ORAL CONTROLLED RELEASE FORMULATION DESIGN AND DRUG DELIVERY

Theory to Practice

Edited by

HONG WEN
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey, USA

KINAM PARK
Purdue University
West Lafayette, Indiana, USA

WILEY
A JOHN WILEY & SONS, INC., PUBLICATION

ORAL CONTROLLED RELEASE FORMULATION DESIGN AND DRUG DELIVERY

ORAL CONTROLLED RELEASE FORMULATION DESIGN AND DRUG DELIVERY

Theory to Practice

Edited by

HONG WEN
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey, USA

KINAM PARK
Purdue University
West Lafayette, Indiana, USA

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

CONTENTS

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.

HONG WEN
Kinam Park

CONTRIBUTORS

Salah U. Ahmed, Abon Pharmaceuticals, Northvale, NJ, USA

Xiaoming Chen, Pharmaceutical Operations, OSI Pharmaceuticals, Cedar Knolls, NJ, USA

Nipun Davar, Transcept Pharmaceuticals, Inc., Point Richmond, CA, USA

Wendy Dulin, Pharmaceutical Development, Wyeth Research, Pearl River, NJ, USA

Linda A. Felton, College of Pharmacy, University of New Mexico, Albuquerque, NM, USA

Sangita Ghosh, Transcept Pharmaceuticals, Inc., Point Richmond, CA, USA

Michele (Xuemei) Guo, Analytical and Quality Sciences, Wyeth Research, Pearl River, NJ, USA

Bhaskara Jasti, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA, USA

Seong Hoon Jeong, College of Pharmacy, Pusan National University, Busan, South Korea

Joseph Kam, Faculty of Medicine, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel

Gemma Keegan, Vectura Group plc, Chippenham, Wiltshire, UK

Mansoor A. Khan, Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA

Mannching Sherry Ku, Pharmaceutical Development, Wyeth Research, Pearl River, NJ, USA

Jaehwi Lee, College of Pharmacy, Chung-Ang University, Seoul, South Korea

Ping I. Lee, Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Jian-Xin Li, Evonik Degussa Corporation, Piscataway, NJ, USA

Xiaoling Li, Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA, USA

Ravichandran Mahalingam, Formurex, Inc., Stockton, CA, USA

Mirela Nadler Milabuer, Faculty of Medicine, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel

Venkatesh Naini, Teva Pharmaceuticals, Pomona, NY, USA

Ali Nokhodchi, Medway School of Pharmacy, Universities of Kent and Greenwich, Kent, UK

Hossein Omidian, Department of Pharmaceutical Sciences, Health Professions Division, Nova Southeastern University, Fort Lauderdale, FL, USA

Kinam Park, Departments of Biomedical Engineering and Pharmaceutics, Purdue University School of Pharmacy, West Lafayette, IN, USA

Zhihui Qiu, Pharmaceutical Development Unit, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Ali Rajabi-Siahboomi, Colorcon Ltd., West Point, PA, USA

Abraham Rubinstein, Faculty of Medicine, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel

Rakhi B. Shah, Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA

Sheri L. Shamblin, Pfizer Global Research & Development, Groton, CT, USA

Yan Shen, Department of Pharmaceutics, School of Pharmacy, China Pharmaceutical University, Nanjing, China

Stephen P. Simmons, Pharmaceutical Development, Wyeth Research, Pearl River, NJ, USA

Shailesh K. Singh, Pharmaceutical Development, Wyeth Research, Pearl River, NJ, USA

John D. Smart, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, UK

Jean M. Surian, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA

Yue Teng, Pharmaceutical Development Unit, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Jiasheng Tu, Department of Pharmaceutics, School of Pharmacy, China Pharmaceutical University, Nanjing, China

Thirunellai. G. Venkateshwaran, Pharmaceutical Development, Wyeth Research, Pearl River, NJ, USA

Hong Wen, Pharmaceutical Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Xiaoguang Wen, WuXi AppTec Inc., Shanghai, China

Jong Soo Woo, College of Pharmacy, Yeungnam University, Gyongsan, Gyeongbuk, South Korea

Hua Zhang, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA

1

INTRODUCTION AND OVERVIEW OF ORAL CONTROLLED RELEASE FORMULATION DESIGN

HONG WEN

Pharmaceutical Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

KINAM PARK

Departments of Pharmaceutics & Biomedical Engineering, Purdue University School of Pharmacy, West Lafayette, IN, USA

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

Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, Edited by Hong Wen and Kinam Park

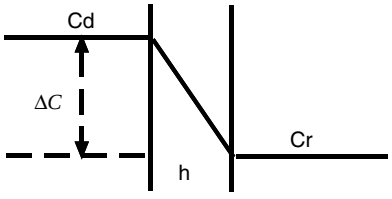
also beneficial for the study of pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug [26, 27].

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.

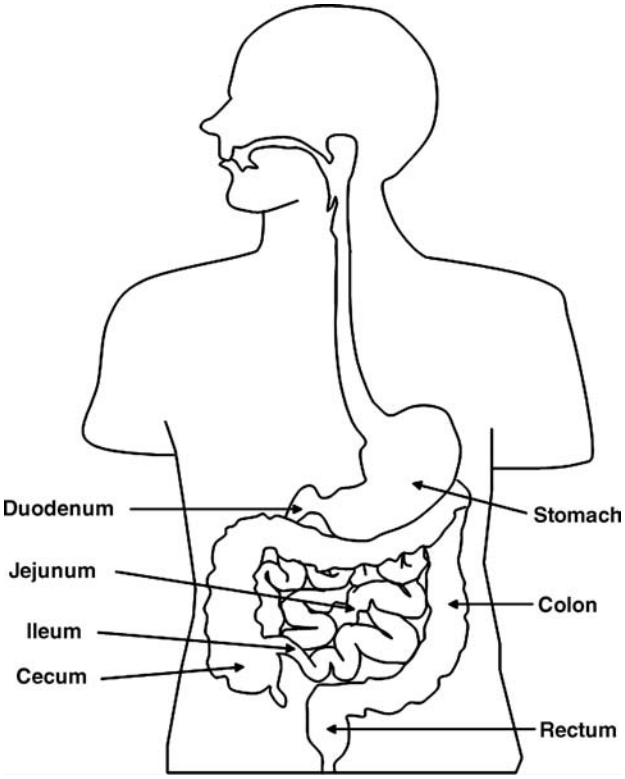


FIGURE 1.1 Upper and lower gastrointestinal tract.

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	

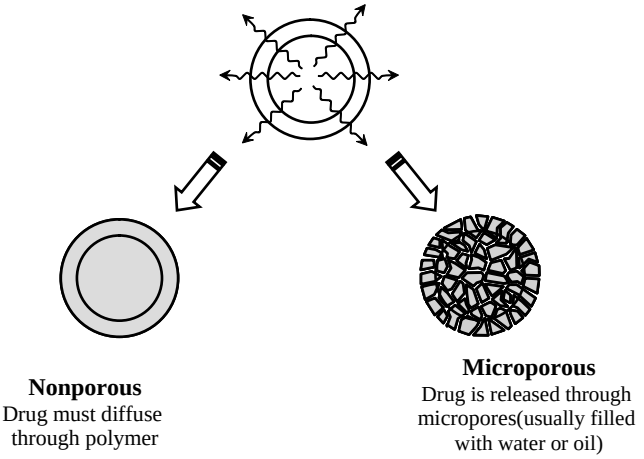


FIGURE 1.2 Diffusion-controlled reservoir systems.

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

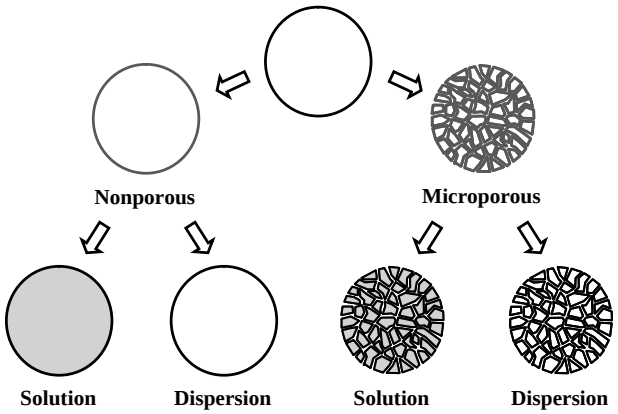


FIGURE 1.3 Diffusion-controlled monolithic systems.

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 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].

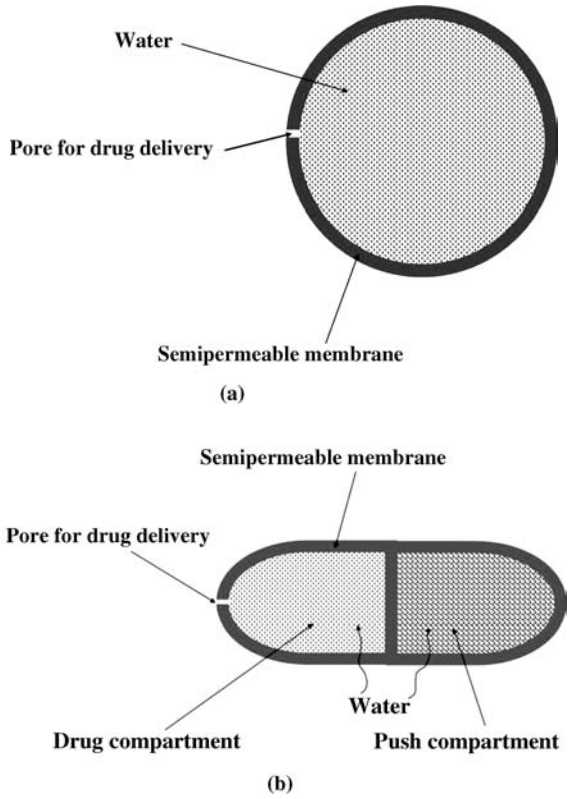


FIGURE 1.4 Brief description of Alza's two OROS® osmotic therapeutic systems: (a) basic osmotic pump; (b) push–pull OROS® system.

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

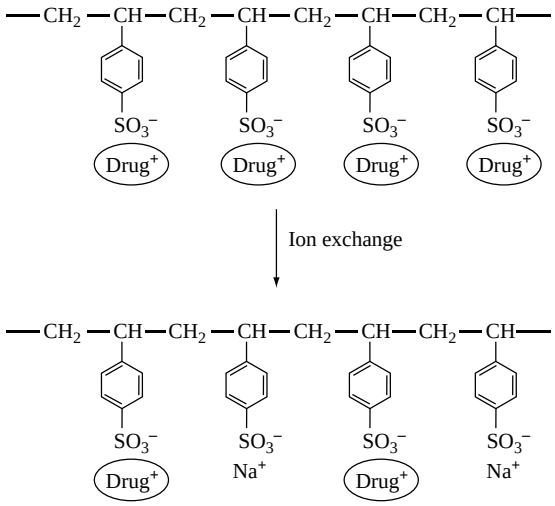


FIGURE 1.5 Ion exchange-controlled systems.

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 $\approx$ 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.).

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(alkylcyanoacrylate), 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 1.3 Common Natural Polymers and Derivatives Used in Oral CR Formulations

Polymer	Comment
HPC	Used in matrix sustained release formulations
HPMC	Widely used in matrix sustained release formulations
EC	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
MC	Not as efficient as HPMC and HPC in slowing down drug release rate [97, 98]
Carboxymethylcellulose, Na	Sometimes used in matrix tablets together with HPMC [99, 100]
Alginate, Na	Besides thickening, gel-forming, and stabilizing properties, it can also easily gel in the presence of a divalent cation such as Ca^{2+} [101]
λ-Carrageenan	
Chitosan	pH-dependent hydrogelation of chitosan matrixes [102]
Heparin	
Xanthan gum	
Starch (thermally modified)	

TABLE 1.4 Polymer Properties Versus Drug Release Mechanisms

Mechanism	Polymer Property
Dissolution	Polymers such as HPMC, soluble in water: molecular weight, viscosity, hydration speed, solubility in water, and so on
Diffusion	Lipophilic polymers, such as ethylcellulose, poly(methyl methacrylate), poly(hydroxyethyl methacrylate), insoluble in water: molecular weight, viscosity, lipophilicity, and so on that can affect drug diffusion through them
Osmosis	Semipermeable membranes such as cellulose acetate: water permeability through them
Ion exchange	Cross-linked resins

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 PHARMCOKINETIC 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),

$$C_{ss} = R_0/CL$$

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 the 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 adsorption 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

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

Device	Comment
Intragastric floating systems (low density)	To make the dosage forms with density less than 1, so that they can float on top of the gastric fluid [121, 122]
High-density systems	Increasing the density of the dosage forms from 1.0 to certain higher values can increase the average GI transit time [123, 124]
Mucoadhesive systems	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]
Unfoldable, extendible, or swellable systems	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 (>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]
Superporous biodegradable hydrogel systems	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]

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 1.6 Commercial Technologies for Gastric Retention Delivery Systems

System	Company
Superporous hydrogel systems	Kos Pharmaceuticals, Inc.
Gastric retention system	DepoMed
West gastroretentive system	West Pharmaceutical Services
OraSert™, OraSite®	KV Pharmaceutical

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].

CODES™ 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 (OCAS™) 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 OCAS™ 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 chocking of a device, potential bacterial growth, and blockage of salivary glands associated with prolonged occlusion.

TABLE 1.7 Commercial Fast-Dissolving Tablet Brands

Technology	Commercial Product
Freeze drying	Zydis® (Cardinal Health)
	Quicksolv® (Mediventure)
	Lyoc® (Lycos, Inc.)
	Pharmaburst™ (SPI Pharma)
Direct compression	DuraSolv®, OraSolv®, OraVescent® (Cima)
	Ziplets™, AdvaTab™ (Eurand)
	QDis™ (Phoqus)
Granulation and compression	WOWTAB® (Yamanouchi)
	Flashtab® (Ethypharm)
	Frosta® (Akina)
	Shear Form (Fuisz Tech)
	OraQuick™ (KV Pharmaceutical)
Molding/cotton-candy process	FlashDose® (Biovail)

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

1. Abdul S, Poddar SS. A flexible technology for modified release of drugs: multilayered tablets. *J. Control. Release* 2004;97(3):393–405.
2. Bartholomaeus J, Ziegler I. Delayed-release formulation of 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol. WO Patent 2003035054, 2003.
3. Lerner EI, Flashner-Barak M, Achthovem EV, Keegstra H, Smit R. Delayed release formulations of 6-mercaptopurine. WO Patent 2005099666, 2005.
4. Prakash A, Markham A. Oral delayed-release mesalazine: a review of its use in ulcerative colitis and Crohn's disease. *Drugs* 1999;57(3):383–408.
5. Sharma SK, Ruggenenti P, Remuzzi G. Managing hypertension in diabetic patients—focus on trandolapril/verapamil combination. *Vasc. Health Risk Manage.* 2007;3(4):453–465.
6. Simon S. Opioids and treatment of chronic pain: understanding pain patterns and the role for rapid-onset opioids. *Med. Gen. Med.* 2005;7(4):54.
7. Alaux G, Lewis G, Andre F. Controlled-release dosage forms comprising a short acting hypnotic or a salt. EP Patent 1005863, 2000.
8. Hainer JW, Sugg J. Metoprolol succinate extended release/hydrochlorothiazide combination tablets. *Vasc. Health Risk Manage.* 2007;3(3):279–288.
9. Ahlskog JE. Treatment of early Parkinson's disease: are complicated strategies justified? *Mayo Clin. Proc*. 1996;71(7):659–670.
10. Divoll M, Greenblatt DJ, Ochs HR, Shader RI. Absolute bioavailability of oral and intramuscular diazepam: effects of age and sex. *Anesth. Analg.* 1983;62(1):1–8.
11. Salzman C, Shader RI, Greenblatt DJ, Harmatz JS. Long v short half-life benzodiazepines in the elderly. Kinetics and clinical effects of diazepam and oxazepam. *Arch. Gen. Psychiatry* 1983;40(3):293–297.
12. Swartz CM, Sherman A. The treatment of tricyclic antidepressant overdose with repeated charcoal. *J. Clin. Psychopharmacol.* 1984;4(6):336–340.
13. Hoffman A, Horwitz E, Hess S, Cohen-Poradosu R, Kleinberg L, Edelberg A, Shapiro M. Implications on emergence of antimicrobial resistance as a critical aspect in the design of oral sustained release delivery systems of antimicrobials. *Pharm. Res.* 2008;25(3):667–671.
14. Awan NA, Amsterdam EA, Vera Z, DeMaria AN, Miller RR, Mason DT. Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction. *Circulation* 1976;54(5):761–765.
15. Anon. Oxymorphone—Endo/Penwest: EN 3202, EN 3203. *Drugs R&D* 2003;4(3):204–206.
16. Anon. Metformin extended release—DepoMed: metformin, metformin gastric retention, metformin GR. *Drugs R&D* 2004;5(4):231–233.
17. Arthur RMF, Mehmel H. A sustained release formulation of isosorbide-5-mononitrate with a rapid onset of action. *Int. J. Clin. Pract.* 1999;53(3):205–212.
18. Klein E. The role of extended-release benzodiazepines in the treatment of anxiety: a risk–benefit evaluation with a focus on extended-release alprazolam. *J. Clin. Psychiatry* 2002;63 (Suppl. 14):27–33.

19. Hutton JT, Morris JL. Long-acting carbidopa–levodopa in the management of moderate and advanced Parkinson's disease. *Neurology* 1992;42 (1 Suppl. 1):51–56; discussion 57–60.
20. Anonymous. Controlled-release budesonide in Crohn's disease. *Drug Ther. Bull.* 1997;35(4):30–31.
21. McCarberg B. Tramadol extended-release in the management of chronic pain. *Ther. Clin. Risk Manage.* 2007;3(3):401–410.
22. Michel MC. A benefit–risk assessment of extended-release oxybutynin. *Drug Saf.* 2002;25(12):867–876.
23. Pieper John A. Understanding niacin formulations. *Am. J. Manage. Care* 2002;8 (12 Suppl.):S308–S314.
24. Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs* 2001;61(15):2221–2228.
25. Michelson EL. Calcium antagonists in cardiology: update on sustained-release drug delivery systems. *Clin. Cardiol.* 1991;14(12):947–950.
26. Khor S-P, Hsu A. The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. *Curr. Clin. Pharmacol.* 2007;2(3):234–243.
27. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. *Int. J. Pharm.* 2004;277 (1–2):141–153.
28. Tuerck D, Wang Y, Maboudian M, Sedek G, Pommier F, Appel-Dingemanse S. Similar bioavailability of dexmethylphenidate extended (bimodal) release, dexmethyl-phenidate immediate release and racemic methylphenidate extended (bimodal) release formulations in man. *Int. J. Clin. Pharmacol. Ther.* 2007;45(12):662–668.
29. Shirwaikar AA, Srinatha A. Sustained release bi-layered tablets of diltiazem hydrochloride using insoluble matrix system. *Indian J. Pharm. Sci.* 2004;66(4):433–437.
30. Shah AC, Britten NJ, Olanoff LS, Badalamenti JN. Gel-matrix systems exhibiting bimodal controlled release for oral drug delivery. *J. Control. Release* 1989;9(2):169–175.
31. Maroni A, Zema L, Cerea M, Sangalli ME. Oral pulsatile drug delivery systems. *Expert Opin. Drug Deliv.* 2005;2 (5):855–871.
32. Ghimire M, McInnes FJ, Watson DG, Mullen AB, Stevens HNE. *In-vitro/in-vivo* correlation of pulsatile drug release from press-coated tablet formulations: a pharmacoscintigraphic study in the beagle dog. *Eur. J. Pharm. Biopharm.* 2007;67(2):515–523.
33. Mohamad A, Dashevsky A. *In vitro* and *in vivo* performance of a multiparticulate pulsatile drug delivery system. *Drug Dev. Ind. Pharm.* 2007;33(2):113–119.
34. Zou H, Jiang X, Kong L, Gao S. Design and evaluation of a dry coated drug delivery system with floating-pulsatile release. *J. Pharm. Sci.* 2008;97(1):263–273.
35. McCall TW, Baichwal AR, Staniforth JN. TIMERx oral controlled-release drug delivery system. *Drugs Pharm. Sci.* 2003;126:11–19.
36. Staniforth JN, Baichwal AR. TIMERx: novel polysaccharide composites for controlled/programmed release of drugs in the gastrointestinal tract. *Expert Opin. Drug Deliv.* 2005;2 (3):587–595.
37. Ritschel WA. Targeting in the gastrointestinal tract: new approaches. Methods Find. *Exp. Clin. Pharmacol.* 1991;13 (5):313–336.
38. Yu LX, Amidon GL. Characterization of small intestinal transit time distribution in humans. *Int. J. Pharm.* 1998;171 (2):157–163.
39. Yu LX, Crison JR, Amidon GL. Compartmental transit and dispersion model analysis of small intestinal transit flow in humans. *Int. J. Pharm.* 1996;140(1):111–118.
40. Youngberg CA, Berardi RR, Howatt WF, Hyneck ML, Amidon GL, Meyer JH, Dressman JB. Comparison of gastrointestinal pH in cystic fibrosis and healthy subjects. *Dig. Dis. Sci.* 1987;32(5):472–480.
41. Gruber P, Longer MA, Robinson JR. Some biological issues in oral, controlled drug delivery. *Adv. Drug Deliv. Rev.* 1987;1 (1):1–18.
42. Wagener S, Shankar KR, Turnock RR, Lamont GL, Baillie CT. Colonic transit time—what is normal? *J. Pediatr. Surg.* 2004;39(2):166–169; discussion 166–169.
43. Bouchoucha M, Devroede G, Faye A, Arsac M. Importance of colonic transit evaluation in the management of fecal incontinence. *Int. J. Colorectal Dis.* 2002;17(6):412–417; discussion 418–419.
44. Arhan P, Devroede G, Jehannin B, Lanza M, Faverdin C, Dornic C, Persoz B, Tetreault L, Perey B, Pellerin D. Segmental colonic transit time. *Dis. Colon Rectum* 1981;24 (8):625–629.
45. Grundy JS, Foster RT. The nifedipine gastrointestinal therapeutic system (GITS). Evaluation of pharmaceutical, pharmacokinetic and pharmacological properties. *Clin. Pharmacokinet.* 1996;30(1):28–51.
46. John VA, Shotton PA, Moppert J, Theobald W. Gastrointestinal transit of Oros drug delivery systems in healthy volunteers: a short report. *Br. J. Clin. Pharmacol.* 1985;19 (Suppl. 2):203S–206S.
47. Alvisi V, Gasparetto A, Dentale A, Heras H, Felletti-Spadazzi A, D'Ambrosi A. Bioavailability of a controlled release formulation of ursodeoxycholic acid in man. *Drugs Exp. Clin. Res.* 1996;22(1):29–33.
48. Heinig R, Ahr G, Hayauchi Y, Kuhlmann J. Pharmacokinetics of the controlled-release nisoldipine coat-core tablet formulation. *Int. J. Clin. Pharmacol. Ther.* 1997;35(8):341–351.
49. Davis SS. Formulation strategies for absorption windows. *Drug Discov. Today* 2005;10(4):249–257.
50. Lindenbaum J, Rund DG, Butler VP Jr, Tse-Eng D, Saha JR. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N. Engl. J. Med.* 1981;305(14):789–794.
51. Saha JR, Butler VP Jr, Neu HC, Lindenbaum J. Digoxin-inactivating bacteria: identification in human gut flora. *Science* 1983;220(4594):325–327.
52. Warrington SJ, Barclay SP, John VA, Shotton PA, Wardle HM, Good W. Influence of site of drug delivery on the systemic availability of metoprolol: comparison of intragastric infusion

and 14/190 Oros administration. *Br. J. Clin. Pharmacol.* 1985;19 (Suppl. 2):219S–224S.

53. Paul W, Sharma Chandra P. Tricalcium phosphate delayed release formulation for oral delivery of insulin: a proof-of-concept study. *J. Pharm. Sci.* 2008;97(2):863–870.
54. Senel S, Kremer M, Nagy K, Squier C. Delivery of bioactive peptides and proteins across oral (buccal) mucosa. *Curr. Pharm. Biotechnol.* 2001;2(2):175–186.
55. Soares AF, Carvalho RdA, Veiga F. Oral administration of peptides and proteins: nanoparticles and cyclodextrins as biocompatible delivery systems. *Nanomedicine* 2007;2 (2):183–202.
56. Amidon GL, Lennernaes H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* 1995;12(3):413–420.
57. Shokri J, Ahmadi P, Rashidi P, Shahsavari M, Rajabi-Siahboomi A, Nokhodchi A. Swellable elementary osmotic pump (SEOP): an effective device for delivery of poorly water-soluble drugs. *Eur. J. Pharm. Biopharm.* 2008;68 (2):289–297.
58. Jacob JS, Bassett M, Schestopol MA, Mathiowitz E, Nangia A, Carter B, Moslemy P, Shaked Ze, Enscore D, Sikes C., Polymeric drug delivery system for hydrophobic drugs. WO Patent 2005084639, 2005.
59. Yu LX. An integrated model for determining causes of poor oral drug absorption. *Pharm. Res.* 1999;16 (12):1883–1887.
60. Backensfeld T. Pharmaceutical preparation with delayed release of an active substance. WO Patent 2000076484, 2000.
61. Liu L, Khang G, Rhee JM, Lee HB. Monolithic osmotic tablet system for nifedipine delivery. *J. Control. Release* 2000;67 (2–3):309–322.
62. Barzegar-Jalali M, Adibkia K, Mohammadi G, Zeraati M, Bolagh Behnaz Aghaee G, Nokhodchi A. Propranolol hydrochloride osmotic capsule with controlled onset of release. *Drug Deliv*. 2007;14(7):461–468.
63. Makhija Sapna N, Vavia Pradeep R. Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine. I. Cellulose acetate as a semipermeable membrane. *J. Control. Release* 2003;89(1):5–18.
64. Wakode R, Bhanushali R, Bajaj A. Development and evaluation of push–pull based osmotic delivery system for pramipexole. *PDA J. Pharm. Sci. Technol.* 2008;62(1):22–31.
65. Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, Vyas SP. Modified push–pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and *in vitro* characterization. *Int. J. Pharm.* 2004;284 (1–2):95–108.
66. Cardinal J. Formulation of controlled/modified release dosage forms. In *AAPS 41st Annual Pharmaceutical Technologies Arden Conference: Oral Controlled Release Development and Technology*, 2006.
67. Rudnic EM, Burnside BA, Flanner HH, Wassink SE, Couch RA, Pinkett JE.Soluble form osmotic dose delivery system for glipizide and other drugs. US Patent 6,361,796, 2002.
68. Rudnic EM, Burnside BA, Flanner HH, Wassink SE, Couch RA.Soluble osmotic drug delivery system. WO Patent 9818452, 1998.
69. Chen C-M, Chou JCH. Polymers for once daily pharmaceutical tablet having a unitary core. US Patent 6,485,748, 2002.
70. Sriwongjanya M, Weng T, Chou J, Chen C-M. Controlled release oral dosage form. WO Patent 9961005, 1999.
71. Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LAF, Sutton SC. Osmotic drug delivery using swellable-core technology. *J. Control. Release* 2004;94 (1):75–89.
72. Thombre AG, Cardinal JR, Fournier LA. A delivery device containing a poorly water-soluble drug in a hydrophobic medium: ruminal delivery application. *J. Control. Release* 1992;18(3):221–233.
73. Johnson BA, Waterman KC.Asymmetric membrane polymeric coating for osmotic dosage form for varenicline, for treatment of nicotine dependency. US Patent 2007248671, 2007.
74. Haslam JL, Rork GS.Controlled porosity osmotic pump for controlled-release of diltiazem L-malate. EP Patent 309051, 1989.
75. Bajpai SK, Bajpai M, Saxena S. Ion exchange resins in drug delivery. *Ion Exchange Solvent Extr*. 2007;18:103–150.
76. Raghunathan Y. Controlled release pharmaceutical preparations. EP Patent 171528, 1986.
77. Raghunathan Y, Amsel L, Hinsvark O, Bryant W. Sustained-release drug delivery system I: coated ion-exchange resin system for phenylpropanolamine and other drugs. *J. Pharm. Sci.* 1981;70(4):379–384.
78. Heil MF, Wilson G. Multi-phase release methscopolamine compositions. US Patent 2008064694, 2008.
79. Jeong SH, Park K. Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. *Int. J. Pharm.* 2008;353(1–2):195–204.
80. Jadhav KR, Chandra M, Kurm SD, Kadam VJ. Ion exchange resins: a novel way to solve formulation problems. *Curr. Drug Ther.* 2007;2(3):205–209.
81. Thombre AG. Assessment of the feasibility of oral controlled release in an exploratory development setting. *Drug Discov. Today* 2005;10(17):1159–1166.
82. Vazquez MJ, Perez-Marcos B, Gomez-Amoza JL, Martinez-Pacheco R, Souto C, Concheiro A. Influence of technological variables on release of drugs from hydrophilic matrixes. *Drug Dev. Ind. Pharm.* 1992;18(11–12):1355–1375.
83. Cao Q-R, Kim T-W, Lee B-J. Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings. *Int. J. Pharm.* 2007;339(1–2):19–24.
84. Huet de Barochez B, Lapeyre F, Cuine A. Oral sustained release dosage forms—comparison between matrixes and reservoir devices. *Drug Dev. Ind. Pharm.* 1989;15 (6–7):1001–1020.
85. Keary CM, Sheskey PJ. Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binders. *Drug Dev. Ind. Pharm.* 2004;30(8):831–845.

86. Sheskey PJ, Keary CM. Process for coating solid particles. WO Patent 2003020247, 2003.
87. Iyer RM, Sandhu HK, Shah NH, Phuapradit W, Ahmed HM. Scale-up of extrusion and spheronization. *Drugs Pharm. Sci.* 2006;157:325–369.
88. Simonoska Crcarevska M, Glavas Dodov M, Goracinova K. Chitosan coated Ca-alginate microparticles loaded with budesonide for delivery to the inflamed colonic mucosa. *Eur. J. Pharm. Biopharm.* 2008;68(3):565–578.
89. Murata Y, Jinno D, Liu D, Isobe T, Kofuji K, Kawashima S. The drug release profile from calcium-induced alginate gel beads coated with an alginate hydrolysate. *Molecules* 2007;12 (11):2559–2566.
90. Huang J, Wong HL, Zhou Y, Wu XY, Grad H, Komorowski R, Friedman S. *In vitro* studies and modeling of a controlled-release device for root canal therapy. *J. Control. Release* 67 (2–3): 2000; 293–307.
91. Zhou Y, Wu XY. Theoretical analyses of dispersed-drug release from planar matrices with a boundary layer in a finite medium. *J. Control. Release* 2002;84(1–2):1–13.
92. Sune NM, Gani R, Bell G, Shirley I. Computer-aided and predictive models for design of controlled release of pesticides. *Comput. Aided Chem. Eng.* 2004;14:301–306.
93. Wu SXY. Computer-aided design for modified release dosage forms (CAD-MRDF). In *AAPS 41st Annual Pharmaceutical Technologies Arden Conference: Oral Controlled Release Development and Technology*, 2006.
94. Patel M, Patel B, Patel R, Patel J, Bharadia P, Patel M. Carbopol: a versatile polymer. *Drug Deliv. Technol.* 2006;6 (3):32–34, 36, 38, 40–43.
95. Alderman DA. A review of cellulose ethers in hydrophilic matrixes for oral controlled-release dosage forms. *Int. J. Pharm. Technol. Product Manuf.* 1984;5(3):1–9.
96. Salsa T, Veiga F, Pina ME. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrixes. *Drug Dev. Ind. Pharm.* 1997;23(9):929–938.
97. Vueba ML, Batista de Carvalho LAE, Veiga F, Sousa JJ, Pina ME. Role of cellulose ether polymers on ibuprofen release from matrix tablets. *Drug Dev. Ind. Pharm.* 2005;31 (7):653–665.
98. Paavola A, Yliruusi J, Kajimoto Y, Kalso E, Wahlstroem T, Rosenberg P. Controlled release of lidocaine from injectable gels and efficacy in rat sciatic nerve block. *Pharm. Res.* 1995;12(12):1997–2002.
99. Obaidat AA, Rashdan LA, Najib NM. Release of dextromethorphan hydrobromide from matrix tablets containing sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose. *Acta Pharm. Turc.* 2002;44(2):97–104.
100. Michailova V, Titeva S, Kotsilkova R. Rheological characteristics and diffusion processes in mixed cellulose hydrogel matrices. *J. Drug Deliv. Sci. Technol.* 2005;15(6):443–449.
101. Tonnesen Hanne H, Karlsen J. Alginate in drug delivery systems. *Drug Dev. Ind. Pharm.* 2002;28(6):621–630.
102. Miller DA, Fukuda M, McGinity JW. The properties of chitosan as a retardant binder in matrix tablets for sustained drug release. *Drug Deliv. Technol.* 2006;6(9):44, 46, 48–50, 52.
103. Bialer M. Pharmacokinetic evaluation of sustained release formulations of antiepileptic drugs. Clinical implications. *Clin. Pharmacokinet.* 1992;22(1):11–21.
104. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 2004;64(6):611–628.
105. Piscitelli DA, Young D. Setting dissolution specifications for modified-release dosage forms. *Adv. Exp. Med. Biol.* 1997;423:159–166.
106. Kamba M, Seta Y, Takeda N, Hamaura T, Kusai A, Nakane H, Nishimura K. Measurement of agitation force in dissolution test and mechanical destructive force in disintegration test. *Int. J. Pharm.* 2003;250(1):99–109.
107. Kamba M, Seta Y, Kusai A, Nishimura K. Comparison of the mechanical destructive force in the small intestine of dog and human. *Int. J. Pharm.* 2002;237(1–2):139–149.
108. Kamba M, Seta Y, Kusai A, Nishimura K. Evaluation of the mechanical destructive force in the stomach of dog. *Int. J. Pharm.* 2001;228(1–2):209–217.
109. Hayashi T, Kanbe H, Okada M, Suzuki M, Ikeda Y, Onuki Y, Kaneko T, Sonobe T. Formulation study and drug release mechanism of a new theophylline sustained-release preparation. *Int. J. Pharm.* 304(1–2): 2005; 91–101.
110. Burke MD, Maheshwari CR, Zimmerman BO. Pharmaceutical analysis apparatus and method. WO Patent 2006052742, 2006.
111. Dowell JA, Hussain A, Devane J, Young D. Artificial neural networks applied to the *in vitro–in vivo* correlation of an extended-release formulation: initial trials and experience. *J. Pharm. Sci.* 1999;88(1):154–160.
112. Young D. *In vitro–in vivo* correlation for modified release parenteral drug delivery systems. *Drugs Pharm. Sci.* 2007;165:141–151.
113. Piscitelli DA, Bigora S, Propst C, Goskonda S, Schwartz P, Lesko LJ, Augsburger L, Young D. The impact of formulation and process changes on *in vitro* dissolution and the bioequivalence of piroxicam capsules. *Pharm. Dev. Technol.* 1998; 3(4):443–452.
114. Mandal U, Ray KK, Gowda V, Ghosh A, Pal TK. *In-vitro* and *in-vivo* correlation for two gliclazide extended-release tablets. *J. Pharm. Pharmacol.* 2007;59(7):971–976.
115. Dutta S, Qiu Y, Samara E, Cao G, Granneman GR. Once-a-day extended-release dosage form of divalproex sodium III: development and validation of a level A *in vitro–in vivo* correlation (IVIVC). *J. Pharm. Sci.* 2005;94(9):1949– 1956.
116. Meron GD. The development of the swallowable video capsule (M2A). *Gastrointest. Endosc.* 2000;52(6):817–819.
117. Podczeck F, Course N, Newton JM, Short MB. Gastrointestinal transit of model mini-tablet controlled release oral dosage forms in fasted human volunteers. *J. Pharm. Pharmacol.* 2007;59(7):941–945.
118. Melia CD, Rajabi-Siahboomi AR, Bowtell RW. Magnetic resonance imaging of controlled release pharmaceutical

dosage forms. *Pharm. Sci. Technol. Today* 1998;1(1): 32–39.

119. Talukder R, Fassihi R. Gastroretentive delivery systems: a mini review. *Drug Dev. Ind. Pharm.* 2004;30(10):1019–1028.
120. Hwang S-J, Park H, Park K. Gastric retentive drug delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* 1998;15 (3):243–284.
121. Nakagawa T, Kondo S-I, Sasai Y, Kuzuya M. Preparation of floating drug delivery system by plasma technique. *Chem. Pharm. Bull.* 2006;54(4):514–518.
122. Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. *Eur. J. Pharm. Sci.* 2005;24(4):363–373.
123. Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. *Int. J. Pharm.* 1995;114(1):1–11.
124. Devereux JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. *J. Pharm. Pharmacol.* 1990;42(7):500–501.
125. Weon KY, Kim DW, Kim JS, Kim K.Gastric retention-type pellet and preparation. WO Patent 2008010690, 2008.
126. Jackson SJ, Bush D, Perkins AC. Comparative scintigraphic assessment of the intragastric distribution and residence of cholestyramine, Carbopol 934P and sucralfate. *Int. J. Pharm.* 2001;212(1):55–62.
127. Park H, Robinson JR. Mechanisms of mucoadhesion of poly(acrylic acid) hydrogels. *Pharm. Res.* 1987;4 (6):457–464.
128. Klausner EA, Lavy E, Stepensky D, Friedman M, Hoffman A. Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. *Pharm. Res.* 2002;19(10):1516–1523.
129. Cargill R, Engle K, Gardner CR, Porter P, Sparer RV, Fix JA. Controlled gastric emptying. II. *In vitro* erosion and gastric residence times of an erodible device in beagle dogs. *Pharm. Res.* 1989;6(6):506–509.
130. Cargill R, Caldwell LJ, Engle K, Fix JA, Porter PA, Gardner CR. Controlled gastric emptying. I. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. *Pharm. Res.* 1988;5 (8):533–536.
131. Lapidot N, Afargan M, Kirmayer D, Kluev L, Cohen M, Moor E, Navon N.A gastro-retentive multi-layered system for the oral delivery of macromolecules. WO Patent 2007093999, 2007.
132. Omidian H, Park K, Rocca JG. Recent developments in superporous hydrogels. *J. Pharm. Pharmacol.* 2007;59 (3):317–327.
133. Yang S, Park K, Rocca JG. Semi-interpenetrating polymer network superporous hydrogels based on poly(3-sulfopropyl acrylate, potassium salt) and poly(vinyl alcohol): synthesis and characterization. *J. Bioactive Compat. Polym.* 2004;19 (2):81–100.
134. Qiu Y, Park K. Superporous IPN hydrogels having enhanced mechanical properties. *AAPS PharmSciTech* 2003;4 (4):406–412.
135. Gemeinhart RA, Park H, Park K. Effect of compression on fast swelling of poly(acrylamide-*co*-acrylic acid) superporous hydrogels. *J. Biomed. Mater. Res.* 2000;55(1):54–62.
136. Asghar LFA, Chandran S. Multiparticulate formulation approach to colon specific drug delivery: current perspectives. *J. Pharm. Pharm. Sci.* 2006;9(3):327–338.
137. Cardinal J. Non-conventional oral controlled drug delivery systems including bioadhesive and site specific systems. In *AAPS 41st Annual Pharmaceutical Technologies Arden Conference: Oral Controlled Release Development and Technology*, 2006.
138. Kaur G, Jain S, Tiwary AK. Recent approaches for colon drug delivery. *Recent Pat. Drug Deliv. Formul.* 2007;1(3):222–229.
139. Patel M, Shah T, Amin A. Therapeutic opportunities in colon-specific drug-delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* 2007;24(2):147–202.
140. Singh BN. Modified-release solid formulations for colonic delivery. *Recent Pat. Drug Deliv. Formul.* 2007;1(1):53–63.
141. Mukherji G, Wilson CG. Enteric coating for colonic delivery. *Drugs Pharm. Sci.* 2003;126:223–232.
142. Kelm GR, Kondo K, Nakajima A. Pharmaceutical dosage form with multiple enteric polymer coatings for colonic delivery. US Patent 5,914,132, 1999.
143. Watanabe S, Kawai H, Katsuma M, Fukui M.Colon-specific drug release system. WO Patent 9528963, 1995.
144. Korstanje C. The improved cardiovascular safety of omnic (tamsulosin) oral controlled absorption system (OCAS). *Eur. Urol. Suppl.* 2005;4(7):10–13.
145. Yang L, Watanabe S, Li J, Chu JS, Katsuma M, Yokohama S, Fix JA. Effect of colonic lactulose availability on the timing of drug release onset *in vivo* from a unique colon-specific drug delivery system (CODES). *Pharm. Res.* 2003;20(3):429–434.
146. Katsuma M, Watanabe S, Kawai H, Takemura S, Masuda Y, Fukui M. Studies on lactulose formulations for colon-specific drug delivery. *Int. J. Pharm.* 2002;249(1–2):33–43.
147. Birudaraj R, Mahalingam R, Li X, Jasti BR. Advances in buccal drug delivery. *Crit. Rev. Ther. Drug Carrier Syst.* 2005;22(3):295–330.
148. Yukimatsu K, Nozaki Y, Kakumoto M, Ohta M. Development of a trans-mucosal controlled-release device for systemic delivery of antianginal drugs pharmacokinetics and pharmacodynamics. *Drug Dev. Ind. Pharm.* 1994;20 (4):503–534.
149. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. *Adv. Drug Deliv. Rev.* 1994;13 (1–2):43–74.
150. Patel M, Patel B, Patel R, Patel J, Bharadia P, Patel M. Carbopol: a versatile polymer. *Drug Deliv. Technol.* 2006;6 (3):32–34, 36, 38, 40–43.
151. Park H, Robinson JR. Mechanisms of mucoadhesion of poly (acrylic acid) hydrogels. *Pharm. Res.* 1987;4(6):457–464.