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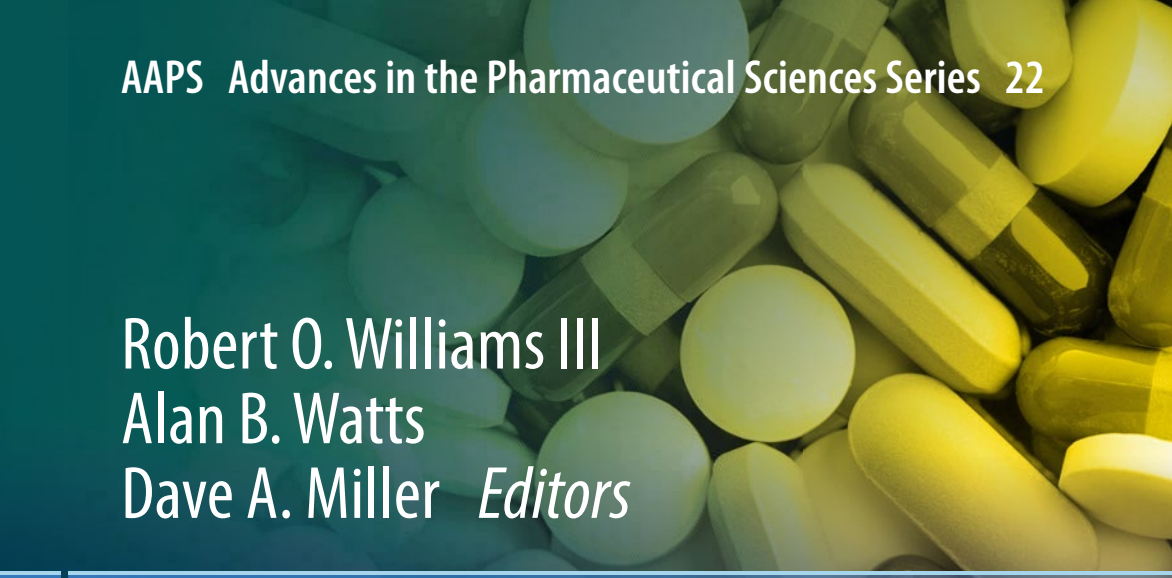

Robert O. Williams III
Alan B. Watts
Dave A. Miller *Editors*

Formulating Poorly Water Soluble Drugs

Second Edition

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Springer

AAPS Advances in the Pharmaceutical Sciences Series

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Volume 22

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Editors

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Editors
Robert O. Williams III
Division of Pharmaceutics,
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA

Alan B. Watts
Division of Pharmaceutics,
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA

Dave A. Miller
DisperSol Technologies, LLC
Georgetown, TX, USA

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We wish to sincerely thank our colleagues and friends who have helped with the first and second editions of this book covering a most important topic of formulating poorly water-soluble drugs. Without your collective insight, wisdom, expertise and time, the books would not have been possible.

Bill, Alan and Dave

To my ever loving and supportive family, Jill, Rory and Maddi, for their patience, encouragement and sense of humor throughout the book writing and editing process. I love you all!

Bill

To Allison, Westley, and Gwendolyn for your constant love and support.

Dave

To my wife-to-be, Avelina, for your love and encouragement, current and future.

Alan

Preface

Over the last three decades, the utilization of high-throughput screening (HTS) methodologies has led to an increase in the number of high-activity therapeutic compounds. In this modern age of drug discovery, improvements in laboratory automation, combinatorial chemistry, target identification, and models of druggable targets have all contributed to a vast improvement in the quality of small molecule therapies. While HTS has produced an increased number of lead therapeutic candidates coming out of drug discovery labs, many of these molecules are poorly water soluble, creating a new challenge for formulation scientists.

It is a central tenet to drug delivery that before a compound can elicit its designed therapeutic effect, it must first be dissolved in physiological fluids. A tendency toward larger molecular weight, lipophilic compounds in HTS efforts have resulted in the majority (over 80 %) of new compounds demonstrating poor aqueous solubility, ultimately resulting in classification as either BCS class II or IV. While it might be possible to overcome poor solubility by simply increasing the drug dose, this approach is not only wasteful, but often results in high variability and potential toxicity. In response, formulation scientists have developed a number of strategies to improve drug solubility. These solubility enhancing approaches vary depending on the desired physicochemical properties, routes of delivery, and manufacturing resources and are highly dependent on the intrinsic properties of the active ingredient. This book is intended to combine and explain the extensive body of literature dedicated toward formulating poorly water soluble compounds. In this single, updated text, we have addressed a breadth of topics in the field of pharmaceutical solubility enhancement and included chapters dedicated to characterization of physiochemical properties, solid-state modifications, advanced formulation design, nonconventional process technologies, advanced analytical characterization, and specialized product performance analysis. In addition, the final chapter discusses special considerations that must be taken from a regulatory perspective due to the novel and unconventional methods used in poorly soluble drug formulation.

In this second edition of our book, we have revised each chapter and added the latest innovations, from industry and academia, aimed toward enhancing the water solubility of drugs. Substantial updates have been considered and added to each

chapter to ensure that this text gives state-the-art applications at the time of publication. In Chap. 1, route-specific challenges in oral, parenteral, and pulmonary delivery are described with added sections for consideration of alternative routes such as ocular and nasal delivery. Approaches to formulation optimization are outlined in Chap. 2 and features expanded discussion of Flory-Huggins theory as well as the latest techniques for characterization of amorphous material. Chapter 3 discusses solid-state approaches (which covers salts, co-crystals, metastable polymorphs, and amorphous forms) with a more in-depth discussion of co-crystal preparation. Mechanical particle size reduction is a well-established approach for solubility enhancement and is described in Chap. 4 with added coverage of novel combination of top-down/bottom-up technologies.

In our fifth chapter, the authors focus on solubilized formulation using co-solvents and complexation. Here, a more thorough focus has been placed on the utility and characterization of cyclodextrins and their extensive use in commercialized formulations. Significant updates have been made to Chap. 6 covering injectable formulations, including an expansion of sections describing disperse systems of emulsions, liposomes, micelles, and nanosuspensions, as well as consideration of intrathecal and intra-articular routes. Chapter 7 reviews lipid-based approaches for solubility enhancement and has been comprehensively updated to include recent thoughts from relevant academic-industrial consortia as well as lipid solidification techniques. An overview of amorphous systems is provided in Chap. 8 and contains increased focus on considerations for choosing spray drying and hot melt extrusion as well as methods for prediction of phase diagrams. In Chap. 9, melt extrusion discussion has been updated with new information regarding extrudate characterization as well as process scale-up. With the increasing application of spray drying for solubility enhancement, the authors of Chap. 10 have added examples from industry and academia published in the past three years that focus on the production of amorphous solid dispersions. Chapter 11 describes particle engineering approaches involving cryogenic technology and has been updated with new applications of spray freeze drying and thin film freezing for oral and non-oral routes. Advancements in particle engineering via controlled precipitation and supercritical fluid precipitation are described in Chap. 12; the chapter has been updated with recent improvements in this rapidly developing field. Emerging technologies such as Kinetisol®, drug-loaded mesoporous carriers, and co-amorphous drug-drug mixtures have also seen extensive new work in recent years, which is reviewed in Chap. 13 of this edition. To coincide with new progressing and analytical technology, Chap. 14 provides an update of the regulatory outlook from the perspective of the FDA on poorly soluble compound formulation. In each of these chapters, our authors have included updated methodologies, applications, and marketed success stories in each of their respective fields. While drug delivery technology is advancing at an increasingly rapid rate, our hope is that this edition serves as the preferred reference that formulation scientists use over the next several years.

In healthcare today, patients are continuing to benefit from improvements in drug discovery through compounds with improved target affinity and reduced off-target effects. New phenotypic discovery processes have led to several first-in-class

therapies; however, without simultaneous advances in formulation technology, many of these breakthrough compounds would not have made it to market. Allowing developers to consider poorly soluble compounds as a feasible lead candidate, rather than a more soluble but less active counterpart, has played a major role in bringing many breakthrough therapies to the clinic. At the time of the publication of the first edition of this book in 2012, ivacaftor, a small molecule breakthrough therapy in Cystic Fibrosis (CF), was newly approved by the FDA. Its discovery is the result of over 20 years of genetics research and application of HTS techniques. Often overlooked, however, is the fact that ivacaftor too is a poorly water-soluble compound, having single-digit bioavailability without specialized formulation. It was the eventual production of ivacaftor as a stabilized amorphous dosage (covered in Chap. 10 of this book) that enabled its development and ultimate approval for the treatment of CF. Improvement of oral bioavailability was particularly important in this patient population giving the GI absorption deficiency inherent in CF. Ivacaftor has led the way in a new class of disease augmenting compounds in CF and has been a seminal moment in the history of CF treatment. This case is merely one example of hundreds provided in this text that describes the utilization of formulation expertise to enable delivery of poorly soluble compounds. In this updated edition, we aim to be a resource for educating current and future scientists on both the established and emerging formulation approaches for poorly soluble medicines that will ultimately enable continued improvement of drug therapy.

The editors would like to thank all authors, both of this second edition and the prior edition, for their efforts and willingness to share their expertise with their fellow pharmaceutical scientists.

Austin, TX, USA — Robert O. Williams III
Austin, TX, USA — Alan B. Watts
Georgetown, TX, USA — Dave A. Miller

Contents

Contributors

Zhengrong Cui Division of Pharmaceutics, The University of Texas at Austin, Austin, TX, USA

James C. DiNunzio Pharmaceutical Sciences and Clinical Supplies, Merck & Co., Inc., Kenilworth, NJ, USA

Zedong Dong Office of Pharmaceutical Quality, Food and Drug Administration, Silver Spring, MD, USA

Daniel Ellenberger DisperSol Technologies, LLC, Georgetown, TX, USA

Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Ping Gao Abbvie Inc., North Chicago, IL, USA

Marco Gil Hovione LLC, Lawrenceville, NJ, USA

Abbe Haser Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Soraya Hengsawas Surasarang Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Siyuan Huang Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Justin R. Hughey Banner Life Sciences, High Point, NC, USA

Justin LaFountaine Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Julien Maincent Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Charlie Martin Leistritz Extrusion, Somerville, NJ, USA

Reto Maurer F. Hoffmann-La Roche AG, Basel, Switzerland

Jason T. McConville Department of Pharmaceutical Sciences, College of Pharmacy, University of New Mexico, Albuquerque, NM, USA

James W. McGinity Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Dave A. Miller DisperSol Technologies, LLC, Georgetown, TX, USA

Javier O. Morales Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile

Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile

Youssef W. Naguib Division of Pharmaceutics, The University of Texas at Austin, Austin, TX, USA

Kevin P. O'Donnell The Dow Chemical Company, Dow Pharma & Food Solutions, Midland, MI, USA

Hannah L. O'Mary Division of Pharmaceutics, The University of Texas at Austin, Austin, TX, USA

Susanne Page F. Hoffmann-La Roche AG, Basel, Switzerland

Hasmukh Patel Office of Pharmaceutical Quality, Food and Drug Administration, Silver Spring, MD, USA

Leena Kumari Prasad Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Hugh D.C. Smyth Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Zachary Warnken Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Alan B. Watts Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Robert O. Williams III Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Nicole Wyttenbach F. Hoffmann-La Roche AG, Basel, Switzerland

Feng Zhang Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Chapter 1
Route-Specific Challenges in the Delivery of Poorly Water-Soluble Drugs

Zachary Warnken, Hugh D.C. Smyth, and Robert O. Williams III

Abstract Poor aqueous solubility of new chemical entities presents various challenges in the development of effective drug-delivery systems for various delivery routes. Poorly soluble drugs that are delivered orally commonly result in low bioavailability and are subject to considerable food effects. In addition, poorly soluble drugs intended for parenteral delivery generally have to be solubilized with large amounts of co-solvents and surfactants, oftentimes resulting in adverse physiological reactions. Ocular delivery of poorly soluble drugs is challenging due to the absorption barriers and clearance mechanisms. Poorly soluble drugs administered nasally are limited by a relatively small administered volume, the geometry of the nasal cavity and the strict safety requirements of the excipients used in the formulation. Finally, successful formulation design of poorly soluble drugs intended for pulmonary administration is hindered by the limited number of excipients generally recognized as safe for this route of delivery and the anatomical and physiological clearance mechanisms found in the airways. In summary, this chapter reviews the specific challenges faced in the delivery of poorly water-soluble drugs via oral, parenteral, and pulmonary administration.

Keywords Oral • Parenteral • Pulmonary administration • Aqueous solubility • Food effects • Metabolism • Biopharmaceutics Drug Disposition Classification System (BDDCS)

1.1 Introduction

Adequate aqueous solubility of new chemical entities (NCEs) is one of the key properties required for successful pharmaceutical formulation development. Solubility is generally defined as the concentration of the compound in a

Z. Warnken • H.D.C. Smyth • R.O. Williams III (✉)
Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, 2409 West University Avenue, PHR 4.214, Austin, TX 78712, USA
e-mail: bill.williams@austin.utexas.edu; zwarnken@utexas.edu; hugh.smyth@austin.utexas.edu

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solution which is in contact with an excess amount of the solid compound when the concentration and the solid form do not change over time (Sugano et al. 2007). Solubility is closely related to dissolution which is a kinetic process that involves the detachment of drug molecules from the solid surface and subsequent diffusion across the diffusion layer surrounding the solid surface. The relationship of solubility and dissolution rate is described by the Nernst–Brunner/Noyes–Whitney equation:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{D\,A}{h}\left(c_s - c_t\right),$$

where $\mathrm{d}M/\mathrm{d}t$ is the dissolution rate, D the diffusion coefficient, A the surface area, h the diffusion layer thickness, c_s the saturation solubility of the drug in the bulk medium, and c_t the amount of drug in solution at time t (Noyes and Whitney 1897; Nernst 1904). The use of high-throughput screening and combinatorial chemistry for the development of NCEs has resulted in an increasingly number of compounds that are characterized by low aqueous solubility (Lipinski 2000). From the Nernst–Brunner/Noyes–Whitney equation, it is evident that compounds characterized by low solubility (c_s) will only establish a small concentration gradient (c_s–c_t), resulting in low dissolution rates. This, in turn, causes many problems in vivo when poorly soluble drugs are administered via various routes of administration. Poorly soluble drugs that are delivered orally commonly result in low bioavailability and high intersubject variability. Additionally, poorly soluble compounds are known to have a higher predisposition for interaction with food resulting in high fast/fed variability (Gu et al. 2007). In order to make low solubility drugs available for intravenous administration, they generally have to be solubilized employing large amounts of cosolvents and surfactants. Problems often arise from the fact that these excipients may not be well tolerated, potentially causing hemolysis and/or hypersensitivity reactions (Yalkowsky et al. 1998). In addition, there is the risk of drug precipitation upon injection due to the subsequent dilution of the solubilized formulation. Depending on the intended target tissue, ocular delivery may be accomplished utilizing various dosage forms, from topical eye drops to more invasive intraocular injections. Anatomical features of the eye form barriers for drug absorption into the eye. Additionally, clearance mechanisms on the surface and inside the eye add challenges to effective drug delivery. Poorly soluble drugs delivered nasally are limited by the small deliverable volumes, nasal mucosal irritation and relatively short retention times for absorption. Finally, formulation design of poorly soluble drugs intended for pulmonary administration is limited by the few excipients already in approved products and generally recognized as safe for this route of delivery. This chapter reviews the specific challenges faced in the delivery of poorly water-soluble drugs for oral, parenteral, ocular, nasal, and pulmonary delivery.

1.2 Oral Route of Administration

Despite significant advances in pulmonary, transdermal, and other sites of drug delivery, the oral route remains the most favored method of administration. Not only are oral drug products conveniently and painlessly administered resulting in high acceptability, they can also be produced in a wide variety of dosage forms at comparably low costs, making them attractive for patients and pharmaceutical companies alike (Sastry et al. 2000; Gabor et al. 2010). In theory, the physiology of the gastrointestinal (GI) tract with its high intestinal surface area and rich mucosal vasculature offers the potential for excellent drug absorption and accordingly high bioavailability (Lee and Yang 2001). Still, oral bioavailability is often low and variable as the process of drug absorption from the GI tract is far more complex and influenced by physiological factors such as GI motility, pH, efflux transporters, and presystemic metabolism; extrinsic factors such as food intake and formulation design; and critically, the physicochemical properties of the drug (Levine 1970; Martinez and Amidon 2002).

Following oral administration of a solid dosage form, the drug must first dissolve in the GI fluids and then be absorbed across the intestinal mucosa to reach the systemic circulation and exert its pharmacological effect. Accordingly, the key properties of potential drug candidates defining the extent of oral bioavailability and thus being vital for successful oral product development include aqueous solubility and intestinal permeability. Based on these two crucial parameters, the Biopharmaceutics Classification System (BCS) assigns drugs to one of four categories: high solubility, high permeability (BCS I); low solubility, high permeability (BSC II); high solubility, low permeability (BCS III); and low solubility and low permeability (BCS IV) (Amidon et al. 1995).

Ideally, a NCE is characterized by high aqueous solubility and permeability (BCS I); yet, only about 5 % of NCEs fulfill this requirement, while approximately 90 % of NCEs are considered poorly soluble in combination with either high or low permeability (BCS II and IV) (Benet et al. 2006). Due to the combination of low permeability and low solubility, BCS IV compounds are generally troublesome drug candidates and, therefore, rarely developed and marketed. BCS II compounds are usually more promising candidates since permeability through the GI mucosa is not a problem. Nevertheless, intestinal absorption is solubility/dissolution rate-limited, oftentimes resulting in low and erratic oral bioavailability.

Overall, problems associated with poorly soluble compounds not only revolve around low oral bioavailability but also involve high susceptibility to factors such as food and metabolism as discussed in more detail in the following sections.

1.2.1 Challenges in Oral Delivery of Poorly Water-Soluble Drugs

Co-administration of oral dosage forms with meals generally results in one of three scenarios: (1) the extent of absorption decreases which is referred to as a negative food effect; (2) the extent of absorption increases corresponding to a positive food

effect; and (3) no substantial change in the extent of absorption takes place (Welling 1996). Given the fact that food intake commonly translates into universal physiological actions, predictions of what scenario will take place may be made based on the physicochemical properties of the drug (Gu et al. 2007). For instance, Fleisher et al. estimated the effect of food on the extent of drug absorption based on the characteristics of the drug as classified by the BCS (Fleisher et al. 1999). Specifically, it was suggested that the extent of absorption of a poorly water-soluble, highly permeable BCS II drug is most likely increased, while it will remain unchanged for a highly water-soluble and permeable BCS I drug. In fact, the same trend was observed by Gu and coworkers, who evaluated the effect of food intake on the extent of absorption, defined as the area under the curve of the time–plasma concentration curve (AUC), by analyzing clinical data of 90 marketed drug products (Gu et al. 2007). For the majority of products containing a BCS I compound (67 %), no statistically significant difference in the AUC in the fasted and fed state was observed. In contrast, more than 70 % of the drug products comprising BCS II or BCS IV drugs exhibited a positive food effect as indicated by a significant increase in the AUC in the fed state compared to the fasted state (Fig. 1.1). Mathias et al. further confirmed this effect by studying in vitro-in vivo relationships of 22 new chemical entities (Mathias et al. 2015).

The positive food effect oftentimes encountered with poorly water-soluble drugs can be primarily ascribed to several physiological changes in the GI environment that ultimately increase drug solubility and dissolution. First of all, the intake of

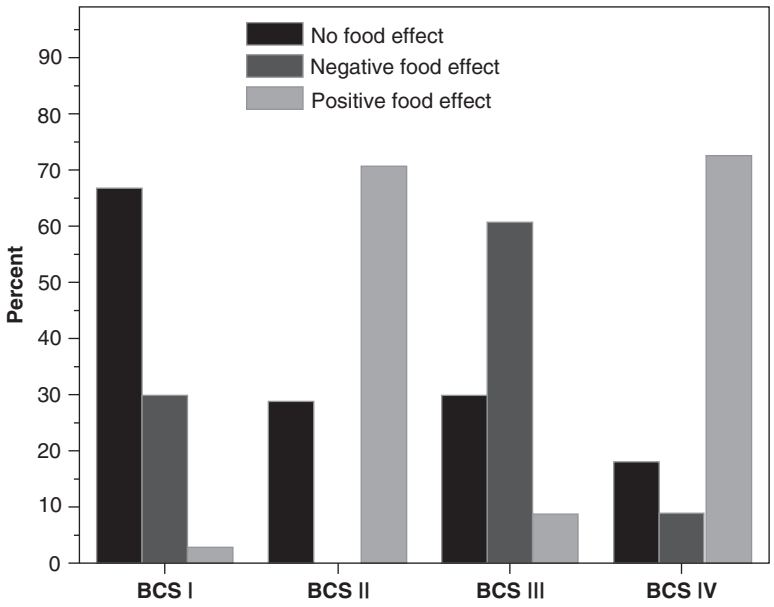

Fig. 1.1 Occurrence of food effects (positive, negative, or no effect) in percent by Biopharmaceutics Classifications System (BCS) category (Gu et al. 2007). Adapted with permission

food is known to delay gastric emptying which, in turn, is beneficial in terms of absorption as it increases the time available for drug dissolution (Charman et al. 1997). Second, a substantial rise in the gastric and intestinal fluid volume in the fed state offers the potential for increased dissolution rates (Custodio et al. 2008; Tanaka et al. 2015). Furthermore, food intake stimulates the release of bile from the gallbladder into the duodenum where its components, primarily bile salts, cholesterol, and phospholipids, solubilize dietary lipids into mixed micelles (Hofmann and Mysels 1987). Similarly, these mixed micelles have the ability to incorporate lipophilic drug molecules potentially boosting drug solubility by several orders of magnitude (Dressman et al. 2007). Bile salts may also enhance the dissolution rate of poorly soluble drugs by improved wetting which is predominantly the case when their concentration stays below the critical micelle concentration. As an example, a study conducted in healthy male volunteers found that the oral bioavailability of danazol, a BCS II drug, was increased by 400 % when administered together with a lipid-rich meal (Sunesen et al. 2005). This can be attributed to the presence of bile salts and lecithin in the small intestine allowing for micellar solubilization of the drug (Anby et al. 2014). In addition, an increase in gastric emptying time from 13 min (fasted state) to 49 min (fed state) was considered to play a role in bioavailability enhancement.

In the case of weakly acidic or basic drugs, which in the aqueous GI environment exist in ionized and unionized form, variations in gastrointestinal pH due to food intake can significantly increase or decrease drug solubility. In healthy subjects, the gastric pH in the fasted state typically lies in the range of 1–3, but may temporarily rise to 4–7 after meal intake (Lee and Yang 2001; Dressman et al. 2007). Studies using the SmartPill®, a telemetric capsule which can monitor pH changes during motility in the gastrointestinal track, found the pH increases to 3.3–5.3 after intake of a high caloric, high fat meal (Koziolek et al. 2015). Since the extent of ionization and consequently the solubility of a weakly acidic drug are greater at elevated pH, food intake may enhance drug dissolution in the stomach. In contrast, the extent of ionization of a weakly basic drug will be reduced at increased gastric pH, resulting in reduced dissolution and/or potential precipitation of already dissolved drug molecules.

Due to their high sensitivity to gastrointestinal changes caused by food intake, poorly soluble compounds are often associated with extremely variable and unpredictable oral bioavailability. Especially in the case of drugs that exhibit a narrow therapeutic window, sub-therapeutic, or toxic concentrations of the drug in the systemic circulation may easily occur. To prevent either scenario, patients generally have to adhere to certain food restrictions, potentially compromising patient compliance, and quality of life.

It should be noted though that the occurrence of food effects may be prevented by selection of an appropriate formulation design. Several formulation approaches that enhance drug solubility and therefore enable class II drugs to act as class I drugs have already been successfully applied to reduce or eliminate fed/fasted variability (Yasuji et al. 2011). These include, among others, nanoparticulate (Jinno et al. 2006; Sauron et al. 2006), self-emulsifying (Perlman et al. 2008; Woo et al. 2008), and solid dispersion-based drug-delivery systems (Klein et al. 2007; Mogalian et al. 2014), all of which will be addressed in depth in upcoming chapters.

The extent of oral bioavailability is affected not only by drug characteristics such as solubility and gastrointestinal permeability but also by a drug molecule's susceptibility to intestinal and hepatic metabolism and active influx/efflux transporters.

The presence of metabolic enzymes of cytochrome P 450 (CYP 450) within the endoplasmic reticulum of hepatocytes and intestinal enterocytes may significantly decrease oral bioavailability of many drugs (Lee and Yang 2001; Paine et al. 2006). Pre-systemic metabolism of drugs is often referred to as first-pass metabolism. Smith et al. suggested that this will particularly be the case for drugs that are lipophilic and therefore easily cross cell membranes, thereby gaining access to CYP enzymes (Smith et al. 1996). Further analysis by Wu and Benet confirmed that highly permeable BCS I and BCS II drugs are primarily eliminated via metabolism, while poorly permeable BCS III and IV drugs are mostly eliminated unchanged into the urine and bile (Wu and Benet 2005; Benet 2010). It should be, however, noted that the low/high permeability characteristics as defined in the BCS reflects the differences in access of the drug to metabolic enzymes within the cells and not necessarily differences in permeability into the cells (Custodio et al. 2008).

Based on their findings, Wu and Benet proposed the Biopharmaceutics Drug Disposition Classification System (BDDCS) in which drugs are categorized in terms of extent of metabolism and solubility as opposed to permeability and solubility used in the BCS (Fig. 1.2). According to the BDDCS, poorly soluble, highly permeable BCS II compounds are characterized by extensive metabolism defined as ≥70 % metabolism of an oral dose in vivo in humans.

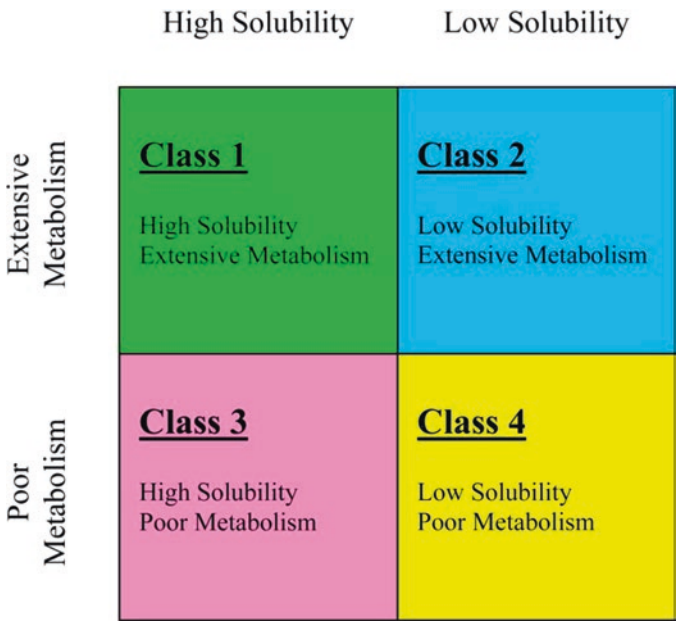

Fig. 1.2 The Biopharmaceutics Drug Disposition Classification System (BDDCS) (Custodio et al. 2008). Reprinted with permission

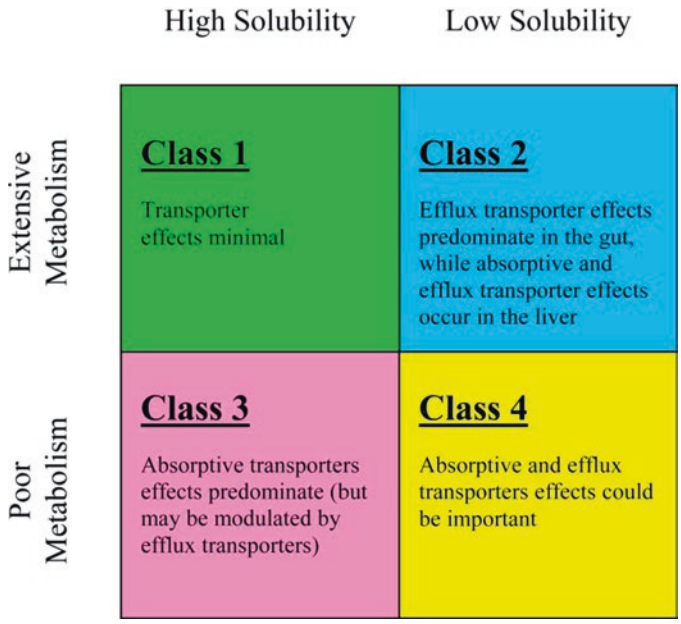

Fig. 1.3 Transporter effects, following oral dosing, by Biopharmaceutics Drug Disposition Classification System (BDDCS) class (Custodio et al. 2008). Reprinted with permission

The BDDCS also considers the influence of active uptake/efflux transporters on drug disposition as shown in Fig. 1.3. Since most BCS II compounds are substrates or inhibitors for P-glycoprotein (P-gp), a transmembrane efflux transporter, it is expected that the interplay of P-gp and metabolizing enzymes will notably influence the extent of metabolic extraction and oral bioavailability of BCS II substrates (Custodio et al. 2008).

Results from a number of studies aimed at understanding the interaction of CYP 450 enzymes and P-gp and its effect on compounds that are dual substrates suggest that both work synergistically to increase pre-systemic metabolism (Hochman et al. 2000). It is assumed that exposure of drugs, which are substrates of P-gp, to intestinal CYP 450 enzymes is increased due to repeated cycles of intracellular uptake and efflux. However, the complexity of metabolic enzyme-P-gp interactions is still only partially understood (Knight et al. 2006; Mudra et al. 2011).

1.3 Parenteral Route of Administration

Parenteral administration is commonly defined as the injection of dosage forms by subcutaneous, intramuscular, intra-arterial, and intravenous (i.v.) routes (Jain 2008). In the case of i.v. administration, the drug is directly delivered to the bloodstream, thereby allowing for rapid distribution to highly perfused organs. The consequently rapid onset of pharmacological effect that is achieved by i.v. administration is critical

for several clinical conditions that require immediate action such as cardiac arrest and anaphylactic shock (Shi et al. 2009). In addition, i.v. administration is advantageous for drugs for which oral delivery would result in low and erratic bioavailability due to gastrointestinal degradation or significant presystemic/first-pass metabolism. Overall, i.v. administration offers excellent control over the actual dose and rate at which the drug is delivered, providing more predictable pharmacokinetic, and pharmacodynamic profiles than obtained after oral administration (Bhalla 2007).

Since i.v. formulations are directly injected into the bloodstream, they are subject to strict regulatory requirements regarding their physical and chemical stability as well as their microbiological characteristics. The latter implicates that products intended for i.v. administration must be sterile and free of pyrogens (Akers 2014). Additionally the pH and tonicity of i.v. products should be carefully considered to prevent irritation, pain, and hemolysis of blood cells. To achieve the highest possible in vivo tolerability for an i.v. product, it should ideally be formulated as an aqueous-based solution that is isotonic and possesses a pH of 7.4. Clearly, this is not feasible for drugs that are characterized by poor aqueous solubility at this specific pH. Generally, poorly soluble compounds may be solubilized by pH adjustment (if the drug molecule is ionizable), the use of organic solvent mixtures, or mixed aqueous/organic cosolvents, and cyclodextrin complexation (Strickley 2004; Bracq et al. 2008). However, all these solubilization approaches are associated with major drawbacks such as increased toxicity or the possibility of drug precipitation upon injection and subsequent dilution (Yalkowsky et al. 1998).

Alternatively, the drug can be formulated in the form of a dispersion of particles which are suspended in aqueous media. The size distribution of intravenous suspensions is critical for safety and distribution of particles in vivo and generally restricted to the submicron range (Wong et al. 2008). Preventing particle agglomeration, aggregation, or crystal growth by adding suitable stabilizers is vital as an increase in particle size could result in the mechanical blockage of small-caliber arterioles and capillaries. The choice of stabilizers and generally excipients accepted for i.v administration is, however, rather limited which presents a common challenge for all formulation strategies mentioned.

1.3.1 Challenges in Parenteral Delivery of Poorly Water-Soluble Drugs

Poorly soluble weak acids or bases may be solubilized by pH modification of the solution to be administered. Yet, if the drug is characterized by very low solubility, pH-adjustment to extreme values might be necessary to achieve the desired drug concentration in solution (Lee et al. 2003). It is recommended, however, that the pH for i.v. infusions should be in the range of 2–10 in order to reduce side effects such as irritation and pain at the injection side (Egger-Heigold 2005).

Side effects may occur not only due to extreme pH values but also due to potential precipitation of the drug upon injection. A change in pH caused by dilution in the bloodstream may reduce the solubility of the drug below the solubility limit resulting in precipitation. Buffer species as well as buffer strength have been identified as key factors influencing drug solubility and consequently precipitation in pH-adjusted formulations (Narazaki et al. 2007). Phenytoin is a weakly acidic drug which is poorly soluble at pH 7.4 and has been reported to precipitate after injection. Addition of a cyclodextrin as a solubilizing agent was shown to reduce the risk of precipitation upon dilution (McDonald and Muzumdar 1998). It is essential to prevent precipitation as precipitated drug crystals may cause inflammation of the vein wall, also known as phlebitis, mainly due to mechanical irritation and prolonged drug exposure at the vein wall (Johnson et al. 2003). Besides, precipitation of solubilized drug molecules may result in erratic or reduced bioavailability as well as altered pharmacokinetics (Yalkowsky et al. 1998). For instance, precipitated particles in the low micron to submicron range may be taken up by macrophages of the reticuloendothelial system resulting in a significantly increased drug plasma clearance rates (Bittner and Mountfield 2002). Furthermore, dissolution of precipitated drug at later time points may increase the terminal half-life as well as the volume of distribution.

Drugs that are not sufficiently solubilized by pH adjustment or drugs that have no ionizable groups may be formulated using organic water-miscible cosolvents and surfactants. Frequently used cosolvents for i.v. formulations are propylene glycol, ethanol, and polyethylene glycols while commonly used surfactants include polysorbate 80, Cremophor EL, and Cremophor RH 60 (Strickley 2004; Bracq et al. 2008). Highly lipophilic compounds may even require formulation in a nonaqueous, organic vehicle comprising only water-miscible solvents and/or surfactants. These are commonly concentrates which are diluted with aqueous media prior to administration. Overall, the number and concentration of organic solvents and surfactants is limited as they may cause side effects. Organic solvents as well as surfactants have been reported to provoke hemolysis, the rupturing of erythrocytes (Reed and Yalkowsky 1987; Shalel et al. 2002). Resulting hemoglobin release into the blood plasma may induce vascular irritation, phlebitis, anemia, kernicterus, and acute renal failure (Krzyzaniak et al. 1997; Amin and Dannenfelser 2006). The hemolytic potential of these additives has been evaluated in numerous studies (Zaslavsky et al. 1978; Ohnishi and Sagitani 1993; Mottu et al. 2001). Yet, conflicting results have been reported due to different methodologies used. Table 1.1 summarizes in vitro hemolysis data for different cosolvent systems obtained in rabbit, dog, and human blood compared to human in vivo data acquired from the literature (Amin and Dannenfelser 2006). For all vehicles a higher percentage of hemolysis is seen for data obtained with human blood followed by rabbit and dog blood; yet, the rank order of different vehicles evaluated is similar for the different species evaluated.

Just like solubilization via pH adjustment, solubilization by means of cosolvents has the limitation of potential drug precipitation (Li and Zhao 2007). Figure 1.4 exemplarily depicts the solubility curve of a drug at different cosolvent levels (squares) compared to the drug concentration curve based on dilution (dots). The saturation solubility of the drug in a 50 % (v/v) cosolvent system is 2.4 mg/mL,

Table 1.1 Detection of hemolysis by in vivo and in vitro methods

Formulation composition	In vivo literature	In vitro (% hemolysis detected)		
		Human blood	Rabbit blood	Dog blood
Normal saline (NS)	No	0.0	0.0	0.0
10 % EtOH in NS	No	0.0	0.0	10.0
30 % EtOH in NS	No	0.0	0.0	2.5
40 % PG in NS	Yes	61.0	37.3	29.7
60 % PG in water	Yes	100.00	96.7	53.4
10 % PG + 30 % EtOH in NS	No	0.0	0.0	0.0
10 % EtOH + 20 % PG in water	No	8.8	0.0	0.3
10 % EtOH + 40 % PG in water	Yes	69.2	52.6	31.5
20 % EtOH + 30 % PEG 400 in water	No	0.0	0.0	3.3

PG propylene glycol, *EtOH* ethanol; Amin and Dannenfelser 2006. Reprinted with permission

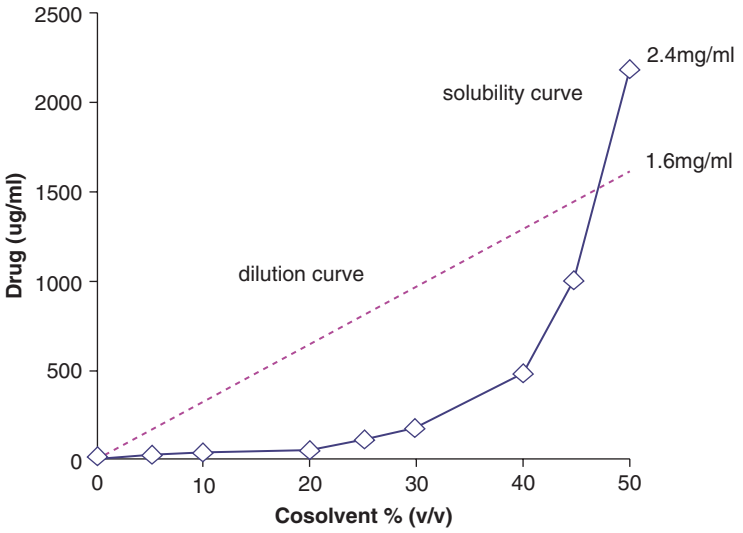

Fig. 1.4 Illustration of precipitation of a drug formulated in a 50 % (v/v) cosolvent system (Li and Zhao 2007). Reprinted with permission

while the drug is formulated at a concentration of 1.6 mg/mL. Upon injection, the concentrations of the cosolvent and drug will decrease linearly due to dilution in the bloodstream. In contrast, drug solubility will decrease exponentially, causing it to fall below the actual drug concentration rapidly. This means that the drug is present in the supersaturated state where it is susceptible to precipitation. It has been suggested that the addition of surfactants to cosolvent formulations, even in small concentrations (0.05–0.5 % w/v), may prevent precipitation upon i.v. administration (Li and Zhao 2007).

The formulation of i.v. products with surfactants, especially in high concentrations, has been associated with acute hypersensitivity reactions characterized by dyspnea, flushing, rash, chest pain, tachycardia, and hypotension (ten Tije et al. 2003). Paclitaxel, a poorly water-soluble molecule with antineoplastic activity, was first formulated in form of a nonaqueous solution for i.v. infusion (Taxol®), in which the drug is solubilized in a mixture of Cremphor EL and ethanol (Singla et al. 2002). This formulation can cause significant hypersensitivity reactions, which are primarily attributed to Cremophor EL, necessitating premedication of patients with steroids and antihistamines. Complement activation due to binding of the hydroxyl-rich surface of Cremophor EL to naturally occurring anti-cholesterol antibodies has been proposed as a possible underlying mechanism for the occurrence of these hypersensitivity reactions (Szebeni et al. 1998). Docetaxel, a semi-synthetic analog of paclitaxel, is solubilized with the nonionic surfactant polysorbate 80 in its marketed formulation Taxotere® (Engels et al. 2007). This concentrate is further diluted with 13 % ethanol in water for injection and saline or dextrose solution before i.v. administration. Like Taxol®, Taxotere® often results in severe side effects specifically, severe hypersensitivity reactions mainly caused due to the presence of polysorbate 80 in the formulation.

The use of surfactants in i.v. formulations may not only cause hypersensitivity reactions but also alter drug pharmacokinetics by interfering with distribution processes, transporters, or metabolic enzymes (Egger-Heigold 2005). It has been reported that Cremophor EL modifies the pharmacokinetics of several drugs such as etoposide, doxorubicin, and paclitaxel (Ellis et al. 1996; Webster et al. 1996; Sparreboom et al. 1996). A study conducted in mice, which received Taxol® (paclitaxel solubilized in Cremophor EL and ethanol) by i.v. injection at three different dose levels, revealed a nonlinear pharmacokinetic behavior of paclitaxel (Sparreboom et al. 1996). In particular, a disproportional increase in c_{max} and a decrease in the plasma clearance upon dosage escalation were observed. In contrast, i.v. administration of a Cremophor EL-free solution of paclitaxel in the organic solvent dimethylacetamide resulted in a c_{max} that varied proportionally with dosage as well as a dose-independent clearance. Studies in mice with Cremophor EL and various other active ingredients have confirmed these findings to be an effect of the surfactant (Liu et al. 2016). The same nonlinear pharmacokinetic was also observed in an in vivo study involving patients with solid tumors who were treated with different dose levels of Taxol® (van Zuylen et al. 2001). It has been suggested that the Cremophor EL-related nonlinear paclitaxel pharmacokinetics is caused by entrapment of the drug into Cremophor EL micelles which function as the primary carrier in the systemic circulation leading to a disproportionate paclitaxel accumulation in the plasma (Sparreboom et al. 1999).

Finally, complexation of poorly water-soluble drugs with cyclodextrins has been explored as an alternative approach for i.v. delivery of these troublesome compounds. Cyclodextrins are cyclic oligosaccharides composed of six, seven, or eight (α-1, 4)-linked α-D-glucopyranose units corresponding to α-, β-, and γ-cyclodextrins, respectively (Brewster and Loftsson 2007). They are characterized by a hydrophilic outer surface and a lipophilic inner cavity, which is capable of accommodating suitable drug compounds. Cyclodextrins employed for parenteral delivery, that is,

hydroxypropyl-β-cyclodextrin, and sulfobutylether-β-cylcodextrin, are derivatives of β-cyclodextrin with increased aqueous solubility and improved in vivo safety profiles (Stella and He 2008). Cyclodextrins oftentimes solubilize drug molecules as a linear function of their concentration. Consequently, dilution of the formulation in the blood stream upon i.v. administration will result in a linear reduction of both drug and cyclodextrin concentration. Based on that, drug precipitation that is oftentimes seen with cosolvent or pH-adjusted systems is very unlikely to occur with cyclodextrin-based formulations. Nevertheless, there are several shortcomings associated with the use of cyclodextrins as means of solubility enhancers. Solubilization by cyclodextrins is not generally applicable to all drug molecules. In order to successfully form a stable cyclodextrin-drug inclusion complex, the drug molecule needs to have the appropriate size, shape, and polarity to fit into the central cyclodextrin cavity (Radi and Eissa 2010). Additionally, cyclodextrins are excreted in the urine and accumulation could occur in patients with renal insufficiency (Stella and He 2008). Drug release from cyclodextrin inclusion complexes after i.v. injection is generally rapid and quantitative, with the main driving force being the dilution in the blood stream (Stella et al. 1999). Problems may however arise for strongly bound drugs with high complex-forming constants where the drug does not rapidly dissociate from the complex potentially altering pharmacokinetics.

1.4 Ocular Route of Administration

Drug delivery by the ophthalmic route is characterized by specialized preparations which are intended to provide direct contact with the eye. Currently the most commonly used commercial eye medications are prepared as eye drops, as they are relatively easy to administer by patients (Vandervoort and Ludwig 2007). However, other ophthalmic dosage forms exist; including gel and ointment-based topicals, intravitreal injections, periocular drug delivery preparations and ocular devices. Each of these possess their own advantages and disadvantages for treating certain diseases of the eye. Ophthalmic formulations are targeted for local treatment of ocular diseases. By using the ophthalmic route of delivery, therapy can be maximized at the site of action while minimizing systemic exposure, reducing the chances for adverse events. Drug delivery to the eye is met with its own unique challenges which must be overcome to achieve therapeutic delivery which can be reliably used by patients.

The eye comprises two main regions, the anterior and posterior compartments, which are separated and delineated by the crystalline lens. The layer at the most anterior portion of the eye is the cornea, a window located in front of the lens that allows light to enter the eye. Eye drops and other topical ophthalmic preparations are intended for absorption across the cornea into the aqueous humor, the fluid residing in the anterior compartment. This is the site of action for many therapeutic agents, largely including those which lower intraocular pressure for treating glaucoma (Weinreb and Khaw 2004). The posterior part of the eye is where the

photoreceptors are located, allowing visual information to be relayed to the brain (Alqawlaq et al. 2012). The chamber in the back of the eye is filled with vitreous humor. Unlike the aqueous humor, this vitreous humor media is more gel-like in nature and contributes to the orbital structure of the eye (Chowhan et al. 2012). The vitreous humor is approximately 4 mL in volume and composed of 98 % water along with hyaluronic acid, collagen fibrils and some phagocytic mononuclear cells (Martens et al 2013; Sebag 2013). Excluding the cornea, the outermost layer of the eye is made up of the sclera. The sclera is a tough fibrous layer which is the white of the eye. Drugs which are administered by periorbital routes may be absorbed through the sclera (Ahmed and Patton 1985). Periorbital routes include peribulbar, subconjunctival, posterior juxtascleral, sub-Tenon and retrobulbar injections, which administer drugs in contact with the sclera for transscleral penetration into the vitreous humor and to the retina. The retinal and vitreal drug bioavailability is about 0.01–0.1 % via these routes, which is much higher than that of topical delivery (0.001 % and less) (Tsuji et al. 1988; Kim et al. 2004; Kaur and Kakkar 2014). Intravitreal injections, injections directly into the vitreous humor, are the most direct method of delivering medications to the posterior portion of the eye. Periorbital, but most often, intravitreal injections can be used for treating conditions like age-related macular degeneration residing in the posterior portion of the eye.

1.4.1 Challenges in Ocular Delivery of Poorly Water-Soluble Drugs

For many topically applied drugs to have efficacy, they must permeate across the cornea membrane. Transcorneal absorption is the predominate mechanism of entrance for small molecules entering the eye (Urtti 2006). However, absorption into the eye from the external environment is hindered by a number of mechanisms resulting in ocular bioavailability which is typically less than 5 % (Urtti 2006). One of these mechanisms is related to the structure of the cornea as depicted in Fig. 1.5. It consists of five layers which drugs must pass through to enter the aqueous humor. The outermost layer of the cornea is the hydrophobic stratified squamous epithelium, beneath this is the Bowman's membrane. The thickest layer of the cornea is a hydrophilic matrix located underneath the Bowman's membrane called the stroma. Following the stroma is the Descemet's membrane then the corneal endothelium, another hydrophobic layer (Edwards and Prausnitz 1998; Friedman et al. 2007). The complexity of the cornea, transitioning from hydrophobic to hydrophilic to hydrophobic layers, makes transcorneal drug transport a challenging route for delivery. Current methods to overcome this barrier include; increasing the dissolution rate of the drugs and including excipients for increased permeability (Li et al. 2013; Nagai et al. 2015). Formulating poorly soluble drugs as a nanosuspension has been shown to increase the ocular bioavailability as well as decrease irritation of the eye (Kim et al 2011).

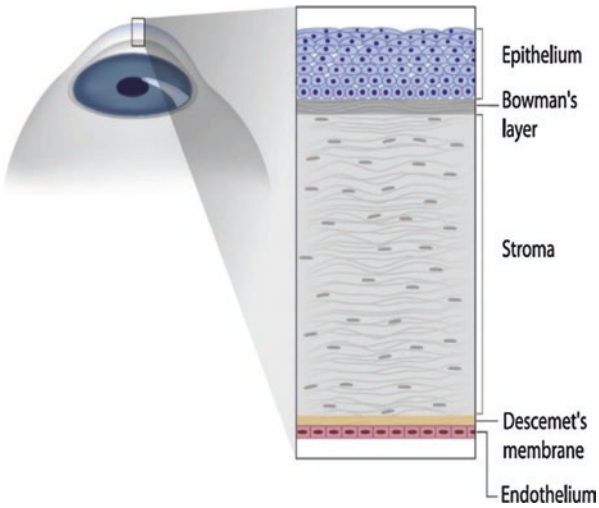

Fig. 1.5 Illustration of the layers comprising the cornea membrane (Sharif et al. 2015). Reprinted with Permission

In addition to the permeability limits for absorption, topically administered drugs are limited by a relatively short residence time in contact with the cornea. The typical volume of the tear film, the liquid layer coating the rostral surface of the eye, is between 5 and 7 μL, but the area as a whole has a maximum capacity of about 30 μL (Foster and Lee 2013). On average, the administered volume from commercial eye drops is 39 μL, ranging from 25.1 to 56.4 μL (Van Santvliet and Ludwig 2004). Volumes delivered above the maximum capacity of the eye are rapidly cleared, one avenue being through the nasolacrimal duct which leads to increased systemic absorption (Van Santvliet and Ludwig 2004). There are several formulation strategies which can be used to help reduce clearance of medications from the ocular surface. Administration of eye drops of smaller volume can be as efficacious as larger volume doses with the same concentration solution by reducing the rate at which the preparation is removed from the site of absorption (Petursson et al. 1984). Formulating poorly soluble drugs, for example acetazolamide or pilocarpine, into eye drops which gel or increase in viscosity after coming into contact with the eye permits the ease of administration of an eye drop with an increase in residence time for absorption (Verma et al. 2013; Miyazaki et al. 2001). Gel and ointment-based formulations can also be utilized to increase contact time for absorption. However, these formulations are typically more difficult to administer than eye drops and suffer from greater dose variability (Chowhan et al. 2012).

Many reports have shown that cyclodextrin formulations can achieve effective drug delivery of poorly water soluble drugs administered ophthalmically (Kristinsson et al. 1996; Sigurdsson et al. 2005; Jansook et al. 2010; Ohira et al. 2015). Cyclodextrins can help improve ocular bioavailability by complexing and solubilizing poorly soluble drugs as well as by acting as permeation enhancers; increasing the diffusion of drugs across the gel-like inner most layer of the tear film (Loftsson et al. 2012). Jansook et al. formulated dorzalamide as a complex with

γ-cyclodextrins which formed reversible mucoadhesive agglomerates in the microparticle range. These suspended particles were found to act as a reservoir for sustaining dorzolamide concentrations within the tear film. This resulted in concentrations detectable for up to 24 h after topical administration, while the commercial formulation was shown to have practically no drug left in the aqueous humor after only 8 h. It has also been reported that cyclodextrins can increase posterior drug delivery of topically applied medications (Loftsson et al. 2007, 2008; Jansook et al. 2010; Ohira et al. 2015) The enhanced posterior delivery is due to the higher permeability of the conjunctiva/sclera membrane compared to that of the cornea (Loftsson et al. 2008). Emulsion drug delivery systems have been reported to increase drug delivery of poorly soluble drugs (Naveh et al. 1994; Calvo et al. 1996; Tamilvanan and Kumar 2011; Ying et al. 2013). Cyclosporin A, a poorly soluble drug used to treat chronic dry eye disease, is commercially available as Restasis®, a viscous emulsion intended for topical eye delivery. Restasis® utilizes castor oil as a disperse phase, which is stabilized with polysorbate 80 and carbomer 1342, to produce an emulsion which is effective and nonirritating to the sensitive eye tissue (Ding et al. 1995; Tamilvanan and Benita 2004).

Intravitreal injections can be used to deliver medications directly into the vitreous humor of the posterior eye. The clearance of medications given intravitreally is often magnitudes slower than that for drugs absorbed into the aqueous humor, resulting in half-lives of days as opposed to hours. The smaller the particles injected into the vitreous humor; the longer the residence time for the particles. For example, Sakurai et al. found that 50 nm polymeric nanoparticles have nearly twice the half-life (10.1 days) of similar 2 μm particles (5.4 days) (Sakurai et al. 2001) when administered by intravitreal injection in rabbits. Due to the relatively long half-life for medications given intravitreally, dosing regimens can be extended to monthly and even quarterly administration for some medications (Kaur and Kakkar 2014). Intravitreal injection administration is more technically difficult than topical delivery to the eye and, therefore, requires the need of healthcare professionals. They also introduce additional risks compared to topical therapy such as retinal detachment, which may be irreversible (Meyer et al. 2011). Intravitreal inserts are designed to further improve the pharmacokinetics by controlling drug release and reduce the number of needed injections. Iluvien®, an intravitreal implant delivering fluocinolone acetonide, lasts for up to 3 years after injection into the eye which maximizes drug delivery to the retina while minimizing systemic and anterior chamber exposure (Kane et al. 2008).

1.5 Nasal Route of Administration

Nasal drug delivery can have many potential advantages and disadvantages over conventional oral drug delivery. Nasal drug delivery can be targeted for treating local, systemic and, more recently, explored for central nervous system (CNS) diseases. Traditionally, nasal delivery has been focused on treating local disease such as nasal congestion, nasal allergies and nasal infections (Illum 2003). Systemic delivery through nasal administration can be advantageous for a number of reasons.

The relatively high vascularization and permeability of the nasal respiratory epithelium often allows for favorable absorption. Additionally, the bioavailability can be increased for drugs which would otherwise undergo significant presystemic metabolism in the liver if given orally.

The nasal cavity (Fig. 1.6) is comprised of three main areas, the vestibule and nasal valve area, the respiratory area and the olfactory area, each of which is divided into two halves by the nasal septum (Clerico et al. 2003). The nasal valve area within

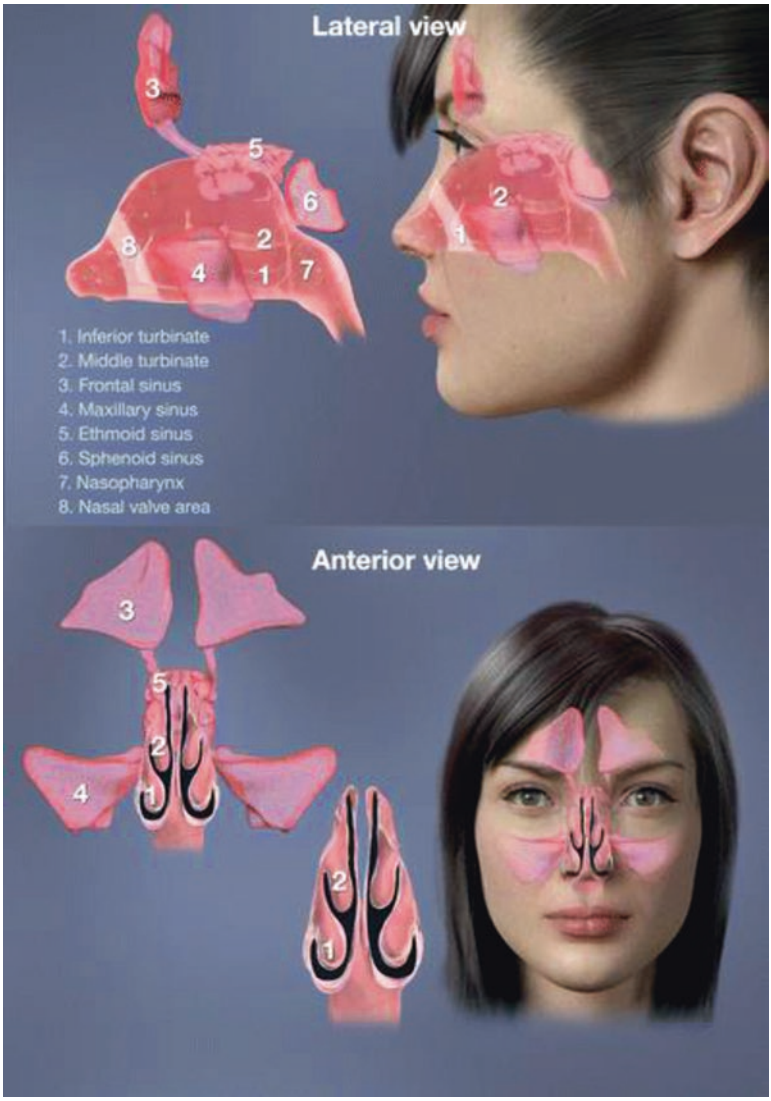

Fig. 1.6 Anatomy of the nasal cavity and sinuses from a lateral (*top*) and anterior (*bottom*) view (Djupesland 2013) (with permission)

the vestibule is the narrowest portion of the nasal cavity and is responsible for the majority of its airway resistance. The respiratory area, posterior to the nasal vestibule, comprises of three turbinates. The inferior, middle and superior turbinates function to produce turbulent airflow within the nasal cavity. The airflow within the nasal cavity is designed to filter and condition the air before it reaches later stages of the respiratory system (Thomas and Ahsan 2008). The olfactory region is located in the uppermost portion of the nasal cavity and is responsible for our sense of smell. The region is comprised of olfactory neuroepithelium, the only place where first order neurons are in contact with the external environment (Lochhead and Thorne 2012).

Nasal drug delivery has been accomplished using several methods. One of the oldest methods of delivering liquids to the nasal cavity is the use of drops. Drops are advantageous as they are low-cost and relatively straightforward to manufacture (Kublik and Vidgren 1998). However, the dose from nasal drops is often difficult to control, the larger drop volume results in rapid clearance compared to sprays, and complex maneuvers can be required for proper administration by patients (Hardy et al. 1985). To overcome the disadvantages of nasal drops, most pharmaceutical liquids on the market today are delivered by meter-dosed pump sprays. Meter-dosed pump sprays accurately deliver volumes between 25 and 200 μL. The particle size of the drops from pump sprays is a product of the device, patient handling, as well as the formulation, which varies based on the viscosity and surface tension of the product (Dayal et al 2004). Although currently not on the market in the United States, nasal formulations can also be delivered as powders. Powder drug delivery provides the highest mass of active ingredients for a given volume, a limiting factor for nasal drug delivery (Kublik and Vidgren 1998).

1.5.1 Challenges in Nasal Delivery of Poorly Water-Soluble Drugs

Systemic absorption of drugs delivered nasally primarily takes place in the respiratory region due to the high surface area, vascularization, and airflow restriction (Kublik and Vidgren 1998). However, the narrow geometry of the nasal valve makes it challenging for dosage forms to deposit in this area. Several studies have shown that a majority of the droplets from meter-dose pump sprays deposit in the anterior third of the nasal cavity, which is mostly comprised of the vestibule and nasal valve area (Suman et al. 1999; Cheng et al 2001; Djupesland et al. 2006; Shah et al. 2014). The area which nasal sprays deposit is influenced by the geometry of the emitted plume. Narrower plume geometries are formed by modifying the device or increasing the viscosity of the formulation. Narrower plume geometries result in greater deposition to the posterior portions of the nasal cavity (Foo et al. 2007). Additionally, to successfully target CNS drug delivery by intranasal administration, drug deposition needs to reach the olfactory region, requiring novel device designs (Djupesland 2013). As the neurons in the neuroepithelium of the olfactory region

are in direct contact with the external environment, drugs can be directly transported from the nose to the brain, bypassing the blood–brain barrier (Dhuria et al. 2010). This can be beneficial for drugs which do not typically cross the blood–brain barrier to therapeutic concentrations, as well as for drugs which otherwise would cause high systemic adverse effects.

Due to the small volume limitations for nasal drug delivery dosages, delivery of poorly water-soluble drugs in quantities that are sufficient for a therapeutic response can be challenging. Many of the commercially available poorly soluble corticosteroids used nasally only require microgram doses for efficacy and are formulated as aqueous suspensions. For drugs requiring higher doses, formulation scientists may use excipients and alter the physical characteristics of the formulation to solubilize the drug to a greater extent. A study whose objective was to achieve CNS-targeted delivery of olanzapine, a drug typically requiring milligram doses for efficacy with limited solubility in water, was formulated in a nanoemulsion to obtain a concentration of 8.5 mg/mL. The formulation, in combination with the targeted delivery, was effective in showing a pharmacodynamic response when dosed in rats (Kumar et al. 2008). Like other routes of administration, cyclodextrins can be used to increase the solubility of poorly water-soluble drugs. Additionally, cyclodextrins can act as permeation enhancers to increase the bioavailability for poorly permeable drugs (Marttin et al. 1998; Kim et al. 2014). Another approach to providing larger doses is using powder delivery formulations. Depending on the bulk density of the powder, quantities up to about 50 mg can be dosed intranasally (Filipović-Grčić and Hafner 2008). A challenge to utilizing formulation parameters to enhance nasal drug delivery is the relatively limited list of inactive ingredients that have been approved in nasal products. Using new formulation technologies that require higher quantities and new excipients for the nasal route of delivery require toxicity studies to assure safety of the nasal mucosa (FDA Guidance for Industry 2005). The pH of the solution may be modulated to affect the solubility and permeability of the poorly water-soluble drugs. Pujara et al. report the nasal mucosa can withstand buffers with pH range of 3–10 with minimal signs of damage based on nasal epithelium irritation studies. Additionally, they found the concentration and type of buffer, including the buffer capacity, play a role in the safety of the formulation to the nasal mucosa (Pujara et al. 1995).

One of the limiting barriers to the bioavailability of drugs delivered nasally is the short residence time due to mucociliary clearance. The respiratory epithelium of the nasal cavity is equipped with motile cilia that beat at 1000 strokes per minute (Illum 2003). This results in a mucus flow rate of 8–100 mm/min in the posterior regions of the nasal cavity, which is directed towards the nasopharynx where it will be swallowed (Kublik and Vidgren 1998). To increase the residence time for nasal absorption of drugs after delivery, formulators add viscosity-increasing and mucoadhesive agents to the formulations (Chaturvedi et al. 2011). To permit effective dosing of the formulation while maintaining an increased residence time, Wang et al. prepared an in-situ gelling formulation utilizing deacetylated gellan gum. Curcumin was formulated as a microemulsion as it is poorly soluble in water. The deacetylated gellan gum was incorporated into the aqueous phase of the microemulsion to facilitate the in-situ gelling action. When the formulation comes into contact with the nasal secretions of