AAPS Advances in the Pharmaceutical Sciences Series 50

Robert O. Williams III
Daniel A. Davis Jr.
Dave A. Miller *Editors*

Formulating Poorly Water Soluble Drugs

Third Edition

aaps®

Springer

AAPS Advances in the Pharmaceutical Sciences Series

Volume 50

The AAPS Advances in the Pharmaceutical Sciences Series, published in partnership with the American Association of Pharmaceutical Scientists, is designed to deliver volumes authored by opinion leaders and authorities from around the globe, addressing innovations in drug research and development, and best practice for scientists and industry professionals in the pharma and biotech industries. Indexed in

Reaxys
SCOPUS Chemical Abstracts Service (CAS) SCImago
EMBASE

More information about this series at http://www.springer.com/series/8825

Robert O. Williams III
Daniel A. Davis Jr. • Dave A. Miller
Editors

Formulating Poorly Water Soluble Drugs

Third Edition

aaps®

Springer

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

Daniel A. Davis Jr.
Division of Pharmaceutics
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA

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

ISSN 2210-7371 ISSN 2210-738X (electronic)
AAPS Advances in the Pharmaceutical Sciences Series
ISBN 978-3-030-88718-6 ISBN 978-3-030-88719-3 (eBook)
https://doi.org/10.1007/978-3-030-88719-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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

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

Bill

To my wife, Sydney. Thank you for always being there with your unconditional love and support!

Danny

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

Dave

Preface

High-throughput screening (HTS) methodologies for lead identification in drug discovery were developed in the 1980s to enable the utilization of advances in genomics and combinatorial chemistry. Since their advent, HTS methodologies have developed rapidly and have been widely adopted in the pharmaceutical industry. Consequently, the number of potential drug candidates identified by HTS has steadily increased over the decades. The HTS approach tends to identify leads with high-molecular weight and lipophilicity, and, consequently, poor water solubility. As more and more leads are identified by HTS, poorly water-soluble drug candidates are emerging from drug discovery with greater frequency. The problem of poor solubility has therefore become pervasive in the pharmaceutical industry recently, with percentages of poorly water-soluble compounds in development pipelines reaching as high as 80–90% depending on the therapeutic area.

Drug dissolution is a necessary step to achieve systemic exposure that ultimately leads to binding at the biological target to elicit the therapeutic effect. Poor water solubility hinders dissolution and therefore limits drug concentration at the target site, often to an extent that the therapeutic effect is not achieved. This can be overcome by increasing the dose; however, it may also lead to highly variable absorption that can be detrimental to the safety and efficacy profile of the treatment. In these cases, solubility enhancement is required to improve exposure, reduce variability, and, ultimately, improve the drug therapy. It is therefore understood that in modern pharmaceutical development, solubility-enhancement technologies are becoming critical to rendering viable medicines from the growing number of insoluble drug candidates.

A pharmaceutical scientist's approach toward solubility enhancement of a poorly water-soluble molecule typically includes detailed characterization of the compounds physiochemical properties, solid-state modifications, advanced formulation design, nonconventional process technologies, advanced analytical characterization, and specialized product performance analysis techniques. The scientist must also be aware of the unique regulatory considerations pertaining to the nonconventional approaches often utilized for poorly water-soluble drugs. One faced with the challenge of developing a drug product from a poorly soluble compound must possess at minimum a working knowledge of each of the above-mentioned facets and detailed knowledge of most. In light of the magnitude of the growing solubility problem to drug development, this is a significant burden especially when

considering that knowledge in most of these areas is relatively new and continues to develop. There are numerous literature resources available to pharmaceutical scientists to educate and provide guidance toward formulations development with poorly water-soluble drugs; however, a single, comprehensive reference is lacking. Furthermore, without access to a vast journal library, the detailed methods used to implement these approaches are not available. The objective of this book is therefore to consolidate within a single text the most current knowledge, practical methods, and regulatory considerations pertaining to formulations development with poorly water-soluble molecules.

The volume begins with an analysis of the various challenges faced in the delivery of poorly water-soluble molecules according to the route of administration, that is, oral, parenteral, and pulmonary. This chapter provides understanding of the formulation strategies that one should employ depending on the intended route of administration. Chapter 2 covers analytical techniques most pertinent to poorly water-soluble drugs with regard to preformulation, formulation characterization, and in vitro performance assessment. Solid-state approaches to overcoming solubility limitations are discussed in Chap. 3. This chapter presents an in-depth review of the solubility benefits obtained via conversion of drug crystals to salts, cocrystals, metastable polymorphs, and amorphous forms. When such solid-state approaches are not viable, particle-size reduction of the stable crystalline form is perhaps the next most straightforward option. In Chap. 4, mechanical particle-size reduction technologies are described, providing a comprehensive discussion of traditional and advanced milling techniques commonly used to increase surface area and improve dissolution rates.

Oftentimes, modification of the API form is not possible and particle-size reduction fails to appreciably increase the dissolution rate owing to the inherent solubility limitation of the stable crystalline polymorph. In these cases, a noncrystalline approach is necessary; perhaps the most straightforward noncrystalline approach is a solution-based formulation. Solution-based approaches are covered by Chaps. 5, 6, and 7 where liquid formulation technologies for poorly water-soluble drugs are presented. Chapter 5 provides a review of solution systems for oral delivery whereby the molecule is dissolved in a suitable nonaqueous vehicle. The chapter discusses the various vehicles available for such systems as well as options for conversion to a final dosage form. Chapter 6 reviews techniques for overcoming compound solubility challenges in developing liquid formulations for parenteral administration, which is of particular relevance as the number and complexity of cancer therapeutics continue to increase. Advanced liquid formulations for oral delivery, self-emulsifying systems, are discussed in Chap. 7. These systems are advancements over traditional solution formulations in that the formulation droplet size formed on contact with GI fluids can be controlled through rational formulation design. Controlling droplet size to the micro- or nanometer scales has been shown to produce significant enhancements in drug absorption.

In many cases, poorly water-soluble compounds also exhibit limited solubility in vehicles suitable for oral liquid formulations. In these cases (assuming

all other previously mentioned options are not viable), an amorphous formulation approach is often necessary. The design of amorphous formulations presents numerous challenges, which much of the latter half of this book (Chaps. 8, 9, 10, 11 and 12) aims to address. These chapters describe the importance of appropriate preformulation studies, formulation design, process selection, as well as considerations specific to the selected process technology. In Chap. 8, a structured, rational approach toward the development of optimized amorphous solid dispersion formulations is presented. Specific emphasis is given to critical preformulation studies, identification of the best excipient carrier system, optimization of drug loading, and process technology selection. Chapter 9 provides a comprehensive guide to the application of hot-melt extrusion technology for the formulation of poorly water-soluble drugs. This chapter provides a detailed overview of the process technology as well as formulation design considerations specific to hot-melt extrusion applications. Spray drying is the subject of Chap. 10, again emphasizing the process technology and formulation development specific to spray drying. Particular focus is given to the development of amorphous spray-dried dispersions owing to its industrial relevance to the production of viable products containing poorly water-soluble drugs. Chapter 11 teaches cryogenic technologies whereby nanostructured particles and amorphous solid dispersions are formed by rapid freezing technologies. The chapter discusses different cryogenic process technologies, formulation design considerations, and downstream processing options. Precipitation technologies for the production of engineered particles and solid dispersions are covered in Chap. 12. Various solvent/antisolvent techniques are discussed along with formulation design principles, particle recovery techniques, and key process design considerations.

Emerging technologies relevant to the formulation of poorly water-soluble drugs are discussed in Chap. 13. These are technologies that have begun to appear in the literature and elsewhere in recent years, which exhibit promise but have yet to mature. Finally, in Chap. 14, regulatory considerations specific to drug products of poorly water-soluble compounds are presented. It is the aim of this chapter to educate formulation scientists regarding unique regulatory aspects to consider for solubility-enhancement approaches, that is, solid-state modifications, particle-size reduction, lipid/solution formulations, and amorphous solid dispersions. This chapter also provides a unique review of case studies for marketed products that employ these solubility-enhancement approaches, highlighting the principal regulatory concerns for each case.

This volume is intended to provide the reader with a breadth of understanding regarding the many challenges faced with the formulation of poorly water-soluble drugs as well as in-depth knowledge in the critical areas of development with these compounds. Further, this book is designed to provide practical guidance for overcoming formulation challenges toward the end goal of improving drug therapies with poorly water-soluble drugs. Enhancing solubility via formulation intervention is a unique opportunity in which formulation scientists can enable drug therapies by creating viable medicines from seemingly undeliverable molecules. With the ever-increasing number of

poorly water-soluble compounds entering development, the role of the formulation scientist is growing in importance. Also, knowledge of the advanced analytical, formulation, and process technologies as well as specific regulatory considerations related to the formulation of these compounds is increasing in value. Ideally, this book will serve as a useful tool in the education of current and future generations of scientists, and in this context contribute toward providing patients with new and better medicines.

The editors sincerely thank all contributors for their dedication toward achieving the vision of this book. It is thanks only to your knowledge and efforts that it was accomplished.

Austin, TX, USA — Robert O. Williams III
Austin, TX, USA — Daniel A. Davis Jr.
Georgetown, TX, USA — Dave A. Miller

Contents

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 may commonly result in low bioavailability and are often subject to considerable food effects. In addition, poorly soluble drugs intended for parenteral delivery may also have to be solubilized with large amounts of cosolvents and surfactants, oftentimes resulting in adverse physiological reactions. Other routes also offer unique opportunities for this class of drug molecules but also their own challenges. Ocular delivery of poorly soluble drugs is challenging due to the efficient absorption barriers and clearance mechanisms. Development of poorly soluble drugs administered mucosally through routes such as the nasal cavity, oral mucosa, and others may be restricted by the relatively small administered volume, the geometry of the administration site, and the excipients commonly used in these formulations. Successful formulation design of poorly soluble drugs' intended alternative routes of administration may be 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 these tissues. In summary, this chapter reviews the specific challenges faced in the delivery of poorly water-soluble drugs via oral, parenteral, and mucosal 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 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

Z. Warnken (✉)
Via Therapeutics LLC, Austin, TX, USA
e-mail: Zwarnken@viatherapeutics.com

H. D. C. Smyth · R. O. Williams III
Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA
e-mail: hugh.smyth@austin.utexas.edu; bill.williams@austin.utexas.edu

R. O. Williams III et al. (eds.), *Formulating Poorly Water Soluble Drugs*, AAPS Advances in the Pharmaceutical Sciences Series 50, https://doi.org/10.1007/978-3-030-88719-3_1

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:

$$\frac{dM}{dt} = \frac{D \cdot A}{h} \cdot (c_s - c_t),$$

where dM/dt 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 without consideration for improving solubility will 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, for example, by employing large amounts of cosolvents and surfactants. Problems often arise when these excipients may not be well tolerated, potentially causing hemolysis and/or hypersensitivity reactions (Yalkowsky et al. 1998). In addition, there may be a 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, and mucosal 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 for systemic 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, be absorbed across the intestinal mucosa, and pass through the liver 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 the 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, reported in 2006 by Benet et al., 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). This is in part a result of contemporary approaches used in molecule discovery and synthesis as well as a necessity for molecule lipophilicity to interact with current molecular targets (Boyd et al. 2019). 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.

In addition to oral dosage forms which are ingested for the intention of drug absorption taking place in the gastrointestinal tract, there are transmucosal oral dosage forms for absorption across the mucosa in the mouth including sublingual and buccal products which bypass the first-pass effect.

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 the 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 food is known to delay gastric emptying

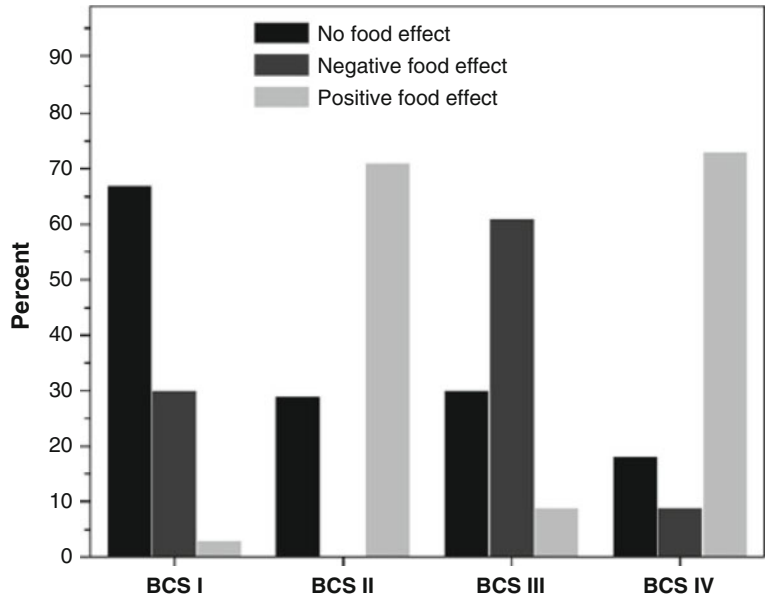

Fig. 1.1 Occurrence of food effects (positive, negative, or no effect) in percent by Biopharmaceutics Classifications System (BCS) category (Gu et al. 2007). (Adapted with permission)

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 that 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 is generally 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, potentially resulting in reduced dissolution and/or potential precipitation of already dissolved drug molecules. Changes in the pH in the stomach and the intestines as well as the transition in pH from the stomach to the intestines can not only directly affect drug solubility but can

also affect the performance of drug delivery systems. Amorphous solid dispersions, for example, using pH-dependent soluble polymers such as hypromellose acetate succinate or hypromellose phthalate can resist drug release in the stomach and target release after the transition to the higher pH environment of the intestines such as with Noxafil® (posaconazole) (Monschkle and Wagner 2019). Another potential complication has been reported by Jara et al., showing how the acidic environment of the stomach resulted in crystallization of a drug from an amorphous solid dispersion, negating the advantages of the drug delivery system if not protected before reaching the intestines (Jara et al. 2021).

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 the 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). Presystemic 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 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 reflect 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 $\geq$ 70% metabolism of an oral dose in vivo in humans.

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 presystemic metabolism (Hochman et al. 2000). It is assumed that

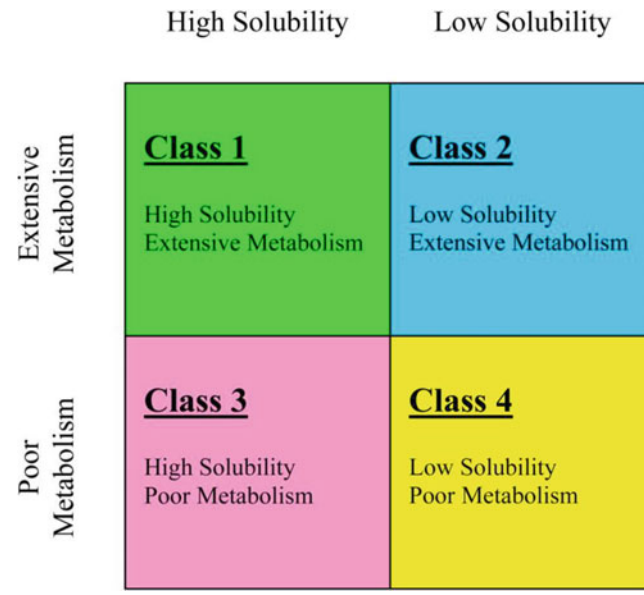

Fig. 1.2 The Biopharmaceutics Drug Disposition Classification System (BDDCS) (Custodio et al. 2008). (Reprinted with permission)

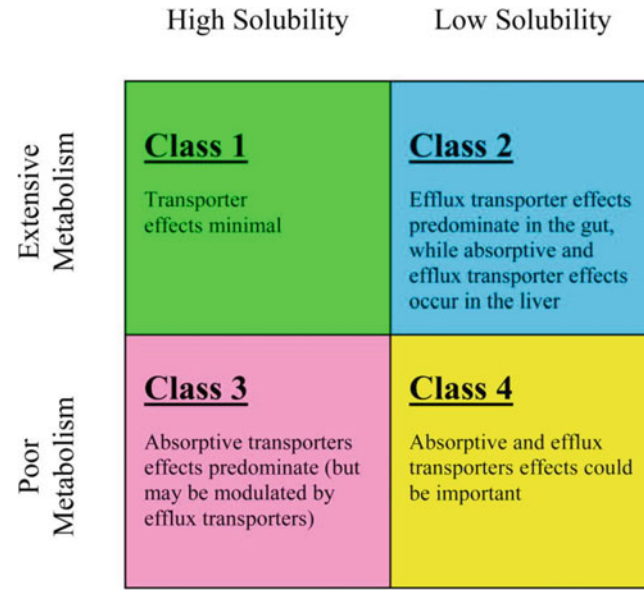

Fig. 1.3 Transporter effects, following oral dosing, by Biopharmaceutics Drug Disposition Classification System (BDDCS) class (Custodio et al. 2008). (Reprinted with permission)

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).

Initial metabolism resulting from the first pass effect in the gastrointestinal tract and the liver can be circumvented with oral dosage forms using transmucosal formulations (Patel et al. 2011). In oral transmucosal formulations, drugs are directly absorbed across the mucosa in the oral cavity into systemic circulation. An array of dosage forms exists to take advantage of this pathway of drug delivery including gums, tablets, films, patches and sprays for applying drugs to different regions

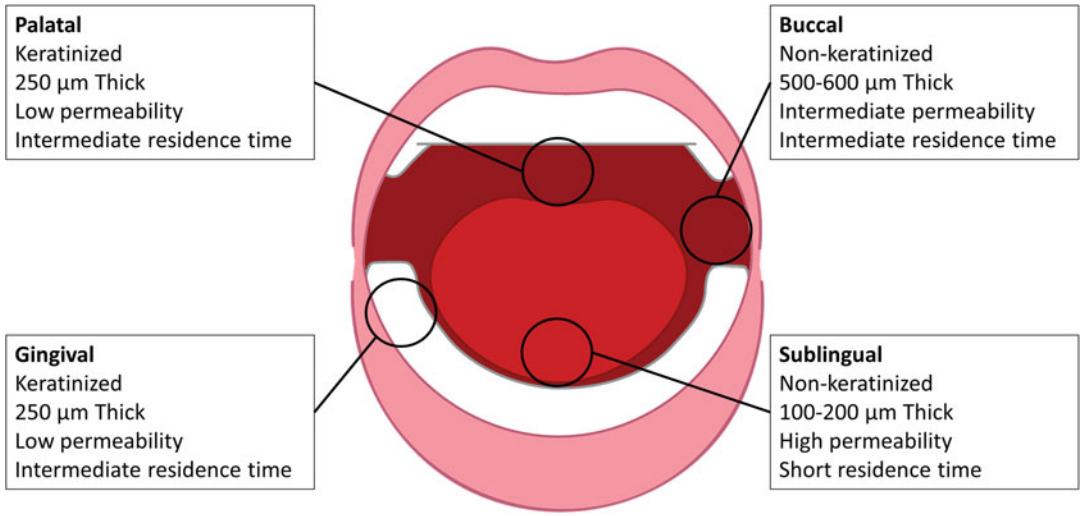

Fig. 1.4 Characteristic of different regions of the oral mucosa as it relates to oral transmucosal drug delivery (Patel et al. 2011)

of the oral cavity. Figure 1.4 depicts the different regions of the oral mucosa as it relates to drug delivery. As many of these dosage forms are easily self-administered and do not require swallowing, they have been used for palliative care treatments such as for breakthrough pain (Lam et al. 2020).

While attractive for particular applications, oral transmucosal delivery of poorly water-soluble drugs comes with its own challenges. Firstly, with particular relevance for poorly water-soluble drugs, is the limited volume available for dissolution. Despite reports of up to 2.0 L of daily salivary secretions, some estimates indicate there is only around 1.1 mL present in the mouth for dissolving drug molecules (Patel et al. 2011). Additionally, drug product residence time can be relatively short depending on the particular dosage form used for transmucosal delivery. Although the relative permeability of the sublingual mucosa is greater due to it being thinner than other regions of the oral cavity and not having a keratinized permeation barrier, delivery by this mucosa can be complicated by shorter residence times of the drug at the site for absorption as it is in contact with salivary secretions which results in swallowing of the drug rather than direct absorption. Some dosage forms such as a mucoadhesive tablets for buccal administration of cannabidiol have shown extended absorption times in vivo in part due to the delivery system as well as the inherent lipophilicity of the molecule resulted in a reservoir in the tissue (Itin et al. 2020). Other challenges to drug delivery using oral transmucosal dosage forms include patient condition, as they may not be suitable for patients that are experiencing nausea and vomiting or also may be a choking hazard for very young or elderly patients. As the dosage forms are meant to remain in the mouth throughout the absorption process, the taste of the drug may also be a complication when using these types of delivery systems.

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, these solubilization approaches are associated with 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 the formulation strategies mentioned. Another consideration is the rapid clearance of nanoparticles following i.v. administration due to opsonization. Formulators should consider the dynamics of the particle surface chemistry during and after administration.

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,

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

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 following opsonization 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 are 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 1.5 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, 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,

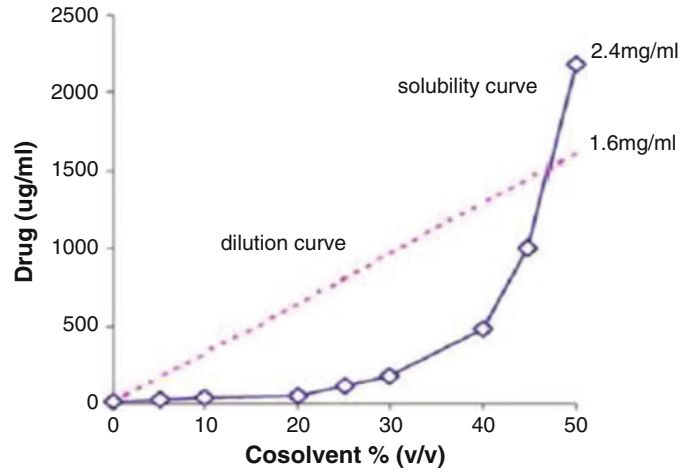

Fig. 1.5 Illustration of precipitation of a drug formulated in a 50% (v/v) cosolvent system (Li and Zhao 2007). (Reprinted with permission)

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 some 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 Cremophor 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 anticholesterol 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 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. 2015). 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).

Alternatively, complexation of poorly water-soluble drugs with cyclodextrins has been explored as an 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-cyclodextrin, 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 can be 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.

Finally, suspending the drug in vehicle can have particular advantages and challenges depending on the drug to be administered. By suspending the drug, it can be possible to avoid excipients which may result in unwanted toxicities. For example, Abraxane®, a nanoparticle formulation of paclitaxel using albumin, is an i.v. product which successfully allows paclitaxel dosing without the need for potentially harmful excipients like the Taxol® product which contains Cremophor EL, which is known to cause hypersensitivities in some individuals (Green et al. 2006). Another advantage that suspended parenteral products can have over solutions can be improved reconstitution times especially for medications which need to me administered rapidly such as Ryanodex® (dantrolene sodium) (Schutte et al. 2011). This formulation approach too has its own challenges, such as limitations on types and concentrations of excipients to stabilize the suspension and particle size limits to avoid being captured in the around 6-micron-diameter capillaries of the lungs (Wong et al. 2008).

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 most often via topical delivery. 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 possesses 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. 1.6. 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, and beneath this is Bowman's membrane. The thickest layer of the cornea is a hydrophilic matrix located underneath Bowman's membrane called the stroma. Following the stroma is 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).

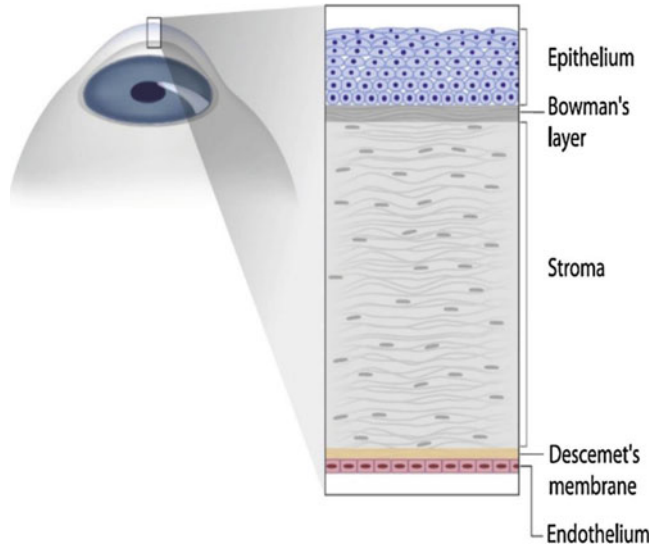

Fig. 1.6 Illustration of the layers comprising the cornea membrane (Sharif et al. 2015). (Reprinted with Permission)

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 dorzolamide 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 hours after topical administration, while the commercial formulation was shown to have practically no drug left in the aqueous humor after only 8 hours. It has also been reported that cyclodextrins can increase posterior drug delivery of topically applied medications (Loftsson et al. 2007; Loftsson et al. 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). Cyclosporine 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). Another barrier recently found to play a role in ocular bioavailability of topically applied therapeutics is mucus and mucus penetration (Popov 2020).

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 (Kuar 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 and systemic diseases 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 allow 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. 1.7) 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 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, is comprised 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 the later stages of the respiratory system (Thomas 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

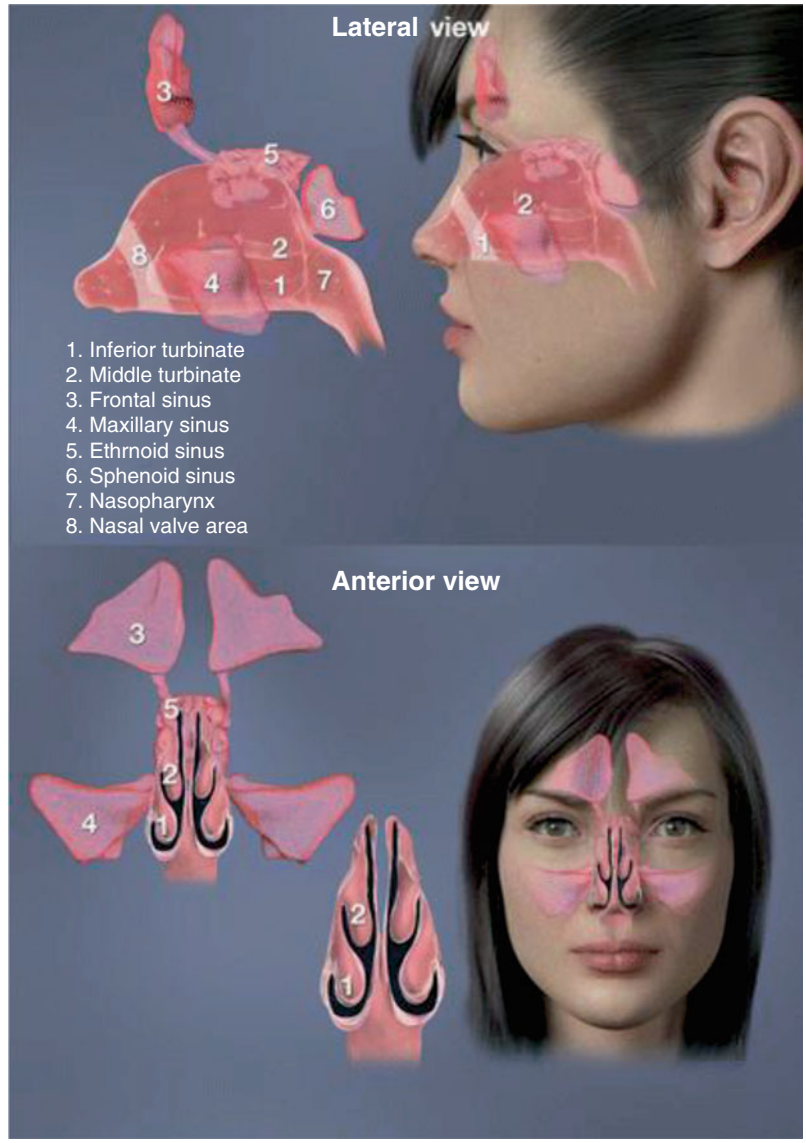

Fig. 1.7 Anatomy of the nasal cavity and sinuses from a lateral (top) and anterior (bottom) view (Djupesland 2013) (with permission)

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). Currently a few marketed nasal formulations are also available as powders in the United States including Onzetra® Xsail® (sumatriptan) and Baqsimi® (glucagon). 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 Viidgren 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-dosed 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 though few studies have linked plume geometry to in vivo deposition patterns in patients. 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 requires 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 the nasal mucosa, it turns from a liquid into a gel due to the presence of ions in the secretions (Wang et al. 2012). Other products, like Nasacort® AQ, take advantage of thixotropic rheological properties in order to have a low viscosity during actuation. However, these products have a higher relative viscosity during shelf life and after intranasal administration compared to during actuation (Kim 2011). Another method of utilizing mucoadhesive excipients in the formulation intended for nasal delivery is to produce microspheres of drug within the excipient. For example, carbamazepine has been spray-dried with chitosan to produce microspheres which provide high bioavailability in sheep when compared to carbamazepine given alone. This could be contributed to the mucoadhesive ability of chitosan; however, in this case, it may also be due to the higher dissolution rate obtained when formulated as microspheres (Gavini et al. 2006).

1.6 Pulmonary Route of Administration

Pulmonary drug delivery may be aimed at treating numerous diseases either locally or systemically. Local therapy of conditions such as asthma or pulmonary infections is advantageous in that drug concentrations at the site of action are maximized while systemic exposure and associated adverse effects are minimized. The pulmonary route of administration also offers several benefits for systemic delivery of drugs including a large absorptive surface area, a thin epithelial barrier, and low metabolic activity (Patton et al. 2004).

The respiratory system comprises the upper airways, including the nasopharynx, trachea, and large bronchi, and the respiratory region, including the small bronchioles and alveoli (Groneberg et al. 2003). It is known that the *trans*-epithelial transport of inhaled compounds will differ significantly among these regions. Transport in the upper airways is generally restricted by its lower surface area, epithelium thickness, and blood flow as well as rapid clearance through the mucociliary escalator. Accordingly, drugs intended for systemic delivery need to be targeted to the respiratory region where high surface area, thinner epithelium, and rich vascularization offer superior conditions for drug absorption (Groneberg et al. 2003; Patton and Byron 2007).

Several factors in regard to the formulation, such as particle diameter, shape, density, or electrical charge, have been shown to influence where and to what extent aerosolized particles deposit in the lungs (Crowder et al. 2002; Saini et al. 2007). Particularly, it has been demonstrated that particles with mass median aerodynamic diameters (MMAD) of 1–3 μm preferentially deposit in the deep lungs (Heyder et al. 1986; Carvalho et al. 2011). Particles with MMAD larger than 5 μm primarily deposit in the upper airways and near-bronchial branching points where they are rapidly cleared, while particles smaller than 1 μm are, to the most part, not deposited in the airways but rather exhaled after inspiration.

Formulations for pulmonary delivery are restricted not only to the appropriate particle size range but also to the use of specific and very few excipients. Generally, excipients intended for use in pulmonary products need to be either physiologically compatible with lung tissue in terms of pH, tonicity, and immunogenic potential or of endogenous nature in order to avoid airway hyper-responsiveness, spasticity,

or inflammation (Tolman and Williams 2009; Pilcer and Amighi 2010).

Several formulations of poorly soluble drugs for pulmonary delivery have been developed and reported in the literature; some of which, like several corticosteroids, have even been marketed. Formulation approaches employed mainly include solubilization in nonaqueous solvents and particle size reduction into the submicron range. Formulation development is however greatly challenged due to the very limited number of acceptable excipients and the fact that these can only be used in small concentrations in order to maintain adequate aerosol performance and prevent adverse physiological effects (Smyth 2006; Mogalian and Myrdal 2007).

1.6.1 Challenges in Pulmonary Delivery of Poorly Water-Soluble Drugs

In order to generate and deliver an aerosol of appropriate size distribution and reproducible dose to the lungs, different devices such as metered dose inhalers (MDIs), nebulizers, and dry powder inhalers (DPIs) have to be employed (Labiris and Dolovich 2003). Depending on the delivery device and the properties of the active pharmaceutical ingredient, inhalation products will be formulated with different types of excipients, i.e., to ensure effective aerosolization performance, to improve physical or chemical stability of the API, or in the case of poorly soluble drugs to enhance solubility/dissolution.

MDIs emit an aerosol driven by a single propellant or a blend of various propellants upon activation of an appropriate valve system. Generally, propellants are subject to strict selection criteria with the key requirements being: benign toxicology, suitable boiling point, solvent capacity, and density, as well as nonflammability (Noakes 2002). Since chlorofluorocarbons (CFCs) exhibit all of these desirable propellant characteristics, they had long been the propellants of choice. However, due to their harmful effects on the ozone layer, it is required that pharmaceutical aerosols have to be reformulated with non-ozone-depleting propellants such as hydro-fluoroalkanes (HFAs). While HFAs are currently still acceptable products on the market, in 2016 the Montreal Protocol which was responsible for the phase out of CFCs incorporated the Kigali Amendment to encourage the removal of HFAs in favor of mechanisms that have lower global warming impact (Panigone et al. 2020). In MDI formulations, the drug is either dissolved or suspended in the propellant(s). In the case of solution-based formulations, it is imperative that the drug has sufficient solubility to allow therapeutic doses to be delivered in a few actuations (Smyth 2003). The use of cosolvents such as ethanol oftentimes enables solubilization of satisfactory amounts of lipophilic drugs in the propellant or propellant mixture of interest. As an example, beclomethasone dipropionate, a slightly water-soluble corticosteroid used in the treatment of asthma, is dissolved in the propellant HFA 134a with the help of ethanol in one of its marketed products (QVAR®). This cosolvent-based approach might however not be applicable for all drugs. Especially, in the case of drugs that are very poorly soluble or require a large delivered dose, great amounts of ethanol might be needed. This may be problematic in terms of aerosol performance as it has been demonstrated that increased ethanol concentrations can considerably affect aerosol characteristics. A study evaluating solubility and product performance of beclomethasone dipropionate in various blends of HFA 134a and ethanol showed that with increasing ethanol concentrations, the solubility of the drug in the propellant was almost linearly increased. However, product performance was greatly reduced at ethanol concentrations above 10% (w/w) as illustrated by a decrease in the respirable deposition (Fig. 1.8; Gupta et al. 2003).

Besides its negative impact on MDI aerosolization performance, ethanol may also cause some irritation of the lung tissue (Coon et al. 1970). However, pulmonary tolerance testing with 150 μL of a 10% ethanol solution conducted in a rat model over 4 days found only limited cellular reactions, including minimal hypertrophy of goblet cells in the lungs and trachea, minimal