FUNDAMENTALS OF DRUG DELIVERY

EDITED BY

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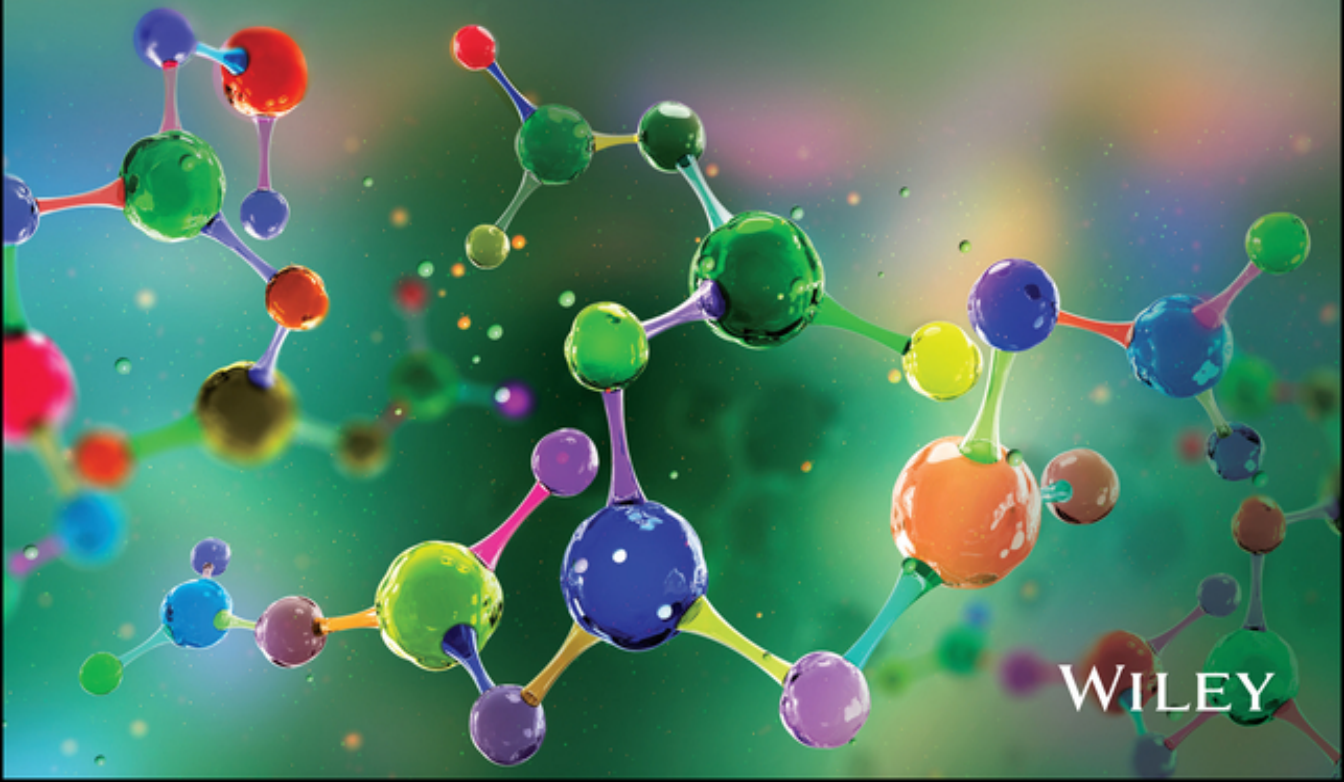

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Preface

Effective, controlled drug delivery has the potential to greatly impact the therapeutic outcome, clinical benefit, and safety of drugs in a wide range of diseases and health conditions. There are a large number of potentially useful drugs with limited effectiveness and/or safety concerns due to poor drug delivery. This may occur because a physiologically relevant concentration is not delivered to the target site, does not remain in contact for a sufficient period, or causes adverse effects because of the resulting high blood concentrations associated with indiscriminate release. Controlled drug delivery systems are designed to carry the drug and release it at the target site in a timely manner, facilitating its absorption and optimizing its physiological action. An effective controlled drug delivery system improves efficacy and safety by controlling the rate, time, and place of drug release within the body, thereby minimizing dose requirements and the potential to interact with non-target body sights that can contribute to undesirable side effects. Drug delivery has evolved from relatively simple systems to modern technologies designed to personalize medicines that have biologically precise drug release in response to real-time monitoring of body parameters.

Controlled drug delivery system development is rapidly evolving with an ever-increasing focus on advanced technologies that bring together a wide range of skilled professions including pharmaceutical scientists, chemical, mechanical, and electrical engineers, chemists, physicists, and clinicians. It is an exciting field that has helped to advance clinical outcomes in almost every health condition, ranging from negating the need for cold-chain storage thus allowing medicines to be transported to the most remote parts of the world, to precision targeting of drugs in cancer treatment. This book is designed to provide an insight into the fundamentals of drug delivery and the important processes in the development of controlled drug delivery systems.

The book is divided into three parts.

Part 1 (Chapters 1–8) introduces the concept of drug delivery and provides a perspective into the challenges, opportunities, and fundamental processes involved in the development of controlled drug delivery systems. It includes a historical perspective and a peek into the future of drug delivery. There is a focus on the drug development process, including the selection of pharmaceutical candidates and evaluation of their physicochemical characteristics with emphasis on the relevance to dosage form design. The role and application of mathematical modeling and the influence of drug transporters in pharmacokinetics and drug disposition complete this section.

Part 2 (Chapter 9–13) is focused on particular challenges in controlled drug delivery and advanced delivery technologies. This includes delivery systems for biologicals, an increasing drug category that presents enormous therapeutic opportunities and equally enormous delivery challenges. The application and recent advances in cell-mediated drug delivery are discussed, and there is a series of chapters on nanotechnology that include fundamentals, applications for targeted delivery, and discussion of the toxicological and safety issues.

Part 3 (Chapters 14–20) provides a "top to bottom" critique of the common administration routes for controlled drug delivery. Each chapter begins with a short introduction and then a more detailed discussion of the physiology pertinent to each administration route, focusing on the barriers to drug delivery. Controlled drug delivery systems that have been evaluated for each route are then discussed before some conclusions summarizing the state-of-the-art and potential future developments. Each chapter includes comprehensive references at the time of writing for those wishing to read the primary literature. *Controlled* drug delivery systems imply that control over dosing resides in the formulation with control over drug release and predictable drug delivery. However, it is apparent that, given the complexities of the biological barriers present for the administration routes, in several cases control over drug delivery arises predominantly from the biological barrier. Although strategies have been developed to reduce these barriers – for example the use of penetration enhancers – it is contentious whether these approaches truly allow *controlled* drug delivery. However, in seeking to provide a comprehensive critique of the current literature, such partially controlled systems have been considered.

We express our thanks to the authors who have contributed to this book. In each case, the chapters are authored by well-respected researchers in the field who have generously provided their knowledge and experience, and continue to contribute to advancing research in their fields. We are also grateful to Jonathan Rose and his team at Wiley who have brought the concepts and chapters to fruition, and shown remarkable patience in dealing with editors who agree with Albert Einstein that "time is an illusion".

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Part I

Product Design, the Essence of Effective Therapeutics

1

Challenges and Innovations of Controlled Drug Delivery

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1.1 Background

A key health care advance over the last century has been the development of drug delivery systems that not only enable effective, safe, and reproducible delivery for optimal therapeutic benefit, but are also chemically and physically stable, aesthetically acceptable, convenient to use, cost-effective and optimized for the most appropriate mode of administration in their target population. There is a wide range of drug delivery systems available for a range of routes of administration, with the aim of achieving local or systemic effects, as shown in Figure 1.1. The most common route of administration is the oral route due to its convenience, cost, and patient acceptance. Injectables include the more common parenteral routes which are intradermal, subcutaneous (SC), intramuscular (IM), and intravenous delivery (Figure 1.1). In addition to the oral route, the most common nonparenteral routes of delivery are topical/transdermal, nasal, pulmonary, ocular, rectal, and vaginal (Figure 1.1). Drug absorption processes for nonparenteral administration generally involve passive and/or active transport across an epithelial barrier and carriage away into the systemic circulation by either local blood flow and/or via the lymphatic circulation. Topical delivery is used for a local effect, such as the treatment of pain, inflammation, or infection of the oropharynx (including nasal, buccal, and sublingual), eye, skin, lung, rectum, and vagina or for systemic delivery.

In this chapter, we introduce the routes of administration of therapeutic and diagnostic compounds to the body, the considerations in designing drug delivery systems, and some examples of the innovations that have contributed new controlled delivery products. The aim is to provide an overview of the topic, with considerable detail provided in the subsequent chapters in this and other volumes in this series.

1.2 Parenteral Dosage Forms

The parenteral route enables precise dosing for drugs that have a narrow therapeutic index, complete dosing for those with poor oral bioavailability to maintain optimal therapeutic concentrations, ready access in patients with swallowing difficulties, or an unconscious patient, and

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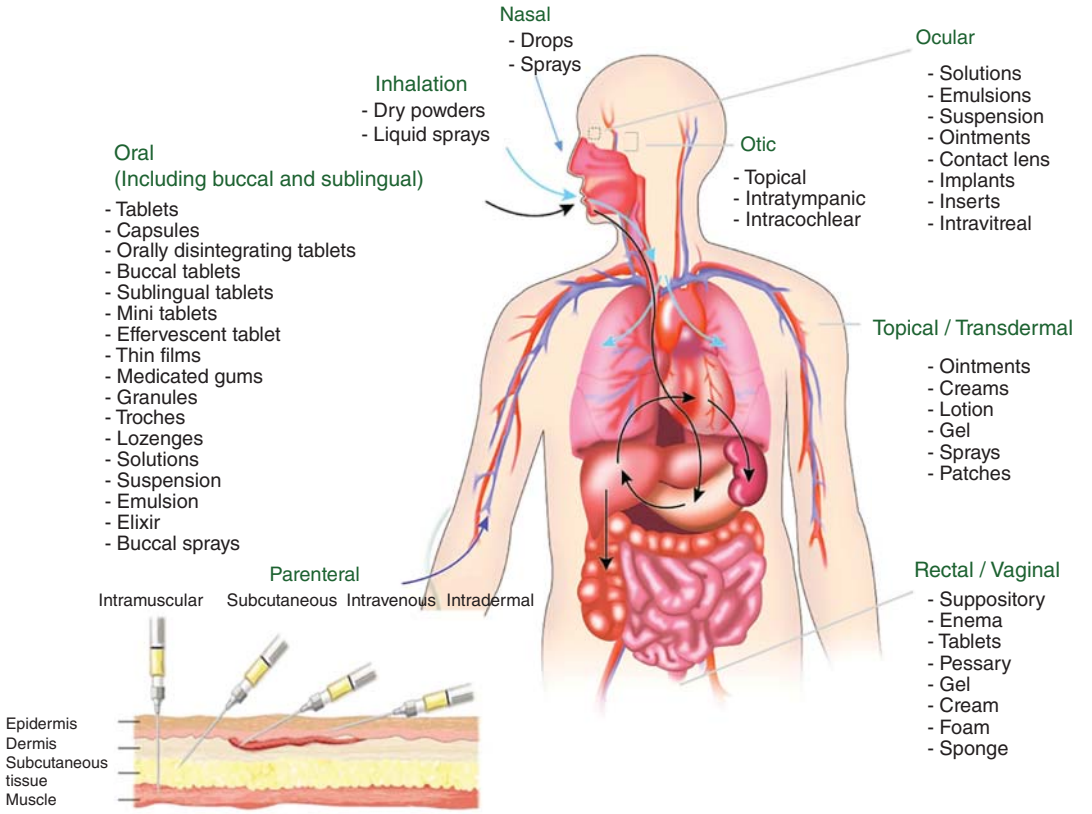

Figure 1.1 Routes of drug administration and associated dosage forms. Source: Khan and Roberts [1]. © 2018 Elsevier.

immediate blood levels of drugs in an emergency. It is used to deliver intravenous fluid replacement and parenteral nutrition fluids and is the preferred delivery route for emerging novel therapeutic molecules, such as proteins, peptides, and biologics. However, parenteral administration requires specialized personnel, and there is a risk of tissue damage, infection, and immune reactions. There is a requirement for sterility in processing, storage, and administration making it more expensive than other conventional drug products. The most common routes used for systemic delivery of a wide range of molecules including biopharmaceuticals, are SC, intravenous (IV), and IM [2] as shown in Figure 1.1. While many parenteral products are solutions, controlled release from formulations such as microparticles or implants composed of biodegradable polymers is also available.

1.2.1 Intravenous Route (IV)

The IV route is used to administer a drug directly into a vein, either as a bolus or by infusion, thus allowing administration of relatively large volumes of fluid. It avoids first pass metabolism and is the preferred choice for rapid pharmacological action, especially in emergencies and anesthesia. However, administration requires medical/nursing supervision, and there are associated risks of infection via the injection site, coagulation of infusion lines, and the possibility of red blood cell

hemolysis, pain, and phlebitis. Effective sterile manufacture and appropriate storage is required to prevent contamination with microbes, pyrogens, and inert particles.

1.2.2 Intramuscular Route (IM)

IM injection enables systemic dosing, high bioavailability, and a rapid onset of action of drugs such as antibiotics, steroids, and narcotic analgesics. It provides a low-cost alternative to IV dosing as demonstrated by Milkovich and Piazza, who reported 10 times lower cost associated with IM compared to IV antibiotics and the opportunity for self-administration and earlier hospital discharge [3]. The IM route avoids many of the administration-related risks of IV administration and can provide a safe, rapid drug administration option in the management of anaphylaxis, where IM dosing of epinephrine was associated with significantly less cardiovascular adverse events compared with IV bolus epinephrine (1.3% vs. 10%) [4] and can be administered rapidly by a teacher, relative, or member of the public. IM injection is associated with pain from needle insertion and care is required to avoid piercing arteries or causing nerve damage.

1.2.3 Subcutaneous Route (SC)

The SC route is cost-effective, amenable to self-injection, minimally invasive, and associated with fewer side effects than the IV route [5]. While adverse reactions to SC dosing are uncommon, edema, pain, inflammation, infection, abscesses, and injection-site reactions may be more common in the elderly [6]. The SC route offers the opportunity for placement of implants that can provide controlled drug release over prolonged periods. Portable devices for SC injection such as insulin pumps, auto injectors, and pen injectors allow optimal dose delivery and self-administration in the management of a range of conditions. Examples include insulin, epinephrine, interferon β-1a (multiple sclerosis), and Enbrel® (auto injectors containing the biologic etanercept for use in arthritis) (https://www.enbrel.com/rheumatoid-arthritis/about-enbrel-for-ra, in).

1.2.4 Other Parenteral Routes

Less common parenteral routes for drug delivery include epidural, intrathecal, intracerebroventricular (ICV), intra-arterial, intra-articular, intracavernous, intralesional, intraosseous, and intravesical injection and infusion. Epidural (outside the dura/spinal fluid sac) and intrathecal (inside sac) routes are used primarily for anesthesia/analgesia. ICV involves injection into the cerebrospinal fluid in cerebral ventricles to bypass the blood–brain barrier. It can be used for drug administration in neurodegenerative disorders such as spinal muscular atrophy or chemotherapeutic agents in gliomas. It is also used as a research tool. Intra-articular injections (into a joint) of anti-inflammatory drugs such as steroids are generally used for the treatment of inflammatory joint conditions such as arthritis, tendinitis, gout, and Carpal Tunnel Syndrome. Vasodilators and vasoconstrictors are administered by intracavernous injection (into the penis) to treat erectile dysfunction. Intralesional steroid therapy is most commonly used in the treatment of hypertrophic and keloid scars, acne cysts, and alopecia areata. Intraosseous influsion (IO) involves injecting directly into the marrow of a bone as an alternative to provide drugs or fluid when IV injection is not available, such as trauma patients with compromised IV access. A needle is inserted through the hard bone cortex into the soft bone marrow to provide immediate access to the vascular system [7]. Intravesicular injection involves administration into the bladder using a catheter, used primarily to instil immunotherapeutic and chemotherapeutic agents in the treatment of bladder cancer.

1.3 Oral Route and Delivery Systems

More than 75% of all doses are given as tablets and capsules due to their ease and low cost of manufacture, stability, convenience in carrying and storing, ease of use, effective taste-masking strategies, and less dosing errors [8]. However, frequent dosing of three to four times a day may be required for drugs with short or immediate elimination half-lives, potentially creating a high pill burden and adherence issues particularly in the older population who may be taking a number of medications to manage multiple conditions. There is clearly enormous potential for controlled drug delivery via the oral route, hence, we have devoted a volume in this series to this topic. Here we provide an overview of the formulation challenges and opportunities offered by the oral route.

While most oral formulations are swallowed intact, as shown in Figure 1.1, immediate release and soluble tablets offer quick therapeutic effect and are particularly suitable for people with swallowing problems such as children and the elderly. Formulation options include tablets that are allowed to effervesce in water, and oral disintegrating tablets, medicated gums, and oral films that can be sucked or chewed before swallowing. Sublingual (placed under the tongue) and buccal (placed between the gum and cheek) tablets, sprays, and patches deliver the drug through the mucosal surfaces of the mouth, providing the added advantage of avoiding first-pass metabolism.

Oral modified release dosage forms include delayed, extended, enteric coated, and other delivery systems that can improve the stability, efficacy, safety, and convenience for patients. They can offer reduced dosing frequency, with improved adherence, clinical outcomes, and a reduction in the need for further clinical intervention such as hospital readmissions [9]. Controlled release technologies include the use of biodegradable polymers, release rate-controlling membranes, microencapsulation, and bioadhesives to enhance drug contact time [10]. Multiparticulate controlled release formulations offer more flexibility for pediatric or elderly patients who have trouble swallowing as they can be filled into sachets or compressed into minitablets [11].

1.4 Nasal Drug Delivery

Intranasal delivery systems are commonly used for treating local conditions (Figure 1.1) such as nasal allergy, congestion, and nasal infections, and are increasingly being used for delivery of opioids, respiratory medicines, vaccines, and other medicines for systemic effect. The thin and highly vascularized nasal mucosal layer enables a fast onset of drug action and avoidance of gastrointestinal tract and hepatic first-pass metabolism [12], and the nasal-associated lymphoid tissue (NALT) offers opportunities for vaccine delivery. The most common delivery systems are nasal sprays and drops administered to the anterior site of the nasal cavity, with the former showing twofold to threefold greater drug bioavailability [13]. The nasal cavity is designed to protect the lungs by filtering inhaled air via its hair follicles and mucous membrane, then transporting those particles down through the esophagus to the stomach by a mucociliary clearance process, thus exposing them to the degradative processes of the gastro-intestinal tract. This clearance process represents a challenge to nasal bioavailability as drug residence time in the nasooral cavity is decreased, resulting in reduced transport into the blood stream. Adhesive polymers, enzyme inhibitors, or the use of novel drug delivery formulations such as liposomes, nanoparticles, microspheres, microemulsions, and penetration enhancers can enhance drug retention and/or penetration across the nasal mucosa [14]. The most favorable candidates for nasal delivery, as shown in Table 1.1, are small lipophilic molecules such as propranolol ($M_W = 295.8$, $\log P_{o/w} = 2.7$), fentanyl ($M_W = 336.5$, $\log P_{o/w} = 4.1$), and estradiol ($M_W = 296.4$, $\log P_{o/w} = 4.3$) [15].