CONTROLLED-RELEASE TECHNOLOGY

Bioengineering Aspects

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K. G. Das

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Regional Research Laboratory
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Contributors

N. F. Cardarelli, Environmental Management Laboratory, University of Akron, Akron, Ohio

R. L. Collins, Physics Department, University of Texas at Austin, Austin, Texas

K. G. Das, Regional Research Laboratory, Hyderabad, India

A. F. Kydonieus, Hercon Division, Health-Chem Corporation, New York, New York

S. A. Patwardhan, National Chemical Laboratory, Pune, India

C. M. Radick, Environmental Management Laboratory, University of Akron, Akron, Ohio

R. M. Wilkins, Department of Agricultural Biology, The University of Newcastle upon Tyne, United Kingdom

L. T. Zeoli, Hercon Division, Health-Chem Corporation, New York, New York

G. Zweig, School of Public Health, University of California, Berkeley, California

Preface

Controlled-release technology probably means many things to specialists in many areas of science and technology. It is an emerging technology for the effective, economic, and safe use of any bioactive toxic chemical or plant nutrient. It provides a unique opportunity to achieve a quantum leap in the benefits of drug therapy by controlling the rate of drug delivery to the site of action. The objective is to achieve selectivity, specificity, and accuracy in delivering the optimum dose of the active ingredient to the desired site at the appropriate time, and to obtain maximum activity on the target while producing minimal effect on the nontarget materials. It is a bridge between polymer and pesticide or drug technologies and may be seen as an attempt to simulate nature's processes.

This technology has its roots in the drug industry. It has spread to other areas such as agrochemicals, plant nutrients, veterinary drugs, and flavors. The high degree of current interest is evident from the amount of work in progress. A few books and many papers are available, and international symposia are held annually.

Some controlled-release formulations have become commercial products. Many are undergoing trials and are in the experimental stage. Developmental work is still in its infancy. Environmental aspects determine the scope and utility of design parameters. Evaluation at the required site of action poses practical problems. The question of chronic vs. acute intoxication offers a challenging problem which evades a satisfactory solution.

Many controlled-release technologies, release mechanisms, design parameters, and chronic vs. acute intoxication are dealt with in this book. Methods for determining release rates and the environmental aspects that govern the commercial success of controlled-release systems are included to make the volume complete.

An overview of controlled-release technology and design parameters are

presented in the first and second chapters, respectively. Chapters 3 through 5 deal with chemical, physical, and microencapsulation approaches to controlled-release technology. Chapter 6 looks at release rates while the last two chapters deal with the environmental aspects of controlled-release technology and on chronic vs. acute intoxication, respectively.

The authors have attempted to make their contributions comprehensive, authoritative, and up-to-date, presenting the state of the art to the extent possible in this fast-growing field. I am very much thankful to all of them for their hearty cooperation and for their excellent contributions. I am indebted to the Director, National Chemical Laboratory, for his great support and to the publishers for their enthusiastic collaboration in publishing this volume.

K. G. DAS

Hyderabad, India
September, 1982

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CHAPTER ONE

An Overview of Controlled-Release Technology

S. A. PATWARDHAN
National Chemical Laboratory, Pune, India

K. G. DAS
Regional Research Laboratory, Hyderabad, India

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1. INTRODUCTION

The concept of controlled release is a novel approach to the safe and effective use of any toxic active ingredient, whether pesticide, drug, or fertilizer. Controlled-release technology promises to solve a myriad of problems that have in common the application of an active toxic compound to a system in such a way as to accomplish a specific purpose while avoiding certain other possible responses. Ideally, the active agent is released at a controlled rate that maintains its concentration in the system within optimum limits for a desired period. The principal advantage of controlled-release technology is that much less of the active ingredient is required for the same period of activity than is recommended in conventional methods of application. Thus, controlled-release technology holds great promise for improving the efficacy of existing drugs and pesticides and for reducing the problems associated with others.

Many insects and microorganisms are known to cause great damage to grains, vegetables, fruits, wood, paper, cotton, wool, rubber, plastics, and leather. In agriculture, crops have often been damaged or destroyed by insects, rodents, and disease. Rodents inflict tremendous damage on crops both in the field and during storage. Insects, mites, mollusks, nematodes, fungi, bacteria, and viruses are responsible for plant diseases. A large number of phytopathogenic microorganisms and insects infest crops, vegetables, and fruits.

Bats, birds, rats, mites, and parasites are a great danger to animal husbandry. Not only do they cause animal unrest and damage to animal hides, but they are also vectors of infectious disease. The danger to human health from various insect pests that are vectors of infectious disease is difficult to evaluate. Epidemic diseases transmitted by pests include encephalitis, typhus, relapsing fever, sleeping sickness, elephantiasis, and malaria.

Most early efforts to alleviate disease were ineffective because the means of transmission were unknown or little understood. As it became recognized that various pests were not only annoying and materially destructive but also life threatening, more effective methods of pest control were developed and practiced. Both mechanical and chemical methods of pest control have a long history. As early as 350 B.C., Aristotle described the use of arsenic compounds for rodent control. In the 1980s we are engaged in the development of biological methods of pest control.

Pest control has now become a part of daily life. Chemicals are used on the farm, in the garden, and in the house to control both plant and insect pests. Large-scale farming practices of the present century have led to the rapid development of agricultural insecticides. Synthetic pesticides such as chlorinated hydrocarbons, organophosphates, and many systemic insecticides were developed to satisfy special requirements. Some synthetic pyrethrins have been found to be efficient and nontoxic to humans.

Pesticides are toxic chemicals. Many pests have developed resistance to common pesticides that have been in long and continuous use. This increased tolerance has resulted in the substitution of more toxic chemicals for less toxic compounds and in the application of larger doses.

In spite of the remarkable advances in science and technology, we have not found a satisfactory solution to eliminate malnutrition, starvation, and disease and to preserve the environment from contamination. Researchers are busy developing high-yield varieties of crops by tissue culture, hybridization, radiation-induced mutation, and other techniques. Controlled-release technology has a significant role in the integrated approach to pest control. The conflict between the absolute need to use pest control agents in agriculture and public health applications and man's great desire to preserve the environment free from toxic materials is still evading a permanent solution. Controlled-release technology aims at increasing the efficiency of active ingredients and at decreasing their quantity and distribution in nontarget systems and in the environment. Until better control techniques become available, chemical control and the necessity for preserving environmental quality can be reconciled by the successful application of controlled-release technology. Localization, prolongation of the desired action with minimal side effects, and one-time application are some of the unique features of controlled-release systems.

2. PESTICIDES

2.1. Historical

In the seventeenth century nicotine was in use as an agricultural insecticide. Later, carbon disulfide was used as a soil sterilant and Paris green was used to control potato beetles. Chemicals were also applied to the bottom of ships to prevent damage and fouling. Pitch, wax and oil-based preparations containing sulfur and salts of arsenic, lead, mercury, and tin were popular before antifouling paints came into existence. Cuprous oxide in shellac or resin base is a known antifouling preparation. Paints containing oxides and salts of mercury, arsenic, and copper were in use in the 1800s. In 1892 the first synthetic organic pesticide, potassium dinitro-*o*-cresylate, was prepared. Fluorine compounds, pyrethrum, and rotenone made their appearance later on.

DDT was reported in 1939 and it quickly became a universal insecticide. Other chlorinated hydrocarbons, BHC, toxaphene, chloradane, aldrin, and dieldrin were subsequently introduced, followed by organophosphates and other synthetic insecticides.

2.2. Conventional Formulations

Chemicals used to destroy any species of pests are called pesticides. Pesticides include substances that stimulate or retard the growth of plants or repel, attract, and sterilize insects and are classified as acaricides, algicides, arboricides, bactericides, fungicides, herbicides, insecticides, molluscicides, nematocides, and zoocides. Insecticides are divided into subgroups: contact, stomach, and systemic. Fungicides are used to control diseases of growing plants and for seed disinfection before planting. Both selective and nonselective herbicides are known which act by contact or systemic modes.

The high economic efficiency achieved with the use of pesticides in agriculture and other areas has favored the rapid development of the pesticide industry. There has been an increase in pesticide production and a continuous change and improvement in chemical formulations. In addition to their high biocidal activity for various pests, pesticide formulations must be safe to handle during both production and use, nontoxic to humans, domestic animals, useful plants, and beneficial insects and microorganisms. Plants treated with any pesticide must after specified periods contain only such residual amounts that complete safety is assured in their use as food not only for animals but also for man.

In many countries standards have been set for the maximum content of pesticides in foodstuffs for both humans and domestic animals. The intervals between plant treatments are so recommended that at harvest the formulation applied should have completely or nearly completely decomposed so that the food materials do not contain amounts of pesticide residues harmful to human health. In determining the degree of toxicity of a formulation, it is necessary to give attention to its chronic toxicity, the possibility of accumulation in the body, the reversibility of the toxic effect, the route of entry, and a number of other factors, as well as the toxicity of the products of its metabolism.

The success of pesticides depends to a large extent on the formulation and the conditions under which the toxicant is brought into contact with the target. Since both the nature of the target organisms and the chemical structures of toxicants vary widely, it is necessary to produce a large number of formulations suitable for practical applications. The most important types of formulations include granules, wettable powders, solutions in water and organic solvents, emulsive concentrates, and aerosols and fumigants. The selection of the most appropriate, efficient, economical, and safe formulation depends on the physicochemical properties of the active agent, its purpose, and the mode of application. Persistent pesticides leave toxic residues and are incorporated into the food chain. The less persistent pesticides tend to be less effective and call for repeat applications and higher doses. Excessive amounts are usually applied to make up for the losses due to biodegradation, evaporation, and leaching. In actual field

applications the quantities are often further increased, since in conventional methods as much as 60–90% never reaches the target organism.

It is desirable to place pest control on a sound quantitative and predictive basis. Conventional pesticide applications are wasteful, since most of the pesticide applied is not used for actual control of the pest but functions as an imperfect reservoir to maintain the critical control level. To achieve satisfactory control for 50 days with a typical nonpersistent pesticide with a half-life of 15 days, the level of conventional application would have to be tenfold the minimum requirement. If the period of control is to be doubled or tripled, the level of application has to be increased 100- or 1000-fold, respectively. Theoretically the addition quantity required to prolong the period of control is only the quantity necessary to replace the fraction lost so that the active ingredient level is maintained for effective pest control.

2.3. Disadvantages of Conventional Formulations

Inorganic compounds used as insecticides and fungicides containing antimony, boron, copper, fluorine, manganese, mercury, selenium, sulfur, thallium, and zinc as active ingredients are known to persist in the soil, and their residues are harmful to crops. Chlorinated hydrocarbons are even more persistent. More than a thousand pesticides are now in common use, a few persist for more than a few weeks or at most months. In the early days there was little anxiety as to possible long-term ecological hazard caused by their use even though there was some evidence that large residues in the soil could be phytotoxic. Small quantities of pesticide residues were reported in plants and animal tissues. There were instances of fish being killed when water was sprayed with antimalarials. Pesticide residues have been detected in the air we breathe, in the streams and lakes that supply drinking water, in the cloth we wear, and in our bodies. Many birds and forest animals have become victims of these poisonous pesticide residues.

Among the environmental contaminants, chemical pesticides occupy a unique position. Their distribution in the environment depends on the way they are applied and on their volatility and solubility. Their persistence in terms of hydrolysis, oxidation, and removal by adsorption is governed by their physical and chemical properties. Biological properties control their utility and toxicity to nontarget living things. The mode of application determines which part of the environment becomes contaminated. Aerial application can contaminate simultaneously, air, soil, and surface water. The fate and persistence of pesticides pose another complex problem. Their translocation, metabolism, and degradation are also complicated.

Toxicological research a decade ago lacked the present conceptual approaches to understand the mechanisms involved in cellular biochemistry relating to

cellular alteration and ultimately to disease states. Over the past decade a gradual evolution in the fields of cellular biology, cytogenetics, and biochemistry have focused attention on the significance of subthreshold toxic stresses to induce responses and pathological changes at the cellular level. Studies are in progress on the biological impact of pesticides on humans and their environment. Protracted cellular insults may occur from chronic exposure to pesticides. Safety measures based on short-term observation of single or multiple exposures to a pesticide are not adequate.

Spurred on by the threat of an impending environmental upset and the critical need to feed the rapidly increasing world population, newer and safer methods of pest control are being quickly developed. Biological control holds great promise. In this approach a species harmless to man, crops, and animals but pathogenic to or a predator of a pest species is reared and released to the pest-infected area. Insects sterilized with irradiation or chemicals or with altered genetic characteristics are released to mate with other members of their species and ultimately eliminate the pest population. In another technique to induce sterility in the wild population, sterilizing agents are introduced into the environment. The use of pheromones as attractants for insects is undergoing fast development. Genetic control is another approach to insect control. These control methods must be explored with great caution.

2.4. Controlled Release

In the recent past many persistent pesticides have been phased out because of the environmental and toxicological hazards they posed. Less persistent, but sometimes more acutely toxic, pesticides have replaced them. The newer pesticides often generate other problems such as greater chances for accidental exposure of humans to highly toxic concentrations, and the need for multiple applications because of lower persistence. Controlled-release technology offers an ideal solution to these problems. The insect growth regulator methoprene is so unstable in the aquatic environment that its practical application is possible only with controlled-release methods. Some of the newer pesticides may never reach the market unless they are stabilized long enough to effect control through controlled-release technology. Economic and environmental advantages are also gained by the constant release of lower concentrations of toxicants than are possible with conventional formulations.

In normal practice, relatively high doses of pesticides, drugs, fertilizers and other biocides are administered at periodic intervals. Immediately following an application the concentration of the active ingredient rises to a high level in the system treated. This initially high concentration may produce undesirable local effects in the target area or contaminate the environment. As time passes, the concentration begins to fall because of natural processes such as elimination,

consumption, or degradation, and before the next application, it may fall below the optimum level for the desired response. Thus the conventional modes of application are usually rather inefficient, since a considerable quantity of the active agent never performs the desired function. These factors inflate the cost of treatment.

In a controlled-release formulation the active ingredient is released at a continuous and constant rate for a predetermined period so that only the target is attacked. The active agent is localized, and the amount released is just enough to achieve the desired effect. In fact, to maintain the pesticide levels by a controlled-release mechanism, the amount of active material needed for 50, 100, and 150 days of control will be about 3, 6, and 8 mg, respectively, instead of the levels of 10, 100, and 1000 mg that are conventionally recommended and used. Minimal damage is caused to nontarget life forms, and environmental contamination is negligible.

One of the problems in controlled-release technology is to combine the active agent with a degradable carrier in an economic manner and achieve a release profile that best suits the requirement. Many techniques are available for the design and preparation of controlled delivery systems. They include dissolving or physically trapping the active agent in an appropriate natural or synthetic polymeric matrix or chemically binding it to a suitable polymer. Pesticides have also been microencapsulated in natural and synthetic polymers. Natural film-forming materials or microcapsules prepared from gelatin, cellulose derivatives, and synthetic polymeric films have been widely used for microencapsulation. Phase-separation reactions and interfacial polycondensation reactions have been successfully applied for microencapsulation of pesticides. Encapsulation of pesticides within starch xanthate matrix has been reported.

3. DRUGS

3.1. Dosage Forms

Great progress has been made in the management of disease through the introduction of many life-saving drugs. These accomplishments in drug development are not balanced by similar growth of drug delivery systems. A drug will not be beneficial to the patient to the maximum extent unless it is delivered to the target area in the right concentration at the right time. The concentration delivered should be such that side effects are minimized and the therapeutic effects are maximized. If the desired target tissue and the site of administration are well separated, the drug may have to pass through many body barriers.

Over the years a variety of modified drugs and dosage forms have been available to control drug action. Dosage forms include prodrug, controlled

release, sustained release, prolonged release, and timed release preparations. In all of these, some degree of control has been obtained over drug placement. A maximization of therapy has not been achieved.

Controlled drug release is the phasing of drug administration so that an optimal amount of drug is made available to cure or control the condition in a minimum time with minimal side effects. Sustained-release and prolonged-release dosage forms prolong drug levels in the body.

3.2. Limitations of Conventional Dosage Forms

The conventional dosage forms, which include tablets, capsules, injectables, and eye drops, share the inability to maintain the drug level in body tissues. The main function of a conventional dosage form is to convey a unit dosage from a container to the body tissues. When a tablet or capsule breaks down to empty its drug content into the stomach, the drug starts dissolving in body fluids and is absorbed into the bloodstream. This leads to the distribution of the drug in the body and to the target tissues. The concentration in the body rises rapidly to a peak, followed by a fall which is determined by its characteristic metabolism and elimination pattern. This cycle is repeated with each dose. With each administration of the drug, its concentration passes through the therapeutic level. Drug concentrations may thus fluctuate between levels that can cause side effects and others that are so low as to be nontherapeutic. This inadequate and inefficient functioning of conventional dosage forms is partly responsible for the toxic side effects of well-established old drugs as well as of the newer ones. Many potent life-saving drugs destined to act only on specific target organs have to cross many body barriers through the bloodstream in high concentrations in order to maintain a therapeutic drug level.

Considerable research has been directed toward a better understanding of the mechanism of drug absorption from the different routes of administration. Studies are also undertaken on the effects of drugs at absorption sites and on the possible injury to subcutaneous and intramuscular sites. Parenteral injection has been recognized as an essential part of therapy. Injectable formulations lead to a local lesion at the site of injection, and satisfactory tolerance requires specific adjustments of solubility, concentration, and volume. An injectable substance with moderate musculoirritative properties can cause a focus of neurosis which is healed by regeneration of striated fibers. Repeated injection of irritating substances results in progressive atrophy of muscle fibers and replacement fibrosis. A number of injections of substances with the lowest irritative index can elicit adaptive lymphatic response. A more serious hazard is nerve injury. Underestimation of the damage caused by repeated injection into the quadriceps femoris muscle has resulted in sequelae of contracture in the upper legs of infants.

3.3 Controlled Release

Over the years, long-acting dosage forms have been developed. Such products are mainly of three types—sustained release, prolonged action, and repeat action dosage forms. These formulations deliver initially the amount required to trigger the desired pharmacological effect. A maintenance dose is supplied at the same rate as the rate of drug removal from the body over the time interval for which the pharmacological response is required, but a constant drug level is not maintained.

In practice it is difficult to design an ideal sustained-release drug dosage formulation, and most dosage formulations are the prolonged-action type. For the development of such formulations there are several stages of activity from inception to completion. The interacting factors relating to the drug, the disease, and the mechanism of prolongation are important to the formulator. The choice of drug is governed by drug properties, the route of drug delivery, whether the therapy is acute or chronic, the nature of the disease, the patient, and the appropriate delivery system. The behavior of the drug in the delivery system and in the body are two important factors that contribute to the success of the system.

An appropriate drug must have the desired therapeutic efficiency, pharmacokinetic behavior, and physicochemical properties that permit effective transfer from the delivery port to the target tissue site. In controlled-release systems, the shorter the half-life of the drug, the more closely will the temporal pattern of its concentration in blood or other body fluids follow the temporal pattern of drug administration. In conventional dosage forms, the rule is the longer the half-life the better. An appropriate drug-delivery module is bioengineered to contain and protect the drug in a reservoir from which it is released at a rate precisely determined by a rate controller. The module also contains an energy source to effect the transfer of drug molecules from the reservoir to the body site. The platform contains the drug-delivery module and ensures correct positioning and safe coupling of the system to the tissue site. The system delivers a drug program whose rate and duration of drug delivery will perform the desired therapeutic function.

Physicochemical properties and biological factors influence the design and performance of sustained-release dosage forms. Among the physicochemical properties, dose size, aqueous solubility, partition coefficient, drug stability, protein binding, and molecular size are important. In most cases, these properties are restrictive rather than prohibitive, making the design of sustained-release systems difficult. The pharmacokinetic properties and biological response parameters have working range for the design of these dosage forms. Absorption, distribution, metabolism, biological half-life, incidence of side effects and margin of safety of the drug have to be examined and evaluated. Some of the limiting

factors in developing an effective sustained-release dosage form are extremes of aqueous solubility, oil/water partition coefficient, erratic absorption properties, multicompartment distribution and binding, extensive metabolism/degradation during transit from delivery site to target tissues, and narrow therapeutic index. Disease state and circadian rhythm have to be considered also, even though they are not drug properties. These limitations can be overcome by the application of physical, chemical, and biomedical engineering approaches singly or in combination.

The term controlled drug delivery is used in a rather loose sense. Delivery of a constant tissue drug level has not yet been achieved. All the successful dosage forms on the market today only prolong drug levels; they do not control the delivery. They do not maximize drug utilization and do not take into account changes in the drug requirement during the course of treatment, that result from circadian rhythm, changes in the pathological state, patient variation, and so on. However, these drug delivery systems are a significant step forward compared to their conventional counterparts with respect to temporal drug level control and patient compliance.

One of the difficulties in developing controlled delivery systems is the technological limitation. Dissolution control systems have limited flexibility. Greater flexibility is possible with drugs in polymers. Orally administered sustained-release formulations have a limited duration of action and offer a formidable challenge, owing to the transit time in the hostile environment of the gastrointestinal tract; this time varies from patient to patient. The difficulties encountered with sustained-release dosage forms that prolong drug levels in the blood are surmountable, since the intramuscular route offers a more controlled environment for their application. The physical modification approach has been tried for prolonging action by administering through the parenteral route.

Implants are the most successful sustained drug delivery systems on the market. They are delivery devices containing the drug in a polymeric capsule or matrix. Silicone and high density polyethylene have been widely used in the manufacture of intrauterine progesterone contraceptive systems because of their physiological inertness and biomedical compatibility (Figs. 1 and 2). Hydron, an implantable hydrogel, and contact lenses are prepared from copolymers of polyhydroxyethyl methacrylate and ethylene glycol dimethacrylate. The Ocusert system was the first in a family of therapeutic systems capable of controlled programmed drug delivery over extended periods. It is used in place of eyedrops or ointments to lower elevated ocular pressure in glaucoma cases and is placed directly under the eyelid for 7 days. A low, constant therapeutic level of pilocarpine is maintained in the eye and reduced side effects (Figs. 3 and 4).

Alza has developed two therapeutic systems for oral and injectable use without the disadvantages of the corresponding conventional formulations. The OROS system is a new form of oral medication that contains a core of solid drug coated with an appropriate polymer membrane (Fig. 5) that is water-permeable