AAPS Advances in Pharmaceutical Sciences Series 3

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

Formulating Poorly Water Soluble Drugs

aapspress
Springer

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

Formulating Poorly Water Soluble Drugs

aapspress
Springer

Editors
Robert O. Williams III
Pharmaceutics Division
College of Pharmacy
University of Texas at Austin
Austin, TX, USA
williro@mail.utexas.edu

Alan B. Watts
Drug Dynamics Institute
College of Pharmacy
The University of Texas at Austin
Austin, TX, USA
abwatts@mail.utexas.edu

Dave A. Miller
Pharmaceutical and Analytical R&D
Hoffmann-La Roche, Inc.,
Nutley, NJ, USA
dave_a.miller@roche.com

ISBN 978-1-4614-1143-7 e-ISBN 978-1-4614-1144-4
DOI 10.1007/978-1-4614-1144-4
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011941579

AAPS Advances in Pharmaceutical Sciences Series

Series Editor

Prof. Dr. Daan J.A. Crommelin

For further volumes:
http://www.springer.com/series/8825

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 indentified by HTS has steadily increased over the past two 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, i.e., oral, parenteral, pulmonary, etc. 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 Chapter 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 Chapter 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 Chapters. 5–7 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 Chapter 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 (Chapters 8–12) 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 Chapter 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 Chapter 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 Chapter 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 Chapter 13. These are technologies that have begun to appear in the literature and elsewhere in recent years that exhibit promise, but have yet to mature. Finally, in Chapter 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, i.e., 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.

Nutley, NJ, USA Dave A. Miller
Austin, TX, USA Alan B. Watts
Austin, TX, USA Robert O. Williams III

Contributors

Michael P. Boquet Global Packaging Technology & Development, Eli Lilly and Company, Indianapolis, IN, USA

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

Duk Soon Choi Pharmaceutical and Analytical Research and Development, Hoffmann-La Roche, Inc., Nutley, NJ, USA

James C. DiNunzio Pharmaceutical and Analytical Research and Development, Hoffmann-La Roche, Inc., Nutley, NJ, USA

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

Ping Gao Global Pharmaceutical Sciences, Abbott Laboratories, Abbott Park, IL, USA

Marco Gil Hovione FarmaCiencia SA, R&D Particle Design, Sete Casas, Loures, Portugal

Justin R. Hughey Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Keith P. Johnston Department of Chemical Engineering, The University of Texas at Austin, Austin, TX, USA

Oskar Kalb F. Hoffmann-La Roche AG, Basel, Switzerland

Charlie Martin Leistritz, Somerville, NJ, USA

Jason T. McConville Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

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

Dave A. Miller Pharmaceutical and Analytical Research and Development, Hoffmann-La Roche, Inc., Nutley, NJ, USA

Javier O. Morales Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Kevin P. O'Donnell, Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Donald E. Owens III Enavail, LLC, Austin, TX, USA

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

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

Jasmine M. Rowe Bristol-Myers Squibb, New Brunswick, NJ, USA

Harpreet Sandhu Pharmaceutical and Analytical Research and Development, Hoffmann-La Roche, Inc., Nutley, NJ, USA

Navnit Shah Pharmaceutical and Analytical Research and Development, Hoffmann-La Roche, Inc., Nutley, NJ, USA

Dawn R. Wagner Formulation Design & Development Pfizer, Inc., Groton, CT, USA

Alan B. Watts Drug Dynamics Institute, 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

Wei Yang Enavail, LLC., Austin, TX, USA

Feng Zhang Formulation and Process Development, Gilead Sciences, Inc., Foster City, CA, USA

Contents

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

Stephanie Bosselmann 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 cosolvents and surfactants, oftentimes resulting in adverse physiological reactions. Finally, successful formulation design of poorly soluble drugs intended for pulmonary administration is mainly hindered by the limited number of excipients generally recognized as safe for this route of delivery. In summary, this chapter reviews the specific challenges faced in the delivery of poorly water-soluble drugs via oral, parenteral, and pulmonary administration.

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 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:

S. Bosselmann • 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: williro@mail.utexas.edu

R.O. Williams III et al. (eds.), *Formulating Poorly Water Soluble Drugs*, AAPS Advances in the Pharmaceutical Sciences Series 3, DOI 10.1007/978-1-4614-1144-4_1,

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

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 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 are not very well tolerated, potentially causing hemolysis and/or hypersensitivity reactions (Yalkowsky et al. 1998). In addition, there is the risk of drug precipitation upon injection and subsequent dilution of the solubilized formulation. Finally, successful formulation design of poorly soluble drugs indented for pulmonary administration is mainly hindered by the limited number of excipients 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 pulmonary delivery.

1.2 Oral Route of Administration

In spite of significant advances in other areas of drug delivery such as pulmonary or topical, oral drug delivery still remains the most favored route 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 unique 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 most essentially 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, an 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

Coadministration 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

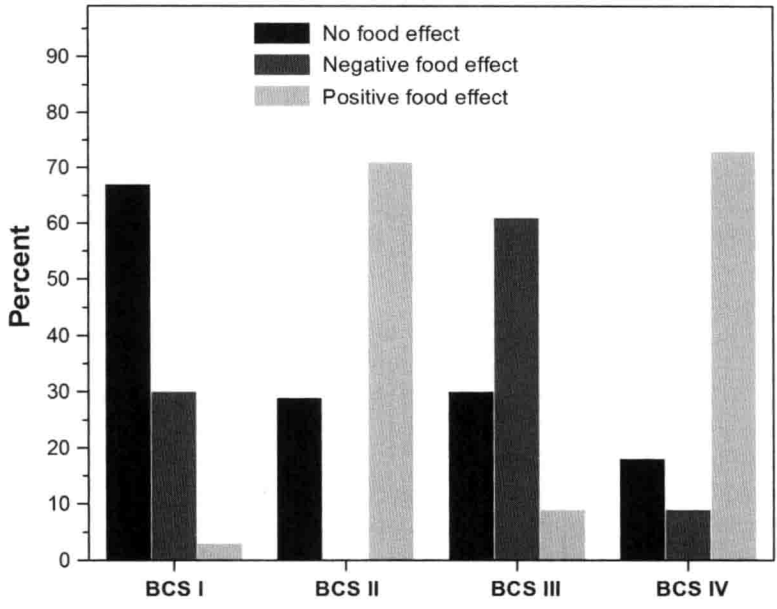

Fig. 1.1 Occurrence of food effects (positive, negative, or no effect) in percent by Biopharmaceutics Classifications System (BCS) category (Gu et al. 2007). Adapted with permission

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).

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 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). 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% (Table 1.1.) when administered together with a lipid-rich meal (Sunesen et al. 2005). This was primarily attributed to the presence of bile salts and lecithin in the small intestine allowing for micellar solubilization of the drug. In addition, an

Table 1.1 Pharmacokinetic parameters and time to 50% gastric emptying ($T_{50\%}$) of danazol administered to healthy male volunteers orally in the fasted and fed state

Treatment	C_{max} (ng/mL)	T_{max} (h)	AUC (h*ng/mL)	Bioavailability (%)	$T_{50\%}$ (min)
Fasted state	25 (±17)	3.1 (±0.7)	120 (±60)	11 (±5.2)	13 (±9)
Fed state	60 (±24)	4.0 (±1.1)	469 (±164)	44 (±12)	49 (±25)

(mean ± SD, $n = 8$; Sunesen et al. 2005). Adapted with permission

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). 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. 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), 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 molecules 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). 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