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Volume 47

CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE AGENTS

Edited by A. C. Tanquary and R. E. Lacey

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PREFACE

The Symposium on Controlled Release of Biologically Active Agents was held under sponsorship of Southern Research Institute in Birmingham, Alabama, April 19 and 20, 1973. The announced purpose of the symposium was to encourage an exchange of information among the experts working in various fields of controlled release and the scientists and technologists interested in applying the concepts. The number of registrants (over 120), the diverse nature of the organizations represented, and the enthusiastic participation of attendees in the discussions testified to intense and broad interests in controlled release. The papers presented at the symposium should serve well to introduce the principles of controlled release and demonstrate a few of the promising applications.

Controlled release is an important step toward improving the delivery of a biologically active agent to its target. Precise administration of an agent can substantially reduce the concentration required for beneficial effects and thus minimize deleterious effects to the organism or to the environment. Through controlled release, older agents whose efficacies are established may prove more reliable, and newer agents whose high potencies or low stabilities have inhibited use may prove more suitable. Controlled release therefore offers both an alternative and a complementary route to the increasingly costly and demanding search for agents of greater specificity.

The papers in this book appear in the order of their presentation at the symposium. The papers may not be identical to the ones presented at the meeting, however, because some of the papers had been condensed by speakers to fit the time allotted, and some of the manuscripts were changed by authors to clarify statements or answer questions raised in the meeting. Moreover, we chose to alter some of the symbols and equations to improve

clarity, especially where these had been used to express diverse meanings.

We are indebted to all of the authors for their co-operation in adhering to rigid manuscript specifications, and also to Mrs. W. Schulman for her untiring efforts in assisting us in our editorial endeavors.

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LIST OF SYMBOLS*

A	surface area (cm^2)
B	number of chain ends per unit volume (cm^{-3})
C	concentration ($g\ cm^{-3}$)
C_s	solubility ($g\ cm^{-3}$)
D	diffusion coefficient (diffusivity)($cm^2\ sec^{-1}$)
F	fraction of agent released
J	flux ($g\ cm^{-2}\ sec^{-1}$)
K	partition (distribution) coefficient
M	total mass of agent in device (g)
M_t	mass of agent released at time t (g)
M_∞	mass of agent released at time t_∞ (g)
P	permeability (DK)($cm^2\ sec^{-1}$)
Q_t	mass of agent released per unit area at time $t(M_t/A)(g\ cm^{-2})$
R_t	total diffusional resistance (cm sec)
R_a	diffusional resistance of water (cm sec)
R_m	diffusional resistance of matrix (cm sec)
R_s	diffusional resistance of solvent (cm sec)
T	temperature (°C or °K as specified)
T_g	glass-transition temperature (°K)
T_m	melt temperature (°K)

*The CGS units express dimensions, not necessarily specific usage: for example, release rates may be given in $\mu g\ day^{-1}$, rather than $g\ sec^{-1}$.

V	volume (cm^3)
V_c	volume of matrix (continuum)(cm^3)
V_f	volume of filler (cm^3)
V_r	volume of receiving fluid (cm^3)
V_s	volume of source (cm^3)
W	mass per unit volume (M/V)(g cm^{-3})
h, ℓ	thickness of membrane (cm)
r	radius (cm)
r_i	inner radius (cm)
r_o	outer radius (cm)
t	time (sec)
$t_{1/2}$	half-time of exhaustion (sec)
t_∞	time of exhaustion (sec)
x	distance from membrane surface (cm)
γ	normalizing parameter (J/C_sD)(cm^{-1})
δ	jump distance (cm)
ε	porosity of matrix
λ	thickness of stagnant fluid boundary layer (cm)
ϕ	frequency of jump (sec^{-1})
τ	tortuosity of matrix

Combined Symbols

dM_t/dt	release rate (g sec^{-1})
dQ/dt	flux (J)(g cm^{-2} sec^{-1})

CONTENTS

INTRODUCTION TO CONTROLLED RELEASE

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Scientists today, more than ever before, are being challenged to provide new, safer, more economical, and more efficient means of providing for the health and well-being of mankind. In almost every instance, the key to meeting these challenges lies in the development of ever more ingenious methods for manipulating biological factors. Historically, scientists have dealt with these problems by designing new biologically active agents. However, whether these agents are pharmaceuticals or agricultural chemicals, use of these agents to produce the desired biological responses is yet fraught with gross inefficiencies that result primarily from inabilities to deliver the agents to their targets (organisms or organs) at the precise time and in the precise quantities required. The results of these inefficiencies are obvious: the use of the agents is costly, and undesirable side-effects (sometimes catastrophic in nature) occur.

To minimize side-effects, scientists have generally concentrated on designing agents having greater specificity and less persistence. However, through a perverse law of nature applying to the design of agents, the less persistent and more specific agents are almost always costly and difficult to administer. The increased difficulties in administering the agents are usually a consequence of labile linkages, since greater potency with minimal persistence or side-effects usually comes from rapid metabolism. And rapid metabolism, in

turn, means effectiveness only within narrow limits of time and concentration. The added costs are usually a result of both the expense of synthesis (since more specific agents tend to be more complex) and the expense of repeated applications.

Recognizing these limitations in the design of agents, scientists are increasingly turning to an alternative approach, that of improving the delivery of the agents, both newer agents and old. This approach is soundly based on the premise that the optimum biological response occurs when the level and time of the availability of the biologically active agent to the target (organism or organ) are optimized. Agent availability is the relationship between the rate of delivery of the agent and the rate of removal of the agent. Removal of the agents means metabolism, chemical decomposition, deactivation, excretion, or other methods by which agents become inactive.

I. CONVENTIONAL AGENT DELIVERY

The designers of biologically active agents expend vast efforts and funds synthesizing, screening, and testing agents. However, once a promising agent has been identified, considerably less effort is usually spent developing the delivery system (i.e., formulating the final dosage form). Standard criteria are usually followed to determine the site of application or route of administration, the unit dose or level of application, and the most convenient application or dosage schedule. In order to understand the importance of the role that delivery plays in our ability to obtain optimum biological response, we should first review the shortcomings of the delivery of agents by conventional techniques.

Agents are usually delivered systemically or topically often at a site somewhat remote from the target (organism or organ). Figure 1 shows schematically the delivery of an agent by conventional techniques. The agent is administered to the biological environment from an appropriate formulation. Route 1 in the figure illustrates the case of "indirect" agent application such as the oral administration of pharmaceuticals or the application of systemic insecticides to the soil to control insects in plants. In this case the agent first enters a reservoir (the digestive tract or ground water) having a volume, V_1. Here the agent becomes diluted.

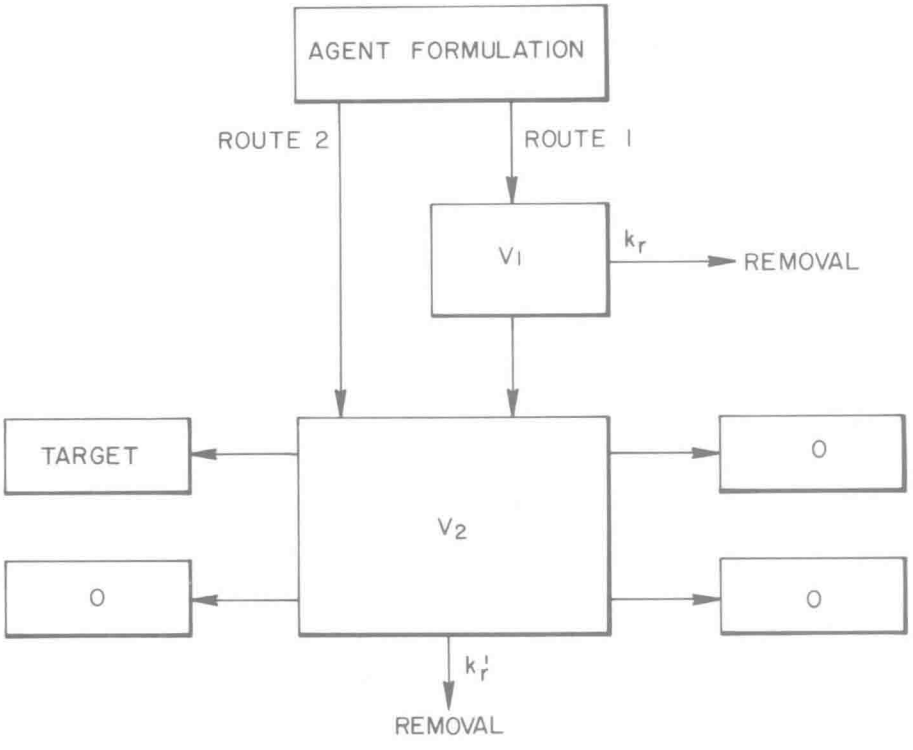

Figure 1. Conventional Agent Delivery

Over a period of time the agent either diffuses into the desired systemic environment (the circulatory system or the plant sap) having volume V_2, or is removed from the site via excretion, metabolism, or chemical deactivation. In the figure, k_r is the rate constant for the rate of removal of the agent from V_1. As the agent enters V_2 it becomes further diluted as it is distributed to the various organs or organisms, O, at least one of which is the target for the agent. The action of the agent on organs or organisms other than the target may result in undesirable side effects. Finally, the agent is metabolized or otherwise irreversibly removed from V_2 at a rate governed by the removal rate constant, k_r'. Route 2 in the figure illustrates a more direct application such as by the intravenous injection of pharmaceuticals or the spraying of crops with pesticides. The first reservoir, V_1, is by-passed in the scheme, but side effects resulting from agent in V_2 affecting non-target organisms or organs can still occur.

When agent is delivered by one of these conventional routes, the level and time of availability of agent to the target cannot be controlled independently. Only the level and frequency of application can be manipulated. The rate of removal of the agent from the biological environment is usually considered to be an "uncontrollable" parameter. At best, the removal of agent can be described by typical reaction kinetics with most biological removal systems being first order or pseudo-first order in agent concentration.

The first-order rate law states that the instantaneous rate of removal is proportional to the amount of agent present. If M/V_2 is the concentration of agent present, the rate of removal, $\frac{d(M/V_2)}{dt}$, of agent can be expressed as

$$\frac{d(M/V_2)}{dt} = k_r(M/V_2) \tag{1}$$

where k_r is the rate constant for removal. The integrated solution to Equation (1) is

$$\ln M/M_o = k_r t \tag{2}$$

where M_o is the amount present at t=0; M_o is thus the amount applied. The rate of removal of the agent from the biological environment is often expressed as the agent half-life, $t_{\frac{1}{2}}$. The half-life is related to the first-order rate constant for removal as follows:

$$\ln 2 = k_r t_{\frac{1}{2}} \tag{3}$$

$$\text{or,} \quad k_r = \ln 2/t_{\frac{1}{2}} = 0.693/t_{\frac{1}{2}} \tag{4}$$

The magnitude of the effect that agent removal has on agent availability can best be illustrated by examples.

Example I. Consider a pharmaceutical agent (drug) designed to combat an infectuous disease and known by pharmacodynamic and toxicological studies to be effective at an optimum systemic level of 5±2 μg/kg (i.e., at levels below 3 μg/kg the drug is only marginally effective, and at levels above 7 μg/kg it may cause undesirable side effects). Assume further that the drug cannot be administered orally, that the half-life for removal in vivo has been determined to be 8 hr, and that patient should be treated for 10 to 14 days.

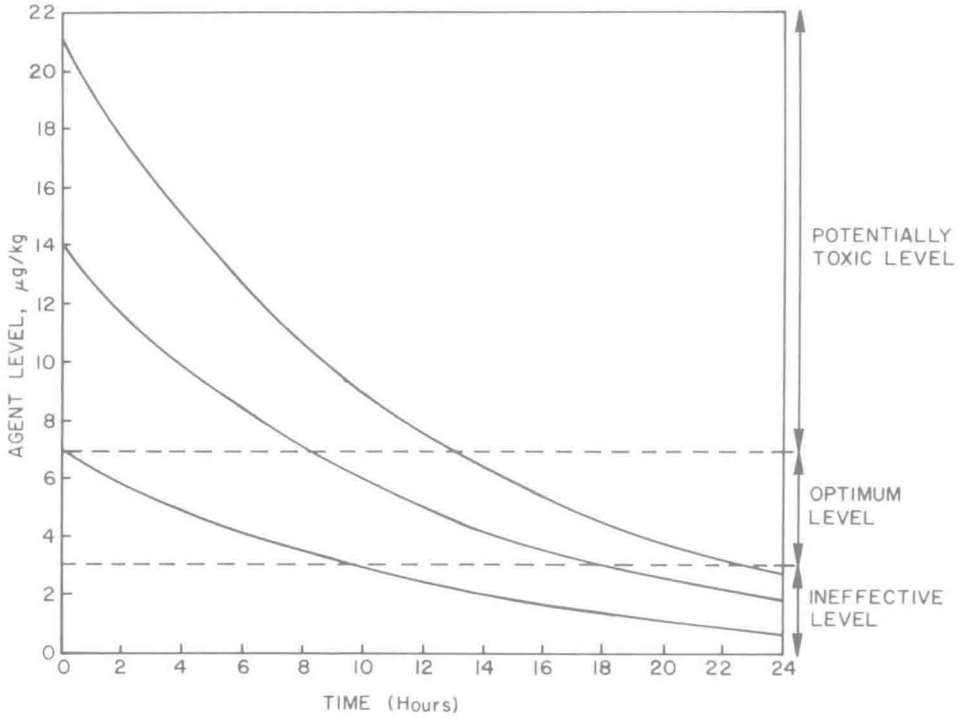

Figure 2. Level and Duration of Agent Availability after Single Injection

Using Equation (4) we can calculate a pseudo-first-order rate constant for drug removal to be 0.0866 hr^{-1}. We can generate the drug availability profile for various dosage levels by applying Equation (2) in the exponential form,

$$M = M_o e^{-k_r t} \qquad (5)$$

Figure 2 shows the levels and durations that can be achieved by single injections of 7, 14, and 21 μg/kg of the drug. A single injection of a 7 μg/kg dose of the drug would obviously provide an effective drug level for about 10 hr. Thirty-two subsequent injections of 5 μg/kg doses at 10 hr intervals would give the desired effect. If dosages of 14 μg/kg were given to reduce the number of needed injections, an effective level could be maintained for about 18 hr, but for 8 hr the concentration of drug is at a hazardous level. If single daily injections were tried, a level of 21