MACROMOLECULAR DRUG RELEASE FROM POROUS IMPLANTS:
SOURCES OF MATRIX TORTUOSITY

by

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The images contained in this document are of the best quality available.
Release of the highly water-soluble proteins Bovine Serum Albumin (BSA), β-lactoglobulin and lysozyme chloride from ethylene-vinyl acetate copolymer (EVAc) matrices was studied at three drug powder particle sizes and ten drug loadings. It was found that at small particles and low loadings, much of the BSA is virtually trapped inside the matrix. Even at higher loadings and particle sizes, where all drug was released, the release rate was orders of magnitude slower than would be predicted for diffusion through water-filled channels, which have previously been shown to be the conduits for drug release.

For the two smaller particle sizes it was found that as loading increases, a sharp transition occurs in the total fraction of releasable drug. This transition is similar to other transitions that are described by percolation theory. A percolation-type model was applied to the data, with qualitative agreement but quantitative disagreement. It was conjectured that the differences are due to inhomogeneities in the drug particle distribution in the matrices.

Three possible mechanisms of retardation of drug release were studied theoretically. It was shown that neither the concentration dependence of the diffusion coefficient of proteins nor the random pore topology are sufficient to account for the slowness of release. However, it was shown that constricted throats connecting pores, which have previously been identified by scanning electron microscopy, can account for the retardation of release. The constricted throats are much larger in diameter than the protein molecules, so the retardation is not due to sieving or hydrodynamic effects. Rather, the constricted throats make it more difficult for diffusing molecules to find their way out of pores.
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I. INTRODUCTION

I.1 Overview of Pharmaceutics

Pharmaceutics has three broad and complementary goals. The first goal is the rational design of new drugs. Those involved in drug design are primarily concerned with biophysical and biochemical interactions associated with disorders to be treated. The second goal is understanding how the body processes drugs. This goal leads one to the subfields of pharmacokinetics, pharmacodynamics, metabolism, and excretory physiology. The third goal is the delivery of drugs or bioactive agents to the proper site. Often the human body provides barriers to successful drug administration, such as the gastrointestinal system and the blood-brain barrier.

One of the concerns of the field of drug delivery is to circumvent physiological barriers to the administration of drugs. A second concern is the rate by which drug is absorbed into the various compartments of the body. Many drugs possess a "therapeutic range" (figure 1) above which the drug becomes toxic and below which the drug is ineffective. Furthermore, it is often desirable to concentrate the drug at the target site, and to keep it away from other tissues. (This localization of drug is called "targeting.") For example, in cancer chemotherapy there
Figure I.1. Time courses of drug plasma levels in response to conventional drug delivery (a and b), and sustained drug delivery (c).
exist many drugs which could effectively kill cancer cells, but are not useful because they are also lethal to nonmalignant cells. It is hoped that one day cancer drugs will be targeted such that only malignant tissues will be destroyed.

The three goals described above are interconnected. The chemical structures of the drug molecule and the receptor determine the pharmacodynamics of drug action and the metabolic pathways by which the drug is removed. Furthermore, rates of drug uptake and removal often determine the rate at which drug should be administered.

1.2 Overview of drug delivery issues

The present work concerns methods of prolonging the delivery of various drugs and maintaining drug concentrations at therapeutic levels. This section provides a brief review of the issues involved in and strategies evolved towards this end.

A common method of sustained drug delivery is the tablet. When ingested, the tablet remains intact until it reaches the appropriate site for dissolution (stomach or gut). The chemical composition of the tablet can be altered to provide desired rates of dissolution.
Tablets provide a simple example of the solution of two problems in drug delivery. Consider for example a drug that is labile in an acid environment but stable in an alkaline environment. To be absorbed the drug must, after swallowing, pass through the stomach, which is strongly acidic. Thus a tablet of this drug should contain a coating or a complexing agent that protects the drug from acid attack. Once having passed through the stomach, the tablet enters the gut, which is alkaline. Thus the coating or complexing agent should also release the drug when in the presence of alkali.

The problems associated with the stability of drugs in the gastrointestinal tract are examples of problems of **bioavailability**. A drug delivery system should maximize the bioavailability of the incorporated drug.

Once a drug is in the circulation, pharmacokinetic considerations become important. Drugs are removed from the circulation via metabolic and excretory processes. A pharmacokinetic parameter of importance is the circulatory **half-life** of a drug. This can be determined by injecting a bolus of the drug directly into the circulation and measuring the circulating drug activity as a function of time.

Often a drug's half-life is very short, and much of the drug may never reach the site of action. Thus bioavailability and pharmacokinetics are intertwined. A
delivery system for such a drug should release the drug into the circulation over a long period of time. On the other hand, a drug that is slowly removed from the circulation (long half-life), does not require sustained administration.

Tablet forms have been designed to alter the rate of absorption of drug from the gut into the circulation. Thus, proper design of a tablet can ensure both bioavailability of the drug and a suitable rate of drug delivery.

Besides tablets, there are several other pharmaceutical preparations whose purpose is to localize and/or prolong the action of drugs. Ointments provide a substrate for drugs which localizes them at the site of application, and prolongs the release of the drug into the skin or mucus membrane on which the ointment is placed. Another example is slow intravenous administration, which in some sense is the most direct method for controlling plasma drug levels, but is generally feasible only for bedridden patients. Drugs such as insulin are often injected in the presence of agents (in the case of insulin, zinc or protamine) which slow the release of free drug into the blood and prevent immediate excretion. Finally, subdermal and intramuscular injections place the drug in an effective depot in the body, and the transport of the drug into the circulation is regulated by physiological processes [1].
1.3 Implants

Unfortunately, tablets, ointments, and injections generally sustain the release and/or absorption of drugs over relatively short time intervals, i.e. hours or days. For many drugs it is desirable to sustain release over periods of weeks, months, or even years. In such cases, implanted devices are generally more useful. In the past 25 years much work has focused on the development of implantable drug delivery systems.

Recently, commercial polymeric systems have been developed for the long term release of pilocarpine (which reduces ocular pressure) [2] and progesterone (for birth control) [3]. Sustained release polymers have also proved useful in several dental applications [4,5].

For macromolecular drugs, it is essential that sustained drug delivery be mediated by an implant. Almost all macromolecules are degraded enzymatically in the stomach or gut before they can be absorbed. Thus enteric administration is ruled out. Furthermore, many macromolecules must be administered in a sustained manner. For example, insulin dosage forms do not provide a good constant basal level. It is felt that many of the long term symptoms of diabetes (e.g. retinopathy, nephropathy) are due to poor control of basal insulin levels, leading to pathological blood glucose levels.
Thus an implantable system which provides improved insulin delivery is desirable.

Despite the fact that macromolecules are among the best candidates for sustained release implants, the only clinically used implants that have been developed thus far are for low molecular weight (<600 dalton) drugs. The reason for this will be discussed in the next section.

Table I provides a list of some macromolecular drugs whose delivery would be efficated by a sustained release implant. Many of these drugs (and others) exist at present in small quantities, so their use in therapy has been limited. However, with the advent of biotechnological techniques such as genetic engineering, many of these drugs may soon be producible in such quantities as to make them clinically useful.

1.4 Reservoir and matrix devices

There are two classes of polymeric implants that are normally considered in sustained release applications [7]. The first class consists of the reservoir devices. In these devices (see figure 2a), a saturated solution of drug is encapsulated by a polymeric membrane. The membrane functions solely as a low permeability barrier. Since the diffusion coefficient of drugs is much lower in the polymer than in
<table>
<thead>
<tr>
<th>Macromolecular Drug</th>
<th>Molecular Weight</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>4700</td>
<td>&lt;5 min.</td>
</tr>
<tr>
<td>Angiotensin I</td>
<td>1200</td>
<td>15 sec.</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>1060</td>
<td>30 sec.</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>3600</td>
<td>&lt;40 MIN.</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>600</td>
<td>2 min.</td>
</tr>
<tr>
<td>Gonadotropic Hormones</td>
<td>30000</td>
<td>0.5-3 hr.</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>22600</td>
<td>&lt;25 min.</td>
</tr>
<tr>
<td>Heparin</td>
<td>3-37,000</td>
<td>&lt;2 hr.</td>
</tr>
<tr>
<td>Insulin</td>
<td>6000</td>
<td>&lt;25 min.</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>1007</td>
<td>2 min.</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
<td>9500</td>
<td>&lt;15 min.</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>1200</td>
<td>4 min.</td>
</tr>
</tbody>
</table>

Table I.1 Macromolecular drugs and their half lives [13].
Figure 1.2. a) Reservoir device.
   b) Monolithic (matrix) device.
water, the reservoir device can retain and slowly release the drug for a long period of time. The second class of implants consists of the monolithic, or matrix devices. In these devices (see figure 2b), drug is dissolved or dispersed inside the polymer. Thus, the membrane functions both as a barrier and as a storage device.

All the examples of sustained release polymers described in section 3 are of the reservoir type. The reservoir type of implant possesses one clear advantage. It is easy to show that as long as the interior drug solution is held at the saturation concentration, a constant, or "zero order" release rate is achieved [7]. However, there are several disadvantages to the reservoir system. First, reservoir devices are not easy to make, as one must surround a liquid solution of drug by the polymer. Second, and more important, if the polymer membrane is somehow ruptured, the device will release all the drug into the patient, with toxic effects.

Monolithic devices, on the other hand, will not disgorge their contents if they are ruptured. However, they have not been as popular as reservoir devices, because it was believed that they could not release drugs at a constant rate. This is true for slabs releasing drugs for which diffusion is rate controlling. In appendix I other cases where monolithic devices can provide zero order delivery are discussed.
For macromolecules, there is another reason why monolithic devices are preferred, if not essential. Most macromolecules have a molecular weight greater than 1000 daltons. Their radii are larger than the characteristic distance between polymer strands in the membrane. Thus the membrane is impermeable to the macromolecule, so a reservoir device cannot work.

1.5 EVAc matrices

Langer and Folkman [8] demonstrated that monolithic devices comprised of ethylene-vinyl acetate copolymer (EVAc), when loaded with various macromolecules in powdered form, release their contents over periods greater than one month. Since then, others have reported the use of such EVAc monolithic implants for bioassays in which the response to a macromolecule was of interest [9-11]. The polymer serves to prevent the macromolecule from diffusing away from the site of interest.

EVAc is biocompatible [12], and has been approved by the Food and Drug Administration for certain medical uses. Further, it is hydrophobic and swells negligibly. These features make EVAc matrices potential candidates for the delivery of macromolecular drugs.

Figure 3 shows typical _in vitro_ release curves for a
Figure 4. Kinetics of release for bovine serum albumin (BSA) from EVAc matrices at various drug loadings and particle sizes. Abscissa is square root of time. Ordinate is cumulative fraction of incorporated BSA that is released.

- ▲ Loading = 0.10, particle size range = 150–180μ
- △ Loading = 0.10, particle size range = 300–425μ
- ■ Loading = 0.30, particle size range = 150–180μ
- □ Loading = 0.30, particle size range = 300–425μ
- ○ Loading = 0.50, particle size range = 150–180μ

Figure I.3. Typical in vitro release kinetics of BSA from EVAc matrices. Reproduced from [13].
protein, Bovine Serum Albumin (BSA) [13]. Note that the abscissa is the square root of time. Thus, 20 hours$^{1/2}$ corresponds to 400 hours. Clearly, protein can be released for months. Also, the fact that release is proportional to the square root of time suggests that diffusion is the rate determining mechanism of release [7].

EVAc, like other polymers, is impermeable to macromolecules. Thus the question was raised: how is it possible to obtain release of the drug? In order to answer this question, it is necessary to describe the fabrication procedure (see figure 4) [14]. Lyophilized or crystalline protein powder is mixed into an EVAc solution in which the solvent is dichloromethane (methylene chloride), an organic solvent. Dichloromethane is a poor solvent for the macromolecular drugs of interest, since the drugs are typically water-soluble. After mixing, the resulting suspension is poured into a cooled (-80 °C) mold. The suspension congeals, and the solvent begins to evaporate. The suspension is then removed from the mold, and the remaining solvent is evaporated over four days.

Figure 5a shows a photomicrograph of a thin (10μ) section of a matrix cast in this manner [15]. It is clear that the polymer and the macromolecular powder phases separate. Figure 5b shows a photomicrograph of a similar matrix after release. It is seen that the powder is
### PREPARATION of SUSTAINED RELEASE POLYMERS

1. **WASH POLYMER in ALCOHOL**
2. **DRY**
3. **DISSOLVE POLYMER in METHYLENE CHLORIDE**
4. **ADD DRY PROTEIN POWDER**
5. **CAST at -80°C**
6. **DRY at -20°C**
7. **DRY at 20°C**
8. **ACTIVATE with PHYSIOLOGICAL SALINE**

![Diagram](image)

**Fig. 1.** Preparation of ethylene-vinyl acetate copolymer (EVAc) matrices by solvent casting.

---

**Figure I.4.** Fabrication procedure for EVAc sustained release matrices. Reproduced from [13].
Figure 1.5. a) $10\mu m$ section of an EVAc matrix loaded with myoglobin before release.
b) $10\mu m$ section of an EVAc matrix, after release is complete.

Reproduced from [13].
dissolved away, but the pores remain. It appears that drug release occurs through a pore network formed by the macromolecule powder, and not through the EVAc itself. Water permeates the pores, causing the drug powder to dissolve and leach out, leaving behind a porous "carcass" through which other drug molecules must pass before leaving the matrix.

An overall picture of the release process has been developed [15]. It is postulated that release of macromolecular drugs from EVAc matrices is mediated by diffusion of the macromolecules through water-filled pores that are formed due to the phase separation of the drug particles from the polymer.

If the diffusion of macromolecules is through water-filled pores in the EVAc implant, then the rate of release should be determined by the diffusion coefficient $D$ of the drug in water and by the smallest dimension $L$ of the device. A characteristic time of release $t_c$ can be computed by the equation

$$ (1) \quad t_c = \frac{L^2}{D} $$

This characteristic time gives an order-of-magnitude estimate of how long it will take for the device to release most of its incorporated drug. For example, for BSA, the diffusion coefficient in water is approximately $7 \times 10^{-7} \text{ cm}^2$/sec [16].
A typical implant we might consider is a slab of depth 0.1 cm. For this case, the characteristic time, given by equation (1) is

\[ t_c = \frac{(0.1 \text{ cm})^2}{(7 \times 10^{-7} \text{ cm}^2/\text{sec})} = 1.4 \times 10^4 \text{ sec} = 4 \text{ hrs.} \]

Considering that figure 3 shows release over periods of months, this result is paradoxical.

Classically, the retardation of diffusion through porous media is attributed to the "tortuosity" of the medium [17]. The channels and pores through which the macromolecules must pass are irregular, and hence sinuous. Thus, the effective distance that a molecule must travel is increased, and equation (1) should be modified to take this into account. Introducing a dimensionless tortuosity factor \( \tau \), the effective depth of the slab becomes \( \tau L \), and equation (1) is replaced by

\[ (2) \quad t_c = (\tau L)^2/D. \]

A tortuosity factor of 2 would increase the release time by a factor of 4, while a tortuosity factor of 10 would increase the characteristic release time hundredfold. Tortuosity factors of at least 10 are required to predict drug release
that will continue for months.

Typical values of tortuosities in porous media such as sands [18] and biological tissues [19] lie between $\sqrt{2}$ and $\sqrt{3}$. To obtain tortuosities greater than 10 would require a highly unusual (and "intelligent") organization of the pore structure in a polymer matrix such that the channels and pores wind so much and also avoid each other. (If channels or pores crossed each other they would provide short cuts for the diffusing molecules. Channels and pores will be defined in chapter II.) Given that EVAc matrices are cast such that drug particles, and hence the pores, are situated at random, it is unlikely that such an organization could exist. Therefore, it is unlikely that tortuosity factors as large as 10 could be due solely to the sinuousness of the pore structure.

A primary goal of this thesis is to achieve an understanding of the retardation of diffusion and release in EVAc matrices. It will be shown that geometrical and topological properties of the water filled pores can provide the basis for the retardation of diffusion.

1.6 Scope of Thesis

This thesis is devoted to the understanding of the slow release of macromolecular drugs from EVAc matrices. Chapter
Chapter IV comprises the experimental effort—a large set of kinetic determinations. It will be seen that not only is drug release slower than might be expected, but also that under certain conditions release becomes so slow that for practical purposes it can be assumed that some of the drug is trapped in the matrix.

In chapter V a model is presented that predicts the total amount of drug released from the matrices, i.e. the amount of drug that will not be trapped. This model also predicts certain aspects of the kinetic curves that can be tested against the kinetic data. Comparison is made between the model predictions and the data of chapter IV. In chapter VI an explanation for the sustained nature of macromolecular drug release from EVAc matrices is provided. Suggestions for further research are provided in chapter VII.

Chapters are written in a self-contained fashion, each with its own bibliography and set of figure, equation, reference, and section numbers. If referral is made to a figure, equation or section from another chapter, the
referral contains the roman numeral for the latter chapter.
Referrals within a chapter do not contain roman numerals.
REFERENCES


II. BACKGROUND ON EVAc SUSTAINED RELEASE MATRICES

II.1 Introduction

This chapter reviews previous work geared towards understanding the mechanism of release of macromolecules from EVAc matrices. In section 2 kinetic studies are reviewed and factors influencing drug release are identified. In section 3, microstructural studies are reviewed. From the information provided by sections 2 and 3, a conceptual model is developed in section 4. This model provides the basis for much of the thesis work.

II.2 Factors influencing release kinetics

II.2.1 Effects of loading and particle size

The two most important variables affecting the release of macromolecular drugs are the drug loading and the drug powder particle size. Drug loading is defined as the weight of drug divided by the total weight of the drug plus the polymer. The drug particle size is the range of (dry) drug particle diameters. The drug powder is sieved to narrow particle size ranges before it is suspended in the polymer solution. This is done to enhance the reproducibility of the release kinetics. Since the powder does not dissolve in the polymer solvent dichloromethane, the powder granules maintain
their integrity as the solvent evaporates (section 1.5).

Thus the drug particle size range translates into the pore size range when the polymer solvent is completely evaporated.

Figure 1.3 shows examples of the effects of particle size and loading on the release kinetics of BSA [1]. Note that the abscissa is the square root of time and the ordinate is the cumulative fraction of drug released. This is obtained by dividing the mass of drug released up to a time point by the total mass of drug originally incorporated into the matrix.

It is obvious that as drug loading increases, the rate of mass transfer should increase, simply because there is more drug inside the matrix. However, figure 1.3 indicates that as loading increases, so does the rate of release per drug molecule. In other words, increasing the drug loading in some sense lessens the resistance of the matrix to release of the drug molecules.

It is also seen in figure 1.3 that at low loadings and particle sizes, not all drug is released from the matrix. Apparently in these cases much of the drug is trapped. This observation will be important in formulating a model for the release mechanism (section 4).
II.2.2 Effects of release media (pH, ionic strength, and temperature)

The effect of pH on release kinetics of BSA has been studied [2]. The slowest release occurs at pH=5.0, which is very close to the isoionic point of BSA [3]. Above pH=5.0 the release rate increases with pH, i.e. as the BSA molecule becomes more negatively ionized.

One experiment has been carried out in which the ionic strength of the release media was varied [2]. In that experiment, the ionic strength did not affect release rates for BSA. However, pH was not controlled, and the pH's of the release media were probably quite close to the isoionic point of BSA (unbuffered water tends to be acidic due to dissolution of air). It has been shown elsewhere that the diffusion coefficient of BSA in water can vary more than twofold with ionic strength if the solution is buffered at physiological pH [4]. Near the isoionic point, however, the diffusion coefficient of BSA is much less affected by ionic strength. Therefore, more complete experiments testing the effect of ionic strength on release rates need to be performed.

As temperature increases, so does the release rate [5]. A plot of the log of the slope of the release curves against inverse temperature (Arrhenius plot) yields an "activation
energy" of approximately 4.5 kcal/mole. This is almost identical to the activation energy derived from an Arrhenius plot for diffusion of BSA in water [6]. This is evidence that the release of BSA is diffusion controlled.

### II.2.3. Effect of coating

When EVAc matrices are fabricated as in figure 1.4, and then dipped several times into a 20% EVAc solution, and if the coating is allowed to dry, the resulting release rates are decreased considerably compared to uncoated EVAc matrices [7]. However, the dipping process does not completely eliminate release. This might seem surprising considering that EVAc is impermeable to macromolecules. Perhaps some of the original polymer in the matrix dissolves during the dipping process, allowing some of the drug to flow into the coating and become exposed again. Alternatively, the coating process may be imperfect, with small defects through which drug could escape.

### II.3 Microstructural studies

#### II.3.1 Optical microscopy

Because the pore sizes are large (~100μm), one can visualize the matrix ultrastructure using light microscopy. Thin (10μm) sections have been obtained using a cryomicrotome
Figures I.5a,b show loaded polymers before and after release, respectively. Phase separation between drug and polymer before release is clear from figure I.5a, and maintenance of the pore structure after release is seen in figure I.5b. Similar photomicrographs of EVAc matrices without drug show no optically detectable pores [8].

II.3.2 Scanning electron microscopy

Due to the small depth of focus allowed by light microscopes, a scanning electron microscope (SEM) was used to obtain information on the pore structure [8]. Figure 1 shows an SEM picture of a pore. The pore is a bulging body, connected to other pores through narrow channels. (By narrow it is meant that the channel diameters are small relative to the diameter of the bulging pores. The channels are still quite large when compared to the size of protein molecules.)

II.4 Conceptual model of the release process

There are several salient points that have been presented in this chapter. First, the EVAc sustained release matrices are heterogeneous materials. The protein powder granules are randomly incorporated into the matrix, and when they leach out they leave behind a highly random porous network. Since the macromolecules do not permeate the polymer itself, they must leach out through the pore network.
Figure II.1. Scanning electron micrograph (SEM) of an empty pore, illustrating a bulging pore body and narrow connecting channel. Reproduced from [1].
Second, at low drug loadings and particle sizes, much of the drug is forever trapped in the matrix. This can be explained as follows: at low loadings, the likelihood that two drug particles make contact is small. Unless a drug particle is at the surface of the polymer matrix, it will likely be completely surrounded by polymer, which the drug cannot penetrate. This is illustrated in figure 2. At low particle sizes, only a small fraction of the drug particles can be on the surface, so that an even greater fraction of the incorporated drug will be trapped. This simple model will be quantitated in chapter VII.

The third important point is that drug release appears to be mediated by diffusion. This is suggested by the activation energy argument of section 2.2 and by the fact that release from slabs follows $t^{1/2}$ kinetics. This does not necessarily mean that diffusion is the only governing process. For example, the concentration gradients that provide the driving force for diffusion may be determined by the drug's solubility. However, the release rates are governed by solubility only through the effect of solubility on the diffusion process.

Since the diffusion is through the water filled pore network, pore geometric and topological factors must account for the slow rate of diffusion. The fourth salient point brought out in this chapter is that the pores seem to be
Figure II.2. Schematic of EVAc sustained matrix.

a) Low drug loading.

b) High drug loading.
connected by narrow "channels" or "throats." In chapter VIII it will be shown that the presence of throats can explain the slowness of the diffusion process.

The porous network might be envisioned as in figure 3, which is a two dimensional conceptualization. We imagine that drug molecules execute random walks through the random maze of figure 3. The field of transport through random media has received much attention in recent years, and in the next chapter a brief review of work in that field is presented.
Figure II.3. Two-dimensional representation of conceptual model of pore structure. Pore topology is random. Pore geometry is characterized by bulging pore bodies connected by narrow throats (channels).
REFERENCES


CHAPTER III. REVIEW OF TRANSPORT IN HETEROGENEOUS MEDIA

III.1 Introduction

In chapters I and II it was indicated that release of macromolecular drugs is caused by diffusion of the drug molecules through a randomly connected, water filled pore network. Because the milieu is random, the boundary conditions for whatever transport equations apply are also random. Clearly one cannot take the approach of examining all possible realizations of a porous medium and calculating the release process for each realization. Rather, the approach one takes is to search for important statistical features of the medium and to model these features in such a way that the transport can be predicted.

The problem of transport in porous and other heterogeneous media has received much attention. This chapter is a review of the work that has been done on this problem. Since heterogeneous media cover a broad range of materials, it is necessary to make some restrictions. Specifically, this review will be restricted to heterogeneous media consisting of two phases, one which is impermeable to the mobile species and one which is permeable. The relationship and applicability of the various reviewed works to the problem of diffusion in EVAc sustained release polymers will be assessed.
III.2 Maxwell-type models

The first attempt at modelling transport through heterogeneous media was made by Maxwell [1]. Maxwell considered the problem of electrical conduction through a dilute suspension of insulating spheres. (Conduction is analogous to steady state diffusion.) He approached the problem by assuming that the spheres are not affected by each others' presence, i.e. the spheres are dilute enough that their induced dipole fields do not interact. He solved Laplace's equation subject to the boundary condition that the normal current at the surface of a sphere is zero. If $\sigma_0$ is the conductivity of the medium into which the spheres are imbedded, $\sigma$ the conductivity of the composite, and $\varepsilon$ the volume fraction of the conductive phase, then Maxwell's result is

$$\sigma = \left[\frac{2\varepsilon}{3-\varepsilon}\right] \sigma_0 .$$

More complicated expressions have been derived for other similar dilute media in which the shape of the suspended insulators is varied (i.e. spheres are replaced by convex shapes such as cylinders [2], spheroids [3], etc.).

In general, these Maxwell-type models are valid only when $\varepsilon$ is near 1. This is because the assumption that the insulators do not affect each other breaks down as the insulator volume fraction $(1-\varepsilon)$ gets large. After the point
where a Maxwell-type model breaks down, no single model is adequate to describe the behavior of the conductivity $\sigma$ as a function of $\varepsilon$. When the insulators start to interact, other statistical factors besides $\varepsilon$ become important. Correlations between positions of the insulators (which are not determined solely by $\varepsilon$) can have a significant effect. For example, an array of regularly spaced insulating spheres in a conductive medium will, at lower values of $\varepsilon$, possess a different overall conductivity than a dispersion of randomly placed insulating spheres placed in the same medium. A recent review by Chiew and Glandt [4] elaborates in much more detail on this point.

In the EVAc system, the operant parameter $\varepsilon$ is the porosity of the matrix, which is considerably less than 1. Thus, the Maxwell-type models, in their simplest form, are not appropriate. In might be argued that one could introduce a higher order statistical characterization of the EVAc matrices, and then predict the transport rates at the lower, realistic values of the porosity $\varepsilon$. However, it should be pointed out that the EVAc sustained release polymers present the direct opposite of the heterogeneous media for which Maxwell-type models are designed. In EVAc polymers, it is the conductive fraction (i.e. the water filled pore space) that is suspended in an insulating medium. The insulating fraction (i.e. the polymer) does not consist of convex particles, as is assumed by Maxwell-type models. For these reasons, Maxwell-type models have not been pursued in this work.
Percolation theory is a relatively young field, having been first introduced in 1957 [5,6]. It derives its name from a problem in the study of flow through porous media. Consider a large rock surrounded by water, and assume that the water wets the rock. Small pores are slowly introduced into the rock, at random positions in the rock. When the porosity is low, pores at the surface of the rock will be wetted, but those pores in the interior of the rock will not, because they are not connected to the surface of the rock (figure 1a). As the porosity increases, more pores connect to the surface of the rock, so more pores are wetted (figure 1b). At a certain critical porosity, denoted $\varepsilon_c$, a network of pores is formed that pervades all regions of the rock, so that water may "percolate" throughout the rock (figure 1c). At the critical porosity, or "percolation threshold," there are still many pores, however, that are not connected to the pervading (or "percolating") pore network. As the porosity increases even further, these isolated pore clusters are recruited into the percolating network (figure 1d).

Figure 1 is reminiscent of figure II.8. A variation of the percolation model will be used in chapter V to analyze the amount of drug that is releasable from EVAc matrices.

Although percolation theory is named for the wetting of
Figure III.1. Stages of formation of a percolating pore network in a porous rock.

a) $\varepsilon<<\varepsilon_c$, b) $\varepsilon<\varepsilon_c$, c) $\varepsilon=\varepsilon_c$, d) $\varepsilon>\varepsilon_c$.
porous rocks, it has found widespread application in several areas of physics that deal with phase transitions [6,7]. In a sense, the onset of a percolating channel in a rock can be viewed as a phase transition. Another phase transition that can be modeled using percolation theory is the transition in a metal/insulator composite from an insulator to a conductor, as the metal fraction is increased [8-11]. Since conduction was used as the framework for discussing Maxwell-type models, the metal/insulator mixture will be used in place of the wetted rock as the vehicle for discussion. Percolation theory has also been applied in the theory of epidemics [6,12], and in the study of two-phase flow through porous rocks [5,6,13,14].

Unlike the Maxwell-type models, percolation models are inherently stochastic. Typically (but not always [15]), a porous or heterogeneous medium is idealized as a regular lattice, the sites of which are either "conductive" or "insulating." (This is called "site" percolation in the literature. For a review of different types of percolation, see [6].) With probability $\varepsilon$, a site is "filled" with conductor, otherwise it is filled with insulator (see figure 2a). A percolation program generates the random lattice using this rule, and then tabulates statistics such as the distribution of sizes of conductive clusters and the fraction of conductors belonging to a cluster that percolates throughout the lattice. If the lattice is large, a clear percolation threshold effect can be seen for the latter statistic (see
Figure III.2. a) A typical percolation lattice of lattice sites containing conductors (filled squares) or insulators (empty squares). Conductor fraction $\xi = 0.56$.

b) Probability $P$ that a conductive site belongs to a percolating cluster, for various 3-dimensional lattices. Redrawn from [7].
figure 2b). Just above the percolation threshold, the fraction of conductors belonging to the percolating cluster rises very quickly, and soon virtually all conductors are recruited.

Figure 2b also shows that, for regular 3 dimensional lattice structures, the percolation behavior, except for the value of the threshold itself, is virtually independent of the lattice structure. That is, the curves in figure 2b can be shifted on top of each other. More precise calculations [7] have shown that the asymptotic behavior near threshold is universal for all 3-D lattice structures. If $P(\varepsilon)$ is the probability that a filled lattice site is in the percolating cluster, then

$$P(\varepsilon) \sim (\varepsilon - \varepsilon_c)^4, \quad \varepsilon > \varepsilon_c .$$

Most quantities associated with percolation networks have a power law dependence with respect to $\varepsilon - \varepsilon_c$. Remarkably, all power law exponents are independent of the actual lattice structure, given a fixed dimensionality of the lattice. (This has been shown to be related to various "universalities" encountered in phase transitions and critical phenomena [16].) However, the critical value $\varepsilon_c$ does depend on the lattice organization, and also higher order properties of the conductive sites.

So far in this section, the only concern has been whether
a mixture of conductors and insulators can conduct current. Nothing has been said about the actual conductivity $\sigma$ of the composite above the percolation threshold. The dependence of the conductivity $\sigma$ on the fraction of conductive sites $\varepsilon$ has been well studied, however [8-11]. Below the percolation threshold $\varepsilon_c$, conductive clusters are isolated from each other, so the overall conductivity of the composite is zero. Above the percolation threshold ($\varepsilon > \varepsilon_c$), the following asymptotic relation holds for 3-D lattices [7]:

$$\sigma \sim (\varepsilon - \varepsilon_c)^{1.5}.$$ 

This is plotted in figure 3. This relationship holds for all types of 3-D lattices, although once again, different lattices give rise to different values of $\varepsilon_c$.

Note that the rise in conductivity is not nearly as fast as the rise in the fraction of conductive sites belonging to the percolating cluster. This is because the percolating cluster contains many regions that are not on the main pathway of current flow, and thus do not contribute to the conductivity of the cluster. These regions are often termed "dead ends." Further, the closer $\varepsilon$ is to $\varepsilon_c$, the more tenuously and tortuously connected the percolating cluster will be.

Equation (3) has been tested for conduction in porous membranes in at least one case: that of perflourinated ionomer
Figure III.3. Plots of percolation probability $P$ and conductivity $\sigma$ of a random simple cubic lattice of conductors and insulators, as a function of $\varepsilon$, the volume fraction of conductors. Reproduced from [9].
membranes [17]. In these membranes, the conductive sites are
water-filled pores whose radii are on the order of tens of
angstroms, so that the pores and insulating regions can be
modelled as belonging to an extensive lattice that is the
membrane. As shown in figure 4, equation (3) fits the data
quite well near the percolation threshold.

The power law dependence discussed above holds only for \( \varepsilon \)
near \( \varepsilon_c \). Away from \( \varepsilon_c \), the lattice structure and higher order
statistical features of the positions of the conductive sites
determine the \( \varepsilon \)-dependence of the percolation probability and
conductivity. "Effective medium" theories [8] have been
developed to explain the dependence of \( \sigma \) on \( \varepsilon \) for \( \varepsilon \) away from
\( \varepsilon_c \), with some success.

Some results have been reported recently [18] on the
conductivity of 3-D lattices of finite depth. For such
lattices there is no threshold \( \varepsilon_c \), since for any \( \varepsilon \) there is a
finite probability that a chain of conductors will span the
depth of the lattice. In general, as the depth gets smaller,
the expected conductivity of the lattice rises.

The problem of diffusion through percolating clusters can
be related to the conduction problem through a suitable
Einstein relation [19,20]. Thus, at first glance it might seem
that the percolation models could explain the slowness of
diffusion of macromolecules through EVAc matrices. After all,
Figure III.4. Conductivity of NAFION® perfluorinated ionomer membranes as a function of volume fraction $\varepsilon$ of membrane that is saline. Dashed line is prediction of percolation theory [eq. (3)]. Reproduced from [17].
as $\varepsilon \to \varepsilon_c$, $\sigma \to 0$. Two things should be pointed out here. First, the lattice sites in a representation of an EVAc sustained release polymer have the dimensions of pores. Since the pores are relatively large compared to the depth of the EVAc matrix, the lattice depth must be small, so the finite depth considerations just described should be included. In fact, it can be shown that the mapping between conductivity and diffusivity is not so clear when the lattices are of finite depth. In particular, diffusing molecules in pores that are near the surface of the membrane do not have to contend with a complicated porous network to be released. Second, transport in EVAc matrices is slow even at high porosities, where equation (3) would seem to predict high conductance (i.e. diffusivity). But notice that (3) is a proportionality. Thus, while the form of the behavior as a function of $\varepsilon$ might be predicted by equation (3), it can be scaled by factors not included in the lattice aspect of the model. For example, the shapes of pores might also affect the rate by which mobile species can move from pore to pore. These scaling aspects will be discussed in the next section.

III.4 Models of influence of pore structure

So far in this chapter, focus has been placed on models that assume the primary factor determining the conductance of a composite medium is the conducting volume fraction. For porous media, this translates into the porosity. In this section
models which deal with the shape of pores are reviewed.

As was stressed in section 2, the pores in EVAc matrices are to be regarded as convex. There are several published models in the field of petrology that handle compacted porous beds and rocks, and these models similarly assume that the pores are convex. Archie [21] showed that many compacted porous media that are saturated with water have a conductance of form

\[ \sigma = \varepsilon^{-m} \]

where \( m \) is called the "cementation factor," which depends on the porous media being studied. The constant \( m \) must be determined empirically, and no model was proposed to predict it based on structural factors in the medium. If \( m \) is large, then the conductance can be quite small, even at large porosities.

Probably the first model that used a postulated pore structure to predict conductivity was due to Owen [22]. Owen proposed a pore structure quite similar to that shown in figure II.9. He then measured the conductance of a Bakelite cube filled with saline (see figure 5). By varying the size of the electrodes, he simulated the effect of constrictions at the pore inlets and outlets. Owen found that the conductance of the cube was almost proportional to the area of the electrodes. This is because the current tends to take the path of least
Figure III.5. Electrical analog of constrictions due to Owen [22]. Electrode width determines resistance. As electrode becomes wider, more saline will conduct current, so resistance decreases. Current is indicated by arrows.

a) Narrow electrode (high resistance)
b) Wide electrode (low resistance)
resistance. With small electrodes, much of the cube is irrelevant for the passage of current.

Michaels [23] arrived at virtually the same result for steady state diffusion, but by using a mathematical model, in contradistinction to Owen's electrical analog. This is not surprising, as the equation and boundary conditions for steady state diffusion are identical to those for electrical conduction. Figure 6a is a schematic of the essence of Michaels' model. Each pore column consists of two pores of different widths. This is analogous to the resistor network (voltage~concentration, current~flow of solute) shown in figure 6b, with the narrow pores having equivalent resistance $R$ and the wide pores having equivalent resistance $r$. ($R/r$ is equal to the inverse ratio of the pore widths.) The network resistance is $(R+r)/2$. For $R\gg r$, this equals approximately $R/2$. Now consider an alternate network of two straight, parallel pores, one wide and one narrow, with the same total length as the previous pore network (see figure 6c). The analogous electrical network is shown in figure 6d. The resistance of this network is $2Rr/(R+r)$. For $R\gg r$ this approximately equals $2r$, which is considerably less than the resistance of the first network.

The difference between the two overall resistances can be explained. In figure 6d, current can choose to flow through the path of least resistance. In figure 6b, all current must
Figure III.6. Model of steady state diffusion through pores with varying width, after Michaels [23]. Solute flows from region of concentration $C^*$ to region of concentration $C$.

a) Wide pores meeting narrow pores.

b) Electrical analog of a.

c) No longitudinal variation in pore width.

d) Electrical analog of c.
flow through a high resistance element.

The previous examples dealt with quasistatic or steady state transport through porous domains. However, diffusion in EVAc matrices is a transient process, so the models of Owen and Michaels do not apply directly. Pismen [24] has presented a general model for transient diffusion in a porous medium. A specialized case of the model will be utilized in chapters V and VI, so only a brief description is provided here. Transport through the porous medium is regarded at two levels. The top level is that of motion on the lattice of pores (which could be a percolation lattice), while the bottom level is the motion within individual pores. A particle is thought to "hop" randomly from pore to pore. The rate of hopping is determined by the shape of the pores. It will be shown in chapter VI that this rate of hopping decreases with the ratio of channel width to pore width.
REFERENCES


CHAPTER IV. RELEASE KINETICS FROM EVAc MATRICES

IV.1 Introduction

Studies of release kinetics of various macromolecular drugs from EVAc matrices have been presented in previous works [1-4]. In none of these studies have the effects of drug particle size and loading been studied systematically. In this chapter, the results of the most comprehensive study of release kinetics of Bovine Serum Albumin (BSA) to date are presented, along with some results on the release kinetics of β-lactoglobulin and lysozyme chloride.

The studies focus on the effects of particle size and loading. Their purpose is to provide a data base against which the models of chapters V and VI can be compared.

IV.2 Materials and Methods

IV.2.1 Materials

The polymer ethylene-vinyl acetate copolymer (EVAc, 40% w/w vinyl acetate) was obtained under the product name ELVAX 40P from DuPont Chemical Co., Wilmington, Delaware.

All proteins were obtained from Sigma Chemical Co., St. Louis, Mo. Proteins used were bovine serum albumin (cat. no.
A4503, m.w. 68000), beta-lactoglobulin (cat. no. L2506, m.w. 18000), and lysozyme chloride (cat. no. L2879, m.w. 14,500).

The antibiotic gentamycin sulfate (crystalline form) was also obtained from Sigma (cat. no. G3632).

The following chemicals were used in the release medium: sodium chloride (Mallinckrodt, Inc., Paris, Ky., cat. no. 4912); sodium phosphate dibasic anhydrous (Mallinckrodt, cat. no. 7917-1); and sodium phosphate monobasic monohydrate (MCB Manufacturing Chemicals, Cincinatti, Ohio).

The solvents dichloromethane (methylene chloride) and xylene were obtained from Mallinckrodt, St. Louis, Mo.

Protein powder was sieved using U.S.A. standard testing sieves, with no. 40,50,80,100,140 and 170 gauge meshes, manufactured by W.S. Tyler, Inc., Mentor, Ohio. Sieves were agitated in a sieve shaker, also obtained from W.S. Tyler, Inc. Drug-polymer suspensions were mixed in Falcon polypropylene centrifuge tubes (VWR cat. no. 21008-940), and vortexed on a Vortex-Genie mixer (Scientific Industries, Bohemia, N.Y., model 12-812). Solutions were cast into glass molds prepared with ordinary window glass cemented with silastic (Dow Corning, Midland, MI). Molds were leveled with a circular level (Fisher Scientific, cat. no. 12-000). Matrices were cut using a #3 or a #6 cork borer (A.H. Thomas,
Phil., PA). Physical dimensions of slabs were measured with a micrometer (Starret Co., Athol, MA).

Wax was obtained from Lancer, a division of Sherwood Medical, St. Louis, MO, under the trade name Paraplast®, in pellet form. Syringe needles were obtained from Becton, Dickenson and Co., Rutherford, NJ.

All quantitative liquid transfers were performed with a Repipet Jr., obtained from Labindustries, Berkeley, CA, or with a Gilson Pipetman.

Spectrophotometric determinations were made on a Perkin-Elmer 553 fast scan spectrophotometer equipped with a super sipper.

IV.2.2 Methods

EVAc slabs containing protein drugs were fabricated in a manner similar to that shown in figure I.4. Ethylene vinyl acetate copolymer (EVAc) was obtained in bead form. The beads were washed several times in distilled water to remove a clay coating added during manufacturing. The beads were then washed exhaustively in ethanol at 37°C to remove butylated hydroxytoluene (BHT), an antioxidant. The clean EVAc was then dissolved in dichloromethane to give either 10% or 8% (w/v) solutions. Protein drug powder was sieved at 4°C.
for 30 minutes using a mechanical shaker, to yield fractions containing particles of specified size ranges.

For each casting, the drug particle size (PS) and (weight/weight) drug loading (L) were prescribed. EVAc solution was placed in a polypropylene tube, and the drug powder was then added. The amounts of EVAc and drug were determined by the prescribed loading, and such that the total mass of polymer and protein equalled 3 grams. (There is one exception to this--one slab was cast with only 1.5 grams total mass--this will be called the THIN slab.) In most cases, 10% EVAc solution was used. At higher loadings the polymer-solvent-drug mixture became very viscous, so the 8% solution was used in those cases. The mixture was vortexed and poured into a leveled, flat 7cmX7cmX1cm glass mold which had been precooled by placing it on a flat slab of dry ice for 5 minutes. The low temperature caused the mixture to congeal into a slab. (The cooling was so fast that no convection currents were observed.) Ten minutes after pouring, the slab was pried loose with a cold spatula and transferred to a wire screen in a -20°C freezer, where it was left for two days. The slab was then transferred to a vacuum dessicator (600 millitorr, room temperature) and left there for two more days. Considerable shrinkage occurred during the drying stages. The result was a rubbery slab with dimensions of approximately 4cmX4cmX1mm (see section 3.2).
The pouring step caused some loss of polymer and protein, which stayed behind in the polypropylene tube, due to the viscosity of the suspension. This was increasingly true as the drug loading increased. However, in all cases the mass of the suspension left behind in the polypropylene tube was only a small fraction of the mass that was poured.

A #6 cork borer (diameter=1.18 cm) was used to punch out five disks from each slab. The weight (mg) and thickness (mm) of each disk was measured. Each disk was then impaled through the center of one of the circular faces by a 5/8", 25 gauge syringe needle. The rear end of the needle assembly was then glued to the inside of a 20 ml scintillation vial cap using RTV silicone rubber. The matrix was pushed back on the needle far enough that a small drop of RTV could also be placed on the needle tip and not touch the matrix. The whole assembly could then be screwed into a scintillation vial. The drop of RTV at the tip prevented the matrix from falling off the needle.

A diagram of the whole assembly is given in figure 1.

Drug release was actuated by placing 16 ml of phosphate buffer (pH=7.4: 11.499 g Na₂HPO₄ and 2.622 g NaH₂PO₄ in 1 liter H₂O) into 20 ml scintillation vials. The buffer also contained the antibiotic gentamicin sulfate, at a concentration of 0.2 mg/ml. The cap-needle-matrix assemblies
were then screwed onto the vials, totally immersing the matrix in the release medium (see figure 1). The vials were placed on a shaker (100 rpm) inside an incubator at 28.5±1°C.

At each timepoint, the cap assemblies were transferred to vials containing fresh buffer. The amount of protein in the old vials was then assayed using UV spectrophotometry. At high protein concentrations, which occurred early in the release, the assay was performed at 280nm. At low concentrations where the 280nm reading was lower than .100, readings were made at 220nm [1].

IV.3 Results

IV.3.1 Introduction

Table 1 lists all the drug-particle size-(weight/weight) loading combinations that were tested. The most extensive study was performed with Bovine Serum Albumin. For two drug particle sizes (particle diameter 90-106μm and 150-180μm), the weight/weight loadings of the slabs were varied from .05 to .50 in increments of .05. The batches of BSA powder received from the supplier did not permit harvesting enough powder of particle size 300-425μm for a full study, so studies were only done with loadings .05,.10,.15,.20,.25 for that case. The THIN slab was cast with particle size 90-106μm and loading .10, but with half the thickness of the
Figure IV.1. Assembly used in release experiments.
<table>
<thead>
<tr>
<th></th>
<th>Loading L</th>
<th>Weight (mg)</th>
<th>Depth (mm)</th>
<th>Estimated Porosity ε</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BOVINE SERUM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.05</td>
<td>141.1 ± 4.9</td>
<td>1.316 ± 0.17</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>90-106 μm</td>
<td>0.10</td>
<td>136.8 ± 5.4</td>
<td>1.276 ± 0.064</td>
<td>0.12 ± 0.03</td>
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<td>1.152 ± 0.073</td>
<td>0.25 ± 0.03</td>
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<td>121.7 ± 5.1</td>
<td>1.110 ± 0.034</td>
<td>0.30 ± 0.02</td>
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<td></td>
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</tr>
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<td>1.102 ± 0.015</td>
<td>0.53 ± 0.01</td>
</tr>
<tr>
<td><strong>BOVINE SERUM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.05</td>
<td>136.5 ± 4.7</td>
<td>1.244 ± 0.042</td>
<td>0.04 ± 0.00</td>
</tr>
<tr>
<td>150-180 μm</td>
<td>0.10</td>
<td>132.5 ± 3.1</td>
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<td>1.100 ± 0.038</td>
<td>0.19 ± 0.03</td>
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<td>1.060 ± 0.029</td>
<td>0.25 ± 0.00</td>
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<td>1.046 ± 0.045</td>
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</tr>
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<td>Albumin</td>
<td>0.05</td>
<td>146.3 ± 6.0</td>
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<td>0.00 ± 0.01</td>
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<td>300-425 μm</td>
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<td>137.9 ± 7.1</td>
<td>1.226 ± 0.102</td>
<td>0.07 ± 0.04</td>
</tr>
<tr>
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<td>0.15</td>
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<td>1.246 ± 0.070</td>
<td>0.16 ± 0.03</td>
</tr>
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<td>0.20</td>
<td>124.1 ± 2.4</td>
<td>1.174 ± 0.038</td>
<td>0.22 ± 0.03</td>
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<td>0.886 ± 0.018</td>
<td>0.32 ± 0.01</td>
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<td></td>
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<td>Albumin-Thin</td>
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<td>49.1 ± 2.6</td>
<td>0.476 ± 0.043</td>
<td>0.15 ± 0.04</td>
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<td>90-106 μm</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-LACTOGLOBULIN</td>
<td>0.10</td>
<td>100.2 ± 7.7</td>
<td>0.920 ± 0.076</td>
<td>0.10 ± 0.03</td>
</tr>
<tr>
<td>106-150 μm</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-LACTOGLOBULIN</td>
<td>0.10</td>
<td>142.7 ± 5.6</td>
<td>1.330 ± 0.037</td>
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</tr>
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<td>300-425 μm</td>
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<td>98.5 ± 4.2</td>
<td>1.020 ± 0.046</td>
<td>0.38 ± 0.02</td>
</tr>
<tr>
<td>LYSOZYME CHLOR.</td>
<td>0.10</td>
<td>141.9 ± 4.6</td>
<td>1.264 ± 0.046</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>106-150 μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LYSOZYME CHLOR.</td>
<td>0.10</td>
<td>135.2 ± 9.3</td>
<td>1.262 ± 0.099</td>
<td>0.12 ± 0.01</td>
</tr>
<tr>
<td>300-425 μm</td>
<td>0.30</td>
<td>128.6 ± 5.4</td>
<td>1.184 ± 0.061</td>
<td>0.30 ± 0.02</td>
</tr>
</tbody>
</table>

Table IV.1 Physical parameters for EVAc disks. Values are mean ± 1 std. dev.
corresponding slab in the "main" sequence. Slabs were also cast with β-lactoglobulin and lysozyme chloride. Again, limitations on the particle sizes available in the batches of these proteins received from the supplier precluded extensive studies, so only illustrative loadings (L=.10,.30) and particle sizes (PS=106-150μm,300-425μm) were tested.

IV.3.2 Physical parameters of slabs

Each row in table 1 summarizes data for five disks that were punched from a mother slab at the specified particle size and loading. Means and standard deviations of the physical parameters (disk weight W and depth d) are listed in the table. Typically, the physical properties of disks taken from the same mother slab show a relative variation on the order of 5-10%.

Some clear trends in weight and depth exist for the BSA slabs. As loading increases, both the weights and the depths of the slabs decrease. This is somewhat surprising, given that all slabs (except the THIN slab) were cast at a total weight of 3 grams. However, a simple physical explanation can be given for this phenomenon. Recall that the polymer and drug are in suspension before casting. At low loadings, the polymer outweighs the drug powder, so the suspension carries a large volume of solvent. At higher loadings, there is less polymer and hence less solvent, so the total volume
of the suspension is smaller. Now the suspensions are poured into molds of fixed horizontal dimensions (7cmx7cm).

Therefore the height of the suspension in the mold must decrease with drug loading. After the suspension "freezes" into a slab, it is removed from the mold, and evaporation can occur from the top, bottom, and horizontal sides of the slab. The thicker the slab, the more likely it is that evaporation will occur through the horizontal sides, thus leading to horizontal shrinkage. Thus the low loading slabs will dry into more horizontally compact, thicker slabs than will the high loading slabs. Since the cork borer provides a constant diameter for the disks, this translates to the observed trends in disk weight.

Some measurements of slab dimensions after drying support this explanation. For example, for slabs containing BSA PS=90-106 µm, the 10% EVAc solution was used for loadings .05-.40. The horizontal dimensions of the slabs were measured after drying, and were found to increase from 

\[(3.7\text{cm})^2 \text{ to } (4.1\text{cm})^2\] as loading increased. For loadings .45 and .50, 8% EVAc was used. Thus, more solvent was added, increasing the depth of the frozen suspensions. Note that at \( L=.45 \) a slight rise in disk weight and depth occurs.

Notice also that the THIN BSA slab (PS=90-106 µm, \( L=.10 \)) has weight and thickness considerably less than half that of the corresponding "main sequence" slab. For the THIN slab,
most evaporation is probably through the top and bottom of the slab, so most shrinkage will be in the vertical direction.

There is a sharp drop in depth and weight between $L = 0.20$ and $L = 0.25$ for BSA, $PS = 300-425 \mu m$. This is due to an anomaly in the fabrication for $L = 0.25$. That slab would not pry from the glass mold after pouring, so the early stage of evaporation was carried out with the slab inside the mold instead of on a screen. This caused evaporation to occur mainly through the top of the slab, leading to a thinner slab than would have resulted otherwise.

There is also a sharp drop in weight, but not depth, between $L = 0.35$ and $L = 0.40$ for BSA, $PS = 150-180 \mu m$. Unfortunately, there is no clear explanation for this.

The decreases in depth and weight with loading also appear to occur for $\beta$-lactoglobulin and lysozyme chloride.

Particle size seems to have a relatively minor effect on physical parameters. There is an indication that depth and weight decrease slightly as particle size increases.

IV.3.3 Porosity

An estimate for the porosity of each EVAc disk was
obtained using the weight and depth measurements in table 1. By porosity is meant the fraction of the disk volume that is not polymer. Thus the pore space is taken to be the region of the disk containing air, drug, or release medium. Let \( W \) be the weight (mg) and \( V \) the volume (cm\(^3\)) of the disk, \( \rho_p \) the density (mg/cm\(^3\)) of the polymer, and \( L \) the \((w/w)\) drug loading. Then the estimated porosity is given by

\[
(1) \quad \varepsilon = 1 - \frac{(1-L)W}{\rho_p V}.
\]

For a disk of depth \( d \) and radius \( r \),

\[
(2) \quad V = \pi r^2 d.
\]

Equations (1) and (2) together yield

\[
(3) \quad \varepsilon = 1 - \frac{(1-L)W}{\rho_p \pi r^2 d}.
\]

For EVAc, \( \rho_p = 965 \text{ mg/cm}^3 \) [2]. Since the cork borer used has an inner diameter of 1.18 cm, \( r = 0.59 \text{ cm} \). \( L \), \( W \), and \( d \) are measurements from section 3.2. The last column of table 1 contains the average estimated porosity values, plus their respective standard deviations.

For \((\text{BSA, } 90-106 \mu\text{m})\), the average porosities are almost equal to the \((w/w)\) loadings. This is also true for \((\text{BSA, } 150-180 \mu\text{m})\), for \( L = 0.05-0.35 \). There was a large increase
in porosity for L=.40-.50. This corresponds to the sharp drop in weight at those loadings. Apparently there was a lot of air incorporated into those slabs during casting.

For BSA, (PS=300-425\,\mu m, L=.05), the computed porosity was 0.00. This may be due to a faulty measurement, most likely of d. For L=.10,.15,.20, the porosities follow the loadings closely. At L=.25, porosity increases to .32.

**IV.3.4 Kinetics**

**IV.3.4.1 Axes of graphs**

Kinetic curves are presented and discussed in this section. These curves represent 1197 hours (50 days) of release. Each point represents the average of five disks at a loading-particle size condition, and the error bars are ±1 standard deviation. The kinetic curves are plotted in a dimensionless (reduced) form. The abscissa is the square root of the reduced time \( \Theta = D_0 t/d^2 \), where \( D_0 \) is the diffusion coefficient (cm\(^2\)/hr) of the drug at infinite dilution in water, and \( d \) is the depth of the disk (cm). The ordinate is the cumulative fraction of drug released \( F_\Theta \), defined as the ratio of the cumulative mass of drug released to the mass of drug originally incorporated in the disk.

Using the dimensionless parameters \( \Theta \) and \( F_\Theta \) facilitates
comparison across experimental conditions, as well as between experiment and theory. $F_\theta$ reflect the release rate per drug molecule. $\theta$ normalizes the effects of matrix depth and the diffusion coefficient of the drug. Plotting $F_\theta$ versus $\theta$ therefore allows the effect of the pore structure of the matrix on diffusion to be studied.

IV.3.4.2 Bovine Serum Albumin

Release kinetics for BSA are shown in figure 2-4. Figures 2 and 3 display results for particle sizes 90-106µm and 150-180µm, respectively. In both cases, the full spectrum of drug loading was tested. Because the curves are bunched at the lower loadings (figs. 2a and 3a), separate graphs were made to enlarge the $F_\theta$ axis and show the low loading curves in more detail (figs. 2b and 3b). For 300-425µm (figure 4), only the low loadings were tested. The diffusion coefficient of BSA was taken to be $2.52 \times 10^{-3}$ cm$^2$/hr [4].

First consider figures 2a and 3a. The two plots show marked similarities. In both cases, drug escapes at an extremely slow rate for loadings less than or equal to .20. As loading increases, the fractional release rate increases. It appears, however, that for loadings less than or equal to .40, release progresses to a certain point, after which it almost stops. There is a tendency for the kinetic curves to
Figure IV.2 Release kinetics of Bovine Serum Albumin (PS=90-106µm), plotted in reduced form.

\[ D_0 = 2.52 \times 10^{-3} \text{ cm}^2/\text{hr.} \]

a) All loadings.
b) Low loadings.
BOVINE SERUM ALBUMIN 90-106um

WEIGHT LOADLING

- 0.50
- 0.45
- 0.40
- 0.35
- 0.30
- 0.25
- 0.20
- 0.15
- 0.10
- 0.05
- NO MATRIX

\[ \theta^{1/2} = \sqrt{D_0 t} \frac{1/2}{d} \]

Figure IV.2a
Figure IV.2b
Figure IV.3. Release kinetics of Bovine Serum Albumin (PS=150-180μm), plotted in reduced form.

\[ D_0 = 2.52 \times 10^{-3} \text{ cm}^2/\text{hr} \]

a) All loadings.
b) Low loadings.
BOVINE SERUM ALBUMIN 150-180um

Cumulative Fraction Released $F_0$

$\sqrt{a} = \sqrt{D_0 t/d}$

Figure IV.3b
Figure IV.4. Release kinetics of Bovine Serum Albumin (PS=300-425µm), plotted in reduced form.

\[ D_0 = 2.52 \times 10^{-3} \, \text{cm}^2/\text{hr.} \]
"hunch over" as loading decreases. That is, concave downward deviations from $t^{1/2}$ kinetics become more apparent with lower loadings.

Figures 2b and 3b show the release behavior at low loadings in more detail. For $L=.05-.20$, it appears that there is an initial burst, followed by extremely slow release. Notice, however, that even at the lowest loadings, there is a small amount released at all timepoints, i.e. release never stops completely.

Figure 4 shows results for (BSA,300-425μm). As in figures 2 and 3, it appears that for $L=.05-.20$, there is a short burst, after which there is an extremely slow but steady $t^{1/2}$ ($\theta^{1/2}$) release of the drug. For $L=.25$, the release is smoother (i.e. no discrete burst). It should be recalled, however, that the $L=.25$ slab is anomalously thin due to differences in the casting procedure (section 3.2).

The cumulative fraction released for the short bursts seen in figures 2b, 3b, and 4 appears to be independent of the loading for $L<.20$, but dependent on particle size. As particle size increases, so does the fraction of drug released in the burst phase. (The values of $F_\theta$ at the end of the burst are approximately .03, .06, and .20 for PS=90-106μm, 150-180μm, and 300-425μm, respectively.) A rough explanation of this trend is that a certain fraction of the incorporated
drug lies on the surface of the disk and is released quickly when the polymer is immersed. For larger particle sizes, it is more likely that a given particle will lie in part on the surface of the disk. The model presented in chapter V quantifies this explanation and does predict the observed trend, although that model predicts higher release levels overall.

A comparison between the THIN disks (90-106 μm, L = .10) and disks at (90-106 μm, L = .10, .15) of the main sequence is shown in figure 5. Because d for the THIN disks is small, the abscissa is expanded. This explains why the burst appears longer for the THIN disk. The value F₀ is higher for the THIN disks than for the main sequence disks because the thinness of the THIN slab implies that a greater fraction of drug particles can touch the surface.

**IV.3.4.4 β-lactoglobulin and Lysozyme chloride**

Kinetic curves for β-lactoglobulin and lysozyme chloride are shown in figures 6 and 7, respectively. The diffusion coefficients for β-lactoglobulin and lysozyme chloride were taken to be 2.82x10⁻³ cm²/hr and 3.74x10⁻³ cm²/hr, respectively [5,6].

For β-lactoglobulin, the loading effect is qualitatively consistent with the observations for BSA. However, the
Figure IV.5. Release kinetics of Bovine Serum Albumin from THIN slab (PS=90-106μm, L=.10), plotted in reduced form.

\[ D_0 = 2.82 \times 10^{-3} \, \text{cm}^2/\text{hr.} \]
BETA LACTOGLOBULIN

Figure IV.6 Release kinetics of β-lactoglobulin, plotted in reduced form.

\[ D_0 = 2.82 \times 10^{-3} \text{ cm}^2/\text{hr.} \]
Figure IV.7 Release kinetics of lysozyme chloride, plotted in reduced form.

\[ D_0 = 3.74 \times 10^{-3} \, \text{cm}^2/\text{hr}. \]
particle size comparison at $L=.10$ gives reversed results—at
the larger particle size, less drug escapes.

Lysozyme chloride shows a burst of release for all three
conditions displayed, followed by a definite slow phase. The
slope of this slow phase is considerably larger than that
observed for BSA and $\beta$-lactoglobulin. There is a reversal in
rate-of-release behavior for lysozyme chloride—for
PS=300-425$\mu$m, the $L=.10$ disks release much faster than the
$L=.30$ disk.

IV.4 Discussion

IV.4.1 Tortuosities and retardation factors

If there were no matrix providing resistance to the
diffusing drug molecules, then the release kinetics, in
reduced form, would follow the equation [7]

\[ F_\theta = 1 - \frac{(8/\pi^2)}{2} \sum_{n=0}^{\infty} e^{-(2n+1)^2\pi^2\theta/(2n+1)^2}. \]

(This assumes that the diffusion coefficient is constant.)
During the early stages of release, $(F_\theta < .6)$, equation (1) has
the simpler form [7]

\[ F_\theta = \frac{(4/\sqrt{\pi})\theta^{1/2}}{2}. \]
Equation (1) is plotted as the dashed "NO MATRIX" curve in figures 2a, 3a, and 4. It is quite clear that the EVAc matrices provide significant retardation of the release, even at the highest loadings.

If the actual kinetic curves in figures 2-7 were linear in $\theta^{1/2}$, then a simple assessment of the retardation due to the matrices would be obtainable. Suppose a kinetic curve has the form

\[
F_\theta = a\theta^{1/2}.
\]

The ratio $R$ of the time required for release from a matrix (eq. 3) to reach a fixed level of $F_\theta$ to the time required for release given NO MATRIX (eq. 2) to reach that level is

\[
R = 16/\pi a^2.
\]

(Note: the ratio of reduced times is equal to the ratio of real times.)

Assume further that retardation is due to an increase in the path length the drug molecules must negotiate. Then the tortuosity factor $\tau$ is equal to the square root of the retardation factor $R$, so that

\[
\tau = R^{1/2} = 4/a\sqrt{\pi}.
\]
The kinetic curves in figures 2-7 are generally not linear in $\theta^{1/2}$, but are concave downwards. Therefore no consistent method exists for comparing the kinetic curves with the "NO SLAB" curve. However, an arbitrary procedure was devised to compute retardation factors and tortuosities. This procedure allows comparison with the modelling results of chapter V.

The method consists of estimating the slopes of the kinetic curves at an early stage of release, but after the original burst. For each curve, the slope

\[(6) \quad a = \frac{(F_{\theta_4} - F_{\theta_2})}{(\theta_{4}^{1/2} - \theta_{2}^{1/2})} \]

was computed, where $\theta_2$ and $\theta_4$ are the values of $\theta$ corresponding to the second and fourth timepoints, respectively. This value of "a" was then plugged into (4) and (5) to yield values of $R$ and $\tau$.

As stated, this method is completely arbitrary. Choice of other timepoints for determining slopes will lead to quite different results. However, as long as the method is applied consistently, it can be used to make comparisons with theory, if a similar procedure is applied to the theoretical curves. This will be done in chapter V.

Computed values of $\tau$ and $R$ are given in table 2. Of
**Table IV.2** Average porosities, tortuosities, and retardation factors.

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<th>Porosity</th>
<th>Tort. Retardation</th>
</tr>
</thead>
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<td>(\tau)</td>
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<td>0.36</td>
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<td>(\tau)</td>
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<th>Tort. Retardation</th>
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<tr>
<td>0.30</td>
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**Notes:**
- BOVINE SERUM ALBUMIN 90-106\(\mu\)m
- BOVINE SERUM ALBUMIN 150-180\(\mu\)m
- BOVINE SERUM ALBUMIN 300-425\(\mu\)m
- BOVINE SERUM ALBUMIN THIN 90-106\(\mu\)m
- \(\beta\)-LACTOglobulin 106-150\(\mu\)m
- \(\beta\)-LACTOglobulin 300-425\(\mu\)m
- LYSOZYME CHLORIDE 106-150\(\mu\)m
- LYSOZYME CHLORIDE 300-425\(\mu\)m
interest is that when comparing BSA (90-106μm) to BSA (150-180μm), the values of T and R are quite similar for equal loadings (especially L>0.25). Also, the tortuosity for the THIN slab (PS=90-106μm, L=.10) is quite similar to the tortuosity for the main sequence BSA (PS=90-10μm, L=.10) slab. At the largest particle size (300-425μm), the tortuosities for BSA disks are lower than the tortuosities measured at similar loadings for the smaller particle sizes. The tortuosities assessed for β-lactoglobulin are close to those measured at corresponding particle sizes and loadings of BSA. The tortuosities for lysozyme chloride are anomalous, reflecting the anomalous behavior of the release curves.

IV.4.2 "Fast" and "slow" phases of release

One of the consequences of the conceptual model presented in chapter II is that at low loading and particle size there should be a significant fraction of drug that is trapped in the polymer matrix, one would expect a premature halt in the drug release after a certain time. As seen in figures 2b, 3b, 4-7, this is not the case. It appears that, at low loadings, release begins with a burst, followed by extremely slow release that follows $t^{1/2}$ ($\theta^{1/2}$) kinetics. It also appears that the slope of the kinetic curves after the burst are approximately the same for L=.05,.10,.15,.20. The slopes after the original burst cluster around the value
\[ a = \frac{dF_\theta}{d\theta^{1/2}} = 0.006. \]

Plugging this value of "a" into equation (6) yields a retardation factor of about 160000.

The persistent, extremely slow release of drug after the burst in disks with low loadings implies that the conceptual model of release from chapter II must be modified. This will be done without abandoning the central theme, however. It is now assumed that release from EVAc matrices proceeds in two phases. The first, or "fast" phase is the evacuation of the interconnecting porous network that extends to the surface of the matrix. The second, "slow" phase is the release of "trapped" drug by an unidentified mechanism.

A strong candidate for the mechanism of the slow phase release is diffusion through defects in the polymer matrix. These defects could be caused by trapping of air as a result of vortexing during fabrication of the slabs, or by the solvent evaporation process.

It will be assumed now that when the release rate from any disk drops below a certain point, then the fast phase is completed. Specifically, if \( \frac{dF_\theta}{d\theta^{1/2}} \) falls below 0.006 (see above), the fast phase is assumed terminated. This criterion allows estimation of the total fraction \( F_m \) of incorporated drug that is in the pore space connected to the matrix.
Table 3 lists the values of $F_\infty$ derived using the above criterion for the disks used in the experiments of this chapter. Figure 8 is a plot of the BSA data in table 3. It is seen that at low loadings, $F_\infty$ increases with particle size. At high loadings, there exists data only for 90-106$\mu$m and 150-180$\mu$m. Because the latter particle size yielded higher porosities than the former, the results for the latter are shifted to the right. If the plot were of $F_\infty$ versus $L$, the points at higher loadings would lie on top of each other.
<table>
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<td>0.04</td>
</tr>
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<td>0.07</td>
</tr>
<tr>
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<td><strong>β-LACTOGLOBULIN</strong>&lt;br&gt;300-425 μm</td>
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<td>0.38</td>
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<td><strong>LYSOZYME CHLORIDE</strong>&lt;br&gt;106-150 μm</td>
<td>0.10</td>
<td>0.07</td>
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<td><strong>LYSOZYME CHLORIDE</strong>&lt;br&gt;300-425 μm</td>
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Table IV.3. Average fraction F∞ of incorporated drug that is connected by pores to the surface.
Figure IV.8 Total fraction $F_{\infty}$ of originally incorporated drug that is released during "fast" phase, as a function of volume loading (porosity) and particle size. Porosities obtained from table 1.
REFERENCES


CHAPTER V. MODELLING THE INCOMPLETENESS OF RELEASE

V.1 Introduction

Previous results, discussed in chapter II, indicate that for low drug loadings, a fraction of the originally incorporated drug remains in the matrix after the release is complete, i.e. there exists trapped drug. At the end of chapter II, a heuristic model was given to explain this phenomenon (see figure II.3). Basically, it was assumed that the drug particles are situated randomly within the matrix. When drug particles are released, they leave behind a porous carcass. Connections between particles allow some of the particles to communicate with the release medium. At low loadings, only particles near the surface can connect to and release their contents into the release medium.

In chapter IV it was shown that this picture is almost correct. After the original "burst" of drug release at low loadings, there is an extremely slow but persistent release of drug. The mechanism for the latter phase is unknown.

The results of chapter IV do not alter the fundamental picture of release, however. It is still possible to maintain that almost all release occurs through the pore network. In keeping with the basic hypothesis on the release mechanism, the data of chapter IV was analyzed with the slow
In chapter III it was indicated that percolation theory describes some similar results from other fields. However, it was pointed out that percolation theory deals with systems in which the characteristic grain size (in the present case, the drug particle size) is much smaller than the characteristic size of the whole system (in the present case, the depth of the matrix) [1,2]. Moreover, percolation theory would predict the size of a cluster of drug particles (and therefore pores) that spans the whole matrix [1,2]. In the EVAc sustained release system, small clusters bordering the surface of the matrix also contribute to release, and these are not counted in typical percolation studies. Thus, there is no theory in the literature with which a direct comparison of the data of chapter IV can be made.

This chapter consists of computer simulations of desorption of drug from matrices that are modelled as percolation lattices. Both the total fraction of drug released and the shape of the release kinetic curves are studied. Section 2 describes the computer representation of the matrix. Section 3 describes the algorithm for computing the total fraction of drug released and presents the results as functions of particle size and loading. Section 4 describes the program for simulating release kinetics and presents the corresponding results. In section 5,
comparison's are made between the theoretical results and the experimental results of chapter IV. It is shown in section 5 that the random pore topology in the simulation does not suffice to explain the slow release observed experimentally. This motivates the work of chapter VI.

V.2 Computer representation of the matrix

The two important lengths characterizing a sustained release matrix are the depth $L$ of the matrix and the drug particle diameter $d_p$. The matrix can be considered to be $N_p = L/d_p$ particles thick.

A simple representation of a random dispersion was chosen for the simulations. The dispersion is modelled as a simple cubic lattice with dimensions $64\times64\times N_p$. That is, there are $N_p$ layers of lattice sites (cubes), and each layer consists of $64\times64 = 4096$ cubes. (It was found convenient to represent lattice sites as bits on a VAX word that is 64 bits long.) Each cube is "filled" either with polymer or with drug. The probability that a given cube is filled with drug is specified by the volume loading, or porosity $\varepsilon$, of the matrix. The fillings of any two cubes in the lattice are statistically independent. That is, whether cube A is filled with drug or polymer does not influence how cube B is filled. The filling of the lattice sites is executed by the VAX MACRO subroutine RANDM, which is listed in appendix II.
The two important fabrication variables, drug loading and drug particle size, can be represented in this scheme. Drug loading is represented via the porosity, or volume loading. It should be noted that the drug loading is normally taken as a weight fraction. Therefore a translation between drug loading and porosity must be derived, either theoretically or experimentally, in order to use the drug loading as a parameter for the present simulation scheme. The second fabrication parameter, drug particle diameter, enters the simulation via the lattice depth $N_p$, once the matrix depth $L$ is specified.

An example of a lattice is shown in figure 1. In this example, $N_p=6$, so the lattice might represent a matrix of depth 1 mm, with drug particle size 150-180 μm. Alternatively, it could represent a matrix of depth 1.5 mm, with drug particle size ~250 μm. For clarity, figure 1 shows only a 10x10x6 core of the full 64x64x6 lattice. Polymer-filled cubes are represented by dashes "-" and drug-filled cubes are marked by "D". The volume loading (porosity) for this example is 0.25. Note that to model a 1 mm deep matrix with a larger drug particle diameter (say 300-425 μm), one simply changes $N_p$ to 3, so that only three layers of the lattice are included in the simulation.

In this chapter a lattice coordinate system is used to facilitate explanations. Each lattice site has coordinates
FIGURE V.1. Illustration of lattice representation of polymer/drug matrix. "-" indicates polymer, "D" indicates drug. Drug particle on lattice site (4,5,3) is circled, and its neighbors are circumscribed by squares. $N_p=6, \varepsilon=0.25$
(r,c,l), corresponding to (row,column,layer). The coordinates r and c vary from 1 to 64, and l varies from 1 to \( N_p \). For example, the encircled drug particle in figure 1 has coordinates (4,5,3).

The lattices described can only provide crude representations of actual controlled release matrices. First, real drug particles do not line up with their centers on sites of a regular lattice. Rather, they are distributed such that the drug particle centers can appear anywhere in the matrix, subject to the constraint that two particles cannot overlap. Thus the very existence of layers is artificial, so that \( N_p \) is a rough parameter. Second, drug particles are not cubic, but are irregularly shaped. However, as evidenced by many studies in percolation theory (see chapter III), these differences should not lead to qualitative differences in model predictions.

V.3 Calculation of total amount of drug released

V.3.1 Description of algorithm

A very simple algorithm was chosen to calculate the total fraction of drug released from the simulated matrices. The main driver for the algorithm is coded as the FORTRAN program USEFUL2, which is listed in appendix II.
Before describing the algorithm, a few definitions are required. Two lattice sites are considered "neighbors" if one and only one of their lattice coordinates differs by 1. If one views the lattice sites as cubes, then two cubes are considered neighbors if they share a square face. In this scheme, diagonally adjacent lattice sites are not neighbors. The neighboring lattice sites of the encircled drug particle of figure 1 are indicated by circumscription with a square. Two drug particles are considered "neighbors" if they are situated on neighboring lattice sites on the simple cubic lattice. Two drug particles are said to be "connected" if there is a chain of neighboring drug particles between them. A "cluster" consists of all drug particles connected to a single drug particle.

A drug particle is considered releasable, and marked by a "§", if it belongs to a cluster that extends to the surface of the matrix. The macromolecules in that particle will eventually find their way out of the matrix through the pore space that is formed around the cluster. If the particle belongs to a cluster that does not extend to the surface of the matrix, then that drug particle is "trapped" within the polymer and cannot release its molecules. (Recall that the polymer is impermeable to macromolecules.) In this case, the particle is marked by a "T".

With these definitions, the algorithm for determining
the releasable fraction of drug can be described. First, all surface lattice sites containing drug are releasable, so the surface drug particles are marked with "$"'s. The surface lattice sites are the top and bottom layers, i.e. $l=1$ and $l=\text{N}_p$. This corresponds to the assumption that drug release occurs through the two broad faces of a matrix. (The consequences of altering this assumption are discussed in section 3.4.) After the initialization, an iterative routine ensues. Each iteration consists of a pass through the lattice in which drug particles are marked with a "$" if they are neighbors to drug particles that are already marked by a "$". After several iterations, all releasable drug particles are marked with a "$". When there is no change in the particle markings, the iterative procedure is terminated. All drug particles not marked with a "$" are then marked with a "T".

The algorithm for determining which drug particles are marked with a "$" is coded in VAX MACRO and listed in appendix II as the subroutine ESCAP2.

The result of the iterative process, when applied to the example lattice of figure 1, is shown in figure 2. To illustrate the algorithm, first consider the particle at site (4,2,3), marked by a circle. It is connected to the surface via the chain of particles (4,1,3), (4,1,2), (3,1,2) and (3,1,1). This chain is marked by diamonds in the figure.
FIGURE V.2. Result of iterative process determining releasable and trapped drug, applied to figure 1. "-" indicates polymer, "$" indicates releasable drug, and "T" indicates trapped drug. Chain of drug particles connecting circled drug particle at (4,2,3) is indicated by circumscription by diamonds. Trapped drug particle at (4,6,2) is circumscribed by a square.
Thus the particle at (4,2,3) is releasable, so it is marked with a "$". On the other hand, the drug particle at site (4,6,2) (marked by a square), is surrounded by dashes "-" (polymer), so it is trapped and thus marked with a "T".

After the iterative routine, the MACRO subroutine COUNTD (see appendix II) counts the number of "$"'s, and also counts the total number of drug filled sites (i.e. "D"'s). The quotient of these two numbers is taken to be the fraction of releasable drug.

V.3.2 Results and Discussion

Simulations were run for $N_p=2,3,4,7,10,12,15$. The results are shown in figure 3. Each point represents an average taken over 10 realizations of random lattices with depth $N_p$ and volume loading $\epsilon$. The case $N_p=2$ is trivial, since the lattice consists only of a top and bottom layer, and all the drug particles in those layers are releasable.

Figure 3 shows that the total fraction released increases with volume loading, and decreases with the number of layers. Clearly, as volume loading increases, the opportunity for a particle to have neighbors increases, so its chances of being in a cluster extending to the surface increases. With fewer layers, a particle can connect to the surface via smaller clusters which can exist at lower volume
Figure V.3. Results of computer simulation of total fraction drug released as a function of volume loading $\varepsilon$ and number of lattice layers $N_p$. 
loadings.

The second result, of course, translates into the prediction that with larger particle sizes at a fixed volume loading, the fraction of releasable drug will increase.

If \( F_\infty \) is the total fraction released and \( \varepsilon \) is the volume loading, then the following limits must hold:

\[
(1) \quad \lim_{\varepsilon \to 0} F_\infty = \frac{2}{N} = \frac{2d_p}{L},
\]

and

\[
(2) \quad \lim_{\varepsilon \to 1} F_\infty = 1.
\]

Both limits are evidenced in figure 3. Limit (1) is a consequence of the fact that two of the \( N_p \) layers are surface layers, and always will release their contents. As \( \varepsilon \to 0 \), the chances of making contact to deeper layers vanishes proportionally to \( \varepsilon \). Limit (1) holds for all homogeneous lattice models of a porous matrix. It will also hold approximately for any model that assumes homogeneous drug distribution, especially for \( d_p \ll L \). Limit (2) is obvious. It is interesting, however, that limit (2) is nearly reached at \( \varepsilon = 0.5 \).

An interesting feature in figure 3 is that the
transition between the region of a small total fraction released to the region of a large fraction released becomes sharper as the number of layers \( N_p \) increases (or the particle size decreases). This is because when \( N_p \) is small, large and small clusters contribute to the releasable drug fraction; when \( N_p \) is large, the majority of the releasable particles come only from the large clusters which do not appear until the volume loading gets larger. As \( N_p \to \infty \), the curves in figure 3 should approach the percolation probability curve for the simple cubic lattice (see section 3.3).

Figure 4 is a heuristic aid for understanding the results of figure 3. Shown are lattices generated for \( \varepsilon = 0.10, 0.30, \) and 0.50, with \( N_p = 6 \). For \( \varepsilon = 0.10 \), practically all releasable drug lies on the surface layers. For \( \varepsilon = 0.30 \), some but not all of the interior drug becomes releasable, because clusters can now be formed. (If \( N_p \) is made larger, then a very clear gradient in the amount of releasable drug can be seen as one proceeds deeper into the lattice at \( \varepsilon = 0.30 \)). For \( \varepsilon = 0.50 \), the clusters are so large that practically all drug particles are releasable. Figure 3 indicates that this will be true no matter how large \( N_p \) is. This will be discussed below.

V.3.3 Comparison to percolation theory

As indicated in section 1, the present simulations are
Figure V.4. Distribution of trapped and releasable drug for three volume loadings $\varepsilon$. $N_p=6$. a) $\varepsilon=.10$, b) $\varepsilon=.30$, c) $\varepsilon=.50$. 

Layer 1 (top) 

Layer 2 

Layer 3 

Layer 4 

Layer 5 

Layer 6 (bottom)
aimed at a slightly different problem than that approached by percolation theory. One difference is that, in order to percolate, a cluster of pores (lattice sites) must reach both surfaces of the matrix (lattice). In the simulations of section 3.1, clusters connected to one of the lattice surfaces are identified.

Simple modifications to the programs of appendix XX permit computation of the percolation probability $P$ as a function of $N_p$ and $\varepsilon$. The results are shown in figure 5, which can be compared with figure 3. One clear difference is that for small $\varepsilon$,

$$\lim_{\varepsilon \to 0} P = 0$$

regardless of $N_p$. Moreover, for all $N_p$ and $\varepsilon$,

$$F_{\infty} > P$$

Limit (3) is due to the fact that as $\varepsilon \to 0$, all particles become isolated and therefore cannot belong to clusters connecting to both faces. Inequality (4) is a consequence of the fact that in order for a particle to be connected to both surfaces, it must be connected to at least one. $P$ does tend to approach $F_{\infty}$ as $N_p$ and $\varepsilon$ increase, however.

Figures 6a,b show a comparison of $P$ and $F_{\infty}$ for $N_p=4$ and
Figure V.5. Results of computer simulation of percolation probability as a function of volume loading $\varepsilon$ and the number of lattice layers $N_p$. 
Figure V.6. Comparison of total fraction released $F_\infty$ and percolation probability $P$ as a function of volume loading $\varepsilon$ for two lattice depths $N_p$. a) $N_p=4$, b) $N_p=15$. 
For $N_p = 15$, respectively. For $N_p = 4$, the surface effects are quite pronounced, and much drug can be released, though not through pore clusters that extend through the matrix. For $N_p = 15$, the surface effects are lesser and a greater fraction of drug is situated in percolating clusters.

These comparisons show that a membrane's "face-to-face" permeability is not necessarily equivalent to its capacity for releasing drug. This may explain unpublished observations that some spent EVA$_c$ matrices are impermeable to drug.

It has been shown [1] for a simple cubic lattice, that at $\varepsilon = 0.50$, virtually all filled sites in a lattice belong to a cluster of infinite extent. This explains the result that for $\varepsilon = 0.50$, practically all drug is releasable, regardless of $N_p$.

V.3.4 Effect of release from matrix rim

A typical sustained release matrix used in the experiments of chapter IV was a disk of diameter 1.2 cm and depth .15 cm. For a drug particle size of 90-106$\mu$m, this means that a "true" representation in a lattice should be a cylinder with diameter of 120 lattice sites and depth 15 sites. (The lattice sites are still cubical, however). This is somewhat larger than the 64x64x15 lattice provided in the
simulations described above. For a drug particle size of 300-425\(\mu\)m, a cylinder-shaped lattice of diameter 20 sites and depth of 4 sites is appropriate. This is smaller than the 64x64x4 lattice used above. Furthermore, in the experiments of chapter IV, release was allowed through the rims of the polymer disks, while for the above simulations, release was only allowed to occur through the two 64x64 faces of the cubic lattice.

For a disk-shaped matrix of diameter \(\alpha\) and depth \(L\), the ratio \(R_A\) of areas of the matrix rim to the area of the two flat faces combined is given by

\[
(5) \quad R_A = \frac{\pi \alpha L}{2 \pi \left(\frac{\alpha}{2}\right)^2} = \frac{2L}{\alpha}.
\]

For the case \(L = 0.15\) cm, \(\alpha = 1.2\) cm, (5) predicts \(R_A = 0.25\). In other words, the simulation described in section 3.1, which does not allow release through the rim, might underpredict release by as much as 25%.

Therefore, it was felt necessary to test whether the results of the simulations presented above are sensitive to the size of the lattice and the boundary condition imposed at the rim of the lattice. This was done using a slightly modified version of USEFUL2. In this version, cylindrical lattices were generated with diameter 8 times the depth (this is the worst case, corresponding to the example of the
previous paragraph). Thus $\alpha$ was chosen to be $8N_p$. For $N_p < 8$ this led to a lattice that fit within the original $64 \times 64 \times N_p$ lattice. For $N_p > 8$, it was necessary to truncate the cylinder to fit the $64 \times 64 \times N_p$ lattice. The simulation was then run for the cases where release can and cannot occur through the rim lattice sites. The values of $F_\infty$ were then compared for the two cases.

Typical results are shown in figure 7. It is seen that the case of release through the rim does predict greater release than the case of no release through the rim. However, it is also seen that the effect is actually quite small. Relative differences of up to 16% are seen, but they tend to occur at the lower loadings. Thus the absolute predictions do not change by much. At higher loadings, drug particles that are releasable through the rim are also likely to be releasable through the flat faces of the disk.

It should be noted that for the cases with $N_p > 8$, the two curves do not represent the full size matrices, and they lie outside the predictions that would have been given if the full sized cylindrical matrices were allowed.

The results of the modified simulations indicate that the simpler $64 \times 64 \times N_p$ matrices are adequate for the present modelling purposes.
Figure V.7. Comparison of total fraction released $F_\infty$ as a function of volume loading $\varepsilon$ between lattices that allow release through their rims (uncoated) and lattices that do not allow release through their rims (coated).
V.4 Simulation of desorption (release) from random lattices

V.4.1 Introduction

The previous section was concerned with calculation of the final total fraction of drug released from a matrix represented by a random lattice. No assumptions were made as to how the drug would be released, and kinetic curves were not computed. Kinetic curves are computed in this section, under the assumption that drug molecules execute random walks on the available lattice sites (i.e. those filled with "$\$"'s). Such random walks are an approximation to diffusion within the pore space.

The simulations serve two purposes. First, they can determine whether random pore topology can produce retardations in release comparable to those seen in the experiments of chapter IV. Second, the simulations give some insight into the shapes of the kinetic curves seen in chapter IV.

V.4.2 Description of the algorithm

Suppose a drug molecule originates at time $T=0$ in lattice cell $(r_0,c_0,l_0)$, and that cell is marked by a "$\$". Then the drug molecule can diffuse out of the lattice. It is
assumed that the molecule is a "tracer" that can diffuse freely within the cluster containing \((r_0, c_0, \lambda_0)\). The diffusion of the tracer molecule can be thought of as a random "hopping" of the molecule from site to site in the releasable cluster.

In the present simulation, the clusters are seen to be open pore space available to a tracer molecule. Physically this means that the drug in all the pores is assumed to be dissolved, and that drug molecules do not interact with each other.

A necessary input to the simulation is the "hopping time," or "residence time" of a molecule in a pore (the two times are identical). In a real matrix, the residence time in a pore is stochastic. However, in the simulation it is assumed that the molecule's residence time is deterministic, and dependent only on the number of neighboring pores ("\$" lattice sites). Specifically, if \(N_{rc\lambda}\) is the number of "\$" sites bordering site \((r,c,\lambda)\), then the residence time for a molecule at \((r,c,\lambda)\) is given in this simulation by

\[
T_{rc\lambda} = \frac{6}{N_{rc\lambda}}.
\]

A site surrounded by six other "\$" sites (the maximum possible in the simple cubic lattice) will then have a residence time of 1. On the other hand, a "dead-end" "\$"
site, which is connected to only one other "$" site, will have a residence time of 6.

The form (6) for the hopping time will be justified in chapter VI. Intuitively, it can be argued that a molecule will leave a cubic site by making repeated attempts at passing through one of the six faces of the cube. Its probability of success on a particular attempt will be equal to $N_{rc}/6$, so the expected number of attempts before success will be given by equation (6).

A dummy lattice site representing the outside of the lattice is added to the simulation. The dummy site is considered a "neighbor" to all surface lattice sites, and might be identified with layers 0 and $N_p+1$. This allows the molecule to leave the lattice, completing the random walk.

The basic simulation step can now be described. Assume that at time $T$, the tracer is situated at site $(r,c,\lambda)$. The number of neighboring lattice sites $N_{rcl}$ and the residence time $T_{rcl}$ are first determined. The simulation then chooses at random (with uniform probability), one of the neighboring sites, and moves the molecule to that site. $T_{rcl}$ is then added to the running time $T$, and the lattice coordinates $(r,c,\lambda)$ are updated. If the new $\lambda$ is either 0 or $N_p+1$, then the molecule has left the lattice (i.e. moved to the dummy site), and the process is terminated. Otherwise, the
simulation step is repeated at the new site.

The tracer molecule was started once at each "$" site on a lattice. Since there are $64 \times 64 = 4096$ sites per layer, this means that approximately $4096N_p e$ walks were performed through the lattice. The final times $T$ required for a tracer to leave the lattice were tabulated as a frequency distribution function $p(T)$. After all the walks were completed, the cumulative fraction released as a function of time, $F_t$, was computed using

$$ F_t = \int_0^T p(T) \, dT. $$

The programs for the simulations are listed in appendix II. The main driver routine is RRWALK, coded in FORTRAN. RRWALK calls the MACRO subroutines RANDM, ESCAP2, and COUNTD, which are described in section 3. There are two other MACRO subroutines, NABOR2 and RAND01. NABOR2 scans the lattice and identifies which "$" sites have left, right, forward, backward, upper and lower neighbors. RAND01 returns a random number uniformly distributed between 0 and 1. Finally, there is a FORTRAN subroutine called NABPR which counts the number of neighbors around a "$" site.

A simulated kinetic curve, which shows the cumulative fraction of drug released as a function of a normalized time, is obtained by plotting $F_t$, calculated using (7), against
The normalization by $N_p$ reflects the fact that $N_p$ is the number of layers, and not the physical depth of the matrix.

V.4.3 Deterministic algorithms for comparison of results

As a standard for comparison, a deterministic computation of random walk in a lattice with $\varepsilon=1$ was performed. This computation will now be described.

Since for $\varepsilon=1$, all lattice sites have a "$\$" and each site has six neighbors, so the hopping time is 1. Let $\Pi^n_\ell$ be the probability that a tracer molecule is situated at a lattice site in layer $\ell$ at time step $n$. At the start of the simulation ($n=0$), the drug molecules are distributed uniformly across all layers, so

\[(8) \; \Pi^n_\ell = 1/N_p \; , \quad \ell=1,\ldots,N_p \; .\]

It is also assumed that the outside of the lattice is a perfect sink (absorber), so

\[(9) \; \Pi^n_0 = \Pi^n_{N_p+1} = 0 \; , \quad \text{for all } n .\]

Consider now the transitions that can occur in the lattice. A cell will receive the tracer at step $n+1$ with probability $1/6$ if any of its six neighbors has the tracer.
But four of the six neighbors are on the same layer as the cell of interest. Thus

$$\Pi^{n+1}_x = (1/6) \left( \Pi^n_{x-1} + 4 \Pi^n_x + \Pi^n_{x+1} \right).$$

Equations (8)-(10) constitute a set of difference equations that describe the probability profile during desorption from the full cubic lattice. To calculate the fraction $F_n$ released at time step $n$, one can use the equation

$$F_n = 1 - \sum_{n=1}^{N_p} \Pi^n_l.$$  

A test was also made to see how different the random walk is from a continuum diffusion. Equation (10) can be rearranged into the form

$$\Pi^{n+1}_x - \Pi^n_x = (1/6) \left( \Pi^n_{x-1} - 2 \Pi^n_x + \Pi^n_{x+1} \right),$$

which is a discretization for the diffusion equation

$$\frac{\partial c}{\partial t} = \frac{1}{6} \frac{\partial^2 c}{\partial x^2}.$$ 

The initial and boundary conditions (8) and (9) translate to

$$\Pi(x,t) = 1 \quad 0 < x < 1, \; t=0,$$

$$\Pi(0,t) = \Pi(1,t) = 0 \quad t > 0.$$

The cumulative fraction \( F_t \) released at time \( t \) was found by solving (13)-(15) and using the fact that

\[
(16) \quad F_t = 1 - \int_0^1 \Pi(x,t)dx .
\]

The solution to (13)-(16) is

\[
(17) \quad F_t = 1 - \left( \frac{8}{\pi^2} \right) \sum_{n=0}^{\infty} \left[ 1/(2n+1)^2 \right] e^{-\frac{(2n+1)^2}{4} \pi^2 t/6} .
\]

It is interesting to note that (12) has the coefficient \( 1/6 \). A corresponding derivation of random walk in one dimension would lead to a coefficient of \( 1/2 \) [3]. The reason for the difference is that there are more choices presented to the particle in three dimensions. This point is closely related to the choice of residence time given by equation (6).

**V.4.4 Results and Discussion**

Runs were performed for \( N_p = 4, 7, 12 \) and \( \varepsilon = .1, .2, .3, .4, .5 \). The values of \( N_p \) correspond to particle sizes that are close to the drug particle sizes used in the experiments. Assuming a matrix depth of 1.2 mm, \( N_p = 4, 7, 12 \) correspond to particle diameters 300\( \mu \)m, 170\( \mu \)m, and 100\( \mu \)m, respectively.

The simulation was typically run for only one realization of a lattice at a given \( N_p \) and \( \varepsilon \). The
simulation for \( N_p = 12 \) took over an hour of CPU time, so it was not practical to run simulations for different realizations given \( N_p \) and \( \varepsilon \). However, the large number of runs per lattice led to smooth kinetic curves. Moreover, preliminary runs, in which two realizations with the same \( N_p \) and \( \varepsilon \) were run, yielded kinetic curves that are almost identical. This is shown in figure 8.

The results for \( N_p = 4, 7, 12 \) are shown in figures 9a, b, c, respectively. Also shown are the respective exact solutions of (8)-(11) for the random walks for \( \varepsilon = 1 \), as well as the continuum diffusion solution given by (17). How close the discrete and continuum solutions are to each other determines how good an approximation the discrete random walk is. As expected, the discrete random walk and continuous diffusion curves converge as \( N_p \) gets large. In analyzing the simulation results, comparisons should be made against the exact discrete curve.

It should be emphasized that there is no absolute time scale for the results. (No mention of lengths or diffusion coefficients went into any of the derivations.) All comparisons are relative.

V.5 Comparison with data

V.5.1 Total fraction of drug released
Figure V.8. Cumulative fraction released $F_e$ simulated by RRWALK.
Two cases run at each volume loading.
Figure V.9. Simulated kinetics of random walk desorption from lattices whose sites are filled at random with drug. Five volume loadings ($\epsilon=.10,.20,.30,.40,.50$) were tested. Results are also shown for "straight" random walks [eqs.(8)-(11)] and for continuous diffusion [eq.(17)].

a) $N_p=4$
b) $N_p=7$
c) $N_p=12$
RANDOM WALK DESORPTION: 4 LAYERS

Figure V.9a
RANDOM WALK DESORPTION: 7 LAYERS

CUMULATIVE FRACTION RELEASED $F_c$

(SQRT TIME)/7

0.0 0.5 1.0 1.5 2.0 2.5 3.0

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Figure V.9b

- 0.50
- 0.40
- 0.30
- 0.20
- 0.10
- STRAIGHT RAND WALK
- STRAIGHT DIFFUSION

Note: The figure represents the cumulative fraction released over time for different layers in a random walk desorption process.
Random walk desorption: 12 layers

CUMULATIVE FRACTION RELEASED \( F_t \)

(SQRT TIME) / 12

0.0 0.5 1.0 1.5 2.0 2.5 3.0

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Figure V.9c

- 0.50
- 0.40
- 0.30
- 0.20
- 0.10

STRAIGHT RAND WALK
STRAIGHT DIFFUSION
Figure VI.8 presents data for the total fraction $F_\infty$ of drug released from BSA disks of various particle sizes and loadings. In figure 10 comparison is made to model predictions. $N_p$ was chosen assuming a matrix depth of approximately 1.2 mm, which is the value of the depth around which most disks clustered (table IV.1). For particle sizes 90-106 μm, 150-180 μm, and 300-425 μm (figures 10a,b,c, respectively), the values of $N_p$ were 12, 7, and 4, respectively.

The model does a poor job at fitting the data quantitatively, although the qualitative trends agree. Both the model and data show sharp transitions at low particle sizes, and weaker transitions as the particle size increases. The model always overpredicts the total fraction of releasable drug. This is especially true at low loadings.

If drug is homogeneously dispersed in the matrix, then the low-loading (low porosity) behavior of the theoretical curve should not be dependent on the higher order details of the drug distribution (e.g. lattice versus amorphous arrangement of drug particles). The disagreement at low loadings indicates that drug may not be homogeneously dispersed in the polymer. Apparently, drug prefers the center of the matrix, and avoids the surface. In some sense, the polymer seems to be "sheltering" the drug particles. The reason for the inhomogeneity is unclear. One might speculate...
Figure V.10. Comparison of results of the USEFUL2 simulation with experimental results of Chapter IV.

a) BSA, 90-106μm (Np=12)
b) BSA, 150-180μm (Np=7)
c) BSA, 300-425μm (Np=4)
Figure V.10a.
BOVINE SERUM ALBUMIN 150-180µm

Figure V.10b.
BOVINE SERUM ALBUMIN 300-425\mu m

THEORY (4 LAYERS)

DATA

Figure V.10c.
that during the drying of the slabs after casting, the polymer solution migrates to the surface of the slabs, moving past the relatively immobile drug particles.

A simple modification of USEFUL2 was programmed to simulate inhomogeneity in the matrices. A "surface factor," $s$, was defined, and the fraction of drug-occupied lattice sites was given by

$$
\varepsilon'(l) = \begin{cases} 
\varepsilon s, & l = 1, n_p \\
\varepsilon(N_p - 2s)/(N_p - 2), & l = 2, \ldots, N_p - 1 .
\end{cases}
$$

(18)

This distribution gives an overall volume loading of $\varepsilon$, but it shifts most of the drug-filled sites into the interior of the lattice.

The results of the simulation for (BSA,90-106µm) are shown in figure 11. For this case, the predicted total release fraction $F_\infty$ at $\varepsilon=.05$ is 0.18, while the observed $F_\infty$ is .03 (table IV.3). Thus, the surface factor $s$ was set to .15 ≡ (.03/18). This value was used for all loadings. As in the "homogeneous" simulation, $N_p$ was set at 12.

The modified model fits very well for $\varepsilon<.25$, but poorly for $\varepsilon>.25$. In fact, for $\varepsilon>.25$, the modified model is worse than the original, simpler model. This can be explained. By
Figure V.11 Comparison of data and predictions of the total fraction release $F_\infty$, for two models. Data is for BSA 90-106\(\mu\)m. "Homogeneous" model assumes drug particles are placed uniformly on lattice. "Surface" model assumes drug particle distribution given by eq. (18) with $s=0.15$. 

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HOMOGENEOUS THEORY

SURFACE THEORY

DATA
pushing drug-occupied sites into the interior of the lattice, those sites become more dense. The percolation threshold is then reached at a lower overall volume loading. Thus the interior becomes well connected. Now the probability is very high that at least one site of the percolating interior cluster can connect to the outside through a drug-filled surface site, even though the density of drug-filled surface sites is very low. Note that the curves for the homogeneous model and the "surface" model cross very near $\varepsilon = .3$, which is very close to the percolation threshold for a simple cubic lattice (figure 5).

Perhaps the postulated inhomogeneities disappear at higher loadings, and this too could be incorporated in the modelling. However, it is the author's opinion that more direct experimental assessment of the distribution of drug particles in the matrix is warranted before more complex models are attempted.

Similar results were obtained for simulations involving the other drug particle sizes.

In summary, neither the simple, homogeneous model nor the more complicated, "surface" model is able to account quantitatively for the total amount of drug released $F_\infty$. However, there are qualitative agreements on the behavior of $F_\infty$ as a function of drug loading and particle size. These
models are a first step towards understanding the topology of the drug particles embedded in the matrix, and its effect on the amount of releasable drug. More complex models should be preceded by more detailed microstructural data.

Before leaving this topic, it should be mentioned that a preliminary experiment, run under slightly different experimental conditions, produced results that were well fit by the model. This experiment, and the application of the model, are discussed in appendix III. The changes in the experimental conditions by themselves should not have altered the accuracy of the model. It is more likely that a nuance in the preparation of the EVAc matrices led to the difference in the results of chapters IV and V and the results presented in appendix III.

V.5.2 Rate of release

A very clear result is that the random pore topology cannot be the sole cause of the retardation of drug release. To see this, consider the curve for $N_p=12$, $\varepsilon=.50$ (figure 9c). The curve does show some retardation, in that it is not parallel to the straight random walk curve. A crude measure of the retardation is the quotient of the time it takes for the two curves to reach some level, say $F_t=0.6$. For the straight random walk, this occurs at $t_{1/2}/12 \approx 0.75$. For $c=0.50$, this occurs at $t_{1/2}/12 \approx 1.25$. Thus, the time
retardation factor is approximately \((1.25/0.75)^2 < 3\). This is orders of magnitude less than the retardation factors observed in the experiments of chapter IV.

The shapes of the simulated desorption curves as a function of volume loading are reminiscent of the experimental curves. As loading decreases, the curves become more hunched over. At all \(N_p\) and \(\varepsilon\), there is an initial "burst" that lies along the straight random walk curve. This corresponds to the desorption of surface particles. At low loadings, virtually all the releasable drug is released almost immediately.

Of course, the simulations were only designed to model the early, "fast" phase of release.
REFERENCES


CHAPTER VI. MODELLING THE SLOWNESS OF RELEASE

VI.1 Overview of Chapter

In chapters I and VI it was shown that release from EVAc matrices is orders of magnitude slower than would be expected from calculations (eq. I.1) involving the dimensions of the matrix and the diffusion coefficient of dilute protein in water. Since it has been shown that a network of waterfilled pore exists \[1\], and since EVAc itself is impermeable to proteins such as BSA, equation I.1 would seem to be the relevant equation. It was also argued in chapter I that channel tortuosity is not sufficient for explaining the slow release of macromolecules from the matrices. Finally, it was shown in chapter VII that the random pore topology cannot explain the overall retardation of release.

In this chapter, two explanations for the retardation of diffusion are investigated mathematically. The first hypothesis, analyzed in section 2, attributes the retardation to a physicochemical property of the protein molecule. The protein is in powdered form when the matrix is first cast, and most of the pore space is filled initially with the powdered drug. The drug solution inside the pores must be very highly concentrated, and therefore viscous. Thus the diffusion coefficient of the drug in the pores may be much lower than the diffusion coefficient of the drug in its
The analysis of section 2 will show, however, that concentration dependent diffusion, by itself, has only a minor effect on the rate of drug release.

The second hypothesis, analyzed in sections 3 and 4, attributes the retardation of release to the pore structure. Section 3 focuses on geometric features of single pores. It is seen in section 3 that equation I.1 is not relevant for length scales greater than that of a single pore, so that equation I.1 should not be expected to hold for porous EVAc matrices.

VI.2 Effect of concentration dependence on diffusion coefficients

VI.2.1 Introduction

Diffusion coefficients of proteins and other macromolecules depend on concentration. In general, macromolecule diffusivity decreases as a function of concentration [2,3], although at very low concentrations diffusivity may increase with concentration, due to electrostatic repulsion between charged macromolecules [4-10]. This increase is most marked when the pH of the solution is far from the macromolecule's isoelectric point and when the ionic strength of the solution is low [7]. Indeed, it was remarked in chapter II that the release rate
of BSA increases as the pH moves away from the isoelectric point of BSA, with ionic strength held constant [10].

In all previous modelling studies of release of macromolecules from EVAc polymers [1,12,13] it has been assumed that diffusion coefficients are constant. This simplifying assumption gives a diffusion equation that is linear. This section examines the concentration dependence of diffusion coefficients. Sections 2.2 and 2.3 review the state of theoretical understanding and experimental measurements, respectively, of diffusion coefficients at high protein concentrations. In section 2.2 the distinction between "tracer" and "mutual" diffusion coefficients is elaborated. It is shown in section 2.3 that while there is widespread agreement that tracer diffusivities decrease significantly with increasing protein concentration, the behavior of mutual diffusivities as a function of concentration is in dispute.

The effect of concentration dependent diffusion on the release process is examined in section 2.4. Numerical and analytical simulations of desorption with various forms of concentration dependence are performed. It is found that, provided the macromolecule's diffusion coefficient remains sufficiently large over an appreciable concentration range, there is very little retardation of the overall desorption process. These simulations argue against a theory of
retardation based on the high macromolecular concentration in the pores.

VI.2.2 Tracer and Mutual Diffusion Coefficients

The concentration dependence of the diffusion coefficient is due to several factors. Einstein showed that macromolecular diffusion is due to thermal collisions of solvent molecules against the macromolecule [14]. The force due to these collisions is opposed by the viscous drag of the solution, characterized by a friction coefficient \( f \). The Stokes-Einstein equation for the diffusion coefficient is

\[
D_T = \frac{kT}{f}
\]

where \( k \) is Boltzmann's constant and \( T \) is the Kelvin temperature of the solution. In the dilute limit, \( f \) is equal to \( 6\pi\nu R \), where \( \nu \) is the solvent viscosity and \( R \) is the radius of the macromolecule.

The Stokes-Einstein equation is strictly valid only at low macromolecule concentrations. At higher concentrations its form can be kept if \( f \) is allowed to represent an effective friction coefficient which accounts for hydrodynamic interactions between the macromolecules [15]. Then \( f \) increases with macromolecule concentration, causing \( D_T \) to decrease with concentration.
\( D_T \) is called the tracer diffusion coefficient, and corresponds to the random motion of a labeled macromolecule in a solution of uniform concentration. However, in our studies we are interested in the mutual diffusion coefficient \( D_M \), which is measured in a solution containing solute gradients. \( D_M \) is defined as the quotient of the flux of solute in a chosen direction divided by the concentration gradient of the solute in that direction. It is \( D_M \) that is important in determining the rate of drug release.

In general \( D_M \) is not equal to \( D_T \), for two reasons. First, as macromolecules flow from regions of high concentration to regions of lower concentration, their volume must be replaced by solvent molecules, causing a countercurrent of solvent molecules. Macromolecules are dragged along in this countercurrent, reducing the net transport of macromolecule.

The second difference between tracer and mutual diffusion coefficients is more subtle. The osmotic pressure in concentrated regions of solute is higher than in less concentrated regions. This is due to hard sphere repulsion and to electrostatic repulsions between the charged macromolecules. Phillies [4] proposed the "generalized Stokes-Einstein" equation for the mutual diffusion coefficient:
In this equation, \( \phi \) is the volume fraction of macromolecule, given by \( \phi = \frac{c}{\rho} \), where \( c \) is the macromolecule concentration (mg/ml) and \( \rho \) is the density of the macromolecule (\( \rho = 1340 \) mg/ml for BSA). \( \left[ \frac{\partial \Pi}{\partial c} \right]_{T,P} \) is the osmotic compressibility of the solution, defined as the rate of change in osmotic pressure with addition of macromolecule to the solution at constant temperature and total pressure. The factor \( 1 - \phi \) in (2) accounts for solute backflow, and clearly decreases with increasing solute concentration. \( \left[ \frac{\partial \Pi}{\partial c} \right]_{T,P} \) increases with concentration, opposing effects of viscosity and solute backflow.

Various authors [4,7,15] have developed expressions for both the hard sphere and electrostatic contributions to the osmotic pressure of protein solutions, allowing theoretical computation of \( \frac{\partial c}{\partial \Pi} \). The hard sphere contribution to \( \frac{\partial c}{\partial \Pi} \) is, to first order, equal to \( 1 + 8\phi \). The electrostatic contribution is modulated by two factors. First, there is the average charge on a macromolecule, determined by the pH and the chloride ion concentration (\( \text{Cl}^- \) can adsorb strongly onto proteins [8]). Second, there is the Debye screening of the macromolecules by the microions in the solution. As the ionic strength increases, the Debye length decreases, and the electrostatic contribution to osmotic pressure also decreases [4,7].
Keller et al. [2] measured tracer and mutual diffusion coefficients of isoionic BSA (pH=4.7) as a function of concentration using a diffusion cell. Mutual diffusion coefficients were assessed by measuring steady state rates of transport through Millipore® membranes from a source chamber at the test concentration to a sink chamber at zero concentration. Tracer diffusion coefficients were measured by establishing small countervailing gradients of 14C-labeled BSA molecules and unlabeled BSA molecules, above a test concentration pedestal. Their results (figure 1) show two salient features. First, both tracer and mutual diffusion coefficients decrease with concentration. Second, it appears that the tracer and mutual diffusion coefficients are identical under the range of experimental conditions tested.

In view of the discussion of section 2.2, it is surprising that $D_T$ and $D_M$ would be indistinguishable, even at the isoionic point. The theoretical literature at present is in dispute on this matter. The hard sphere contribution to as stated above, is equal to $1+8\phi$, which more than compensates for the $1-\phi$ factor due to solvent backflow. Anderson and Reed [7] argue that the friction coefficient $f$ covaries locally with the hard sphere component of $\frac{\partial C}{\partial \Pi}$, so that $f$ and $\frac{\partial C}{\partial \Pi}$ cannot be averaged separately before computing equation (2). By averaging the quotient of $\frac{\partial C}{\partial \Pi}$ and $f$, 
Figure VI.1. Tracer and mutual diffusion coefficients of BSA for pH=4.7. Reproduced from Keller et al.[1] Abscissa converted from volume fraction to concentration.
Anderson and Reed were able to justify theoretically the results of Keller et al. Anderson and Reed's model predict equality of $D_M$ and $D_T$ only for those conditions where electrostatic effects are negligible.

Keller et al. obtained an empirical relation for the BSA diffusivity:

\[(3) \quad D_T(c) = D_M(c) = D_0 \tanh \gamma c / \gamma c ,\]

where $D_0 = 7.0 \times 10^{-7} \text{cm}^2/\text{sec}$ and $\gamma = 0.016 \text{ml/mg}$ for BSA. This expression, with a different $D_0$, also held for hemoglobin.

Anderson [3] proposed an alternative expression for the diffusivity of BSA, viz.

\[(4) \quad D_T(c) = D_M(c) = D_0 (1 - \phi)^{6.5} = D_0 (1 - c / \rho)^{6.5} .\]

This relation provides a good experimental fit to the data of Keller et al., and is consistent with known sedimentation velocities of BSA as a function of concentration.

All studies of concentration dependence of $D_M$ and $D_T$ of BSA above its isoionic point indicate that $D_{M} > D_{T}$ [5,9]. Near physiological pH (7.4), it appears that $D_T$ behaves roughly as described by Keller et al. [9], but $D_M$ increases with concentration at low BSA concentrations. This behavior of $D_M$
has been verified by quasielastic light scattering [5,8], centrifugation [9], Rayleigh interferometry [10], and capillary techniques [6,9]. An example of a plot of \(D_M vs. c\) at \(pH=7.4\) is shown in figure 2. The increase in \(D_M\) with concentration is not dramatic, and it can be assumed, for modelling purposes, that \(D_M\) is approximately equal to \(D_0\), at least up to \(c=240\,\text{mg/ml}\).

It should be noted that diffusion coefficients have not been measured for BSA above 325 mg/ml. In EVA\(_c\) polymer systems the concentrations of the macromolecules in the pores can be as high as 1000 mg/ml, which is well above the range over which diffusion coefficients have been measured. It is possible that the diffusion coefficient suffers a significant drop as the concentration approaches solubility. At very high concentrations, other factors such as excluded volume and entanglements may play a significant role. Neither of these factors are considered in the generalized Stokes-Einstein treatment. Note that at solubility for BSA (\(C_s=585\,\text{mg/ml}\) [16]), protein occupies a solution volume fraction of \(C_s/\rho = 585/1340 = 0.44\).

In summary, the mutual diffusion coefficient may decrease significantly with concentration. Thus it is necessary to see whether the slowness of protein release from EVAc matrices is due to the fact that diffusion occurs in a region of high macromolecule concentration. We now turn to
Figure VI.2. Mutual diffusion coefficient of BSA, for pH=7.4. Reproduced from [5].
VI.2.4 Effect of concentration dependence of diffusion coefficients on desorption from slabs

VI.2.4.1 Introduction

In this section it is assumed that concentration does affect the diffusion coefficient of a macromolecule. How much concentration dependence affects the overall desorption (release) rate from a slab will be assessed. In section 2.4.2 the steady state diffusive flux across a slab, given a concentration dependent diffusion coefficient, is derived. The steady state case provides some heuristics for interpreting transient desorption. In section 2.4.3, numerical and analytical calculations are made for the transient diffusion (desorption) case.

VI.2.4.2 Effect of concentration dependence on steady state diffusion

If the concentration dependent diffusion coefficient $D(c)$ is known, then it is easy to calculate the diffusive flux across a membrane from a reservoir at a given concentration into a perfect sink [17]. Assume a membrane of thickness $\delta$ separates two chambers of a diffusion cell, with the concentrations in the chambers held at $C^*$ and 0 (see...
Also assume that porosity and tortuosity effects are absorbed into the diffusion coefficient. At any depth $x$ in the membrane, in the steady state,

$$\frac{3}{2} \left[ \frac{D(c)}{\partial x} \right] = 0,$$

or

$$D(c) \frac{\partial c}{\partial x} = F_S,$$

where $F_S$ is a constant. Integrating over $x$,

$$\int_{0}^{\delta} D(c) \frac{\partial c}{\partial x} dx = F_S \int_{0}^{\delta} dx.$$

Changing variables on the left hand side of (7) from $x$ to $c$,

$$F_S(C^*) = \left[ \int_{0}^{c^*} D(c) dc \right] / \delta.$$

But $-F_S$ is the flux through the membrane. For the concentration independent case, i.e. $D(c) = D(0) = D_0$ for all $c$,

$$F_{0S}(C^*) = D_0 C^*/\delta.$$

The ratio of the concentration dependent flux to the concentration independent flux is then

$$R_S(C^*) = \frac{F_S(C^*)}{F_{0S}(C^*)} = \frac{\int_{0}^{c^*} D(c) dc}{D_0 C^*}.$$
Figure VI.3. Schematic of test cell for measuring steady state diffusion through a membrane of depth $\delta$. 
Now \( F_S(C^*) \) might be viewed as the flux produced by an effective diffusion coefficient \( D_{es}(C^*) \) acting on a concentration gradient \( C^*/\delta \), i.e.

\[
F_S(C^*) = D_{es}(C^*)C^*/\delta
\]

where, using (8),

\[
D_{es}(C^*) = \left[ \int_{0}^{C^*} D(C) dC / C^* \right].
\]

Thus, \( R_S(C^*) \) is also the ratio of \( D_{es}(C^*) \) to \( D_0 \).

Apparently, the steady state rate of transport is not determined solely by the slowest step, which is diffusion in the high concentration regime.

VI.2.4.3. Calculation of transient concentration dependent diffusion: theory

Explicit analytical solutions for the transient desorption of a slab with concentration dependent diffusion coefficients do not exist [15]. The situation must be analyzed by computer.

 Rather than attempting to solve the problem of desorption from a slab of finite depth with a prescribed \( D(c) \), we have chosen to solve the semi-infinite desorption
case. (Desorption is into a perfect sink.) This is a much simpler problem, as will be seen below, and because the early behavior for a finite slab is virtually identical to the early behavior for a semiinfinite slab.

The concentration dependent case is solved by making a transformation. Within the semiinfinite slab, the transient diffusion equation

\[ \frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left[ D(c) \frac{\partial c}{\partial x} \right], \quad 0 < x < \infty \]

with boundary conditions

\[ c(x=0, t) = 0, \]
\[ c(x=\infty, t) = C^*, \]

and the initial condition

\[ c(x, t=0) = C^*, \quad 0 < x < \infty \]

holds. Setting \( \eta = x/2\sqrt{D_0 t} \) (Boltzmann transformation) and \( D(c) = \frac{\dot{c}}{D(c)} \) equations (13-16) become

\[ -2\eta \frac{dc}{d\eta} = \frac{d}{d\eta} \left[ \dot{c} \frac{dc}{d\eta} \right] \]
\[ c(0) = 0 \]
\[ c(\infty) = C^* , \]
which is an ordinary differential equation boundary value problem.

First consider the case where \( D(c) = D(0) = D_0 \) for all \( c \). Then (17) becomes

\[
(17') \quad -2\eta \frac{dc}{d\eta} = \frac{\partial^2 c}{\partial \eta^2}
\]

which, when subject to (18) and (19), has the solution [12]

\[
(20) \quad c(\eta) = C^* \text{erf}(\eta).
\]

For the concentration dependent case, (17)-(19) were solved using a fourth order Runge-Kutta scheme [16]. Because this scheme is designed for first order differential equations, it was necessary to transform the second order equation (17) into a system of first order equations:

\[
(21) \quad \frac{dc}{d\eta} = c' \\
\frac{dc'}{d\eta} = -(2\eta c' - c' \frac{2d\tilde{D}}{dc})/D(c).
\]

The details of the numerical computations for the concentration dependent case are described in appendix IV.

Once having solved for \( c \), given any expression for \( \tilde{D}(c) \), the flux out of the semiinfinite slab as a function of time
was obtained by applying the inverse Boltzmann transformation (i.e. \( x = 2\sqrt{D_0t}\eta \)):

\[
(22) \quad -F_T = D_0 \frac{dc}{dx} \bigg|_{x=0} = (1/2)\sqrt{D_0}/\tau \frac{dc}{d\eta} \bigg|_{\eta=0}.
\]

For example, for the concentration independent case, (20) and (22) yield

\[
(23) \quad -F_{OT} = C^*(D_0/\pi t)^{1/2}.
\]

As in the steady state case, \( F_T \) and \( F_{OT} \) can be used to derive a constant effective diffusion coefficient \( D_{eT}(C^*) \).

Set

\[
(24) \quad F_T(C^*) = C^*(D_{eT}/\pi t)^{1/2}.
\]

Then the ratio \( R_T(C^*) \) of \( D_{eT} \) to \( D_0 \) is given by [using (22) and (24)]

\[
(25) \quad R_T(C^*) = D_{eT}/D_0 = \left[ F_T(C^*)/F_{OT} \right]^2.
\]

Using (22) and (23) in (25),

\[
(26) \quad R_T(C^*) = (\pi/4C^*)^2 \left( \frac{dc}{d\eta} \right)^2 \bigg|_{\eta=0}.
\]
VI.2.4.4 Application to specific diffusivity models

The diffusivity models of Keller et al. [2] and Anderson [3] were studied, extrapolated to 1000 mg/ml. These models were studied because they provide the "worst case" of concentration dependence. (It was concluded in section 2.3 that at physiological pH, the diffusion coefficients are much higher than those predicted by the Keller and Anderson models.) Graphs of the two model diffusivities, given by equations (3) and (4), are shown in figure 4a. The two model diffusivities are quite similar up to 325 mg/ml, although the curve shapes are somewhat different. Above 325 mg/ml, the Anderson model predicts a lower diffusivity than the Keller model.

The ratios $R_T(C^*)$ and $R_S(C^*)$ for the Keller and Anderson models are shown in figure 4b.

Besides the Keller and Anderson models, another set of models was tested in which $D(c)$ behaves similarly to the former models in the low concentration regime, but with $D(c)$ approaching 0 faster at high concentrations. We call these "Butterworth" models, because the form of $D(c)$ is similar to that of a Butterworth filter:

\[
(27) \quad D(c) = [1+(c/c_0)^n]^{-1},
\]
Figure VI.4

a) Model concentration-dependent diffusion coefficients, given by Keller et al. [2] and Anderson [3] (eqs. 2 and 3, respectively).

b) Values of $R_S(C^*)$ and $R_T(C^*)$ (see text) for Keller and Anderson models.
where $c_2$ is the concentration such that $D(c_2) = D_0/2$, and $n$ is an exponent that determines how sharply the diffusion coefficient drops near $c_2$, and also determines how close to zero $D(c)$ comes as $c$ gets large.

"Butterworth" simulations were run for $c_2 = 125$ mg/ml and $n = 2, 3$. These parameters give curves for $D(c)$ that share many of the features of the Keller and Anderson models of $D(c)$. The curves for $D(c)$ are shown in figure 5a. The resulting $R_T(C^*)$ and $R_S(C^*)$ for the Butterworth models are shown in figure 5b.

A limiting case of interest is the "Butterworth" case with $n = \infty$, where the diffusivity is equal to $D_0$ up to concentration $c_2$, at which point it drops to zero. (Essentially, this means that $c_2$ is the solubility of the diffusing molecule.) There is an analytical solution for $R_T(C^*)$ in this case, which is [19]

\[
R_T(C^*) = \begin{cases} 
1 & C^* \leq c_2 \\
\left\{ c_2/(C^* \text{erf}(\eta^*)) \right\}^2 & C^* \geq c_2
\end{cases}
\]

where

\[
\sqrt{\pi} \eta^* \exp(\eta^{*2}) \text{erf}(\eta^*) = c_2/(C^*-c_2) .
\]
Figure VI.5a) "Butterworth" (n=1,2,∞; \( c_2 = 125 \text{ mg/ml} \)) model concentration dependent diffusion coefficient.

b) Value of \( R_S(C^*) \) and \( R_T(C^*) \) for Butterworth models.
For $C^* \gg c_2$, the simplest asymptotic form of (29) is

\[(30) \quad R_T(C^*) \sim (\pi/2)(c_2/C^*) \, .\]

It is easy to see that for the steady state case,

\[(31) \quad R_s(C^*) = \begin{cases} 
1 & C^* \leq c_2 \\
\frac{c_2}{C^*} & C^* > c_2 
\end{cases} \, .\]

VI.2.4.5 Discussion

The plots in figures 4 and 5 have some surprising features. First, it appears that there is relatively little reduction in the effective diffusivity for transient desorption, even though in the concentrated region of the slab the diffusion coefficient is much lower than in the dilute region. It is also apparent that the shapes of the curves in figures 4 and 5 depend mostly on the shape of $D(c)$ at low values of $c$. The fact that $D(c)$ is much lower at high concentrations in the "Butterworth" and Anderson models than in the Keller model is not reflected in the prediction of the two models for the overall desorption rates.

Figures 4b and 5b indicate that the effective diffusion
coefficient is reduced by a factor of at most 5, given the functional forms of $D(c)$ chosen. However, it should be recalled that there is strong evidence that mutual diffusion coefficients do not fall off in the manner shown in figures 4a and 5a. The results presented should be treated as "worst case" estimates of the effect of concentration dependent diffusivity on the effective diffusion coefficient. [For example, if it is assumed that the diffusion coefficient is constant up to 400 mg/ml, then (28) and (29) predict a reduction in diffusivity by a factor of less than 2.]

Because the characteristic desorption time given by equation I.1 is inversely proportional to the effective diffusion coefficient, it appears that the concentration effect can retard release by no more than a factor of 5. This is not nearly sufficient to account for the observed time scale of release.

The second salient feature of the graphs is that concentration dependence has a slightly smaller effect on the effective diffusion coefficient for the transient desorption case than for the steady state case.

It is somewhat surprising that the concentration dependence of the diffusion coefficient has so little effect on the desorption of the slab. At present, we only have numerical evidence that this is a robust prediction, and we
cannot offer an analytic proof that this should always be so. However, a heuristic explanation of the phenomenon may be helpful. Figure 6 diagrams the situation. Imagine that the protein in the slab becomes highly concentrated at some depth $x^*$. To the left of $x^*$ the diffusion coefficient is relatively high, so that that region quickly becomes very dilute. But then the gradient near $x^*$ becomes very large. This steep gradient offsets the low diffusivity at $x^*$, and the drug at depth $x^*$ falls quickly down that gradient. This offset by the gradient is what makes the overall desorption behavior very robust to changes in the concentration dependence. (Figure 6 is actually the concentration profile for a slab whose diffusivity is given by the $n=3$ Butterworth model with $C^*=1000$ mg/ml.)

VI.2.5 Summary

In this section it has been shown that, although diffusion coefficients can be very low at high concentrations, this does not come close to explaining the retardation of release. Therefore, the slowness of release from EVAc matrices must be attributed to other factors.
Figure VI.6. Concentration profile of slab with high value of $C^*$. Note sharp drop in concentration between regions of low and high diffusivity.
VI.3 Models of the effect of pore geometry

VI.3.1 Introduction

In chapter III, the model of Pismen [18] for diffusion through porous media was described cursorily. The model looks at diffusion over two length scales. The first scale (the "macro" scale) is the scale of the whole porous medium. Pore topology effects are important on the macro scale. These were considered in section V.4. It was assumed that diffusing molecules "hop" from pore to pore with a particular hopping rate. The second scale (the "micro" scale) involves single pores. Given the geometry of a pore, the distribution of first passage times of a molecule through that pore can be calculated. The first passage time is then identified with the hopping time on the macro scale.

In this section the effect of pore geometry on first passage times is examined. Figure II.1 illustrates an important feature of pore geometry. It appears that pores, rather than being interconnected tubes, are varicose bodies, connected to each other via narrow "channels." The effect this might have on the "hopping time" between pores is illustrated in figure 7. Roughly speaking, when the diffusing molecule enters a pore, it must find an outlet before it can exit that pore and make further progress. However, because the pore outlets are very narrow, they are
Figure VI.7. Schematic of Brownian particle in a constricted pore. The particle bangs into the wall several times before finding the pore exit.
difficult to find. The molecule has numerous collisions with the pore wall before it finds an outlet. It is the author's view that these constricted channels between pores are the basis for the slow diffusive release from EVAc matrices.

It should be emphasized that although the constricted channels are very narrow compared to the pores themselves, the channel diameters are orders of magnitude larger than the diameters of macromolecules (e.g. the radius of BSA is \(~35 \text{ Å}\) [6], while the channel radii are on the order of \(10 \text{ µm}\) [Figure II.1]). Models of restricted diffusion of molecules through narrow pores [21,22] do not apply here.

In section 3.2 a method is described for computing first passage time distributions in regions of arbitrary shape. In section 3.3, this method is applied to simple pore geometries that permit analytical solutions. It is shown that the size of a pore is not the only parameter determining first passage times through the pore. In section 3.4 a Monte Carlo simulation using a pore structure similar to that shown in figure II.3 is performed, and the results are discussed.

VI.3.2 Development of first passage time equations

VI.3.2.1 Introduction

Consider a pore with geometry shown in figure 8. It is
Figure VI.8. Schematic of situation for which first passage time distributions are solved. Solute obeys diffusion equation inside pore. Two types of boundaries: absorbing and reflecting. Concentration at absorbing boundary is zero. Normal solute flux at reflecting boundary is zero.
assumed that the diffusion equation

\[ \partial_t c = D \nabla^2 c \]  

holds inside the pore. D is the diffusion coefficient of the molecule in water. It is assumed that the diffusion coefficient is independent of concentration. Two types of boundaries are assumed. One is perfectly absorbing and corresponds to a pore outlet, while the other is perfectly reflecting, corresponding to pore walls. The boundary conditions for the diffusion equation (32) are then

\[ c = 0, \text{ absorbing boundary,} \]

and

\[ \partial_n c = 0, \text{ reflecting boundary,} \]

where \( \partial_n \) signifies the normal derivative of \( c \) at the boundary (see figure 8). Diffusion occurs in \( d \) dimensions (later examples will use \( d=1,2 \) and 3). Two derivations are made. In section 3.2.2, the full first passage time distribution equation is derived. In section 3.2.3, the mean first passage time equation is derived. The latter often contains sufficient information for our purposes and is much simpler than the full distribution equation.
VI.3.2.2 First passage time distribution

Assume that a diffusing particle is placed at time 0 at position $X$ in the interior of the pore. Define

$$P(T;X) = \text{Prob}[\text{A Brownian particle starting at } X \text{ reaches an absorbing boundary at time } T].$$

Note that $P(T;X)$ is a cumulative distribution function (c.d.f.). $P(T;X)$ can be derived by discretizing time and passing to the limit. In a short time $t$, the particle will move to position $X+x$. By choosing $t$ small enough, it can be guaranteed with arbitrary certainty that the particles will not have hit the pore boundary between times 0 and $t$. From $X+x$ the particle must get to an absorber before time $T-t$. Let $G_t(x)$ be the probability density function (p.d.f.) of the displacement $x$ after time $t$. Then the following equation holds:

$$(35) \quad P(T;X) = \int_{V} P(T-t;X+x)G_t(x)dx,$$

where $V$ is the interior of the pore. (Again, $t$ is chosen so small that $G_t$ is effectively zero long before $X+x$ nears the pore boundary.)

For a Brownian particle, $G_t(x)$ is Gaussian in each direction, i.e.
(36) \[ G_t(x) = \prod_{i=1}^{d} \left[ \exp\left(-x_i^2/4Dt\right)/\sqrt{4\pi Dt} \right] , \]

where \( x_i \) is the \( i \)'th component of \( x \).

The integrand in (35) is now expanded in \( x \):

(37) \[
P(T;X) = \int \left[ p(T-t;X) + \sum_{i=1}^{d} P_i x_i + \sum_{i,j=1}^{d} P_{ij} x_i x_j + \text{h.o.t.} \right] G_t(x) dx ,
\]

where \( P_i = \frac{\partial p}{\partial x_i} \) and \( P_{ij} = \frac{\partial^2 p}{\partial x_i \partial x_j} \) and \( \text{h.o.t.} \) denotes higher order terms. Plugging (36) into (37) obtains

(38) \[
P(T;X) = P(T-t;X) + \sum_{i=1}^{d} x_i \int G_t(x) dx + \text{h.o.t.}
\]

The linear terms and the quadratic cross terms of the Taylor series vanish in the integration due to the symmetry properties of \( G_t \). The integrals in (38) are well known [22], so (6) becomes

(39) \[
P(T;X) - P(T-t;X) = DtV^2 P + \text{h.o.t.}
\]

Dividing both sides by \( t \) and letting \( t \to 0 \), the higher order terms vanish, and the result

(40) \[
\partial_t P = DV^2 P
\]

is obtained. The cumulative probability distribution of the first passage time for a Brownian particle obeys the
diffusion equation, with the same diffusion coefficient as the particle itself.

The initial and boundary conditions for (40) in a pore as diagrammed in figure 8 can also be derived. If the molecule is not on the pore boundary, then a finite time will be required to reach the absorbing boundary. Therefore, the "initial" condition is

(41) \( P(0; \mathbf{x}) = 0 \), for \( \mathbf{x} \) inside the pore.

On the other hand, a particle residing in the absorbing portion of the pore boundary requires no time to reach an absorbing boundary, so a boundary condition is

(42) \( P(0; \mathbf{x}) = 1 \), for \( \mathbf{x} \) on an absorbing boundary.

The boundary condition for a reflecting pore wall is somewhat more difficult to obtain. To do so, assume that the wall is smooth enough so that at any point on the wall a continuous unit normal vector exists. A blow-up of the pore region near a point \( \mathbf{x} \) on the wall is shown in figure 9. Locally, the wall looks like a flat surface, and the vector of displacement \( \mathbf{x} \) can be set in coordinates such that \( x_1 \) is normal to the wall, and the other components run "along" the wall's tangent plane. A Brownian particle starting at point \( \mathbf{x} \) will have Gaussian displacements along all components
Figure VI.9. Local geometry near reflecting pore wall, represented by tangent plane of wall. $x_1$ is normal to tangent plane, while $x_2$ and $x_3$ lie on tangent plane.
except $x_1$. The $x_1$ displacement will be distributed according to a reflected Gaussian distribution $g_1(x) [22]$, viz.

$$g_1(x_1) = H(x_1) \exp(-x_1^2/4Dt)/\sqrt{\pi Dt},$$

where $H(\cdot)$ is the Heaviside step function. The joint distribution of all displacements is then

$$g_t(x) = H(x_1) \prod_{i=2}^d \exp(-x_i^2/4Dt)/\sqrt{4\pi Dt}.$$ 

Plugging (44) into (37) obtains, after some manipulation,

$$P(T;X) = P(T-t;X) + 2\sqrt{Dt/\pi P_1} + DtV^2P + h.o.t.$$ 

Dividing through by $t$ yields

$$[P(T;X)-P(T-t;X)]/t = 2\sqrt{D/\pi t}P_1 + DV^2P + h.o.t.$$ 

Notice that the term multiplying $P_1$ in the right hand side of (46) approaches infinity as $t \to 0$. However, the left hand side, in that limit, becomes $\delta_tP$, which is not infinite, since there is no "sticking" of the particle to the wall. Therefore, the boundary condition at the wall must be

$$\delta_n P = P_1 = 0.$$ 

It has been shown that, for the class of pores
considered here, the equation and boundary conditions for first passage times are the same as the corresponding equations for diffusion through such pores. Only the initial conditions are different.

VI.3.2.3 Mean first passage times

Again assume a diffusing particle is placed at time 0 at position $X$ in the interior of the pore. Of interest is the average time $\overline{T}(X)$ required to reach an absorbing boundary. After a short time $t$ the particle is displaced to $X+x$. From there it must reach the absorbing boundary. There will be a mean time $\overline{T}(X+x)$ required to reach the absorber from $X+x$. Averaging over all possible $x$ yields

$$
(48) \quad \overline{T}(X) = t + \int \frac{G_t(x)\overline{T}(X+x)}{V} \, dx ,
$$

where $G_t(x)$ and $V$ are defined as in the previous section. Expanding $\overline{T}$ in the integrand (and using subscript notation for partial derivatives of $\overline{T}$),

$$
(49) \quad \overline{T}(X) = t + \int \frac{G_t(x)[\overline{T}(x) + \frac{d}{dt} \overline{T} + \frac{1}{2} \sum_{i=1}^{D} \sum_{j=1}^{2} \frac{d}{dt} \frac{d}{dx} \overline{T}_{ij} + h.o.t.] \, dx}
$$

which, after evaluation using (36), becomes

$$
(50) \quad \overline{T}(X) = t + \overline{T}(X) + DtV^2 \overline{T} + h.o.t.
$$
Dividing by \( t \), cancelling, and letting \( t \to 0 \), obtains the final result

\[
(51) \quad \nabla^2 \bar{T} = -1.
\]

This partial differential equation requires no initial conditions, so it is simpler than the p.d.e. for the full first passage time distribution. Using arguments of the previous section, it can also be shown that the boundary conditions for (51) are

\[
(52) \quad \bar{T}(X) = 0, \quad X \text{ on an absorbing boundary},
\]

and

\[
(53) \quad \frac{\partial}{\partial n} \bar{T}(X) = 0, \quad X \text{ on a reflecting boundary}.
\]

**VI.3.3 First passage times in model geometries**

**VI.3.3.1 Introduction**

In this section, equations (51)-(53) for the mean first passage time are solved in three geometries. It will be shown that the distance over which a particle must diffuse is not the only factor determining its first passage time.

The model geometries are diagrammed in figure 10. In
Figure VI.10. Geometries of model pores for which mean first passage times can be solved.

a) Straight pore.
b) Cylindrically conical pore.
c) Spherically conical pore.
all three geometries, the side and rear walls are reflecting, and lie along natural manifolds for various coordinate systems. This allows two and three dimensional physical situations to be reduced to one dimensional analysis.

In all cases, the mean first passage time is calculated for a particle starting on the wall (reflecting boundary) farthest from the absorbing boundary. The length units are scaled such that the distance between the starting point and the absorbing boundary is equal to $l-\lambda$, where $\lambda$ is the parameter to be varied. Since the effect of geometric properties is independent of particle diffusivity, it is assumed without loss of generality that $D=1$. [To translate times calculated here to those for a particle of diffusivity $D$ in a pore whose length scale is given by $a(l-\lambda)$, simply multiply the results below by the factor $a^2/D$.]

In the following examples, $\bar{T}(r;\lambda)$ is defined as the mean first passage time for a particle starting at coordinate $r$ in a pore whose parameter is $\lambda$.

VI.3.3.2 Straight pore (figure 10a)

The mean first passage time for a straight pore depends only on the distance $r$ into the pore. The geometry is rectangular, so $\nabla^2 = \frac{\partial^2}{\partial r^2}$, and the appropriate equation and boundary conditions are
(54) $\frac{\partial^2 T}{\partial r^2} = -1$ ,

(55) $T(\lambda ; \lambda) = 0$ , and

(56) $\frac{\partial T}{\partial r} \bigg|_{r=1} = 0$ .

The solution of (54)-(56) is

(57) $\bar{T}(r; \lambda) = \frac{[(\lambda^2 - r^2) - 2(\lambda - r)]}{2}$ .

For a particle starting at $r=1$, (55) becomes

(58) $\bar{T}(1; \lambda) = \frac{(1-\lambda)^2}{2}$ .

As $\lambda \to 0$, $T(1; \lambda) \to 1$ .

VI.3.3.3 Cylindrically conical pore (figure 10b)

The mean first passage time for this case depends on the radial position $r$ in the pore. The geometry is cylindrical, so $\nabla^2 = \frac{1}{r} \frac{\partial}{\partial r} (r \frac{\partial}{\partial r})$, and (51)-(53) become

(59) $\frac{1}{r} \frac{\partial}{\partial r} (r \frac{\partial T}{\partial r}) = -1$ ,

(60) $T(\lambda ; \lambda) = 0$ , and

(61) $\frac{\partial T}{\partial r} \bigg|_{r=1} = 0$ .
The solution of (59)-(61) is

\[(62) \quad \overline{T}(r; \lambda) = (\lambda^2 - r^2)/4 + \ln \sqrt{r/\lambda}, \]

so

\[(63) \quad \overline{T}(1; \lambda) = (\lambda^2 - 1)/4 - (\ln \lambda)/2. \]

As $\lambda \to 0$, $\overline{T}(1; \lambda) \sim -(\ln \lambda)/2$.

VI.3.3.4 Spherically conical pore (figure 10c)

Once again, the mean first passage time depends only on the radial position $r$ in the pore. The geometry is spherical, so $\nabla^2 = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \frac{\partial \overline{T}}{\partial r})$, and (51)-(53) become

\[(64) \quad \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \frac{\partial \overline{T}}{\partial r}) = -1, \]

\[(65) \quad \overline{T}(\lambda; \lambda) = 0, \quad \text{and} \]

\[(66) \quad \left. \frac{\partial \overline{T}}{\partial r} \right|_{r=1} = 0. \]

The solution of (64)-(66) is

\[(67) \quad \overline{T}(r; \lambda) = (\lambda^2 - r^2)/6 + (1/\lambda - 1/r)/3, \]

so
\( T(1; \lambda) = (\lambda^2 - 1)/6 + (1/\lambda - 1)/3 \).

As \( \lambda \to 0 \), \( T(1; \lambda) \sim 1/3\lambda \).

VI.3.3.5 Discussion

Three geometries with identical fundamental length scales \((1-\lambda)\) have been presented, with very different resulting mean first passage times. Equations (58), (63), and (68) are shown (log-log) in figure 11. The difference is seen most strongly in the case of spherically conical pores.

A partial explanation of this phenomenon is as follows. As \( \lambda \to 0 \), the surface area of the absorber in the straight pore remains constant. The surface areas of the absorber in the cylindrically and spherically conical pore, on the other hand, vary respectively as \( \lambda \) and \( \lambda^2 \). Thus the time needed to find the absorber must be greatest for the spherically conical pore, followed by the time needed for the cylindrically conical pore. This explanation is incomplete, since the surface area of the absorber does not by itself determine \( T \); other geometrical, and possibly dimensional effects, must be contributing.

VI.3.4 First passage times in square pores with constricted inlets and outlets
RELATIVE MEAN FIRST PASSAGE TIMES

Figure VI.11. Comparison of first passage times as functions of parameter $\lambda$ for pores with geometries shown in figure 10.
VI.3.4.1 Introduction

The purpose of section 3.3 was to obtain analytical results that illustrate that the length scale of a pore is not the only factor determining first passage times. This is a crucial concept in understanding diffusion through porous media. The pore geometries discussed in section 3.3, while easy to analyze, are not realistic, and in this section more plausible pore geometries are investigated by the Monte Carlo method.

Figure 11.3 contains a conceptual model, in 2 dimensions, of the EVAc matrix pore structure. The water-filled pore space is modelled as a network of "cells" containing bulging "pores" that are connected to each other via narrow "channels" or "throats." (In this chapter, "throats" will be the term used.)

Section 3.4.2 describes the important geometric parameters within the cells, as well as the boundary conditions for the overall first passage time problem. Since the pore geometry is not simple, no closed form solutions exist (unlike in section 3.3), so a Monte Carlo simulation is performed instead. Section 3.4.3 contains a solution of a simple first passage time problem. In section 3.4.4 it is shown how to use the results of section 3.4.3 to compute, using a Monte Carlo method, first passage times in the more
complicated geometries of section 3.4.2. In sections 3.4.5 and 3.4.6 results of the simulations are presented and discussed.

VI.3.4.2 The geometric setting

Consider two adjacent pores, taken from the lattice of figure II.3. A typical example is shown in figure 12. The unit cell in the lattice has diameter \( \xi \). The pore bodies are assumed to be at the centers of their respective cells, and the connecting throats are bisected by the cell boundaries. The points where the pore bodies meet the throats are called "outlets."

Simulations are initiated by placing a particle on the perpendicular bisector of the throat connecting the two pores, as shown in figure 12. The computer then simulates a Brownian motion for the particle, until the particle reaches a perpendicular bisector of one of the other throats of either of the two pores. The time taken to reach the bisector is taken to be the first passage time through the pore.

Brownian motion is executed through a connected pair of pores, since in a random walk there is no guarantee that a particle, starting out in one direction, will continue in that direction. In fact, the diffusing particle may cross
Figure VI.12. Example of two adjacent pores taken from lattice in figure II.3.
the original bisector any number of times. It may even
journey into one of the pores and return to the original
throat and make its way into the other pore, etc.

For simplicity, two restrictions are imposed on the pore
model of figure 12. First, it is assumed in the simulation
that adjacent pores are mirror images, reflected through the
cell boundary. This is equivalent to placing a reflecting
boundary at the bisector between the two pores. Second, it
is assumed that outlets are in the centers of sides of pores.

The resulting model pore geometry for the simulations is
illustrated in figure 13. The parameters in the simulation
are the number of outlets \( n_T \), the width \( w \) of the outlets
(throats), and the half-length \( z \) of the throats. Note that
instead of assuming a fixed overall cell size as in figure
12, the diameter of the central pore body is fixed at 2.
Thus \( w \) and \( z \) are considered dimensionless, and the effect of
their relative sizes on first passage times can be assessed
without the confounding effect of a growing overall pore
dimension. One can scale the dimensionless first passage
times to real times for a pore in a cell of fixed dimension
by using the scale factor \( \frac{\xi^2}{(2+2z)^2} \).

There are seven possible outlet configurations, as shown
in figure 14. Since configurations 6 and 7 in that figure
are mirror images of configurations 1 and 3, respectively,
Figure VI.13. Parameters for simulation of Brownian motion through constricted pores.

\( n_T \) = Number of outlet throats.

\( w \) = Outlet width.

\( z \) = Half-length of throat.
Figure VI.14. Pore outlet configurations. Configurations 6 and 7 are mirror images of 1 and 3, respectively, so only 1-5 are tested in Brownian motion simulations.
they must yield the same first passage time distributions, so only configurations 1-5 are tested.

As usual, the diffusion coefficient is assumed without loss of generality to be 1.

Before further describing the Brownian motion simulation, it is necessary to make two derivations. This is done in the next section.

VI.3.4.3 First passage out of a square

Consider a Brownian particle in two dimensions whose path starts at the origin. Surround the origin by a square with boundaries $x=\pm 1$ and $y=\pm 1$. Of interest is the probability distribution of the "hitting time" $T$, which is the time required for the Brownian particle to reach the boundary for the first time. Also of interest are the mean $T$ of that distribution and the probability distribution of the "hitting spot," i.e. the point on the boundary where the Brownian particle makes its first contact.

Once again, the diffusion coefficient is set to 1.

The full probability distribution for $T$ is determined first, by an imbedding procedure, illustrated in figure 15a. $P(T,X)$ is the cumulative distribution function (c.d.f.) of
Figure VI.15  
a) Imbedding approach for determining cumulative probability distribution $P(T;x,y)$ of the "hitting time" $T$. See text for explanation.

b) Imbedding approach for determining mean hitting time $\bar{T}$. See text for explanation.
the time $T$ required to reach the boundary, starting from a point $X=(x,y)$ in the interior of the square. $P(T,X)$ is obtained by solving equations (40), (41) and (42), with the whole boundary of the square taken to be absorbing. The result is

$$P(T,X) = 1 - \frac{4}{\pi^2} \left[ \sum_{n=0}^{\infty} \frac{1}{2n+1} e^{-\frac{(2n+1)^2\pi^2 T}{4}} \cos((2n+1)\pi x) \right] \cdot $$

$$\cdot \left[ \sum_{n=0}^{\infty} \frac{1}{2n+1} e^{-\frac{(2n+1)^2\pi^2 T}{4}} \cos((2n+1)\pi y) \right].$$

The desired cumulative distribution of first hits for a particle starting at the origin is given by

$$P(T) = P(T, X=0) = 1 - \frac{4}{\pi^2} \left[ \sum_{n=0}^{\infty} \frac{1}{2n+1} e^{-\frac{(2n+1)^2\pi^2 T}{4}} \right]^2.$$ 

The corresponding probability density function (p.d.f.) $p_1(T)$ is obtained by differentiating (70) with respect to $T$:

$$p_1(T) = \begin{cases} 
\sum_{n=0}^{\infty} \frac{1}{2n+1} e^{-\frac{(2n+1)^2\pi^2 T}{4}} \cdot \\
\sum_{n=0}^{\infty} (-1)^n (2n+1) e^{-\frac{(2n+1)^2\pi^2 T}{4}}, & T>0 \\
0, & T=0 
\end{cases}$$

The special case for $T=0$ is needed because the second summation in (71) is divergent at $T=0$. 
Plots of $P_1(T)$ and $p_1(T)$ are shown in figures 16a,b, respectively.

The mean hitting time $\bar{T}_1$ is similarly obtained by imbedding into a more general problem (figure 15b). For any point $X=(x,y)$, the mean hitting time $T(X)$ is the solution of equations (19) and (20), viz.

\begin{equation}
T(X) = \frac{1}{2} - \frac{(x^2+y^2)}{4} - \frac{(16/π^3)}{\cdot}
\end{equation}

\begin{equation}
\sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)^3 \cosh(2n+1)\frac{π}{2}} \left( \frac{\cos(2n+1)\frac{πx}{2} \cosh(2n+1)\frac{πy}{2}}{(2n+1)^3 \cosh(2n+1)\frac{π}{2}} \right)
\end{equation}

The algebraic portion of (72) is a particular solution of (19), while the series portion is used to match the boundary conditions (52). The desired value $\bar{T}_1 = \bar{T}(X=0)$ is then

\begin{equation}
\bar{T}_1 = \frac{1}{2} - \frac{(16/π^3)}{\sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)^3 \cosh(2n+1)\frac{π}{2}}} \approx 0.295.
\end{equation}

[Note: $\bar{T}_1$ can also be computed by taking the expected value of $T$, using equation (71) for the p.d.f. of $T$.]

Given a particular value of $T$, the probability distribution of the hitting spot on the boundary can be derived. First note that the square is symmetric, so the probability of landing on any side is equal to $1/4$. It can be supposed without loss of generality that the particle lands on the side given by $x=+1$, $-1 \leq y \leq 1$. Define
Figure VI.16a) Cumulative distribution function (c.d.f.) $P_1(T)$ of hitting time $T$ for Brownian particle starting at origin and ending on square box of radius $l$.

b) Probability distribution function $p_1(T)$, derived by differentiating $P_1(T)$. 
\( Q_1(y;T) = \text{Prob}\{\text{Particle lands in } [-1,y) \text{ at time } T, \text{ and this is the first hit}\} \)

and

\[ q_1(y;T) = \text{associated p.d.f.} = \frac{dQ_1}{dy}. \]

To obtain \( q_1(y;T) \) a one dimensional diffusion equation describing the motion of the particle in the \( y \) direction is solved, with absorbing boundaries at \( y=1 \), and with the initial "mass" concentrated at the origin:

\(\begin{align*}
\partial_t c &= \delta_{yy} c, \\
c(\pm 1, t) &= 0 \text{ for } t>0,
\end{align*}\)

and

\(\begin{align*}
c(y,0) &= \delta(y),
\end{align*}\)

where \( \delta(\cdot) \) is the Dirac delta function, also known as the unit impulse function. \( c(y, t) \) is the "concentration" of particles diffusing in the \( y \) direction, never having hit \( y=\pm 1 \). Then

\(\begin{align*}
(77) \quad q_1(y;T) = \frac{c(y,T)}{\int_{-1}^{1} c(y,T) dy}
\end{align*}\)
The solution of (76)-(78) is

\[
(79) \quad c(y,t) = \sum_{n=0}^{\infty} e^{-\frac{(2n+1)^2}{2} T/4} e^{-\frac{(2n+1)^2}{2} T/4} \cos(2n+1)\pi y/2 
\]

which, when plugged into (77) and (78), yields respectively

\[
(80) \quad q_1(y;T) = (\pi/4) \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} e^{-\frac{(2n+1)^2}{2} T/4} 
\]

and

\[
(81) \quad Q_1(y;T) = \frac{\sum_{n=0}^{\infty} \left[\sin\left(\frac{(2n+1)\pi y}{2}\right)ight] (-1)^n}{2 \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} e^{-\frac{(2n+1)^2}{2} T/4}} 
\]

As \( T \to \infty \),

\[
(82) \quad q_1(y;T) \to (\pi/4)\cos(\pi y/2) 
\]

and

\[
(83) \quad Q_1(y;T) \to (1/2)[1+\sin(\pi y/2)] 
\]

A plot of \( q_1 \) for several values of \( T \) is illustrated in figure 17. As expected, the most probable values of \( y \) become more concentrated toward the center (\( y=0 \)) as \( T \) approaches.
Figure VI.17. Probability distribution of "hitting spot" $y$, assuming that particle lands at $x=1$, given the hitting time $T$. 
zero. However, it appears that the function \( q_1 \) does not vary greatly with \( T \). Indeed, \( q_1(y;T=.295) \) (dotted curve) is visibly indistinguishable from \( q_1(y;T=\infty) \) (dashed curve). The furthest deviation from those two curves shown in figure 17 is for the case \( T=.06 \), for which \( P_1(T)=.0155 \). That is, for less than 2 percent of the values \( T \) will the distribution of the \( y \) values be more concentrated near \( y=0 \) than is indicated by the plot of \( q_1(y;T=.06) \). In the following section, this relative insensitivity of \( q_1 \) (and \( Q_1 \)) to \( T \) is used to simplify the simulation procedure.

The above results can be generalized to the case of a particle with diffusion coefficient 1 executing Brownian motion in a square with boundaries \( x=\pm \rho \) and \( y=\pm \rho \). Let \( P_\rho \), \( p_\rho \), \( q_\rho \), and \( Q_\rho \) be the probability functions analogous to \( P_1 \), \( p_1 \), \( q_1 \) and \( Q_1 \), respectively. For diffusion, time scales as length squared, so the following relations hold:

\[
\begin{align*}
(84) \quad P_\rho(T) &= P_1(T/\rho^2) , \\
(85) \quad p_\rho(T) &= p_1(T/\rho^2) , \\
(86) \quad q_\rho(y;T) &= q_1(y/\rho;T/\rho^2) , \\
(87) \quad Q_\rho(y;T) &= Q_1(y/\rho;T/\rho^2) , \\
(88) \quad \bar{T}_\rho &= .295 \rho^2 \bar{T}_1
\end{align*}
\]
VI.3.4.4 Description of the Monte Carlo Brownian motion simulation

In this section a description of the Monte Carlo Brownian motion procedure is given. The actual simulation is performed by the FORTRAN program called RSPASS, which is listed in Appendix V. The reader should refer to figure 13 in the following paragraphs.

It is assumed that the Brownian particle has just entered the pore at a uniformly random position along the north throat bisector at time $0$. The symmetry across the north throat bisector allows one to consider the north throat bisector to be a reflecting boundary. The first step is to move the particle from the bisector to the inlet to the central pore body. This consists of a reflected random walk over a distance $z$. The expected (mean) time required for the particle to traverse the distance can be shown, using methods similar to those of section 3.3.2, to be

\[ t_0 = .5z^2 \]
Because the origin of the particle on the bisector is uniformly distributed, the particle's position along the inlet after the first step is also uniformly distributed.

The position of arrival at the inlet is designated $X_0$, which is set as the initial point for an interactive procedure, illustrated in figure 18. Suppose that after $n$ iterations the Brownian particle is at the position $X_n$, and the time since the start of the run is $t_n$. A square box of radius $\rho_n$ is drawn around $X_n$, where $\rho_n$ is the largest radius such that the box lies within the boundaries of the pore (here the "pore" includes both the central pore body and the half-throats). If $X_n$ lies on the pore boundary, then $\rho_n$ is the largest radius such that half the box lies within the pore. Now the mean time for the particle to hit a point on the box for the first time was been shown [eq. (88)] to be

$$\bar{T} = 0.295 \rho_n^2.$$

The point on the box where the particle makes its first hit is generated at random. First the side of the box (north, south, east or west) is chosen with equal probabilities, and then the position along that side is generated according to the p.d.f. $q_\rho$ (or c.d.f. $Q_\rho$) given by equations (89) and (90). If $X_n$ lies on the pore boundary and the particle is told to land on a point outside the pore, the program simply reflects the particle across the pore boundary.
Figure VI.18. Illustration of procedure for simulating Brownian motion through a model constricted pore.
(possibly reflected) hitting point is then taken to be $X_{n+1}$, the time is updated by

$$ t_{n+1} = t_n + T_n, $$

and a new iteration commences.

The iterative process continues until the particle hits one of the nonreflecting throat bisectors. The final value of $t_n$ is the first passage time $T_p$ through the pore, where $m$ is the number of walks that have thus far been executed in the pore. If the particle hits the reflecting (north) bisector, the procedure is restarted, but the time is not reset to zero.

The program keeps a running mean $T_{P_m}$ and standard deviation $s_{P_m}$ of the first passage times $T_{P_m}$ computed for the pore by the algorithm described above. When the coefficient of variation of the mean, defined by

$$ (93) \quad \tau_m = (s_{P_m}/\sqrt{m})/\overline{T_{P_m}} $$

is less than a prescribed tolerance, the program assumes that the mean first passage time has been computed to sufficient accuracy. (This criterion was not tested until 100 passages were executed for a single pore.) The program then prints $\overline{T_p}$ and $s_P$, which are the final values of $T_{P_m}$ and $s_{P_m}$.
For each combination of throat half-length z and throat width w, and for each of the pore configurations shown in figure 14, RSPASS calculates an estimate of $T_p$.

The procedure described here has some advantages over standard techniques involving random walks on discrete grids. First, the present procedure allows the particle to land anywhere in the pore—it is not constrained to land on grid points. Neither time nor space are discretized. Second, its speed and accuracy are not dependent on the choice of grid size. To be accurate, the lattice spacing for a discrete random walk must be determined by the smallest feature of the geometry, which in this case is usually the throat width. Thus, as the throat width decreases, the number of required lattice points becomes larger, and the interpoint spacing becomes smaller. Thus, all walks take more iterations to accomplish. (The number of steps to complete a random walk is inversely proportional to the square of the lattice spacing.) By drawing boxes of maximal size, the procedure described here saves much time. For example, if the particle is located near the center of the pore, then the box drawn around it fills almost the whole central pore body, and the particle jumps a long distance in a single iteration.

A variant of RSPASS, called RSPASSD, was also written, which took into consideration that the hitting times for the $\rho$-boxes $T_\rho$ are in fact randomly distributed, with a
distribution calculated using equations (70), (71), (84) and (85), and that the hitting spot probabilities depend on $T_p$ in a manner prescribed by equations (80), (81), (86) and (87).

RSPASSD in fact represents the rigorously correct algorithm. However, it requires the generation of more random variables and table lookups than does RSPASS, and generally requires 50% more computing time. It will be shown in the next section that the results of RSPASS are essentially the same as those of RSPASSD. For this reason, RSPASS was used.

VI.3.4.5 Results of the Brownian motion procedure

Figure 19 shows a comparison of values of $T_p$ generated by RSPASS and RSPASSD for the respective pore configurations shown in figure 14a-e. Parameters used were $z = 0.02, 1.0, 0.5, 0.2, 0.1$. The tolerance $\Gamma$ was set to 0.05. Thus, the estimates provided by the programs are accurate to within 5%. The results for RSPASS and RSPASSD are virtually identical. It was found in both cases that an average of about 350 passages were needed to bring the $\Gamma$ below 0.05 for a given pore geometry. Therefore, it was decided to use RSPASS in the subsequent simulations.

For the main set of simulations, RSPASS was run with seven values of $w$ (2.0, 1.0, 0.5, 0.2, 0.1, 0.05, 0.02) and three values of $z$ (0.5, 1.0, 0.02). For each $(w, z)$, all five pore configurations shown in figure 14 were run. This led to
Figure VI.19. Comparison of mean first passage times $T_p$ computed using RSPASS and REPASSD.

- $\bullet$ - RSPASS results.
- $\blacksquare$ - REPASSD results.
5X7X3=105 runs. The error tolerance was chosen to be 5% as before, and on the average about 350 passages were required to bring the error below that point.

Each passage consisted on the order of $10^2-10^4$ steps consisting of box drawing and random jumping. Table 1 gives a distribution of stepsizes (i.e. box radii) for a sample run ($z=0.01, w=0.1$). Notice that most of the stepsizes are between 0.001 and 0.1. However, there are also many between 0.1 and 1. For $w=0.1$, an appropriate stepsizes on a finite lattice would be 0.01. A single step of size 0.1 is equivalent to 100 steps with size 0.01, while a step of size 1 is equivalent to $10^4$ steps with size 0.01. Thus this is a very efficient procedure for executing random walks.

From $\bar{T}_P$, a retardation factor due to pore geometry, $R_P$, is calculated, using

$$\begin{align*}
(94) \quad R_P &= \frac{\bar{T}_P}{0.5(2+2z)^2},
\end{align*}$$

where $0.5(2+2z)^2$ is the mean first passage time for a particle in a straight ($w=2$, configuration 2) pore whose pore body and throats have total length $2+2z$ (see section 3.3.2).

The values of $\bar{T}_P, s_P$, and $R_P$ are listed for all cases in table 2. One feature is that $s_P$ is always of similar magnitude as $\bar{T}_P$, implying a wide distribution of values of
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<th>.001-.01</th>
<th>.0001-.001</th>
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<td>.361</td>
<td>.350</td>
<td>.088</td>
<td>.003</td>
</tr>
<tr>
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<td>.117</td>
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<td>.094</td>
<td>.003</td>
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</table>

**Table VI.1** Frequency distribution of stepsizes for simulation of Brownian motion through constricted pores. 

z = .01, w = .1.
\[ z = 0.5 \]

<table>
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<tr>
<th>CONF.</th>
<th>( n_T )</th>
<th>( \bar{T}_P )</th>
<th>( s_P )</th>
<th>( R_P )</th>
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Table VI.2. Mean first passage times \( \bar{T}_P \), standard deviations \( s_P \), and retardation factors \( R_P \).

Conf. = outlet configuration,

\( w \) = throat width,

\( z \) = throat half-depth,

\( n_T \) = number of outlets.
<table>
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<th>( s_P )</th>
<th>( R_P )</th>
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Table VI.2. (Continued)
### Table VI.2 (Continued)

#### z=0.02

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This explains why so many passages are required to achieve 5% accuracy in estimating $T_p$. To achieve 1% accuracy would require 25 times as many passages per configuration.

Many of the values of $R_p$ displayed in table 2 are less than 1. This occurs where there are wide outlets to shallow throats (large $w$, small $z$) on sides of the central pore body that are adjacent to the inlet (north) side. This allows particles to "cut corners," as illustrated in figure 20.

In the subsequent analysis, only those cases with throat width $w$ less than or equal to 0.2 (i.e. 1/10 the diameter of the pore body) will be considered. This eliminates the problem of cutting corners. Moreover, the decoupling of the macro and micro length scales can occur only if pores have sharp definition. When the throats are almost as wide as the pores, the pore lattice is less well defined.

It was believed, prior to running the simulation, that the throat width $w$ would be the most important parameter in determining $R_p$, because the narrower the throats (i.e. outlets), the harder it should be for a Brownian particle to find them. Figure 21 shows the the dependence of $R_p$ on $w$, for each value of $z$. In each case, different symbols correspond to the five throat configurations. The values of $R_p$ are virtually the same for outlet configurations 1 and 2 ($n_T=1$), and for configurations 3 and 4 ($n_T=2$). This is
Figure VI.20. Diffusing particles can "cut corners" if throats are wide and shallow.
especially true for \( z' = 0.5 \).

For a fixed value of \( z \), \( R_p \) increases when \( n_T \) and \( w \) decrease. If one compares, for fixed \( z \), the dependences of \( R_p \) on \( w \) for different values of \( N_p \), one sees that they are approximately parallel on the log-log plot. In fact, the relation

\[
R_p(z,w,n_T) = \frac{k(z,w)}{N_p},
\]

where \( k(z,w) \) is an undetermined function, holds quite well.

As \( z \) increases with \( w \) and \( N_p \) held fixed, \( R_p \) increases. This can be seen by comparing figures 21a, b, and c.

An unsuccessful attempt was made to separate the \( z \) and \( w \) dependences. For \( z = 0.5 \), the dependence

\[
R_p = \frac{k_z}{n_T w},
\]

where \( k_z \) depends on \( z \) alone, works fairly well (lines in figure 21a). However, for \( z = 0.1 \) and 0.02, (95) does not come close to describing the dependence of \( R_p \) on \( z \) and \( w \).

**VI.3.4.6 Discussion**

The results of section 3.4.5 show that one can obtain
Figure VI.21. Retardation factors $R_p$ as a function of throat width $w$ and length $z$, for different throat configurations. Lines are for equations $R_p = k_z / n_T w$, where $n_T$ is the number of outlet throats, and $k_z$ depends on $z$ alone.

a) $z = 0.5$

b) $z = 0.1$

c) $z = 0.02$
$z = .5$

**Figure 21a**

- **CONFIG. 1**
- **CONFIG. 2**
- **CONFIG. 3**
- **CONFIG. 4**
- **CONFIG. 5**

**Graph Details**
- **Y-axis:** Retardation Factor $R$ ranging from 0.01 to 100.0
- **X-axis:** Throat Width $w$ ranging from 0.01 to 1.00

The graph demonstrates the relationship between retardation factor and throat width for different configurations.
$z = .1$

**Figure 21b**
z = .02

Figure 21c
arbitrarily high retardation factors within a pore by appropriate choice of the parameters $z$, $w$ and $n_T$.

That $R_p$ should decrease with $n_T$ is obvious, since the fewer outlets, the longer it takes for a particle to find an outlet. In section V.4, the mean hopping time from pore to pore was set to the equivalent of $1/n_T$. This form is now justified. It should be noted that if one combines the results of section V.4 with the results of section 3.4.5, then the $1/n_T$ factor must not be used twice.

The effect of $z$ and $w$ are intertwined. For fixed $z$, $R_p$ decreases as $w$ increases. This is expected, because increasing $w$ increases the chance that the diffusing particle finds an outlet. However, unlike for $n_T$, the dependence of $R_p$ on $w$ varies with $z$ in an as yet undetermined manner.

As $z$ increases with $w$ fixed, $R_p$ increases. This was not expected initially. However, there is a qualitative explanation. The central pore body can be regarded as a "trap" from which a Brownian particle must escape in order to make progress. However, to make progress the particle must not only find an outlet, but it must traverse the narrow throat. Because the particle is executing a random walk, it will often "slip back" into the central pore body after it has entered the throat. Once it reenters the central pore body, the particle can become lost again. The longer the
throat, the greater the chance that this will happen.

The largest retardation factor obtained in the simulation was approximately 16 (see table 2). This is considerably smaller than the retardations observed experimentally (table IV.2). The simulated retardation factor of 16 was obtained for \( w = 0.02 \), so the throat is \( 0.02/2 = 1/100 \)th the diameter of the pore body. (We will say for this case that there is a constriction factor of 100.) It appears that one must impose very severe constrictions in order to obtain retardations consistent with experimental observations. It should be recalled, however, that the simulations were performed in two dimensions, while the real system is three-dimensional. To obtain a constriction factor of 100 in three dimensions is easier than in two dimensions. Consider a cubic pore of diameter 2 (figure 22). An outlet of diameter \( w = 0.2 \) has area \( (0.2)^2 = 0.04 \), which is \( 1/100 \) the area of the cubic face. Thus a constriction factor of 100 is obtained with a diameter dimension of 10.

There is another aspect of dimensionality that deserves theoretical consideration. In section 3.3 it was shown that a spherically conical pore yields a retardation factor that grows much faster with the inner radius \( \lambda \) than does the retardation factor for a cylindrically conical pore. The difference could not be linked directly to the rates at which the area of the outlets decrease as \( \lambda \) decreases.
Area ratio = \((\frac{.2}{2})^2\) = \(\frac{1}{100}\)

Figure VI.22. For cubic pore, the constriction factor is the square of the ratio of the cube diameter to the throat diameter.
Dimensionality itself seems to play a role. This suggests that simulated Brownian motion should be executed through three-dimensional model pores in order to truly assess the effects of constrictions on retardation.

Finally, a discussion of the relationship between the "micro" scale simulations just described and the "macro" scale simulations described in section V.4 is appropriate. The main theme of the "micro" discussion has been that Brownian particles cannot find their way out of constricted pores. In the "macro" case, greater retardation occurs at lower volume loadings because at these loadings the lattice is less well connected, and particles often wander into regions of the lattice that do not allow forward progress to the lattice surface. In effect, retardation on the macro scale is also due to particles getting lost. Thus the retardations seen on the macro scale and on the micro scale can be seen as two aspects of the same phenomenon.

VI.4 Combination of factors slowing release

In this study three factors retarding release have been identified:

1. High concentration of drug in pores,
2. Random pore topology, and
3. Constricted pore geometry.
Factors 1 and 2 were shown to be by themselves insufficient to explain the experimentally observed retardations. Parameters can be chosen for factor 3 which yield any desired retardation factor. However, the results of two-dimensional simulations indicate that those parameters may not be physically realistic.

Experimental retardation factors of approximately 150 were observed for .50 w/w BSA-loaded EVAc matrices. Factor 1 was shown in section 2 to yield a retardation factor between 2 and 4. Factor 2 yields a factor of approximately 3. As these factors are independent of each other, they can be multiplied to yield a factor between 6 and 12. This leaves a factor of between 150/12=12.5 and 150/6=25 to be explained by constrictions in the pore geometries. This factor must be achieved without including the $1/n_T$ factor twice. This is a much more reasonable demand on the geometric explanation than the original factor of 150.
REFERENCES


CHAPTER VII. SUGGESTIONS FOR FURTHER WORK

Chapters VI, V and VI all suggest further work. The data of chapter IV show certain irregularities, and when it was compared with the model of chapter V, there were discrepancies in unexpected places. Moreover, the model fit a previously gathered set of data (appendix III) quite well.

This suggests that there are unknown variables introduced when the matrices are cast that affect the release behavior. A thorough study of what happens physically during the casting process would be very valuable. For example, the rate of solvent evaporation and the viscosity of the polymer solution may be crucial variables in the formation of pore structure.

A careful assessment of the distribution of drug in the matrix should be made. This may aid in understanding the results of chapter IV and V.

Chapter VI suggests two areas of pursuit. First, the behavior of retardation as a function of model pore parameters should be investigated in three dimensions. This should be done partly because the real pores are three dimensional. It should also be done because the analysis of the conical pores indicates that dimensionality may play an
important role in determining retardation factors. If this is true for cubic vs. square pores, it would be very interesting both on theoretical and practical grounds.

A weakness of the approach taken in this study is that models are developed that contain parameters that at present are not accessible experimentally. In particular, the constriction model of chapter VI is based on SEM observations that show that pores are connected via narrow throats. However, these observations are purely qualitative, and constriction factors have not been assessed quantitatively. The development of experimental techniques that allow the determination of the constriction parameters of section VI.3 would be an extremely important breakthrough, not only for the study of EVAc controlled release matrices, but for porous media in general.
APPENDIX I. ZERO ORDER RELEASE FROM MONOLITHIC DEVICES

Monolithic drug delivery devices are often criticized because they normally do not provide zero order (constant rate) release. This is certainly true for the case of a slab that releases drug by diffusion. Consider a slab whose geometric parameters are shown in figure 1. Assume that within the slab,

\( \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \) 
\( -L < x < L, \)

where \( c(x,t) \) is the concentration (mg/ml) of the drug at time \( t \) and position \( x \) in the matrix, and \( D_e \) is the effective diffusion coefficient of the drug in the slab. Also assume the following initial and boundary conditions

\( (2) \quad c(x,t) = C^*, \quad t=0, \)
\( (3) \quad c(\pm L,t) = 0, \quad t>0. \)

If \( M_t \) is the cumulative mass of drug released through a unit area of the slab, then it is well known [1] that

\( (4) \quad M_t = \left[ \frac{8L C^*}{\pi} \right] \sum_{n=0}^{\infty} \exp\left[-D_e(2n+1)^2 \pi^2 t/4L^2\right]. \)

While \( M_t/M_\infty < 0.6 \) (where \( M_\infty \) is the total amount of drug that will be released through a unit area), the asymptotic form
Figure AI.1. Geometric parameters of slab and concentration profiles of drug solution for slab. Release is governed by simple diffusion and all solute is dissolved. [eqs. (1)-(3)].
holds. Thus the release is said to follow $t^{1/2}$ rather than zero order kinetics. Using a Boltzmann transformation (see section VI.2.4.3), it can be shown that if $D_e$ depends on drug concentration, then the early kinetics are still $t^{1/2}$. Also, cylindrical and spherical monolithic devices release drug originally at $t^{1/2}$ rates, although the downward departure of release kinetics from $t^{1/2}$ in these cases occurs earlier than in the slab case [2].

In this appendix it is shown that there are several circumstances in which it is possible to achieve or approximate zero order release with matrix devices. The methods presented below are not suitable for all drugs, and their limitations will be indicated.

Case 1: A dissolution front exists and dissolution is the rate determining step for drug release.

This case is illustrated in figure 2. Drug dissolves slowly at the position of the front $x_f$ at rate $R_d$ mg/(cm$^2$ sec). Once having dissolved it diffuses through the region $0 < x < x_f$ with diffusion coefficient $D_e$. The characteristic time for dissolution is

$$t_{diss} = \frac{\rho d}{R_d}.$$
Figure A1.2. Concentration profile of slab for which release is dissolution controlled [eqs. (8)-(10)]. A is drug loading.
where $\rho$ is the density of the drug (mg/cm$^3$) and $d$ is the diameter of a drug molecule (cm). The characteristic time for diffusion is

\begin{equation}
(9) \quad t_{\text{diff}} = \frac{x_f^2}{D_e} .
\end{equation}

So long as

\begin{equation}
(10) \quad t_{\text{diff}} \ll t_{\text{diss}}
\end{equation}

holds, the release per unit area will be given by

\begin{equation}
(11) \quad M_t = R_d t .
\end{equation}

This case probably applies at the start of the release process to many drugs that are dispersed in a matrix. Note that $t_{\text{diff}}$ is dependent on $x_f$, which increases with time. Thus, while this case may be applicable right at the start of the release process, as the front reaches deeper into the matrix (i.e. $x_f$ increases), the inequality (10) will not hold. Just how long (10) holds depends on the drug. When the inequality (10) is reversed, i.e. $t_{\text{diff}} \gg t_{\text{diss}}$, the situation described below in case 3 becomes operative.

**Case 2: Mixed dissolution and diffusion.**

This case is illustrated in figure 3. At all depths $x$
Figure AI.3. Concentration profile of slab in which dissolution and diffusion are both occurring [eq. (13)]. $A$ is drug loading, $C_s$ is drug solubility.
in the matrix there exist two phases of drug: a dissolved phase and an undissolved phase. The dissolved drug diffuses with diffusion coefficient $D_e$. The rate of drug dissolution is a function of the concentration of the dissolved drug and the drug's solubility concentration $C_s$, i.e.

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + f(C_s, c) .$$

If the undissolved phase is maintained throughout the slab, then after a time a steady state will be reached, so (12) becomes

$$D \frac{\partial^2 c}{\partial x^2} + f(C_s, c) = 0 .$$

Thus the concentration profile of dissolved drug is constant, and the release rate is constant. When the undissolved phase starts to vanish (this will happen first at $x = +L$), $t^{1/2}$ kinetics will take over. Since $c=0$ at $x = +L$, the undissolved phase will disappear at the surface at time

$$t_d = (A - C_s)/f(C_s, 0) ,$$

where $A$ is the initial drug loading (i.e. the total concentration of drug in the dissolved and undissolved states).

The case where
(15) \( f(C_s,s) = k(C_s - c) \),

with \( k \) constant, has received considerable attention lately, and full solutions for this case have been presented and tested against the observed release of certain low molecular weight drugs [3,4].

**Case 3: Drug has low solubility, but dissolution is instantaneous at the dissolution front.**

This situation is diagrammed in figure 4. At the front \( x_f \), the dissolution rate matches the rate of diffusion. Diffusion is assumed to be in a quasi steady state. For slabs (figure 4a), it has been shown [5] that

(16) \( M_t = [D C_s (2A - \epsilon C_s)]^{1/2} \) (the Higuchi equation),

where \( \epsilon \) is the matrix porosity, \( A \) is the drug loading \( \text{(mg/cm}^3) \), and \( C_s \) is the drug solubility.

The above equation predicts \( t^{1/2} \) kinetics. However, by considering release from a coated hemisphere (figure 4b), it can be shown [6] that the total drug released \( Q_t \) obeys the following equation:

(17) \( \frac{dQ}{dt} = 2\pi C_s D \epsilon r_f/(r_f - a) \),
Figure A1.4. a) Concentration profile of drug in slabs in which drug dissolution rate at front $x_f$ matches diffusion rate [eq. (16)]. $A$ is drug loading, $C_s$ is drug solubility.

b) Drug configuration in coated hemisphere with dissolution front at $r=r_f$. 
where \( a \) is the radius of the small aperture and \( r_f \) is the radial position of the dissolution front. Clearly \( r_f \) increases with time. For \( r_f \gg a \) the term in parentheses asymptotes to 1, so that equation (17) becomes

\[
\frac{dQ}{dt} = 2\pi C D a \cdot \]

The zero order release will continue until \( r_f = R \), where \( R \) is the outer radius of the hemisphere. Details of the actual time course of release can be found in [6]. Hemispheric systems have been shown experimentally to provide zero order release of drugs with low solubility [7].

Case 4: Hemispheric device containing drug in solution.

In [7] it is demonstrated that BSA can be released from a hemispheric device with zero order kinetics. Since the solubility of BSA is high (585 mg/ml [8]), it is unlikely that the constant release is due to the mechanism of case 3. It will be shown here that it is possible to approximate zero order release even when all the drug is in solution. The demonstration will be limited to the case where the diffusion coefficient is constant.

The geometry of the situation is illustrated in figure 5a. Within the hemispere, the diffusion equation (cast in spherical coordinates) holds, i.e.
Figure AI.5.  

a) Coated hemisphere containing drug that is all in solution.

b) Profile of \( u = rC \) at time 0. \( C^* \) is initial concentration.
The pertinent initial and boundary conditions are

(20) \[ c(r,t) = C^* \quad \text{for} \quad t=0, \]

and

(21) \[ c(a,t) = 0 \quad \text{for} \quad t>0 \quad \text{(perfect sink)}. \]

If we set \( u(r,t) = r c(r,t) \), then (19)-(21) become

(22) \[ \frac{\partial u}{\partial t} = D e^{\frac{2}{\partial t^2}} \]

(23) \[ u(r,t) = r C^* \quad \text{for} \quad t=0 \quad \text{and} \quad a < r < R, \]

and

(24) \[ u(a,t) = 0 \]

Now the mass release rate through the aperture is given by

(25) \[ \frac{dQ}{dt} = 2\pi a^2 D e^{\frac{\partial}{\partial r}}(u/r)_{r=a} = 2\pi a^2 D e^{\frac{\partial^2}{\partial r^2}} \left( (u/r^2)_{r=a} \right) \]

\[ = 2\pi a D e^{\frac{\partial}{\partial r}} \left. \right|_{r=a} \]

The profile of \( u \) at time 0 is shown in figure 5b. One can
break the profile into two parts. Because $D_e$ is assumed constant, (25) can be solved by solving for each of the parts and adding the two solutions. The top, "triangular" portion of the profile has constant slope $C^*$. For a considerable amount of time after the release has started, the slope will be maintained near $r=a$. (The decay in the profile will start at $r=R$ and work its way towards $r=a$.) While the slope is maintained, (25) gives, for the triangular part of the profile,

\[(26) \quad \frac{dQ(I)}{dt} = 2\pi a D_e C^* \]

The bottom, "rectangular" part of the profile is analogous to a slab with a constant initial condition. For the rectangular part of the profile it is easy to see that for early times,

\[(27) \quad \frac{dQ(II)}{dt} = 2\pi a C^* \left[ \frac{D_e}{\pi t} \right]^{1/2} \]

Therefore the total release rate is

\[(28) \quad \frac{dQ}{dt} = \frac{dQ(I)}{dt} + \frac{dQ(II)}{dt} = 2\pi a D_e C^* + 2\pi a C^* \left[ \frac{D_e}{\pi t} \right]^{1/2} \]

When $\frac{dQ(I)}{dt} \gg \frac{dQ(II)}{dt}$, zero order release will hold as long as the triangular portion of the profile maintains its slope near $r=a$. 
REFERENCES


APPENDIX II: PROGRAMS FOR CHAPTER V

This appendix contains listings of the programs described in chapter V. A brief description of the organization of the lattice representation is also given to aid interpretation of the code, much of which is coded in VAX MACRO. The reader of the following paragraphs should be familiar with VAX MACRO, plus the data structure on the VAX.

Lattices are $64 \times 64 \times N_p$. Since VAX quadwords are 64 bits long, a whole row of lattice sites is stored in a quadword. This allows parallel logical operations. A quadword is REAL*8 in FORTRAN. A layer consists of 64 consecutive quadwords. A lattice is therefore a REAL*8 FORTRAN array with dimension $(64, N_p)$. Quadwords are 8 bytes long, so each layer is $8 \times 64$ consecutive bytes of storage.

For some operations it is easier to use VAX longwords, which are 32 bits long.

In USEFUL2 and RRWALK, array A represents the lattice of "D"'s, generated by the subroutine RANDM. A one bit in array A corresponds to a "D", while a zero bit corresponds to a "-". Array B corresponds to the lattice of "$"'s, calculated from A using the subroutine ESCAP2. The array NEI in RRWALK is actually six consecutive lattices, generated from B in the subroutine NABOR2. The six lattices contain bits that are
set if the corresponding bit in $B$ has left, right, up, down, forward, or backward neighbors, respectively.
C USEFUL2--MAIN DRIVER ROUTINE DETERMINING TOTAL RELEASABLE
C DRUG AS FUNCTION OF VOLUME LOADING AND PARTICLE
C SIZE
C
REAL*8 A(64,15),B(64,15)
INTEGER*4 DEPTH,LOADNG,SEED,KOUNTA,KOUNTB,NITER
DIMENSION IDEPTH(10),LOAD(10),AVG(10,10)
DATA LOAD/5,10,15,20,25,30,35,40,45,50/
C
TYPE *,'GIVE ME NDEPTH,IDEPTH'
ACCEPT *,NDEPTH,(IDEPTH(I),I=1,NDEPTH)
TYPE *,'NOW GIVE ME SEED IN HEX'
ACCEPT 100,SEED
100 FORMAT(Z8)
DO 1 I=1,NDEPTH
DEPTH=IDEPTH(I)
TOTCEL=4096.*DEPTH
DO 1 J=1,10
LOADNG=10*LOAD(J)*1024/1000
AVLD=0.
SSQ=0.
DO 2 K=1,10
CALL RANDM(A,LOADNG,DEPTH,SEED)
CALL ESCAP2(A,B,DEPTH,NITER)
CALL COUNTD(A,DEPTH,KOUNTA)
CALL COUNTD(B,DEPTH,KOUNTB)
TRUELD=KOUNTA/TOTCEL
AVLD=AVLD+TRUELD/10.
OUT=FLOAT(KOUNTB)/FLOAT(KOUNTA)
AVG(I,J)=AVG(I,J)+OUT
SSQ=SSQ+OUT*OUT
2 CONTINUE
AVG(I,J)=AVG(I,J)/10.
SIG=SQRT(SSQ/10.-AVG(I,J)*AVG(I,J))
1 TYPE 200,DEPTH,NITER,LOADNG/1024.,AVLD,AVG(I,J),SIG
200 FORMAT(215,F5.2,3F7.3)
OPEN(UNIT=3,FILE='USEFUL2.OUT',TYPE='NEW',
FORM='FORMATTED')
1 DO 3 J=1,10
WRITE(3,300)LOAD(J)/100.,(AVG(I,J),I=1,NDEPTH)
300 FORMAT(10F7.3)
STOP
END
RANDOM MATRIX GENERATOR USING POWER RESIDUE METHOD
RON SIEGEL 10/28/82

CALL RANDM(A,IPERC,IDEPTH,ISEED)
A = OUTPUT ARRAY DIMENSIONED 64XIDEPTH
EACH ARRAY ELEMENT IS A QUADWORD (REAL*8)
CONTAINING 32 BITS WHICH ARE EITHER SET OR CLEARED
DEPENDING ON WHETHER THE CORRESPONDING CELL
IS OCCUPIED BY DRUG OR POLYMER
IPERC = VOLUME LOADING--BETWEEN 1 AND 1024
IDEPTH = DEPTH OF SLAB IN PARTICLE SIZE UNITS
ISEED = RANDOM NUMBER GENERATOR SEED WHICH IS
REPLACED AT THE END OF THE SUBROUTINE

.TITLE RANDM
.ENTER RANDM,R<2,R3,R4,R5,R6,R7,R8>
A_P=4
PERC_P=8
DEPTH_P=12
SEED_P=16

MOV L A_P(AP),R2 ;ARRAY POINTER
MOV L @PERC_P(AP),R3 ;LOADING
MOV L @DEPTH_P(AP),R4 ;SLAB DEPTH
ASHL #7,R4,R4 ;TIMES 128 TO GET ARRAY SIZE
MOV L @SEED_P(AP),R5 ;SEED FOR RANDOM NUMBER

MOV L #69069,R6 ;MULTIPLIER INTO R6
MULL2 R6,R5 ;ONE CYCLE OF RANDOM NUMBER GENERATOR

; THIS IS THE MAIN LOOP

ALOOP: MOV L #32,R1 ;BIT COUNTER IN LONGWORD
CLRL R7 ;GET RID OF GARBAGE IN R7

DLOOP: MULL2 R6,R5 ;THIS IS THE RANDOM NUMBER GENERATOR
INCL R5

BICL3 #OX003FFFFF,R5,R8 ;RESIDUE BETWEEN 0 AND 1023
ROTL #10,R8,R8 ;PUT INTO LOW ORDER
CMPL R8,R3 ;DETERMINE WHETHER OR NOT
ADWC R7,R7 ;TO FILL (AND SHIFT)
SOBGTR R1,DLOOP ;MOVE TO NEXT CELL (BIT)

MOV L R7,(R2)+ ;PUT 32 CELLS INTO ARRAY
LWORD
SOBGTR R4,ALOOP ;MOVE TO NEXT LONGWORD

MOV L R5,@SEED_P(AP) ;DONE--UPDATE RANDOM NUMBER SEED
RET ;AND GET OUT OF HERE

.END
.TITLE ESCAP2
; COUNTS NUMBER OF DRUG FILLED CELLS IN A CUBIC
; LATTICE THAT CAN ACCESS THE SURFACE (TWO FACES) OF
; THAT LATTICE
; RON SIEGEL 10/14/81
; MODIFIED FOR TWO SIDED RELEASE 2/17/83
; CALL ESCAP2(A,B,IDEPTH,NITER)
; A = INPUT ARRAY CONTAINING LATTICE IN QUESTION.
; EACH ARRAY ELEMENT IS A QUADWORD (REAL*8)
; AND THE DIMENSION IS 64XIDEPTH
; CONTAINING A ROW OF 64 CELLS (BITS) WHICH ARE
; SET TO ONE IF CELL CONTAINS DRUG.
; B = OUTPUT ARRAY CONTAINING LATTICE IN WHICH THE
; CELLS (BITS) ARE SET IF THE CORRESPONDING CELL
; IN A IS SET AND CONNECTED TO THE SURFACE OF
; A. EACH ELEMENT IS A QUADWORD (REAL*8) AND
; THE DIMENSION IS 64XIDEPTH. EXTRA ROW
; IS FILLED WITH ZEROS FOR CONVENIENCE.
; IDEPTH = DEPTH OF MATRIX (INTEGER*4)
; NITER = NUMBER OF ITERATIONS REQUIRED
; A_P=4
; B_P=8
; DEPTH_P=12
; NITER_P=16
.ENTRY ESCAP2,®,M<R2,R3,R4,R5,R6,R7,R8,R9>
;
MOVL A_P(AP),R0 ;ADDRESS OF INPUT LATTICE
MOVL R0,R4
MOVL B_P(AP),R1 ;ADDRESS OF OUTPUT LATTICE
MOVL @DEPTH_P(AP),R2 ;DEPTH OF LATTICE
ASHL #9,R2,R3 ;MULTIPLY BY NUMBER OF BYTES
; PER LAYER
ADDL R3,R4 ;R4 POINTW TO END OF A
ADDL R1,R3 ;R3 NOW POINTS TO END OF B
MOVL R3,R5 ;SO DOES R5
CLRL @NITER_P(AP) ;INTERATION COUNT
;
COPY FIRST LAYER OF A TO FIRST LAYER OF B AND
ZERO OUT LAYER OF B AFTER END OF LATTICE
;
DECL R2 ;DEPTH-1
DECL R2 ;DEPTH-2
MOVL R2,SAVDEP ;WE'LL NEED THIS LATER
MOVZBL #64,R2 ;64 ROWS PER LAYER
COPY: MOVQ (R0)+,(R1)+ ;FRONT SURFACE
MOVQ -(R4),-(R3) ;BACK SURFACE
SOBGTR R2,COPY
TSTL SAVDEP
BNEQ PROCED
RET ;IF SO THEN WE'RE DONE
;
PROCED: MOVL R0,SAVO ;POINT TO BEGINNING
MOVL R1,SAV1 ;OF SECOND LAYER
; NOW ZERO OUT REST OF B
ZEROB: CLRQ (R1)+
        CMPL R1,R3
        BLSS ZEROB

; NOW COMES THE MAIN PART
; WE ITERATE UNTIL SATISFACTION ACHIEVED, I.E.
; NO CHANGE IN THE B LATTICE
;
ITERLP: INCL @NITER_P(AP) ;INCREMENT COUNT OF
        CLRW DIFF ;THIS WILL BE SET IF B
                    ;CHANGES AT ALL
        MOVL SAV0,R0 ;START OF A MATRIX (LAYER 2)
        MOVL SAV1,R1 ;START OF B MATRIX (LAYER 2)
        MOVL SAVDEP,R2 ;DEPTH-2 (THIS PROCESSING
                    ;EXCLUDES TOP AN BOTTOM
                    ;LAYERS)
;
       層 INITIALIZE PROCESSING FOR LAYER
        LAYER: MOVZBL #64,R9 ;COUNTER FOR ROWS
                MOVQ 512(R1),EDGE ;SAVE BEGINNING OF NEXT LAYER
                CLRQ 512(R1) ;SO WE CAN CLEAR IT
                        ;(ELIMINATES EDGE PROBLEMS)
                MOVZBL #1,SWITCH ;INDICATES WE'RE ON FIRST ROW
;
        末 ROW LOOP
        ROW: MOVQ (R0)+,R3 ;ROW OF A
                MOVQ (R1),R5 ;ROW OF B
                MOVQ R5,SAV64 ;SAVE TO TEST LATER FOR
                    ;CHANGES
                ASHQ #1,R5,R7 ;LEFT NEIGHBORS
                ASHQ #1,R5,R5 ;RIGHT NEIGHBORS
                BICL2 #0X80000000,R6 ;GET RID OF SIGN BIT
                BISL2 R7,R5 ;LOGICALLY OR LEFT
                BISL2 R8,R6 ;AND RIGHT
                BISL2 -512(R1),R5 ;AND DOWN ONE
                BISL2 -508(R1),R6 ;LAYER AND
                BISL2 512(R1),R5 ;UP ONE
                BISL2 516(R1),R6 ;LAYER
                BISL2 8(R1),R5 ;AND BACKWARD
                BISL2 12(R1),R6 ;ONE ROW
                SOBGEQ SWITCH,ANDEM ;AND UNLESS THE FIRST ROW,
                BISL2 -8(R1),R5 ;DO IT FORWARD
                BISL2 -4(R1),R6 ;ONE ROW
;
        ANDEM:  MCOML R5,R5 ; MCOML AND BICL TOGETHER
                MCOML R6,R6 ; CONSTITUTE A LOGICAL AND
                BICL2 R5,R3 ; LOGICALLY AND FINAL RESULT
                BICL2 R6,R4 ; WITH A MATRIX ENTRIES
                MOVQ R3,(R1)+ ; AND ADVANCE
                CMPL R3,SAV64 ; ANY CHANGES IN B MATRIX?
                BNEQ SDIFF
                CMPL R4,SAV64+4
                BEQL GOBACK
;
        SDIFF: MOVW #1,DIFF ;SET "DIFFERENT" FLAG
        GOBACK: SOBGTR R9,ROW ;GO TO NEXT ROW OF 64
MOVQ     EDGE,(R1)                     ;RESTORE FIRST ROW OF NEXT
SOBGT    R2, LAYERJ                  ;LAYER
          ONE PASS THROUGH
TSTW     DIFF                        ;GO TO NEXT LAYER OF 64X64
BNEQ     ITERJ                       LATTICE
          ;ANY CHANGES?
          ;IF SO GO BACK AND DO IT
          ;AGAIN
          ;OTHERWISE, WE'RE DONE

;ALL DONE WITH
RET

;LAYERJ: JMP LAYER
ITERJ: JMP ITERLP

SAVO:   .LONG  0
SAVI:    .LONG  0
SAVDEP:  .LONG  0
SWITCH:  .LONG  0
DIFF:    .WORD  0
SAV64:   .QUAD  0
EDGE:    .QUAD  0
.END
.TITLE COUNTD
; COUNTS NUMBER OF ON BITS IN A 3D LATTICE
; RON SIEGEL 10/19/81
;
.ENTRY COUNTD, @R2,R3,R4,R5>
A_P=4
DEPTH_P=8
KOUNT_P=12
;
CLRL R0 ; COUNTER OF "ON" BITS
CLRL R5 ; WORD COUNTER
MOVL A_P(AP), R1 ; STARTING ADDRESS
ASHL #7, @DEPTH_P(AP), R2 ; DEPTH MULTIPLIED BY 128
;
NEWORD: MOVL (R1)+, R3 ; GET NEXT WORD
TWOS: BEQL TSTEND ; ALL OUT OF ONE BITS?
INCL R0 ; IF NOT, INCREMENT BIT COUNT
MNEG R3, R4 ; TWO'S COMPLEMENT AND
BICL2 R4, R3 ; WORD IN QUESTION TO ITSELF
BRW TWOS ; AND KEEP GOING
TSTEND: AOBLSS R2, R5, NEWORD ; LOOP BACK TILL DONE
MOVL R0, @KOUNT_P(AP) ; RESULT
RET
.END
RRWALK--MAIN DRIVER ROUTINE FOR RANDOM WALK IN RANDOM LATTICE SIMULATION

RON SIEGEL 1/5/84

REAL*8 A(64,15), B(64,16)
REAL*8 LFT(64,15), RGT(64,15), UP(64,15), DN(64,15)
REAL*8 FOR(64,15), BAK(64,15), NEI(64,15,6)
INTEGER BIN(4000), DEPTH, DEPTH1
INTEGER*4 ISEED
DIMENSION NWHICH(6)
EQUIVALENCE (LFT(1,1), NEI(1,1,1))
EQUIVALENCE (RGT(1,1), NEI(1,1,2))
EQUIVALENCE (UP(1,1), NEI(1,1,3))
EQUIVALENCE (DN(1,1), NEI(1,1,4))
EQUIVALENCE (FOR(1,1), NEI(1,1,5))
EQUIVALENCE (BAK(1,1), NEI(1,1,6))

TYPE *, 'GIVE ME LOADING AND DEPTH'
ACCEPT *, LOAD, DEPTH
DEPTH1=DEPTH+1
TYPE *, 'GIVE ME A SEED INTEGER'
ACCEPT *, ISEED
CALL INIT01(ISEED)
LOADNG=10*LOAD*1024/1000
CALL RANDM(A, LOADNG, DEPTH, ISEED)
CALL COUNTD(A, DEPTH, KOUNTA)
CALL ESCAP2(A, B, DEPTH, NITER)
CALL NABOR2(B, LFT, RGT, UP, DN, FOR, BAK, DEPTH)
DO 30 IZ1=1, DEPTH
DO 31 IY1=1, 64
DO 31 IX1=0, 63
CALL NABPR(NEI, 15, IX1, IY1, IZ1, NNAB, NWHICH)
IF(NNAB.EQ.0) GO TO 31
IZ=IZ1
IY=IY1
IX=IX1
KSTEP=0
T=0.
9 KSTEP=KSTEP+1
CALL NABPR(NEI, 15, IX, IY, IZ, NNAB, NWHICH)
CUM=0.
RNAB=NNAB
T=T+6./RNAB
CALL RAND01(X)
DO 10 I=1, 6
CUM=CUM+NWHICH(I)/RNAB
IF(X.LT.CUM) GO TO (11, 12, 13, 14, 15, 16), I
10 CONTINUE
11 IX=IX-1
GO TO 9
12 IX=IX+1
GO TO 9
13 IZ=IZ+1
IF(IZ.EQ.DEPTH1)GO TO 20
GO TO 9
14 IZ=IZ-1
IF(IZ.EQ.0)GO TO 20
GO TO 9
15 IY=IY-1
GO TO 9
16 IY=IY+1
GO TO 9
20 KWALK=KWALK+1
IT=T+.5
IF(IT.GT.4000)GO TO 25
BIN(IT)=BIN(IT)+1
GO TO 31
25 KOVER=KCOVER+1
31 CONTINUE
30 CONTINUE
OPEN(UNIT=2,FILE='RRWALK.OUT',TYPE='NEW',
1 FORM='FORMATTED')
COUNTA=KOUNTA
WRITE(2,5000)0,0.,0.
DO 35 IT=1,4000
T=IT
IF(IT.GT.1)BIN(IT)=BIN(IT)+BIN(IT-1)
35 WRITE(2,5000)ITSQRT(T),BIN(IT)/COUNTA
5000 FORMAT(I5,2F7.3)
TYPE *,'KOVER/COUNTA=',KOVER/COUNTA
STOP
END
.TITLE NABOR2
; DETERMINE NEIGHBORS SHARING A FACE WITH EACH SUBCUBE IN A
; LATTICE.
; SINK ON TWO FACES OF LATTICE.
; RON SIEGEL 1/4/84
; SUBROUTINE NABOR2(T,L,R,U,D,F,B,DEPTH)

.SUBROUTINE NABOR2(T,L,R,U,D,F,B,DEPTH)

.ENTRY NABOR2, @M<R2,R3,R4,R5,R6,R7,R8>

T_P=4 ;TEST LATTICE
L_P=8 ;CELLS OF T WITH LEFT NEIGHBORS
R_P=12 ;RIGHT
U_P=16 ;UP
D_P=20 ;DOWN
F_P=24 ;LEFT
B_P=28 ;BACKWARDS
DEPTHP=32 ;DEPTH OF LATTICE

; TAKE CARE OF LEFT AND RIGHT FIRST
MOVLT_P(AP),R0 ;START OF TEST LATTICE
MOVLL_P(AP),R1 ;START OF "LEFT" LATTICE
MOVLR_P(AP),R2 ;START OF "RIGHT" LATTICE
MOVLODEPTH_P(AP),R3 ;DEPTH OF LATTICE IN LAYERS

LR1: MOVZBL #64,R4 ;# ROWS PER LAYER
LR2: MOVQ (RO)+,R5 ;ROW OF 64 CELLS
ASHQ #1,R5,R7 ;LEFT NEIGHBORS
MCOMLR7,R7,R7 ;MCOML AND BICL3
BICL3 R7,R5,(R1)+ ;DEPOSIT LEFT NEIGHBORED
BICL3 R8,R6,(R1)+ ;INTO L ARRAY
BICL3 R7,R5,R5 ;DO AGAIN
BICL3 R8,R6,R6 ;BUT INTO (R5,R6)
ASHQ #1,R5,R7 ;AND PUT INTO LEFT NEIGHBOR
MOVLR7,(R2)+
BICL3 @=X80000000,R8,(R2)+
SOBGTR R4,LR2 ;LOOP BACK IF STILL MORE ROWS
SOBGTR R3,LR1 ;LOOP BACK IF MORE LAYERS

; UPS AND DOWNS
MOVLT_P(AP),R0 ;START OF "UP" LATTICE
MOVLU_P(AP),R1 ;START OF "DOWN" LATTICE
MOVZBL #64,R4 ;COPY FIRST LAYER OF
UD1: MOVQ (RO)+,(R2)+ ;TEST LATTICE TO
SOBGTR R4,UD1 ;"DOWN" LATTICE (I.E. CONNECT
; TO SINK)
MOVLT_P(AP),R0 ;RESTORE RO TO BEGINNING OF
;TEST LATTICE
MOVLODEPTH_P(AP),R3 ;ONLY DEPTH-1 COMPARISONS
DECL R3 ;BETWEEN LAYERS

UD2: MOVZBL #128,R4
UD3: MCOMLR512(R0),R5
BICL3 R5,(R0),(R1)+
BICL3 R5,(R0)+,(R2)+
SOBGTR R4,UD3
SOBGTR R3,UD2
MOVZBL #64,R4
UD4:
MOVQ (R0)+,(R1)+
SOBGTR R4,UD4
; FORWARDS AND BACKWARDS
MOVL T_P(AP),R0
MOVL F_P(AP),R1
MOVL B_P(AP),R2
MOVL @DEPTHP(AP),R3
BF1:
CLRQ (R1)+
CLRQ 504(R2)
MOVL #126,R4
BF2:
MCOML (R0)+,R5
BICL3 R5,4(R0),(R1)
MOVL (R1)+,(R2)+
SOBGTR R4,BF2
ADDL #8,R0
ADDL #8,R2
SOBGTR R3,BF1

; RET
.END
SUBROUTINE NABPR -- DETERMINES WHICH NEIGHBORS OF A SITE ARE FILLED

RON SIEGEL 1/4/84

SUBROUTINE NABPR(NEI, NEIDIM, IX, IY, IZ, NNAB, NWHICH)
LOGICAL*4 BTT
INTEGER*4 IROW(2)
REAL*8 NEI(64, NEIDIM, 6), ROW
DIMENSION NWHICH(6)
EQUIVALENCE (ROW, IROW(1))

IF (IX .LT. 32) THEN
   J = 1
   IX32 = IX
ELSE
   J = 2
   IX32 = IX - 32
ENDIF

NNAB = 0
DO 1 I = 1, 6
   ROW = NEI(IY, IZ, I)
   BTT = BJTEST(IROW(J), IX32)
   IF (BTT) THEN
      NWHICH(I) = 1
      NNAB = NNAB + 1
   ELSE
      NWHICH(I) = 0
   ENDIF
1 CONTINUE
RETURN
END
.TITLE RAND01
.ENTRY RAND01,@M<>
; SUBROUTINE RAND01(X)
; RETURNS RANDOM VALUE BETWEEN 0 AND 1
MULL3  #69069,R,RO     ; COMPUTE RANDOM INTEGER
INCL   RO               ; AS A LONGWORD
MOV L  R0,R             ; PUT BACK IN STORAGE
BICL2  #$X00000000,RO   ; ELIMINATE SIGN BIT
CVTLF  R0,R1            ; MAKE FLOATING POINT
DIVF  RMAX,R1,@4(AP)    ; DIVIDE INTO LARGEST POSSIBLE
                        ; NUMBER
RET

; .ENTRY INIT01,@M<>    
; SUBROUTINE INIT01(ISEED)    
; SEEDS RANDOM NUMBER GENERATOR
MOVL  @4(AP),R          ; THIS IS THE SEED
CVTLF  #$X7FFFFFFF,RMAX ; THIS IS THE LARGEST
                        ; POSSIBLE NUMBER
RET
R:   .LONG  0
RMAX: .LONG  0
.END
APPENDIX III. A SECOND SET OF DATA

Before the set of experiments described in chapter IV were run, a preliminary set of data was gathered and compared to the model of the total fraction released. The experimental conditions were slightly different. For this set of data, the model fit quite well, as opposed to the case of chapters IV and V. In this appendix, the modified experimental conditions and the corresponding modifications to the model are described briefly, and a comparison between data and theory is made.

BSA, particle size 150-180µm was incorporated into EVAc by the method described in section IV.2. After the disks were punched out of the slabs, they were coated on one circular face and around the rim with wax, leaving one circular face exposed. The disks were then placed in unbuffered saline and release of BSA was monitored.

The only change in the model of section V.3 was that only drug-filled lattice sites on the top layer (l=1) were initially set to "$\$". For $l=1$ for $l=N_p$, drug-filled sites were ultimately set to "$\$" only if they belonged to connected clusters extending all the way to $l=1$. This amounted to a small modification of the subroutine ESCAP2 (see appendix II).
The results of the release experiments and the model fit for \( N_p = 6 \) (the average depth of these disks was approximately 1.05 mm) are shown in figure 1. The model provides a good fit to the data.
Figure AIII.1. Total fraction released for a preliminary set of BSA disks released through only one face. Curve is fit of modified model that only allows release through one side. PS=150-180 m, average depth=1.05mm. Model assumes 6 layers.
APPENDIX IV: NUMERICAL PROCEDURE AND COMPUTER PROGRAM FOR CONCENTRATION DEPENDENT DIFFUSION

In this appendix we describe the solution technique for the nonlinear second order differential equation (ODE)

\[
-2\eta \frac{dc}{d\eta} = \frac{d}{d\eta} \left[ \frac{\gamma(c) dc}{D(c) d\eta} \right]
\]

subject to the boundary conditions

\[
(2) \quad c(0) = 0
\]

\[
(3) \quad c(\infty) = C^*.
\]

\(\gamma(c)\) is bounded by 1.

Equation (1) is first recast as a system of first order ODE's:

\[
(4) \quad \frac{dc}{d\eta} = c'
\]

\[
\frac{dc'}{d\eta} = \left( 2\eta c' - c \frac{d\gamma}{dc} \frac{d^2 D}{dc^2} \right) / D(c).
\]

Equations (4), subject to (2) and (3), constitute a nonlinear two point boundary value problem, for which a simple numerical solution cannot be found. However, the problem can be converted to an initial value problem by replacing eq. (3)
with

\[(3') \quad c'(0) = S\]

where \(S\) is chosen by the analyst. The solution to \((2),(3'),(4)\) converges, as \(\eta \to \infty\), to a particular value \(C^*\), which depends on \(S\).

The system \((2),(3'),(4)\) is solved using the FORTRAN program BDRK. BDRK is the main driver routine that calls the subroutine ODEsolver, which implements a fourth order Runge-Kutta finite difference scheme, with variable stepsize. At the \(n'\)th step of the Runge-Kutta procedure, the stepsize \(\Delta \eta_n\) is set to \(\hat{D}(c_n) \Delta \eta_0\), where \(\Delta \eta_0\) is specified by the user. \(c_n\) is the concentration at the \(n'\)th step. The variable stepsize is implemented because the system becomes very stiff when \(D\) gets small.

The program performs the above procedure for many values of \(S\), so that a plot of \(S\) versus \(C^*\) may be generated. Since \(S\) is proportional to the flux out of the semiinfinite slab, this plot will be proportional to the desired plot of flux versus initial concentration.

The program BDRK must be loaded with the user-supplied FUNCTION subprograms DIFF and dDdc, which provide the computation of \(\hat{D}(c)\) and \(d\hat{D}/dc\). Also, SUBROUTINE ID, which
passes back a name for the model, must be provided. The name passed back is used in output filenames.

A listing of BDRK, along with the subprograms necessary for the Keller diffusivity model, is provided in this appendix.
COMPUTES RATIOS RT(C*) AND RS(C*).
RT IS COMPUTED BY INTEGRATING D(C).
RS IS COMPUTED BY SOLVING THE BOLTZMANN TRANSFORMED
DIFFUSION EQUATION WITH CONCENTRATION DEPENDENT
DIFFUSION COEFFICIENT.

DIMENSION C(125), RATIO(125), RATIOS(125), SL(125), D(125)
CHARACTER*6 MODEL
TYPE '*', 'GIVE ME DETA'
ACCEPT '*', DETA
SLOPE=0.
OLDC=0.
OLDD=1.
RINT=0.
DO 1 I=1, 100
SLOPE=SLOPE+30.
SL(I)=SLOPE
CALL ODESOLVER(DETA, SLOPE, CI, ETAS)
IF(CI.GT.1000.)GO TO 3
C(I)=CI
DI=DIFF(CI)
RATIOI=(SLOPE/CI)/(2./SQRT(3.14159))
RATIO(1)=RATIOI*RATIOI
D(I)=DI
RINT=RINT+.5*(DI+OLDD)*(CI-OLDC)
RATIOS(I)=RINT/CI
TYPE '*', SLOPE, CI, DI, RATIOS(I), RATIO(I)
OLDC=CI
OLDD=DI
II=I-1
CALL ID(MODEL)
OPEN(UNIT=1, FILE=MODEL//'.OUT', TYPE='NEW',
1 FORM='FORMATTED')
ZERO=0.
ONE=1.0
WRITE(1,1000) ZERO, ONE, ONE, ONE
DO 2 I=1, II
WRITE(1,1000) C(I), D(I), RATIOS(I), RATIO(I)
CLOSE(1)
STOP
1000 FORMAT(F7.2, F10.5, 2F10.4)
END

ODESolver SOLVES DIFF EQ. USING RUNGE-KUTTA WITH
VARIABLE STEPSIZE

SUBROUTINE ODESolver(dE, sl, z, etas)
eta=0.
z=0.
y=sl
1 data=diff(z)*dE
call rk(eta, y, z, data, yl, zl)
if(abs(z-zl)/deta.lt.1e-3)return
eta=eta+deta
y=y1
z=z1
goto 1
END

C RUNGE-KUTTA ONE-STEP

SUBROUTINE RK (X0,Y0,Z0,dE,Y1,Z1)
CY1=dE*DER(X0,Y0,Z0)
CZ1=dE*Y0
CY2=dE*DER(X0+dE*.5,Y0+CY1*.5,Z0+CZ1*.5)
CZ2=dE*(Y0+CY1*.5)
CY3=dE*DER(X0+dE*.5,Y0+CY2*.5,Z0+CZ2*.5)
CZ3=dE*(Y0+CY2*.5)
CY4=dE*DER(X0+dE,Y0+CY3,Z0+CZ3)
CZ4=dE*(Y0+CY3)
Y1=Y0+(CY1+2.*CY2+2.*CY3+CY4)/6
Z1=Z0+(CZ1+2.*CZ2+2.*CZ3+CZ4)/6
RETURN
END

C BOLTZMANN-TRANSFORMED DIFFUSION EQUATION
C IN VECTOR FORM

FUNCTION DER (t,dC,C)
s=dDdC(C)
f=Diff(C)
DER=-dC*(s*dC+2.*t)/f
RETURN
END
C DIFFUSIVITY PROFILE GIVEN BY KELLER, CANALES, AND YUM

SUBROUTINE ID(MODEL)
CHARACTER*6 MODEL
MODEL='KELLER'
RETURN
END

FUNCTION Diff (C)
gam=21.3/1340.
gC=gam*C
IF (gC.EQ.0.) THEN
Diff=1.
ELSE
Diff=TANH(gC)/gC
ENDIF
RETURN
END

FUNCTION dDdC (C)
gam=21.3/1340.
gC=gam*C
IF (gC.EQ.0.) then
  dDdC=0.
else
  const=gam/gC
  S=SECH(gC)
  dDdC=const*(S*S-TANH(gC)/gC)
ENDIF
RETURN
END

FUNCTION SECH(X)
IF (ABS(X).GT.30) then
  SECH=0.
else
  SECH=1/COSH(X)
ENDIF
RETURN
END
APPENDIX V. The RSPASS program

This appendix describes and provides listings for RSPASS and its subroutines. This set of routines calculates and tabulates mean first passage times of particles diffusing through pores with constricted outlets (throats). The reader should refer to section VI.3.4.

RSPASS is the main driver routine for SUBROUTINE RPASS, which in turn calls SUBROUTINES SQUARE and RNOS2. RSPASS accepts from the user a random number generator seed, and the throat widths w (array DIAM) and half-lengths z (array DPTH), for which all combinations are tested. RSPASS sends that throat half-length and width information. RSPASS also sends to RPASS information on the throat configuration, via the arrays Cl and C2. If a side of the central pore body, indexed by I, contains an outlet to a throat, then Cl(I)=-DIAM/2 and C2(I)=+DIAM/2. If there is no outlet on that side, then Cl(I)=1 and C2(I)=-1.

RPASS executes the iterative routine described in VI.3.4. SUBROUTINE SQUARE determines the radius of a box around the particle for a particle located in the central pore body. For particles in throats, the radius of the box is determined in RPASS itself. The MACRO subroutine RNOS2 returns two uniformly distributed random numbers IP and IS. IS ranges from 1 to 4, and is used to determine the side of
the box on which a particle lands. IP ranges from 0 to 1023, and is used to determine the position along the side on which the particle lands. The position is given by \( Q_1^{-1}\left(\frac{IP+1}{1025}\right) \), where \( Q_1 \) is given by equation (VI.83). \( Q_1^{-1} \) is computed and stored in table form in RSPASS.
C RSPASS--TABULATES MEAN FIRST PASSAGE TIMES FOR PORES
C WITH THROATS OF VARIOUS WIDTHS (DIAM),
C HALF-LENGTHS (DPTH), AND CONFIGURATIONS
C
LOGICAL*1 FILE(11)
INTEGER*4 ISEED
DIMENSION T(1000),NARR(4),TB(4),KS(4,5)
DIMENSION DIAM(20),DPTH(10)
COMMON /PROBS/AHIT(0:1023)
COMMON /PARAMS/C1(4),C2(4)
DATA KS/1,1,0,0, 1,0,1,0, 1,1,1,0, 1,1,0,1, 1,1,1,1/
TYPE *,'GIVE ME ISEED/NDEPTH,DPTH/NDIAM,DIAM'
ACCEPT *,ISEED
ACCEPT *,NDEPTH,(DPTH(IL),IL=1,NDEPTH)
ACCEPT *,NDIAM,(DIAM(ID),ID=1,NDIAM)
TYPE *,'FILENAME?'
ACCEPT 100,(FILE(I),I=1,10)
FORMAT(10A1)
TYPE *,'FRACTIONAL ERROR TOLERANCE'
ACCEPT *,TERROR
FILE(11)=0
OPEN(UNIT=2,FILE=FILE,TYPE='NEW',FORM='FORMATTED')
DO 20 IP=0,1023
P=((IP+1)/1025.1)
20 AHIT(IP)=2./3.1415928*ASIN(2.*P-1.)
CALL RINIT(ISEED)
DO 50 IL=1,NDEPTH
DEPTH=DPTH(IL)
DO 50 ID=1,NDIAM
D=DIAM(ID)
D2=D/2.
DO 40 JC=1,5
DO 1 I=1,4
IF(KS(I,JC))2,3,2
2 C1(I)=-D2
C2(I)=D2
GO TO 1
3 C1(I)=1
C2(I)=-1
1 CONTINUE
TT=0.
T2=0.
DO 16 I=1,4
NARR(I)=0
16 TB(I)=0.
I=0
10 I=I+1
CALL RPASS(DEPTH,TI,IS)
T(I)=TI
NARR(IS)=NARR(IS)+1
TB(IS)=TB(IS)+TI
TT=TT+TI
T2=T2+TI*TI
IF(I.LT.100)GO TO 10
TBAR = TT / I
TSTD = SQRT(T2 / I - TBAR * TBAR)
FERROR = TSTD / SQRT(FLOAT(I)) / TBAR
IF(FERROR .GT. TERROR) GO TO 10

TYPE 1000, DEPTH, D, JC, TBAR, TSTD, I

1000 FORMAT ('0LENGTH=', F5.3, ', DIAM=', F6.3, ', CONFIG.', I2,
1 'TBAR, TSTD=', 2F10.3, ' I=', I5)

DO 17 IS = 1, 4
IF(NARR(IS).EQ.0) GO TO 17
TB(IS) = TB(IS) / NARR(IS)

TYPE *, IS, NARR(IS), TB(IS)

17 CONTINUE

40 WRITE(2, 2000) DEPTH, D, JC, TBAR, TSTD, NARR, TB

2000 FORMAT (2F6.3, I3, 2F8.3 / 4I5, 4F8.3)

50 CONTINUE
STOP
END
C RPASS--COMPUTES FIRST PASSAGE TIME THROUGH PORE
C WITH THROATS.
C REFLECTION AT INLET THROAT BISECTOR ASSUMED.
C
SUBROUTINE RPASS(DEPTH,T,ISIDE)
LOGICAL LSIDE
INTEGER*4 IR1,IR2,IR3,IS,ISIDE
REAL L
COMMON /CONST/CONST1,CONST2,PI4,PIPI
COMMON /PARAMS/C1(4),C2(4)
COMMON /PROBS/AHIT(0:1023)
DATA PI/3.1415928653/
T=0

C FIRST GET TO INLET
D2=DEPTH*DEPTH
T=T+.5*D2
YT=0.
CALL RNOS2(IR3,ISIDE)
XT=C1(1)+(C2(1)-C1(1))/1024.*IR3
ISIDE=1

C WHEN IN AN THROAT...

10 C11=C1(ISIDE)
C21=C2(ISIDE)
DELX=0.
DELY=0.

15 IF(YT.LT..0001)YT=.0001
L=AMIN1(DEPTH-YT,XT-C11,C21-XT)
IF(L.LT..000001)L=AMIN1(DEPTH-YT,C21-C11)
T=T+.295*L*L
CALL RNOS2(IP,IS)
XINC=AHIT(IP)*L
IF(XT-C11.GT..000001)GO TO 16
GO TO (17,12,17,12),IS
16 XINC=ABS(XINC)
GO TO 19

17 XINC=ABS(XINC)
GO TO 19

18 XINC=-ABS(XINC)
GO TO (11,12,13,14),IS
19 YT=YT+L
XT=XT+XINC
IF(DEPTH-YT.GE..000001)GO TO 15
IF(ISIDE.EQ.1)GO TO 2
RETURN

12 XT=XT+L
YT=YT+XINC
IF(YT)20,15,15

13 YT=YT-L
XT=XT+XINC
IF(YT)20,15,15

14 XT=XT-L
YT=YT+XINC
IF(YT)20,15,15
C GET BACK INTO CENTRAL PORE BODY
20 LSIDE=.FALSE.
   GO TO (21,22,23,24),ISIDE
21 Y=1.+YT
   X=XT
   GO TO 40
22 X=1.+YT
   Y=-XT
   GO TO 40
23 Y=-1.-YT
   X=-XT
   GO TO 40
24 X=-1.-YT
   Y=XT
   GO TO 40
C C WHEN IN THE CENTRAL PORE BODY...
C
30 CALL SQUARE(X,Y,L,ISIDE,LSIDE)
   T=T+.295*L*L
   CALL RNOS2(IP,IS)
   XINC=AHIT(IP)*L
   GO TO (31,32,33,34),IS
31 DELX=XINC
   DELY=L
   GO TO 35
32 DELX=L
   DELY=XINC
   GO TO 35
33 DELX=XINC
   DELY=-L
   GO TO 35
34 DELX=-L
   DELY=XINC
35 IF(LSIDE)GO TO (36,37,38,39),ISIDE
   GO TO 40
36 DELY=-ABS(DELY)
   GO TO 40
37 DELX=-ABS(DELX)
   GO TO 40
38 DELY=ABS(DELY)
   GO TO 40
39 DELX=ABS(DELX)
C
40 LSIDE=.FALSE.
   X=X+DELX
   Y=Y+DELY
   IF(Y.LE..9999)GO TO 41
   Y=1.
   LSIDE=.TRUE.
   ISIDE=1
   IF(X.LT.C1(1))GO TO 30
   IF(X.GT.C2(1))GO TO 30
YT=0.
XT=X
GO TO 10
41 IF(X.LE..9999)GO TO 42
X=1.
LSIDE=.TRUE.
ISIDE=2
IF(Y.LT.C1(2))GO TO 30
IF(Y.GT.C2(2))GO TO 30
YT=0.
XT=-Y
GO TO 10
42 IF(Y.GE-.9999)GO TO 43
Y=-1.
LSIDE=.TRUE.
ISIDE=3
IF(X.LT.C1(3))GO TO 30
IF(X.GT.C2(3))GO TO 30
YT=0.
XT=-X
GO TO 10
43 IF(X.GE-.9999)GO TO 30
LSIDE=.TRUE.
X=-1.
ISIDE=4
IF(Y.LT.C1(4))GO TO 30
IF(Y.GT.C2(4))GO TO 30
YT=0.
XT=Y
GO TO 10
END

SUBROUTINE SQUARE(X,Y,L,ISIDE,LSIDE)
REAL L
INTEGER*4 ISIDE
LOGICAL LSIDE
COMMON /PARAMS/C1(4),C2(4)
ABSX=ABS(X)
ABSY=ABS(Y)
C TAKE CARE OF CORNER DEAD ENDS
IF(ABSX.LE..99)GO TO 30
IF(ABSY.LE..99)GO TO 30
X=X*.99
Y=Y*.99
ABSX=ABS(X)
ABSY=ABS(Y)
LSIDE=.FALSE.
GO TO 2
30 IF(LSIDE)GO TO 5
C' IF IN INTERIOR OF CENTRAL PORE BODY...
IF(ABSY.GT.ABSX)GO TO 1
ISIDE=1
IF(Y.LT.0.)ISIDE=3
GO TO 2
ISIDE=2
IF(X.LT.0.)ISIDE=4
L=AMIN1(1.-ABSX,1.-ABSY)
IF(L.NE.0.)RETURN
LSIDE=.TRUE.
C IF ON BOUNDARY OF CENTRAL PORE BODY...
CC1=C1(ISIDE)
CC2=C2(ISIDE)
GO TO (3,4,3,4),ISIDE
IF(X.GT.CC1)GO TO 31
L=AMIN1(X+1.,CC1-X)
RETURN
31 L=AMIN1(1.-X,X-CC2)
RETURN
4 IF(Y.GT.CC1)GO TO 41
L=AMIN1(Y+1.,CC1-Y)
RETURN
41 L=AMIN1(1.-Y,Y-CC2)
RETURN
END
.TITLE RNOS\$2
.ENTRY RNOS2, @M<R2>
IT=4
IS=8

; MOVL STORE, R0
MOVL #69069, R1
MULL R1, R0
INCL R0
BICL3 #X03FFFFF, RO, R2
ROTL #10, R2, @IT(AP)

; MULL R1, R0
INCL R0
BICL3 #X3FFFFFFF, RO, R2
ROTL #2, R2, R2
INCL R2
MOVL R2, @IS(AP)
MOVL R0, STORE
RET

; .ENTRY RINIT, @M<>
MOVL @4(AP), STORE
RET
STORE: .LONG 0
.END
BIOPHGRAPHICAL NOTE

The author, Ronald Alan Siegel, was born February 1, 1954, in Oakland, California. He attended Condon Elementary School, Roosevelt Jr. High School, and South Eugene High School, all in Eugene, Oregon. He graduated cum laude from the University of Oregon in 1975, majoring in Mathematics. That year, he was awarded the prize for Outstanding Mathematics Student.

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While at M.I.T., the author taught courses in electrical circuit theory and sensory-motor physiology.

The author worked as a computer programmer at Oregon Research Institute, Eugene, Oregon, from 1969-1975, and at Systems Control Inc., Palo Alto, California, from 1975-1976, as a research analyst. In 1978 he worked as a research engineer at Scientific Systems, Inc., Cambridge, Massachusetts. He has served as a consultant with Abbot Laboratories since 1982. He is currently Assistant Professor of Pharmaceutics and Pharmaceutical Chemistry, School of Pharmacy, University of California at San Francisco, San Francisco, California.

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Publications


Patent Application

J.M. Cohen, R.A. Siegel, and R. Langer, "Pressure Casting Technique for Producing Polymer Matrices for the Sustained Release of Macromolecules."