Advances in the Technology for Controlled-Release Pesticide Formulations

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**INTRODUCTION**

**Categories of Pesticide Formulations**

The science of pesticide formulation covers a very broad field, as it deals with the development, production, and storage of the formulations, as well as with the interaction of pesticides with the environment, including plants, insects, animals, soil, air, and water (1–5).

Pesticide formulations can be classified into the following types:

- Aqueous solutions
- Emulsifiable concentrates
- Dispersion concentrates (aqueous and nonaqueous flowables)
- Wettable powders
- Dry flowables (water-dispersible granules)
- Controlled-release formulations
- Others (dusts, aerosols, etc.)

The choice of formulation is influenced by the following factors: the physical properties of the pesticide (melting point, solubility, and volatility), the chemical properties of the pesticide (hydrolytic stability, thermal stability, and irradiation stability), the mode of application of the formulation (soil, foliar), the crop to be treated and the agricultural practices, the biological properties of the pesticide (crop selectivity, transport through soil or grass cover, and LD$_{50}$ for mammals and non-mammalian species), and economic considerations.

This chapter covers methods of pesticide encapsulation and formulation, controlled-release techniques for pesticide application, and the current trends in the use of encapsulated natural products. Pesticides are conventionally applied to crops by periodic broadcasting or spraying. Very high, and possibly toxic, concentrations
are applied initially, and these often decrease rapidly in the field to concentrations that fall below the minimum effective level. As a result, repeated applications are needed to maintain pest control (6). The formulation of a pesticide must thus be designed to meet the multifaceted demands of efficacy, suitability to mode of application, and minimization of damage to the environment. Controlled-release formulations meet these demands in that they enable smaller quantities of pesticide to be used more effectively over a given time interval and in that their design enables them to resist the severe environmental processes, i.e., leaching, evaporation, and photolytic, hydrolytic, and microbial degradation, that act to eliminate conventionally applied pesticides (6).

**Release Patterns from Encapsulated Formulations**

In most instances, the rate of removal of a conventionally formulated pesticide follows first-order kinetics (6–9). The time \( t_e \) that an effective level of pesticide is maintained after a single application is given by:

\[
t_e = \left( \frac{1}{k_r} \right) \ln \left( \frac{M_\infty}{M_e} \right)
\]

where \( M_e \) is the minimum effective level, \( M_\infty \) the amount of agent applied initially, and \( k_r \) the removal rate constant (6).

It follows from Equation (1) that for an increase in the effective duration of action of a conventionally applied pesticide, an exponentially greater quantity of the pesticide would be required. If, however, the pesticide could be maintained at the minimum effective level by a continuous supply from a controlled-release system, then the optimum performance of the pesticide would be realized, and in that case, the duration \( t_0 \) of action of the pesticide would be given by:

\[
t_0 = (M_\infty - M_e)(k_d M_e)
\]

where \( k_d \) is the rate constant for pesticide delivery from the controlled-release device (6).

The relationship between the concentration of application and the duration of action of a pesticide is shown in Figure 1 for a conventional formulation and for a controlled-release formulation (6). The area between the two curves represents the amount of pesticide that is wasted. It is apparent that for a short duration of effectiveness, e.g., one week or less, the efficiency of the conventional method is adequate. As the duration of effectiveness increases, the efficiency of the conventional system decreases exponentially (Fig. 1).

The different release rates, from an encapsulated pesticide formulation, are a function of the concentration of the remaining encapsulated pesticide. For the case of a pesticide core enclosed in a polymeric membrane, when the release rate is independent of the pesticide concentration (in effect, the thermodynamic activity remains constant), pesticide release is governed by zero-order kinetics; in effect, \( dC/dt = k_d[C]^0 = k_d \), where \( C \) is the concentration of pesticide remaining in the microcapsule. When first-order kinetics are followed, the release rate is directly proportional to the remaining \( C \); in effect, \( dC/dt = k_d[C]^1 \), indicating that the concentration of the remaining pesticide decreases exponentially with time. In the third type of release kinetics, the release rate is proportional to the square root of time, i.e., \( t^{-1/2} \). A comparison of the kinetic release patterns (Fig. 2) shows that the release rates of zero-order and \( t^{-1/2} \) formulations exceed that of the first-order formulations for equivalent pesticide quantities. The optimal rate of solute delivery from controlled-release devices is often a constant rate of zero-order release. Thus, a benefit of pesticide formulations comprising a core of pure pesticide encapsulated in a
polymeric membrane is related to zero-order kinetics. This implies that the release rate and duration of release are not related to each other and can be independently optimized. Release rates can be readily controlled by adjusting membrane thickness, microcapsule surface area, and membrane permeability, while duration of activity is controlled by the quantity of pesticide encapsulated.

Two frequently used material combinations in controlled-release systems are membrane-coated reservoirs and monolithic matrices, which are based on diffusion

![Figure 1](image1.png)

**Figure 1** Relationship between the level of application and the duration of action for conventional and controlled-release formulations. The graphs are plotted using Equations (1) and (2) and assuming that the half-life of the pesticide is 15 days and the minimum effective level is 1 g/acre. *Source:* From Ref. 6.

![Figure 2](image2.png)

**Figure 2** Release kinetics of controlled release formulations. *Source:* From Ref. 10.
of the pesticide ingredient through polymer barriers. Other less common configurations are liquid membranes comprising a liquid within the pores of inert porous matrices, and laminated polymeric membranes whose release profiles are also based on diffusion through homogeneous barriers. Irrespective of the geometry of the matrix, i.e., flat wafer, hollow tube, microcapsule, or tablet) zero-order release (in effect \( \frac{dC}{dt} = k_dC_0 = k_d \)) for encapsulated pesticides is expected under the following conditions: (i) when the thermodynamic activity of the pesticide solute within the reservoir remains constant and (ii) if pesticide transport to and from the membrane surfaces is rapid. Under these conditions, controlled release for the three most common geometries are given by the following equations (10):

- **Slab:** \( \frac{dQ}{dt} = \frac{ADS}{l} \)
- **Cylinder:** \( \frac{dQ}{dt} = 2\pi hDS/\ln(r_o - r_i) \)
- **Sphere:** \( \frac{dQ}{dt} = 4\pi DS[r_o r_i/(r_o - r_i)] \)

where \( \frac{dQ}{dt} \) is the quantity of material released per unit time (g/sec), \( D \) the diffusivity of the pesticide through the polymer membrane (cm\(^2\)/sec), \( S \) the solute solubility within the polymer membrane (g/cm\(^3\)), \( A \) the surface area of the slab, \( l \) the membrane thickness, \( h \) the length of the cylinder, and \( r_o \) and \( r_i \) are the outer and inner radii, respectively, of a cylinder or sphere.

The minimum effective dose \( M_e \), the kinetics \( k_d \) of pesticide release from the source, and the rate of elimination \( k_r \) of the pesticide from the site of application determine the quantity of pesticide to be applied for a given duration of activity. For example, for a pesticide formulation that is applied to a water surface, the rate of removal of free pesticide from the surface is expected to decrease exponentially; in effect, \( \frac{dC_{pes}}{dt} = -k_rC_{pes} \) where \( \frac{dC_{pes}}{dt} \) is the rate of change of pesticide concentration, \( k_r \) the rate constant of removal, and \( C_{pes} \) the concentration of the free pesticide. Encapsulated formulations with a zero-order release rate from the microcapsules may be described kinetically by \( \frac{dQ}{dt} = k_d \), where \( k_d \) is the constant input rate from the microcapsules into water and \( \frac{dQ}{dt} \) the quantity of pesticide released per unit time. Upon application of such a depot, a steady state will be reached when the rate of pesticide release to the surface equals the rate of removal, then \( \frac{dQ}{dt} = k_rC_{pes}V = k_d \) and \( C_{pes} = k_d/k_r \), where \( V \) is the apparent water surface volume containing the microcapsules. From this equation, it can be seen that \( C_{pes} \) is a function of two kinetic constants, \( k_r \), which is determined by the solubility of the free pesticide in water, the evaporation rate, the sensitivity of the pesticide to ultraviolet (UV) radiation, and oxygen, the temperature, and the wind velocity, and \( k_d \), which is determined by the physicochemical properties of the microcapsules. A steady state close to the minimum effective concentration can be maintained only if \( k_d \) is sufficiently large relative to \( k_r \). However, this \( k_d \) must be achievable with a single dose of reasonable size.

**Advantages of Controlled Release**

In addition to the advantages described above, controlled-release pesticides have other important advantages over conventional formulations (6):

- reduction of mammalian toxicity for highly toxic substances,
- extension of duration of activity for an equal level of active agent,
reduce evaporative losses and flammability of liquids,
- reduction of phytotoxicity,
- protection against environmental degradation,
- reduction of leaching into the earth and transportation into streams,
- reduction of contamination of the environment,
- increased convenience of use by conversion of liquid materials into solids and flowable powders,
- separation of reactive components,
- control of the release of active agents,
- decreased costs as less active material is needed,
- convenience of handling.

For the most part, microencapsulation of a pesticide is utilized when slow or controlled release of the active material is desired. It is also possible to produce microencapsulated formulations of pesticides for which the object is not necessarily controlled release, but rapid release, as is required in formulations for foliar applications. Such compositions contain the pesticide in small microcapsules with relatively thin encapsulating wall membranes, allowing for relatively quick release of the total contents of the microcapsules. Even though controlled release may not be the objective of such formulations, they nevertheless carry the advantages of reduced oral and dermal toxicity and minimization of dust formation in comparison with the nonmicroencapsulated material. In addition to the pesticide itself, the core of the microcapsules may also contain solvents, surfactants, and materials such as titanium dioxide or zinc oxide to minimize ultraviolet damage.

Although the advantages of controlled release are impressive, the disadvantages of the technology must not be forgotten. Each formulation has to be examined individually, and the positive and negative aspects weighed carefully (6). The following aspects of controlled-release formulations—some of which may be deleterious—thus require careful appraisal: (i) the costs of the materials and processing of the controlled-release preparation, which may be substantially higher than those of standard formulations, (ii) the fate of the polymer matrix (see below) and its effect on the environment, (iii) the fate of polymer additives such as plasticizers, stabilizers, antioxidants, and fillers, (iv) the environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation, or biological agents, and finally (v) the cost, time, and probability of success in securing government registration of the product, if required (6).

STANDARD MICROENCAPSULATION PROCESSES FOR PESTICIDES

General Methods of Encapsulation

A variety of techniques have been proposed for the production of microcapsules (11–14). Indeed, one source suggests that hundreds of methods are to be found in the scientific and patent literature. In general, the methods for microencapsulation may be classified as follows:

- separation from an aqueous solution,
- formation by polymer–polymer incompatibility,
- interfacial polymerization,
- polymerization in situ,
- drying from a liquid state,
solvent evaporation from an emulsion,
gelation in the liquid state by cooling, and
desolvation.

Physical techniques, such as spray drying or fluidized bed reactions, are not usually suitable for encapsulation of pesticides. Similarly, addition polymerization is not suitable as many pesticides contain P, N, or S atoms, which are known to be radical scavengers, or because the compounds may not be stable in acid or alkali media. Interfacial polymerization is the method of choice for encapsulation of highly toxic insecticides, as the active ingredient is completely enveloped by the polymer, and in most cases, release takes place via diffusion. This technique facilitates a dramatic decrease in toxicity. Both phase separation and interfacial-polymerization techniques may be used for nontoxic pesticides. The only technique suitable for biological pesticides is phase separation; with any other technique the active ingredient, which in this case is a biological microorganism, would not be able to cross the envelopes surrounding it.

Interfacial Polymerization

The technique for the microencapsulation of pesticides by interfacial polymerization comprises two stages. In the first stage, a liquid, molten, or dissolved pesticide containing a dissolved monomer—together comprising the organic phase—is agitated at a high speed in an aqueous solution, with emulsifiers and stabilizers. In the second, interfacial polymerization at the droplet surface is completed by the addition of a second water-soluble monomer to the continuous aqueous phase. The resulting aqueous slurry may be used as such or the pesticide-containing capsules may be recovered as a dry powder. When the pesticide is water miscible, it is also possible to carry out interfacial polymerization by emulsifying the liquid or molten pesticide in an organic phase, such as high-boiling petroleum ether.

The following factors influence the performance of the capsules:

1. **Composition of the polymeric capsule wall:** The monomers can be chosen to produce a variety of interfacial polycondensation products to be used as wall materials, e.g., polyamides, polyesters, polyureas, polyurethanes, or polycarbonates. Within each of these categories, a range of polymers may be produced, depending on the starting monomers. It is also possible to vary the wall composition by forming copolymers in a simple process that is based on a mixture of oil-soluble or water-soluble monomers.

2. **Degree of cross-linking:** For cases in which a higher degree of wall integrity is essential, multifunctional monomers are used.

3. **Capsule wall thickness:** The thickness of the capsule wall is a function of the concentration of the monomers. In the production of the capsule, the wall continues to thicken until all of the available monomer is consumed.

4. **Capsule size:** The size of capsules is determined by the degree of agitation and by the type of emulsifying agent used in the continuous phase. Capsule size can be varied from an average diameter of a few microns to a millimeter. If the formulation is to be sprayed, then the diameter of the capsule must be less than 100 μm.

5. **Physical form of the product:** The final product may take the form of an aqueous slurry or microcapsules that can be filtered off, washed, and dried to a free flowing powder. Aqueous slurries are indeed useful in the
formulation of pesticides, as they need only to be diluted with water in order to be ready for field application as a sprayable product. In addition, they are cheaper, being more economical to manufacture.

6. **Additives**: A range of additives, such as UV light absorbers, antioxidants, and synergists, may be dissolved in the oil phase (pesticide) being encapsulated. It should be remembered that these additives must be soluble in the oil and must not react with the monomers.

Typically, effective pesticide formulations with zero-order release kinetics comprise microcapsules containing a pesticide core surrounded by a thin polyurea membrane formed by interfacial polymerization between a polyisocyanate and a polyamine (15,16). The latter polymers are generally preferred because they can form thin but strong and robust films around the pesticide core, and the conditions of formation are relatively mild. In a typical procedure for the microencapsulation of a pesticide, a hydrophobic oil phase containing an aromatic polyisocyanate as the membrane former is dissolved in a suitable nonwater miscible liquid containing the active component. The immiscible phase containing the isocyanate and the active ingredient is then emulsified (to approximately the desired size of the final microcapsules) in an aqueous solution containing stabilizing components such as surfactants or steric stabilizers, for example, polyvinyl alcohol (PVA). To the aqueous solution are added water-soluble polyfunctional reagents, such as amines, which rapidly react with the isocyanate groups at the interface between the immiscible droplet and the water phase to form a thin polyurea film. Sufficient time is allowed for all the isocyanate to react with the polyamine to form urea moieties. The resulting microcapsules have a thin, but strong, polyurea membrane surrounding the immiscible droplets. The membrane thickness is directly proportional to the mole fraction of the polyisocyanate (17). This interfacial-polymerization process is especially suitable for encapsulating water-dispersible formulations containing water-insoluble liquid pesticides, for example, insecticidal pyrethroids such as lambda-cyhalothrin, permethrin, cypermethrin, and many others, or relatively low-melting pesticides, such as the herbicides napropamide and fluazifopbutyl.

A recent example of the use of polyurea microcapsules for reducing toxicity and environmental impact is the encapsulation of the organophosphate insecticide, nematicide cadusafos (S,S-di-sec-butyl O-ethyl phosphorodithioate). The encapsulated product features significantly reduced human toxicity, less environmental impact, and enhanced stability but is as effective as the nonencapsulated formulation (18). Microcapsules of cadusafos are formed by microemulsion, followed by interfacial polymerization of a polyfunctional monomer such as polymethylene polyphenyl isocyanate with a polyfunctional amine to form an aqueous suspension of microcapsules with a polyurea shell surrounding a core of cadusafos. The components of the membrane are chosen such that the shell is sufficiently impenetrable to the cadusafos to reduce mammalian toxicity (skin, oral, and inhalation toxicity) of the formulation—in comparison with aqueous microemulsion cadusafos formulations of equivalent concentrations—and without loss of pesticidal activity or physical and chemical stability—in comparison with nonmicroencapsulated formulations.

Microencapsulation by interfacial polymerization may reduce the initial efficacy of pesticides exhibiting a low “knockdown effect.” It is thus desirable to develop formulations with reduced toxicity that have good initial activity together with long-term effectiveness; for example, haloacetanilides [e.g., alpha-chloroacetanilides,
such as alpha-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-acetanilide] that have been encapsulated in polyurea shells, produced by interfacial methods using phase-transfer catalysts or using different polyamines in the aqueous phase, have reduced initial effectiveness (19,20). It is possible to perform interfacial polymerization, which results in a polyurea shell, without adding amines or phase-transfer catalysts to the water. In this case, the interfacial polymerization is carried out by using the reaction of the polyisocyanate (e.g., polymethylene polyphenylisocyanate and isomeric mixtures of toluene diisocyanate) with water to form an amine, which then reacts with other isocyanate groups to give a polyurea, without the addition of catalysts of other reactive components (21). With this approach, the encapsulation method can produce formulations with equivalent initial herbicidal activity while at the same time reducing both the number of applications required and the mammalian toxicity, compared with the nonencapsulated formulations.

The issue of large microcapsules with slow sustained release versus small approximately 5-μm capsules that provide both rapid initial release (due to the larger surface to volume area) and reduced mammalian toxicity becomes important when a rapid knockdown effect is required or when small capsules are needed to facilitate migration through soil or surface grass. Despite the demand for controlled-release formulations that exhibit an early knockdown effect followed by sustained release of the active material, little work has been done on the production of stable, very small, rapid-release pesticide microcapsules. The reason for this situation is that such small microcapsules (typically less than 5 μm), which have extremely thin polymer shell walls, are difficult to produce uniformly and reproducibly. In a recent patent assigned to Dow, U.S. small, microencapsulated pesticide (e.g., chlorpyrifos) formulations were produced by an interfacial polycondensation reaction between PVA and a polyamine (e.g., diethylene triamine) in the aqueous phase with a polyisocyanate (e.g., Voranate M220) (22). It was shown that it is indeed possible to produce such small microcapsules with improved storage stability, i.e., with no leaching of the active material from the microcapsules. The use of PVA is important in the production of such microcapsules. The pendant –OH groups of the PVA, present during the polycondensation reaction that forms the microcapsule walls, react with the isocyanate to form a polyurethane group. The mixture of polyurethane and polyurea (formed between the polyamine and the isocyanate) components in the encapsulating membrane changes and gives a membrane permeability that differs from that of a polyurea membrane. By using PVA as a reactant in the encapsulation reaction and varying the time before the addition of the polyamine, the polyurethane/polyurea ratio can be varied as a way of optimizing the characteristics of the encapsulating membrane; for example, as each polymer type has a different permeability, the polyurethane/polyurea ratio can thus control active ingredient release rates as well as the microcapsule diameter and the thickness of the encapsulating membrane wall. In addition, PVA forms—on the surface of the capsule—hydrophilic pendants, which act as a steric barrier to prevent aggregation during production and storage, to facilitate spray drying for dry microcapsule formulations, and to enhance subsequent redispersion in water just before use.

Microencapsulated pesticides are generally sold in the form of the aqueous suspensions in which they are produced. There is, however, a need for dry water-dispersible powders for certain applications. Dry formulations that can easily be mixed with water to produce a sprayable material have the following advantages: (i) higher pesticide loading, (ii) easy removal from containers, (iii) less environmental contamination, (iv) longer shelf life, and (v) smaller volumes providing for more
economical transportation and storage. Dry formulations are usually prepared by
spray drying an aqueous suspension of microcapsules of the water-insoluble pesticide,
together with a spray-drying adjuvant; for example, the water-soluble polymer PVA
or polyvinyl pyrrolidone (PVP), a salt such as ammonium sulfate or sodium, potas-
sium, or calcium chloride, a surfactant, or some other water-soluble or water-disper-
sible material, such as gum, clay, or silica (23). While all the above mentioned spray
drying adjuvants can be used for relatively large thick-walled microcapsules of pesti-
cides, the list of adjuvants, suitable for producing water-dispersible formulations of
microcapsules of relatively small particle size with relatively thin walls, is limited to
synthetic and natural polymers such as PVP, PVA, polyethylene oxides, ethylene/
maleic anhydride copolymer, methyl vinyl ether-maleic anhydride copolymer,
water-soluble cellulose, water-soluble polyamides or polypeptides, copolymers or homo-
polymers of acrylic acids, water-soluble starches and modified starches, natural gums
such as alginates and dextrans, and proteins such as gelatins and caseins (24).

To enhance the efficiency of pesticide formulations, signal substances such as
pheromones, kairomones, or other attractants may be added to insecticides in micro-
encapsulated form or bound in water-soluble polymers (25). The release of the signal
substances at the infested sites leads to migration of the pests to these sites, where
they are exposed to the pesticidally active compounds and destroyed. This type of
insect control is known as the “attract-and-kill” method. For the compositions to
be effective over a sufficiently long period of time, the attractants must be formulated
in such a way that they can be released in a controlled manner and are protected
against environmental degradation by factors such as light, oxygen, moisture, and
high temperatures.

To date, a wide range of insecticides, herbicides, and fungicides have been
encapsulated by interfacial polymerization within a variety of polymeric shells, with
polyurea and polyurethane being particularly popular. The company that introduced
encapsulated pesticidal formulations to the market is the Pennwalt Corporation.
Their first insecticidal product, Penncap-M (encapsulated methylparathion), was
followed by KNOX OUT 2FM (encapsulated diazinon), Penncaptrin (encapsulated
permethrin), and Pennphos (encapsulated chlorpyrifos), and later by the herbicide
trifluralin (26). The Pennwalt polyurea envelope, synthesized by the reaction of poly-
isocyanate with amines and acid chlorides, and the method of encapsulation are
described in the patents (26–29).

Another company active in the market is the Stauffer Chemical Company,
whose interest lies mainly in encapsulated herbicides. The Stauffer process
for the production of the polyurea envelope differs from that of Pennwalt in that
the isocyanate also serves as a source of amine. In the reaction process, some of
the isocyanate is converted into the amine, which then reacts with the remaining
isocyanate (30–33).

A number of other companies are also involved in the production of encapsu-
lated biocides and herbicides. Among these, Monsanto Chemical Company markets
encapsulated alachlor under the trade name of Lasso. The envelope for the alachlor
formulation is also based on polyurea and polyurethane, and the method and
chemicals—isocyanates, amines, and emulsifiers—used by Monsanto are described
in the patent literature (34–38). Lever Israel produces NO-ROACH (encapsulated
diazinon), Chimgat 2000 produces De-Bugger® (encapsulated pyrethroids) and Effect-
tive Ultra (encapsulated propoxur), and Mahkteshim manufactures Master 25
(encapsulated chlorpyrifos) (39). In all the products mentioned above, the toxicity
of the formulation is at least one-tenth that of the emulsifiable concentrate, and the
duration of efficacy is longer without a reduction of insecticidal activity. Several other companies (40–44) have used polyurethane or polyurea shells as envelopes for pesticides; among the biggest of those are Hoechst, Bayer AG (45), and Ciba-Geigy (46).

The process for the production of encapsulated pesticides—in this case diazinon and pyrethroids (Pictures 1–3)—is presented in Scheme 1 (47).

So far, we have discussed the interfacial-polymerization technique in which polyureas, polyurethanes, and polyamides are used as the envelope for the pesticides. We have also made a passing reference to envelopes made from other polymers, including urea–formaldehyde and melamine–formaldehyde polymers, polyesters, epoxy, and polysilane. The formulations based on these polymers as envelopes have, so far, not been successfully commercialized.
Phase Separation

The second technique used in pesticide encapsulation is phase separation. The capsule obtained by this method is generally of the matrix type. This technique is suitable only for nontoxic and biological pesticides, as encapsulation into matrix-type capsules does not considerably reduce the toxicity of the product. An advantage
of this mode of encapsulation is that, should the need arise, it is possible to grind the formulation, as in most cases the active ingredient is absorbed onto and within the polymer matrix.

In the phase separation technique, the active ingredient is suspended in a solution of the wall material. The wall polymer is then induced to separate out as a viscous liquid phase by coacervation (i.e., by adding a nonsolvent), by lowering the temperature, by adding a second polymer, or by a combination of these methods. Coacervation, which may be simple, complex, or of the “salting out” type, is manifested as turbidity, droplet formation, or the separation of liquid layers as described below.

Simple coacervation occurs when a water-miscible nonsolvent (e.g., ethanol) is added to an aqueous polymer solution, causing the formation of a separate polymer-rich phase. A typical example of a simple coacervation system is water/gelatin dissolved in water; this system is, however, difficult to control, so it is little used in practice.

Complex coacervation takes place by the mutual neutralization of two oppositely charged colloids in aqueous solution. One of the most widely used methods of microencapsulation by this process is the use of a solution of positively charged gelatin (pH < 8), which forms a complex coacervate on being neutralized with negatively charged gum arabic. Other polymer systems may be employed, and other electrolytes may be used with gelatin. Complex coacervation is closely related to the precipitation of colloidal material from solution in that it immediately precedes

![Scheme 2](image)

**Scheme 2** Production of encapsulated *Bacillus thuringiensis israeliensis* (Bti).
precipitation. The process was originally developed in the 1950s—with gelatin and gum arabic as the two colloids—for the coating of carbonless copying paper.

In salt coacervation, the polymer is separated out from the aqueous solution by salting out, typically by adding an electrolyte to an aqueous polymer solution. The method may be used to encapsulate water-insoluble oils or dispersed solid particles, but it is difficult to control the microcapsule size and the agglomeration of particles. The system may be stabilized by altering the pH or temperature.

The polymers that can be used in the phase separation technique are summarized below (6):

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<tr>
<th>Natural polymers</th>
<th>Synthetic elastomers</th>
<th>Synthetic polymers</th>
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<tr>
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<td>Chlorinated polyethylene</td>
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<td>Ethylenevinylacetate</td>
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<td>Carboxymethylcellulose</td>
<td>Ethylene/propylene/diene terpolymer</td>
<td>Poly(ω-xylylene)</td>
</tr>
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<td>Hydrin rubber</td>
<td>Polycrlylate</td>
</tr>
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<td>Silicone rubber</td>
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**ADVANCES IN ENCAPSULATION TECHNOLOGIES**

**Biological Pesticides**

In addition to currently used synthetic pesticides, there are strong environmental and regulatory incentives to use “natural pesticides.” For example, biological pesticides, such as bacillus thuringiensis israeliensis (Bti) and trichoderma harzianum, have been encapsulated in matrix-type capsules in which envelopes are produced from two types of polymer—natural polymers such as alginate or synthetic polymers such as polyethylene (48–51). The methods of encapsulation are shown in Schemes 2 and 3. For example, the most common tactic used to control the larvae of the gypsy moth Lymantria dispers (L.) (Lepidoptera: Lymantridae), a destructive pest infesting cork oak forests in the eastern United States, Europe, and Asia, relies on the use of Bti-based insecticides (48).

**Insect Growth Regulators (IGR)**

In addition to currently used synthetic pesticides such as organophosphates, organochlorines, carbamates, and petroleum oils, use of encapsulated insect growth regula-
tors (IGR), for example, methoprene or pyriproxyfen, is increasing. For example, ALTOSID®, produced by Wellmark International, and developed in its encapsulated slow-release form by Southwest Research Institute (SwRI), is a mosquito larvicide used in the United States to reduce mosquito infestations by preventing immature mosquito larvae from becoming disease-spreading adults. The active ingredient, methoprene, is an insect growth regulator that interferes with normal mosquito development.

**Essential Oils as Natural Pesticides**

Alongside the use of natural pesticides like pyrethroids and bacterial larvicides, there has been a recent upsurge in the development of essential oils as “green pesticides” for such applications as larvicides, and moth and lice repellants (52–54). Formulations of essential oils are designed to compete with currently used pesticide products that are either highly toxic or very expensive or are harmful to the environment. In fact, before the development of the modern chemical and pharmaceutical industries, essential oils were used in many areas of daily life as antiseptic and

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**Scheme 3** Production of encapsulated *Trichoderma.*
disinfectant materials in pharmaceutical and cosmetic applications, e.g., as antimicrobial (antiviral, antibacterial, and antifungal) and larvicidal agents. With time, the toxic effects modern synthetic chemicals have on the environment have become apparent, and there is now an effort to replace them with the same essential oil agents that they replaced.

Many “green” materials, including essential oils, are less efficient and more expensive than the synthetic chemicals they seek to replace. There is thus a need to produce these green materials with a smaller effective dosage and increased effectiveness by enhancing the duration of activity per dose. This need is met by encapsulation of the oils, which are then released at a constant rate over a long period of time, thus increasing the duration of activity per dose and lowering the quantity needed and hence reducing the cost of the product. Encapsulation also stabilizes the volatile essential oils with respect to evaporation, UV degradation, and oxidation, and facilitates the ease of application.

The patent literature on encapsulated essential oils can be divided into four categories as follows: (i) patents describing all methods of encapsulation and a wide range of polymer encapsulants but giving limited examples and claims, (ii) patents based on a solid core containing the essential oils, with and without subsequent coatings, (iii) patents describing the encapsulation of essential oil droplets or emulsions in a polymer shell by coacervation or adsorption of preformed polymers, and (iv) patents relating to the encapsulation in microorganisms.

A number of examples from the patent literature follow. Encapsulated formulations of essential oils containing terpenoids are good lice repellents; these are safe, efficacious, pleasant smelling, and relatively inexpensive and are not toxic to man and animals (54). The encapsulation facilitates both quick action and delayed release. A number of synthetic and natural agents, including biodegradable natural or synthetic polymeric microparticles (including microspheres and microcapsules), liposomes, cyclodextrins, various surfactants, and polymers that decrease the volatility of the terpenes, have been developed for delaying the release of the essential oils. For example, positively charged chitosan microcapsules have been used to facilitate the sustained release of essential oils that act as biodegradable lice-repelling agents (55). In the encapsulation process, which is based on coacervation, an oil-in-water emulsion is first produced by homogenizing the oil in an aqueous solution containing an anionic emulsifier. The emulsion so obtained is then added to an aqueous chitosan solution with continuous homogenization of the mixture to give a stable dispersion. Finally, the emulsion is converted into microcapsules by the initiation of coacervation by the addition of a suitable electrolyte and changing the pH.

Another example is the use of *Rosmarinus officinalis* and *Thymus herbabarona* oils as effective larvicides instead of Bti-based preparations against the larvae of the gypsy moth (56). For formulating these oils, encapsulation is carried out by means of the phase separation process of coacervation, followed by freeze-drying. The essential oil is dispersed in an aqueous solution of gelatin (10%, w/w) at 40°C and emulsified with a high-shear mixer. Na2SO4 is then added to start the coacervation. The resultant gelatin microcapsules are cross-linked with glutaraldehyde at a basic pH, filtered off, rinsed with cold water, and dehydrated by freeze-drying. The process gives aggregates containing spherical units of about 0.2 μm in diameter in a high encapsulation yield (over 98%) with both rosemary and thyme oils. In these particles, the core of essential oil is encapsulated in a cross-linked gelatin shell. It was found that the microcapsules exerted a larvicidal effect at a
concentration similar to that usually employed for localized treatments with microgranular synthetic pesticides. As formulations of essential oils, prepared as described above, appear to be able to protect the core material against environmental degradation, they therefore could be considered for use as controlled-release systems.

Water-Soluble Pesticides

Most technologies for pesticide encapsulation have been developed for pesticides with low water solubility. There is, however, a class of water-soluble pesticides that would also benefit from microencapsulation, such as the acid or salt form of paraquat, diquat, glyphosate, dicamba, ioxynil, bromoxynil, bentazon, acifluorfen, and fomesafen. In one approach to encapsulation of such water-soluble ingredients, the active ingredient is embedded in a matrix of urea/formaldehyde polymer. The first step in this encapsulation procedure is the preparation of a water-in-oil emulsion from a water-immiscible liquid, a water-soluble urea–formaldehyde or melamine–formaldehyde prepolymer with methylol groups (−CH$_2$OH), the water-dispersible material to be encapsulated, an emulsifier, and water (57). The emulsion is then cured or treated to produce microcapsules by solidification of the urea–formaldehyde prepolymer resin to form a matrix encapsulating the droplets and permitting the separation of solid polymeric capsules containing the water-dispersible material. Curing is initiated with an amphiphatic catalyst, i.e., a catalyst that is soluble in

Table 1 Biological Efficacy After 24 hours of De-Bugger® Against the Flour Beetle (*Tribolium castaneum*)

<table>
<thead>
<tr>
<th>Pyrethroid formulation</th>
<th>% Mortality at the concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>De-Bugger®</td>
<td>0</td>
</tr>
<tr>
<td>EC</td>
<td>50</td>
</tr>
</tbody>
</table>

*Note*: 0 (zero), control (without pesticide—water only) in the case of the capsules and solvent in the case of the EC product.

*Abbreviation*: EC, emulsifiable concentrate.

<table>
<thead>
<tr>
<th>Pyrethroid formulation</th>
<th>% Mortality at the concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>De-Bugger®</td>
<td>0</td>
</tr>
<tr>
<td>EC</td>
<td>60</td>
</tr>
</tbody>
</table>

*Note*: 0 (zero), control (without pesticide—water only) in the case of the capsules and solvent in the case of the EC product.

*Abbreviation*: EC, emulsifiable concentrate.
both the water and oil phases of the emulsion. In a more recent approach to forming a shell surrounding the aqueous core—instead of a matrix—a surface-active proton-transfer catalyst that is soluble in the organic liquid, but only slightly soluble in the aqueous phase, is used to initiate an interfacial condensation reaction of the prepolymer at the water/oil interface (58). In this condensation reaction of the prepolymer, a polyurea–formaldehyde shell is formed around the water droplet instead of a matrix being formed within the water droplet. In a typical procedure, a urea–formaldehyde and/or melamine–formaldehyde prepolymer with methylol groups is dissolved in water, and the aqueous phase is emulsified in an organic liquid phase containing one or more surface-active agents. Self-condensation of the prepolymer in the aqueous phase of the discrete droplets adjacent to the interface is obtained by heating the emulsion to a temperature between 20°C and about 100°C with a proton-transfer catalyst.

Table 3  Biological Efficacy of De-Bugger® Against Fleas and Ticksa

<table>
<thead>
<tr>
<th>Sex</th>
<th>Type</th>
<th>Level of infestation</th>
<th>Presence of parasites after days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Type</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M Mongrel</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>F Mongrel</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>F Ridgeback</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>F Mongrel</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>M Mongrel</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>F Mongrel</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>M Pointer</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>M German shepherd</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>M German shepherd</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>F Belgium shepherd</td>
<td>Fleas + ticks</td>
<td>High</td>
<td>+ 0 0 0 0 0</td>
</tr>
<tr>
<td>M Spitz</td>
<td>Fleas</td>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>F Spitz</td>
<td>Fleas</td>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>F Spitz</td>
<td>Fleas</td>
<td>1–2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>F Terrier</td>
<td>Fleas</td>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>F Terrier</td>
<td>Fleas</td>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>M German shepherd</td>
<td>Fleas</td>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>F German shepherd</td>
<td>Fleas</td>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
</tbody>
</table>

*The experiment was performed in an animal shelter in Tel-Aviv, Israel under the supervision of the Chief Veterinarian. The spraying was done directly on the dogs. No untoward side effects were observed. Spraying on dogs heavily infested with ticks and fleas with De-Bugger® gave excellent results: after the first spraying the dogs remained without fleas and ticks for 28 days. After the second spraying, the dogs were free of fleas and ticks for 60 days. It is well known that the commercial product keeps the dogs free of ticks and fleas for a very short time (i.e., a few days).
QUALITY CONTROL

For any biocide formulation, the following parameters must be determined: the amount of active ingredient, particle-size distribution, shelf life, biological release rate, toxicity, and efficacy. As the first two parameters are well documented, they will not be described here. The tests for determining the other parameters are described in detail below.

Storage Stability

A sample of the microencapsulated pesticide formulation is kept in a closed vessel in an oven maintained at 54°C for two weeks or at 40°C for six weeks. The amount of the active ingredient in the product is analyzed before and after heating, and the formulation is considered stable if the amount of active ingredient does not change.

Release Rate of Pesticide

The apparatus used for this test is illustrated in Figure 3. One gram of encapsulated pesticide is placed on a plate, which is then sealed in a cylindrical glass vessel. The vessel is provided with a digital thermometer, and inlet and outlet tubes. The inlet tube is equipped with a flowmeter to control the volume of air introduced into the vessel. The temperature of the system is maintained at a predetermined value by an external heater. An air stream carries the released pesticide out of the vessel into a beaker containing ethanol. The amount of pesticide in the ethanol is determined, and the release rate calculated as a function of time.

Toxicity to Fish

A solution of the pesticide formulation is obtained by mixing the formulation in water in a high-shear mixer for five minutes. Ten fish are kept in a 16-L aquarium under the following optimal conditions: water quality as close as possible to pH 7.0 (neutral), water temperature 23–25°C, and good strong light for least 12 hours a day (more light makes them grow too fast). The test is performed in a room free of insecticidal contamination. Adult fish of either sex are supplied with adequate standardized food (Europet basic food) before and after the experiment. Food is withheld for two days before the experiment. After addition of the pesticide to the fish tank, mortality is checked after 3, 6, 24, 48, 72, and 96 hours. The time taken for 50% and 95% mortality (LT₅₀ and LT₉₅) are then determined from the results.

Acute Oral Toxicity to Mice

Adult male mice (2–2.5 months of age) weighing 25 to 30 g are supplied with standardized mouse food for the period of the experiment. A solution of the pesticide formulation is obtained by placing a small amount of pesticide in water in a vortex mixer for five minutes. Pesticide solution, 1 mL of solution per 20 g body weight, is taken in a 2-mL syringe and introduced into the stomach of the mouse via the mouth. Mortality is checked at 0, 5, 24, 48, 72, 96, 120, 144, and 168 hours, and LD₅₀ is determined.
Efficacy

In this method, which measures the susceptibility of a population of cockroaches (*Blattella germanica*) to a given insecticide, the cockroaches are exposed to standard insecticide residues in a Petri dish, and mortality is determined. Solutions of the insecticide formulation are obtained by mixing it with water in a high-shear mixer for five minutes. Filter papers are put into this solution, removed, placed in a Petri dish, and dried in a hood. The cockroaches should be obtained, as far as possible, from the same area, and kept in a suitable container until required. It is preferable to use adult males for the test, but if it is not possible to obtain enough males, females may be used. The test should be carried out in a room free of insecticidal
The cockroaches are given adequate standardized food before the experiment. They are anesthetized with carbon dioxide before being put into the insecticide-containing Petri dish. The Petri dish is then placed in an experimental vessel, which is maintained at 25°C to 30°C and relative humidity greater than 25%. From the results, the time taken for 50% and 95% knockdown (LT₅₀ and LT₉₅) can be determined. (A cockroach is considered knocked down if it fails to move, on being returned to its normal posture.) Picture 4 shows the capsule attached to the leg of a cockroach.

**CASE STUDY: DE-BUGGER®**

De-Bugger® (encapsulated pyrethroids) is manufactured and distributed by Chimgat 2000 under license from Ben-Gurion University of the Negev, Beer-Sheva, Israel. The LD₅₀ of De-Bugger® for mice, determined by the test described above, is 12,500 mg/kg, and the LD₅₀ for golden orfe fish 2200 µg/L. The biological efficacy of this encapsulated formulation versus that of the emulsifiable concentrate against cockroaches, flour beetles, house flies, and fleas and ticks is shown in Figure 4, Tables 1, 2, and 3, respectively.

**SUMMARY**

This chapter covers methods of encapsulation, controlled-release techniques for pesticide application, and current trends in the use of encapsulated natural products. The benefits incurred from the microencapsulation of many pesticides such as improved shelf life, reduced toxicity and environmental damage, reduction in the number of required applications, and enhanced efficacy far outweigh the cost of the encapsulation process. In the case of “biological, natural, or green pesticides,” encapsulation is necessary, if the materials are to compete with synthetic pesticides, such as the limited stability of the former under field conditions occurring because of
radiation, oxidation, and evaporation, and because of the high cost, which hinders multiple applications. Physical techniques, such as spray drying or fluidized bed reactions, are not usually suitable for encapsulation of pesticides. For most commercial encapsulated pesticides, the process of choice is interfacial polymerization, followed by phase separation and coacervation. Interfacial polymerization is used for highly toxic insecticides, as the active ingredient is completely enveloped by the polymer, and in most cases, release takes place via diffusion. Both phase separation and interfacial-polymerization techniques may be used for nontoxic pesticides. The only technique suitable for biological pesticides such as Bti and T. harzianum is phase separation: with any other technique the active ingredients would not be able to cross the capsule envelope. In addition to currently used synthetic pesticides, such as organophosphates, organochlorines, carbamates, and petroleum oils, the use of encapsulated IGR such as methoprene or pyriproxyfen is continuously increasing.

Alongside the use of natural pesticides, there has been a recent upsurge in the development of essential oils as green pesticides for such applications as larvicides, and moth and lice repellants. Essential oils may be encapsulated by a variety of techniques including interfacial polymerization and phase separation. Ongoing R&D to improve the final formulations of encapsulated pesticides has produced dry products that may be readily reconstituted in water for spray application, the combination of microcapsules with long-term release properties with more rapidly releasing microcapsules for a quick knockdown effect, and the addition of slow-release attractants to encapsulated pesticides.

REFERENCES