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Oral Controlled-Release Delivery

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INTRODUCTION

Among all the routes of drug administration that have been explored for the development of controlled-release (CR) systems, the oral route has by far achieved the most attention and success. This is due, in part, to the ease of administration as well as to the fact that gastrointestinal physiology offers more flexibility in dosage-form design than most other routes. Development of an oral CR dosage form for a given drug involves optimization of the dosage-form characteristics within the inherent constraints of gastrointestinal (GI) physiology.

Although significant clinical advantages have been obtained for CR formulations, most such dosage forms are still designed on an empirical basis. An understanding of varied disciplines, such as GI physiology, pharmacokinetics, and formulation techniques, is essential in order to achieve a systematic approach to the design of oral CR products. The scientific framework required for development of a successful oral controlled drug delivery dosage form consists of an understanding of three aspects of the system, namely, (1) the physicochemical characteristics of the drug, (2) relevant GI anatomy and physiology, and (3) dosage-form characteristics. The anatomy and physiology includes insight into the basic physiology of the gut as well as the absorptive properties of the GI mucosa. Often one encounters additional factors, including the disease being treated, the patient, and the length of therapy. Given that it is usually not practical to alter the physicochemical characteristics of the drug, design of controlled-delivery systems generally optimizes dosage-form characteristics relative to the GI environment.

The objective of this chapter is to review oral CR systems, with a focus on dosage-form characteristics and GI physiology. Since an understanding of the basic concepts of CR systems is vital for future development, particular emphasis will be on the rationale and mechanism of such delivery systems.

Definitions

The term CR implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics, and known mechanism of release. Also included in this term are systems that provide control over movement of the dosage form through the GI tract and/or deliver the drug to a specific area within the GI tract for either local or systemic effect. This chapter will deal only with dosage forms intended to be swallowed orally and will thus exclude buccal and rectal areas of delivery.

Advantages/Disadvantages of Oral CR Dosage Forms

The goal of oral CR products is to achieve better therapeutic success than with conventional dosage forms of the same drug. This goal is realized by improving the pharmacokinetic profile as well as patient convenience and compliance in therapy. Improvement is perhaps the major reason for so much attention being focused on drugs used in chronic therapy; e.g., diuretics, cardiovascular, and CNS agents. Some of the advantages of oral CR dosage forms are

1. Reduced dosing frequency
2. Better patient convenience and compliance
3. Reduced GI side effects and other toxic effects
4. Less fluctuating plasma drug levels
5. More uniform drug effect
6. Lesser total dose

The ideal system possesses all of the above advantages. In most cases, however, there is little direct evidence of a more uniform drug effect, and success has to be based on circulating plasma drug levels. Also, a lesser total dose is based on the assumption that the drug shows linear pharmacokinetics, which in many cases, as will be discussed below, may not be achieved.

On the other hand, oral CR formulations suffer from a number of potential disadvantages. These include:

1. Generally higher cost
2. Relatively poor in-vitro/in-vivo correlation
3. Sometimes unpredictable and often reduced bioavailability
4. Possible dose dumping
5. Reduced potential for dose change or withdrawal in the event of toxicity, allergy, or poisoning
6. Increased first-pass metabolism for certain drugs

Unpredictable and poor in-vitro/in-vivo correlations and bioavailability are often observed with such formulations, especially when the drug release rate is very low or drug absorption from the colon is involved. Dose dumping is a phenomenon where a large amount of the drug is released in a short period of time, resulting in undesired high plasma drug levels and potential toxicity.

Drug Candidate Criteria

A number of drug characteristics need to be considered in evaluating drug candidates for oral CR dosage forms. Some of these characteristics are discussed here.

Dose

Dose limitation is a major factor to consider in many routes, especially for transdermal and buccal patches. In oral systems, however, total drug dose is infrequently a limiting factor. A total dose of several grams may be administered orally as single or multiple units to obtain and maintain adequate drug levels. Nevertheless, for drugs with an elimination half-life of less than 2 h as well as those that are administered in large doses, a CR dosage form may need to carry a prohibitively large quantity of drug.

Biological Half-Life

In general, drugs with short half-lives (2-4 h) make good candidates for CR systems. For drugs with half-lives shorter than 2 h, a prohibitively large dose may be required to maintain the high release rate. Additional factors, such as the reduced rate of absorption from the distal small intestine and colon, may also reduce the rate of drug input to less than that required for adequate drug levels. On the other hand, drugs with elimination half-lives of over 8 h are commonly sufficiently sustained in the body after a conventional oral dose to make sustained release unnecessary.

Therapeutic Range

The range of plasma drug levels between the minimum effective and toxic levels is known as the therapeutic range. Oral CR formulations are valuable for maintaining plasma levels within a narrow therapeutic range. In fact, a valid rationale for formulating drugs with half-lives of over 8 h as CR formulations is to maintain plasma drug levels within a narrow range. By reducing the rate of drug release, it is possible to produce a flatter plasma-level curve and avoid toxic drug concentration in the body. Another means of expressing safe and effective plasma drug levels is the therapeutic index, which is discussed in detail later.

GI Absorption

Most CR formulations are dissolution-controlled, and drug release rate from the dosage form is the rate-limiting step. It is assumed that, once released, the drug is rapidly transferred from the gut lumen to blood. Therefore, efficient drug absorption from the GI tract is a prerequisite for a drug to be considered for use in an oral CR dosage form. In general, the absorption rate for most drugs decreases as the dosage form moves beyond the jejunum. As long as the absorption rate remains above that of the release rate, this change does not affect plasma levels. However, once past the ileocecal junction, a variety of factors generally reduce the drug absorption rate to below acceptable values. This creates a time limit of about 6–9 h during which the drug can be delivered in a predictable manner. For drugs that are absorbed passively, gut wall permeability shows a consistent pattern, even though the rate of drug absorption may decrease progressively. But for compounds that are absorbed via an active transport mechanism, absorption from the GI tract may not be consistent. For such drugs, and for many others, an acceptable rate of absorption may exist only from a limited portion of the small intestine, which may further limit their suitability for CR systems.

Aqueous Solubility

Absorption of poorly soluble drugs is often dissolution rate-limited. Such drugs do not require any further control over their dissolution rate and thus may not seem to be good candidates for oral CR formulations. However, the rate of dissolution of free drug particles decreases with time due to a reducing surface area. CR formulations of such drugs may

be aimed at making their dissolution more uniform rather than reducing it. Drugs with good aqueous solubility make good candidates for CR dosage forms. Since the GI environment changes considerably in terms of pH, as well as viscosity, it is desirable that the dissolution rate be independent of such variables; indeed, with systems such as the elementary osmotic pump, dissolution may be rendered independent of pH and viscosity.

Stability to Wide pH Range, GI Enzymes, and Flora

Irrespective of the system employed, an orally administered drug must be exposed to the luminal contents of the gut before it is absorbed. Stability of the drug in the GI content is therefore important to ensure a complete and reproducible drug input into the body. Typically the drug must be stable in the pH range of 1 to 8. Unlike a conventional dosage form, a CR formulation is exposed to the entire range of GI pH, enzymes, and flora. If some degree of colonic absorption is expected, stability to the metabolizing effect of the colonic bacterial population is also required.

First-Pass Metabolism

Saturable hepatic metabolism may render a drug unsuitable for oral CR. This is because systemic availability for such drugs is highly reduced when the input rate is small. First-pass metabolism will be discussed in detail in the section on pharmacokinetic and pharmacodynamic considerations.

PERTINENT BIOLOGICAL PARAMETERS

Design of oral delivery systems, both conventional and CR, have to date been based largely on an empirical understanding of GI physiology. Insight into the biological aspects of oral delivery is more important for CR systems than it is for conventional dosage forms, because, in order to exert control over the rate of drug release, as well as movement of the dosage form through the GI tract, a number of factors such as motility, pH, ionic strength of luminal content, differential absorption, etc., come into play.

Listed below are some of the factors that influence delivery of drugs to the GI tract. These factors show considerable inter- and intrasubject variation, as well as variations due to disease state and circadium rhythm.

Some biological factors influencing the performance of oral CR products include:

1. GI motility and transit time
2. Blood flow
3. Environment of the GI tract
   (a) Luminal contents and pH
   (b) Mucus
   (c) Ileo-cecal junction
   (d) Gut flora
   (e) GI immunology

GI Anatomy

In order to set the stage for subsequent discussion of GI physiology, a brief overview of the functional anatomy of the human GI tract is presented.

Figure 1 shows a schematic representation of the GI tract, and Table 1 [1] lists some of the characteristics of the GI tract that are relevant to drug delivery.

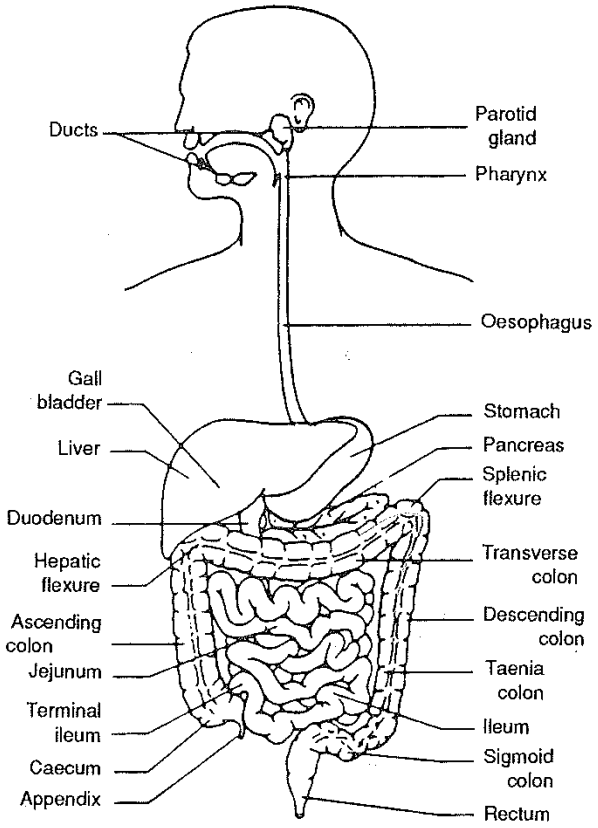

Figure 1 Schematic representation of the GI tract.

Under physiological conditions, gastric absorption of most drugs is insignificant. Factors contributing to limited absorption from the stomach include the limited surface area, the lack of villi on the mucosal surface, a relatively thick layer of mucus on the stomach lining, and the short residence time of most drugs in this organ.

Contents of the stomach pass through the antral area by an opening called the pylorus, into the proximal duodenal part of the small intestine. The gastroduodenal junction controls traffic between the stomach and duodenum, allowing unidirectional passage from the former to the latter, although a duodeno-gastric reflux has been observed in many species. Contents of the gall bladder (bile) and pancreas are emptied into the proximal duodenum, as are some duodenal secretions including bicarbonate. The other end of the small intestine, the terminal ileum, passes into the colon via a junction known as the ileo-cecal valve. Unlike the stomach, the small intestine has on its mucosal surface numerous villi, which impart an enormous surface area. There is a progressive decrease in surface area from the proximal to the distal small intestine and colon. As a result, most nutrients and drugs are absorbed predominantly from the proximal small intestine.

Table 1 Characteristics of the GI Tract

Section	Area (m^2)	Liquids secretion (l/d)	Reaction (pH)	More important constitutents	Transit time of food (h)
Oral cavity	About 0.05	0.5-2	5.2-6.8	Amylase Ptyalin Mucins	Short
Esophagus		0	—	—	Very short
Stomach	0.1-0.2	2-4	1.2-3.5	Hydrochloric acid Pepsin Rennin Cathepsin Lipase Intrinsic factor	0.25-3
Duodenum	About 0.04	1-2	4.6-6.0	Amylase Glucohydrolase Galactohydrolase Lipase Trypsin Chymotrypsin Bile acids	1-2
Small intestine	4500[a]	0.2	4.7-6.5	Like in duodenum	1-10
Large intestine	0.5-1	About 0.2	7.5-8.0	Mucus Bacteriums	4-20

[a] Taking intestinal microvilli area into account; without them, about 100 m^2.

The primary function of the colon is to store indigestible food residues. The luminal content of the colon is much more viscous than that of the small intestine. The colonic mucosal surface lacks villi, thus reducing its exposed surface area. It also contains a variety of bacteria, which are normal residents of the GI tract.

Gastrointestinal Motility

An important consideration when contemplating use of CR dosage forms in the GI tract is the continuous motility of this organ. The pattern and force of the motility vary depending on whether the animal is in a fed or a fasted state [2].

Figure 2 [3] shows a representation of the typical motility patterns in the interdigestive (fasted) and digestive (fed) state.

It is now well documented that there are two modes of GI motility patterns in humans and animals that consume food on a discrete basis; the digestive (fed) mode and the interdigestive (fasted) mode [4]. The characteristic of fasting GI motility is a cyclic pattern which has been fully characterized in both dogs and humans. This cyclic pattern of motility, which originates in the foregut and propagates to the terminal ileum, can be divided into four distinctive phases: phase I, representing a quiescent period with no electrical activity and no contractions; phase II, the period of random spike activity or intermittent contractions; phase III, the period of regular spike bursts or regular contractions at the maximal frequency that migrate distally; and phase IV, the transition period between phase III and phase I.

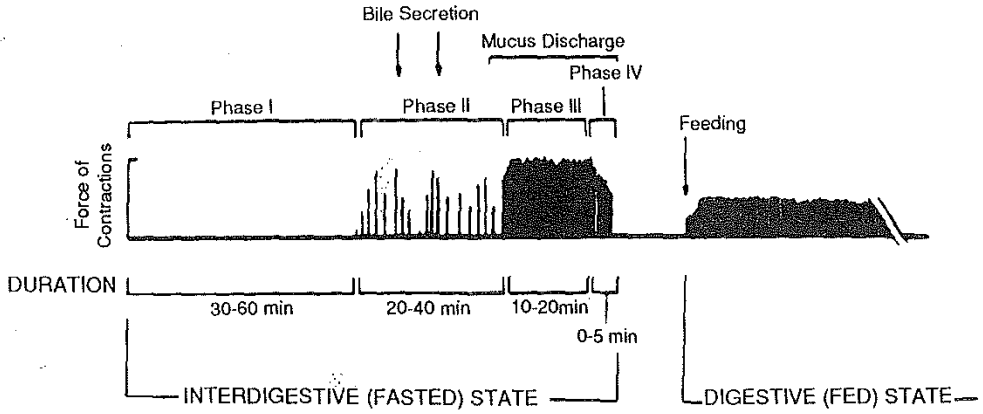

Figure 2 Pictorial representation of the typical motility patterns in the interdigestive (fasted) and digestive (fed) state. (From Ref. 3.)

The average length of one complete cycle, commonly known as the interdigestive migrating motor complex (MMC), ranges from 90 to 120 min in both humans and dogs [5]. Certain disease conditions, such as bacterial overgrowth, mental stress, and diurnal variations, or a combination of the above factors, can affect the length of the total cycle or its individual phases [6–8]. Phase III, also known as the housekeeper wave, serves to clear the digestive tract of all indigestible materials from the stomach and small intestine. Nondigestible solids when administered during phase I are emptied from the dog stomach only during phase III [9]. Shear forces involved during this phase can pose a problem for bioadhesive systems in the GI tract; consequently, any system that is designed to remain in the stomach during the fasted mode must adhere to the membrane strongly enough to withstand the force of the housekeeper wave.

A characteristic feature of cyclic motor activity is its association with the secretory gastrointestinal component. Gastric, pancreatic, and biliary secretory components of the MMC in the human duodenum indicates that the migratory motor and secretory activity constitutes two aspects of the same periodicity [10]. It may be concluded that under fasting conditions both motor and secretory activities of the stomach, gut, pancreas, and liver change periodically to provide both mechanical and chemical means of intestinal housekeeping.

Feeding results in interruption of the interdigestive motility cycle of the GI tract and in the appearance of a continuous pattern of spike potentials and contractions called postprandial motility. A minimum amount of gastric content appears to be necessary in order to change motility from an MMC to postprandial. It has been shown that oral administration of 150 ml of water during phase I changes the fasted motor activity to a fed-like pattern in dogs [11]. A normal meal changes the motility pattern to a fed state for up to 8 h, depending on caloric content of the food [12].

GI Transit

The single most limiting biological factor in the development of once-daily oral CR systems is the transit time of a dosage form through the GI tract. Of particular importance in this

context is the residence time of a dosage form in certain parts of the GI tract, since drug absorption may not be possible through the entire lining of the gut. Like the motility pattern, transit patterns of both solids and liquids through the gut also vary depending on whether the person is in a fasted or a fed state. Accordingly, these two types of transit patterns will be discussed separately.

Transit Patterns in the Fasted State

Gastric emptying. *Liquids*: The process of distintegration and dissolution starts in the stomach. Transit of liquids already present in the stomach and administered with the dosage form can play an important role in this process. Gastric emptying of liquids in the fasted state is a function of the administered volume of liquid [11]. For small volumes, generally less than 100 ml, gastric emptying is controlled by the existing phasic activity. Liquids empty at the onset of phase II, and most of the fluid is gone before arrival of phase III. Volumes larger than 150 ml show a different transit pattern and empty with a characteristic discharge kinetics irrespective of phasic activity. These kinetics can be approximated by a plot of first-order or square root of volume remaining in the stomach versus time, the slope of the curve in both cases being a function of caloric content of the meal. Figure 3 shows the cumulative volume emptied as a function of time when different volumes of water are administered during phase I in the dog. This difference in transit behavior between large and small volumes is due to the fact that small volumes do not change the existing motility pattern in the stomach, while large volumes convert

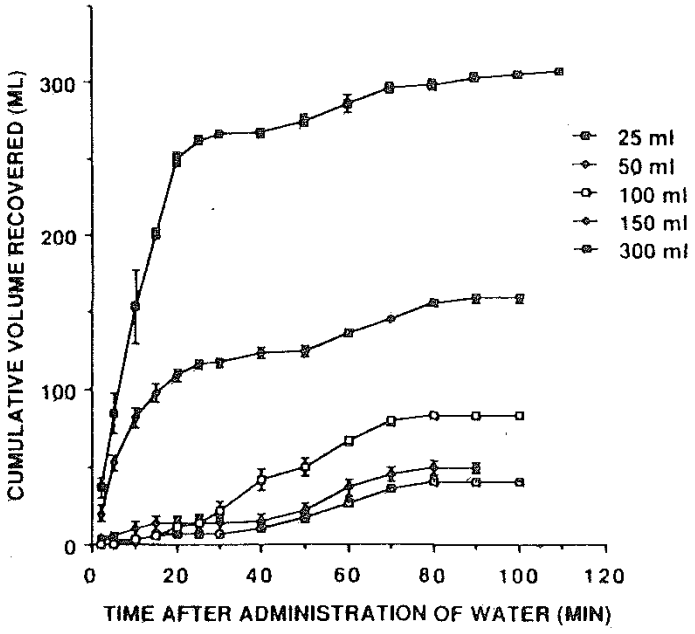

Figure 3 Commulative volume recovered as a function of time after administration of different volumes of water (25–300 ml) 15–20 min after cessation of high antral activity in fasted dogs. (From Ref. 11.)

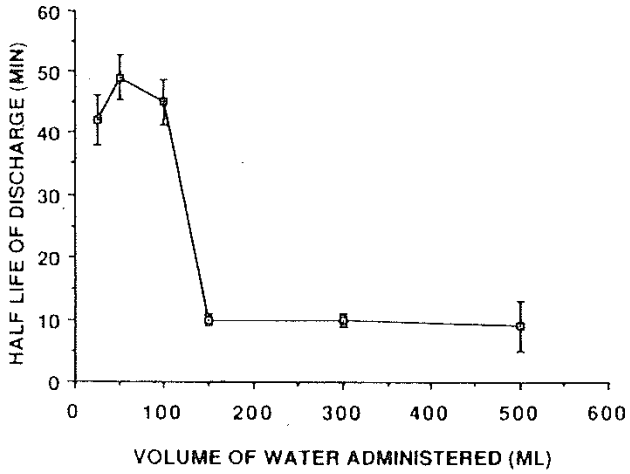

Figure 4 Time taken for the discharge of half of the administered volume of water given 15–20 min after cessation of high antral activity, plotted against the volume of test solution. (From Ref. 11.)

the fasted state to a fed-like state, which in turn creates the fed-state motility pattern. The time taken for discharge of 50% of a large volume of liquid is 8–12 min, as shown in Fig. 4.

Thus a dosage form given with a small volume of liquid can stay in contact with that liquid in the fasted state from 0 to 60 min, depending on the phase of activity at the time of administration. Dissolved drug in the media will then be emptied into the duodenum almost as a bolus. This emptying pattern of liquids in the fasted state is independent of the presence of any indigestible solids in the stomach [13].

Gastric emptying of indigestible solids: Indigestible solids, which include most solid dosage forms, empty from the stomach as a function of their size. Solids of particle size smaller than 1 mm can empty with the liquid, especially if the liquid viscosity is high. Solids of size 2 mm or more do not empty until arrival of phase III activity, at which time they empty as a bolus [13]. In the fasted dog, onset of the gastric emptying of solids is variable, depending on proximity of the time of ingestion to the next phase III activity. Thus, a solid dosage form can stay in a fasted stomach anywhere from 0 to 120 min. Also in fasted dogs, gastric emptying of solids is independent of size, density, and surface characteristics [14].

Thus, manipulation of density and shape of solids does not seem to be a viable approach, although some studies have claimed otherwise. The only possibility may be to increase the size of the dosage form to a degree that it cannot pass through the pylorus until degraded, or perhaps convert the stomach to a fed state, thus initiating the retropulsion phenomenon in the antral area which will keep the dosage form from emptying. Moreover, distribution of multiunit dosage forms administered during the fasted state is questionable in light of the observation that solids empty during phase III as a bolus.

Intestinal transit: During phase I of the fasted state, when contractions are minimal, there is little or no movement of content through the intestine. Flow of materials is

progressively faster during phases II and III. Segregation of liquids and solids also occurs, so that fluids tend to move during phase II and solids during phase III.

Transit of solids through the small intestine is variable because motor activity may not be sufficiently strong to move the solids. This implies that, during the fasted state, there is relative motion between the dosage form and the luminal fluid content. Shear forces and constant fluid movement around the dosage form may explain the sometimes-observed higher in-vivo bioavailability compared with in-vitro release.

For multiunit dosage forms, once the particles have left the stomach, there is little, if any further spreading of particles in the intestine [15]. Since particles usually leave the stomach as a bolus during the fasted state, multiunit dosage forms may not serve their intended claim of dispersion. These findings are consistent in both humans and dogs. Once in the colon, however, particles do show a tendency to disperse, perhaps due to high viscosity.

Fed State Transit Behavior

Gastric emptying of liquids and solids. Following ingestion of a meal the fundus expands to accommodate the meal without an appreciable increase in intragastric pressure. This phenomenon is known as receptive relaxation. Once in the stomach, food starts emptying almost immediately. Liquids empty faster, compared to solids, the rate of emptying being controlled by feedback mechanisms from the duodenum and ileum. Solids are handled differently by the stomach according to their particle size. In general, solids are not emptied in the fed state unless they have been ground to a particle size of 2 mm or less. Thus, there is a sieving mechanism in the fed stomach, and meal viscosity seems to influence this mechanism. Since grinding and mixing takes place in the antral area, dosage forms will tend to reside in this area due to their large size. Multiunit dosage forms, however will disperse and empty with food and thus achieve a considerable degree of distribution.

Another event that follows feeding is gastric secretions. Depending on the nature and volume of the ingested meal, gastric volume may actually remain constant during the first hour of emptying, the volume emptied being replaced by gastric secretions. Thus, in the fed state more fluid is available for dissolution. Total time for gastric emptying varies from about 2 to 6 h.

Intestinal transit during the fed state. The contents of the small intestine move faster during the fed state compared with phase III transit during the fasted state. This helps move smaller particles more rapidly, but larger particles are unaffected by this flow and thus travel relatively slowly. Regardless of the nature of the digestible fluid and particles, the intestinal transit time for both liquids and solids is around 3–4 h, in both the fasted and fed state. The constancy of intestinal transit can be important in colonic drug targeting.

Studies of dosage forms such as tablets, capsules, and particles have shown transit patterns similar to those of nutrients. Thus most dosage forms administered in the fasted state empty in 0–90 min. In the fed state, nondisintegrating tablets and capsules stay in the stomach for 2–6 h and are discharged only at the onset of fasted activity. However, small particles and disintegrating dosage forms will empty with food. In all instances, the small bowel transit time is 3–4 h.

In summary, the total transit time of nutrients and dosage forms in humans from the stomach to the ileo-cecal junction is approximately 3–6 h in the fasted state, and 6–10 h in the fed state. This puts an approximately 10-h delivery limit on drugs that are absorbed only from the small intestine.

Environment of the GI Tract

Blood Flow

The GI tract is a well-perfused organ, receiving about 30% of the total cardiac output. Changes in blood flow can only affect the absorption of compounds with high intestinal permeability. Generally, lipid-soluble molecules and those small enough to penetrate the aqueous pores are absorbed rapidly and show blood flow-dependent absorption. Since the absorption rate of many drugs shows an intermediate dependence on blood flow, relatively large changes in blood flow are required to produce a significant change in the absorption rate [16]. Splanchnic blood flow increases considerably after a meal, reaching its peak after a heavy meal. In fact, any distention in the stomach causes an increase in intestinal blood flow to some degree, and this increase can last for up to 1 h. Therefore, dosage forms given with large volumes of water (200 ml or more) could facilitate drug absorption by inducing an increase in blood flow. Indeed, this may be a partial explanation of the higher bioavailability observed for some dosage forms when given with a large volume of water.

Luminal Contents and pH

The GI tract offers a pH range of 1–8 for drug delivery systems, and Table 1 lists the pH range for different parts of the GI tract. Table 1 also lists a variety of acids, enzymes, and special factors present in the gut. This varying pH and composition of the luminal content affects performance of orally administered dosage forms in several ways. The pH of the bulk solution not only affects the release rate and dissolution of drug, it also determines the ratio of charged and uncharged species for ionizable drugs, thus affecting the rate of absorption. The pH is different in the fasted and fed states, and certain disease states may also alter the pH.

The gastric pH in the resting state is generally between 1 and 3 in both dogs and humans [17]. Upon feeding or distending the stomach to over 150 ml, gastric secretion is stimulated. Ingested food, however, may have a considerable buffering effect on gastric content and help maintain the pH above 4 for up to 1 hour [18]. Eventually, gastric pH returns to its base level, i.e.,1–3. Thus, basic drugs have a better chance of dissolution in the stomach, provided the dosage form stays in the stomach for a sufficient time.

Intestinal pH varies between 4 and 7.5 depending on location. The duodenal pH ranges between 4 and 6, whereas most of the intestine has a pH near neutrality. Substantial bicarbonate and bile secretions during the fed state may push duodenal pH toward the basic side. The colonic pH is normally above 7 and can be as high as 8, and in certain cases, bacterial metabolism may alter the pH in the large bowel.

The pH of the mucus membrane has been shown to be fairly constant throughout the GI tract. The thick mucus layer is considered to be the pH barrier in the stomach, higher pH at the membrane being a result of the sodium-dependent transcellular bicarbonate transport system.

GI Mucus

Specialized goblet cells located throughout the GI tract continuously secrete mucus. Fresh mucus on the surface of the membrane is very thick. Away from the membrane and closer to the lumen, mucus is dilute and less viscous. Chemically, mucus is a glycoprotein network holding a variable amount of bound water.

The thickness of the mucus layer varies depending on the region of the GI tract. The primary function of mucus appears to be protection of the surface mucosal cells from

acid and peptidases. In addition, it also serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses.

Mucus is considered to be an absorptive barrier in the GI tract, since it acts as a stagnant diffusion layer. For small-molecular-weight compounds, it merely adds to the stagnant diffusion layer through which compounds must diffuse before reaching the membrane. However, for large molecules such as peptides, it may offer some added resistance due to the expanded network of glycoproteins.

Many substances can interact with mucus and change its physicochemical characteristics. This interaction can also result in a change in absorption of these compounds. Tetracyclines have been shown to complex with mucus and have their transport delayed [3].

Ileo-Cecal Junction

The ileo-cecal junction serves primarily to ensure unidirectional flow of material from the small to the large bowel. Due to the large water-absorptive capacity of the colon, the colonic content is considerably more viscous than ileal chyme. This presents a problem for absorption of most drugs, since mixing and hence availability of drug to the absorptive membrane is not efficient.

Gut Flora

The intestinal flora may play an important role in the metabolism of certain foreign compounds. Many drugs are metabolized by enteric bacteria, including sulfasalazine and acetyl salicylic acid. The human colon has over 400 distinct species of bacteria and has up to 10^{10} bacteria per gram of content [19]. Among the reactions carried out by these bacteria are azoreduction and enzymatic cleavage, e.g., by glycosidases [20]. These bacterial degradation processes present an interesting concept of drug delivery, i.e., use of drug complexes that are degraded by bacteria. These will be discussed in greater detail later in this chapter.

Immunology of the GI Tract

The entire gastrointestinal tract is exposed to an immense and diverse range of potentially antigenic materials, primarily from food but also from a number of pathogenic and nonpathogenic microorganisms. In response to this antigenic challenge, the GI tract is populated by an abundance of immunological elements, both as individual lymphoid cells and as organized lymphoid tissue. When challenged by an antigen, these elements produce IgA antibodies, which by virtue of their secretory component are able to traverse the epithelial layer and appear at the epithelial surface and in the lumen of the GI tract [21]. IgA antibodies are primarily responsible for providing an immunological barrier against mucosal penetration of antigens encountered by the GI tract.

There are no studies available on antigen absorption from the stomach. In terms of nonspecific immune reactions, production of acid and pepsin is thought to denature most ingested antigens and bacteria and thus relieve the stomach of the necessity of having an active immune system. The intestinal tract, consisting of the small intestine, caecum, and large intestine, has a well-developed immune system that is both specific and nonspecific.

Antigen uptake from various parts of the intestine is important not only from an immunological point of view, but also in the context of drug delivery, because it may provide an opportunity to deliver large molecules, including peptides and proteins, provided they can be protected from degradation in the intestine and localized at the site of uptake. Two compartments through which antigen absorption might occur are the villous mucosa

and Peyer's patches. Through the formation of pinocytotic vesicles at the base of the microvilli the villous mucosa is able to absorb molecules as large as horseradish peroxidase and ferritin [22]. This process has also been implicated in maternal immunoglobin uptake by the neonate. However, the amounts absorbed are generally too small to be of any therapeutic significance.

Gastrointestinal Absorption

Intestinal Permeability

Absorption in the GI tract takes place predominantly in the small intestine because of its large surface area and the high permeability of the lining membrane. The luminal surface of the mucosa is organized such that the surface area available for contact with intestinal contents is greatly amplified. Since the epithelium of the intestinal membrane consists of only a single layer of loosely packed cells, the permeability of this membrane is high. A variety of routes exist for drug and nutrient passage through this membrane. Drugs can pass directly through the cell membranes into the underlying blood vessels (transcellular) or permeate through the spaces between the cells (paracellular). Attempts have been made to correlate various physiochemical properties of molecules and the permeability in order to determine their rate and predominant route of passage through intestinal tissue. For relatively lipophilic drugs, which permeate largely via the transcellular route, the pH partition hypothesis and the three-aqueous-compartment model generally explain the absorption characteristics, unless some active transport mechanism exists in the system. The three-compartment model has additional refinements over the pH partition hypothesis. These include the treatment of the absorption process in dynamic terms rather than an equilibrium state, and better representation of the true physiological situation in that both the transcellular and paracellular pathways are included. Also, it does not involve a complex and ill-defined microclimate at the mucosal surface. Small hydrophilic compounds are apparently absorbed through aqueous pores or channels formed by protein components in the membrane. There can be segmental differences in absorption of different kinds of drugs in the intestine, but most absorption takes place in the first half of the small intestine.

For conventional dosage forms, the major concern is the bioavailability from each dose. As long as most of the administered dose is absorbed as completely as possible, within a given period of time, the outcome is acceptable. Thus, if absorption takes place only from a part of the GI tract, it may not have much significance for conventional dosage forms. However, the situation is not the same for CR formulations. Since these systems are designed to stay in the GI tract for longer periods of time and continuously release drug during their entire stay, efficient abortion from the entire GI tract is a prerequisite for optimal performance of such systems. In general, drugs with high membrane permeability are rapidly absorbed from the entire lining of the gut, although the rate of permeation may vary. Variation in drug absorption rate does not have significance as long as it is significantly greater than the drug-release rate from the dosage form. This is because, for most drugs, the rate at which the drug is presented at the site of absorption is the rate-limiting step in the absorption process. However, for drugs that show intermediate or low permeation through the GI lining, the situation may be different. There is potential for such drugs to have permeation rates less than their rate of release from the dosage form, thus making the rate of GI absorption limiting. If one considers the fact that most drugs are absorbed efficiently from the first half of the small intestine, there is the possibility that drug input into the body declines as the dosage form moves closer to the ileo-cecal junction.

Certain drugs show a differential absorption, being absorbed predominantly from a particular segment of the small intestine. This segment is also referred to as the "window of absorption." Such drugs are bioavailable only if released before or at the absortion window, because any drug released after the dosage form has cleared the absorption area is simply passed into the feces. This effect may be pronounced for drugs that are transported by an active transport mechanism, because active transport tends to show well-defined segmental differences in the GI tract.

Colonic drug absorption is typically believed to be poor and variable [23]. This is attributed to high viscosity of the colonic content and lack of microvilli on the mucosal surface. Unlike the small intestine, where a multitude of drug absorption mechanisms exist, colonic absorption appears to be primarily a simple diffusion process through the lipid membrane, with no evidence to date of any carrier mediation [24]. Bacterial degradation may also be a contributing factor to poor colonic absorption. This may be of particular importance to controlled drug delivery systems which are aimed at a once-daily dosing. Some degree of colonic absorption is necessary for oral delivery beyond 6–8 h. Recently, however, it has been shown that some drugs, including theophylline and metoprolol, are absorbed from the colon [23,25].

Effect of Food on Drug Absorption

The presence of food in the GI tract can often have a marked and sometimes variable effect on drug absorption [26,27]. Food can increase or decrease the rate or extent of absorption of a drug, or delay the onset of absorption. A change in the extent of absorption is usually due to the direct or indirect interaction of food with the formulation or drug, while a delay in absorption is usually a result of delayed gastric emptying. These effects

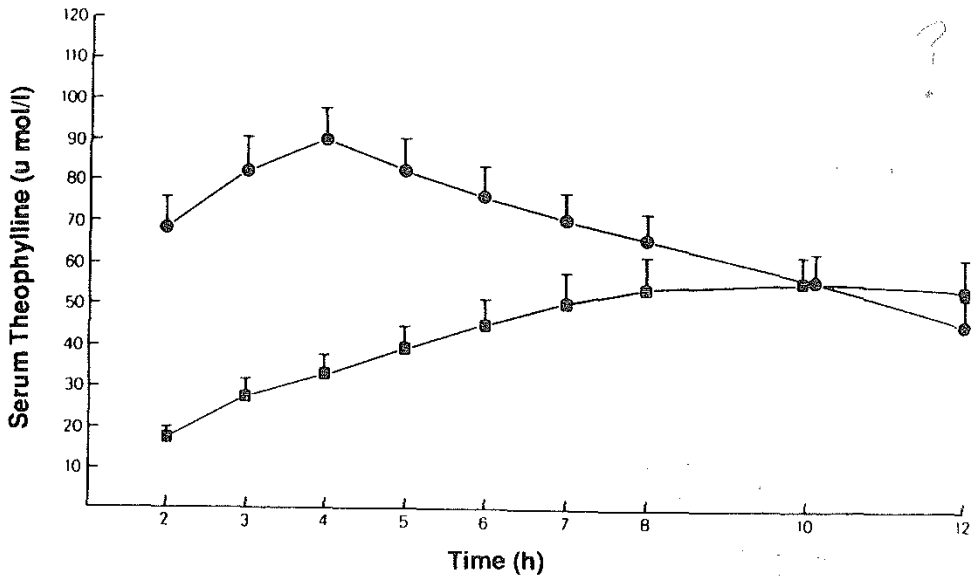

Figure 5 Serum theophylline concentrations after a single dose of a prolonged release product to fasted (●) and fed (■) children. (From Ref. 26.)

are so variable that the same drug may appear under different categories of food effects, depending on the nature of the food and the formulation.

In general, food prolongs the gastric residence time of nondigestible solids for up to 6 h. Thus, formulations designed to release their drug in the intestine only (enteric coated), when administered with food will show an increase in the lag time for absorption. However, for formulations designed to release drug independent of pH, gastric residence time does not affect drug release and subsequent absorption, unless the drug is unstable in an acid environment. For such formulations, food generally improves the bioavailability. This effect can be seen in Figure 5, which compares bioavailability of a sustained form of theophyllin in the fasted and fed states [26]. The relationship between variations in the gastric residence time and the absorption of procainamide from a wax-matrix sustained-release tablet in humans has been reported [5]. Unlike enteric-coated aspirin, gastric retention of a procainamide dosage form does not delay absorption of the drug, but shows a slight increase in AUC and C_{max}. Food can have a marked influence on the GI distribution of multiunit dosage forms, provided they are 2 mm or smaller.

PHARMACOKINETIC CONSIDERATIONS

Kinetic Parameters

From a release kinetics standpoint, there are three categories of oral delivery systems, conventional, first-order slow release, and zero-order release. Variations within these systems are possible in terms of free drug load for a burst effect or additional coatings to introduce a lag time before drug release begins. Figures 6a, 6b, and 6c show typical in-vitro/in-vivo mass balances of such systems. These curves are applicable assuming that drug release from the dosage form is the rate-limiting step. For a CR system, there is a small amount of drug in the form of solution in the gut. Most of the drug resides either in the dosage form or in the body. However, for conventional systems, there is a period of high drug content in the gut lumen as a solution, which is then rapidly absorbed to give a characteristic peak associated with administration of such dosage forms.

The goal of a CR formulation is to improve therapy by reducing the ratio of the maximum and minimum plasma drug concentration (C_{max}/C_{min}) while maintaining drug levels within the therapeutic window. In a conventional dosage form, a relatively large C_{max}/C_{min} is typically observed due to rapid absorption of drug into the body. This ratio is considered relative to another term known as the therapeutic index. For practical purposes, the therapeutic index of a drug can be defined as the ratio of the maximum drug concentration in blood that can be tolerated without appreciable side effects to the minimum drug concentration needed to produce and maintain a desirable pharmacological response. Therefore, the goal of any therapy is to give a drug with sufficient frequency and dose so that the ratio C_{max}/C_{min} in plasma at steady state is less than the therapeutic index and drug levels are always maintained at effective concentrations.

Two intrinsic properties of the drug determine the frequency with which a drug must be given as a conventional dosage form in order to keep the C_{max}/C_{min} ratio within the therapeutic index: the therapeutic index and the biological half-life. For a rapidly absorbed and distributed drug, the ratio of maximum to minimum concentration in plasma at steady state is given by [1]

$$\frac{C_{max}}{C_{min}} = e^{kT} \tag{1}$$

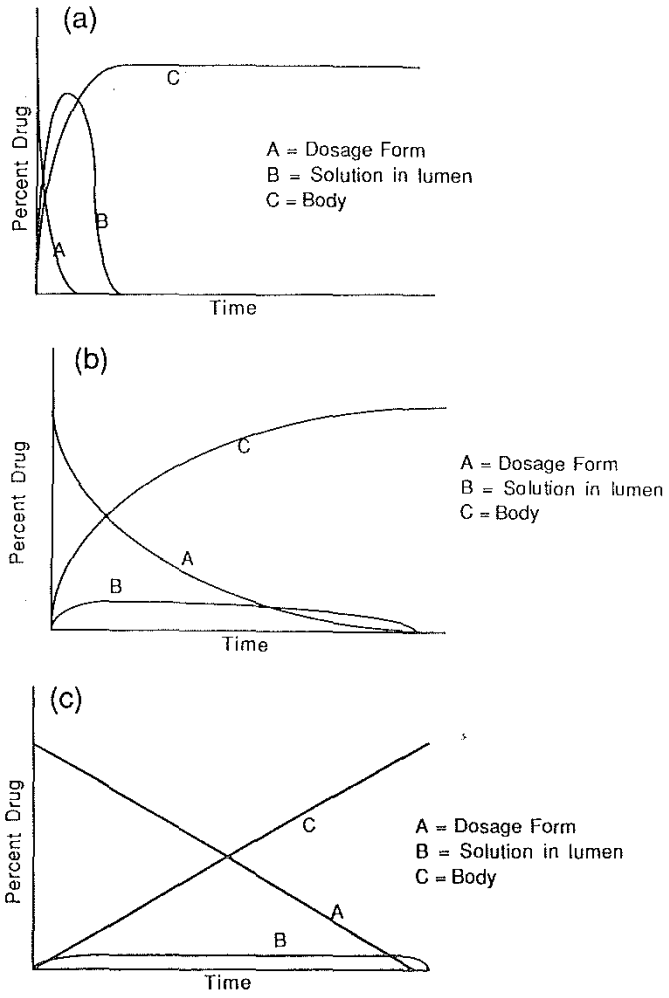

Figure 6 Hypothetical curves for drug fraction in dosage form, solution in gut, and body after oral administration of (a) a solid conventional-dosage form; (b) a first-order slow-release dosage form; (c) a zero-order-release dosage form.

where

k = first-order elimination rate constant

T = dosing interval

Example: A rapidly absorbed and distributed drug is administered twice a day and has an elimination half-life of 3 h. Calculate C_{max}/C_{min} at steady state.

Using Eq. (1):

$$\frac{C_{max}}{C_{min}} = e^{kT} = e^{(0.693/3)(12)} = 16.0$$

Since C_{max}/C_{min} should be less than the therapeutic index (TI), it follows that:

$$T < t_{1/2}\left(\frac{\ln TI}{\ln 2}\right) \tag{2}$$

For a drug with therapeutic index of 2, the dosing interval should not exceed more than one biological half-life of the drug. For drugs with short biological half-lives ($t_{1/2}$ = 2–5 h) and low therapeutic indices ($T < 3$), dosing has to be unreasonably frequent to maintain desired drug levels in the body. This situation is observed for a number of drugs, including theophylline and procainamide. Therefore, from a pharmacokinetic standpoint, there are two approaches to the design of formulations that give desirable therapeutic concentrations at a reasonable dosing frequency. The first approach is to select a drug that has a $t_{1/2}$ value long enough to be administered as infrequently as once or twice a day. Certain drugs, including warfarin, digoxin, and phenobarbital, fall into this category. But for a given medical condition, a drug or its analog with a suitable $t_{1/2}$ may not be available. In general, most drugs demonstrate relatively short half-lives and thus need to be formulated according to the second approach, which involves modification of the drug formulation in such a way that the drug input into the body is slowed. Such formulations are particularly suitable for drugs with short half-lives and low therapeutic indices, and are used in chronic therapy—e.g., antiarrhythmics.

In principle, in order to keep a constant plasma drug level, the drug input rate into the body should be zero-order. While many systems promise zero-order release based on in-vitro situations, in-vivo profiles are seldom the same due to a number of physiological constraints and variations as discussed earlier. In general, it is easier to design systems that release drug with first-order kinetics, but at a slow enough rate that the drug is delivered from a single dose over a period of up to 12 h. Drug release rate and plasma drug levels from zero-order or first-order release can be computed from equations derived with the following assumptions: (1) Drug absorption, metabolism, and elimination are first-order processes; (2) the rate-limiting step in drug input is the release rate of drug from the formulation; (3) the drug shows linear pharmacokinetics.

Plasma drug concentration, C, following a single dose of a first-order-release formulation can be calculated by [28]:

$$C = \left[\frac{Dk_r}{V(k_r - k_{el})}\right][\exp(-k_{el}t) - \exp(-k_r t)] \tag{3}$$

where

D = drug in sustained-release form
V = volume of distribution
k_r = rate constant for drug release ($k_r << k_a$)
k_a = rate constant for drug absorption
k_{el} = rate constant for drug elimination ($k_{el} > k_r$)
t = time

In most situations, k_r is smaller than k_{el} and presents an example of a "flip-flop" model. From the above equation, it is obvious that the plasma drug levels are a function of k_{el} and k_r (assuming that $k_r << k_a$). As k_r decreases, the drug profile is lowered and prolonged for a given k_{el}.

C_{max} and C_{min} at steady state can be calculated as:

$$C_{max} = \frac{D[\exp(-k_{el}t_{max})]}{V[1 - \exp(-k_{el}T)]} \tag{4}$$

$$C_{min} = \left[\frac{k_r D}{V(k_r - k_{el})}\right]\left\{\frac{\exp(-k_{el}T)}{[1 - \exp(-k_{el}T)] - \exp(-k_rT)/[1 - \exp(-k_rT)]}\right\} \tag{5}$$

where

$$t_{max} = 2.3\log\left\{\frac{k_r[1 - \exp(-k_{el}T)]/k_{el}[1 - \exp(-k_rT)]}{k_r - k_{el}}\right\} \tag{6}$$

Using the above equations, one can calculate the dose and the dosing interval required in order to achieve a given dosage-form index. In general, drugs with short half-lives and low therapeutic indices must be given no less frequently than twice a day.

Following a single dose of a zero-order-release formulation, plasma drug concentration can be calculated as [28]:

$$C = \frac{K_0}{Vk_{el}[1 - \exp(-k_{el}t)]} \tag{7}$$

where K_0 = zero-order drug release rate constant.

Example: A zero-order-release device releases drug at a rate of 12 mg/h. Given that $k_{el} = 0.15$ and $V = 70$ liters, calculate the plasma drug concentration at 6 h after dosing and at plateau.

Using Eq. (7):

$$C_{6h} = \frac{12 \text{ mg/h}}{(70 \text{ liters})(0.15\text{h}^{-1})(1 - e^{(0.15)(6)})} = 1.92 \text{ mg/liter}$$

$$C_{plateau} = \frac{12 \text{ mg/h}}{(70 \text{ liters})(0.15 \text{ h}^{-1})} = 3.42 \text{ mg/liter}$$

Example: A wax matrix tablet containing 250 mg of drug released 90% of its drug load as a zero-rate release over 12 h, the rest being eliminated in the feces. Calculate the plasma drug concentration at 3, 6, and 12 h after first dose. Given $V = 60$ liters, clearance (Cl) = 15 liters/h.

Using Eq. (7):

$$k_{el} = \frac{Cl}{V} = 0.25 \text{ h}^{-1}$$

$$K_0 = \frac{(0.9)(250)}{12} = 18.75 \text{ mg/h}$$

$$C_{3h} = \frac{18.75}{(60)(0.25)(1 - e^{(0.25)(3)})} = 0.33 \text{ mg/liter}$$

$$C_{6h} = 0.48 \text{ mg/liter}$$

$$C_{12h} = 0.59 \text{ mg/liter}$$

In both first-order- and zero-order-release systems, the time required to achieve desired drug levels in the body depends on the elimination-rate constant. The slower the elimination, the longer it takes to reach steady state.

Bioavailability

Factors affecting the bioavailability of a drug after its oral administration include incomplete absorption from the GI tract, presystemic clearance (gut metabolism and liver first-pass effect), and degradation of drug in the gut lumen. These factors may vary in their magnitude depending on whether a drug is given as a conventional dosage form or as a CR formulation. Incomplete drug release from a CR dosage form will constitute an additional factor contributing to the loss of drug prior to its absorption. Among these factors, first-pass liver metabolism is particularly susceptible to change when changing the drug input rate.

First-Pass Liver Metabolism

After absorption from the GI tract, the drug must first pass through the liver before it reaches systemic circulation. This is because blood drainage from the entire GI tract, with the exception of the buccal cavity and lower rectum, goes to the liver via the hepatic portal vein. Since the liver is the principal site of metabolism for a number of drugs, a fraction of the absorbed drug may be eliminated through metabolism by the liver before it reaches the general circulation. This fraction is a function of the susceptibility of the drug to liver microsomal enzymes for metabolism and is measured in terms of a parameter called extraction ratio. Because of this presystemic metabolism, which is also referred to as the "first-pass" effect, an oral dose of a drug may have incomplete bioavailability despite its complete absorption from the GI tract.

A number of drugs have been identified as having a significant first-pass effect, and many of these have been shown to obey Michaelis-Menten kinetics in the therapeutic dose range [29]. Factors that affect first-pass metabolism are (1) liver enzyme activity (2) blood flow (3) plasma protein binding, and (4) plasma drug concentration. All of these factors can play important roles, depending on the nature of the drug and its interaction with liver enzymes.

The major difference between conventional and CR oral dosage forms is the rate of drug input into the body. The amount of drug absorbed during any 24-h period is usually comparable. Therefore, if linear kinetics of drug metabolism are involved, one should expect no difference between the pharmacokinetic parameters of the two dosage forms. However, linear pharmacokinetics do not always apply in real situations. One such example is propranolol, which accumulates during repeated oral administration to a greater extent than predicted from its half-life and area under the curve after a single oral dose [30]. This type of nonlinearity is commonly referred to as "dose-dependent kinetic." Such nonlinearity may also arise from other saturable processes arising during the course of drug absorption and disposition [31]. In addition, certain disease conditions, such as renal insufficiency, can also lead to dose-dependent kinetics for certain compounds.

Dose-dependent kinetics can be an important factor in considering the design and evaluation of CR systems. This is because the rate and pattern of drug delivery with a conventional dosage form are considerably different from those with a CR dosage form. Most important among saturable processes from an oral delivery standpoint is the saturable first pass liver metabolism effect. Experimental observations indicating dose-dependent and saturable first-pass metabolism include: (1) increase in dose-normalized bioavailability with increase in dose and (2) decreased clearance at steady state compared to a single dose. A consequence of dose-dependent kinetics is that bioavailability will decrease with

a decrease in the rate of absorption after oral administration of the same dose. If one considers that a decreased rate of drug absorption from the GI tract is the primary goal of most CR formulations, drugs showing saturable kinetics will need special attention, and indeed, they may be unsuitable for such formulations.

Michaelis-Menten enzyme kinetics can be employed to better understand saturable liver metabolism. The equation describing the rate of drug metabolism is

$$\text{rate of metabolism} = \frac{V_{max}C}{K_m + C} \tag{8}$$

where

V_{max} = maximum rate of metabolism

C = drug concentration in plasma

K_m = Michaelis-Menten constant measured as plasma drug concentration at metabolism rate of $V_{max}/2$

The K_m value is a measure of the approximate concentration above which saturability becomes evident.

For drugs like phenytoin, which show saturation of liver enzymes at relatively low concentrations (therapeutic concentration), increase in dose results in a disproportionate increase in bioavailability and circulating drug levels because both first-pass metabolism and systemic metabolism (clearance) are saturable. Propranolol and alprenolol show similar dose-dependent behavior [32,33].

Therefore, bioavailability from an oral dose is an important parameter to consider when contemplating a CR dosage form for oral use. Generally, drugs with medium to high extraction ratio and saturable first-pass metabolism make unsuitable candidates for CR. Alternatively, an appropriate change in the release rate may be incorporated into the dosage form to compensate for the increased loss due to first-pass effect. This approach may be possible for drugs with low to medium extraction ratios. Thus, dose-dependent nonlinearity can present a serious limitation for development of oral CR formulations.

Pharmacokinetic Analysis

An important consideration in oral CR formulations is the selection and use of appropriate models to assess in-vivo pharmacokinetic parameters. Most important in this regard is the measurement of the in-vivo release rate and its correlation with in-vitro dissolution profiles. Such information can help evaluate as well as refine oral delivery systems. One can use either a compartment model approach or a relatively recent "noncompartmental" or "model-independent" approach in such studies. In both approaches, the kinetic processes are assumed to be first-order, linear, and irreversible.

The compartment model methods assume that the drug concentration-time profile can be described by one of many pharmacokinetic models. The data are evaluated by using an equation consistent with the assumed model by using either the method of residuals or a nonlinear least-square regression analysis. Standard equations for one- or multicompartment models are used to estimate pharmacokinetic constants, including the absorption rate constant. The problem with model-based methods is that for drugs showing multicompartment kinetics, one cannot be sure about the relative nature of the absorption and distribution rate constants. Additional factors such as drug degradation and metabolism in the gut, gastric emptying, and GI motility can further complicate the analysis.

An alternative to curve-fitting the data is construction of percent absorbed-time plots, which do not require assumption of the order of the absorption rate. The Wagner-Nelson method [34] has been widely used for this purpose, but it gives best estimates for drugs showing one-compartment kinetics only. The Loo-Riegelman method [35] can be applied to linear multicompartment pharmacokinetic models. It requires blood-level data after both oral and intravenous administration.

However, in recent years, model-independent methods based on statistical moment theory have gained popularity for estimating absorption rate constants of orally administered drugs. Noncompartmental analysis assumes input, end elimination, as well as sampling from the central compartment. In addition, these methods assume that metabolism of the drug is exactly the same after oral and intravenous administration, which is not the case for certain drugs such as quinidine and propranolol.

Noncompartmental analysis based on statistical moment theory usually utilizes the area under a plot of drug concentration versus time as the basis for estimating the kinetic parameters. It can be applied to any compartmental model provided that the pharmacokinetics are linear. Its advantage is that it permits a wide range of analysis that is usually adequate to characterize the pharmacokinetics of a drug [36–38].

Mathematically, the moment method considers the time course of in-vivo drug concentration as a statistical distribution function F(t), whose n-th moment can be expressed as

$$t^n F(t)\, dt$$

In pharmacokinetics, F(t) is plasma drug concentration. The first three moments can be defined as follows:

$$AUC = \int c\, dt$$

$$MRT = \frac{\int tc\, dt}{\int c\, dt} = \frac{AUMC}{AUC}$$

$$VRT = \frac{\int t^2 c\, dt}{\int c\, dt}$$

where

AUC = area under the curve
MRT = mean residence time
VRT = variance of the mean residence time of drug in body
AUMC = area under the first moment curve

From these moments, one can calculate bioavailability and the absorption rate constant as follows:

$$\text{Bioavailability} = F = \frac{AUC_{oral}}{AUC_{iv}} \quad \text{for equal dose}$$

$$MAT = MRT_{oral} - MRT_{iv}$$

where MAT is the mean absorption time for a first-order drug absorption:

$$MAT = \frac{1}{k_a}$$

given that k_a is the apparent first-order absorption rate constant.

For a zero-order absorption process,

$$MAT = \frac{T}{2}$$

where T is the total time during which the absorption takes place.

Other pharmacokinetic parameters, including clearance, half-life, apparent volume of distribution, and metabolism kinetics can be similarly calculated.

Another example of the statistical moment theory is the method of deconvolution, introduced by Rescigno and Segre [39]. The following scheme described a physical system that transforms input into output:

drug $-$ (A)t $\rightarrow$ body $-$ (B)t $\rightarrow$ plasma levels

For an orally administered drug, A(t) represents the rate for in-vivo drug release, and B(t) represents plasma drug concentration. Computing B(t) from A(t) is called convolution, and conversely, computing A(t) and B(t) is called deconvolution. This equation can be written as

$$B(t) = G(t - T)\, A(t)\, dT$$

The Laplace transform of the above equation is

$$B(s) = g(s)\, A(s)$$

where B(s), g(s), and A(s) are the Laplace transforms of B(t), G(s), and A(t), respectively. A number of numerical deconvolution methods have been reported [40]. A practical example of the application of this method is given in the next section.

Pharmacodynamics

While pharmacokinetic parameters provide useful information regarding the time course of the drug and its metabolites in the body, they may not be representative of the pharmacological response or therapeutic effectiveness of a dosage regimen. This is due, in part, to the fact that the plasma drug concentration is not necessarily at equilibrium with drug concentration at the receptor site. Also, owing to individual variations in drug-receptor interactions commonly observed with drugs other than antibiotics, plasma drug concentration may not be the best way to evaluate the success of therapy. Due to a combination of pharmacodynamic and pharmacokinetic variables, a single dose-response curve does not apply to a population. Factors that contribute to pharmacodynamic variability include intersubject variability in drug-protein binding in plasma, rate and pattern of metabolism for drugs forming active metabolites, drug concentration at the receptor site, affinity and/or activity of drug-receptor interaction, and balance between pharmacological response and toxicity.

IN-VITRO/IN-VIVO CONSIDERATIONS

In-Vitro Considerations

In a conventional oral delivery system, drug content is released within a short period of time and plasma drug levels peak at a given time, usually within a few hours after dosing.

Since the dosage form will encounter gastric content or possibly proximal duodenal content, in-vivo disintegration and dissolution conditions are relatively well defined. In such a case, an in-vitro dissolution profile is based on the fastest possible dissolution rate, and can have a direct correlation with in-vivo bioavailability. But this kind of arrangement is simply not possible with CR systems. For oral CR products, in-vitro testing is not aimed at how fast, but at how uniformly the drug is released. The uniformity of drug release is measured in terms of a predetermined rate of release. The deviations from release rate can be either too slow or too fast from the desired value. Optimal dissolution profile is determined by drug properties, which include the biological half-life, and therapeutic plasma levels of the drug. For drugs with longer half-lives, the initial release period should provide enough drug for a minimum effective plasma drug level. Subsequently, the release rate can drop to maintain drug levels. For drugs with relatively short half-lives, however, release rates may have to be more or less the same throughout due to rapid elimination of the drug from the body. A variety of in-vitro dissolution characteristics of CR dosage forms set them apart from conventional formulations. These include the following:

1. Dissolution is measured in terms of optimum drug release rate, not the fastest release rate.
2. The optimum release rate is usually an intermediate value and is related to the required biologic input function.
3. Dosage forms are designed for different release patterns, e.g., first-order versus zero-order, both with or without a rapid-release component.
4. Disintegration may or may not precede the process of dissolution.
5. In-vitro medium may not adequately mimic the pH, motility, and viscosity variations of the GI tract to which the dosage form will be exposed.

Despite a large variety of CR dosage forms, and variations in drug release rate, kinetic models that describe drug release are generally of two types, i.e., first-order and zero-order. In addition, both these models may have an initial period of rapid drug release conforming to first-order kinetics.

Testing Procedures

Current USP (XXI) guidelines for in-vitro dissolution tests for CR products are limited. CR products are referred to the USP as modified-release dosage forms and are further classified as sustained-release and delayed-release products [41]. Sustained-release systems are those that allow at least a twofold reduction in dosing frequency when compared to the same drug in conventional dosage form. A delayed-release dosage form is one that releases its drug at a time other than immediately after administration, e.g., enteric-coated tablets.

The dissolution test apparati for such formulations are basically the same as those or conventional dosage forms, i.e., the rotating basket method (apparatus 1) or the paddle method (apparatus 2). The following dissolution procedure and interpretation are quoted directly from USP XXI, chapter on drug release <724>, and apply to all modified-release dosage forms. A list of articles subject to extended-release definition has been published in *Pharmacopeial Forum*.

Acceptance Table 1

Stage	Number Tested	Criteria
S_1	6	No individual value lies outside the stated range and no individual value is less than the stated amount at the final test time.
S_2	6	The average value of the 12 units ($S_1 + S_2$) lies within the stated range and none is more than 10% of labeled content outside of the stated range; and none is less than the stated amount at the final test time.
S_3	12	The average value of the 24 units ($S_1 + S_2 + S_3$) lies within the stated range, and not more than 2 of the 24 units are more than 10% of labeled contents outside of the stated range; and not more than 2 of the 24 units are less than the stated amount at the final test time.

Extended-release Articles—General Drug Release Standard

Time—The test-time points, generally three, are expressed in terms of the labeled dosing interval, *D*, expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three stages unless the results conform at either S_1 or S_2. Limits are expressed in terms of the percentage of active ingredient dissolved. The limits embrace each value of Q_t, the amount dissolved at each specified fractional dosing interval.

Enteric-coated Articles—General Drug Release Standard

Use Method A or Method B and the apparatus specified in the individual monograph. Conduct the *Apparatus Suitability Test* as directed under *Dissolution* (711).
Method 4.

Procedure (unless otherwise directed in the individual monograph)—

Acid phase—Place 750 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus at the rate specified in the monograph for 2 hours (±5 minutes).

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer phase*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2*.

Acceptance Table 2

Stage	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

In-Vivo Considerations

Despite recent improvements in and general guidelines for in-vitro evaluation of CR formulations, such tests are more useful in ensuring product uniformity than predicting in-vivo performance of a dosage form. In-vivo tests for CR formulations are based on drug concentrations in plasma/blood, or cumulative urinary excretion of a drug and/or its metabolities. These parameters can be treated in a number of ways to obtain different kinds of plots or kinetic constants, which can then be correlated with corresponding in-vitro parameters. However, in-vivo parameters are subject to a number of unpredictable physiological factors which can affect both drug release and absorption. Some of these factors have been outlined earlier in this chapter. Continuously changing conditions, as the delivery system moves through the GI tract, can exert a significant effect on performance of CR systems. A major objective, therefore, should be to design a system that compensates for the effect of the GI environment on the rate of release.

In-Vitro/In-Vivo Correlations

A valid in-vitro/in-vivo correlation is one which allows prediction of the in-vivo performance of a dosage form from its in-vitro dissolution profile. It is desirable to obtain a suitable mathematical equation describing a quantitative correlation of a particular in-vivo variable with an in-vitro variable. In-vivo variables are obtained from concentration-time plots of either plasma drug concentration or urine drug excretion. Parameters such as AUC, absorption rate constant, specific blood levels at a particular time, etc., may also be used for this purpose. Corresponding in-vitro parameters will typically be drug concentrations at specific times.

Most CR formulations are designed to release the drug at a rate slower than its rate of absorption, making the drug release rate limiting. Thus, plasma drug concentrations can be correlated with in-vitro drug release rate as long as this assumption is valid. Generally, model-independent methods, such as the moment method and convolution/deconvolution methods, have been shown to be suitable for this purpose.

The deconvolution method has been utilized successfully in estimating the in-vivo dissolution rate during development of a 24-h dosage form of a nonsteroidal anti-inflammatory agent [42]. Figure 7 shows in-vitro dissolution profiles of two experimental sustained-release tablets which were later tested in humans. The dissolution rates were determined in a spin filter apparatus. Figure 8 shows blood-level profiles of the two sustained-

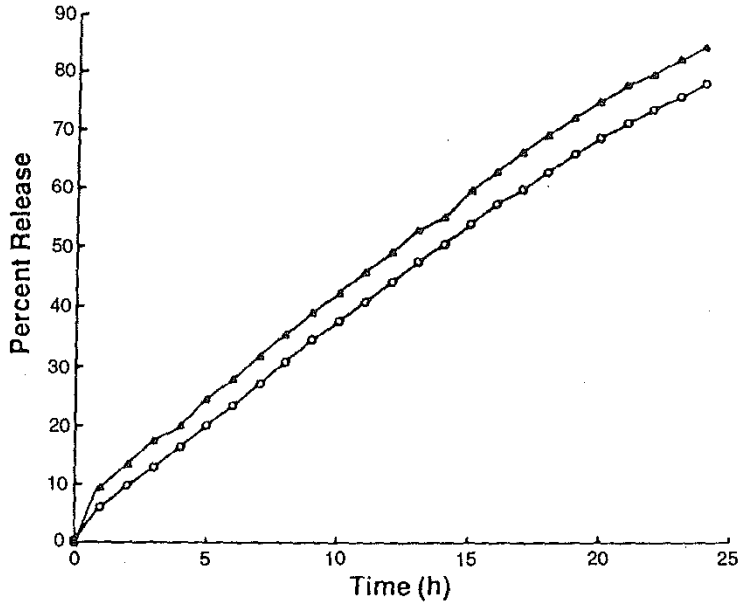

Figure 7 In-vitro profiles of two sustained-release tablets. (From Ref. 42.)

release tablets (A, B) and a fast-release 100-mg tablet given twice at 12-h time intervals. The in-vivo dissolution rate profiles were computed as shown in Fig. 9 using blood-level data and numerical deconvolution. It is obvious from the plots that both tablets show similar in-vivo release rates and complete bioavailability. Figure 10 shows a linear correlation that is observed between in-vitro and in-vivo dissolution rates.

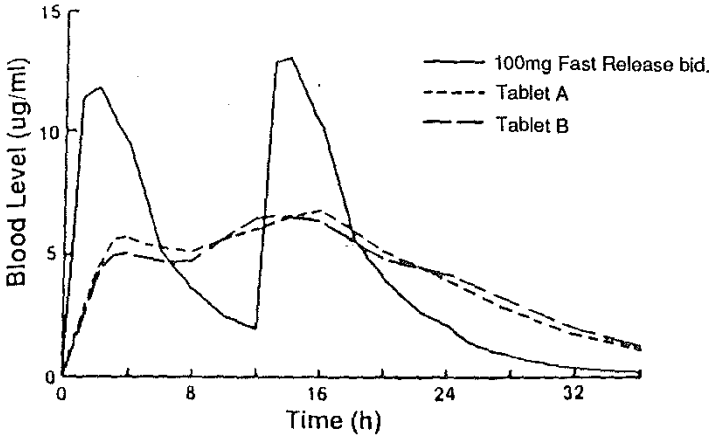

Figure 8 Serum levels of two 200-mg sustained-release (A, B) and 100-mg fast-release tablet. (From Ref. 42.)

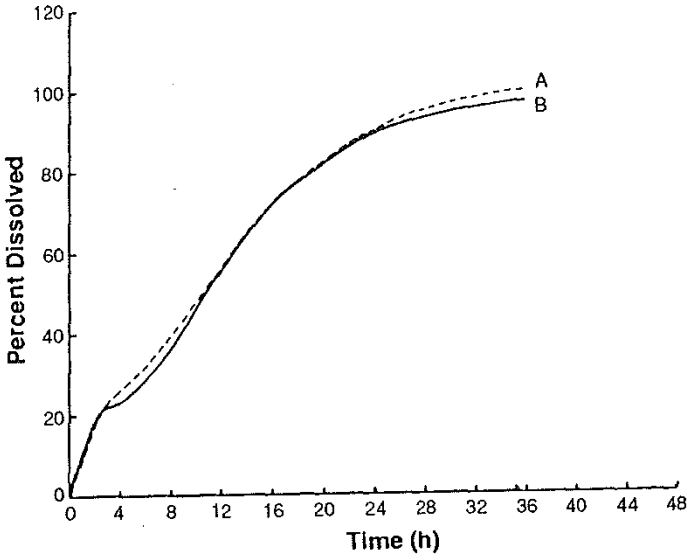

Figure 9 In-vivo dissolution profiles by numerical deconvolution. (From Ref. 42.)

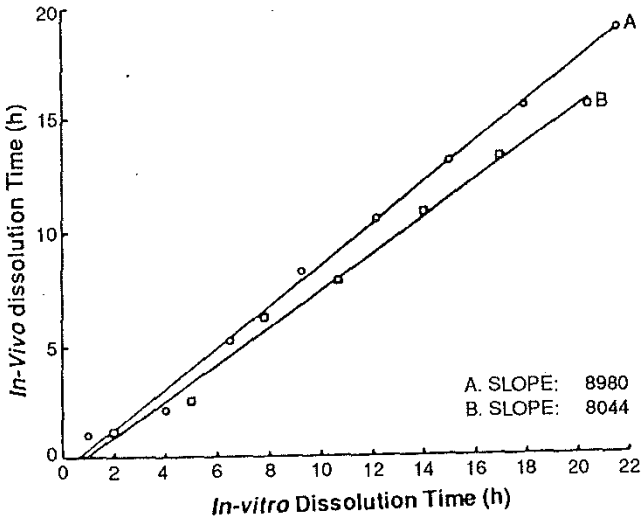

Figure 10 In-vitro/in-vivo correlation of a sustained-release formulation of a nonsteroidal anti-inflammatory drug. (From Ref. 42.)

BIOPHARMACEUTICAL CONSIDERATIONS

The success of a therapy depends on selection of the appropriate delivery system as much as it depends on selection of the drug itself. It is well recognized that a dosage form, whether conventional or CR, can have a significant effect on bioavailability, and indeed make a difference between success and failure of therapy.

For conventional oral dosage forms, a major concern is bioavailability of the drug. Selection of a dosage form is often based on how rapidly and completely the drug is available. In this regard, both from intuition as well as experimental observations, systemic availability of a drug is maximum from an aqueous solution and minimum from a coated tablet, with suspensions, capsules, and tablets showing intermediate bioavailabilities in that order. Deviations from this rule are sometimes observed. The picture, however, is different for CR formulations, where one rarely has a choice of solution or suspension dosage forms. The concern in CR drug delivery is not only bioavailability, but also uniformity of drug input into the body.

The rate and extent of drug absorption from CR dosage forms is determined by the rate of release from the dosage form. This is based on the assumption that absorption from the entire GI tract is efficient enough not to be rate-limiting, although this may not be true in many practical situations. In most situations, a common observation with respect to bioavailability from dosage forms is that in-vitro as well as in-vivo availability from CR formulations is less than from a conventional dosage form. Possible explanations for this observation are as follows:

1. Drug release is not complete from a CR formulation, especially for those designed to release drug for periods longer than 6 h at a low release rate.
2. There is a greater degree of preabsorption degradation and metabolism in the GI tract, particularly for saturable degradation processes or colonic delivery systems.
3. First-pass metabolism for CR formulations may be higher.
4. Drug release may be at a site of poor absorption, e.g., the colon.
5. Fewer dissolution media are available for CR dosage forms, especially in the terminal ileum.
6. There is differential absorption from the GI tract, i.e., drug absorption takes place in a limited area.
7. GI residence of the dosage form may be variable and unpredictable.

As with conventional dosage forms, considerable differences in performance among different CR products of the same drug are frequently observed. The variables responsible for the observed differences are more often in the case of CR dosage forms due to greater complexity involved in their design. Various kinds of devices may involve different mechanisms and kinetics of drug release, and they may be subject to different biological constraints in the GI tract. This will result in considerable variation in plasma drug profiles for similar doses. Theophylline has been formulated in a variety of sustained-release formulations that show significant variations in the rate as well as the extent of absorption from the GI tract. Indeed, some of these products show no reduction in release rate compared to that of a conventional dosage form of theophylline [43,44]. Certain classes of drug, including theophylline, show a considerable intersubject variation in pharmacokinetics. This fluctuation can result from variable absorption or different rates of metabolism. Thus, individualization of dose may be required for such compounds. Indeed, such a study has been done for TheoDur, a sustained-release formulation of theophylline

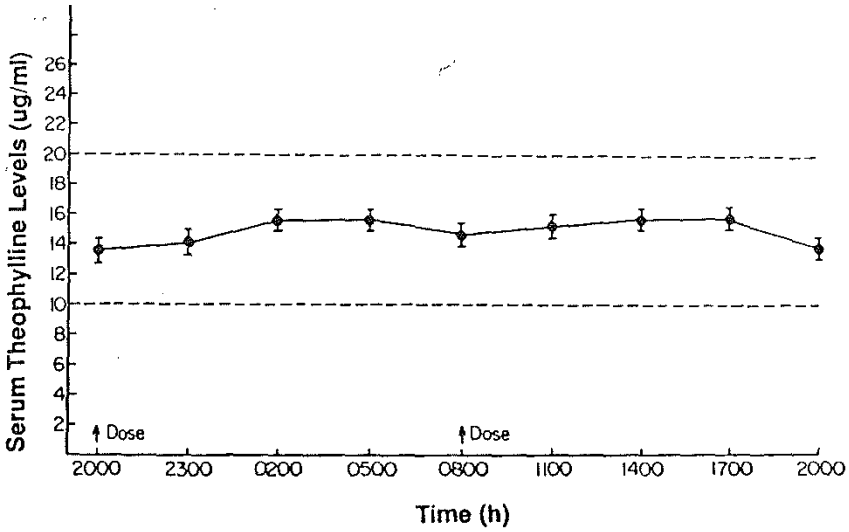

Figure 11 Mean 24-h serum theophylline levels for 20 asthmatic children on a mean TheoDur dosage of 10.0 mg/kg/dose every 12 h. (From Ref. 45.)

[45]. The daily dose needed to produce an average blood level of 15 μg/ml ranged from 6.1 to 16.3 mg/kg, showing an almost threefold difference in dose requirement. The blood levels resulting from such doses were remarkably stable, as shown in Fig. 11 [45]. A peak-to-trough ratio of less than 2.0 was observed in most cases.

An example of the formulation effect on blood levels of CR dosage forms is a report on metoprolol [46]. Two formulations containing the same amount of drug were compared, a conventional sustained-release tablet and an elementary osmotic pump with a release rate of 19 mg/h. As is evident from Fig. 12, the osmotic pump device shows relatively less variation in drug plasma levels [46]. Another interesting observation from this plot is that the plasma metoprolol levels from the osmotic pump show stability between 8 and 18 h, despite the fact that the pump was made to deliver the drug for only 10 h. This leads to the conclusion that either in-vivo drug release is slower than the in-vitro rate, or the drug-release rate from the pump may not be the rate-limiting step; instead, the drug continues to be absorbed long after its delivery has stopped.

No systematic study has been reported that evaluates the performance of different kinds of CR devices for oral use. An understanding of dosage-form interaction with the GI environment is necessary to explain the observed differences. In general, for solid CR dosage forms, one would expect flatter plasma drug levels from zero-order-release formulations, compared with first-order-release formulations. For multiunit formulations, appropriate distribution in the GI tract may be the key to obtaining consistent blood levels. Unless given with a large quantity of food, a dosage form designed to release drug for every 6 h will release some fraction of its drug load in the colon. Knowing that drug absorption from this part of the GI tract may be erratic and incomplete, the observed differences in bioavailability of such dosage forms should not be surprising.

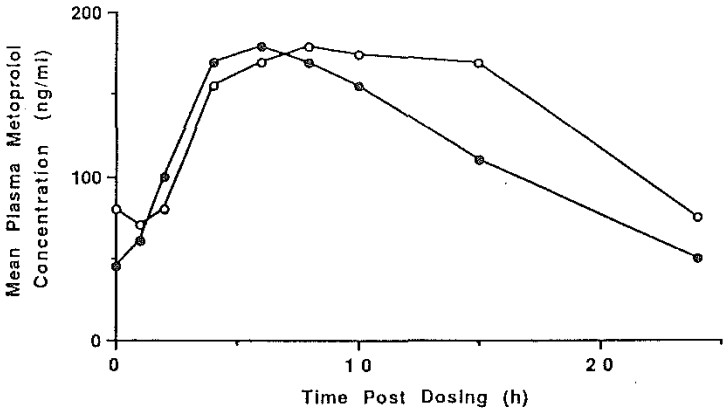

Figure 12 Mean steady-state plasma levels of metoprolol in healthy subjects after repetitive dosing of an osmotic pump (○) and a conventional CR product (●). (From Ref. 46.)

Drug devices that are designed to stay in a particular segment of the GI tract, e.g., bioadhesive systems and large size to delay gastric emptying, must take into account the stability of the drug in that environment. Degradation due to pH or enzymes may reduce bioavailability of such dosage forms. Also, single-unit forms, intended to stay at the pylorus or ileo-cecal junction, may release enough drug in their immediate vicinity to cause local toxicity or irritation. Design must also account for possible bacterial degradation, and variable and poor absorption from the colon and rectum.

STRATEGIES AND DESIGN OF ORAL CONTROLLED-RELEASE SYSTEMS

The design and fabrication of oral CR systems has been reviewed recently by a number of authors [47]. These reviews are extensive concerning the technology involved in the fabrication of such systems and the underlying mechanisms of release. Table 2 lists some of the technological approaches to the fabrication of oral CR systems [1]. The present section will focus on the basic principles involved in conception and development of new approaches to oral CR drug-delivery systems. Emphasis will be on the rationale of design of systems and their interaction with the GI environment.

Most oral CR systems are solids, although a few liquids, all of them suspensions, have recently been introduced. The following classification of such systems is chosen because it includes not only the conceptual approach of design, but some elements of physiology of the GI system as well.

1. Continuous-release systems
   a. Dissolution control
   b. Diffusion control
   c. Dissolution and diffusion control
   d. Ion-exchange resins
   e. Osmotically controlled devices
   f. Slow-dissolving salts or complexes
   g. pH-independent formulations

2. Delayed-transit and continuous-release systems
   a. Density-based systems
   b. Size-based systems
   c. Bioadhesive-based systems
3. Delayed-release systems
   a. Intestinal release
   b. Colonic release

The design of oral CR dosage forms is aimed at presenting the drug to the absorptive membrane of the GI tract at a predetermined rate. The majority of such systems rely on dissolution, diffusion, or a combination of both mechanisms, to control drug release rate in the gastrointestinal lumen. Whatever the mechanism may be, as long as the drug release rate from the dosage form is significantly smaller than the rate of drug absorption, there is little drug in solution in the gut. The drug is absorbed by the GI mucosa as soon as it is released. On the other hand, when drug absorption is the rate-limiting step, there is a high concentration of drug in solution in the gut lumen. Plasma drug concentration in release rate-limited processes reflect drug release rate from the dosage form. Before a decision about a system, based on a particular mechanism, is made, drug properties such as solubility, dose requirements, stability, and absorption rate must be considered. These issues have already been discussed in previous sections. Desired in-vivo kinetics of drug release will also play a part in decision making.

Continuous-Release Systems

Dissolution Control

Continuous release for extended periods can be obtained by employing dissolution as the rate-limiting step in drug release. Certain drugs are slow-dissolving due to their intrinsic low aqueous solubility and thus act as natural sustained-release products. Digoxin and griseofulvin are examples of slow-dissolving drugs. A few others, such as aluminum aspirin and benzamphetamine pamoate, produce slow-dissolving forms when they come in contact with aqueous media [48].

For compounds with high aqueous solubility, one needs to reduce the solubility rate by some mechanism. Unless a chemical modification of the drug in question is involved, the approach to control the rate of dissolution of such compounds will be based on either or both of the following techniques:

1. Increase in the stagnant diffusion layer
2. Encapsulation or coating which erodes or slowly dissolves

Stagnatnt-layer control. If the dissolution process is diffusion layer-controlled, i.e., the rate of diffusion through an unstirred water layer on the solid surface to the bulk of solution is rate-limiting, an increase in the stagnant diffusion layer works effectively. In such a system, flux J (mg/s) is given by

$$J = -D\left(\frac{dc}{dx}\right) \tag{9}$$

where

D = diffusion coefficient (cm^2/s)

$\frac{dc}{dx}$ = concentration gradient from the solid surface to bulk solution (mg/ml/cm)

Table 2 Principles of Technological Possibilities for the Manufacture of Oral Extended-Release Dosage Forms

Method and type of factors used to achieve extended release	Examples of use excipients	Kind of drug release	Kinetics of drug release	Possibilities of release rate regulation	Examples of dosage forms
1. Binding					
(a) Chemical binding (slightly soluble salts or complexes)	Tannic acid, polygalacturonic acid, albumins, pectins	Slow dissolution of salts, esters hydrolysis, complex dissociation	First-order under, some conditions zero order	Selection of salt or complex forming substances	Tablets, capsules, liquid suspensions
(b) Physical-chemical binding	Ion-exchange resins	Ion exchange	First-order	Variation of binding strength depending on chemical stuctures of the resin or adsorbents and the drug	Tablets, capsules, liquid suspensions
	Absorbents	Desorption			
2. Coating					
(a) Insoluble membrane	Ethyl cellulose	Diffusion, partitioning	Zero- or first-order	Membrane porosity and/or thickness	Granules, pellets, microcapsules, film tablets
	Polymers	Diffusion	Zero-order	Membrane porosity and thickness	Oros osmotic pumps
(b) Soluble membrane					
(i) pH-Dependent solubility	Polymers of methacrylic acid and its esters, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate	Drug dissolution after coating; disintegration, repeat release	First- or second-order	Substitution and/or polymerization degree, membrane thickness	Multilayer tablets, coated granules or pellets with varying disintegration time, ultiple-unit capsules, liquid suspensions

(ii) Enzyme-dependent solubility	Lipids, proteins	Drug dissolution after coating, disintegration	First-order	Changes in the chemical composition	Coated granules or pellets with varying disintegration time, tablets from mixed granules, multiple-unit capsules
(iii) Liquid membrane	Glycerides and surfactants	Diffusion and partitioning	Zero- or first-order	Oil-to-water phase ratio, droplet diameter in the dispersed phase	Multiple emulsion
3. Embedding					
(a) Hydrophilic carrier (gel-forming base)	Methylcellulose, gelactose mannate, alginic acid or sodium alginate, polyacrylic acid	Slow diffusion from viscous gel, very slow pH-dependent dissolution of the matrix	First- or second-order	Polymerization degree, drug-to-carrier ratio	Multiplayer tablets with slow-release cores, capsules
(b) Hydrophobic carrier					
(i) Soluble carrier (digestible base)	glycerides, waxes, fatty alcohols, fatty acids	Release when the surface layer is continuously eroded in the gastrointestinal fluids	$Q = \sqrt{t}$ First- or second-order	Changes in the chemical composition influencing the lipase sensibility, melting point, self-emulsifying properties, drug-to-carrier ratio	Eroding tablets, multilayer tablets with slow-release cores, capsules, liquid suspensions
(ii) Insoluble carrier (non-digestible base)	Polyethylene, polyvinylchloride, polycinylacetate, waxes, calcium sulphate	Immediate release from the surface, after that, continuous diffusion (leaching principle)	$Q = \sqrt{t}$	Tablet porosity, compression conditions, addition of soluble solids, drug-to-carrier ratio	Matrix tablets

The material flow rate through a unit area A from a dosage form can be defined as

$$J = \left(\frac{1}{A}\right)\frac{dm}{d_t} \tag{10}$$

The gradient dc/dx can be expressed in terms of diffusion-layer thickness, and the concentration gradient across this layer as

$$\frac{dc}{dx} = \frac{C_b - C_s}{h} \tag{11}$$

where

C_b = concentration in the bulk solution

C_s = concentration on the solid surface, which is usually the same as the saturated solution

h = diffusion-layer thickness

The above equation assumes that the concentration gradient across the diffusion layer is linear.

Thus, the rate of material flow will be

$$\frac{d_m}{d_t} = -\left(\frac{DA}{h}\right)(C_b - C_s) = kA(C_s - C_b) \tag{12}$$

where $k = D/h$ = intrinsic dissolution rate constant.

If A, D, h, and the concentration difference remain constant, the release rate will be constant. In practice, however, all of these parameters may change continuously, especially surface area.

For release rate from a diffusion layer-controlled system, the following general equation may be more useful:

$$\frac{M_t}{M} = 1 - \left(\frac{1 - K_0 t}{C_0 a}\right)n \tag{13}$$

where

M_t = amount released at time t (mg)

M = total amount released (mg)

a = half-thickness of dosage form (cm)

n = constant shape factor: n = 3 for a sphere, n = 2 for a cylinder, and n = 1 for a slab

Example: The intrinsic dissolution rate constant of a drug is 5×10^{-5} cm/s. Calculate the rate of dissolution in milligrams per hour from a tablet of surface area 2.5 cm^2 under sink conditions. The solubility of the drug is 50 mg/ml.

Using Eq. (12):

$$\frac{dm}{dt} = (5 \times 10^{-5}\ \text{cm/s})(3600\ \text{s/h})(2.5\ \text{cm}^2)(50\ \text{mg/cm}^3)$$

$$= 22.5\ \text{mg/h}$$

Matrix dissolution control is the most commonly employed technique to achieve dissolution control. The rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This rate of penetration of the dissolution media can be controlled by the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet. The porosity of the tablet can be altered by changing the compression force in a tablet. Size and shape of particles can also affect porosity of the dosage form.

Wax-impregnated tablets are examples of matrix dissolution systems. Wax-impregnated particles can be prepared either by aqueous dispersion or by a congealing process. The aqueous dispersion method simply involves spraying or placing the wax-drug mixture in water and collecting the resulting particles. Alternatively, one may use the spherical agglomeration technique, where drug particles are suspended in an aqueous media, stirred with wax at high temperature, and then cooled while stirring. Particle size can be controlled by the speed of stirring. In the congealing method, drug is mixed with wax material and either spray-congealed or congealed and screened.

A variety of wax matrix materials can be used for such formulations. Among these are hydrogenated castor oil and carnauba wax. Important factors affecting drug release are the physical properties and chemical composition of the wax used, and the composition of the dissolution media. Surfactants are typically added to improve the release rate. Sorbitan monostearate is used in a concentration range of 0.1 to 5% for this purpose.

A slow-release procainamide tablet, releasing drug through matrix dissolution, has been compared to conventional dosing [49]. Wax matrix tablets showed less plasma-level fluctuations of procainamide and could be administered every 8 h to keep drug concentration within therapeutic range. There is a good correlation between bioavailability and the in-vitro dissolution profile.

A major disadvantage of stagnant layer-controlled systems is that they fail to give a zero-order release; i.e., release rate progressively decreases with time. This is a result of an increased diffusional distance and decreased surface area at the penetrating solvent front. Geometry changes can help reduce this problem to some degree. Also, the drug release rate is influenced by the nature of the GI content, particularly by the viscosity of the dissolution media.

Encapsulation dissolution control. The basic approach in encapsulation is the coating of drug particles with a slowly dissolving material. Coated particles can be compressed directly into tablets or placed into gelatin capsules. Since the time required for dissolution of the surface coat is a function of coat thickness and its aqueous solubility, good control of the release rate can be achieved. One can obtain a repeat or continuous release of drug by using granules of varying coating thickness.

A wide range of drugs have been formulated as sustained-release coated granules and compressed into tablets. These include antispasmodic-sedative combinations, phenothiazines, and aspirin [48].

There are several ways to prepare drug-coated beads or granules. Usually inert beads are coated with drug, followed by coating with a slowly dissolving material. It is common practice to include some uncoated drug particles in the dosage form to give an initial priming dose.

An illustration of this approach is the formulation of dextroamphetamine sulfate. The release rate of dextroamphetamine sulfate could be effectively controlled by varying the wax coating thickness [50]. Also, by using a selected blend of different coating materials, a desired rate of release can be obtained.

Microencapsulation is another approach which is analogous to encapsulated dosage forms, except that it involves a much smaller size of particle. This process is normally used to convert liquid or semisolid materials into solid particles by coating them with another solid material. It appears that a portion of drug becomes embedded in the coating during this process, and this drug is provided in a sustained fashion as the coat dissolves.

Coacervation is one of the commonly employed techniques to microencapsulate materials. This process utilizes the interaction of two oppositely charged polyelectrolytes in water to form a polymer-rich coating solution called a coacervate. This coacervate encapsulates the liquid or solid to form an embryo capsule. Other techniques used for microencapsulation include interfacial polymerization, electrostatic method, precipitation, hot melt, salting out, and solvent evaporation.

The thickness of a microcapsule coat can be adjusted from less than 1 μm to 200 μm by changing the amount of coating material.

Microencapsulation has an additional advantage in that sustained drug release can be achieved with better GI tolerability. Microencapsulated aspirin and potassium chloride are examples of better GI tolerance. Core of the microcapsules can consist of pure drug, buffered drug mixtures, or wax-core formulations. A dual approach to dissolution control is possible by using a slowly dissolving coat on wax-core beads.

Diffusion Control

Diffusion-controlled systems fall into two basic categories:

1. Reservoir devices
2. Matrix devices

Reservoir devices. In reservoir devices, a water-insoluble polymeric material encases a core of drug. Drug release through the system occurs by partition through the coating membrane. Drug penetrates the membrane and diffuses to the other side, and eventually into the dissolution media.

The rate of diffusion across the membrane is governed by Fick's law:

$$J = -D\frac{dc}{dx} \tag{14}$$

where

J = flux

D = diffusion coefficient

$\frac{dc}{dx}$ = change in concentration with distance x within the membrane

At steady state:

$$J = D\frac{c}{l} \tag{15}$$

This is an integrated equation where l is the diffusional path length, which in an ideal case is the membrane thickness. In terms of amount of drug released:

$$\frac{dm}{dt} = ADK\frac{c}{l} \tag{16}$$

where

A = area

K = partition coefficient of drug between solution and membrane

K is defined as the drug concentration ratio in the membrane and core. This is an important parameter controlling the rate of drug release. In such a system it is relatively easy to keep all parameters more or less constant so that a zero-order rate can be achieved. However, in an in-vivo situation, deviations are usually observed.

Example: Calculate the rate of flux in milligrams per minute from a diffusion-controlled device when $A = 1.4\ cm^2$, $D = 10^{-6}\ cm^2/s$, $c = 20$ mg, $l = 50\ \mu m$, and $k = 5$.

Using Eq. (16):

$$\frac{dm}{dt} = (1.4\ cm^2)(10^{-6}\ cm^2/s)(60\ s/min)\frac{(20\ mg/cm^3)(5)}{0.005\ cm}$$

$$= 1.68\ mg/min.$$

Insoluble coatings can be applied to a drug core by a variety of techniques. Commonly used approaches are press coating and air-suspension coating. For smaller particles intended for tablets or capsules, microencapsulation techniques are generally used. Uncoated drug may be enclosed in the system to provide an initial rapid dose.

Figure 13 shows the release characteristics of a reservoir dosage form for salicylic acid [51]. Varying rate of release can be obtained depending on the membrane thickness. The coating material used in this case was hydroxypropyl cellulose.

Several parameters are crucial in maintaining a constant rate of drug release from the reservoir system. These include:

1. Polymer ratio in the coating
2. Film thickness
3. Hardness of microcapsules

Among these factors, film thickness is an easily manipulated parameter to obtain the desired release rate. Figure 14 shows the release rate of clofibrate as a function of the wall thickness of gelatin-sodium sulfate microcapsules [52].

Hydroxypropyl cellulose and polyvinyl acetate are commonly used polymers used as an insoluble permeable coat. A laminated diffusion controlled drug-hydroxypropyl cellulose matrix coated with hydroxypropyl cellulose and polyvinyl acetate has shown zero-order drug release [53]. The drug-containing core serves as a reservoir exerting some control over the duration of drug release, while the coat serves as a diffusion-controlled, rate-limiting membrane. Ratio of polymers in the coat determines the release rate of drug.

Drug particles can be coated in a fluidized bed with aqueous dispersions of polymers. These dispersions typically contain additives known as plasticizers to help the polymer stick to pellets uniformly. Dibutyl sebacate is a commonly used plasticizer in such formulations. Permeability additives may be needed to enhance the release rate of drugs.

Cellulose derivatives contain a few carboxyl groups. Therefore rate of diffusion through the membranes tend to be pH-dependent. This can make the drug release rate different in the stomach and intestines. However, the differences in permeabilities are generally small.

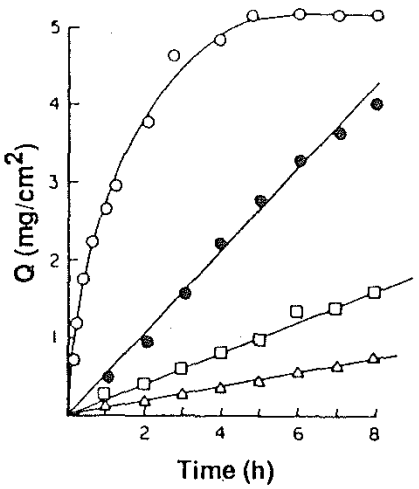

Figure 13 Drug release from films containing 20% salicylic acid in hydroxypropyl cellulose as the reservoir layer. ○, no membrane layer; (●), 0.164-mm hydroxypropyl cellulose-polyvinyl acetate (8:2) membrane; □, 0.204-mm hydroxypropyl cellulose-polyvinyl acetate (6:4) membrane; △, 0.164-mm hydroxypropyl cellulose-polyvinyl acetate (6:4) membrane. (Plotted with data obtained from Ref. 51.)

Some parameters controlling drug release from pellets of guaipnesin coated with an aqueous ethyl cellulose dispersion have been reported to include thermal post-treatment of the coating, plasticizer content, and the pH and ionic strength of the dissolution medium.

Different types of poly (vinyl alcohol) can be cross-linked to varying degrees to control the degree of swelling and hence the rate of drug release [54]. One such study reported cross-linking of three types of poly (vinyl alcohol) by glutaraldehyde to form water-swellable materials possessing a three-dimensional, molecular network [55]. With proxyphylline and theophylline as model drugs, release rates could be controlled by varying the degree of cross-linking of the polymers. Figure 15 shows the effect of type of alcohol on the release of proxyphylline from micromatrices at a fixed degree of cross-linking and drug load. Different rates of release of theophylline could be obtained by varying the cross-linking ratio of micromatrices produced from Elvanol 71-30 with a fixed drug load of 4% as shown in Figure 16.

Matrix devices. The matrix approach employs a system where the drug is compressed with a slowly dissolving or insoluble polymer. The rate of drug availability is controlled by the rate of penetration of the dissolution medium through the matrix and to the surface of the unit. As the drug dissolves, the diffusional path length increases because the polymer matrix is insoluble. With proper design of the system, an initial loading dose can be provided from the drug particles on or near the surface of the tablet. Once pores have

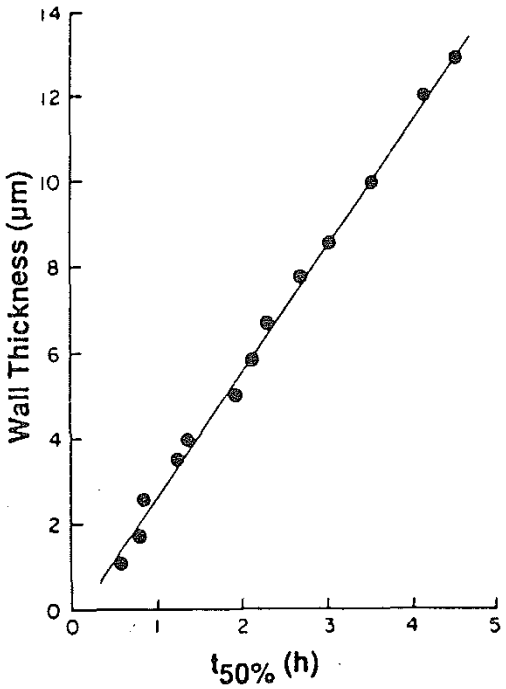

Figure 14 Wall thickness of microcapsules as a function of in-vitro $t_{50\%}$ release time of clofibrate. (From Ref. 52).

been created, drug release will slow down. Obviously, the rate of release will not be zero-order, as may be desired, because, as the diffusional length increases, the rate of dissolution falls. However, if one uses a slowly dissolving polymer matrix, where the matrix itself dissolves at a certain rate so as to keep the diffusional length more or less the same, it can result in a zero-order release.

In such a system, the rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution. Higuchi's equation can be used to express the release rate from such systems:

$$Q = \left(\frac{DE}{T(2A - EC_s)C_s t}\right)\frac{1}{2} \tag{17}$$

where

Q = drug released in g per unit surface area
D = diffusion coefficient of drug
E = porosity of the matrix
T = tortuosity of the matrix
C_s = solubility of drug in release medium (g/ml)
A = concentration of drug in the tablet (g/ml)

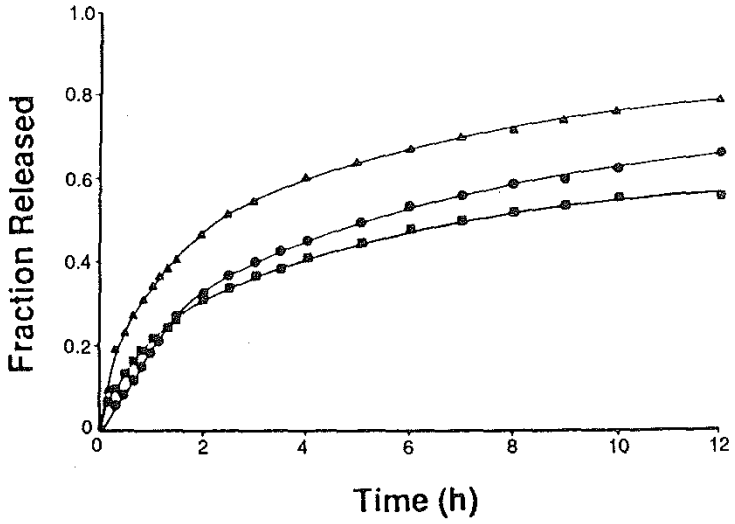

Figure 15 Effect of the type of poly(vinyl alcohol) on the release of proxyphylline from micromatrices cross-linked at a ratio, X, of 0.20 and loaded with 14% drug. Type of PVA: Elvanol 71–30 (▲); Mowiol 40–88 (■); Mowiol 66–100 (●). (From Ref. 55.)

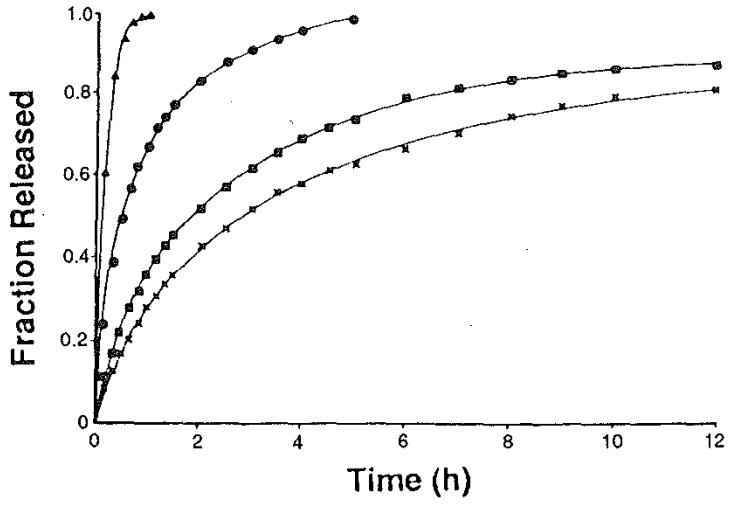

Figure 16 Effect of the cross-linking ratio on the release of theophylline from micromatrices produced from Elvanol 71–30 and loaded with 4% drug. Cross-linking ratio, X: 0.05 (▲); 0.10 (●); 0.15 (■); 0.20 (X). (From Ref. 55.)

The following assumptions are made in deriving this equation:

1. A pseudo-steady state is maintained during release.
2. $A >> C_s$; that is, excess solute is present.
3. $C = 0$ in solution at all times (perfect sink).
4. Drug particles are much smaller than those in the matrix.
5. The diffusion coefficient remains constant.
6. No interaction occurs between the drug and the matrix.

Since the goal is to keep all the parameters constant, for the purpose of treatment, Higuchi's equation can be reduced to:

$$Q = kt^{1/2} \tag{18}$$

Therefore, a plot of amount of drug released versus the square root of time should be linear if the rate of drug release is diffusion-controlled. The rate of release in a matrix system can be altered by varying any of the variables in the equation.

Three major types of matrix systems are fatty, plastic, and hydrophilic matrices. Fatty matrices consist of waxes and are generally prepared by dispersing the drug and excipients in molten wax, followed by congealing and coating. Nondigestible hydrophilic gums such as hydroxypropylmethylcelluose or sodium carboxymethylcellulose are mixed with drug and compressed to make hydrophilic matrix tablets. When such a tablet is exposed to an aqueous medium, rapid drug release occurs initially, but release slows as the gum swells. Such formulations generally have poor control over release, and their performance varies considerably with varying GI conditions.

Diffusion- and Dissolution-Controlled Systems

Some systems employ diffusion as well as dissolution control over the drug release rate. The dosage form consists of a drug core encased in a partially soluble membrane. When placed in the appropriate mileu, the soluble part of the membrane dissolves away, creating pores in the remaining coat. This allows for entry of aqueous media into the core and allows dissolution of the drug. An example of such a coating would be a polymer coating consisting of ethylcellulose and methylcellulose. The latter dissolves, leaving the ethylcellulose coat intact. The release profile from such a system can be described by the following equation:

$$\text{release rate} = AD\frac{(C_1 - C_2)}{l} \tag{19}$$

A = surface area

D = diffusion coefficient of drug

C_1 = concentration of drug in the core

C_2 = concentration of drug in the dissolution medium

l = diffusion path length

Surface area in such a system can be easily controlled by varying the fraction of soluble material in the coating. Also, by incorporating more than one soluble material with different rates of solubility, one can increase the release rate after a certain period of time. This can be useful in oral systems designed to deliver for more than 12 h. Since colonic absorption may not be as efficient and complete as intestinal absorption, an

increased release rate could compensate for reduced absorption to maintain a constant input of drug into the body.

Ion-Exchange Resins

Polymers containing groups of exchanging ions can be used to obtain extended delivery preparations of ionizable drugs. These polymers, also known as ion-exchange resins, contain ionizable groups. Thus, they may contain acidic-reacting groups such as phenolic, carboxylic, or sulfonic (cation ion-exchange resins), or basic groups, such as amino or quaternary ammonium groups (anion-exchange resins). These reacting groups of ion-exchange resins can be used to bind drugs, basic drugs to acidic cation ion exchangers, and acidic drugs to basic anion ion exchangers.

The following simplified equation describes the release of a basic primary amine drug from a cation exchanger when in contact with a dissolution medium containing an ionic compound XY:

$$\underset{\text{resin-drug complex}}{(R{-}SO_3{-}H_3N^+{-}R)} + (X^+Y^-) = \underset{\text{resin}}{(R{-}SO_3{-}H^+)} + \underset{\text{active drug}}{(H_3N^+{-}RY^-)}$$

Drug release, especially with strong acidic groups, is primarily a function of the ionic strength of the gastrointestinal fluid, with pH having little effect other than ionic. The extended release rate of drug is a result of slow diffusion of drug molecules through the resin particle structure. Release rate can be modified by alteration of the resin particle dimensions and chemical composition of the resin. The release rate can be further controlled by coating the drug-resin complex using one of the encapsulation processes described earlier. A mixture of the coated and uncoated complex can then be used to obtain a desired rate of release. A drug-resin complex of phenyl propanolamine administered every 12 h for 2 weeks has been shown to provide the same plasma concentrations as a solution of the drug administered every 5 h [56]. Prolongation of therapeutic effects have also been reported for noscaine, an antitussive, when the drug-resin complex was administered [57].

The preparation of drug/ion-exchange complex can be accomplished by either incubating the resin with the drug solution or passing drug solution through a column loaded with the appropriate resin. In both processes, enough time is allowed for the drug to displace the suitable ion from the resin. Resins are used in their salt form because they often swell as salts when placed in aqueous medium. This facilitates drug permeation into the resin.

Osmotically Controlled Devices

Osmotically controlled systems utilize osmotic pressure as the driving force to release drug at a constant rate. A cross-sectional view of an elementary osmotic pump is shown in Fig. 17 [47]. It consists of a drug core surrounded by a semipermeable membrane coating which has one orifice [58,59]. Water imbibed from the environment crosses the membrane at a controlled rate and causes the drug solution to exit through the delivery orifice. it delivers drug at a rate independent of gastrointestinal pH and motility. The delivery rate is controlled by osmotic properties of the core as well as membrane area, thickness, and permeability to water.

The mathematical relationship used to describe the drug release rate from an osmotic system can be written as

$$\left(\frac{dm}{dt}\right)_{t=T} = \frac{kA\pi S}{h} \tag{20}$$

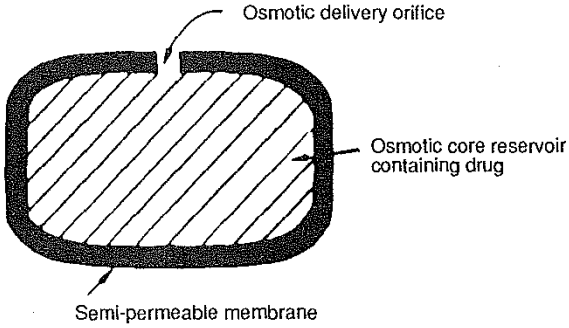

Figure 17 Schematic representation of an elementary osmotic pump. (From Ref. 47.)

where

m = released amount of drug (mg/h)
t = time from zero to T (h)
T = time at which the entire drug core has gone into solution (h)
k = osmotic permeability constant of the membrane (cm^3/h)
A = area of the membrane (cm^2)
h = membrane thickness (cm)
π = total osmotic pressure
S = drug solubility (mg/ml)

From the above equation, it is clear that the drug release rate will be zero-order between the starting time and the time when the entire drug core dissolves. After time T, drug release follows first-order kinetics. Generally, 80% of the drug is released at a constant rate and the rest as first-order release.

Example: An osmotic pump has a total surface area of 2.5 cm^2 and a membrane thickness of 200 μm. The solubility of the contained drug is 200 mg/cm^2. Calculate the zero-order delivery rate in milligrams per hour. The value of $k\pi$ is 5.0×10^{-2} cm^2/h.

Using Eq. (20):

$$\frac{dm}{dt} = \frac{(5.0 \times 10^{-2})(200)(2.5)}{0.02} = 12.5 \text{ mg/h}$$

Drug solubility is an important parameter in determining release rate. For compounds with low solubility, the osmotic pressure developed in the system may not be enough to ensure the desired drug release rate. In such situations, one can use highly soluble substances, generally salts, which serve to increase the osmotic gradient across the membrane and increase the release rate. Thus, the pump core may consist of pure drug, or drug and other additives, to achieve the desired release rate. Potassium chloride and mannitol are commonly employed osmogens to improve the release rate for poorly soluble drugs. On the other hand, certain drugs may be too soluble to provide a saturated solution for a long time. In such cases, the saturated solution is diluted too rapidly, causing a premature and

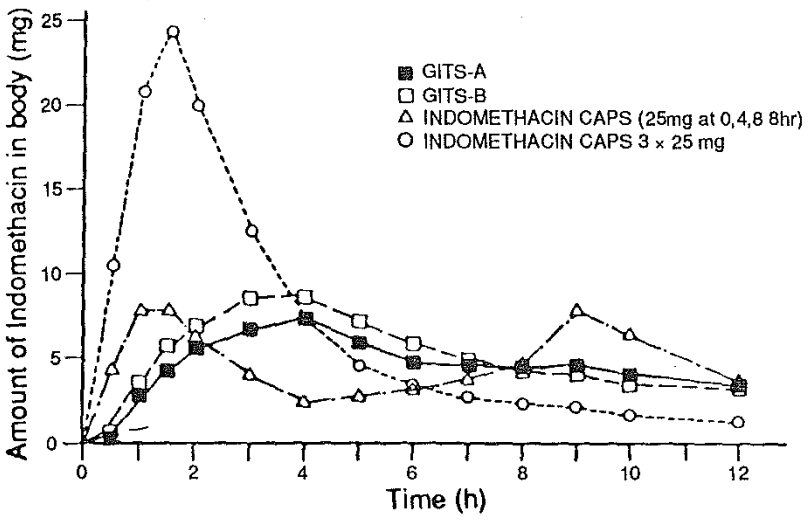

Figure 18 Mean body levels of indomethacin after administration of two osmotic pumps (GITS) each containing 75 mg with different release rates, three indomethacin capsules taken together, and three indomethacin capsules taken at 0, 4, and 8 h. (From Ref. 62.)

rapid fall in the pumping rate. For compounds with high solubility, the choice of a less soluble salt or ester can be a solution.

From a technology standpoint, osmotic devices are little more than coated tablets. A compressed core is coated with the water-insoluble but permeable polymer, and a small hole is drilled through this coating on one side of the tablet [60].

One such system has been developed for indomethacin [61,62]. As shown in Fig. 18, plasma-level excesses encountered with capsules were avoided by using osmotic devices. Bioavailability of indomethacin from osmotic pumps was 85% relative to capsules.

Typical membrane materials for osmotic devices are derivatives of polysaccharides, which include cellulose esters and cellulose ethers. Examples are various cellulose acylates, cellulose acetoacetate, etc. In addition to the polymeric material for the wall, the coating solution usually contains a stabilizing agent that imparts physical and chemical integrity to the wall, a flux enhancer to achieve the desired rate of fluid permeation, a plasticizer that gives flexibility to the wall, and a dispersant to blend the materials well. The final coating membrane must be rigid and capable of maintaining the structural integrity of the drug delivery system during the course of drug release.

Several modifications of the elementary osmotic pump pressure-controlled drug delivery system have been developed. One such system consists of two compartments separated by a movable partition. The osmotically active part imbibes water, swells, and moves the partition to expel the contents of the other compartment. Another modification is a pump without an orifice so that the osmotic pressure simply ruptures the device to release the contents as a bolus. By controlling membrane permeability, such a device could be used to target certain areas of the GI tract.

Osmotic devices can also be designed as multiunit dosage forms. Such formulations will consist of relatively small particles of drug core, coated with a water-permeable

membrane, and dispensed in a capsule. A delivery orifice can be made by either laser drilling as in an osmotic tablet, or by using a channeling agent in the coat which dissolves in the dissolution media to create tiny holes. Such devices have the potential of being less irritating, especially when strongly GI-irritating additives or drugs such as potassium chloride are used. Although osmotic devices are essentially independent of the GI environment, they may be unpredictable in a high-viscosity region such as the colon.

Slow-Dissolving Salts or Complexes

A salt or complex of drug that is only slightly soluble in gastrointestinal fluids can provide an extended release of drug without further control over its release rate. For such a function amine drugs can form slightly soluble salts with tannic acid [63]. The process of complex formation is usually a simple acid-base reaction, as in the case of amines and tannic acid. Solutions of both compounds in suitable solvents are mixed together and the resulting complex precipitated by the addition of another solvent or salt.

Drug-polymer complexes can be employed to provide extended release of drug. The complex releases the drug molecule either due to its degradation, as in the case of certain dye complexes with dextran, or simply due to equilibrium because drug is not bound covalently to the polymer.

pH-Independent Formulations

Since pH in the GI tract varies considerably and continuously as the formulation moves through it, pH-independent formulations are particularly attractive for oral use. These formulations are prepared by blending an acidic or basic drug with one or more buffering agents; e.g., primary secondary, or tertiary salts of citric acid, granulated and coated with appropriate materials. These materials are permeable to GI fluids so that dissolution can occur through the dosage form, but the dosage form cannot disperse and lose buffer. When gastrointestinal fluid passes through the membrane, buffering agents adjust the pH to an appropriate, predetermined, constant pH at which the drug dissolves and permeates out at a constant rate regardless of the external pH.

The buffer ingredients chosen must be compatible with the drug and other excipients and should also be physiologically acceptable. The amount of buffer must be sufficient to ensure a buffer effect throughout the drug-release period. The proportion of buffer material and drug depends on the relative permeability of both through the coating membrane.

Delayed-Transit and Continuous-Release Systems

As discussed previously, the length of in-vivo delivery by oral CR products is severely limited due to a short GI-transit time of solids and liquids. In addition, GI transit time tends to show considerable inter and intra-subject variation. This can also make drug delivery both variable and unpredictable. As a result, most oral dosage form are limited to a 12-hour period.

Several efforts have been aimed at prolonging residence time of the delivery devices in the GI tract. Given the nature of GI motility, the only viable approach appears to be to delay gastric emptying; because once a dosage form is emptied from the stomach, little can be done to retard its movement through the intestine. Indeed, most approaches have been aimed at delaying gastric emptying, although success in this regard has been limited to date. Such devices would use any of the mechanisms discussed so far to control the rate of the drug delivery except that they will be modified to stay in the GI tract for longer

periods of time. Since the stomach is the most likely target, it is obvious that the drug in question must be stable to gastric contents. Some of these approaches to prolong GI residence time are discussed in this section.

Density-Based Systems

Results of studies using variable-density dosage forms or pellets have been conflicting. The basic approach will be either high- or low-density pellets.

High-density approach. In the high-density approach, the density of the pellets must exceed that of normal gastric contents, i.e., approximately 1.2 g/cm^3, and therefore should be more than 1.4 g/cm^3. Claims have been made about longer gastric as well as intestinal residence times of such pellets when density is increased from 1 to 1.6 [64]. From studies done in this laboratory, however, such delays in gastric emptying or intestinal transit were not observed for pellets of densities of up to 2. In fact, glass beads with a density of 4 were emptied from the stomach in the same manner as pellets with a density of 1.

Low-density approach. The low-density approach forms the basis of formulations known as buoyant tablets or capsules. The approach is based on the assumption that a formulation with a density less than that of gastric contents will float on the surface of the gastric content and thus escape gastric emptying. It sounds reasonable in principle but neglects the basic physiology of gastric emptying. Gastric fluid empties fast, usually in a matter of minutes, and one would have to continuously drink prohibitively large volumes of water in order to keep enough volume in the stomach to prolong retention. Also, gastric motility would make it impossible for any device to stay afloat, regardless of its density.

Certain low-density materials such as polystyrene may be used for such systems. A modification of low-density materials may be a drug reservoir containing entrapped air to make it lighter than water, as shown in Fig. 19 [47]. From our basic knowledge of the process of gastric emptying, it seems unlikely that a density-based system will be viable.

Size-Based Systems

Studies have consistently shown that the size of a dosage form administered in the fasted state has little effect on its transit time through the GI tract. In the fed state, however, dosage forms of size greater than 2 mm show a longer transit time, the difference being due entirely to delayed gastric emptying. In order to achieve delay in gastric emptying

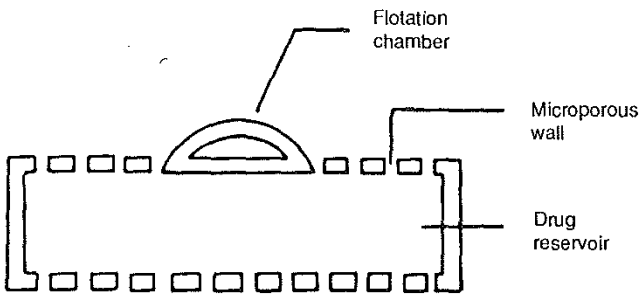

Figure 19 Schematic representation of a drug delivery system with flotation chamber. (From Ref. 47.)

long enough to allow once-a-day dosing, the dosage form has to be 2.5 cm or larger to prevent it from passing through the pylorus. Degradation of the device, after a certain period of time, will enable it to pass through. Such dosage forms may not be practical to swallow, unless they are made to swell or somehow inflate in the stomach.

Bioadhesive Systems

Bioadhesives are materials that can bind to a biological membrane and are capable of being retained on that membrane for an extended period of time. This binding, which usually takes place due to interfacial forces between two surfaces, can be added directly to the membrane surface (cell layers), or to a coating on the membrane surface, such as the mucin layer. The bioadhesive material itself may be biological or nonbiological in nature and source, although in a drug-delivery context, it is usually a nonbiological macromolecular or hydrocolloid material. The term "mucoadhesive" is commonly used for materials that bind to the mucin layer on a biological membrane, but throughout this section, the general term bioadhesive will be used. Besides acting as platforms for sustained-release dosage forms, bioadhesive polymers can themselves exert some control over the rate and amount of drug release, and thus contribute to the therapeutic design of such systems.

A bioadhesive delivery system that adheres to the stomach will be able to provide a continuous dose of drug into the intestine for extended periods of time. However, there are a number of problems, as listed below, associated with development of a suitable adhesive for the stomach.

1. Gastric motility will be a dislocating force for the adhesive. This motility is particularly strong during phase III of the fasted state. During the fed state also, the stomach is in a state of continuous motility, with substantial retropulsive forces acting, particularly in the antral area. In addition, the presence of food may make it difficult for such polymers to attach to the gastric mucosa. Only bioadhesives that bind strongly enough to withstand these shear forces will be practical.
2. Most adhesive polymers studied thus far actually attach to the mucin layer on the mucosal membrane. In the stomach, the mucin turnover rate is substantial, in both the fed and fasted states. Thus, the adhesive will attach to mucus, and be detached along with the mucus when it is released from the membrane. Further attachment of the polymer may not be possible because all the active binding sites on the adhesive will be covered with mucin.
3. The pH of the stomach, which normally ranges between 1.5 and 3.0, may not be suitable for bioadhesion. This is not the case for the polyacid polymers such as cross-linked polyacrylic acid, where the predominant mechanism of bioadhesion is through hydrogen bond formation.
4. Unlike areas such as the buccal cavity, the GI tract is not directly accessible to place an adhesive system on the mucosa. In the absence of a mechanical force to achieve the initial attachment, such systems may have trouble attaching to the membrane.

However, all of these problems can be overcome, either by designing suitable polymers, or by incorporating certain ingredients in the dosage form which will modify conditions in the immediate vicinity of the dosage form to maximize bioadhesion. One approach would be to develop adhesive polymers that attach to the epithelial membrane,

instead of mucin. Incorporation of a mucolytic agent in the formulation may create a local mucosal-free surface and attach to it, although it will raise the question of causing physical insult to the membrane or making it more susceptible to attack by acid and enzymes in the stomach.

Similar problems can be anticipated in the intestine, but the pH may be more helpful in this region. The key to success of a bioadhesive polymer in these areas seems to lie in an understanding of the adhesive phenomenon at a molecular level, to a degree that suitable adhesives can be designed to attach to specific areas in the GI tract. This area of research is ongoing and needs to be pursued vigorously.

Delayed-Release Systems

Delayed-release systems for oral controlled delivery are the ones aimed at delivering drug to a particular area of the Gi tract, instead of delivering the drug continuously immediately after ingestion. This site-specific delivery can be aimed at systemic absorption, as in case of enteric-coated tablets, or for local effects. Certain disease conditions of the colon and rectum could be treated by delivering drugs specifically in the desired area. These systems can provide one or more of the following advantages over other oral CR systems:

1. Bypass areas of potential drug degradation, e.g., the stomach for acid-labile drugs, the stomach and jejunum for peptidase-labile drugs
2. Achieve local effects in the lower GI tract without much systemic absorption or side effects
3. Reduce GI discomfort in the upper area
4. Deliver drugs to a specific absorption site to achieve a high concentration at the absorptive membrane, e.g., delivery to Peyer's patches or colon bacteria

Delayed-release devices can be divided into two categories, intestinal-release and colonic-release devices.

Intestinal Release

Enteric-coated tablets are examples of the intestinal-release approach. This approach is usually used for acid-labile drugs. In the case of aspirin, prevention of gastric irritation is the aim. However, enteric-coated formulations tend to be unpredictable in their bioavailability. Enteric-coated erythromycin tablets are well known for their unpredictable and variable bioavailability. In addition to protection from stomach acid, a drug can also be protected from most of the intestinal enzymes if it is released in the terminal ileum. In this area, additional routes of absorption could be utilized to deliver certain drugs such as macromolecules via Peyer's patches, and very hydrophobic drugs via the lymphatic route.

Peyer's patches, which are organized mucosal lymphoid tissues of the gut, play an important role in regulating the immune response to orally presented antigens. They are generally larger and more numerous in the distal than in the proximal small intestine and are usually present on the antimesenteric circumference of the intestinal wall. Their size and number vary from species to species, with as many as 100 in humans [65]. Peyer's patches consist of a collection of lymphoid follicles that occupy the full thickness of the small intestinal mucosa.

It is well documented that Peyer's patches are able to internalize particulate matter, bacteria, and marker proteins [22]. Both soluble and colloidal substances enter Peyer's

patches by vesicular transport through specialized epithelial cells. Some of the cells covering Peyer's patches have microfolds and have been called microfold or "M" cells. These cells have been demonstrated to be involved in antigen uptake, and serve as an explanation for uptake of high-molecular-weight soluble and colloidal proteins.

Due to their capability of absorbing large molecules, Peyer's patches present a potential site for delivery of macromolecules. The exact nature of the surface characteristics of these patches is not yet fully understood, but if adhesive systems are to be devised to attach to or around them, a successful delivery system for large molecules may emerge.

Lymphatic absorption presents a viable route of absorption for compounds with certain characteristics, chiefly the hydrophobicity or partition coefficient of the drug. Factors controlling lymphatic uptake of drugs are not well understood yet, but the partition coefficient of the compounds seem to play a dominant role. It appears that a compound has to have a very high partition coefficient in order to be taken up predominantly by the lymphatic route. Most absorption into the lymphatic system is via two mechanisms, chylomicrons and large-molecule uptake by pinocytosis. Chylomicrons are small spherical particles made up almost entirely of dietary fat and cholesterol and are specifically internalized into the lymphatic vessels. Thus, any compound that can be incorporated into chylomicrons will also be taken up by the lymphatic system. Since lymphatic drainage does not go through the liver, drugs absorbed by this route will not be subject to first-pass liver metabolism.

Colonic Release

Despite a small absorptive surface area, the potential for delivery through the colonic mucosa still exists because the desired rate of absorption from CR formulations is generally not very high. Another factor in drug absorption through the colon is the physical nature of the luminal content. Once past the ileo-cecal junction, gut content thickens quickly and considerably due to increased absorption of water. This puts an additional constraint on the dosage form from a drug-release standpoint. Although no systematic study has been reported to date to evaluate drug diffusion through the viscous colonic contents, there is little doubt that both the rate and the extent of drug release are compromised.

There are basically two approaches toward delivering drugs through the colon: (1) use of bioerodible polymers to protect drug during its passage through the upper GI tract, and (2) use of prodrugs that are activated by bacterial degradation or metabolism. The use of bioerodible polymers to control the release of drugs is based on a pH gradient which exists in the GI tract or on high levels of enzymatic activity in the lower GI tract.

Copolymers of methacrylic acid and methyl methacrylic acid, and cellulose acetate phthalate are examples of pH-sensitive bioerodible polymers. They have been used to coat 5-aminosalicylic acid, an anti-inflammatory agent, for its selective delivery to the colon to treat inflammatory bowel disease [66].

Copolymers of styrene and hydroxyethylmethacrylate, cross-linked with divinyl-azobenzene, can be designed to be susceptible to cleavage by the azo-reductase activity of the colonic microflora. Through the use of such polymers, attempts have been made to deliver insulin and other peptides, including vasopressin, via colonic absorption [67].

An example of a colon-specific prodrug is sulfasalazine, an azo compound degraded by the azo-reductase activity in the colon. One of its degradation products, 5-aminosalicylic acid, is thought to be the ingredient active against local inflammation. Glycoside-linked drugs are another example of prodrugs designed for activation in the colon by glycosidase activity.

SUMMARY

The oral route of drug delivery continues to attract the most attention with respect to development of CR systems. Research during the last three decades has established the scientific framework leading to development of a number of oral CR systems. Most of these are polymer-based systems in which the drug release rate is controlled by a membrane or matrix of a polymeric material. However, relatively few of these devices have proved to be useful therapeutic systems, due mainly to biological constraints of the gastrointestinal tract. The next challenge, therefore, is to increase our understanding of the physiology of this route in order to optimize drug delivery. This task will involve the incorporation of tissue, cellular, and molecular elements of GI physiology into the design of oral CR systems. Of particular significance among these are transit time studies, a detailed picture of the GI permeability to drug molecules, and GI motility. This will enable the pharmaceutical scientist to either optimize the dosage form to the GI environment or find ways to perturb GI physiology in a noninvasive way to deliver drugs. Specific regions of this organ should also be explored for delivery of peptides and proteins. Control over the movement of a dosage form and achieving some degree of colonic absorption are necessary in order to design systems to deliver drugs for more than 12 h with a single dose.

PROBLEMS

1. The therapeutic dose of a rapidly and completely absorbed drug is 450 mg/day, given 8 h apart as an osmotic pump device which delivers 75% of its load as a zero-order release, and the rest is retained in the dosage form. Half-life of the drug is 3 h, and rate of clearance is 50 liters/h. Calculate the amount in each dose, the release rate from the pump, and plasma drug concentration at 8 h after the first dose (μg/ml).
2. A drug shows a DI index of 3.2 from a controlled-release dosage form, and has a therapeutic index of 5. Can you evaluate the therapeutic value of the dosage form?
3. List three potential advantages of multinunit dosage forms over single-unit dosage forms.
4. An orally administered drug as a conventional tablet form shows 60% bioavailability when given as 250 mg t.i.d., and 80% bioavailability when given as 375 mg b.i.d., indicating a saturable presystemic drug elimination process. Suggest some noninvasive or invasive animal experiments to study the contribution of saturable, enzymatic degradation in the GI tract, gut wall metabolism, and first-pass liver metabolism. Note that more than one process can be involved.
5. The pharmacokinetic parameters of a drug, as determined from i.v. data, are as follows:

$$\text{Desired SS blood level} = 10 \text{ mg/liter}.$$
$$V = 15 \text{ liters}.$$
$$k_{el} = 0.2\ h^{-1}.$$
$$F = 1.$$

   (a) If you were to device a zero-order-release formulation for oral administration, what rate of drug release would be required in order to maintain the desired blood levels in the body?

(b) How long will it take to reach 90% of plateau levels with the above release rate?

6. A controlled-release drug device releases the drug by a zero-order-release rate of 12 mg/h. It contains 288 mg of drug load.
   (a) Complete the following table. The pharmacokinetic parameters are as follows:

$$ka = 12\,h^{-1}.$$
$$V = 1000 \text{ liters}.$$
$$k_{el} = 0.12\,h^{-1}.$$

Time (h)	Amt. in body (mg)	Amt. in dosage form (mg)	Amt. in gut lumen (mg)
0.25			
0.5			
1			
2			
4			
6			
8			
12			
16			
20			
24			

   (b) Obtain a drug amount-versus-time plot for body (curve A), dosage form (curve B), and gut lumen (curve C).
   (c) In an in-vivo study, curve B was observed to shift to the right 6 h after dosing, with a corresponding downward shift in curve A. Curve C showed no change. Give some possible explanations for this shift.
   (d) After another 6 h (12 h after dosing), curve B shifts further to the right, curve C shows a slight rise, and curve A falls further down compared to the in-vitro results. Explain the events that could be responsible for this observation.
   (e) Give two approaches that could be used to keep the in-vivo curves closer to those of in-vitro curves.
   (f) Assuming that the dosage form is administered every 24 h and the in-vitro and in-vivo curves overlap, what will be the drug amount in the body at steady state?

7. A typical osmotic device comes in the shape of a tablet, with a tiny hole drilled through the semipermeable membrane on one side of the tablet. The usual range of the size of this orifice is 100–250 μm. Explain why such a range is chosen. What might happen if the size is smaller than 100 μm or larger than 250 μm?
8. The following information is available about two new antidepressant drugs:

	Drug A	Drug B
MW	260	580
pK_a (base)	9.5	8.4
Aqueous solubility (mg/ml)	10	2.0
Oral bioavailability (% from soln.)	55	75
Absorption rate constant (k_a)	10	5
Therapeutic index	4	8
Apparent volume of distribution (liters)	80	2200
Clearance (liters/h)	50	170
Minimum effective concentration (ng/ml)	170	60

(a) Evaluate, on a comparative basis, the first six parameters above in order to assess the suitability of both drug candidates for formulation as an oral controlled-release system. Based on your evaluation, indicate the better candidate.

(b) Based on the overall evaluation, which drug candidate would you choose and why?

(c) Complete the following table:

	Drug A	Drug B
Target blood level (μg/liter)		
Zero-order release rate desired (mg/h)		
Loading dose (mg)		

(d) Both of the above drugs were formulated as slow first-order-release formulations as follow:

	Drug A	Drug B
Dose/unit	250 mg	250 mg
Release rate constant (k_{rel})	0.3 h^{-1}	0.2 h^{-1}

Assume the same F as from solution. No loading dose is given. Calculate the dosage form index at steady state for both drugs for the following dosage-form regimens:

(i) One unit given every 6 h
(ii) Two units given every 12 h
(iii) Four units given every 24 h

(e) Which dosage regiment of those above would you choose for Drugs A and B? Explain your choice.

ANSWERS

1. (a) Amount needed = 450/3 = 150 mg, but since only 75% of drug load is delivered, the amount required in dosage form is 150 × 100/75 = 200 mg.
   (b) Release rate = 200/8 = 25 mg/h.
   (c) Using Eq. (7), c = 0.019 μg/ml.
2. In order to assess the therapeutic success of a dosage regimen, one needs to know the desired blood levels in addition to the TI and DI. The fact that DI < TI for the above formulation does not necessarily mean that the plasma drug levels fall within the effective range. It is possible that C_{max} and C_{min} at steady state overlap with the toxic levels or with minimum effective levels of drug. In both these cases, therapy will fail. Therefore, from a pharmacokinetics standpoint, the goal of a therapy is to maintain the drug levels within therapeutic window as well as to keep DI < TI.
3. (a) Better gastrointestinal tolerance
   (b) Less chances of dose dumping
   (c) Better colonic absorption
4. Perform an in-situ intestinal perfusion experiment, using well-washed-out intestine to eliminate gut lumen enzymes. Collect blood samples from the portal vein in one experiment, and from the hepatic vein in the other.
   (a) 100% bioavailability from the hepatic vein will indicate that the gut lumen enzymes are solely responsible for degradation.
   (b) The difference between the portal and hepatic venous drug levels will indicate the contribution of liver metabolism.
   (c) Less than 100% availability from portal vein drug levels will indicate a contribution from gut wall metabolism.
5. (a) $c = k_0/Vk_{el}$; k_0 = 30 mg/h
   (b) 90% of 10 mg/liter = 9 mg/liter
   $c = k_0(1 - e^{-k_{el}t})/Vk_{el}$; t = 1.1 h
6. (a) The equations are as follows:

$$\text{Amount in body} = (k_0/k_{el})(1 - e^{-k_{el}t})$$

$$\text{Amount in dosage form} = 288 - k_0t$$

$$\text{Amount in gut lumen} = (k_{el}/k_a)(1 - e^{-k_a t})$$

Time (h)	Amt. in body (mg)	Amt. in dosage form (mg)	Amt. in gut lumen (mg)
0.25	2.95	285	0.0095
0.5	5.82	282	0.0099
1	11.3	276	0.01
2	21.3	264	0.01
4	38.1	240	0.01
6	51.3	216	0.01
8	61.7	192	0.01
12	76.3	144	0.01
16	85.3	120	0.01
20	90.9	48	0.01
24	94.4	0	0.01

(c) Since the shift in curve B is to the right, the drug release rate is falling (k_0 < 12 mg/h). This is further evident from the fact that curve A shifts downward, as a result of reduced drug input. However, no shift in curve B means that k_a holds up steady. Possible reasons for this observation could be increased gut lumen viscosity or lower GI motility. The dosage form at this time is probably in the terminal ileum.

(d) The rise in curve C means that k_a has lowered, in addition to a further drop in k_0. The dosage form at this time is definitely in the colon, and highly viscous contents contribute to slower dissolution as well as diffusion of drug.

(e) (i) Use a multiunit dosage form, with a portion of particles releasing drug only after 6 or 12 h to compensate for reduced k_0.

(ii) Administer a nonabsorbable, nondegradable, and highly hydrophillic polymer, e.g., polymethacrylic acid, to maintain adequate fluid levels around the dosage form and help sustain drug dissolution and diffusion.

(f) Using Eq. 7, c = 100 mg.

7. Drug diffusion takes place with osmotic pressure as well. For this range, the rate of drug release due to simple diffusion is negligible compared to the total release rate, but does not restrict the solution movement. Size smaller than 100 μm may make the orifice the rate-limiting step for drug release. Size larger than 250 μm may allow an unacceptably high rate of drug diffusion. Since drug diffusion is affected by a variety of GI variables including viscosity and the hydrodynamics of GI contents, this may result in an unpredictable release rate.

8. (a) (i) MW: Drugs with MW less than 600 usually do not pose problems with respect to absorption from the GI tract. Drug A, with a MW of 260, does not seem to be a problem at all, but B, with a MW of 580, approaches 600. Yet it shows a slightly higher bioavailability than A. Since a complete absorption profile is not given, drug B could pose some absorption problems in the terminal ileum and colon. Consequently, although both drugs are below the 600 limit, based on MW alone, drug A will be a better choice.

(ii) Pk_a: Both drugs are basic, with Pk_a higher than the pH of GI tract at all times. Thus they will be mostly in an un-ionized form through most of the GI tract. In this respect, both drugs are equally suitable for controlled-release formulations.

(iii) Aqueous solubility: An aqueous solubility of 2 mg/ml seems to pose no problem for controlled-release dosage forms because the desired rate of release is usually small. Also, k_a for both drugs is fairly high, so not much drug will stay in the GI tract during the entire process of drug release. Thus, solubility does not seem to be an important factor for these drugs.

(iv) Bioavailability: Less than 100% bioavailability from solution usually indicates drug loss due to degradation or metabolism. Liver first-pass metabolism could be a contributing factor. Since the data are only from solution dosage form and no effect of dose on bioavailability has been evaluated, a saturable presystemic clearance process is a possibility, especially for drug A. Apart from that, drug B will be a better choice simply due to its higher F.

(v) k_a: Since most controlled-release formulations are designed to have the drug release rate as the rate-limiting step, the value of k_a should be much higher than that of k_0 (the drug release rate). Values of 5 and 10 h^{-1} seem high enough for this purpose. Nevertheless, k_a has been determined from a solution dosage form, and, thus, reflects absorption kinetics only from the upper small intestine. Considering that k_a generally falls from the proximal to the distal part of the small intestine, drug A, with a value of 10 h^{-1}, will be a better choice.

(vi) TI: TI alone is of limited value in determining suitability for controlled release. From the given values of V_{app} and Cl, one can get an estimate of k_{el}, which seems much higher for drug A (50/180 liters/h) compared with drug B (170/2200 liters/h). Thus, DI for B will be much smaller compared to that of A. Given that the TI for B is also higher, controlled release may not offer much advantage over the conventional dosage form. [This will be more evident in part (d) of this problem.] Therefore, once again A will be a better choice.

(b) Based on the above parameters, drug A makes a better candidate for formulation as a controlled-release product in all respects except oral bioavailability. Unless a saturable metabolic clearance is documented for A, it should be chosen.

(c)

	Drug A	Drug B
Target blood level (MEC × TI/2)	340 μg/liter	240 μg/liter
Zero-order release rate (C·Cl/F)	31 mg/h	30.6 mg/h
Loading dose (C·V/F)	111 mg	704 mg

(d) Use Eq. (6) for t_{max}, Eq. (4) for C_{max}, and Eq. (5) for C_{min}.
For drug A:

One unit every 6 h:
$$t_{max} = 2.1 \text{ h}$$
$$C_{max} = 0.52 \text{ mg/liter}$$
$$C_{min} = 0.45 \text{ mg/liter}$$
$$DI = \frac{0.52}{0.45} = 1.2$$

Two units every 12 h:
$$t_{max} = 3.0 \text{ h}$$
$$C_{max} = 0.67 \text{ mg/liter}$$
$$C_{min} = 0.21 \text{ mg/liter}$$
$$DI = \frac{0.67}{0.21} = 3.2$$

Four units every 24 h:
$$t_{max} = 3.5 \text{ h}$$
$$C_{max} = 1.16 \text{ mg/liter}$$
$$C_{min} = 0.01 \text{ mg/liter}$$
$$\frac{1.16}{0.01} = 116$$

For drug B:

One unit every 6 h:
$t_{max} = 2.7$ h
$C_{max} = 0.18$ mg/liter
$C_{min} = 0.18$ mg/liter
$DI = \frac{0.18}{0.18} = 1.0$

Two units every 12 h:
$t_{max} = 4.4$h
$C_{max} = 0.20$ mg/liter
$C_{min} = 0.15$ mg/liter
$DI = \frac{0.20}{0.15} = 1.3$

Four units every 24 h:
$t_{max} = 6.4$ h
$C_{max} = 0.24$ mg/liter
$C_{miin} = 0.09$ mg/liter
$DI = \frac{0.24}{0.09} = 2.6$

(e) The choice should be the most infrequent dosing where DI < TI and pla levels stay between MEC and toxic levels.

Drug A: The choice is regimen (ii), i.e., two units every 12 h, bec TI = 0.68/0.17 = 4 and DI = 0.67/0.21 = 3.2.

Drug B: The choice is regimen (iii), i.e., four units every 24 h, bec TI = 0.48/0.06 = 8 and DI = 0.24/0.09 = 2.6.

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