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ScienceDirect
Advanced Drug Delivery Reviews 60 (2008) 717–733
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption ☆

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Received 1 August 2007; accepted 31 August 2007
Available online 28 November 2007

Abstract

The ability to predict drug disposition involves concurrent consideration of many chemical and physiological variables and the effect of food on the rate and extent of availability adds further complexity due to postprandial changes in the gastrointestinal (GI) tract. A system that allows for the assessment of the multivariate interplay occurring following administration of an oral dose, in the presence or absence of meal, would greatly benefit the early stages of drug development. This is particularly true in an era when the majority of new molecular entities are highly permeable, poorly soluble, extensively metabolized compounds (BDDCS Class 2), which present the most complicated relationship in defining the impact of transporters due to the marked effects of transporter–enzyme interplay. This review evaluates the GI luminal environment by taking into account the absorption/transport/elimination interplay and evaluates the physiochemical property issues by taking into account the importance of solubility, permeability and metabolism. We concentrate on the BDDCS and its utility in predicting drug disposition. Furthermore, we focus on the effect of food on the extent of drug availability (F), which appears to follow closely what might be expected if a significant effect of high fat meals is inhibition of transporters. That is, high fat meals and lipidic excipients would be expected to have little effect on F for Class 1 drugs; they would increase F of Class 2 drugs, while decreasing F for Class 3 drugs.
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Keywords: Absorption; BCS; BDDCS; Disposition; Elimination; Food effects; Interplay; Transporter

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Lipid-Based Systems for the Enhanced Delivery of Poorly Water Soluble Drugs".

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doi:10.1016/j.addr.2007.08.043

1. Introduction

Food–drug interactions have been widely associated with alterations of pharmacokinetic and pharmacodynamic parameters and proven to have significant clinical implications [1,2]. The influence of concomitant food intake prompted the Food and Drug Administration (FDA) to issue a guidance for industry entitled, "Food-Effect Bioavailability and Fed Bioequivalence Studies" [3]. As a result, it is common to find medication labeling containing language denoting that maximum effect is achieved if the drug is administered with a meal. Conversely, some drug products show a decrease in the extent of availability and decreased efficacy with meal coadministration. Of course there are very many drugs for which food–drug interactions are non-existent or negligible.

The effect of food on the extent of availability is a significant concern during drug development. Ideally, it is most advantageous if a recommendation of oral drug administration can be provided independent of meal considerations. A food–drug interaction model would be beneficial in the early stages of development when preclinical predictions could be of particular use and service to the industry. Although various *in vitro* and *in vivo* models can be found [4–7], to date no standard system exists to predict drug absorption and the effect of food.

The role of food, and its subsequent digestion, in oral drug absorption may be attributed to a myriad of variables ranging from the chemical characteristics of the drug itself to the postprandial changes in the gastrointestinal (GI) tract. Therefore, when attempting to predict variations in pharmacokinetics it is imperative to consider not only the physiochemical properties of the drug, but the GI luminal environment as well. In this review, we evaluate the GI luminal environment by taking into account the absorption/transport/elimination interplay and we evaluate the physiochemical property issues by taking into account the importance of solubility, permeability and metabolism. Here, we concentrate on combining these aspects into a comprehensive system to predict disposition and the role of food on drug absorption.

2. The Biopharmaceutics Classification System

2.1. The BCS and the FDA

The oral absorption of a drug is fundamentally dependent on that drug's aqueous solubility and gastrointestinal permeability. Extensive research into these fundamental parameters by Amidon et al. [8] led to the Biopharmaceutics Classification System (BCS) that categorizes drugs into four groups, Class 1–Class 4 (Fig. 1). The BCS classifies compounds based on the critical components related to oral absorption. Centrally embracing permeability and solubility, the objective of the BCS is to allow prediction of *in vivo* pharmacokinetic performance of drug products from *in vitro* measurements of permeability and solubility.

In 2000, the FDA promulgated the BCS as a science based approach to allow waiver of *in vivo* bioavailability and bioequivalence testing for immediate release solid dosage forms for Class 1 compounds, highly soluble and highly permeable drugs, when such drug products also exhibit rapid dissolution [9]. In brief, bioequivalence is achieved if the generic product shows the same rate and extent of bioavailability with rate evaluated in terms of C_{max} and extent measured in terms of AUC. The criteria include a 90% confidence interval around point estimates of the ratios of C_{max} and AUC, test/reference, falling within 0.8–1.25 on a log normal distribution.

2.2. Framework of the BCS

As depicted in Fig. 1, the BCS sorts drugs on a scale in terms of solubility versus permeability. A drug substance is considered

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