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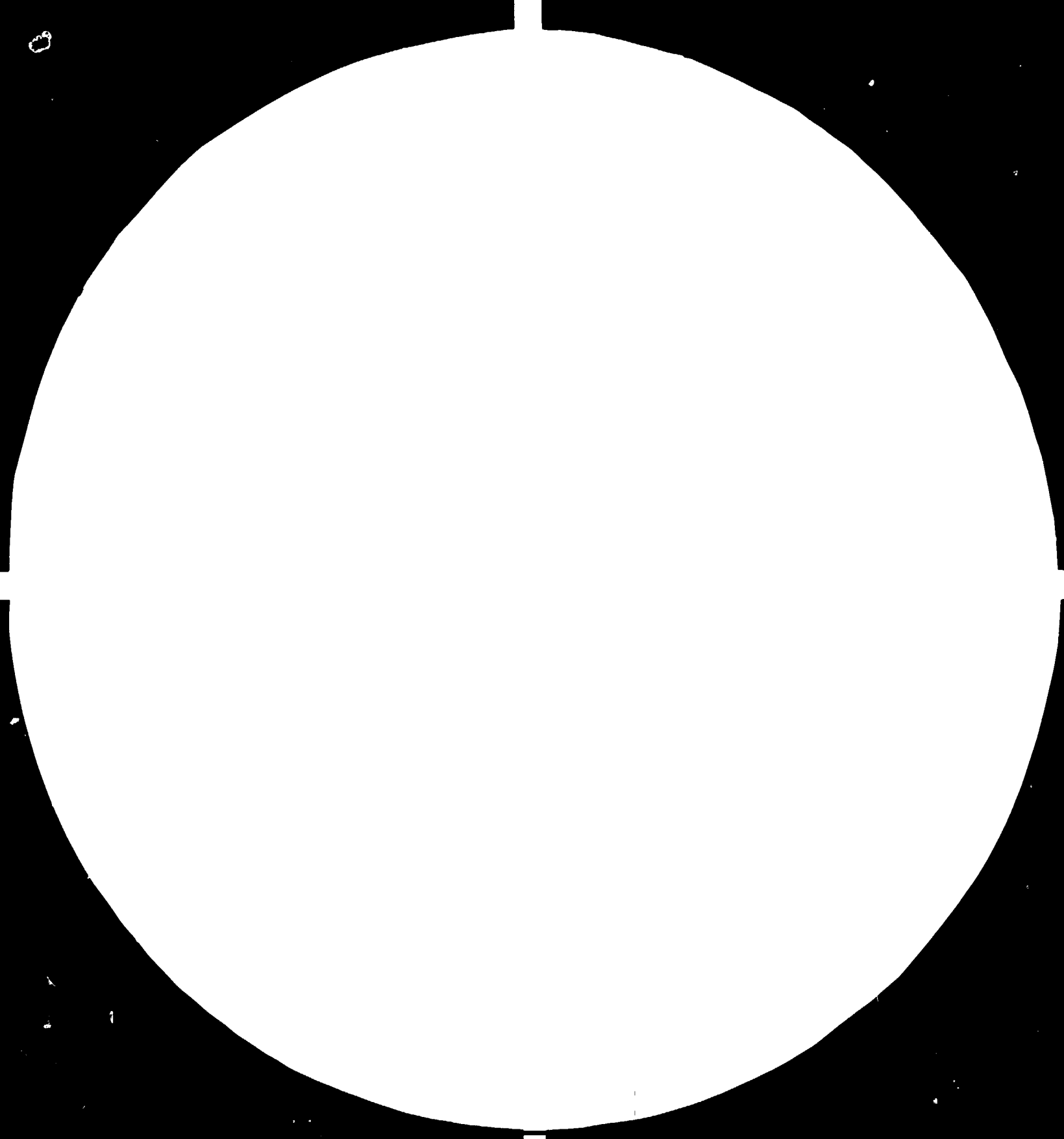

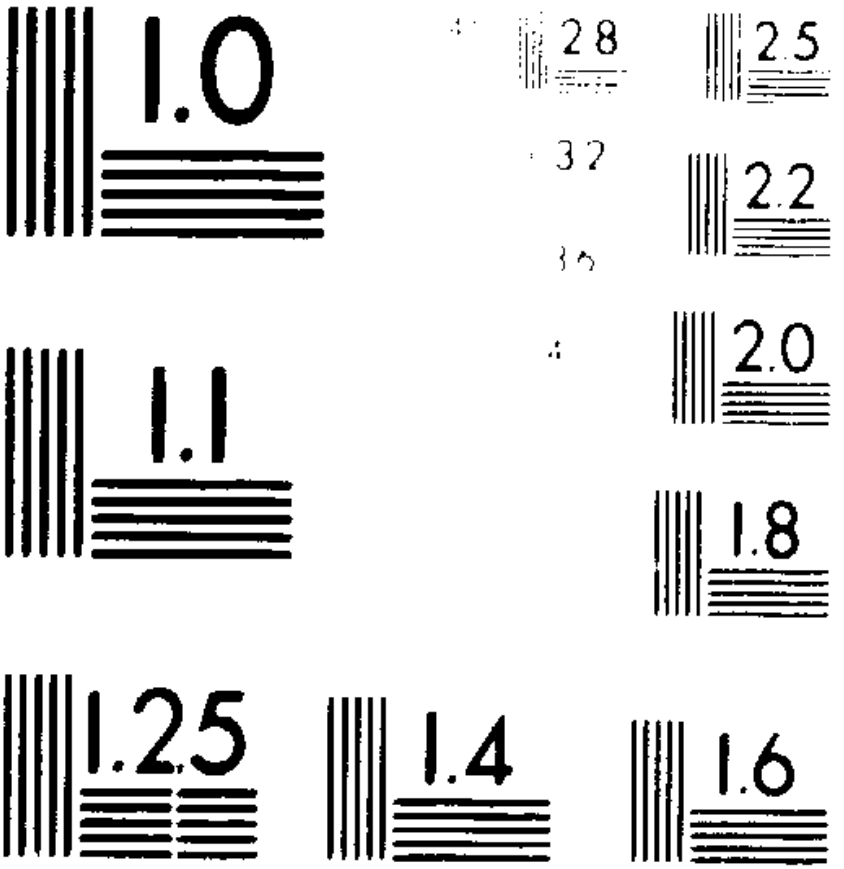

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DP/IND/80/003

INDIA

Technical Report*

Mission 1-16 June 1984

Prepared for the Government of the Republic of India

by the United Nations Industrial Development Organization,

acting as executing agency for United Nations Development Programme

Based on the Work of Danny H. Lewis

consultant on controlled release technology

United Nations Industrial Development Organization

Vienna

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1. SUMMARY OF FINDINGS

This report is based on the visit of the UNIDO consultant Danny H. Lewis to the National Chemical Laboratory (NCL), Poona, India, from 1-16 June 1984. The NCL project involving controlled-release pesticides was reviewed as related to DP/IND/80/003. The general programme organization and critical areas of research had been formulated at NCL with the guidance and recommendations of three previous experts on controlled release. Therefore, the objective of this mission was to review the programme progress and to discuss state-of-the-art technologies in controlled release with the appropriate NCL staff. Because of the continuous progress achieved by the laboratory, the role of each expert will necessarily change.

The overall program was found to be steadily progressing, and there is considerable evidence of technical accomplishment on the part of the NCL personnel. The present observations made and the review of reports submitted by the previous three experts clearly confirm that the program has advanced at a satisfactory pace since its conception. The research is currently divided into two general aspects based on pesticide application. As expected each of the areas exhibit significant technical achievements but also several hurdles yet to be crossed.

The program of highest priority involves development of a controlled-release formulation of temephos (Abate®)

a mosquito larvicide. Studies on a natural rubber/abate monolithic dispenser have been abandoned, at least temporarily, and a second product based on polyethylene is now being tested. The polyethylene/abate composition has exhibited long-term release in laboratory tests and is now (June, 1984) being evaluated in a few selected mosquito breeding sites in the local community. It is recognized by the staff that the present fabrication method for that product is not ideal, and more sophisticated extrusion techniques will likely improve the performance of the system. New equipment will be required for that work.

The second major program, which is currently receiving slightly lower priority, involves the development of a controlled-release carbofuran product for rice insect control. Considerable progress has been made with granular formulations based on starch and starch derivatives. Recently, experimental work was initiated on other formulation techniques and materials. Primarily, these efforts involve microencapsulation of the pesticide in synthetic polymers. Several complications have been identified in regard to the methods of evaluation of the carbofuran materials in actual rice insect control, expecially in the pilot field laboratory. No clear results have yet been achieved.

A significant effort is underway in the microencapsulation of other insecticides including fenitrothion and phorate in various synthetic polymers. Application as a sprayed dispersion

for mosquito control in the intended use.

The author demonstrated alternative microencapsulation processes to the laboratory staff. Both fenitrothion and carbofuran were successfully microencapsulated in polystyrene by a solvent-evaporation process during the author's visit. Several suggestions were made in regard to the interfacial polymerization technique currently being studied by the staff. More reproducible microcapsule formulations were achieved by the interfacial process during the expert's visit.

A considerable effort was devoted to discussing the analytical characterizations of the many controlled-release systems. The importance of rapid and thorough determinations of active content and laboratory release profile was emphasized to the staff. The author found a wide range of modern analytical instrumentation available and a highly competent staff, but a need for better understanding of the interpretation of the controlled-release data.

Several major seminars were presented by the author to the laboratory staff at large. These were designed to emphasize the latest formulation techniques and the importance of thorough and rapid characterization of prototype formulations. One particular seminar revealed to the staff the use of fibrous polymers as a unique approach to pesticide delivery. This led to further detailed discussions and specific laboratory plans in that area in regard to mosquito control.

Equipment items needed by the staff include a laboratory-scale extruder, sieving equipment for microcapsules, a centrifugal film-casting apparatus, and a greenhouse for entomology studies.

The program still suffers from the lack of an intermediate level program director to carefully coordinate the handling and analysis of all experimental data and to coordinate daily laboratory collaborations between the diverse staff involved in the project. This appears to be the major deficiency of the project. Overall, the project can be expected to result, in time, in useful pesticide formulations. Serious consideration should be given to maintaining this type of effort for at least five additional years beyond the current project. It has been the experience of the author that it can take as much as five years to establish the techniques and required background knowledge before any practical applications can be expected.

It is vital that the staff continue to establish communication with recognized laboratories in this field. Scientist from NCL should be supported with training programs in the U.S. and Europe at selected centers.

2. INTRODUCTION

The objective of this project is to develop controlled-release pesticide formulations of special utility in India. This is a major aspect of DP/IND/80/003 initated in 1981 and scheduled to conclude in 1986. The rationale and advantages of controlled-release products have been well documented in the reports of previous authors and consequently will not be repeated here.

It is worthwhile to emphasize the importance of utilizing natural polymers readily available in India as excipients for delivery of the active agents. Most synthetic polymers would be prohibitive in terms of cost and would certainly be unacceptable in this situation. Many years of related study in the U.S. have revealed that, even there, synthetic polymers are usually too expensive for use in bulk pesticides. Nevertheless, it is imperative that the NCL staff establish broad experimental knowledge with both synthetic as well as natural polymers in order that practical achievements can be realized in the less costly materials.

It is obvious that the scientists at NCL are conscious of the cost factor in material selection and are quite capable in identifying native materials for this study.

3. RECOMMENDATIONS

Major

(1) Designate a senior scientist as the project coordinator. It is imperative that someone below the level of Deputy Director be responsible for the day-to-day coordination of the various groups now involved in the project. These now include polymer formulation, polymer engineering analytical, and entomology. The facilities and personnel capabilities are in place. A middle-management coordinator is needed to maximize the efforts of all involved. The Deputy Director is responsible for the overall implementation of the project; however, he obviously cannot be expected to review data as it becomes available on all the different formulations and plan details of the experiments.

(2) Place a greater emphasis on the gathering and interpretation of analytical data regarding each controlled-release pesticide formulation. Careful coordination between the formulation staff and the entomology or analytical groups to allow improved formulations to be developed based on the latest efficacy and/or analytical results.

(3) Submit proposal for a second major project to commence at the completion of the current program in 1986. It is critical that this initial effort be expanded to allow ample opportunity to develop into a center of excellence in controlled-release technology.

(4) Ensure that all staff take adequate safety precautions when processing or otherwise handling pesticides. This is especially important with high-temperature compression molding or extrusion.

(5) Conduct a wide range of experiments using state-of-the-art microencapsulation procedures such as solvent-evaporation techniques with synthetic and natural polymers in order to broaden general working knowledge of controlled-release technology.

(6) Investigate melt-extrusion techniques for fabrication of synthetic polymers containing insecticides, particularly Abate®.

(7) Utilize simple melt-flow equipment such as melt-flow indexes and Instron Melt Flow instrument to generate preliminary samples for feasibility studies.

(8) Perform analysis on controlled-release insecticide samples exposed to field conditions for various time intervals. These data will provide the valuable in vitro - in vivo correlations desperately needed for the long-term success of the project.

(9) Procurement of the following equipment:

(a) Melt extruder (laboratory scale) to be used by the formulation group. Appropriate mixing equipment is required as well.

(b) Microcapsule Wet-sieve apparatus with appropriate set of sieves ranging from 20 to 400 microns to

be used by the formulation group. This is critical because duration of release is usually directly dependent upon microcapsule size.

(c) Ancillary glassware to allow preparation of microcapsules according to solvent-evaporation procedures (including a strobe light for measurement of stir rates).

(d) A centrifugal film-casting apparatus for preparing nonporous polymeric films.

(e) A suitable small-scale greenhouse facility for the entomology group. This should be a high priority purchase during 1984.

(10) Conduct room-temperature and accelerated vapor-phase in vitro studies using gas chromatograph on some of the mosquito insecticide formulation.

(11) Utilize scanning electron micrographs to assist in characterizing the pesticide microcapsule (and granular) formulations. Detect presence of unencapsulated pesticide, assess surface morphology and establish microcapsule size.

(12) Investigate efficacy of pesticide/polymer "sprayed paint formulations" for insect control on building surfaces.

(13) Investigate extruded fibrous polymers in simple short filaments or as coils of fiber in mosquito larvicide delivery systems.

(14) Abandon chemical methods of analysis and emphasize instrumental methods such as HPLC and UV.

(15) Long-range plan should include identification of a biodegradable excipient for the delivery of mosquito larvicides such as Abate®.

Minor

(1) Scientists from NCL should attend the annual meeting of the Controlled Release Society. (1985 meeting scheduled for Europe.)

(2) Training of NCL scientists in Europe and the U.S. is imperative. The following organizations were suggested as possible training sites.

(a) Southern Research Institute, Birmingham, Alabama
Dr. Donald R. Cowsar, Director, Applied Sciences

(b) Washington University, St. Louis, Missouri
Dr. Robert Sparks, Department of Chemical Engineering

(c) University of Akron, Akron, Ohio
Polymer Science Department, Dr. Frank Harris, Professor

(d) University of Gent, Gent, Belgium
Dr. Entiene Schacht, Professor

(3) Provide training for one senior staff of the entomology group in use of radioisotopes, possibly in Europe.

(4) Start library subscription to new Journal of Controlled Release, the offical journal of the Controlled Release Society.

(5) NCL staff submit more papers to appropriate controlled release journals in order to become identified as a center of excellence in this field of research.

4. PROJECT STATUS

1. Controlled-Release Mosquito Larvicide

Earlier studies on a long-acting mosquito larvicide based on Abate® incorporated in natural rubber have been terminated. Even though considerable progress was demonstrated on that specific task, a few significant problems have caused the project team to consider alternative approaches to this product. Consequently, a high priority effort is continuing on development of a controlled-release mosquito larvicide, but different polymeric matrix materials are being studied in current work. A system lasting thru one breeding season (8-9 months) is sought.

Current work is devoted to the compression molding of polyethylene sheets containing Abate®. Extensive in vitro studies in 1-liter jars are being conducted to determine the rate and duration of release under these laboratory conditions. The mosquito larvicide program was moved to a high priority project about 2-3 months ago and the project team meets regularly and a written monthly report is submitted. Excellent bioassay studies by the entomology group have been completed in small trenches and holes in an outdoor test area at the laboratory. The bioassay shows efficacious levels of the pesticide being released.

On approximately June 15, 1984, a limited field trial was initiated with the polyethylene/Abate® system. This

study, organized during the consultant's visit, was planned with the local malaria control authorities. This study will provide valuable field data on the current system.

It is not unlikely that work will be resumed on the natural rubber system once sufficient data are available on the new polyethylene formulations. The rubber formulation was temporarily abandoned because of retirement of a key scientist in charge of formulation work, problems with reproducibility and nonuniformity of the product.

The consultant discussed the importance of melt-extrusion fabrication techniques for this project and plans were made to initiate work on polyethylene fibers and strips prepared by extrusion rather than compression molding. Higher loadings of pesticide must be achieved to make this product acceptable from a practical viewpoint.

2. Controlled-Release Carbofuran for Rice Insect Control

The project team has made considerable progress in the formulation of various controlled-release carbofuran products. A major effort has resulted in a prototype starch xanthate formulation for this purpose. The product is a fine granule loaded with 55% by weight of the active insecticide. Much work has been devoted to identifying a suitable vegetable oil to be incorporated into the starch matrix to further regulate the controlled release of the insecticide.

Recently, the formulation team has initiated experimental

work on the microencapsulation of carbofuran in other polymers. The staff has accomplished much in this area as three principal microencapsulation technologies have now been investigated and are available now for use on future product development programs in the laboratory. These include phase separation, interfacial polymerization, and solvent-evaporation procedures.

The entomology group has suffered a few significent setbacks on the rice pest control work. Even though the carbofuran project is apparently at a lower priority than the mosquito larvicide work, a number of rather involved experiments have been conducted. The lack of a greenhouse facility at the laboratory is one of the major problems with this work. Entomology staff have experienced severe logistical problems in procuring the appropriate sucking type insects from farms. For example, transportation is not readily available and when it rains, insects are not available.

Further problems lie in the methodology development with testing a systemic insecticide based on controlled-release concepts. The group has made progress in identifying the problems and is now in a better position to properly evaluate the exciting new microcapsule formulations coming available.

During the consultant's visit, carbofuran was microencapsulated in a polystyrene matrix by means of a solvent-evaporation process. The technique was repeatly demonstrated to the

formulation staff and future experimental work was planned. The key variables in regard to release rate control were discussed and an experimental plan was devised to allow investigation of these key variables including microcapsule size, percent insecticide loading, etc.

3. Other Projects

It was observed that the formulation staff is moving with confidence into the development of additional controlled-release products of special interest to India. Additional insecticides including fenitrothion and phorate have recently been incorporated into various polymeric matrices such as starch borate and polyurea.

Fenitrothion is being studied as a mosquito control agent for application as a sprayed dispersion onto buildings and other constructions. Interfacial polymerization techniques have been developed by the formulation staff for this insecticide. The author was able to provide further suggestions as to details of the microencapsulation procedure which afforded more reproducible product.

During the author's visit, fenitrothion was also microencapsulated successfully in polystyrene by means of a solvent-evaporation procedure. The microcapsules were examined by a scanning electron microscope and found to be of high quality. Further analytical characterization will be

conducted to determine usefulness in the intended application.

Phorate is a highly toxic soil nematode insecticide. The high toxicity of this product is a prime reason for development of a controlled-release formulation. Starch borate has been used as an excipient for phorate in the form of granules to be broadcast in the soil. The laboratory staff has recently initiated experiments to prepare a styrene/ starcn graft polymer for this project. The availability of modified excipients will allow further versatility in controlling the release of phorate from the formulation.

Plans were made during the author's visit to microencapsulate phorate by means of the other techniques in polyurea and polystyrene excipients.

5. GENERAL OBSERVATIONS

The project appears to be moving forward with significant progress being made each year. There is a high degree of enthusiasm among the staff as to the potential of controlled-release pesticides. The personnel have excellent academic and work experience qualifications to allow investigations in this field. At this point, three or four of the staff have gained a good working knowledge of controlled-release technology including theory, process techniques, nomenclature, etc. This level of knowledge is a direct consequence of their involvement on the UNIDO program.

The laboratory is well equipped, with the exception of the key items mentioned earlier, for this type of work. A large number of modern state-of-the-art analytical instruments are available and being used on this project.

The library is still lacking in a wide range of reference materials on the subject; however, a few key reference books are now in the hands of the laboratory staff.

The laboratory has one of the worlds best glassblowing shops, and its importance was evident during the author's visit when a special glass apparatus was quickly constructed to allow microencapsulation by a new technique.

The author presented four seminars to the staff during his visit. These were quite comprehensive in scope and

were designed to teach various principles and processes as related to controlled-release technology. They were:

a. Microencapsulation: Theory, Characterization, and Processes

b. Controlled-Release Fibers

c. Controlled-Release Pesticides

d. Controlled-Release Pharmaceuticals

Many long discussions were held with various team members and each suggestion or recommendation was thoroughly explained. Separate meetings were held with staff in each of the divisions including entomology, polymer formulations, analytical, chemical engineering, and organic chemistry. In addition to the main topic of controlled-release technology, the author was able to also have informal discussions and an exchange of ideas on other technical subjects related to polymer science.

6. CONCLUSIONS

The project has been successful thus far. However, even more progress could be realized if an intermediate-level coordinator was present. The various team leaders and diverse disciplines involved make daily coordination of this type of project quite difficult. Full advantage of the available knowledge and data is not being realized because of a weak project coordination effort.

The team should not deviate from the original plan of utilizing low cost natural polymers as excipients. This is critical for any pesticide project, but especially important in this instance. However, to establish the laboratory as a center of excellence in this field, the recent move to study techniques with a few synthetic polymers is wise and should be encouraged.

Overall strategy should include extending this type of project for at least five years beyond the original target.