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BIOSCIENCE AND ENGINEERING

DP/IND/80/003

Technical report*

Prepared for the Government of India
by the United Nations Industrial Development Organization (UNIDO)
acting as executing agency for the United Nations Development Programme

Based on the work of J. Heller,
Consultant on Controlled Release Technology

United Nations Industrial Development Organization
Vierna, Austria

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ABSTRACT

This report describes a review of the controlled release portion of Project DP/IND/80/003 and is based on a visit that took place at the National Chemical Laboratory (NCL) in Pune, India between October 21 and October 30, 1986.

The bulk of the visit consisted of detailed discussions with Mr. Rajagopalan and his group on their work on carbofuran encapsulation and plans for future activities in controlled release. Academic research being carried out by staff members in pursuit of their Ph.D. degrees was also reviewed.

The status of the abate project was discussed with Dr. Sharma and discussions with a number of other scientists were also carried out. In general, work carried out by the controlled release (CR) group is of high quality, but too narrow in scope and suggestions for expansion of their activities were made. It was further recommended that all CR activities at NCL be better coordinated and that as a minimum, a computerized high performance liquid chromatograph (HPLC) be purchased and dedicated to the CR program.

CONTENTS

I INTRODUCTION

The development of controlled release formulations for pesticides is one of the components of the project Bioscience and Engineering, DP/IND/80/003 started in 1981 and scheduled to terminate in 1986.

The rationale of CR pesticide formulations is now well established and the basic advantages are decreased amounts of the toxic agent necessary for achieving desired control, extension of duration of action and decreased toxic hazards for applicators.

While cost is generally not a significant factor in CR formulations intended for human therapeutics, CR formulations for agricultured applications must be low cost items. Therefore, the development of such systems can not tolerate expensive raw materials or expensive manufacturing procedures. Furthermore, although biodegradability is a much overemphasized requirement, it is preferable that any polymer used in CR formulations be biodegradable.

For these reasons, CR formulations using either microcapsules or monolithic dispersions are satisfactory fabrication procedures and the use of abundant, naturally occurring polymer such as starch or cellulose are also satisfactory materials. However, readilly available, inexpensive synthetic polymers such as various rubbers are also satisfactory materials, particularly when the rubber is used in latex form.

This report summarizes extensive discussions held with various NCL staff members and makes recommendations based or these discussions.

II SUMMARY OF DISCUSSIONS HELD AT NCL

A. Development of Carbofuran Delivery Systems

This work is being carried and under the direction of Mr. Rajagopalan by Dr. H. Narain, Mr. N. Amarnath, Mr. C. Bhaskar, and Mr. P. G. Shukla. An additional member of the group Dr. (Mrs.) S. Vaidya works on a project sponsored by Sandoz. This project was not reviewed.

The carbofuran CR work started out about five years ago with the basic premise that the polymer must be cheap and that a 60 day protection of the crop is adequate.

The following systems were investigated for carbofuran encapsulation:

1. Crosslinked poly(vinyl alcohol)

Poly(vinyl alcohol) is complexed with an adduct of a 1,3-diol and boric acid and microcapsules prepared by a phase-separation process. This system required pure carbofuran and released the active agent too fast. In addition, PVA is too expensive. Thus, this system was abandoned.

2. Starch-Xanthate

This sysstem has been extensively investigated by Shasha and coworkers at the USDA Laboratories in Peoria, Illinois. Dr. Shasha visited NCL in March 1983 and again late 1984. Because starch is cheap, readilly available and biodegradable, this represents a good choice. Although starch xanthate is made under alkaline conditions, it is gelled in an acidic pH so that the alkaline instability of carbofuran is not a problem.

Use of this system, however, is not without problems. Among them is the hazardous nature of CS_2 used in xanthate preparation, poor storage stability and evil odor of the xanthate. Furthermore, it has a somewhat limited scope of release rates and has to be compounded with inert fillers to prolong carbofuran release for the desired length of time.

3. Polystyrene

This is a moderately priced polymer and microcapsules can be readilly prepared by a solvent evaporation technique. During

microcapsule preparation, carbofuran tends to migrate to the surface of the microcapsules so that release is too fast. However, this problem could be solved by additional work.

4. Urea-Formaldehyde

This is an excellent procedure and depending on the ratio of urea to forraldehyde, materials having a range of crosslink densities and consequent range of release rates can be prepared. Because a very fine powder is produced (a few microns), this product is useful in seedcoat applications.

5. Starch-Urea-Formaldehyde

Another excellent and novel (patent to be filed) procedure was developed, where starch is crosslinked by a urea-formaldehyde resin. The process is somewhat analogous to the starch-xanthate process without any of its disadvantages. The effect of various parameters and product properties is currently under investigation.

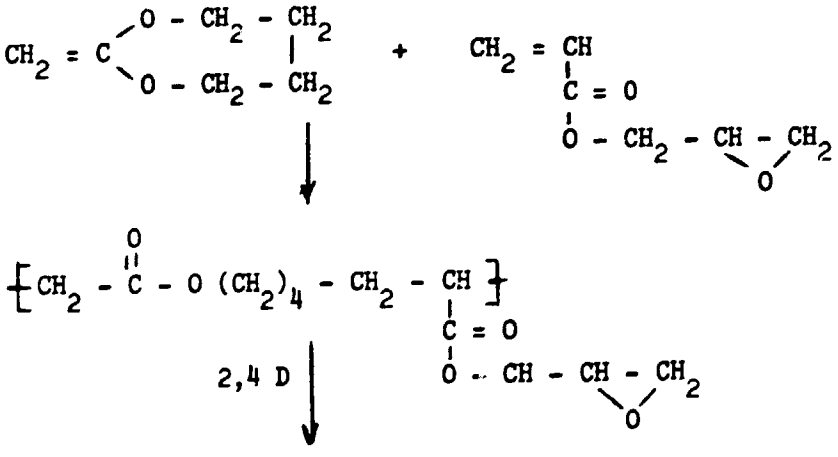
B. Academic CR Research

Limited involvement in academic research is under way or contemplated.

1. Pendant Drug

During his stay with Professor Harris, Dr. H. Narain initiated some work on the chemical attachment of 2,4-D to a biodegradable polymer backbone.

The following reactions were carried out.



polymer-drug adduct

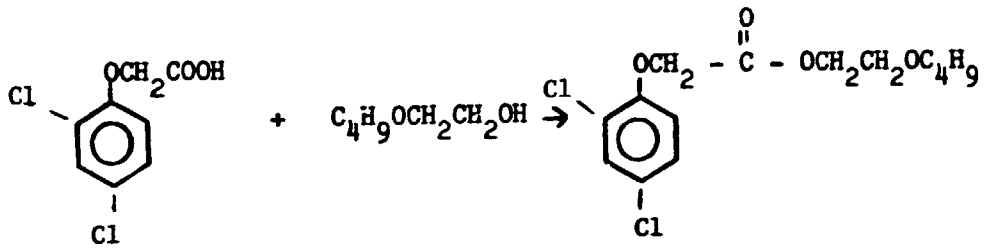
It is unlikely that this will result in a commercially viable product due to high cost.

2. Swelling Systems

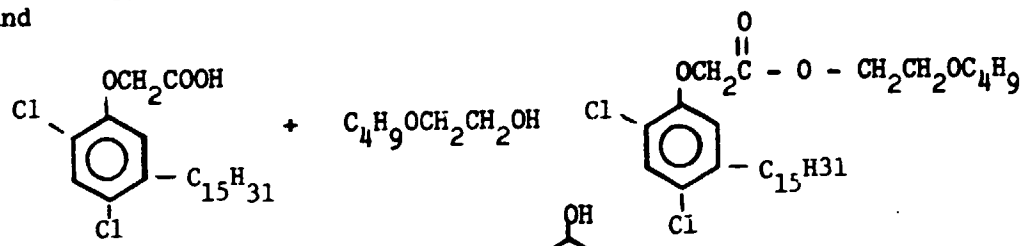
Mr. Shukla is considering studying swelling systems (Case II Swelling) as a Ph.D. thesis work.

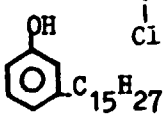
3. Herbicide

Mr. Amarnath is studying the release of a 2,4-D derivative and the same derivative containing a $C_{15}H_{31}$ derivative from rubber latices. The objective is to see what effect the $C_{15}H_{31}$ side-group has a rate of release and activity against hyacynth.



and



The C_{15} derivative is prepared from  which is isolated from Cashew nut shell, which is very abundant in India.

The release of the C_{15} derivative is slower than the derivative without the C_{15} group and its activity against hyacynths is slower, presumably because it is taken up by the plant at lower rates.

However, W. Amarnath's conclusion are based on single experiments so that no statistical analysis of the results could be made. Therefore, unless more experiments are carried out the results subjected to established statistical evaluating the results of this study are at best an indication of trends only.

C. Development of Abate System

This work is being carried out under Dr. R. N. Sharma, Head Entomology. This effort is not part of the CR Program under Mr. Rajagopalan, nor is entomology part of the Polymer Chemistry Division. Instead, it is part of the Synthetic Organic Chemistry Division.

Dr. Sharma's group has developed a very clever dispenser where the abate is placed in a container and allowed to diffuse out through a rate-limiting hydrogel such as an acrylamide gel. The dispenser has a number of exits which are supplied to the user plugged. By unplugging a specified number of exits, release can be regulated for a specific body of water. The device is anchored just below the surface of the body of water being treated. Very simple instructions are provided so that even semi-literate workers can place the device.

D. Other Non-CR Research

During the visit to NCL, discussions with other polymer scientists, not engaged in CR, were carried out. The major purpose of those discussions was to get a feeling for the scope of polymer activities at NCL as they might relate to CR activities. Some of those discussions are summarized below.

1. Dr. S. D. Vernekar

Works an epoxidized polybutadiene in order to prepare materials closely resembling butyl rubber. About 50% of the double bonds are epoxidized. This is an interesting approach, but the long term stability of the product due to reactivity of epoxide groups is of concern and the product will need to be compounded with appropriate stabilizers.

2. Dr. S. S. Mahajan

Works on polymer blends such as polyphenylene oxide and polystyrene. Even though this is a General Electric product, India does not recognize composition of matter patents, only process patents. Consequently, if a process different from GE can be developed, the product would lie outside the scope of GE patents.

Dr. Mahajan is also working on a cellulose acetate modified by reaction with phenyl isocyanate for desalination membranes. Hollow fibers are not used due to inability to fabricate these. Instead, thin films sandwiched between perforated metal plates are used.

3. Dr. J. C. Sehra

Works on polymer blends such as Nylon 6 and polystyrene which are not mutually compatible and consequently phase-separate. However, by adding as little as 1-2% of a Nylon-polystyrene graph copolymer, the two become compatible. This research is important for producing polymer alloys.

4. Dr. Shrinivasan

Works on polyurethanes that use natural products available in India such as castor oil. In general, work on polyurethanes in India is

hindered by the unavailability of essential monomers such as di-isocyanates, polyesthers, etc.

5. Dr. S. Gundiah

Carries out very academics highly theoretical work on theories dealing with conformation of polyelectrolytes such as poly(methacrylic acid) and partially hydrolyzed polyacrylamide.

III SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

The 10 day visit to NCL consisted of: (a) discussions with polymer scientists, (b) tour of NCL physical facilities, and (c) delivery of two 50 minute lectures.

A. Discussion with Polymer Scientists

These have been summarized in the body of the report. In general, I found the caliber of science practiced at NCL to be of very high quality and the staff highly competent and quite enthusiastic about their research.

I found that the work carried out by Mr. Rajagopalan's group on the carbofuran delivery is first rate. The important parameters of performance, cost and manufacture constraints were recognized at the onset and a successful product developed in a reasonable amount of time.

I consider this group well qualified to continue their involvement in CR and with adequate help and support from management, this group has the potential of becoming a leader in CR work in India.

However, the work is too narrowly focussed on carbofuran. Thus, if this group is to become a significant contributor to CR and if this group is to become a center of excellence, then this involvement must be broadened.

Mr. Rajagopalan suggests that oral drug delivery for human therapeutics be seriously considered and I agree. However, a jump from the pesticide field to human therapeutics is a big step which cannot be made without full realization of regulatory requirements in terms of toxicological studies to be carried out in appropriate animal species, good manufacturing practice (GMP) and good laboratory practice (GLP). Also, consideration must be given to pharmakokinetics and pharmacodynamics in selecting drugs and in selecting the delivery regime. Thus, additional expertise will need to be coordinated with this expanded program.

I suggest that another area of therapeutics that should be considered is animal health. However, entry into the veterinary field will require a careful study of India's need so that consultations with veterinary experts need to be carried out.

Clearly, this broadening of CR activity does not mean that the pesticide field be abandoned. Quite the contrary, this activity should

be continued and because the methodologies developed for carbofuran are clearly applicable to other pesticides, additional industrial support should be readilly available.

It is not clear to me why abate delivery is being carried out outside the CR group, or at the very minimum, why the CR group does not actively participate in this effort. I would strongly recommend that those activities be consolidated.

It is also not clear why the only abate delivery system is the so-called "satellite." Although this is a very clever and useful device, it is only applicable to relatively large bodies of water and only works if algae coating is not severe. Thus, it seems that the abate delivery project neglects a very significant source of mosquito larvae breeding which takes place in small water puddles, which accumulate after rain or irrigation.

It would therefore seem appropriate to involve the CR group to develop formulations that can be sprayed or otherwise applied to these small bodies of water.

It would further seem that some effort should be devoted to preventing, or at least, minimizing algae growth. Thus, it is conceivable that polymer surfaces can be coated to prevent this growth or that an algacide could be incorporated into the polymer.

B. Physical Facilities

These are outstanding in terms of availability of sophisticated, modern instrumentation, but are lacking in equipment placed in laboratories and dedicated to the activity of the laboratory.

For example, the CR group uses ultraviolet spectroscopy to follow drug releases. This method, of course, only works with compounds that have adequate UV spectra, but most importantly does not recognize the presence of absorbing impurities that can be released along with the drug.

I would strongly recommend that a sophisticated, computerized HPLC be purchased and placed in the CR laboratory, or at least be made available for the exclusive use of that group. This instrument should have a variable wavelength UV detector and an automated injector. As the activity of the group expands, so will the number of samples that have to be analyzed. The automated injector with associated computer to operate the instrument and reduce data will allow essentially 24 hour unattended operation. Such an instrument can be purchased from Waters for about $60,000. We have a number of such instruments in our CR laboratory at SRI and we suggest that NCL consider the purchase of the following systems, listed in decreasing sophistication and price.

System #1

For HPLC and room temperature GPC

Model 840 - Chromatography Control and Data Station - Based on DEC Pro 380 with Waters single system LC and GPC software	17,600
Model 712 WISP - autosampler - with interface board for 840	11,500
Model 490 Programmable Multiwavelength Detector UV/VIS detector	10,000
Model 410 Differential Refractive Index Dectector	7,000
Model 510 Pumps (2) with 840 interface	13,100
Column Oven and Temperature Controller	1,500
	60,700

System #2

For HPLC only

Model 840 Chromatography Control and Data Station Based on DEC Pro 380 with Waters single system LC software	15,100
Model 712 WISP - autosampler with interface board for 840	11,500
Model 490 Programmable Multiwavelength Detector UV/VIS	10,000
Model 510 Pump (2) with 840 interface	13,100
	49,700

System #3

HPLC only

Model 680 Gradient Controller and Model 510 Pumps (2)	13,500
Model 481 UV/VIS Detector	7,000
Model 712 WISP - autosampler	10,000
Model 740 Data Module	2,900
	33,400

System #4

HPLC only

Model 680 Gradient Controller and Model 510 Pumps (2)	13,500
Model 481 UV/VIS Detector	7,000
Model U6K Manual Injector	1,500
Model 740 Data Module	2,900
	24,900

C. Lectures Delivered

I delivered two 50 minute lectures on the general methodologies of controlled release with heavy emphasis on biodegradable polymers. The purpose of the lectures was to expose NCL personnel to the latest advances in CR methodologies in an organized and systematic manner.

The lectures were well attended and generated a significant amount of discussion.

Due to the relative isolation of Indian CR scientists from the mainstream of CR activities which occur principally in Europe and in the US, it is most important to maximize the interaction of Indian Scientists with prominent workers in CR. For this reason, lectures by visiting experts and attendance of key CR meetings should be maximized as available funding allow. I recommend that two meetings be regularly attended. These are the annual meeting of the Controlled Release Society which takes place late June or early July, and the biannial meeting that takes place in Salt Lake City, Utah, organized by Professors Kim and Anderson. This latter meeting is an excellent meeting in that all papers are invited lectures so that the quality is generally excellent. The meeting has a limited attendance so that early registration is recommended. The next meeting is late February 1987.