



TREATISE ON CONTROLLED DRUG DELIVERY

Fundamentals • Optimization • Applications



edited by
Agis Kydonieus

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Preface

Controlled-release delivery of chemicals is practiced in nature on a routine basis. Examples include the oxygenation of blood by the diffusion of oxygen through the alveolar walls, the flow of nutrients and waste through cellular membranes, and the control of body temperature by the permeation and evaporation of water from the epidermis. The development of controlled-release devices is an attempt to simulate nature's processes so as to deliver a drug to a target organ at a specified rate for a specified period of time, and to accomplish the optimum therapeutic effect while keeping undesirable side effects to a minimum. With the development of *targeted* and *self-regulating* therapeutic systems, we are now attempting to mimic nature. Although we still have a long way to go, solid advances have been made in both the scientific and commercial development of controlled-release systems. Transdermal nitroglycerin devices control half a billion dollars of the angina pectoris market worldwide, and once-per-day oral tablets based on osmotic pressure and erodible-system design are being introduced into the marketplace at an ever-increasing rate.

In this book we have attempted to present a concise, readable, and in-depth presentation of the fundamentals, applications, and optimization of controlled-release systems. Each chapter starts with the basics and progresses into the most difficult thoughts and mathematical concepts. Interspersed within the chapters are examples and solved problems to aid in the understanding of the material. Specific attention was paid to the methodologies for modifying drug release and to the application of release kinetics to the design and optimization of controlled-release formulations. Separate chapters are presented discussing the mechanisms, characteristics, and mathematics of erodible devices, as well as the development and performance testing of implantable and oral osmotic pumps. Particularly strong are the chapters on controlled-release fundamentals, including those on the kinetics of solute release and on diffusion controlled matrix systems, written by scientists instrumental in molding these areas.

The second part of the book examines in depth the applications of controlled release. The most important routes of drug administration—oral, parenteral, transdermal, and nasal—are discussed in separate chapters. The pharmacokinetics, pharmacodynamics, and biological and biopharmaceutical parameters pertinent to each route of administration are presented for both peptide and nonpeptide drugs. How polymers, adhesives, control membranes, and other formulation parameters are used to design optimal systems are discussed, including polymers for osmotic, erodible, and diffusion-controlled systems. Chapters on veterinary and pesticide applications are also included to aid in the cross-fertilization of ideas between the delivery of drugs and other biologically active agents.

The volume provides an introductory but detailed treatise on the principles and applications of controlled release and, with nearly 1000 references, it can be used as a valuable source of the most recent literature for the expert in the field. However, the book is written in a readable, basic, didactic format, with solved examples and end-of-chapter problems, allowing for this volume to be used as an educational tool or text for the practicing scientist and the student alike.

Several friends and associates should be given credit for their helpful suggestions and criticisms. Special thanks should go to Dr. Bret Berner for reviewing several parts of the manuscript and providing invaluable suggestions. I am indebted to my associates Dr. John Wille and Ms. Stefanie Decker for reviewing and contributing to the chapter on transdermal delivery. I am also indebted to the chapter authors for their guidance and encouragement, as well as for their cooperation in adhering to strict manuscript specifications. A lot of thanks are also due to Joan VanDerveer for her efforts in typing and assisting in the editorial and administrative endeavors.

Agis Kydonieus

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1

Fundamental Concepts in Controlled Release

Bret Berner and Steven Dinh *CIBA-GEIGY, Ardsley, New York*

BASIC CONCEPTS

Controlled-release drug delivery combines well-characterized, reproducible dosage-form design with clinical pharmacology, in particular, steady-state pharmacology. The steady-state biology defines the required input or the desired drug delivery profile. A systems approach to experimental design allows the necessary quantitation of the biological response.

In the simplest model (Fig. 1), the fate of the drug may be characterized by a single compartment, which is described by the plasma concentration of drug with time. The concentration of drug bound to the receptor site versus time reflects the pharmacodynamics or biological response, whether it be related to drug efficacy or adverse reactions. With constant drug inputs into the plasma compartment, steady-state conditions are achieved, and the pharmacokinetic/pharmacodynamic problem simplifies to an equilibrium distribution between the plasma and the receptors. At steady state, the plasma concentrations will help predict the biological response, and the required drug delivery profile may be related to that input rate resulting in those steady-state plasma levels associated with the ED_{50} for efficacy while minimizing side effects.

Controlled-release drug delivery design involves the application of physical and polymer chemistry to dosage-form design to produce a well-characterized and reproducible dosage form that controls drug entry into the body within the specifications of the required drug delivery profile. This design typically includes additional characterization of the drug's permeation through the appropriate biological membrane and any first-pass metabolic effects prior to entry of the drug into systemic circulation. Conventional tablets fail this definition in their lack of characterization and control of absorption. The controlled-release dosage form should be tailored so that variations in component characteristics lead

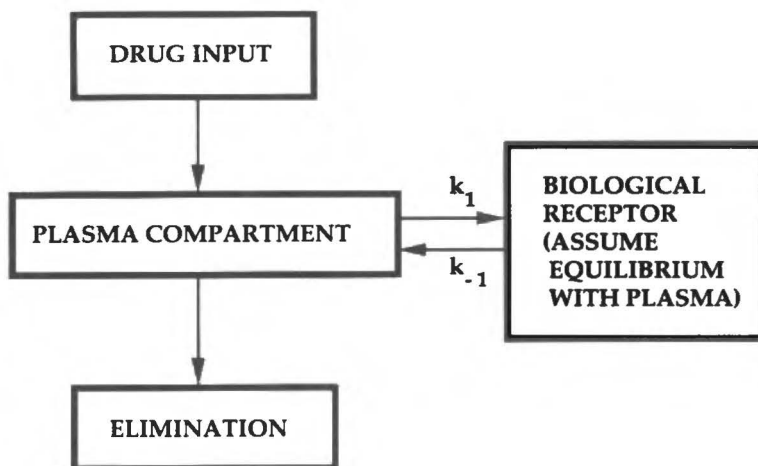


Figure 1 A simple pharmacokinetic model

to predictable alterations in release profiles. This release profile should also include appropriate control over absorption of the drug into the body.

In a similar fashion, *sustained release* indicates merely a dosage form that has its dissolution profile extended in time rather than designed and characterized to achieve a desired drug delivery profile. The classical example of a sustained-release dosage form is a wax matrix of phenylpropanolamine, which extends the period of drug release in the gastrointestinal tract beyond the short half-life (4.9 h) of the drug in the plasma [1]. An osmotic pump for phenylpropanolamine that produces (1) an initial loading burst of drug, (2) followed by a constant delivery rate of drug, and (3) a rapid exponential decay in the release rate timed for a mean gastrointestinal transit time is an example of a *controlled-release* dosage form for the same drug [2]. Plasma levels achieved by sustained-release dosage forms for phenylpropanolamine generally peak well above therapeutic levels, while controlled-release dosage forms, when properly designed, do not. For this controlled-release dosage form for phenylpropanolamine, the drug input rate was deconvoluted from the plasma levels, and the rate calculated from these levels agreed well with the theoretical and experimental in-vitro drug-delivery profile obtained in dissolution testing. The desired profile allows phenylpropanolamine to function as an appetite suppressant while minimizing the classical stimulant side effects of the drug. A suitable profile also extends the duration of efficacy and allows for a more convenient dosage form. In contrast, the sustained-release dosage form achieves the convenience of an extended duration of action [3], but its delivery is less reproducible, and it fails to avoid undesired side effects.

Controlled-release drug delivery currently involves control of either the time course or location of drug delivery. While control of the time course of drug delivery is the more classical approach, *site-specific* or *targeted delivery*, which involves drug delivery to a specific organ or class of cells or physiological compartment, e.g., to cancer cells or to hepatocytes or across the blood-brain barrier, is possible. Currently, this approach is mostly in the research stage.

Delivery rates from temporal controlled-release systems may be characterized in terms of their kinetics and physical processes. Of particular interest are zero-order systems, those systems for which the release of drug is constant with time, t , or proportional to

t^0 . Typical zero-order systems involve diffusion of the drug through a membrane, where the steady-state flux determines the constant delivery rate. In practice, these membrane systems are either initially loaded with drug in the membrane to provide an initial burst followed by a period of constant release, or they have a time lag prior to steady-state diffusion across the membrane.

Perhaps the most common controlled-release delivery devices exhibit delivery rates that initially are proportional to $t^{-1/2}$. This square-root-of-time dependence reflects mass transport by sorption/desorption in monolithic systems [4,5].

Zero-order systems can, in principle, allow for selection of precise efficacious plasma levels after titration for interindividual variation. At steady state, plots of drug levels in plasma should reflect the biological response, and studies over a range of plasma levels should resemble in-vitro enzyme kinetics. For example, angiotensin converting enzyme (ACE) converts angiotensin I (AI) to angiotensin II (AII). Through multiple mechanisms, this translates into an increase in mean arterial pressure (MAP). One of the most direct means of controlling hypertension is to use ACE inhibitors [6]. By giving constant simultaneous infusions of the enzyme substrate (AI) and the ACE inhibitor (a competitive inhibitor of ACE, benazeprilat) and, at the same time, measuring the mean arterial pressure, one obtains a curve of the in-vivo response versus delivery rate (Fig. 2), which is an in-vivo competitive inhibition curve [7]. By curve-fitting these data to a competitive inhibition model, one may calculate an in-vivo IC_{50} . The desired drug delivery rate is approximately twice the rate that corresponds to this IC_{50} . A zero-order delivery system could then be

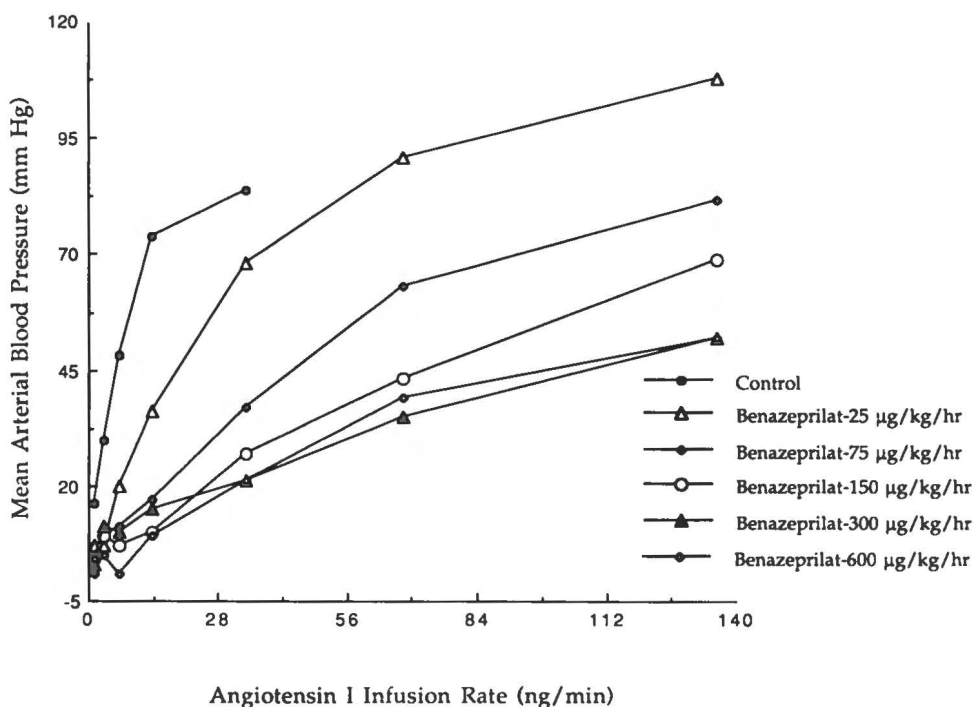


Figure 2 Increase in mean arterial blood pressure in the SHR in response to the administration of angiotensin I, during the steady-state infusion of benazeprilat.

designed to deliver at this rate, and constant plasma levels of drug would result. In a conventional dosage form for an instantaneous input of a drug with a moderate half-life, the initial plasma level overshoots the IC_{50} to compensate for the subsequent decline of the plasma levels due to drug elimination with a falling input rate of drug. Consequently, the initial level of a drug with a short half-life might be 10 times the IC_{50} .

With zero-order delivery, it may be important to select plasma levels that avoid adverse drug reactions. Side effects and efficacy may be associated with different sets of biological receptors, and each set may have very different IC_{50} s or local drug distributions; i.e., side effects and efficacy may be associated with steady-state plasma levels that are quite different. If the therapeutic window is sufficiently large, i.e., the plasma level for the side effect is sufficiently higher than that for the desired efficacy, then a zero-order dosage form may permit drug efficacy without that side effect. The classical pharmacological case is use of scopolamine to prevent motion sickness. The desired drug delivery rate is 5 $\mu\text{g/h}$, while delivery rates for the side effects of dry mouth and drowsiness are 15 and 35 $\mu\text{g/h}$, respectively [8]. Based on these results, the transdermal system for scopolamine was designed as a zero-order dosage form that delivers 5 $\mu\text{g/h}$. More generally, the drug clearance [9,10] from plasma can be calculated from the AUC, the area under the curve to infinite time, for a curve of plasma concentration versus time for a fully bioavailable dosage form, preferably an intravenous infusion, as follows:

$$\text{clearance} = \frac{\text{dose}}{\text{AUC}} \quad (1)$$

The desired steady-state drug input rate may then be obtained from

$$\text{drug input rate} = (\text{target plasma level}) \times (\text{clearance}) \quad (2)$$

A second potential advantage of zero-order dosage forms is improved efficiency of delivery of the drug. Steady-state delivery of the drug may be more efficient when the distribution of the drug into the receptor compartment is much slower than elimination from the receptor compartment; in Fig. 1 $k_1 \ll k_{-1}$. The extent of the added efficiency may be surprisingly large. For example, the dopamine autoreceptor agonist, CGS 15855A, requires 0.4 mg/kg by i.p. injection in rats to lower striatal dopamine metabolites [11]. However, in rats given 40 $\mu\text{g/day}$ by continuous infusion from an osmotic minipump, the effect of lowering striatal dopamine metabolites is saturated [12]. This example emphasizes a concern of zero-order drug delivery. Within 2 weeks of continuous infusion of the drug in rats, the effect of even a 400- $\mu\text{g/day}$ delivery rate of CGS 15855A on dopamine metabolites disappears; i.e., there is complete tolerance.

This issue of tolerance has led to much controversy relative to treatment of angina with nitrates, so that nitrate-free intervals are proposed [13]. More complex delivery profiles may be used to balance tolerance and intervals of efficacious protection. Modulatable controlled-release profiles may be important for drugs with large circadian rhythms. Iontophoresis, phonophoresis, and light-activated systems are being considered for complex time-dependent drug delivery profiles. While the classical chronotherapy problem is enhanced delivery of insulin before a meal, many of these technologies are awaiting application to a therapy. Light-activated systems may have applications in localized or targeted cancer treatments and are being applied to the use of psoralens in skin cancers [14].

ROUTES OF DRUG DELIVERY

The justification for a controlled-release dosage form over a conventional tablet is either to optimize therapy or to circumvent problems in drug absorption or metabolism. Without this therapeutic rationale, a controlled-release dosage form would be unlikely to succeed as a product. The variety of routes available for drug delivery corresponds to the list of biological membranes in the human body: buccal, nasal, and vaginal mucosa, the gastrointestinal tract including the colon and rectum, the eye, and skin. We should further add to this list parenteral delivery, including implants and targeted delivery. Let us briefly review some of the reasons and approaches for each of these routes of administration. While prodrugs can be applied in each of these routes, use of these compounds has been extensively reviewed and will not be discussed in this chapter [15,16].

The GI Tract

Oral drug delivery is the most popular route and, as such, its advantages and limitations define the rationale for the other routes. The drug is absorbed through the various membranes along the gastrointestinal tract as the dosage form migrates through the GI tract. The pH of the stomach is approximately 2. The emptying time from the stomach is highly variable, but its mean is 4 h. Liquids may show a different pattern of emptying and empty in as fast as 15 min [17,18]. The pHs in the duodenum and the ileocecal junction are, respectively, 5.8 ± 0.8 and from 6.5 to 8.5 [19], but the microscopic pH near the membranes may be of the order of 6.1 near the jejunal membranes, as opposed to 7.2 in the bulk fluid [20,21]. Transit through the small intestine is more regular and is of the order of 4–6 h [34]. Entrance into the colon may be accompanied by a 0.5- to 1.0-unit increase in pH, and transit is highly variable giving a total GI transit time varying from less than a day to several days [22]. Drugs may be susceptible to degradation by different means in different regions of the gut—in particular, by hydrolysis in the stomach, by enzymatic digestion such as proteolysis in the small intestinal fluid, by metabolism in the gut wall, and by microorganisms in the colon. It should be noted that many individuals have diseases of the GI tract for which many of the above generalizations are not valid [22].

Other concerns for many drugs are extensive metabolism in the liver which is directly perfused by the portal blood supply leaving the intestine prior to entering the systemic circulation. This first-pass metabolism can lead to highly variable or poor absorption of drug into the systemic circulation. Finally, after absorption, metabolized or intact drug may be excreted into the bile and recirculated into the intestine.

Given these complications, prediction of drug absorption in the GI tract is difficult, but simple models correlating (1) oil solubility or melting point with absorption through a lipid membrane [23,24], or (2) water solubility as an additional variable to account for an “unstirred layer” in series with the intestinal membrane [25], or (3) more complex hydrodynamic models of perfusion [26–28] facilitate the estimation of drug absorption.

The thrust of controlled-release efforts in oral delivery has been limited mostly to four areas: (1) dosage forms with well-defined controlled-release delivery profiles, (2) extension of the transit time of dosage forms either through retention or drug delivery continuing into the colon, (3) enhancers for improved absorption of peptides, and (4) targeted delivery to the colon. Regardless of the approach, extensive in-vitro permeation studies, perfusions or infusions in animals, intubation studies in humans, and studies on

transit of the dosage form are needed to characterize an oral dosage form for clinical development.

Oral Controlled-Release Dosage Forms

Varied oral controlled-release dosage forms have been developed, from coated pellets to microcapsules [29], to ion-exchange resins [30]. Hydrogels and osmotic pumps are two of the more important classes of oral controlled-release dosage forms. Hydrogels allow for extremely reproducible loading and delivery with an unusually wide range of specially tailored delivery rates, and also allow relatively easy removal of monomers, cross-linking agents, or other species with unacceptable toxicological profiles. Most hydrogels deliver as monolithic systems; i.e., drug release is proportional to the square root of time once the system is swollen with water. The search for zero-order monolithic oral delivery systems has become a "holy grail" of controlled-release and has included extensive work on novel geometries [31], Case II diffusion [32], and dissolution-controlled systems [33].

Osmotic pumps have seemingly offered the capability of tailoring delivery profiles—in particular, constant infusions—to the desired rate. To date, the tailoring has been limited by practical osmotic pressures, drug solubilities, and the nature of the membrane. The principle of drug release from osmotic pumps is simply one of water diffusing into the capsule down a water activity gradient across a membrane [2]. This water then exerts a constant pressure to force the drug out through a small hole in the capsule. While osmotic pumps for phenylpropanolamine hydrochloride and ascorbic acid are currently marketed, systems for metoprolol, albuterol, nifedipine, and prazosin may soon be available. Early adverse drug reactions related to ulceration after use of an indomethacin osmotic pump led to its withdrawal from the market and the irrational association of the osmotic pump with gastrointestinal side effects. The well-established side effects of ulceration with systemic administration of indomethacin combined with prolonged depression of prostaglandin synthesis for cytoprotection are more appropriate hypotheses.

Temporal control of the dosage form is currently a subject of academic research [34–36]. Several hydrogels display sensitivity to external stimuli. For example, certain hydrogels with mixtures of hydrophobic and hydrophilic groups exhibit temperature behavior analogous to surfactant solutions, that is, lower critical solution temperatures. At these temperatures, the gels exhibit large changes in swelling, which may be utilized for drug loading or release. Certain ionic hydrogels exhibit pH-dependent phase changes, while other gels seem to exhibit continuous swelling changes with pH. Recently, temperature-sensitive gels have been combined with a small fraction of ionic monomers to increase the magnitude of the swelling effect from phase changes with pH [34]. Some of these pH-sensitive gels have been suggested as replacements for enteric coating to prevent emptying in the stomach or to target the gel to the colon where a small pH change may occur. Applications other than oral delivery, such as iontophoresis or an insulin-releasing implant, have been suggested for these polymers [37].

Extension of GI Transit

Retention of dosage forms in the GI tract could be useful to decrease the frequency of dosing to once daily or less or in cases where there is an established absorption window in the GI tract, i.e., a unique region of the GI tract where drug absorption occurs. While carrier mechanisms are being investigated, the presence of absorption windows has often not been verified. Irritation to the colon or bacterial degradation in the colon may be a more frequent rationale for an apparent absorption window.

Bioadhesion to soft mucosa or mucus lining the GI tract has received considerable attention recently [38,39]. These applications are not just for prolonging retention, but also for localizing delivery. In addition to applications to oral dosage forms, bioadhesion to buccal, vaginal, and ocular mucosa has been investigated. Hydrogel adhesion to mucosa, a tissue which is highly swollen with water, may depend on entanglements and hydrogen bonding; for these applications polyacrylic acid and carboxymethylcellulose have received considerable attention [40–42]. Adhesion to mucus is complicated by sloughing of the mucus layer and by changes in the structure of mucus upon isolation. Negative charges from sialic acid with a pK_a of 2.6, in particular, and hydrogen bonding can play a role in adhesion to mucus. Polycarboxophil has been shown to double the bioavailability of chlorothiazide in rats due to prolonged gastric retention, but the results were less pronounced in humans and dogs [39,43]. The relationships among the necessary forces, particle size, and release rate remain to be established. Bioadhesion combined with localization in the intestine has been considered for targeting peptides to Peyer's patches, but the absorption characteristics, and distribution between the systemic and lymphatic circulation are not well established. While bioadhesive dosage forms exhibit some promise, extensive technical and toxicological barriers must be overcome.

A second approach to prolonged retention has been to prevent or delay gastric emptying with dosage forms of various size and density or which swell to become too large to pass through the pylorus. However, successful modification of actual emptying has been limited, with these dosage forms exiting within the variability of the emptying time of solids [44,45].

Finally, the dosage form may continue delivering drug to the colon where degradation or poor absorption is not an issue, and once-daily, controlled-release dosage forms may be obtained for at least a substantial proportion of the population.

Oral Protein Delivery

The combined macromolecular and hydrophilic exterior nature of proteins minimizes passive transport across lipophilic barriers, and the size and continuity of aqueous porous pathways in the GI tract are far from established. In addition, proteins and peptides are susceptible to proteolysis. While amino acids and di- or tripeptides are actively transported in the small intestine [46], often with further degradation, the extent of transport of larger oligopeptides is less clear, except that it is substantially diminished. These carriers may play a role in absorption of L-methyldopa or perhaps angiotensin-converting enzyme inhibitors in the diacid form [47,48]. In-vitro methodology to characterize such carrier systems, such as intestinal cell lines [49] and in-situ perfusion models, may be used to evaluate the extent of oligopeptide transport.

Other approaches to peptide delivery have included use of protease inhibitors to minimize degradation in the small intestine and the classical ion-pair absorption [50], which has never been verified for any anionic or cationic drug. The use of micelles or lipid vehicle systems [51] is being tested to take advantage of the chylomicron flux into the lymphatic system or as a means of overcoming hepatic first-pass metabolism. However, the absorption of drugs from the lymphatic to the systemic circulation is not well characterized.

Enhancers of oral absorption may act by increasing passive transport across the small intestine, colon, or rectum [52–58]. Such alterations in gross barrier properties may require interactions of a magnitude that may cause cellular disruption, inflammation, or, at a more minor level, biochemical changes. Enhancers might be used in localized bursts,

where the damage is contained, and repair mechanisms can handle alterations within the realm of normal physiological wear. At steady state, enhancers might be used at sufficiently low concentrations to avoid damage. The steady-state approach suffers from the further problem that the enhancer may be absorbed much more rapidly than the drug, or the enhancer may be diluted and provide only a local effect. Two classes of compounds have been studied as enhancers: (1) surfactants such as bile salts, nonionics, long-chain acyl carnitines, and nonionic glycerides; and (2) chelating agents, such as EDTA, salicylates, and phosphate derivatives. Careful toxicological evaluation of these enhancers will be required. While 60 mg/rat of sodium 5-methoxysalicylate increased the oral bioavailabilities of a hexapeptide somatostatin analog, insulin, and horseradish peroxidase, this was at the expense of mucosal damage [57], which got progressively worse. Histology is used to test for gross damage, and more sensitive biochemical tests have not been included. While there are intriguing data in the literature, no systematic characterization of the extent, mechanism, or minimization of damage has been reported.

Colonic Targeting

Targeting drugs to the colon has been suggested both to treat diseases of the colon and to deliver proteins orally from a region where there is little protease activity. The assumption of minimal proteolysis in the colon has not been carefully evaluated experimentally. To target insulin or vasopressin to the colon, an approach was borrowed from studies targeting prodrugs to the colon. Drugs are incorporated into azopolymers, which remain intact upon passage through the upper GI tract. The drugs are released in the colon when the azopolymers are degraded by colonic bacteria [59,60]. More recently, colonic bacterial glycosidases were used to release insulin selectively in the colon. A second approach to colonic targeting is to release the drug following passage through the small pH change from the ileum to the colon [19]. While this pH change may be readily demonstrated, it is not yet clear that the magnitude of this change is sufficiently large to overcome inter- and intraindividual variation. Although colonic targeting is an intriguing method for peptide delivery, current absorption data are based on pharmacodynamic measures rather than plasma levels relative to i.v. infusion or direct transport measurements. Consequently, the extent and variability of colonic absorption of peptides are difficult to assess from existing data.

While the use of suppositories and rectal delivery are remarkably unpopular in the United States, the relatively high permeability of the rectal mucosa and the ease of application have led to the investigation of this route for peptide delivery and delivery of drugs with oral-absorption problems. Many of the enhancer studies with the GI tract were performed on the rectal mucosa, and the aforementioned critique is still valid. Rectal delivery can only in part circumvent the hepatic first-pass metabolism. A hydrogel morphine suppository to relieve pain for 24 h was tested and found to be too variable and absorption too slow for use in acute pain [61].

Transdermal Delivery

Transdermal drug delivery has received perhaps the most attention of these alternatives. Commercial systems are available for scopolamine to treat motion sickness [8], nitroglycerin for angina [62], estradiol for postmenopausal syndrome and perhaps eventually to prevent osteoporosis [63], and clonidine as an antihypertensive [64]. New Drug Applications (NDAs) have been filed for transdermal administration of nicotine for smoking cessation [65–67], fentanyl for analgesia and in anesthesia for relief of moderate to severe

surgical pain for an extended duration [68–70], and testosterone for male hormonal insufficiencies. A transdermal system for a D2 or autoreceptor agonist for Parkinson's disease is well into clinical trials [71]. The regimen for these transdermal systems varies from 1 day to 1 week, although skin tolerability is a concern for the longer-duration patches. Recently, trials relating efficacy of transdermal nitroglycerin to time have suggested that chronic daily application leads to tolerance, which may be avoided by wearing the transdermal patch for 10–14 h and then removing it at night.

To pass transdermally, the drug must diffuse across the epidermis to the dermis, where it is carried into the systemic circulation. This direct route into the systemic circulation avoids hepatic first-pass metabolism. The outermost 10–20 μm of the epidermis, the stratum corneum [72], is composed of sheets of keratinized squamous epithelium with the cells joined by tight junctions. There is virtually no metabolic activity in the stratum corneum. The stratum corneum comprises at least 90–95% of the diffusional resistance of the skin. The viable epidermis is the metabolizing layer, approximately 100 μm thick, from which the stratum corneum originates. It has been suggested that this layer is the dominant barrier for passage of extremely lipophilic compounds, although this has never been conclusively demonstrated. To measure skin permeation in vitro, diffusion of a drug across human stratum corneum should be determined from a saturated solution, i.e., unit activity, in an infinite donor reservoir; in-vitro skin permeation that is measured in this manner may be used to predict in-vivo drug delivery. This simple arrangement allows the physical and electrochemistry developed for classical membranes to be utilized without change for skin permeation.

A main function of the integument is to isolate the interior body tissue from its environment, and this is achieved by a combination of the remarkable barrier properties of stratum corneum and by its exceptional immune system. The barrier properties limit transdermal delivery to readily permeable, highly potent drugs. Skin permeation classically may be related to solubility in oil [73], that is, ideal solution theory [74]. The flux of a drug across skin may decrease exponentially with its molecular volume [23,75]. While until recently it appeared that the permeation of polar compounds through stratum corneum was negligible, recent work has indicated that water solubility may also play a role in skin permeation [76,77].

Much work has concentrated on finding enhancers to improve skin permeation [78]. Surfactants may alter protein structure or fluidize lipids as reflected by the discontinuous increase in skin permeation with surfactant concentration or by the FTIR spectra with and without these surfactants [79,80]. Absorption of polar compounds may be enhanced by surfactants with head groups of greater hydrophilicity, or nonpolar and polar compounds when surfactants are mixed with other solvents, such as diols or ethanol [78,81]. In general, there is an excellent correlation between the ability to increase skin permeation with a surfactant and skin irritation. While hairless mouse skin and other animal skins may be qualitative models for aqueous skin permeation in humans, with enhancers the correlation is not nearly as good [82]. Ethanol can increase permeation of nonpolar species by increasing their solubility in the stratum corneum without altering their diffusion constants [83–85]. Ethanol is the only solvent used in a commercial transdermal system where the relationship between the flux of the drug, estradiol, and that of the solvent has been characterized [73,86].

For many drugs the limiting factor in transdermal delivery is not poor permeation, but skin tolerability. Primary irritation, consisting of erythema (redness), edema (swelling), or pain, the classical inflammatory trio, may result from a variety of drugs. While solvents

or surfactants may also cause irritation, the skin irritation of drugs may be instigated by local pH changes in the epidermis caused by a permeating drug. For drugs that permeate skin at comparable rates, the pK_a of the drug may help predict relative skin irritation [87,88].

A second, more serious skin-tolerability concern is contact sensitization resulting from repeated exposure to an antigen, which is the drug or system component; the immune system becomes alerted to a hapten, an antigen-protein complex, and quite severe erythema, edema, generalized rash, etc., may ensue. The classical example of a sensitizing agent is poison ivy [89,90]. Transdermal clonidine has become the most-studied transdermal sensitizer to date [91]. While guinea pig or mouse-ear-swelling models may generally be used to predict positive human sensitization responses, they do not indicate that clonidine is a sensitizer in humans with an incidence close to 20%. To date, only one instance has been reported where an individual who was sensitized to clonidine by the transdermal route was also sensitized to clonidine given orally. A recent patent application attempts to address this issue by incorporating corticosteroids into the patch, but given the extensive systemic effects of corticosteroids, an appropriate risk-benefit evaluation should be conducted [92].

The design of transdermal systems falls into two basic types: membrane-controlled and monolithic [93]. When the skin is rate-controlling, both types of systems exhibit zero-order delivery. With individuals with abrasions or exceptionally high skin permeability, the membrane systems may offer a safety advantage. Elegant systems that allow some temporal control of delivery are in development. Some systems allow activation of membrane permeation by diffusion of water from the skin, the transepidermal water loss or TEWL [94], or by mechanical activation by a breakable heat seal [95]. The common elements of current transdermal systems are a drug reservoir, a backing which is impermeable to drug over the system lifetime, an adhesive and release liner to attach the system to skin with minimal tolerability concerns, and appropriate pouching to achieve the desired shelf life.

Iontophoresis, or the use of electrical current to drive drugs across the skin, although noted in the last century, has received much attention recently as a means of increasing skin permeation and for temporal variation in drug delivery [96,97]. Careful attention to the use of nonpolarizable electrodes, well-characterized redox reactions, the use of constant current, etc., allows a fairly simple picture to emerge [98]. With the exception of some long-time relaxations, which may be modeled in a fashion similar to those observed in collagen and bone [99], the equivalent circuit for stratum corneum is a solution resistance in series with parallel membrane capacitor and resistor. The membrane impedance reflects diffusion in bulk solution within a restricted volume fraction and weak ionic selectivity. Current ranges need to be restricted to limit skin irritation, and at higher levels, pain [100,101]. In systems with polarizable electrodes, irritation may be related to pH changes. Substantial increases in drug permeation may be observed at small currents. Extensive use of iontophoresis exists in "sports medicine" applications, but its therapeutic application has not yet begun.

Given the limitations and concerns over transdermal delivery, it is its convenience, accessibility, and simplicity that have led to its early development compared to other routes.

Buccal Delivery

Buccal delivery of drugs, at first glance, seems to offer a combination of the advantages of transdermal and oral delivery. A buccal device or a sublingual tablet offers the easy

application and removal of transdermal delivery without the excellent barrier properties of the stratum corneum and with less immune activity than the epidermis. Furthermore, hepatic first-pass metabolism may be avoided. The buccal route is restricted by its limited surface area, concerns of taste and comfort in a highly innervated area, the difficulties of adhesion to a mucosal surface for extended periods without the danger of swallowing or choking on a device, and potential bacterial growth or blockage of salivary glands associated with prolonged occlusion. Sublingual or buccal dosage forms have been developed for nitroglycerin [102], ergotamine [103], nicotine [104], buprenorphine [105], methyl testosterone [102], and nifedipine [123]. Even small peptides, such as oxytocin, have been shown to cross the buccal mucosa [106]. While the gingiva and periodontal pockets have somewhat different anatomy and physiology, it is convenient to mention dental applications of controlled release, including release of fluorides or release of antibiotics from fibers placed in periodontal pockets [107].

While human oral mucosa, like skin, is a stratified epithelium, the hard palate tends to have a cornified epithelial layer, but the buccal mucosa is a nonkeratinized tissue with an average thickness of 580 μm [108]. Keratohyalin granules have been identified in human buccal tissue, but in contrast to many rodent buccal models, there is no stratum corneum. Intercellular connections in buccal tissue are characterized by desmosomes and gap junctions, and the tissue is a somewhat leaky epithelium. Although it is believed that the buccal mucosa has a weak immune response compared to skin, buccal tissue has a reduced number of Langerhans cells, which appear to function in the immune response to antigens in oral mucosa in the same fashion as in the viable epidermis [109].

Most of the in-vivo data on buccal permeation of drugs is derived from the experimental paradigm developed by Beckett and Triggs [110]. With this method, a known concentration and volume of drug are kept in the subject's mouth for a fixed amount of time, spit out, and the drug absorption is calculated as the difference in the total amount of drug. In-situ perfusion cells [111] have also been developed, but both techniques suffer from the same drawbacks: (1) absorption is not distinguished from adsorption or metabolism; and (2) the drug's affinity for water may dominate the absorption measurement. This second aspect of the methodology has led to the conclusion that un-ionized species dominate buccal permeation and that transport follows the partition coefficient [112].

The polar shunt pathway has been largely neglected in the understanding of buccal permeation. Sodium diclofenac in its ionized form has been shown to permeate buccal mucosa extremely rapidly in dogs and in humans [113,114]. Dipolar ions, such as angiotensin-converting enzyme inhibitors [115] and TRH [111,116], also permeate quite extensively. The measurement of these permeants has relied on both in-vivo studies from saturated solutions where plasma AUC was compared with intravenous administration or in-vitro methods, such as Ussing chambers. Permeation through buccal mucosa is very rapid compared to skin, but perhaps an order of magnitude or more slower than through intestinal or nasal tissue [113,117].

Peptide and protein permeation through buccal mucosa has been reported based on pharmacodynamic measurements. The bioavailability of oxytocin given transbuccally seemed to be on the order of a few percent. The usual aminopeptidases are present in buccal tissue, and degradation may be a concern [118,119]. Furthermore, the extent of peptide permeation is unclear, and some histological papers suggest barrier layers for high-molecular-weight markers such as horseradish peroxidase [120]. A buccal tissue culture model is in development, but it is from the hamster cheek pouch, which contains a cornified layer [121]. Careful study of the transport and biochemistry of buccal mucosa will continue with some newer, more appropriate models.

Nasal Delivery

In comparison to the aforementioned routes, nasal delivery currently has a greater capability of delivering peptides and poorly orally absorbed drugs with reasonable bioavailabilities and without encountering hepatic first-pass metabolism. Absorption of TSH, ACTH, buserelin, growth hormone, and LHRH have been measured by the nasal route using pharmacodynamic responses relative to i.v. administration [122]. The nasal delivery of nafarelin acetate, an LHRH analog, has been further quantitated by plasma levels versus i.v. administration [123]. Through the use of adjuvants, such as sodium deoxycholate, insulin has been absorbed intranasally [124]. Such adjuvants may both limit the aggregation of insulin and act as enhancers on the tissue. With these enhancers, extensive toxicological tests must be performed. To date, such toxicology has been limited to histological studies of necropsy tissue, but more sensitive biochemical studies of nasal mucosa are needed.

Nasal anatomy is designed to provide sizable resistance to air flow and to control the humidity and temperature of inhaled air. The nasal septum divides the nasal passage into two, and each passage is convoluted by the turbinates. Large particles have difficulty passing the nasal valve, a constriction. The mucosal lining contains both the goblet cells, which secrete the mucous that flows slowly to the nasopharynx and is swallowed, and the cilia, which aid this transport, plus submucosal glandular structures. The nasal mucosa has been studied *in vitro* in Ussing chambers and is a leaky mucosa [125]. Transport appears to be by parallel lipoidal and shunt pathways with oil and water solubilities and molecular weight providing an approximate indication of structure-permeation relationships [126]. Large proteins appear unable to cross the mucosa to any significant degree. Small peptides, such as oxytocin and somatostatin analogs, can show bioavailabilities comparable to those with i.v. injection [117].

The *in-situ* rat perfusion model, in which the inlet and outlet concentrations are measured, is a popular model for nasal drug delivery [127]. While this method has been used to predict nasal delivery of certain compounds, other animal models, such as sheep or primate, may be preferred, even though they are less convenient [128].

Drugs may be administered intranasally as aerosols, powders, or small particulates. Sterility, stability, toxicology, and effects on delivery of adjuvants should be evaluated. Design of a nebulizer device is also a key to reproducible dosing, and there is an extensive literature on the design of these devices. Plasticizers and other excipients in plastic or gaskets may interact with the formulation, so that their effects must be evaluated [129]. Although nasal delivery presents a route for achieving relatively high bioavailabilities of small peptides, there is an opportunity for innovation in reproducible controlled-release nasal formulations.

Ocular Delivery

Ocular delivery involves localized treatment of the eye, unlike the previous routes, which are meant for systemic drug delivery. Ocular prodrugs are the simplest example of site-specific delivery, but as new chemical entities, they require a drug discovery program. The so-called soft drugs [130], compounds that are active locally when applied topically to the eye but that degrade rapidly to an inactive form in the systemic circulation, are examples of new chemical entities designed for localized delivery.

Drug applied to the eye is continually drained by the lachrymal fluid, which has a mean volume of 7 μl per eye and a pH of 7.4. Inside the cornea is the aqueous humor, a 0.01–0.02% protein solution with a volume of some 300 μl and a turnover rate of

approximately 180 $\mu\text{l/h}$. The permeation barrier, the cornea, is classically viewed as a hydrophilic layer, the stroma, sandwiched between two hydrophobic layers, the epithelium and the endothelium [131,132]. A partition coefficient near unity is necessary for transport through the cornea. Indeed, the lack of transport of drugs with partition coefficients differing from unity may result from the long time lag for permeation and not from low permeability [133]. Parallel shunt pathways through the multilaminar may also operate. Melting point, as a predictor of the ideal solubility and molecular weight, can provide an order-of-magnitude estimate of the flux across the cornea [134].

Most in-vivo studies of ocular absorption involve application of a finite dose of drug in a non-steady-state measurement. In a recently developed paradigm [135,136], after a brief application, the eye is washed. Under the near sink conditions that hold on both sides of the cornea, the amount absorbed equals the product of the surface area, the time of application, and the steady-state flux; i.e., steady-state transport properties are easily inferred from the non-steady-state measurement. In other in-vivo models, the eye is perfused [137]. Diffusion measurements are also routinely performed in vitro in diffusion cells, but the electrical properties of this tissue are only recently being defined [138].

Irritation, including erythema, edema, and severe pain, must be considered with any drug, excipient, or enhancer to be applied to the eye. Like the skin, the eye is a well-defined site for the use of an enhancer for drug transport, provided both drug and enhancer are nonirritating.

Most drug products are drops or ointments, and retention in the eye is a concern for controlled release. To prevent drainage, ointments with a large viscosity may be formulated with such hydrophilic polymeric thickeners as certain cellulose or starch derivatives. A hydrophobic formulation may also be useful. Ocular controlled-release devices have been designed, but patient comfort and convenience must be carefully considered. A small membrane-controlled reservoir insert, Ocusert, which delivers pilocarpine to treat glaucoma, has met with limited success. Hydrogel contact lenses may be used as drug-delivery devices, with release proportional to the square root of time. These devices are reproducibly loaded with drug in the laboratory or clinic, but difficulties in home use might be an issue unless disposable lenses become common. Soft contact lenses have also been used for controlling release of pilocarpine.

Intrauterine and Intravaginal Delivery

Intrauterine and intravaginal delivery are the two routes used primarily for fertility control [139]. While numerous intrauterine devices (IUDs) have previously been on the market and may have functioned to provide a sustained release of copper and to irritate the uterine endometrium, one of the few remaining commercial devices in the United States is a membrane-controlled device, Progestasert; it releases progesterone at the rate of 65 $\mu\text{g/day}$ for 1 year. With this low-release rate, endometrial proliferation is suppressed [140].

Intravaginal delivery may have applications beyond birth control. The two existing vaginal implants are (1) silicone elastomer vaginal rings releasing the contraceptive gestagen, medroxyprogesterone acetate, from a dispersed monolithic matrix; and (2) estrogen-progestin vaginal implants using a similar design, but with polyethylene glycol dispersed throughout the silicone matrix [141,142]. The linear release of these devices arises from the lipophilicity of the steroids and the unstirred water layer in series with the rather permeable vaginal membrane.

The human vagina is lined along its 10- to 15-cm length with a mucosal membrane

and is lubricated by vaginal secretions. While the pH is generally between 4 and 5, it is cyclically dependent through the influence of estrogen on glycogen deposition. Among body tissues, 3% glycogen content is second only to that in the liver [142]. Estrogen also causes cornification and thickening of the vaginal mucosa, and consequently, transport may be cyclic. A variety of microorganisms and potential pathogens may proliferate in the vagina, and this may be important for understanding drug metabolism and the constraints of the device design. The permeability of the vaginal membrane has been suggested to be closer to nasal mucosa than to buccal mucosa [143]. Given its convenience for self-implantation, the high permeability, and its ease of controlling the delivery, peptide delivery by the vaginal route is being investigated.

Parenteral Delivery

For life-threatening diseases or those in which the quality of life is drastically impaired, parenteral controlled-release administration either by injectables or by implants may be appropriate. It is appropriate to distinguish between depot formulations, which typify sustained release, and true controlled-release administration. There are numerous examples of depot formulations where drug delivery is controlled by solubility either through insoluble salts, oil emulsions, or other approaches [144]. Another route to parenteral controlled release is through the use of infusion pumps of varying degrees of sophistication. Direct infusion into physiological compartments, for example, intrathecal infusion of baclofen or neuropeptides [145], may permit therapies in debilitating diseases, but diffusion of the drug within the target organ is still being investigated [146]. Miniaturization of mechanical devices and improved biocompatibility of materials will make these devices more acceptable.

For most pharmaceutical applications, subcutaneous implants must answer both long-term toxicological concerns and ease of removal to terminate drug therapy. There have been two basic approaches to the use of polymers, conventional and biodegradable. While biodegradation avoids removal of the system after its use, metabolism of the polymer, its monomer, its dimer, and low-molecular-weight polymers must be extensively evaluated, and biodegradation should occur within a time frame that is slow compared to drug release to allow for system removal.

Acute and chronic inflammation and foreign-body reactions to implants are another major concern [147]. Extensive work has been done relating surface free energy, steric hindrance, surface mobility, and other approaches to minimize protein adsorption [148]. Investigations of the blood compatibility of materials have been adapted to accommodate subcutaneous implants, and similar tests of pathology and durability may be developed.

Given the aforementioned issues, development of implants as commercial products is quite slow. Several varieties of implants with different geometries, i.e., beads, fibers, etc., are being investigated for cancer chemotherapy; e.g., a polyanhydride-based device containing carmustine is used to treat brain tumors and a HEMA copolymer hydrogel uses 5-fluorouracil [149]. Several implantable systems have been described containing narcotic antagonists for use in heroin addicts [150]. Examples of biodegradable implants are poly(l-lactic acid) fibers to release levonorgestrel as a contraceptive [149] and poly(orthoesters) to release 5-fluorouracil or LHRH analogs [151].

Some of the more glamorous research in this area involves the development of self-regulating implants, especially for administration of insulin. Two of the approaches used include immobilization of the enzyme, glucose oxidase [152], to form a bioresponsive

membrane and a glycosylated insulin con A complex in which glucose binding to con A [153] displaces insulin. The great potential of implants has yet to be achieved. A subcutaneous implant that releases levonorgestrel through silicone rubber capsules is one of the closest to reaching the marketplace [149].

The element of targeting or site-specific delivery is often linked with new controlled-release delivery systems. Such targeting is currently only in the research stage. In perhaps the simplest form, some sort of carrier such as liposomes, colloidal particles, albumin, nanoparticles, or water-soluble polymer conjugates is employed [154,155]. Particle filtration can be used to localize larger particles in the lungs [156], but it is not clear that this localization aids the distribution of the drug to the appropriate target cells [157]. Many particles injected into the circulation are rapidly taken up by the reticuloendothelial system (RES), specifically, the Kupffer cells of the liver [158]. The uptake or kinetics of uptake of such particles may be altered by the use of surface coatings such as poly(oxyethylene) or poloxamers [159]. Water-soluble macromolecular conjugates may include antibodies to target the conjugate, and then the drug may be released by lysosomal enzymes after being internalized into the cell [155,159]. Numerous strategies for targeting drugs including antibodies, rheoviruses, and immunotoxins, have been suggested [154], but this field is largely in its infancy and needs specific problems identified for it to be developed. The difficulties in the analytical methodology have made quantitation and kinetic/dynamic studies in this field slow in coming. One of the more advanced applications is the use of liposomes to deliver immunomodulators for cancer and antiviral therapy, but even this approach is just beginning in the clinic [160].

POLYMER PROPERTIES INFLUENCING DRUG PERMEATION

Controlled drug release is based on diffusion through polymers, erosion of polymers, and special polymer characteristics such as osmotic and ion-exchange properties. In a unidirectional reservoir system, for instance, understanding diffusion through polymers can guide material selection for the system components to regulate the fluxes of active ingredients. The next two sections review some of the important properties of polymers that influence drug permeation, and how these properties can be characterized.

Mass Transfer

Let us begin by examining the migration of a species, such as an active ingredient, across a polymeric film by passive diffusion. The activity gradient of the species across the film provides the driving force. For convenience, however, activity is replaced by concentration following the relationship

$$\text{activity} = (\text{activity coefficient}) \times (\text{concentration}) \quad (3)$$

In the simple case of constant mass transfer properties, the flux of a species through a polymeric film [4] is given by

$$\text{flux} = \left(\frac{\text{area}}{\text{length}} \right) \times (\text{permeability}) \times (\text{concentration difference}) \quad (4)$$

Area is the surface through which a species is diffusing, and length is the film thickness. Permeability is given by the product of partition coefficient and diffusivity:

$$\text{permeability} = (\text{partition coefficient}) \times (\text{diffusivity}) \quad (5)$$

The concentration difference in Eq. (4), which is measurable, refers to concentrations of a diffusing species located on both external surfaces of the film. However, the diffusional driving force, when expressed in terms of concentration, comes from the concentration gradient on both interior surfaces of the film. The partition coefficient relates the concentration in the interior to that at the exterior surface of the film, by the ratio of their respective activity coefficients. The implicit assumption made is that equilibrium is established at the interface. Partition coefficients from a saturated solution simplify the interpretation. From a saturated solution, the partition coefficient is a ratio of the solubilities in the solvent and the film. Physically, the partition coefficient describes the relative affinities of the diffusing species for the solvent and the polymeric film. For instance, nonpolar species tend to partition into nonpolar materials. The amount partitioned can be measured from sorption/desorption experiments. Diffusivity is the component of permeability that accounts for the geometric constraints encountered by the diffusing species in weaving across the polymeric film. Consequently, diffusivity increases as the free volume of the polymer increases relative to the dimensions of the diffusing species. In turn, the internal structure of a polymer depends on molecular weight, chain regularity, chain flexibility, and the strengths of the intermolecular and intramolecular forces. We will investigate these factors in more detail, and examine how they affect the polymer bulk properties.

Molecular Weight and Molecular-Weight Distribution

Polymers are macromolecules that are made up of many repeat units. The chemical composition of a repeat unit or monomer is the basic building block, which can be characterized by elemental analysis and various spectroscopic methods. The number of repeat units gives the molecular weight of a single polymer chain. However, reactants usually do not polymerize at the same time and at the same rate during synthesis. Consequently, a distribution of chain lengths is formed. This means that molecular weight is an average quantity made up of contributions from all polymer chains, but there is no unique way to assign this value. Therefore, a number of averaging methods [161] have been introduced, each attempting to emphasize a certain population of chain length.

The first moment-average or number-average molecular weight is sensitive to the low-molecular-weight species, and is defined by

$$M_n = \frac{\sum N_i M_i}{\sum N_i} \quad (6)$$

where N_i is the number of polymer chains (i), each having a molecular weight (M_i). Colligative properties are related to M_n through their dependencies on the number of species. This also suggests that experimental methods for determining colligative properties, such as osmometry, ebulliometry (boiling-point elevation), and cryoscopy (melting-point depression), can be used to obtain M_n .

The second moment-average or weight-average molecular weight is more sensitive to the higher-molecular-weight species, and is defined by

$$M_w = \frac{\sum N_i M_i^2}{\sum N_i M_i} \quad (7)$$

Light scattering is commonly used to measure the weight-average molecular weight. Many properties, such as toughness or mechanical properties associated with large deformations, can be correlated to M_w .

Since the number-average and weight-average molecular weights describe opposite ends of the molecular-weight spectrum, their ratio provides an estimate of the breadth of the molecular-weight distribution. The polydispersity index is the ratio of M_w/M_n . The polydispersity index equals 1 for a monodisperse polymer, and is greater than 1 otherwise.

The third moment-average or z-average molecular weight adds even more weight toward the high-molecular-weight species, and is defined by

$$M_z = \frac{\sum N_i M_i^3}{\sum N_i M_i^2} \quad (8)$$

Experimentally, electron microscopy and centrifugation have been used to measure the z-average molecular weight. Physical properties, such as elasticity, have been shown to depend on M_z . In addition to M_z , average molecular weights with higher weighting factors can be defined accordingly. For completeness, there is also a viscosity-average molecular weight (M_v), which is obtained from viscosity measurements. In a polydisperse polymer, the relative magnitude of these average molecular weights follows

$$M_z > M_w > M_v > M_n \quad (9)$$

Molecular weight reflects the size and size distribution of a polymer. While we might expect qualitatively that diffusivity decreases with increasing molecular weight, the critical factor that governs diffusivity is determined by the overall microstructure of the polymer in the presence of diffusing and other foreign species. Let us first consider the macroscopic behavior of a polymer and then investigate how the microstructure of a polymer is constructed.

Material Characteristic Time

From a phenomenological perspective, the physical behavior of a material can be predicted from the characteristic time of the material (λ), and the process time scale (θ) to which the material is subjected. The material characteristic time is an intrinsic property of a material. However, it is an average quantity from a spectrum of characteristic times that reflects the distribution of polymer chain lengths within a polymer. These material characteristic times can be determined experimentally from rheological techniques. The process time scale is the duration of a process, such as diffusion or a mechanical deformation. Reiner [162] coined this dimensionless ratio of time scales, the Deborah number ($De = \lambda/\theta$). When the Deborah number is very small ($De \ll 1$), the response is termed "viscous," according to the nomenclature in fluid and solid mechanics. In the corresponding case of diffusion, the polymer molecular relaxation is much faster than the duration of the diffusion. In this situation, diffusion can be modeled by Fick's law, with a diffusivity that can depend on temperature, concentration, and molecular weight. At the other extreme of a very large Deborah number $De \gg 1$, the response is classified as "elastic." For this case, polymer diffusion takes place in a glassy polymer, and Fick's law has been used quite successfully to model diffusion in this regime. Consequently, diffusion can be characterized by Fick's law in two situations, where the Deborah number is either very small or very large. In both cases, the amount of penetrant absorbed in or desorbed from a polymer film is proportional to the square root of time. This type of diffusion is designated as case I diffusion. When the Deborah number approaches unity ($De \approx 1$), the relaxation and the diffusion time scales are of the same order of magnitude. In this case, diffusion in polymers exhibits a number of anomalous behaviors. For instance,

the amount of penetrant absorbed or desorbed in a polymer film no longer follows a square-root-of-time dependency. Instead, it approaches a linear relationship with time. The extreme case of non-Fickian diffusion is known as case II diffusion. While we have seen the importance of determining the material characteristic time, and the utility of the Deborah number of classify Fickian and non-Fickian diffusion, let us investigate how the polymer microstructure may give rise to these macroscopic behaviors.

Polymer Microstructures

The conditions and routes of synthesis can lead to three general classes of polymer topologies. These are the linear, branched, and network polymers [163], which can be characterized experimentally. For instance, branching can be detected by IR, NMR, and radiolysis. The cross-link density in network polymers can be determined from swelling data, sol-gel analysis, and viscometry. Linear polymers, as sketched in Fig. 3a, contain two free ends. Branched polymers contain more than two free ends, and thus can form numerous topologies as shown in Fig. 3b. Network polymers are formed by cross-linking polymer segments, as shown in Fig. 3c. Some of these networks have interesting structures and unique properties, such as the high thermal stability of ladder polymers. Hydrogels are of particular interest for controlled-release applications, because their intriguing networks enable this material to pick up enormous amounts of water while remaining water-insoluble and retaining their mechanical strength [164].

The interactions within a polymer chain and between polymer chains depend on the chemical composition and ordering of the functional groups. The chemical makeup of a polymer gives rise to intramolecular forces that determine the local stiffness and flexibility

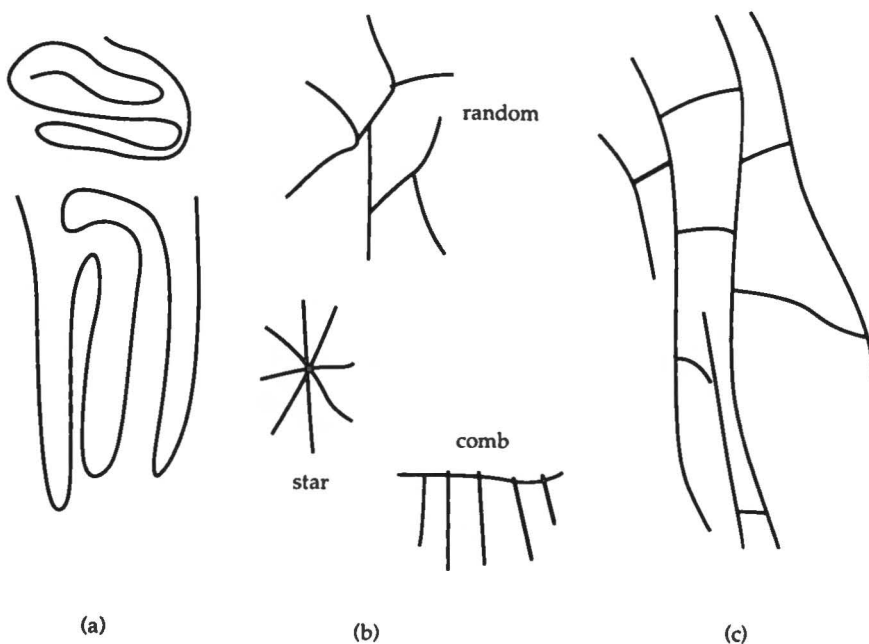


Figure 3 Schematics of linear, branched, and network polymers: (a) linear polymers, (b) branched polymers; and (c) network polymers.

of polymer segments. For instance, double bonds and ring structures along a polymer backbone stiffen the polymer chain, while insertion of oxygen along the chain increases flexibility. In general, diffusivity is higher in polymers containing flexible chains. Molecular interactions also occur between polymer chains. In this case, the polarity of functional groups gives rise to repulsive and attractive forces, which control the positioning of the groups and the separation of the chains.

The ordering of the functional groups can also come about from stereoisomerism, such as *cis-trans* isomers and tacticity, produced during synthesis. Tacticity is the arrangement of functional groups along a carbon chain. The *isotactic* and *syndiotactic* structures exhibit regularities along a carbon backbone, while random placement of the groups gives rise to an *atactic* structure. The effect of tacticity on macroscopic properties increases as the distance between polymer chains decreases to form crystal lattices. As an example, the densities of isotactic, syndiotactic, and atactic polymethyl methacrylate are, respectively, 1.22, 1.19, and 1.188 g/cm³. The isotactic form has the highest degree of regularity, increases the packing density, and therefore the bulk density. Qualitatively, diffusivity decreases as density increases because of the reduced amount of free volume.

The net effect of these molecular interactions gives rise to different polymer morphologies [165], which are generally classified as amorphous, semicrystalline, or crystalline. The popular analogy for an amorphous polymer is a bucket of worms, because the polymer segments are in constant motion. This phase is usually marked by disorder, and consequently does not give clear X-ray diffractions. Since intermolecular-chain interaction is minimal, the polymer can be deformed and shaped into films or other useful geometries. Diffusivity is normally high in an amorphous polymer because of its relatively high free volume. Semicrystalline polymers contain a mixture of amorphous and crystalline phases. Consequently, these polymers can still be deformed, particularly by raising temperature to enhance molecular motion. Crystalline polymers are characterized by a high degree of order among the polymer chains. As a result, they produce colorful patterns in cross-polarized light. However, they are not readily deformable by thermal energy, and may decompose instead of melting. Consequently, a solvent is needed to partially dissolve these polymers, so that they can be shaped into useful objects. An additional processing step may then be required to remove the solvent by either evaporation or extraction. Diffusivity is low in the crystalline phase because of the reduced free volume.

As expected, polymers can be in different morphological phases at equilibrium, depending on pressure and temperature. The effect of pressure is negligible in most cases. However, temperature can significantly alter the mobility of the polymer segments by thermal energy. Let us investigate the effects of temperature.

Transition Temperatures

The melting temperature (T_m) and the glass transition temperature (T_g) are two important transition temperatures of polymers. Above the melting temperature, a polymer is in a molten state, and is completely amorphous. The melting temperature, a first-order transition, is characterized by a sharp change in specific volume. However, not all polymers exhibit a melting temperature. Highly crystalline polymers usually do not melt, because their collective intermolecular forces are comparable or exceed their covalent bond strengths. Very often, degradation can occur before melting, because covalent and secondary bonds are severed.

As temperature decreases below the melting temperature, the polymer chain mobility

decreases. If the polymer chains can be ordered even on a local scale, then crystallization can take place. The rate of crystallization then increases with decreasing temperature, but eventually reaches a maximum. With further drop in temperature, the rate of crystallization decreases because of decreasing polymer chain mobility. Ultimately, a certain temperature is reached where virtually no segmental motion can occur. This temperature is the glass transition temperature. The polymer is in a glassy state below the glass transition temperature.

The glass transition temperature is a second-order transition because the associated change in specific volume is not discontinuous as it is at the melting temperature. Furthermore, the glass transition temperature depends on the history and time scale of the experiment, and changes slightly according to the rate of heating or cooling of a sample. Since the glass transition temperature depicts segmental mobility, factors that hinder motion would increase T_g . For instance, stiff chains, ring structures, bulky side groups, and polar groups in a polymer would all contribute to a higher glass transition temperature. This brings up an interesting problem on how to modify the glass transition temperature, particularly relative to room temperature or body temperature, where most of these polymers are to be used.

The glass transition temperature can be modified by changing the strength of the secondary forces within the polymer. This can be accomplished by introducing an additive, such as a plasticizer, to the polymer. For instance, addition of dioctyl phthalate lowers the glass transition of polyvinyl chloride and softens this polymer, which by itself is brittle at room temperature. However, the relationship between the glass transition temperature of the mixture and the amount of plasticizer needs to be determined experimentally. Another approach to modifying the glass transition temperature is to form a copolymer. The glass transition temperature of the copolymer can be estimated from the glass transition temperatures of each homopolymer by the empirical relationship

$$\frac{1}{(T_g)_{\text{copolymer}}} = \frac{\omega_1}{(T_g)_1} + \frac{\omega_2}{(T_g)_2} \quad (10)$$

where the temperatures are in kelvins, and ω_1 and ω_2 are the weight fractions of the homopolymers.

The ability to modify the glass transition temperature provides an interesting approach to develop systems with some temporal control of delivery [94]. As described earlier, the delayed onset of drug permeation from a system can be triggered by the back-diffusion of water from the skin. In this case, a drug normally could not permeate across a glassy polymeric membrane. However, when the system is applied on skin, water from the skin plasticizes the membrane and activates drug permeation.

Solubility Parameter

The addition of a second component, such as a drug or a solvent, to a polymer can change the strength of the polymer intermolecular forces, and therefore the physical properties of the polymer. Diffusivity would then depend on the availability of free volume in this multicomponent system. The strength of the intermolecular forces of a polymer is measured by its cohesive energy density (CED). The solubility parameter of a polymer (δ) is an alternative description of the intermolecular forces; it is related to the cohesive energy density as follows:

$$\delta = (\text{CED})^{1/2} \quad (11)$$

The solubility parameter can be determined by various methods, such as intrinsic viscosity and swelling measurements. The solubility parameters for many polymers are tabulated in handbooks [166]. The compatibility between a polymer and another polymer, or a polymer and a solvent, can be estimated from their respective solubility parameters. For instance, a polymer would swell or dissolve in a solvent that has a similar solubility parameter, and would precipitate from a solvent with a significantly different solubility parameter. A poor solvent is also known as a theta solvent. Similarly, the theta temperature is the temperature at which a solvent becomes a theta solvent for a polymer. The extent of interaction between a polymer and a solvent is characterized by the Flory-Huggins interaction parameter (χ). This interaction parameter is proportional to the difference in solubility parameters, and is given by the following equation:

$$\chi = \alpha + \frac{V_1}{RT} (\delta_1 - \delta_2)^2 \quad (12)$$

where α is a lattice constant for the polymer, the subscripts 1 and 2 refer to the polymer and the solvent, respectively, V_1 is the polymer molar volume, R is the gas constant and T is temperature. Two materials are likely to be compatible if the value of χ is small.

Diffusivity

The concept of free volume has been widely used to model diffusivity [167] in amorphous polymers above and below the glass transition temperature. The transport mechanism is modeled by a migration of the penetrant through holes or free volume within the polymer. Therefore, the rate of transport is based on the probability of creating a hole of sufficient size to accommodate the penetrant, and the probability for this penetrant to have sufficient energy to enter this hole. At temperatures significantly higher than the glass transition temperature, both probabilities must be taken into account to estimate diffusivity. However, near the glass transition temperature, the amount of free volume is small, so the probability of encountering holes of sufficient size dominates mass transfer. Below the glass transition temperature the amount of free volume is small, and the redistribution of holes within the polymer is negligible because segmental motion is virtually nonexistent. The size and the distribution of the holes at any temperature below the glass transition temperature are the same as those that were “frozen in” at the glass transition temperature. Consequently, the rate of cooling controls the diffusivity directly. Numerous mathematical models have been proposed to estimate diffusivity based on this diffusion mechanism. All of these models are semiempirical because of the difficulties in predicting free volume from first principles.

POLYMER CHARACTERIZATION

This section provides an overview of experimental methods used to characterize the properties of polymers.

Molecular Weight and Molecular-Weight Distribution

Most methods developed to measure molecular weight involve dissolving the polymer in a solvent. Dilute solutions are often used to avoid additional complications from viscoelastic effects. The experimental methods are then divided into those that measure absolute molecular weights and those that provide relative molecular weights. Both approaches

are presented below for the measurement of the various average molecular weights defined earlier.

End-group analysis is used to obtain the number-average molecular weight up to approximately 20,000. The key to this method depends on the availability of analytical techniques to detect and count functional groups on a polymer chain. For instance, hydroxyl, carboxyl, and amino end groups can be titrated.

Osmometry can also be used to determine the number-average molecular weight. The key to this method depends on the availability of a semipermeable membrane to measure the osmotic pressure in a polymer solution. The osmotic pressure is then related to M_n by

$$\pi = \frac{RT}{M_n} C + BC^2 \quad (13)$$

where C is concentration and B is a virial coefficient. The number-average molecular weight is then obtained from the intercept of a plot of π/CRT versus C .

Ebulliometry (or boiling elevation) and cryoscopy (or freezing depression) are based on the Clausius-Clapeyron equation, to relate changes in boiling and freezing points to the number-average molecular weight. This relation is given by

$$M_n = \frac{RT^2V}{\Delta H} \left(\frac{C}{\Delta T} \right)_{C \rightarrow 0} \quad (14)$$

where V and ΔH are the specific volume and heat of transition, respectively. Experimentally the boiling and freezing points of a polymer solution are compared sequentially to that of a solvent by differential thermometers or thermistors arranged in a Wheatstone bridge circuit. Both methods are limited to M_n up to approximately 30,000 because of foaming and crystallization problems with high-molecular-weight polymers.

Light scattering provides a means of measuring the weight-average molecular weight by applying Lord Rayleigh's electromagnetic theory, which shows that the intensity of scattering is proportional to the square of the particle mass. Experimentally, the intensity of scattered light from an incident source, such as a laser, is measured at different angles from polymer solutions of different concentrations. In dilute solutions, the Debye equation relates intensity, concentration, and M_w as follows:

$$\frac{HC}{\tau} = \frac{1}{M_w} + \frac{2\beta C}{M_w} \quad (15)$$

where H is determined experimentally from refractive index (n) and specific refractive increment (dn/dC) measurements. H is constant for a polymer in a solvent at a given temperature, and is calculated by the following equation:

$$H = \frac{32\pi^3 n^2}{N_0 \lambda^4} \left(\frac{dn}{dC} \right)^2 \quad (16)$$

where N_0 is Avogadro's number, and λ is the wavelength of the incident source. The turbidity (τ) is calculated from the intensity of scattering at 0° and 90° , and β is a constant. The weight-average molecular weight is then obtained from the intercept of a plot of HC/τ versus C .

Ultracentrifugation can be used to measure the weight-average and z-average molecular weights. This method takes advantage of an equilibrium that is established between

centrifugal and diffusional forces in a dilute polymer solution. For a given angular velocity (Ω), concentration, refractive index, and specific refractive increment are measured at two locations (r_1 and r_2) within the ultracentrifugation cell. The weight-average molecular weight is related to concentration measurements by

$$M_w = \frac{2 RT \ln(C_2/C_1)}{(1 - \bar{V}\rho)\Omega^2 (r_2^2 - r_1^2)} \quad (17)$$

where $\bar{V}$ is the polymer partial specific volume and ρ is the solution density. The z-average molecular weight is related to refractive index and specific refractive increment by

$$M_z = \frac{RT}{(1 - \bar{V}\rho)\Omega^2} \frac{[(1/r)(dn/dr)]_2 - [(1/r)(dn/dr)]_1}{(n_2 - n_1)} \quad (18)$$

The solution viscosity reflects the space that a polymer occupies in a solvent, and therefore provides a measure of molecular weight. The viscosity of a dilute polymer solution (η) can be conveniently determined in capillary viscometers of the Ostwald-Fenske or Ubbelohde type by recording the time required for a volume of solution to flow through a capillary tube. By repeating this measurement in various solution concentrations, the intrinsic viscosity ($[\eta]$) can be extrapolated at infinite dilution from the following relationship:

$$[\eta] = \left(\frac{\eta - \eta_s}{\eta_s C} \right)_{C=0} \quad (19)$$

where η_s is the solvent viscosity. The intrinsic viscosity is then related to viscosity by the Mark-Houwink equation, which is an empirical relationship with two constants (K') and (a):

$$[\eta] = K' M^a \quad (20)$$

The exponent (a) varies from a value of 0.5 in a poor solvent to a maximum of 1. The values of both constants, which are functions of temperature, solvent, and polymer, are tabulated in polymer handbooks [168]. Based on the intrinsic viscosity measurement, Schaefgen and Flory [169] defined a viscosity-average molecular weight by

$$M_v = \left(\frac{\sum_{i=1}^{\infty} N_i M_i^{1+a}}{\sum_{i=1}^{\infty} N_i M_i} \right)^{1/a} \quad (21)$$

From this definition, $M_v < M_w$; except for the case of $a = 1$, $M_v = M_w$.

The above methods for measuring absolute average molecular weights are time-consuming. For a rapid evaluation of molecular weight, gel-permeation chromatography (GPC), or more precisely liquid exclusion chromatography, provides a relative measure of molecular weight [170]. In GPC, a polymer solution is injected into a column of porous beads. Initially, a concentration gradient is established between the liquid phase and the porous beads, to cause fractions of smaller polymer molecules to diffuse into the beads. Since a solvent is continuously passed through the column, the larger polymer molecules are eluted first. With the larger molecules depleted, the concentration gradient between the beads and the solvent phase causes the smaller polymer molecules to diffuse back out of the beads, and eventually eluted from the packed column. Consequently, the molecular weight and the molecular-weight distribution can be obtained by comparing the elution time of the unknown sample to a set of standards. Although standards of narrow-molecular-

weight-distribution polymers at different molecular weights are often not available these measurements are still useful for relative comparisons against an acceptable sample, such as one used for quality control.

The zero-shear-rate viscosity of a polymer melt can also be used as a relative measure of molecular weight. From the molecular theories of polymer melts [171], such as entanglement [172] and reptational models [173], the zero-shear-rate viscosity is proportional to molecular weight raised to an exponent that ranges between 3 and 3.5. Consequently, a relative measure of molecular weight can again be obtained from the ratio of viscosities of a new sample and a known sample.

Rheological Measurement of Material Characteristic Time

In addition to obtaining polymer flow properties and molecular weight, rheological measurements provide a means to determine the material characteristic time of a polymer. Various types of rheometers, such as cone-and-plate and parallel-disk rotational viscometers, can be used to measure the shear viscosity as a function of shear rate at a given temperature [174]. Figure 4 shows a typical response of the dependency of shear viscosity (η) on shear rate ($\dot{\gamma}$), plotted on a log-log scale. At low shear rate, the zero-shear-rate viscosity (η_0) is independent of shear rate, and depends only on temperature:

$$\eta = \eta_0 \quad (22)$$

The shear viscosity then decreases with increasing shear rate. The linearly decreasing shear viscosity on a log-log plot can be conveniently represented by a power-law model:

$$\eta = m \dot{\gamma}^{(n-1)} \quad (23)$$

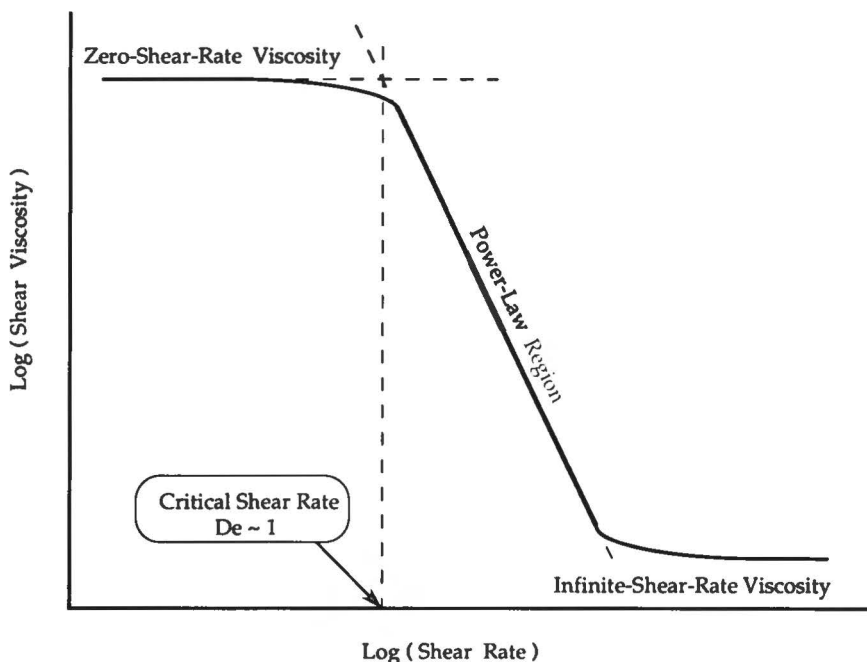


Figure 4 Log-log plot of shear viscosity as a function of shear rate.

where the power-law coefficient (m) is a function of temperature and (n) is the power-law index. For some polymers, the shear viscosity may become independent of shear rate at very high shear rate. This viscosity is the infinite-shear-rate viscosity (η_∞).

The use of the Deborah number simplifies the interpretation of the material response. In shear flow, the process time scale is approximately equal to the reciprocal of shear rate ($1/\dot{\gamma}$). The Deborah number is then given by

$$De = \lambda \dot{\gamma} \quad (24)$$

At low shear rate ($De \ll 1$), a viscous response is observed, as indicated by a constant shear viscosity. In this region, hydrodynamic forces are extremely weak, and do not interfere with the molecular motion of the polymer, driven primarily by Brownian forces. Consequently, molecular weight radius of gyration, and other molecular parameters can be obtained by combining the low-shear-rate data and molecular models. As shear rate increases, the time scale of the shear flow approaches the polymer relaxation time. Here, the shear viscosity begins to depend on shear rate, and the onset of non-Newtonian behavior sets in. Since $De \approx 1$, the longest material characteristic time (λ_L) can be estimated at the critical shear rate ($\dot{\gamma}_c$) where the zero-shear-rate viscosity intersects the shear viscosity from the power-law model:

$$\lambda_L = \frac{1}{\dot{\gamma}_c} \quad (25)$$

Hence the material characteristic time can be estimated from a simple shear flow measurement. More elaborate experiments and analyses would be required to map out the spectrum of material characteristic times [175].

Transition Temperatures

Differential thermal analysis (DTA) and differential scanning calorimetry (DSC) are two commonly used techniques to determine transition temperatures [176]. In differential thermal analysis, the temperature difference between a sample and a reference material is recorded when both specimens are heated or cooled at a controlled rate. Figure 5 shows a schematic DTA curve, in which the temperature difference is plotted against the temperature of the environment where the sample and the reference material are tested. In differential scanning calorimetry, the energy required to maintain a zero temperature difference between a sample and a reference material is recorded when temperature is scanned at a controlled rate. The output from a DSC experiment is similar to a DTA experiment, except that the ordinate of a DSC curve shows the amount of energy required to maintain a zero temperature difference. This energy can also be represented in the form of a heat capacity, as shown in Fig. 5. The area under a peak in a DSC curve is related directly to a change in enthalpy, whereas the area under a peak in a DTA curve is a complex function of sample geometry, heat capacity, and heat losses.

In general, narrow peaks are indicative of first-order transitions, such as the melt temperature, in both DTA and DSC curves. Second-order transitions, such as the glass transition temperature, occur at inflection points in both curves; and chemical reactions are depicted by broad peaks. The specific heat capacity (c_p) can also be calculated from

$$c_p = \frac{\Delta Q}{m \Delta T} \quad (26)$$

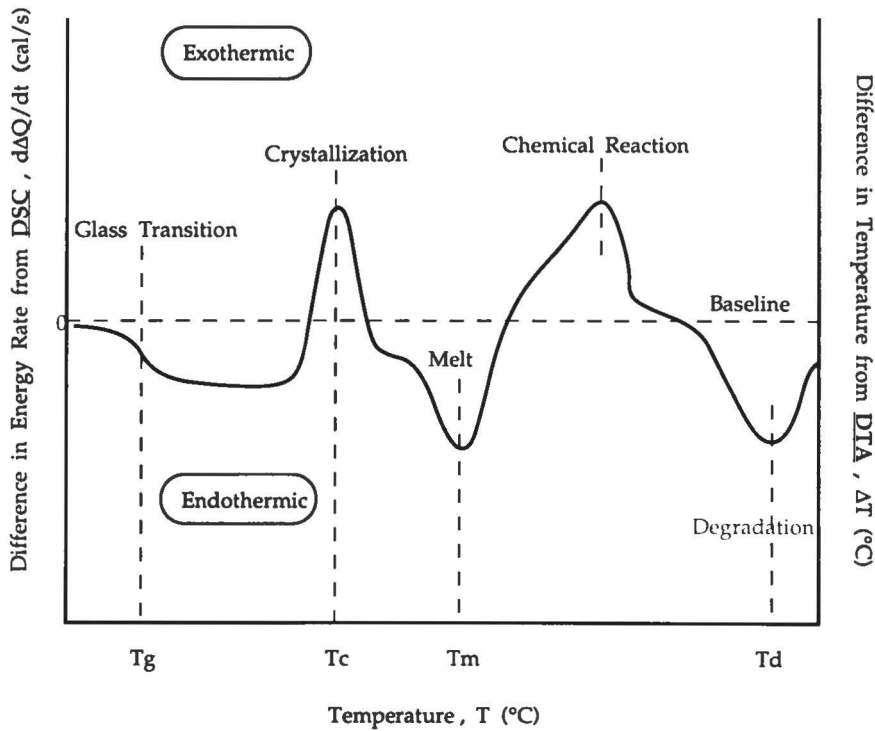


Figure 5 Schematic of a DTA or DSC curve.

where ΔQ is the energy required to change the temperature of a sample of mass (m) by ΔT . Additional thermodynamic properties can be determined from the heat capacity data. Enthalpy is given by

$$\Delta H = \int_0^T c_p dT \quad (27)$$

entropy is given by

$$\Delta S = \int_0^T \frac{c_p}{T} dT \quad (28)$$

and Gibbs free energy is given by

$$\Delta G = \Delta H - T \Delta S \quad (29)$$

Lastly, an estimate of the degree of crystallinity can be obtained from

$$\delta_c = \frac{(c_p)_a - c_p}{(c_p)_a - (c_p)_c} \quad (30)$$

where $(c_p)_a$ and $(c_p)_c$ are, respectively, the specific heats of the amorphous and crystalline standards.

Permeation in Polymers

As discussed earlier, permeability is a lumped parameter, consisting of the product of partition coefficient and diffusivity, that is used to characterize the transport of a species

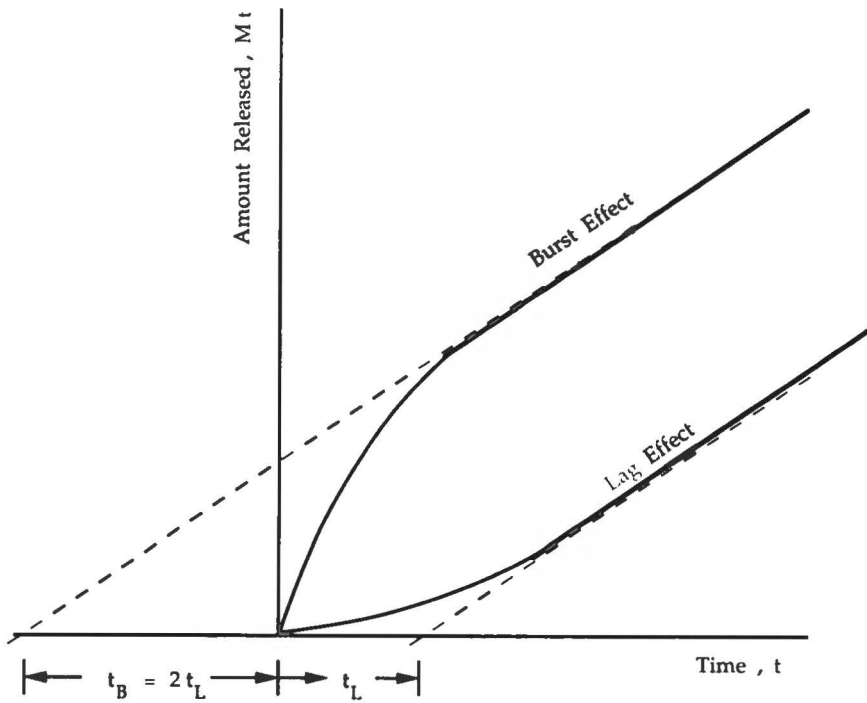


Figure 6 Amount permeated across a membrane as a function of time.

across a polymer. The partition coefficient and the diffusivity can be measured from a simple permeation experiment. A polymeric film is clamped between a donor cell that contains a saturated solution and a receiver cell in which the concentration of the permeating species is measured as a function of time. Both cells are well stirred to minimize the boundary-layer mass transfer resistances. Figure 6 shows a typical plot of the amount released (M_t) versus time [177]. The amount released is initially nonlinear and then approaches steady state. The initial nonlinearity exhibits a burst or a lag effect, depending on whether the membrane is initially saturated or devoid of the diffusing species, respectively. Diffusivity ($\mathcal{D}$) can be obtained from the time to reach steady state in both cases, since

$$\mathcal{D} = -\frac{L_m^2}{3t_B} = \frac{L_m^2}{6t_L} \quad (31)$$

where the burst time (t_B) and the lag time (t_L) are intercepts on the time axis extrapolated from the amount released at steady state, and L_m is the membrane thickness. Permeability ($\mathcal{P}$) is evaluated from the slope at steady state, which is constant, and is given by

$$\mathcal{P} = \frac{L_m}{A \Delta C} \left(\frac{dM_t}{dt} \right)_{\text{steady state}} \quad (32)$$

where A and ΔC are, respectively, the membrane surface area and the bulk concentration difference between the donor and receiver cells. The partition coefficient ($\mathcal{K}$) is then calculated from

$$\mathcal{K} = \frac{\mathcal{P}}{\mathcal{D}} \quad (33)$$

In addition to permeation experiments, partition coefficient and diffusivity can be determined by sorption/desorption measurements, radioactively tagged penetrants, and a variety of spectroscopic methods.

CONCLUSION

Within the voluminous literature and list of technologies regarding controlled drug delivery, interesting applications can be found for almost any conceivable biological membrane or therapeutic area, with most academic and industrial pharmaceutical institutions contributing. However, few applications have yet found their way to the market. This observation may be surprising even in light of the long development time in the pharmaceutical industry and the effort required to change established R&D processes. Perhaps the greatest drawback to the success of controlled drug delivery is the isolation of the technology from the therapeutics. Coordination of technology and therapeutics is needed in a rational drug development process that is initially governed by the steady-state pharmacology and later by the clinical pharmacology.

PROBLEMS

1. A very potent drug has a half-life of 3 min and an extensive hepatic first-pass metabolism. Discuss the relative merits of an oral, a sublingual immediate-release formulation, a sustained-release sublingual formulation in which some of the drug is swallowed, and a transdermal patch.
2. For a drug to be delivered by a zero-order device, the desired effective plasma level is 10 ng/ml and the clearance is 1 liter/min. Calculate the required steady-state delivery rate of drug.
3. Construct a phase diagram for copolymers of poly(acrylic acid) and poly(methacrylate) with T_g 's of 379 and 278 K, respectively.
4. The fluxes from saturated solutions of drug in either water or propylene glycol were measured across a membrane. Assume that neither the drug nor the solution affects drug permeation across the membrane, i.e., ideal membrane approximation. If the solubilities of the drug in water and propylene glycol are 10 and 1 mg/ml, respectively, what is the ratio of their fluxes across the membrane?
5. Given a minimum dosing interval for an implant of 6 months and a maximum drug loading due to size constraints of 0.5 g, calculate the required drug potency for use in an implant. Comment on the toxicological concerns of using an implant.
6. Discuss the relative merits of oral, buccal, nasal, and transdermal delivery of the small peptide, oxytocin.
7. Discuss the effects on membrane permeation of (a) glass transition, (b) cross-linking density, (c) plasticizer content, (d) molecular-weight distribution of the polymer, (e) molecular volume of the drug, (f) solubility parameters of the drug and membrane, and (g) surface topology of the membrane.
8. Two batches of the same copolymer are processed under different temperature conditions to yield membranes with different permeation properties. Discuss some of the methods that might be used to characterize this phenomenon.

ANSWERS

1. The large first-pass metabolism would cause an oral dosage form to produce erratic plasma levels, and the half-life would necessitate a controlled-release

dosage form. If the therapeutic window were extremely large, then an oral controlled-release dosage might be viable. The sublingual immediate-release formulation could be used only for very short-term effects, and a sublingual sustained-release formulation would circumvent both concerns. A transdermal formulation might be possible for a very potent drug, would also circumvent the metabolism and half-life issues, and would probably have better patient acceptance than the buccal route.

2. From Eq. (2),

$$\text{drug input rate} = (10 \text{ ng/ml}) (1000 \text{ ml/min}) (60 \text{ min/h}) = 0.6 \text{ mg/h}$$

3. From Eq. (10), the glass transition temperatures for any copolymer composition will be linear with the weight fraction, and this line will connect the two T_g 's for the two homopolymers.
4. Saturated solutions are at unit activity and are in equilibrium with the solid drug regardless of the choice of solvent. Since the driving force for diffusion is the activity gradient, for an ideal membrane, the flux from any saturated solution will be the same. This is, then, a method of testing for solvent effects on membranes.
5. The required drug potency for an implant may be estimated as (0.5 g)/180 days) or approximately 2.7 mg/day. That is, extreme potency is required, and this estimate may be somewhat large. An implant needs to be capable of being removed rapidly in emergencies, and inflammation and foreign body reactions are of particular concern.
6. Oxytocin requires rapid delivery and would be broken down by peptidases in the gut. An oral dosage form is therefore unlikely. Peptide permeation through skin is unlikely in sufficient doses, although iontophoresis might be a possibility. However, this may be too elaborate a technology for this task. A sublingual formulation may be possible, but the bioavailability is somewhat poor and variable. Nasal delivery would provide the most bioavailable and rapidly absorbed formulation of oxytocin.
7. Membrane permeation (a) decreases with increasing T_g , (b) decreases with increasing cross-linking density, (c) increases with plasticizer content, (d) typically decreases with polymers or (e) drugs of increasing molecular weight or volume, (f) is largest when the two solubility parameters are identical, and (g) can increase or become variable due to irregular surface topography.
8. To analyze this problem, SEM and TEM will allow one to visualize differences in the membrane, and either DSC or thermomechanical analysis will help in understanding the thermal properties. If crystallinity is an issue, cross-polarizers may help visualize changes and X-ray diffraction may prove useful.

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Factors Influencing the Kinetics of Solute Release

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INTRODUCTION

During the past 40 years a substantial number of drug delivery systems have been introduced to the marketplace, and considerable effort has been expended in the development of new delivery concepts. There are a number of reasons for this continued interest in developing new systems, as has been emphasized in Chapter 1 of this book. First, recognition of the possibility of repatenting successful drugs by applying the concepts of controlled drug delivery, coupled with the increasing expense of bringing new drug entities to the marketplace, has provided justification for continued research on and development of these products. Second, the idea of improving the therapeutic efficacy and safety of new drug entities by more precise spatial and temporal placement within the body as compared to conventional delivery systems is attractive. This second goal will result in less total drug being required, thereby decreasing side effects and increasing the efficiency of treatment by reducing frequency of dosing.

There are other reasons for the development of these products beyond the obvious therapeutic advantages of controlled drug release. For example, patient compliance is a chronic problem for all self-administered drugs and is a sufficiently compelling reason in itself to warrant an alternative delivery system. Indeed, in recent years this has been recognized as a very important component of successful drug therapy. Economic justification is sufficient for designing controlled-release products as well. This is particularly true in a critical care, hospital setting in which drugs are administered intravenously. Systems that eliminate the need for manual reconstitution or admixing will result in labor reduction and time savings to the clinical health-care professional, and ultimately result in improved therapy. In addition, drug delivery systems that overcome drug stability problems inherent in conventional dosage forms warrant attention as well. For example,

in the case of intravenous drug administration, some drugs cannot be practically formulated in a ready-to-use sterile aqueous solution because of their significant instability in an aqueous environment. In these cases, an in-line drug delivery system in which the drug is formulated in the solid state to improve stability is attractive. The drug would be delivered intravenously in the solution phase by controlling its dissolution kinetics as a large-volume parenteral solution flows through the system via an administration set.

For many years, controlled drug release or delivery was attainable only by intravenous infusion. In this mode of administration, the rate at which a drug of known concentration is delivered to the bloodstream can be controlled or changed according to the therapeutic requirements of the patient. In this form of drug delivery, control is achieved by the use of a flow control pump or, in the case of gravity-flow infusion, by the plumbing/valving of the administration set. More recently, this ideal of controlled drug delivery has been approached through the design of polymer systems in which the drug is dissolved or dispersed, coupled with an increased understanding of the factors influencing the kinetics of drug release. This fundamental concept (drug dissolved or dispersed in a polymer) represents a commonality with regard to the approach taken in designing drug delivery systems for a breadth of administration modes (transdermal patches, bioadhesive platforms, microencapsulated products, monolithic implants, etc.). Typically, the objective in a controlled drug delivery system is to have drug release from the dosage form be the rate-limiting step for drug availability. In this fashion, drug availability is controlled by the kinetics of drug release rather than absorption. Therefore, central to the development of successful controlled delivery systems is the synthesis of the principles of molecular transport in polymeric materials, as well as a firm understanding of the variables that influence the transport processes. This understanding will allow more efficient drug delivery system design once the drug delivery rate requirements are known based on pharmacokinetic/pharmacodynamic considerations.

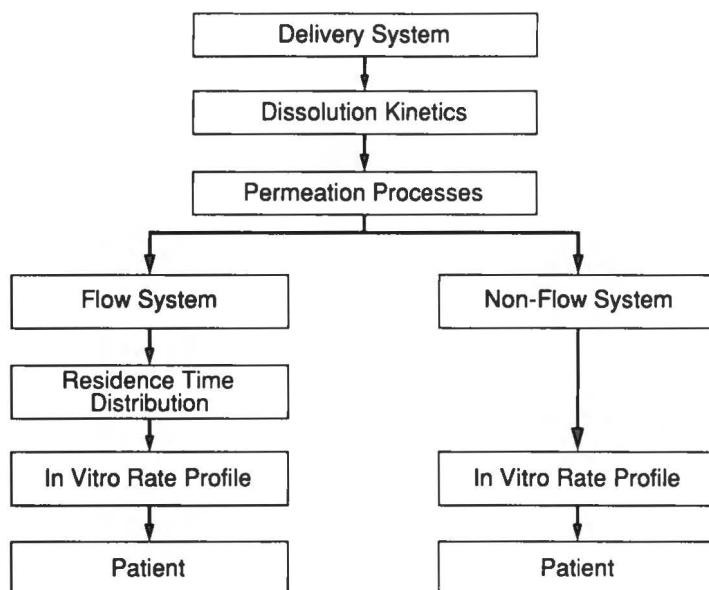


Figure 1 Schematic diagram of solute release from a drug delivery system.

Figure 1 is a generalized flow diagram illustrating the processes involved in solute release from most drug delivery systems. The nonflow system is representative of the situation for most drug delivery systems in which the drug is eluted into a relatively stagnant milieu. The flow system applies, for example, in the case of in-line drug delivery systems in which a large-volume parenteral solution continuously flows through a cartridge containing the formulated drug. Drug is released into this flowing stream and is delivered intravenously in solution phase via the administration set. This chapter, using Fig. 1 as the guide, critically reviews the factors which influence the kinetics of solute release using a quantitative, physical-model approach. It describes the diffusion and partition coefficients of solutes, how these coefficients are measured/computed, and the role they play in defining solute release kinetics. The effect of viscosity and concentration on diffusion is described. Membrane and matrix parameters important to drug release, as well as polymeric drug solubility considerations, are discussed. The chapter also describes the particularly important effect in flow-through intravenous drug delivery systems in which the drug is delivered via an administration set. Finally, approaches for designing and/or optimizing drug delivery systems based on pharmacokinetic/pharmacodynamic requirements are also considered.

PRINCIPAL SYMBOLS, CONSTANTS, AND ABBREVIATIONS

Note: The units presented in the following list are suggested by the authors. In general, any consistent set of units may be used in all equations in this chapter, except the equations derived empirically, such as Eq. (5). These empirical equations are valid only when specific units are used.

A: surface area, cm^2

Å: angstrom

a: general symbol for the radius of a cylinder, sphere, or the half-thickness of a slab; constant equal to k_m/K , used in Eq. (130)

a_i : radius of a cylindrical or spherical cavity

b: dimensionless constant defined by Eq. (131)

C: time-dependent solute concentration, either in the bulk or in a polymer, mg/ml

C_B' : molar density of the solvent, g-mol/cm^3

C_b : solute concentration in the bulk; solute concentration in the receptor solution, used in Eq. (116)

C_{b0} : initial solute concentration in the bulk; initial solute concentration in the receptor solution, used in Eq. (117)

C_{b1} : solute concentration in the solution phase adjacent to face 1 of the polymer, mg/ml

C_{b2} : solute concentration in the solution phase adjacent to face 2 of the polymer, mg/ml

C_b^* : solute concentration in the polymer phase adjacent to the interface between the bulk and the polymer, used in the section on membrane and matrix parameters with the absence of boundary-layer diffusion, mg/ml

CED: cohesive energy

C_M : solute solubility in the polymer, mg/ml

$\bar{C}_M$: mole fraction solubility in polymer, defined by Eq. (158)

C_0 : solute concentration in the polymer phase adjacent to the interface between the bulk and the polymer, used in the section on recipient environment and in Fig. 16 with the presence of boundary-layer diffusion, mg/ml

- C_s : solute solubility in the liquid phase, mg/ml
 C_T : total solute loading dose in the polymer, equal to the amount of solute per unit volume of the entire matrix, mg/ml
 D : diffusion coefficient of solute molecules in the liquid phase or solvent, cm^2/s
 $D(C)$: diffusion coefficient of solute as a function of concentration, cm^2/s
 $\bar{D}$: dispersion coefficient, cm^2/s
 D_{am} : diffusion coefficient in the amorphous polymer, cm^2/s
 D_{calc} : calculated diffusion coefficient, cm^2/s
 D_D : drug diffusion coefficient in the donor-side boundary layer, cm^2/s
 D_e : effective diffusion coefficient of solute molecules in the polymer phase, cm^2/s
 D_{exp} : diffusion coefficient determined by experiment, cm^2/s
 D_m : diffusion coefficient in the polymeric membrane or matrix equivalent to D_e , cm^2/s
 D_{M1} : diffusion coefficient of a diffusant of unit molecular weight, used in Eq. (19)
 D_0 : diffusion coefficient at infinite dilution, cm^2/s
 D_R : drug diffusion coefficient in the receptor-side boundary layer, cm^2/s
 d : characteristic length, cm
 $E(t)$: residence time distribution function of a flow system, 1/min
 $E(\tau)$: dimensionless residence time distribution function of a flow system
 E_v : molar energy, used in Eq. (157)
 $E_{all}(t)$: overall residence time distribution function, 1/min
 ΔE : penetration energy
 $\text{erf}(x)$: error function with argument x
 $\text{erfc}(x)$: complementary error function = $1 - \text{erf}(x)$
 F : flow rate, ml/min
 f : proportionality constant used in Eq. (112)
 $f(\xi_p)$: a function dependent on the mesh size ξ_p
 Fa : faraday, 96,500 C/g-equiv
 FF : a function defined by Eq. (213)
 $FF(R_{L1})$: functional value of FF at $R = R_{L1}$
 $FF(R_{L2})$: functional value of FF at $R = R_{L2}$
 $FF(R_{R1})$: functional value of FF at $R = R_{R1}$
 $FF(R_{R2})$: functional value of FF at $R = R_{R2}$
 $FF_{1/2}$: functional value of FF at the halfway point, determined in the first step of the half-interval iterations
 $G(C)$: dimensionless variable defined by Eq. (175)
 g_1 : physical parameter, used in Eq. (12)
 g_2 : physical parameter, used in Eq. (12)
 g_3 : constant defined by Eq. (15)
 ΔH_f : molar heat of fusion
 ΔH_f^* : energy required for dissociation of the solute molecules from their crystal lattice
 ΔH_f^{**} : energy required for solvation of the solute molecules into polymer structure
 h : boundary-layer thickness, cm
 h_D : boundary-layer thickness on the donor side, cm
 h_0 : thickness of the boundary layer having constant viscosity, cm
 h_R : boundary-layer thickness on the receptor side, cm
 $\text{ierfc}(x)$: integrated complementary error function = $1/\pi^{1/2}\exp(-x^2) - x \text{erfc}(x)$
 J : diffusion flux, rate per unit area, $\text{mg}/(\text{cm}^2\text{-s})$

- $J_0(x)$: Bessel function of the first kind of order 0
 $J_1(x)$: Bessel function of the first kind of order 1
 $J_{\max}$: permeation flux from a saturated solution, $\text{mg}/\text{cm}^2\text{-s}$
 K : partition coefficient (polymer/bulk), dimensionless
 K_D : partition coefficient (polymer/bulk) on the donor side, dimensionless
 K_n : partition coefficient for the compound with a chain length of n carbons, used in Eq. (148)
 K_0 : partition coefficient for the reference homolog, used in Eq. (148)
 K_{ps} : partition coefficient of the solute from the pore to the solvent, used in Eq. (7)
 K_{rs} : restriction coefficient dependent on the ratio of molecular radius to pore radius, used in Eq. (7)
 K_R : partition coefficient (polymer/bulk) on the receptor side, dimensionless
 k_D : mass transfer coefficient in the donor cell, cm^2/s
 k_m : mass transfer coefficient, cm^2/s
 k_R : mass transfer coefficient in the receptor cell, cm^2/s
 k_0 : infusion rate, mg/min
 L : length of a cylinder or tube, cm
 l_s : characteristic length of the solute molecule, used in Eq. (13)
 ℓ : thickness of membrane, cm
 M : molecular weight, dalton
 $\bar{M}_c$: number average molecular weights between crosslinks, used in Eq. (12)
 $\bar{M}_c^*$: value of $\bar{M}_c$ below which no diffusion of the solute molecules can take place, used in Eq. (12)
 M_{it} : cumulative amount of solute released at time t , following the intrinsic kinetics, mg
 M_{it}' : fictitious amount of drug release at time t , determined from the plot of M_t versus $t^{1/2}$ of the apparent release profile, as illustrated in Fig. 23
 M_{i1}' : value of M_{it}' at time t_1 , determined from the plot of M_t versus $t^{1/2}$ of the apparent release profile, as illustrated in Fig. 23
 M_{i2}' : value of M_{it}' at time t_2 , determined from the plot of M_t versus $t^{1/2}$ of the apparent release profile, as illustrated in Fig. 23
 $\bar{M}_n$: number-average molecular weight before cross-linking, used in Eq. (12)
 M_0 : initial mass used in Eq. (24), mg
 M_t : cumulative amount of solute released at time t , mg
 $M_t(i)$: cumulative amount of solute released of datum point i
 $\hat{M}_t$: estimated (computed) value of M_t at time t
 M_∞ : cumulative amount of solute released at infinite length of time, mg
 m : molality, $\text{g-mole per 1000 g of solvent}$
 N_0 : Avogadro's number, $6.023 \times 10^{23}/\text{g-mol}$
 P : permeability coefficient
 Q_{it} : intrinsic release rate
 Q_m : swelling ratio
 Q_0 : initial rate; transport rate of the reference diffusant, mg/s
 Q_t : diffusion rate, dissolution rate, release rate, or permeation rate at time t , mg/s
 $Q_t(i)$: release rate of datum point i
 $\hat{Q}_t$: estimated (computed) release rate at time t
 Q_∞ : diffusion rate, dissolution rate, or permeation rate at steady state, mg/s
 R : gas-law constant, equal to $8.314 \times 10^7 \text{ g-cm}^2/\text{s}^2\text{-g mol-K}$

- $R(t)$: radius or distance of receding boundary, cm
 Re : Reynolds number, equal to (dU/ν) , Eq. (114), dimensionless
 R_i : inner radius of a cylinder or sphere
 R_{L1} : value of the radius, $R(t)$, on the left-hand side, determined in the first step of the half-interval iterations
 R_{L2} : value of the radius, $R(t)$, on the left-hand side, determined in the second step of the half-interval iterations
 R_{Lk} : value of the radius, $R(t)$, on the left-hand side, determined in the k -th step of the half-interval iterations
 R_{R1} : value of the radius, $R(t)$, on the right-hand side, determined in the first step of the half-interval iterations
 R_{R2} : value of the radius, $R(t)$, on the right-hand side, determined in the second step of the half-interval iterations
 R_{Rk} : value of the radius, $R(t)$, on the right-hand side, determined in the k -th step of the half-interval iterations
 R_o : outer radius of a cylinder or sphere, cm
 r_A : radius of diffusant molecules, cm
 r : radius of a sphere or a cylinder, cm
 r_s : characteristic radius of a solute molecule
 Sc : Schmidt number, equal to ν/D , Eq. (115), dimensionless
 ΔS_f : entropy of fusion, cal/mol-K
 Sh : Sherwood number, equal to $k_m d/D$, Eq. (113), dimensionless
 S_0 : initial slope of the dimensionless concentration profile defined by Eq. (182)
 T : absolute temperature, K
 T_f : forming temperature of polymer
 T_M : melting temperature, K
 $t(i)$: time of datum point i
 $\bar{t}$: mean residence time, min
 t_{lag} : lag time
 t_{lag}' : apparent lag time
 U : mean velocity of flow; effective velocity, cm/s
 u_0 : maximum velocity of flow, cm/s
 V : volume, ml
 V_A : molar volume of solute molecule A, $\text{cm}^3/\text{g-mol}$
 V_A' : molar volume of solute molecule A at its normal boiling point, $\text{cm}^3/\text{g-mol}$
 V_B : partial molar volume of a solvent
 V_c : volume of central compartment
 v_a : volume fraction of equilibrium amorphous polymer
 v_c : volume fraction of equilibrium crystalline polymer
 v_p : volume fraction of polymer
 v_s : volume fraction of solvent or swelling-agent
 $W(i)$: weighting factor of datum point i
 w : polymer concentration in weight-percent, used in Eq. (10)
 Z_+ , Z_- : valences of cation and anion, respectively
 α : shear rate; pharmacokinetic constant; $V_1/(KV_2)$ defined by Eq. (33)
 β : pharmacokinetic constant
 γ : the ratio of the solute molecule radius to the pore radius; correction factor used in Eq. (125); activity coefficient