## Journal of Macromolecular Science, Part A

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

# The Controlled Release of Bioactive Compounds from Polymeric Systems

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**To cite this Article** Allan, G. G. , Friedhoff, J. F. , McConnell, W. J. and Powell, J. C.(1976) 'The Controlled Release of Bioactive Compounds from Polymeric Systems', Journal of Macromolecular Science, Part A, 10: 1, 223 — 244

**To link to this Article: DOI:** 10.1080/00222337608068097

**URL:** http://dx.doi.org/10.1080/00222337608068097

J. MACROMOL. SCI.--CHEM., A10(1&2), pp. 223-244 (1976)

# THE CONTROLLED RELEASE OF BIOACTIVE COMPOUNDS FROM POLYMERIC SYSTEMS

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The ability to effect profound changes in the growth and behavior of living systems through the application of minute quantities of biologically active compounds has lead to development of the multibillion dollar pest control industry. Indeed, the introduction of modern chemical pesticides was originally thought to represent the "ultimate weapon" in man's age-old battle with pests [1]. Not until the late fifties and early sixties was it recognized that the continued use of this weapon, in its present form, might well result in a Pyrrhic victory for man. As a consequence of this realization, the concept of efficient pest control has undergone considerable modification in recent years. The undesirable secondary and tertiary effects of the highly successful long-lived pesticides has caused their use to be severely restricted [2]. An additional general concern is the often gross excess of applied pesticide in relation to that necessary to achieve control of the pest in the target area. For example, depending on the method of application and the climatic conditions, as much as 60 to 90% of the applied pesticide never reaches its objective [3]. In addition, the effective concentration of the pesticide is further reduced by leaching and soil erosion after application [4,5].

Unfortunately, when one examines the other side of the coin, represented by short-lived easily biodegraded pesticides, the results, in terms of the duration of pest control, tend to be economically discouraging, precisely because of the rapidity of degradation after application. Consideration of Fig. 1 provides a visual estimation of this deficiency. Here the calculated duration of a typical nonpersistent pesticide with a half-life of 15 days is represented by curve A. Assuming the loss of pesticide is the result of a unimolecular reaction, then the application of a level just above the minimum necessary for pest control (say 1 mg) would provide protection for only a day or so. To achieve practical periods of protection of 50, 100, or 150 days, the level of application would have to be increased 10-, 100-, or 1000- fold, respectively. In contrast, the theoretical level required to achieve these periods of protection is only that amount needed to continuously maintain the minimum effective level of 1 mg. Ideally then, the pesticide should be continuously provided from some efficient reservoir at a rate exactly equivalent to the rate of loss that occurs after the initial minimum treatment. If a pesticide were applied using just such an efficient reservoir, then the amounts needed to provide 50, 100, and 150 days of protection would be represented by curve B in Fig. 1. The area between curves A and B represents logarithmically the amount of pesticide wasted in conventional treatments and indicates how much room exists for improvements in application techniques.

A viable solution to the problems outlined above utilizes the potential of pesticide-polymer combinations as a means of securing the localized, continuous release of an easily biodegraded pesticide in the correct amount over an appropriate time period. In recent years a remarkable number of such pesticide-polymer formulations have been proposed [6-79]. In the more primitive forms, a pesticide Ⓟ is adsorbed on an inert substrate Ⓢ. Although this is often described as a physical operation, it is more helpful from a fundamental point of view, in our opinion, to regard it as a chemical process, albeit one of low energy. Thus we now have a quasi-

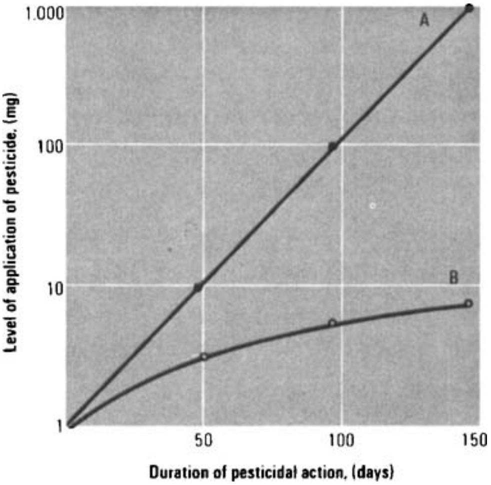

Fig. 1. Duration of pesticidal action for practical (A) and ideal (B) application techniques.

chemical structure Ⓢ—Ⓟ , which by definition is biologically inactive, and insulated from the deteriorating effects of the macroenvironment. If the combination is to provide control, then the following sequence of steps must take place:

$$\text{Ⓢ}\text{—}\text{Ⓟ} \xrightarrow{K_r} \text{Ⓢ} + \text{Ⓟ} \xrightarrow{K_\rho} \text{consumption}$$

However, the cleavage of Ⓢ—Ⓟ requires an energy input and is governed by a rate constant $K_r$, which is theoretically calculable from the theory of absolute reaction rates [80] where:

$$K_r = (RT/N_oh)e^{-F/RT}$$

and the symbols have their usual meanings. Thus there is an inverse dependence of $K_r$ on the free energy of formation of Ⓢ—Ⓟ. This in turn implies that, for a given quantity of combination Ⓟ, the higher the energy of the linkage, the longer will be the period of release. Since all forms of controlled release pesticides can be regarded as being a spectrum of bonded pesticides (some bonded with more energy and some bonded with less), the level and duration of release of a toxicant can be varied with the type of bonding employed in the formulation. Of course, boundary conditions on the energy of bonding do exist, and the bond type should be chosen so that $K_r$ has a reasonable value. Otherwise, for formulations with low $K_r$ values it is difficult to maintain Ⓟ at a suitable level without changing the capacity factor tremendously, i.e., without adding huge quantities of the combination initially. Conversely, a significant reduction in the amount of pesticide applied and a longer term controlled release cannot be anticipated from formulations with high $K_r$ values. Thus combinations relying on low energy bonds such as Van der Waals attractions, as is the case for pesticides adsorbed on materials like walnut shells, simple clays, or silica gels [6,8-10], show limited utility in extending the duration of control or in reducing the amount of pesticide applied. However, a range of bond energies which do provide reasonable values of $K_r$ can be achieved through the chemical bonding of pesticides to polymer backbones.

## CHEMICAL ATTACHMENT

Chemically bonded pesticide-polymer combinations can readily be synthesized by conventional, organic chemical procedures wherein the attachment can take any one of the forms illustrated in Fig. 2. The simplest of these has the pesticide attached as a pendent substituent on a natural or synthetic water-soluble or -insoluble polymer having a replaceable hydrogen as formulated in

$$\text{Polymer—X—H} + \text{RCOOH} \underset{\text{environment}}{\overset{\text{synthesis}}{\rightleftarrows}} \text{Polymer—X—COR} \qquad (1)$$

where X = N, O, or S. Obviously, the pesticide must contain a structural moiety suitable for use as a link to the macromolecule, and the carboxyl group is only one of the many alternatives possible. In the mid-sixties several patents were issued which embodied this concept. The earliest claim [31] utilized chlorinated phenol esters of tri- and tetracarboxylic benzene acids to achieve fungicidal properties in alkyd resin coatings. A recent patent [17,18] of a

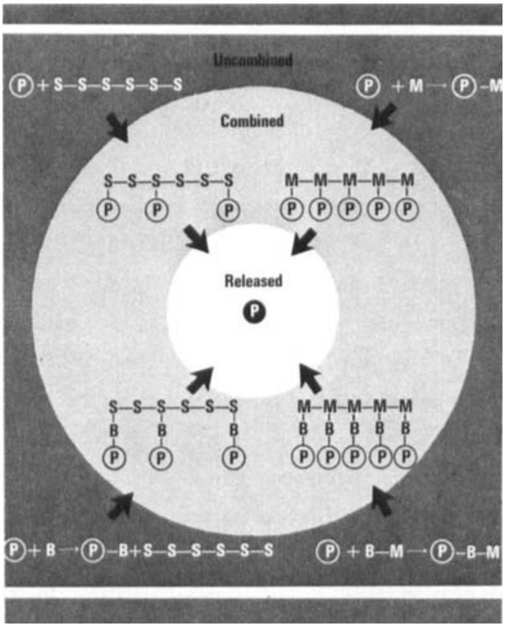

Fig. 2. Synthetic routes to controlled release of chemical combinations.

more general nature reports the utilization of forest wastes and other low cost materials for the production of sustained release herbicides. An example of this type of combination is the direct bonding of herbicide acids to the hydroxyl groups of natural waste products such as bark and lignin.

For pesticides which cannot be directly attached on a substrate to form a bond of suitable stability, a bridging entity may be interposed (Fig. 2). An example of this would be the linking of pesticide alcohols to a polysaccharide substrate by means of a phosphate or diurethane bridge [81]. Alternatively, the pesticide may be initially converted to a polymerizable derivative, e.g., vinyl 2,4-dichlorophenoxyacetate, which is then homo- or copolymerized to give a wholly synthetic pesticide-polymer [82] as illustrated in Fig. 2.

For all of these variants, side-chain degradation occurs in the biological environment. The chemical bonds holding the pesticide within its polymeric prison are sequentially broken to provide a sustained release of the biocide over an extended period of time. The rate of release will be determined not only by the nature of the pesticide-polymer bond, but also by the chemical characteristics of the pesticide and the polymer, the dimensions and structure of the resultant macromolecular combination, and the hydrophilicity of neighboring groups. For example, carboxylic acid groups introduced (via acrylic acid) in copolymers of 2,3,5-trichloro-4-pyridyl methacrylate and acrylic acid produce dramatic changes in the rate of release of 2,3,5-trichloro-4-pyridinol. Thus, because the carboxylic acid groups increase the hydrophilicity and catalyze the hydrolysis of the ester linkage between the herbicide and the polymer, the higher the percentage of acrylic acid the shorter the period of protection [83]. The dimensions of the pesticide-polymer combination as well as the solubility of the polymer backbone also play important roles in determining the release rate of a biocide [29].

Where the polymeric backbone is water soluble, the rate of hydrolytic degradation ($R_h$) for n sperical particles (radius r and density $\rho$) in a water-saturated heterogeneous surface reaction is given by

$$R_h = n\rho 4\pi r^2 \, dr/dt \qquad (2)$$

and by

$$R_h = nK_h 4\pi r^2 C_o \qquad (3)$$

where $C_o$ is the initial per unit area concentration of pesticide-polymer linkages on the surface of a particle of radius $r_o$, and $K_h$ is the hydrolysis rate constant. Since each pesticide molecule released by hydrolysis exposes another linkage beneath, $C_o$ is a constant and the duration of pesticide release ($D_{pr}$), by combination of Eqs. (2) and (3), can be predicted from the relationship

$$D_{pr} = \rho r_o/K_h C_o \; - \; (R_h \rho^2/nK_h{}^3 C_o{}^3) \qquad (4)$$

or by

$$D_{pr} = A - BW^{-1/2} \qquad (5)$$

where A and B are constants and W is the amount of pesticide-polymer combination used. The validity of the above equations as a predictive tool was demonstrated by measuring the persistence of herbicidal activity exhibited by a combination synthesized by the partial acylation of polyvinyl alcohol with 2-methyl-4-chlorophenoxyacetyl chloride [29]. The validity of this analysis is demonstrated by a plot of A as the reciprocal of the level of application of active ingredient versus the duration of herbicidal action. The curve obtained is clearly linear (Fig. 3).

Conversely, when the polymer backbone selected is water insoluble, the rate of degradation ($R_d$) can be expressed as

$$R_d = Wdc/dt \qquad (6)$$

or by

$$R_d = K_dWC \qquad (7)$$

where W is again the amount of pesticide-polymer combination used, C is the concentration of pesticide per unit weight contained therein at time t, and $K_d$ is the degradation rate constant.

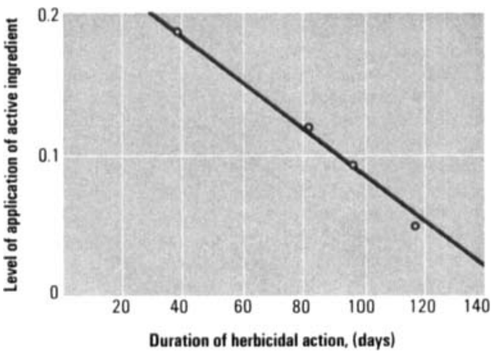

Fig. 3. Dependence of the duration of herbicidal action on the level of application for a chemical combination of 2-methyl-4-chlorophenoxyacetic acid with a water-soluble polymer. (Level of application = liter/mg applied.)

The duration of effectiveness ($D_{pr}$) for this type of controlled release herbicide-polymer combination, by combination of Eqs. (6) and (7), is therefore given as

$$D_{pr} = (1/K_d)\ (\ell n\ W - \ell n\ R_d/K_d) \tag{8}$$

or

$$D_{pr} = M \log_{10} W - N \tag{9}$$

where M and N are constants. Experimental confirmation of the usefulness of Eqs. (8) and (9) in the design of controlled release pesticide-polymer combinations is demonstrated in the release rates of herbicide acids, via ester cleavage, from cellulose and lignin (Fig. 4) [29]. Clearly the constants M and N change for each combination and are determined by the nature of the pesticide-polymer bond and by the chemical and physical characteristics of the resultant macromolecule. Therefore, by proper selection of bond energies coupled with variations in the chemical and physical microenvironment of the bonding site, a wide range of different release rates is obtainable. Practical application of these findings is now being utilized for the selective suppression of unwanted weeds and deciduous brush.

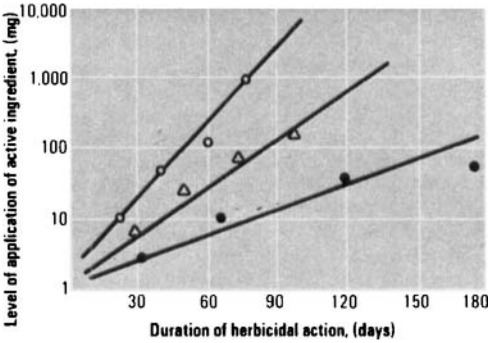

Fig. 4. Dependence of the duration of herbicidal action on the level of application for 2,4-dichlorophenoxyacetic acid (2,4-D) in chemical combination with water-insoluble polymers. (O) 2,4-D Alone; (Δ) 19.7% 2.4-D/Douglas fir bark; (●) 39% 2,4-D/kraft lignin.

As an example of this utilization, the reforestation of commercial forest lands with coniferous species is often severely retarded by the rapid invasion of unwanted vegetation in these plantations [84]. In spite of the recognition of this problem, its control by herbicide application is far from straightforward. The characteristics of the problem require the application of a herbicide with selective toxicity to the unwanted vegetation only, and with a period of duration on the order of several years. The most promising materials, in terms of their selective toxicity, are the chlorophenoxybutyric acids [85]. Unfortunately, these butyric acid herbicides are readily enzymically oxidized in the soil to the corresponding chlorophenoxyacetic acids, which have considerable toxicity to conifers [84]. In this case the controlled release concept is being utilized to perform a dual function: to greatly increase the duration of effectiveness achieved through a single application of the herbicide and to protect the butyric acid herbicide from soil oxidation to the corresponding acetic acid analog.

To achieve this goal, ester combinations of 2,4-dichlorophenoxybutyric acid with bark were synthesized, and their selective toxicity to western red alder (Alnus rubra Bong.) in the presence of Douglas fir (Pseudotsuga menziesii (Mirb. Franco) was evaluated. The results clearly indicated a favorable effect from this type of treatment, and the lower levels of application showed no damage to the conifer while effectively eliminating the red alder [84]. A field evaluation of the practicality of this approach was therfore initiated [86]. The field site near Sedro Woolley, Washington covers an area of 10,000 $yd^2$, experiences an annual rainfall of 30 to 40 in., and contains approximately 800 Douglas fir seedlings. The seedlings were treated with bar combinations containing 37% esterified herbicide at four levels of application. After one growing season the height increase for the treated seedlings was more than double that of the controls. At the same time the vegetation level, on a scale of 1 to 10, was an average of 2 for the area around treated seedlings in contrast to a reading of 8 for the area around untreated seedlings. To assess the possible effect of varying climatic conditions on these results, field trials of a similar nature have been initiated near Glenwood (annual rain fall 25 to 30 in.) and Gray's Harbor (annual rainfall 90 to 100 in.), Washington.

The compete suppression of vegetation is also being investigated in field trials utilizing controlled release formulations of the herbicides 2,4,5-trichlorophenoxyacetic acid and 2-chloropropionic acid as esters of bark and crab shells. These materials, when applied on railroads, firebreaks, and power-line right-of-ways, provided complete suppression of all vegetation for a period of 2 years at the highest level.

Although these two vegetation control examples demonstrate the potential of chemical attachment as a viable method of improving the efficiency of pest control, this approach is precluded for a large number of biologically active compounds due to their lack of functional moieties amenable to polymeric attachment. Fortunately, this restraint can be overcome by the incorporation of such compounds into polymeric matrices.

## CONTROLLED RELEASE FROM POLYMERIC MATRICES

Efforts to secure improvements in the volatility, solubility, toxicity, and period of duration for a wide variety of biologically active materials, through polymer incorporation, have been reported in the literature [11-28]. While at first glance they appear to be a hodgepodge of different concepts and inventions, they all can be separated into two major classes. The simplest classification involves the pesticide interacting with the polymer to afford a solid solution wherein the low energy of individual interactions is supplemented by the additional constraint of diffusion through appreciable masses of plastic. Notable examples in this class include Shell's No Pest Strip [88-90] and the increasingly popular flea collars for cats and dogs. Physical combinations in which the active ingredient is dispersed or encapsulated in a polymeric matrix in which they have low solubility comprise a second classification. This concept has been discussed in the pharmaceutical literature for the prolonged dissemination of birth control hormones [91], and it forms the basis of Pennwalt's new microencapsulated methyl parathion [92].

## SOLID SOLUTION FORMULATIONS

The equations which describe diffusion from solid polymeric solutions are well-known and characterized [93-95]. In particular, descriptions and mathematical analyses for diffusion-controlled release systems, especially in the pharmaceutical field, are numerous [95-101]. Although each analysis is predicated on a unique set of predetermined boundary conditions, in all case release is moderated by the rate of diffusion of the active component to the polymer surface as well as the rate of its subsequent detachment therefrom. Fundamentally, these two constraints on release are governed by the concentration and diffusivity of the active compound in the polymer, and by the geometry, surface area, and surface resistance of the pesticide-polymer combination.

The functional relationship between concentration and diffusivity, common in the description of diffusion within polymers, results from the additional mobility imparted to the polymer segments by the plasticizing diffusant [102]. Thus, as the plasticizer concentration decreases with time, the free volume within the polymer becomes exponentially harder to generate and the diffusivity decreases, often by several orders of magnitude. Quantitatively, this concentration dependence can be expressed in equation form as

$$D_c = e^{ac}$$

where $D_c$ is the diffusivity at concentration $c$, and $a$ is a positive real constant. In addition, even if the diffusivity is assumed to remain constant throughout the period of release, the flux or driving force of diffusion has been shown by Fick's law [103] to decrease with decreasing concentration of the diffusant. Thus the mathematical description of diffusion in solid solutions, as a result of the above considerations, is represented by the following nonlinear, parabolic partial differential equation [104]:

$$\frac{\partial c}{\partial t} = D\nabla^2 c + \frac{dD}{dc}\left(\frac{\partial c}{\partial x}\right)^2$$

where the change in concentration of the active component with time ($\partial c/\partial t$) varies with the change in concentration (c) and diffusivity (D) throughout the polymeric matrix. Numerical solutions of this equation predict release rates which decrease exponentially with time [104]. However, variations in the geometry of the pesticide-polymer combination show limited ability in overcoming this proclivity. For example, normalized computer models of the release rate from cylindrical and planar geometries show relative release rates, after 50% of the biocide has been dissipated, which are only 30 and 100% greater than the rate of release from a spherical conformation with an equal surface to volume ratio [104]. Moreover, a substantial improvement in the efficiency of solid solutions can be realized by coating the formulation with an enveloping film through which diffusion of the active component is slow [89]. In this instance the rate of release is no longer controlled by diffusion of the biocide to the matrix surface, but instead it is controlled by the subsequent step of detachment into the environment. Thus the rate-controlling resistance is concentrated at the surface of the polymer matrix, and the solid solution functions as a reservoir maintaining a constant flux on the outer envelope of diffusion-resistant polymer. As a result, the concentration and diffusivity of the active component remain constant in the surface coating, thereby linearizing the rate of loss of the pesticide from the polymer matrix. The magnitude of this effect is amply demonstrated in Fig. 5, where the proportion of biocide released from plane geometry solid solutions is plotted versus time for various dimensionless surface transport coefficients (k) [104]. Clearly, for high surface resistances (k = 1, 0.5, or 0.1) the release rate is effectively constant. Therefore, formulations in which the surface resistance is increased by surface coatings represent an efficient method of applying a constant dosage of active ingredient over an extended period of time.

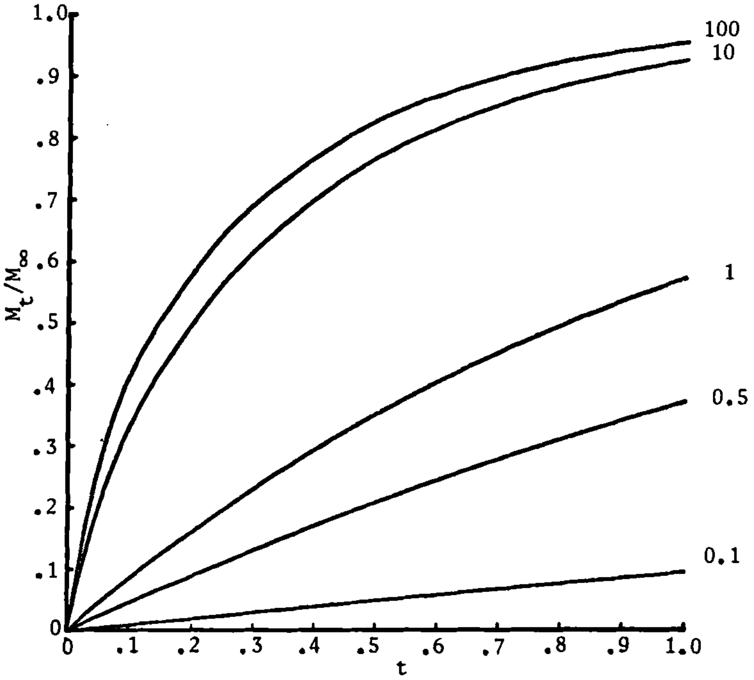

Fig. 5. The proportion of pesticide released as a function of time for the indicated values of k (the dimensionless surface transport coefficient).

The basic factors influencing the design of this type of controlled-release system are the chemical and thermodynamic compatibility of the resultant pesticide-polymer matrix. While chemical reactions between the pesticide and polymer are to be avoided, thermodynamic compatibility is a prerequisite to the formation of stable solid solutions of pesticides within polymer matrices. Through modification of the solubility parameter theory originally developed by Hildebrand and Scatchard [105-107], relatively simple guidelines are available for assessing the thermodynamic free energy of mixing. Thus pesticides which are probably compatible with a polymer may be easily selected by comparing their respective solubility parameters [104]. This ability is demonstrated in a recent patent which claims a new controlled-release method based on novel polymer mixtures in which the applicable polymers and pesticides are delineated by solubility parameter ranges [108]. It should be recognized, however, that every pesticide will not be amenable to solid solution formulation. In fact, the formation of stable solid solutions is largely limited in scope to relatively nonpolar compounds. The primary difficulty in extrapolating the solid solution concept to more polar compounds lies in their inherent incompatibility with the common commercial flexible polymers [104]. However, this disability forms the basis of an alternative general formulation concept which utilizes solid suspensions of the active component in a polymer matrix.

## SOLID SUSPENSION FORMULATIONS

A solid suspension or dispersion refers to a mixture of one or more active ingredients in a polymeric carrier or matrix. The attainment of a finely divided state of biocide particles within the polymer is critical to the success of this type of sustained release formulation since a pseudo-steady state between the rate of solute release from the matrix and the rate of particle fragment dissolution within the pellet must be established. In this manner the rate of release is still governed by diffusion of the biocide through the polymer. However, the suspended particles now maintain a constant concentration of the biocide within the matrix phase.

Predictive equations for the release rates from such solid suspension formulations have been developed by Higuchi and others [98-101] using the following set of restrictions: (1) the rate-limiting step is diffusion of the pesticide within the matrix; (2) a pseudosteady state exists between the release rate and the rate of particle dissolution; (3) the initial concentration of the active component in the matrix greatly exceeds its solubility in the polymer; (4) the initial matrix porosity is negligible; and (5) the receiving medium is a perfect sink. Under these assumptions [99] the total release of biocide (Q) after some time (t), for the case of a planar geometry, is given by

$$Q = [(D_m t(2A - C_s)C_s)]^{1/2}$$

where $D_m$ is the diffusivity of the active component in the polymer phase, A is the concentration per unit volume of the active component in the polymer matrix, and $C_s$ is the solubility of the active compound in the polymer phase. This class of formulations offers an improvement over simple solid solutions in terms of the constancy of release. However, it still suffers an everdecreasing rate of release. Consideration of the diffusion pathlength, as a function of time, offers a clear explanation of the phenomena. During the period of release, the suspended biocide is depleted from the surface inward. Thus the thickness of the depleted zone, through which diffusion must take place, steadily increases with time. Hence the change in the amount of active ingredient released per unit area corresponds to this change in the thickness of the depleted zone and so the decrease in the release rate varies with the square root of time. Nonetheless, the efficiency and lifetime of the active material are substantially improved, and numerous pharmaceutical investigators have considered variations of this release mechanism [109]. When the active component is only sparingly soluble in the environmental eluent, one such variation is particularly useful.

Thus, when the eluent solution bathing the formation is capable of penetrating the matrix through pores or capillaries, then the rate of release becomes dependent on the dissolution, leaching, and subsequent diffusion of the biocide out of the pellet along a tortuous path. Therefore, the equation describing the release rate of an active component from a porous, solid suspension takes the following form [99]:

$$Q = [(D_f e/T(2A - eC_s)D_s t)]^{1/2}$$

where Q is the mass per unit surface area of biocide leached from the matrix at time t, $D_f$ is the diffusivity of the biocide in the permeating fluid, e and T are the porosity and tortuosity factors for the matrix, respectively, A is the concentration per unit volume of the bioactive component in the matrix, and $C_s$ is the solubility of the diffusant in the permeating fluid. The validity of this equation for the release of biologically active compounds from a tablet matrix of polyethylene was demonstrated by Desai et al. [110]. As predicted, a linear relationship for the release of sodium salicylate was found experimentally when Q was plotted against the square root of time.

It is clear from the above discussions that no one type of formulation can be the ideal candidate for all applications. Rather, the delivery system employed will largely be determined by the physicochemical characteristics of the active component and the duration and rate of release desired. In addition, the character of the environment in which the formulation is placed cannot be overlooked.

The above derivations, while applicable for aqueous media, may require modifications to compensate for the soil environment. The pertinent differences between aqueous and soil conditions are numerous and include the presence of soil particles, variances in water content, cyclical temperature changes, biological activity, erosion forces, and possibly even chemical reactivites [104,111-114]. The integration of all of these factors to provide a suitable formulation-ecosystem balance is the necessary prerequisite to achieving efficient pest control. Clearly, such pesticide-polymer combinations are likely to be of special value for the economic control of pest infestations where systemic chemicals are effective but do not possess a sufficient period of activity. This sitution abounds in forest management, particularly in the tropics where increasing efforts are being made to specifically cultivate commercially valuable tree species.

A typical acre of tropical forest contains perhaps 150 trees species of which only one or two are commercially useful. However, planting efforts to extend the numbers of valuable trees such as Spanish cedar or mahogany in tropical forests have been frustrated in the Americas by devastating attacks of a lepidopteran shootborer, Hypsipyla grandella Zeller [104, 115-117]. The larvae of this moth tunnel into the stems of developing seedlings causing crippling distortion or death. Conventional protection by pesticides is economically impossible because applications of systemic insecticides last only 2 to 3 weeks under the climatic conditions of frequent, heavy rainfall and high biological activity [118]. However, these same readily biodegraded organophosphate and carbamate insecticides, when formulated as solid suspensions in a fatty polyamide, give much longer periods of protection - over 13 months in the best case [113]. These trees have thus been protected from the massive attack potential of eight pest generations. Modified designs which will extend and linearize this period of protection for a period of 3 years are now being evaluated in Costa Rica, Puerto Rico, and the Virgin Islands.

## CONCLUSIONS

Although not all-inclusive, the release mechanisms and examples reviewed in this paper reveal the very extensive breadth and depth of the controlled release technology which has been researched over the last 10 years and which is now more than adequate to deal with the vast majority of existing pesticides.

The current combined and mounting pressures of pesticide shortages and concern for the quality of the environment will inevitably increase the rate at which the obsolete and wasteful conventional application techniques are discarded.

However, it is the belief of the authors that the pace of introduction of controlled-release technology has been funereal from a societal point of view. To remedy this situation in the pesticide area, research should now emphasize development of the existing reservoir of technology so that practical and sensible new delivery systems can be expeditiously introduced.

## REFERENCES

[1] M. Grosser, Zoecon Corp. 1970 Annual Report, 19 (1970).

[2] Chemical Week, 110(25), 34 (1974).

[3] Canadian Wildlife Service, Ministry of Fisheries and Forestry, Ottawa, Canada, 4, 1971.

[4] Chemical and Engineering News, 42(46), 26 (1964).

[5] K. A. Hassall, World Corp Protection, Vol. 2, Chemical Rubber Co., Cleveland, 1969.

[6] H. A. Benesi, V. P. Sun, and E. S. Loeffler, U.S. Patent 2,868,688 (January 13, 1959).

[7] H. L. Morrill, U.S. Patent 2,739,052 (March 20, 1956).

[8] J. W. Nemec and E. A. Nolan, U.S. Patent 3,194,730 (July 13, 1965).

[9] W. Benzel, U.S. Patent 3,127,235 (March 31, 1964).

[10] W. P. Reeves, U.S. Patent 3,376,191 (April 2, 1968).

[11] C. G. L. Furmidge and J. M. Osgerby, J. Sci. Food Agric., 18, 269 (1967).

[12] F. Marson, J. Appl. Chem., 19, 93 (1969).

[13] R. J. Geary, U.S. Patents 3,074,845 (January 22, 1963), 3,162,573 (December 22, 1964).

[14] R. T. McFadden, R. R. Langher, and L. L. Wade, U.S. Patents 3,212,967 (October 19, 1965), 3,223,513 (December 19, 1965), 3,228,830 (January 11, 1966).

[15] N. F. Cardarelli, U.S. Patents 3,417,181 (December 17, 1968), 3,074,848 (January 22, 1963), 3,223,510 (December 14, 1968).

[16] G. E. Barnsley, J. K. Eaton, and J. Malone, British Patent 898,915 (June 14, 1962).

[17] G. G. Allan, Belgian Patent 706,509 (December 15, 1967).

[18] G. G. Allan, Canadian Patents 855,181 (November 3, 1970), 863,310 (February 9, 1971).

[19] H. D. Grown, A. B. Patel, S. V. Chattopudhyay, and S. N. Pennington, Enzymologia, 35, 215 (1968).

[20] G. H. McKibben, D. D. Hardee, T. B. Davich, R. C. Gueldner, and P. A. Hedin, J. Econ. Entomol., 64(1), 317 (1971).

[21] Chemical and Engineering News, 49(37), 20 (1971).

[22] S. C. Khanna, T. Jecklin, and P. Speiser, J. Pharm. Sci., 59, 614 (1970).

[23] S. C. Khanna and P. Speiser, Ibid., 58, 1114 (1969).

[24] S. J. Desai, P. Singh, A. P. Simonelli, and W. J. Higuchi, *Ibid*., *55*, 1230 (1966).

[25] A. F. Caprio and W. Horback, U.S. Patent 2,460,377 (February 1, 1949).

[26] F. B. Folckemer, R. E. Hanson, and A. Miller, Belgian Patent 648,606 (November 30, 1964), U.S. Patent 3,318,769 (May 9, 1964).

[27] J. W. Miles and J. E. Woehst, *Adv. Chem. Ser*., *86*, 183 (1969).

[28] T. J. Roseman, *Chem. Eng. News*, *49*(14), 13 (1971).

[29] G. G. Allan, C. S. Chopra, A. N. Neogi, and R. M. Wilkins, *Nature (London)*, *234*, 349 (1971).

[30] E. Baltazzi, U.S. Patent 3,343,941 (September 26, 1967).

[31] R. L. Broadhead, U.S. Patent 3,179,608 (April 20, 1965).

[32] E. Kolb, U.S. Patent 2,387,591 (October 23, 1945).

[33] J. E. Lloyd and J. G. Matthysse, *J. Econ. Entomol*., *59*(2), 363 (1966).

[34] C. W. Murray, U.S. Patent 2,286,636 (June 16, 1942).

[35] G. Faerber, British Patent 826,831 (January 20, 1960).

[36] D. Werner, U.S. Patent 3,607,863 (September 21, 1971).

[37] A. Williams, *Sustained Release Pharmaceuticals*, Noyes Development Corp., Park Ridge, New Jersey, 1969, p. 272.

[38] I. Fox, G. A. Rivera, and I. G. Bayona, *J. Econ. Entomol*., *62*, 1246 (1969).

[39] C. G. Wright, *Ibid*., *64*, 278 (1971).

[40] T. L. Harvey and J. R. Brethour, *Ibid*., *63*(5), 1688 (1970).

[41] C. H. Stockman, E. H. Bollinger, and R. N/ Naranch, *Mosq. News*, *30*, 584 (1970).

[42] R. N. Wilkinson, W. W. Barnes, A. R. Gillogly, and C. D. Minnemeyer, *J. Econ. Entomol*., *64*(1), 1 (1971).

[43] A. R. Clark and M. M. Clark, U.S. Patent 3,592,910 (July 13, 1971).

[44] U. R. Hattangadi, V. R. Shah, and D. S. Hattangadi, Indian Patent 116,080 (June 20, 1970).

[45] M. V. Fogle and G. E. McGowan, South African Patent 7,002,725 (December 2, 1970).

[46] S. S. Wasti and F. R. Shaw, *J. Econ. Entomol*., *64*(1), 224 (1971).

[47] M. Vlig and N. V. VanBreen, German Patent 1,802,684 (May 13, 1971).

[48] R. H. Czurak and R. M. Thompson, German Offen. 2,040,000 (April 22, 1971).

[49] J. C. McCool, German Patent 1,010,314 (June 13, 1957).

[50] M. Dima, A. Carpov, and S. Maxim, Rev. Roum. Chim., 13, 485 (1968).

[51] O. B. Wurzburg, W. Herbst, and H. M. Cole, U.S. Patent 3,091,567 (May 28, 1963).

[52] M. L. Beasley and R. L. Collins, Science, 169, 769 (1970).

[53] CIBA Ltd., German Patent 1,936,748 (January 29, 1970).

[54] J. S. Pierce, U.S. Patent 2,503,297 (April 11, 1950).

[55] R. W. Simmons, A. E. Markham, and E. G. King, U.S. Patent 3,287,209 (November 22, 1966).

[56] C. H. Boehringer Sohn., French Patent 1,447,479 (July 29, 1966).

[57] Upjohn Co., British Patent 929,407 (June 19, 1963).

[58] J. E. Vandegaer and F. G. Meier, U.S. Patent 3,515,882 (April 20, 1971).

[59] J. E. Vandegaer, U.S. Patent 3,577,515 (May 4, 1971).

[60] J. G. Wagner, French Patent 1,468,601 (February 10, 1967).

[61] W. B. Hemson, Abstracts of 162nd ACS Meeting (September 13, 1971).

[62] A. T. Jancosek and J . S. Brown, U.S. Patent 2,906,744 (September 29, 1959).

[63] C. W. MacMullen, U.S. Patent 3,299,566 (January 24, 1967).

[64] T. H. Shepherd, U.S. Patent 3,299,566 (January 24, 1967).

[65] PPG Industries, German Patent 1,945,873 (January 22, 1970).

[66] J. F. Vartiak, U.S. Patents 3,360,356 (December 26, 1967), 3,413,109 (April 19, 1967).

[67] Diamond Shamrock, Farm Chem., 52 (1967).

[68] CIBA Ltd., Netherland Patent 6,401,097 (August 12, 1964).

[69] L. L. Danielson, Weeds, 15, 60 (1967).

[70] G. G. Allan, C. S. Chopra, A. N. Neogi, and R. M. Wilkins, Tappi, 54, 1293 (1971).

[71] C. Haremcki, J. R. Nuss, and P. H. Williams, Proc. Northeast Weed Control Conf., 1969, 76.

[72] K. S. Knyazeua, A. M. Klechetova, L. N. Pdogina, and I. V. Khorkina, Inst. Byt. Obsluzh., 3, 115 (1963).

[73] S. V. Knylov and K. A. Timisyazeva, Nauch. Konf., 29, 69 (1957).

[74] K. Nakayama, L. Koiwa, and K. Noguchi, Nippon Sakumotsu Gakkai Kiji, 37, 645 (1968).

[75] H. L. Pierce, U.S. Patent 3,172,754 (March 9, 1965).

[76] M. Rubin, U.S. Patent 3,269,900 (August 30, 1966).

[77] J. D. Stone and L. M. Stahler, U.S. Patent 2,904,423 (September 15, 1959).

[78] M. L. Dunham and F. M. O'Connor, Union Carbide, U.S. Patent 3,359,092 (December 19, 1967).

[79] J. E. Yaffe and R. E. Sellers, U.S. Patent 3,274,052 (September 20, 1966).

[80] F. Daniels and R. A. Alberty, Physical Chemistry, 3rd ed., Wiley, New York, 1966.

[81] G. G. Allan and J. C. Powell, Sven. Papperstidn., In Preparation.

[82] R. M. Wilkins, "The Design of Polymers for the Sustained Release of Selected Herbicides," M.S. Thesis, University of Washington, Seattle, 1969.

[83] A. N. Neogi, "Polymer Selection for Controlled Release Pesticides," Ph.D. Thesis, University of Washington, Seattle, 1970.

[84] G. G. Allan, C. S. Chopra, and R. M. Russell, Int. Pest Control, 14(2), 15 (1972).

[85] J. H. Rediske and G. R. Staebler, For. Sci., 8, 353 (1962).

[86] G. G. Allan, C. S. Chopra, M. W. Maggi, A. N. Neogi, and R. M. Wilkins, Int. Pest Control. 15(3), 24 (1973).

[87] G. G. Allen, J. F. Friedhoff, and J. C. Powell, In press.

[88] J. W. Gillette, J. R. Harr, F. T. Lindstrom, D. A. Mount, A. D. St. Clair and L. J. Weber, Residue Rev., 44, 161 (1972).

[89] F. T. Lindstrom, A. D. St. Clair, and C. E. Wicks, Special Report 399, Oregon State University, Corvallis, Oregon, 1973.

[90] I. Fox, G. A. Rivera, and I. G. Bayona, J. Econ. Ent., 62, 1246 (1909).

[91] D. R. Mischell and M. E. Simkin, Fertil. Steril., 21, 99 (1970).

[92] Pencap M, Technical Bulletin, Pennwalt Corp., Morovia, California, 1973.

[93] J. Crank and G. S. Park, eds., Diffusion in Polymers, Academic, Oxford, 1956.

[94] J. Crank, The Mathematics of Diffusion, Clarendon Press, Oxford, 1956.

[95] G. L. Flynn, S. H. Yalkowsky, and T. J. Roseman, J. Pharm. Sci., 63, 479 (1974).

[96] Y. W. Chien, H. J. Lambert, and D. E. Grant, Ibid., 63, 365 (1974).

[97] J. W. Ayres and P. A. Laskar, Ibid., 63, 351 (1974).

[98] P. Dothisiri, and J. T. Carstensen, Ibid., 62, 1468 (1973).

[99] T. Higuchi, Ibid., 52, 1145 (1963).

[100] T. Higuchi, Ibid., 50, 874 (1961).

[101] T. Higuchi, Ibid., 56, 315 (1967).

[102] A. Aitken and R. M. Barrer, Trans. Faraday Soc., 51, 116 (1955).

[103] A. Fick, Poggendorffs Ann., 94, 59 (1855).

[104] S. C. Roberts, "Principles and Practice of Controlled Release Insecticide-Polymer Blends," Ph.D. Thesis, University of Washington, Seattle, 1974.

[105] J. H. Hildebrand and R. L. Scott, The Solubility of Nonelectrolytes, 3rd ed., Reinhold, New York, 1950.

[106] J. H. Hildebrand and R. L. Scott, Regular Solutions, Prentice-Hall, Englewood Cliffs, New Jersey, 1962.

[107] G. Scatchard, Chem. Rev., 8, 321 (1931).

[108] A. W. VanBreen, U.K. Patent 1,321,044 (June 20, 1973).

[109] "Symposium on Controlled Release of Biologically Active Agents," Southern Research Institute, April 19-20, 1973.

[110] S. J. Desai, P. Singh, A. P. Simonelli and W. J. Higuchi, J. Pharm. Sci., 55, 1230 (1966).

[111] C. G. L. Furmidge, Pestic. Sci., 3, 745 (1972).

[112] C. G. L. Furmidge, A. C. Hill and J. M. Osgerby, J. Sci. Food Agric, 17, 518 (1966).

[113] J. M. Osgerby, Pestic. Sci., 3, 753 (1972).

[114] J. R. Coppedge, R. A. Stokes, R. E. Kinzer, and R. L. Ridgway, Econ. Ent., 67(2), 292 (1974).

[115] R. M. Wilkins, "Suppression of the Shootborer, Hypipyla grandella (Zeller) with Controlled Release Pesticides," Ph.D. Thesis, University of Washington, Seattle, 1972.

[116] G. G. Allan, R. I. Gara and R. M. Wilkins, Turrialba, 20, 478 (1970).

[117] G. G. Allan, R. I. Gara and R. M. Wilkins, Int. Pest Control, 16(4) (1974).

[118] D. DeBach, Biological Control of Insect Pests and Weeds, Reinhold, New York, 1964.