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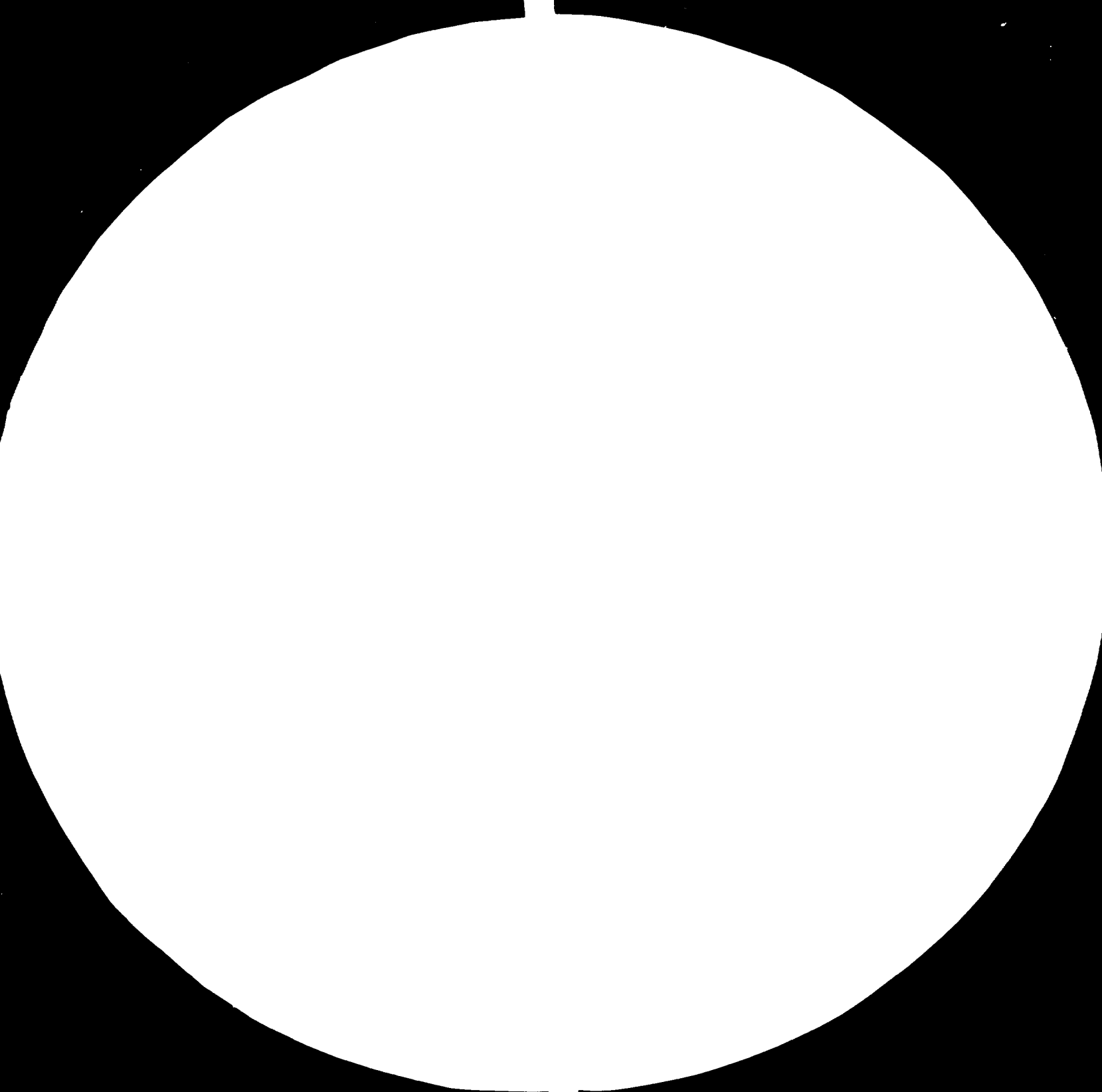
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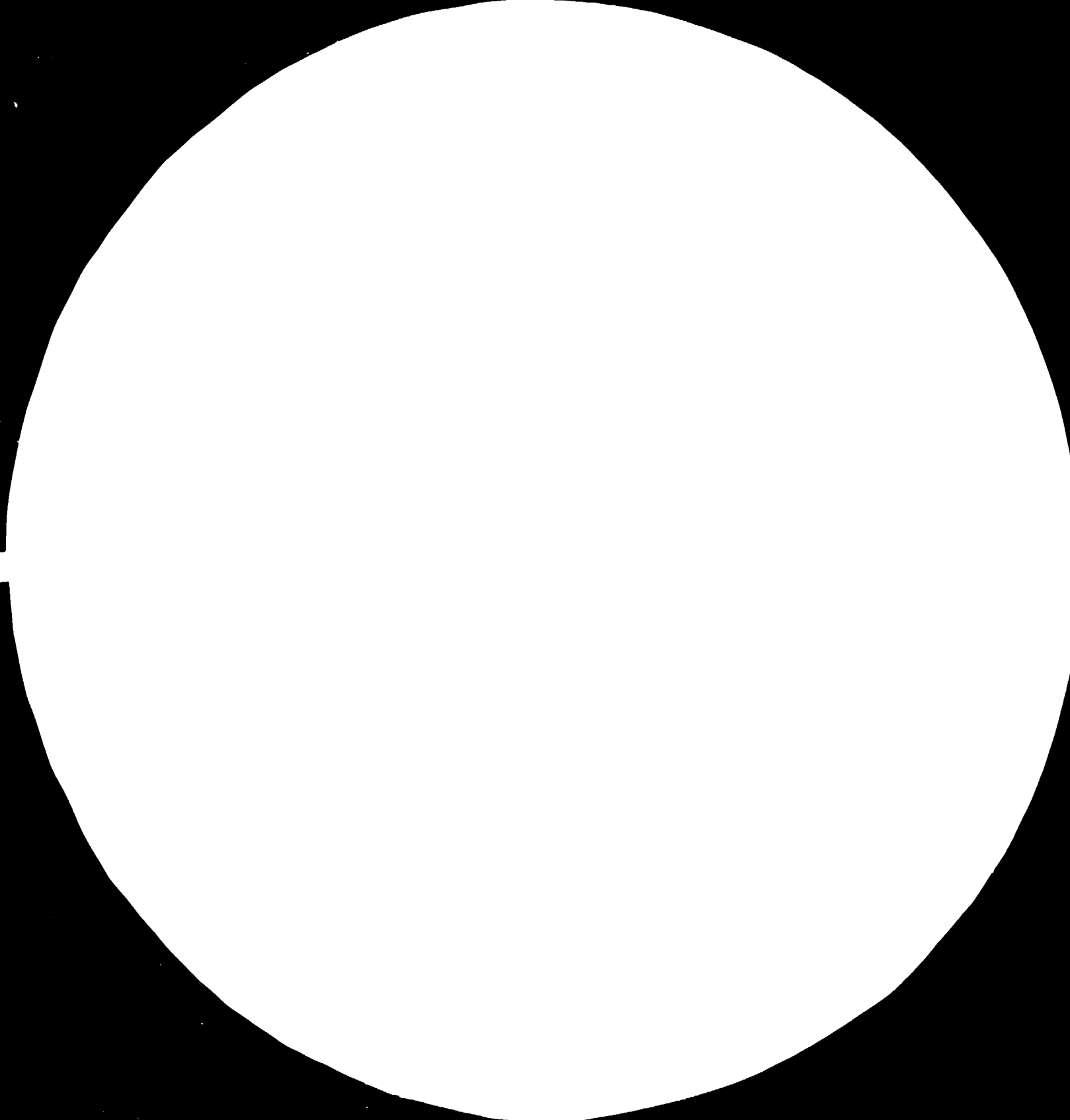
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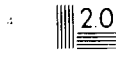
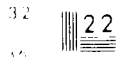
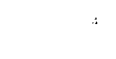
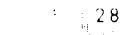
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August 1983
ENGLISH

PROSPECTS OF INDIGENOUS MEDICINAL PLANTS
IN THE DEVELOPMENT OF PHARMACEUTICAL INDUSTRY
IN THE DEVELOPING COUNTRIES

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1. INTRODUCTION

The developing regions of the world have experienced significant growth in population resulting in about 100 per cent increase in the last thirty years. The expansion in health care programmes in most of these regions could not be maintained to cope up with the increasing requirements. As a result, a large percentage of the people are deprived of the essential health services.

The constant increase in the requirements of pharmaceuticals in the developing countries, which remained deprived of industries related to manufacture of pharmaceuticals, and progressive trend for pharmaceuticals of synthetic origin in the West have adversely affected the growth of industries based upon medicinal plants. This situation has thus rendered the health care programmes in most of the developing countries almost entirely dependent on the foreign sources they can ill-afford under the prevailing economic conditions.

In order to improve upon the fast deteriorating health facilities in the economically depressed countries the development of the pharmaceutical industries in general and the industries based upon medicinal plants in particular are of vital importance and are expected to offer the following benefits:

- . the pharmaceutical products would be available more readily and at economical prices,
- . the drugs essential for country diseases profile will be produced locally ensuring constant and adequate supplies,
- . the naturally occurring medicinal plants will find economically beneficial exploitation supplementing the growth of appropriate industrial infrastructure and employment.

2. OBJECTIVES

The overall objective of this study is to explore the means to assist the developing countries in improving their national health services by development of pharmaceutical industry based upon locally available medicinal plants.

Following the substance of basic objective the study has been designed to incorporate salient features of techno-economic considerations related to the following specific objectives:

- 2.1 To analyse technological requirements and highlight the economic implications of the undertakings based on medicinal plants potentials in the developing countries.
- 2.2 To assess the potentials for appropriate pharmaceutical industry based upon the medicinal plants of established therapeutic value in order to improve availability of pharmaceuticals to the health services and to replace imports of finished products through substitution with local products.
- 2.3 To evaluate the possibilities for establishment/expansion of the processing industry for production of raw materials and therapeutic substances from indigenous medicinal plants in order to improve the economic exploitation of local resources.

3. HISTOKICAL BACKGROUND

Medicinal plants, the pioneer material in the development of apothecary and earliest known tools to combat disease, have to enjoyed the predominant role in the progress of pharmaceutical sciences till the onset of revolutionary progress in the field of synthetic chemistry and biological sciences and their entry in the era of modern therapeutics.

As recently as the period of World War II, the medicinal plants and the derived substances maintained a predominant share in the production of pharmaceuticals and even today, after the introduction of many synthetic substances in therapy, the utilization of medicinal plants is substantial. While some substances of plant origin have been replaced by synthetics, other new ones have found entry either as such or as important starting materials for synthetic production of compounds of significant therapeutic value.

It will not be justified to assume that the present declining trends in utilization of medicinal plants is solely because of substitution with synthetics. The fact remains that most of the medicinal plants or the therapeutic substances derived therefrom are still being used and some have even maintained their unmatched therapeutic supremacy.

There are many reasons for the apparent growth of the share of synthetics and undoubtedly a good deal of it has been at the expense of natural products. While, if not more, an equally important reason is the quest for new remedies, especially since the World War II, which have been predominantly steered towards synthetic approaches while attention towards products of plant origin remained minimal. Additionally, there is a full range of new synthetic drugs and alternates exclusively used either for those diseases for which the cures were hitherto unknown or for the diseases which could not be diagnosed and remained untreated in earlier periods.

Not underscoring the value of drugs of synthetic and biological origin, it is a fact that instances of disfavour/rejection of synthetic drugs are not infrequent. Many of these have had short spans of popularity, others remain on the list of questionable efficacy and therapeutic value and some have even

been declared dangerous to health and withdrawn. Natural therapeutic agents, barring losing preference for other reasons, have never been discredited or withdrawn from therapeutic use. Exclusion of therapeutic agents of plant origin from the official monographs is not so frequent and even after exclusion, such drug still retains the therapeutic status. In any case the official monographs are compiled according to the needs, practices and trading environments of the country of origin and any exclusion does not necessarily reflect on its therapeutic efficacy.

Tropical regions of the world produce a variety of botanical flora in abundance and many of the plant species possess substances of great therapeutic value. In the course of industrial development, these regions were unable to keep pace with the rate of progress in the West and consequently, like all other sectors of industry, the industries based on the medicinal plants were established almost exclusively in the West rendering the developing countries merely the suppliers of raw materials.

4. CLASSIFICATION OF THE PROCESSING TECHNOLOGIES OF MEDICINAL PLANTS

Depending upon the ultimate use of the medicinal plant, the methodology for the processing differ from one plant to the other involving varying degrees of technological skills from simple "pulverization of dried crude drug" to "isolation of pure substances" and "complex chemical modifications". The technologies involved under specific conditions, therefore, can be fairly distinctly classified into four levels depending upon the required know-how and the degree of skill and proficiency. (Fig. 1).

4.1 Process Level I - Crude drugs

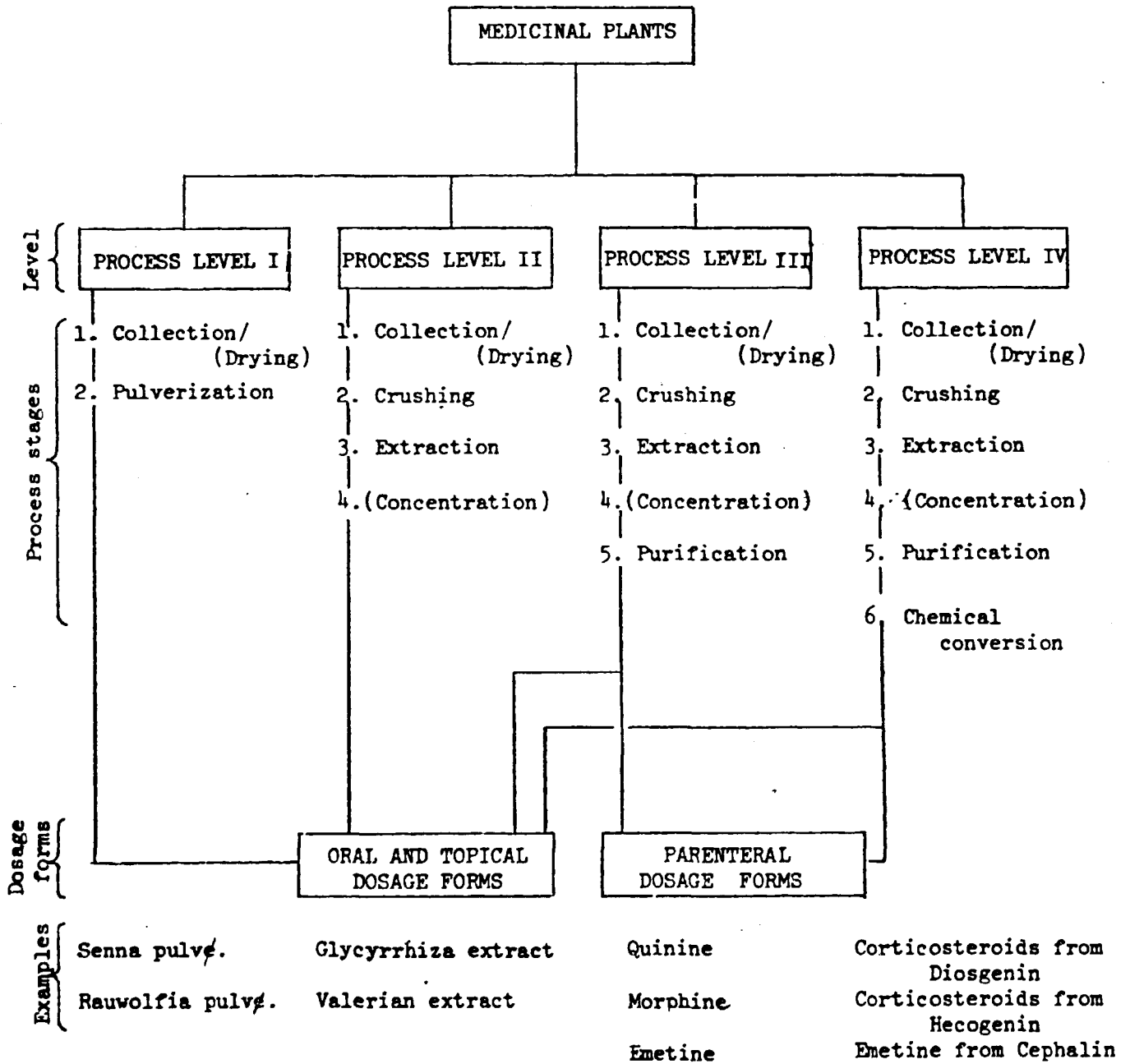
The crude drugs possessing adequate strength of the therapeutic substances can be employed directly as raw materials. For this purpose the dried crude drug is merely pulverized and after standardization of therapeutic potency can be formulated into the dosage form alone or in a desired combination. Senna leaves and Rauwolfia roots are two typical examples to illustrate the crude drugs in this category.

4.2 Process Level II - Total extracts

In order to obtain the therapeutic substances in relatively more concentrated state, the extraction of medicinal plants is the most widely employed technique. Added advantage of this process is that the material can be offered with a predetermined standard of therapeutic activity. The extraction techniques applied for multifareous purposes are summarized below:

- (i) galenicals including tinctures, spirits, liquid extracts etc. for use as components for prescription filling, such as tinctures of Ipecacuanha and Beladonna.
- (ii) extracts such as that of Glycyrrhiza for direct consumption or as raw material for manufacture of dosage form,
- (iii) extracts of crude drugs for isolation and production of pure therapeutic substances and raw materials for synthetic modifications such as quinine, diosgenin etc.

Figure I: Technology levels in processing of medicinal plants



4.3 Process Level III - Pure therapeutic substances

Production of pure substances from crude drugs necessarily call for well established process know-how and advanced level of operational skill. The technology is designed to isolate the substances in purest possible form required as raw materials for more refined dosage forms or as starting material for synthetic manufacture of therapeutically active substances. Production of alkaloids of Opium, Beladonna and Cinchona and cardiac glycosides of Digitalis are some examples where this level of technology is employed. Diosgenin and hecogenin, starting materials for synthesis of corticosteroids are also produced employing the same level of technology.

4.4 Process Level IV - Synthetically converted therapeutic substances

Highly advanced level of chemical technology is involved for production of certain therapeutic substances. At this level of technology a pharmacologically inactive substance derived from plant source is subjected to successive chemical conversions to obtain a therapeutically active substance. The chemical conversion technology has also been fruitfully applied in order to increase the activity of a therapeutic substance or to eliminate/reduce the side effects of an otherwise important substance.

5. TECHNO-ECONOMIC ANALYSIS OF THE PRODUCTION LEVEL OF DRUGS FROM MEDICINAL PLANTS

5.1 Crude medicinal plants

5.1.1 General considerations

In developing countries many species of medicinal plants are collected from the the natural habitat but the major commercial commodities are mostly derived from planned cultivation. Many of the plantations were originally organised in developing countries by or in collaboration with the ultimate consumers of the crude drugs based in the developed economies of West with ensured lifting of the crops but in recent decades this system has been greatly disrupted mostly because of lack of adequate management and marketing abilities.

In order to circumvent the present difficulties faced both by the growers and the consumers of medicinal plants, to regain the lost markets by ensuring supplies according to the requirements and thus to develop healthy competition of the crude drugs with the alternate sources by maintaining stable prices equally attractive both to the producers and consumers, the collection and cultivation of the medicinal plants in the developing countries will have to be developed in an organized and scientific way.

The techniques required for planned collection and cultivation of the crude drugs and their pre-treatment prior to shipment are being practiced since long in developing regions of the world where the crude drugs are found. What is required is the planning and good management through adequately trained and experienced personnel and guided by objective national policies evolving the desired commercial infrastructure leading to the following objectives:

- . sufficient quantities to meet the demand
- . guaranteed quality of the product in terms of authenticity and purity
- . stable market prices
- . ensuring regular and scheduled supplies.

5.1.2 Cultivation and/or collection

In a region of natural habitat or cultivation, assessment should be first made for the crop yield potential and if justified, plans should be developed for expansion of the crop propagation. These plans, however, must be cautiously drawn evaluating the market potential and export and whether sufficient land could be allocated for this purpose without affecting the cultivation of other more important agricultural produce.

The therapeutic value of medicinal plant often varies from species to species occurring in the same natural habitat and the market price is determined on the basis of therapeutic contents of the crude drug. Analytical screening of the various available species to select the most preferred botanical species for propagation is very important to ensure attractive market outlook and, therefore, should form an integral component of the crop propagation programme and cultivation should be planned of preferred species only.

The investments and recurring expenditures involved in production of the crop being constant, scientific knowledge based plans regarding improvement in crop yield through proper selection of climate, soil quality, fertilizer aids and plantation and harvesting seasons should be carefully drawn and implemented to obtain the crops in higher yields and with superior qualities. The techniques to develop hybrids of the medicinal plants yielding higher contents of therapeutic substances and varieties resistant to infestation should also be investigated and superior hybrids introduced for plantation in order to increase the financial returns.

In case of those medicinal plants which are collected from natural habitat only, it is of vital importance to determine the optimum level of collection ensuring constant natural regermination and, accordingly, the collection should never exceed a level reducing future yields and endangering extinction. If an increased level of collection can be commercially justified then plans should be developed for increasing propagation. This can be best achieved through introduction of scientifically planned cultivation. Excepting scientific cultivation, there are other techniques such as avoiding plucking of immature plants, protection of seedlings and clearing the habitat of other growths to facilitate preferred propagation of the medicinal plants and increasing yields. These measures will take time to increase the potential yield and till such time the harvesting level should be judiciously controlled.

The plants can get exposed to various kinds of infestations and fungus attacks which result in deterioration or even total destruction of the plants. The infestation often being selective for plant species, such occurrence is more serious in case of plantations under cultivation as the infestation will spread fast causing destruction of entire crop. Prior knowledge of such infestation and its possible time, according to the season and plant age, is very important to adopt advance preventive measures. In any case it is also desirable that constant vigil be maintained for possible onset of the infestation in order to arrest it at early stage. The use of insecticides, although cost inducing, can be made but care has to be taken in choice of the insecticide so as not to contaminate the plants and carried over

in the harvested crops. Some end users have strict restriction in this regard which should be known to the growers so that the use of such insecticides which are not permitted to be present in the crude drugs could be avoided or the supplies should be freed of them before shipment.

5.1.3 Preparing and drying

Except in case of those drugs which are subjected to extraction in the freshly collected condition, all other drugs are freed from unwanted parts of the plant, cleaned of extraneous matter, dried and prepared for transportation. Suitability of these processes are essential to obtain the material of desired quality and have to be followed carefully and systematically.

The age of the plant and season for collection, both are important in determining the final quality of crude drug as in many plants the contents of therapeutic substance may vary considerably according to season of collection and age of the plants at the time of harvesting.

The therapeutic substances are either found in specific botanical parts of the plant or are unequally distributed in different parts. The techniques to obtain crude drug of high quality has thus strong bearing on the necessary precautions during preparation.

- i. If more than one species are found in the habitat, as far as possible the collection of species will be separate and processing well segregated.
- ii. During harvesting, proper techniques should be employed to avoid loss of or damage to the desired parts of the plant especially if it is root or subsoil rhizome (part of stem).
- iii. After harvesting, the parts of plant containing therapeutic substance should be separated from the unwanted parts carefully.

- iv. While still fresh, the material should be properly cleaned and/or washed well to remove extraneous matter, especially the remains of soil from the roots and rhizomes.
- v. After cleaning, the material should be cut, sliced or broken down to the specifications according to the supply requirements.
- vi. Drying of the crude drugs can be carried out in the sun as well as in the shed with sufficient ventilation but in any case adequate provision should be made for protection of the harvest from rain and excessive heat during drying and if possible the conditions should be improvised to facilitate and expedite drying. Drying is normally carried out in sheds of suitable capacity where the drug is spread on racks arranged in several horizontal layers and well separated from each other for free aeration and ventilation. The drying time should be carefully adjusted depending upon the atmospheric conditions such as temperature and relative humidity. At the final stages it is advantageous to determine the total moisture contents to ensure that they are within the specified limits. In order to maintain the keeping quality, it is preferable to dry the crude drugs to the point till the moisture is well below 15 per cent.

5.1.4 Grading, packing, storage and transportation

- i. The collection and drying of crude drugs, if centrally controlled, is based on species but in cases when the crude drug is procured from individual collectors after drying, it is necessary to conduct macroscopic examination of each lot and the procured materials be segregated and graded according to the species which should remain well identified to avoid mix-ups.
- ii. Periodic collection should be cross-sectionally sampled and subjected to quality evaluation with respect to content of therapeutic substances and the collections not meeting the specification should be identified and segregated from the normal stocks. In some cases it may be possible to blend the low potency

collections in suitable proportions with high potency stock to obtain a standard potency stock for sale.

- iii. Packing of crude drug also requires attention in order to protect it from fungus or mould attack, infestation and losses during storage, transportation and shipment.

Depending upon the physical nature of the crude drug it is packed in bundles, bales or gunny bags which could allow constant aeration. Each package is fully identified for the materials, botanical identity, origin of collection, grade, harvesting references and packed lot reference. The packaging must be strong to protect the crude drug from damage and losses during shipment and transportation and the identification tags/labels, durable so as not to get torn/defaced during handling.

- iv. The warehouse where the crude drugs are stored before shipment should be weather protected allowing for ventilation and aeration. The stocks of crude drug are stacked in a manner so as to avoid mix-up of different grades and also with other crude drugs. It should have adequate protection against rodents and other possible infestations. The disposal of crude drug for sale should be on the principle of first-in first-out basis ensuring that stocks do not get over aged. In case of doubt in the quality of older stocks, these should be subjected to evaluation prior to shipment to ensure that the shipment still meets the required quality standards.

5.1.5 Market exploration and export

Market potential assesment of crude drugs is the prerequisite for commercial collection/cultivation in order to ascertain the economic viability of such undertakings. There are numerous factors which can be beneficially used to evaluate the market potential, to attract buyers and to develop the

trade credibility in terms of regularity in supply, maintenance of quality and ensuring profitable returns on investment.

First and foremost is the assessment of the world market, present supply position, future prospects of growth or decline of the market, and possibly information regarding the future trading plans of the crude drug producers of the world. A realistic assessment of such information will enable the grower to determine the future plan depending upon the demand level trends and advance measures could be taken to maintain the cultivation/collection levels at a desired level.

Availability of the up-to-date trends and forecast regarding the world prices would enable the growers to plan the trade better. Detailed information about the established buyers and constant efforts to locate prospective customers will help in establishment of trade on sound footing.

The management for export of crude drugs should be based on sound system with full realisation of the customers, needs, honouring the commitments, regular and committed schedules of deliveries, assurance in maintenance of agreed qualities in each supply and prompt intimation to the customers of any departure from delivery schedules, quantity or quality. These measures are of great importance in promotion of business and to gain confidence of the customers resulting in long lasting dealings.

In order to develop advance plans for expansion or diversification of the business, it is extremely desirable that a constant liaison be maintained with the established customers to acquire an up-to-date information on the quality and changes in specifications, periodic demand levels and delivery schedules, short term market-trends and long range forecasts.

Systems should be practiced in the management to make early estimates of the harvesting quantity and anticipated quality of the crude drug, their comparison with the committed supplies and in case any discrepancy or deviation is anticipated, to liaise with the customers in order to take agreement for the anticipated changes in the supplies and also to provide reasonable margin of time so that the customer may arrange additional/alternate supplies in time.

For those crude drugs which can be stored for longer periods without deterioration, it is preferable to maintain certain level of running inventory. This would help the customers to draw additional supplies in cases of increased demand, or loss of consignment and to fill any orders from new customers. With properly organized system, the running inventory in the stocks will never age more than the duration between the harvesting of the crude drugs.

Standardised costing systems, which are extremely useful to set the sale prices, should be instituted and periodically reviewed in order to incorporate necessary changes depending upon the world price trends and factors to maintain the economic viability of the trade. It is, however, important especially in case of established customers, that the price changes should be fully negotiated to the satisfaction of both sides before being effected.

5.2 Official galenicals and established dosage forms

5.2.1 Scientific considerations and technological principles

The therapeutically active substances are usually present in very small proportions in the medicinal plants and the percentages of these may also vary considerably.

Conversion of crude drugs into galenical forms has thus been evolved for maintaining uniformity in supplies of crude drugs and also to standardize the pharmacological activities, to establish the therapeutic dosage, to preserve the active constituents against possible deterioration during storage of crude drugs and to economize the costs and space of storage, handling, transportation and shipments of otherwise voluminous quantities. The process also provides unit components for use in formulation of pharmaceuticals and prescription dispensing.

i. Unit operations

Based upon the specific requirements and the end-use of the processed material, the technologies involved in manufacture of these products vary to a certain degree from one material to the other. The established technologies in commercial practice are divided into four distinct steps:^{1/}

- a. Crushing and/or pulverisation
- b. Maceration
- c. Extraction
- d. Concentration/drying

a. Crushing and/or pulverisation: As the first step the crude drug is prepared in a form which could be easily extracted. The crude drug is crushed into a physical state so as to allow exhaustive extraction with minimum use of solvent employed for this purpose. The degree of disintegration of the drug is determined by the nature and the physical characteristic of the drug. For example coarse crushing/shredding of freshly harvested material (Glycyrrhiza) to fine comminuted powder (Nux Vomica). Normally it is preferred to crush the crude drug up to relatively coarse form for ease during extraction but due to varying natural textures of materials it is not always possible.

b. Maceration: The second stage is pre-treatment of the prepared material with the solvent of extraction, in some cases with a suitable chemical reactant to liberate the active materials into extractable form. This stage is more important in case of dried materials where the solvent must be allowed to penetrate deep into the crushed drug material to improve the extraction efficiency. Here again the conditions of

1/ Remington's Pharmaceutical Science, p. 1461

maceration vary from drug to drug and in some cases even elevated temperatures (digestion) are employed to expedite the process. The processing at elevated temperatures, however, is restricted to crude drugs possessing thermostable substances only.

The selection of a suitable solvent, which is based upon coefficient of extraction of active materials, low solubility of other plant materials, inertness towards active ingredients, ease of removal from the extractive, cost and availability, minimal hazardous properties and recoverability, perhaps is the most vital factor to determine the efficiency and economics of undertakings based upon crude drugs.

c. Extraction: Of the techniques practised in extraction of crude drugs, "percolation" is the most efficient and economical and accordingly is employed more widely. There are, however, limitations in such cases where the drug cannot be extracted exhaustively in coarsely powdered form and must be finely ground. In such unusual cases maceration/decantation is the more favoured technique although it requires larger volumes of solvent.

Percolation is carried out by packing the macerated crude drug in deep cone-like vessels called percolators, provided with bottom outlet valve and open top with well sealed loose covers, in presence of the solvent to ensure uniform density of packing of the drug permitting even flow of solvent through the material. At this stage the extractive from the drug is slowly collected from the bottom valve while fresh solvent is constantly replenished from top to permit the drug to remain constantly covered with fresh solvent.

The exhaustive extraction point can be determined through a gravimetric evaluation of total solids in the percolate. Normally the percolate in an amount thrice the quantity of crude drug is sufficient for exhaustive extraction. The first 66 per cent of the percolate carrying most of the extractives is processed further to obtain the end-product while the last percolate, containing very low extractive contents is recycled for extraction of subsequent lot.

The percolation process can also be designed in the form of series of successive percolators depending upon the amount of crude drug to be processed.

d. Concentration: The main extract from the percolation is subjected to solvent removal process such as evaporation and/or distillation. The evaporation method is usually employed when the solvent recovery is not of economic significance and where the material can be subjected to elevated temperatures without resulting in potency deterioration. The concentration process is carried out in suitably designed distillation units under reduced pressure to remove the solvent at lowest possible temperatures. The system is connected with solvent recovery installations composed of suitable condensers, chillers and receivers.

The removal of the solvent is monitored constantly and as soon as the product attains the required concentration the distillation is discontinued. The final product is collected from the concentrator and subjected to drying under reduced pressure if pure extract is the end-product.

ii. Galenicals

The commercial products from the medicinal plants termed galenicals, depending upon the end-use are offered in several consistencies like prepared powders, tinctures, fluid extracts and extracts.^{2/}

a. The prepared powders are merely powdered dried crude drugs of declared potency or the potency adjusted to a standard by addition of inert material, often the exhausted mark of the same drug.

b. The tinctures are alcohol based extracts of crude drugs with adjusted potency usually representing one or two gramme of crude drug in ten millilitres of tincture. These are used as such in pharmaceutical dispensing and prescription filling.

^{2/} Various official compendia such as British Pharmacopeia, United States Pharmacopeia.

c. The fluid extracts are prepared by concentrating the percolate under reduced pressure to obtain a liquid each 1 ml of which represents an activity equivalent to 1 g of the crude drug. It usually contains certain percentage of alcohol as preservative.

d. The extracts are prepared by total removal of solvents from the percolate and when necessary by adjusting the extracted mass or powder with inert materials to a standard potency. In the commerce the extracts are found in semi-solid, piular and powder forms possessing standard potency. These are the forms of extractives which have wide application in manufacture of dosage-form and pure substances in pharmaceutical industry.

iii. Solvent recovery

Solvent is the major cost component in the manufacture of galenicals and its extent of recovery affects the product cost considerably. Marc, the exhausted crude drug after extraction process contains about 50 per cent solvent^{3/} and except in case of water, this solvent must be recovered by distillation. The vacuum distillation system for production of liquid and solid extracts is also provided with an efficient cooling unit for optimum recovery of solvent.

The processes for recovery of solvents require consumption of utilities and equipment occupancy and results in unavoidable losses during distillation and accordingly the following alternate uses are preferred to avoid recovery costs as far as possible.

The last percolate which contains rather small quantity of extractive is used directly for:

- a. extraction of fresh lot of drug,
- b. after quality determination as volume making-up solvent for tinctures and liquid extracts of the same product.

^{3/} Observation in operation of galenical manufacturing plant.

Most of the plant-derived therapeutic substances in the crude extract are susceptible to heat and accordingly great care is exercised during solvent removal from the extract especially high boiling solvents like water. Some of the plant extracts, due to presence of saponin-like substances, cause frothing problems during distillation under reduced pressure and almost in all cases when the extract attains high consistency, removal of last quantities of solvent causes operational difficulties and requires great care to avoid deterioration of quality of the end product. The technological innovations have resulted in development of efficient and relatively simple processes like "climbing film evaporation" and "drum drying" where the material is exposed to higher temperature for a limited duration with minimal effect on the natural characteristics of the product. "Spray drying" is yet another modern technique gaining increasing popularity for production of extracts in powdered form.

iv. Extraction of steam volatile substances: The steam volatile substances of pharmaceutical significance are almost exclusively derived from plant resources and are grouped in the official monograph in the category of essential oils barring such substances as camphor.

The essential oils are produced mostly by the process of steam-distillation of the crude drug and in some cases by distillation per se. In yet other cases they are also produced by "expression" of fresh material to retain the natural fragrance which otherwise is injuriously affected by heat treatment.

The technology for production of essential oil again does not require involved techniques and can be carried out with the equipment very similar if not identical to the equipment required for processing of crude drugs.

In general, the technique required for production of essential oils and other steam volatile substances is based upon the following unit processes:

a. Steam distillation

Crushing of the crude plant in dried or in certain cases in freshly collected state.

Steam distillation of the crushed material suspended in water.

Separation of the steam volatile material from the distillate where it forms separate layer on top of the aqueous distillate.

Dessication and purification through redistillation to obtain refined product.

Packaging in hermetically sealed containers compatible with the product.

b. Distillation per se: Usually this technique is employed to obtain volatile substances from oleoresins. The distillation is carried out without the presence of water or use of steam because the volatile substances are difficult to separate from the distillate if steam-distillation process is employed.

c. Expression: The fresh material is manually or mechanically pressed under water for releasing the essential oil from the organic tissue. The essential oil forms a separate layer on the aqueous surface which is separated, dried with suitable dessicant and purified through decantation/filtration.

5.2.2 The basic requirements for large-scale production of galenicals from crude medicinal plants

Processing of the medicinal plants, dried or fresh, varying in constituents and species, all require similar techniques involving the four stages of operation discussed earlier and a unit designed on these principles can be used or appropriately modified to process large varieties of crude drugs.

Most of the crude drugs are extracted with commonly available and low cost solvents such as water, alcohol, methanol and mixtures therefrom. In some instances, where fatty and oily material is to be removed from the final product, petroleum solvent is used at specific stage of the process to remove fatty matter.

The crude drugs usually offer about 10 per cent extractive^{4/} on the dried basis while the percentage of extractives from fresh material is much less and depends upon the moisture contents present in the fresh material. There are exceptions such as glycyrrhiza where the total solid extractive may be 30 per cent or more^{5/} on the dry weight basis. The total volume of extractive may also vary depending on the techniques employed and extraction efficiency of the process developed.

In production of tinctures, the volume of the solvent used is not of consequence as the final volume of the product has to be made up with still more solvent. In case of extraction for other galenicals, where solvent is removed and/or recovered, however, it is very important to develop the process requiring minimal use of solvent for extraction, a major aspect to economise the cost of the final product from consideration such as plant capacities, solvent inventory levels, processing time, operation losses and solvent recovery costs.

i. Process unit description: The illustration selected for this study is based upon a plant operation capacity of 200 kilograms of dried crude drug or its equivalent of fresh supply per day. With such a capacity the unit will be capable of processing 50 tons of crude drug annually. For normal considerations such a unit is small but has been selected based upon several considerations:

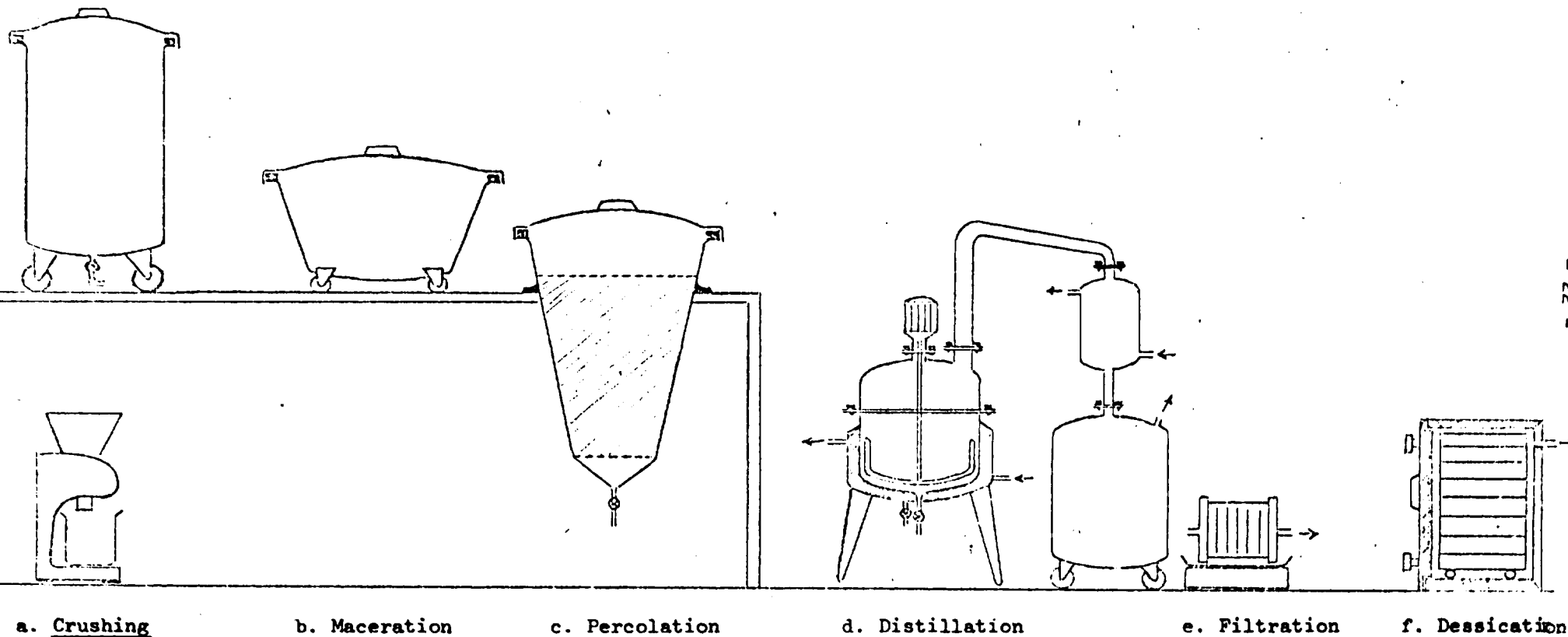
^{4/} Studies on numerous medicinal plants, both roots and leaves (author's own experience)

^{5/} Medicinal plants and their derivatives, UNCTAD, Geneva, 1982, p.135

- a. The unit is based upon conventional operation techniques without employing advanced technologies/equipment.
- b. It requires low initial investments and will be viable even in the areas of relatively low crop yields.
- c. Provisions have been retained to double or even triple the capacities in case of increased product demand with minimal investments and also retaining the possibility of processing up to three products at one time.
- d. In case of needs it can also be used as source of plant derived raw materials for the dosage form manufacturing unit based upon the medicinal plant available in the country.
- e. Being small in capacity and requiring relatively low investments, it can be installed as pilot-plant in those locations where larger undertaking may not be advisable to start with.
- f. The unit could also be used for processing new sources of drugs for investigational and research purposes.

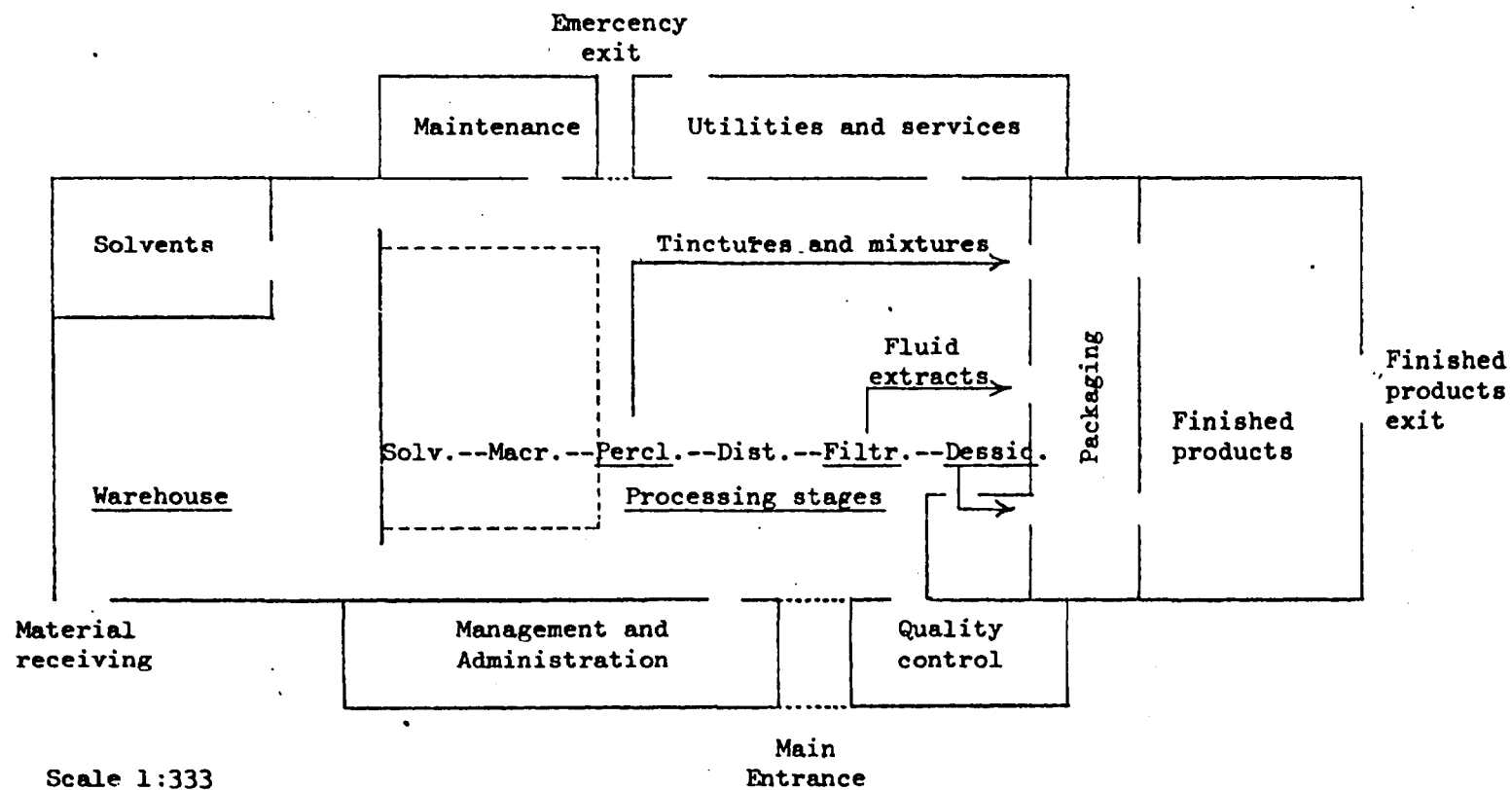
The schematic diagram of process flow and plant design including the layout are illustrated in Figure II and Figure III respectively, incorporating necessary considerations of capacities of all pertinent functions of the unit as outlined below:

Figure II. Processors flow: Illustration of a medicinal plant extraction unit



Note: Drawing is schematic representation and not according to true scale.

Figure III. Design of building for manufacture of galenicals



ii. Functional capacities assessment^{6/}

- | | |
|---|---|
| 1. <u>Warehousing:</u> of dried crude drugs (two-month inventory) | 5,000 kg |
| Larger warehousing is not needed because of close vicinity of source of supply. | |
| The solvent will be stored in original suppliers drums | 10,000 ltrs |
| 2. <u>Crushing/grinding</u> | 125 kg.
(or equivalent fresh material) |
| 3. <u>Solvent preparation</u> | 500 litres |
| 4. <u>Pre-treatment (maceration)</u> | 200 kg. |
| Fresh material will not be subjected to pre-treatment | |
| 5. <u>Extraction:</u> i. Percolation | 200 kg |
| ii. Maceration | 200 kg |
| 6. <u>Filtration:</u> | 600 litres |
| 7. <u>Solvent recovery/removal:</u> | |
| i. Vacuum distillation (50/60 litres per hour) | 400 litres |
| ii. Vacuum drying | 40 kg. |
| 8. <u>Recovered solvent storage:</u> | 600 litres |
| Alternately it can be stored in the original containers | |
| 9. <u>Storage of bulk products</u> | |
| To the extent of waiting time for quality control release | |
| 10. <u>Subdivision and packaging</u> | |
| i. Tinctures and mixtures therefrom | 2 000 litres |
| and/or ii. Liquid extracts | 200 kg. |
| and/or iii. Extracts | 40 kg |
| 11. <u>Finished product storage</u> | |
| i. Tinctures and mixtures therefrom | 5 000 litre bottles |
| and/or ii. Liquid extracts | 500 1 kg. bottles |
| and/or iii. Extracts | 500 1 kg. tins |
| 12. Quality control laboratory | |
| 13. Plant management and administration office. | |

^{6/} These assessments have been made from the capacities data of a plant for manufacture of galenicals in a developing country.

iii. Building^{7/}

Based upon the process unit capacities outlined earlier the building is designed and equipped incorporating the following features:

a. Land and location: An approximately six thousand square meter plane piece of land slightly elevated from the surroundings and away from the congested residential areas would be preferable. The location also should not be in the vicinity of other installations causing air pollution and the site selection should be based upon the availability of utilities and communications means from the source of crude drug and to destinations of finished products. The buildings for a complete process unit, retaining provisions for expansion to three times the original production capacity, would occupy about one fourth of the land leaving enough open space for other plant services such as material deliveries/despatch traffic, personnel conveniences, disposable materials area and security systems.

b. Civil structure: There are no special or critical requirements. It should be simple structure with uniform floor level throughout and well ventilated. There should, however, be adequate segregation between various operational functions and security provision necessary for the required controls and product quality and integrity. The internal structure of the building should retain provision for ease of modification in case of future changes.

As a broad based guideline, the different functions of the unit will bear the following covered floor spaces:

1. Warehousing (crude drugs and packaging)	350 sq. meters
2. Processing operations area	700 " "

^{7/} These assessments are based upon the experience of operating a small galenicals manufacturing unit in a developing country. The capacities are based on multi-product operations and are subject to adjustment/change for specific undertaking.

3. Utilities and services	100 "	"
4. Warehousing (finished products)	200 "	"
5. Quality control	50 "	"
6. Repair and maintenance	50 "	"
7. Management and administration	100 "	"

c. Internal layout: Internal layout of the building should be preferably based upon the principle of one directional process flow incorporating the crude drug warehouse at one side and that of finished products on the other with the processing functions in the middle. The services such as quality control, utilities and maintenance should also be conveniently located for ease of communication.

d. Finishing of the building: There are no particular specifications mandatory for internal finish of the building and thus cost of construction is usually minimal. Certain practical considerations, however, should be borne in mind:

- . The crude drug storage should be well ventilated and protected from weather conditions and rodent or any other kind of infestation.
- . The processing area should also be well ventilated to eliminate solvent vapours and dust.
- . The area for processing of extracts, if these are hygroscopic in nature, should be kept free from atmospheric moisture during the operation and packing.
- . Bottling, subdivision and container sealing area should be free from airborne pollutions.
- . Areas required for the remaining functions could be finished in economical commercial type of building.

The layout presented in Figure III is based upon the considerations appropriate for developing countries and useful when the circumstances permit construction of a new facility. Under limiting circumstances an available building could be converted for this purpose incorporating the fundamental guidelines of the operations outlined in the preceding discussions.

iv. Machinery and equipment:^{8/}

a. Processing/production

<u>Item</u>	<u>Capacity</u>	<u>Number</u>
1. Weighing scale	200 kilogram	1
2. Solvent holding containers	200 litre	3
3. Grinder (dry drugs)	50 kg/hr.	1
4. Crusher/shredder (fresh drugs)	100 kg/hr.	1
5. Maceration pots	100 kg	4
6. Percolator	200 litre	2
7. Circulation pumps (stainless steel)	250 litres/hr.	2
8. Collection containers	100 litres	4
9. Concentrator (vacuum type)	60 litres/hr.	1
10. Filter press (multiple plates)		1
11. Storage tank (recovered solvents)	200 litre	3
12. Drying/dessicating unit (vacuum type)	40 kg	1
13. Liquid subdivision unit 1000 cc.	350/hr.	1
14. Bottle sealing machine	350/hr.	1
15. Extract subdivision scale (1 kg.)	25/hr.	1

In addition, the processing operation will also require miscellaneous gadgets, tools and similar ancillary items for measuring, manipulation, handling and movement, transportation, washing and cleaning and other miscellaneous jobs.

b. Utilities and plant services

1. Steam generator (pressure 10 bar)	150 kg/hr.	1
2. Central vacuum system (0.06 bar)	10 tons	1
3. Chilled water unit	10 tons	1

^{8/} These capacities are based on multipurpose operation concept and are subjected to revision according to specific needs.

c. Quality control

Phase 1

1. Analytical balance (0.1 mg accuracy)	1
2. Moisture balance (infra-red)	1
3. Drying oven (laboratory scale)	2
4. Vacuum oven (laboratory scale)	1
5. pH meter	1
6. Viscometer	1
7. Centrifuge (laboratory model)	1
8. Alcohol determination apparatus	2
9. Formulation development kit (laboratory model)	1
10. Vacuum pump (laboratory model)	1

Phase 2

11. U.V. spectrophotometer	1
12. I.R. spectrophotometer	1
13. Kjeldal apparatus	1
14. Thin layer chromatographic unit	1
15. Column chromatographic apparatus	1
16. Soxhlet apparatus	1
17. Muffle furnace	1

The laboratory instrument listed under phase II will be needed if investigational and exploratory work is to be undertaken.

Laboratory glassware, procelainware and auxiliaries
Laboratory re-agents and solvents.

v. Plant personnel identification and qualification^{9/}

Managerial: Plant manager	Commercial pharmacist	1
Technical: Production pharmacist	Industrial pharmacist	
Quality control pharmacist	Qualified analyst	1
Foreman	Mechanical engineering	1
Trained operators	Pharmacy diploma	5
Trained analyst	Pharmacy diploma	1
Trained technicians	Engineering diploma	1
Untrained personnel		2
Driver		1

^{9/} The given staffing appears top-heavy for the planned plant capacity but the managerial, engineering and non-technical staff strength being minimal for plant operations will not increase with subsequent expansion of productivity.

vi. Quality and packaging considerations

Standards of quality and packaging specifications both are determined by the ultimate use or destination of the end product. In case of products for domestic use the product specifications will be subject to the national health regulations and the packaging will be according to distribution and mode of consumption in the hospital and retail pharmacy practices.

The products manufactured for use as raw materials at other locations in the country or for export will be according to the specifications agreed upon by the end-user or the buyers.

The product pack-size, container and outer packing for export purposes, however, must be suitable to retain the quality and robust to withstand the handling and movements during transportation and shipment.

The immediate containers and outer shipper/crate both should bear the necessary identifications of the product, source and destination.

vii. Plant operations systems and procedures

Satisfactory performance of the plant always requires carefully developed systems and well designed procedures for all functions of the plant as it is vital that the plant operation be backed-up by proper co-ordination of each function.

viii. Plant management and finance

Overall management is the key function of the plant through which the activities are co-ordinated towards the desired objectives. Based on the projected forecasts, this function ensures that the needs of different functions are adequately satisfied and is instrumental in monitoring the performance leading to the planned productivity. This function is vested with sufficient authority for independent planning of the plant activities

co-ordinating product demand forecast, procurements, personnel and other needs and production, quality standards and distribution of the products. The function will also possess adequate financial disbursement authority and financial resources to meet the operating costs.

5.2.3 Module for manufacture of extracts from Glycyrrhiza and Cephelis species

For the purpose of this exercise, the selection of medicinal plants is made on the following considerations:

- the plants are expected to retain the therapeutic importance for the foreseeable future especially in the developing countries,
- these are widely cultivated in several developing countries in commercial quantity,
- production will find reasonable consumption locally as well as in other developing countries,
- processing technology is available in some developing countries which could be made available,
- the processing techniques are less involved and the product relatively stable and as such the adaptation of technology will not pose unsurmountable problems.

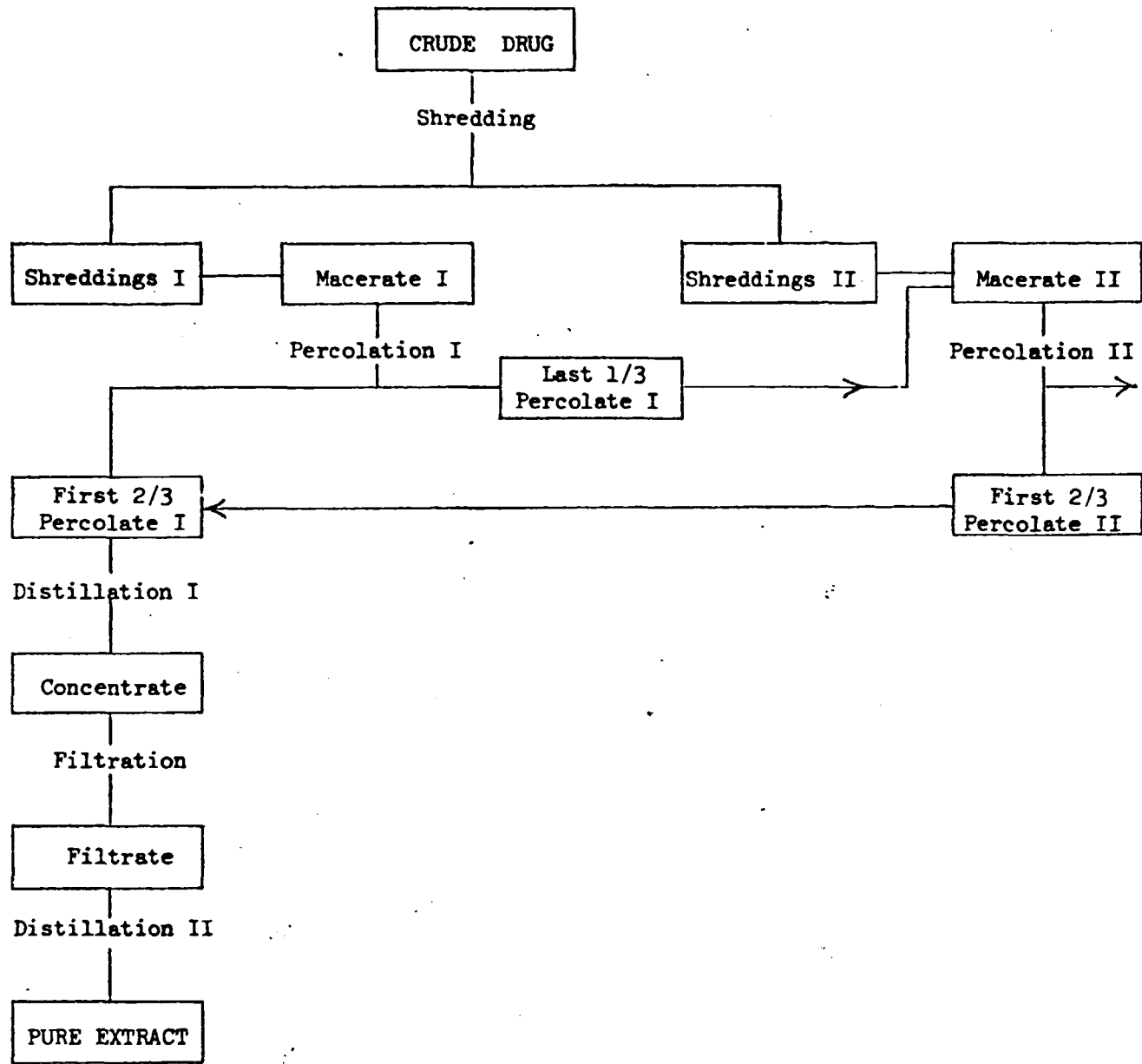
i. Glycyrrhiza Extract

The process (Figure IV) is based upon extraction of shredded fresh or dried roots of glycyrrhiza by percolation with hot water followed by concentration under reduced pressure. The concentrate after being subjected to filtration is transformed to pure extract under reduced pressure.

The manufacture can be carried out in a production facility described earlier with deletion of items 2, 3, 11, 13 and 14 of the machines.

Further increase in capacity can be achieved by operating the unit in extended, double or, if need arises, even in three shifts. Such planning will offer a production capacity which can be substantially increased during harvesting seasons without resorting to additional capital investment.

Figure IV: PROCESS FLOW: Glycyrrhiza Extract Production



Drug: Glycyrrhiza		Product: Pure Extract N.F. XX		
Process step No.	Process step	Sub-step	Unit Operation	Capacity
1	Crushing/Shredding		Mechanical	200 kg
2	Pre-Treatment		Maceration with water at 100°c	200 kg
3	Extraction		Percolation with water at 100°c	400 kg
4	Concentration	I	Distillation-reduced pressure	200 l/hr
5	Filtration		Filter press	200 l/hr
6	Final Solvent Removal	II	Distillation-reduced pressure	
7	Subdivision/Packaging	i	Liquid filler (1000 ml syringe)	200 l/day
		ii	Gravimetric	100 kg/day

ii. Liquid Extract of Ipecacuanha

The process of production is based upon extraction of crude drug by maceration technique. The finely powdered Ipecacuanha roots are macerated with 70 per cent ethanol for at least 72 hours in a closed container. The extract is removed by filtration and the mark is freed of residual extract by washing with additional quantities of solvent. The total extract is subjected to distillation under reduced pressure. The concentrated residue thus obtained is adjusted to standard potency by dilution with sufficient quantity of 70 per cent ethanol.

The tincture of Ipecac also is produced by the same method except that the total extract is filtered and subjected to quality evaluation. In the subsequent step its volume is adjusted with 70 per cent ethanol to a standard potency product (Note: Concentration is not required.)

The manufacture of the liquid extract can be carried out in the facility described in Figure II with deletion of items Nos. 4,6, 12 and 15.

Drug: Ipecacuanha		Product: Ipecacuanha fluid extract NSP XVI	
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Process step No.	Process step	Unit Operation	Capacity
1	Grinding	Mechanical	50 kg
2	Soaking/maceration	Maceration with 70% ethanol at r.t.	100 kg
3	Filtration	Filter press	50 l/hr
4	Solvent removal	Distillation under reduced pressure	50 l/hr
5	Volume adjustment	-	-
6	Subdivision/Packaging	Volumetric dosing at 1000 ml	350/hr

5.2.4 Commercial and economic data

i. Glycyrriza glabra L. and other species

The table No. 1 provides a detailed study of global trade, market, and origins and destination of commercial crude drug and pure extract during the year 1980.^{10/}

The total trading of crude drug and the pure extracts combined was of the value of over 45 million US dollars. The major importers were the United States of America and Japan totalling about 27.5 million dollars. The European Economic Community was the largest importer of pure extract of the value of 12.5 million dollars.

China was by far the largest exporter valuing about 18 million dollars followed by Afghanistan with 6.8 million dollars. The developing countries exported 8,694 tons of crude drug and 3,773 tons of pure extract. Iran followed by Turkey were the major exporter of pure extract with smaller share by some other Middle Eastern countries.

^{10/} Derived from the trade and price statistics provided in medicinal plants and their derivatives, UNCTAD, Geneva, 1982, pp. 139-144

Table 1 Glycyrrhiza (Liquorice root)
(World Trade 1980)

I. Total Import	Roots		Pure extract	
	Q ^{a/}	V ^{b/}	Q	V
USA (1981)	11 985	12 000	2 869	5 750
Japan	9 693	9 700	-	-
E.E.C.	5 121	5 100	6 240	12 500
United Kingdom	469	500	-	-
TOTAL WORLD	27 268	27 300	9 109	18 200
II. Total Export				
	Q	V	Q	V
China, USSR and Israel	16 457	16 500	2 391	4 800
Total developing countries	8 694	8 500	3 773	7 500
Within EEC countries	2 117	2 100	2 945	6 000
III. Major exporting countries				
	Q	V	Q	V
China	13 702	13 700	1 558	3 100
USSR	2 722	2 700	-	-
Iran	319	300	2 282	4 600
Afghanistan	6 719	6 700	-	-
Turkey	531	530	862	1 700
Others	1 125	1 100	629	1 300

a/ Q = quantity : tons

b/ V = Value: US\$ thousands (cif)

Note: Value figures have been rounded off.

Significant fluctuations in the trade are observed and accordingly the individual country figures should be considered with caution.

Out of a total of 8,694 tons of crude drug exported, the share of Afghanistan was 6,719 tons followed by Turkey and Iran with 531 tons and 319 respectively, while the remaining 1,125 were the export of several countries combined.

It is clear from these figures that the developing countries, almost all of which belong to Western South Asia and South Asia, have a potential for establishment of processing units for about 10,000 tons of crude drug excluding the quantities required for domestic consumption. In this study it is not possible to provide statistics for consumption of extract of glycyrrhiza in developing regions but in view of the therapeutic significance and the population levels it can be safely assumed that the potential is substantial.

ii. Cephalis ipecacuanha and C. acuminata

In absence of sufficient statistics of trading quantities and stable price levels of ipecacuanha it is almost impracticable to work out sensible and realistic market trends and future prospects. Certain approximations and assessments, however, can be deduced from the scanty information available at hand.

- a. The world trading, mostly that of *C. acuminata*, could be assessed in the tune of approximately 100 tons annually most of which is obtained from Brazil and India with smaller amounts from Malaysia.
- b. In the recent years, the trading of crude drugs has been considerably disrupted due to supply problems from the origins in Latin America and commencement of production of natural alkaloid in India.
- c. Due to extreme scarcity of the commodity in the trading centres of the world, the price has recorded unrealistically sharp increases to the extent of threefold escalation between January 1980 and September 1982. As a result the stockists of crude drugs in the West, are reluctant in ipecac trading.

d. Although the synthesis of emetine has been successfully carried out and natural alkaloid is also facing competition with other therapeutic alternates of synthetic origin but the ipecacuanha market can still be maintained, especially in the developing countries, where it has extensive use as cough expectorant and as antiamoebic.

5.3 Raw materials and bulk substances production by chemical unit process

In quest for more specific therapeutic substances of single chemical entity, the production of pure therapeutic substances from medicinal plants gained increasing interest in the first half of this century. Many important drugs were transformed into modern medicaments for diversified modes of administration hitherto not possible such as parenterals. The availability of chemically pure therapeutic substances thus opened new avenues in the manufacture of dosage forms with exacting standards, better stability, controlled administration and improved palatability and presentation gradually replacing "the mixture", "the powder", "the pills" etc. from the pharmacy shelves.

5.3.1 Scientific considerations and technological principles

The galenicals, although enriched, contain the therapeutically active substances still in relatively low concentration due to many other inert organic chemicals present in the crude drug and being carried through during the extraction. Further purification and isolation of pure substances require higher degree of techniques and skill although employing established principles of chemical technology. Based upon somewhat similar principle of elimination of insoluble inert materials during the production of galenicals, the procedures for production of pure substances diversify further to employ other physical properties such as selective solubility, fractional crystallization, adsorption characteristics and even in situ chemical conversions in progressive elimination of soluble inert substances and leading to refinement of the therapeutic substances up to pure crystalline stage.

Although the early steps in this technology for processing of crude drugs are more or less similar as required for production of galenicals but in the

subsequent stages advanced know-how and skill is essential, for critical control of process conditions--monitoring the quality of product and optimum yield on the one hand and recycling/recovery of solvents and regeneration of process-aid materials on the other--the vital factors to determine the economics and efficiency of the process. In addition, it also requires effective environmental controls and judicious handling techniques for avoiding hazards of contact/exposure to pharmacologically potent pure substances.

The technology for manufacture of pure substances from medicinal plants differ from product to product in finer details but is broadly based on one standard process flow (Fig. V) incorporating the major routes for commercial scale production of pure substances.

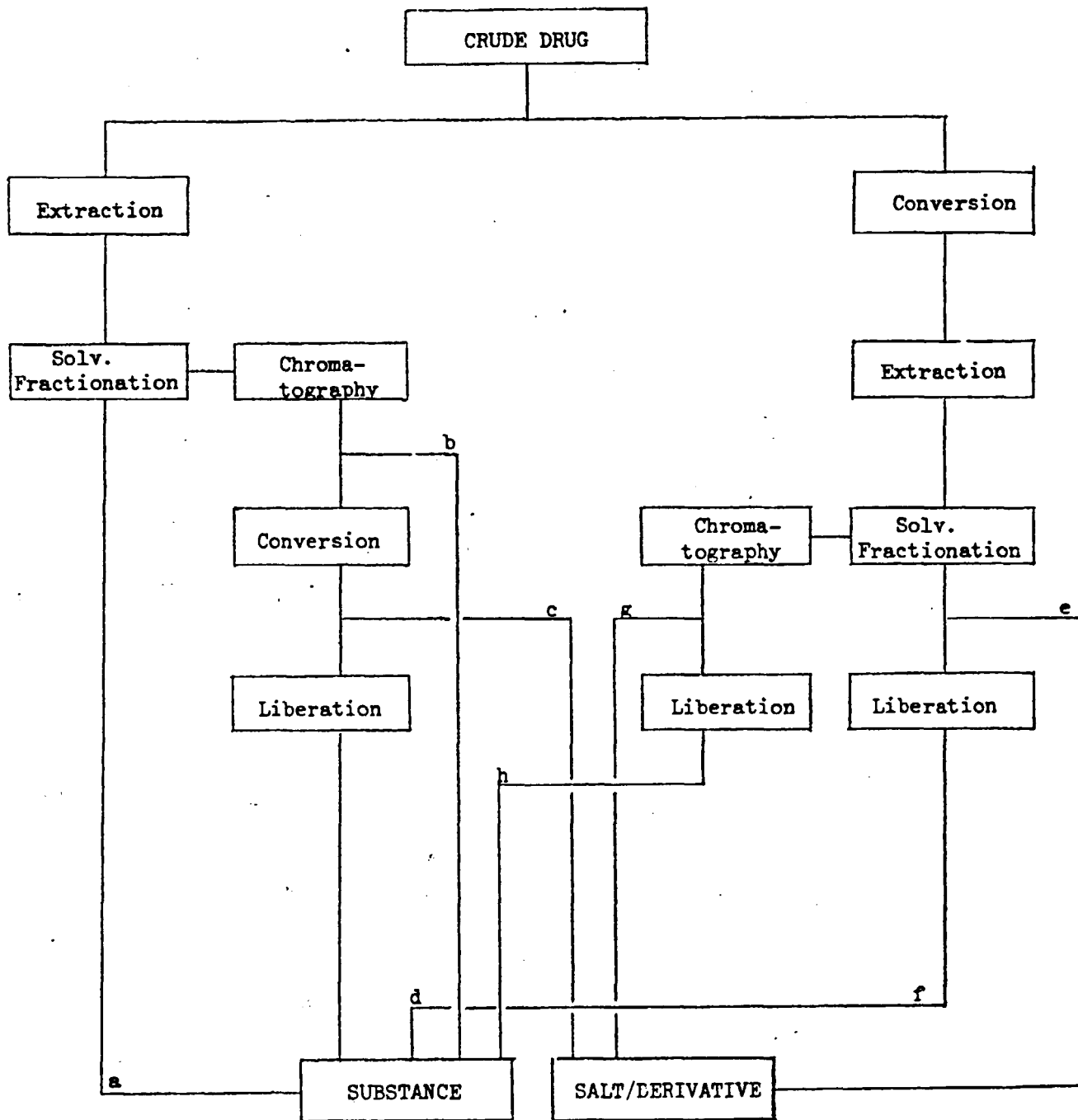
i. Chemical unit process description

Depending upon the physical characteristics of the substance and its mode of occurrence in the plant, experiments are carried out on small-scale to develop economical methods requiring minimal manipulation and offering high yield of the end product. This method is then scaled up for commercial purposes. The technologies differ considerably for individual products but fall into the following basic stages:

- a. Extraction
- b. Solvent partitioning
- c. Isolation of the therapeutic substance
 - c¹. direct techniques
 - c². conversion techniques
- d. Recrystallization

a. Extraction The crude drug is subjected to extraction following one of the methods described earlier. Depending upon the nature and mode of occurrence of the therapeutic substance, the crude drug may be chemically treated during the maceration stage in order to liberate the substance for ease of extraction. The percolate of the drug is then concentrated to the consistency required for subsequent purification steps.

Figure V: Process Flow: Pure substances production: General scheme



b. Solvent partitioning: The process is based upon preferential solubility of the therapeutic substances in particular solvent. For this process the extract is dissolved in water or dilute alcohol and agitated with an immiscible organic solvent. After separation of organic layer, the therapeutic substance is obtained in a crude state by removing the solvent. It still contains other chemically related substances and smaller quantities of other impurities.

c. Isolation of therapeutic substance: The techniques employed at this stage are designed on the basis of physical characteristics of the therapeutic substance and nature and extent of presence of other analogous chemicals and impurities.

c¹. Direct techniques

- . If the therapeutic substance has preferential crystallization possibility by virtue of its physical characteristics or predominance in quantity, the material is subjected to direct crystallization through a suitable solvent system to obtain the pure substance.

- . In case of existence of therapeutic substance in smaller proportion and/or in presence of other chemical analogues in relatively significant proportions to interfere with selective crystallization of pure substance, adsorption chromatographic technique is employed, which apart from eliminating the impurities also resolves other chemical analogues with simultaneous purification of the therapeutic substance.

The process of chromatography is of relatively recent development and is an effective tool for isolation of even minute quantities of substances. The technique is fairly versatile in nature and can be applied on the crude extract, on the isolated mixture of substances or their converted derivatives and also to resolve crystalline mixtures of substances. It also offers advantage of offering highly purified material in almost quantitative yields.

The chromatographic techniques are based on the simple principle of differential adsorption capacity of various components of the mixture on the solid stationary phase of adsorbant packed in a tubular column against a moving liquid phase. The technique has been further refined by making use of varying elution power of solvents and mixture of solvents through which absolute separation of individual components of a complex mixture of substances may be possible.

The simplest example which has long been used is removal of coloured impurities of an organic substance by treating its solution with activated charcoal which adsorbs the impurities and the pure colourless substance is carried through with the organic solvent.

A large variety of solid phase adsorbents suitable for a variety of applications are now commercially available.

c² Conversion techniques

The therapeutic substances found in nature usually occur in the form of salts, glycosides, saponins and other organic complexes because of which direct purification may not always be successful or may offer poor yields. Chemical conversion of such substances at certain stage of purification techniques has been successfully used to facilitate purification and fractionation of mixture of substances of otherwise similar physical characteristics. Some methods which are generally used are briefly described below:

. Liberation by chemical treatment

Cinchona alkaloids are converted into free bases before extraction of the crude drug and converted into inorganic salts at the stage of final crystallization.

. Liberation by hydrolysis

Diosgenin, occurring as sapogenin glycoside is liberated by acid hydrolysis within the plant tissue before isolation.

. Conversion by chemical modification

Cephaline, removed during production of emetine from ipecacuanha, offers additional quantity of emetine upon methylation.

. Conversion into chemical derivative

Complex mixtures of alkaloids and glycosides are converted to derivatives of specific nature to offer improved resolution into pure compounds during fractional crystallization or chromatographic purification techniques.

d. Recrystallization: This is the final stage in production of pure substances when the trace impurities in a material of otherwise single entity are eliminated to yield pure substance. In case of some drugs, especially where the final isolation of the substance is achieved through adsorption chromatography, this stage of purification may not be necessary.

Techniques other than crystallization such as "sublimation", "steam distillation" and/or "distillation under vacuum" are also employed in refining of therapeutic substances but these are employed for natural products of specific characteristics like camphor, essential oils etc.

The therapeutic substances which are non-crystalline in nature or which are difficult to crystallize even in pure state are isolated in the form of a salt or an organic derivative which can be crystallized to offer the pure substance.

ii. Solvent and other process-aids recovery

The unit operation for manufacture of pure therapeutic substances is evidently based upon the technology where solvents are the predominant component followed by process-aid materials like adsorption media for chromatographic columns. Efficient solvent recovery and material reclamation systems, therefore, are integral components of the function which ultimately determine the economics of the process especially in case when such items are expensive and of imported origin. Depending upon the process technology, various practices starting from "judicial usage" to "solvent recovery" are applicable at different stages:

- a. Solvent used should be low in cost and preferably available within the country
- b. Process should be developed employing minimum solvents
- c. The "spent solvent" should be preferably reused as such as far as possible
- d. System for recovery of the solvents must be one of the vital functions of the operation
- e. Adequate measure should be practiced to avoid evaporation and other accidental loss of solvents.

The process-aid materials like adsorption-medium for chromatographic column are expensive and are used in large quantities in processing certain crude drug. Usually the suppliers do provide methods for regeneration if these are of such nature and the plant should have adequate facility for this purpose.

5.3.2 Basic requirements for large-scale manufacture of pure raw materials and bulk substances

Manufacture of pure substances from the medicinal plants is based on principles such as partitioning between solvents, simple chemical reactions, adsorption chromatography and crystallization and does not appear to be involved. In practice, however, certain processes could be almost as sophisticated as synthetic chemical processes and unless the process used has not been well designed and carefully followed it will meet with little success.

Although the general process can be divided in four major steps but in practice and due to incorporation of intermediary steps some processes may be much more involved. In certain instances even when the technologies are based upon well known differential solubility principles in organic solvents and the processes have been described in good detail in the literature, the critical aspect of know-how are not readily available and because of this, adaptation of technology apparently based upon simple processes, also face difficulties in spite of the fact that relevant patents for production of these therapeutic substances have long been expired.

i. General process concept

Manufacture of pure therapeutic substances from the medicinal plant is carried out using selectively designed processes for each crude drug in order to obtain desired purification with optimum yield. Figure V illustrates two general sequences of operation starting from crude drug to final pure substance. Depending upon the process technology specific for a crude drug the sequences would lead to pure substance by carrying out the process up to the specified point. It is obvious that to reach a given point requires varying number of processing steps and accordingly, in order to minimize the process cost and operational losses of material at each additional step, it is endeavoured to perfect a process requiring minimal steps. This approach, however, is primarily guided by the nature and quantity of the therapeutic substance present in the drug and the quality requirements of the end product.

The technology being based on established principles of chemical engineering, it is the degree of perfection in development of commercial scale process and the level of technological skill, especially during the later stages, in control of process conditions, monitoring the yields and quality and maintenance of environmental control, where high degree of skill and perfection is mandatory.

ii. Process unit description

Initial stages of processing of crude drugs are identical with the processes described for manufacture of galenicals and accordingly and extension of the plant building (Figure III) sufficient to accommodate pure substances manufacturing facility will be required. In case the plant is designed to manufacture only pure substances then the section for finished product warehouse can be converted to accommodate the facilities for production of pure substances after desired internal alterations and finishing.

Since the technology for production of different pure substances employ same machinery and equipment, such unit will be able to function as multipurpose plant for production of pure substances derived from different crude drugs.

Computation of working capacity of such plant is almost impossible because of yield of pure substances greatly vary in different crude drugs; Cinchona bark contains an between 6-16 per cent total alkaloids and Cephalis alkaloidal contents vary between 1.7 - 4.0 per cent. Therapeutic substances in Digitalis and Belladonna are as low as 1.0 per cent and 0.30 per cent respectively. By applying the "rule of thumb" however, the plant capacity can be based upon taking the extraction of crude drug as "key function" and computation of the capacity of the purification unit basing 5 per cent availability of therapeutic substance in the crude drug.

iii. Functional capacities

a. Crude drug extraction	200 kg per day
b. Liquid/liquid partitioning	20 kg
c. Chromatography	5 kg
d. Chemical conversion	5 kg
e. Crystallization/filtration	5 kg.

The above functional capacities have been proposed on the basis of processing 200 kilograms of the crude drug containing about 10 per cent extractable matter and 2 per cent of the therapeutic substance along with other chemical analogues in smaller quantities. Capacities of these functions can be correctly computed only after ascertaining the relevant data of the crude drugs to be processed.

iv. Buildings

In view of the extent of usage of solvents and the degree of purification in the production of therapeutic substances certain features should be incorporated in the building design:

- a. The electrical installations should be explosion-proof which will include motors, switch gear and illuminations
- b. Adequate ventilation/exhaust system should be installed
- c. The operation areas, especially at the final stages of processing should be free from air-borne dust

d. Various steps of operation should be planned maintaining process flow and segregation.

v. Machinery and equipment

Extraction of crude drugs being integrated with the production of pure substances, the requirements for machinery and equipment for all functions described in the preceding section dealing with the production of extracts will be required with addition of the following equipment for production of pure substances.

<u>No</u>	<u>Equipment</u>	<u>Brief description</u>
1	Separator	For partitioning between two immiscible liquid phases
2	Chromatography column	Stationary solid phase
3	Reaction vessel	For simple chemical conversion at room temperature and atmospheric pressure
4	Distillation unit	For concentration and solvent recovery
5	Crystallizer	

vi. Personnel

The requirements of the personnel will be the same as detailed for the production of galenicals. The trained operators rendered free from processing and packaging of the "extracts" will be utilized for the section producing pure substances.

vii. Quality and packaging

Each batch of the therapeutic substance will be subjected to rigorous quality evaluation in accordance with the requirements of finished product specifications based on international standards.

Therapeutic substances are packed in suitable size glass containers with air-tight closures and sealed to avoid pilferage. The label should bear full

identification of the product according to international practices and national regulations.

Pure therapeutic substances possess potent pharmacological properties and necessary precautions should be exercised during handling and packaging in order to avoid dust inhalation and physical exposure.

5.3.3 Module for manufacture of pure therapeutic substances from medicinal plants

Choice of medicinal plants

The selection of the medicinal plants to illustrate the process technology for production of pure substances is based upon the following considerations:

- a. Almost entire supply of these medicinal plants is obtained from the developing regions of the world either through cultivation or collection from natural habitat.
- b. The derived therapeutic substances are of great value and can find considerable consumption in developing countries and export to developed countries.
- c. Technology for commercial production of pure substances from these plants is relatively easy to adopt, requiring modest investment on equipment and can be acquired as process patents are no more effective in most of the cases.

i. Reserpine

Reserpine is obtained from the roots of *Rauwolfia serpentina* and *Rauwolfia vomitoria*. The best alkaloidal yields are obtained from *R. serpentina* with 0.7 - 3.0 per cent alkaloidal contents. Reserpine is usually 10 per cent of the total alkaloids.

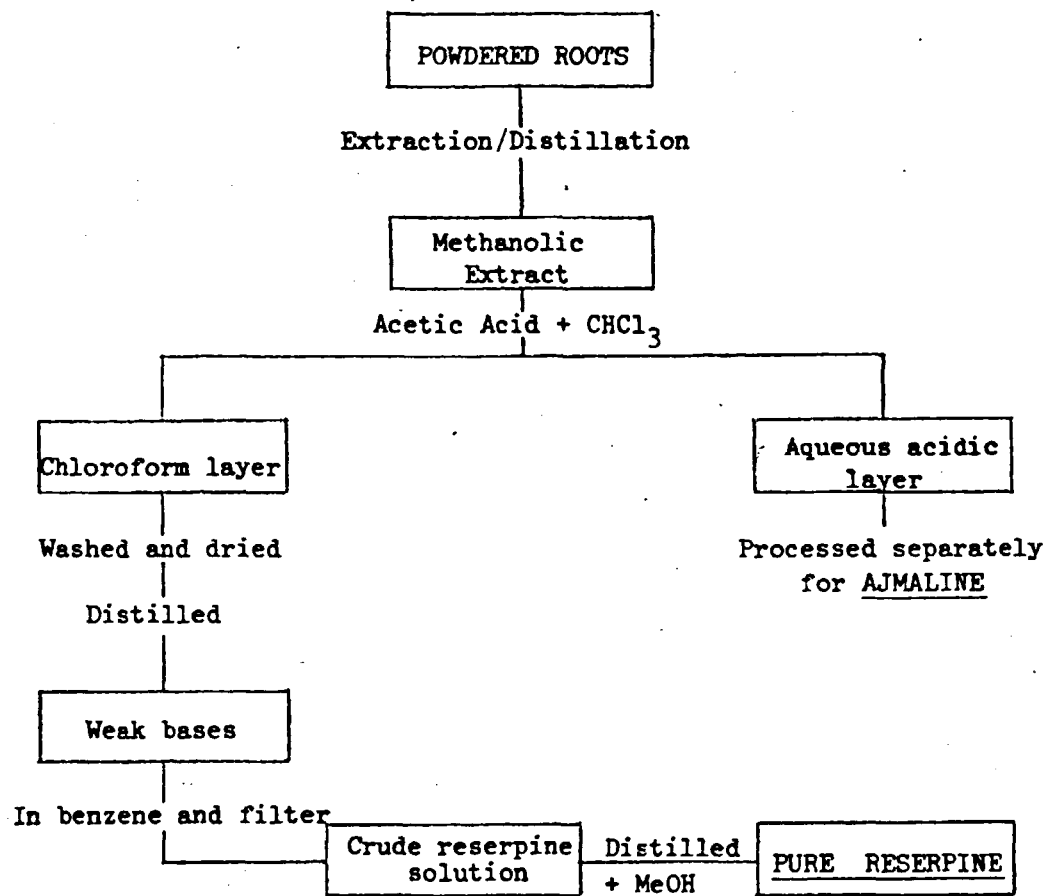
There are numerous patented processes for manufacture of reserpine, most of them based on chromatographic principle of isolation of reserpine. The alkaloid reserpine being a "weak base" it can be first separated from "stronger bases" by treatment with weak acid and the non-salt-forming portion can be further purified by a suitable technique.

The process^{11/} briefly outline below, is perhaps one of the simplest to adapt and is based on isolation by partitioning between immiscible solvents and purification by crystallization. (Figure VI)

- a. Pulverised Rauwolfia roots are extracted with methanol and the methanolic extract is subjected to distillation under reduced pressure to remove methanol.
- b. The extract is taken in 15 per cent acetic acid and the weak bases are isolated by extraction with chloroform (The acidic aqueous layer is processed separately for production of Ajmaline and other stronger bases).
- c. The chloroform extract containing reserpine is washed with water, dried over anhydrous sodium sulfate and the residue recovered by removing the chloroform under reduced pressure.
- d. The residue is dissolved in benzene and insoluble matter removed by filtration. The benzene is then removed from the solution by distillation under reduced pressure to obtain the crude reserpine substance.
- e. The pure reserpine in white crystals (melting at 262-263° C) is obtained by recrystallization of crude reserpine from methanol

^{11/} Ciba, Schweiz. Pat. 313 680 (1952)

Figure VI: Unit process: Production of reserpine
from Rauwolfia roots



ii. Quinine and Quinidine

Quinine and Quinidine, the two major alkaloids of Cinchona bark which also contains numerous analogous alkaloids in smaller quantities, are obtained by liberation of free alkaloids in situ in the crude drugs and extraction of the free bases with organic solvent immiscible with water. The isolation of pure alkaloids is based upon the principle of differential solubilities/crystallization of the sulfates. The sequence of unit processes is illustrated in Figure VII and briefly outlined below.

The average contents of total alkaloids in the dried roots vary between 6 and 16 per cent depending upon the species. Similarly the yield of quinine also differs from 10 per cent to even 90 per cent of the total alkaloids in certain species.

The unit process outlined here is generally used and is based on simple process technology:

- a. The powdered crude drug is treated with slaked lime and 5 per cent aqueous sodium hydroxide.
- b. The liberated alkaloids are extracted with hot petroleum or toluene.
- c. The alkaloidal extracted is distilled under reduced pressure to obtain the crude alkaloidal mixture.
- d. The alkaloidal mixture is dissolved in diluted sulfuric acid by heating, filtered if necessary, and cooled. Upon cooling the pure quinine crystallizes out as sulfate.
- e. The aqueous mother liquor is then treated with alkali to liberate the bases and extracted with selected organic solvent which yields quinidine upon recrystallization.

5.4 Commercial trends in medicinal plant trade

The present world consumption of the crude drugs is estimated to be about 551 million dollars annually.^{12/} A large variety of medicinal plants in

^{12/} Data compiled by the United States Statistical Office and I.T.C.

varying quantities are included in this estimate but eight major drugs alone represent 20 per cent of this trade.^{13/} The share of herbal remedies, medicinal teas and other drugs not included in the category of ethical pharmaceuticals was not possible to extrapolate as the available statistics have not been classified on this basis.

In the recent decades the commercial supply of the medicinal plants has been seriously disrupted due to numerous reasons. As a result of this disruption, serious problems have been encountered both by the cultivators and buyers. Major problems, generally ascribed to erratic supply position, are enumerated below.

i. Short supply The situation has caused non-availability of sufficient quantity of crude drugs to the processor causing artificial escalation in prices not benefiting to the grower in any way, redundancy in processing capacities due to shortages and at times increase in the production cost of the end-product due to utilization of crude drugs of inferior quality.

ii. Over supply Periodic overflow of crude drugs in the world market has resulted in "glutt" when processors could not "lift" the stocks causing abnormal crash of prices and loss of sales directly affecting the cultivators and ultimately resulting in loss of incentive in collection or cultivation, cycling back to periods of short supply.

Such a vicious cycle of fluctuating supply and prices of crude drugs, has, in certain cases, compelled the end-users to either develop their own plantations of crude drugs in locations ensuring constant supply or switch over to synthetic processes to obtain the therapeutic substances or raw materials even when such approaches may not be economically favourable.

^{13/} Medicinal plants and their derivatives: UNCTAD, Geneva, 1982

Aside from the large varieties of herbs used in traditional medicine, ninety-nine medicinal plants and species have been identified,^{14/} either growing in the natural habitat or being cultivated in many countries of Africa, Latin America and Asia, which have continued to find their use in modern medicine. Further scrutiny of these medicinal plants with respect to therapeutic significance, extent of occurrence, level of consumption, world trade indices and future potential of commercial exploitation has enabled to identify twenty medicinal plants (Table 2) considered to be of high priority for the establishment of related commercial and industrial undertakings in developing countries. These undertakings, however, will have to be planned depending upon the level of technology available and designed at relatively small scale retaining provisions for expansion especially towards higher levels of technology in the future.

5.4.1 Present status of trade

In recent years, the trends in the trading of medicinal plants have taken a turn towards the worse with the result that the producer and traders have become shy and consumers either reluctant to depend upon supplies or are diversifying their activities. This highly undesirable status will seriously jeopardize the prospects for developing countries if corrective measures are not taken forthwith.

The supply of major commodities is erratic and unpredictable which adversely affects the world prices causing serious setbacks both to the growers and consumers. The price of ipecacunha, for instance, trebled in a period of less than two years due to short supply. The excess supplies of cinchona bark in the recent past has resulted in sharp decline in the world prices inflicting serious blow to cultivators. Declining supplies of Mexican diosgenin during the period 1963-1980, forced consumers to gradually switch over to alternate materials. As a result the Mexican share of corticosteroids

^{14/} Medicinal and Aromatic Plants for Industrial Development;
A. Tcheknavorian-Asenbauer and Wijezekera, R.O.B., UNIDO/IO.505 June 1982,
p.87.

Table 2 A list of preferred medicinal plants for the manufacture of pharmaceuticals in the developing countries

No.	Plant species	Plant part used	Therapeutic substance present ^{a/}	Occurrence			Origin ^{b/}	Market potential
				Africa	America	Asia		
1	Acacid species	Stem	Gum	x	-	-	W	sustained and good
2	Agave sisalana	Leaf juice	(Hecogenin)	x	x	x	C	" " "
3	Aloes species	Leaf juice	Aloin	x	x	-	CW	good
4	Atropa beladonna	Leaf and roots	Atropine	-	-	x	C	domestic/regional
5	Cassia species	Leaf and roots	Sennosides	x	x	x	W	domestic/regional
6	Cantharus roseus	Leaf and root	Vinblastin Vincristin	x	x	x	CW	good
7	Cephalis species	Roots	Emetine (Cephaline)	-	-	x	C	sustained and good
8	Cinchona species	Bark	Quinine Quinidine	x	x	x	CW	sustained and good
9	Cleviceps purpurea	Whole	Ergometrine (Ergotamine)	-	x	x	C	domestic/regional
10	Digitalis lanata	Leaves	Digoxin	x	-	-	C	domestic/regional
11	Dioscorea species	Tuber	(Diosgenin)	x	x	x	CW	sustained and good
12	Ephedra species	Whole	Ephedrine	-	-	x	W	domestic/regional
13	Glycyrriza species	Rhizoms	Extract	-	-	x	W	sustained and good
14	Hyascyamus species	Roots	Hyocyamine	x	-	-	W	domestic/regional
15	Papaver somniferum	Latex	Codein (Morphine)	-	x	x	C	sustained and good
16	Physostigma venenosum	Seeds	Physostigmine	x	-	-	W	good
17	Pilocarpus species	Leaves	Pilocarpine	-	x	-	W	good
18	Plantago vata	Seeds - Husk	Ispagula	-	-	x	C	sustained/good
19	Rauwolfia species	Roots	Reserpine Ajmaline	x	-	x	W	sustained and good
20	Ricinus communis	Seeds	Castor oil	x	x	x	CW	sustained and good

^{a/} The names in brackets are raw material used for synthetic modifications to therapeutic substances
^{b/} w = wild growing; c = cultivated.

precursors, which was 375 tons out of 500 tons total world requirements in 1960 stumbled down to 165 tons while the world production soared to 2,100 tons in 1980. The share of synthetic precursors during the same period has increased from nil to 220 tons.^{15/}

In the wake of increasing demand for a natural product, the inability of the source country to meet the challenge is a vivid example of how a market of otherwise great potential can be lost.

The situation could have been averted by promptly stabilising the supplies and promoting the cultivation of dioscorea and agave sisalana, both of which can be commercially used for production of steroid precursors and widely found in natural habitat of all the three developing regions.

National policies to prohibit export of crude drugs without ensuring sufficient local production capabilities for export has also contributed in affecting the market stability and inducing potential erosion.

5.4.2 Location of industries based on medicinal plants

In some developing countries industries based on medicinal plant have been established but in comparison to the world market, the production share of their establishment is very small. Only 20 per cent of the world requirement of about 500 tons of quinine can be processed in the developing regions while over 60 per cent of the glycyrrhiza roots are still exported in crude form. Rauwolfia and most other medicinal plants are almost entirely exported in crude state.

The medicinal plants based industries are located in only selected and newly industrialized developing countries. Dosage-form manufacturing facilities, although existing in many developing countries but most of these are based upon imported raw materials, and where ever a natural product is employed as raw material, even that is imported in purified, extract or

^{15/} ITC field investigations. Medicinal plants and their derivatives, UNCTAD, Geneva, 1982, p.127.

prepared form. In spite of this status, the cost of production of pharmaceutical dosage-forms manufactured in developing countries is considerably less as compared to developed countries.

5.4.3 World requirements of medicinal plants and future potential

Estimation of the world requirements of medicinal plants appears to be a fruitless exercise due to the fact that the statistics specifically for medicinal plants are not normally compiled separately, data of consumption in developing countries is not available and even the estimation of real requirements in the developing countries is not possible due to inadequacy of health-care programmes. The assessment of the export quantities is also not easy because the relevant data for all drugs cannot be found and even in most other cases the information is not sufficient to make sensible assessments. Suggestive indications, however, can be derived from the import indices^{16/} of the developed economies regarding some crude drugs of significant trade value summarized below:

	<u>Crude drug</u>	<u>Quantity (tons)</u>	<u>Value (US \$ 1000)</u>
1	Cinchona bark	10 000	14 000
2	Digitalis lanata	1 000	2 000
3	Glycyrrhiza roots	45 000	45 000
4	(Diosgenin)	455	11 500
5	(Papain)	300	3 600
6	Plantago ovata	15 000	17 000
7	Rauwolfia	200	500
8	Senna leaves/pods	7 000	3 400
		<u>78 955</u>	<u>97 000</u>

The figures are close approximations with rounding off and merely offering a cursory overview.

^{16/} Extracted from product profile data of medicinal plants and their derivatives, UNCTAD, Geneva, 1982.

5.4.4 Cost comparison consideration for medicinal plants and
respective pure substances

Comparison of world prices of the pure therapeutic substances with the equivalent amount of crude drug was considered a valuable tool in assessing the potential benefits for establishment of industries based on medicinal plants in the source countries. Efforts in this direction, however, remained limited because of lack of information regarding prices. Citing the example of cinchona bark and quinine, where sufficient data was available, however, a general pattern of the price comparisons can be evolved:

Quinine sulfate (Q.A.A. 75%)	US \$ 100.00/kg
Cinchona bark (Q.A.A. 5%)	US \$ 1.44/kg
(Q.A.A. = Quinine anhydrous alkaloid)	

Note: According to above equations, 15 kg of cinchona bark (US \$21.60) would offer 1 kg of quinine sulfate (US \$100.00).

It is evident from the above illustration that the cost of pure quinine is almost five times the equivalent amount of a low grade cinchona bark. This comparison is based upon the "destination" price of cinchona bark and the component of supplementary benefit of production of quinidine from the bark has not been accounted for. Comparison employing "at-source" price of cinchona bark and including the factor of "quinidine yield" thus will result in significantly greater difference in the above exercise.

The comparison of prices of crude drugs at source with those at the international trade centres can be fully visualised by citing the example of Rauwolfia serpentina. It was being exported from India at 0.517 per kilogram while a major trade source in the Federal Republic of Germany quoted at 2.15 dollars per kilogram.

It was not possible to present additional examples to illustrate the price comparisons of pure substances with those of equivalent crude drugs because in case of several major commodities either the price of crude material or that of pure substance is not quoted. In some other cases the available prices were unreliable and unauthenticated.

5.4.5 Consumption of medicinal plants and purified substances in developed and developing regions of the world

In absence of adequate statistics any realistic estimates are impossible to develop regarding the consumption ratio of the medicinal plants between the developing and developed regions of the world and only circumstantial assessments can be made.

Almost all the medicinal plants which dominate the world trade in the west are also employed for treatment of diseases commonly encountered in the developing regions and in fact are more acceptable in the clinical practices. On the other hand, and although the health services are not adequate in the developing regions, the quantum of consumption is estimated to be still substantial and expected to increase considerably with improvement in health services.

With all logical considerations it will be safe to assume that given due expansion of health facilities and establishment of medicinal plants-based industries, the medicinal plants will find far more consumption in the developing regions than the present level.

5.5 Technology development considerations

The technology for processing of medicinal plants has gradually developed along with the advances made in the chemistry of plant products and has ultimately achieved precision levels to produce highly refined therapeutic substances. The technological developments, however, have been entirely made in the developed countries which continued to draw the raw materials from the developed regions with no serious attempts to transfer the technologies to the source countries except for the sake of convenience from operational point of view or because of impractical conditions for transportation of crude drugs.

Because of the distant location of processing facilities, the drying and preparing functions for making the drug worthy of shipment and "crushing and maceration" of dried crude drug at the plant location became inevitable but under the conditions suiting to manufacturers, the cost of these additional

steps was tolerated. The other reason for such approach was that the industries based on certain locally available crude drugs were already established in the west and only transportation of crude drugs, obtained at low costs from abroad was required for keeping the installations at higher utilisation level.

In the wake of the advances in pharmaceutical sciences in the West, the medicaments derived from plants have not been able to maintain the previously held degree of preference and consequently the attention towards this sub-sector of pharmaceutical industry remained limited to bare necessity. The situation of drug supply in the developing countries, however, is very different and grossly short even in case of the drugs essential for minimal health care and which these countries can hardly afford due to financial limitations. Under such conditions, the ways and means have to be evolved in order to improve the supply of pharmaceuticals at price levels economical to the developing countries.

The first step in this direction, logically is to enable the developing countries to develop appropriate technologies for production of drugs economically and based upon the degree of competence available at their disposal. Admittedly, the development of pharmaceutical industry, especially under limitations of infrastructure and know-how, is a time-consuming process but the early stages can be developed relatively speedily.

5.5.1. Cultivation/Collection of crude drug

Organized on sound footings, the cultivation and collection of medicinal plants can offer a steady source of foreign exchange by ensuring regular supplies and reasonable returns. The steady supplies, and efficiently conducted trade will compete well with the alternate sources like synthetics and may result in restoration of markets and the expansion potential can be safely predicted. Although most of the naturally occurring therapeutic substances have been chemically synthesized in the research laboratories but except few simple ones like ephedrine, have not been able to compete with the natural products and because of the prohibitive cost for synthesis, may not be able to find commercial justification as long as the natural products continue

to remain in good supply. Undoubtedly some of the synthetic substitutes are available in the commerce today but only because of shortages and uncertainty of supplies of natural parallels.

5.5.2 Industries based on crude drugs

It has been illustrated that a therapeutic substance is far more costly as compared to the equivalent crude drugs while it has been well established that in most of the crude drugs the therapeutic activity is at least same as the equivalent amount of pure substance. On the contrary, observation have been recorded that the presence of other natural substances in the crude drug sometimes may increase the therapeutic activity^{17/} and even act as moderator for the side effects exhibited by the pure therapeutic substance. It has also been observed that sometimes chemical cleavage of natural moiety results in alteration or total loss of therapeutic activity of natural extract.^{18/}

From the pharmaceutical point of view many medicinal plants can be directly converted into modern pharmaceutical dosage forms such as tablets, capsules, syrups, liniment, ointments, etc. and can be conveniently administered orally or topically--the most widely used modes of administration.

Examples for some of the possibilities with wider potential of use are appended below:

<u>Crude drug</u>	<u>State</u>	<u>Dosage form</u>	<u>Therapeutic use</u>
Atropa Beladonna	extract	plaster	Antispasmodic
Cinchona bark	powder	table/capsule	antimalarial
Digitalis lanata	powder	tablet/capsule	cardiotonic
Glycyrrhiza roots	extract	syrup	expectorant
Ipecacuanha roots	powder	capsule/tablet	expectorant and antiamoebiasis

^{17/} Problems relating to the preparation and use of extracts from medicinal plants, A. Bonati, *Fitoterapia* Li, 1980, pp. 35-37.

^{18/} Studies in the alkaloids of *Rauwolfia Serpentina* Benth and mode of their occurrence, Part II, S. Siddiqui, S.A. Warsi, M. Alauddin, *Pak. J. Sci. Ind. Res.* 1959, 2, p.80.

Plantago ovata	seeds	as such	laxative
Rauwolfia roots	powder	tablet/capsule	hypotensive
Senna leaves/pods	powder	tablet/capsule	laxative

The technology development for conversion of the crude drugs directly or after simple extraction to modern dosage-form requires such know-how and skill which can be expediently evolved in countries of even lower development level without resorting to large investment towards plant building and machinery and can also be economically justified at relatively low capacity levels.

The countries establishing such industries need not possess all the required crude drugs resources because the crude drugs can be imported from other developing countries. Even under such arrangements the cost of the finished products will remain significantly lower than the products based on refined therapeutic substances and synthetics.

6. RESEARCH AND DEVELOPMENT

Research and development is a vital component of sound infrastructural base for establishment of any sector of industry but in case of pharmaceutical industry it has deeper roots.

The field of research and development in pharmaceutical industry is particularly wide and extremely diversified in nature. The undertakings related to discovery of new therapeutic agents, synthetic approaches and development of high level process technologies all require well developed educational, scientific and industrial infrastructure and must be adequately backed by financial resources. Fruitful results can only be obtained through painstaking efforts by highly trained and experienced personnel, extended period of pursuit, enduring patience and large investments. In view of the importance of this aspect for industrial development and its enormous scope, it is considered more appropriate that detailed consideration in this regard should form subject matter of an entirely separate study.

In the present study, therefore, the research and development aspects related to first and second levels of technological competence have been covered with the understanding that research carried out at this level can be

directly translated into practice to improve upon the performance, efficiency and product quality. These aspects of research and development are more beneficial on the face of changing pattern of trade of medicinal plants in contrast with the pre-World War II years when the industrial processing facilities remained exclusively with the developed economies and the processing technologies were accordingly evolved to suit the then existing trade and industrial practices. During World War II, the short supplies of crude drugs forced the researchers in West to alternate synthetic sources for self-reliance and this trend is ever increasing with little attention towards exploration of plant sources. Under this situation the developing economies will have to resort to their own efforts to make beneficial use of raw materials at their disposal and development of technological skill to suit their economic conditions.

There are numerous prospective areas related to research and development work based upon economic utilization of medicinal plants which are briefly outlined in this study in order to help facilitate the research and development programmes in developing countries depending upon the immediate needs and technological level to be attained.

6.1 Crude medicinal plants

Studies can be steered in the following direction:

- i. Agronomical investigations towards plant propagation, optimisation of crop yield and improved methods for cultivation and collection.
- ii. Phytochemical investigations to improve the quality of crude drugs, increase in the yield of therapeutic contents, and introduction of superior species.
- iii. Utilisation of techniques for improved hybrids development and attempts in genetic manipulation for development of better varieties of crude drugs.

6.2 Galenicals and dosage forms

The technology for production of galenicals should be reinvestigated in view of the availability of crude drugs in freshly harvested form. New processes development work can be organised on the following lines:

- i. elimination of drying process of crude drug after conducting experimental extraction of freshly harvested crop.
- ii. development of simpler and more efficient techniques for extraction using fresh drugs. The tissues of fresh crude drug are still intact and solvents can more efficiently extract the therapeutic substances of the material in relatively coarse state. Observations have been made that the solvent preferentially extracts the therapeutic substances ^{19/} from freshly harvested undried material yielding extracts more enriched with active substances.
- iii. Studies for development of improved extraction processes suited to the working conditions and innovations to improve the quality, yields and the processing costs.
- iv. Studies towards economisation by process improvements, solvent recycling techniques and exploration of alternates to solvent recovery.
- v. Research and development undertakings related to development of dosage-forms using crude drugs and galenicals as raw materials:
 - a. Dry dosage-forms incorporating powdered crude drugs.
 - b. Dry and liquid dosage-forms using extracts as vehicle and/or active material along with other drugs or synthetic substances.
 - c. Topical dosage-forms using dried extracts and essential oils as active ingredients alone or in combination with synthetics.

^{19/} Studies in the alkaloids of Rauwolfia serpentina Benth and mode of their occurrence Part I: A new hypotensive factor and alkaloid complexes from roots S. Siddiqui and M. Alauddin: Pak. J. of Sci. and Ind. Research, 1958, pp.1-3.

6.3 Pure raw materials and bulk substances

The research and development work related to the synthetic routes involved in the chemical unit process require advanced academic background and extended experience. In the course of development of early levels of technology, therefore, any approach in this direction may not be advisable. Full understanding with respect to the scientific background and principles of the acquired technologies, by itself will take considerable period of time before a sound infrastructure could be developed towards advanced research possibilities.

7. SCENARIOS

In view of the plausible potentials for the development of pharmaceutical industry based on medicinal plants it is foreseen that with serious efforts on the part of developing countries and moderate degree of technical support from the developed countries, it is possible that:

- i. By the year 1990 the early and middle level processing of the medicinal plants will be entirely carried out in the source countries offering substantial support to the national health care programmes and ensuring steady supply of raw and intermediate materials for export markets.
- ii. By the year 2000 the developing countries will acquire capabilities for propagation of sufficient quantities of the medicinal plants to satisfy the world demand competing healthily with the alternate synthetic approaches and will attain technological skill to convert the crude drugs into pure therapeutic substances and synthetic precursors economically and in sufficient quantity to satisfy the growing world requirements.

8. BENEFITS AND CONSTRAINTS

The benefits, both to the producers of crude drugs and to the consumers, which could be derived by establishment of medicinal plants based processing and industrial undertaking, are numerous but in order to achieve the desired results these undertakings should be systematically planned initially by organising the cultivation and collection of medicinal plants in a scientific way followed by establishment of related industries.

8.1 Benefits

8.1.1 Developing countries

- i. The pharmaceutical services to the national health programmes will be available to wider section of the population at more economical cost.
- ii. The source country will draw more economic benefit of the produce which offers nominal earnings at present.
- iii. The end product will incur substantially reduced production cost with better chances of competing with alternate sources.
- iv. Regularity in supplies and assurance of quality of the products will stabilise the market and help ensure future prospects.
- v. Industrial infrastructure of the source country will improve with provision of industrial employment.

8.1.2 Developed countries

- i. The supplies and quality of the crude drugs will be ensured eliminating the price fluctuations, shortages and over stocking problems.
- ii. The end-products of crude drugs will be available in adequate quantity and through agreed schedules.

- iii. There are good chances that processing in the source country may result in reasonable decrease in the prices of end-products.

8.2 Constraints

The circumstances which did not permit establishment of industries based upon medicinal plants in the source countries go back into the history when the relevant technologies were developed and established preferentially in West. As a consequence, the developing countries are now confronted with numerous constraints:

- i. The developing countries have no effective hold on the prices of the crude drugs which they produced
- ii. The suppliers are constantly confronted with hazards of market instability and sharp declines in prices
- iii. The technologies for processing of crude drug have not developed in the developing countries and they are unable to acquire these from technology holders
- iv. Necessary know-how for such undertakings is not available
- v. The infrastructure needed for such undertaking is also weak in developing countries.

9. SUMMARY OF THE FINDINGS

The world trading in medicinal plants was of the value of 551 million dollars in 1980 showing a cumulative growth of 55 per cent over a period of preceding four years. This figure includes many herbs which have found increasing use as medicinal teas and in health foods but at the same time the medicinal plants supplies which do not appear in the international trading are not included. With the presently collected statistics it is not possible to develop accurate assessments.

The international trading of medicinal plants has been subjected to serious set backs during the last 20-30 years mainly as a result of deterioration in the market stabilities with respect to supplies, prices and quality of crude drugs.

Declining trends have been observed in the demand of certain commodities of major commercial interest also but in view of the therapeutic importance it appears that the market status can be regained through stabilization of the supplies and ensuring the quality.

Reliable consumption trends, trade statistics and prices of most of the important commodities are not available because these are either subject to extreme fluctuations or not even quoted due to contractual arrangements. Under these circumstances a sensible forecast of future trends is difficult to develop.

A great majority of commercially and therapeutically important medicinal plants are obtained and collected in many developing countries but exported to the industrialized countries in crude drugs form for further processing.

Twenty medicinal plants, identified on the basis of commercial importance and wider therapeutic value are extensively found in developing regions of the world. These are expected to retain their therapeutic/commercial value in the foreseeable future.

There is strong evidence to support that scientifically organized collection and cultivation and well planned trading systems are the prerequisites to ensure recapturing the market for medicinal plants and for the future growth potential.

There are good prospects for collection/cultivation of selected medicinal plants in the developing countries and economically viable if planned as a proper business undertaking.

Numerous important medicinal plants are under organized cultivation in developing countries and further improvements in cultivation techniques offer good prospects.

The developing countries, in absence of industries based on medicinal plants, are unable to draw full economic benefit of their valuable natural resources. In addition to value added economic benefit, the industrial establishment will also provide support to the health services of the developing countries.

It has been well accepted that the pharmaceutical dosage-forms based upon crude or semi-refined drugs as raw material are of equal therapeutic value and as such the cost intensive production of pure substances is not always necessary particularly in case of dosage-forms for oral administration.

The infrastructure for cultivation and lower level processing of medicinal plants is available in many developing countries and can be restructured for improved economic production of crude drugs and semi-refined raw materials.

Capabilities towards advanced methods and technologies are yet to be instituted in the developing regions in the following fields:

- Modern agronomic techniques for crop propagation, yield improvements and upgrading of medicinal plants.
- Technology for synthetic modification of natural substances for production of therapeutically active compounds.
- Capabilities in:
 - resource finding,
 - negotiations for acquiring know-how and technologies,
 - bilateral and contractual agreements for transfer of technology,
 - management of industrial undertakings.

10. CONCLUSIONS AND RECOMMENDATIONS

In order to develop more meaningful projection related to the future prospects of medicinal plants in the pharmaceutical industries, further exploratory studies are necessary to secure sufficient trade indices and particularly those of major commodities. These studies would greatly help in making realistic assessments regarding the present constraints, to recommend measures to stabilize the trading in medicinal plants and to ensure future potentials.

The present declining or erratic trends are detrimental to the trade in crude drugs but these are merely the result of disorganized trading and supply pattern because the co-ordinated supply arrangements for some drugs have been all along operating smoothly.

In case of most of the medicinal plants reviewed, it is apparent that there is no threat to these drugs from synthetic alternates at least in the foreseeable future. The trade set-backs suffered by certain commodities in the recent past have actually been inflicted by newer sources of the crude drugs taking advantage of the difficulties in obtaining supplies from traditional sources.

There are positive indications that given a chance through well designed programme for cultivation/collection and dependable trading environments the future prospects of the medicinal plants can be well secured.

The future prospects of the medicinal plants as raw materials for pharmaceutical dosage-forms within the developing regions is presently in a state of neglect and effective exploitation of this potential in supplementing the health care programmes in the developing countries is expected to generate further increase in demand of the crude drugs.

Sparing the medicinal plants based industries requiring higher levels of technological expertise, other industries can be established in the developing countries generating the value added benefits supplementing the economic growth of the developing countries and for which sufficiently large quantities of raw

material can be made available. In view of the weakness in the industrial infrastructure of the developing regions, however, the planning for establishment of these industries will have to be phased out in accordance with the technological capabilities levels. Such approach would permit sustained and effectively beneficial growth of industrial undertakings based on medicinal plants.

The first and foremost objective should be for measures towards stabilization and expansion of trading aspects by compilation of the relevant statistics and commercial data followed by organized collection and cultivation systems to ensure regular and adequate supplies matching the demand projections.

In the subsequent stage, the industrial undertakings for early level processing of medicinal plants should be established in selected developing regions capable of providing sufficient raw materials for economic viability of industrial set-up. The demand levels both for domestic consumption as well as for export of the produce will have to be carefully estimated and projected to ensure success of these industrial undertakings.

With the advancement of appropriate infrastructural framework, the medicinal plant based industries requiring advanced technological levels can be gradually introduced in the industrial development plans but the establishment of such industries, which are highly specialized and cost intensive, great caution has to be exercised and should be best introduced through collaborative arrangements with technology holders to ensure complete transfer of technology, efficiency of performances and ensured sale of the finished products.

