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UNIVERSITY OF STRATHCLYDE

UNIDO COURSE ON

"THE DEVELOPMENT OF ADVANCED PHARMACEUTICAL FORMULATIONS"

9th-14th January 1994

Course Organisers:

Professor Neil B. Graham
Dr. Tony L. Whateley

UNIDO WORKSHOP - PROGRAMME

"THE DEVELOPMENT OF ADVANCED PHARMACEUTICAL FORMULATIONS"

6 Nights 5 Days
9th - 14th January, 1994
Venue
Strathclyde Graduate Business School
199 Cathedral Street, Glasgow, G4 OG2, Scotland

Leaders: Professor Neil B. Graham Department of Pure and Applied Chemistry
Dr. Tony L. Whateley Department of Pharmaceutical Sciences

Sunday 9th January

18.30 - 20.00pm	Arrival - Cocktails + Buffet Supper

Monday 10th January

09.00 - 09.15	Professor Neil B. Graham. Welcome
09.15 - 10.15	Professor Neil B. Graham "An Introduction to Controlled Release"
10.15 - 11.10	Dr. Russell Paterson "Principles of Diffusion and Molecular Transport I"
11.10 - 11.30	Tea Break
11.30 - 12.30	Professor Neil B. Graham "The Applications of the Dosage of Practical Programmed Delivery Systems"
12.30 - 13.30	Lunch
14.00 - 15.00	Dr. Russell Paterson "Principles of Diffusion and Molecular Transport II"
15.30 - 17.30	Practical Laboratories
17.30 - 18.30	Group Discussion with Course Staff

Tuesday 11th January

09.00 - 10.30	Professor Ian W. Kellaway "Liposomes"
10.30 - 11.00	Coffee
11.00 - 12.30	Professor Ian W. Kellaway "Nasal and Lung Delivery"

12.30 - 13.30	Lunch
14.00 - 15.00	Group Discussion with Course Staff
15.00 - 17.00	Practical Laboratories

Wednesday 12th January

09.00 - 10.30	Professor Jonathan Hadgraft "Transdermal Delivery I"
10.30 - 11.00	Coffee
11.00 - 12.30	Professor Jonathan Hadgraft "Transdermal Delivery II"
12.30 - 13.30	Lunch
14.00 - 16.00	Practical Laboratories
16.00 - 17.00	Group Discussion with Course Staff

Thursday 13th January

09.00 - 10.00	Dr. Tony L. Whateley "Microspheres and Microencapsulation"
10.00 - 11.00	Professor Clive G. Wilson "GI Tract Transport and Delivery"
11.00 - 11.30	Tea Break
11.30 - 12.30	Mr. R.F. Weir "Regulatory Considerations"
12.30 - 13.30	Lunch
14.00 - 16.00	Practical Laboratories
16.00 - 17.00	Group Discussion with Course Staff

Friday 14th January

09.00 - 10.00	Dr. Tony L. Whateley "Biodegradables"
10.00 - 10.30	Tea Break
10.30 - 11.30	Dr. Tony L. Whateley "Multiple Emulsions"
11.30 - 13.00	Forum to discuss specific problems of delegates

13.00	Lunch
14.30	Coach to Ross Priory on Loch Lomondside and Workshop Closing Dinner

Practical Sessions

1. Preparation of liposomes - TLW
2. Preparation and sizing of biodegradable microspheres - TLW
3. Characteristics of release from hydrogels using USP Dissolution Apparatus - NBG
4. Particle sizing of nasal aerosol delivery systems - TLW
5. Computer simulation of diffusion and pharmacokinetics - CGW, RP, NBG, and TLW
6. Demonstrate of gamma-camera, CGW

Practical Sessions

	Group A	Group B
Monday	Computer Simulation of Diffusion	Diffusion Coefficient on Hydrogel
Tuesday	Automatic Membrane Permeability System	Diaphragm Cell
Wednesday	Preparation of Micropheres (R105)	Sizing of Microspheres and Aerosols (R105)
Thursday	γ-Camera Demonstration (R403)	Preparation of Liposomes (R105)

INSTRUCTIONAL STAFF

Course Organisers:

Professor Neil B. Graham	Department of Pure & Applied Chemistry University of Strathclyde, Glasgow
Dr. Tony L. Whateley	Department of Pharmaceutical Sciences University of Strathclyde, Glasgow

Lecturers:

Professor Jonathan Hadgraft	The Welsh School of Pharmacy University of Wales College of Cardiff, Cardiff, Wales
Professor Ian W. Kellaway	Welsh School of Pharmacy University of Wales College of Cardiff, Cardiff, Wales
Dr. Russell Paterson	Department of Chemistry University of Glasgow, Glasgow
Mr. Robert F. Weir	Controlled Therapeutics (Scotland) Ltd East Kilbride, Glasgow
Professor Clive G. Wilson	Department of Pharmaceutical Sciences University of Strathclyde, Glasgow

LABORATORY DEMONSTRATIONS

INSTRUCTIONAL STAFF

Christopher R. Moran	Department of Pure & Applied Chemistry University of Strathclyde, Glasgow
Marion McNeill	Department of Pure & Applied Chemistry University of Strathclyde, Glasgow
Sam McFadzean	Department of Chemistry University of Glasgow, Glasgow
Tony L. Whateley	Department of Pharmaceutical Sciences University of Strathclyde, Glasgow
Isabel Crossan	Department of Pharmaceutical Sciences University of Strathclyde, Glasgow
Pauline Fallon	Department of Pharmaceutical Sciences University of Strathclyde.Glasgow

Laboratory Sessions

Automatic Multi-Cell, Multi-Lambda Membrane Permeability System
Christopher R. Moran

Measurement of the Diffusion Coefficient of Proxyphylline in a Fully Hydrated Poly(ethylene oxide) hydrogel
Release of Proxyphylline from a Dispersion in a Poly(ethylene oxide) Xerogel in the Form of a) A Tablet and b) A Sphere
Marion E. McNeill

Theory of the Diaphragm Cell
Sam McFadzean

Preparation of Liposomes
Tony L. Whateley

Particle Sizing of Microspheres and Aerosols
Tony L. Whateley and Pauline Fallon

Preparation of Microspheres
Isabel Crossan and Tony L. Whateley

Demonstration of Gamma-Camera
Clive G. Wilson

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Professor Neil B. Graham

POLYMERIC INSERTS AND IMPLANTS FOR THE CONTROLLED RELEASE OF DRUGS

Neil B. Graham and David A. Wood

TABLE OF CONTENTS

I. INTRODUCTION

Polymers are intrinsic to all living sytems, and life as we know it could not exist without the presence of organized large molecules. They fill a number of roles of which three may be clearly identified as follows.

1. Contributing mechanical strength to skeletal structures exemplified by bones, sinews, and muscles in humans and to cell membranes in all life at the cellular level
2. Providing very specific chemical action, as for example, their function as enzymes, RNA, DNA, and certain hormones
3. Controlling the concentration of small molecules in intra- and extracellular fluids by acting as membranes with precise diffusion characteristics or as adsorption centers to maintain a low, precisely controlled level of dissolved low molecular weight species

The increasing basic knowledge of the chemistry and biochemistry of cellular and body functions combined with an expanding analysis of the engineering operation of body parts has led in the past decade to an explosion of research into three areas related to (1) prosthetic devices, (2) polymeric drugs, and (3) drug carriers and devices for the controlled release of drugs. This chapter will discuss the latter class (3) with some additional brief reference to (2) as in reality overlap occurs between these classifications.

The principles of controlled release of biologically active compounds are found in a multitude of applications as varied as preventing barnacles from adhering to ships' bottoms, promoting the growth of trees, keeping flies out of houses and fleas off pets, to the particular focus of this work, that of the prophylaxis and treatment of human diseases. The usual method for drug administration is by taking tablets at intervals during the day. This technique is far from ideal as it provides wide variations in plasma levels at different times as shown in Figure 1 for a patient taking four tablets per day. For every drug there is a so-called therapeutic index which measures the ratio of the plasma level of the drug causing toxic side effects in a defined proportion of subjects to the level which is therapeutically ineffective. Obviously, drugs with high therapeutic indexes are the most desirable and those with low values will be suspect because of the probability of plasma levels becoming either too high or too low with undesirable consequences in both cases. A controlled release dosage form should achieve the "desired level" providing more consistent protection without toxic effects. The removal of the necessity for a patient to comply to a prescribed dosage regimen is also a major advantage of such systems.

Certain drugs, such as the prostaglandins, are rapidly metabolized to inactive compounds and effectively eliminated from the body. In this way the organism protects itself against continuation of the often dramatic effects induced by minute quantities of such active materials. For their application in therapy, a continuous adminstration is often necessary and a simple controlled release device provides an attractive alternative to an i.v. infusion.

Yet another benefit of controlled release is in reducing the patient exposure to a massive excess of drug over that required at the desired site of action. Normal therapy involves a gross overkill technique in which the entire body is subjected to drug when only a small local concentration is required.

The benefits of controlled release devices can thus be summarized as follows:

1. To improve the control of systemic blood levels of drug
2. To localize drug action at a particular site
3. To eliminate patient compliance problems

Major research effort is currently being made to apply the principles of physical chemistry,

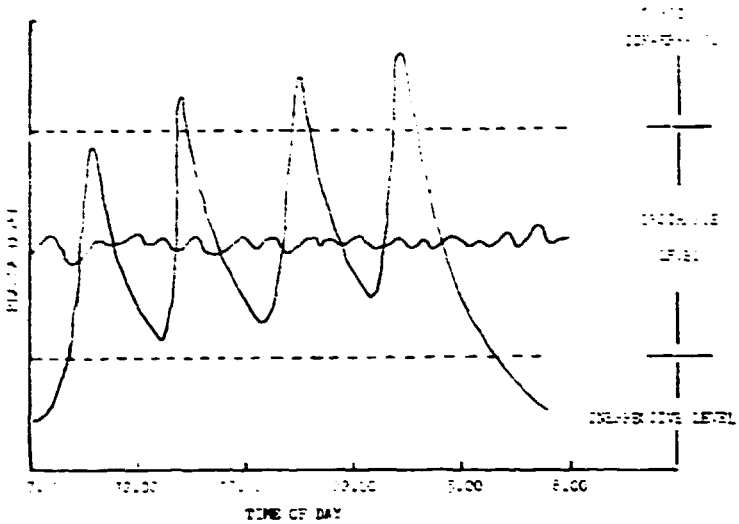


FIGURE 1. Hypothetical plasma level of drug with conventional multidosing schedule (e.g., four tablets daily) compared with controlled release device.

polymer science, and engineering to the design of controlled release devices for human and veterinary application. The pace of advance is rapid, and it is perhaps surprising the precision that has already been achieved in the release of drugs from quite complex polymeric devices and a high degree of precision promises to be obtained from even simpler polymer systems.

Conventional hydrophobic polymers, as rate controlling membranes or matrices, often will not provide a high enough release rate for short-term applications — particularly when water-soluble drugs are being used. They also have a significant disadvantage in that for surgical implantation (rather than insertion) in general two minor operations are required (i.e., for both implantation and removal of the device). Water-swollen matrices, commonly called hydrogels, will provide high permeation rates for water-soluble drugs while biodegradable polymer matrices offer a major potential improvement in the design of controlled release devices for implantation as they may decompose in vivo to nontoxic products which are readily eliminated from the body.

These sophisticated delivery devices can be conceived in many different shapes and sizes. Such devices could be utilized without surgery as inserts into accessible body cavities such as the conjunctival sac of the eye, the ear, mouth, GI tract, rectum, uterus, and vagina or merely placed in contact with the skin as in a transdermal therapeutic system.

An understanding of the physical and organic chemistry of the polymers used for these devices is most important if they are to be well-designed and this will be emphasized for the various types of controlled release devices. The principles involved are reasonably well-defined, but the precise predictions of the physical chemist can often be complicated or even confounded by the added complexity encountered when the device is placed in living tissue which may encapsulate, degrade, calcify, or swell it. An interdisciplinary approach is required for successful research in this field.

II. PHYSICAL FORMS OF DRUG-POLYMER COMPOSITES AS INSERTS AND IMPLANTS

All physically controlled drug release devices can be classified into two distinct types as shown in Figure 2: (1) matrix devices in which the drug is dispersed throughout the polymer or can in some cases be completely soluble in the polymer and (2) membrane devices in which a core of drug is enveloped by a polymeric membrane. These two fundamental types form the basis for systems with a variety of geometrical configurations and topography.

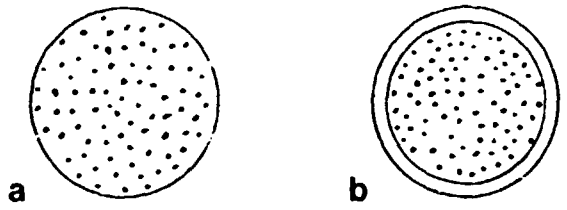


FIGURE 2. Schematic representation of controlled release devices. (a) Matrix device with dispersed drug; (b) membrane device with reservoir of drug.

Matrices are composed of solid polymer in which the drug is dissolved or dispersed. In most cases the loading of the drug exceeds its solubility in the polymer and the drug is present as a homogeneous dispersion of fine particles. These types are also referred to as monolithic devices and can be prepared by a variety of methods. With thermoplastic polymers, such as poly(lactic acid), a drug is dispersed in the melt which can be transfer molded as beads or extruded into rods.[1] Films can be prepared by casting from a common solvent system[1,2] and spray-drying from a solvent produces injectable powders.[3] When the polymer cannot be processed in this way, the polymerization reaction is often carried out in the presence of drug. Using this method, reactive liquids are polymerized by thermal curing[4] or irradiation[5] in molds to produce highly cross-linked matrices. In the case of hydrogels, it may be more convenient to prepare the polymeric device in a desired form prior to loading with a solution of the drug.

The membrane devices consist of a reservoir of drug, often dispersed in solvent, enveloped by a polymeric membrane which controls the rate of release of the drug to the surrounding medium. Microscopic devices take the form of microcapsules[6,7] or nanocapsules[3] while macroscopic devices can take a variety of shapes with the hollow cylinder being the most easily fabricated and most widely studied.[9,10] In general, a hollow tube of polymer is cut to the desired length and sealed at one end; the lumen is then filled with drug and the other end is sealed.

This chapter concentrates on the above types of formulation which involve the polymer as a "physical carrier". However, it should be noted that polymers are increasingly being used as "chemical carriers" in controlled release applications. In this case the drug molecules are linked to a polymeric backbone,[11,12] perhaps by spacer groups, or can be monomers or comonomers used to prepare polymeric molecules.[13,14] These polymers may be either soluble or insoluble in the body fluids at the time of administration. These approaches to drug therapy introduce the fields of polymeric drugs,[15,16] affinity labeled drugs,[17,18] and biologically active polymers.[19,20]

III. RELEASE MECHANISMS AND PREDICTION OF RELEASE PROFILES

The release of drug from any of the different forms of drug-polymer composites, described above, must be predictable and often a constant release rate (zero order) is desired. For many years a considerable amount of mathematical analysis of the theoretical rates of diffusional[21,22] release from the various fixed geometrical configurations has been reported and correlated with experimental results. Three other basic rate determining mechanisms can control the release profile of drug, these being found in swelling, boundary-layer controlled, and erodible devices. The basic concepts involved in the treatment of each of these mechanisms are given below and are followed by a discussion of how these and polymer structure are related.

A. Membrane Devices

Diffusion of a solute, such as a drug molecule, through a polymer occurs as random

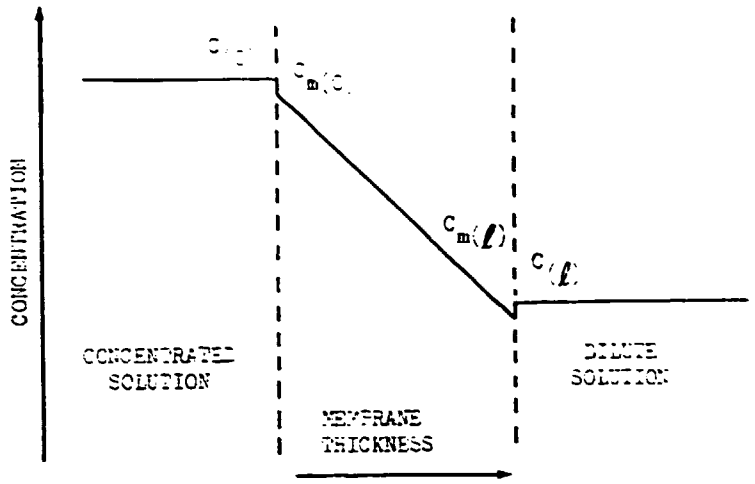


FIGURE 3. Diffusion of solute across a polymeric membrane showing concentration differences.

molecular movement and because a concentration gradient exists between the polymer phase and the external phase the drug tends to diffuse down the concentration gradient. It is generally assumed that the processes involved obey Fick's first law which for diffusion in a nonporous solid polymer membrane can be expressed as:

$$J = -D \frac{dC_m}{dx} \tag{1}$$

Where J is flux (g cm^{-2} sec^{-1})
C_m is the concentration of the permeant in the membrane (g cm^{-3})
$\frac{dC_m}{dx}$ is the concentration gradient, and
D is the diffusion coefficient (cm^2 sec^{-1})

The negative sign reflects that the direction of flow is down the gradient.

Figure 3 shows the arrangement found for a membrane which separates two solutions of different concentration. It is assumed that the concentration of permeant in the surface layer is in equilibrium with either side. Therefore, if K is the partition (or distribution) coefficient of the solute between the two phases;

$$C_{m(0)} = K C_0 \text{ upstream } x = 0$$

$$C_{m(\ell)} = K C_\ell \text{ downstream } x = \ell$$

In the steady state

$$J = \frac{D (C_{m(0)} - C_{m(\ell)})}{\ell} \tag{2}$$

$$= \frac{D \Delta C_m}{\ell} \tag{3}$$

where ℓ is membrane thickness. Usually the concentration in the membrane is not known and ΔC is measured as the concentration difference between the two sides so that:

$$J = \frac{D\,K\,\Delta C}{\ell} \tag{4}$$

The terms D and K are not always easily measured and frequently values of permeability (P) are quoted where

$$P = D\,K \tag{5}$$

Therefore for a membrane device with constant activity, such as one with a saturated solution of the permeant over a large excess of insoluble material, the steady state release rate is expressed by:

$$\frac{dM_t}{dt} = \frac{A\,D\,K\,\Delta C}{\ell} \tag{6}$$

where M_t is the mass released and A is the surface area of the device. When the concentration of drug in the surrounding body fluids is maintained at an extremely low level (i.e., sink conditions), the term ΔC in Equations (4) and (6) can be replaced by C_s, the saturated concentration of drug in the reservoir.

In membrane devices, particularly seen with steroid-silicone systems, "burst" and "lag" effects are found. Newly prepared devices require a period of time to establish a concentration gradient within the membrane and a "lag" effect is found if drug release from the device is assessed. When devices of this type have been stored for some time, the membrane becomes saturated with drug and a "burst" effect, observed as a higher release rate, is found until the concentration gradient associated with the steady state is established. Burst or lag effects are commonly encountered in most types of devices.[23] Inert[24] and biodegradable[25] matrices may often exhibit burst effects due to the presence of crystals of the drug at the surface[26] which readily dissolve when the device is placed in an aqueous environment.

B. Release from Monoliths with Dissolved Drug

The exact solutions for the desorption of solutes from a medium of given simple geometry (e.g., sphere, cylinder, and slab) are available in standard works.[27,28] However, these equations are clumsy for routine use and several approximate solutions can be used for early time and late time release (Table 1). An even simpler unifying equation for the simple geometric forms can be used if less rigourous treatment is acceptable; in this the fraction released at time, t, is given by:

$$\frac{M_t}{M_\infty} = 2\frac{S}{V}\left(\frac{Dt}{\pi}\right)^{1/2} \tag{7}$$

where M_t is the amount of drug released after time, t, M_∞ is the amount present initially, and S and V are the surface area and volume of the device. Practically "blocks", short cylinders, and disks are met more frequently and solutions for these are available in three dimensions where "end-effects" and "edge-effects" require to be taken into account.

C. Release from Matrices with Dispersed Drug

In many cases, the solubility of a particular drug in a given polymer is much lower than that required to provide an adequate amount of drug in a device of limited size. When this situation is encountered, the drug is assumed to be homogeneously dispersed as small particles throughout the polymer. The release kinetics of this type of system were derived by Higuchi,[29] using a model which assumes that the solid drug dissolves from the surface layer and that

Table 1
APPROXIMATE SOLUTIONS FOR DIFFUSIONAL RELEASE OF SOLUTES FROM SLABS, CYLINDERS AND SPHERES (SEE TEXT FOR DEFINITIONS OF SYMBOLS)

Geometry	Early time	Late time
Slab r = thickness	$\frac{M_t}{M_\infty} = 4\left(\frac{D\,t}{\pi\,r^2}\right)^{1/2}$	$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\exp\left(\frac{-\pi^2\,D\,t}{r^2}\right)$
Cylinder r = radius	$\frac{M_t}{M_\infty} = 4\left(\frac{D\,t}{\pi\,r^2}\right)^{1/2} - \frac{D\,t}{r^2}$	$\frac{M_t}{M_\infty} = 1 - \frac{4}{(2.405)^2}\exp\left(\frac{-(2.405)^2\,D\,t}{r^2}\right)$
Sphere r = radius	$\frac{M_t}{M_\infty} = 6\left(\frac{D\,t}{\pi\,r^2}\right)^{1/2} - 3\,\frac{D\,t}{r^2}$	$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left(\frac{-\pi^2\,D\,t}{r^2}\right)$

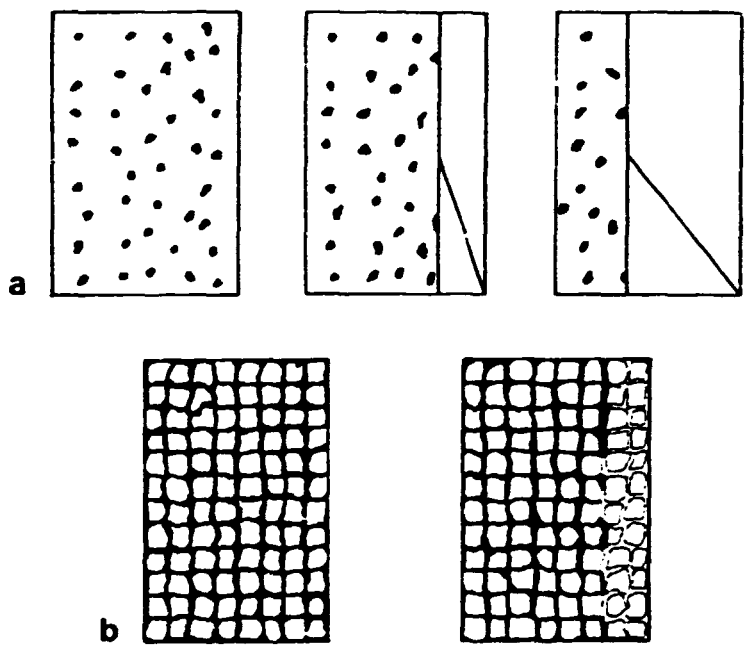


FIGURE 4. Models of drug release from polymeric devices. (a) Drug dispersed in continuous polymer; (b) drug dispersed in capillary channels of a porous polymer matrix.

this layer becomes exhausted of dispersed drug particles, as shown in Figure 4a. From the figure the dependence of concentration gradient with time is apparent. The validity of this matrix-controlled model has been demonstrated in several experimental studies.[30,31] In particular, the visual appearance of cylinders containing dispersed particles of steroid has shown a gradual depletion of the steroid from the surface layer which progressed towards the core with time.[32] The derivation of the Higuchi Equation (8) relies on Fick's first law and assumes:

1. A Pseudosteady state exists.
2. The drug particles are small compared to the average distance of diffusion in the device.
3. The diffusion coefficient is constant.
4. Perfect sink conditions exist in the external medium.

$$Q = (C_s\,D_s\,(2A - C_s)\,t)^{1/2} \qquad (8)$$

and when

$$A \gg C_s \qquad Q = (2 C_s D_s A t)^{1/2} \tag{9}$$

where Q is the amount of drug released at time, t, C_s is the solubility of drug in the polymer, and A is the amount of drug present initially.

The most important point to note from these equations is that the amount of drug released is related to the square root of time (Q-$t^{1/2}$ relationship) essentially throughout the lifetime of the device. Whereas with monoliths with dissolved drug a Q-$t^{1/2}$ relationship is found initially and the second half of the release decays exponentially (see Table 1). Higuchi suggested that the Equation (8) would be valid only for systems in which A is greater than C_s by a factor of three or four. More recently, the model has been developed and the newer equations can be used with more accuracy over a wider range of conditions.[33,34]

D. Release from Devices with Capillaries and Pores

All of the above models were based on simple diffusion of a permeant molecule in a homogeneous polymer phase. If, however, the polymer phase is discontinuous, such as in the situation where a considerable volume fraction of drug has been compressed into an infinite slab with a polymer powder, the situation is more complex. The small extent of diffusion through the polymer is neglected and it is assumed that diffusion occurs predominantly in the capillaries between polymer particles and through the pores left behind as drug particles dissolve and are replaced by the permeating liquid (Figure 4b). Account must be taken of the increase in the length of the diffusional path around the inert polymer particles and the effective cross-section of diffusion must be reduced to allow for the fact that the cross-section available for diffusion is that of the permeant-filled holes left behind by the drug particles after dissolution and not the total volume of the inert polymer-drug-permeant combination.

Higuchi[35] developed a similar equation to that above Equation (8) for release of drug from one face of an inert granular matrix containing a dispersion of drug. The increased path length in the capillaries using a tortuosity factor ($\tau = 3$) and the cross section of pores left by the dissolved drug by a porosity factor (ϵ) were taken into account. This provides an equation,

$$Q = (C_s D_s \frac{\epsilon}{\tau} (2A - \epsilon C_s) t)^{1/2} \tag{10}$$

where C_s and D_s are the solubility and diffusion coefficient of the drug in the permeating fluid. The terms Q, A, and t have similar definitions as in Equation 8 and again a Q-$t^{1/2}$ relationship is predicted. Higuchi deduced a related equation for the release from spheres of the same composite structure. More recently, the basic Higuchi models have been developed for more practical shapes — disks, biconvex tablets, and cylinders.[36-38]

Since it was first introduced, the Higuchi Equation (10) has frequently been applied to experimental data, particularly inert granular matrix tablets of the sustained-action type for oral administration. In some cases, the fundamental parameters have been studied in great detail. Values for C_s and D_s for a particular drug can be determined readily using conventional techniques. Desai et al.[39-42] studied the release of various drugs and model compounds from polyethylene and poly(vinyl chloride) matrices and described the components involved in the porosity term, ϵ, and how to evaluate them. When the matrix tablets were subjected to vacuum treatment prior to study, tortuosity values obtained experimentally for poly(vinyl chloride) were in the range 1.5 to 4, which is in good agreement with theoretical values.[42] Similar studies with polyethylene matrices produced tortuosity values in the range 7 to 10

when a surfactant was added to the elution medium to wet the polymer.[41] Both types of polymer required some pretreatment before ideal release behavior was found and the differences in tortuosity values was attributed to the different particle size and density of the polymer powders. Apparent tortuosity values of the order of a thousand were found with polyethylene matrices when surfactant was not used to aid the removal of air from within the pores. In further extensions of these studies, the theoretical equations for the release of two noninteracting[43] and two interacting drugs[44] were presented and compared with experimental data.

Increasingly, other polymers (generally hydrophilic) are being included as additives to formulations in an attempt to modify the release rate from the major polymer component. In this way, the addition of gelatin or sodium alginate to silicone cylinders was found to increase the release rate of morphine sulfate (hydrophilic drug.)[45] When 20% alginate was added to the formulation, the devices swelled with water forming microscopic pores and channels and about 90% of the drug was released after 10 days compared to 9% from devices without alginate. The release of morphine sulfate was found to follow second-order kinetics and a loss of alginate was observed throughout most of the period of drug release. The release of macromolecules, such as proteins, from ethylene-vinyl acetate copolymers[46] may occur by a similar mechanism involving the uptake of water by osmotic pressure resulting in the formation of microchannels.

E. Release from Hydrogels

With hydrogels a considerable proportion of the device is composed of water which may be several times the dry weight of the polymer. When the hydrogel is initially swollen and contains water-soluble drug, the release equations given previously (i.e., Table 1) can be applied. Davis[47] deduced the following empirical expression to calculate the apparent diffusion coefficient of any soluble drug in any hydrogel,

$$D_p = D_0 \exp -(0.05 + 10^{-6}M)P \qquad (11)$$

where D_p is the diffusion coefficient of the solute in the swollen polymer gel containing P% (by weight) of polymer; M is the molecular weight of the solute; and D_0 is the diffusion coefficient of the solute in water. The study involved both cross-linked poly(acrylamide) and poly(vinylpyrrolidone) hydrogels and solutes with a wide range of molecular weight (125,000 to 150,000) and included radio-labeled rabbit immunoglobulin, bovine serum albumin, insulin, a prostaglandin, and sodium iodide.

Various forms of the Higuchi Equations (8) and (10) have been used to describe the release of drugs from hydrogels,[48] and in a study by Chien and Lau,[49] the diffusion coefficient in the gel D_m ($D_m = D_w^s$) was related to the degree of cross-linking.

The release kinetics from initially dry hydrogels, as would be expected, are complicated by the added consideration of the diffusion of solvent into the polymer. Good[50] has derived equations where the diffusion coefficient is a time dependent variable and fitted experimental data based on the release of a water-soluble drug (tripelenamine·HCl) from a poly(2-hydroxyethyl methacrylate) hydrogel. This hydrogel had a low degree of swelling and the water uptake was approximately balanced by the loss of drug, and the dimensions of the device were assumed not to change during release. Recently, the much more complex situation of diffusion from a device which is simultaneously swelling,[51,52] and undergoing dimensional change, has been analyzed.

F. Boundary-Layer Controlled Release

With drugs which are very poorly water soluble, the external medium in contact with the polymer phase may become saturated with drug and the release from the device is effectively

stopped until drug has diffused out of the unstirred boundary layer. As an example of this phenomenon, also termed partition controlled release, Chien et al.[53] studied the release of estradiol diacetate from silicone devices and found a desirable zero-order (Q-t relationship) release when the steroid was poorly soluble in the eluting medium (water). However, when increasing proportions of poly(ethylene glycol) were added to increase the solubility of the steroid in the eluting medium, the release profile changed to a typical matrix-controlled type ($Q\text{-}t^{1/2}$ relationship).

The boundary-layer effect has considerable implications in vivo[54] where the composition and the movement of the eluting medium may vary from site to site. The effect should be considered when in vitro release kinetics are compared with in vivo release[49,55-57] and the in vitro methodology designed to favor reasonable correlation. If the release characteristics of a device change with the rate of stirring in an in vitro test, it is a strong indication of some measure of boundary control.

G. Release from Erodible Devices

Hopfenberg[58] considered controlled release from erodible slabs, cylinders, and spheres. Where a single zero-order process controls erosion, the theoretical equations can be rearranged in the form

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_0 a}\right)^n \qquad (12)$$

where k_0 is the single zero-order rate constant for the erosion process. C_0 is the uniform initial concentration of drug, M_t is the amount of drug released at time, t, and M_∞ is the total amount of drug present initially. For the infinite slab, $n = 1$ and a is the half-thickness; for the cylinder, $n = 2$ and a is the radius; for the sphere, $n = 3$ and a is the radius. From the analysis, it is evident that zero order is only obtained from the infinite slab and that delivery rates from cylinders and spheres should decrease with time. It is implicit in the overall concept that a boundary exists between unaffected polymer and the previously degraded material and that the rate determining step occurs at the boundary . Specifically, water sorption by the polymer and the diffusion of the drug out of the matrix have negligible effect on release rate. Cooney[59] discussed the effect of geometry on the dissolution of pharmaceutical tablets presenting the common shapes and suggesting that spheres and cylinders with internal bores cross and clover leaf-shapes may offer better release profiles.

Devices which undergo surface erosion have been reported,[60] however, at this time, most biodegradable systems have release profiles complicated by water sorption, degradation in the bulk, and diffusion of the drug from bulk polymer.

IV. FUNDAMENTALS OF POLYMER CHEMISTRY FOR THE CONTROLLED RELEASE OF DRUG FROM POLYMERIC MEMBRANES AND MATRICES

In controlled release applications, the drug molecule is chosen for its biological action in a particular therapy and therefore is generally not considered to be a variable. Furthermore, in any proposed application the amount (dosage level) released over a chosen time scale from a particular dosage form are the desired objectives at the outset.

The physicochemical properties of the drug can have significant effect on its release from any polymeric system and molecular size, concentration, and solubility both in body fluids and the polymer are of extreme importance.

Perhaps the most important parameter in any controlled release system is the diffusion coefficient of the drug in the polymeric device. The rate of diffusion of one molecule through a medium depends mainly upon:

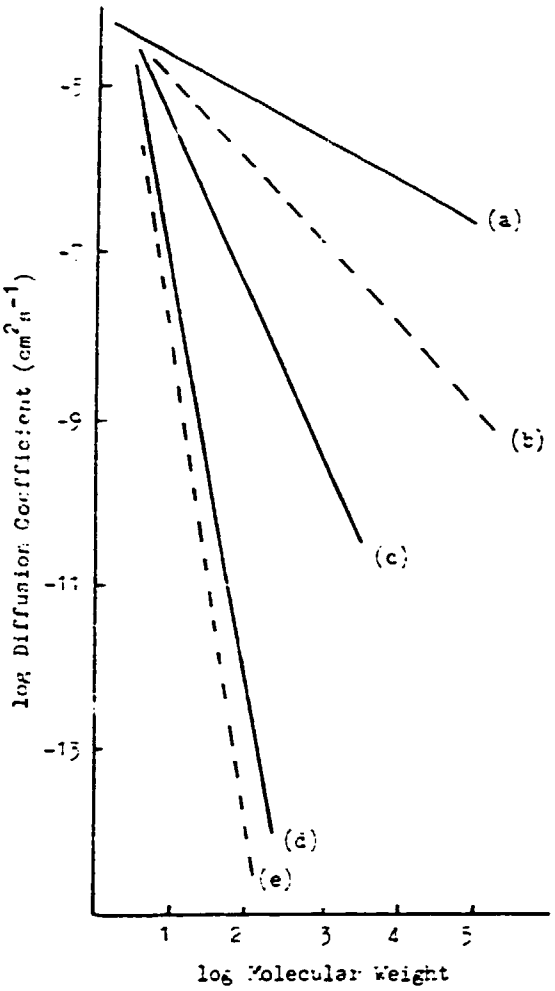


FIGURE 5. Relationship between log molecular weight of drug and its diffusion coefficient in different media. (a) Aqueous solution; (b) possible plot for a hydrogel; (c) a natural rubber; (d) an organic glass (polystyrene); and (e) possible plot for a cross-linked glassy polymer (some data from Reference 23).

1. The thermodynamic driving force which can approximate to a function of a concentration difference
2. The size of the diffusing molecule
3. The resistance to molecular movement presented by the medium

A. Physical States and Structure of Polymers

The density of a polymer, indeed any particular material, will usually decrease in the order crystalline state, glassy state, rubbery state. This change in density is related to the molecular holes or free volume present in each state. This free volume increases from lowest in the crystalline state to highest in the rubbery state. As the free volume represents the holes into which diffusing molecules jump as they move down a concentration (or chemical potential) gradient, it is easy to postulate in general terms how diffusion coefficients increase as one goes from the crystalline to the glassy and then to the rubbery state. This is illustrated in Figure 5 in which the difference in both diffusion coefficient in different states can be seen and also how the different states show markedly different changes in their response to the diffusion of larger molecules. This plot demonstrates clearly why water-swollen hydrogels provide such appropriate systems for the short-term release of water-soluble drugs by providing the highest available diffusion coefficients amongst polymer matrices.

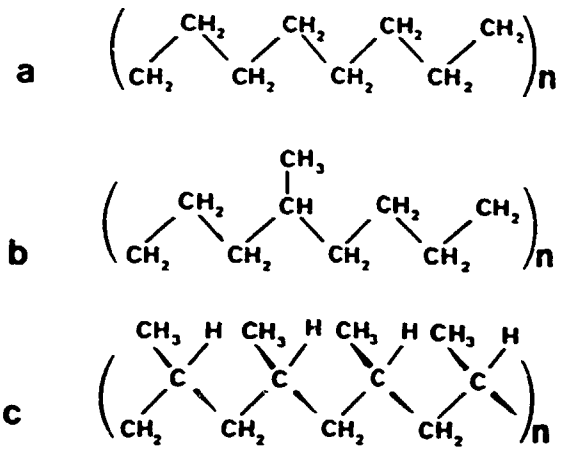


FIGURE 6. Polyethylene and ethylene/propylene structures producing rubber or crystalline polymers. (a) Crystalline; (b) rubbery; and (c) crystalline.

In the glassy state, polymers are hard, rigid, and often brittle.[61] There is a low level of molecular movement and the rate of diffusion of large molecules is very low. On heating at a defined rate, the glassy solid changes to a more flexible rubbery solid over a given small temperature range. Above this so-called glass transition temperature (T_g), the polymer is in the rubbery state and, if not constrained by some molecular interaction or bonding, will exhibit fluid flow. The fluid flow is prevented in many useful plastics by the presence of phase separation, crystallites, or cross-linking.

Crystallites can form in polymers when long sequences of the polymer chain have a stereoregular structure. The simplest example of this is polyethylene as shown in Figure 6. An approximate relationship T_g = (0.5 to 0.66) T_c is found to hold for many polymers (where T_c in degrees Kelvin is the temperature at which the crystallites melt). The main point to note is that $T_c > T_g$ and as polymers are never 100% crystalline such polymers above their T_g contain rubbery portions bound together with varying proportions of crystalline domains through which many chains pass.

Block or graft copolymers as represented in Figure 7 are comprised of long sequences of two or more different polymers. As high molecular weight chains rarely dissolve in each other such block or graft copolymers form a mixture of domains in which polymer separation has occurred and the units of each species have aggregated. If one type of these separate domains is glassy or crystalline while the other is rubbery, the effect is to prevent flow of the chains and hence bulk polymer.

The need for polymers with a range of precise requirements, as in controlled release applications, has led increasingly to the study and use of copolymers. Three broad groups of polymers used in controlled release can be divided into (1) inert hydrophobic, (2) inert hydrophilic, and (3) bioerodible. Examples of these three classes are given later. However, it should be noted that classification is far from simple and many of the devices which have been studied to date have been relatively complex. Classification of groups of polymers should be treated with caution because, for example, the "acrylates" can be

1. Inert hydrophobic, e.g., poly(methyl methacrylate)
2. Inert hydrophilic, e.g., poly(hydroxyethyl methacrylate)
3. Bioerodible, e.g., poly(methyl 2-cyanoacrylate).

B. The Swelling of Cross-Linked Polymers

The ability of a polymer to swell with a given solvent is governed by the free energy of mixing of the solvent with the polymer and by the density of the cross-linking.[62,63] The

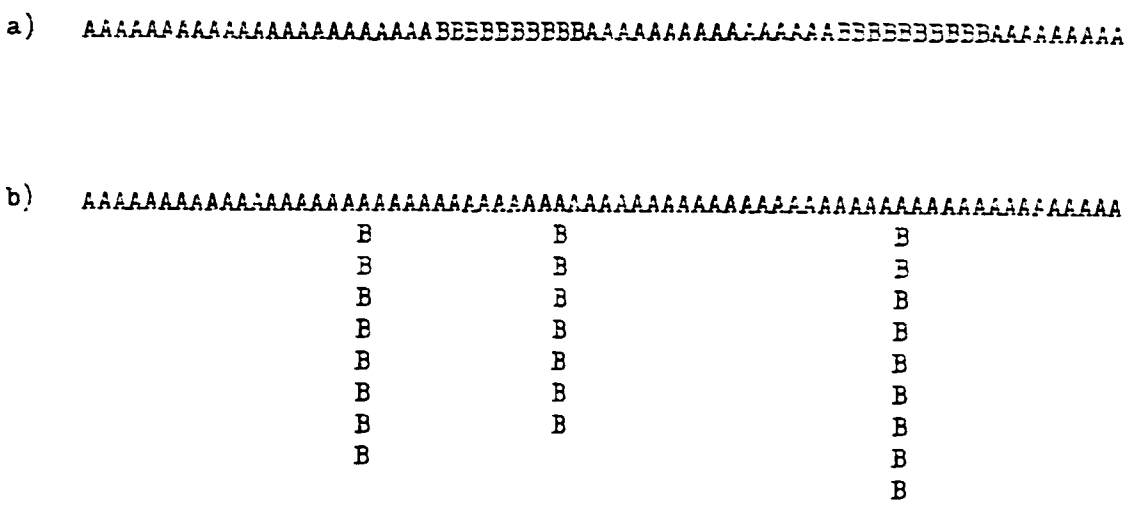


FIGURE 7. Simple representation of (a) block and (b) graft copolymers, where A and B represent units derived from different monomers.

Table 2
DIFFUSION OF ^{3}H-LABELED PROGESTERONE THROUGH VARIOUS POLYMER MEMBRANES

Polymer	Progesterone diffused (%)
Polydimethylsiloxane (Silastic®)	100
Polyamide (nylon)	1.0
Acetylcellulose (cellophane)	0.1
Fluorethylene	0.1
Polyester (Mylar®)	0.1
Polycarbonate (Lexan®)	0.1
Polyethylene	0.1
Polystyrene copolymer (Cr 37)	0.1

From Kincl, F. A., Benagiano, G., and Angee, I., *Steroids*, 11, 673, 1968. With permission.

theoretical analysis of the swelling is complex and will not be discussed here. The combination of a polymer with a swelling solvent which might be a plasticizer in the case of a commonly used membrane such as ethylene/vinyl acetate copolymers or water in the case of hydrogels is commonly used to moderate and control the diffusion of drugs through polymers.

The degree of swelling is increased by reducing the cross-linking density. As diffusion coefficients also increase with increasing swelling this can be used as a means of controlling the rate of release of incorporated soluble drugs.

C. Diffusivity of Drugs in Polymers

Table 2 shows the relative permeabilities of ^{3}H-labeled progesterone in a range of different polymeric membranes[64] and the difference between silicone rubber, with its very flexible backbone, and the other common polymers is readily apparent. The effect of soaking membranes in plasma prior to diffusion experiments with steroid was examined in another study.[55]

In addition to molecular size of the diffusing molecule other physicochemical properties are extremely important. The permeation of a molecule through a membrane is not only dependent upon its diffusion coefficient, but also its solubility in the polymer and its dis-

Table 3
AVERAGE DIFFUSION RATE OF VARIOUS STEROIDS ACROSS SILICONE MEMBRANES

Steroid	Diffusion rate*
19-Norprogesterone	1353
Progesterone	469
Testosterone	317
Megestrol acetate	236
Norethisterone	73
Estradiol	61
Mestranol	43
Corticosterone	21
Cortisol	6

* $\mu g/(100\ mm^2)\ (0.1\ mm)\ (24\ hr)$.

From Kincl, F. A., Benagiano, G., and Angee, I., *Steroids*, 11, 673, 1968. With permission.

tribution coefficient between the polymer and the external medium. The effect of small changes in the structure of steroid molecules on their release from silicone[64] is shown in Table 3. Detailed studies[65-67] have since been carried out to relate the effect of these slight changes which have negligible effect on molecular size, but considerable effect on solubility. Similar studies have been reported for the release of steroid from hydrogels.[68]

Other additives apart from the drug may produce significant effects and can be used to modify the release profile. The effects of fillers[67,69] and plasticizers have been extensively studied while copermeant enhancement[70] and the addition of hydrophilic polymers[45] to produce a heterogeneous polymer matrix with microchannels appear to add further design variables. In the latter approach, as discussed previously, high molecular weight water-soluble materials (e.g., proteins) can be released from a hydrophobic polymer by the formation of microchannels.

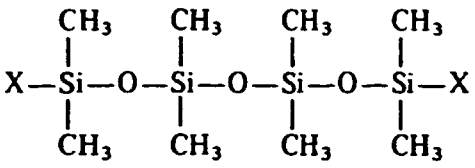
V. HYDROPHOBIC NONDEGRADABLE DEVICES

The release of biologically active compounds from "inert" synthetic polymers has been the subject of a considerable amount of research for many years and probably most classes of polymer have been screened in some controlled release application or another. Table 2 showed some which were studied as potential membranes for the release of steroids. Inert synthetic polymers have also been investigated as the wall material of microcapsules and many processes and applications have been reported. It is clear that in many cases the release rate of drug from simple macroscopic devices would be inadequate for most applications. However, two groups of polymers which showed some potential, the silicones and the substituted polyethylenes discussed in some detail below, have been the subject of concentrated study and their advantages and limitations have become apparent.

A. Silicones

Silicone rubber[71] has been used in a variety of biomedical applications due to its inertness and good biocompatibility. In 1964, Folkman and Long[72] reported the use of this polymer in sustained release formulations.[73]

The backbone of the silicone polymer is made up of alternating silicon and oxygen atoms and the most widely used member of the family is poly(dimethylsiloxane). This material can be prepared as a fluid elastomer or a resin and is available commercially as Silastic®.



Silicone polymers end-blocked (group denoted X above) with CH_3, are unreactive and generally used as fluids. Alternatively, chains can have reactive hydroxyl end groups which may be cross-linked by curing at room temperature and these are used to prepare molded or cast devices. This type of polymer has been widely studied in implants and inserts for the controlled release of steroids,[66,67,74] chloroquine,[75] pyrimethamine, indomethacin,[76] atropine, and histamine.[77] The devices are generally macroscopic implants of both the membrane and the matrix type. Chien and Lambert[78] developed a system with microsealed compartments (10 to 200 μm) containing drug in a hydrophilic solvent enclosed within a matrix of silicone polymer. By careful choice of the composition of the hydrophilic solvent [e.g., aqueous solutions of poly(ethylene glycol)], the release rates of various drugs could be controlled over a wide range. A microsealed device of this type which delivered deoxycorticosterone acetate, was used to study the production of metacorticoid hypertension in rats.[79]

While the flexibility of the backbone of the silicone polymer in combination with the saturated solubility level of hydrophobic drugs in the polymer allows adequate release rates to be obtained, the release of hydrophilic drugs will be considerably slower due to their lower solubility. Attempts to increase the permeability of the silicone poiymer to hydrophilic drugs employed the addition of a considerable proportion of hydrophilic polymer (e.g., sodium alginate) to produce microchannels, as described above. Devices modified in this way have been used to study morphine induced tolerance and physical dependence in animals.[80]

B. Substituted Polyethylene

High density polyethylene is used in a variety of biomedical applications and the low density material has been used in the fabrication of a contraceptive intrauterine device which also releases progesterone.[81] The local release of a steroid, such as progesterone, has a synergistic effect on the contraceptive action of the device which is provided by its physical presence. This local direct drug action in the uterus reduces systemic side effects to undetectable levels and normal menstrual cycles occur. For controlled release devices, it is usual to add other monomers to provide a range of copolymers with the desired characteristics (see Figure 8). Thus, the Progestasert® device (Alza Corportion) uses an ethylene-vinyl acetate copolymer (9% vinyl acetate) as a rate controlling membrane. In this way a constant release of 65 μg/day of progesterone is obtained for a period of 1 year.[82,83] Another device developed by the Alza Corporation, and approved by the FDA in the U.S. is the Ocusert Pilo. The device, composed of two membranes of ethylene-vinyl acetate copolymer, is inserted into the cul-de-sac of the eye and provides a constant release of pilocaprine for the reduction of intraocular pressure in glaucoma. The two devices available, Pilo 20 and Pilo 40, release at a rate of 20 or 40 μg/hr for 1 week and offer much better control than eye drops instilled several times daily and remove problems with patient noncompliance.

The effect of the comonomer ratio of ethylene and vinyl acetate on the in vitro release of hydrocortisone from molded devices was studied by Fu et al.[84] It was found that increasing the proportion of vinyl acetate, thereby changing crystallinity, increased the release rate. In another study, an ethylene-vinyl acetate copolymer (40% vinyl acetate) was used to prepare

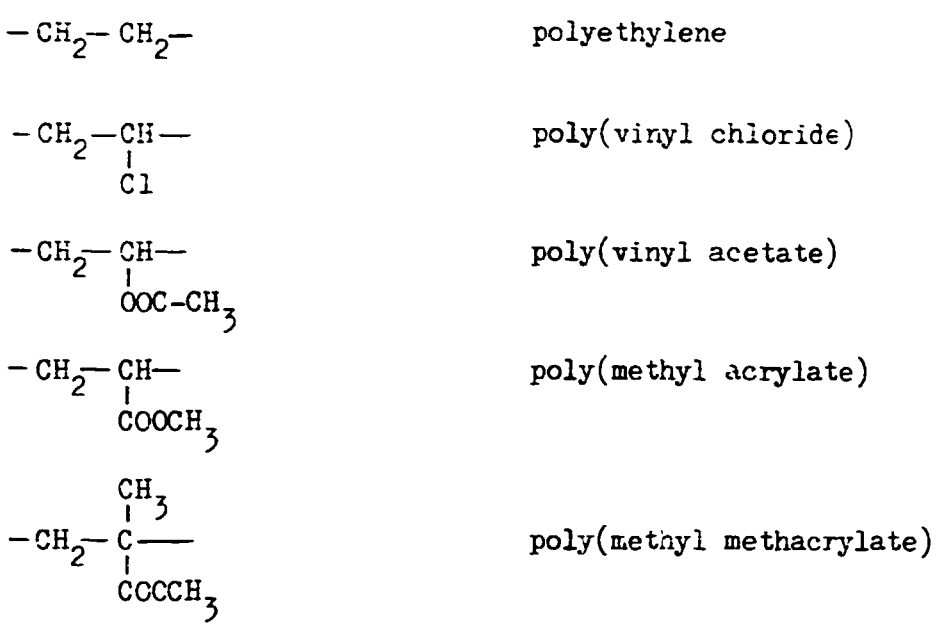


FIGURE 8. Some examples of the repeating units of substituted polyethylene polymers which have been used in controlled release devices.

pellets which released biologically active macromolecules (e.g., soy bean trypsin inhibitor, lysozyme, alkaline phosphatase, catalase, insulin, heparin, and DNA) for times in excess of 100 days at relatively constant rates depending on the particular preparation.[46] It was suggested that copolymers of this type could be used to prepare carriers for a wide range of enzymes and other biologically active macromolecules which would release at desired rates.[85] While it seems likely (see before) that the hydrophilic macromolecules would draw water into the matrix and swell it with the formation of microchannels, it was noted in that study that once the macromolecule had been released the membrane was not permeable to molecules of similar size.

Both polyethylene and poly(vinyl chloride) have been used to prepare matrix tablets by compression of the powdered polymer with hydrophilic drug and under certain conditions were found to obey the Higuchi Equation (10). Similar studies have been carried out with copolymers of methyl acrylate and methyl methacrylate.[86,87] Recently, methyl methacrylate membranes have been applied to a core of poly(hydroxyethyl methacrylate) and the resulting trilaminate device has provided zero order release of tetracycline for periods in excess of 100 days.[88] The trilaminate devices, when implanted intraperitoneally in rats, were used in a pharmacokinetic study of tetracycline.[89]

Surgeons using methyl methacrylate as a bone cement in total replacement of joints, especially hip joints, have found that the addition of antibiotics to the cement prior to use significantly reduced the incidence of infection. Several studies have been carried out[90,91] and the effect of several antibiotics on the mechanical properties has been reported.[92,93] The concept led to the evaluation of implantable beads of poly(methyl methacrylate) containing gentamycin for the treatment of chronic bone infections.[94] Such beads have been found in vitro and in vivo to provide adequate release locally for several months while serum concentrations were low thereby minimizing the risk of problems with side effects.

Devices composed of cross-linked diethylene glycol dimethacrylate have been prepared by γ-irradiation of the frozen monomer at $-78°C$.[95,96] Mixtures of the monomer with a variety of anticancer drugs were molded, frozen, and irradiated.[5] The effect of the incorporation of other polymers (e.g., poly(ethylene glycol), poly(methyl methacrylate), and poly(vinyl acetate) at 10% of the total weight) on the release profiles of the drugs were briefly discussed. It was found that the rate of release could be greatly enhanced by some of these incompatible additives which formed microchannels in the glassy matrix.

It is readily evident that a very diverse range of devices can be prepared from simple polymers, such as the two groups discussed above. Various constraints are placed by the solubility of the drug and the desired duration of action and in general each case has to be studied in some detail.

VI. HYDROGEL SYSTEMS

Hydrogels comprise a large group of polymers which swell to a considerable degree with water. They have attracted considerable interest in prosthetic applications such as contact lenses or promising nonthrombogenic surfaces and in the context of this chapter as matrices for the controlled release of drugs. Their most interesting attribute is their high permeability to water-soluble drugs which is in contrast to the low permeability of these materials often obtained with hydrophobic polymers such as silicones. Their physical strength and durability in the dry and swollen states are important factors in their practical application and some indications of how these can be optimized are discussed later. They obey the release equations described earlier and can be obtained in monolithic slab, cylinder, or spherical configurations and also in envelope or matrix forms, all with the kinetics predicted by the well-developed mathematical models. Powders of hydrogels can provide injectable formulations which may be further developed.[97] The kinetics of release from devices which are changing their dimensions during their effective lifetime have recently been modeled, while other studies on systems which both lose crystallinity and swell simultaneously have been shown to provide constant rates of drug release from a monolithic device — something which is very useful, but not to date predicted by theory. Polymers can be designed which are hydrophobic at one pH and change to hydrophilic hydrogels at another. These can be used to design matrices which only release their contained drug at a particular pH. These points of design will be discussed in more detail below.

A. The Polymers Used in Hydrogels

Any water-soluble polymer which can be rendered insoluble by cross-linking or incorporation into a block or graft copolymer (Figure 7) in which the other component is a hydrophobic unit can in principle be used as a hydrogel for the delayed or controlled diffusion of molecules which may or may not be drugs. Probably the best-known and most widely used hydrogel for such purposes is cross-linked collagen which is used as the basis of photographic films as well as in the pharmaceutical industry. While cross-linked collagen has been used for microencapsulation, it is not a very suitable polymer for preparing monolithic hydrogel devices with consistent performance properties especially if low degrees of swelling are desired. For this consistency with ease of preparation, research has favored the synthetic polymers of hydroxyethylmethacrylate,[50,98] acrylamide[47] and its *N*-sugar substituted derivatives,[99] *N*-vinylpyrrolidone[47,48] and poly(ethylene oxides),[100-104] as shown in Figure 9. Poly(glutamic acid)[102] and cross-linked dextrans and starches[97] have also been used. The most desirable hydrogels should be very strong and tough, but not brittle in the dry state, swell to a reproducible degree in water, buffer, or plasma, and be strong in the swollen state. Practically, the drug/polymer composite should be readily obtained in the desired geometry by a process capable of scaling up to production. It should not contain any toxic residues of monomer, initiators, stabilizer, or drug modified by the polymerization process. Although polyacrylamide has been the focus of some academic study, the risk of residual carcinogenic monomer might well rule it out in practice. The largest amount of work has been done on hydroxyethylmethacrylate which is unfortunately brittle as a homopolymer and has a relatively low degree of swelling (42%). In many studies it is polymerized with a cross-linking agent in aqueous solution containing drug and the residual initiation fragments and monomer are not removed.

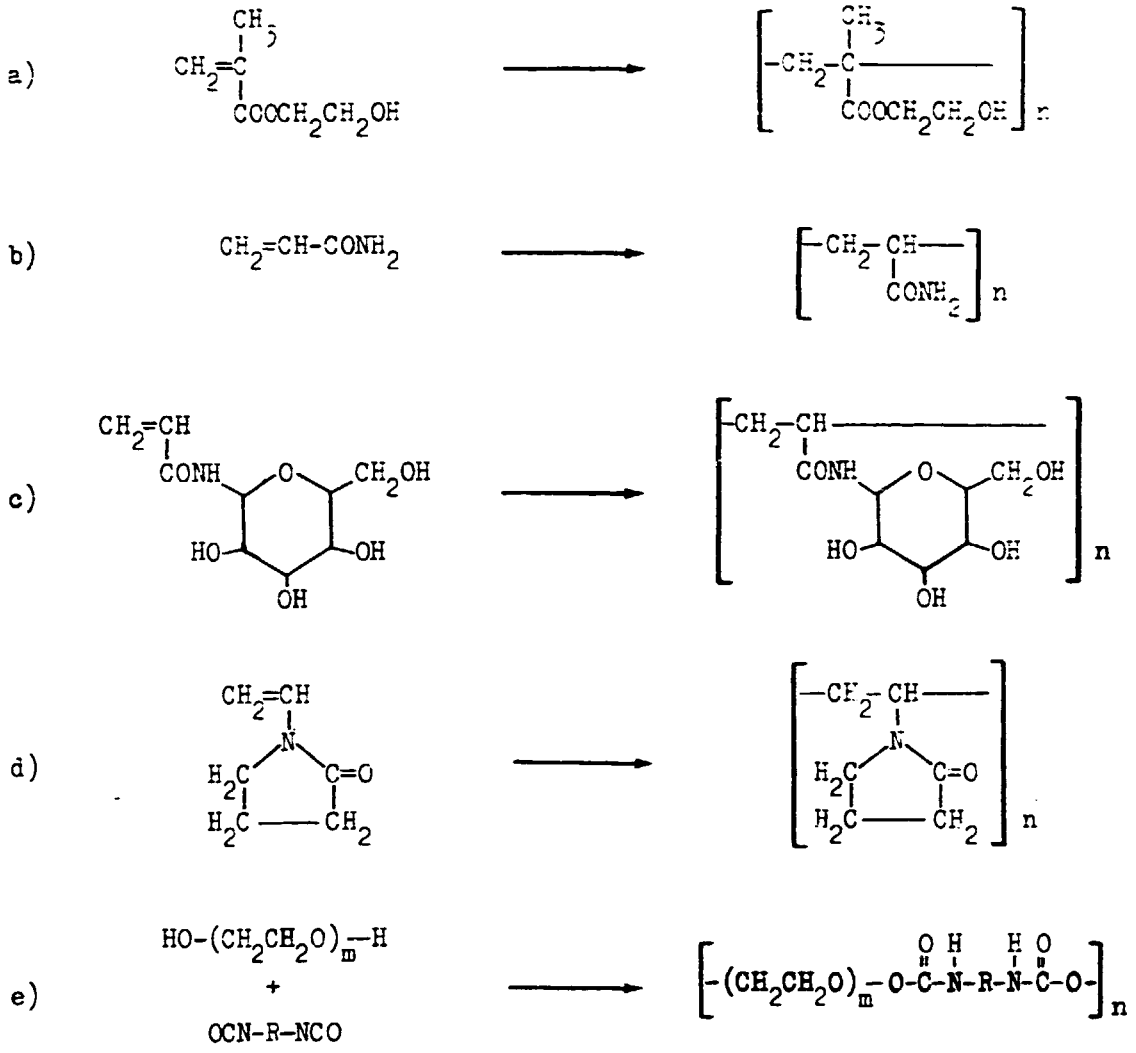


FIGURE 9. Structures of some commonly used hydrogels. (a) Poly(2-hydroxyethyl methacrylate) (HEMA); (b) polyacrylamide; (c) *N*-substituted derivative of polyacrylamide; (d) poly(vinyl-*N*-pyrrolid-2-one); (e) polyurethane prepared from poly(ethylene glycol) and a diisocyanate.

There is little difference in the release characteristics normally attributable to the chemical nature of the hydrogel for basically amorphous polymers.[47] The big differences arise from control of physical parameters such as the water content, degree of cross-linking, crystallinity, and morphology, i.e., if two or more phases are present. Thus, much recent research has been concerned with obtaining stronger hydrogels from what are essentially block or graft copolymers of either a thermoplastic or thermoset nature. Ciba-Geigy[101] has obtained cross-linked hydrogels of poly(ethylene oxide) capped with double bonds and subsequently co-polymerized with hydrophobic monomers to obtain polyphase systems which are claimed to have improved physical strength. ICI[104] achieved a similar multiphase system which also has the distinct advantage of retained polymer solubility allowing washing and purification of the polymer combined with the thermo-forming properties of a linear block copolymer. This allowed thin films to be obtained by the application of pressure and heat.

Another promising development along these lines by Graham et al.[103] involves cross-linked polymers of poly(ethylene oxide) using diisocyanates and polyols to provide cross-linking. If poly(ethylene glycols) of molecular weights above 2000 were used dry gels containing up to 50% crystalinity could be obtained. The crystallites act to reinforce an already quite perfect polymer network to provide a tough polymer akin in its physical properties to low density polyethylene. By control of the degree of cross-linking, hydrogels

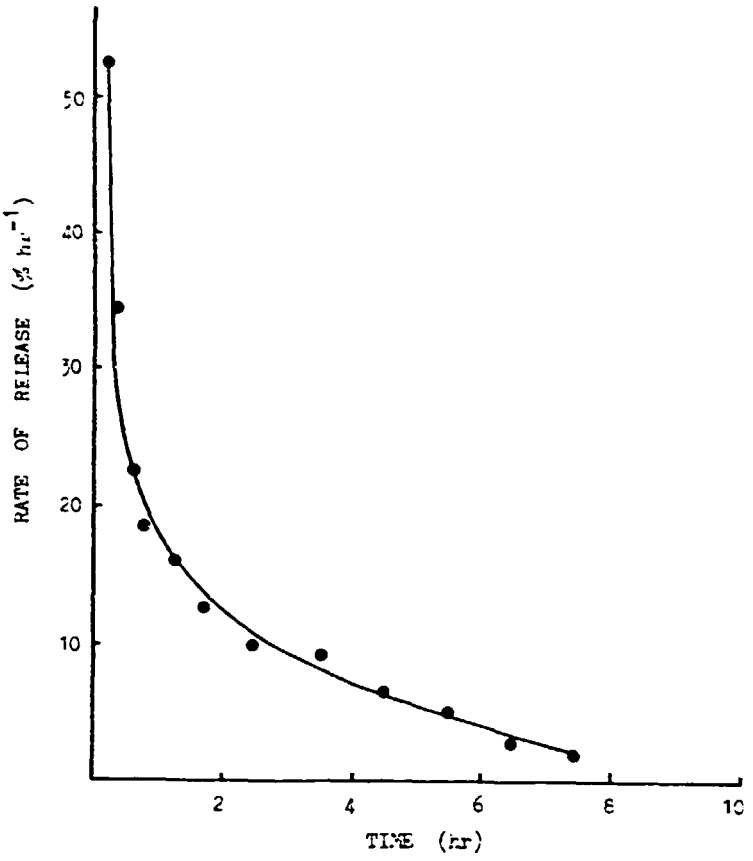


FIGURE 10. Release of prostaglandin E_2 from an initially fully swollen hydrogel based on poly(ethylene glycol) at 37°C and pH 7.4 (rate $\propto t^{-1.2}$ relationship).

capable of swelling with water to typically five times their dry weight could be made. In the fully swollen state these polymers behaved like any other hydrogel, releasing their contained drug at a rate proportional to (time)$^{-0.5}$ (Figure 10), but in the dry state slices of the polymer released a considerable proportion of the contained drug at a constant rate (Figure 11). This is because of a balance struck between decreasing drug release from an unswollen crystalline core and a physically coupled increasing permeability of the swelling outer layer. This constant release from a monolithic hydrogel is of obvious clinical importance and its first use has been in aiding the performance in delivery of pregnant women suffering from a so-called unripened cervix at full term.[105]

The above polymer in the form of a small vaginal pessary containing between 5 and 15 mg of prostaglandin E_2, depending on the assessed requirements of the individual patient, was inserted into the vaginal vault on the eve of the predicted delivery date. The uniform release of the prostaglandin E_2 over 12 to 24 hr induced cervical ripening and significantly reduced the need for a Caesarian operation as well as inducing normal and shortened labor with reduced pain in many patients. A major benefit of this device is that the prostaglandin E_2 which is normally quite unstable on storage was shown to be largely unchanged after 14 months storage at 4°C. This points to these drug-in-dry-hydrogel devices having enhanced practical application because of this ability to protect the contained drug from degradation or isomerization. This ability of hydrogels to stabilize prostaglandin E_2 has been confirmed in another briefly reported study using dry cross-linked starch gels.[106]

Other attempts to obtain constant rates of release from either fully swollen[88] or initially dried down[50] hydrogels have been reported in various studies. Lee et al.,[107] for example, have taken a drug containing monolithic cylinder prepared from derivatives of poly(methacrylate) and adsorbed and polymerized additional cross-linking monomers into

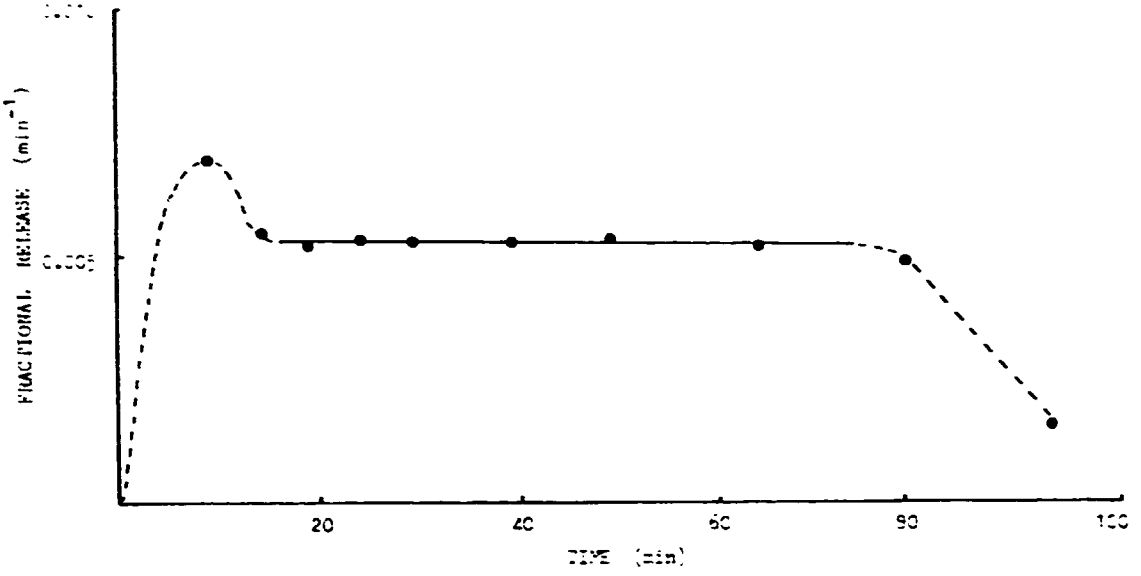


FIGURE 11. Release of promethazine hydrochloride from an initially dry, crystalline hydrogel based on poly(ethylene glycol) (rate ∝ t relationship for 37% of total release).

the external surface. This produces a skin around the device which has a lower degree of swelling than the core and as a result has a lower permeability to the contained drug. This skin becomes the rate controlling step of drug diffusion out of the device which is effectively converted into an "envelope" configuration for which the rate is predicted and found to be constant with time. Other related devices for the release of fluoride to teeth have also been reported.[108]

Cores of drug coated with rate controlling membranes have been used in even more sophisticated ways. Thus, by the incorporation of covalently bound carboxyl groups it is possible to obtain hydrogels which swell under basic conditions,[98] while swelling under acidic conditions can be obtained by the covalent incorporation of basic groups such as amine. Such groups have been incorporated into both vinyl and urethane polymers. An elegant example of such a use has been reported by Fildes of ICI,[109] who encapsulated a core tablet of quinoxaline di-*N*-oxide with a nylon copolymer containing basic groups in its backbone made by interfacial or condensation polymerization (Figure 12). These coatings were essentially unswollen at a pH of 7, but became highly swollen hydrogels at pH 4 and thus, having a high permeability to water-soluble drugs at this latter pH, released the contained drug in 4 hr. This arrangement was made for the purpose of protecting the drug in the rumen of cattle where the pH is around 7 and allowing release of the drug in the abomasum where the pH is around 4.

An example of systems of low swelling under neutral conditions, but releasing at high pH, is provided by the urethane polymers containing glucuronolactone.[110] The lactone group is not involved in the formation of a network by reaction of the hydrogens in this molecule with isocyanate. In high pH conditions the lactone ring opens and allows the polymer to dissolve if it is not cross-linked or to swell if it is cross-linked. These fundamental ideas were well-described in an early patent to the Czech Academy of Sciences[98] on the controlled release from vinyl hydrogels.

An even greater degree of sophistication has been developed by the Alza Corporation in their Oros® devices. In these, a solid tablet is coated with a hydrogel into which coating a very fine hole is introduced by a laser beam. In its simplest form, an elementary osmotic pump,[111] such as the Oros® device, consists of a membrane with an orifice in it (Figure 13a). In this type of device the membrane allows the passage of water, following an osmotic gradient, into the core which contains the drug which acts as an osmotic driving force for

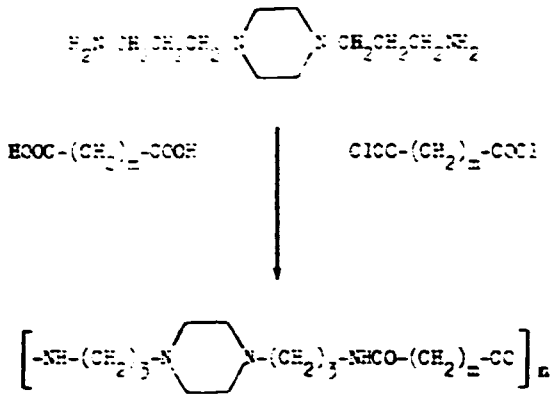


FIGURE 12. Structure of a polyamide polymer which responds to the pH of its environment (i.e., swells at about pH 4 while remaining unswollen at pH 7).

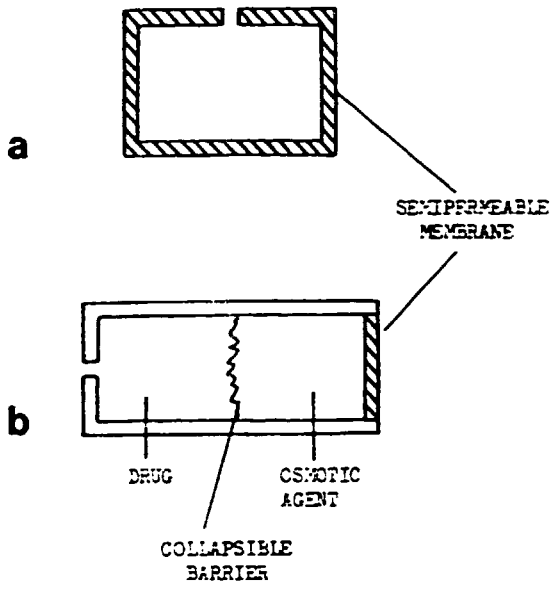


FIGURE 13. Schematic representation of osmotic pumps. (a) Elementary type; (b) pump with collapsible membrane separating drug compartment from osmotic agent.

water transport. The ingress of water is balanced by a saturated solution of drug being pumped out through the orifice. More sophisticated variations are available[112,113] (e.g., Figure 13b) in which the drug compartment is separated, by a movable barrier, from another compartment which contains an osmotic agent.

In principle there is no reason why any of the above devices cannot be utilized for use as inserts or implants in addition to their use orally. There has been a considerable amount of work done on devices for the controlled administration of drugs which come under a heading of bioengineering and are beyond the scope of this chapter. One should be mentioned, however, in the context of hydrogels as it is a commercial and very useful research tool for the study of the pharmacology and pharmacokinetics of drugs.[114] This is the Alzet® Osmotic Minipump. The implantable Alzet® device provides a typical delivery rate of 1 μℓ/hr for 1 week and is small enough for implantation in animals as tiny as mice. Before implantation the pump is primed by injecting the desired drug solution into the orifice. Several water-soluble drugs have been investigated using these devices, and poorly water-soluble steroids have been delivered using polyethylene glycol as solvent.[115]

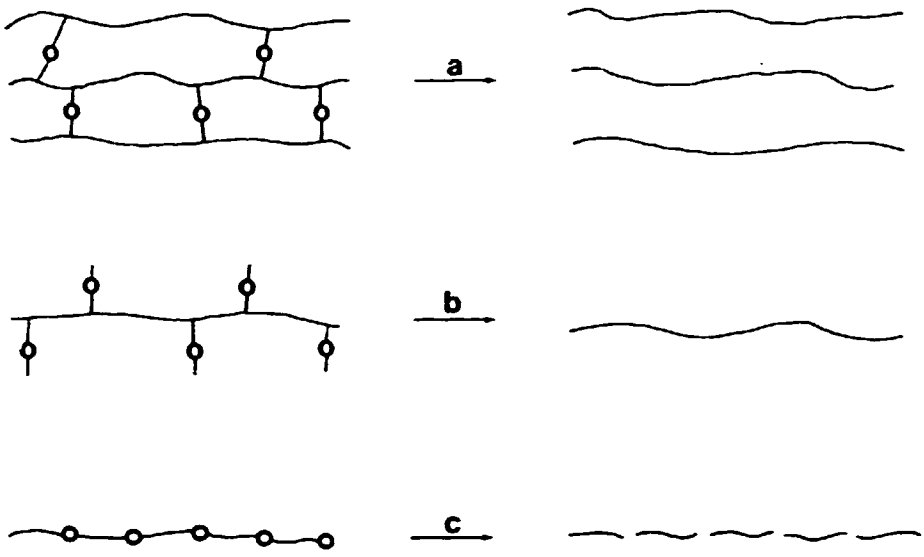


FIGURE 14. Schematic representation of three basic types of bioerodible polymers where -O- denotes a hydrolyzable linkage (see text for description).

VII. BIODEGRADABLE AND BIOERODIBLE SYSTEMS

The use of biodegradable polymers in drug delivery systems[116] allows the implantation of the device without the need for its removal after the drug has been released. The terms biodegradable, bioadsorbable, and bioerodible are frequently used interchangeably. The term bioabsorbable has long been associated with surgical sutures which gradually dissolve in the body. Bioerodible polymers may erode by slow dissolution as a result of side-group hydrolysis or ionization while the polymer backbone remains undegraded — frequently the erosion occurs as a surface phenomenon. Biodegradable is a more general term which is applied to many different materials other than polymers[117] including drugs,[118] surfactants, insecticides, and synthetic compounds in general.[119,120]

Three basic classes of polymer are generally recognized in biodegradable systems (Figure 14):

1. Water-soluble polymers which are insolubilized by hydrolytically unstable cross-links
2. Linear polymers which are initially water insoluble which become solubilized by hydrolysis, ionization, or protonation of pendant groups, but which do not undergo backbone cleavage
3. Polymers which are water soluble and degrade to small soluble products by backbone cleavage

In general, biodegradation takes place by a hydrolysis reaction when the device is placed in the aqueous environment of the body. In some cases enzymes have been found to accelerate the degradation reaction considerably.[121,122] Perhaps the most important consideration with biodegradable implants is whether the degradation products are nontoxic and readily eliminated from the body. Standards have been proposed to allow a comparison between the cytotoxicity of novel biodegradable polymers and established ones.[123] Polymers which undergo erosion of the type (2) above would probably not be suitable for implantation because a high molecular weight polymer is not readily excreted from the body. However, this can be put to advantage by using surface eroding polymers as inserts, as opposed to implants, the degradation products of which would be less liable to be absorbed due to their high molecular weight. Heller and Trescony[124] have used partial esters of maleic anhydride copolymers to prepare devices which release drug by dissolution of the polymer. The rate

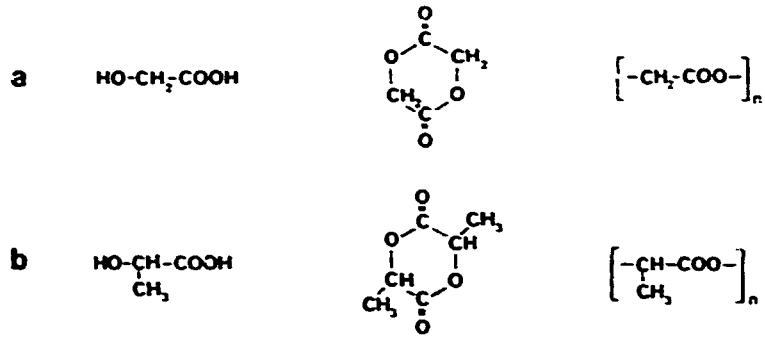


FIGURE 15. Structures of (a) glycolic acid (b) lactic acid, their cyclic dimers (glycolide and lactide), and homopolymers.

of surface erosion is controlled by the particular ester group and the pH of the environment. In a development of this system, the polymeric devices were coated with a hydrogel containing urease. The presence of urea resulted in the production of ammonium ions which accelerated the erosion, and the drug release, by a reversible mechanism. The Alza Corporation has patented an intrauterine device which bioerodes, and thereby releases drug, in the uterus.[125] A particular advantage of this type of device is that its shape can be designed for maximum retention in the uterus.

Polymers which undergo surface erosion are, almost by definition, hydrophobic while containing readily hydrolyzable groups. Workers at Alza have developed several novel polymers of this type which also undergo backbone cleavage to low molecular weight molecules which would therefore be of potential application in biodegradable implants.[126-128] The polymers have been given the general name Chronomer® and include hydrophobic poly(orthoesters) and poly(orthocarbonates). Heller,[129] one of the inventors, reviewed bioerodible drug delivery systems from a general point of view and included these as a possible group of polymers which could be used as implants. Choi,[130] another of the inventors, has described the development of these polymers for use in biodegradable systems. The Alza bioerodible polymers have been studied for controlled release of narcotic antagonists for the treatment of narcotic addiction[131] and of steroidal contraceptives for fertility control.[132]

Studies with polymers which undergo backbone cleavage have been restricted mainly to copolymers of lactic and glycolic acid[133,134] (Figure 15). Biodegradable drug delivery systems based on these polymers have shown the potential of this form of administration and have been reviewed by Wise et al.[135] The four main areas of application have used steroidal contraceptives,[25,136,137] narcotic antagonists,[1,138-140] antimalarials,[3,141,142] and anticancer drugs.[143,144] The forms in which these drug-polymer composites have been studied in vivo and in vitro include implantable cylinders,[136] spheres,[141] and films[139] and injectable microcapsules[137] and powdered formulations.[139] The polymers are generally prepared from the cyclic dimers of lactic and glycolic acid (i.e., lactide and glycolide) (Figure 15). Lactic acid has an asymmetric carbon atom, and therefore exists as two optical isomers. The different isomers and the racemic mixture produce polymers with significantly different properties. Poly(L-lactic acid), having steroregular sequences in the chain, has about 37% crystallinity while poly(DL-lactic acid) is totally amorphous.

Water uptake by a series of copolymers of L-lactic and glycolic acid has been studied recently by Gilding and Reed.[145] Poly(L-lactic acid) is the most hydrophobic and crystalline of the series and has the lowest equilibrium water content. With increasing the glycolic acid content, the degree of crystallinity and hydrophobicity decrease resulting in an increase in the equilibrium water content. A maximum of about 30% water uptake is found with the 30:70 copolymer (lactide to glycolide), thereafter with the onset of crystallinity the water content decreases.

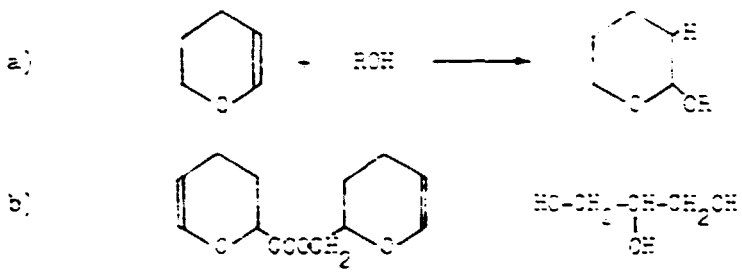


FIGURE 16. Biodegradable polymers based on dihydropyrans. (a) Reaction of dihydropyran with an alcohol; (b) typical monomers used to prepare cross-linked biodegradable polymers for drug delivery systems.

The presence of water in this type of polymer allows degradation to occur in the bulk amorphous region of the polymer matrix. Moiseev et al.[146] have considered the role of water, trace elements, and enzymes in the macrokinetics of polymer degradation in general and discussed the hydrolysis of poly(glycolic acid) in some detail. While the degradation of these polymers in the bulk complicates the prediction of the release profiles, it can have the fortuitous advantage of compensating for the decrease in release rate found with cylindrical or spherical devices which undergo surface erosion. Thus, a crudely constant release of ^{14}C-norgestrel from cylinders of poly(lactic/glycolic acid), in the rat, has been followed for 2 years.[136] Attempts to correlate release with the molecular weight of the polymer have shown that these systems can be difficult to design. Woodland et al.[138] found no significant differences in the release rate of cyclazocine from composites prepared from poly(lactic acid) with molecular weight of 45,000 and 70,000. However, when poly(lactic acid) with molecular weight of about 150,000 and 450,000 was used to prepare implantable beads containing sulfadiazine, the amount of drug released after 90 days was about 40% from beads prepared from the higher molecular weight material compared to 80% with the lower weight material.[141] Further, small changes in the structure of the drug molecule may have profound effects on release rates. The in vivo release from particles of poly(lactic acid) of naltrexone, cyclazocine, and naloxone after 60 days was 68, 38, and 26%, respectively, while in vitro release studies showed considerably faster rates.[139]

Sterilization of poly(lactic/glycolic acid) copolymers by irradiation is known to affect their properties and is found to alter the molecular weight distribution.[145] Ethylene oxide sterilization has been used prior to in vivo studies with these devices.[147] Closely related polyesters may offer modified properties and poly(dioxanone) has been evaluated as a bioabsorbable suture material which can be sterilized by irradiation without significant loss of physical properties.[148] Poly(caprolactone) has recently been studied as a potential biodegradable polymer for controlled release of contraceptive steroids.[2,10]

Graham et al.[149] have developed a series of biodegradable polymers which possess both ester and glycosidic linkages and can be prepared using the well-known reaction of 3,4-dihydro-2H-pyran with alcohols to give a tetrahydropyranyl ether (Figure 16a). Monomers which contain two such dihydropyran groups, linked by an ester group, can form linear polymers with diols or can be used to prepare cross-linked matrices when multifunctional alcohols are used as comonomers[4] (Figure 16b). Drugs can be incorporated into the reaction mixture prior to molding and curing, and the resulting thermosetting polymers provide release over prolonged periods of time. Such formulations have been found to release ^{14}C-labeled norethisterone in baboons for over 10 months. Related systems prepared by mixing preformed polymer with the antimalarial drug pyrimethanime have protected mice against *Plasmodium berghei* infection for at least 3 months. The range of possible monomers in addition to formulation variables has shown that devices have the potential to release drug over periods ranging from a few hours to in excess of 1 year.[149]

The identification of suitable biodegradable polymers for drug delivery systems has been relatively difficult, due to the number of properties required of the material for this application, and it is perhaps not surprising that polymers which have already been studied, and gained some acceptance, in other biomedical applications are attractive candidates. One such class is the poly(amino acids) and their derivatives which can be prepared with a wide range of properties and have been studied in several different disciplines. The in vivo degradation rate of copolymers of L-leucine and L-aspartic acid has been found to be dependent upon the degree of hydrophilicity of the polymer.[150] The resorption of sutures prepared from poly(glutamic acid) is delayed by partial esterification with lower alcohols,[151] while copolymers of glutamic acid and leucine form a biodegradable matrix which is well tolerated in rats.[152] Several studies have shown the potential of poly(glutamic acid) as a drug carrier in cancer chemotherapy where *p*-phenylene mustard[153] and cyclophosphamide[154] have been bound to the polymer.

Another class of biomedical polymer with potential use in biodegradable drug delivery systems is the poly (alkyl 2-cyanoacrylates). The alkyl 2-cyanoacrylate monomers have been used as biodegradable tissue adhesives in a variety of applications.[155] The butyl monomer is regarded as the most suitable due to a combination of its spreadability on biological fluids, rate of polymerization.[156] and its low toxicity.[157] The ability of the monomers to polymerize in the presence of water was exploited by Florence et al. to prepare microcapsules containing aqueous solutions of protein by *in situ* interfacial polymerization of butyl 2-cyanoacrylate in water-in-oil emulsions.[158] Microcapsules containing enzymes and other proteins have a variety of potential biomedical applications as demonstrated in many studies by Chang[159] and by other groups.[160] The possibility of using biodegradable polymers as the membranes of these "artificial cells" may encourage further study of these systems which have shown potential in therapy of substrate-dependent tumors and enzyme-deficiency diseases when nondegradable polymers have been used. Couvreur et al.[161,162] have prepared nanoparticles (200-nm diameter) from methyl and ethyl 2-cyanoacrylate monomers and studied the adsorption of several antineoplastic drugs. By virtue of their size, structure, and drug sorptive properties these nanoparticles have considerable potential as biodegradable lysosomotropic carriers and their tissue distribution, after i.v. injection in the rat, has shown their targeting potential.[163]

VIII. ROUTES OF ADMINISTRATION AND TARGETING

As mentioned previously, polymeric inserts and implants can provide both prolonged release and a localized release of a drug at a particular site. With inserts the localized action can be obtained by placing the device in the vicinity of the receptor organ; thus a direct action on, for example, the eye or uterus is possible. Recently the Alza Corporation has described ocular inserts which can direct the release of drug to a particular region of the eye.[164] Other body cavities may favor a sustained release for systemic action. These more traditional routes, particularly the GI tract, are associated with a shorter duration of action with a time scale of hours, and a zero order release may not be optimal if the drug is absorbed from a particular region of the GI tract.[165] The vaginal and rectal routes may also have limited potential as sites for sustained release of certain drugs which are absorbed into the systemic circulation.[166,167] The use of transdermal delivery systems is rather new because the skin has traditionally been viewed as a barrier, but development in this area is probable. Synthetic polymers are also being investigated as wound dressings which deliver topical antimicrobial drugs.[168]

Traditionally, implants and depot injections have been designed to provide a prolonged release with a time scale of days, weeks, or even months. Considerable effort is being made in this area to extend the duration of action and to improve reproducibility of release. Implants

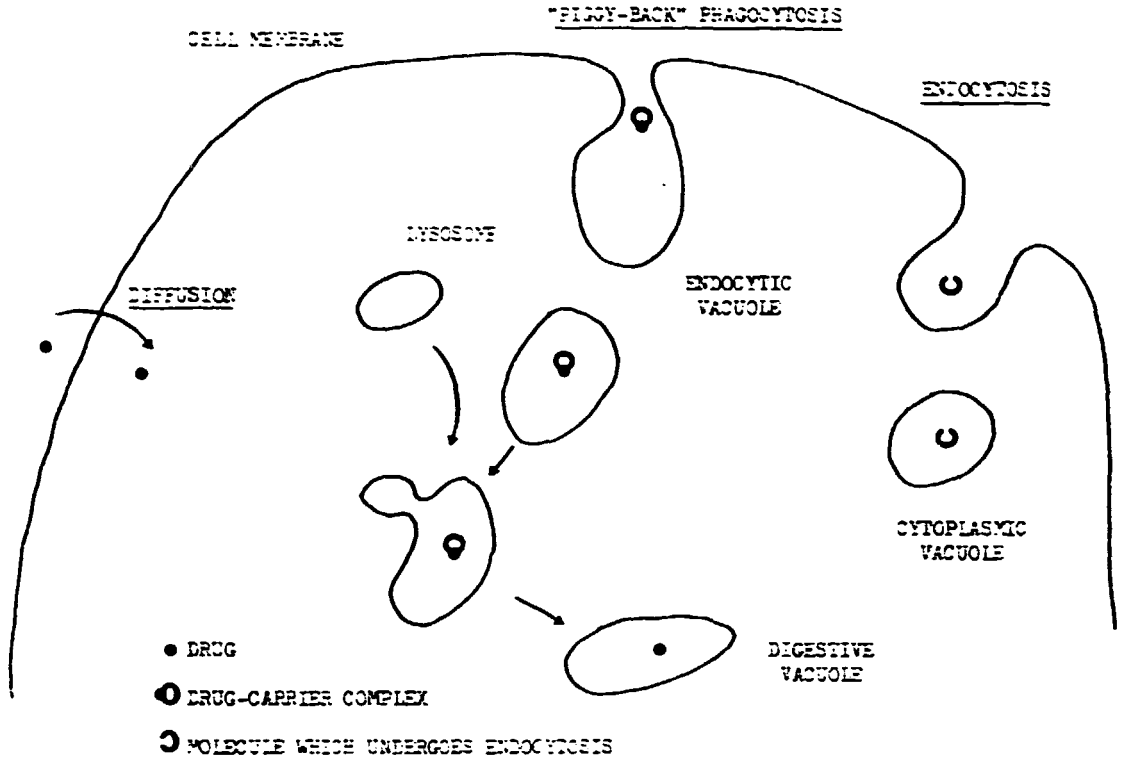


FIGURE 17. Diagramatic representation of entry of biologically active molecule into phagocytic cell.

also have some potential to localize action, as for example, the implantation of a device inside bone cavities for the treatment of chronic bone infections as described previously.[94]

More recently there has been considerable interest in the use of drug carriers in targeting therapy.[169] Many experimental approaches have been investigated particularly by the use of liposomes[170,171] and polymers, both natural and synthetic, as carriers. In many systems the targeting is accomplished by the selective uptake of the drug-carrier system by phagocytic cells following injection (Figure 17).

The macrophage[172] is a type of cell which is present throughout the body, in some cases as specialized cells (e.g., Kupffer cells of the liver). Characteristically, macrophages have the ability to take up large amounts of particulate matter of relatively large size (e.g., bacteria and protozoa) and have a highly developed ability to discriminate between particles of different types. These cells ingest solid or fluid matter by interiorizing part of their plasma membrane.[173,174] Where the material ingested is a particulate solid, the process is termed phagocytosis. The term pinocytosis is used where liquid droplets are engulfed, and the general term endocytosis encompases both cases. "Piggy-back" phagocytosis describes the way in which a substance, not normally ingested, gains entry to the cell by being phagocytosed along with a particle which is selectively taken up by the macrophage.[175] There is considerable interest in this type of approach for cancer chemotherapy and antimicrobial therapy for diseases in which the causative organism is localized within fixed macrophages.

Many attempts have been made to bind drugs and antibodies to a polymeric carrier which ideally will bind with, for example, tumor cells and subsequently release the active drug molecule. Poly(glutamic acid) was used as a biodegradable carrier for *p*-phenylene mustard and an antibody and the conjugate was found to suppress tumor growth in mice.[153] Dextran has been used as a carrier of daunomycin.[18] Unfortunately, a high degree of specificity for the target cells has not been achieved in most studies and systemic side effects still occur. In an attempt to avoid the use of biochemical differences between the target cell and normal cells to obtain specificity, the use of magnetic microspheres has been studied.[176,177] In this

method magnetic particles are incorporated into the drug-carrier system and by the application of a magnetic field can be localized at a particular site in the body.

IX. POLYMER-TISSUE INTERACTIONS AND BIOLOGICALLY ACTIVE POLYMERS

The possible interactions between implanted polymers (such as drug delivery systems) and body tissues are manifold, and over recent years a tremendous amount of research interest has revealed the complexities and provided fundamental knowledge. The complexities of these potential interactions are readily appreciated if one considers that living tissues consist of a wide variety of soluble low and high molecular weight compounds and insoluble structural components in dynamic equilibrium. Similarly, drug delivery systems can have present both low and high molecular weight material which is either soluble or insoluble. At present, little detailed information is available on the effects that these interactions may have on the release of drugs from delivery systems. "Medical grade" polymers and the control of additives have removed most of the problems associated with the leaching of toxic low molecular weight compounds. However, the uptake of lipid-soluble compounds from the body into poly(dimethylsiloxane) devices has been reported.[178]

Previously it was thought that "inert" polymers could be implanted without problem and bland or minimal responses with a wide range of polymers have been reported. However, the physical presence of an implanted polymer can cause foreign body tumorigenesis[179] and the shape and size of polymeric implants can produce different tissue responses.[180] Microporous hydrogels are encapsulated while the same polymer with a macroporous structure allows ingrowth of capillaries[181] or calcification.[182]

The adsorption of plasma proteins onto synthetic surfaces has been, and continues to be, the subject of a tremendous amount of research. The adsorption behavior of the particular proteins is dependent upon the hydrophilic/hydrophobic character of the surface. This field, in which the material in question is generally insoluble in the body fluids, still requires to be reviewed in terms of the "current understanding"[183] and our understanding of the interactions with soluble polymers is perhaps less clear.

Soluble polyelectrolytes of diverse nature have been found to exhibit biological activity. Synthetic heparinoid polymers have been designed and studied,[184] but many polymers with no apparent resemblance to natural macromolecules have been found to possess significant activity. The Pyran copolymer (divinyl ether-maleic anhydride copolymer, DIVEMA) has been the subject of many studies,[20,185] while its detailed structure is still uncertain.[186] DIVEMA has been found to exhibit antitumor, antiviral, antibacterial, antifungal, anticoagulant, and antiarthritic activity in addition to being an inducer of interferon and a macrophage activator. Both the biological activity and the toxicity of the material are related to its molecular weight. DIVEMA is by no means unique and other anionic polyelectrolytes display some biological activity. The antiviral activity of poly(acrylic acid) is related both to its molecular weight and tacticity.[187] However, atactic poly(methacrylic acid) has been reported to be devoid of antiviral action while the activity of the isotactic form is just detectable.

Even simple neutral water-soluble polymers can interact with living systems to a significant degree. Block copolymers of poly(oxyethylene)-poly(oxypropylene) (e.g., Pluronic®-F68) have been used in priming solutions for cardiopulmonary bypass and several advantages were found including an antisludging effect and a decrease in hemolysis.[188] However, poly(ethylene glycol) has been found to cause cell fusion, the mechanism of action being believed to be related to the reduction of the surface potential of the cells when the polymer adsorbed onto their surfaces.[189] Another study demonstrated that linking poly(ethylene glycol) to the enzyme catalase produced a conjugate which was nonimmunogenic, while experimental animals remained immune competent to the unmodified enzyme.[190] Poly(ethylene glycol)

has also been used to study intestinal permeability in man because it is presumed to be nontoxic and nondegradable.[191]

Nevertheless, implanted polymeric prosthetic devices and controlled release implants and inserts have now been safely used in humans for many years. Increasingly, as the factors involved at the implant-tissue site are studied and the fact that even "inert" polymers have physicochemical properties, the trend is to design systems which interact with the living environment in a desired manner. With insight and imagination the complexities are becoming better understood. The current increase in cost of getting new drug entities to the market will guarantee that significant developments of controlled release systems will improve drug therapy for the treatment and prophylaxis of disease.

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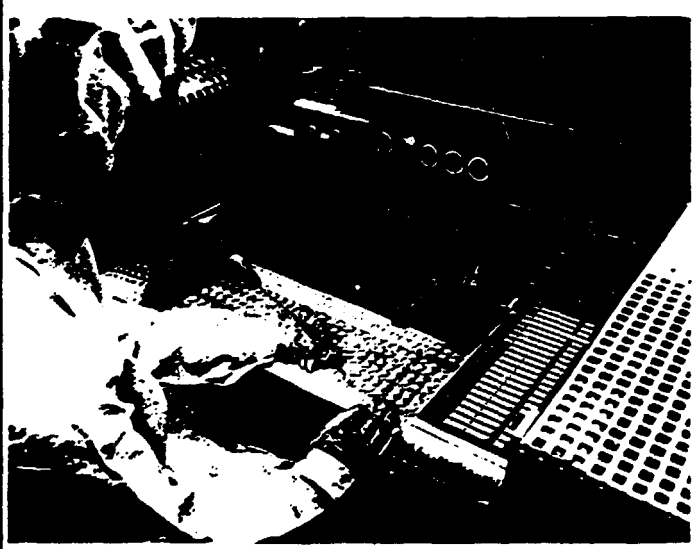
Controlled Drug Delivery Systems

NEIL B GRAHAM

Drug delivery systems can play a significant part in the therapeutic efficacy of the agent being formulated. Professor Graham looks at the past developments which led to the delivery profiles currently in commercial use. He also looks to the future of biodegradable implants, and targeted, responsive and pulsed drug delivery systems. New therapies may result from either a new or an older drug in a precise programmed delivery form; the field is challenging, socially beneficial, and potentially very profitable.

The past half century has seen the growth of the pharmaceutical industry based on new chemical entities which have done so much to improve health. From simple analgesics such as aspirin, through antibiotics like the penicillins and cephalosporins, and on to the myriad of agents to treat every condition from head to toe, the past 50 years have been a credit to the skills of the synthetic organic chemists and microbiologists, who have produced this large variety of chemical entities by either synthetic or fermentation methods. The recipients of these powerful products have taken them in various forms, such as tablets, liquids, capsules and other less common units. These delivery systems can play a significant part in the therapeutic efficacy of the agent being formulated.



The therapeutic agent is a combination of drug and delivery system

The therapeutic agent is thus a combination of a drug and a delivery system and it is almost impossible to separate the two. Initially, delivery systems were for instant delivery of the agent and as such were to some extent taken for granted. The problems of instant delivery were well known. The peaks and troughs of plasma levels lead to excessive concentrations and undesirable side effects, and to inadequate concentrations which provide insufficient cover for the condition being treated (see Fig 1). This led to the concept of a therapeutic index,[1] defining the ratio of plasma levels of agent which provides effective therapy to that providing freedom from undesirable reactions in 50 per cent of the test population.

The introduction of a time dimension into controlled drug delivery leads to the idea that the active agent, the drug, should be released at specified rates over defined time periods. The precise control of the release in such a programmed manner can lead not only to more convenient dosage forms but also to an improved therapy, though it must be clearly understood that it is only the first of a number of steps towards obtaining the appropriate plasma levels. This review will provide a selection of past developments leading to the delivery profiles in commercial use today and, with a knowledge of some of the ideas being currently evaluated, try to project forward into the future.

Polymers in controlled delivery

Polymers can be made in an enormous range of compositions which can exist in three major states: a crystalline solid; an amorphous hard glass; or an amorphous rubber which can be, if desired, plasticised by a suitable lower molecular weight liquid. The diffusion coefficients for a given diffusate will normally increase as one passes from a glass to a rubber to a plasticised rubber and as the free volume also increases. The free volume may be thought of as the volume fraction of molecular size holes which must be available for diffusion to occur. The change in the diffusion coefficient in going from a glass to a solvent-swollen polymer can be as much as ten decades (billion), depending on the molecular weight of the diffusate.

The general form of the relationship between the logarithm of the diffusion coefficient and that of the molecular weight of the diffusate is given in Figure 2. In general there is a need to provide more data on the prediction of the diffusion coefficients for high molecular weight diffusates, as the delivery of high molecular weight peptides and proteins arising from the biotechnology revolution is becoming of considerable importance. This will be referred to later. However, as the diffusion coefficient clearly depends on the polymer selected for use, the ready availability of such a wide variety of these materials clearly provides a very versatile tool for the design and construction of controlled delivery systems.

The equation governing normal Fickian diffusion from an infinite flat slab configuration of material for the first 60 per cent of the release is given by:

$$M_t/M_\infty = 4[Dt/\pi l^2]^{\frac{1}{2}}$$

where M_t is the change in the amount of the diffusate at time t, M_0 is the amount of diffusate present at time zero, D is the diffusion coefficient and l is the thickness of the slab. π has its normal meaning.

It can be readily seen that the variation of the thickness provides a further control factor which can be used. Rate controlling films can be from a few microns to millimetres, thus providing a further four decades of possible time control. By means of these two simple but powerful parameters the resistance to diffusion can, in principle, be varied over a range of some 14 decades. As polymers can be synthesised and fabricated relatively readily they are very useful for accessing this potential.

The earliest use of this principle was in the production of granules coated with wax or shellac, in which the coating provided some considerable prolongation in the release of agents such as antihistamines and decongestants. The 'tiny time pills' of Smith Kline and French were born in the 1950s and a major new treatment for hayfever, sinus problems and colds opened up what is still a major market today. Microencapsulation for obtaining sustained delivery of up to 24 hours is being used on an increasing scale for many drugs even though it is now quite old technology.

Chemists and chemical engineers

The principles of mass transport and diffusion are the familiar domain of chemists and chemical engineers, so it is perhaps not surprising that the field of controlled delivery has been increasingly invaded by scientists with these skills. Pharmacists tended to utilise techniques and materials which have provided well proven safety and reproducibility. This is highly commendable from the points of view of quality, safety and efficacy, but was a somewhat inward looking approach from which radical new departures were perhaps less likely. Today many of the major innovations in controlled and programmed delivery are being generated by non-pharmacists.

The Alza Corporation (Palo Alto, California) took the simple principle of using thin polymer layers as precise rate controlling membranes and developed a number of elegant delivery systems. These were for the sustained and constant delivery of very active agents which needed guaranteed and precise control for microgram to milligram quantities per day. Thus the *Ocusert* for the treatment of glaucoma, delivering pilocarpine from a small device inserted in the conjunctival sac of the eye, was very elegant but not commercially very successful.[2] It is shown diagrammatically in Figure 3. The *Progestasert*, delivering milligram quantities per day of progesterone from an interuterine contraceptive device (IUD), was very effective for periods of years providing reduced bleeding when compared with a non-medicated IUD.[3]

Transdermal delivery, utilising a rate controlling membrane in the device to overcome the variability of human skin, initiated a market which rapidly grew into hundreds of millions of dollars. The first devices were developed for astronauts who became sick in space. The precise delivery of scopolamine via a little patch placed behind the ear made a significant contribution to the relief of this problem and has resulted in the product *Transderm-Scop* for the relief of travel sickness.[4] Then fol-

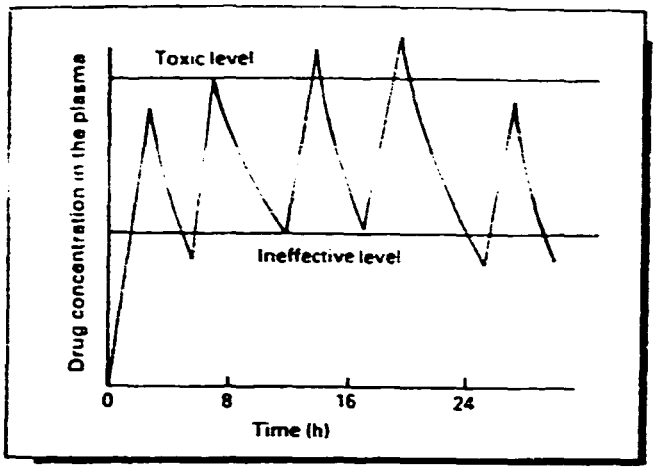


Fig 1 The fluctuations in plasma levels which can result from taking instant delivery pills four times daily

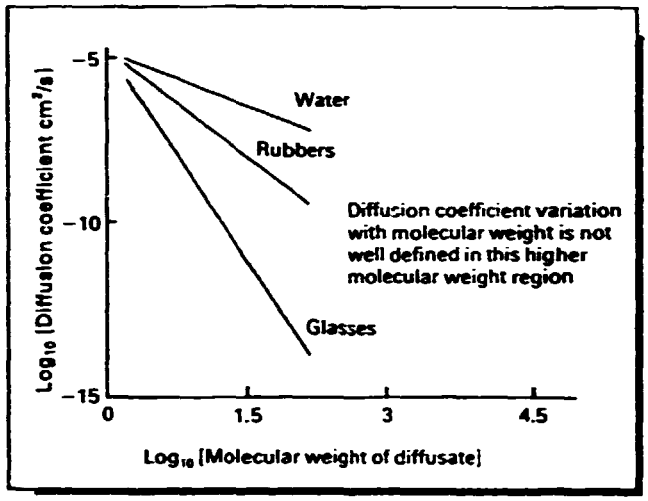


Fig 2 The change in $\log_{10}$ [diffusion coefficient] with $\log_{10}$ [molecular weight of diffusate] in water, rubbers and glasses

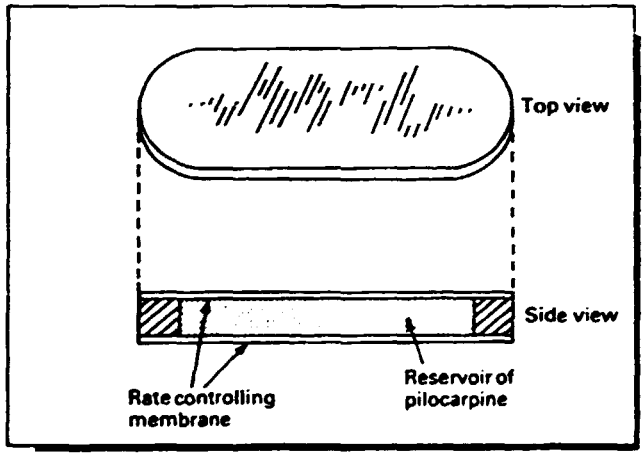


Fig 3 The Ocusert *ocular sustained delivery device for pilocarpine*

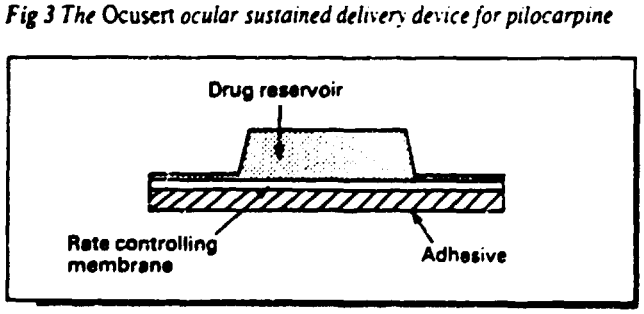
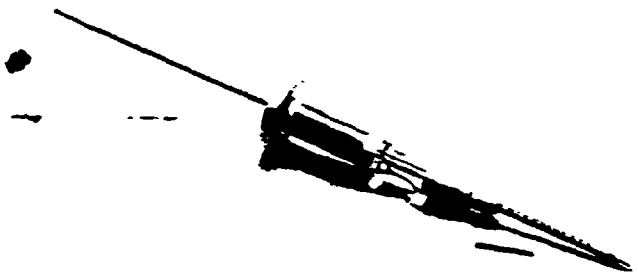


Fig 4 A transdermal delivery system to be placed on the skin for delivery of the agent over several days

lowed a scramble for the market for the transdermal delivery of glyceryl trinitrate from a variety of patches attached to the skin. A number of other therapeutic agents, including clonidine, have been delivered from these patches. A recent example is delivery of estradiol and/or progesterone for post-menopausal hormone replacement therapy. It is not by choice that these systems are utilised only for agents active in very small quantities, for the permeability of the skin is so small that only very low fluxes of relatively low molecular weight compounds are possible and the agents able to be delivered in this manner are severely restricted. The design of a typical skin patch is shown in Figure 4.



ICI's Zoladex: fastest-growing product in its class

Alza developed an ingenious and novel approach to obtaining constant drug delivery from a tablet by the use of a semi-permeable membrane coating on a tablet of water-soluble drug

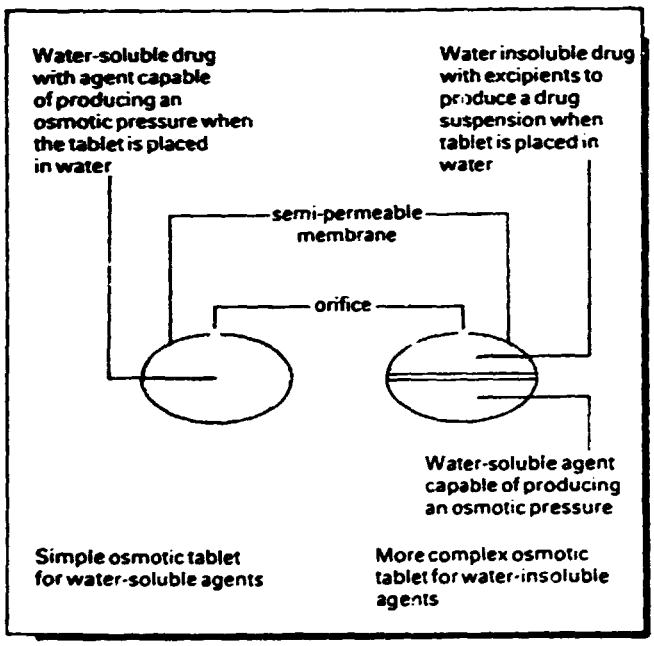


Fig 5 Osmotic tablets for drugs of different water solubilities

with an agent which would develop an osmotic pressure. When immersed in water or aqueous fluid the semi-permeable membrane would allow water to be imbibed and the resulting solution developed an osmotic pressure within the tablet. By incorporating a tiny drilled or laser-punched hole in the semi-permeable membrane the internal pressure caused a constant flow of the contained solution to be squirted out of the hole. So long as the inflow through the semi-permeable membrane was greater than, or equal to, the outflow through the hole a pressure would be maintained and a constant flow of drug solution produced. This device, in its simple form, has been licensed for use with a number of active agents. A recent example is *Volmax*, a Glaxo product for the sustained release of salbutamol sulphate for treating asthma. A more sophisticated two compartment system has been developed for use with relatively water-insoluble drugs. Utilising this system Pfizer has developed and obtained a product license for the sustained oral delivery of *Nifedipine*, an insoluble calcium channel blocker for the treatment of hypertension. The construction of both the simple and more complex osmotic devices are shown in Figure 5.

Most polymeric membranes are hydrophobic and water-soluble drugs often have a very low solubility in the membrane thus providing an extremely low flux. It is possible to crosslink water-soluble polymers and obtain a product membrane which can be highly swollen with water and in which the water-soluble drugs will have a much higher solubility and will permit a potentially high flux. These materials are called hydrogels in the water swollen state and xerogels in the dry state.[5-8]

Hydrogels

Common hydrogels in use for biomedical and pharmaceutical applications include those based on poly(hydroxyethylmethacrylate), poly(vinylpyrrolidone), poly(vinylalcohol), poly(ethyleneoxide) and dextrans. Many natural hydrogels such as gelatin, cellulosic derivatives, alginates and others are also commonly encountered.

Among these hydrogels those based on poly(ethyleneoxide) have several unique features which make them an attractive group of materials. They are particularly biocompatible and they can be partially crystalline. They appear not to be recognised by the normal body defence mechanisms so that they can disguise and protect such agents as enzymes circulating in the blood,[9] or they can provide particularly blood-compatible materials which not only show a low level of non-thrombogenicity but also a very low level of activation of complement.[10] Water-swollen hydrogels can provide fluxes of as high as grams per day of water-soluble agents and they thus are in a different class than other continuous polymeric membranes.

A major feature discovered in the study of hydrogels was that the use of a xerogel impregnated with a drug could provide practically constant release for a significant fraction of the contained drug. This was contrary to the expectations of normal Fickian diffusion and is in fact what is referred to as Case II diffusion. By use of this discovery it is possible to formulate

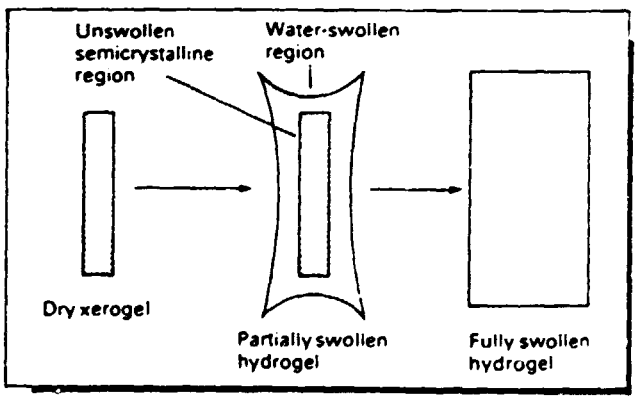


Fig 6 The swelling of a semi-crystalline xerogel of polyethyleneoxide in water

very safe devices for, unlike the membrane coating technique, there is not a core reservoir of drug to rupture and potentially cause some untoward incident by the sudden drug dumping. The drugs to be used in single membrane devices should not be life threatening if the total dose is dumped. In a monolithic hydrogel device it is not possible to dump the dose even if the device is cut up into pieces! The added feature of controllable crystallinity in the hydrogels based on poly(ethyleneoxide) provides a toughening mechanism for the materials which aids their fabrication into devices but also gives an extra measure of control over the release profile.[12]

The problem encountered with the use of monoliths, that of obtaining reasonably constant rates of release, has been largely solved by utilising the dried down xerogels. The precise release pattern cannot yet be analysed and predicted mathematically, as the solution involves a complex set of moving boundaries and changing concentrations and dimensions. The mechanism of obtaining the pseudo-constant rates of release can however be readily understood by a simple qualitative explanation.

A xerogel slice of a crosslinked but partially crystalline poly(ethylene oxide) swells on the exterior but remains dry in the interior for a long time. The exact length of time is determined by the thickness of the slice. During swelling the slice takes up a configuration as shown in Figure 6. In this the exterior is swollen to some degree less than the equilibrium value

Transdermal delivery: a space age spin-off

and the degree of swelling decreases as the core is approached. The total swelling is slowed by the crystallinity of the core which physically constrains the swelling until all of the crystallites have finally been melted by interaction with water. The result, insofar as the release of a contained drug is concerned, is to flatten the release profile. The release pattern which would pertain without the swelling would be a rapidly decreasing rate with progressing time. The swelling of the exterior however provides a steadily increasing diffusion coefficient which counteracts this decreasing rate. If an appropriate balance can be struck an effectively constant rate can be obtained up to the point of complete swelling, usually to about half of the contained drug (see Fig 7).[12]

An example of the application of hydrogel technology is a

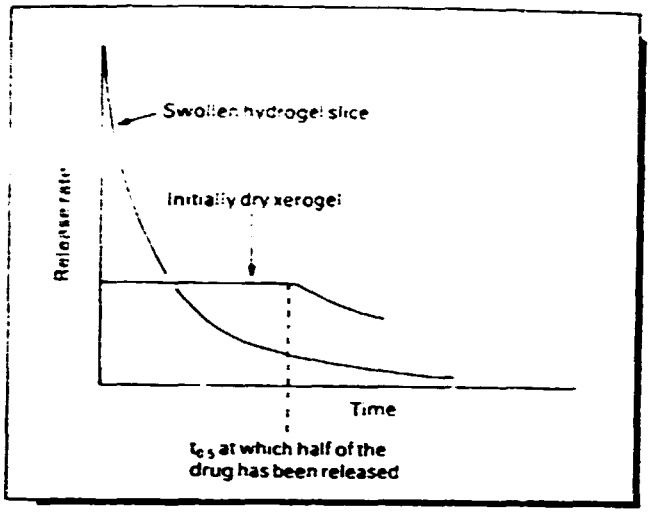


Fig 7 Comparison of typical drug release profiles from a fully-swollen hydrogel and a dried xerogel

delivery system for prostaglandin E_2 for the ripening of the cervix in women at full term in labour.[13,14] This product has now been granted a product licence in the UK and Ireland and is marketed under the name *Propess* by Roussell. The principle will be applied to other drugs to produce new therapies.

Biodegradable delivery systems

Simplistically it might be thought that an ideal delivery system would utilise a polymer which would be biodegraded by the body and, after presentation orally or by some other method such as implantation, would be absorbed harmlessly. Prolonged delivery and treatment over periods of weeks or months from a single implant might thus be envisaged without the necessity of removing the implant empty shell at some subsequent time. The problems of proving the toxicological safety of such novel materials is however very large and for the past decade this approach fell somewhat into disfavour with the opinion developing that the difficulties were too great. However with the advent of the sudden explosion in active agents from the combination of genetic engineering, biotechnology and peptide synthesis there has been a resurgence of interest in biodegradable matrices which were seen as a possible solution to the urgent need for delivery systems for these products. The product licenses awarded, for example, for delivery of a peptide analogue of luteinising hormone-releasing hormone under the

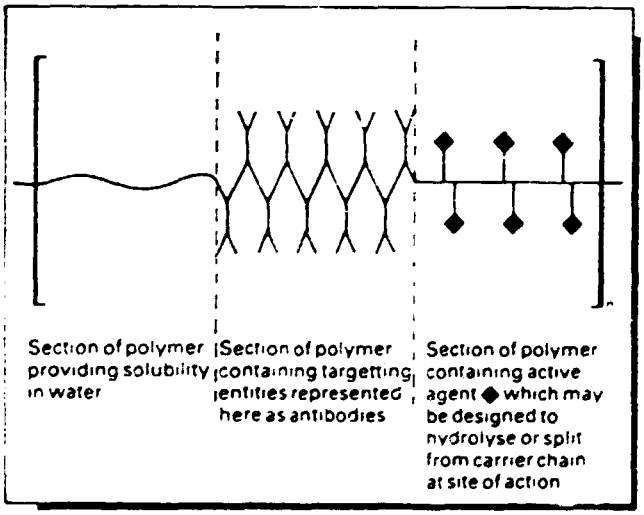


Fig 8 Proposed design of a polymer which is in principle capable of delivery and targeting a drug to a particular receptor site in the body

trade names *Zoladex* and *Decapeptyl – CR* provided a watershed. These products are indicated for the treatment of male prostatic cancer and the hormone is presented as an implant or microcapsules of a lactic glycolic acid copolymer which releases the hormone over a month. *Zoladex* is said in ICI's 1990 annual report to be the fastest growing product in its class. There is now, as a result, a resurgence of interest in biodegradable delivery systems and other product licences will be granted in the future.

The future

As it can take from seven to 15 years for a new delivery system to progress from conception to sale, the major products to reach the marketplace over the next ten years must already be much more than gleams in an inventor's eye. The four novel areas which seem most promising are those involving biodegradable implants, targeted delivery, responsive delivery and pulsed delivery.

The concept of targeted delivery includes any technique which allows a drug to locate at a particular body site where it is needed for its physiological effect. When used in this manner a smaller quantity of drug can often be used to the same or greater therapeutic effect. The therapeutic index is increased and the potential side effects are reduced. The targeting can be, in its simplest form, by containing the drug in particles which are sieved by part of the circulatory system. This has been used as an approach to the treatment of tumours.[16] At the other extreme the targeting is in theory able to be attained by the attachment of moieties such as antibodies to a water-soluble polymer containing the covalently attached drug.[17] If the antibody is specific for a receptor on the particular cell to be treated, then the antibody-containing complex might well act as the designer 'magic bullet'. The design of such a molecule is shown in Figure 8. In the Figure the polymer is represented as a block copolymer for convenience. It could also be a random or graft copolymer.

'Responsive' or 'intelligent' polymers are already known. Thus membranes have been devised which will release insulin in response to the presence of glucose[18,19] and release naloxone in response to morphine.[20] These are as yet far from practical but represent a promising beginning for delivery systems which begin to mimic the responsive nature of the glands in the body.

Finally, pulsed delivery in which a dosage form delays the release of a contained active agent has already been demonstrated. Thus the possibilities of delivery during the sleeping period become possible and the developing knowledge of the requirements of chronobiology can begin to be addressed.

There is a major current activity in research and development in the field of controlled and programmed delivery, driven both by the desire to produce new and improved therapy, and by the potentially large financial rewards. The field is challenging in the extreme and most satisfying because of the clear benefits to all society should the efforts be blessed with success. There will be many such successes over the next decade and beyond.

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Professor Graham is at the Department of Pure and Applied Chemistry, University of Strathclyde, Thomas Graham Building, 295 Cathedral Street, Glasgow G1 1XL

Dr. Russell Paterson

TRANSPORT AND DIFFUSION IN MEMBRANES CONCEPTS, CHARACTERISATION AND SIMULATION.

by

Russell Paterson

Director Colloid and Membrane Research Laboratories,
Department of Chemistry
University of Glasgow
Glasgow G128QQ
Scotland UK

OUTLINE OF THEORY OF TRANSPORT PROCESSES:

Diffusion processes are only one class of spontaneous processes by which chemical systems may reach equilibrium or, if certain restrictions are imposed, a steady state. Classical thermodynamics requires that there will be a net increase in the entropy of the system and surroundings during any spontaneous process. Irreversible thermodynamics shows us how this rate of production of entropy can be expressed as the sum of products of flows and thermodynamic driving forces within the system. It provides the most general of all possible system dynamic descriptions, its scope extends to all non-equilibrium processes in all energy domains (for example, electrical, chemical, thermal) and is fully capable of describing energy transduction between them.

In this theory, the local rate of production of entropy, σ and consequently hte rate of dissipation of free energy, $\Phi = T\sigma$ to specific irreversible processes occurring within the system. For any local volume, this dissipation function, Φ, is defined by the sum of products of the flows in the system and their conjugate forces, eqn.(1).

$$\Phi = f'_q\left(-\frac{dT}{T}\right) + f_v(-dP) + \sum f_i(-d\mu_i^c) + i(-dV) + \sum f_r A_r \geq 0 \qquad (1)$$

These are, respectively the flows of; heat, f'_q: volume, f_v; molecules f_i; electric current, i; and the rates of chemical reactions, f_r, within each element. The conjugate forces (termed efforts in bond graph theory) are defined by the local differences in temperature, T: hydrostatic pressure, P; chemical potential, μ_i^c; and electrical potential, V across the element and by the affinities, A_r, of the chemical reactions in the element.

In this way the thermodynamics of irreversible processes defines precisely the fundamental scheme of flows and forces for all possible processes in all familiar energy domains.

Tel: 44 41 339 8855 ext5500 FAX 44 41 330 4888

Experiments performed exclusively in each domain have produced simple, linear constitutive relationships between flows and forces:

$$f_q = \left(\frac{\theta_q A}{l}\right)(-\Delta T)$$

$$f_v = \left(\frac{\theta_p A}{l}\right)(-\Delta P)$$

$$f_i = \left(\frac{D_i A}{l}\right)(-\Delta C_i)$$

$$i = \left(\frac{\kappa A}{l}\right)(-\Delta V)$$

where $(\kappa A/l) = R$, the electrical resistance of the material.

These are the well-known transport equations of Fourier, Darcy, Fick and Ohm, respectively. All take the general form of eqn.(2), in which flow is defined by an effort (or force) e, divided by a resistance, R.

$$f = \frac{e}{R} \qquad (2)$$

In non-equilibrium thermodynamics there is provision for coupling phenomena: That is a force or effort applied to one species will affect the flow of another. A simple example is found in electrokinetics in which a voltage applied to a membrane or capillary will not only cause ions to flow and generate an electrical current (as in Ohm's law) but also produce a flow of water. This is the phenomenon of electro-osmosis. In this case water flows when there is now force (effort) applied to it (such as an osmotic or pressure difference). The water is pulled along, through the membrane by the moving ions: coupling. Ion pumps in biological membranes use the affinity of a chemical reaction (usually ATP hydrolysis) to drive ionic flows, even against their concentration gradients.

These effects can be described precisely by irreversible thermodynamics, but this application is out with the scope of this lecture. We will consider here only diffusion systems an d exclude coupling phenomena. It is worth noting however that such effects exist and will occur in apparently simple diffusion systems and that they may be exploited at some later stage in the formulation of advanced drug release and other bio-medical applications.

Most drug delivery systems are diffusion controlled by a membrane, pessary or other device. It is necessary therefore to be able to assess the capability of new membrane materials by measuring their diffusion coefficients, D_i and permeabilities, $P = (DA\alpha)/l$, to drug molecules. (α is the distribution coefficient for the permeant between membrane and solution, $\alpha = \overline{C}/C$. This term appears because Fick's law, as given above, relates the diffusional flow to the concentration difference in the membrane from one surface to the other, while the practical permeability, as measured in the laboratory, relates the diffusional flow to the concentration difference of permeant between the two solutions on either side of the membrane and so the α factor is required.

To solve the diffusion equations for practical systems and so obtain solutions to particular diffusion problems with defined initial states and set boundary conditions is a major mathematical task involving considerable creativity. A number of books deal with this

subject and give mathematical solutions for large number of common problems, such as diffusion across a membrane or diffusion in spheres or cylinders or other simple geometric forms. Three standard texts, for reference, are listed in the bibliography. (Solutions to heat conduction problems are exact analogues to those of diffusion and historically heat transport problems were solved first, hence the relevance of the book by Carlslaw and Jaeger.)

The complexity of the mathematical solutions, even for simple diffusional problems involving simple shapes, constant diffusion coefficients and elementary boundary conditions, involve complex mathematics and yield complex solutions. As a result it is common to use approximate solutions applicable only in the initial initial or final stages of the diffusion process. A series of such solutions are given in Professor Graham's paper, in Volume I. It is quite clear therefore that diffusion processes commonly devised to obtain controlled release or even the study of diffusion across multilayer membranes (both artificial and natural, as across skin layers) cannot be predicted mathematically. It is necessary to consider computer simulation techniques for the design and prediction of membrane processes.

In this paper the applicability of Network Thermodynamics is explored. The systems which will be described were developed in the author's own laboratory as part of an on-going research programme. The original source references [1,2,3,4,5] give the basic concepts of the method which are introduced in more succinct form here.

Simulation of Transport Processes

The equations of Fourier, Darcy, Fick and Ohm all take the form of eqn.(2), in which the flow is defined by the size of the applied effort, e, dmultiplied by a reciprocal resistance, R. The term resistance is used by analogy with Ohm's law and as a reminder of the purely dissipative role of such processes. (The reciprocal of the resistance is of course the permeability and the equations could equally well have been expressed in terms of permeabilities.) The representation of the diffusion or transport system can be made in a very compact way using the bond graph notation of Paynter, [2]. In bond graph terms eqn.(2) is the constitutive relationship of a generalised resistor, relating effort to flow. The products of efforts and flows, as defined by the dissipation function, have the dimensions of power. In the notation of Paynter [2], power flow is represented by a power bond, pointing in the direction of the half arrow, fig.1a and power dissipated, by fig.1b, symbolising a resistor with constitutive relationship, eqn.(2).

If the power entering a resistive element e_1f_1 and leaving it is e_3f_3, the power dissipated is e_2f_2, given by their difference, eqn.(3).

$$e_2f_2 = e_1f_1 - e_3f_3 \qquad (3)$$

Since a resistor is a series element, flows are conserved, eqn.(4)

$$f_1 = f_2 = f_3 \qquad (4)$$

To represent eqns.(3) and (4), bond graph notation employs a 'through' or 1-junction, fig.1d, in which all power bonds shared a common flow.

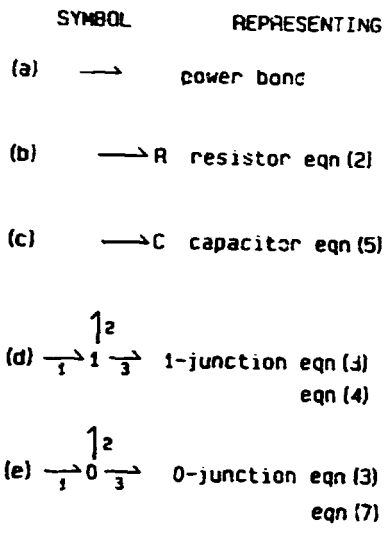

Figure 1: Basic bond graph symbols and their constitutive relationships.

Of particular interest to chemical diffusion studies is the capacitative role of an elemental volume in the non steady state. The relationship between effort and flow is now one of a capacitor, described by eqns.(5) and (6), in which **C** is the capacitance, relating the charge, q (defined as the time integral of the flow) to the effort.

$$e = e_o + \mathbf{C}^{-1} q \qquad (5)$$

where

$$q = \int_{t=0}^{t} f dt \qquad (6)$$

In a chemical system the 'charge', q, is simply the number of moles of the permeant species in the local volume element and, since the effort is defined as the chemical potential, the capacitance is not a simple constant. The local effort at any time, t, is determined by its initial value, e_o and the subsequent history of accumulation or depletion of permeant in the element, eqn.(5). For a chemical capacitor therefore, the difference between the power entering and leaving, eqn.(3), is that stored (reversibly) without dissipation, fig.1c. The junction conditions are now those of a parallel element at constant effort, combining eqn.(3) and (7) and represented by an O-junction, or constant effort junction, fig.1e.

$$e_1 = e_2 = e_3 \qquad (7)$$

The capacitative role of an element is defined by eqns.(3), (5) and (7) and represented by fig.2b.

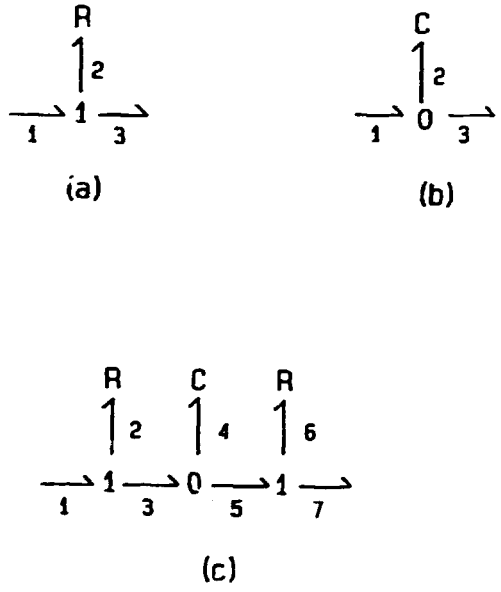

Figure 2: Resistor and Capacitor elements separately, and combined as a lumped diffusion bond graphs, a, b,and c, respectively.

In electrical circuits the role of capacitor and resistor are separate, but in chemical systems they are combined in each element of the medium. To model an element however, it is usual to separate them formally and mathematically. It is common (although not mandatory) to split the elemental resistance into two parts (often equal) as in fig.2c, where power enters the element by bond 1 and leaves by bond 7. In its passage power is dissipated in R_2 and R_6 and stored in C_4. Such a bond

graph, which, on its own, incorporates all the relevant functions of a diffusion element is termed a 'lump'. A 1-lump model of a diffusion element, is therefore characterised by a single capacitor, C_2 and two resistances R_2 and R_6, whose sum equals the total membrane resistance.

The precision of quantitative modelling is greatly improved if the system is subdivided into a number of lumps, each characterised by its own resistance, capacitance and local effort. The greater the degrees of sub-division, the more closely the bond graph will approach a true continuum of states.

Bond graph notation includes a number of additional functional elements [3], but the only one to be used here is the source of constant effort, SE, as shown in fig.3.

[The bond graph model of a simple membrane was demonstrated in the lecture by a hydraulic analog. In place of resistors there were capillaries (which resist flow) and in place of capacitors, simply ve. . al tubes at regular interval along the capillary path. In non-steady state conditions the flows entering and leaving the vertical (capacitor) tubes would not be equal and so the level in the tube would either rise or fall changing the pressure and so the effort or driving force on the liquid which drives the liquid at that point in the system. The source of effort, SE, and the terminal capacitor, C, are, in this hydraulic analog merely a constant head device and a collecting volume or receiver (a beaker), respectively. Because the laws of transport are analogous for heat, water flow, diffusion and electrical current, as noted, then such a hydraulic model is an exact analog of our diffusion bond graph. The bond graph can however be used to develop sets of differential equations, (such as eqns.(8),(9),(10),(11)) which may then be solved by standard computational methods, by computer.]

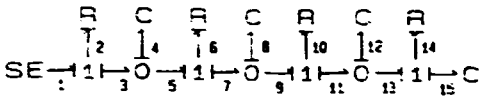

Figure 3: A three lump bond graph of membrane through which diffusion occurs between a constant source, SE, and a limited collecting volume represented by the terminal capacitor, C.

(A source of constant effort is a capacitor with (near) infinite capacity, leaving its effort (effectively) unaltered, in the time scale of the experiment, eqn (5). It imposes 'infinite bath' conditions. Limited volumes of homogeneous (well-stirred) solution or gas are modelled in the bond graph as capacitors. Unstirred layers of solution at surfaces or layered membrane structures, merely provide additional lumps in the model, each with its own characteristic resistance and capacitance, fig. 2c. A 3-lump bond graph model for diffusion in a membrane exposed to a constant source, **SE**, on one side and a limited collecting volume, **C**, on the other, is shown in fig.3. In a 3-lump model only three internal efforts and charges are defined within the membrane phase. For an **n**-lump model, **n** such efforts are defined, one in each contiguous lump, to define a 'staircase' of efforts, which will approximate ever more closely to a smooth profile as the number of lumps in the model is increased.

CHARACTERISTIC EQUATIONS OF STATE

For all one-dimensional diffusion schemes, simple bond graphs of the type shown in fig..3 are required. With the bonds numbered as shown, the model may be expanded to as many lumps as required. Using the constitutive relationships for each element and beginning with the flows, $\dot{q}$, into each capacitor in turn, it is always possible to characterise a bond

graph with **n capacitors** in terms of **n** first order differential equations [3]. For the three lump, four capacitor, SE-C bond graph, shown in fig. (3) the four characteristic 'state-space' equations are,

$$\dot{q}_4 = e_1 R_2^{-1} - (C_4^{-1}R_2^{-1} + C_4^{-1}R_6^{-1})q_4 + (C_8^{-1}R_6^{-1})q_8 \quad (8)$$

$$\dot{q}_8 = (C_4^{-1}R_6^{-1})q_4 - (C_8^{-1}R_6^{-1} + C_8^{-1}R_{10}^{-1})q_8 + (C_{12}^{-1}R_{10}^{-1})q_{12} \quad (9)$$

$$\dot{q}_{12} = (C_8^{-1}R_{10}^{-1})q_8 - (C_{12}^{-1}R_{10}^{-1} + C_{12}^{-1}R_{14}^{-1})q_{12} + (C_{15}^{-1}R_{14}^{-1})q_{15} \quad (10)$$

$$\dot{q}_{15} = (C_{12}^{-1}R_{14}^{-1})q_{12} - (C_{15}^{-1}R_{14}^{-1})q_{15} \quad (11)$$

Eqn.(9), which defines the flow $\dot{q}_8$, into the middle capacitor, C_8, is typical any additional lumps which may be added to the bond graph to increase its precision. Such 'state-space' equations contain only three terms and involve only the central capacitor, and those on either side of it. A system in which no efforts are defined will decay from its initial non-equilibrium state to equilibrium (free response). Typically the source of constant effort is replaced by a limited volume of diffusant in which case a capacitor, **C**, will replace the effort source on bond #1, fig. 3. The state space equations will be unaltered except that the effort, e_1, eqn.(9), will be replaced by the constitutive relationship of the new capacitor, q_1/C_1 and an additional first order equation in $\dot{q}_1$, analogous to eqn.(11), is required. The same bond graph and state-space equations apply to single phase diffusion in, for example, sheets rods of membrane or columns of liquid in free diffusion [7].

The state-space equations, once defined, are easily integrated numerically from any chosen initial state, defined by the source effort (if defined) and the charges (moles) in each capacitor. Numerical integrations were performed using standard methods.

FICKIAN DIFFUSION MODELS

To illustrate bond graph procedures, we may consider Fickian systems initially. Although the treatment is in no way restricted to such systems, they are convenient for these demonstrations, not least because rigorous mathematical solutions available in the literature [8][9] against which bond-graph simulations may be readily compared. In particular, since the amount of computation increases greatly with increasing reticulation, it is of primary interest to determine the minimum lumped description consistent with quantitative modelling.

It is usual to define the permeability, P, of a membrane by eqn.(12),

$$f = \overline{P}\Delta c \quad (12)$$

where Δc is the concentration difference across the membrane. For a Fickian system

$$\overline{P} = \frac{\overline{D}A\alpha}{l} \quad (13)$$

where $\overline{D}$ is the diffusion coefficient, A the area, and l, the thickness of the membrane. The distribution coefficient, α defines the equilibrium ratio of the concentrations of diffusant in membrane to contact solution (or gas) phase, $\overline{c}/c$. A comparison of eqns.(2) and (12) shows the (fickian) bond graph resistance to be the reciprocal of the permeability, $\overline{P}$, eqn.(14).

$$R = \frac{1}{\overline{P}} = \frac{l}{\overline{D}A\alpha} \quad (14)$$

Eqn.(14) may be applied to each slice or lump in the bond graph model, and since all efforts are referred to the external phase (solution or gas) this definition allows that the membrane itself may be made up of different layers of differing thicknesses, each with its own diffusion and distribution coefficients. In this way multilayer membranes may be modelled. Using the Fickian model we may show in a similar fashion that the capacitance of a lump (or collecting volume capacitor) is simply αV, eqn.(15), [7][10].

$$C = V\alpha \qquad (15)$$

since

$$\dot{q} = \frac{d\bar{n}}{dt} = V\frac{d\bar{c}}{dt} = V\alpha\left(\frac{dc}{dt}\right)$$

where $\bar{n}$ and $\bar{c}$ are moles and concentrations, respectively in the membrane phase.

On the Fickian model chemical potential is no longer taken as effort, it is replaced by concentration. The constitutive equations for capacitors and resistors remain unaltered (eqns.(2),(5) (6)) and state-space equations (such as eqns.(8)-(11) for a three-lumped model membrane (fig.3)) remain, with resistances and capacitances defined as above, eqns.(2) and (5). Bond graph techniques may be used in a Fickian model, but since the product of effort and flow no longer defines power the treatment must be considered pseudo-thermodynamic. Fully thermodynamic treatments are necessary if flows are coupled [5][11].

APPLICATIONS

Simple Diffusion:

Figure 4 shows the effect of varying the size of the collect ing volume upon the quantity of gas, q(t), which will diffuse through a thin sheet of membrane into a collecting volume (terminal capacitor) when it is exposed to a constant pressure of that gas on its outer side. This example is taken from [10]. The upper curve represents the infinite volume case and with a ten lump or larger reticulation the bond-graph predictions agree to better than 0.1% with the mathematical solution.

Limited collecting volumes present no additional complexity, and merely involve a changing in the value of the final collecting volume capacitance, fig..3. Bond graph simulations for an experimental volumes of 1.5 ml and 0.1 ml are shown in fig.4 (middle and lower curves, respectively).

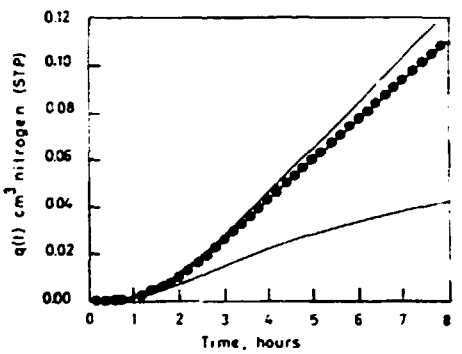

Figure 4: Simulation of the quantity of nitrogen, q(t), diffused from a constant pressure source (53.37mm Hg) through a planar membrane into a collecting volumes of 1000cm^3 (upper curve), 1.4980cm^3 (middle) and 0.1000cm^3 (lower curve). Filled circles mark experimental data [12] for collecting volume 1.498cm^3. Membrane: (ethylene-propylene co-polymer film), area; 45.6cm^2; thickness, 0.1013cm, N_2 solubility 7.118×10^{-4}Barrers, D,3.09×10^{-7}cm^{2}s^{-1}.

The dotted curve superimposed on the former shows that this prediction is in excellent agreement with experimental data [12]. The ease of simulation of infinite band limited volume conditions is to be contrasted with the extreme complexity of dealing with the same problem mathematically [8][9]. The bond graph model provides not only output and flux data, but also predicts experimentally inaccessible concentration profiles in the membrane phase as a function of time, fig.5

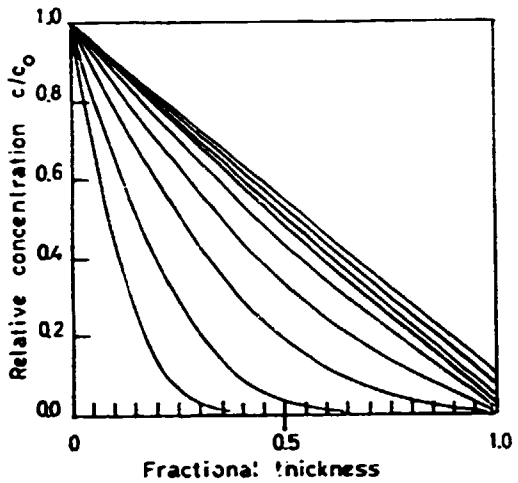

Figure 5: Concentration profiles within the membrane, obtained for the experimental system (collecting volume 1.498 cm^3), using a 20-lump bond graph. Concentrations have been plotted at the centre of each lump and joined to give smooth concentration profiles.

These local membrane concentrations are easily obtained since during the computer simulation, the charge (moles of diffusant) in each lump volume is obtained at each integration step. From this simple bond graph, all the classical diffusion and heat transport properties of slabs, (infinite) cylinders, spheres etc may be simulated. Gas diffusion was chosen here solely because suitable data were available for comparison, the treatment is equally viable for membrane/solution systems and with little modification to thermal diffusion problems.

For systems with a free response the source of effort (SE) is replaced by a capacitor (C) as noted in the theory above. Figure 6 illustrates the release of diffusant from a membrane dipped into a well stirred solution, and fig.7 the decay of the same membrane from a linear, steady state concentration profile with the membrane clamped between solutions of equal volume.

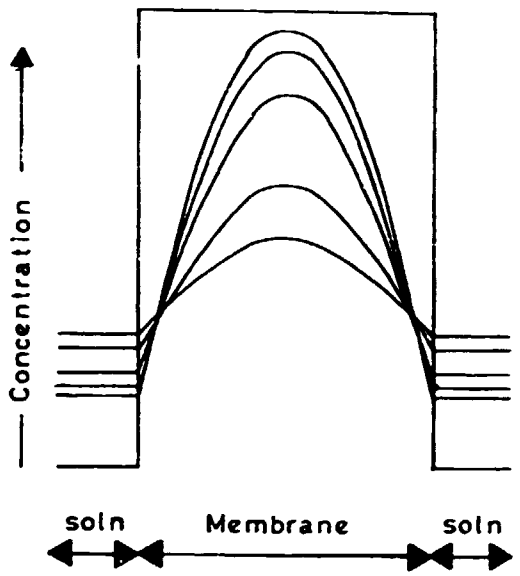

Figure 6: Concentration profiles obtained when a membrane is dipped into solvent. Time span ten minutes, edge effects ignored. Membrane: area 1.5810cm^2, thickness 0.0632 cm, D $1 \times 10^{-4} cm^2 s^{-1}$, alpha 10.0 and solution volume 2ml. Concentrations are shown on the common (solution) reference, in the membrane phase $\bar{C} = C\alpha$.

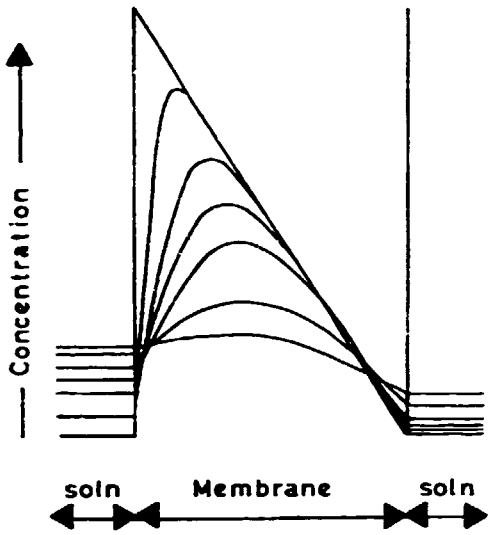

Figure 7: Decay from an initial linear concentration profile steady state. The membrane (as fig.6) now clamped between two solutions (each 1ml).

Diffusion problems in which the membrane or diffusion medium is made up of layers, or, when diffusion polarisation occurs at the interface between two phase (for example solution and membrane) are solved by adding further lumps to the model each with its own volume and diffusion (transport) parameters.

The systems so far simulated have well known mathematical solutions and were used to check the quantitative capabilities of the bond graph models and to set degrees of reticulation (number of lumps) and the step times ofr integration to obtain quatitative simulations. As systems simulated get much more complicated only simulation techniques can be used.

For example for non-steady state diffusion through a multilayer membrane, fig.7a.

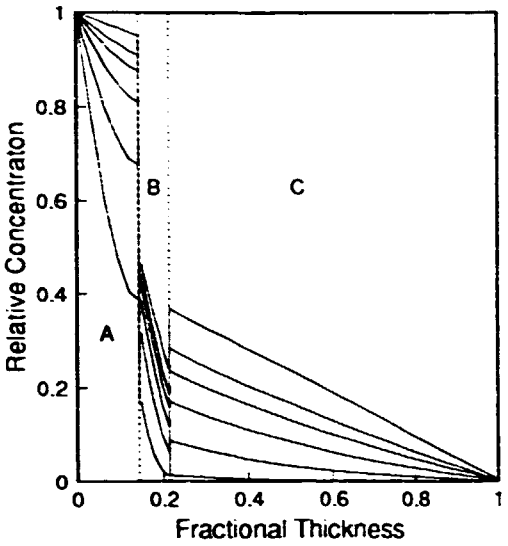

Figure 7a: Non steady state diffusion through a multilayer membrane/solution system, in a time lag experiment. Simulation of a bilayer membrane: active layer, B, 5um, support layer C, 55um, and unstirred solution layer, A, 10um. The distribution coefficients and diffusion coefficients of A,B and C were 1, $2x10^{-5}$; 0.5, $2x10^{-6}$ and 0.8, $1.15x10^{-5}$, respectively. A sixty lumped model was used.

Non-linear Systems:

Since the state-space equations are integrated numerically, the resistance, capacitance, and source terms may be redefined after each incremental integration step-time. This allows precise prediction of non-linear processes in which diffusion coefficients are known to change either as functions of time or as determined by their concentration dependence, progressively altering resistance coefficients during the process, eqn.(14). Such factors as swelling, which alter the lump volume, affect both resistance and capacitance values eqns.(14)(15). Constant drug release devices have been devised using polymers which swell. Such devices depend upon the fact that as drug diffuses out of the polymer device and concentration profiles flatten out, the expected steady reduction in efflux, is compensated by the increase in the diffusion coefficient in the swelling layers.

As an example of the implementation of network thermodynamics to problems of this nature a computer simulation of caffeine infusion from a tea leaf is presented. This particular problem was chosen because a near complete set of experimental data were available [13]. The analogy between this phenomena and drug release from a swelling hydrogel polymer however is **exact.**

A tea leaf is sufficiently thin so that diffusion from the edges of the leaf can be ignored. The problem then becomes that of diffusion from the faces of a swelling plane sheet. Also for added convenience diffusion into an infinite medium only was considered, this ensures that distribution coefficients, α may be ignored eqns(14),(15). The leaf considered had an initial thick ness, $2l$ (.08 mm) and an area, A ($1mm_2$). The overall volume of the leaf was considered to increase linearly with time finally doubling its volume relative to the dry membrane after 60 seconds. These experimentally determined properties do not provide sufficient information for computer modelling. The Network model requires not just the total swelling but also water penetration profiles as functions of time and position in the leaf. In addition the local diffusion coefficients must be known as functions of the degree of swelling. Since for the test system these detailed relationships had not been measured, experimentally reasonable assumptions were made.

Two methods for predicting the water profile were used. The first assumed that it remained linear through the leaf, penetrating from a fully swollen surface at time zero. The position of the water front was then calculated to give an overall swelling rate which agreed with experiment.

Volumes were considered to swell isotropically. The water profiles calculated on this basis are shown at 2 second intervals in fig.8 in which distance is expressed as the fractional thickness relative to the fully swollen leaf.

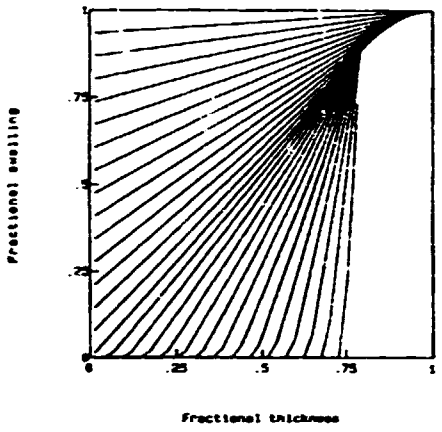

Figure 8: Successive swelling profiles, at 2s intervals, calculated from penetrating front algorithm. Distances measured from the centre of the leaf, expressed as fraction of the fully swollen length.

The dry membrane at time zero has a fractional thickness of 0.8. The second algorithm used, perhaps less realistic, considered the profile to invade the leaf sharply such that volumes were either fully swollen or completely dry. These profiles are unremarkable and are not presented here.

It was assumed that the diffusion coefficient changed due to tortuousity factors alone. There are many relationships available which predict the effects of tortuousity. Prager's derivation, [14] has been used here. This provides the relationship between the degree of swelling at each location and the local diffusion coefficient. The specific tortuousity

correction is not critical in this simulation. In fact, the implementation of Prager's relationship, in this particular model, results in an almost linear function between the diffusion coefficient and fractional swelling. The experimental diffusion coefficient for the fully swollen leaf, $\overline{D}_o$ was $5.0 \times 10^{-7} cm^2 s^{-1}$. Thereafter the diffusion coefficient is predicted by Prager's factor to decrease to $\approx 4 \times 10^{-7} cm^2 s^{-1}$ at .75 fractional swelling, $\approx 3 \times 10^{-7} cm^2 s^{-1}$ at 0.5, and $\approx 1.6 \times 10^{-7} cm^2 s^{-1}$ at .25. In the dry leaf membrane the diffusion coefficient was taken as zero. For the penetrating front example this rapidly changing diffusion coefficient is of particular importance.

Using the network methods outlined above the concentration profiles of diffusant (caffeine) were predicted at 2s intervals during the swelling - diffusion process, fig.9.

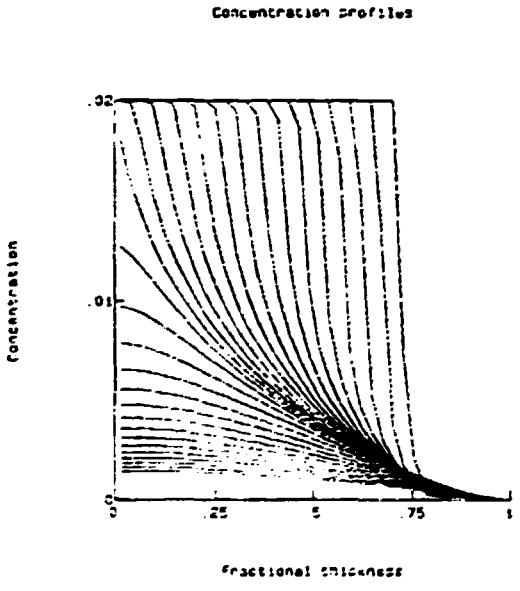

Figure 9: Successive concentration profiles for caffeine within the swelling leaf, at 2s intervals, corresponding to fig.8.

In this example the total amount of caffeine in the tea leaf at time zero was 1.6×10^{-5}mmol (.02mmolml^{-1}). Concentrations have been plotted relative to the fully swollen thickness and at the same time as for the water profiles shown in fig.8. In this way each concentration profile may be compared to the corresponding swelling profile in the leaf. Figure 10 gives the simulated release of caffeine using the penetrating front algorithm for water uptake (curve 1), and the sharp front algorithm. (curve 2).

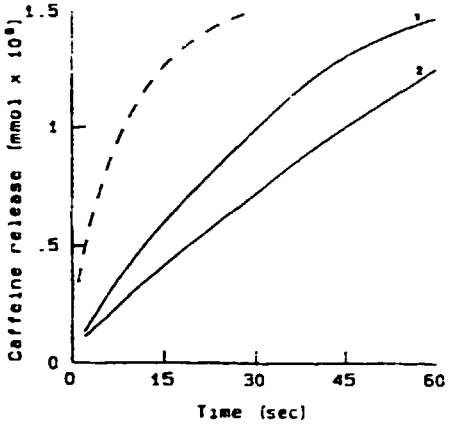

Figure 10: A comparison of caffeine release predicted using the penetrating front and sharp front algorithms for solvent invasion, curves 1 and 2, respectively. Dashed line, comparative release from a fully swollen leaf at equal caffeine loading.

These may be compared with the mathematical solution for release from a fully swollen leaf [9], shown as a dashed line on this figure.

Hydrogel constant release devices operate on the same principle and it is clear that system dynamic modelling of this type will be of considerable use in their design.

Morphine release from a swelling hydrogel has also been simulated. The hydrogel, initially dry, was in the form of a slab, thickness 0.28cm, area 2.75cm^2 and loaded with

0.23mmolcm^{-3} morphine. On immersion in water, it swelled to twice its dry volume, with a half-time of two hours. The swelling profile was the same as fig.8 for the tea leaf except that the profiles were recorded at 8 minute intervals rather than 2 second intervals. Morphine concentration profiles in the swelling hydrogel are shown in fig.11 at 8 minute intervals up to 4 hours.

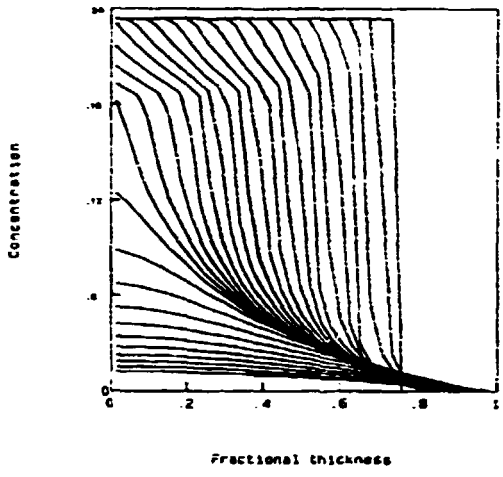

Figure 11: Successive concentration profiles for morphine within the swelling, hydrogel at 8 minute intervals.

The near constancy of the concentration gradient at the outer face, indicates a steady release of drug and this is confirmed by the predicted release into the environment, fig.12

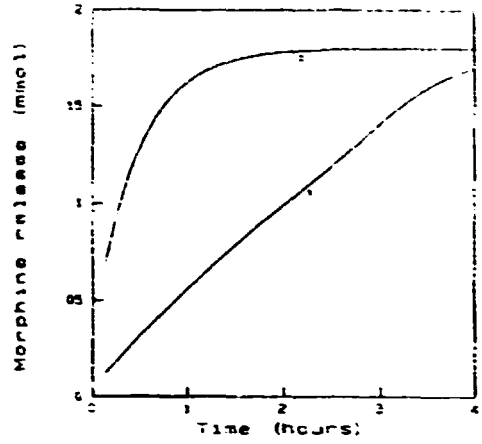

Figure 12: A comparison of morphine release predicted using the penetrating front algorithm for solvent invasion and that from a fully swollen hydrogel, curves 1 and 2, respectively.

The lower curve, being linear, indicates a constant release. The upper curve, for comparison, is the expected release from the fully swollen hydrogel, similarly loaded.

A further illustration of simulations involving variable diffusion coefficients is found in ion exchange. The ion fluxes of exchanging ions (a and b) are coupled through the electrical potential and a common diffusion coefficient Dab is obtained, (using Nernst-Planck theory) which is strongly concentration dependent, eqn.(16).

$$\overline{D}_{ab} = \left\{ \frac{\overline{D}_a \overline{D}_b (Z_a^2 \overline{c}_a + Z_b^2 \overline{c}_b)}{\overline{D}_a Z_a^2 \overline{c}_a + \overline{D}_b Z_b^2 \overline{c}_b} \right\} \qquad (16)$$

Figure 13 illustrates the evolution of a membrane, initially in the hydrogen form and bathed on both side with hydrochloric acid when the left hand side solution is changed to NaCl at time zero.

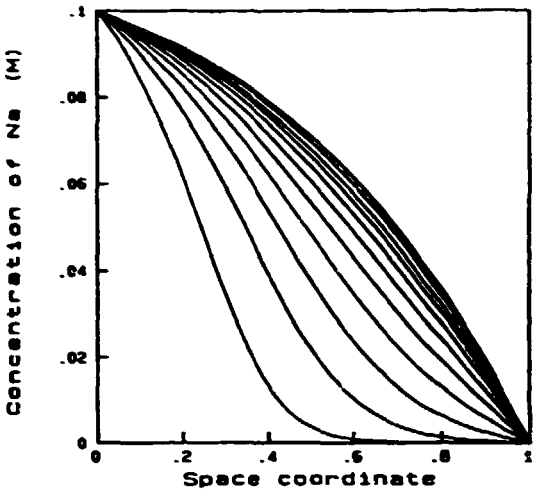

Figure 13: Simulation of approach to steady state diffusion for Na^+/H^+ exchange across a cation exchange membrane, as ref [15]. Sodium concentration profiles at 5,10,15,20,25,30,35,40,45,55,75 and 110s, thereafter invariant as steady state is reached.

The system is that described by Helfferich and Ocker [15] with a membrane thickness 0.1cm, modelled by a 30-lump bond graph. Twelve successive sodium concentration profiles are shown, the final two (at 55s and 75s) effectively superimpose as a steady state is approached.

Variable Input Systems:

The source of effort (SE, fig..3) need not be constant in the bond graph simulation, it need only be known as a function of time. In the thermal bond graph the heat gains and losses through such barriers as walls or insulating layers as a function of varying external temperature would provide a useful application.

In membrane studies the author has applied this principle to determine the system behaviour of a membrane exposed to regular square concentration (or pressure) waves [16]. As the source concentrations oscillates, concentration waves travel through the membrane. The emergent wave is much reduced in amplitude and out of phase with the signal input wave.

From the phase shift, the diffusion coefficient of the permeant may be obtained. Bond graph and mathematical simulations are compared with measured concentration waves, fig.14.

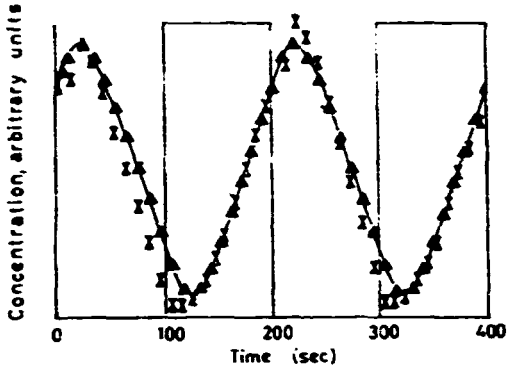

Figure 14: Phase shift between square concentration wave input at the surface of a membrane and the emergeant wave detected at the opposite side in a small collecting volume: ----- mathematical solution - Δ bond graph ; X experimental - taken from [16]. System: dialysis membrane: permeant KCl : detector, conductivity probe.

Square concentration waves were generated using a spray technique. The same technique conveniently allows the determination of diffusion coefficients and permeabilities by the time-lag method [17]. In both cases bond-graph simulations were used to optimise the design of the experimental detection equipment.

The oscillator experiment can now be performed under automatic control using fully computerised equipment recently built in the author's laboratory.

The latest version uses a multi-time lag system. The external solution is stepped from an initial condition of equilibrium (when it is equal to that in the collecting volume) to a higher level and back again at regular intervals in what turns out to be repetitive time-lag experiment, fig.14a.

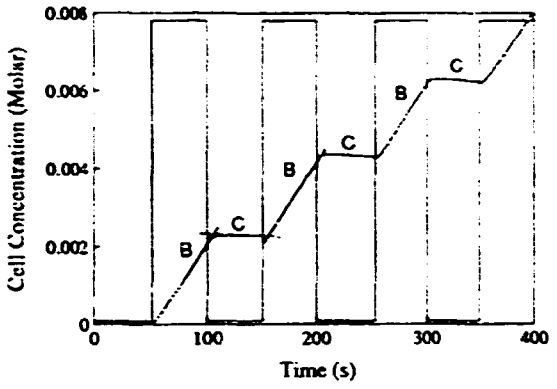

Figure 14a: Experimentally observed emergeant concentration waves from a stepped oscillator experiemin with an anotec membrane 0.02um pore size bilayer membrane, with oscillations between 0.1KCl and water alternately, switch period 100s, collecting volume,2.44cm^{3}and exposed membrane area, 0.771 cm^2, [19].

Intersections between linear portions A and B give repeated estimates of time lags $\tau = l^2/6D$ and the slope of A - slope of B provide repeated estimates of the permeability. The method has enormous advantages over conventional method in that a large number of precise estimates of diffusion coefficient and permeability, P, eqn.(13), are obtained in a single experiment.

Coupled Systems:

Coupled systems are strictly outwith the scope of this paper, but such systems have been simulated in the author's laboratory and include both chemical coupling between molecular fluxes and electrochemically coupled systems of importance in electrically driven membrane processes such as electro-dialysis, in batteries, or in applications such as chlor-alkali production. (Here we distinguish the free diffusion of two ions in a process of ion exchange (treated above) from multi-ionic electrodiffusion since such systems require a full coupling analysis and cannot be described in terms of a simple diffusion model). In fig.15 concentration profiles for chloride and hydroxide are shown in a simulation of a cation exchange membrane set between two concentrated solutions, one of sodium chloride, the other sodium hydroxide. In this simulation a current densities of 3000 Am^2, was used, as in the chlor-alkali cell and as seen in fig.15, concentration profiles are non-linear, being strongly influenced by the electric fields. Network thermodynamics is particularly useful (possibly uniquely so) in coupling and energy transduction modelling. This is due to its unified approach to all energy domains, based upon flows and efforts, defined by the dissipation function eqn.(1).

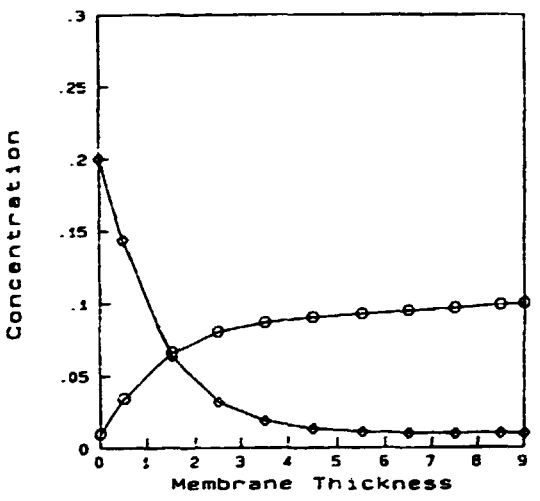

Figure 15: Illustration of membrane profiles for chloride * , and hydroxide o , in a cation exchange membrane in which the current density is 3000Am^2 modelling the behaviour expected in Nafion membranes in use in chlor-alkali cells.

Two-dimensional diffusion:

The extension of bond graph models into the second dimension is relatively simple. The bond graph, fig.16 is an extended 2D lattice with directional resistances R_x and R_y space equations are obtained as before and the progress of diffusion in two dimensions may be predicted.

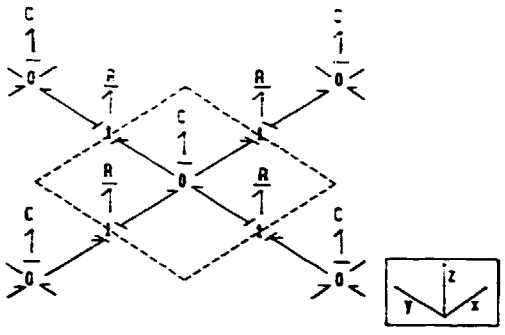

Figure 16: Bond graph for two dimensional diffusion [6].

Concentration profiles become 3D objects and may be displayed as in fig.17.

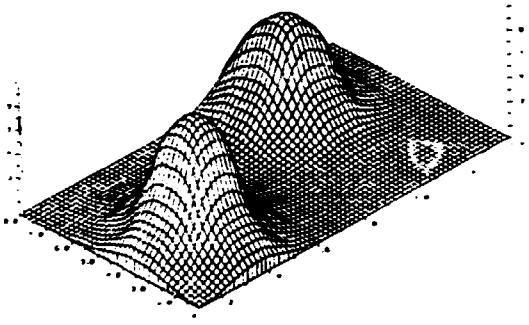

Figure 17: Simulation of free diffusion in a plane.

This is a concentration profile of a diffusion system in which two high concentration spots set asymmetrically interdiffuse on a rectangular plane. To test the quantitative aspects of the model, several systems were simulated for which analytical models were available. These include effusion from a cube through four contiguous faces and from a limited cylinder (disc or pill). The edge effects caused by additional diffusion paths around the edge of a clamped disc were analysed by Barrie, Barrer and Rogers [18]. Figure 18 shows a bond graph simulation of the concentration profiles for such a membrane in the steady state.

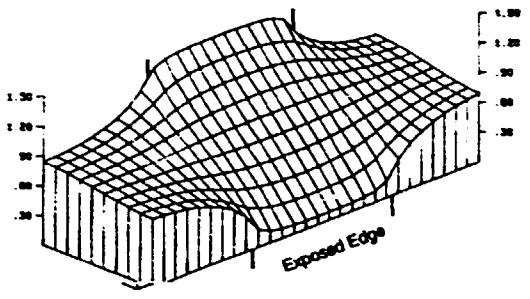

Figure 18: Steady state concentration profiles across a planar disc with edge effects.

The local fluxes are, as always, determined in these bond graph simulations. Quantitative agreement with the theoretical model was obtained, Table 1. Clearly all the additions extensions to the linear bond graph discussed above for one dimensional cases can be transferred to two- and even three-dimensional systems.

Table 1: edge effects on steady state fluxes through a planar membrane : a comparison of the analytical solution [18] and bond graph simulations

$\frac{l}{a}$	$100\frac{(b-a)}{a}$	$100\frac{(J-J_o)}{J_o}$	
		Analytical*	**Network****
0.2	18	7	6
0.4	18	13	14
0.6	18	19	19
0.8	15	21	21

The membrane disc : thickness, l; radius, b; exposed radius, a.
The steady state flux, J, with edge diffusion effect, may be compared with J_o: the corresponding flux with no edge effect $(b-a)$.

* Percent increase in flux predicted by the analytical method of Barrer, Barrie and Rogers [18].

** Corresponding results obtained using a 10x10 bond graph.

Network thermodynamics and the bond graph theory combine to give a universally applicable system dynamics for membrane systems. It is clear that such a theoretical tool

could (and should) have a major role in the design an modelling of new membrane processes and the optimisation of existing ones.

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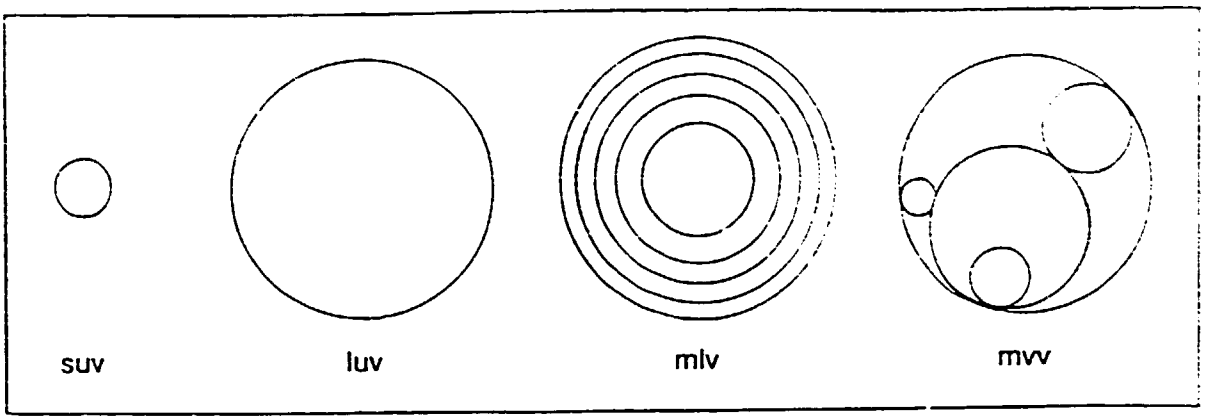
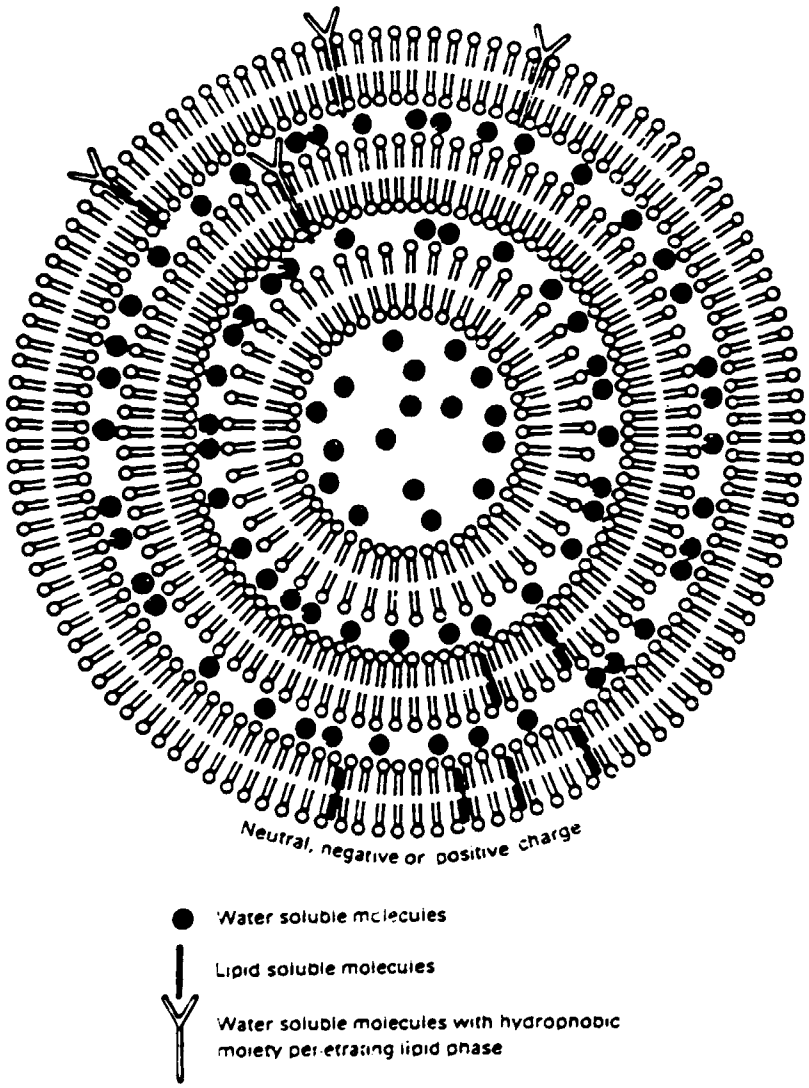
Professor Ian W. Kellaway

LIPOSOMES AS DRUG DELIVERY DEVICES.

IAN W. KELLAWAY,
WELSH SCHOOL OF PHARMACY,
UNIVERSITY OF WALES,
CARDIFF.

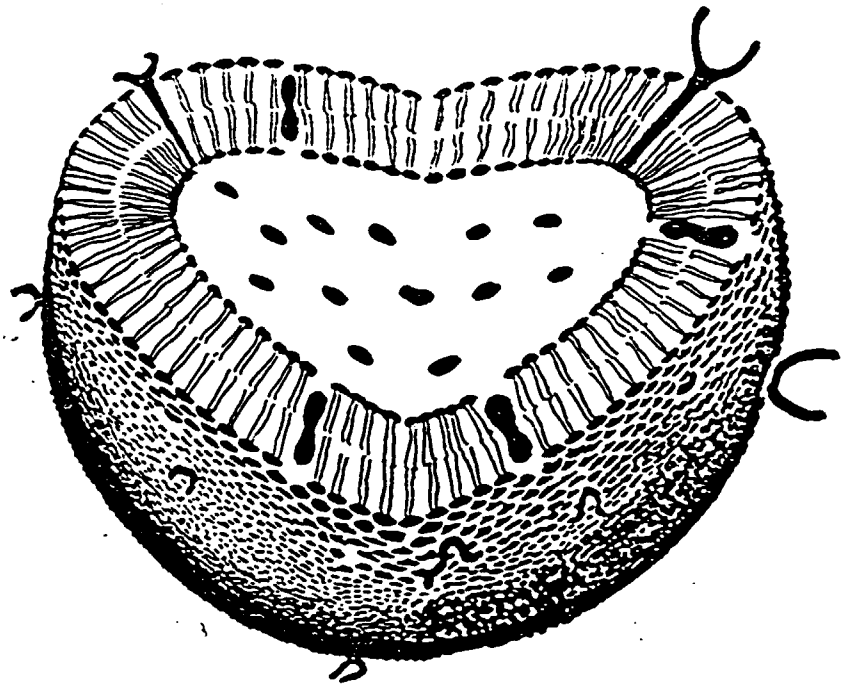


Morphology of the different liposome structures; suv: small unilamellar vescicle; luv: large unilamellar vescicle; mlv: multilamellar vesicle; mvv: multivesicular vesicle.



Schematic diagram of multilamellar liposome.

SCHEMATIC REPRESENTATION OF A UNILAMELLAR VESICLE

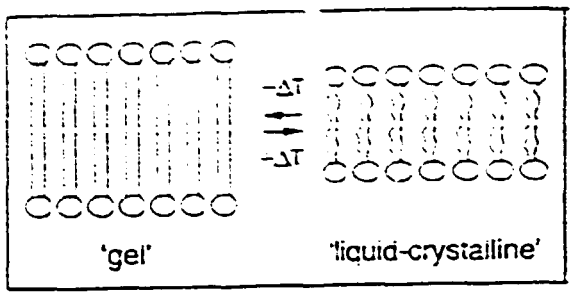


phospholipid

hydrophilic drug

hydrophobic drug

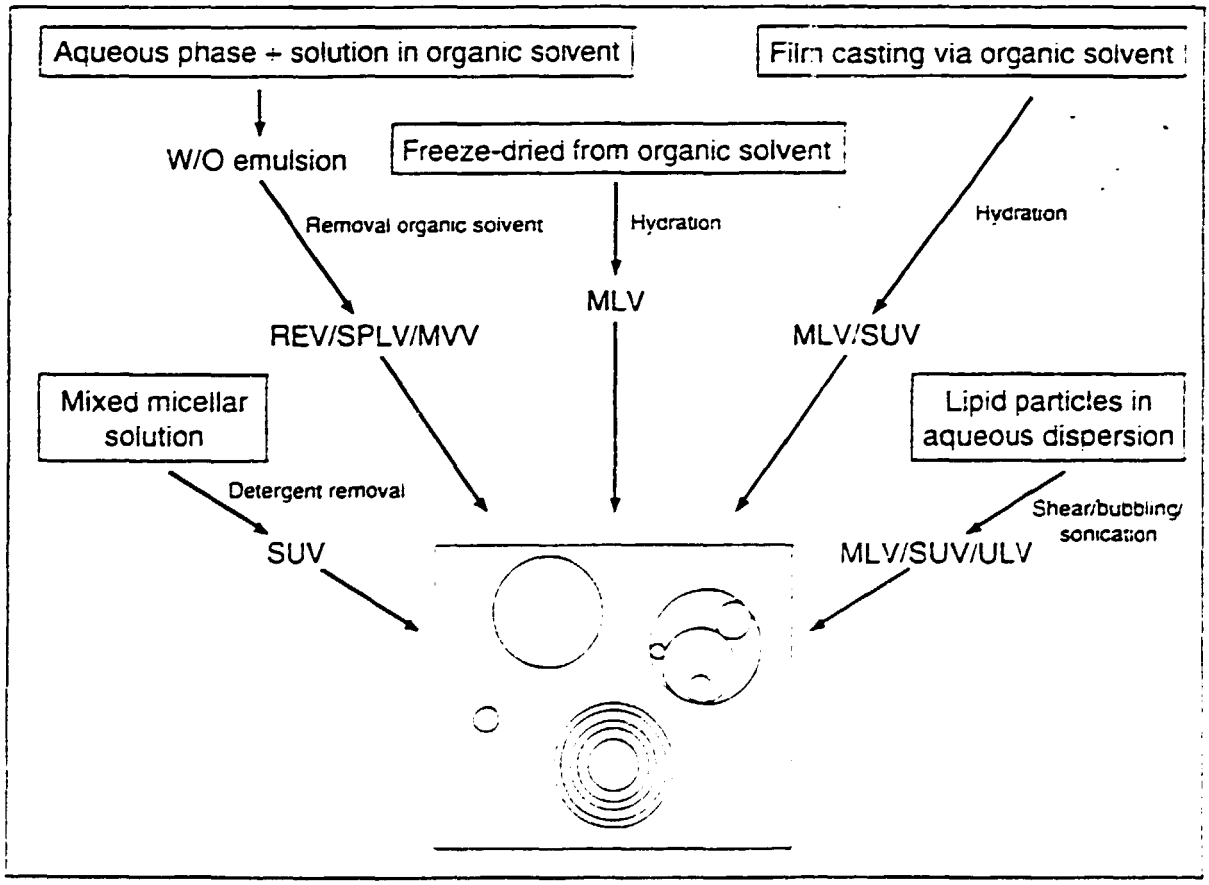
targeting moiety



A schematic view of the 'gel'-'liquid-crystalline' transition of the bilayer.

Transition temperature of some phospholipids regularly selected for liposome preparation.

Phospholipid	T_m (°C)
Egg phosphatidylcholine	-15 to -7
Brain phosphatidylserine	6 to 8
Dipalmitoylphosphatidylcholine	41
Hydrogenated soy-bean phosphatidylcholine (phospholipon 100H®)	51



Schematic diagram of regularly used methods used for liposome preparation. The commonly obtained type of vesicle is indicated. REV — reverse-phase evaporation vesicles; SPLV — stable plurilamellar vesicles; ULV — unilamellar vesicles.

CLINICAL RATIONALE FOR DRUG CARRIERS.

1) GREATER SELECTIVITY THAN ACHIEVABLE BY DRUG DESIGN ALONE.

2) LARGE DRUG PAY-LOAD PROTECTED WITHIN CARRIER PARTICLE FROM DEGRADATION.

3) DECREASED TOXICITY BY CONTROL OF DRUG AND METABOLITE LEVELS IN BLOOD AND ORGAN SITES.

4) CELLULAR UPTAKE BY VARIOUS MECHANISMS ——— ENHANCED CELLULAR DRUG LEVELS.

5) ALTERED PHARMACOKINETICS ———— REDUCED TOXICITY AND ENHANCED THERAPEUTIC EFFECTS.

POTENTIAL LIPOSOMAL - TARGETING BENEFITS.

1) ENDOGENOUS, BIODEGRADABLE, NON-TOXIC CONSTITUENTS.

2) WIDE RANGE OF COMPONENTS

——— LIPOSOMES OF DIFFERENT PHYSICAL AND BIOLOGICAL PROPERTIES.

——— DESIGN FOR SPECIFIC TARGET.

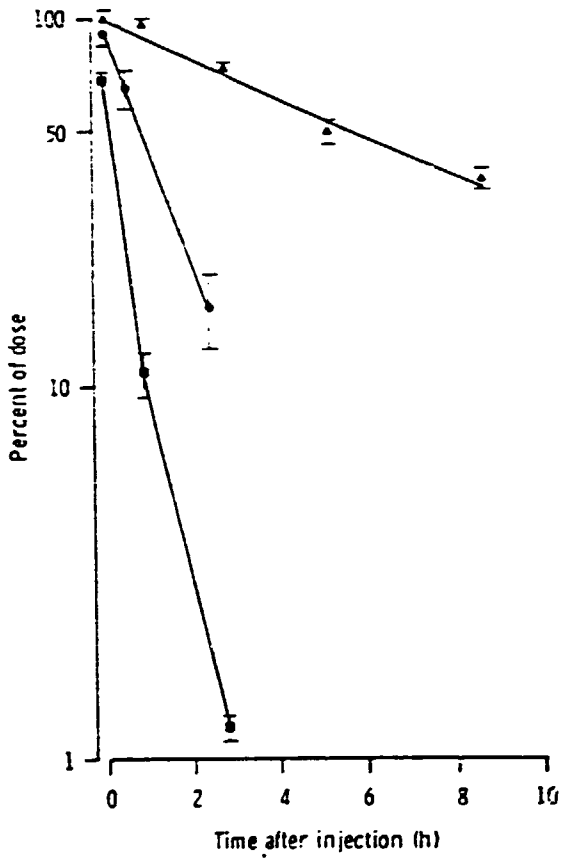
3) NO CHEMICAL REACTIONS AND MILD PREPARATION CONDITIONS

——— OPTIMAL DRUG STABILITY.

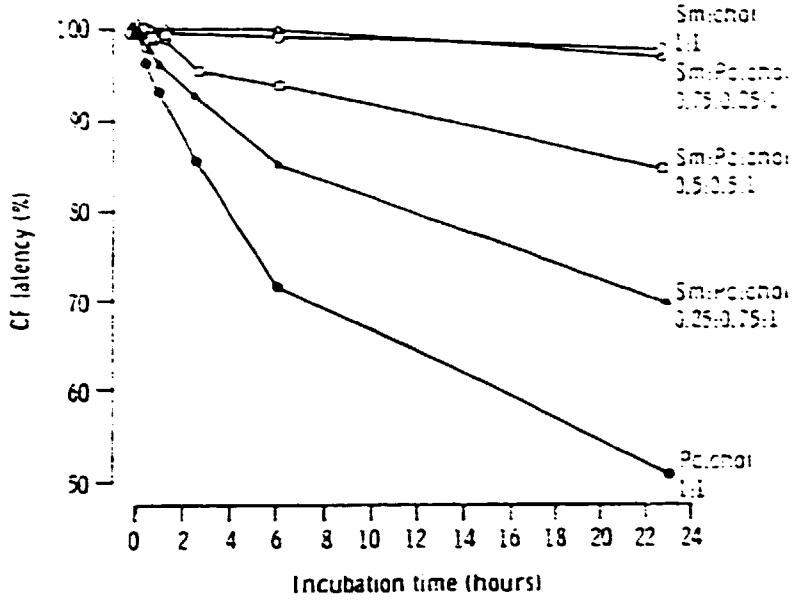
4) IN ADDITION TO CELL ENTRY BY ENDOCYTOSIS ——— FUSION ALBEIT AT LOW EFFICIENCY.

5) READY MODIFICATION OF SURFACE PROPERTIES (MEMBRANE FORMING LIPIDS, ADSORPTION OF MACROMOLECULES; COVALENT ATTACHMENT OF TARGETING ENTITIES).

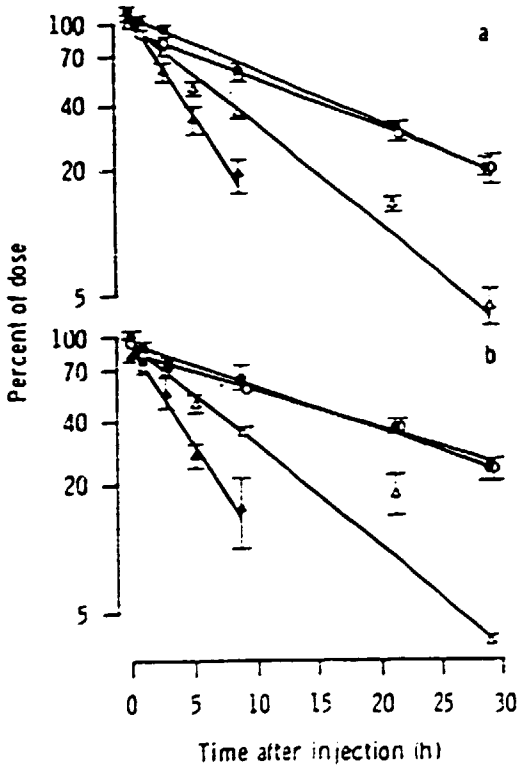
6) POSSIBLE IN VIVO TRIGGERING OF DRUG RELEASE (pH, TEMPERATURE, PHOTOCHEMICAL MODULATION).



Effect of size on the clearance of liposomes from the circulation of mice. Mice were injected intravenously with CF-containing liposomes composed of equimolar cholesterol and DSPC. Vesicles given were reverse phase evaporation filtered through polycarbonate filters of 0.4 (■) and 0.2 (●) μ diameter or small unilamellar (▲), all at a dose of 21 mg phospholipid per kg body weight.

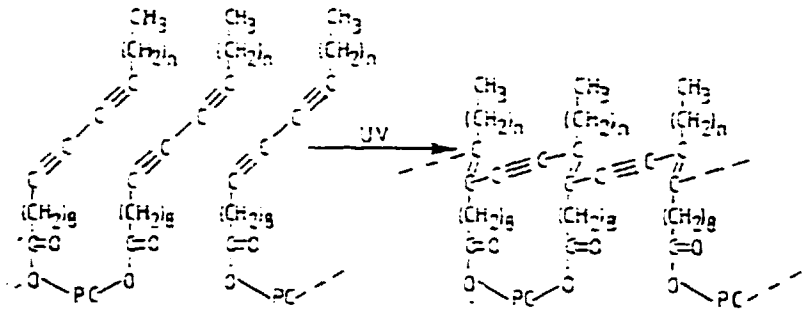


The effect of phospholipid composition of liposomes on their permeability in plasma. Small unilamellar liposomes containing quenched CF and composed of SM (△), 77% SM, 23% PC (○), 47% SM, 53% PC (□), 23% SM, 77% PC (▲), and PC (●) were incubated in the presence of mouse plasma at 37°C. All liposomal preparations contained cholesterol, equimolar to total phospholipid. CF latency values at time intervals are percent of total CF present.

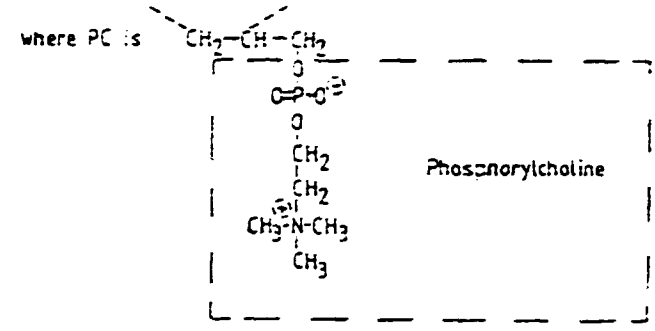


Effect of dose on clearance of small unilamellar liposomes from the circulation of mice. Mice were injected intravenously with liposomes composed of equimolar cholesterol and DSPC and containing CF (a) and ^{14}C-DSPC (b). Amounts of phospholipid given were 0.2 (▲), 0.6 (△), 1.2 (○), and 2.0 (●) mg per mouse.

EXAMPLE OF POLYMERIZED VESICLES.



where PC is



Effect of ganglioside G_{M1}, cholesterol, or combination of the two on blood, RES ratios for liposomes of varying compositions, 2 h post-injection (mean ± SD, n = 3)

Composition	Size (μm)	Blood/RES	% remaining in vivo
PC	0.17	0.010 ± 0.005	56.0 ± 5.4
PC:CH, 2:1	0.17	0.13 ± 0.08	78.1 ± 0.04
PC:G_{M1}, 1:0.07	0.17	0.17 ± 0.12	79.4 ± 5.9
PC:CH:G_{M1}, 2:1:0.14	0.16	1.7 ± 0.5	75.6 ± 3.7
PC:CH:ASG_{M1}, 2:1:0.14	0.16	0.62 ± 0.44	64.8 ± 1.6
DSPC	0.17	0.015 ± 0.002	91.2 ± 2.00
DSPC:CH, 2:1	0.17	0.007 ± 0.00	101.2 ± 2.4
DSPC:G_{M1}, 1:0.07	0.17	2.0 ± 0.02	76.7 ± 3.1
DSPC:CH:G_{M1}, 2:1:0.14	0.17	3.2 ± 1.0	64.6 ± 3.5
SM	0.17	0.02 ± 0.01	27.1 ± 3.1
SM:CH, 2:1	0.17	0.7 ± 0.2	71.9 ± 4.4
SM:G_{M1}, 1:0.07	0.17	5.7 ± 1.8	12.4 ± 0.7
SM:CH:G_{M1}, 2:1:0.14	0.17	4.6 ± 0.6	72.1 ± 1.5
SM:PC, 4:1	0.17	0.6 ± 0.2	69.0 ± 3.3
SM:PC:CH, 4:1:3	0.17	0.12 ± 0.06	69.9 ± 2.2
SM:PC:CH:SO_4, 4:1:3:0.35	0.17	0.43 ± 0.21	78.4 ± 1.4
SM:PC:G_{M1}, 4:1:0.35	0.16	3.3 ± 0.3	61.8 ± 2.9
SM:PC:CH:G_{M1}, 4:1:3:0.35	0.16	1.5 ± 0.6	88.5 ± 3.0
SM:PC:ASG_{M1}, 4:1:0.35	0.16	0.9 ± 0.5	80.3 ± 2.5

G_{M1} and ASG_{M1} concentrations are expressed as the molar ratio of total phospholipid. The ratio of % injected counts in blood to % injected counts in liver plus spleen is termed blood/RES ratio

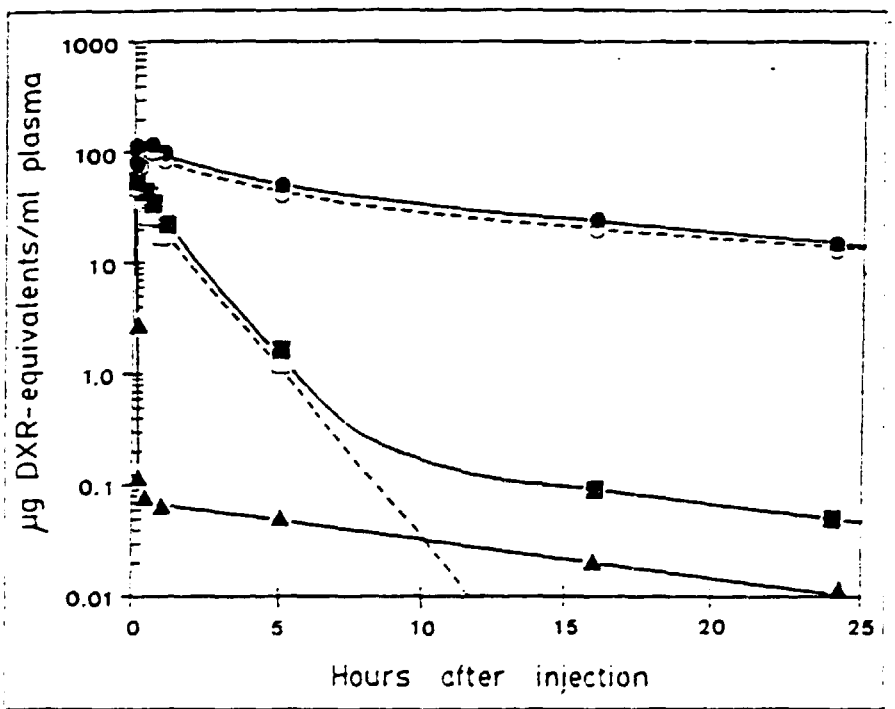
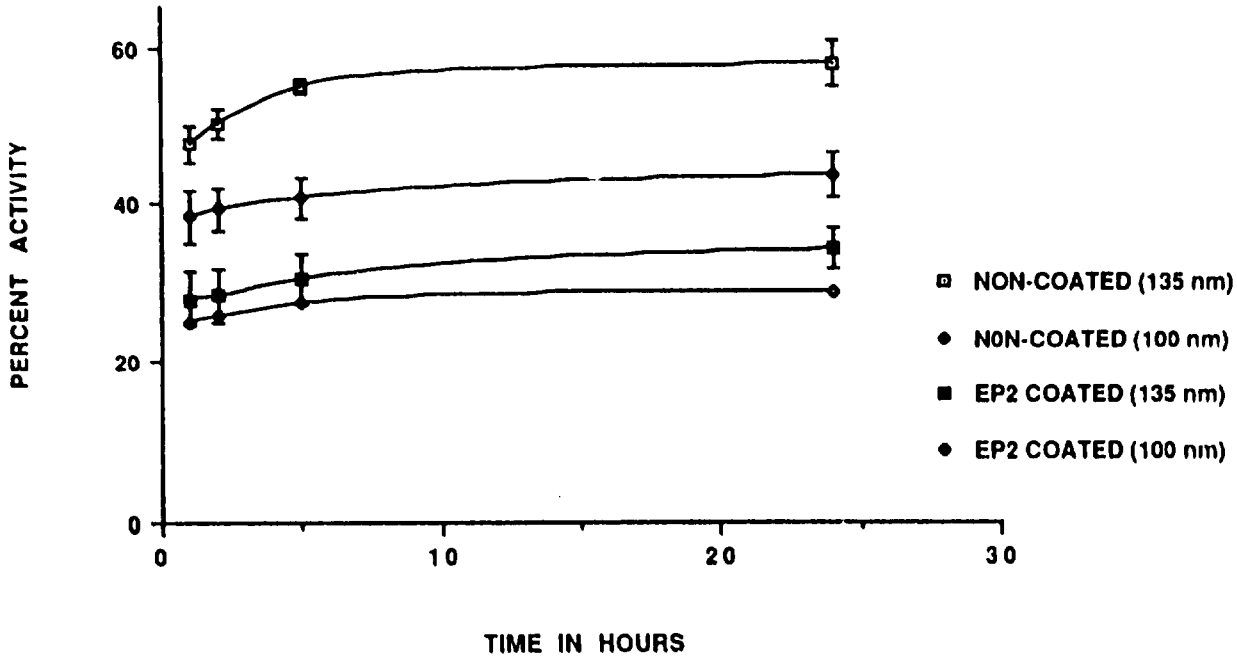


Figure 1. Plasma clearance of free and liposome-encapsulated DXR after IV injection in mice. Symbols represent observed values; lines represent computer-predicted values. Filled symbols and solid lines stand for total DXR concentrations in plasma; open symbols and dashed lines indicate concentrations of liposome-associated DXR in plasma. ▲ = free DXR. ■, □ = DXR encapsulated in PG-PC-Chol. ●, ○ = DXR encapsulated in HPI-HPC-Chol. DXR dose = 10 mg/kg; phospholipid dose = 0.14 mmol/kg for PG-PC-Chol and 0.20 mmol/kg for HPI-HPC-Chol. Sampling times: 5 min, 10 min, 30 min, 1 hr, 5 hr, 16 hr, and 24 hr. Note that concentrations of PG-PC-Chol liposome-associated DXR were undetectable at the 16- and 24-hr time points.

Activity associated with the liver/spleen of 67-Ga labeiled DPPC:chol (1:1) liposomes following intravenous adminstration into rabbits. STATIC STUDY



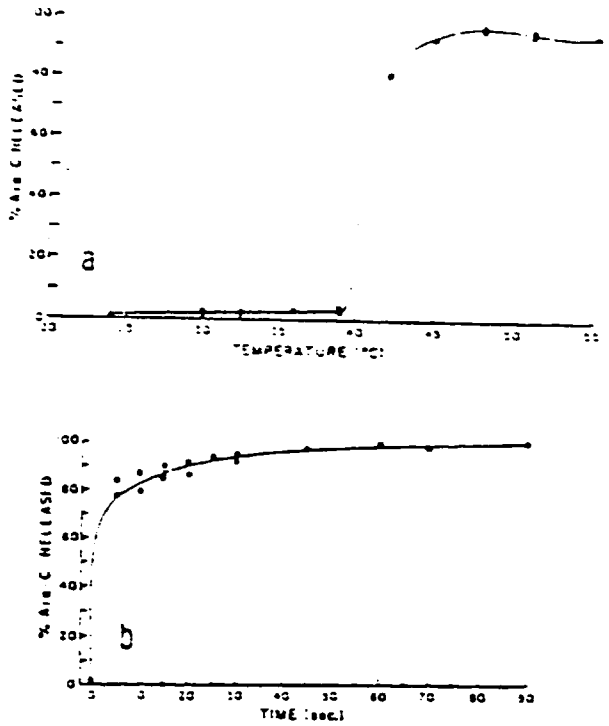
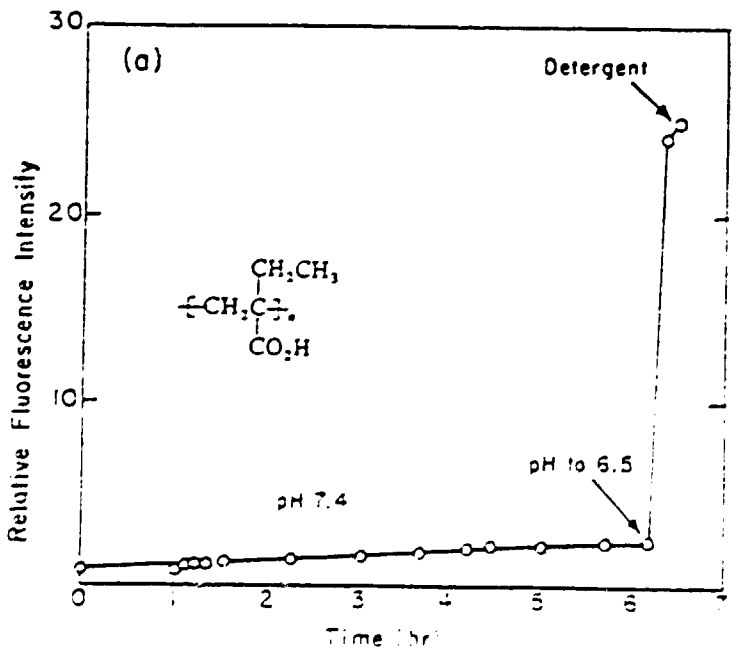


Fig. 6. Temperature-sensitive release of ^{3}H-cytosine arabinoside (ara-C) from DPPC:DSPC (5.5:1) large unilamellar vesicles.
(a) Vesicles were incubated in 100 μl capillaries in 50% mouse serum for 1 minute. Free and encapsulated ara-C were then separated in a Beckman air-driven centrifuge and counted. A dramatic increase in release was obtained at 40°C. The lipid concentration was 3 mg/ml.
(b) Time-course of ara-C release from the same vesicles. The bath was set at 45°C, and the time constant for equilibration of temperature was 1.2 seconds. Six seconds sufficed for near total release, and subsequent experiments with smaller capillary tubes have shown 2 seconds to be adequate.



Efflux of 6-carboxyfluorescein from sonicated phosphatidylcholine vesicles suspended in 50 mM Tris-HCl, 100 mM NaCl, 0.03% PEAA at indicated pH. Figure 3a above. Egg yolk phosphatidylcholine.

Table 1. Liposomally entrapped drugs tested for gastrointestinal application

Drug	References
Hydrophilic	
Insulin	Patel and Ryman (1976, 1977a,b), Dapergolas and Gregoriadis (1976, 1977), Patel *et al.* (1978, 1982), Hashimoto and Kawada (1979) Tragl *et al.* (1979), Weingarten *et al.* (1981), Kawada *et al.* (1981), Arrieta-Molero *et al.* (1982), Shenfield and Hill (1982), Dobre *et al.* (1983)
Glucose oxidase	Dapergolas *et al.* (1976)
d-Tubocurarine	Dapergolas and Gregoriadis (1977)
Angiotensin II	Papaioannou *et al.* (1978)
1-β-D-Arabinofuranosylcytosine	Rustum *et al.* (1979)
Gentamycin	Morgan and Williams (1980)
Factor VIII	Hemker *et al.* (1980), Kirby and Gregoriadis (1984)
Factor IX	Ueno *et al.* (1982a)
Heparin	Ueno *et al.* (1982b)
Cysteamine	Jaskierowicz *et al.* (1985)
Lipophilic	
Vitamin K	Nagata *et al.* (1984)
Dolichol	Kimura *et al.* (1989)
Indomethacin	Soehngen *et al.* (1988)

Table I. Liposome-based products in clinical development. Except as noted, all are administered intravenously

Indication	Drug	Phase
Anticancer	Daunorubicin	
	'DaunoXome'	I/II
	Doxorubicin	
	L-Dox	I
	TLC D-99	II
	MTP-PE	II
Bronchodilator[a]	Orciprenaline (metaproterenol)	
	'Metasome'	II
	Salbutamol (albuterol)	II
γ-Imaging agent	^{111}Indium	
	'Vescan'	III
MAI in AIDS patients	Gentamicin	
	TLC G-65	I
Systemic mycoses	Amphotericin B	
	'ABCD'	II
	'ABLC'	II
	'AmBisome'	–[b]

a Inhaled.

b Marketed in Europe.

Abbreviations: MTP-PE = muramyl tripeptide phosphatidylethanolamine; MAI = *Mycobacterium avium intracellulare*; AIDS = acquired immune deficiency syndrome.

DRUG DELIVERY TO THE LUNG

Ian W. Kellaway, Welsh School of Pharmacy, University of Wales College of Cardiff, Cardiff CF1 3XF.

INTRODUCTION

Drug delivery to or via the respiratory tree has been a long-standing pharmaceutical objective. For locally acting agents it is desirable to confine the action of the drug to the lung in order to eliminate unintended side effects which might result following absorption and distribution to other extravascular sites. Oral inhalation is often the preferred route in order that such effects be minimised. The large surface area for absorption provided by the alveolar region, together with reduced extracellular enzyme levels compared with the gastrointestinal tract, ensures that pulmonary administration is a potentially attractive route for the delivery of systemically active agents including the new generation of biotechnology molecules.

RESPIRATORY TRACT MORPHOLOGY AND PHYSIOLOGY

The lung is a specialized tissue with the prime function of gaseous exchange involving oxygen absorption and carbon dioxide and water elimination. Efficient exchange results from a surface area of approximately $70m^2$ and an air-blood barrier of between 0.36 and 2.5 um. It has been estimated that the daily air mass handled by the human lung is approximately 13kg. The lung therefore provides a great potential for toxicity by air-borne toxins and, in addition, some substances that are poorly absorbed in the gut are well retained by and absorbed within the lung.

For convenience, the respiratory tract is often compartmentalised into the following three regions (Table 1):

1. The oropharyngeal (OP) or nasopharyngeal (NP) compartment consists of the mouth or nares and includes the respiratory airways down to the larynx.

2. The tracheobronchial (TB) region begins at the larynx and includes the trachea and the ciliated bronchial airways down to the terminal bronchioles.

3. The pulmonary (P) or functional gaseous exchange region comprises the respiratory bronchioles, alveolar ducts, alveolar sacs, atria and alveoli.

The terms 'upper' and 'lower' respiratory tract are frequently encountered and correspond to the NP, together with the trachea and the P plus bronchial regions respectively.

The NP compartment can entrap larger particles whose inertia causes impaction in the nasal passages or entrapment by nasal hairs. Clearance is believed to occur either by particle solution and distribution into blood or, for less soluble materials, physical clearance by mucociliary transport with subsequent swallowing. The posterior region of the nose is subject to mucociliary clearance whereas particles deposited in the anterior region will only be cleared by such actions as wiping, sneezing or blowing.

A relatively small fraction of all inhaled particles will deposit in the TB region. TB deposition may occur by a variety of mechanisms but principally by inertial impaction, sedimentation and Brownian diffusion - the latter restricted to submicron particles. Mouth breathing of aerosols - the normal route of pulmonary delivery of medicinal agents - by-passes the nasal removal of large particulates, which therefore are deposited in the throat and regions of the TB area. The mucociliary escalator ensures rapid removal (hours) of insoluble deposited particles; soluble particles will dissolve and may enter the blood stream. Mucus is removed by the cilia at a rate which increases as the diameter of the airways increases. This, in conjunction with the tendency for smaller particles towards deeper penetration of the lung, ensures that larger particles are cleared more rapidly. It is for this reason that particle clearance kinetics from this compartment cannot be described by a single rate, although estimates of clearance half-time of 0.5, 2.5 and 5 hr have been quoted for the larger, intermediate and finer airways respectively.

For particles to deposit in the deepest compartment (pulmonary region) successful penetration beyond the NP and TB regions must occur with subsequent retention on the pulmonary surfaces as a result of settling, diffusion and interception processes, the relative contribution being, to a large extent, governed by particle size. The residual volume (approximately 1.2 l of air) ensures that for some particles the time to achieve deposition may be considerably longer than a single breathing cycle and, in some instances, may be minutes rather than seconds. Several mechanisms ensure clearance from this region and include dissolution with absorption, phagocytosis of particles by macrophages with translocation to the ciliated airways, lymphatic uptake of particles and the possibility of direct passage of particles into the bloodstream.

These three compartments were adopted by the ICRP Task Group in their deliberations on the relationship between fraction deposited and particle aerodynamic diameter and subsequently applied to the mouth breathing of monodispersed aerosols (Fig.1). These theoretical profiles are in reasonable agreement with experimentally determined curves (Fig.2).

CELLS AND TISSUES OF THE RESPIRATORY TRACT.

The ultrastructure of the trachea and large bronchi consists of a variety of cells although ciliated and goblet cells predominate. Serous, basal, brush, undifferentiated, Clara and Kulchitsky cells are also present. In the bronchioles, ciliated cells are dominant and Clara cells progressively increase distally along the airways. Goblet cells and serous cells also decrease distally and are absent in terminal bronchioles. Undifferentiated brush, basal and Kulchitsky cells are an uncommon occurrence. The cells and tissues which play an important role in drug deposition and clearance are now described in more detail.

CILIATED MUCOSA

This tissue lines the rear portion of the nose, the larynx and the tracheo-bronchial tree. The cilia are hair-like projections which beat in a coordinated fashion to move the overlying mucus blanket in a direction towards the throat where the mucus is swallowed. The mucus which is primarily an acid glycoprotein, is produced from goblet cells which are

interspersed with the ciliated cells; both cell types are attached to the basement membrane. The mucus is a viscoelastic, tacky fluid which is responsible in conjunction with the cilia for the removal of particulates from the tracheobronchial regions. The efficiency of the 'mucociliary escalator' depends on the quantity and quality of mucus and the number and synchronisation of the cilia. Drugs can alter the viscoelastic properties of mucus and range from mucolytics such as N-acetyl cystine, which reduces the viscosity and elasticity, to mucospicics such as the tetracyclines which enhance both the viscous and elastic nature of the mucus gel. There appears to be a range of mucus elasticity within which cilia can effect transport.

Viral and bacterial infections can lead to changes in both the quantity and quality of the mucus and, in more severe cases, clearance is only possible through the action of coughing or sneezing.

ALVEOLI

The alveoli are polyhedral structures generally less than 300 um in diameter, surrounded by thin walled epithelial cells on all but one side which is open to the atmosphere. The epithelial cells are of several types: Type I are thin cells, overlying a basement membrane some 20 - 40nm thick. A much thicker cell (type II) has a surface covered with microvilli which greatly increase the surface area with the air stream. These cells produce and secrete 'lung surfactant' which is composed of lipid-rich lipoproteins (85 - 90% lipid by weight). The lipid composition is dominated by phosphatidylcholine with dipalmitoyl present in unusually high percentages. This 'cocktail' leads to the generation of low, stable surface tensions, preventing collapse of the lung. Proteins present include serum albumin, together with 10 and 35 kDa non-serum proteins. The latter allow the rapid formation of phospholipid surface films in the alveoli. Respiratory distress syndrome is an example of a disease state related to abnormalities in lung surfactants. Type III, or alveolar brush cells, overlie the alveolar basement membrane and protrude into the airspace with their large microvilli. Other cell types include interstitial cells and macrophages. The alveolar macrophages are mobile, nucleated cells which surround and endocytose small particles. Functions of maintaining sterility by engulfing and killing microorganisms, together

with 'dust collecting' have been ascribed to these cells. Both positive and negative chemotactic responses have been demonstrated by alveolar macrophages. Certain dusts may be cytotoxic to macrophages, for example coal, asbestos and silica. An upper limit of 3 um has been suggested for a phagocytic uptake.

PULMONARY DRUG SELECTIVITY AND PROLONGATION OF THERAPEUTIC EFFECTS

(a) Prodrugs

In addition to improved selectivity of action in the lung relative to other organs, it is possible to obtain prolongation of therapeutic effects and enhancement of pulmonary activity by the design of appropriate prodrugs. Lung accumulation from the blood pool is achieved by many drugs which are both highly lipophilic and strongly basic amines. Such drugs exhibit very slowly effluxable lung pools.

Lung tissue exhibits high nonspecific esterase activity (3) which is species dependent and capable of cleaving carboxylate or carbonate ester linkages. In vivo prodrug conversion to active drug moiety can be controlled by use of different aliphatic or aromatic coupling agents, together with stereochemical modifications.

Terbutaline is an example of a bronchodilator drug for which a number of prodrugs exist (Fig. 3). Terbutaline exhibits little affinity for lung tissue being rapidly absorbed following inhalation with peak plasma concentrations occurring within 0.5h. The di-isobutyryl ester (Ibuterol) results in an increased bioavailability of 1.6 fold over terbutaline following oral administration. However, it is 3 times as effective as terbutaline post-inhalation in inhibiting bronchospasm. Enhanced effects are attributable to more rapid absorption and better tissue penetration. Bambuterol is the bis-N,N-dimethylcarbonate of terbutaline and as such is well absorbed from the gastrointestinal tract and is relatively resistant to hydrolysis leading to a sustained release oral product. However, it is not readily metabolised in the lung which precludes its administration by the pulmonary route.

(b) Polyamine active transport system

The cell types which accumulate polyamines such as the endogenous putrescine, spermidine and spermine, together with compounds such as paraquat, are the Clara cells and the alveolar Type I and Type II cells. The uptake process is saturable and energy dependent. Table 2 illustrates the dependence of both Ki (inhibitory constant) and A (= 1000/Ki) a measure of the affinity of a compound for the polyamine receptor on molecular structure (4). A is seen to decrease with N-methylation and conformational restriction, but to increase for N-(4-aminobutyl)aziridine. Previously, in a study of putrescine inhibition by α,ω-diaminoalkanes, the inhibitory potential increased with chain length, plateauing at 1,7 diaminoheptane (5).

(c) **Rate control achievable by employing colloidal drug carriers.**

Control of the duration of local drug activity and of the plasma levels of systemically active agents may be achievable by employing a colloidal carrier possessing appropriate drug-release characteristics. Tracheobronchial deposition of such carriers may not be desirable as their clearance will occur in a relatively short time period on the mucociliary escalator. Pulmonary deposition will, in contrast, result in extended clearance times which may be dependent upon the composition of the colloid. The mechanism by which clearance is effected will also vary, but will involve alveolar macrophage uptake, with subsequent metabolism or deposition on to the mucus blanket in the ciliated regions or lymphatic uptake. Colloidal carriers, of which liposomes an example, can therefore control both drug delivery rates and availability. Technological problems, however, exist such as the design of delivery devices to ensure deposition in the appropriate regions of the lung without degradation or loss of entrapped drug. Toxicological considerations, foremost amongst which is the processing of the colloid, also require to be addressed.

I. LIPOSOMAL DRUG DELIVERY TO THE LUNGS see reference 6.

(a) Clearance of liposomes from the human lung

Farr et al. (7) administered ^{99m}Tc-labelled DPPC liposomes to the lungs of healthy volunteers by means of an air jet nebuliser (Hudson). Pulmonary deposition was dependent on breathing pattern and the droplet size distribution of the aerosol. As clearance rates were related to the depth of penetration, it was not possible to show differences between liposomes of different size or type (Table 3). A fraction of the liposome dose which was deposited in the tracheobronchial region was largely cleared by the mucociliary mechanism over 6 - 8 h. However, approximately 60% was retained at 20 h and probably represents the fraction of the dose reaching the alveolar regions. Such clearance kinetics would be appropriate for achieving sustained release of drugs administered as a liposomal dosage form to the lungs.

(b) Pharmacokinetics of liposomal drugs

In 1989 Taylor et al. (8) reported on the influence of liposomal encapsulation on sodium cromoglycate pharmacokinetics in five healthy volunteers. Sodium cromoglycate 20 mg was inhaled from a Hudson air jet nebuliser (172 kPa) as a solution and encapsulated in DPPC/cholesterol (1:1) liposomes. Liposomal drug produced detectable levels in plasma taken 24 and 25 h post inhalation. The free drug produced peak plasma levels more than sevenfold higher than the liposomal drug but was not detectable (i.e. smaller than 0.5 ng ml^{-1}) in 24 h samples (Fig.4). The decline in plasma levels following inhalation of liposomal drug (reflecting the absorption phase) was best described by a biexponential equation with the two absorption rate constants differing by more than an order of magnitude. The authors attributed the rapid absorption phase as due to free or surface adsorbed drug while the slow drug absorption phase was attributed to drug release from the liposomes. The presented data are the first to demonstrate the ability of liposomes to extend the duration of drug plasma levels in man following pulmonary administration.

(c) Therapeutic efficacy

There is a lack of data in man regarding the clinical efficacy of liposomal drugs administered to the airways. Bronchodilator effects and duration of action have been reported for liposomal Beta-2 adrenergic agonists in the guinea pig (9). Airways resistance was measured following intratracheal instillation of free and liposomally entrapped drug (metaproterenol or albuterol). Liposomal metaproterenol was less effective than the same dose of free drug interpreted by the authors as liposomal drug release being too slow to achieve the concentration required for bronchodilator effects (Table 4). Liposomal albuterol in contrast produced an effect which was sustained for a longer duration than the free drug (Fig. 5).

(d) Technological aspects

Nebulization is the simplest method of administering liposomes to the lung, although Taylor et al. (10) have indicated the importance of vesicle size and composition in maintaining liposome integrity (and hence entrapped drug) during the nebulization process.

An alternative approach is to employ a lyophilized liposome preparation in conjunction with a unit-dose dry powder inhaler. The production and stability of lyophilized liposomes to aerosolisation (11) has been reported.

II. DRUG-POLYMER COMPLEXES

The conjugation of cromoglycate (CG) to a dextran carrier was shown to modify its pharmacokinetic profile compared with the free drug after intratracheal administration to rabbits (12). Conjugation prolonged CG residence with a reduction in C_{max}. The half life was increased from 83 $\pm$ 13 min (free drug) to 171 $\pm$ 24 for the conjugate (Table 5).

III. DRUG-CYCLODEXTRIN COMPLEXES

Salbutamol forms complexes with β cyclodextrins and a complex with hydroxypropylbetacyclodextrin (HP-β-CYD) was shown to increase t_{max}, absorption half-life and decrease the C_{max} following intratracheal administration to

rabbit lungs (Table 5) [13]. However, complexation did not alter the post peak decline of salbutamol indicating that the absorption was not slowed sufficiently to produce absorption rate limited kinetics. The bioavailability was also reduced to about 30%. The complex dissociated rapidly within the lung. Such an approach of using drug-CYD complexes to prolong pulmonary drug release profiles may be enhanced for drugs exhibiting stronger complexes with CYDs.

DELIVERY OF DRUGS TO THE SYSTEMIC CIRCULATION BY THE PULMONARY ROUTE

The large surface area, thin epithelial membrane provided by Type I cells and a rich blood supply, ensures that many compounds are readily transported from the airways into the systemic circulation. Gaseous anaesthesia and oxygen therapy are examples of efficient clinical utilisation of the pulmonary absorption process. Compounds are absorbed by different processes including active transport and passive diffusion through both aqueous pores and lipophilic regions of the epithelial membranes. Absorption can be both rapid and efficient; for example, sodium cromoglycate is well absorbed from the lung whereas less than 5 per cent is absorbed from the gastrointestinal tract.

Small lipophilic molecules, such as the gaseous anaesthetics, are absorbed by a non-saturable passive diffusion process. Hydrophilic compounds are absorbed more slowly and generally by a paracellular route. Aqueous pores are, by virtue of their size, capable of controlling the rate and extent of hydrophilic compound absorption. Sodium cromoglycate is absorbed by both active and passive (paracellular) mechanisms. The rates of absorption by the paracellular route decreases as the molecular weight of the compound increases.

The efficiency of absorption from the lung is species dependent. For example, insulin is absorbed from the human lung (14) but less efficiently than in the rat (15) or rabbit (16). Human growth hormone (molecular weight 22 kDa) is absorbed from the lungs of hypophysectomised rats with an estimated bio-equivalence of 40 per cent relative to the subcutaneous route and an absolute bioavailability of 10 per cent, sufficient to induce growth (17). A nonapeptide (leuoprolide acetate) has been shown to have an absolute bioavailability following aerosolization to healthy male

volunteers of between 4 and 18% which, when corrected for respirable fraction, corresponds to 35 - 55%.

Protein absorption, however, is postulated to occur through the extremely thin Type I cells by the vesicular process of transcytosis. The passage from lung to blood of proteins in the rat has recently been shown to increase during inflammatory conditions with the observed transport correlating to the severity of the lung injury (19). The pulmonary route therefore warrants further investigation for the systemic delivery of peptides and proteins.

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TABLE 1. The compartmentalisation of the respiratory tract

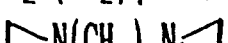
COMPARTMENT	DEPOSITION	CLEARANCE	PATHOLOGY
NP Nasopharyngeal	Impaction Diffusion Interception Electrostatic	Mucociliary Sneezing Blowing	Inflammation Ulceration Cancer
TB Tracheobronchial	Impaction Sedimentation Diffusion Interception	Mucociliary (hours) Coughing	Broncho- spasm Obstruction Cancer
P Pulmonary	Sedimentation Diffusion Interception	Solubilization Phagocytosis Interstitial (hours to years)	Inflammation Oedema Emphysema Fibrosis Cancer

As reported by the Task Group on Lung Dynamics of the International Commission of Radiological Protection

TABLE 2

POLYAMINE ACCUMULATION

INHIBITORY EFFECTS OF PUTRESCINE DERIVATIVES ON THE UPTAKE OF PUTRESCINE [$H_2N(CH_2)_4NH_2$ 2HCl] INTO RAT LUNG SLICES

	INHIBITOR CONSTANT Ki (uM)	AFFINITY FOR RECEPTOR A $(mM)^{-1}$
N-methylation		
$H_2N(CH_2)_4NHCH_3$ 2HCl	8	125
$H_2N(CH_2)_4N(CH_3)_2$ 2HCl	11.5	87
$(CH_3)_2N(CH_2)_4N(CH_3)_2$ 2HCl	100	10
Conformationally restricted analogues		
$H_2NCH_2CH \overset{Z}{=} CHCH_2NH_2$ 2HCl	40	25
Aziridines		
$H_2N(CH_2)_4N$	7.5	133
 $N(CH_2)_4N$	31.5	32

M.C.O'SULLIVAN, B.T.GOLDING, L.L.SMITH, I.WYATT. Biochem. Pharmacol. 41 (1991) 1839 - 1848.

TABLE 3

PULMONARY RETENTION OF NEBULIZED ^{99m}Tc-LABELLED DPPC LIPOSOMES IN VOLUNTEERS (n=4) (REF. 7)

MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation.

Type	Mean size (μm)	Aerosol Analysis		6-h retention ± S.E.M. (%)
		MMAD (μm)	GSD	
MLVs	2.90	3.7	1.5	87.5 ± 2.1
SUVs	0.07	3.2	1.5	76.8 ± 5.1

Inhibition of response to histamine by metaproterenol

TABLE 4

	Free metaproterenol		Liposome metaproterenol	
	27.9 ug	125.0 ug	27.9 ug	125.0 ug
	Resistance responses			
- 15 min	+0.21 ± 0.06	+0.35 ± 0.10	+0.24 ± 0.04	+0.32 ± 0.08
0 time		MPS instillation		
+ 15 min	+0.05 ± 0.02*	+0.03 ± 0.01*	+0.28 ± 0.07	+0.16 ± 0.02*
+ 1 hr	+0.14 ± 0.01	+0.07 ± 0.02*	+0.25 ± 0.06	+0.21 ± 0.07
+ 2 hrs	+0.23 ± 0.05	+0.08 ± 0.05*	+0.29 ± 0.06	+0.26 ± 0.08
+ 3 hrs	+0.30 ± 0.04	+0.18 ± 0.08	+0.33 ± 0.08	+0.27 ± 0.09

The total lung resistance responses to bronchoconstrictor challenge with histamine before and after intratracheal instillation of metaproterenol sulfate. Mean values ± SEM are shown. The asterisk (*) denotes significant reduction in response to histamine compared with baseline controls.

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TABLE 5. Cromoglycate pharmacokinetic parameters (mean ± s.e.m.) after i.v. and i.t. administation of SCG and i.t. administration of a cromoglycate-dextran conjugate (CG-Dx).

	SCG (i.v.)	SCG (i.t.)	CG-Dx (i.t.)
$t_{1/2}$ (min)	7 ± 0.7*	83 ± 13*	171 ± 24*
t_{max} (min)		20 ± 5	75 ± 37
C_{max} (ng/ml)[a]		348 ± 122	184 ± 25
F (%)		36 ± 11	41 ± 6

[a]Normalized for a 4 mg/kg dose
*Significantly different ($p<0.05$) from other treatments (2-way ANOVA and Duncan's multiple range test)

TABLE 6

Summary of the pharmacokinetic parameters (mean ± SE; n = 4) of salbutamol and its complex with HP-β-CYD after i.t. administration to rabbits

	Salbutamol (free)	Salbutamol-HP-β	HP-β-salbutamol
t_{max} (min)	13.6 ± 2.4	23.0 ± 1.2	107.0 ± 4.5
C_{max} (ng/ml)	1035.5 ± 81.5	524.6 ± 43.8	22770 ± 2500
$t_{1/2\alpha}$ (min)	145.3 ± 18.6	168.5 ± 21.4	64.0 ± 2.9
$t_{1/2\beta}$ (min)	10.6 ± 4.2	32.7 ± 6.1	26.2 ± 7.8
F (%)	109.2 ± 8.1	80.6 ± 8.0	67.3 ± 8.8

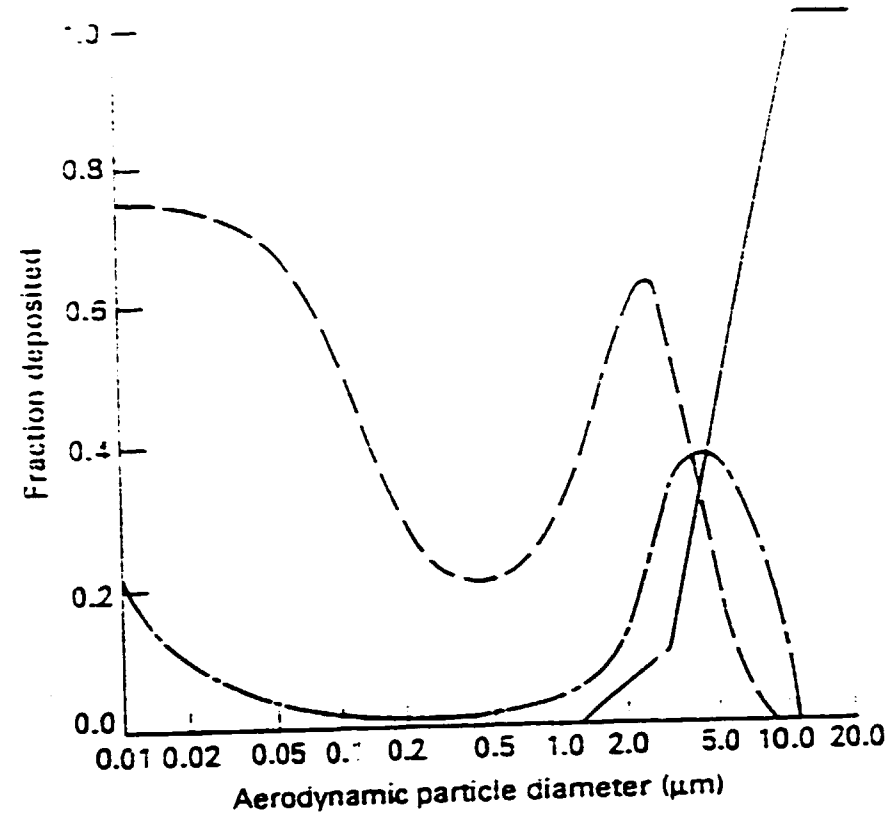


Figure 1 Theoretical deposition of monodisperse aerosols inhaled by healt human adults in the 'head' (——), tracheobronchial (— – — –) and pulmonary (– – – –) regions of the respiratory tract during normal mouth breathing. (Adapted from reference 1)

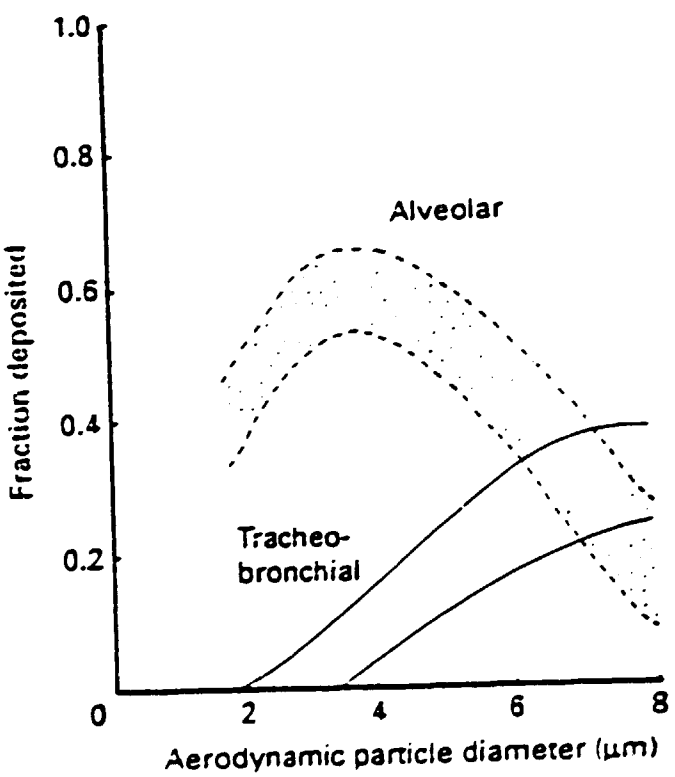
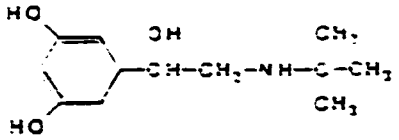


Figure 2 Particle diameter dependence of alveolar and tracheobronchial deposition for mouth breathing. Tidal volume 1 l, breathing frequency 7.5/mi mean flow rate 250 cm^3/s, inspiration/expiration times 4 s each. (Adapted fro

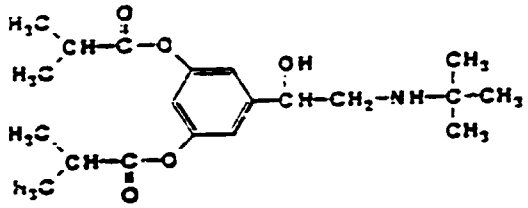
Fig 3.

PULMONARY PRO-DRUG EXAMPLES

TERBUTALINE PRO-DRUGS

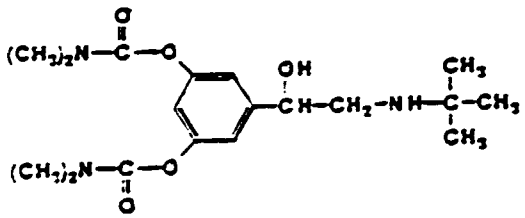


TERBUTALINE



IBUTEROL (DI-ISOBUTYRYL ESTER)

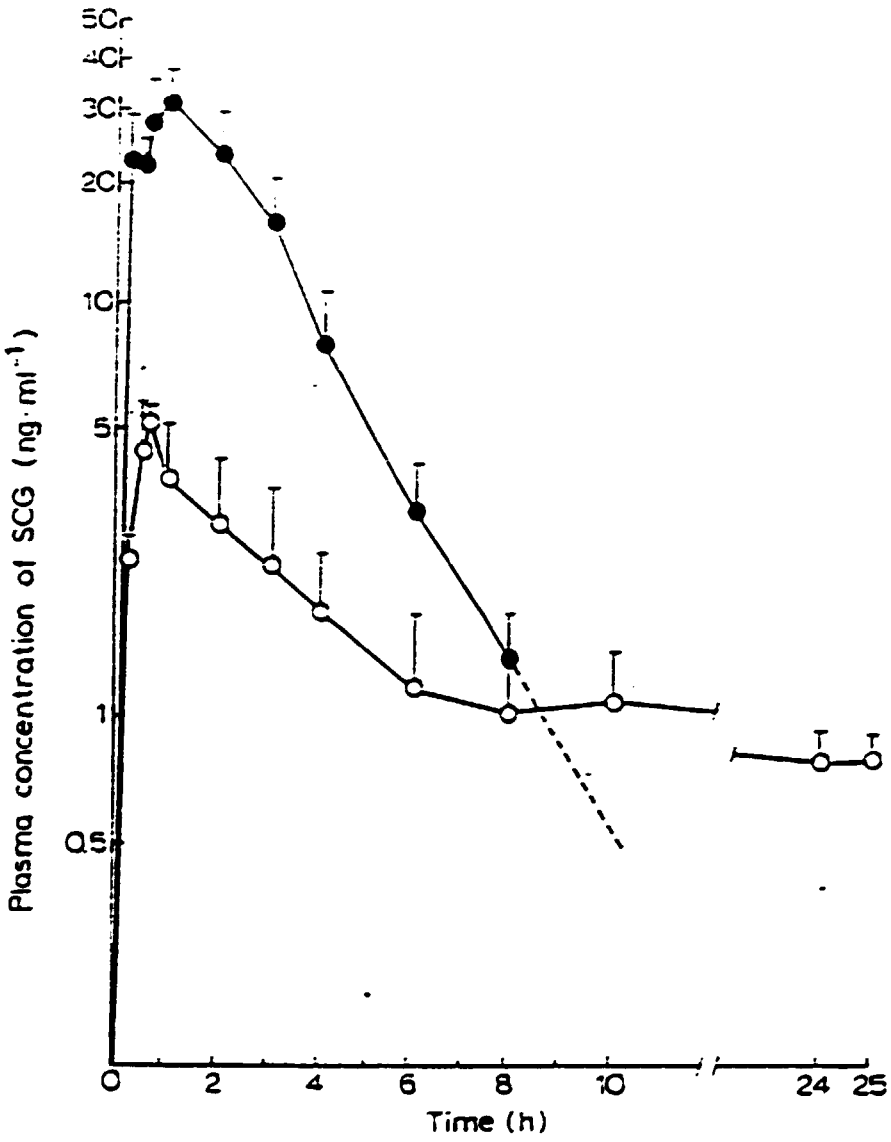
3 times as effective in inhibiting bronchospasm 5 min post inhalation due to better tissue penetration



BAMBUTEROL (BIS-N,N-DIMETHYLCARBAMATE)

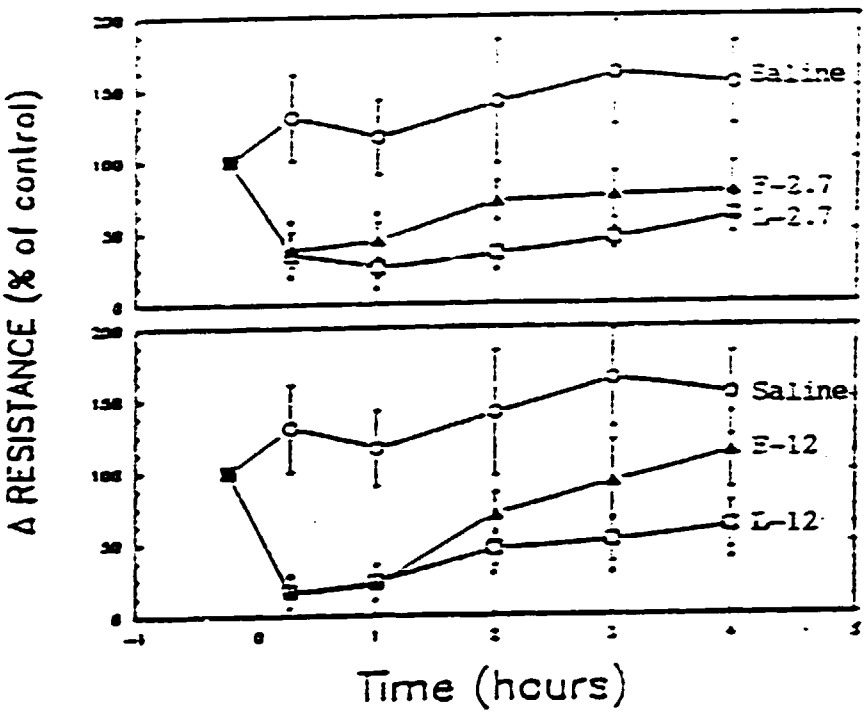
Not metabolised in the lung therefore ineffective by inhalation

Fig 4.



Plasma levels following nebulization of 20 mg sodium cromoglycate (SCG) to volunteers. point is a mean±S.E. (●). Free SCG (N=5); (○) liposomal SCG (N=4) (Ref 8)

Fig 5



Figure—Comparison of the effect of free and liposome albuterol on the airways resistance response to histamine.

The mean percentage change of R from baseline ± SEM in response to histamine after intratracheal instillation of free (n = 13) or liposome (n = 9) encapsulated albuterol at 2.7 or 12.0 μg/100 grams body weight. Responses after saline (50 μl/100 g) are included for comparison. The asterisk (*) denotes a significantly smaller response to histamine than in the baseline control or saline experiments.

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Professor Jonathan Hadgraft

TRANSDERMAL DRUG DELIVERY: PROBLEMS AND POSSIBILITIES

Authors: **Victoria M. Knepp**
Department of Pharmaceutical Chemistry
University of California at San Francisco
San Francisco, California

Jonathan Hadgraft
The Welsh School of Pharmacy
University of Wales Institute of Science
and Technology
Cardiff, Wales

Richard H. Guy
School of Pharmacy
University of California at San Francisco
San Francisco, California; and
Department of Dermatology
School of Medicine
University of California at San Francisco
San Francisco, California

Referee: Gary W. Cleary
Cygnus Research
Redwood City, California

I. INTRODUCTION

A primary function of human skin is to provide a barrier to the ingress of foreign compounds into the body.[1] It must be stated that, on the whole, given the enormous range of chemicals with which man comes into contact, the skin performs this role with considerable success. Thus, an initial reaction of surprise to the concept of transdermal drug delivery for systemic effect is not unreasonable. One might ask, "Why administer compounds across a membrane which has been designed rather specifically to inhibit such transport?" Some answers to this question are attempted in this review.

The concept of a small topically administered bandage containing, and capable of delivering, sufficient medicine for a day or longer is elegant and attractive. An alternative to oral administration is, in many cases and for large numbers of individuals, an important option that is infrequently available. The control of drug input, which is potentially available with transdermal delivery (Figure 1), is also alluring. The saw-tooth profile of drug concentration in the biophase vs. time, characteristic of conventional dosing regimens, can be damped by administration via the skin. A clear advantage for drugs of narrow therapeutic index is thereby implicated.[2]

Enthusiasm for topical drug input to elicit systemic effect must be tempered, however, by recognition of the fact that skin represents one of the most formidable barriers of biology. It is also a tissue which registers insult in a manner designed to discourage repeat events. Hence, transdermal delivery is presently limited to potent drugs which elicit no, or minimal, local irritating effects.[3] A few simple calculations serve as an initial guide to the feasibility of transdermal delivery for some representative "candidate" compounds. Assume, for the purpose of illustration, that a transdermal device exists which is capable of providing zero-

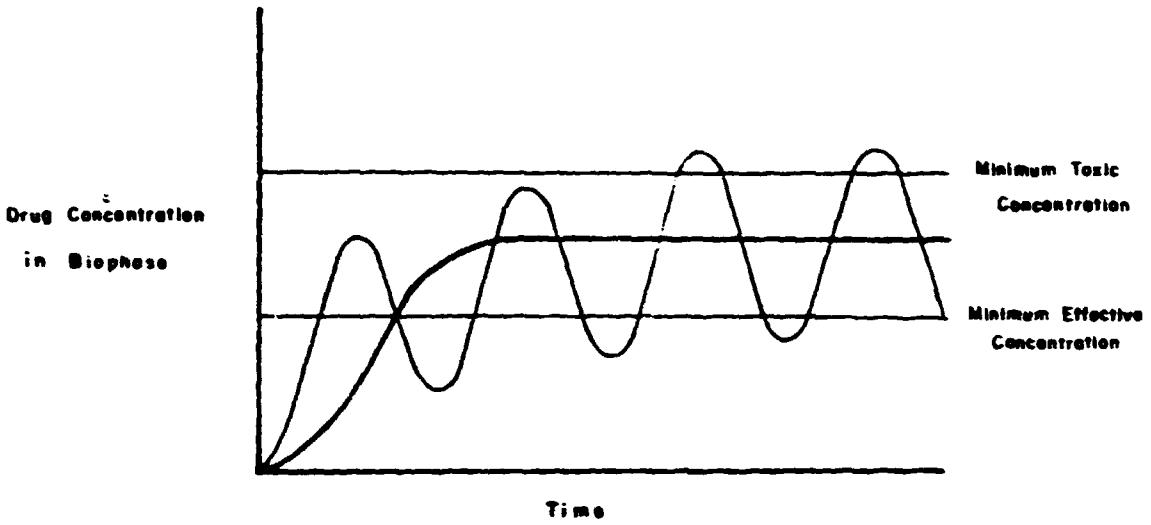

FIGURE 1. Schematic representations of drug levels in the biophase as a function of time following conventional (e.g., oral) multiple-dosing (oscillating line) and sustained (e.g., transdermal) drug delivery (horizontal line).

order delivery to the skin surface at a rate (k_o μg/cm²/hr) slightly less than the maximum flux (J_m μg/cm²/hr) of a model drug across the stratum corneum. Taking J_m = 35 μg/cm²/hr, then a value of k_o = 25 μg/cm²/hr is appropriate.[4] If if the target plasma concentration of the drug is C_T μg/mℓ, it follows that Equation 1 must hold at steady state:

$$A \cdot k_o = Cl \cdot C_T \quad (1)$$

where A cm² is the area of the patch and Cl cm³/hr is the drug clearance. Setting k_o less than J_M is desirable to retain drug input control within the delivery system and to avoid variability associated with differential skin permeabilities within a patient population.[4] Given this constraint, Equation 1 contains only A as a manipulative parameter. In other words, if inherent skin permeability cannot be increased in some way, then the input function can be maneuvered only within the confines of $k_o < J_m$ and that A be "reasonable".

The limitations can be emphasized with reference to Table 1 in which an initial pharmacokinetic feasibility assessment of transdermal delivery is performed for an arbitrary selection of compounds. Clearances and target therapeutic plasma levels were obtained from the literature;[5] k_o was fixed at 25 μg/cm²/hr; and the value of A required by solution of Equation 1 was calculated for each drug. The results clearly indicate the nonfeasible candidates (aspirin, acetominophen, cimetidine, indomethacin) for which A is unacceptably large. In the case of aspirin, for example, the calculated A is approximately nine times that of a normal adult's skin surface area! For economic and practical reasons, a delivery system area of 50 cm² is a reasonable upper limit. The remaining drugs pass the initial screen, although it should be emphasized that the theophylline calculation is for pediatric purposes only.[6] For clonidine, digoxin, estradiol, and scopolamine, A is very small and a reduction in k_o is indicated so that a patch of manageable dimensions can be fabricated. This is exactly the strategy that has been followed in the development of the marketed clonidine, estradiol, and scopolamine systems (see below).

However, this simplistic approach leaves a number of questions unanswered. Is a percutaneous flux of 25 μg/cm²/hr possible for all compounds? Probably not, and some degree of input control may therefore need to be sacrificed. How long will be required for the attainment of C_T following application of the patch? The half-life of the drug can be of some use here, but if absorption through the skin is slow (the usual case), an unacceptably long approach to the target level may be apparent. Which of the "feasible" candidates will

Table 1
FEASIBILITY SCREEN FOR REPRESENTATIVE TRANSDERMAL DELIVERY "CANDIDATES"

Drug	Cl (cm³/hr)[a]	C^{ss} (μg/cm³)	A^{ss} (cm²)[b]
Acetaminophen	23,076	15	13,846
Aspirin	29,085	150	174,510
Cimetidine	48,510	1	1,940
Clonazepam	4,032	0.025	4.0
Clonidine	12,054	0.001	0.48
Digoxin	6,800	0.002	0.54
Estradiol	66,859	0.0001	0.27
Indomethacin	9,049	0.5	181
Isosorbide dinitrate	174,636	0.001	7.0
Nitroglycerin	4,213,440	0.0001	17
Propranolol	48,594	0.02	39
Scopolamine	43,330	0.0002	0.35
Theophylline	138	5	28

[a] Calculated for a 70 kg adult *except* in the case of theophylline, the assessment of which is for a 2.5 kg preterm infant.
[b] The total body surface area of a 70 kg, 1.83-m-tall adult is approximately 19,000 cm². The values in this column are calculated using Equation 1 with k_p = 25 μg/cm²/hr.

elicit a local irritating effect on the skin? There are no simple nor reliable methods to predict skin irritation from a compound's structure and properties unless information pertinent to a closely related homolog or analog is known.[7]

It should be clear, therefore, that transdermal drug delivery presents nontrivial challenges (independent of formulation itself) while offering certain unique opportunities. The goal of this review is to place these difficulties and attributes in perspective and to indicate strategies which can evaluate the likelihood of successful transdermal delivery for different drug moieties. The organization of the paper is as follows: (1) the advantages and disadvantages of transdermal drug delivery are enumerated; (2) the delivery systems developed for the transdermal route are described and compared; (3) pharmacokinetic and pharmacodynamic observations following transdermal delivery are reviewed for several drugs and the efficiency of the administration route is evaluated; (4) approaches to the selection of transdermal drugs are considered and a kinetic model for delivery and percutaneous absorption is reviewed; (5) the potential application of penetration enhancers to expand the range of possible transdermal drug candidates is discussed; and (6) conclusions and prognoses for the future are offered.

II. ADVANTAGES AND DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY

Drug delivery via the skin to elicit systemic effect offers several advantages over more conventional methods of administration including the following:[3]

1. Steady-state drug concentrations within the therapeutic window can be maintained. The "peaks and valleys" associated with conventional multiple-dosing regimens are avoided (Figure 1). This precise control over plasma drug concentration enables the selectivity of drug action to be enhanced and decreases unwanted side effects.
2. Gastrointestinal tract variables such as erratic or incomplete absorption are circum-

vented. Hepatic first-pass metabolism, which can severely limit the systemic availability of a drug, is elimated.

3. An alternative route to oral administration is provided for those situations in which patient variables (e.g., geriatric or pediatric cases; nausea and vomiting symptoms) preclude conventional dosing.
4. A substitute parenteral form of therapy is possible without the inconvenience and anxiety associated with IV infusions, boluses, or IM injections.
5. Transdermal therapeutic systems are able to extend significantly the duration of action of many drugs, thereby reducing the frequency of drug dosing necessary with conventional dosage forms. This reduction may lead to enhanced patient compliance and, consequently, more effective therapy.
6. When medical needs demand, therapy can be terminated quickly and simply by removing the system.

These important attributes of transdermal drug delivery are counterbalanced by a number of major drawbacks, any one (or more) of which may be sufficient to preclude its use:

1. The skin is an excellent barrier to chemical penetration into the body.[1] The stratum corneum is a tough, resilient, hydrophobic membrane through which drug diffusion is slow. In order to gain systemic access, a transporting molecule must breach this layer and then partition into the much more aqueous in nature viable epidermis and dermis. Balanced physicochemical properties (i.e., reasonable solubility in oil and in water; moderate or low molecular weight; conservative lipid-water partitioning characteristics) are prerequisite for a successful penetrant, therefore.
2. As percutaneous absorption is slow, the drug must be pharmacologically potent because the concentration of active species in the biophase will be low. Currently, very few drugs whose effective plasma concentrations exceed 1 to 10 ng/mℓ are seriously considered for delivery transdermally.
3. In addition to the above pharmacokinetic limitation, there may exist a (potentially) more restrictive pharmacodynamic disadvantage. The excellent barrier nature of the skin means that continuous transdermal delivery will produce rather steady drug concentrations in the biophase. Such a situation is not necessarily optimal from a pharmacological point of view and may exacerbate the potential for tolerance development (see below).
4. Local, unwanted biological effects may also occur. The drug and/or contact system of the transdermal device must not elicit irritant or allergic reactions within the skin at the site of application. Cutaneous binding and metabolism remain, at this time, unknowns, the significance of which await clearer demarcation and quantitation.
5. Transdermal delivery systems are relatively expensive compared to conventional dosage forms. They may contain large amounts of drug, of which only a small percentage may be used during the application period.

III. TRANSDERMAL THERAPEUTIC SYSTEMS

The objective of a transdermal therapeutic system is to deliver drug into the body at a controlled, efficacious rate such that inter- and intrapatient variations in skin permeability are overcome. Thus, the rate-limiting step in transdermal drug absorption is ideally provided by the delivery system and not the skin. At this time, a number of transdermal delivery systems have been described. They may be classified broadly into three general categories:

A. Membrane Moderated

A reservoir containing the drug is enclosed on all sides, bar that through which drug i

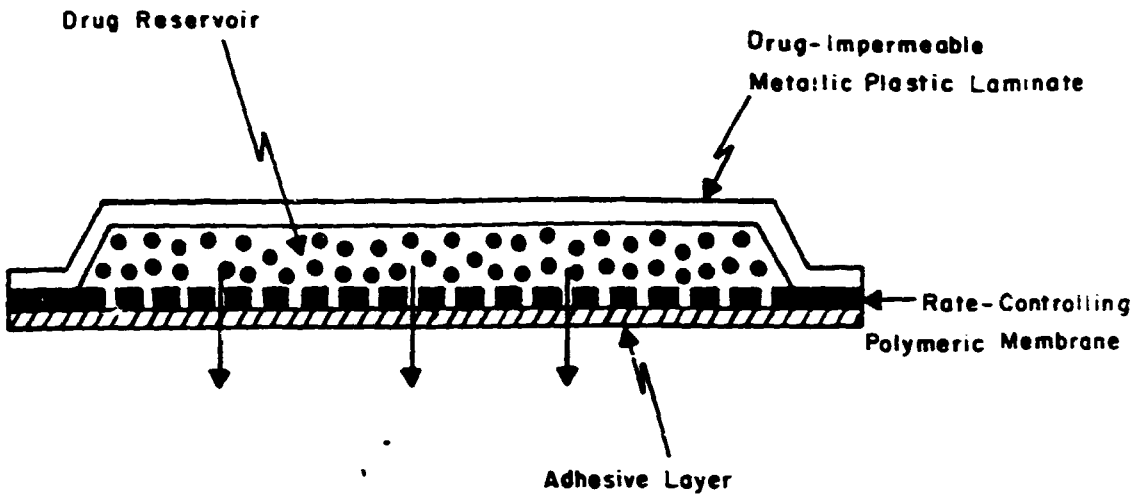

FIGURE 2. Diagram of a membrane-moderated transdermal drug delivery system.

released, by an impermeable laminate (Figure 2). The releasing face of the reservoir is covered by a rate-controlling polymeric membrane. Different release rates are achieved by variation of the polymer composition and the thickness of the membrane. The devices of this type, which have been described, include the following:

1. Transderm Scop (CIBA-GEIGY). This system consists of a backing of aluminized polyester film; a reservoir of mineral oil and polyisobutylene containing 1.5 mg of scopolamine; a rate-controlling membrane of microporous polypropylene; and an adhesive layer of mineral oil, polyisobutylene, and scopolamine. The system is programed to deliver 0.5 mg of scopolamine at a constant rate to the systemic circulation for approximately 3 days. In vitro, there is an initial burst of drug which has been liberated from the adhesive, followed by zero-order release from the reservoir into an aqueous sink of approximately 3.8 $\mu g/cm^2 \cdot hr^{\frac{1}{2}}$.
2. Transderm Nitro (CIBA-GEIGY). The components of this system are an impermeable backing of aluminized plastic; a reservoir of nitroglycerin adsorbed to lactose and dispersed in a colloidal suspension of silicone dioxide and silicone medical fluid; and a rate-controlling membrane of ethylene/vinyl acetate copolymer. The system adheres to the skin by a hypoallergenic silicone adhesive. It is available in 5, 10, 20, and 30 cm^2 areas delivering 2.5, 5.0, 10.0, and 15.0 mg of nitroglycerin into an aqueous receptor phase at around 40 $\mu g/cm^2/hr$ between 2 and 24 hr following an initial rapid burst effect.[9]
3. Catapres TTS (BOEHRINGER-INGELHEIM). In this system, the components are a backing material of pigmented polyester; a reservoir of clonidine, mineral oil, polyisobutylene, and colloidal silicone dioxide; and a rate-controlling membrane of microporous polypropylene. An adhesive formula of clonidine, mineral oil, polyisobutylene, and colloidal silicone dioxide affixes the system to the skin. It is available in sizes of 3.5, 7.0, and 10.5 cm^2 with delivery rates of 100, 200, and 300 μg of clonidine per day. The in vitro release rates into an aqueous solution from these devices are between 1.5 and 2.0 $\mu g/cm^2/hr$.
4. Estraderm (CIBA-GEIGY). This system is similar to that of the Transderm Nitro and Catapres TTS systems described above. The reservoir in this case consists of estradiol solubilized in ethanol. Because this system is currently awaiting FDA approval,* little information as to its construction has been published.
5. The Hercon company has developed a nitroglycerin transdermal patch which recently

*Now approved.

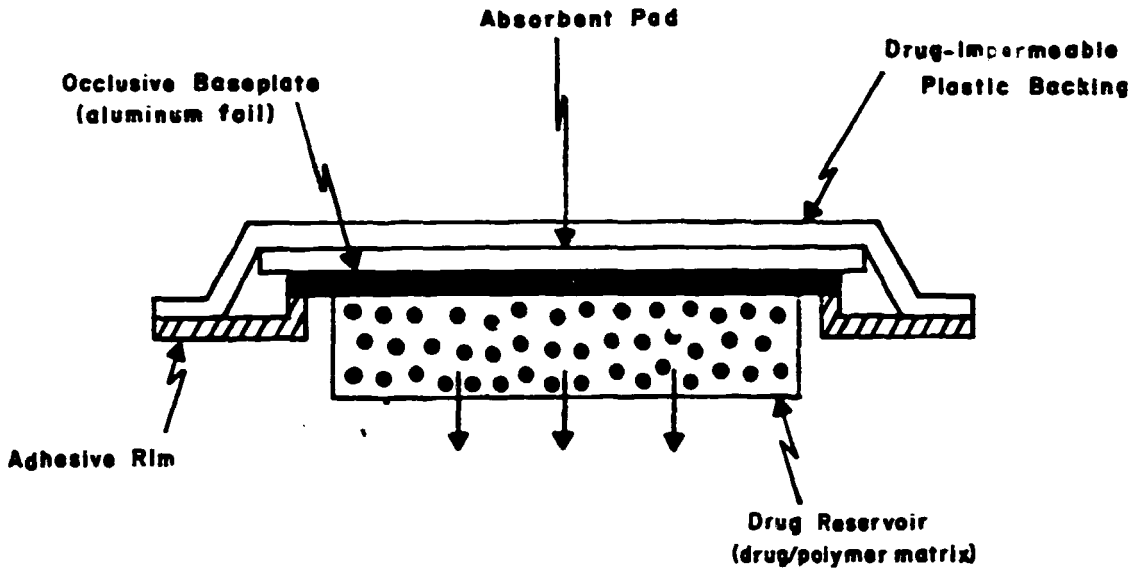

FIGURE 3. Diagram of a matrix dispersion-type transdermal drug delivery system.

has been granted FDA approval. This system consists of an outer layer impervious to nitroglycerin; a reservoir containing the drug; and a rate-controlling membrane in contact with the skin. In vitro, a representative 1 in.^{2} system released approximately 18 mg of nitroglycerin in 8 hr.[10]

B. Matrix Diffusion Controlled

The reservoir is manufactured by homogeneously dispersing the drug in a polymer matrix which is then molded into a disc with a defined surface area and thickness (Figure 3). Drug release from the device into the body is controlled by diffusion through the matrix reservoir material. Devices of this type include the following:

1. The Nitrodur (KEY/SCHERING-PLOUGH) system, which consists of a nonpermeable aluminum foil backing; a gel-like matrix of glycerin, water, lactose, polyvinyl alcohol, povidone, sodium citrate, and nitroglycerin; and a medical-grade microporous tape to adhere the system to the skin. It is available in dosage strengths which deliver 2.5 mg (5 cm^2), 5 mg (10 cm^2), 7.5 mg (15 cm^2), 10 mg (20 cm^2), and 15 mg (30 cm^2) in 24 hr.
2. The Nitrodur II (KEY/SCHERING-PLOUGH) system, a more elegant formulation of the Nitrodur system, contains nitroglycerin in an acrylic-based polymer adhesive with a resinous cross-linking agent. The system is available in 5, 10, 15, 20, and 30 cm^2 sizes, delivering 2.5, 5.0, 7.5, 10.0, and 15.0 mg in 24 hr, respectively.
3. The Deponit TTS (PHARMA-SCHWARZ), a device currently available only in Europe. It consists of a flexible carrier foil about 20 μm thick which is impermeable to nitroglycerin; an adhesive film about 300 μm thick of polyisobutylene resin which is charged with nitroglycerin; and a protective foil approximately 100 μm thick which is impermeable to nitroglycerin and is peeled off before use. A 16 cm^2 system delivers 5 mg in 24 hr in vivo. In vitro, the system releases 7.1 mg in 24 hr.[11]

C. Microsealed

The microsealed category is represented by the Nitro-Disc (SEARLE) device (Figure 4). In this system, the reservoir is formed by dispersing nitroglycerin adsorbed to lactose in a hydrophilic solvent system of 10 to 30% (v/v) polyethylene glycol in distilled water, which is subsequently distributed in a silicone elastomer by mechanical force to form thousands

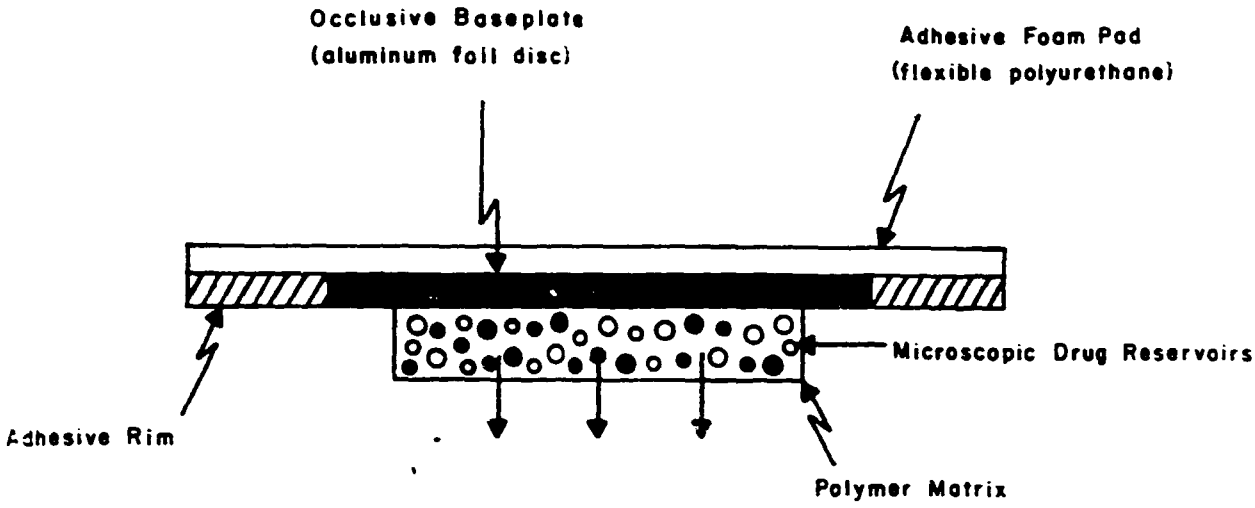

FIGURE 4. Diagram of the microsealed transdermal drug delivery system.

of microscopic drug compartments. Drug release is controlled by diffusion through the polymeric matrix. It is available in 8 cm^2 (Nitrodisc 5) and 16 cm^2 (Nitrodisc 10) sizes delivering 5 and 10 mg in 24 hr, respectively.

IV. PHARMACOKINETICS AND PHARMACODYNAMICS OF TRANSDERMALLY DELIVERED DRUGS

A. Estradiol

in preventing or reversing these symptoms.[15] However, orally administered estradiol undergoes massive first-pass liver and gut metabolism to estrone,[16,17] and leads to the induction of several liver proteins.[18,19] Delivery of estrogen by this route also maintains the plasma concentration ratio of estradiol (E2) to estrone (E1) at the postmenopausal level of 0.2 to 0.3, rather than achieving the ideal premenopausal level of 1 or more.[20] Estrogen replacement therapy via transdermal delivery has been proposed, therefore, as a way in which (1) the total daily dose of estrogen, which is required to achieve plasma levels comparable to those of a premenopausal woman, can be reduced; (2) the extensive liver metabolism experienced by oral forms of the drug can be avoided, and the E2/E1 ratio thereby returned to the premenopausal level; and (3) the induction of liver proteins can be reduced or eliminated.

To determine whether nonorally administered estradiol would provide effective physiologic replacement without altering hepatic function, Laufer et al.[21] studied 20 postmenopausal women before and after 3 weeks of treatment with either prototypical estrogen transdermal systems or placebo. In the treatment group, the subjects of which replaced their systems every 3 days for 21 days, the mean values of estradiol and estrone rose significantly from baselines of 7 ± 1 and 16 ± 1 pg/mℓ, respectively, to 72 ± 6 and 37 ± 3 pg/mℓ. When these end-of-treatment values were compared to premenopausal control subjects, it was found that the mean estradiol values were not significantly different, whereas mean estrone levels were significantly lowered. The corresponding values in the placebo group did not change from baseline (Figure 5A). No significant changes were noted in the concentrations of the hepatic proteins renin substrate and thyroxine-binding globulin, nor were there any alterations in the binding capacities of cortisol-binding globulin and sex hormone-binding globulin in either population, indicating that when delivered transdermally, estradiol has limited effect on hepatic function.

The decline in ovarian function and subsequent loss of endogenous estrogen at the menopause are associated with many symptoms including hot flashes, atrophic vaginitis, and osteoporosis.[12-14] Estrogen replacement therapy has been shown to be at least partially successful

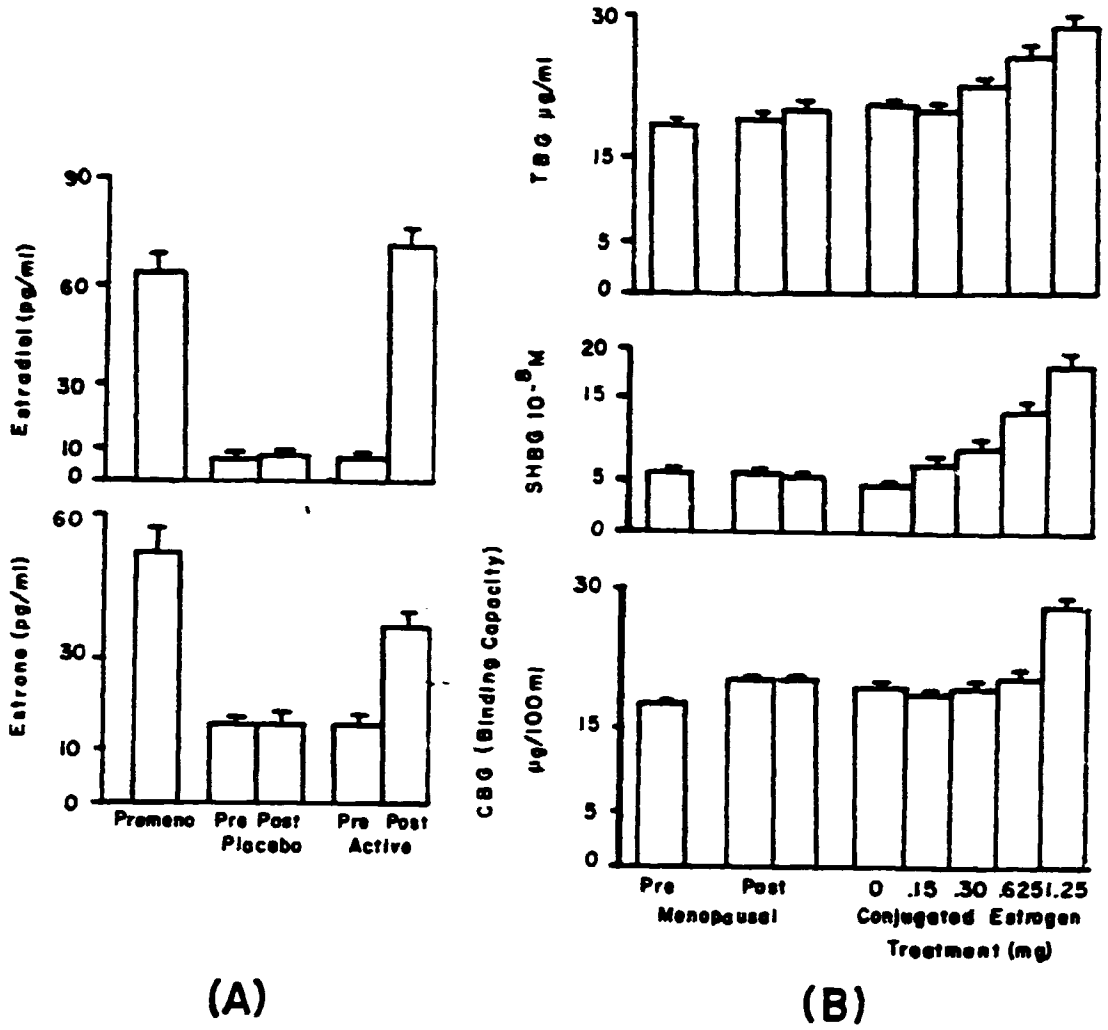

FIGURE 5. (A) Plasma concentrations of estradiol and estrone in premenopausal subjects, postmenopausal subjects both before and after 3 weeks of treatment with placebo patches, and postmenopausal subjects both before and after 3 weeks of treatment with active patches.[21] (B) Plasma concentrations of corticosteroid-binding globulin, sex hormone-binding globulin, and thyroxin-binding globulin in postmenopausal women both before and after 6 weeks of treatment with transdermal estradiol, and after 6 weeks of orally administered conjugated estrogens.[18]

In a more recent study, Powers et al.[22] compared the pharmacokinetics of transdermally delivered vs. orally administered forms of estradiol to 14 postmenopausal women. The mean baseline pretreatment levels of estradiol and estrone were 7.4 and 32.2 pg/mℓ, respectively. The average steady-state values during the application period of 3 different Estraderm systems (delivering 0.025, 0.05, and 0.1 mg/day) were 23, 39, and 74 pg/mℓ, respectively, for estradiol, and 33, 41, and 59 pg/mℓ for estrone. Oral administration of Estrace (micronized estrogens, 2 mg/day) and Premarin (conjugated estrogens, 1.25 mg/day) resulted in serum estradiol levels of 66 and 31 pg/mℓ, respectively, and estrone levels of 334 and 152 pg/mℓ (mean steady-state values, measured 24 hr after the third dose). Again, no significant elevation of hepatic proteins was found following transdermal administration of the drug (Figure 5B).

This system demonstrates quite elegantly the advantages that can be gained through rate-controlled transdermal drug delivery. In essence, this system allows for a more physiologically correct estrogen replacement pattern by:

1. Maintaining the correct estradiol to estrone ratio, thus avoiding excessive tissue accumulation of estrogens
2. Avoiding the induction of hepatic proteins

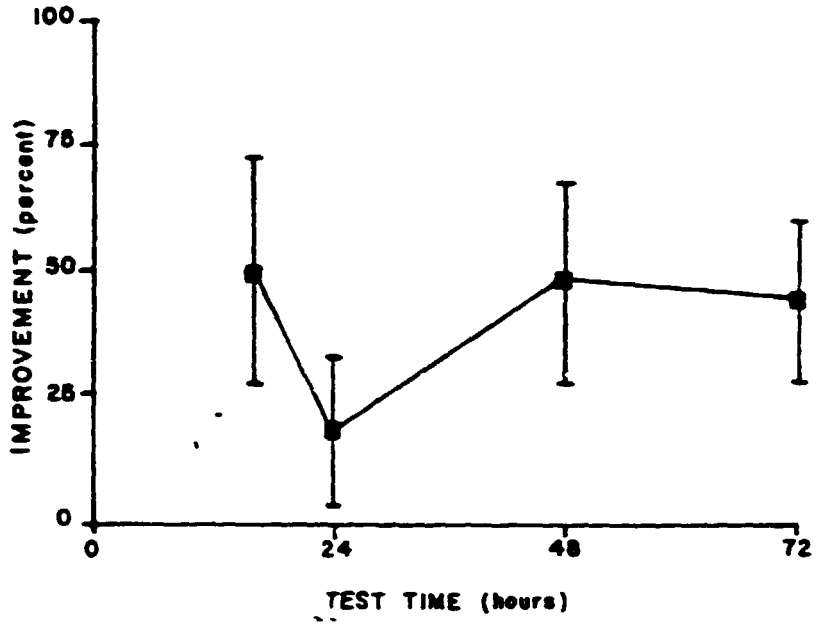

FIGURE 6. Percent improvement (± SEM; n = 9), as a function of time, in the prevention of motion sickness (as measured by the number of stressful head movements made in a rotating chair) following administration of transdermal scopolamine.[26]

3. Bypassing first-pass hepatic metabolism, thereby reducing the total daily dose of estradiol required

Studies have also shown that there is a quick return to baseline urinary excretion of endogenous estrogen compounds upon removal of the system.[20] This will allow the physician to provide cyclical therapy, further improving the ability of this system to mimic the state of the premenopausal woman.

B. Scopolamine

Of the wide range of antiemetic agents with which to treat motion sickness, scopolamine has been shown to be superior.[23,24] However, its use is limited due to the short half-life of the drug, and the appearance of dose-related side effects such as drowsiness, dry mouth, blurred vision, and, in cases of higher dosage, mental confusion and hallucinations. The aim of transdermally delivered scopolamine is to eliminate the relatively high plasma concentrations of drug which normally follow oral or intramuscular administration, and, hence, to minimize side effects and attain a superior pharmacokinetic profile. Schmitt et al.[25] determined that during the steady-state phase of scopolamine administration, the transdermal system was functionally equivalent to an intravenous infusion.

Homick et al.[26] evaluated the time course of effectiveness of transdermally administered scopolamine in the prevention of motion sickness induced by exposure to coriolis stimulation in a rotating chair. They observed a highly variable response, with an overall 40% improvement ($p < 0.05$) in test scores 16 to 72 hr after application of Transderm-Scop systems to 11 subjects (Figure 6). Such variability was also noted in a study performed by Graybiel et al.,[27] where the efficacy of transdermal scopolamine was compared at 12 and 72 hr postadministration. In 6 subjects, after 12 and 72 hr, the number of beneficial responses were 4 and 0, respectively. On repeating the test in the same subject population, the corresponding figures at the same time points were 4 and 3.

McCauley et al.[28] compared the efficacy of transdermally administered scopolamine to orally administered dimehydramine and either orally or transdermally administered placebo

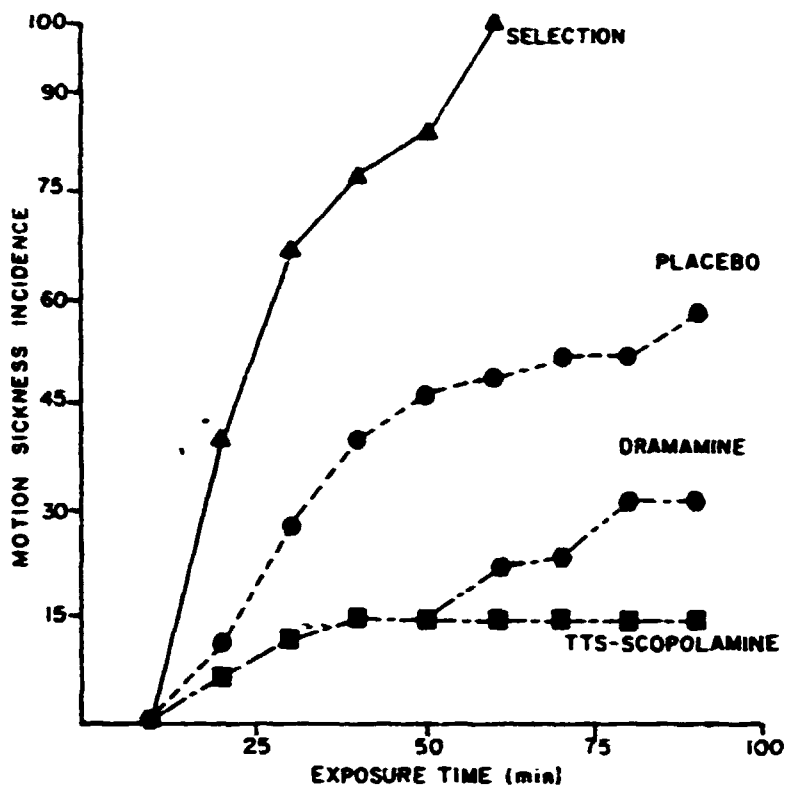

FIGURE 7. Reduction in motion sickness incidence as a function of exposure time to vertical oscillation and treatment modality (no treatment, placebo treatment, oral dramamine treatment, and transdermal scopolamine treatment).[28]

in the prevention of motion-induced nausea in a vertical oscillator. Thirty-five subjects were utilized in a double-blind crossover study. It was found that a placebo effect reduced the motion sickness incidence [(MSI); the percent of subjects vomiting within 90 min] from 100 to 59%, whereas dimenhydramine reduced the MSI to 32%. Scopolamine further reduced the MSI to 16% (Figure 7). Other investigators[29,30] reported similar results when comparing the same treatment modalities aboard vessels at sea.

The occurrence of side effects following transdermal scopolamine was minimal in all these studies. However, Homick et al.[26] noted that one or more side effects (including dry mouth, drowsiness, blurred vision, and irritation at the site of application) were reported during 60% of test trials when the topical system was used. It should be noted, however, that all of these symptoms except blurred vision were also reported with placebo treatment.

C. Clonidine

Hypertension is associated with an increased risk of premature cardiovascular complications. Antihypertensive therapy decreases the incidence of these events, but effective results hinge on patient compliance which is increased when side effects are few and administration is convenient. Thus, a transdermal therapeutic system, Catapres TTS, has been developed to provide rate-controlled, continuous release of the antihypertensive drug clonidine for a 7-day period. Such a lengthening of the dosage interval should increase patient compliance as well as minimize the dose-dependent side effects, such as dry mouth and sedation, which occur with oral dosage forms of the drug.

A crossover clinical study[9] compared Catapres TTS with oral Catapres. Seventeen subjects were randomly assigned to one of two regimens: either two Catapres TTS devices (5 cm^2 total area) for 7 days on the upper outer arm, or 0.1 mg of oral Catapres every 12 hr for 4 days. With the transdermal system, plasma concentrations of clonidine gradually increased.

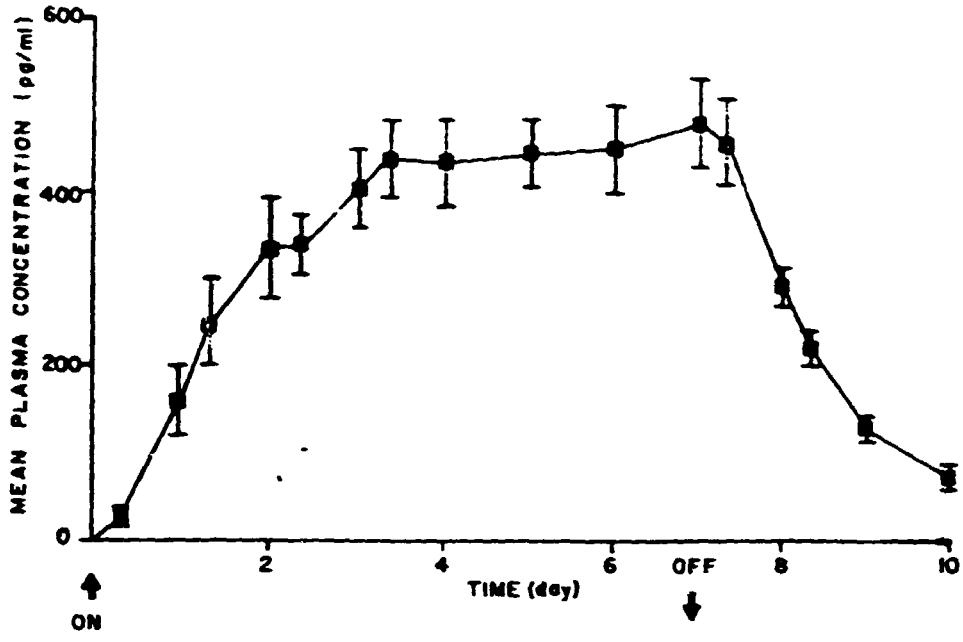

FIGURE 8. Plasma concentrations of transdermally administered clonidine (5 cm^2 system) as a function of time (± SEM; n = 17). Arrows indicate application and removal of the system.*

attaining an average steady-state value of 400 pg/mℓ on day 3 of the study (Figure 8). This value remained constant during the remainder of the application period. With oral administration, plasma levels of clonidine peaked at an average value of 800 pg/mℓ on day 4 of the study. Plasma "trough" concentrations averaged approximately 400 pg/mℓ by day 3 of the study.

MacGregor et al.[31] found mean steady-state plasma clonidine concentrations of 0.39, 0.84, and 1.12 ng/mℓ with 3.5, 7.0, and 10.5 cm^2 devices, respectively, with no significant differences when the site of application was rotated. Diastolic blood pressure fell by at least 10% in 37 patients, and was normalized (i.e., less than 90 mmHg) in 64% of the patients tested (total number of patients was 85).

Weber et al.[32] compared Catapres TTS (3.5 cm^2) patches to placebo patches in their ability to reduce diastolic blood pressure in 20 patients with essential hypertension. Blood pressure was reduced to less than 90 mmHg in 12 of 20 patients wearing the active patches. When these 12 responders were placed on placebo patches, blood pressure rose to its pretreatment value. Plasma concentrations were similar to those observed in other studies.

D. Nitroglycerin

Nitroglycerin (GTN) has been used in the treatment of angina pectoris for over 100 years. It is frequently prescribed in the sublingual form, a route which results in the immediate relief of anginal pain. Unfortunately, the duration of action of sublingual GTN is extremely short because of the drug's rapid elimination from the body; hence, it cannot be given via this route as prophylaxis against further angina attacks. Oral preparations, although longer acting, also provide relatively brief therapeutic effect due to extensive first-pass hepatic metabolism; hence, orally, GTN must be administered four to six times per day. This extreme sensitivity of GTN to metabolism, and its corresponding short biological half-life, suggest the drug as an excellent candidate for transdermal delivery.

Transdermal nitroglycerin in the form of an ointment has been available for over 30 years, and has been shown effective in the prophylaxis of angina attacks.[33] However, the use of the conventional topical dosage form is limited by:

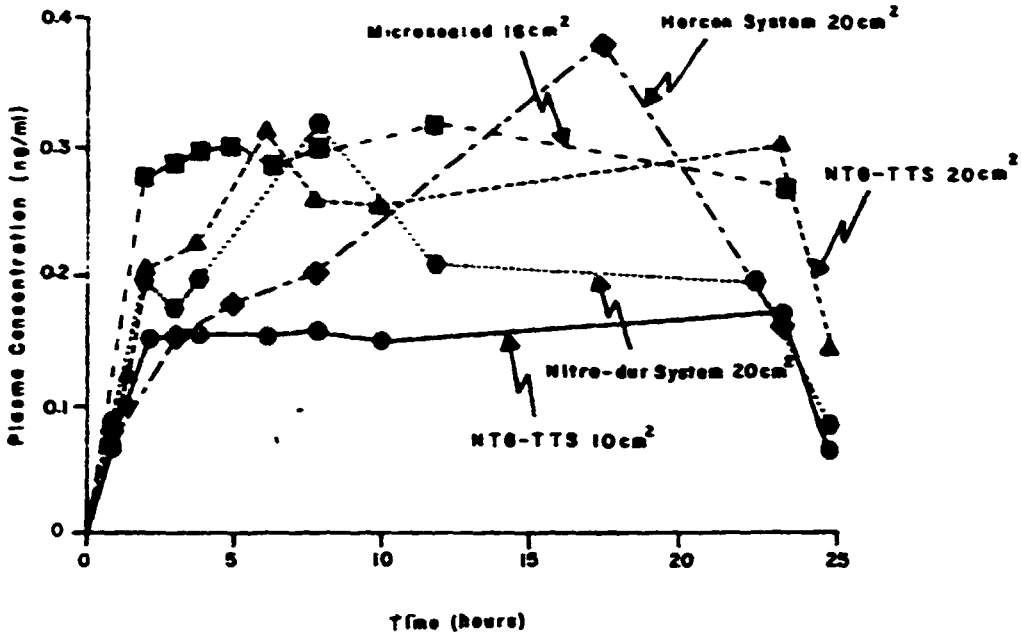

FIGURE 9. Plasma GTN concentrations as a function of time following administration of the various GTN transdermal systems.[10,35-38]

1. The difficulty in obtaining reproducible dosage, in terms of the amount of drug applie and the area of application.
2. The release of GTN from these ointment bases is rather rapid and, as a result, the ra of drug input into the systemic circulation is controlled by the skin. Therefore, GT plasma levels may vary considerably both within and between patients because inter- and intraindividual variations in skin permeability.
3. Metabolism of GTN by skin microflora[34] may be greater with this formulation tha with the newer transdermal devices in which most of the drug is physically protecte within the device.
4. Patient compliance: the ointment should be spread as evenly as possible over a rath large surface area, and then covered with an occlusive material (such as Saran® wra to minimize loss of drug to the patient's clothing,etc. The dosage interval of t ointment is every 8 hr.

The need to provide a dosage formulation of GTN which would overcome the abo problems and give prophylactic protection against angina pain led to the development transdermal delivery systems of GTN. To date, four systems — Nitrodisc, Nitrodur, Tra derm Nitro, and Hercon — have been conditionally approved by he FDA for once-da dosing of GTN.

Although the fabrication and the principles of release control of different nitroglyce transdermal systems differ, remarkably similar plasma levels are found in vivo follow their administration (Figure 9). For example, when 16 cm² Nitrodisc systems were appl to 12 healthy volunteers, plasma concentrations remained constant over the 32-hr study 280 pg/mℓ.[35] The mean plasma concentrations of 12 volunteers wearing the Transderm N system ranged from 175 to 300 pg/mℓ over 28 hr;[36] in another study, volunteers wearing 10 and 20 cm² systems achieved steady-state plasma concentrations of 160 and 250 pg/r respectively, between 2 and 24 hr.[37] The Hercon system resulted in mean steady-state plas concentrations of 176 ± 79 pg/mℓ over 72 hr when applied to 16 healthy male volunteer Finally, application of the Nitrodur system to 6 healthy human volunteers resulted in aver steady-state plasma concentrations of 201 pg/mℓ.[38] The obvious implication of these

is that GTN input to the systemic circulation is probably controlled in large part by the skin rather than by the devices themselves.

Although now used extensively on a daily-dosing basis, controversy exists as to the efficacy of the transdermal GTN devices. Several studies indicate that nitrate tolerance can occur as soon as 24 hr after onset of prolonged steady-state plasma levels of GTN.

Reichek et al.[39] studied the effect of high and low dose transdermal GTN compared to placebo on exercise tolerance (bicycle protocol, NIH). At 4 hr, the bicycle exercise time increased by 7% with low dose therapy (9.4 mg/day Nitrodisc); however, this was not significantly different than the response seen in placebo-treated subjects. On the other hand, improvements of 29 and 39% ($p < 0.01$) were achieved during high dose treatment with the 24 mg/day Nitrodisc and 22 mg/day Transderm Nitro systems, respectively. Increases in exercise time were indistinguishable from placebo at 24 hr for all forms of therapy, and even at high doses the peak effect on exercise tolerance was 50% of that obtained with sublingual GTN. Crean et al.[40] compared the 10 cm^2 Transderm Nitro system to placebo in 10 patients in a randomized, double-blind, double-crossover trial of 4 1-week periods. Efficacy was evaluated by exercise testing, ST segment recording, and the number of angina attacks experienced by each patient. The net result was that the number of anginal attacks was not decreased over placebo, nor was the time to angina different between therapies; there was no reduction in consumption of sublingual nitrates, and the time to 1 mm ST segment depression was the same as for placebo. A subsequent[41] study tested the Nitrodur 10, 20, and 30 cm^2 systems in 11 patients and found improved treadmill walking time at 2 and 4 hr postinitiation of the study ($p < 0.05$), but not at 24 hr. After sustained therapy with the 30 cm^2 system for 1 to 2 weeks, no difference in walking time was seen over placebo. Hollenberg and Go[42] studied the short- and long-term effects of Nitrodur on exercise tolerance using a computerized analysis of ST segment changes. Significant improvements were seen at 4 and 7 hr. As a group, the patients demonstrated an improvement of 31% ($p < 0.0001$) for all dose levels. Sublingual GTN, however, induced an even greater improvement than the highest dose of transdermal GTN ($p < 0.003$), and the effects of Nitrodur were attenuated after 2 and 4 weeks.

On the other hand, a study by Thompson[43] using the maximally tolerated dose of GTN in the Nitrodisc system found that, at 2 hr, the mean duration of exercise time increased from 11.3 to 14.4 min ($p < 0.05$), and that at 26 hr, the mean duration of exercise was still elevated to 14.1 min compared to the placebo-treated value of 11.8 min ($p < 0.05$). This represents a 30% increase at 2 hr, and a 25% increase at 26 hr. The consumption of nitrates also decreased by 63% over the time course of the study. Georgopoulos et al.[44] administered Transderm Nitro (5 mg) for 1 to 2 weeks in a placebo-controlled, double-blind crossover study of 13 patients. Although exercise duration was not measured, the exercise-induced depression of ST segment at matched treadmill times was decreased by 50%. The daily frequency of anginal attacks decreased by 67%, and the daily consumption of nitrates decreased by 63%. No tolerance was observed over the 14 days of the study. Finally, Scardi et al.,[45] in a double-blind, randomized, placebo-controlled study, found a statistically significant increase ($p < 0.01$) in total duration of exercise, exercise duration to 1 mm ST segment depression, maximal workload, and total work performed at both 4 and 24 hr after dosing with both the 20 and 40 cm^2 Transderm Nitro systems.

Clearly, the results of these trials are mixed, with several studies showing statistically significant increases in exercise time at 2 and 4 hr after application of the last patch, whereas only two studies demonstrated a significant increase in exercise time after 24 hr. These investigations differ significantly in their criteria for entry and efficacy, as well as in the use of concomitant medications. Study designs vary also: some are crossover, some placebo controlled, some randomized, and some double blind. The patient populations in these studies are also very small, making the statistical interpretations difficult. Finally, there is a question

of tolerance of the exercise protocol in these studies, i.e., there is a "training effect" with repeated exercise testing, especially with those patients who have participated in previous studies. Until more standardized protocols and larger patient populations are used, interpretation of these studies will remain difficult. Currently, a major multicenter clinical trial involving the Transderm Nitro, Nitrodur, and Nitrodisc GTN systems is underway, with particular emphasis on the pharmacological behavior of GTN.

V. DRUG SELECTION

The choice of a compound for transdermal delivery depends upon a number of factors which may be grouped conveniently into three categories: biological, physicochemical, and pharmocokinetic.[46]

A. Biological Criteria

1. The drug must be potent, requiring a parenteral daily dose of milligrams or less. In most cases, this limitation translates into an effective plasma concentration in the nanogram per milliliter range.
2. Drugs subject to an extensive hepatic first-pass effect on oral dosing may benefit by transdermal administration. Dose amount and dosing frequency may be significantly reduced in this way.
3. As for all forms of sustained or prolonged delivery, drugs with short (rather than long) biological half-lives are most appropriate.
4. The drug should not elicit a major cutaneous irritant or allergic response. The definition of "major" in this context is difficult to specify. The clonidine system, for example, has been launched successfully despite a relatively high rate of irritancy provocation.[47]
5. Because transdermal delivery typically provides constant drug input, it is important that the pharmacological effect of the agent be suited to this absorption pattern. The possible induction of tolerance must be carefully monitored, therefore (see above discussion on nitroglycerin).
6. Sensitivity of the drug to cutaneous metabolism[48] within the viable epidermis or to degradation by surface microflora[34] is clearly undesirable. Current understanding of these areas is sketchy, and methods for their evaluation are poorly developed.

B. Physicochemical Criteria

The sequential events that a drug must undergo in order to become systemically available following application in a transdermal device are[3]

1. Transport within the delivery system to the device-skin surface interface
2. Partitioning from the delivery system into the stratum corneum
3. Diffusion through the stratum corneum
4. Partitioning from the stratum corneum into the viable epidermis
5. Diffusion through the viable tissue
6. Uptake by the cutaneous microcirculation and subsequent systemic distribution

It follows that diffusion and partitioning are the key physical processes pertinent to transdermal delivery.

Diffusion—Drug transport is determined primarily by the molecular size and the level of interaction with the medium through which diffusion is taking place (viz. delivery system, stratum corneum, viable epidermis). Most currently used drugs have molecular weights (M) less than 1000 g/mol and the effect of size on diffusion coefficient may be adequately described by a power dependency (e.g., the Stokes-Einstein equation: $D \alpha M^{-1/3}$) or,

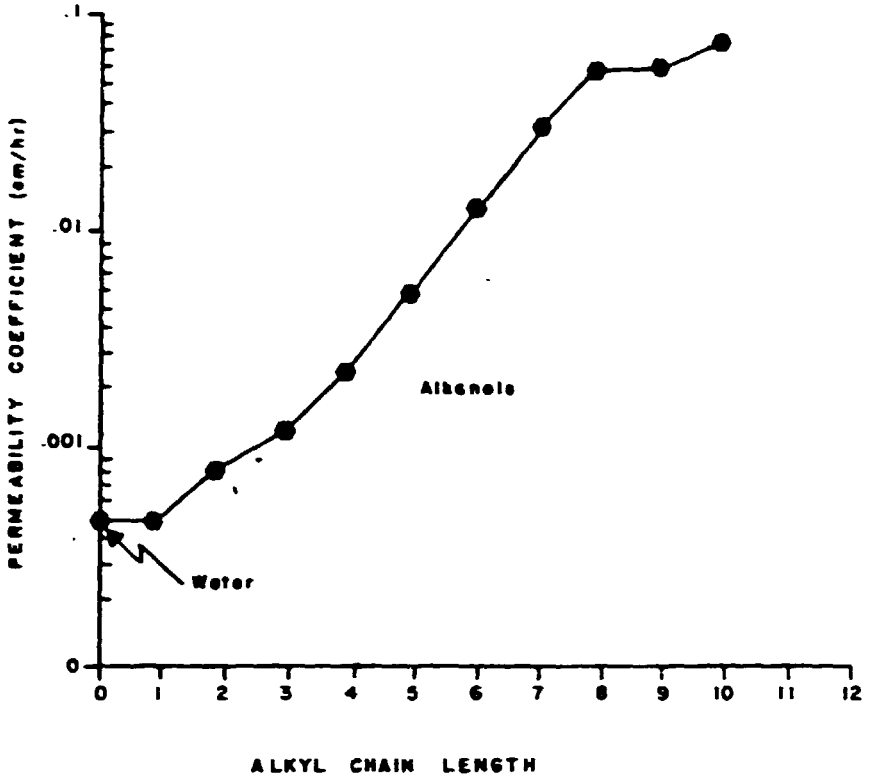

FIGURE 10. Permeability coefficients plotted vs. alkyl chain length for a series of n-alkanols.[54,55]

sometimes, by an exponential function.[49] Generally, these relationships are not particularly powerful and predict that D is much less sensitive to M than, for example, the viscosity of the medium through which the drug is diffusing.

Partitioning—The partitioning criteria for a transdermal candidate are demanding. The molecule must favor the stratum corneum over the device, and the relative affinity of the drug for stratum corneum and viable tissue must be reasonably balanced. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin. Correlations between skin absorption and various oil-water partition coefficients have been reported. Percutaneous penetration through human skin has been related to both heptane-aqueous buffer[50] and octanol-water partition coefficients.[51] Linear free energy relationships have been established between steroid absorption across human skin and (1) benzene solubility[52] and (2) log K (octanol/H_2O).[53] The in vitro penetration of the series of n-alkanols has been compared to the corresponding values of K (ether/H_2O).[54,55] A linear correlation was found up to octanol, but the behavior of subsequent homologs indicated that a change of rate-limiting step was occurring when the penetrant hydrophobicity reached a certain level (see Figure 10). Mechanistically, a plausible explanation for this observation is that stratum corneum to viable epidermis transfer becomes a slower process than stratum corneum permeation for very lipid-soluble drugs. Therefore, an oil-water partition coefficient is a useful qualitative indicator of penetration, the reliability of which is least at the extremes of solute partitioning behavior.

C. Pharmacokinetic Criteria

The dependence of transdermal drug delivery on diffusion and partitioning across stratum corneum and viable tissue implies that the feasibility of the process may be predictable from the physicochemical properties of the drug. Recently, a linear kinetic model has been developed for this purpose and has been validated successfully using in vivo data for nitroglycerin, clonidine, estradiol, scopolamine, and timolol.[56-59]

packing structure of the ordered lipids that Elias[62] has observed in the intercellular channels.* Until a systematic study is conducted on a range of these materials, the exact manner in which they operate is open to conjecture. Hydration has been suggested as the way in which urea elicits its action, and perhaps the most ubiquitous, but infrequently recognized, penetration enhancer is water. In nearly all instances, hydrated skin is more permeable than dry skin. The examples most usually quoted are the corticosteroids which penetrate through occluded skin more extensively than they cross nonoccluded tissue.[1] Perhaps water as a penetration enhancer is one of very few substances which satisfies the six stringent requirements enumerated above.

Thus, it would, in general, be desirable to find an agent whose properties are similar to water, but which demonstrates a more powerful enhancement effect. A commonly cited accelerant is dimethylsulfoxide (DMSO), a colorless liquid with excellent solvent properties. It is miscible with water and many organic liquids, and is reasonably easily incorporated into formulations. The versatility of DMSO is exemplified by its ability to accelerate the penetration of a wide range of compounds including steroids, organic dyes, barbiturates, griseofulvin, phenylbutazone, antibiotics, and quaternary ammonium compounds. Despite considerable investigation, the mode of action of DMSO is not completely understood. It has been suggested that the enhancer replaces integral water within the stratum corneum to form a continuous network through the skin. A recent systematic study, performed in vitro using hairless mouse skin,[63] however, implies that DMSO impairs barrier function by eluting solvent-soluble components from the stratum corneum; in addition, delamination of the horny layer and denaturation of its proteins also seem to contribute in diffusion enhancement.

While the properties of DMSO indicate that it does act as an excellent penetration enhancer, there are problems associated with its use. Concentrations above 60% are required to significantly increase the percutaneous absorption of solutes and, at these high concentrations, DMSO can produce erythema and wheals. Another side effect of DMSO is caused by the metabolite dimethyl sulfide which causes a characteristic foul taste and bad breath. Widespread use of DMSO, therefore, is not common, although it has been used as a solvent for idoxuridine in the treatment of herpes zoster and herpes simplex skin infections.

Other sulfoxides have been examined as penetration enhancers, particularly the alkylmethyl derivatives having the general structure $RSOCH_3$.[64] The optimum chain length appears to be C_{10} to C_{12}, and these compounds have the advantage that their degradation products are less odorous than dimethyl sulfide.[65] They are also active at low concentrations (Figure 12), but the effect appears limited to the enhancement of polar or ionic molecules. It is possible that the activity of these substituted sulfoxides is due to their nonionic surfactant character and that they interact with and alter the structure or conformation of the skin proteins. From a consideration of their molecular structure, they may also be expected to disrupt the structured lipids in the intercellular channels. Phosphine oxides such as the dodecyldimethyl derivative have also been shown to enhance skin penetration.[65]

Chemically related to dimethylsulfoxide are dimethylacetamide (DMAC) and dimethylformamide (DMF). These have been used as penetration enhancers and have been shown to be effective for both griseofulvin and hydrocortisone.[1] It is clear that the dipolar aprotic nature of these solvents is of importance in their mode of action. Although they are not quite as effective as DMSO, they are better tolerated by the skin. However, they have not been subject to widespread evaluation. Other simple solvents, for example, ethanol, have been considered as enhancers. The estradiol delivery system [20] contains a significant amount of ethanol which almost certainly assists the percutaneous absorption of the drug.

Urea is used clinically to enhance skin penetration. Two hydrocortisone preparations

* The latter mechanism has been strongly implicated by recent work from Potts et al. (*J. Invest. Dermatol.*, 86, 478, 1986). It was shown that *cis*-vaccenic acid enhanced percutaneous absorption and caused a concomitant increase in the fluidity of stratum corneum lipids

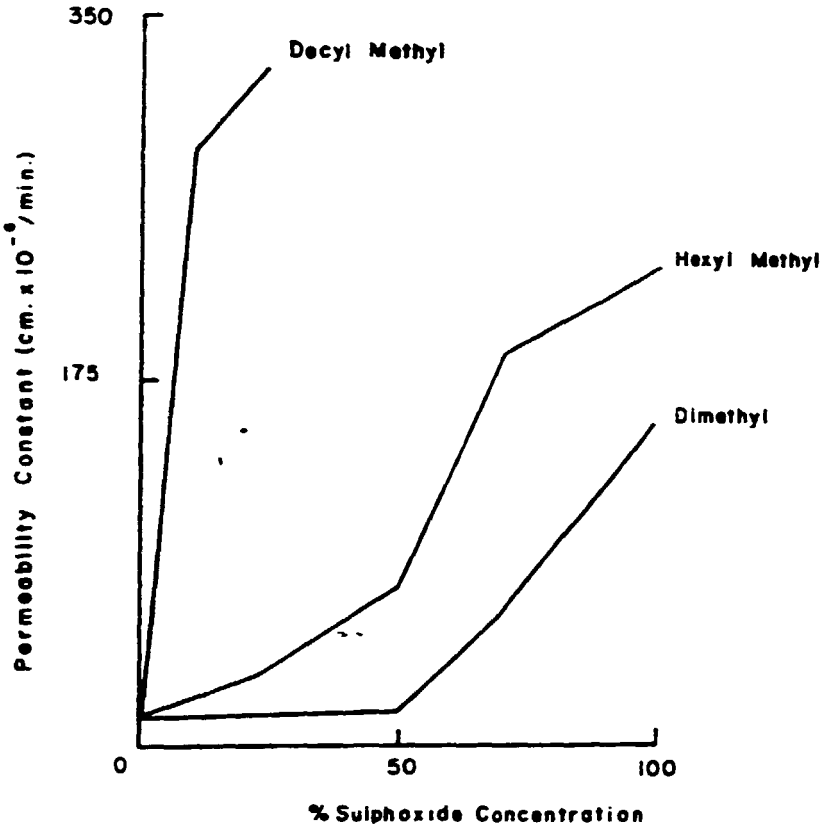

FIGURE 12. Effect of three alkyl sulfoxides as a function of concentration on the in vitro steady-state permeation of salicylic acid across excised human skin.

contain urea to optimize the delivery of drug to the lower regions of the skin. Urea may induce two changes to the barrier function of the skin: (1) it increases the hydration of the stratum corneum, and (2) after prolonged contact, it acts as a keratolytic agent. At low concentrations, the mechanism of action is probably related to the hydration effect. It appears that urea acts rapidly as an accelerant.[66] Using hexyl nicotinate as a model penetrant, the time of onset of erythema was measured in vivo in humans following topical application and was used to assess percutaneous penetration. In oily cream BP, hexyl nicotinate at 0.1% penetrates the skin to give a time of onset of erythema of 14.3 min. Addition of 10% urea decreases this time to 11 min. More extensive data obtained following nicotinate delivery in aqueous cream BP with and without urea are shown in Table 2. However, for use in commercial formulations, urea must be stabilized to prevent degradation. For this reason, its accelerant properties have not been widely exploited.

Pyrrolidone derivatives have been examined as accelerants, and 2-pyrrolidone and *N*-methyl pyrrolidone, in particular, have been shown to be active. They have been examined with a range of solutes including griseofulvin, theophylline, tetracycline, and ibuprofen (see Figure 13).[67-71] At high concentrations, pyrrolidones can be irritating to the skin.

Recently, considerable attention has been directed toward 1-dodecylazacycloheptan-2-one (Azone®), which may be considered to be a "chemical combination" of pyrrolidone and decylmethyl sulfoxide. It has the ring structure associated with the pyrrolidone (albeit a seven-membered ring) and the long alkyl chain with mild polar head group associated with the alkyl sulfoxides. Azone® is a clear colorless liquid which may be incorporated into gel, cream, lotion, or solution formulations. It appears to have low irritancy and is active, at low concentrations, in enhancing the percutaneous absorption of a range of compounds[72-77] including corticosteroids, erythromycin, clindamycin, fusidic acid, griseofulvin, 5-fluorouracil, indomethacin, and hydroquinone. Typical concentrations of Azone® required for

Table 2
PENETRATION ENHANCEMENT BY UREA

Hexyl nicotinate concentration (%)	Erythema onset times (min) (mean ± SE) Urea concentration (%) 0	5	10
0.05	18.5 ± 0.5	17.2 ± 0.4	14.4 ± 0.2
0.1	12.9 ± 0.5	11.9 ± 0.3	10.5 ± 0.2
0.2	11.1 ± 0.4	9.6 ± 0.3	8.1 ± 0.2
0.5	8.7 ± 0.4	8.2 ± 0.4	6.6 ± 0.2
1	7.1 ± 0.3	6.9 ± 0.3	5.1 ± 0.3

Note: Times (in minutes) of onset of erythema (mean ± SE; n = 20) induced by hexyl nicotinate delivered from aqueous cream BP as a function of drug and urea concentration in the vehicle.

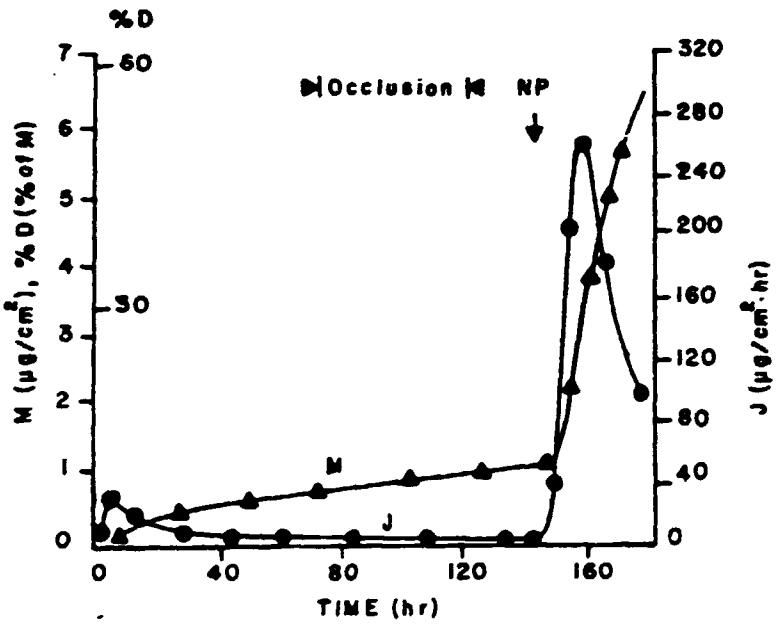

FIGURE 13. In vitro penetration data through dermatomed human skin for ibuprofen applied from an acetone vehicle. The effects of occlusion and the addition of *N*-methyl-2-pyrrolidone (NP) are shown. M is the cumulative amount penetrated; %D is the percent of the applied dose; and J is the derived flux.[67]

optimum effect range between 0.1 and 5%. For this reason, this agent may have particular use in transdermal delivery systems. However, more recent evidence[76,77] suggests that the action of Azone® may depend critically upon the presence of other components in the vehicle (e.g., propylene glycol) and that a degree of synergism may be involved in the promotion effect.

There are other miscellaneous compounds which have been considered as penetration enhancers: propylene glycol has already been mentioned and various amines have been examined. *N,N* diethyl-*m*-toluamide (DEET) has been investigated by Windheuser et al.,[78] and at 5% enhances the penetration of a range of compounds across hairless mouse skin. In a steroid blanching test, it has also been shown effective in vivo in human skin. Since DEET has been used for many years as an insect repellent at concentrations ranging from 10 to 100%, it seems possible that this agent has potential as a penetration enhancer.

One of the major difficulties associated with accelerants is their lack of specificity. They will enhance the absorption of other vehicle components and any impurities will be taken into the circulation. The toxicological implications of this must be considered in the formulation and all the materials must be ultrapure. This is possibly the reason for the lack of accelerants presently in commercial products. However, a fuller understanding of their mechanism of action will perhaps aid the development of compounds with greater specificity. An additional problem, also unresolved at this time, is that the penetration enhancing ability of, and the level of local skin toxicity induced by, the popular promoters are generally highly correlated. In other words, the best promoters of percutaneous absorption cause the most severe irritation. If disruption or destabilization of bilayer structures is a component of their mechanism of action, then this observation is, perhaps, not surprising, and may impose a limitation on the potency of enhancers that can be used practically. However, despite their disadvantages, penetration enhancers will undoubtedly remain a major consideration in the development of transdermal drug delivery systems.

Finally, mention should be made of two alternative methods to achieve penetration enhancement: (1) the use of prodrugs and (2) iontophoresis. Neither of these approaches can claim any existing applications in transdermal drug delivery for systemic effect. The philosophy of the prodrug concept is generally straightforward in its use with respect to the skin: to prepare a labile, more lipophilic precursor of the drug which has improved skin permeability but rapidly hydrolyzes once it has breached the stratum corneum. The area of topical prodrugs has been reviewed recently in some depth.[79] Iontophoresis has been recognized as a means of driving charged materials across lipoidal membranes for a considerable time. There is evidence to indicate that ionic species can be driven across the skin by this technique.[80] However, the problems associated with both formulation of suitable delivery systems and long-term passage of current at a specific skin site remain unresolved. It follows, therefore, that a significant amount of work remains to be performed before the potential use of these alternative approaches is clearly defined.

VII. CONCLUSIONS

In recent years, transdermal drug delivery has elicited a significant response in the pharmaceutical sciences. To a certain degree, the early promise has been realized with the successful and pending introductions into the market of a number of dosage forms. However, initial enthusiasm, which might be characterized (with hindsight) as somewhat excessive, has now been tempered with recognition that the transdermal route of administration has significant limitations and unique formulation requirements. Selection of drug candidates requires a thorough understanding of the kinetics and mechanism of percutaneous absorption, and a careful evaluation of the pharmacodynamic profile is needed for optimal efficacy. These issues can now be tackled more rationally because of developing intelligence in the necessary areas. The notion of skin penetration enhancement remains an enigma with the equation relating promotion to toxicity (local or systemic) undefined. Subsequent advances in transdermal delivery will be much harder to achieve because, in a sense, the most obvious candidates for this mode of input have now been considered. The learning experience, though, has been valuable and has delineated important questions, the answers to which must be known for further progress. There is no doubt that the next efforts will advance our comprehension of the skin's barrier function and of the mysteries of dermal penetration. Transdermal delivery remains, therefore, a challenge that will demand attention for the foreseeable future and will ultimately yield further basic science and commercially applicable rewards.

ACKNOWLEDGMENTS

Financial support was provided by NIH (GM-33395), by Liposome Technology, Inc. (Menlo Park, Calif.), and by a Special Emphasis Research Career Award to RHG from the Centers for Disease Control — National Institute of Occupational Safety and Health (KO1-OH-00017-03).

We thank Cynthia Lorence for the illustrations, and Andrea Mazel for manuscript preparation.

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transdermal drug delivery

historical background

advantages and disadvantages

selection of drug candidates

system designs

future developments

CARDIFF

historical background

systemic toxicity

- nicotine. pesticide use in agrochemical workers
- nitroglycerin. headaches in workers in armaments factories.
- hexachlorophene toxicity after topical application to infants.

Therefore drugs placed on skin may penetrate it in sufficient amounts to induce systemic effects

ALZA Corporation (early to mid 70's) developing transdermal patch containing scopolamine for travel sickness. From research papers other drug candidates intimated. Showed importance of physicochemical properties.

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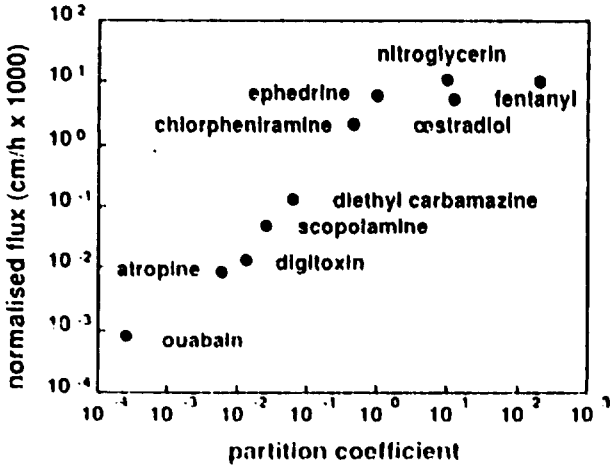
relationship between flux and partition coefficient



from above graph, compounds on market: scopolamine, nitroglycerin, œstradiol, fentanyl.

Others under development include: testosterone & other steroid hormones (combination patch, œstradiol plus progestogen), nicotine, clonidine, bupranolol, timolol, buprenorphine.

Why the interest?

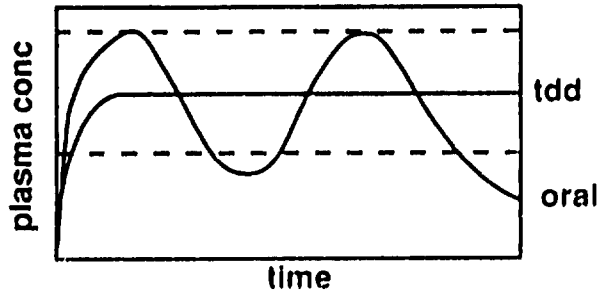
Michaels et al. A.I Ch.E.J.,21 (1975) 985-996.

CARDIFF

Advantages of transdermal delivery i

*System controls delivery***

constant levels in the plasma



minimization of intra- & inter patient variability.

sustained drug levels in the plasma

dosing frequency reduced (1, 3, 7 days). Improved patient compliance

drug input terminated easily

instantaneous drop in plasma levels

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Advantages of transdermal delivery ii

Avoidance of first pass metabolism

lower daily doses

less variability in plasma levels

eg nitroglycerin subject to extensive first pass effects

peptide delivery using iontophoretic systems. Avoids some of the instability problems of peptides eg hydrolysis in the gi tract, first pass metabolism

Disadvantages of transdermal delivery ii

Limited to potent drugs

System not skin should provide rate control but skin is good barrier and large amounts of drug cannot permeate.

maximum daily dose ~ mg per day.

maximum attainable flux across the skin therefore important.

influenced by physicochemical properties of drug

modified by penetration enhancers.

Since skin barrier not insignificant difficult to design systems with complex release patterns.

Difficult to deliver very lipophilic drugs

build up in stratum corneum, rate of transfer into viable tissue slow, enhancers tend to act on polar drugs.

Disadvantages of transdermal delivery iii

Difficult to deliver ionised drugs

- many drugs are acids or bases, skin surface pH ~5, should not deviate significantly from this. pK of drug important
  - local delivery of cromoglycate
  - peptides, ionization state & maybe molecular size problems, does skin have molecular weight cut off?
  - mask ionization by chemical modification or ion pair formation to increase solubility in skin lipids
  - use iontophoresis

Disadvantages of transdermal delivery iv

Limited phamacokinetic clearance range

- half life of elimination: as with all sustained delivery systems not appropriate for drugs with long biological half life.
- if volume of distribution large, small quantities of drug that penetrate the skin will be dispersed in large volume and plasma concentrations will be small.

Allergic & irritant responses.

- unlike above problems these cannot be predicted and need to be investigated at very early stage of development programme.
  - drug
  - formulation components
  - exacerbation by solvent or enhancers
    - clonidine

Disadvantages of transdermal delivery v

May be metabolized.

phase I and II enzymes present in viable epidermis.

some enzymes present in stratum corneum eg cholesterol sulphatase.

microflora

steroid esters

nitroglycerin

staph. epidermidis.

Tolerance.

can be induced as result of constant plasma levels

nitroglycerin (gtn) patches relabelled

new design strategies for gtn delivery

selection of drug candidates

daily dose and potency

a few mg per day

clearance kinetics

not long half life, small volume of distribution.

tolerance

any predictable problems?

allergic or irritancy

if not NCE, any adverse reactions reported?

physicochemical properties.

partition characteristics

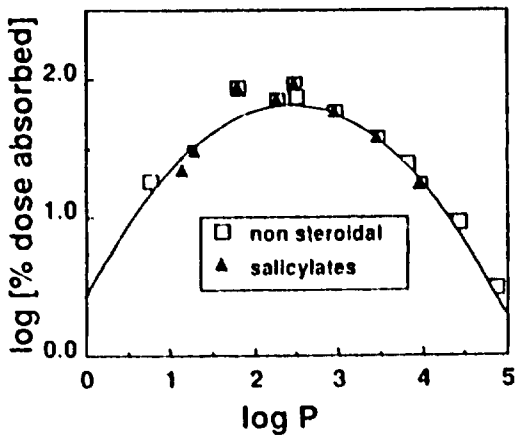
molecular weight

solubility in water and oils

melting point

partition characteristics

appears to be optimum partition behaviour for transdermal delivery. eg delivery of NSAIDs and salicylates.



usual to use octanol water values from measurement or Hansch data base.

Yano et al., Life Sci. 39 (1986)1043-1050.

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molecular weight

not much known about molecular weight cut off. In general diffusion coefficients are related to molecular volume and to a first approximation the diffusion rate through the stratum corneum can be estimated by assuming it is inversely proportional to the cube root of the MW.

Part of the problem of establishing the relative effects of MW,partition, solubility etc is the difficulty in designing appropriate skin diffusion experiments and being able to deconvolute the data.

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solubility i

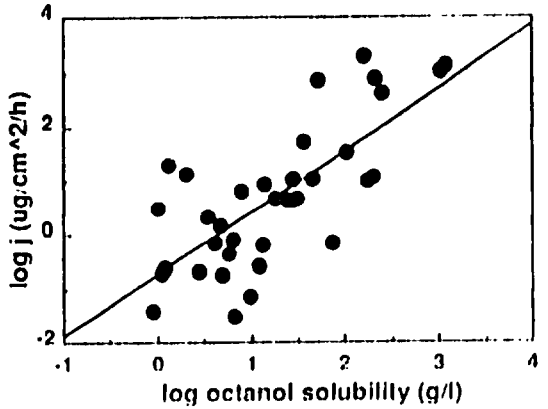
The skin has layers which are both lipophilic and hydrophilic in nature. Therefore transport into the systemic circulation will be favoured by "balanced" solubility in both oils and water.

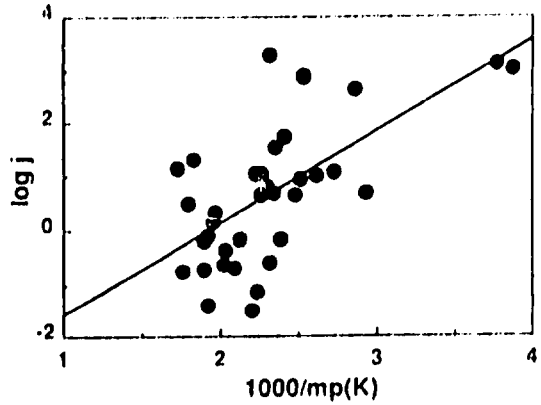
Solubility can be related, through thermodynamic parameters, to melting point. Basically the mp is a refection of the intermolecular forces which have to be broken before a substance can go into solution. In general terms the lower the mp the faster the rate of penetration through the skin.

Nitroglycerin and nicotine are both delivered transdermally, they have low mp and penetrate the skin well.

solubility ii

effects of octanol solubility & mp on drug flux for a range of substances.



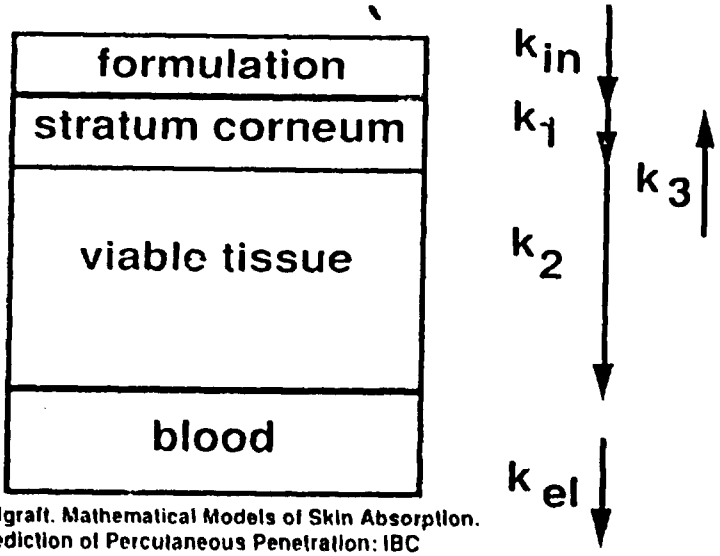


Kasting et al (1987). In *Skin Pharmacokinetics.* B.Shroot, H. Schaeffer, Eds. S. Karger, Basel p138

modelling transdermal delivery i

since the physicochemical properties of a drug are important determinants in the rate at which it crosses the skin, ought to be able to build up a model to act predictively.

$$k = D / l^2$$



J.Hadgraft. Mathematical Models of Skin Absorption. In Prediction of Percutaneous Penetration: IBC Technical Services Ltd., Eds R.C.Scott, R.H.Guy and J.Hadgraft. (1990) 252 - 262

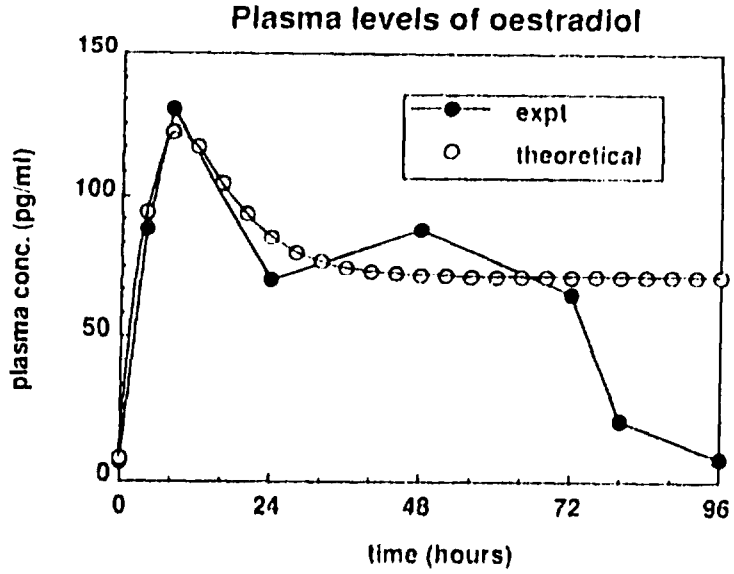
CARDIFF

modelling transdermal delivery ii

modelling achieved using STELLA on the Apple Macintosh.

useful for complex input functions, considering solubility constraints complex elimination kinetics & multiple dosing.

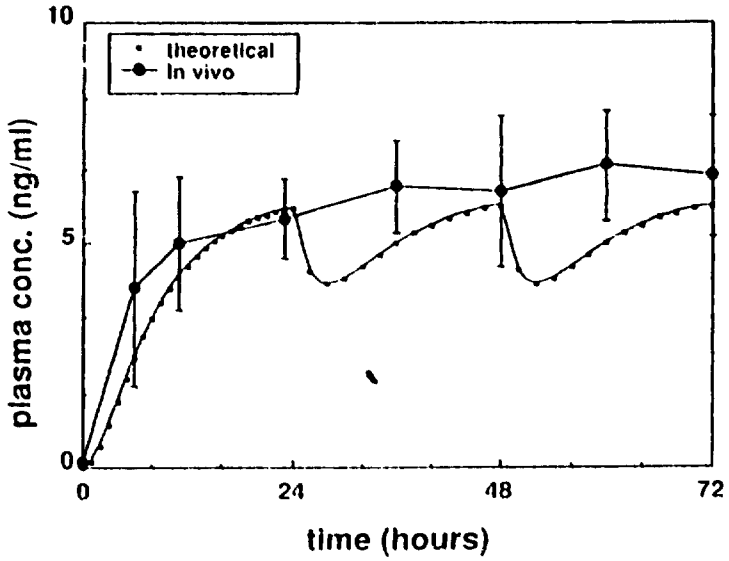
œstradiol



CARDIFF

modelling transdermal delivery iii

bupranolol



R.H. Guy and J. Hadgraft. Int. J. Pharm. (1986) 32, 159-163.

CARDIFF

in vitro skin diffusion studies

determine the maximum flux (J_{max}) of drug across excised *human* skin. This gives estimate of the input of the drug into the systemic circulation, equate this to the known clearance kinetics to give estimate of the plasma levels that can be achieved using the transdermal route.

$$J(max)\ A = Cl\ .c_p$$

provides confirmation of mathematical feasibility studies and confidence in continuation of developmental programme.

V.M. Knepp, R.H. Guy and J. Hadgraft. Transdermal drug delivery : problems and possibilities. CRC Critical Reviews in Therapeutic Drug Carrier Systems. Volume 4, Issue I (1987) pp 13-37.

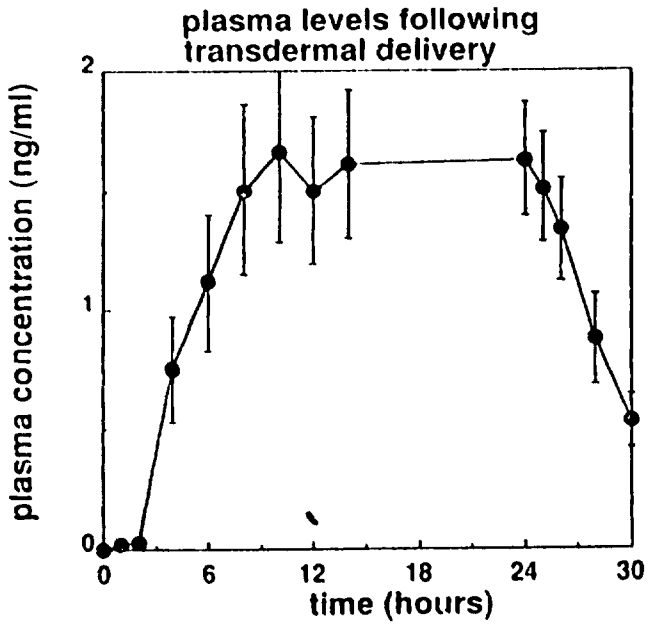
CARDIFF

in vitro - in vivo correlation : Rolipram

concept -> feasibility

mathematical model ->*in vitro* experiment

in vitro data confirm mathematical simulation and suggest that attainable levels are approximately 4 ng/ml.
volunteer study (n=6)



Hadgraft etal., Pharm. Res. (1990) 7, (12), 1307 - 1312

CARDIFF

in vitro - in vivo correlation : pre-term infants

preterm infants difficult to dose

small blood volume, poorly formed gi tract (erratic absorption)

stratum corneum not present at "birth" and therefore very permeable.

ethanol

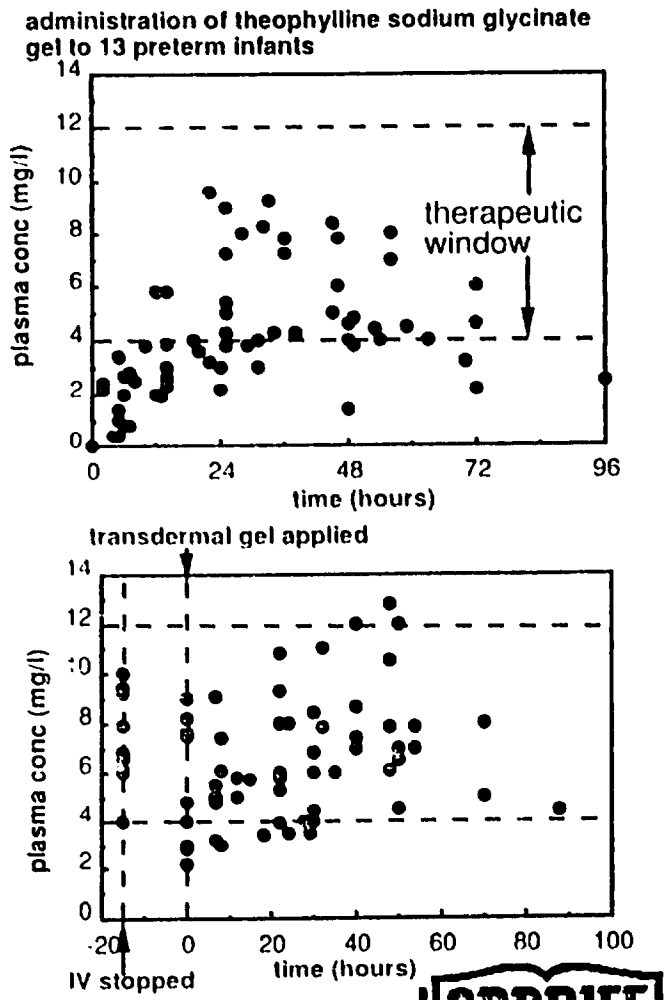
theophylline given to treat breathing difficulties but has narrow therapeutic window.

mathematical feasibility study shows that TDD can be used. Simple gel formulation produced and tested *in vivo.*

Evans et al. J. Pedriatrics 107 (1985) 307-311.

CARDIFF

in vitro - in vivo correlation : pre-term infants ii

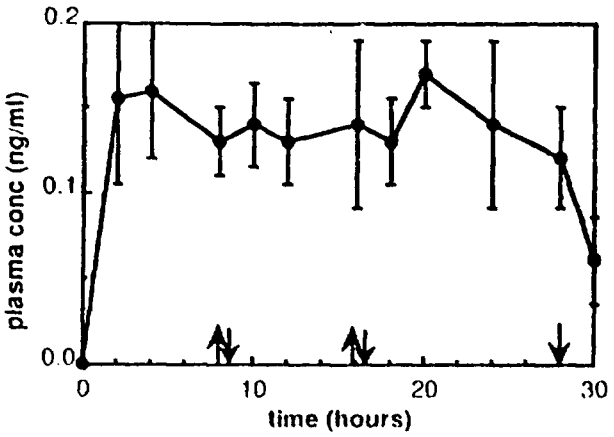


system designs

consider transdermal delivery of gtn

- *simple ointment*
- *Nitrodur ii*
  - matrix type
- *Nitrodisc*
  - microsealed drug delivery system
- *Deponit*
  - matrix, inhomogeneous drug distribution
- *Transderm-Nitro*
  - membrane moderated

Simple ointment



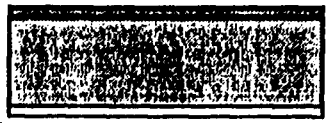
gtn plasma concentrations (mean ± se, n = 12) following application of 400 mg of 2% ointment over a skin area of 10 sq cm. at t=0, t=8 and t=16h.

Chu et al. Angiology 35 (1984) 545-552.

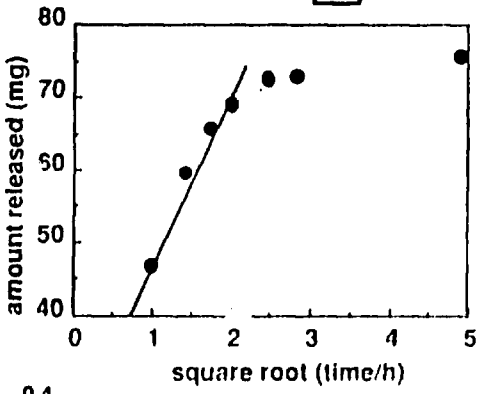
CARDIFF

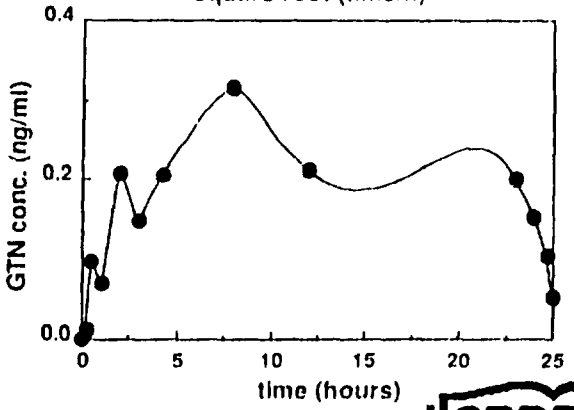
Nitrodur ii

homogeneous matrix system eg acrylate



backing membrane
polymeric matrix which may be adhesive
adhesive layer

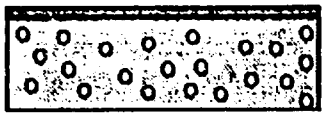




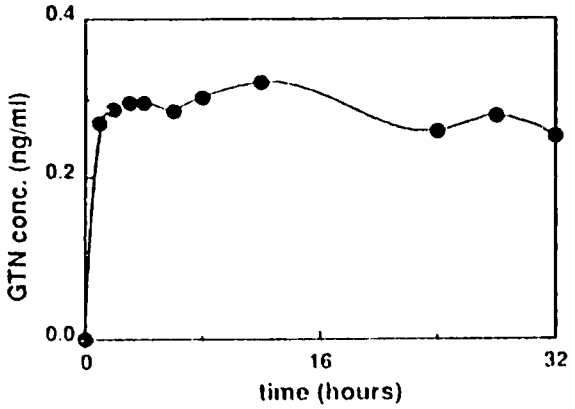
Chien. Amer. Heart J. 108 (1984) 207-216.

CARDIFF

Nitrodisc



backing membrane
polymeric matrix containing "solvent" droplets
adhesive layer



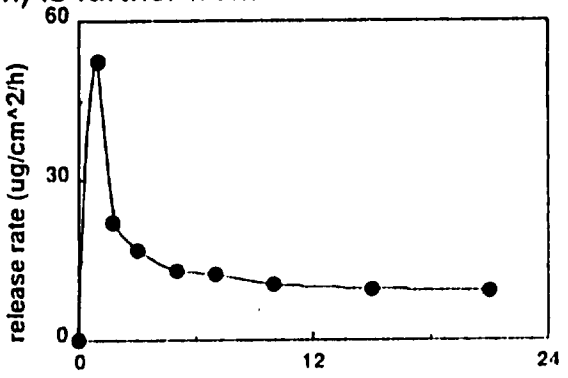
Karim. Drug Dev. Ind. Pharm., 9 (1983) 671-689.

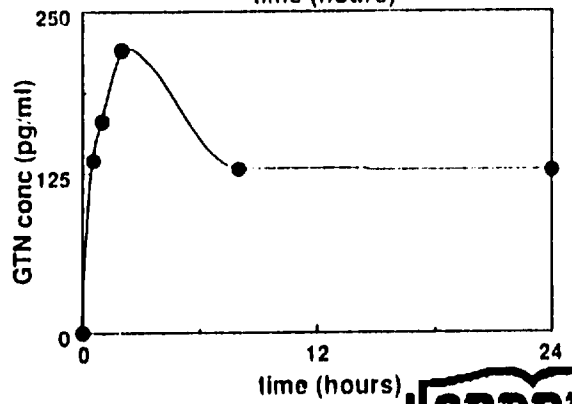
CARDIFF

Deponit

backing membrane
polymeric matrix, containing gtn in solution & on lactose.

matrix built up in several layers so that more lactose (plus gtn) is further from skin surface.



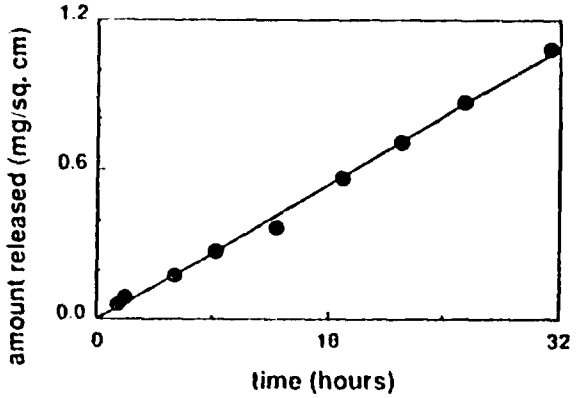


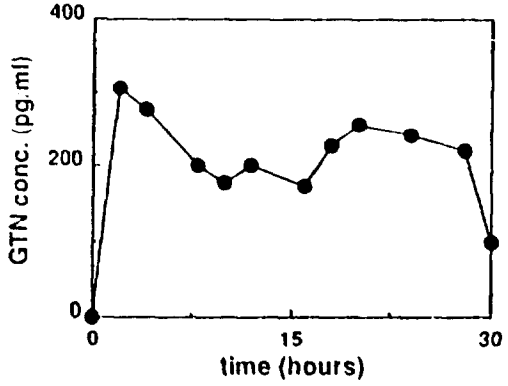
Wolff et al. Pharm. Res. 2 (1985) 23-29.

CARDIFF

Transderm-Nitro

backing membrane
drug reservoir,usually suspension
rate controlling membrane
adhesive, may be annulus round
patch edge

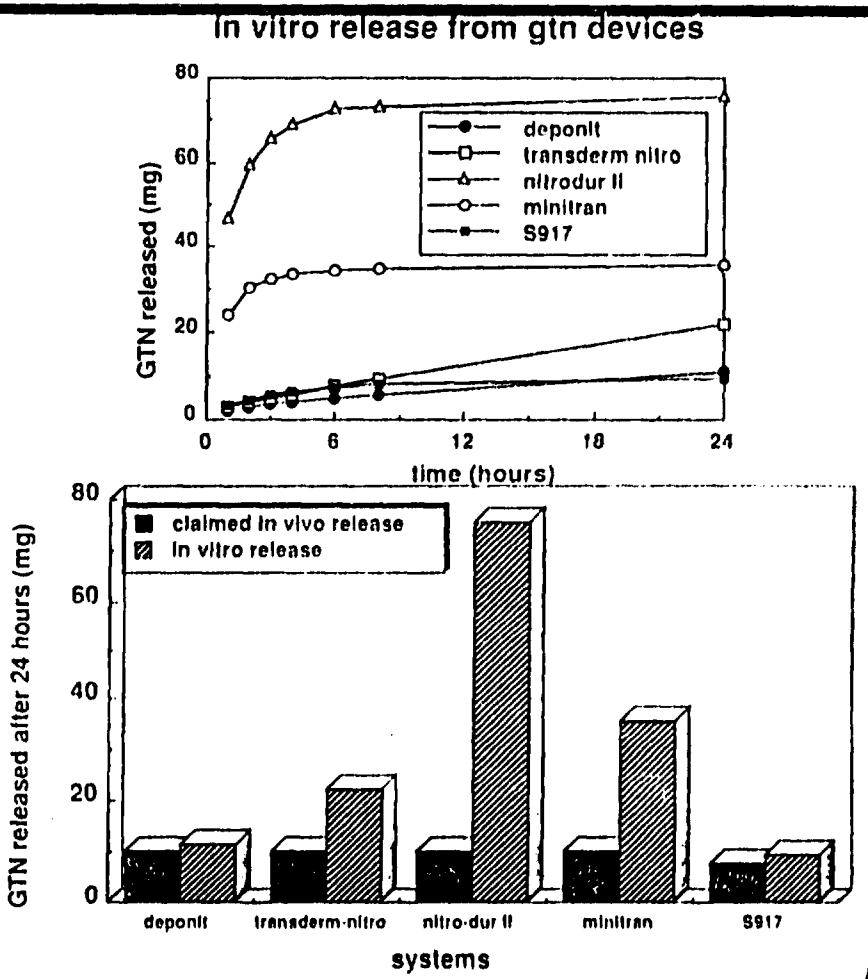




Chu et al. Angiology 35 (1984) 545-552.

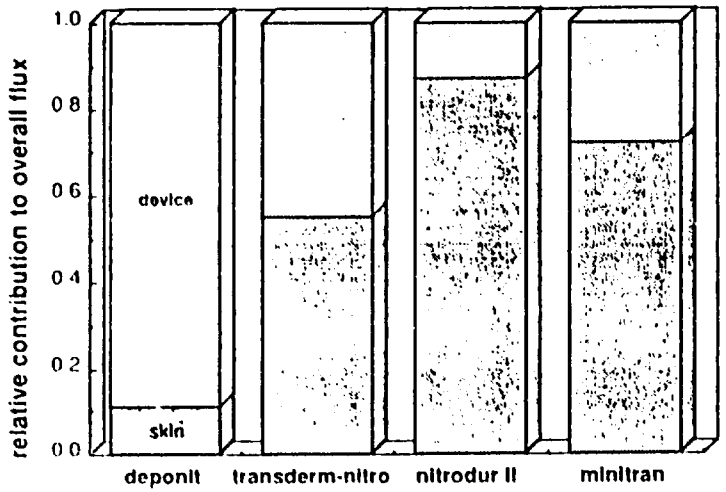
CARDIFF

System vs. skin control?



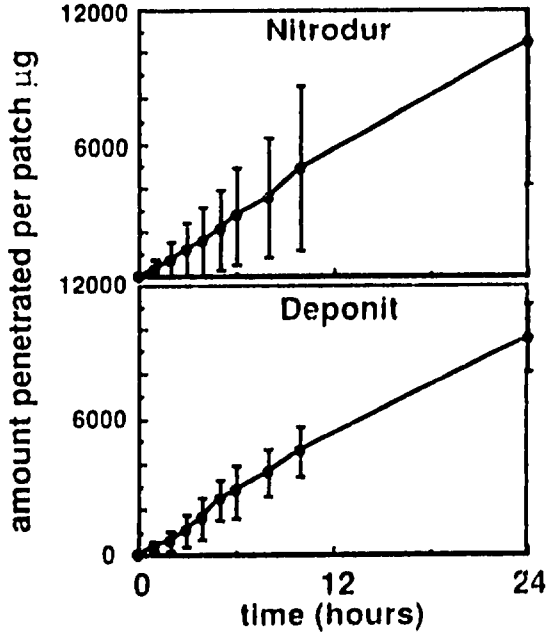
CARDIFF

System vs. skin control?

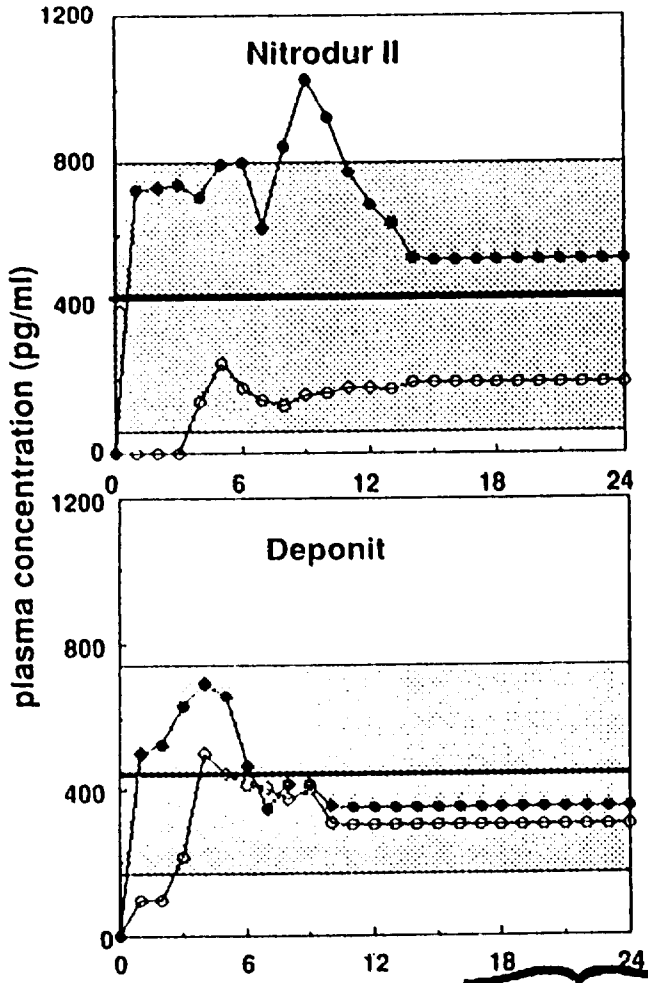


predicting gtn levels from in vitro experiments i

measure *in vitro* flux of gtn through excised human skin (dermatomed to 220μm). Compare Nitrodur II and Deponit. Calculate rates of gtn input and couple with known clearance kinetics using STELLA.



predicting gtn levels from in vitro experiments ii



CARDIFF

future

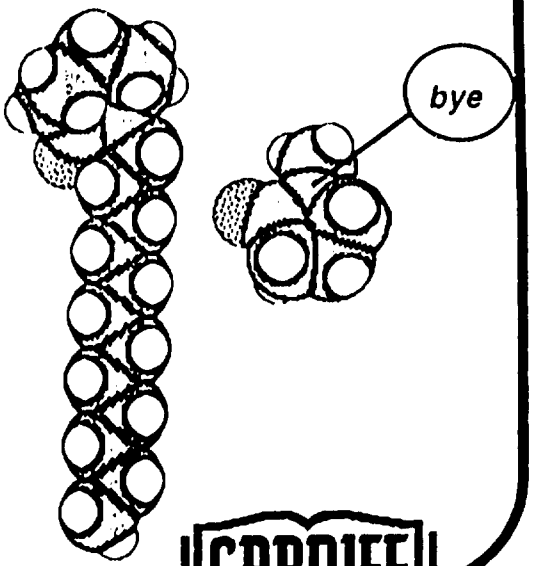
mechanisms of skin penetration / enhancement will be better understood.

will produce greater confidence in predictability.

molecular graphics will be used to predict drug lipid interactions.

modelling diseased states?

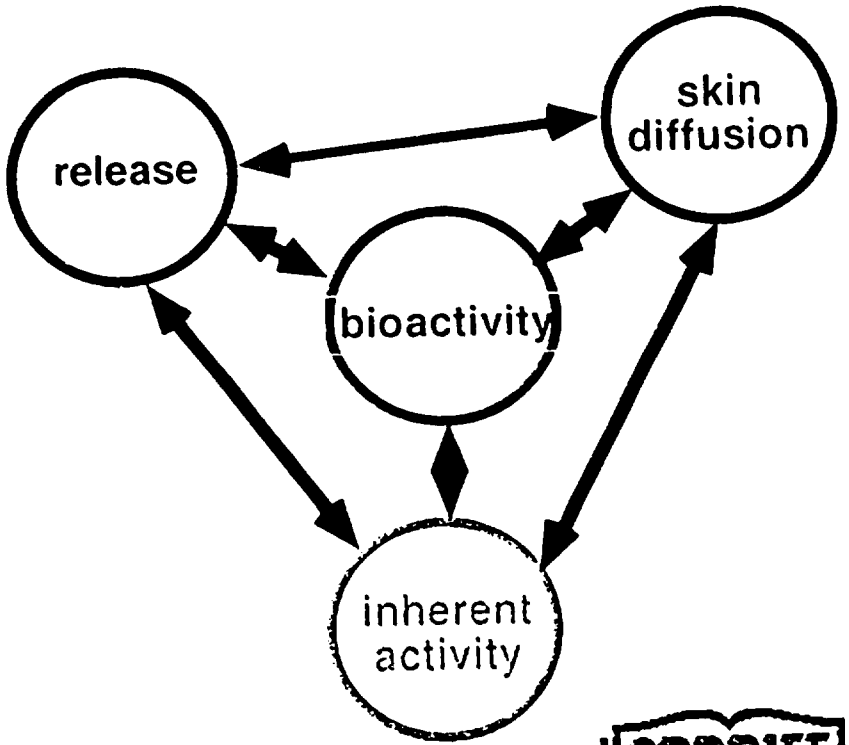
metabolism.



CARDIFF

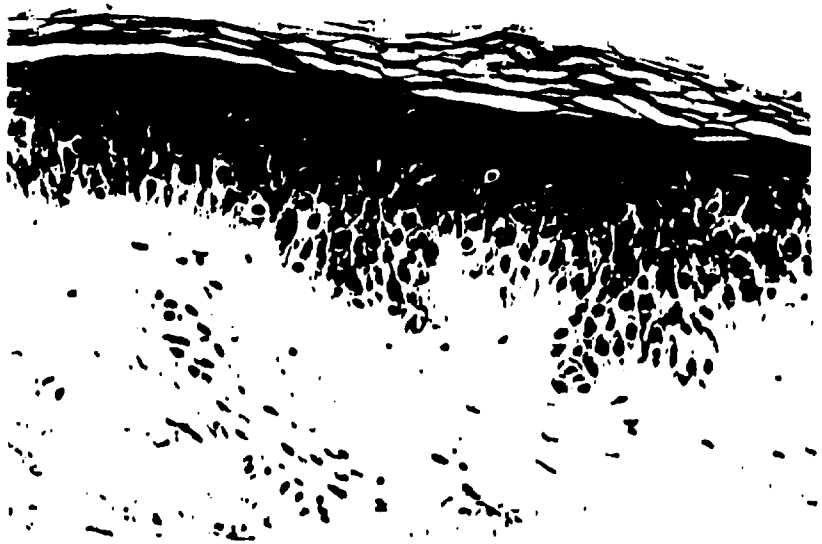
percutaneous absorption

factors affecting topical and transdermal delivery



CARDIFF

route of penetration

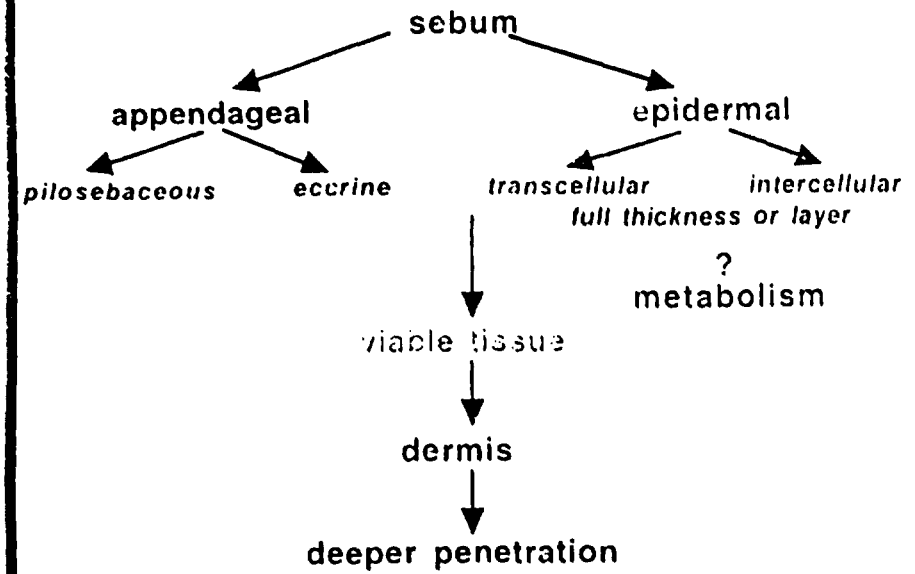


principal barrier: stratum corneum unless drug very lipophilic

how does drug cross stratum corneum?

various routes postulated

route of penetration



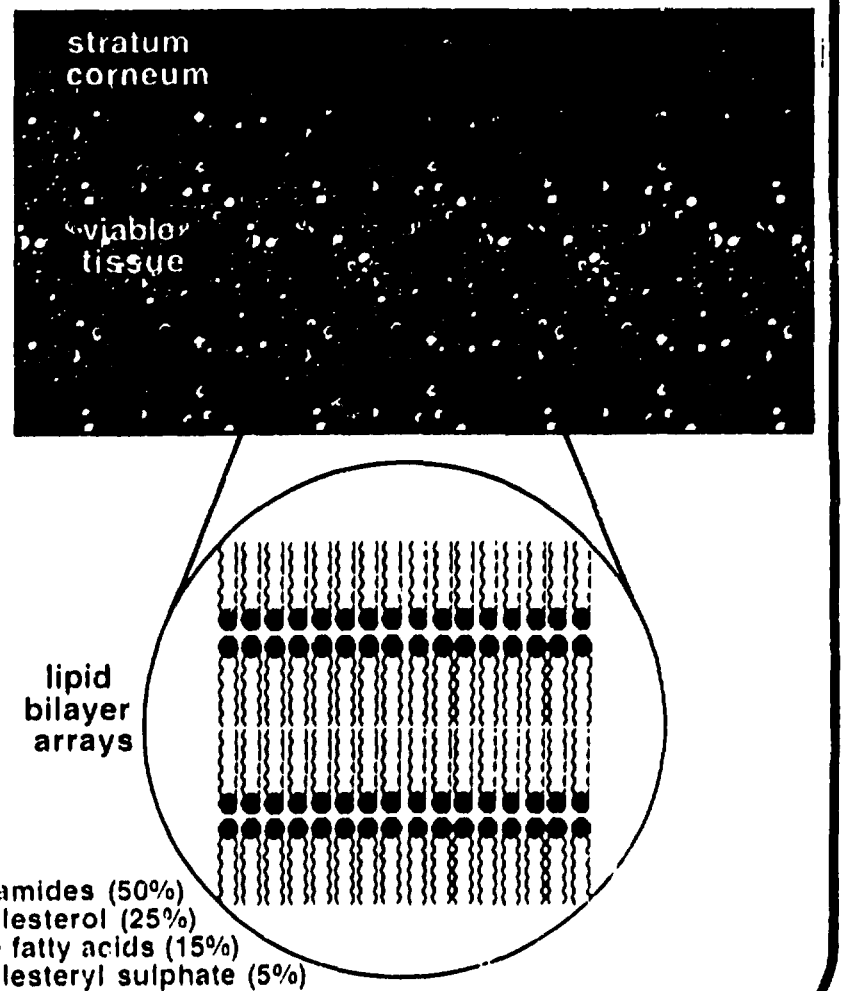
diffusional pathlength >>15μm

visualisation studies

lipids in skin

1st transfer process, partition into skin lipids

schematic representation of skin



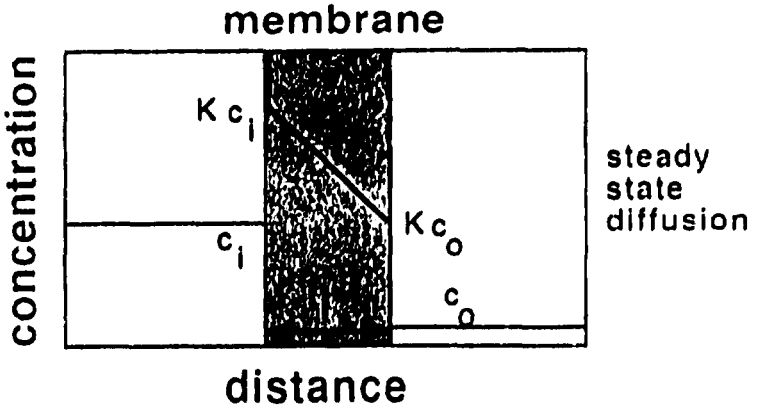
release from formulation

can control penetration eg particle size effects:

comparison of absorption of 0.025% fluocinolone acetonide from white soft paraffin, degree of vasoconstriction (n=10)

preparation	mean	range
coarse particle	0.7	0 - 2
micronized particle	1.4	0 - 2
dissolved in 5% propylene glycol	1.8	1 - 2

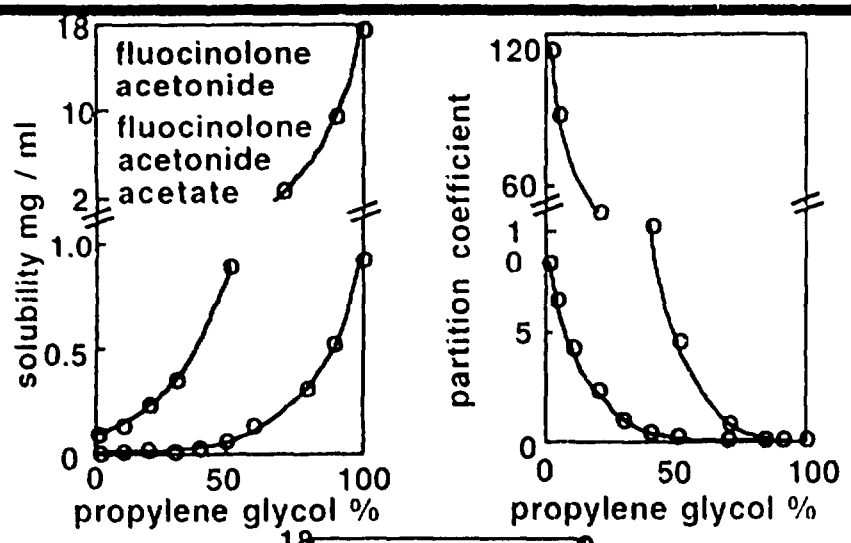
partitioning & solubility

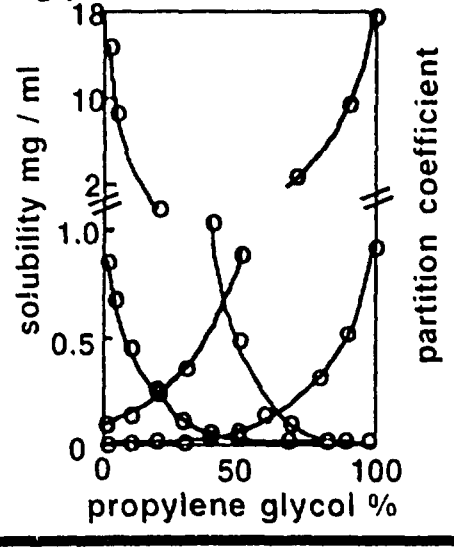


$$J = D\frac{K(c_i - c_o)}{l}$$

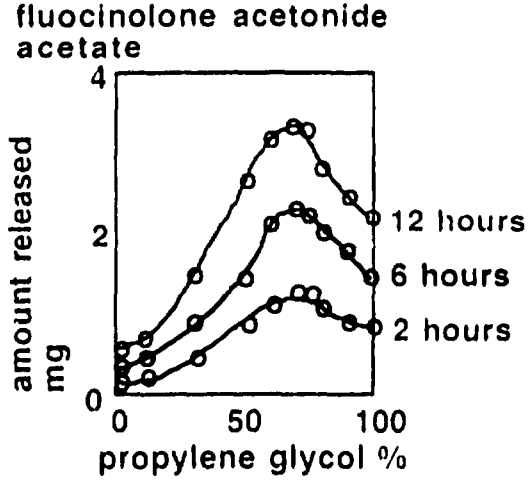
permeability coefficient = KD/l

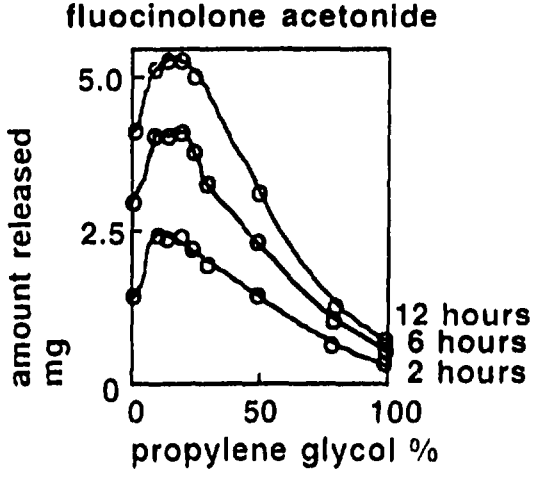
fluocinolone & fluocinonide



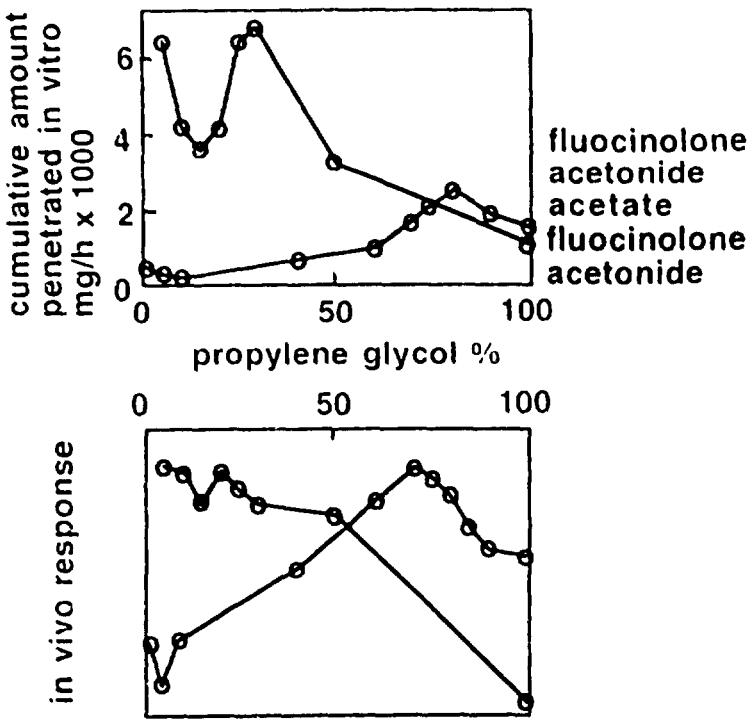


fluocinolone & fluocinonide ii





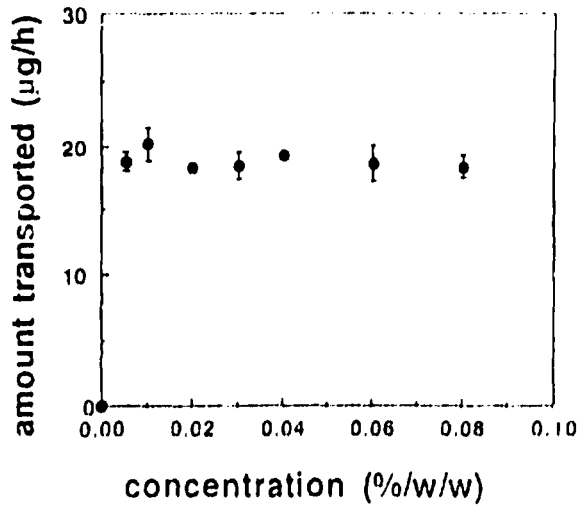
fluocinolone & fluocinonide iii



thermodynamic activity

saturated solutions have thermodynamic activity of 1. Can create different solutions that have different drug concentrations but the same degree of saturation. If the formulation components do not alter the permeability characteristics of the skin, the flux through the skin will be the same.

penetration of HCA through silastic

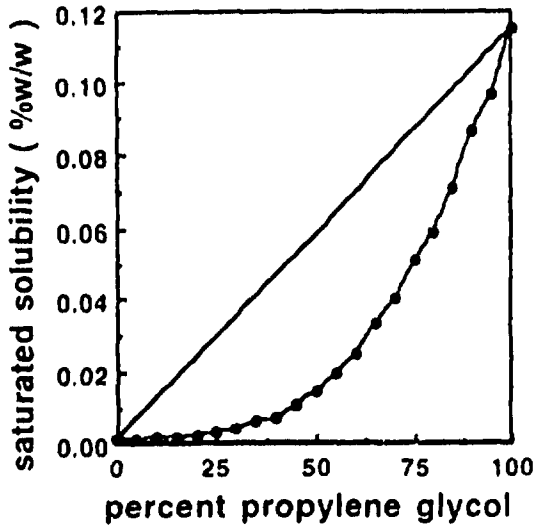


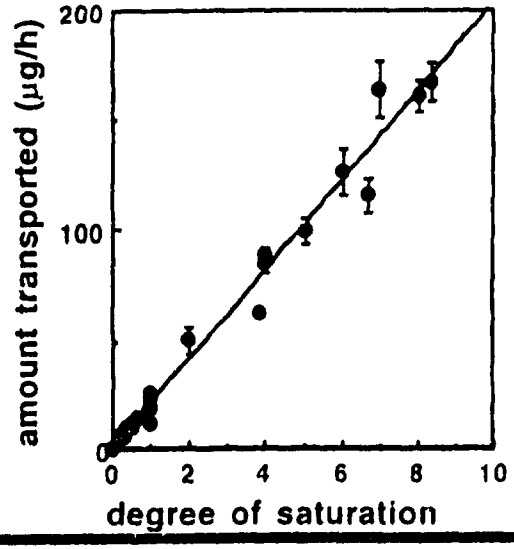
penetration of methyl nicotinate

glycerol %	MN	time of erythema (min)
0	0.04M	4.3
10	0.04M	4.4
40	0.04M	4.7
60	0.04M	4.8
80	0.04M	6.2
100	0.04M	11.5

glycerol %	MN	time of erythema (min)
0	0.07M	4.0
60	0.08M	4.2
80	0.1M	4.3
100	0.2M	4.7

supersaturated systems

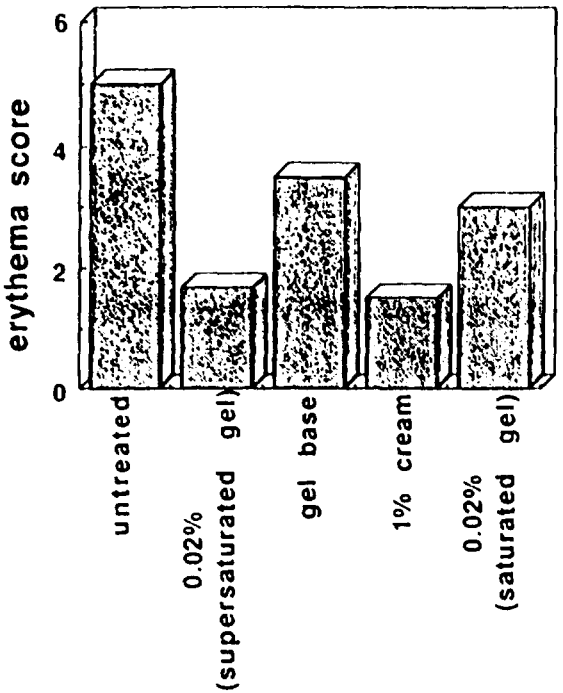




steroid blanching studies

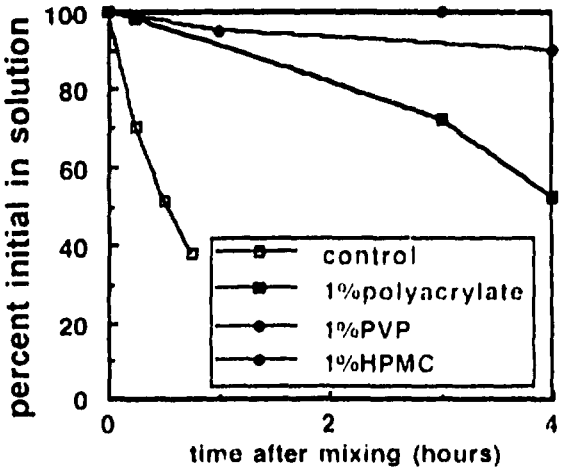
surfactant induced erythema

16 volunteers



stability considerations

need to incorporate polymer additives

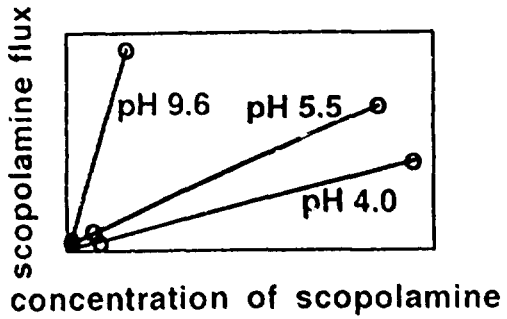


more recent studies show that HPMC can stabilise for at least 72 h.

Formulation design needs twin pack storage to keep components separate.

ionisation

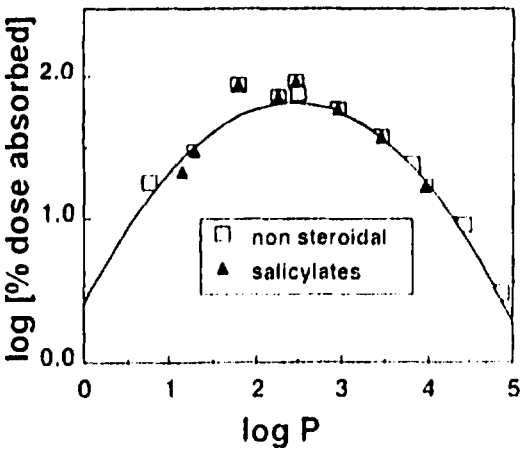
skin surface pH 4.2 - 5.6



delivery of sodium cromoglycate prodrugs

partition coefficient

appears to be optimum partition behaviour for transdermal delivery. eg delivery of NSAIDs and salicylates.



usual to use octanol water values from measurement or Hansch data base.

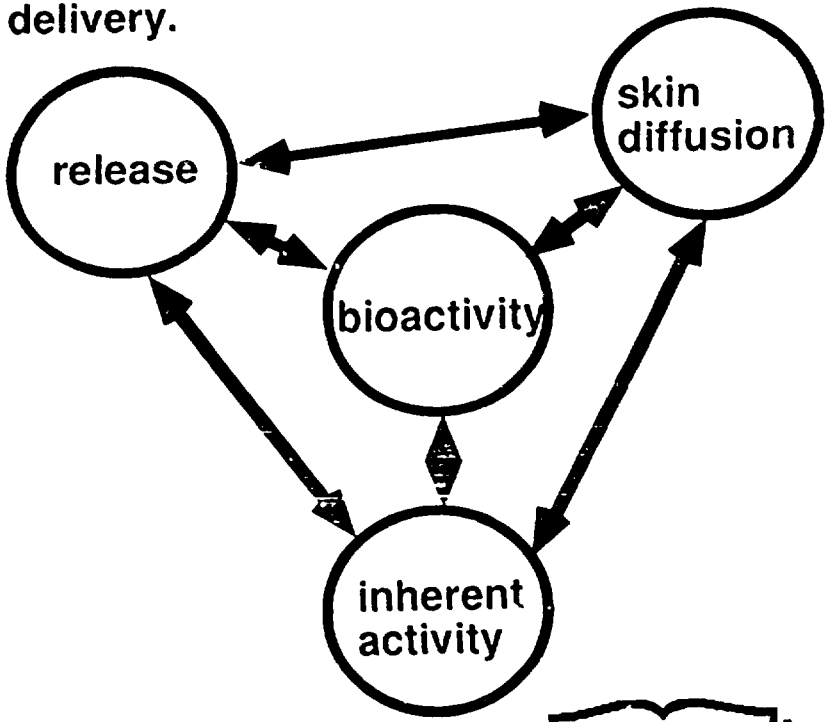
Yano et al., Life Sci. 39 (1986)1043-1050.

Penetration enhancers

Materials that favourably alter the transport properties through the skin.

Chemical & physical enhancement

Uses in topical and transdermal drug delivery.



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Penetration enhancers ii

ideal characteristics

- no inherent pharmacological action
- non toxic
- non allergenic
- specific in action
- immediate action with predictable duration
- chemical & physical compatibility with drug
- odourless, colourless, tasteless, inexpensive

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Penetration enhancers iii

Need to be able to identify what enhancer to choose. Will be a function of the physicochemical properties of the penetrant.

In order to identify this correctly should appreciate the mechanism of action of the different enhancers. This can only be achieved by first understanding the rate controlling steps in percutaneous absorption and the route of penetration.

For most materials transfer through the stratum corneum is the slowest step and therefore the one to study.

Route of penetration via lipid rich intercellular channels, see idealized model of the skin.

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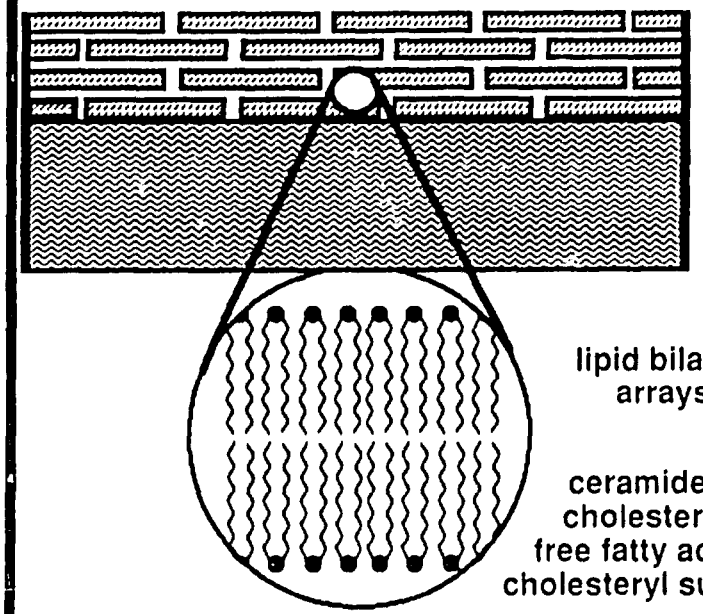
schematic model for skin



enhancers act on lipids:
a. modify disorder, affecting D
b. modify solubility properties.

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Mechanism of action summary

Can alter the following

partitioning into the skin

- intrinsic solubility of the drug in the skin lipids

diffusion through the skin

partitioning from skin lipids to viable tissue.

Most studies have concentrated on the ways in which enhancers interact with the structured skin lipids.

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Methods of studying interaction with structured lipids

skin

extracted skin lipids

other model structured lipids eg dppc

- thermal analysis
- fourier transform infra red
- nuclear magnetic resonance
- electron spin resonance
- x-ray diffraction
- neutron scattering
- fluorescence spectroscopy
- monolayer models
- liposome models

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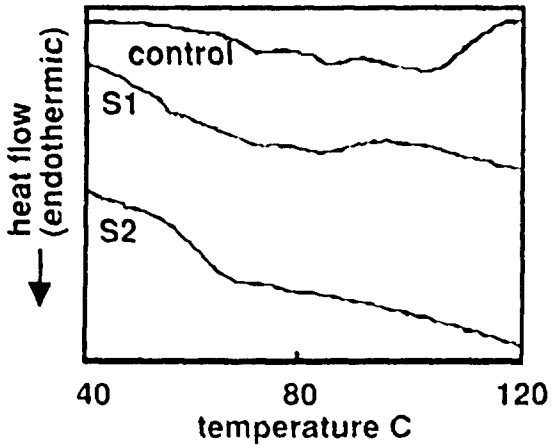
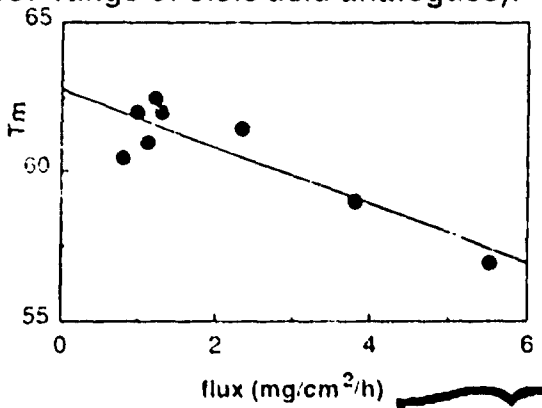
thermal analysis

differential scanning calorimetry



relationship between Tm and flux of salicylic acid, (enhancers: range of oleic acid analogues).



Golden et al J.Pharm. Sci. (1987) 76, 25.

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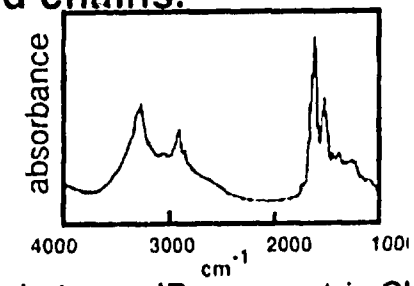
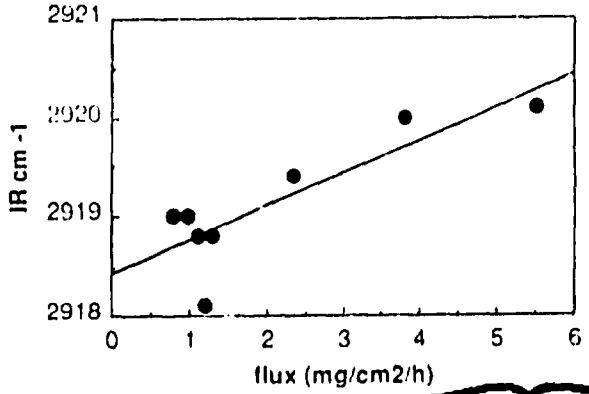
fourier transform infra red i

The CH symmetric (2850 cm-1) and asymmetric (2920cm-1) stretching frequencies reflect the disorder of the alkyl lipid chains.



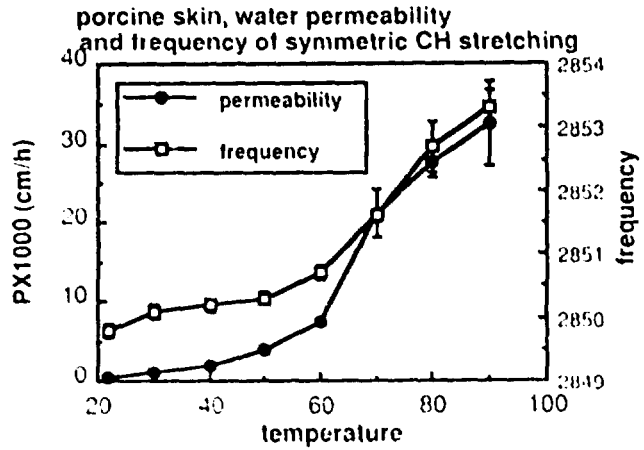
relationship between IR asymmetric CH stretching frequency and flux of salicylic acid (enhancers: range of oleic acid analogues).

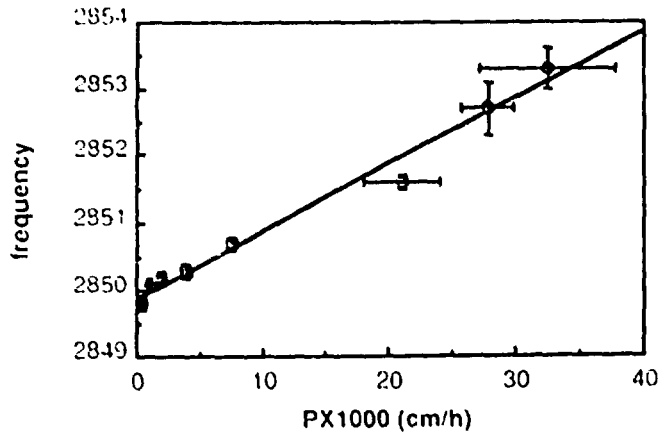


Golden et al J.Pharm. Sci. (1987) 76, 25.

CARDIFF

fourier transform infra red ii





Potts & Francoeur, Proc. Natl. Acad. Sci. 87 (1990)

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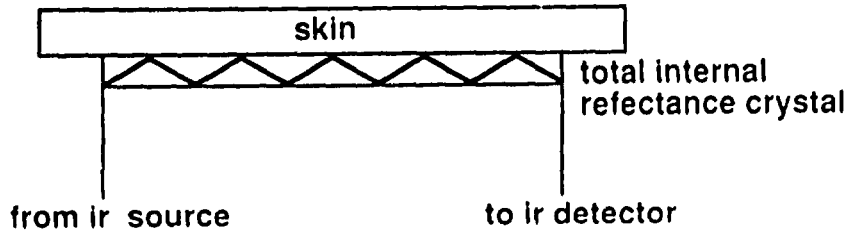
fourier transform infra red, in vivo



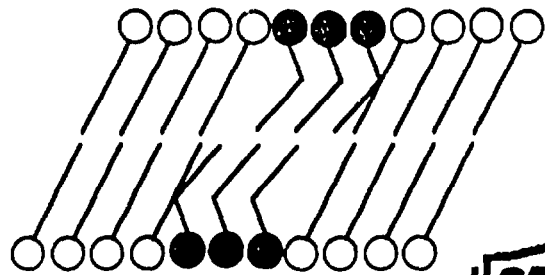
ir only penetrates superficial layers

effects of enhancers on skin lipids

concentration of drug in skin

stripping experiments: depth profile.

oleic acid experiments with perdeuterated material suggests OA pools and increased drug transfer at interfacial defects.



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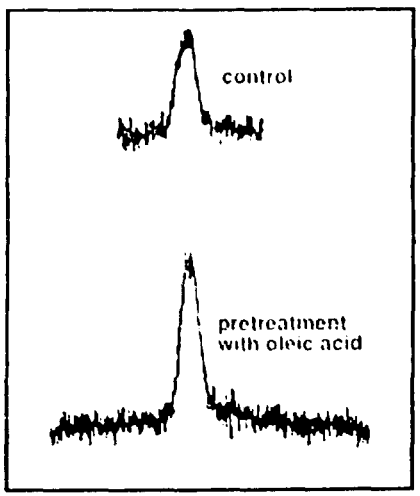
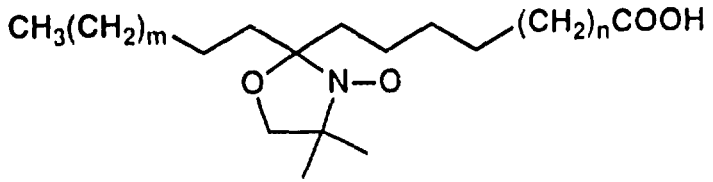
nmr

Can use nmr to monitor in vitro diffusion rates of drugs within the stratum corneum. Need a drug with appropriate "nuclear probe" eg F. Studies conducted on esters of flurbiprofen and influence of oleic acid on diffusion. Width of spectral band gives indication of D.



esr

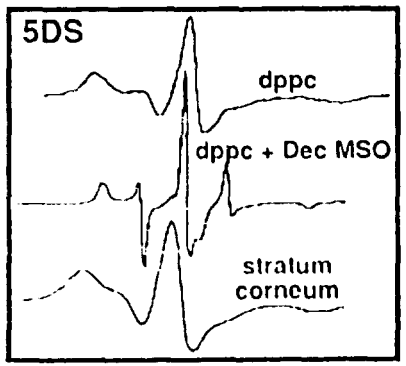
spin probes, (eg doxylstearic acid) can be incorporated into stratum corneum or model structured lipids (dppc liposomes).



the esr spectrum gives information about the molecular environment in which the spin probe is located.

By changing the position of the spin label on the doxyl stearic acid can determine the relative disordering of the acyl chains as a function of the distance from the head group.

comparison of esr spectrum, stratum corneum and dppc liposomes



from spectrum determine order parameter, a measure of the "fluidity" of the microenvironment experienced by the spin probe.

Gay et al. Int J. Pharm. 49 (1989) 39-45

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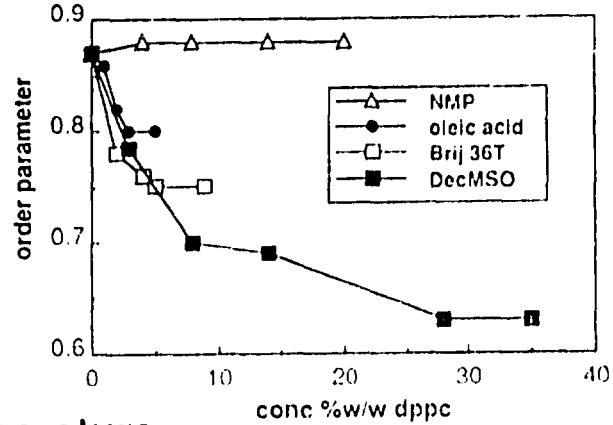
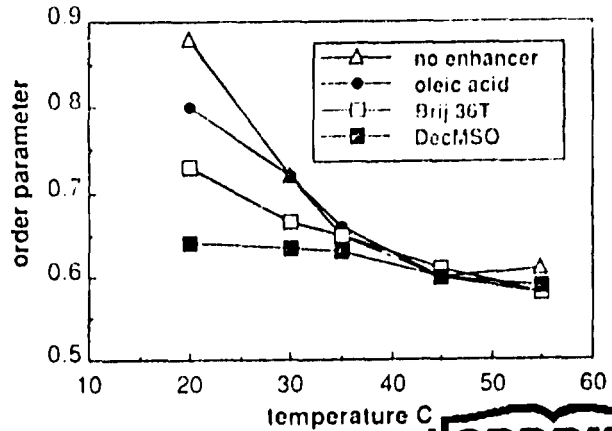
effect of enhancer conc. and temp. on order parameter (dppc)

concentration



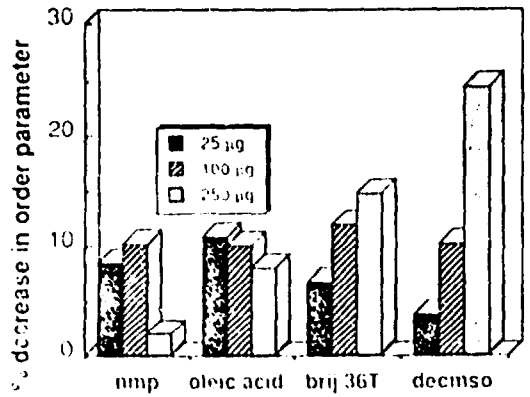
temperature



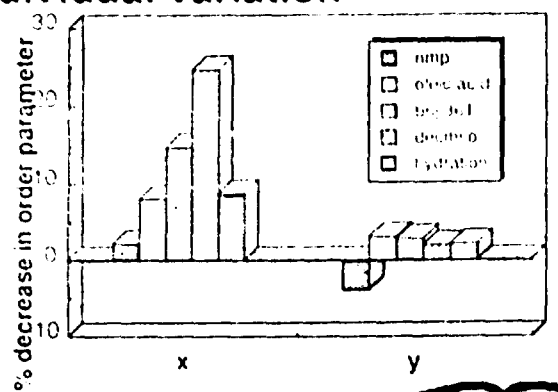
CARDIFF

effect of enhancer conc. on order parameter (stratum corneum)

concentration



inter individual variation



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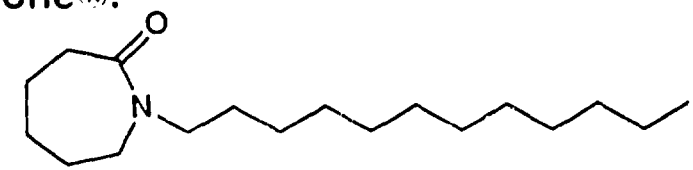
x ray diffraction and neutron scattering

x-ray diffraction on stratum corneum samples provides information about the interlamellar spacing of the lipids. This does not appear to be affected by the presence of enhancers such as Azone®.



will provide information about mechanism of insertion into lipid bilayers

neutron scattering also provides information about interlamellar spacing. It can also give information about location of deuterated materials in the bi (or mono-) layers. Experiments with dppc liposomes suggest pooling of oleic acid and "soup spoon" conformation of Azone

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fluorescence spectroscopy

stratum corneum "doped" with fluorescent probes cf stearic acid spin probes. The fluorescence life times and frequencies give information about the microviscosity in which the probe is located. Similar experiments to the esr ones have confirmed in skin that there is a gradation in fluidity along the acyl chains. There is a more ordered, rigid structure close to the head groups. This suggests that molecules like Azone are effective because they reduce this ordering and facilitate diffusion of the permeant.

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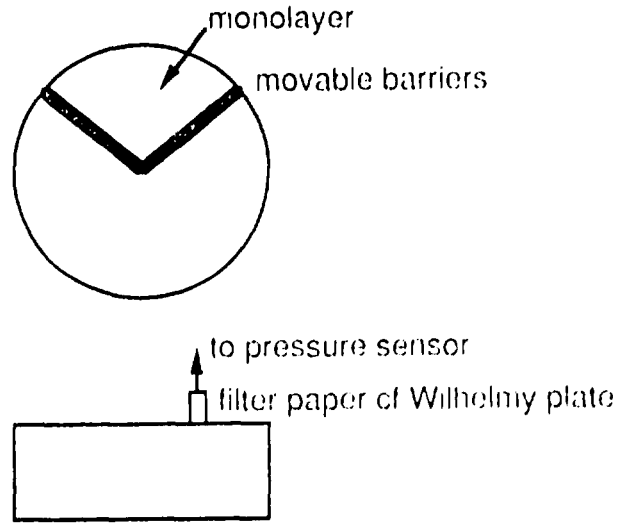
monolayer models i

Langmuir trough with dppc monolayer. Determine π A curve and hence calculate area per molecule.

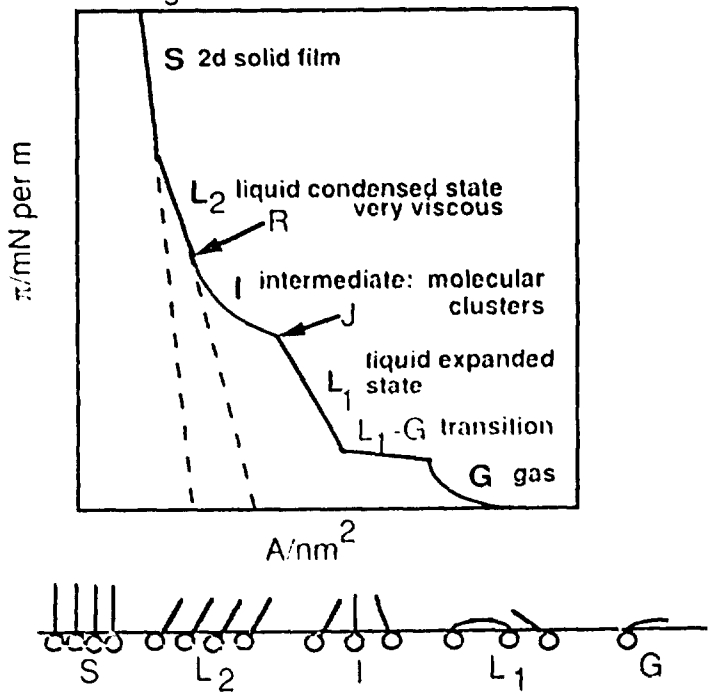
Langmuir Trough



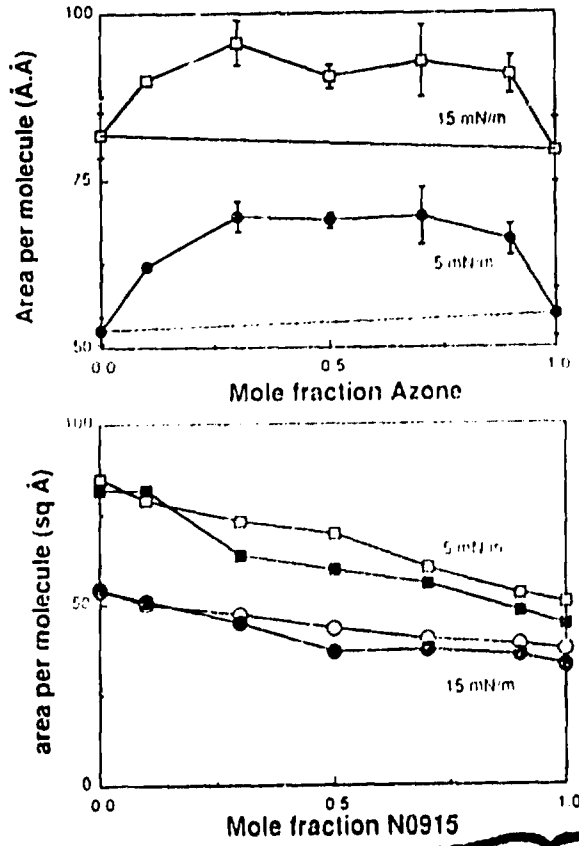
CARDIFF

monolayer models ii

schematic diagram for tetradecanoic acid



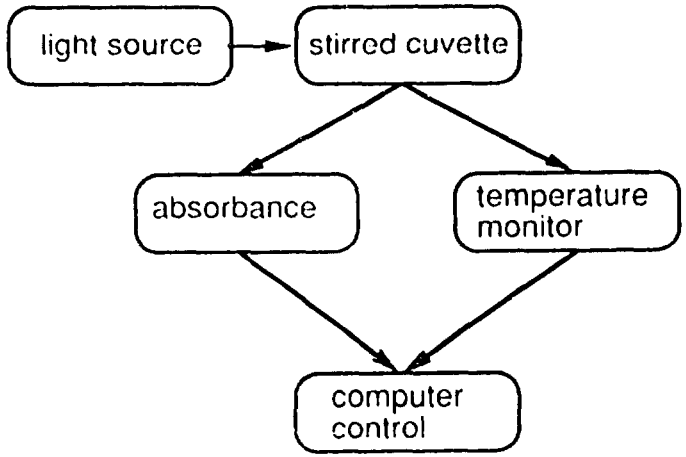
monolayer models iii



D. Lewis and J. Hadgraft, Int. J. Pharm., (1990) 65 211 - 218

membrane fluidity i

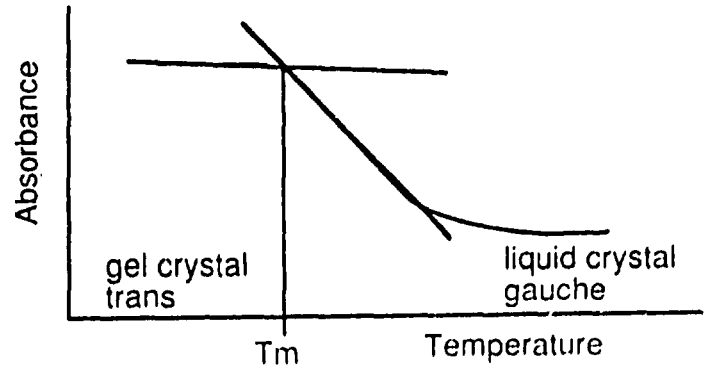
as liposomes go through their phase transition temperature, refractive index gradient changes - detected spectrophotometrically as change in scattered light.

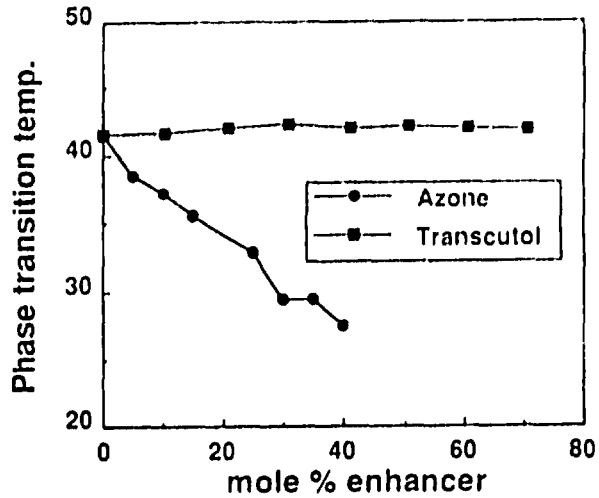


J.C. Beastall et al. Int. J. Pharm. (1988) 43, 207-213.

CARDIFF

membrane fluidity ii





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membrane fluidity iii

for compounds that act by fluidising skin lipids the degree of enhancement appears to be related to gradient of line at low enhancer concentration. One "Azone" like material raises phase transition temperature and retards the absorption of compounds through the skin.

examples

dimethyl sulphoxide

decyl methyl sulphoxide

propylene glycol

N methyl pyrrolidone

NN diethyl toluamide

Azone

Silicones

non ionic surfactants eg brij 36T

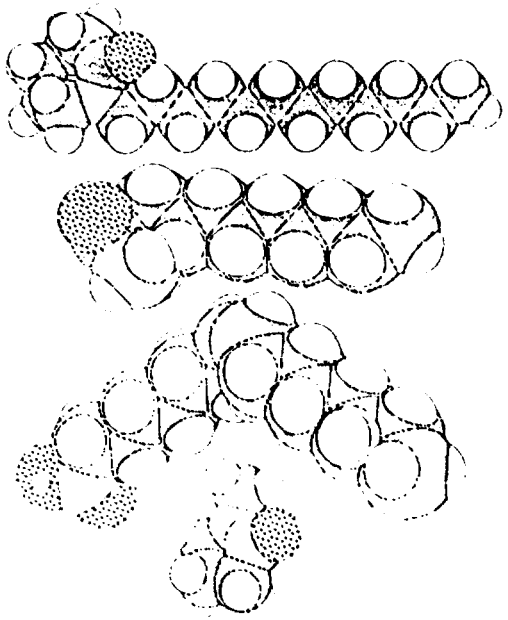
ionic surfactants

oleic acid

terpenes

Transcutol

molecular graphics & solubility parameters



shapes and polarity important determinants in how enhancers interact with lipids, solubility parameters of the solvent type enhancers will show how they may favourably modify skin lipid properties to enhance drug solubility

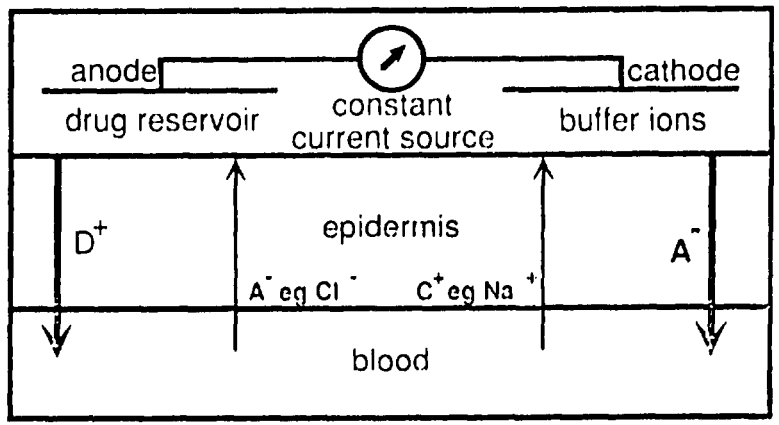
CARDIFF

physical enhancement

iontophoresis and phonophoresis

iontophoresis, application of electric current to skin (<1 mA sq. cm, voltage ~10V.

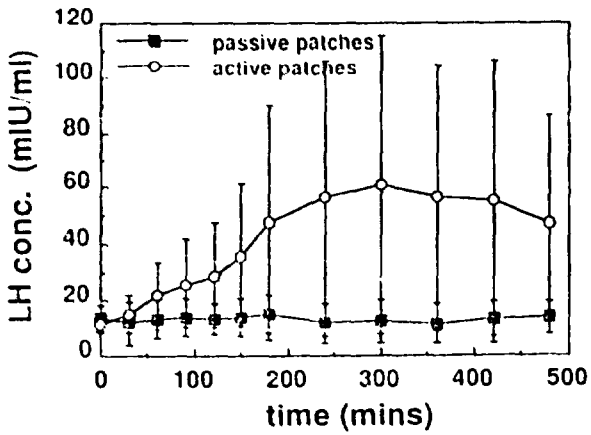
Mechanism



CARDIFF

iontophoresis

delivery of leuprolide, nonapeptide (1209D). luteinising hormone releasing hormone (LHRH) analogue. Physicochemical properties suggest very small unenhanced flux across skin. Blood levels of LH determined with & without iontophoresis (70 cm2, 9V, 0.2mA)



Meyer et al., Clin. Pharm. Ther., 44 (1988) 607-612.

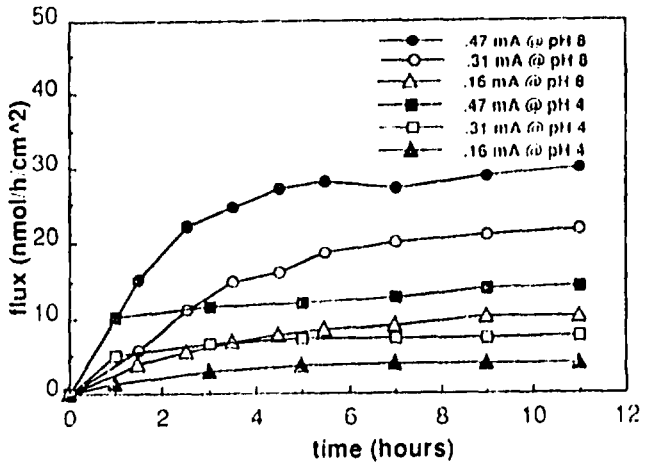
CARDIFF

iontophoresis

patient acceptability
- mild tingling
- slight erythema

acceptability to regulatory authorities
- damage to skin

patient control
- effect of current (thyrotropin releasing hormone (TRH)



both ionized &non ionized drug have enhanced penetration - electroosmosis

Burnette et al., In Transdermal drug delivery, Eds Hadgraft & Guy, Marcel Dekker (1989) 247-291.

CARDIFF

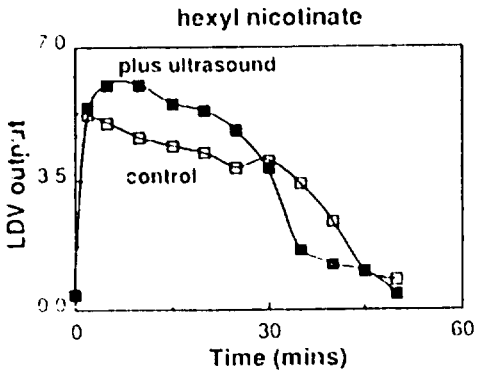
phonophoresis i

application of ultrsound to skin, may act by supplying energy to disorder skin lipids.

steroids

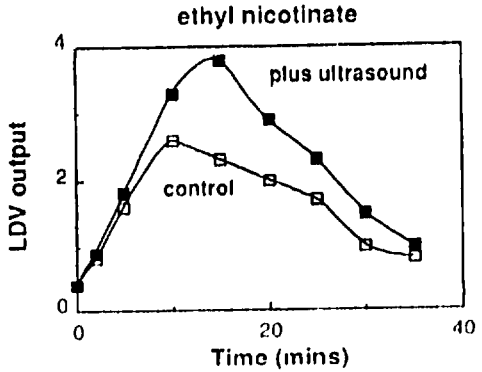
local anaesthetics

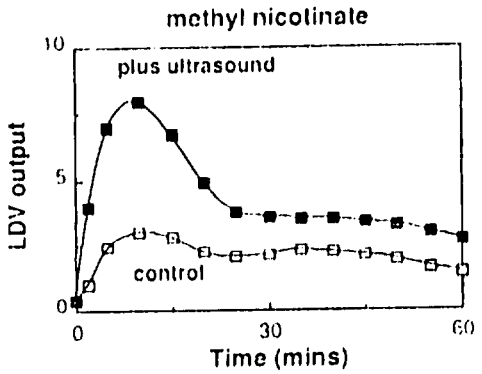
esters of nicotinic acid



Benson et al., Pharm. Res. (1991) 8, (2), 204 - 209

phonophoresis ii





Dr. Tony L. Whateley

MICROENCAPSULATION AND MICROSPHERES FOR DRUG DELIVERY

T. L. Whateley

Department of Pharmaceutical Sciences

University of Strathclyde

Glasgow, G1 1XW

CONTENTS

INTRODUCTION

Two recent books relating to microencapsulation, microspheres and nanoparticles in pharmaceutical, medical and biomedical applications have been published in 1992:

"Microcapsules and Nanoparticles in Medicine and Pharmacy"

M. Donbrow, CRC Press Inc, 1992

and "Microencapsulation of Drugs"

T. L. Whateley (ed.) Harwood Academic Publishers, UK, 1992.

These two books supplement and bring up to date the books:

"Microencapsulation and Related Processes"

P. B. Deasy, Marcel Dekker, 1984.

and "Biomedical Applications of Microencapsulation"

F. Lim (ed.) CRC Press, Inc., 1984.

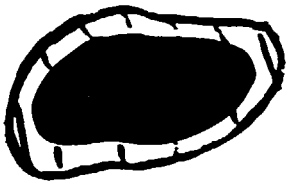
Jalil and Nixon (1992) have recently reviewed the microencapsulation of drugs with biodegradable materials.

Microcapsules and microspheres can be described as small particles (in the 1-500μm size range) for use as carriers of drugs and other therapeutic agents. The term 'microcapsule' has become the term for systems having a definite coating or shell encapsulating the contents in the form of a particle. The term 'microsphere' describes a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles. The distinction between the two terms is illustrated in Figure 1, using mitomycin C, a cytoloxic agent, as an example.

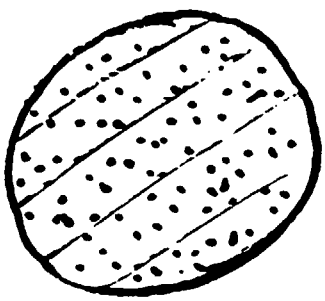
Microcapsules tend to be difficult to prepare in the lower end of the size range indicated above, due to their methods of preparation : hence, they are restricted in the routes of administration to which they are suitable. Microcapsules have wide application for the oral delivery of drugs for the following reasons:-

MICROENCAPSULATED MITOMYCIN C

Drug particles coated with ethyl cellulose



MICROSPHERES CONTAINING CYTOTOXIC (& OTHER DRUGS)



MONOLITHIC

UNIFORM DISTRIBUTION (Molecular dispersion or dispersion of crystals)

FIGURE 1

(a) sustained release is possible; the coating acts as a barrier to drug release. Various mechanisms of release are possible.

(b) taste masking (e.g. for chloroquine, an anti-malarial drug).

(c) protection of drug contents from moisture and/or oxygen.

(d) to allow the combination of incompatible constituents by the protection of one or more component by microencapsulation.

This lecture will concentrate on microspheres, which can be prepared in a wide range of sizes e.g. from nanometres (nanospheres) up to hundreds of micrometres (microspheres). In particular, there is much interest currently in the use of biodegradable polymers for the preparation of microspheres containing a wide range of therapeutic agents. Biodegradable microspheres can, of course, be used for parenteral administration and there is now on the market microsphere preparations for sub-cutaneous administration. Given the wide range of sizes possible, such biodegradable microspheres can be administered intravenously, intra-arterially, sub-cutaneously and intra-muscularly (as well as by the oral route where limited uptake is possible for specific applications).

As discussed under 'Biodegradable Polymers for Drug Delivery' the polymeric system of choice is currently poly(lactic acid) and the co-polymer poly(lactic-co-glycolic acid). The properties, degradation, drug release of these systems has been previously dicsussed.

Some current applications of biodegradable microspheres will be discussed followed by a detailed discussion of methods available for their preparation, with emphasis on the microencapsulation of protein and polypeptide drugs.

Applications of Drug Loaded Biodegradable Microspheres

1. Sustained Release of Polypeptides/Proteins from Sub-Cutaneous Depot Injections

   The development of 'Zoladex', a once-a-month sub-cutaneous implant to deliver the polypeptide, goserelin, was the first drug delivery system based on the biodegradable poly(lactic-co-glycolic acid) (PLGA) polymers. A product, based on microspheres of

PLGA is also on the market, Prostap SR. This product consists of microspheres of mean size 20μm prepared from a polymer of molecular weight 14,000. The method used in their preparation, involving a w/o/w multiple emulsion solvent evaporation process, will be described later in this paper. The injection vehicle for the microspheres contains carboxy methyl cellulose (CMC) in order to increase the viscosity of the medium and to ensure that the microspheres remain in suspension during the administration. A 23 gauge needle can be used for the once-a-month sub-cutaneous injection rather than the larger 16 gauge needle needed for the Zoladex implant, which can necessitate the use of local anaesthetic.

2. Delivery and Targeting by Intra-venous Injection

The delivery and targeting of drugs using microspheres and nanoparticles has been investigated extensively by Davis and Illum (e.g. 1989). By modification of the surface of the microspheres, by, for example, adsorption of non-ionic block co-polymeric surfactants (poloxamers and poloxamines) it has been possible to avoid the normal uptake in the liver by the mononuclear phagocyte system (MPS). Circulating depot release systems should be possible using biodegradable microspheres. The targeting of drugs using microspheres is illustrated in Figure 2 with the use of the example of targeting to the liver.

FIGURE 2 ***TARGETING OF DRUGS TO LIVER***

1st ORDER TARGETING	:	*to organ* *e.g. i/a microspheres* *20-80μm* *i/v colloidal particles* *0.1-2μm*
2nd ORDER TARGETING	:	*to tumour* *e.g. i/a microspheres plus angiotensin II*
3rd ORDER TARGETING	:	*selective uptake by tumour cells*

3. Targeting to Tumours by Intra-arterial Administration

The concept underlying regional chemotherapy is an attempt to increase the therapeutic index of the drug by increasing the concentration of drug within the organ harbouring the metastatic deposits with decreased concentration of cytotoxic drug in the systemic vascular compartment.

Microspheres in the size range 20-50μm will be trapped in the capillary bed of the liver following intra-hepatic arterial administration. Second order targeting (i.e. to the tumour(s) rather than to the whole organ) can be achieved by the concurrent administration of angiotensin II (AT II), a vasoconstrictor, which restricts arterial flow to the normal liver but does not affect the capillary blood flow network of the tumour. Delivery of microspheres loaded with mitomycin C (MMC) in this manner has three advantages:

(1) Systemic levels are low, with consequent reduction in side effects.

(2) The sustained release of MMC from the trapped microspheres extends the timescale of exposure of the tumour cells to cytotoxic drug. The embolic effect of the microspheres increases retention of drug at the site of release. This whole process has been termed 'chemoembolisation'.

(3) In the case of a cytotoxic drug such as MMC, which requires bioreduction for activation, the reduced oxygen levels consequent on embolism by the microspheres may enhance the therapeutic efficacy of MMC.

With MMC microencapsulated with ethyl cellulose we have shown that peak plasma levels could be reduced from 812 (±423) ng/ml for free MMC in solution to 80 (± 75) ng/ml for microencapsulated MMC administered as a bolus via the hepatic artery. A Phase I clinical trial showed that the dose of microencapsulated MMC could be increased to 40mg without toxicity. (Goldberg *et al*, 1991; Anderson *et al*, 1991; Whateley *et al*, 1992). However, ethyl cellulose is not biodegradable and we

have been developing methods for the incorporation of MMC into microspheres of the biodegradable and acceptable poly(lactic-co-glycolic acid). Our experience with this system will be used to illustrate the sections of this lecture on the preparation of PLGA microspheres.

4. Delivery of Cytotoxic Drugs to Brain Tumours

The use of cytotoxic drugs to treat malignant brain tumours is limited by drug exclusion from the brain by the blood-brain-barrier. Chemotherapy is limited to a few drugs with high lipid:water partition coefficients, such as the nitrosourea, carmustine (BCNU). Gliomas do not tend to metastasise outwith the CNS and therefore lend themselves to a regional chemotherapy approach where a high drug concentration is generated at the tumour site.

There has been work on the use of BCNU sustained release implants using the surface eroding, biodegradable polymer bis(p-carboxyphenoxy) propane-sebacic acid, a hydrophobic polyanhidride. BCNU is rapidly degraded in aqueous media and is protected within the surface eroding, hydrophobic polyanhydride (Brem, 1990, 1990a; Domb *et al*, 1991).

We are developing PLGA microspheres loaded with the stable, water soluble drug, carboplatin. The biodegradable and acceptable PLGA is suitable for this application with carboplatin and there is the advantage that the hydrophilic cytotoxic drug will not pass the blood-brain-barrier into the systemic circulation.

5. Oral Delivery of Vaccines

There is increasing evidence that small microspheres (<1μm) can be absorbed from the gastro-intestinal tract to a limited extent, probably via the Peyer's patches of the intestinal walls. Possibly only 1 particle on 10^5 is absorbed, making the mechanism unattractive for drug delivery, in general. However, such an uptake can be adequate to generate an immune response.

Some recent examples of the development of oral vaccines based on microspheres include the following:

Ovalbumin (as a model system); O'Hagen *et al*, 1992

Malaria; Bathurst *et al*, 1992

Staphylococcal Enterotoxin B Toxoid; Gilley *et al*, 1992 and Staas *et al*, 1991.

Preparation of Microspheres of Poly(lactic-co-glycolic acid)

A number of microsphere properties have to be otpimised:

(1) Mean size and size distribution

(2) Surface properties

Re-suspension in an aqueous vehicle for injection without aggregation or sedimentation must be possible: for this a mean size <50μm is normally required together with hydrophilic surface properties.

(3) Drug loading

(4) Drug release rate

(5) Degradation rate of matrix

Other aspects such as sterility, apyrogenicity and residual solvent content (e.g. CH_2Cl_2) clearly have also to be satisfactory.

The discussion of the various methods of preparing drug loaded microspheres of PLGA will be illustrated by our experience in attempts to prepare microspheres in the size range 30-50μm loaded with the cytotoxic agent mitomycin C.

Emulsion-Solvent Evaporation Methods

These are the most commonly used methods : there are several variations of the basic oil-in-water method which will be discussed first :

Oil-in-Water Method

Figure 3 illustrates the basis of this process. The inner, oil phase of the emulsion consists of dichloromethane, CH_2Cl_2, in which the PLGA is dissolved together with

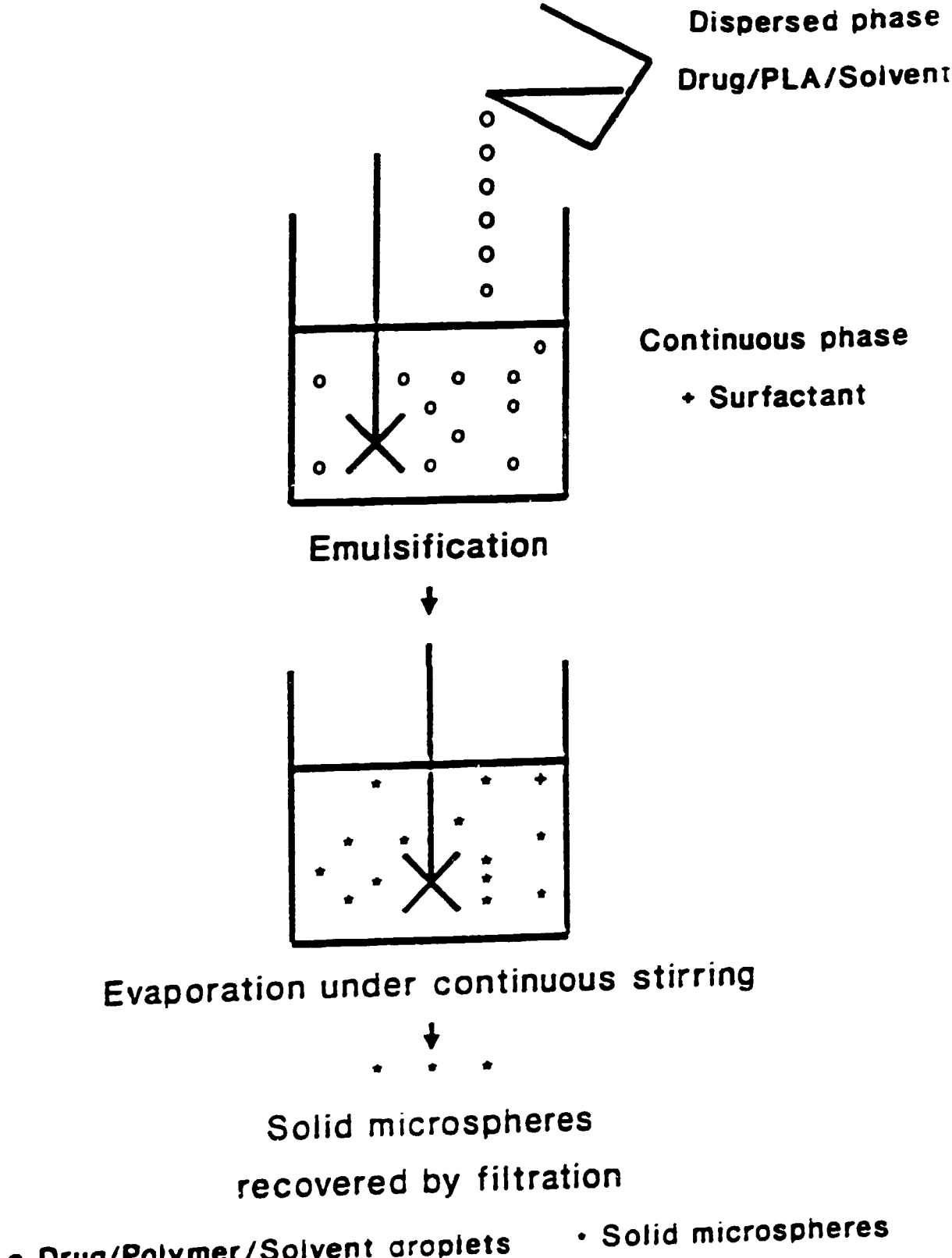

Dispersed phase
Drug/PLA/Solvent
Continuous phase
+ Surfactant
Emulsification
Evaporation under continuous stirring
Solid microspheres
recovered by filtration
o Drug/Polymer/Solvent droplets
• Solid microspheres

FIGURE 3

the drug to be incorporated into the microspheres. The emulsion is formed in water containing, typically, poly(vinyl alcohol) (PVA) as stabiliser for the formed microspheres.

The oil-in-water method has the advantages :

(a) efficient incorporation of lipophilic drugs

(b) wide-range of sizes readily prepared e.g. from large (100μm) to nanoparticle size (<1μm), essentially controlled by stirring rate and conditions.

(c) microspheres have hydrophilic surface properties which allows ready re-suspension without aggregation.

However, this method has the disadvantage that the incorporation of water soluble drugs is very low due to the partitioning of the drug into the large external aqueous phase of the emulsion. The water soluble drug will not be soluble in the inner CH_2Cl_2 phase and will be there as a suspension of drug particles : sonication has been used to improve this suspension process.

Cisplatin has been successfully incorporated into PLGA microspheres (100-200μm diameter) using the oil-in-water method with the external aqueous phase being saturated with cisplatin to reduce partitioning of the drug from the CH_2Cl_2/polymer phase.

We have used a similar approach to prepare PLGA microspheres (30-50μm diameter) containing mitomycin C with loadings of up to 25% for intra-arterial targeting to liver metastases from colorectal tumours. The rate of release of mitomycin C increased rapidly with drug loading e.g. the time for 50% release was 9 hr and 50 hr for drug loadings of 25% and 12% respectively. In these systems the drug is dispersed in the microsphere matrix as discrete crystals and the higher release rate for the higher loaded microspheres can be ascribed to the fact that an interconnecting network of crystals exists at high loadings allowing connected

pathways to form as the crystals dissolve. At lower drug loadings, the crystals in the interior are isolated and are released only on massive degradative breakdown of the microsphere matrix. This mechanism of release is considered in more detail under the discussion of drug release from biodegradable polymers.

This o/w preparative method for water-soluble drugs is sensitive to a number of variables, see Table 1. In addition we have found that batch-to-batch variation in the PLGA polymer makes it difficult to reproduce mitomycin C loaded microspheres.

The incorporation of the poloxamer, Pluronic L101, into the CH_2Cl_2 oil phase at the 10% level was effective in improving the incorporation efficiency for mitomycin C microspheres, possibly by a solubilisation effect. However, residual droplets of the Pluronic L101 surfactant remain in the final product microspheres.

TABLE 1

Variables in the o/w Emulsion-Solvent Evaporation Process for the Incorporation of Water-Soluble Drugs in PLGA Microspheres

Phase volume of organic phase

Phase volume of aqueous phase

Loading of polymer in organic phase

Loading of drug in organic phase

Presence of oil-soluble surfactant in organic phase (e.g. Pluronic L101)

Ultrasonication of organic phase

Stabiliser/surfactant in aqueous phase

Saturation level of drug in aqueous phase

Stirring method and rate

Jalil and Nixon (1990) also studied the variables for the o/w process for both poly(L-lactic acid) and poly(DL-lactic acid) for the water-soluble drug, phenobarbitone and compared the o/w process with an oil-in-oil method, which is now described.

Oil-in-Oil Method

In order to be able to incorporate water soluble drugs efficiently, the use of acetonitrile as the inner 'oil' phase was developed. The external phase is liquid paraffin containing a surfactant (e.g. Span 40) and solvent evaporation takes place at, typically, 55°C over a period of 4 hr.

A serious drawback to the o/o method is the difficulty of obtaining small microspheres (e.g. <50μm). This method had been used by Tsai *et al* (1968) to prepare poly(lactic acid) microspheres containing mitomycin C; however, these microspheres were of size ca 95μm. Microspheres of these sizes are difficult to administer clinically via an in-dwelling hepatic arterial catheter. As this oil-in-oil method is well-suited to the incorporation of water soluble drugs we have attempted to prepare smaller PLA microspheres (e.g. 20-50μm) containing mitomycin C by this method.

Jalil and Nixon (1990) made an extensive and thorough study of the factors influencing the preparation and properties of microspheres of poly(L-lactic acid) and the incorporation of a model, water-soluble drug, phenobarbitone. Both the oil-in-oil and oil-in-water emulsion solvent evaporation processes were investigated. Although high loadings of the drug were obtained using the oil-in-oil method, the microspheres were large.

In their studies on controlling microsphere size in the o/o method, Jalil and Nixon (1990) found that increased stirring rate and increased surfactant concentration (in the external light light paraffin phase of the emulsion) reduced the size of the

microspheres. A range of Spans (sorbitan esters of fatty acids) and Brijs (polyoxyethylene ethers of fatty acids) were investigated (see Figure 4). There was no correlation between the HLB of the emulsifier and microsphere size. The packing of the emulsifier at the interface appeared to affect microsphere size: close packed straight chain saturated fatty acid containing emulsifiers produced smaller microspheres than loose packed emulsifiers containing, for example, three fatty acid chains or a cis-double bond.

Span 40 which was found to give the smallest microspheres, at 2% concentration in light liquid paraffin was used in our studies and a variety of stirring methods and speeds investigated, including the use of a Silverson stirrer. Using the Silverson stirrer at 55°C resulted in microspheres of diameter 60-70μm.

The problem of obtaining small (i.e. <50μm) microspheres from this o/o method was examined by Jalil and Nixon (1990) who found that initially (i.e. 2 mins. after the mixing of the two phases under stirring) small (i.e. << 50μm) droplets of the acetonitrile + polymer phase were observed under the microscope. However, after 8 mins. coalescence had occurred and only large (i.e. < 50μm) droplets were present. We have observed this same phenomenon: it appears that as the solvent (acetonitrile) begins to evaporate out of the droplets, with consequent increase in polymer concentration, coalescence occurs and it seems impossible to obtain conditions of stirring and concentration/nature of surfactant emulsifier to prevent this coalescence during evaporation of the acetonitrile polymer solvent. We are currently investigating this problem further.

A further problem with PLGA microspheres prepared by this oil-in-oil procedure is that they tend to aggregate when re-suspended in aqueous vehicles: this will be due to the hydrophobic nature of the surface from the o/o emulsion procedure with a lack of any hydrophilic stabilising agent (a function served by the poly(vinylalcohol) in the

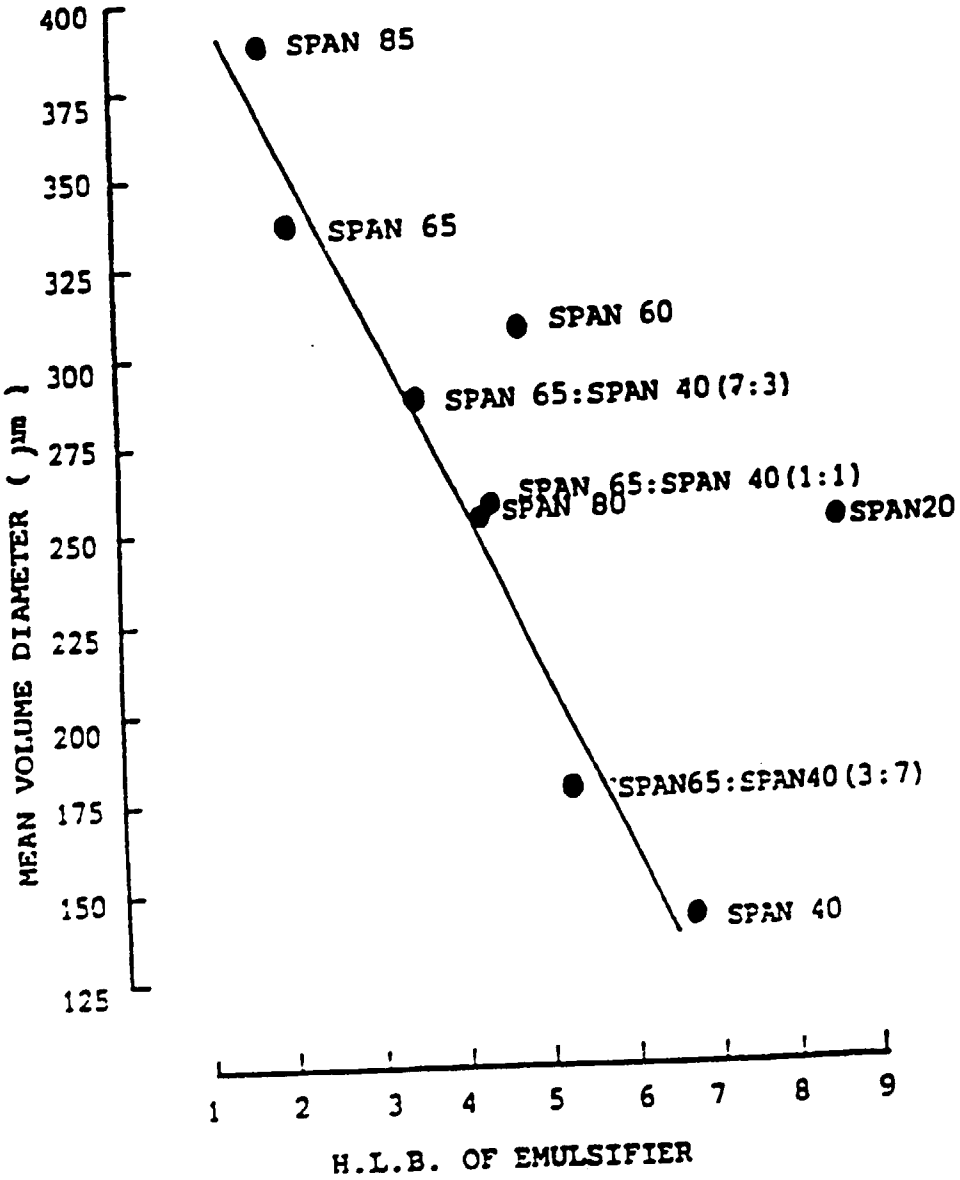

400
375
350
325
300
275
250
225
200
175
150
125
MEAN VOLUME DIAMETER (μm)
SPAN 85
SPAN 65
SPAN 60
SPAN 65:SPAN 40(7:3)
SPAN 65:SPAN 40(1:1)
SPAN 80
SPAN20
SPAN65:SPAN40(3:7)
SPAN 40
1
2
3
4
5
6
7
8
9
H.L.B. OF EMULSIFIER

FIGURE 4

oil-in-water method).

The release rate of phenobarbitone has been reported to increase rapidly with temperature of evaporation i.e. rate of removal of solvent influences the porosity.

Water-in-Oil-in-Water Multiple Emulsion Method

For drugs which are very soluble in water (e.g. the protein and polypeptide drugs) a multiple emulsion method has proved to be very effective. Typically the polypeptide in water (e.g. 0.5ml) is dispersed into PLGA in dichloromethane (e.g. 10ml) to give a water-in-oil emulsion. This w/o emulsion is then dispersed into an aqueous phase (e.g. 200ml) containing PVA and the dichloromethane allowed to evaporate. This process is illustrated in Figure 5. This process overcomes the insolubility of water-soluble drugs in CH_2Cl_2 and has been used commercially for the preparation of microspheres containing LHRH analogues for s/c injection. The possible disadvantages are that denaturation of a protein drug can occur at the H_2O/CH_2Cl_2 interface and that there may be residual water remaining in the microspheres affecting the rate of degradation and stability of the product.

Multiphase Microspheres

The multiple emulsion approach has been taken a step further recently to have a system with 4 phases: a w/o/'o'/o system. The three steps in such a procedure are:

1. An aqueous solution of the drug is dispersed in soybean oil (w/o).
2. This w/o emulsion is dispersed into acetonitrile plus polymer (w/o/'o')
3. This w/o/'o' emulsion is dispersed into liquid paraffin (w/o/'o'/o) and the acetonitrile allowed to evaporate.

The advantage of this procedure is that the drug (e.g. a protein) does not come into contact with a dichloromethane/water interface. Large (200μm+) microspheres are obtained (Iwata and McGinity *et al.* 1992). Figure 6 shows the difference between a multiphase microsphere and a normal monolithic microsphere.

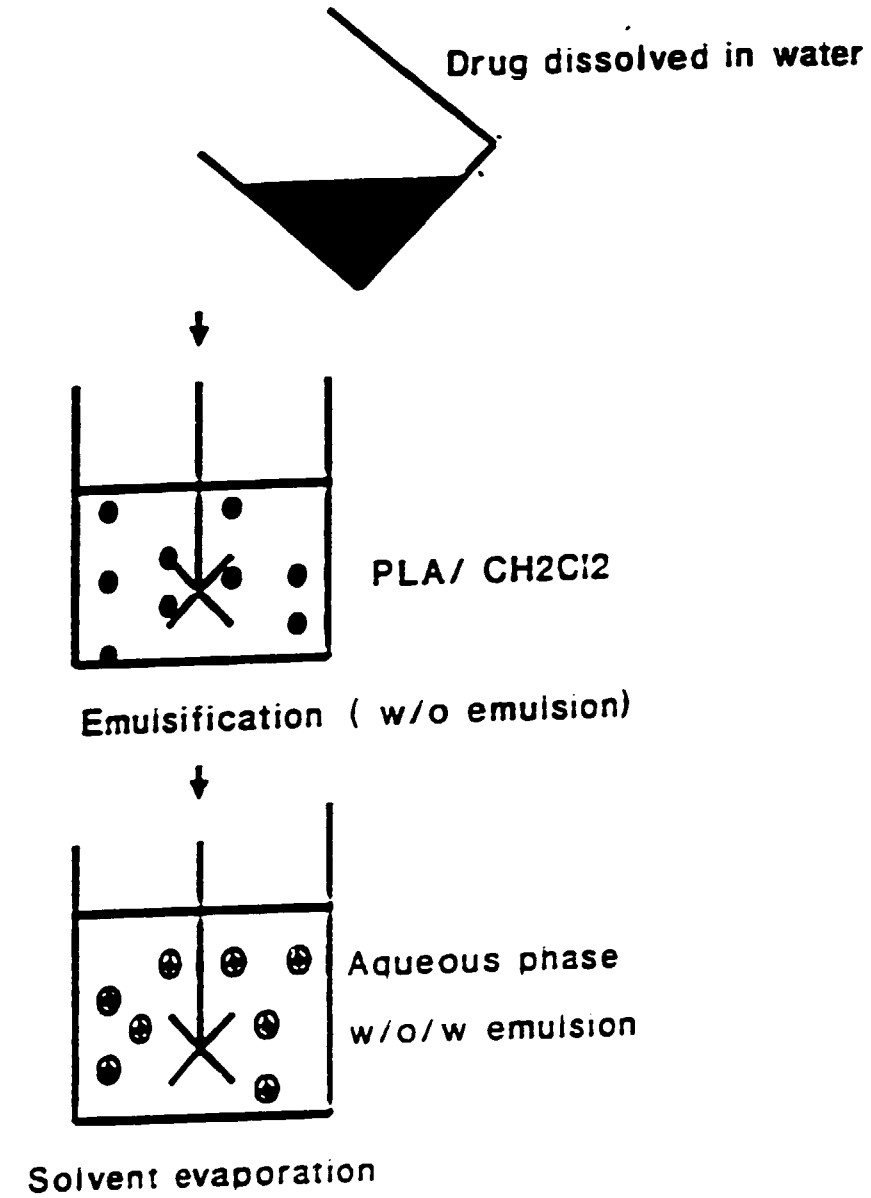
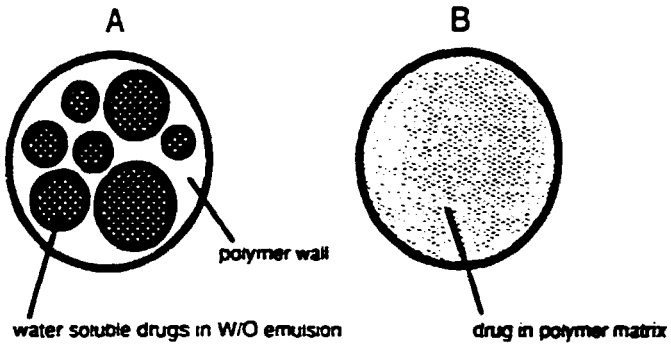

Drug dissolved in water
PLA/ CH2Cl2
Emulsification (w/o emulsion)
Aqueous phase
w/o/w emulsion
Solvent evaporation
microsphere formation
Solid microspheres
recovered by filtration

FIGURE 5



Schematic features of a multi-phase microsphere (A)

FIGURE 6

Coacervation (Phase Separation)

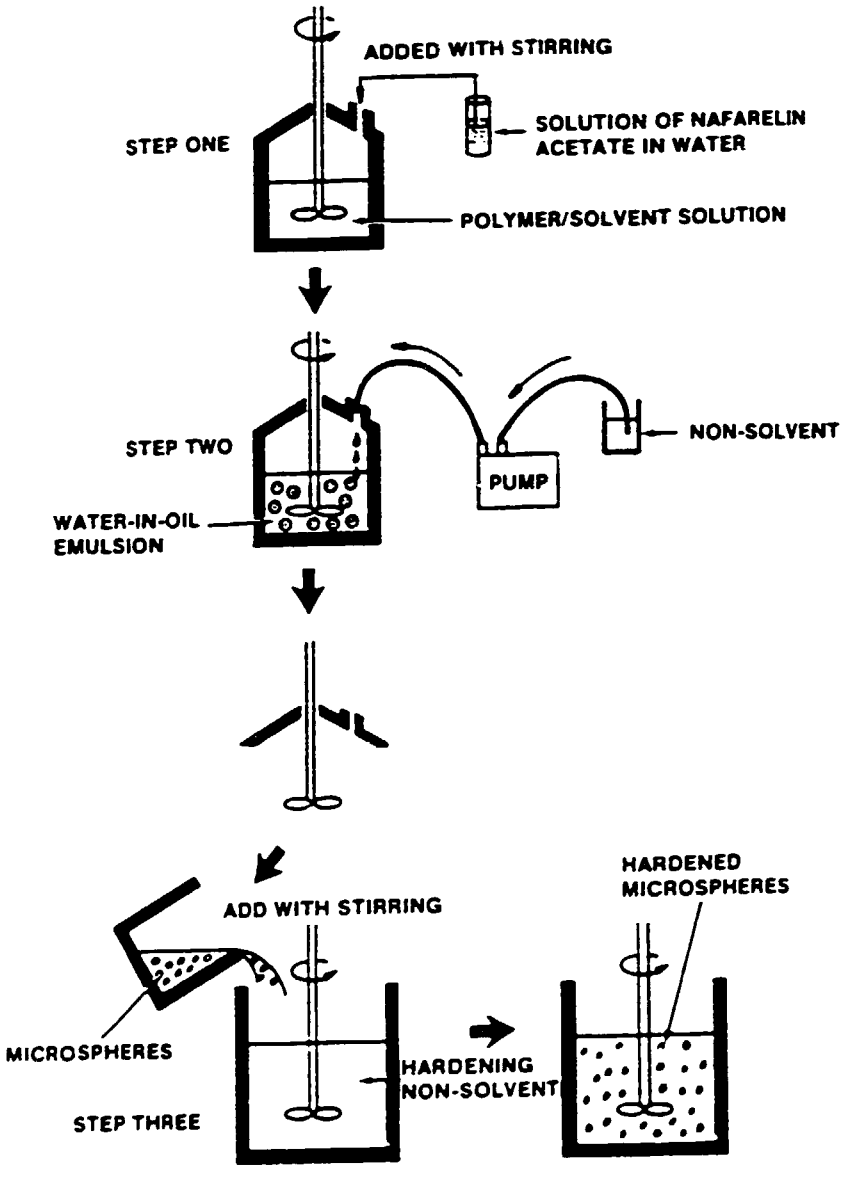
Phase separation of PLGA by non-solvent addition (coacervation) can be brought about by the addition of silicone oil to a solution of PLGA in dichloromethane (see Figure 7). The triangular phase diagram (Figure 8) has been established giving the information for the formation of a stable coacervate droplet phase. Typically, microspheres can be prepared with 3.8% poly(L-lactide) in CH_2Cl_2 plus 10% BSA (relative to polymer mass). At 12°C the addition of 47% ($^{W}/w$) silicone oil (relative to total mass) results in coacervate droplets containing drug particles which can be solidified and hardened in octamethylcyclotetrasiloxane or n-heptane. Encapsulation efficiency was 80% with 95% of microspheres less than 70μm.

This method has advantages for water soluble drugs. However, batch to batch variation of PLGA has caused problems: both the coacervation process and release rate profile are affected by the presence of PLGA oligomers.

An aqueous solution of the drug can be used to form a w/o emulsion in CH_2Cl_2 plus polymer: the non-solvent is then added, precipitating the polymer around the water/drug droplets of the emulsion. This approach has been used to prepare microspheres containing polypeptide drugs for monthly s/c drug delivery.

Other Methods of Preparing PLGA Microspheres

A freeze-drying technique for the preparation of microspheres containing the hormone calcitonin has been described. A mixture of calcitonin and poly(glycolide)



Phase Separation Microencapsulation

FIGURE 7

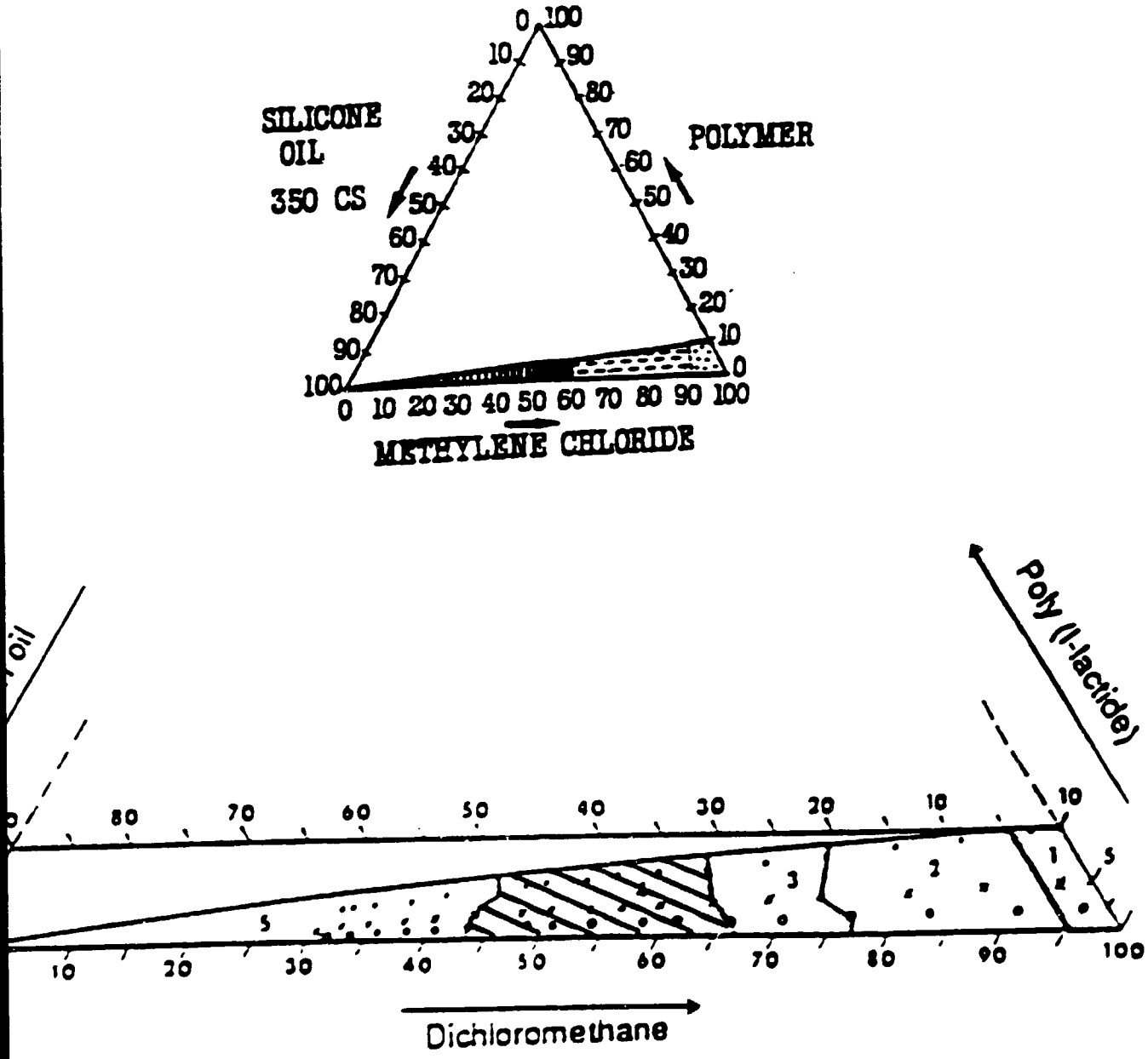

SILICONE
OIL
350 CS
POLYMER
METHYLENE CHLORIDE
Poly (l-lactide)
Dichloromethane
1
2
3
5

FIGURE 8

in hexafluoroacetone is dispersed in carbon tetrachloride: this suspension is freeze-dried and washed with CCl_4. Loadings of up to 7.5% calcitonin were obtained with 90% of microspheres under 5μm in diameter (Lee *et al*, 1990).

A novel method involves spraying a suspension of lyophilised protein particles (1-5μm) suspended in a PLA/CH_2Cl_2 solution through an ultrasonic nozzle into liquid nitrogen covering some ethanol. The liquid nitrogen is allowed to evaporate and the CH_2Cl_2 is taken into the liquid ethanol (see Figure 9). Encapsulation efficiences of 95% are reported with sizes of 50-60μm. Some enzymes have been microencapsulated without loss of activity e.g. ribonuclease and horse radish peroxidase (Khan *et al*, 1992).

An interesting hot-melt method was described by Wichert and Rohdewald (1990) and this is illustrated in Figure 10. An advantage is that contact of active agent with chlorinated solvents is avoided.

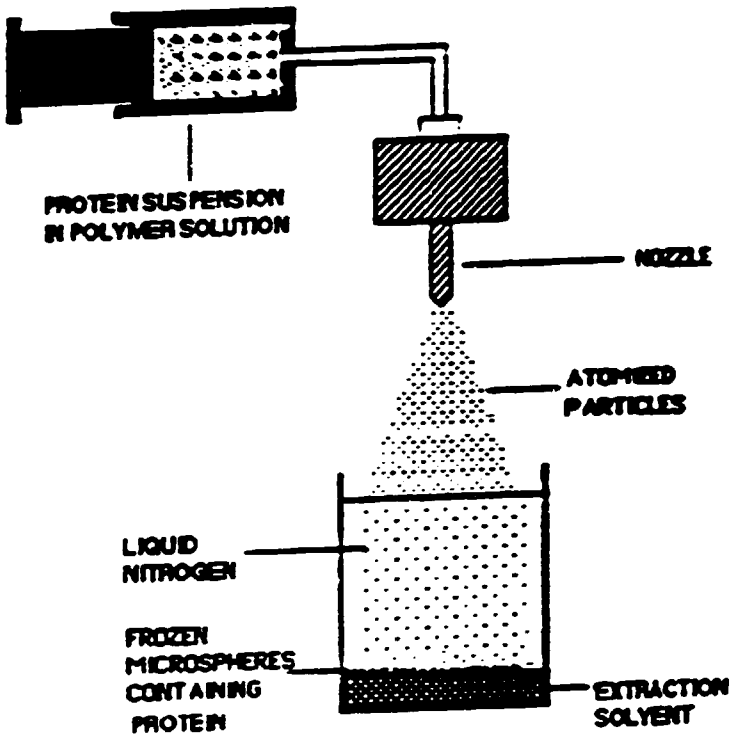
Release of Drugs from PLGA Microspheres

The release of drugs from PLGA materials has been considered under the lecture on Biodegradable Polymers for Drug Delivery. Similar factors and mechanisms clearly apply also to microsphere systems of PLGA.

The additional factor of the effect of particle size on drug release is illustrated in Figure 11, which shows the expected increase in release rate with decreasing size for PLA microspheres containing butamben.

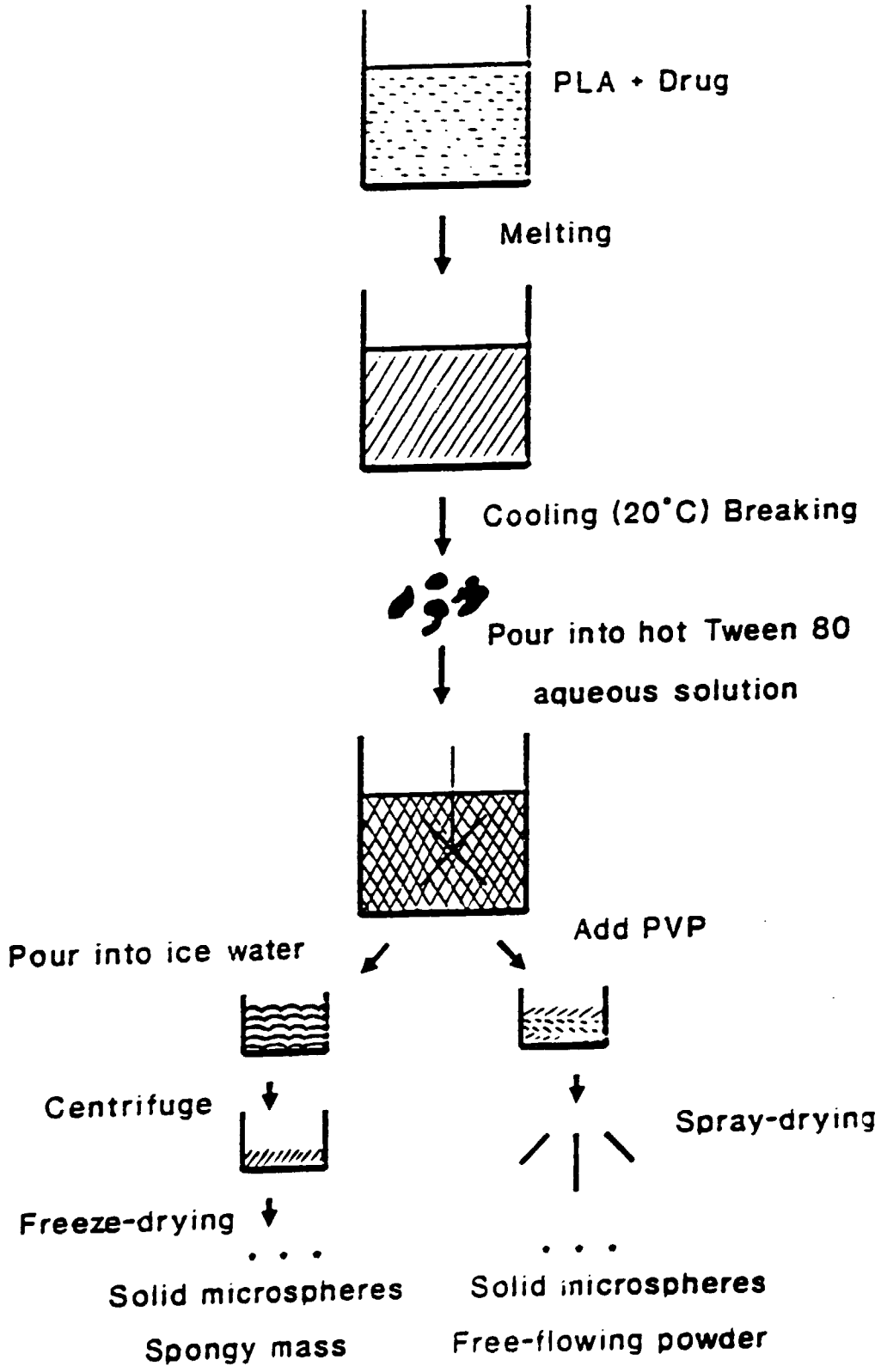
The effect of polymer molecular weight on the release of fluphenazine is clearly shown in Table 2 These results correlate with the increased rate of degradation of the lower molecular weight polymers, as discussed previously. It is interesting to note that the presence of acidic or basic drugs in PLGA matrices can increase the rate of degradation.

The effect of drug loading is also illustrated in Table 2; as discussed under drug



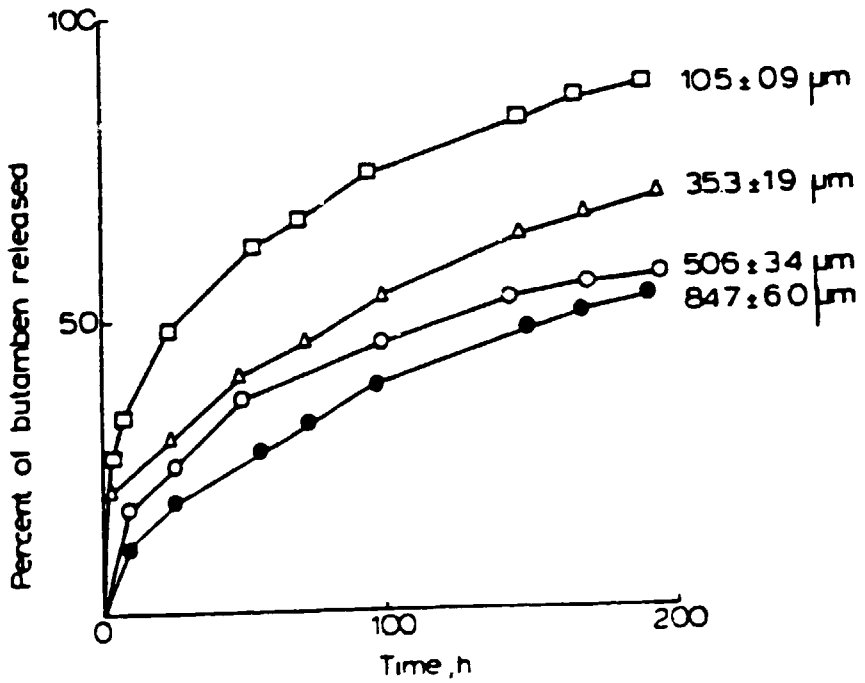
A schematic diagram showing the fabrication of microspheres.

FIGURE 9



Microsphere preparation by melting method (Wichert and Rohdewald 1990

FIGURE 10



Effect of size on release patterns from polylactic acid microspheres.

FIGURE 11

release from biodegradable polymers, higher drug loading, in general, results in a faster rate of release. The effect of polymer molecular weight is also clearly illustrated by the data (Ramtoola *et al*, 1992).

TABLE 2

FLUPHENAZINE IN POLY(D,L-LACTIDE) MICROSPHERES

POLYMER MOLECULAR WEIGHT	***TIME FOR 50% RELEASE***
2,000	***44 day***
16,000	***164 day***
109,000	***2.3% in 37 day***
FLUPHENAZINE LOADING	
10%	***48 day***
20%	***17 day***
30%	***5 day***

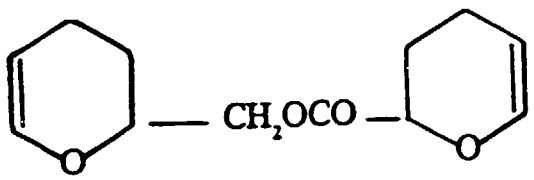
Recent Developments in Microencapsulation

Surface polymerisation of an adsorbed layer on a solid particle has recently been developed as a microencapsulation technique (Graham and Amer, 1992). The microencapsulation of potassium chloride will be taken as an example of the application of the method to provide a sustained release product.

Boron tri-fluoride etherate, as a catalyst in the cationic polymerisation process, is adsorbed onto potassium chloride crystals in heptane. The crystals activated with catalyst are separated and re-dispersed into heptane containing the monomer, for example, 3,4-dihydro-2H-pyranyl-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate), the structure of which is shown in Figure 12 together with the mechanism of polymerisation. Surface polymerisation of the monomer takes place following the

mechanism in Figure 12 and the potassium chloride crystals are microencapsulated by the polymer.

The release rate from the surface encapsulated potassium chloride was constant over a period of 30 minutes with a time for 50% release of 15 minutes. This technique has also been used to microencapsulate β-estradiol.



3,4-dihydro-2H-pyranyl-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate).

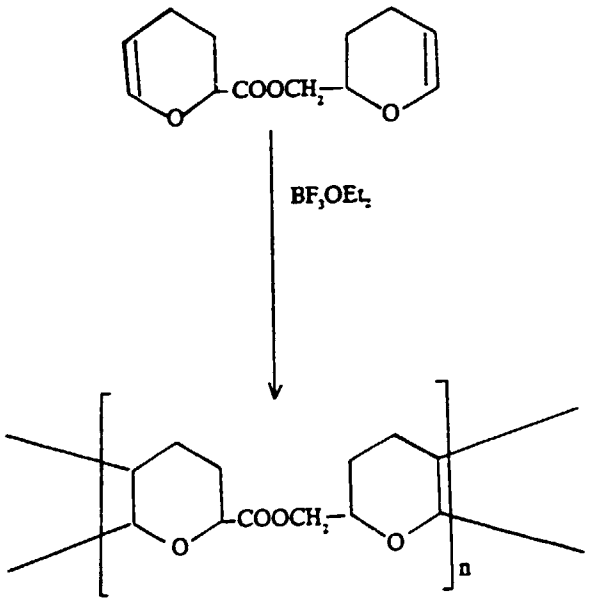


FIGURE 12

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