MIGUEL GIMENO SIERRA*, BORJANA LUBURA
Jesmond Bioscience GmbH, Weimarerstrasse 104, Vienna 1190, Austria


Miguel Gimeno Sierra


Borjana Lubura

Maximizing returns through re-formulation:
re-formulation strategies for old molecules

KEYWORDS: Chemical molecules, type of formulations, capsule suspension, insecticides, pyrethrum, PBO.

Abstract One of the reasons for the development of new and improved formulations in the sector of agro- and biocidal products is the emergence of resistance of various weeds and insects towards older molecules. In order to overcome this resistance as well as certain physic-chemical incompatibilities and to improve the activity and decrease the toxicity, improved chemical formulations were developed. This paper focuses on one main example which is a summary of the efficacy study for an insecticidal product based on actives, Pyrethrum (PYR) and Piperonyl butoxyde (PBO) by applying the microencapsulation technology.

INTRODUCTION

There are three groups of chemical molecules which are dominant in the area of crop protection which are grouped in various ways according to their activity, mechanism of action, timing and method of application, chemical family or their selectivity. They belong to herbicides which are substances that kill or inhibit growth of weeds, insecticides which are substances that kill arthropod pests, and which are very important in combating human and animal diseases and fungicides which are substances that destroy or prevent the growth of pathogenic fungi. All three belong to pesticides. Some of them are designed to control a broad range of weeds or insect pests, while others are designed to control only selected types of the same. In this regard, proper timing will lead to adequate weed or insect control, while improper application timing may result in a failure to control either of them adequately.
The table 1 summarizes some of the commonly used herbicides.

In the middle of the 19th century an insecticidal powder derived from dried flower heads of the genus Pyrethrum (Chrysanthemum) was introduced from Africa to central Europe. The insecticidal components were identified as Pyrethrins which were used as precursors to generate.
The synthetic pyrethroids can be separated into two classes according to the poisoning action they induce.
The table 2 shows some of the commonly used insecticides representing the two classes.

Despite the availability of so many chemicals, there is always a scope for the replacement of formulations of some older

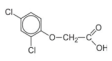
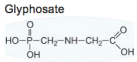
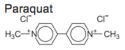
Term	Definition	Example
Selective	Herbicide formulated to control specific weeds with a material that is toxic to some plant species but less toxic to others.	2,4-dichlorophenoxyethanoic acid (2,4-D) 
Nonselective (a.k.a. Broad spectrum)	Herbicide formulated to control both broadleaf and grass weeds.	Glyphosate  Paraquat  Diquat 

Table 1.

molecules with improved ones, especially those where resistance is becoming a problem. Glyphosate which is a broad-spectrum herbicide as listed in the table 1, is the world's most-selling crop protection chemical. However, due to its extensive use during so many years, several species of glyphosate resistant weeds emerged. Consequently, glyphosate will need to be combined with other herbicides to overcome the resistance of weeds that cannot be controlled otherwise. Another reason for the development for new and improved formulations in the sector of agro- and insecticidal products are their re-registration processes which are currently ongoing in many regions of the world, including Europe. These processes aim to ensure that all these kind of products meet modern safety and environmental standards with

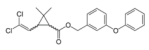
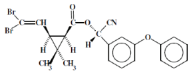
Term	Definition	Example
Type I pyrethroids	They cause hyperactivity and incoordination.	Permethrin 
Type II pyrethroids	Type II pyrethroids contain an α-cyano substituent inducing nerve depolarization and subsequently paralysis of the insect.	Deltamethrin 

Table 2.

minimum danger exposure to human. In order to develop highly profitable products by introducing specific methods of formulation, chemicals or molecules need to meet certain criteria such as:

- high activity in a various spectrum of weeds, insects or fungi;
- high selectivity, thus allowing the product to be applied at low rates and without affecting non-target organisms with no emergence of resistance towards target weeds or pests;
- chemical and metabolic stability, so that it survives in sunlight which is related to how the product has been formulated, however at the same time without being so stable that it persists in the environment.

Selection of appropriate formulation technology is a challenging task but it is still a crucial parameter in order to eliminate any kind of incompatibilities of chemicals used in formulation process and at the same time improve their activity without interfering with the physicochemical properties especially when more than one active is used for the same product.
Microencapsulation is a powerful technique which offers significant advantages to accurately control the delivery and release rate of microencapsulated active ingredients (A.I.s) over long periods for weeks or months solving incompatibilities issues related to actives.
By minimizing or eliminating problems associated with incompatibilities such as instability or application of less effective formulation types, microencapsulation provides the possibility to create products with improved or even new valuable properties, e. g. more selective to pests and also safer by reducing the operator hazard and risks to natural habitats.
The choice of a solvent or a mobility modifier plays an important role as the higher viscosity of the core of the capsule supports the slow or fast release rate.
Required release behavior of the core material can be controlled by processing of microcapsules on different particle size.
In this regard, small particles with thin walls and low cross-linking density allow the fastest possible release, while large particles with thick wall and high cross-linking density have the slowest possible release. This is the most practical way to change release rates and thus achieve compatible actives in order to balance efficacy, toxicity or physicochemical stability of the formulation.
Chemical stability is also one of the main characterises of microencapsulated sensitive actives against oxidisation or UV light and therefore it also helps to eliminate the degradation during the process of product formulation which otherwise may lead to decrease of storage stability.
Preparation of microcapsules for a prolonged, timely tailored and safe action can be achieved by the process called "*in situ*" interfacial polymerisation emulsification. This method is based on the emulsification of the oil phase containing active ingredient into the aqueous phase. The formation of microcapsule polyurea-glycoluryl wall (Patent number WO 05/058476 CONTINUOUS MULTI-MICROENCAPSULATION PROCESS FOR IMPROVING THE STABILITY AND STORAGE LIFE OF BIOLOGICALLY ACTIVE INGREDIENTS) via a reaction between the wall forming materials - which include monomers such as isocyanate and certain pre-polymers - and cross-linking agent occurs at the interphase of the oil droplets and aqueous phase containing protective colloids. The curing of the polymeric wall is accelerated by increasing the temperature up to 60 - 80°C.
A timely tailored and controlled release rate depends upon use of specific percentage and rate of the wall-forming materials which determinate the thickness of the polyurea wall, which in turn becomes inert after polymerisation.
Hydrocolloids and other surfactants are added to formulation in order to maintain the stability by controlling the osmotic pressure before the products application.
The release rate and duration of the activity are governed by capsule particle size, wall thickness and wall permeability.
The process of release from the microcapsule can be triggered by molecular or a solvent diffusion through the pores of the capsule wall. The microcapsule releases the active immediately whereas the speed of diffusion is controlled by the thickness and porosity of the capsule wall. The example of the above description is depicted in the Figure 1.

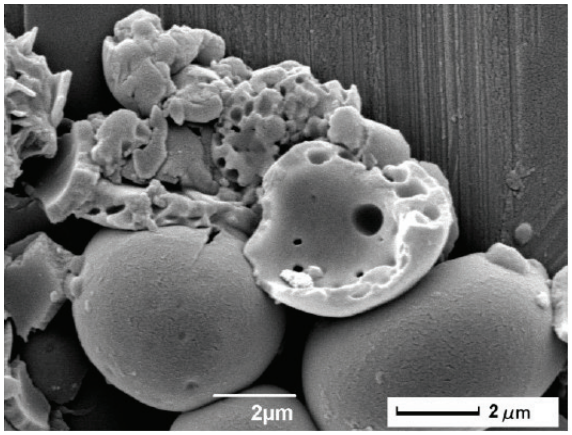


Figure 1.

Normal and Reverse Phase Microencapsulation
Normal phase microencapsulation is referred to the formation of a wall around oil droplets of the A.I.(s) by O/W emulsion process. The A.I.(s) need to be liquid or soluble in oil and essentially non soluble in water.
Reverse phase microencapsulation is referred to the formation of a wall around water droplets of the A.I.(s) by W/O emulsion process. The A.I.(s) need to liquid or soluble in water and essentially non soluble in oil.
The combination of capsules from both technologies in one single final product can solve the typical chemical and physical incompatibility of the A.I.(s) with different solubility parameters avoiding chemical degradation of

physical incompatibility. Examples are the main herbicides listed in the Table 1 and Sulfonylureas or a combination with herbicides, insecticides and fungicides that are soluble in oil. In order to show the application of the technology, an example including a combination of two A.I.(s) enclosed in the same microcapsule is described in the next section. This combination leads to the increase of activity and stability having the synergist delivered at the target with the A.I.

MATERIALS AND METHODOLOGY

The study was undertaken in summer of 2016 in order to assess the efficacy profile of an insecticidal product, containing two active ingredients, Pyrethrum and PBO. Pyrethrum is non photo-stable with low residual effect needing a synergist, PBO. The typical formulation is EC in aerosol form or old/classic CS formulation using the PBO in a solution of EW. In order to overcome these challenges, the product was formulated as a single capsule suspension based on the microencapsulation technology "*in situ*" emulsion polymerisation.
The trial was done in order to evaluate the efficacy of the product against the following target organisms, *Musca domestica* (house fly), *Blattella germanica* (German cockroach) and *Tegenaria domestica* (house spider) by exposing them on ceramic tiles and concrete impregnated with three different dosages at 25, 35 and 50 mL/m^2.
The treatments were done by using one-use hand-held sprayers and Good Practice procedure was used to apply the intended dosage +/-3%. The droplets were thin enough to wet the surfaces without leaking and without excessive vaporization in the air.
The treated tiles were randomly assigned among the total treated area and not handled before complete drying.
The untreated materials were treated with water. 4 replicates were conducted by using 3 doses of the product.

RESULTS AND DISCUSSION

In the conditions of this trial, with the product formulated, the insect's strains and methodology used, PYR CS and PBO CS has shown a very high efficacy at 100% already at the lower dose of 25 mL/m² as depicted in the Figure 2. The Figures 3 and 4 show the efficacy of the same product at the other two tested dosages, 35 and 50 mL/m^2.

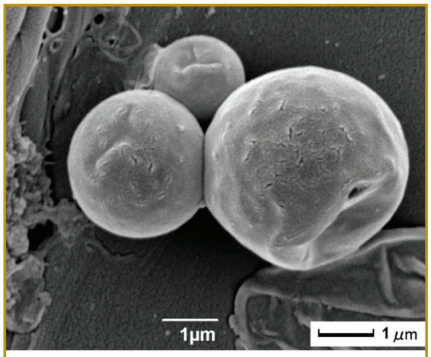


Figure 5.

From the above presented results we can conclude that the semi-permeable capsule wall protects PYR and PBO formulation from the air, light or other conditions that would otherwise break it down quickly and two more.

As an example of this microcapsule containing PYR and PBO and the type of the surface (cracks) is depicted in the electronic microscopic figure 5.

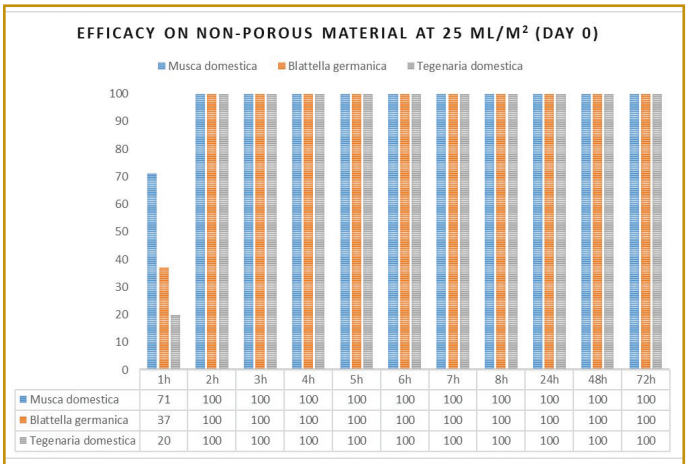


Figure 2.

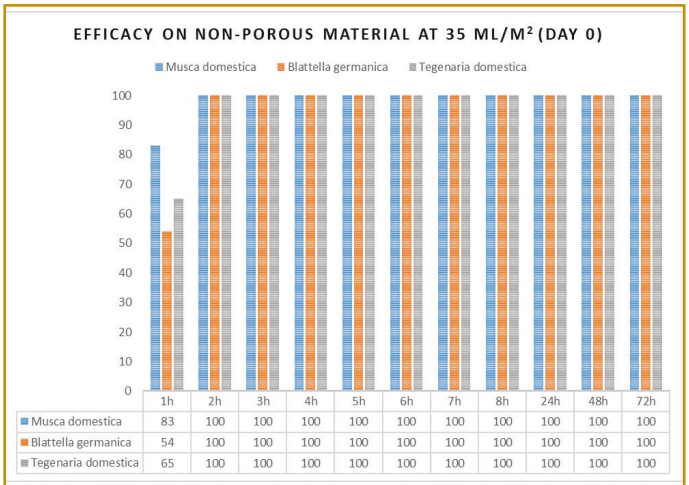


Figure 3.

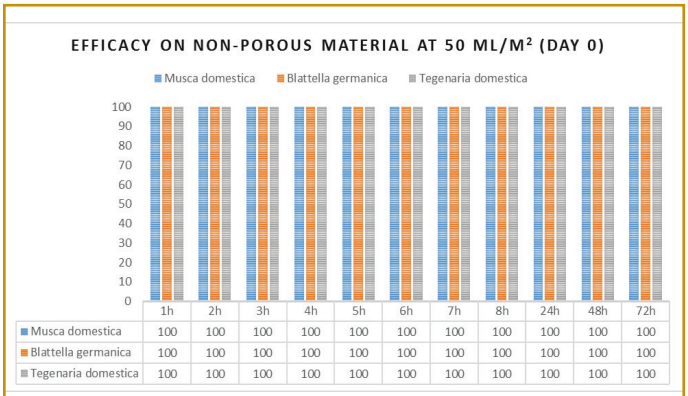


Figure 4.

The achieved results show the high performance of this type of the formulation when combining two actives, PYR and PBO in the same microcapsule.

REFERENCES

Serrano B. 2016. Laboratory testing of a dose range of insecticidal products intended to control various pests. T.E.C. Laboratory, 1-17.