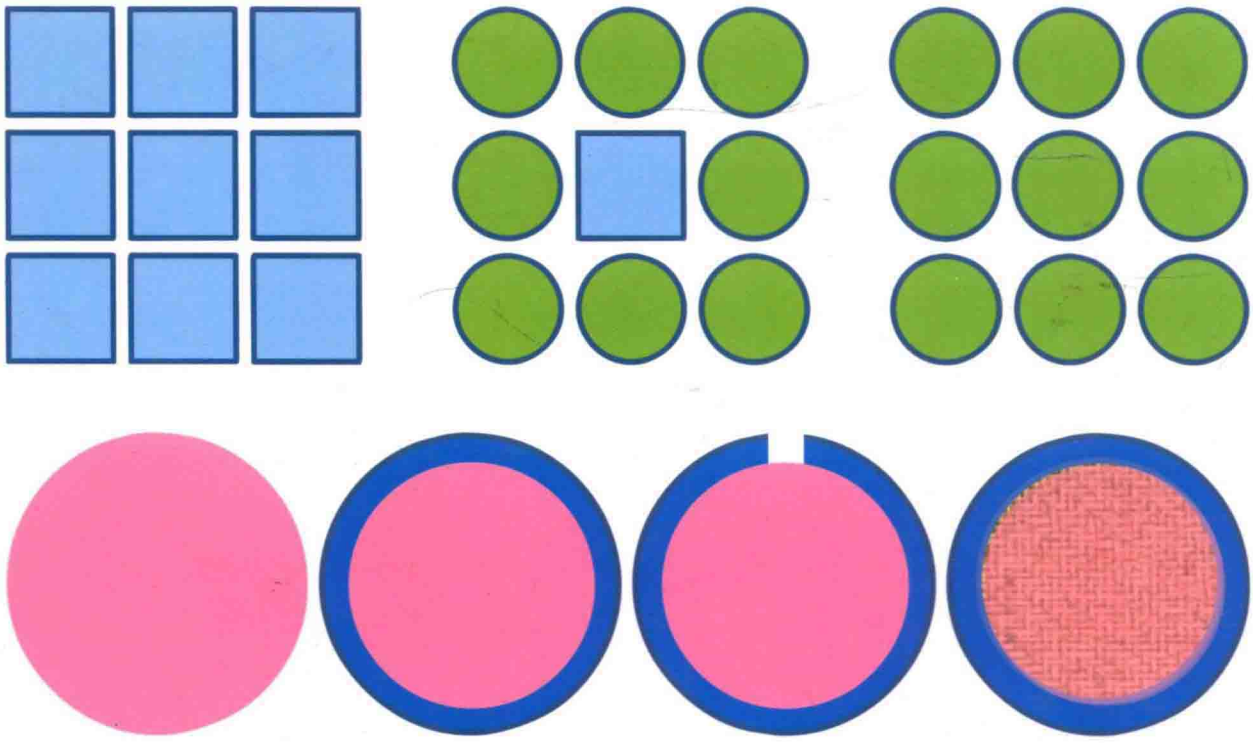
Oral Controlled Release Formulation Design and Drug Delivery

Theory to Practice

Edited by

Hong Wen and Kinam Park



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WILEY
A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Oral controlled release formulation design and drug delivery : theory to practice / edited by Hong Wen, Kinam Park.
p. cm.
Includes bibliographical references and index.
Summary: "This book describes the theories, applications, and challenges for different oral controlled release formulations. This book differs from most in its focus on oral controlled release formulation design and process development. It also covers the related areas like preformulation, biopharmaceutics, in vitro-in vivo correlations (IVIVC), quality by design (QbD), and regulatory issues"–Provided by publisher.
ISBN 978-0-470-25317-5 (cloth)
1. Drugs–Controlled release. 2. Oral medication. I. Wen, Hong, 1967- II. Park, Kinam.
[DNLM: 1. Delayed-Action Preparations. 2. Administration, Oral. 3. Drug Design. QV 785 O6248 2010]
RS201.C64O725 2010
615'.6–dc22

2010013930

Printed in Singapore

10 9 8 7 6 5 4 3 2 1

ORAL CONTROLLED RELEASE FORMULATION DESIGN AND DRUG DELIVERY

PREFACE

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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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., β-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

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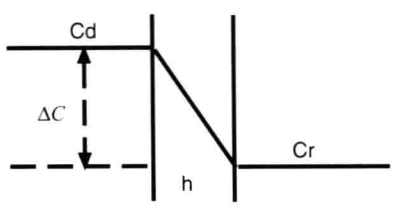
also beneficial for the study of pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug [26, 27].

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 (ΔC) between drug donor (C_d) and receptor (C_r), that is, between drug dosage surface and bulk medium.



Fick's first law states that

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

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 cm^2/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.

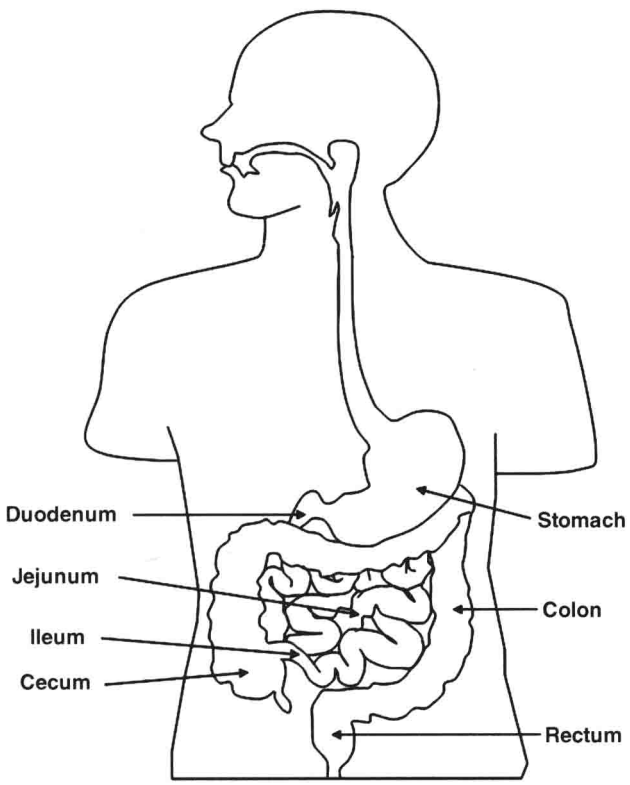


FIGURE 1.1 Upper and lower gastrointestinal tract.

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].

TABLE 1.1 The pH Values and the Transit Time at Different Segments of the Human GI Tract [37–41]

	Fasting Condition		Fed Condition	
Anatomical Site	pH	Transit Time (h)	pH	Transit Time (h)
Stomach	1–3.5	0.25	4.3–5.4	1
Duodenum	5–7	0.26	5.4	0.26
Jejunum	6–7	1.7	5.4–6	1.7
Ileum	6.6–7.4	1.3	6.6–7.4	1.3
Cecum	6.4	4.5	6.4	4.5
Colon	6.8	13.5	6.8	13.5

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 coat 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 gastroretentive 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, pK_a, 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]

$$\text{Mass}(t) = \int_0^t \iint_A PwCw \, \mathrm{d}A \, \mathrm{d}t$$

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.

TABLE 1.2 Controlled Drug Release Mechanisms and Related Formulation

Mechanism	Related Formulation Approach
Dissolution	Encapsulated dissolution system (reservoir system) Matrix dissolution system
Diffusion	Reservoir system 1. Nonporous membrane reservoir 2. Microporous membrane reservoir Monolithic device 1. Nonporous matrix a. Monolithic solution b. Monolithic dispersion 2. Microporous matrix a. Monolithic solution b. Monolithic dispersion
Osmotic	
Ion exchange	

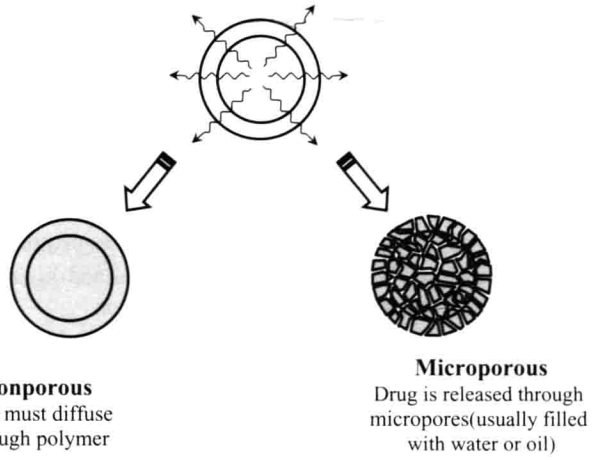


FIGURE 1.2 Diffusion-controlled reservoir systems.

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

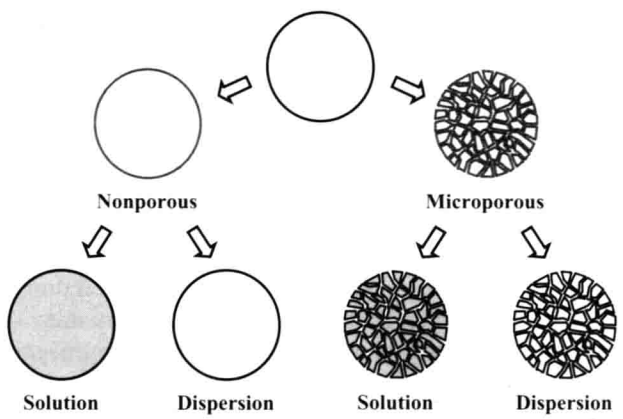


FIGURE 1.3 Diffusion-controlled monolithic systems.

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

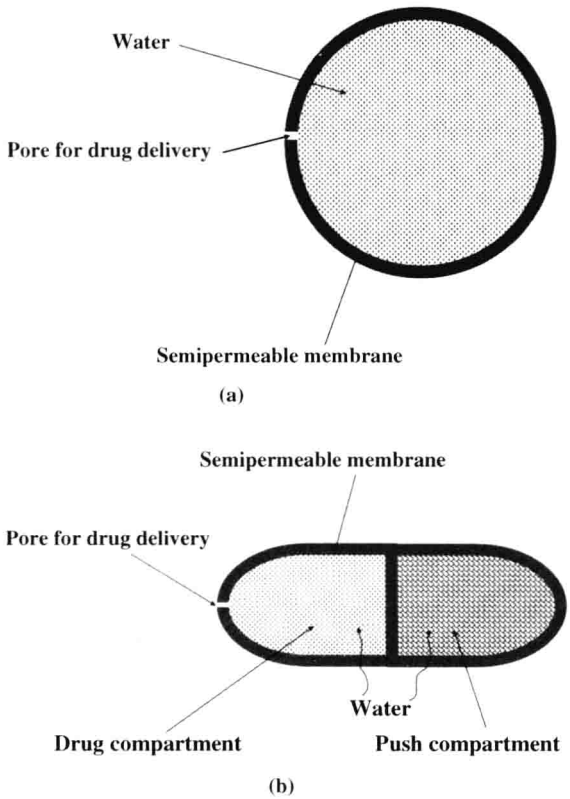


FIGURE 1.4 Brief description of Alza's two OROS® osmotic therapeutic systems: (a) basic osmotic pump; (b) push–pull OROS® system.

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

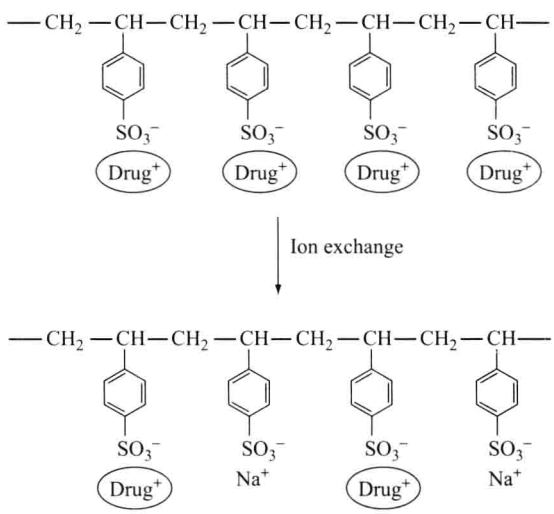


FIGURE 1.5 Ion exchange-controlled systems.

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 spheronization, 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.).