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Review

Regional intestinal drug permeation: Biopharmaceutics and drug development

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ABSTRACT

Over the last 25 years, profound changes have been seen in both the development and regulation of pharmaceutical dosage forms, due primarily to the extensive use of the biopharmaceutical classification system (BCS) in both academia and industry. The BCS and the FDA scale-up and post-approval change guidelines were both developed during the 1990s and both are currently widely used to claim biowaivers. The development of the BCS and its wide acceptance were important steps in pharmaceutical science that contributed to the more rational development of oral dosage forms.

The effective permeation (P_{eff}) of drugs through the intestine often depends on the combined outcomes of passive diffusion and multiple parallel transport processes. Site-specific jejunal P_{eff} cannot reflect the permeability of the whole intestinal tract, since this varies along the length of the intestine, but is a useful approximation of the fraction of the oral dose that is absorbed. It appears that drugs with a jejunal $P_{eff} > 1.5 \times 10^{-4}$ cm/s will be completely absorbed no matter which transport mechanisms are utilized. In this paper, historical clinical data originating from earlier open, single-pass perfusion studies have been used to calculate the P_{eff} of different substances from sites in the jejunum and ileum.

More exploratory *in vivo* studies are required in order to obtain reliable data on regional intestinal drug absorption. The development of experimental and theoretical methods of assessing drug absorption from both small intestine and various sites in the colon is encouraged. Some of the existing human *in vivo* data are discussed in relation to commonly used cell culture models. It is crucial to accurately determine the input parameters, such as the regional intestinal P_{eff}, as these will form the basis for the expected increase in modeling and simulation of all the processes involved in GI drug absorption, thus facilitating successful pharmaceutical development in the future. It is suggested that it would be feasible to use open, single-pass perfusion studies for the *in vivo* estimation of regional intestinal P_{eff}, but that care should be taken in the study design to optimize the absorption conditions.

Contents

1. Introduction

The biopharmaceutical classification system (BCS) (Amidon et al., 1995) and the FDA guidelines for scale-up and post-approval changes (SUPAC) were developed during the 1990s, and both have

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facilitated the development of pharmaceutical products over the last two decades. *In silico* models and simulations of drug absorption, distribution and excretion, which are becoming increasingly important in the development of oral pharmaceutical products, aim to reduce time, effort and costs by decreasing the number of *in vivo* bioequivalence studies needed. One recent European research effort working in this area, extensively covered in this special issue of the European Journal of Pharmaceutical Sciences (EJPS), is the IMI OrBiTo (Oral Biopharmaceutics Tools) project. The main objective of OrBiTo is to develop novel experimental and theoretical simulation tools (*in silico*) to be used in pharmaceutical research and development, and the regulation of oral pharmaceutical products (http://www.imi.europa.eu/content/orbito).

Membrane transport proteins are known to influence the absorption of some drugs. The Biopharmaceutics Drug Disposition Classification System (BDDCS) was developed to predict the influence of these proteins on biopharmaceutic and pharmacokinetic (PK) processes and parameters (Wu and Benet, 2005). A recently published compilation of the BDDCS classifications for 927 drugs (includes 30 active metabolites). Of the 897 parent drugs examined, 80% are administered orally (Benet et al., 2011). Discussions are also under way on the advisability of substituting the degree of metabolism of the drug in drug development simulations as an alternative surrogate for the extent of intestinal permeation and the fraction of the dose absorbed (fa) (Chen et al., 2011). The BCS and the BDDCS classify approved drugs and new drug candidates into four categories using the same solubility criteria, but differ in their permeability criteria and have different purposes (Benet, 2013). The BCS system is currently widely applied in regulatory affairs and has a significant direct industrial impact (Ungell et al., 1998; Lennernas and Abrahamsson, 2005; Amidon et al., 2011; Dahan et al., 2012). Together, the BCS, the BDDCS, modeling, and simulation are central to the evolution of biopharmaceutical and PK concepts and have a large impact on drug discovery, drug development and regulatory strategies in the pharmaceutical industry (Benet, 2013; Smith, 2013).

The BCS has recently been extended to form the Developability Classification System (DCS) (Butler and Dressman, 2010). This revised system has been designed to have a greater focus on drug developability and specifically to predict what pharmaceutical factors are critical to *in vivo* performance and critical quality attributes. For instance, DCS introduced the concept of solubility limited absorbable dose (SLAD), which might be able to more easily titrate the dose above which gastrointestinal (GI) absorption is likely to be limited by intestinal solubility.

More exploratory *in vivo* studies are needed to clarify regional drug absorption along the intestine, especially in the colon. The development of experimental and theoretical methods of directly assessing the permeability of distal parts of the GI tract in humans is particularly encouraged. It is now recognized that important differences between *in vivo* models, species, and *in vitro* transport models in the Ussing chamber and cell monolayers (such as the Caco-2 model) do not fully serve the purpose of improving the accuracy of *in silico* absorption models. Developing new *in vivo* methods would stimulate the development of more relevant and complex *in vitro* absorption models, and would form the basis of an accurate, physiologically based PK (PBPK) model of GI drug absorption (Darwich et al., 2010; Poulin et al., 2011; Agoram et al., 2001; Parrott et al., 2009). The importance of accurately determining the input parameters in such a model cannot be overstated; this step is crucial for increasing the acceptance of these models in simulating GI drug absorption.

The experimental and *in silico* models applied in the design and development of oral pharmaceutical products need to improve to be able to better predict the key biopharmaceutical and PK processes. The main biopharmaceutical parameters for an active pharmaceutical ingredient (API) include its physical, chemical, and biological properties, the design and composition of the pharmaceutical formulation, and the extent and manner of GI absorption. The permeation of drugs through the intestinal wall varies along the small and large intestine and is extensively influenced by any transport mechanisms involved (Ungell et al., 1998; Tannergren et al., 2009; Sjoberg et al., 2013) (Sugano et al., 2010). It is important to distinguish between these transport routes and to identify the main membrane transport mechanism(s) for each drug. It is recognized that no *in vitro* model can accurately predict the permeability of the small intestine to compounds, which have slow passive diffusion and/or carrier-mediated transport as the main transport mechanism (Sun et al., 2002; Lennernas, 2007a, 2007b; Dahan et al., 2009b; Larregieu and Benet, 2013).

The primary objective of this review is to present and critically discuss the differences in permeability between various regions of the human intestine, as estimated by the effective permeation (P_{eff}) of drugs through the intestinal wall, and to relate these human *in vivo* data to *in vitro* cell culture data.

2. Definition of intestinal absorption and bioavailability

Most orally administered drug products have pharmacological and adverse effects that to various degrees are related to the rate and/or extent of the absorption and bioavailability (F) of the API. In a regulatory context, F is defined as the rate at and extent to which an API is released from the pharmaceutical dosage form to become available in the general circulation (often the plasma compartment). F is mainly dependent on three general but rather complex serial processes: the fa, the extent of first-pass extraction of the drug by enzymes in the gut wall (E_G), and the extent of first-pass extraction of the drug in the liver (E_H) (Eq. (1)) (Amidon et al., 1995; Wu et al., 1995).

$$F = \text{fa} \cdot (1 - E_G) \cdot (1 - E_H) \quad (1)$$

Accordingly, the rate (mass/time) and extent (fa = mass/dose) of drug absorption following oral administration *in vivo* are influenced by: the ratio of dissolved drug (solubility) to the administered dose; the rate and extent of chemical degradation or metabolism in the lumen, GI luminal complex binding, and GI transit; and the P_{eff} across the intestinal mucosa. The P_{eff} and the dissolved and free drug luminal GI concentrations are the key variables controlling the fa (Amidon et al., 1995, 2011; Sun et al., 2002; Tannergren et al., 2003b). The successful development of a theoretical PBPK model for GI drug absorption requires *in vivo* P_{eff} data for a set of drugs representing the different absorption properties of different intestinal segments.

3. Permeability of human jejunum to drugs and nutrients *in vivo*, estimated as P_{eff} determined by double-balloon perfusion

The single-pass, double-balloon perfusion system is a directly measured parameter of intestinal drug transport that is not influenced by other factors such as the extent or rate of metabolism, methods of transit or lumen conditions. The estimation of P_{eff} is based on the rate of disappearance of the drug from the perfused jejunal segment, where the difference between the concentrations of substance entering and leaving the tested segment is determined (or the rate of its appearance in the segment if direct intestinal secretion is examined). The absorption conditions, such as pH, osmolality, fluid correction and recovery of the perfusion fluids, which differ significantly among the clinical methods applied, need to be considered in the design and evaluation of these experiments. The human jejunal P_{eff} values estimated using these methods are