ORAL CONTROLLED RELEASE FORMULATION DESIGN AND DRUG DELIVERY

Theory to Practice

Edited by

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ORAL CONTROLLED RELEASE
FORMULATION DESIGN AND DRUG DELIVERY
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As researchers in the fields of pharmaceutical sciences and drug development, we all understand the importance and challenges related to the design of oral controlled release formulations. The oral administration has been the first choice of drug delivery when a new drug is developed because of its easiness of administration and high acceptance by patients. Naturally, the oral formulations occupy the majority of all dosage forms. For this reason, there have been numerous research articles, patents, and books describing various aspects of development and clinical applications of oral formulations. A number of books dealing with various topics in oral drug delivery have been available, but they are either not comprehensive in topics or were published a while ago, necessitating update. We thought that it would be highly useful to prepare a new comprehensive book, covering all the major topics of oral controlled release formulation ranging from basics to practice that can serve as a useful reference book to the scientists in academia, industry, and government. Many practical examples in the book will be especially useful to graduate students and those scientists who do not have pharmaceutical background and training.

Since we initiated this book, we received many valuable suggestions from scientists active in the field on the structure and contents of the book. The book covers not only the fundamentals of preformulation, biopharmaceutics, and polymers, but also practical aspects in formulation designs, all of which are critical to achieving successful formulation development. The book also includes the most updated topics, such as new drug delivery technologies, quality by design (QbD), regulatory consideration for drug development, and competition between brand drugs using life cycle management (LCM) and generic drugs. In each chapter of the book, both theory and practical examples have been introduced to help readers understand the topic and apply the knowledge gained from the book directly to their own work. Since each chapter contains not only updated scientific information, but also authors’ own experiences on a specific topic, the book as a whole provides many practical tips in formulation development, serving well as a reference book.

We want to thank all the authors for their hard work in writing their chapters, sharing knowledge, and making this book successful. Our thanks also go to all the reviewers who provided invaluable inputs for the chapters. We are also grateful to John Wiley & Sons, Inc. for agreeing to publish this book, and our special appreciation goes to Jonathan Rose who has been infinitely patient and supportive during the preparation of this book.

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INTRODUCTION AND OVERVIEW OF ORAL
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1.1 FUNDAMENTALS OF ORAL CONTROLLED
RELEASE FORMULATION DESIGN AND DRUG
DELIVERY

1.1.1 Overview

Due to the difficulty in developing new drugs, more and more emphasis has been given to developing new drug delivery systems for existing drugs as well as new chemical entities. Drugs can be delivered to patients by more than one route and by more than one type of dosage form. Even though “dosage form” and “drug delivery system” are used interchangeably, “drug delivery system” implies that a technology has been used to deliver a drug to the desired body site for drug release with a predetermined rate. Among various drug delivery systems, oral controlled release (CR) formulation is the most commonly used in pharmaceutical industry.

Delayed release, sustained release, and repeat action formulations are the three most common controlled release formulations [1, 2]. The most widely used example of delayed release form is enteric coated tablets [3, 4] or capsules, in which drug will not release in gastric fluid, that is, acidic environment, until it reaches the intestine, that is, neutral environment. In sustained release formulations, a portion of drug is released immediately, and the remaining drug is released slowly over an extended period of time, normally over 12–18 h. In fixed dosage combination (FDC), immediate release (IR) formulation for one drug and sustained release (SR) for another drug [5] or the same drug in both IR and SR formulation parts are popular approaches [6, 7]. For example, metoprolol succinate extended release and hydrochlorothiazide immediate release combination tablets have additive antihypertensive effects [8]. In Sanofi-Aventis’ Ambien CR, there is a biphasic profile of dissolution, where the first phase is an IR phase and the second phase is a prolonged release phase [7].

For those drugs where prolonging blood levels of the drugs have no therapeutic advantages, there is no need to develop their controlled release formulations [9]. For example, drugs with a long half-life \( t_{1/2} \) (e.g., diazepam [10, 11] and amitriptyline [12]), drugs whose maintained effect is undesirable (e.g., \( \beta \)-lactamase antibiotic (amoxicillin) may induce emergence of resistant bacteria [13]), and drugs that require immediate effect (e.g., nitroglycerin for heart attack) [14] are not suitable in controlled release formulations.

1.1.2 Advantages and Disadvantages

In addition to extending the patent life of those drugs whose patent protection are expiring, there are many other benefits for patients by using an oral controlled release formulation [15–17]. They include maintenance of optimum drug concentration and increased duration of therapeutic effect [18], improved efficiency of treatment with less amount of drug [19], minimized side effects [20–23], less frequent administration [24], and increased patient convenience and compliance [18, 25]. The controlled release formulations are
also beneficial for the study of pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug [26, 27].

Like any other formulation, there are some disadvantages of oral controlled release formulations. In most cases, the amount of drug contained in the dosage form is higher than a single dose of conventional dosage forms. If the drug reservoir of a controlled release formulation is damaged and release the drug all at once, the drug concentration may go above the toxic level. Therefore, the potential of dose dumping has to be taken into consideration in controlled release formulation design. Furthermore, once the drug release begins, it is difficult to stop the release even if it is necessary. In addition, the cost of producing the controlled release formulation is higher than that of the conventional dosage forms. The relative higher production cost can be compensated if the benefit of the controlled release formulations is immediate and obvious to the patients.

1.1.3 Fundamental Release Theories

Based on different drug release mechanisms, quite a few drug release theories have been developed, which will be elaborated in the corresponding chapters. For all different types of controlled release systems except osmosis-based systems, the drug concentration difference between formulation and dissolution medium plays a very important role in drug release rate. The drug concentration can be affected by its solubility, drug loading, and/or excipients used. Besides drug concentration difference, the dissolution rate of polymer carriers can affect drug release rate in dissolution-controlled systems, and the diffusion speeds of both drug and dissolution medium inside polymer(s) can affect drug release rate in diffusion-controlled systems. For osmosis-based and ion exchange-based systems, the drug release can be affected by other factors as well. Overall, for most CR formulations, drug release can be affected by one or more mechanisms. Here, a few fundamental theories will be briefly discussed.

Fick’s first law of diffusion is used in steady-state diffusion, in which the concentration within the diffusion volume does not change with time. The drug release rate is determined by drug release surface area (S), thickness (h) of transport barrier (such as polymer membrane or stagnant water layer), and the concentration difference (∆C) between drug donor (Cd) and receptor (Cr), that is, between drug dosage surface and bulk medium.

Fick’s first law states that

$$ M = JSt = \left( \frac{D \Delta C}{h} \right) St $$

where M is the total amount of solute crossing surface area S in time t, J is the flux rate, and D is the diffusion coefficient of the drug molecule in the unit of cm²/s.

Fick’s first law did not take into account the drug concentration changes with time in each diffusion volume, which have been taken into consideration by Fick’s second law of diffusion. Based on Fick’s second law, drug accumulation speed (dC/dt) is determined by drug diffusivity (D) and the curvature of drug concentration:

$$ \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial^2 t} $$

Most commonly seen drug release rate for oral controlled release formulation is first-order release and/or zero-order release. Most oral controlled release formulations based on matrix and coating approaches are close to first-order release. Alza’s osmotic pump and Egalet’s erosion tube can release drugs at zero order. Based on the shape of release profile, there are five major release profiles: zero-order release (constant release rate); first-order release (decreasing release rate); bimodal release (two release modes, which can be either two separate immediate release modes or one immediate release mode followed by one sustained release mode [28–30]); pulsatile release (multiple release modes and multiple peaks of release rate [31]); and delayed release (e.g., enteric coated tablets [32–34]).

The two important phenomena in controlled release formulations are the lag time effect and the burst effect. In diffusion control system, if fresh membrane is used, it takes time for drug molecules on the donor side to appear on the receptor side. Under the sink condition, drug molecules will be released at constant rate into the receptor side and the steady state is reached. The time to reach the steady state is known as the “lag time.” However, if the membrane saturated with a drug is used, a “burst effect” will be observed at the beginning of drug release. Gradually, the drug concentration inside the polymer membrane will decrease until the steady state is reached. Actually, for matrix approach controlled release formulation, because it takes time for polymer molecules to form hydrogel, “burst effect” is also a common phenomenon.

TIMERx™ is very versatile hydrogel-based controlled release technology, which can provide different release kinetics for a wide range of drugs by manipulating molecular interactions. The release profiles range from zero order to chronotherapeutic release. This technology does not need complex processing or novel excipients, but still achieves
desired drug release profiles using a simple formulation development process. TIMERx™ is a pregranulated blend composed of synergistic heterodisperse polysaccharides (usually xanthan gum and locust bean gum) together with a saccharide component (generally dextrose). Different drug release kinetics can be achieved based on the synergism between the homo- and heteropolysaccharide components in the system. Finally, the drug release rate is controlled by the speed of water penetrating into the matrix [35, 36]. The material has good compressibility and can be mixed or granulated with drug and other necessary excipients to be compressed into tablets.

1.1.4 Limiting Factors for Oral CR Formulations

There are a few unique properties of the gastrointestinal (GI) tract that make development of oral CR formulations rather difficult. Figure 1.1 shows schematic description of the GI tract. Based on histology and function, the small intestine is divided into the duodenum, jejunum, and ileum, and the large intestine is divided into the cecum, colon, rectum, and anal canal. W. A. Ritschel reported the average length, diameter, and absorbing surface area of different segments of the GI tract, and the data clearly show that jejunum and ileum (small intestine) have similar surface absorbing areas that are significantly larger than those of other segments [37]. For most drugs, there is better drug absorption in the upper GI tract, which is also consistent with the significant higher surface absorbing area in the upper GI tract.

1.1.4.1 Relatively Short Gastric Emptying and Intestinal Transit Time and Varying pH Values

Because oral dosage forms will be removed from the GI tract after a day or so, most oral CR formulations are designed to release all drugs within 12–18 h. The values in Table 1.1 show the approximate transit time in different GI segments. The presence of food in the stomach tends to delay the gastric emptying. Among different foods, carbohydrates and proteins tend to be emptied from the stomach in less than 1 h, while lipids can stay in the stomach for more than 1 h [37–41]. As a convenient resource, Gastroplus™ can provide rough estimation on the transit times and pH values of the GI tract under different situations and help to calculate corresponding drug PK profiles.

Table 1.1 shows that the small intestinal transit time is more reproducible and is typically about 3–4 h [38, 39]. Thus, the transit time from mouth to cecum (the first part of large intestine) ranges from 3 to 7 h. Colonic transit is highly variable and is typically 10–20 h [42–44]. Since most drugs are absorbed from the small intestine, the time interval from mouth to cecum for oral controlled release dosage forms is too short, unless the drug can be equally well absorbed from the large intestine. Thus, the release profiles of most oral controlled release dosage forms can be effective for only about 8 h. If the drug can be absorbed from the large intestine, the time interval for drug absorption can be increased to 1 day. Thus, certain drugs can be delivered for 24 h by a single administration of an oral controlled release dosage form. But many drugs require more than one administration if they have the upper GI tract absorption window and short half-life, unless the release of those drugs can be controlled at the upper GI tract with special design. The study on the GI transit time of once-a-day OROS® tablets of both oxprenolol and metoprolol showed that the median total transit time was 27.4 h with a range of 5.1–58.3 h [45, 46].

![FIGURE 1.1 Upper and lower gastrointestinal tract.](image)

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<tr>
<th>Anatomical Site</th>
<th>Fasting Condition</th>
<th>Fed Condition</th>
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<td>Stomach</td>
<td>1–3.5</td>
<td>4.3–5.4</td>
</tr>
<tr>
<td>Duodenum</td>
<td>5–7</td>
<td>5.4</td>
</tr>
<tr>
<td>Jejunum</td>
<td>6–7</td>
<td>5.4–6</td>
</tr>
<tr>
<td>Ileum</td>
<td>6.6–7.4</td>
<td>6.6–7.4</td>
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<tr>
<td>Cecum</td>
<td>6.4</td>
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<tr>
<td>Colon</td>
<td>6.8</td>
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TABLE 1.1 The pH Values and the Transit Time at Different Segments of the Human GI Tract [37–41]
1.1.4.2 Nonuniform Absorption Abilities of Different Segments of GI Tract  
Drug transport across the intestinal epithelium in each segment is not uniform, and in general, it tends to decrease as the drug moves along the GI tract. Because drug absorption from different regions of the GI tract is different, the residence time of drug within each segment of the GI tract can profoundly affect the performance of the oral controlled dosage form, that is, the absorption of drug.

If a drug is absorbed only from the upper segment of the GI tract, it is known to have a “window for absorption” [47]. For the drugs with window for absorption, adjusting drug release rate on different segments of the GI tract may be needed to compensate decreased absorption, in order to maintain relatively constant blood concentration. For example, to achieve a plateau-shaped profile of plasma concentrations at steady state throughout the 24 h dosing interval, nisoldipine coated core (CC) controlled release formulation releases drug slowly in the upper GI tract that has fast absorption and quickly in the colon that has decreased absorption rate [48]. Besides adjusting drug release rate, increasing the residence of drug formulations at or above the absorption window can also enhance the absorption for those drugs. Currently, two main approaches have been explored: bioadhesive microspheres that have a slow intestinal transit and the gastrointestinal permeable dosage system [49].

1.1.4.3 Presystemic Clearance  
For some drugs, presystemic clearance may occur at some sites of the GI tract and affect drug absorption. Degradation of orally administered drugs can occur by hydrolysis in the stomach, enzymatic digestion in the gastric and small intestinal fluids, metabolism in the brush border of the gut wall, metabolism by microorganisms in the colon, and/or metabolism in the liver prior to entering the systemic circulation (i.e., first pass effect). Such degradations may lead to highly variable or poor drug absorption into the systemic circulation. For example, digoxin undergoes microbial metabolism before absorption [50, 51]. For this type of drugs, for which presystemic clearance is determined by the site of absorption, drug bioavailability can be enhanced by restricting drug delivery to the upper segment of the gut, or to the stomach. For example, the same amount of metoprolol was administered at the same rate using a continuous 13.5 h intragastric infusion or a OROS® tablet; at 6–15 h after dosing, the intragastric infusion had higher plasma concentration than metoprolol OROS® tablet [52].

1.1.4.4 Poor Absorption of Peptide and Protein Drugs  
It is very difficult to develop oral formulations for peptide and protein drugs. First, peptide and protein drugs are unstable under the harsh conditions in the GI tract and can be degraded by enzymes. Second, even if the structures of peptide and protein drugs are maintained, absorption of high molecular weight drugs, for example, insulin, through the epithelial cells of the GI tract is very difficult at best. So far, much research has been done to develop new technologies for oral peptide and protein delivery [53–55]. For example, Emisphere’s eligen® Technology has been used in the development of oral drug delivery for peptide and protein drugs such as salmon calcitonin, insulin, and recombinant human growth hormone (rhGH) (http://www.emisphere.com/pc_pp.asp).

1.1.4.5 Difficult In Vitro–In Vivo Correlation  
Establishing in vitro–in vivo correlation (IVIVC) will be very valuable in predicting drug in vivo performance based on in vitro dissolution tests. However, it is sometimes difficult to establish IVIVC for oral controlled release formulation due to many factors, such as variable transit time in different segments of the GI tract, nonuniform absorption abilities of different segments of the GI tract, and presystemic clearance.

1.2 PREFORMULATION AND BIOPHARMACEUTICAL CONSIDERATIONS FOR CONTROLLED RELEASE DRUGS

Many parameters of drug substances can affect the controlled release formulation design and drug absorption from the formulation. Many properties of drug substances, such as pH–solubility profile, pKa, permeability, particle size distribution (PSD), thermal properties, hygroscopicity, compactibility, and excipient compatibilities, can affect oral CR formulation design, processing, storage, and drug absorption. However, in the in vivo process of drug release to drug absorption, the major factors are drug solubility, permeability, and stability. Based on drug aqueous solubility and gastrointestinal permeability, drugs have been classified into four biopharmaceutical drug classes [56].

1.2.1 Aqueous Solubility  
For Biopharmaceutical Classification System (BCS) Class II drugs with poor water solubility but good permeability, the absorption of a drug is often limited by dissolution rate. If a drug’s solubility is lower than 0.1 mg/mL, the drug is not a suitable candidate for diffusion-controlled formulation, but still feasible using other approaches such as dissolution-controlled or osmosis-based systems [57, 58]. Furthermore, drugs with solubility less than 0.01 mg/mL show dissolution-limited bioavailability, and thus have inherent controlled release property.

For drugs with high solubility, it is also pretty challenging to design controlled release formulations with high drug loading like more than 80% using the matrix dissolution system. Because the drug diffusion force from the high drug concentration in the matrix system will be strong, it will be
difficult for the minimal amount of polymer to control the diffusion process. However, with new technology such as hot-melt extrusion, the drug loading can be significantly increased to even higher than 90%. Furthermore, BCS Class III drugs with high solubility but poor permeability are even more difficult to deliver in controlled release dosage forms. For those poorly permeable drugs, the drug absorption is controlled by the cellular absorption of the drug rather than the release from the dosage form, but localized high drug concentration can still benefit drug absorption.

Drugs with pH-dependent solubility can present difficulties in the drug delivery. Table 1.1 shows different pH values at different segments of the GI tract. One frequent challenge in developing poorly water-soluble free-base drug is that the free-base drug can dissolve to a greater extent in stomach due to acidic environment, but may precipitate out in the small intestine due to high pH; however, the maximum adsorption may occur in the small intestine. For some water-insoluble free-base drug compounds, when comparing the AUC (area under drug plasma concentration curve) of different CR formulations with different release profiles, sometimes the AUC of slow release can be higher than the AUC of fast release, which may be due to the precipitation of drug in the intestine, that is, neutral pH environment.

1.2.2 Permeability

For absorption to occur from the GI tract, drug molecules have to penetrate through the cellular membranes. The total drug absorption can be described as [56]

\[
\text{Mass}(t) = \frac{t}{0} \int PwCw \ dA \ dt
\]

where Mass is the total mass of drug absorbed, \( P \) and \( C \) are the permeability and drug concentration at certain time and location, respectively, and \( A \) is the adsorption surface area. Drug permeability can be affected by many factors, such as the location of the GI tract, drug concentration in the case of carrier-mediated transport, and so on. Considering the three major processes of drug absorption, transit flow, dissolution, and permeation, Lawrence Yu proposed an integrated absorption model to estimate the fraction of dose absorbed and to determine the causes of poor oral drug absorption [59].

To have desired bioavailability for the poorly permeable drugs, the equation shows the importance of localized high drug concentration, as well as the transit time of a drug in different segments of the GI tract. All these factors affect the absorption of poorly permeable drugs much more significantly than drugs with high permeability. The permeability and transit time of a drug can be affected by many factors, such as food, interpersonal variance, formulation design, and so on, and all these variables make establishing IVIVC very difficult for poorly permeable drugs in oral controlled release formulations.

Uncharged form of a drug is preferentially absorbed through the cellular membrane. For charged form, the pH value of the environment, shown in Table 1.1, can affect the drug absorption significantly. If polymer membranes are used in oral controlled release formulations, the drug diffusion through polymer membranes can also be affected by environment pH based on the drug’s pK_a.

1.2.3 Physicochemical Stability

The drugs unstable in acidic environment cannot be delivered in the stomach, and enteric coating has been widely used to release drugs in neutral small intestine environment. Drugs that are degraded in the GI tract may undergo more degradation when slowly released in stomach from the controlled release formulations.

Similar to immediate release formulations, both physical and chemical stability of drug substances are very important in formulation design, process development, and storage. The forced degradation studies of drug substances can check the drug stability under heating, acidic, basic, oxidative, and lighting (both UV and visible light) environment, which are very useful information in formulation design. Furthermore, excipient compatibility studies are commonly used to select suitable excipients. In process development, whether drug substances are moisture sensitive will be critical in wet granulation, and whether drug substances are heat sensitive will be critical in hot-melt extrusion granulation, and so on. For those drugs that have different crystal forms such as hydrous/anhydrous and polymorphisms (especially enantiotropic polymorphisms), the potential crystal form transformation during processing and storage has to be taken into careful consideration.

1.3 OPTIMAL FORMULATION AND PROCESS SELECTION FOR CONTROLLED RELEASE DRUGS

1.3.1 Controlled Release Formulation Mechanisms and Related Approaches

Although there are hundreds of commercial products based on controlled release technologies, there are only a few distinct mechanisms in controlled drug release. Oral controlled release formulations are designed mainly based on physical mechanisms, rather than chemical degradation, enzymatic degradation, and prodrug approach. Table 1.2 lists the types of controlled drug release mechanisms commonly used in oral controlled release formulations. All controlled release formulations are designed based on one or combination of a few mechanisms.
### 1.3.1.1 Dissolution-Controlled Formulations

In the encapsulated dissolution system (reservoir system), the drug release is determined by the thickness and the dissolution rate of the polymer membrane surrounding the drug core. Once the coated polymer membrane dissolves, all the drug will release like immediate release formulation. In general, small beads are designed based on this approach. Tablets are not preferred due to potential dose dumping if the tablet coating is broken. By adjusting membrane thickness on small beads, desired release profile can be achieved. The coated drug beads can be either compressed into tablets or filled into capsules.

In the matrix dissolution system, the most commonly used system in pharmaceutical industry, drug is homogeneously distributed throughout the polymer matrix. As the polymer matrix dissolves, drug molecules are released, also called “erosion controlled release.” Actually, for both encapsulated dissolution system (reservoir system) and matrix dissolution system, drugs may release through diffusion mechanism as well based on the properties of drugs and polymers. In the matrix dissolution system, since the size of the matrix decreases as more drug is released, the amount of drug released is also decreased, that is, resulting in a nonzero-order release.

### 1.3.1.2 Diffusion-Controlled Formulations

In diffusion-controlled formulations, drug molecules have to diffuse through a polymer membrane [60] or a polymer matrix to be released. Diffusion-controlled formulations can be divided into reservoir and monolithic systems, depending on whether a drug is surrounded by a polymer membrane or distributed through the polymer matrix. Different diffusion-controlled reservoir systems have been shown in Figure 1.2. In nonporous reservoir systems, drug molecules have to diffuse through the polymer membrane, but in microporous reservoir systems, drug molecules are released by diffusion through micropores that are usually filled with either water or oil.

In addition to nonporous and microporous systems, diffusion-controlled monolithic systems can be further classified based on the concentration of loaded drug. The monolithic system is called monolithic solution if a drug is loaded by soaking a polymer matrix in a drug solution, in which the drug concentration inside the matrix cannot be higher than the drug solubility, if the partition coefficient of a drug is 1. If the drug loading is higher than the drug solubility, shown as black dots in Figure 1.3, the monolithic system is called monolithic dispersion.

### 1.3.1.3 Osmosis-Based Formulations

Osmosis, the natural movement of water into a solution through a semipermeable membrane, has been used in the development of zero-order release drug delivery systems. Not solutes, only water can diffuse through the semipermeable membrane. For different polymer membranes, their water vapor transmission

### Table 1.2 Controlled Drug Release Mechanisms and Related Formulation

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Related Formulation Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution</td>
<td>Encapsulated dissolution system (reservoir system), Matrix dissolution system</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Ion exchange</td>
</tr>
</tbody>
</table>

FIGURE 1.2 Diffusion-controlled reservoir systems.

FIGURE 1.3 Diffusion-controlled monolithic systems.
value can differ widely, and selection of a semipermeable membrane depends on the nature of the application. Overall, the release rate in osmosis-based systems depends on osmotic pressure of release medium.

In the development of osmosis-based controlled release formulations, cellulose acetate has been used most frequently [61–63]. Alza Corporation developed two different types of osmotic devices, known as OROS® osmotic therapeutic systems, as shown in Figure 1.4. Both OROS® osmotic systems can deliver drugs at continuously controlled rate for up to 24 h, independent of GI environment. However, the manufacturing processes for both OROS® osmotic systems are pretty complex. Compared to basic osmotic systems that can deliver only water-soluble drugs, “push–pull” osmotic systems can deliver water-insoluble drugs as well [64, 65].

Both the original Alza patents have expired, and many new approaches have been developed so far, such as modifying formulation compositions, alternate membrane coating, and so on [66]. For insoluble drugs such as nifedipine, EnSoTrol system of Shire Laboratories contains a nonswelling solubilizing agent that enhances the solubility of insoluble drugs and a nonswelling wicking agent dispersed throughout the composition that enhances the surface area contact of the drug substances with the incoming aqueous liquid [67, 68]. The single composition osmotic tablet (SCOT®) of Andrx can deliver insoluble drugs as well [69, 70]. In the SCOT®, osmosis leads to swelling and disruption of coating; after membrane disruption, core matrix erodes and releases drug at controlled rate. In the swellable core technology of Pfizer, two model drugs, tenidap and sildenafil, have been released at similar rate despite significant differences in their physicochemical properties [71, 72]. For alternate membrane coatings, there are several unique approaches such as asymmetric membrane coating of Pfizer [73] and Merck osmotic delivery system [74].

1.3.1.4 Ion Exchange-Based Formulations

Ion exchange-controlled release systems use ion-exchange resins that are water-insoluble polymeric materials containing ionic groups [75]. Drug molecules can attach onto the ionic groups with opposite charge through electrostatic interaction. Thus, the drug molecules can be replaced with other ions with the same charge and released from the ion-exchange resin, as shown in Figure 1.5. The drug release from ion-exchange systems depends on replacement of the drug molecules by other electrolytes. To have a more predictable drug release, the ion-exchange resins can be coated with water-insoluble polymers such as ethylcellulose (EC) to provide diffusion-controlled drug release. Overall, the rate of drug release depends on the area of diffusion (i.e., surface area of resin particles), cross-linking density, ionic strength (i.e., concentration of replacing ions such as Na⁺ or K⁺ for cationic drugs and Cl⁻ for anionic drugs), and coating of the drug–resin complex.

There are a few advantages of the ion exchange-controlled systems. First, they are convenient to adjust individual dose especially for pediatrics and geriatrics. Second, the GI tract irritation is substantially reduced due to the slow release in

![FIGURE 1.4](image-url)  
**FIGURE 1.4** Brief description of Alza’s two OROS® osmotic therapeutic systems: (a) basic osmotic pump; (b) push–pull OROS® system.

![FIGURE 1.5](image-url)  
**FIGURE 1.5** Ion exchange-controlled systems.
small quantities. They can effectively provide taste abatement because all drug molecules are initially bound to polymer chains. Suspension of ion-exchange resins was first developed by Pennwalt Pharmaceutical Company, and the system is called the Pennkinetic system [76, 77]. One of the Pennkinetic systems that is commercially available is Delsym® in which poly(styrene sulfonic acid) resins loaded with dextromethorphan are coated with ethylcellulose for delivery up to 12 h. Corsym® delivers codeine and chlorpheniramine. Nowadays, ion-exchange approaches have not only proved to be safe and effective, but also attracted more and more attention considering their uniqueness [78–80].

1.3.2 Various Process Approaches

Based on the dissolution-, diffusion-, and osmosis-based controlled release formulation mechanisms, oral CR formulations can be roughly divided into three approaches: matrix tablets, multiparticulates, and osmotic tablets [81]. Even though many processes can be used in different formulation approaches, the preferred processes for different formulation approaches are different.

1.3.2.1 Processes for Matrix Tablets

Matrix tablets contain both hydrophilic CR systems [82] and lipophilic CR systems [83, 84]. The drug release from hydrophilic systems involves both diffusion and dissolution (i.e., matrix erosion), and from lipophilic systems is only under diffusion control. Most traditional processes such as dry blend (direct compression), roller compaction, wet granulation, fluid bed granulation, foam granulation [85, 86], and melt extrusion granulation can be used to make both types of matrix tablets. The process selection for matrix tablets is similar to the process selection for immediate release tablets. The major factors involved in process selection are drug loading, flowability, and compactibility. Both wet granulation and fluid bed granulation may not be optimal for moisture-sensitive drugs, and melt extrusion granulation may not be suitable for thermally unstable drugs. For different processes, the maximal drug loading may follow approximately in the order of melt extrusion granulation > wet granulation > roller compaction ≈ fluid bed granulation > direct compression.

1.3.2.2 Multiparticulates

Multiparticulate CR systems contain both drug layered beads and microspheres. Fluid bed coating, very useful in preparing various multiparticulate CR systems, uses three different spraying methods: top spray, bottom spray (Wurster process), and tangential spray. The top spray method is commonly used for fluid bed granulation, sometimes for particle coating as well. The bottom spray (Wurster) coating is the usual method in particle/bead coating. For the multiparticulate CR systems, Wurster coating is very useful in drug layering on nonpareils as well as functional coating. The tangential spray (rotary) method can achieve similar film quality as Wurster coating; however, it is more difficult to scale up.

In addition to fluid bed granulation, many other approaches have been used to prepare microspheres/beads, such as extrusion and spherization, hot-melt extrusion granulation, spray congealing, and roller compaction. Extrusion–spheronization is a usual pelletization process for making pellets that are amenable for both immediate and controlled release formulation preparation [87]. Calcium can induce alginate to form beads, which have been widely used in controlled release formulation design. The beads can be collected by filtering and drying, or one-step spray drying [88, 89].

1.3.2.3 Osmotic Tablets

Preparation of osmotic tablets can be roughly divided into three parts: drug layer and/or sweller layer, membrane(s), and microscopic hole(s) for drug release. For drug layer and sweller layer, traditional processes can be used to make granules similarly. For elementary osmotic pump, that is, only drug layer, monolayer tablets can be compressed easily. For the “pull–push” osmotic pump, that is, with both drug layer and sweller layer, drug layer and sweller layer need to be compressed into bilayer tablets. After membrane(s) has been coated onto the core tablets, holes for releasing drug from membrane are normally created by laser drilling. However, in Merck osmotic delivery system [74], high concentrations of porosigens inside cellulose acetate will generate holes for drug release.

1.3.3 Computer-Aided Design

Computer-aided design (CAD) uses mathematical and numerical techniques to study drug release kinetics. With the help of CAD, it is possible to save both cost and time in drug development, as well as create better quality products. In order to use CAD in oral CR formulation development, the approximate workflow is listed below [90–93]:

- Understand delivery systems and related drug release mechanisms.
- Build models and determine related parameters.
- Execute numerical analysis.
- Identify discrepancies, adjust model, and analyze results.
- Design formulation-based computer-aided design to achieve desired release profiles.

Many formulation and process factors can affect drug release, and among them, five formulation factors may be most critical in influencing release kinetics. They include drug and excipient’s properties, especially drug solubility, tablet shape and size (i.e., dimension), tablet surface area, drug loading, and coating (coating materials, coating thickness, etc.).
1.3.4 Scale-Up

After formulation and process has been determined, based on scientific understanding and collected process data, several DoEs (design of experiments) will be designed and executed to study the critical process parameters and their effective ranges. Nowadays, QbD (quality by design) becomes more and more important in developing robust manufacturing process to get qualified drug product. After DoEs, pilot size batches of plus and minus process set point conditions and/or set point conditions will be made to further understand process parameters to help scale up to commercial size manufacturing.

1.4 POLYMERS FOR CONTROLLED RELEASE FORMULATION DESIGN

1.4.1 Categories

Even though there are a lot of different synthetic polymers, not many have been used in pharmaceutical industry especially in oral CR formulation. Although biodegradable polymers such as poly(lactic acid) and poly(glycolic acid) are widely used in parenteral sustained release and implant drug release systems, they are not commonly used in oral CR formulations. Most common synthetic polymers used in oral CR formulation are poly(vinyl alcohol) (PVA), poly(acrylic acid), poly(ethylene oxide) (PEO), poloxamers, pluronics, and polymethacrylate. Poly(acrylic acid) and its derivatives are commonly used in enteric coating due to their insolubility at low pH. Carbopol is a high molecular weight cross-linked poly(acrylic acid) polymer [94]. Polymethacrylate and derivatives, main compositions of Eudragit®, are very commonly used for sustained release coating.

In pharmaceutical industry, much more natural polymers or their derivatives than synthetic polymers have been used in oral CR formulations. Among the three subclasses of natural polymers, proteins, polysaccharides, and nucleotides, only polysaccharides are widely used in oral CR formulations.

Cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), ethylcellulose, and methylcellulose (MC) are the most commonly used polymers in oral CR formulations [95, 96]. For each cellulose derivative, different grades can also have significantly different properties in terms of molecular weight, viscosity, solubility, hydration, and so on; thus, different grades can be used for different purposes. Besides cellulose derivatives, many polysaccharides especially dietary fibers have been used in drug development. Table 1.3 lists the commonly used natural polymers or their derivatives in oral CR formulations.

Different from the polymers used in dissolution-controlled release systems, the polymers in diffusion-controlled systems are generally water insoluble. Some commonly used polymers for diffusion-controlled systems (reservoir and monolithic systems) are cellulose (e.g., ethylcellulose), collagen, nylon, poly(alkyleneacrylate), polyethylene, poly(ethylene-co-vinylacetate), poly(hydroxyethyl methacrylate), poly(hydroxypropylethyl methacrylate), poly(methyl methacrylate), polyurethane, and silicon rubber.

1.4.2 Polymer Properties

For polymers used in oral CR formulations, there are several important properties that can influence formulation design especially drug release rate, as shown in Table 1.4. Besides drug release kinetics, polymer properties can also affect process development. For example, in melt extrusion granulation, polymer glass transition temperature \( T_g \) is very important because the process temperature in melt extrusion granulation falls between polymer \( T_g \) and melting temperature \( T_m \) of drug substance. Other polymer properties such as flowability, compactibility, and so on are also very important in process development. The effects of polymer properties on

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC</td>
<td>Used in matrix sustained release formulations</td>
</tr>
<tr>
<td>HPMC</td>
<td>Widely used in matrix sustained release formulations</td>
</tr>
<tr>
<td>EC</td>
<td>Insoluble in water. Widely used in coating for sustained release applications. Also used in matrix tablets for diffusion-controlled CR formulation, that is, lipophilic matrix</td>
</tr>
<tr>
<td>MC</td>
<td>Not as efficient as HPMC and HPC in slowing down drug release rate [97, 98]</td>
</tr>
<tr>
<td>Carboxymethylcellulose, Na</td>
<td>Sometimes used in matrix tablets together with HPMC [99, 100]</td>
</tr>
<tr>
<td>Alginate, Na</td>
<td>Besides thickening, gel-forming, and stabilizing properties, it can also easily gel in the presence of a divalent cation such as Ca(^{2+}) [101]</td>
</tr>
<tr>
<td>( \lambda )-Carrageenan</td>
<td>pH-dependent hydrogelation of chitosan matrixes [102]</td>
</tr>
<tr>
<td>Chitosan</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Xanthan gum</td>
<td></td>
</tr>
<tr>
<td>Starch (thermally modified)</td>
<td></td>
</tr>
</tbody>
</table>
oral CR formulation design and process development will be further discussed in a related chapter.

Plasticizer is a material that enhances the flexibility of the polymer with which it is mixed and reduces the $T_g$ of the mixture. Examples of plasticizers are glycerin, glyceryl triacetate (triacetin), poly(ethylene glycol) (PEG), and propylene glycol. Plasticizers are commonly used in film coating to help polymer(s) achieve desired film quality. Besides, since plasticizers reduce the stiffness of polymer molecules, they can increase the diffusion rate of drug molecules through the polymer matrix or polymer membrane. Except preparing amorphous drug products, the process temperature for melt granulation should be below drug melting temperature and above polymer $T_g$. Therefore, by reducing polymer $T_g$ through adding suitable plasticizer, the process temperature for melt granulation can be lowered.

### 1.5 PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

#### 1.5.1 PK/PD Principles

To design a controlled release drug product, besides disposition and absorption pharmacokinetic parameters, a complete understanding of the concentration–response relationship is also very important. Quantification of pharmacodynamics of a drug will enhance the development of a controlled release drug product and, importantly, should lead to faster regulatory approval.

The drug ADME (adsorption, distribution, metabolism, and elimination) process is a very complex process and can be affected by many factors such as physicochemical properties, physiologic constraints, and biochemical principles. To determine suitable dosage, the most useful PK parameter is total plasma clearance (CL). The CL is meaningful because of its relationship with dosing rate and plasma concentration at steady state ($C_{ss}$). For a zero-order input ($R_0$),

$$C_{ss} = \frac{R_0}{CL}$$

The above equation shows that the plasma concentration, which is important in achieving a desired effect and avoiding undesired toxicological effect, is mainly controlled by the drug input rate and the plasma clearance. Even though the equation is most routinely used for a constant i.v. infusion, it is still meaningful for oral controlled release formulations especially in the case of a zero-order release. For most drugs, the drug input rate is mainly controlled by the drug release rate.

The above equation is a very simplified scenario in which the drug is assumed to obey linear PK principles, that is, the clearance is constant and first-order elimination is observed at several doses. Considering the interpersonal variability, a range of input rates need be calculated to check whether there exist serious toxicities at upper range end of input rate. If the undesired toxicological effect does occur at relatively high input rate, the input rate should be adjusted toward lower end of the therapeutic range.

The drug plasma elimination half-life ($t_{1/2}$) is not directly needed for determining the input rate for a controlled release drug product. However, it will help evaluate the usefulness of a controlled release formulation. A compound with $t_{1/2}$ more than 12–24 h is considered a poor candidate for once-daily controlled release formulation. For a compound with $t_{1/2}$ relative short but not extremely short, its treatment can be improved by a controlled release formulation. For an immediate release formulation, the dosing interval is primarily determined by $t_{1/2}$. However, for a CR formulation, the dosing interval is more affected by the maximum drug input and the drug release rate.

Besides improving patient compliance, a controlled release formulation can help reduce undesired toxicological effects especially for drugs with narrow therapeutic window by reducing $C_{max}$ [103, 104]. Oral controlled release formulation can help maintain drug blood concentration within its therapeutic window for longer time and decrease the plasma concentration fluctuation.

#### 1.5.2 Dissolution Profiles and Testing Conditions for Target Dissolution Profiles

The in vitro release rate, that is, dissolution profile, for a dosage form, though not strictly a PK parameter, is clearly quite critical to the eventual regulatory approval and the effectiveness of the controlled release delivery system. From a PK perspective, this process is very important because in most scenarios it is the rate-determining step leading to drug in the plasma and at the active site. The drug release rate must be reproducible, and ideally be unaffected as much as
possible by physiologic factors, and, as a final result, provide the desired therapeutic plasma concentration.

Dissolution tests not only are useful in formulation design and quality assurance, but can also help to get biowaiver for scale-up, postapproval changes. For the fixed dosage combinations, after high strength formulations have achieved bioequivalence with free combination formulations, dissolution tests can help low strength formulations to eliminate the need for bioavailability studies, that is, biowaiver. Note that the drug release dissolution method may not always be the same as the biorelevant dissolution method. The biorelevant dissolution method can predict plasma concentration curves based on changes of dissolution profiles. Ideally, dissolution specifications should be set so that all formulations whose dissolution profiles fall within specifications are bioequivalent [105].

Dissolution specifications are usually established based on drug substance properties and dissolution profile evaluation. For oral CR formulations, their dissolution tests meet regulatory requirements if the quantities of drug substance released conform to the harmonized USP (711), or EuPharm 2.9.3 and JP 15 for EU and Japan, respectively. For oral CR formulations, dissolution apparatus can be USP Type I, II, IV, and VII, that is, rotating basket, rotating paddle, flow-through cell, and reciprocating holder. In dissolution medium selection, besides stability, sensitivity of assay, and so on, sink condition in which the final drug concentration is at least three times lower than a saturated concentration is needed.

Current USP dissolution tests exert minimal mechanical force on solid dosage forms, which is different from the reality in human gut that exerts about 1.5–1.9 N force on solid dosage forms [106–108]. In vivo, different from IR tablets, mechanical forces can obviously affect the dissolution process much more in sustained release matrix tablets [109]. A peristaltic dissolution test developed by Matthew Burke applied mechanical compression to simulate gastric contractions and peristalsis action in SR matrix formulations [110]. The test can be added to a USP Type II apparatus directly or utilized in established dissolution methods.

1.5.3 IVIVC

Like most drug substances, an adequate demonstration of the in vitro release profile should be established within appropriate limits for controlled release formulations. A reasonable release profile must match with the claims of the particular product. Furthermore, adequate in vivo studies should be conducted to show the capability of the release system in controlling the drug release, that is, an IVIVC needs to be established. There are many models that may be used to establish the IVIVC. However, for drugs with complex absorption scenarios such as drugs with low permeability or narrow GI adsorption window, it may be difficult and even not feasible to establish the IVIVC [111–113]. Besides, many scenarios such as enter hepatic cycle, poor permeability, and so on make IVIVC very difficult. For drugs dissolving rapidly but with low permeability, no IVIVC may be expected [56].

However, there are still many reports of successfully establishing IVIVC for oral CR formulations [114, 115]. For example, Dutta et al. established an internally and externally validated level IVIVC model during the development of a once-daily extended release (ER) tablet of divalproex sodium, using multiple formulations with varying release rates. The in vivo absorption–time profile was inferred by deconvoluting of the PK profile against the unit disposition function (UDF). In the established IVIVC model, in vivo absorption was expressed as a function of in vitro drug dissolution profile. Therefore, plasma profiles of the extended release formulations could be established by convoluting in vitro drug release profiles with the UDF.

1.5.4 Others

Besides dissolution, visualization is also a good tool to evaluate oral CR formulations in human. There are several visualization tools currently available:

1. Wireless M2A Capsule Camera first designed by Given Imaging Inc. As the capsule travels through the GI tract, while light-emitting diodes flash the gastrointestinal tract, the microchip camera can capture thousands of images and send to a data recorder [116].

2. Gamma scintigraphy is a technique in which a short-lived radioactive isotope is incorporated into a dosage form, and the location of the dosage form in the GI tract can be noninvasively imaged with a gamma camera. Therefore, the observed transit of the dosage form can be correlated with the rate and extent of in vivo drug absorption [117] (http://www.scintipharma.com/html/what_is_gamma_scintigraphy_.htm).

3. Single photon emission computed tomography (SPECT) can be used together with any gamma imaging study, if a three-dimensional image is needed.

4. Magnetic resonance imaging (MRI), similar to gamma scintigraphy, also offers a powerful noninvasive method for picturing events inside controlled release dosage forms. It can keep track of drug release processes such as hydration, diffusion, and so on and help understand drug release mechanisms. Furthermore, the unique information collected from MRI studies may help in problem solving and formulation development [118].

1.6 NONCONVENTIONAL ORAL CONTROLLED DELIVERY SYSTEMS

Oral route is the most convenient and preferred route of administration. Besides sustained release formulations, there
are several site-specific oral delivery systems, such as gastric retention devices, buccal controlled release formulations, and so on. For those drugs that may degrade in acidic environment, enteric coating can prevent drug release at low pH of the stomach and release drug at neutral environment of the small intestine. Overall, the drug absorption rates are best maintained by a delivery device that releases the drug at its optimum absorption sites.

### 1.6.1 Gastric Retention Devices

Because most drugs are absorbed in the upper small intestine, the absorption of the drugs will be improved if the oral controlled release dosage forms are maintained in the stomach. For drugs with a "window of absorption," gastric retention devices will be even more critical to achieve desired bioavailability (Table 1.5). As long as a drug is stable in acidic environment, using gastric retention devices, drugs can be delivered for longer period of time in the stomach than the conventional dosage forms. The approaches that have been used to achieve long-term gastric retention are listed in Table 1.6. The same topic is described in more depth in Chapter 12.

#### Table 1.5 Devices Used a Platform for Gastric Retention [119, 120]

<table>
<thead>
<tr>
<th>Device</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intragastric floating systems (low density)</td>
<td>To make the dosage forms with density less than 1, so that they can float on top of the gastric fluid [121, 122]</td>
</tr>
<tr>
<td>High-density systems</td>
<td>Increasing the density of the dosage forms from 1.0 to certain higher values can increase the average GI transit time [123, 124]</td>
</tr>
<tr>
<td>Mucoadhesive systems</td>
<td>Coating the dosage forms with mucoadhesive polymers such as poly(acrylic acid) that can adhere to the mucus layer of the gastric tissue [125–127]</td>
</tr>
<tr>
<td>Unfoldable, extendible, or swellable systems</td>
<td>Gastric retention by large dimension and rigidity can be used to improve bioavailability for drugs with narrow absorption window. By unfolding multilayer polymeric films, the extended absorption phase (&gt;48 h) of riboflavin administered in a gastroretentive dosage form (GRDF) led to four fold increased bioavailability in dogs [128]. Cargill et al. reported that large single-unit dosage form with devices of different shapes could prolong gastric retention in dogs, and among them, tetrahedrons and rings are most efficient [129, 130]. InTec Pharma developed Accordion Pill™ platform using expanding geometries [131]</td>
</tr>
<tr>
<td>Superporous biodegradable hydrogel systems</td>
<td>The swelling of superporous biodegradable hydrogels can be very fast, with ratio over 1000. However, the traditional superporous hydrogels may not be strong enough to withstand gastric contraction. With IPN (interpenetrating network) with polyacrylonitrile, the mechanical properties of superporous hydrogels have been improved up to 50 times, and thus could be used to develop gastric retention devices for long-term oral drug delivery [132–135]</td>
</tr>
</tbody>
</table>

#### Table 1.6 Commercial Technologies for Gastric Retention Delivery Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superporous hydrogel systems</td>
<td>Kos Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Gastric retention system</td>
<td>DepoMed</td>
</tr>
<tr>
<td>West gastroretentive system</td>
<td>West Pharmaceutical Services</td>
</tr>
<tr>
<td>OraSert™, OraSite®</td>
<td>KV Pharmaceutical</td>
</tr>
</tbody>
</table>

### 1.6.2 Colon-Specific Delivery Systems

To design a successful colon-specific drug delivery system for a drug, before the drug reaches the colon, it needs to be protected from degradation and release in the upper GI tract. Of course, the system needs to release the drug at the colon that has close to neutral pH [136]. Colon-specific drug delivery is critical for drugs intended for localized treatment, mainly inflammatory bowel diseases, irritable bowel syndrome, and colon cancer, or for drugs like proteins and peptides exhibiting maximal systemic absorption from the colon.

Several approaches have been generally used in designing colon-specific delivery systems [137–140], and they include pH-modulated/enteric systems [141], time-controlled (or time-dependent) systems, microbially controlled systems, and luminal pressure-controlled systems. Among these approaches, formulations that release drugs in response to colonic pH, enterobacteria, or time are most widespread formulation technologies. In microbially controlled systems, prodrugs and biodegradable polymers will be degraded by colon-specific enzymes. In time-controlled systems, drug release has to be delayed at least 5 h to reach the colon. Many factors make the development of colon-specific drug delivery systems very challenging, such as extreme pH conditions, gastric enzymes, diet, varying transit time in the GI tract, disease, and so on. For the pH-dependent systems, the drug may be prematurely released in lower small intestine (pH 7.5).

Based on the pH-dependent approach, Procter & Gamble developed Asacol® (mesalamine) delayed release tablets, in
which the pH-sensitive polymer coating on tablets is designed to release drug at pH > 7 in the terminal ileum and beyond, that is, to the colon (http://www.asacol.com/ulcerative-colitis-treatment/asacol.jsp) [142]. Based on programmed intervals, PORT systems can deliver multiple doses and/or drugs and achieve colon-specific drug delivery based on timing [137].

CODESTM of Yamanouchi Pharmaceutical Co., Ltd. (now part of Astellas Pharma Inc.) is a colon-specific drug delivery system based on enzyme degradation. The drug core is prevented from degradation or drug release prior to the colon by first an enteric coating and then a cationic polymer coating for passage through the small intestine to the cecum. Note that a saccharide, lactulose, which will be degraded to organic acids when exposed to the enteric bacteria in a lower gastrointestinal tract, is included in the drug core formulation. pH changes in the large intestine trigger erosion of the cationic polymer, and lactulose diffuses through the cationic polymer and is degraded by cecal microflora. Organic acids produced by the microflora dissolve the cationic polymer and cause the drug to be released colon specifically [143]. In another oral controlled absorption system (OCASSTM) of Yamanouchi, the coating gels rapidly and hydrates completely in the upper gastrointestinal tract, thus enabling the gradual drug release as the tablet system travels throughout the GI tract, including the colon where water is poorly available and the drug release is difficult to achieve. The hydrophilic gel-forming polymer matrix tablets of OCASSTM prevent degradation of drug prior to intestinal delivery and also allow the formulation of single daily doses and ensure stable drug release by minimizing the effects of individual differences and food consumption on drug absorption. Omnic-OCAS™ was developed by applying OCAS™ technology to tamsulosin for the treatment of functional symptoms of benign prostatic hyperplasia [144–146].

### 1.6.3 Buccal Controlled Release Dosage Forms

There are several main advantages of buccal delivery [147–149]. Barrier property of buccal membrane is much reduced compared to the skin, and extensive presystemic clearance occurring for some drugs after oral administration can be avoided. Also, it allows faster onset of drug action and is highly useful for a short duration ranging from a few minutes to several hours. These properties result in improved patient compliance, ease of dosage form removal in emergencies, robustness, and good accessibility.

The limitations and disadvantages in buccal drug delivery are limited surface area for absorption, concerns on taste and comfort in a highly innervated area, difficulties of adhesion to a mucosal surface for extended periods without the danger of swallowing or choking of a device, potential bacterial growth, and blockage of salivary glands associated with prolonged occlusion.

<table>
<thead>
<tr>
<th>Table 1.7 Commercial Fast-Dissolving Tablet Brands</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
</tr>
<tr>
<td>Freeze drying</td>
</tr>
<tr>
<td>Direct compression</td>
</tr>
<tr>
<td>Granulation and compression</td>
</tr>
<tr>
<td>Molding/cotton-candy process</td>
</tr>
</tbody>
</table>

Carbopol, a synthetic high molecular weight cross-linked water-soluble poly(acrylic acid), is commonly used as a bioadhesive in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications [150–152]. Other polymers such as karaya gum, xanthan gum, and glycol chitosan also have strong adhesion to the mucosal membrane; however, concentrations greater than 50% (w/w) are needed for them to produce sustained drug release [153].

### 1.6.4 Fast-Dissolving Tablets

Fast-dissolving tablets are designed to take orally without water and without swallowing; therefore, they are very useful for patients with swallowing problem, and also during outside activities when there is no access to water [154–156]. In general, these tablets can disintegrate within 10–30 s. There are four technologies used in preparing fast-dissolving tablets, and each one has its advantages and disadvantages, which will be elaborated in a separate chapter in this book. Table 1.7 lists some commercial fast-dissolving products and their manufacturing technologies [154–156].

### 1.7 REGULATORY AND LEGAL ASPECTS OF CONTROLLED RELEASE

#### 1.7.1 Applicable Guidelines and Acceptance Criteria

If a controlled release formulation is used for new chemical entity, the NDA filing will include the related information on oral controlled release formulations. However, if a controlled release formulation is used for an existing drug, a new drug application is required for approval. Of course, for an existing drug, data would be available to support any preclinical information as to what the drug would do and its safety.
However, if more dosage is used than previously approved dosage form, a safety level especially toxicity needs to be established. Overall, drug in a new controlled release formulation needs to demonstrate its safety and effectiveness before a new drug application can be filed. In general, time to review and approve the NDA will be shorter than the original NDA for the new chemical entity.

### 1.7.2 Patent Protection of Controlled Release Products

With regard to oral CR formulations, besides formulation compositions, some useful related information have been included to provide more patent protection [157]:

1. **Formulation**: type of preparation, excipients, *in vitro* drug release profile, chemical and physical stability, scale-up, and new processes for preparation of drug substance or formulation.

2. **In Vivo Performance**: PK/PD information, such as $T_{max}$, $C_{max}$, AUC (area under curve), efficacy, and side effects.

3. **Others**: controlled release profiles, enteric coating, fast-dissolving tablets, multiphase releases, and so on.

Considering the complex scenarios for patent protection for oral CR formulations, it is always valuable to plan early, discuss with patent attorney early, and file all necessary patents as early as possible. Besides orange book, it is also helpful to review all related patents and exclusivities.

### 1.7.3 Generic Versus Innovator Products

Even though brand drug companies face huge pressure from generic companies, controlled release formulation design is still a very useful tool in extending the life cycle for some drugs. For example, even though the drug substance of Ambien CR™ (Sanofi-Aventis), zolpidem tartrate, already lost patent protection, Ambien CR™ still garners sizeable revenue for the brand company. Developing a new oral CR formulation for an existing drug can extend drug life cycle through two aspects, exclusivity from regulatory agencies and formulation patent(s). Utilizing novel drug delivery technologies can substantially increase the overall efficacy of the drug and convenience and compliance by the patients. Such benefit should maintain the advantages of the innovator products even after their patent protections have expired.

**REFERENCES**


REFERENCES


REFERENCES

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