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Biopharmaceutic classification of drugs revisited

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ABSTRACT

The biopharmaceutics classification system (BCS) was based on the tube model of the intestinal lumen. This model considers constant drug permeability along the intestines, a plug flow fluid with the suspended drug particles moving with the fluid, and dissolution in the small particle limit. Since then the research work focusing on drug gastrointestinal (GI) absorption phenomena and processes rely on the classical laws of transport, diffusion and kinetics; however, the homogeneous assumptions associated with the well-stirred Euclidean media, where the classical laws of diffusion and kinetics apply, have been questioned in the past. In this work we explore the biopharmaceutic classification of drugs using a heterogeneous pseudo steady-state model of oral drug absorption. The fraction of dose absorbed (F_{abs}) was expressed as a function of two time-dependent processes where time dependent coefficients govern drug absorption and non-absorption processes. Fundamental drug properties like the absorption potential are correlated with F_{abs} and allow the biopharmaceutic classification of drugs taking into account the heterogeneous aspects of oral drug absorption. This analysis reveals that for Class I drugs no time dependency is expected for both absorption and non absorption processes since the gastric emptying is controlling the absorption of Class I drugs while the completion of absorption ($F_{abs} > 90\%$) is terminated along the first part of the jejunum. Due to the biopharmaceutical properties of Class II, III and IV drugs, these drugs travel throughout the GI tract and therefore both absorption and non absorption processes will exhibit time dependency. Thus, the calculation of F_{abs} (<90%) for Class II, III and IV is dependent on the estimates of the time exponents of time dependent coefficients controlling drug absorption e.g. dissolution, uptake or non absorption e.g. precipitation.

1. Introduction

In a recent review (Macheras et al., 2013) dealing with the science and regulation of oral drug absorption it was stated that "orally administered drug compounds should possess biopharmaceutical properties that enable them to achieve therapeutic concentrations at their site of action". This statement is associated with the ever burning problem of our inability to correlate explicitly the drug characteristics e.g. dose, lipophilicity, solubility and permeability with the rate and extent of oral absorption (Charkoftaki et al., 2012). The first attempt towards the semi-quantitative prediction of the extent of absorption as a function of fundamental drug properties was attempted in 1985 when the concept of absorption potential (AP) was developed (Dressman et al., 1985):

$$AP = logPF_{non}\frac{S_0V_L}{D} \quad (1)$$

where P is the 1-octanol-water partition coefficient, S_0 is the intrinsic solubility, D is the dose, V_L is the volume of the intestinal fluids and F_{non} is the unionized fraction of drug at pH 6.5. Indeed, a sigmoid relationship between the fraction of dose absorbed F_{abs} and AP was found for nine drugs examined (Dressman et al., 1985). A quantitative approach for the prediction of F_{abs} as a function of AP was published a few years later, (Macheras and Symillides, 1989). F_{abs} was defined in terms of a first-order absorption rate constant k_a and a first order rate constant leading to non-absorption k_n:

$$F_{abs} = \frac{k_a}{k_a + k_n} \quad (2)$$

using a homogeneous pseudo steady-state model of oral drug absorption. k_a was considered proportional to AP, $k_a = \lambda(AP)$, whereas k_n was considered proportional to 1/AP, $k_n = \mu/(AP)$.

An explicit relationship between F_{abs} and AP was developed:

$$F_{abs} = \frac{(AP)^2}{(AP)^2 + (\mu/\lambda)F_{non}(1-F_{non})} \quad (3)$$

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and drugs were classified into three categories according to their AP values (Macheras and Symillides, 1989).

Further to the above, in 1986, the mixing tank model was introduced (Dressman and Fleisher, 1986) to describe the absorption process in the intestine. The model described the intestine as a well stirred compartment (mixing tank), where dissolution and absorption take place simultaneously and a first-order decrease of drug is considered because of transfer out of the intestinal tank. Although in its simplest form, the mixing tank model does not consider the intestinal transit process, it can be modified to include the mean intestinal transit time as a time constraint after which absorption is terminated (Sinko et al., 1991).

In mid '90s, the two seminal articles by Amidon and co-workers (Oh et al., 1993; Amidon et al., 1995) on the microscopic analysis of oral drug absorption using a homogeneous tube model, lead to the development of BCS (Amidon et al., 1995) and the subsequent publication of the relevant US Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory guidelines (FDA, 2000; EMA, 2010; FDA, 2015). The BCS has evolved in many different directions. One of the most important is the development of the biopharmaceutics drug disposition classification system (BDDCS) (Wu and Benet, 2005) which uses metabolism instead of permeability in its classification. In parallel, the BCS-based biowaiver as a means to prove bioequivalence has attracted the interest of scientists for a number of reasons e.g. economic benefits (Cook et al., 2010), publication of biowaiver monographs for immediate-release solid oral dosage forms and development of biorelevant media for Class II compounds (Fagerberg et al., 2010). Furthermore, various theoretical-experimental aspects of the BCS (Amidon et al., 1995) and the relevant guidelines (FDA, 2000; EMA, 2010; FDA, 2015) such as solubility-dissolution criteria (Rinaki et al., 2003; Yazdanian et al., 2004; Rinaki et al., 2004; Varma et al., 2012), kinetic solubility and supersaturated phenomena (Box and Comer, 2008), volume utilized for solubility measurements (Rinaki et al., 2003; Butler and Dressman, 2010), highest dose strength (Charkoftaki et al., 2012; Daousani and Macheras, 2015), dual drug classification (Bergström et al., 2014a), non-continuity of classification (Macheras and Karalis, 2014), early pharmaceutical profiling to predict oral drug absorption (Bergström et al., 2014b) and new frames of reference for mapping drugs in the four classes of the BCS and BDDCS (Chatzizacharia and Hatziavramidis, 2015) are important scientific and regulatory advances in oral drug absorption.

All literature data listed above for GI phenomena and processes rely on the classical laws of transport, diffusion and kinetics; this means that the processes are taking place in well-stirred Euclidean media whereas the classical laws of diffusion and kinetics apply and the movement of drug follows the fundamental law "the mean square displacement, $\langle \bar{x} \rangle^2$, of the random walker-drug is proportional to time". This 'homogeneous' approach has been questioned in the past (Macheras and Argyrakis, 1997; Pippa et al., 2013) for GI phenomena-processes, and heterogeneous approaches have been formulated (Macheras and Iliadis, 2016). The term "heterogeneous" is used here for GI processes taking place in disordered media or media under topological constraints where classical diffusion-kinetics laws do not apply. Whenever this principle cannot be applied i.e. $\langle \bar{x} \rangle^2 \propto t^{\beta}, \beta \neq 1$, then it is said that the process is anomalous. In these cases, fractal like kinetics (Kopelman, 1988; Macheras, 1995; Macheras and Dokoumetzidis, 2000) is used for the description of time evolution of these processes. This is so since fractal like kinetics can describe mathematically the impact of the spatial heterogeneity on the kinetics of heterogeneous processes. Fractal kinetics arises whenever processes are studied in understirred media or under dimensional or topological constraints. As a result of these conditions either the reactant species do not re-randomize their position as a function of time or the species of interest in transport studies does not move (diffuse) in accordance with the law, $\langle \bar{x} \rangle^2 \propto t$. Therefore, time coefficients and not rate constants govern the kinetics of drug reactions or transport under these conditions. During the last fifteen years, several applications of fractal kinetics as well as fractional kinetics have been published in the biopharmaceutics-pharmacokinetics literature (Kalampokis et al., 1999a; Kalampokis et al., 1999b; Dokoumetzidis and Macheras, 2009; Kytariolos et al., 2010; Dokoumetzidis et al., 2010; Dokoumetzidis and Macheras, 2011; Hennion and Hanert, 2013).

In this work we explore the impact of the heterogeneous character of drug absorption processes on biopharmaceutic classification, fraction absorbed, carrier mediated transport and variability. To this end, a heterogeneous pseudo steady-state model of oral drug absorption was utilized; this model is a modified version of its classical analogue (Macheras and Symillides, 1989). F_{abs} was expressed as a function of two time-dependent processes where time dependent coefficients govern drug absorption and non-absorption processes.

2. Methods

2.1. Homogeneous aspects of oral drug absorption

As already mentioned, the development of BCS was based on the homogenous tube model of the intestinal lumen (Oh et al., 1993; Amidon et al., 1995). The main characteristics of the model are i) constant drug permeability (passive diffusion) along the intestines ii) a plug flow model with the suspended drug particles moving with the fluid and iii) dissolution in the small particle limit following the classical Noyes-Whitney relationship (Dokoumetzidis and Macheras, 2006). Due to the oversimplified assumptions of the homogenous tube model of the intestinal lumen and in order to improve the prediction of oral drug absorption in humans, mixing tanks in series with linear transfer kinetics from one to the next with the same transit rate constant have been utilized to obtain the characteristics of flow in the human small intestine (Yu et al., 1996a; Yu et al., 1996b; Yu and Amidon, 1998). This type of analysis coupled with experimental observations revealed that seven mixing tanks (compartments) in series better describe the drug transit in the GI lumen. In parallel, the analysis associated with the nonlinear processes of BDDCS (metabolism and carrier mediated transport) in the GI tract rely on Michaelis-Menten kinetics. In these cases, the two parameters, namely, the maximum rate of metabolism or transport (V_{max} or J_{max}, respectively) along with the corresponding Michaelis constant, k_M control the kinetics of the processes. It should be recalled here that due to the saturation characteristics of this type of kinetics, the drug dose becomes an important variable for the analysis of the absorption data. All above remarkable scientific-regulatory advances, created a real explosion in the development of mechanistically-physiologically based software packages e.g. GastroPlus™ (Simulations Plus, Lancaster, CA), SimCyp® (Certara Inc., St. Louis, MO) for the prediction of oral drug absorption.

2.2. Heterogeneous aspects of oral drug absorption

Almost twenty years ago, a provocative article entitled "Gastrointestinal drug absorption: is it time to consider heterogeneity as well as homogeneity?" (Macheras and Argyrakis, 1997) introduced the concept of "fractal like kinetics" (Kopelman, 1988) in biopharmaceutics-pharmacokinetics for drug absorption processes taking place in the understirred media of GI lumen. A plethora of recent studies dealing with various aspects of gastrointestinal physiology provide a clear heterogeneous picture for the drug absorption processes and the composition of the GI lumen contents. For example, scintigraphic studies demonstrate that the colonic transit time varies enormously (Wilson, 2010), regional intestinal drug permeability and the available mucosal area vary remarkably along the GI tract (Sjögren et al., 2015; Olivares-Morales et al., 2015), the GI fluids are not homogeneously distributed along the gut and "fluid filled-pockets" as well as "dry segments" have been observed and quantified (Schiller et al., 2005; Mudie et al., 2014), most of the high intra- and inter-subject variability as well as the subject by formulation interaction encountered in bioequivalence studies are associated with the heterogeneous uncontrolled conditions of the GI tract (Kim et al.,