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REVIEW

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韓國科學技術研究所 生物高分子研究室

Controlled Release —Technique, Theory, and Application—

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Abstract

The primary intention of this paper is to present a broad introduction of controlled-release technology. Discussions are centered on techniques of formulation and release mechanisms of active ingredients. Aspects of practical application of this technology, together with some actual examples, are also provided.

1. Introduction

During the last few decades, a significant success has been achieved in the synthesis of biologically-active chemicals such as pharmaceuticals, biocides and fertilizers. However, it does not seem that man has been utilizing these valuable and costly materials in efficient ways.

Urea, when dispersed on paddy fields, dissolves in water almost completely within a day. Only thirty per cent of the fertilizer is absorbed by the rice plant, and the rest, seventy per cent of it, flows wastefully into the river. Such examples are plenty. Most pharmaceuticals or biocides are employed in a little excess amount to maintain a longer biological effectiveness in the organ or environment. As a result, the use of the chemicals becomes costly, and sometimes undesirable side-effects or hazards occur.

Controlled release is a technology aimed at the improvement of such inefficiency and at the reduction of possible hazards in the delivery of active agents. By use of the controlled-relase technology, the release of the active agent at the target place (organ or organism) can be made timely and appropriate in concentration.

In older days, the term "slow release" or "sustained release" has been used instead of the present "controlled release" or "programmed release" to denote the slowly-releasing nature of active agents from a formulation. Recent techniques, however, extended such limitations. Controlled release possesses broader meaning. A specially-designed rivet[1] may be illustrated as an example. The rivet is coated with microcapsules

containing anti-corrosion primer. As the rivet is inserted into a hole for binding metal plates, the capsules rupture and the primer is released to seal the opening between the rivet and the hole. Products of the same concept are the bolts precoated with adhesive-containing capsules. Upon installation, the adhesive is released, ensuring a tight, rattle-free bond. In this manner, the formulation of controlled release is not simply restricted to the slow release of active agents, but it allows the release under specified situations whether the release rate is slow or not.

The primary purpose of this paper is to review the basic techniques and applications of controlled release. In addition, the fundamental theories on the release mechanism and rates of the active agents from various types of formulation are discussed. An effort is made to use only the references that are locally available.

2. Techniques of Formulation

In one way or the other, the intrinsic properties of polymer materials are widely utilized in the application of controlled-release technique. However, the utilization of materials other than polymer should never be underestimated.

Cowsar[2] lists typical methods of the controlled-release formulations (or delivery systems) as follows: (a) capsules of polymeric material filled with a solid or liquid agent or, with a suspension or solution of agent in a fluid, in which the release of agent is controlled by Fickian diffusion through the capsule wall; (b) a heterogenous dispersion of particles of agent in a solid polymeric matrix, which can be either biodegradable or non-biodegradable, and which controls the release of agent by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion; (c) a laminate of agent and polymeric material made by coating a film of biodegradable or non-biodegradable material with solid agent, and then forming the film into a sealed "sandwich" or "jelly roll", which controls the release of agent by diffusion, by erosion, or by both; (d) a heterogeneous dispersion or solution of agent in a water-swellable hydrogel matrix, which controls the release of agent by a slow surface-to-center swelling of the matrix by water and subsequent diffusion of the agent from the water-swollen part of the matrix; (e) liquid-liquid encapsulation of the agent in a viscous solution of polymer, which controls release of agent by slow diffusion through or dilution of the media; (f) chemical bonding of the agent to a polymeric backbone, as by pendant amide or ester linkages, which controls the release of agent by hydrolysis; and (g) formation of macromolecular structures of the agent via ionic or covalent linkages, which controls the release of agent by hydrolysis, thermodynamic dissociation or microbial degradation of this linkages.

In addition to the aforementioned methods, several elaborate devices have been proposed. Merrill[3] suggested an externally controllable implant. The use of "chemodes" or "dialytrodes" for the perfusion of a specific locus with drug was proposed by Siegel and Atkinson[4]. A combination of various methods may also produce an excellent delivery system.

For the coating or encapsulation of the active agent with wall materials (Method(a)), a number of techniques are available. Thermoplastic polymer membrane may simply be heat-sealed while it contains the active agent in it. If the active agent is in the form of solid particles, it can be spray-coated in a rotating drum as in the case of sulfur-coated urea[5]. Other technique, which commands a broad popularity today, is microencapsulation.

Microencapsulation is a technique of wrapping small entities in individual and protective coatings. The principal reasons of this miniature packaging can be listed under the following four categories:

(a) To protect reactive materials from their environments until time of use.

(b) To permit safe and convenient handling of toxic or noxious materials.

(c) To provide for controlled, sustained release of materials.

(d) To permit liquids to be handled as solids.

Luzzi[6], in his review article, briefly explains the following fundamental methods of microencapsulation, i. e., (a) coacervation, (b) phase separation, (c) interfacial polymerization, (d) electrostatic method and (e) mechanical method. Coacervation describes a

phenomenon of phase separation in a colloid solution. It is subdivided into two categories: simple coacervation and complex coacervation. Briefly, simple coacervation ususally deals with systems containing only one colloidal solute, while complex coacervation deals with systems containing more than one[7]. By and large, coacervation is closely related to the polyelectrolytic properties of polymers[8]. Discussions on the natural poly-electrolytes are given by Whistler[9]. Gutcho[10] presents a complete list of U.S. patents since 1960 relating to the capsule technology and microencapsulation. The proceedings of ACS symposium on microencapsulation held at chicago in 1973 have been published[11]. Methods of mechanical microencapsulation are described by Goodwin and Somerville[12]. More references on microencapsulation are available[13,14,15].

Information on the compatibility between active agent and polymer is vital to the study of the dispersion or dissolution of one in the other (Methods(b) &(e)). The theory by Hildebrand[16] allows one to examine the solubilities in liquids and polymers, liquid-liquid miscibility, and the like by using solubility parameters[17,18]. Solubility parameters of a number of polymers are tabulated in literatures[19,20]. The conventional polymer processing techniques[21] are employed in the manufacture of the polymer/active agent composite.

An active agent may be chemically combined with a polymer (Methods (f), (g)) by synthesizing hydrolizable graft polymers or degradable copolymers. According to Neogi and Allan[22], the characteristics of polymeric biocides are largely determined by: (a) the nature of biocide-polymer bonds; (b) the chemical characteristics of the monomers and comonomers; and (c) the dimension and structure of the polymer molecule as governed by degree of polymerization, degree of crosslinking, and the stereochemistry. This subject is discussed in literatures[23,24].

According to Cowsar[2], the factors that must be considered by designers of controlled release systems are the following: (a) the optimum level of agent necessary to obtain the desired biological response; (b) the mechanisms and rates of all agent removal systems operable in the biological environment; (c) the kinetics and mechanism of the delivery of agent from the release system chosen; (d) the influence of the biological environment on the mechanism and kinetics of release; (e) inherent restrictions on the physical and chemical properties of the delivery system materials dictated by the particular application. Factors (a) and (b) are pre-determined by the characteristics of selected target place and, therefore, they are not usually controllable by designers. Factor (e) is related to such limitations as reversibility, biodegradability, and acceptability of residues. Designers are mostly concerned with factors (c) and (d), which may be controlled by use of a suitable device associated with the delivery system.

In the following section, current theories on the kinetics and the mechanism of the delivery of agent from various release systems are introduced.

3. Release Mechanisms and Rates

Controlled-release formulations may be divided into two types: (a) a reservoir device which encloses an active agent, liquid or solid, with a semipermeable membrane; (b) a monolithic device in which an active agent is dispersed or dissolved. The monolithic device may be bio-degradable or hydro-degradable, or may stay undeformed.

Mass Balance

In principle, concentration of an active agent in the environment where a formulation is empolyed is determined by a simple mass balance between the realease rate of the agent from the delivery system (input rate) and the consumption rate of the agent in the environment(output rate). As mentioned in the previous section, the output rate is usually predetermined by the characteristics of a selected environment. A common type of the equations assumed for the output rate is:

$$R_o = -k_o C^n$$

k_0 is the proportionality constant, C is the concentration of an active agent in the environment, and n is an empirical factor that designates the order of

"consumption-reaction"-such term is used because the dissipation of the agent in the environment is hypothetically considered as a chemical reaction. It is the input rate of the active agent that is substantially controllable by designers through changes in types of formulation.

Pulse System and Zero-order System

For a pulse delivery system, where the input is given by an instantaneous pulse, e. g., spray-type insecticide, the release kinetics may be derived as follows:

$$C=C_o e^{-k_1 t} \tag{1}$$

where C_0 is the pulse input in concentration.

On the other hand, the release kinetics of the "zero-order" delivery system, where the input is constant through out the lifetime of the system, may be expressed:

$$C=\frac{I}{k_0}(1-e^{-k_1 t}) \tag{2}$$

where I is the constant input in concentration per unit time. In this expression, the order of the consumption-reaction, n, is assumed as unity. *Figs.* 1-a and b show the plots of Eqs. (1) and (2). It is evident from the comparison of these two results that the zero-order system is advantageous in maintaining a constant concentration in a given environment. The zero-order release is attainable by selecting an appropriate semipermeable membrane as a barrier material for diffusion control or by utilizing other techniques such as capillary action, osmotic pump, etc.

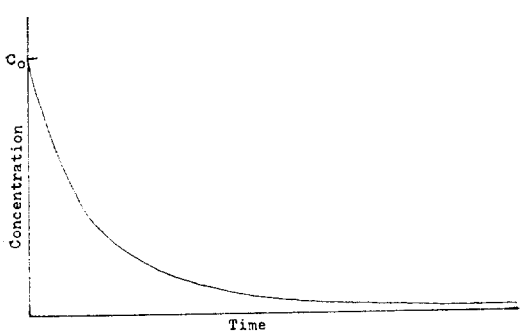

Fig. 1-a. Concentration change of a pulse system.

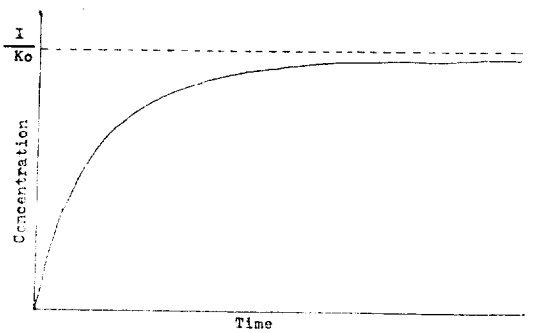

Fig. 1-b. Concentration change of a zero-order system.

Nonconstant Input Reservoir Device

For several reasons, however, it is sometimes impractical to maintain unit thermodynamic activity of the active agent(hence, constant input) in the reservoir. Even in those cases where unit activity is initially established, continual loss of the active agent or dilution by the imbibed solvent can eventually produce a situation where the agent activity falls with time. An example of the mathematical treatment of such nonconstant input system is presented by Baker and Lonsdale[25]. A reservoir of volume V_1 is separated by a membrane of thickness L and surface area A from the environment of volume V_2. The time-dependent amount of the active agent in the reservoir is M_{1t}, and that in the environment is M_{2t}. The total mass of the agent, M_∞, is given by

$$M_\infty=M_{1t}+M_{2t},$$

and, if all the agent is initially present in the reservoir,

$$M_{1t}=M_\infty \ at \ t=0. \tag{3}$$

The concentrations and masses are related as follows:

$$M_{1t}=C_{1t}V_1$$
$$M_{2t}=C_{2t}V_2.$$

Using appropriate terms such as diffusivity, D, and distribution coefficient, K, the rate of permeation can be expressed as

$$\frac{dM_{1t}}{dt}=-\frac{ADK}{L}(C_{1t}-C_{2t})$$
$$=-\frac{ADK}{L}\left(\frac{M_{1t}}{V_1}-\frac{M_{2t}}{V_2}\right). \tag{4}$$

Integration of Eq(4) after substituting for M_{2t} yields,

$$M_{1t}=\frac{M_\infty}{V_1+V_2}\left[V_2\exp\left\{\frac{-ADK(V_1+V_2)t}{V_1V_2L}\right\}+V_1\right] \quad (5)$$

Differentiation of Eq. (5) gives the release rate:

$$\frac{dM_{1t}}{dt}=-\frac{M_\infty ADK}{V_1L}\exp\left\{\frac{-ADK(V_1+V_2)t}{V_1V_2L}\right\}. \quad (6)$$

Equation(6) indicates that the release rate decreases exponentially with time. A useful information obtainable from Eq. (5) is the "half-time", $t_{1/2}$, or the time required to release a half of the active agent. This is the time at which $M_{1t}=M_\infty/2$; substitution of this into Eq. (5) leads to:

$$t_{1/2}=-\frac{V_1V_2L}{ADK(V_1+V_2)}\,ln\left(\frac{V_2-V_1}{2V_2}\right). \quad (7)$$

The half-time increases linearly with the membrane thickness, L, and decreases inversely with the surface area, A.

Monolithic Devices

When an active agent is intimately mixed with a polymer or with any solid matrix in a monolithic device, the device can be subdivided into two cases. The first case is that the active agent is simply dissolved in, or equilibrated with, polymer, and the other is when the agent is dispersed in excess in a polymer.

Dissolved Device

For the dissolved case, the desorption of an agent from the matrix of a slab geometry is expressed by

$$M_t/M_\infty=4(Dt/\pi L^2)^{1/2} \quad \text{for} \quad 0\leq\frac{M_t}{M_\infty}\leq 0.6 \quad (8)$$

as an early time approximation, which holds over the initial portion of the change, and by

$$M_t/M_\infty=1-\frac{8}{\pi^2}\exp\left(\frac{-\pi^2Dt}{L^2}\right) \quad \text{for} \quad 0.4\leq\frac{M_t}{M_\infty}\leq 1.0 \quad (9)$$

as a late time approximation which holds over the final portion of the desorption curve. The release rates are:

$$\frac{dM_t}{dt}=2M_\infty\left(\frac{D}{\pi L^2t}\right)^{1/2} \quad (10)$$

for the early time approximation, and

$$\frac{dM_t}{dt}=\frac{8DM_\infty}{L^2}\exp\left(-\frac{\pi^2Dt}{L^2}\right) \quad (11)$$

for the late time approximation.

It is noted that the release rate changes inversely with the square root of time in the initial stage, and then decreases exponentially with time as the desorption proceeds.

An equation for the half-time is

$$t_{1/2}=0.0492L^2/D, \quad (12)$$

and the release rate at that time is given by

$$\left(\frac{dM_t}{dt}\right)_{t_{1/2}}=16DM_\infty/\pi L^2. \quad (13)$$

Extension of the above treatments to the cases of other geometry such as cylinder or sphere is straightforward[26,27].

Dispersed Device

In the dispersed case, when the total concentration of the agent, C_o(dissolved plus dispersed), is larger than the solubility in the polymer, C_s, the release kinetics have been derived by Higuchi[28] using the model illustrated in *Fig.* 2. In this model, it is assumed that the agent dissolves from the surface layer of the device first and, when this layer becomes exhausted of the agent, the next layer begins to be depleted. The interface between the region containing only dissolved agent thus moves into the interior as a front. Starting from Fick's law for the slab, the release rate is:

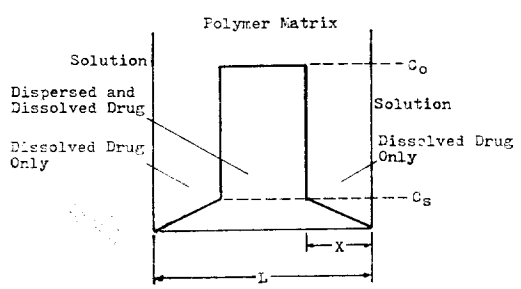

Fig. 2. A diffusion model for a dispersed device (Ref. 25).

$$\frac{dM_t}{dt}=\frac{ADC_s}{x}, \tag{14}$$

and at time t, from mass balance considerations,

$$\frac{2x}{L}=\frac{M_t+AxC_s/2}{M_\infty} \tag{15}$$

Combining Eqs. (14) and (15), and upon integration,

$$M_t^2=ADC_s\left(\frac{2}{L}-\frac{AC_s}{2M_\infty}\right)M_\infty t. \tag{16}$$

M_∞ is the amount of the agent, initially contained in one half of the slab, i.e.,

$$M_\infty=AC_0L/2.$$

Rearrangement of Eq. (16) gives

$$M_t=A[DtC_s(2C_0-C_s)]^{1/2}, \tag{17}$$

or

$$M_t\simeq A(2DtC_sC_0)^{1/2} \text{ for } C_0\gg C_s. \tag{18}$$

The release rate at time t is then given by:

$$\frac{dM_t}{dt}=\frac{A}{2}\left[\frac{DC_s}{t}(2C_0-C_s)\right]^{1/2} \tag{19}$$

$$\simeq\frac{A}{2}\left[\frac{2DC_sC_0}{t}\right]^{1/2} \text{ for } C_0\gg C_s. \tag{20}$$

A point worth noting here is that the fractional release as well as the release rate is proportional to the square root of the agent loading and can thus be easily varied by incorporating more or less agent. In addition, the release rate in the dispersed case is considerably less variable, the rate being inversely proportional to the square root of time throughout, than in the dissolved case where the rate decreases exponentially with time in the late stage of depletion. Above results have been validated by many experiments[29~35]. Similar treatments are possible for different geometries[36~39].

Degradable Device

Another case of devices that deserves a brief analysis here is when the monolithic matrix containing an active agent degrades in a solvent. An example is a pharmaceutical tablet which degrades in the gastric solution. A spherical model of initial radius r_0 is considered. The sphere is assumed to degrade in the solvent at a constant rate of k, i.e., $dr/dt=k$, thus releasing the active agent within the degraded part. The degradation proceeds until $t=r_0/k$. The release rate is

$$\frac{dM_t}{dt}=4\pi kC_0(r_0-kt)^2, \tag{21}$$

where C_0 denotes the concentration of the agent in the matrix. It is evident that the rate decreases rapidly with time.

Initial Effects

In addition to analyses on the steady-state release mechanisms, Baker and Lonsdale[25] also discussed on the initial effects of the release, i.e., release before the introduction of steady-state, especially for the zero-order reservoir device. Initial effects can be divided into two kinds, i.e., burst effect and time lag. Burst effect occurs when the surface of the membrane is saturated with an agent at the moment of an application of the device ($t=0$), and time lag occurs when the membrane is initially devoid of the agent as in the case of a fresh-made product. Following Crank[26], flux of the agent for each of the effects is obtained as

$$J/J_\infty=1+2\exp\left(-\frac{D\pi^2t}{L^2}\right) \tag{22}$$

for the burst-effect case, and as

$$J/J_\infty=1-2\exp\left(-\frac{D\pi^2t}{L^2}\right) \tag{23}$$

for the time-lag case. Here L denotes the thickness of membrane, and J_∞ is the steady-state flux. The total amount of agent, M_t, which has diffused through a membrane at steady-state time t is given by

$$M_t=\frac{DC_0}{L}\left(t+\frac{L^2}{3D}\right) \tag{24}$$

for the burst-effect case, and by

$$M_t=\frac{DC_0}{L}\left(t-\frac{L^2}{6D}\right) \tag{25}$$

for the time-lag case. The time-lag is $-L^2/3D$ for the former, and $L^2/6D$ for the latter. *Figure* 3 shows changes of the released amounts with time for the two cases. Such initial effects are not rare in the actual experiments, hence they should not be overlooked.

More discussions are accessible on mechanisms and

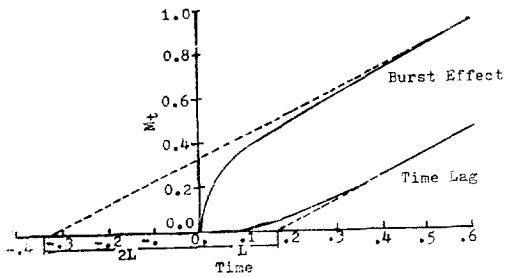

Fig. 3. Burst effect and time lag ($C_0l=1$, $D/L^2=1$) (Ref. 25)

rates of the release in literatures[40-42].

4. Applications

Applications of controlled-release technique that are currently commercialized or under development may be classified under the following four major fields; (a) pharmaceuticals, (b) biocides, (c) fertilizers and (d) others.

Pharmaceuticals

Biological activities of most pharmaceuticals are very sensitive to their concentration in the target place, and sometimes even a little excess of concentration may induce crucial hazards to the user. As a result, pharmaceuticals have been the most popular and urgent objects in the application of controlled release.

Miller and Anderson[43] used coacervation technique for the microencapsulation of aspirin. In their process, coating material, ethylcellulose, is dissolved in cyclohexane, and, while aspirin particles are dispersed in the mixture, temperature is lowered to induce coacervation. A little amount of butyl rubber is added as a phase separation inducing agent.

Later, Anderson, et al[44] improved this method. Polyethylene is substituted for butyl rubber, and aspirin is pre-treated with an acid buffering salt solution to retard its hydrolysis during the encapsulation process.

Fat-soluble vitamins are easily oxidized when exposed to oxygen. Ohtaki[45] encapsulated vitamin in order to protect it from oxidation before reaching the target place, and also to furnish an appropriate release rate. In his process, vitamin is mixed with wall materials such as dextrin, gelatin and CMC, and the mixture is atomized into an air current containing dehydrating solvents at an elevated temperature. An improved process[46] has been patented especially for the microencapsulation of vitamin A.

One of the most popular pharmaceuticals that are under research for controlled release is contraceptive. Sillicone rubber (polydimethylsiloxane) has been studied to offer a good delivery system for contraceptive steroids[36]. At Alza corporation, an intrauterine device that releases progesterone through silicone rubber at low constant rates is under development. The device contains the equivalent dosage of three oral pills, and the amount released daily is low enough not to interrupt the normal menstrual cycle. More references are obtainable on this subject[37,47,48].

Hormones, enzymes and other pharmaceuticals are also investigated for controlled release[49-52].

Biocides

Pesticides for the control, suppression, or destruction of plant or animal pests play a vital role in our daily life, both economic and esthetic. Although these biologically active compounds have been very effective in selectively suppressing undesirable weeds and insects, thereby increasing productive capacity of food grains and dairy products[53] and irradicating many diseases caused by insect vectors, there has been achieved very little control over the persistence of activity of these materials. Geary[54] patented a process in which the pesticide is adsorbed on a carrier and then coated with a urea-formaldehyde resin. Many insecticides have been mixed with polymers to obtain biocidal formulations which have an extended life yet provide an increase in the safety of otherwise toxic compounds[55]. No-Pest Strip[56] patented by Shell Chemical Company is an example of such.

Recently, Choi, Kwon and Moon[57] improved this method. Microencapsulation of pesticides by phase separation or interfacial polymerization is covered by many patents[58-62].

Neogi and Allan[22] illustrate one example of the field tests on the effectiveness of controlled-release

herbicides. Their result shows that, after one growing season, the height increase for the treated (with controlled-release pesticide) seedlings of Douglas fir is double that of the untreated ones, and at the same time, the competitive vegitation, western red alder, is reduced to one-third. Baltazzi[63], in his patent, claims that alkyd resins with chemically bonded herbicides have a longer effective life than the herbicide alone. Another patent[64] claims the utilization of forest wastes and other low-cost materials to produce sustained-release herbicides.

Long-term control of barnacles on ships has been achieved by coating the underwater surfaces with paints containing the trimer of phenarsazine chloride or the polyacrylate of tributyltin hydroxide[65,66]. Chlorinated phenols have been incorporated into alkyd resins as esters, and coatings of the resin are claimed to have fungicidal properties[67]. Pentachlorophenyl acrylate, a well known fungicide, has been homo and copolymerized with other monomers to result in polymers which are fungicidal[68].

Fertilizer

One approach to achieving controlled release of fertilizers has been to alter the chemical or physical characteristics of the fertilizer material to reduce the product solubility. A typical example of this approach is the utilization of urea-formaldehyde resin material[69-72]. Continued research on compounds with reduced solubility has led to the development of oxamide[73], the metal ammonium phosphates[74] and the like[75].

Recently, there has been a significant amount of research on the method of covering fertilizer granules with water-resisting or impermeable coatings. Materials investigated as coating agents include various plastics or resin substances[76], waxes and paraffin compounds[77] and sulfur[78]. The principal problem of this method is the provision of a coating which presents optimum resistance to moisture and other environmental conditions existing in soil.

Patents on controlled-release fertilizers up to 1968 are described by Powell[79]. More recent discussions on the subject are presented in literatures[80-85]. Substantially, various advantages of controlled release fertilizers are to a certain extent offset by their high cost. As a result, the general opinion at present is that slow-release fertilizers should be specialty products, limited to certain soil type and rainfall combinations and to specific cropping situations.

Others

With a broad sense of controlled release, carbonless carbon paper patented by Green and Schleicher[86-88] may be regarded as an example of the applications. In this innovation, a colorless dye-base in the encapsulated oil droplets is coated on the top of one sheet of paper, while the bottom of a second sheet is coated with acidic dye. Application of pen, pencil, or machine pressure ruptures the capsules and produces a visible color.

Another example is the controlled release of flavors or fragrances. Stabilized flavors, made by removing water and trapping the flavor within a coating matrix are increasingly used in dry food products[89]. Sustained release of fragrances are also commercialized in many cosmetic industries[90]. Adhesives or toxic odors may be microencapsulated in such a way that the capsules are ruptured (to release the core materials) under characteristic conditions such as abrupt changes in pressure and/or temperature. Many references as well as commercial products are available[91-100].

5. Future

As described in the previous sections, contolled release has a good potential in its application. However, an accomplishment of the application is currently restricted due to the following problems.

(a) High cost for the manufacturing of controlled-release products.

(b) Lack of information on the release mechanisms of active agents from delivery systems.

(c) Chronic side effects due to the persistence of active agents in the environment, i.e., residue effect, especially in the case of controlled-release biocides.

More investigations on these problems are highly urged in the future.

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