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INDIA

Technical report: Pesticide Formulation Development *

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

Based on the work of A. R. Woodford, Consultant in
Pesticide Formulation Development

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Vienna

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I should like to thank all those people both in UNDP and at the R&D Centre at Dundahera who helped me through this my first assignment with the PDPI. In particular I should like to thank Dr. Khetan for his general guidance and help throughout my stay. I should also like to thank Dr. Ramdas and all his laboratory staff for their great assistance throughout. Without their cooperation it would have been impossible to achie : all that we did. In addition I would also like to thank Dr. G. Baldit for his helpful comments and advice throughout my visit.

Finally I would like to thank all the rest of the staff at the Centre for the way in which they helped me over many little problems.

ABSTRACT

This report summarises the work and discussions which took place during the authors visit to the PDPI R&D Centre at Dundahera. Some considerable time was spent on the procedure and techniques used to develop and optimise flowable formulations and a blue print process was drawn up to provide a guide for future developments in this field. Included are also guidelines for the specifications which are required to control both the process of manufacture and quality of any agrochemical product.

The discussions which took place on various topics are summarised and these include, emulsifier characterisation, storage stability testing, micro emulsions and emulsion flowables. Most of these were only briefly covered due to the short time available.

A number of recommendations are included and a number of essential pieces of equipment are recommended, including a more rapid particle measuring instrument, a Malvern Particle Size analyser, a conventional microscope and a stereomicroscope.

Recommendations are also made concerning the technical training of the laboratory staff, on whose skill much of the success of the formulation unit will depend.

Recommendations

1. The formulation laboratory should be equipped with a modern instrument for particle size determination. The author recommends the Malvern Laser Particle Size Analyser but any equivalent instrument would do. Without the means of rapidly and accurately determining particle size, progress in the development of both flowables and water dispersible granules will be held up. The existing Micron Particle Sizer is slow, difficult to use and subject to operator variability.

2. A good miscroscope will be required as a qualitative measure to assess particle size and distribution, and a stereo microscope for the examination of granules and larger particles. The author recommends the following:

Olympus Research Microscope model BHT 312
Olympus Photomicrographic system model PM 10M with exposure meter model EMM 7
Micro-projection screen model AH-MPS-W
Olympus Stereo Microscope SZH 131 + SZH KPO polarising attachment
Universal Illuminator LSD-W + TGHM Transformer
Olympus Polarizing Filter Set BH-POL

A projector is included in this list as this will prove particularly useful in the proposed training courses to be held at the Centre.

3. The laboratory needs to be better equipped with the general run of laboratory ware. In the development of formulations much of the work is done in beakers and measuring cylinders and other similar apparatus and an adequate supply of these is essential. Much work on emulsifiers requires samples to be stored undisturbed for several hours, if not days to get a meaningful measure of their stability. It is also advantageous to have much of this type of apparatus in plastic. Firstly this greatly reduces loss due to breakage and secondly, as most of the newer formulation developments are water based plastic is quite suitable.

4. With the ever increasing use of electronically controlled equipment such as balances it is essential that a stabilised voltage is available.

For any accurate work, the balances used must give realiable results. Often analytical balances are adequately catered for but it is equally important that the general purpose laboratory balances are also reliable.

5. Emphasis must continue to be placed on the multidisciplinary nature of formulation development. Discussion and consultation can greatly assist in achieving the desired objective and minimise wasted time.

6. The success or failure of any formulation development unit is very dependant on the technical ability of the staff carrying out the bench tests. It is strongly recommended that this staff, that is the bench chemists who work for example under Dr. Ramdas, are given training in general laboratory techniques as applied to formulation development. In particular Mr. R.M. Sarin from Dr. Ramdas's laboratory and Mr.S.N.Gupta from the Pilot Scale unit are recommended for such training. This training should preferably be in the laboratories of Company actively carrying out such work and,because of language problems, the suggested order of country preference is U.K., Holland, Germany and then any others.

7. During the course of this visit it became apparent that the project in general was short of man-power and it is with this background that the following reommendations are made. It is recommended that the Formulation Development unit under Dr.Ramdas is augmented. An additional person with background of Colloid and Surface Chemistry has just been recruited and this will help to increase the effectiveness of this unit. However, it is recommended that the unit is further increased immediately by the addition of a further person at the level below SSA to work under the new man and once the two new persons are trained then a further person should be added at the lower grade. This would give two persons of SSA level and four at Analyst grade plus laboratory attendant working under Dr. Ramdas and tnis should be a suitable staff level for the next two years unless the number of projects significantly increases.

It is also recommended that an additional SRA is appointed to the analytical section and that Mr.M.L.Gupta of this section is transferred to Formulation to fill one of the proposed junior posts. It is most important that the Analytical Section is well staffed with persons capable of developing and operating instrumental analytical

techniques and equipment. Much of the work carried out in Formulation development requires good quality analytical support for storage stability testing, checking assays and active ingredient stability and this can only be provided by a well staffed Analytical Section.

It is recommended also that their is no further expansion of the clay mineralogist section and that consideration is given to integrating this section more closely with Formulation.

8. It is recommended that work on sponsored projects should take high priority. It is in this area that any achievements will give the most direct benefit and enhance the standing of the R&D Centre in the eyes of the Indian Pesticide Industry. For similar reasons, the replacement of imported technology should be o high priority.

Although the shelf of projects made a useful starting point the priorities of that list should now be revised to give more priority to these projects directly related to industrial needs. The current sponsored projects or those of direct current interest must head the list. Thus suspension concentrates and emulsion flowables and coated granules should head this list. Projects such as water dispersible granules and microencapsulation where there is perhaps only limited plant availability, should be given low priority.

9. It would also help the project to develop further the consultancy service to provide a specialised service to the Pesticide Industry to provide plant design and even complete installation if required. This subject will possibly be covered more fully in Dr. Baldit's report.

INTRODUCTION

During the preliminary briefing discussions with Dr. Hussein and Dr. Khetan it was clear that one of the primary objectives of the authors visit was to consider the practical aspects of formulation development and to assist in establishing procedures and techniques which would help to develop the 'know-how' necessary for successful formulation development in an R&D Centre. This background would then enable the staff at the Centre not only to provide the required service to Industry, which is one of its objectives, but also to run meaningful training programmes both in the practical and more Research oriented sense.

Before the author's arrival, a number of projects had been identified and work started on some of these, some in fact being mainly completed. Those in which the author became involved are detailed below. The topics are identified by the number of the project in the 'shelf of projects' which had been previously agreed. Throughout the report the R&D Centre at Udyog Vihar, Dundahera will be referred to as 'the Centre'.

1. **Evaluation of Surfactants** - Project 2

Considerable work had already been completed on this topic and a very useful report prepared by Dr. Ramdas was in draft. The author was invited to comment on this and some possible improvements were proposed. Although the list contains much useful information, because the suppliers are reluctant to give any details of the chemical composition it becomes difficult to choose between products of the same HLB without some information on solubility. The author therefore suggested to Dr. Ramdas that the inclusion of solubility data on solvents representing the different ranges likely to be encountered in pesticide formulation would greatly increase the usefulness of this list. The solvents proposed were Xylene, an aliphatic hydrocarbon, a glycol and a mineral oil. Work is to be started to obtain this data for inclusion in the Table.

One point of major concern to the Indian Pesticide Industry is the apparent absence of 'generic emulsifiers'. All the products available for pesticide use are of the mixed anionic/nionionic emulsifier type

mainly designed for use in emulsifiable concentrates. If any progress is to be made towards more modern formulation techniques then a broader range of surfactants is required. For some of the newer types of formulation a range of wetting, dispersing and binding agents is required in order to have a reasonable degree of flexibility and to cope with a wide range of active ingredients.

Later during this visit it was found that other types of surfactant are available from Hico where the recommendations are for use in washing powders or other detergent applications. It was then pointed out that any review of surfactants should be on as broad a base as possible and cover supplies to any industry using surfactants. For example paints, leather tanning, cotton scouring, textiles, detergents, soaps and general cleaners etc. are all industries which use surfactants and may provide a useful source of surfactants for pesticide formulation development.

It is important to have a greater emphasis on cooperating with surfactant suppliers with respect to the work of this Centre. Surfactants play a major role in almost all types of formulation and cooperation between the R&D Centre and Surfactant Manufacturers can only be of benefit to the Industry.

2. **Suspension Concentrate** - Project 5

On arrival at the Centre the author found that a lot of development work had already been carried out in the development of a carboxin Flowable. As at the same period Dr. Baldit UNIDO Expert in Chemical Engineering was also at the Centre setting up a Pilot scale Flowable plant it was opportune to place the main emphasis on this project. This gave the possibility of taking at least one project right up to pilot plant scale trials.

A programme of work was then started to try to meet the above objectives. After examination of the process development it was apparent that there were a number of areas where changes should be tried. These were mainly with the objective of simplifying the procedure by rounding off the quantities used and making the blending operation easier to

carryout. For example the gel solution used in the laboratory had a very high viscosity and thus was difficult to pour and transfer. By including some ethylene glycol in this stage, the viscosity was greatly reduced and the handling made very much easier. Further the thickening agent presented a similar problem and again by using the ethylene glycol it was possible to reduce the viscosity of this stage also. This additionally gave the opportunity to put the dyestuff in at this last stage as well thus avoiding having the product coloured until the final mix was prepared.

During these changes it was necessary to check that the properties of the finished product remained unchanged and that no alterations were necessary tc the miling conditions. At this time also specifications were drawn up for the intermediate stage so that the pilot scale work could be checked during the processing.

It was at this point that the need for a better and faster method for particle size analysis became apparent. On the pilot scale the throughput rate for the Dynomill was around 3.5 l. per min. and as only 50 l batches were being made the milling was completed in about 15 min. As the Micron particle size analysis took about 40 min. to 1 hour, the pilot scale run had to be delayed for that time before any indication of the particle size being achieved could be obtained. This is obviously an unacceptable state of affairs and one which can only lead to delays and even to an inability to ever achieve an equlibrium state in the mill.

Finally a suitable procedure for pilot scale manufacture was drawn up and a copy of the final laboratory process was left with Dr. Khetan. An outline of the recommended process is given in Appendix II. This process represents a first proposal for pilot scale to work to. It may of course be changed as a result of development work by pilot scale but it is essential that a document of this sort is provided as a basis on which they can start work.

In addition in Appendix III some outline speicfications for all the components, are included. These are put forward as tentative specifications from which final specifications can be produced as a result of practical experience.

Since the main use of this product is as a seed dressing it was suggested that the product must be tested to ensure that it is suitable for its intended use. Some tests were therefore carried out to determine the seed coating obtained when this product was used at the field use rate.

Seed dressing is either carried out by commercial houses or by the farmer himself. As the latter is the use most likely to encounter difficulty in obtaining uniform coverage, a simple test was carried out in which the requisite quantity of flowable was added to the seed and shaken to disperse the carboxin.

These tests showed that at the use rate, the product used 'as is' did not give adequate coverage of the seed in the simple mixing procedure used. Tests were therefore carried out at various dilutions and it was found that diluting 1 pt of suspension with 2 pts of water gave an acceptable commercial coating. It was not considered to be economically acceptable to make the formulation at less than 40% w/w but it was considered that this formulation would still be acceptable with the recommendation to dilute as indicated above.

The work on this topic has been described in considerable detail so that it can be used as a sort of blueprint for future development of flowable formulations, and in effect as a guide to formulation development in general. It is intended to emphasise the multidisciplinary nature of the work and the need to have a broad outlook over all the aspects of the product under development. This is shown in the above exercise where exchange of ideas between the various disciplines led to changes in the formulation. In order to better emphasise the various inputs necessary, the various areas consulted are listed below.

a) Discussion with pilot scale. These led to alterations of the order of mixing and laboratory confirmation of the effect these changes made on the properties of the product.

b) Discussion with Biologists. To determine the dose and type of seed coverage required. In this case no alterations were necessary but in the general case such discussion could lead to alterations and perhaps even in the extreme case, complete reformulation.

A summary of these points and some additional important ones are given in Appendix I. This list is not all embracing but is intended to provide an aide memoier to help ensure that all related areas and disciplines are taken into consideration during formulation development.

3. **Shelflife Studies** Project No. 3

This topic was not one of the major subjects dealt with during this visit. However, the subject is so intimately tied in with formulation development that some discussions of the subject was considered necessary.

The shelf life of an Agrochemical product is taken to be the length of time that the product can be stored under normal ambient conditions and still give the same biological performance. This general statement, unfortunately leaves many questions without an answer. When does the product begin to loose biological efficacy? Can this be determined simply on its chemical composition or must its physical properties be considered also? These and many other questions must be clarified in order to establish a meaningful assessment of product Shelf Life.

One common misconception is to assume that the normal limits placed on the active ingredient content of a formulation are related directly to biological activity. Although the concentration of any formulation is based on its biological activity, this concentration is chosen to cover a wide range of field conditions and to ensure that under all conditions the product will continue to work. For this reason it is rarely possible to be more precise than say 25% in discussing biological activity. This is of course a much wider tolerance than the 5% allowed in manufacturing and it would be very difficult to see any difference in biological performance over this range.

It is therefore necessary when discussing this subject to have clearly in mind the objectives and to consider the needs of both the farmer and the manufacturer. It is important to protect the farmer and

to give him confidence in the quality of any product he uses but it is equally important to consider the manufacturer and not to set criteria which he cannot economically meet.

The limits set in a product specification are there to ensure that the product has been manufactured correctly and should not be used to establish Shelf Life. Separate criteria have to be established for this.

It is against this background that the following points have been drawn up.

i) The usual criterion for Stability is 2 years in the actual Sales pack when stored under good conditions. Storage conditions must be indicated as it cannot be guaranteed that any product will survive if stored badly.

ii) Test conditions

The following are some common European test conditions.

	Test Interval					
	Initial	1st week	1 month	3 months	1 year	2 year
Ambient	X			X	(X)	X
37 °C	X		X	X	(X)	
50 °C	X	X	X	(X)		

The tests in parenthesis are optional. These are of course not to be suited to Indian conditions and the temperature will need to be increased. A possible range would be Ambient, 40°C, 60°C.

Once these temperatures are decided then the same test intervals as indicated above should be used.

The tests are normally carried out in glass, the material of the sales pack and if possible in the actual sales pack.

iii) The tests carried out.

Both chemical and physical tests are carried out and in general the product is tested against the standard specifications.

Care must be exercised in the choice of analytical method used for the active ingredient to ensure that it really detects degradation. It may therefore be necessary to use a different method from that used for normal production quality control. This test must, of course always be confirmed on the actual formulation being sold.

The physical tests need only be those which indicate changes in performance which might affect field activity and usually are concerned with suspensibility, wetting, emulsification etc.

iv) The tests at high temperature are normally only used as a guide and not as an absolute indication of stability. If degradation does occur it is possible that this may not be significant at lower temperatures. It is essential that the tests are continued at ambient temperature as in the end, the test after 2 years is the only really true criterion with respect to stability.

v) **Interpretation.** - The basic criteria should be that the product still complies with the specification after 2 years storage under ambient conditions. However, if the product shows any instability it is necessary to consider whether it is still suitable for its intended use. One criterion which is commonly used is to take it that if the active content drops below 10% of its initial figure it is still suitable for immediate use but not for further storage. This seems to be a reasonable compromise since if at the end of a 2 year test period the product is still within the specification then it is still suitable for sale as though it had just been manufactured. It is obvious therefore that to give a shelf life that insists on the product meeting the original specification is meaningless.

It is important that this topic is discussed with the local Registration Authority to establish just what criterion is acceptable to all parties concerned. It will then be possible to direct these studies to provide the relevant data.

6. These studies must form an integral part of the formulation development work and should be started as soon as possible. Even if the finished pack is not known tests should be started in

glass and a likely plastic container. The time taken for these tests is so long that much effort can be wasted if formulation stability is left until all the formulation work is completed.

4. **Emulsion Flowables** - Project No. 11

As some work had been carried out on normal flowables it was considered that this topic would follow on well from that work. Although some development work had been carried out at the Centre it was not at such an advanced stage as with Carboxin. No completely satisfactory formulation had been prepared and therefore any work carried out would have to await the results of storge stability tests before any really useful conclusion could be reached. This would obviously extend beyond the time of this visit but at least some work was started.

Preliminary work consisted of reappraising the best of the available agrochemical surfactants and setting up a testing procedure to get a first evaluation of the products. A further study will be made when the range of surfactants is received from Hico.

Based on the work already carried out some tests were started to evaluate the effects of order of addition of the components. and some tests were started to see the effect of including a protective colloid.

5. **Controlled Release.**

Some work had already been carried out at the Centre to prepare granular formulation based on Basalin. The object of the work, which was at the request of BASF, India was to provide a presentation which overcomes the instability of the normal E.C. It was considered that a controlled release granule could provide the requisite properties.

Preliminary tests had shown that a premade wettable powder could be coated on to marble chips and that by coating with polyethylene glycol a controlled release effect was achieved.

The preparation procedure being used was examined and some modifications were investigated with the objective of eliminating the milling stage. This would give a significant cost reduction and a simple process.

* Basalin is the BASF brand name for formulation of Fluchloralin.

Trials were started to investigate the possibility of adding the Basalin premix directly to marble chips with some success. However, much more work is necessary to get a workable procedure and this had to be left as an ongoing project.

Conclusion and comments

As a result of this visit it is the author's opinion that at the present time, it is of more use to the Centre to receive real practical help in the various techniques used in formulation development than to concentrate on more theoretical aspects. The latter is of course very important and cannot be ignored but at this relatively early stage in the life of this R&D unit it is considered to be more important to have some practical evidence of ability in respect of this type of work.

Some useful work had already been carried out and the author was able to supplement this and to propose some new ideas particularly in the area of flowables. However, because of the limited time available some of the other topics of interest could only be dealt with superficially although some experiments were started on emulsion flowables and pan granulation. This work can be further progressed at any subsequent visit.

One important part of this work which was not covered was that of Safety, both from the user and formulators point of view. As this R&D unit will undoubtedly, in the future have to handle quite toxic products this subject must be dealt with as soon as possible. Safety routines in the laboratory and elsewhere should be instituted and adhered to and general safety records kept. Unfortunately it is not possible to cover all these topics in one visit but they must not be forgotten.

Appendix I

FORMULATION CHECK LIST

1. **Client's Requirements**

   a) What type of formulation
   b) What is the required field use rate
   c) What is the method of application
   d) What is the ideal volume rate. This with the field use rate gives the concentration to be aimed for.
   e) Are there any other requirements such as compatibility with other pesticides, special packaging, or unusual storage stability requirements.

2. **Biologist's Requirements**

   a) Are there any special points which should be noted which may affect the biological activity.
   b) Are there any special tests which could be used to confirm the suitability of the formulation.

3. **Analyst's Requirements**

   a) Provide analysts with samples of formulation as soon as possible to check analytical methods for the active ingredient in case the formulation affects the analytical method.

   b) Prepare samples for storage stability tests, both chemical and physical, and start tests as soon as possible.

   c) Discuss any special methods which may have to be developed for any ingredients. For example the gelling agent in the flowable discussed earlier in this report.

4. **Material Supplies**

   a) Discuss all ingredients with the supplier to ensure that the items are readily available, and of consistent quality.

b) Draw up a specification for each item in collaboration with the supplier as quality of some items can have a very significant effect on the performance of any formulation. Good examples are the surfactants and gelling agents or thickners.

5. **Pilot Scale Requirements**

a) Check whether the nature of the ingredients affect the handling on a large scale. For example dustiness, lumps, high viscosity, can all cause problems.

b) Are there any problems in combining the different stages in the process.

c) Do the differing viscosities of the various stages make mixing on a large scale difficult.

d) What modifications to the formulation would assist in its preparation on Pilot scale.

Appendix II

A PROCESS FOR THE PREPARATION OF A FLOWABLE FORMULATION

Summary - A formulation and procedure is described for the preparation of a pesticide flowable. This is based on a Dynomill process in which a premix containing the pesticide is first Dynomilled and then mixed with a gel solution concentrate. Finally a suspension stabilising solution is added and the whole mixed until homogeneous.

In describing the procedure, control points are included to ensure the correct operation of the process.

Specifications for the finished product, the intermediates and the raw materials are also given in Appendix III.

1. Formulation Composition

This section must contain the complete formulation composition expressed in gm./kg. or gm./litre. The formulation must also quote the purity of the ingredients used.

2. Preparative Procedure for a 50 kg. Batch.

This procedure must be based on actual laboratory experience scaled up. 50 kg. is chosen because this is a convenient size for pilot scale to operate.

2.1 Equipment

This section must list all the relevant equipment required to operate the process. This includes the vessels, mill, special stirrers etc.

2.2 Procedure

Stage 1

Components

Here are listed all the components required for this stage.

Method

In this section precise method is described.

For example

Add Component A
Stir until in solution
Add Component B.
Mix until completely wetted and dispersed.

Continue in this way until the whole method for completing stage 1 is described.

Stage 2

Repeat in the same manner as for Stage 1 and do likewise for all the remaining Stages.

2.3 Specifications.

The above procedure should include tests between the relevant stages to ensure product quality. Thus there should be a test after Dynomilling and before going further to ensure that the particle size is correct and there should be a test to ensure that the gel has the correct viscosity.

In addition the procedure must include a tentative specification for the finished product.

Some typical specifications for a Carboxin Flowable are given in Appendix III.

Appendix III

SAMPLE SPECIFICATIONS

Finished Product Specification		Carboxin 40% w/w Flowable
1.	Appearance	Pink opague mobile suspension which when added to water immediately disperses.
2.	Wt./ml.	Record. Expected to be about 1.155g
3.	Colour	Not significantly different from a standard sample.
4.	Assay (as carboxin)	39.0% w/w to 41.0% w/w
5.	Particle size	Not less than 95% less than 5 micron not less than 65% less than 1 micron
6.	Viscosity	Using Brookfield 6 rpm 12 rpm 30 rpm 60 rpm. To be based on the laboratory results.
7.	Dispersion	Approximately 20 ml washed through a 44 micron sieve should leave no residue.

Note : This specification is put forward as a tentative manufacturing specification and should be modified in the light of experience. It is for this reason that the specification for wt./ml. is left as 'record.' In addition limits should finally be set for the viscosity when more data are available from the Pilot Scale trials.

PE 80 Specification		
1.	Appearance	Pale yellow granular powder
2.	Viscosity	A test must be used based onthe material used in the development stage but must also be agreed withthe supplier to ensure continuity of supply.

Ethylene Glycol Specification	See the supplier's specification whereever possible.
Rhodamine B Specification	
Tamol DN Specification	
Atlox 3409 Spepcification	

Carboxin Specification

1.	Appearance	Pale yellow powder.
2.	Assay	Not less than 97%
3.	Sieve Test	Place 10 gm on a 44 micron sieve and wash through with water containing enough Tamil DN to wet the powder. There should be no residue.
4.	Identity	The IR spectra should match that of standard sample of carboxin.

In Process Specifications

Specifications must be provided for the particle size of the milled technical pesticide as it leaves the Dynomill. Specifications must be provided for the viscosity of the gel solution before it is added to the milled product. This is most important since it is very difficult to make any changes after the finished product has been prepared.