CONTROLLED RELEASE TECHNOLOGY, AGRICULTURAL

1. Pesticide Controlled Release Formulations

Controlled release formulations (CRF) aim to make available pesticides at rates appropriate for efficient control of pests under field conditions. These formulations are combinations of the pesticidal active agent with inert materials that protect, and release, the active agent according to the pest control needs. A depot or reservoir of active agent, within the releasing device or particle, is released at a defined rate, or variable rate, into the environment over a specified period. The releasing systems are usually solid and can vary in size from microparticles to large devices several centimetres across. However, the aspect that differentiates CRF from conventional formulations such as emulsifiable concentrates, wettable powders, soluble liquids, water-dispersible granules, etc, is time and the kinetics of release are central to CRF. In contrast, in the case of conventional formulations, complete availability of the active agent is usually considered to be immediate or rapid following deployment.

Controlled release formulations can be used with a wide range of pesticides, including inorganic substances, conventional low molecular weight organic substances, high molecular weight substances such as peptides or proteins, microbials (such as mycopesticides), and semiochemicals (which, eg, pheromones, modify pest behavior). Applications may be found in agriculture, veterinary, and public health sectors, and may be aimed at controlling a variety of pest organisms such as insects, mites, rodents, nematodes, weeds, and microorganims as well improving crop production with plant growth regulators. Within the term of "controlled release" there exist a variety of release types such as extended, slow, fast, delayed, programmed, sustained, pulsed, etc.

As for all pesticide formulations, CRF need to be applied, or placed, in the field appropriately for targeting the pests. In crop protection, this usually means application to the crop, or crop area, by means that achieve good distribution. Such distribution depends on how the pesticide moves to the target organism following application and often needs small particle size to provide this. Thus, the standard application methods of spraying and granules are important in agricultural pesticide delivery, which in turn limits the device size of the controlled release systems deployed. Greatest advances in CRF in agriculture have thus been found with sprayable, and to a lesser extent, granular methods. More specialized methods, eg, based on pheromones or baits, have been commercially possible using larger devices (1).

Most CRF are based upon macromolecules (usually polymers) as the inert components (sometimes combined with clays, salts, etc). The reason is because large molecules tend not to move in the environment (being often water insoluble and nonvolatile) and they can entrap small and large molecules such as pesticides. Thus, formulation with polymers provides the construct needed to entrap the pesticide and to build into the resulting depot device the mechanism for reliable release rates. Such polymers are best degradable so as to remove them from

the environment following their use. In selecting polymers for formulation, cost is of great importance in agriculture, when compared to medical drug delivery systems where benefits are considered more commercially valuable.

Thus, controlled release technology aims to manipulate the bioavailability of the pesticide in the local environment following application (2). This approach has many benefits compared to conventional formulations that include increased safety to the environment, workers, and consumers. Lower concentrations of released pesticide in the environment leads to reduced losses, such as leaching, evaporation, degradation, and binding. Reduced losses may mean better pest control, less nontarget impacts, reduced crop phytotoxicity, and safer formulations. Numerous benefits have been given on behalf of controlled release formulations, including

Protection of active ingredients from environmental degradation.

Manipulation of bioavailability and persistence.

Reduction of toxicity and operator hazards.

Reduction of phytotoxicity to seeds and crops.

Improved selectivity between target and nontarget organisms and usage in integrated pest management (IPM).

Reduction in repellency (also reduction in odors).

Allows coformulation, especially of incompatible pesticides (eg, of chemical and microbial pesticides).

Permits elimination of solvents.

Improves formulation of actives with phase changes near ambient temperatures.

Improves handling qualities of formulations and ease of cleaning sprayers.

Possible reduced application rates.

However, these advantages have been known for some decades [in fact, an early publication on a site specific release formulation of an insecticide dates to 1948 (3)] but their exploitation has been slow to develop in commercial practice. The first microcapsule formulation came on the market in 1974 (4); since then uptake represents only a small portion of total pesticide formulations. This is in contrast to the drug sector where controlled release and delivery has been rapidly expanding.

This slow uptake in the pesticide market may be related to the increased costs of the new technology on a product basis (but not on an "effect" basis) and there is a need for a change in attitude to pest control. However, there are also technical problems involved in active agent delivery in the open environment that may restrict extensive uptake. Renewed interest in good pesticide delivery could be prompted by the inexorable increase in limitations on pesticide numbers and their use as the U.S. Environmental Protection Agency (EPA), and other organizations, phase out more pesticides. New active ingredients coming to the market are currently fewer and registration is slow and expensive. In this situation, the commercial benefits of new safer controlled release formulations may be starting to outweigh the perceived disadvantages and the usual route of new molecule introduction.

2. Principles of CRF for Use in The Environment

2.1. Pesticide Delivery. As with all treatments, based on biologically active molecules, targeting is fundamental to its success. If the substances do not reach the pest, then logically no control will be achieved. Delivery to the target pest is considered both in time and place; sometimes the pesticide moves toward the target [eg, with foliar herbicides (5)] and sometimes the target moves toward the pesticide [residual insecticides (6)]. Thus, the efficiency of this delivery process can be defined as the ratio of the amount of pesticide reaching the pest divided by the amount applied, per unit cropping area. For many pest organisms the amount of pesticide needed for control can be ascertained, thus giving some idea of the efficiency of the delivery process. This delivery process is the sum of the placement methods, ie, spraying, granules, bait, etc, and the subsequent movement of the pesticide combined with the movement and growth of the pest itself. Sometimes, the pesticide is activated following application, in which it is chemically transformed into a more pesticidal substance. Transfer of the pesticide occurs through contact and also in mobile phases such as air and water.

2.2. Losses and Half-Life. During delivery, the pesticide is lost by a multitude of processes. The most rapid loss mechanisms cause the greatest amount of loss in which the pesticide is removed from the cropping location. These include spray drift, evaporation, leaching, run-off, sorption, dispersal, and dilution below active concentrations. Slower loss mechanisms include degradation of the pesticide caused by light (photodegradation), by biological processes (especially by microorganisms in soil) and chemical processes (such as hydrolysis and oxidation) (7). Degradation produces breakdown products (metabolites) that may be more or less toxic than the parent molecule and may be more or less prone to movement away from the application site. The environmental hazard of the metabolites may be greater than the pesticide but usually degradation represents a reduction of the pesticidal activity and overall toxicity. Alternatively, the pesticide, and its metabolites, may be bound into plants or into the organic matter (or clay) of soil.

The tendency for any pesticide to be degraded is characteristic of its molecular properties and can be expressed in the DT_{50} (time for 50% disappearance) or $t_{1/2}$ (half-life), typical values for agricultural soils. This value is based on a pseudo-first-order kinetic for loss. Pesticides with long half-lives, which persist for long periods are more effective in pest control, and are thus more efficient in contacting the pest, than those with short half-lives. However, such pesticides are less desirable environmentally, as long persistence can allow the substance to migrate, or otherwise cause detrimental impacts, such as by entering the food chain if having a high partition coefficient. In contrast, other bioactives may have short half-lives, thus requiring large application rates to provide an adequate period of effective control. This can be demonstrated in Figure 1, where the durations of control provided by two pesticides, P-1 with a half-life of 15 days and P-2 with a half-life of 50 days, are shown. Both require a minimum active level of 1 mg to provide control and the two plots "A" compare the periods of control, on a logarithmic basis. It can be seen that the faster degrading pesticide P-1 requires an initial application of 1000 mg, whereas the slower degrading P-2

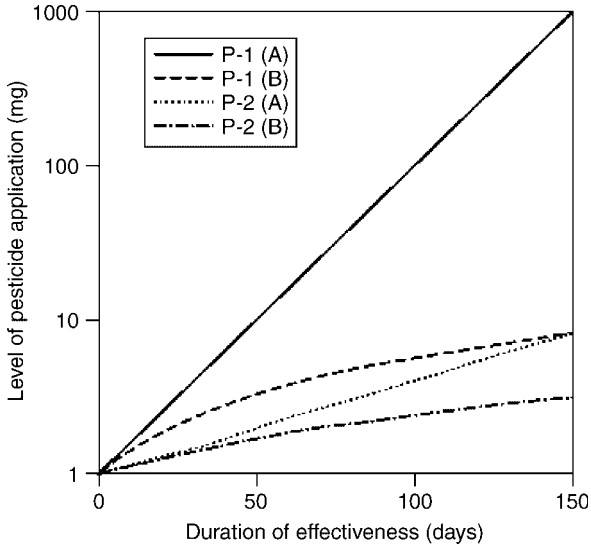

Fig. 1. Relationships between the level of application and the duration of action of two pesticides, P-1 and P-2, with differing half-lives, for conventional (**A**) and controlled release (**B**) formulations.

only needs 8 mg to be effective up to 150 days. In this case, the high initial concentration in the environment forms a reservoir or depot albeit exposed to degradation and losses that is available above the level required for control (ie, 1 mg) for the duration of the control period. Thus, the proportion of pesticide that is lost (ie, wasted) increases as the half-life decreases.

2.3. Controlled Delivery. As pesticide loss is concentration dependent, reducing environmental concentrations will reduce losses. If the concentration at the target pest could be kept at the minimum (or just above) for effective pest control by continuous supplementing for that portion lost or dissipated then the overall losses could be minimized (8). Keeping this minimum for the duration of control needed would represent the ideal approach with highest possible level of efficiency of delivery.

To maintain the concentration at the target, pesticide needs to be supplied at the same rate at which it is dissipated. Thus, the supply can be set equal to the loss, as in the following equation:

$$\text{Rate of supply } \frac{dS}{dt} = \frac{dM}{dt} \quad \text{rate of loss} \tag{1}$$

where $S =$ pesticide supplied and $M =$ the amount at time, t. By approximating the loss processes occurring in the environment, the rate of loss at any time is directly proportional to the amount of the pesticide

$$\text{The rate loss } \frac{dM_t}{dt} = -kM_t \tag{2}$$

where M_t is the amount of the pesticide at time t and k is the loss coefficient. After integration this gives the relationship:

$$\ln \frac{M_t}{M_0} = -kt \tag{3}$$

and M_0 is the amount of pesticide applied.

The time taken for the initial pesticide application M_0 to dissipate and fall to the minimum level required at the pest for control t_m is

$$t_m = \frac{1}{k} \ln \frac{M_0}{M_m} \tag{4}$$

which is used to plot the logarithmic lines in Figure 1 (lines "A").

If the pesticide is delivered from a formulation at a continuous rate to replace that which is lost in the environment

$$\frac{dS}{dt} = kM_t \tag{5}$$

$$dS = kM_t\, dt \tag{6}$$

The incremental change is thus given by

$$\frac{M_0 - M_m}{M_m} = kt_m \tag{7}$$

By using this relationship, the amount released from the formulation to replace that lost and to prevent the environmental amount to falling <1 mg can be calculated (8). This provides the curves "B" in Figure 1 for each of the two pesticides. It can be seen that the amount needed to give 150-days control has now fallen to 7.9 mg for P-1 (from 1000 mg) and to 3.1 mg for P-2 (from 8 mg). The areas between the two sets of curves logarithmically represents the pesticide that is lost and that only serves the purpose of a degradable reservoir. The amounts saved at shorter periods are less than for 150 days. By comparing the two sets of curves, the potential for saving is substantially greater for the pesticide with the short half-life. In fact, using an ideal controlled delivery system for this pesticide produces an efficiency over the 150 days equivalent of using the second pesticide with the longer half-life.

Controlled release formulations, combined with other aspects of pesticide application, thus offer the feasibility of improving pesticide delivery, reducing losses and benefitting the environment. The above model is based on many assumptions, including a constant and uniform environment. The agricultural situation is characterized by continual fluctuation and thus the theoretical objective can only be partially realized. However, it does demonstrate that compounds of short persistence (such as insect pheromones) may be used effectively in place of long persistent compounds when appropriately formulated. Loss kinetics for any individual pesticide vary depending on the environmental location

considered; eg, loss by evaporation or photodegradation at the surface of plants may be much more rapid than published data giving half-life values for soils (7).

3. Types of Formulation: Physical, Chemical, Biological

3.1. Physical Systems, Matrix, and Reservoir. The role of delivery of pesticides is becoming more recognized as it has been a much neglected part of pest management. In a recent book arising from the IUPAC meeting on pesticides, the position of delivery was placed second only to the discovery of new biologically active molecules. Indeed, with the widespread advent of proteinaceous pesticides, the ability to deliver these to the crop plant using genetically modified varieties has reached the level of 100% efficiency, but not with 100% bioavailability or delivery to the pest organism. However, this ability does not apply to all pest problems and situations and it is desirable to maintain a multiplicity of pest management methods (including conventional pesticides) and controlled release formulations as described here have an important role in good delivery. In terms of IPM, controlled delivery has a major contribution to the combination of pesticides with biocontrol methods when compared to conventional formulations.

For environmental application of pesticide delivery, controlled release formulations have been traditionally divided into chemical and physical types (9). More recently, a third approach has appeared, biological, partly in response to delivery requirements for genetically engineered pesticides. The types of controlled release formulations described to date can be categorized as follows:

Chemical

Backbone linking.

Side-chain bonding.

Matrix degradation.

Carrier molecules such as cyclodextrins.

Physical

Reservoir

with membrane (micro- and macroencapsulation, coated solids, laminates and large devices).

without membrane (hollow fibers, porous solids, and foams, gels, osmotic pumps).

Monolith or matrix (films, paint, sheets, slabs, pellets, strips, granules, microparticles, powders, and microspheres).

Biological

Living, or dead, cells (microorganisms) as delivery mechanisms.

All formulation types have been prepared and tested but not all have reached commercial practice. The more important types are described in the following, but this description is not comprehensive and the opportunities are only

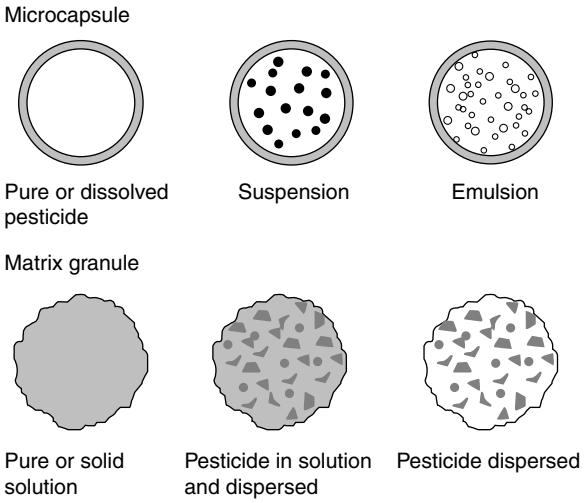

Fig. 2. Various configurations of capsule and matrix formulations.

limited by innovation and development of new approaches (10). The basic configurations of CRF are given in Figure 2.

3.2. Kinetics and Characteristics. There is a great deal of variation in the release kinetics of pesticides from the various formulation types described above. However, based on mathematical treatment the main types of release kinetics are represented in Figure 3. In order to discern the kinetics, the rate-controlling step needs to be identified (11). This should be done under controlled conditions, ie, in the laboratory, but it does not necessarily follow that this will be

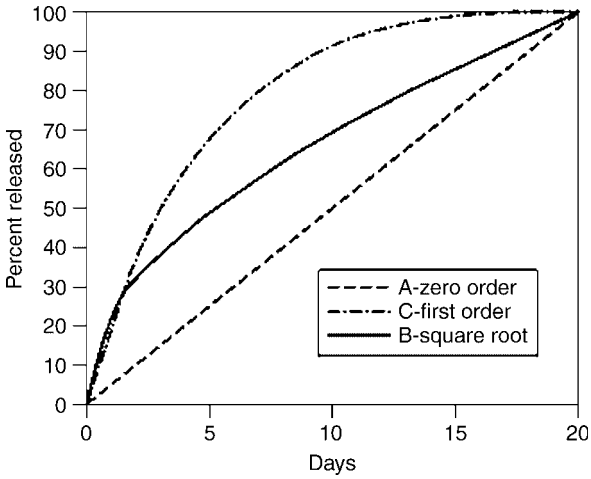

Fig. 3. Cumulative release provided by various release kinetics. (A) Constant release, independent of time (zero order) such as that possible from a membrane reservoir device free of lag time or initial burst effects, (B) matrix or monolithic sphere with square root time release, (C) first-order release.

true in the environment where the formulation is to be used. To study the basic kinetics, ie, those independent of the environment, the formulation has to be placed under "sink" conditions. These prevent the released pesticide from accumulating in the immediate vicinity of the surface of the formulation and slowing the release rate. The type of test environment will depend on the interfacial transport mechanism, especially movement into aqueous media or into the vapor phase or uptake by a biological system (12). Ideally, release kinetics ought to be determined under field conditions, but this often presents insurmountable problems (especially those resulting from the variability of the open environment) and instead the biological response to the released pesticide is observed over time to validate the performance of any formulation.

3.3. Mechanisms of Release. *Constant Release (Zero Order).* In the Figure 3, Line A represents release from a reservoir system with a large core relative to the wall mass. This could be a microcapsule releasing by steady-state diffusion through a uniform nonerodible wall. Transport through the polymer membrane (or matrix) occurs by a dissolution–diffusion process, where the active ingredient first dissolves in the polymer and then diffuses across the polymer to the external surface where the concentration is lower. The diffusion is in accordance with Fick's first law:

$$J = -Ddc_m/dx \tag{8}$$

where J is the flux of pesticide, D is the diffusivity, and dc_m/dx is the concentration gradient of the active ingredient. The rate remains constant as long as the internal and external concentrations of the pesticide and the concentration gradient are constant. A lag phase may occur while the system reaches this steady state (7).

Release by Erosion. The rate is independent of the concentration of pesticide remaining in the device. This zero order is also typical of certain surface erodible devices but their geometry is important and only laminar shapes produce a true constant rate as the device is eroded from one or both faces (2). Cylindrical, spherical, and irregular granular shapes provide a decreasing rate (as these particles lose surface area as erosion proceeds) and the overall release rate can be sustained only if hollow (concave) surfaces are available. These erodible systems have not been substantially exploited in pesticide delivery, mainly due to cost. Erosion can occur by dissolution of surface polymer or by degradation of the matrix, the best examples of which are the many polyesters such as *d,l*-polylactic acid or polyhydroxybutyrate. In this case, erosion may be through bulk hydrolysis of the polymer (13).

Release From Reservoir Systems. Most controlled release systems, including microcapsules, are positively rate dependent on temperature that makes effective delivery during cool night periods when interspersed with hot days (such as that required for pheromone release for control of nocturnally mating insect pests) problematic. For microcapsules, if the activity of the pesticide within the reservoir decreases then the release rate will also decrease; this effect will vary according to the capsule dimensions. This leads to a consideration of the polydispersity, or the range of sizes in a given number of microparticles. Although the release rate from individual particles may be constant, the duration

of this release will varying according to the size of each particle. Thus small particles become depleted before large particles and the overall release from a population of particles will decrease with time. This has been shown in laboratory and field tests where overall first-order rates from microcapsules (Penncap-M; 20–40 μm) have been observed (14).

Release from Polymeric Matrices. In nonsurface erodible matrix systems, diffusion of the active ingredient occurs from the interior of the particle to the surface. This gives rise to a declining rate of release according to the square root of time ($t^{-1/2}$) as shown by curve B in Figure 3. In practice, the approximate Higuchi model (15) applies and is true up to 60–70% of release, typically from a sphere or microsphere. The pesticide may be dissolved or dispersed in the polymer; for dissolved pesticide the second phase of release is by first-order kinetics. For dispersed pesticide, the $t^{-1/2}$ kinetics last for almost all the release. These kinetics are a special case of the generalized description (16) of proportional release (at time t) from matrix or monolithic devices, as follows:

$$\frac{M_t}{M_\infty} = kt^n \tag{9}$$

where k is a constant incorporating characteristics of the polymer and the pesticide, and n is the diffusional exponent and indicative of the transport mechanism. In these cases, $n = 0.5$ and indicates Fickian diffusion as the rate-controlling step in release.

3.4. Swellable Matrices. In matrix systems, where water uptake or swelling can occur, such as may be possible in moist soil or water, the rate-controlling step may be solid-state diffusion or relaxation of the polymer by incoming water or a combination (17). Thus, the time exponent of the equation characterizing the release rate (18) may vary from 0.5 (square root of time) for Fickian diffusion to 1.0 (zero order) for swelling according to the nature of the matrix and the pesticide. Generally, the higher the water solubility of the pesticide, the faster will be its rate of release. Less polar molecules with high partition coefficients tend to transport slower. In the case of irregular particles, such as granules, and where polydispersity exists, the overall time exponent will typically be less than the corresponding value for microspheres. For diffusion controlled systems, a typical low value is $n = 0.43$ (18).

First-Order Release. Finally, in situations where a chemical reaction liberates the active species, or where boundary conditions are rate limiting, the rate of release depends on the concentration in the solid phase (19), and first-order kinetics are seen as in Figure 3 as curve C. Where more than one mechanism (including diffusion) operates, then complex release patterns occur.

4. Design and Preparation of Controlled Release Formulations

4.1. Chemical Methods. Chemical methods involve the formation of a chemical bond with the pesticide and another molecule; this bond is then broken in the field to allow the release of the pesticide. The bond energy relates to the

ease of breaking and thus the rate of release of the pesticide (20). Where the structure of the pesticide permits, it can be homopolymerized through a condensation reaction and the pesticide forms the backbone of a resulting high molecular weight polymer, which is in effect a polymeric propesticide. In the environment, this polymer depolymerizes to release the original pesticide, usually from each end of the chain (unzipping). Often breakdown of such homopolymers is slow and there is need for copolymerization with another appropriately functional monomer. Pesticides capable of homo- or copolymerization are few and include those containing functional groups such as amino, hydroxyl, and carboxyl groups.

A second approach to chemical-based formulations is where the pesticide is attached to a side chain of a high molecular weight polymer or macromolecule. This polymer may be either preformed, and the pesticide is then bound to appropriate side-chain functional groups, or the pesticide is first attached to a polymerizable monomer that is subsequently polymerized to yield the pesticide bound polymer (21). Again the release rate will depend on the energy of the bond holding the pesticide to the polymer that then undergoes scission to release the pesticide moiety (20).

The third approach to chemical-based release of pesticides is where the active is trapped in a network of a cross-linked polymer. Chemical breakdown of this polymer then allows the release of the pesticide. This mechanism incorporates physical processes of diffusion within the release mechanism.

The first two of the chemical release mechanisms usually involve covalent bonding of the pesticide and the formation of a molecular species different to the original structure. As a result of the registration requirements of new pesticide molecules, this approach implies considerable additional costs that outweigh the putative formulation benefits. Thus, true chemical approaches are often proscribed in favor of physical methods.

4.2. Physical Methods. Physical methods are divided into two general approaches. The pesticide is entrapped within a physical structure either at a molecular or microdomain level or the pesticide in the form of a reservoir is enclosed within a polymeric envelope (2). In the first, the pesticide is mixed with the polymer (or other material with high energy density) to form a monolithic structure or matrix. Release is normally by means of diffusion through the matrix or dissolution and erosion of the matrix. In the second approach, structures are based upon a reservoir of the pesticide enclosed by the polymer, from nanoscale up to centimeter-sized devices. The shapes of these devices are varied and include spherical such as microcapsules, and laminar or layered structures with the reservoir bounded by permeable membranes. These membranes provide a permeable barrier that controls the release rate. Other mechanisms of release include capsule rupture and erosion of the membrane.

As these "physical" methods provide the most important technologies for CRF of pesticides they will be presented in more detail in the this section.

4.3. Reservoir Based Formulations with Membrane. In this method, a reservoir or depot of the pesticide is bounded by a polymeric membrane, which protects (and separates) it from the environment and also provides a mechanism for its release. Thus, the specifications for the chemical nature and

structure of this membrane are critical in the performance of such formulations. This makes for exacting requirements in the manufacturing processes if the desired release rates are to be consistently obtained in the field.

The method most suitable for use for pesticides is microencapsulation, where particle sizes are of the order of 10–100 μm and can be delivered by standard agricultural spraying. Microencapsulation has been defined (22) as the placing of a layer on the surface of a single *liquid* droplet. Conversely, coating refers to the covering of a single *solid* particle, whereas a matrix particle contains the solid or liquid active agent dispersed throughout a binding material. Even though these matrix particles are usually granular, they can be similar in size to microcapsules and are also intended for spraying as suspensions, they should be considered as matrices, and are covered below.

4.4. Microencapsulation. Microencapsulation has now been commercially practiced for >30 years, following the first application of the technology to carbon-less copying paper. Pesticide formulations based on microcapsules appeared in 1974 with the product Penncap-M containing the insecticide methyl parathion (4). Since then, many microcapsule suspension formulations have been introduced and form the major group of CRF.

Production of microcapsules is based on three main methods (23). The oldest, that of phase separation or coacervation, uses emulsification to produce core droplets containing the pesticide dispersed in a immiscible phase in which the wall material is dissolved, but then precipitates around the core droplets. Interfacial encapsulation is done by emulsifying or dispersing the pesticide solution in a continuous phase and a polymerization reaction takes place at the interface. Finally, in the physical methods the wall material is spread around the pesticide containing core to make the microcapsule.

Microcapsule Preparation by Interfacial Polymerization. The polymer forming the wall of the microcapsule can be made by addition or condensation poymerization or by *in situ* condensation polymerization. Addition polymerization using unsaturated monomers and free-radical generating catalysts may start with the monomer in the pesticide-containing dispersed oil phase and the water-soluble catalyst in the aqueous phase. Other combinations of monomer and catalyst distributed between the two phases are possible but less practical. Pesticide impurities can interfere with the polymerization producing unsatisfactory capsules (24).

The condensation route to wall polymers is the best method for pesticide encapsulation. In this process the two reactive monomers, one dissolved in each of the two phases (of the emulsified oil/pesticide in water), polymerize at the interface and generate the wall material. Typically the oil-phase monomers are polyfunctional isocyanates (A) or acid chlorides (B) and the water phase reactants are polyalcohols or amines. Compounds sufficiently reactive are chosen such that when they meet at the interface the condensation polymer forms the capsule wall (Figure 4). Alternatively, the two reactants (a diol and a diisocyanate) and a low boiling solvent make up the oil phase of the emulsion along with the pesticide. When heated, the solvent evaporates bringing the monomers together at the droplet surface to form the capsule wall (25).

The resulting polyamide wall tends to be weak and soft, but the polyurea and polyester produce tough strong materials (26). Other combinations of

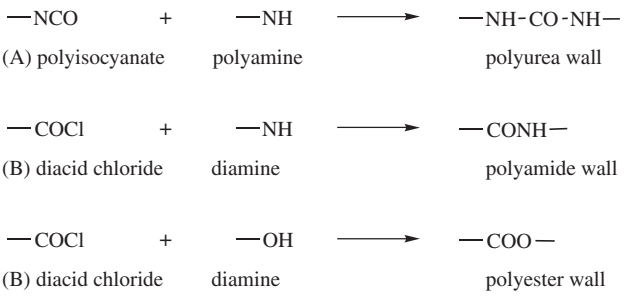

Fig. 4. Various routes to capsule wall formation through condensation polymerization.

reactants give tough and strong polyurethane walls [polyamine and bis-(haloformate) or polyol and polyisocyanate] or epoxy walls (amine and epoxide).

For *in situ* condensation polymerization, only the oil-phase isocyanate reactant is used (27). When the emulsion is heated the isocyanate reacts with water at the interface to form an amine that then reacts in turn with remaining isocyanate. The resulting polyurea wall material formed is thin and strong providing good release properties for environmental applications. The permeability (the product of the diffusion coefficient and the solubility coefficient) of the wall can be varied by incorporating cross-linking monomers into the oil phase. A typical monomeric system is toluenediisocyanate (TDI) and polymethylene-polyphenylisocyanate (PAPI), a multifunctional monomer that causes cross-linking of the wall polymer (see Fig. 5). Both isocyanate monomers react with water at their own rates.

Forming the wall is only part of the successful microcapsule formulation. Recombination during microcapsule formation or subsequent storage to give large irregular shapes is a problem. Protective colloids offset this and reduce loss of the active ingredient into the continuous phase. Commercial colloids

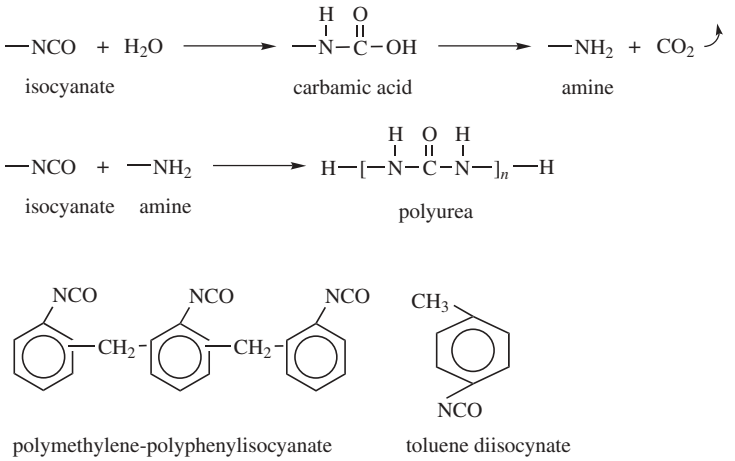

Fig. 5. Monomers and polymer forming reaction for *in situ* microcapsule wall formation.

used include poly(methyl vinyl ether/maleic anhydride) cross-linked with poly-(vinyl alcohol), styrene/maleic anhydride coplymers, vinylpyrrolidone/vinyl acetate copolymers, vinylpyrrolidone/styrene copolymer, and lignin sulfonate. A typical capsule suspension formulation made in this way may have up to 60% of the active ingredient, solvent (up to 20%), polymer (5–10%), protective colloids (1–20%), emulsifiers (1–5%), ultraviolet (uv)-protectant (0–5%), buffer (5%), viscosity/structure modifiers (2–10%), and water to make up the bulk (24).

Microcapsule Preparation by Phase-Separation Methods. The earlier methods used for pesticide microencapsulation were based on phase separation. There are two main approaches to coacervation, based on phase separation. Simple coacervation is when an aqueous solution of a hydrophilic polymer separates into two phases (solid and liquid) on addition of salt, alcohol, or other water-miscible solvents (27). An example would be the phase separation from an aqueous solution of poly(vinyl alcohol) by a nonsolvent such as propyl alcohol or by a salt solution, such as sodium sulfate. Complex coacervation occurs when polymers in solution with opposite electric charge come together and separate from the water. The most common example of complex coacervation is based on gelatin and gum arabic, two natural hydrophilic colloids. The process involves gelatin solution mixed with the core material in oil that is emulsified and the gum arabic added. The emulsion is heated and the phase separation is induced by dilution, reducing pH, or cooling. If the pH is reduced <4.5, the gelatin is then below its isoelectric point (pH 4.5) and its charge becomes positive; it then reacts with the gum arabic that has a residual negative charge and coats the oil droplets. Alternatively, phase separation can be caused by dilution. The emulsion would then be cooled and treated with formaldehyde to cross-link and strengthen the capsule wall.

Phase separation can also be produced from solutions of polymers in organic solvents. By addition of a nonsolvent for the polymer to the solution containing the core material the polymer will precipitate around the emulsified core to form microcapsules (28). This can allow for the encapsulation of aqueous solutions or suspensions of pesticides. For example, such an aqueous solution can be emulsified in oil containing the dissolved polymer. Addition of the nonsolvent to the oil phase separates out the polymer that can then form the wall around the water droplets.

Microcapsule Preparation by Physical Methods. These work by passing the two phases, core and wall material, through a small opening such that the wall material coats the core (29). This coating can be achieved using biliquid extrusion nozzles or with centrifugation in which the two liquids pass through many orifices. These allow the wall material to be cooled or dried after leaving the nozzle thus forming a rigid wall structure. These processes generally give high wall to core ratios and cannot be used to prepare very small microcapsules (<100 m).

4.5. Coating of Solid Particles. Covering a solid particle with a polymeric wall is usually referred to as coating although the product may be termed a microcapsule. Various methods may be used with degrees of uniformity of the wall structure (30). Pan coating is well established in which the core particles (>1–2 mm) are tumbled in a rotating drum while the coating solution is sprayed slowly; warm air circulates to remove the solvent. For smaller particles, a

Table 1. **Acute Mammalian Toxicities for Encapsulated and EC Formulations of Methyl Parathion and Diazinon**[a]

Formulation	Rat oral LD_{50} mg/kg	Rabbit dermal LD_{50} mg/kg
diazinon (EC)	350	600
Knox Out 2FM	>21,000	>10,000
methyl parathion (EC)	25	400
Penncap M	600	>5,450

[a] After Ref. 39.

fluidized bed is needed. The core particles (down to 100–150 μm) are fluidized in a rising air current and the coating solution slowly sprayed into the bed. Spray drying in which the core material and the coating solution is atomized and the droplets dried rapidly in hot air gives poorer quality of encapsulation. There are numerous other methods for encapsulation, many specialized for specific applications.

4.6. Examples of Microcapsule Formulations. Even though the first microcapsule formulation (using phase-separation technology) was introduced into commerce in 1960 for the purpose of releasing ink in carbonless copying, it was not until 1974 that the first pesticide microcapsule appeared (14). This was Penncap M, methyl parathion encapsulated within a polyamide/polyurea wall material, prepared from the reaction of sebacoyl chloride and polymethylene polyphenylisocyanate with ethylenediamine and diethylenetetramine, suspended in water (240 g/L). This product showed reduced toxicity and extended insect control, and was followed by a similar formulation based on diazinon for indoor control of cockroaches. Superior and extended pest control was achieved, compared to conventional formulations. Mammalian toxicity was reduced as can be seen for these microcapsule formulations in Table 1. These pioneering formulations were followed by similar types using other insecticides such as ethyl parathion, permethrin, cypermethrin, and chlorpyriphos.

Microcapsule formulations have been made, based on pesticides, for control on crops and soils, on timber and other surfaces for structural and indoor pests, on seeds and livestock. A few examples of microcapsule formulations from the 60 or more currently available worldwide are in Table 2. An electron micrograph of a pesticide microcapsule formulation is shown in Figure 6. Each particular

Table 2. **Selection of Some of the Microcapsule Formulations**

Trade name	Active ingredient	Wall material	Company
Penncap M	methyl parathion	polyamide/polyurea	Atochem
Knox Out 2FM	diazinon	polyamide/polyurea	Atochem
Micro-Sect	pyrethrin/synergist	polyurea	3M
Kareit MC	fenitrothion	polyurethane	Sumitomo
Sumithion MC	fenitrothion	polyurethane	Sumitomo
Lumbert	fenitrothion	polyurethane	Sumitomo
Icon	lambda-cyhalothrin	polyurea	Syngenta
Karate Zeon	lambda-cyhalothrin	polyurea (thin wall, low cross-linking)	Syngenta

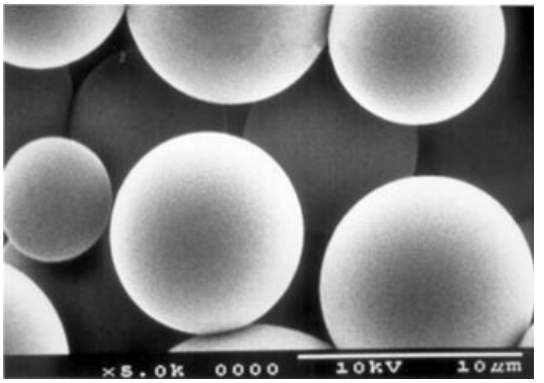

Fig. 6. Electron micrograph of a pesticide microcapsule formulation.

formulation is designed for its specific application and method of use. Variables that can be exploited for this purpose include capsule size and size range, wall thickness, wall permeability and strength (provided by degree of cross-linking), nature of wall material, adjuvants and other formulation constituents. Release is usually through diffusion of the active agent through the capsule wall but other mechanisms can be used, such as rupture triggered by mechanical, erosion or degradation, thermal processes, or by osmotic swelling. An example of how encapsulation variables can influence release has been provided by Tsuji for a fenvalerate formulation (31). This polyurethane microcapsule was prepared by interfacial polymerization of polyisocyanate and ethylene glycol and to have various wall thicknesses and mass median diameters.

Efficacy against the important brassica pest, diamond-back moth (*Plutella xylostella*), was assessed and it was found that the LC_{50} value decreased for the larger capsules (diameter D) when wall thickness (T) was constant and for the thinner wall when the diameter was kept constant. For any batch of microcapsules, the ratio of diameter (expressed as the mass median diameter in μm) to the wall thickness (in μm) can be determined. This value D/T can be interpreted as relating to the strength of the capsules. As the ratio D/T increased, the 48 h LD_{50} value decreased. This means that the rupture of the capsules, by insects or other factors, is the important factor in biological efficacy. The availability of the insecticide depends on the strength of the capsule and thus the persistence of action of such microcapsule formulations will depend on having an optimum diameter/wall ratio with the wall thickness, neither too thin or too thick. Other similar microcapsules (MC) formulations for use in agriculture have been made based on insecticides fenitrothion and fenpropathrin, that also showed better safety to sensitive crops and to nontarget organisms such as fish. In extending this technology, formulations based on permethrin were developed for use in transplanted rice, and on fenitrothion and fenobcarb for aerial application in rice for bug and planthopper control.

The mechanism of release for these capsules, ie, by rupture or breakage, is suitable for controlling insect pests on surfaces. Formulations were developed for the control of cockroaches (based on fenitrothion or cyphenothrin), for termites

(based on fenitrothion either applied to surfaces or incorporated into the glue of plywood), and for mosquitoes and flies on aggressive surfaces such as cement (based on fenitrothion and lambda-cyhalothrin). In the case of cockroach control, the pick up of microcapsules and the efficient delivery (often by grooming and ingestion of dust plus capsules) can give control of individuals resistant to diazinon or fenitrothion.

Formation of microcapsules by *in situ* interfacial polymerization (where the monomers are entirely in the oil phase of the capsule core) yields microcapsules with a high core/wall ratio and a bilayer wall with an outer layer ($\sim$0.05 μm) and an inner reinforcing spongy layer (0.5 μm). This method has been used to encapsulate a range of insecticides, pheromones, and herbicides, many of which have been available commercially (32). The capsule size may be varied from submicron to 100-μm diameter and the permeability selected for rapid or slow release of the pesticide. Release is by diffusion through the wall rather than rupture. For an effective formulation, the capsule suspension formed after polymerization needs protective stabilizers, dispersants, flow etc, to provide a high active ingredient content with good shelf-life and acceptable handling at dilution.

Applications for MC formulations include seed treatment (especially where an insecticide may be phytotoxic at dosages required), soil treatment of insecticides and herbicides, and treatment of surfaces for cockroach and mosquito control.

4.7. Laminate Formulations. The laminate system comprises a reservoir layer of pesticide-containing polymer sealed between two other plastic layers (33). The two outer layers of this multilaminate structure protect and release the active ingredient by diffusion driven by the concentration gradient. Often one of the layers is impermeable and functions as a support for adhesion to suitable surfaces. At the surface, the pesticide is continually removed by evaporation, degradation, leaching, or by mechanical contact by humans, insects, moisture, wind, dust, or other agents.

The form and structure of the laminate varies according to the active agent and the intended application. The laminate may be used as a sheet for covering surfaces or may be cut into strips, ribbons, wafers, flakes, confetti, or even into granules or sprayable powders. Laminate strips (2.5×10 cm) consisting of a reservoir of an insecticide in poly(vinyl chloride) (PVC) on a base of impermeable Mylar sheet and covered with a 0.127-mm layer of PVC have been developed for indoor cockroach control (Hercon Insectape). The insecticides include chlorpyrifos, diazinon, and propoxur. The tape is intended to be affixed to cockroach frequenting surfaces and provide control for up to 3–5 months, especially valuable in areas where spraying is not desirable.

The laminate tape may also be used in its strip form as part of a collar for control of ticks and fleas on pet animals. Durations of control of these pests have been demonstrated to be up to 8 months for tick control.

An important application is for release of insect pheromones and attractants for insect control. A combination of the insecticide propoxur with the cockroach attractant periplanone-B provides 1 month of control in a laminate bait strip. Delivery of volatile compounds to the atmosphere surrounding crops is a crucial part of the mating disruption technique for many insect pests (34). The number and disposition of devices releasing the volatile pheromones depends

on the pest, crop, and other environmental factors. Laminates can thus be dispersed in the crop as individual large devices (adhesive strips) or as small flakes or confetti applied by aircraft (applied with adhesive to ensure retention towards the top of the crop canopy) according to the control requirements. Among a number of crop pests, an important use has been for pink bollworm in cotton. The use of a plastic film for controlling release of pheromones can take the form of the laminate, or film enclosing a reservoir of the active agent on a porous substrate, or even in the form of polyethylene bags, vials, tubes, and caps.

4.8. Reservoir Based Formulations Without Membrane. Reservoir systems that lack a bounding membrane to protect and regulate the release are usually designed for liquid actives that are volatile. The liquid is held in place through capillary forces and is released in the vapor phase. The rate of evaporation is regulated by diffusion of the vapor through the static air phase above the liquid surface. The simplest example is the hollow fiber, which is a fine polymeric capillary closed at one end and filled (or partially filled) with the liquid active (35). This diffuses through the air column to the opening from where it disperses. This method has been mostly developed to deliver many of the volatile sex pheromones for insect pest control to maintain a minimum concentration in the air surrounding the crop to be protected.

Operating by a similar process are the porous and foam polymers. The active is held in the pores of the structure and released by diffusion through the pores to the surface where it moves away from the particle. The diffusion is driven by evaporation or by dissolution in environmental water that penetrates the porous particle. Highly absorbent polymers such as Culigel have been developed for delivery in water bodies for mosquito control (36).

4.9. Matrix Formulations. These formulations, also known as monolithic, consist of a uniform continuous phase with the pesticide dissolved or dispersed throughout. Their preparation is generally easier, requiring less process control, but can exhibit a rich variety of release types according to the material and structure of the matrix. An almost endless selection of materials are available for the matrix. Elastomers (rubbers) as well as thermoplastics and thermosetts can be used and many applications for pesticides have been developed using the technologies of the rubber and plastics industries (9). Generally, a range of additives such as plasticizers, light protectants, pigments, antioxidants, processing aids, etc, are usually included (37). The products can be produced in a number of forms or shapes, especially sheets, ropes, extruded cylinders, slabs, and granules. As release is inversely related to device size, the production of simple powders involves difficulty in uniformity as well as minimal reduction in release kinetics compared to conventional formulations. Many of the large formulation types are, or have been, popular for aquatic applications, such as for insect and mollusc vectors of human disease causing organisms, with few applications in agriculture. Examples have been larvicidal sheets containing temephos, malathion, or chlorpyrifos using polyamide, PVC, polyethylene, and polyurethane. Current survivors of this approach are thermoplastic formulations of chlorpyrifos (Dursban 10CR), of dichlorvos (No Pest PVC strips), and of tributyltin fluoride (Ecopro 1330) for controlling freshwater snails (*Biomphalaria glabrata*) the vector of *Schistosoma mansoni*, the causal agent of bilharzia (38). Monolithic systems such as these require appropriate plasticizers to promote

migration of the pesticide to the surface, even so a substantial proportion will still remain entrapped when the rate of release declines below effective levels. This is less of a problem with elastomers where diffusion is faster (due to lower intermolecular forces) at similar temperatures.

4.10. Pesticide-Containing Films. In the agricultural field, the use of plastic mulch and plastic films for plant growing has become widespread, as it advances and enhances cropping when temperatures are low. It also encourages pests, particularly weeds and disease causing agents. The use of pesticides in these conditions can cause problems (eg, crop phytotoxicity), not least a result of the need for reapplication after the film has been laid. Incorporation of the pesticide into the film obviates both of these problems. Release of the pesticide can occur predominantly on the underside of the film and transported away (to the soil/crop) by condensation (39). Pesticides can be incorporated into agricultural films prior to their being formed by blown extrusion or into other forms such as sheets, tapes, cords and ropes, and chopped pieces such as confetti. Herbicides incorporated into ethylene–vinyl acetate copolymer EVA films are said to reduce by 2–4 times the amounts needed in covering early season vegetables such as cabbage, sweet corn, and celery. Using coating processes, films may be applied to seeds (40) that provides a very effective means of controlled delivery of pesticides to the seed region and to the emerging seedling.

4.11. Matrix Particles. Small particles based on a matrix can range in size from powders (microparticles) to granules (fine to macrogranules) to pellets (41). Microspheres can be considered as the matrix equivalent to microcapsules. Most controlled release granules are matrix based, although some have a solid core or reservoir of pesticide (with a coating).

4.12. Microparticles. Size matters; release rates depend on surface area, ie, a function of the square of the radius of a spherical particle and thus larger particles release for longer and are able to manipulate the external availability of the pesticide. Small microparticles are therefore limited in their scope for controlling release but can be used in traditional spraying of dispersions onto soils and crops as well as for seed dressing. Suspension concentrate formulations of matrix microparticles have been developed based on various rosins, phenolic resins, waxes, and bitumens. These have focused on lipophilic pesticides such as trifluralin and chlorpyrifos, and reductions in volatility have been demonstrated (41).

4.13. Granules. Whereas microparticles refer to sizes up to 100-μm, granules are typically 0.5–2.0 mm (fine granules 0.3–1.0 mm, microgranules 0.1–0.6 mm, macrogranules 2–6 mm). Granular controlled release formulations can be achieved by coating as well as from matrices. Although controlled release granules have not been as popular as microcapsules, there have been significant developments for applications to soil especially where extended control is required.

Cane grubs are a widespread pest problem in sugar cane growing and attack the roots of the plant over long periods. Conventional control has used persistent organochlorine insecticides applied at or soon after planting to optimize placement and residual protection. The introduction of long release granule formulations of short-lived insecticides such as chlorpyrifos (suSCon Blue) allowed the phase out of the organochlorines while giving good protection to the sugar

Table 3. **Acute Oral Toxicities of Controlled Release (suSCon) Granules Compared to Technical Grade Pesticides**[a]

Product	Acute oral rat LD_{50}
suSCon Blue (140 g/kg chlorpyrifos)	>1000 mg/kg
Technical chlorpyrifos	135–165 mg/kg
Marshal suSCon (100 g/kg carbosulfan)	>1000 mg/kg
Technical carbosulfan	185–250 mg/kg
suSCon Fu Ming (100 g/kg phorate)	319 mg/kg
Technical carbosulfan	1.6–3.7 mg/kg
G22001 (140 g/kg parathion)	578 mg/kg (male)
Technical parathion	3.6 (female) 13 (male) mg/kg

[a] After Ref. 43.

cane (42). The formulation is a 2-mm diameter extruded cylindrical granule of polyethylene containing 140 g of active ingredient per kilogram with an additive that sustains release by pore formation, through leaching by soil moisture. Single applications at planting can provide up to 3-years protection through the first harvesting and to several follow-on ratoon crops. This approach to pest control has since been extended to other problems, especially of concealed insects where systemic insecticides can be used effectively. Shoot borers in sugar cane and forestry, termites and weevils in forestry and ornamentals, borers and nematodes in a number of crops are examples of potential targets.

In addition to improved delivery and replacing persistent organochlorine pesticides with nonpersistent compounds controlled release granules also provide reduced toxicity of the product. For example, the acute oral toxicity of these granules are much reduced compared to unformulated or conventional sprayable formulations, as shown in Table 3.

Other granule formulations are based on biodegradable polymers that also offers the possibility of using wastes and byproducts from biological industries such as farming and forestry. New uses for cornstarch developed by the USDA included processes for the formulation of pesticides based on cross-linking of starch (43). The method involves the use of a corotating twin-screw extruder for mixing and gelatinizing starch with water (90–95°C), introducing the pesticide and providing the extrudate, which is then cut and dried to give the pelleted product. Hydrogen bonding occurs between the starch molecules (a process called retrogradation) to give a water-insoluble matrix entrapping the pesticide. Release occurs following soil placement by swelling. Evaluation of this granule formulation, especially of herbicides, has shown good efficacy at the same time reducing environmental losses and detrimental effects on surface and groundwater quality (44). In field experiments, significant reductions in herbicide volatility, surface runoff losses, and leaching have been observed compared to commercial formulations. These effects are particularly noticeable very shortly after application, when commercial formulations make the herbicide rapidly available at high concentrations.

Another natural polymer type abundantly available is the polyphenolic lignin. This aromatic macromolecule, which occurs in terrestrial plants, is obtained as a water-insoluble waste or byproduct from the pulping of wood. Its

natural protective attributes, which it contributes to the success of plants, can be exploited to protect, and deliver, pesticides (45). It can be melt processed with compatible pesticides (similar polarity) by blending or screw extrusion to provide granules or powders. Release of pesticides from the granules declines with time and depends on diffusion kinetics according to a swelling-diffusion model (46). Formulations based on a wide range of soil-applied pesticides have been evaluated and field trialed extensively. For example, carbofuran-containing lignin-based granules in tropical flooded rice gave good control of virus disease (through controlling the insect vector of the virus) but using one-third of the amount of pesticide compared to conventional formulations (47). This approach afforded safe handling to applicators and reduced risks (to bare feet) during the transplanting of the rice seedlings. A wide range of pesticides have been controlled release formulated by this method.

Other matrix methods for the preparation of granules can use gelating polymers such as alginic acid and other polyelectrolytes. This approach effectively entraps pesticides through cross-linking with polyvalent ions such as Ca^{2+}; combined with adsorbents, useful release profiles can be obtained (48). This method of preparation, using mild conditions in aqueous media at ambient temperatures, is used for formulating microbial pesticides to protect and extend the active lives and release of propagules of such living pesticidal agents (49). A wide range of bacteria, fungi, viruses, protozoa, and nematodes have been formulated by this method, and related methods, to provide effective sustained formulations.

5. Biological Methods

Finally, the use of living cells (eg, yeast) as encapsulating materials has been under investigation for many years. The problems associated with the encapsulation of pesticides within preformed cells have been overcome by using proteinaceous pesticides such as the toxin from *Bacillus thuringiensis* (Bt). The genes for the production of the toxin have been introduced into the soil bacterium *Pseudomonas fluorescens*, the toxin is expressed and is seen as a crystalline inclusion. Following production by fermentation, the cells are killed and fixed to provide the capsule formulation that is registered for use on brassicas (50).

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Chemosphere
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