European Journal of Pharmaceutical Sciences 95 (2016) 82–87

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Biopharmaceutic classification of drugs revisited

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ARTICLE INFO

Article history:
Received 12 February 2016
Received in revised form 26 July 2016
Accepted 2 August 2016
Available online 3 August 2016

Keywords:
BCS
Fraction absorbed
Oral absorption
Heterogeneous
Variability

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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http://dx.doi.org/10.1016/j.ejps.2016.08.001
0928-0987/

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.,

2012). Special emphasis should be also given to the extreme variability found in all physicochemical measurements in aspirates dealing with the characteristics of the human intestinal fluid such as bile salt composition, pH and buffer capacity at different locations (duodenum and jejunum) in the fasted state (Perez de la Cruz Moreno et al., 2006). Overall, the inter- and intra-subject differences in intestinal lumen contents coupled with their time-site-dependent character can explain the larger portion of the extreme variability observed in the in vivo dissolution/release/precipitation studies based on human aspirates (Perez de la Cruz Moreno et al., 2006; Clarysse et al., 2009a; Clarysse et al., 2009b; Macheras et al., 2013; Bergström et al., 2014b).

The fraction of dose absorbed is the crux of the matter for the early studies (Macheras and Symillides, 1989; Oh et al., 1993) focusing on the analysis of drug absorption and the biopharmaceutic classification of drugs as well as on the most recent ones (Sugano and Terada, 2015), dealing with the rate limiting factors of oral drug absorption. Indeed, this latter work provides a theoretical aspect associated with the complexity of GI absorption and an overview of the theoretical relationships between the different concepts, by introducing the fraction of dose absorbed classification system (FaCS) and discussing its applications for food effect prediction, active pharmaceutical ingredient form selection, formulation design, and biowaiver strategy.

2.3. A heterogeneous-dynamic pseudo steady-state model of gastrointestinal absorption

2.3.1. Pharmacokinetic considerations

As delineated above, non-homogeneous conditions prevail in the GI lumen. Therefore, fractal kinetics (Kopelman, 1988) is a more realistic way to describe drug processes in the GI lumen. This type of kinetics is associated with time-dependent rate coefficients, k, and not rate constants:

$$k = k_1 t^{-h} \ (t \neq 0) \tag{4}$$

where k_1 is a constant not dependent on time with units $(\text{time})^{h-1}$ and h is a pure number different than zero. The value of the exponent h is linked with two different phenomena: the geometric disorder of the medium and the imperfect mixing of the GI contents. Building on these concepts, a heterogeneous model of drug GI absorption can be formulated by employing global time-dependent rate coefficients to describe absorption and non-absorption processes. According to Eq. (4), these rate coefficients for absorption (k_a) and non-absorption (k_n) processes, can be

$$k_a = k_{a1} \quad t^{-m} \ (t \neq 0)$$

$$k_n = k_{n1} \quad t^{-n} \ (t \neq 0)$$

Assuming pseudo steady-state conditions, F_{abs} can be written:

$$F_{abs} = \frac{k_{a1} t^{-m}}{k_{a1} t^{-m} + k_{n1} t^{-n}} = \frac{1}{1 + \mu t^{\lambda}} \tag{5}$$

where $\lambda = m - n$ is a unitless quantity and $\mu = (k_{n1}/k_{a1})$ is a proportionality constant with $(\text{time})^{-\lambda}$ units.

The use of global time-dependent coefficients for absorption (k_a) and non-absorption (k_n) processes follows the general principles of the species anomalous diffusion (Kopelman, 1988) in disordered media like those of the GI lumen; besides, the time dependent character of the fundamental drug absorption processes, namely, drug dissolution and release has been demonstrated for Weibull- or power law-kinetics, respectively (Macheras and Dokoumetzidis, 2000). Also, time-dependent coefficients have been used for the description of supersaturated dissolution data following a reaction-limited model of dissolution (Charkoftaki et al., 2011). Similar approaches based on probabilistic concepts have been utilized for the description of GI transit (Kalampokis et al., 1999a) and absorption (Kalampokis et al., 1999b).

2.3.2. Biopharmaceutical considerations

The pharmacokinetic approach delineated above can be extended to the biopharmaceutical aspects assuming that the governing rate constants k_{a1} and k_{n1} are proportionally and inversely proportional to AP (Macheras and Symillides, 1989), respectively:

$$k_{a1} = \xi AP$$

$$k_{n1} = \rho \frac{1}{AP}$$

where ξ and ρ are proportionality constants with $(\text{time})^{m-1}$ and $(\text{time})^{n-1}$ units. Substituting the last two equations to Eq. (5) one obtains:

$$F_{abs} = \frac{\xi AP t^{-m}}{\xi AP t^{-m} + \rho \frac{1}{AP} t^{-n}} = \frac{1}{1 + \frac{\rho}{\xi} \frac{1}{(AP)^2} t^{m-n}} = \frac{1}{1 + \frac{\varepsilon}{(AP)^2} t^{\lambda}} \tag{6}$$

where $\varepsilon = \rho/\xi$ is a constant in $(\text{time})^{-\lambda}$ units. For $\lambda = 0$, Eqs. (5) and (6) are not dependent on time i.e. they are reduced to the classical analogue (Macheras and Symillides, 1989).

2.3.3. Biopharmaceutic classification of drugs-fraction absorbed

According to common wisdom, Class I drugs have a "homogeneous" behavior since they not only are absorbed extensively ($F_{abs} > 90\%$) but obviously non-absorption processes are not involved in their absorption, as depicted in Fig.1A. In fact, the gastric emptying is controlling the absorption of Class I drugs while the completion of absorption ($F_{abs} > 90\%$) is anticipated to be terminated along the first part of the jejunum.

Contrary to Class I drugs, the drugs of Classes II, III and IV travel throughout the GI tract because of their biopharmaceutical properties are termed "heterogeneous" (Macheras and Argyrakis, 1997) and exhibit incomplete absorption ($F_{abs} < 90\%$), Fig.1B. Therefore, the kinetics of absorption and non-absorption processes will exhibit time dependency for the drugs of Classes II, III and IV. This is clearly reflected in Eqs. (5) and (6) which demonstrate the time dependency of F_{abs}. Since this is a pseudo steady-state model, the more reasonable time estimate associated with Eqs. (5) and (6) could be the mean

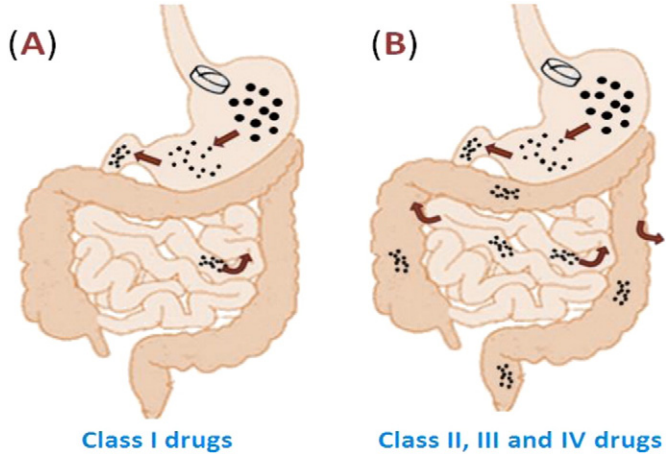

Fig. 1. A pictorial view for the GI absorption of (A) the homogeneous Class I drugs (Fabs >90%) and (B) the heterogeneous Class II, III and IV drugs (Fabs <90%). These terms are used here to underline that gastric emptying controls the absorption of Class I drugs while heterogeneous absorption and non-absorption processes are involved in the absorption of Class II, III and IV drugs.

gastrointestinal transit time, T. However, T is a highly variable parameter and therefore, different arbitrary "effective" T values, close to the physiological observations reported can be considered e.g. 12 or 24 h.

The "rule of unity" was proposed in 2006 by Yalkowsky et al. (2006). They introduced a new absorption parameter, π, to predict the absorption efficiency of orally administered drugs that are passively transported. In reality, the "rule of unity" is a semiempirical model based on the AP concept (Dressman et al., 1985; Macheras and Symillides, 1989). According to this model, drugs are classified as "well absorbed" when their absorption values, π, correspond to >50% of the administered dose, whereas those with absorption values corresponding to <50% of the dose are classified as "poorly absorbed." The fraction of dose absorbed was related to parameter π (Papadopoulou et al., 2008), allowing experimentally based estimates for the volume of intestinal contents; moreover, scientifically based changes for the current BCS were suggested.

Based on the above, an estimate for εt^{λ} was derived, 1.91 ± 0.68 from the fit of Eq. (6) to F_{abs} values (<90%) for Class II, III and IV drugs using the absorption parameter π instead of AP, Fig. 2. This estimate reveals that a large number of (ε, λ) pairs for a given "effective' time T, can describe the extent of absorption as a function of π for a highly diverse set of Class II, III and IV compounds, Fig. 2. For example, for $\lambda = 0.7$ (Kopelman, 1988) and $T = 24$ h the value for ε is 0.21 $h^{-0.7}$. The homogeneous case ($\lambda = 0$) can be also considered (Macheras and Symillides, 1989). This can lead to a global estimate for the ratio of absorption and non-absorption rate constants, k_a/k_n. In all cases, this analysis supports the heterogeneous character of GI absorption for Class II, III and IV. In addition, the analysis demonstrates a continuous three zones biopharmaceutic classification system (Fig. 2), as it has been suggested previously using the classical-homogeneous approach (Macheras and Symillides, 1989) as well as the ABΓ system published recently (Macheras and Karalis, 2014).

As a last point, one may not forget the role and the effect of different formulation types on drug behavior and classification. Indeed, the choice of formulation is of critical importance in the establishment of safe and effective products administered orally, due to its major role in determining the rate and extent of absorption from the GI tract. This fact is more critical in cases of active substances with low solubility characteristics, i.e. compounds belonging to BCS class II and IV.

Especially for BCS Class II drugs, due to their reasonable membrane permeability, the rate-limiting step of absorption is the drug dissolution. Therefore, following an appropriate formulation design, these drug dosage forms could potentially behave as BCS Class I drugs having enhanced bioavailability. There is a number of formulation strategies that could be applied to improve the bioavailability of poorly soluble drugs. Approaches such as crystal modification, micronization, amorphization, self-emulsification, cyclodextrin complexation and pH modification have been extensively presented and reviewed in the scientific literature (Pouton, 2006; Kawabata et al., 2011). For example, the effect of cyclodextrin complexation on the biopharmaceutics behavior of praziquantel, a Class II drug, resulted in drug dosage forms that would behave as a BCS-Class I, depending on the dose administered (Maragos et al., 2009). Another notable example is cyclosporine. Despite its low and anomalous solubility (Ismailos et al., 1991) the commercially available microemulsion formulation, Neoral®, exhibits consistent absorption (Wahlberg et al., 1995).

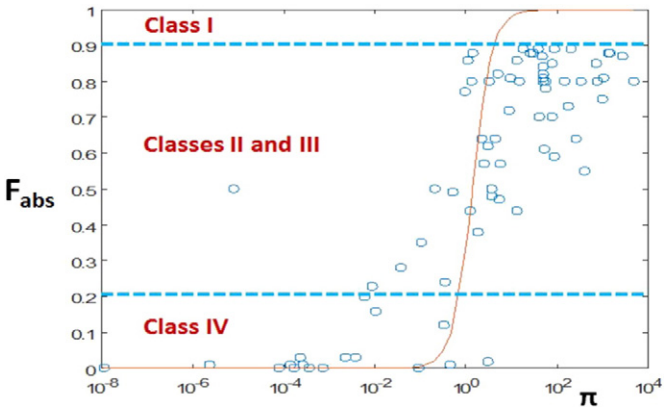

Fig. 2. Plot of fraction of dose absorbed versus absorption parameter π. Key: (o) observed data from Yalkowsky et al., 2006; continuous line, prediction based on Eq. (6). The horizontal lines at $F_{abs} = 90\%$ and $F_{abs} = 20\%$ are the border lines for Class I and IV, respectively.

On the other hand, BCS class IV drugs exhibit challenging molecular properties such as low solubility and low permeability, i.e. both factors are rate-limiting steps for absorption. Therefore, physiological parameters, such as gastric emptying time and gastrointestinal transit time, mostly influence the absorption of such molecules, leading to large inter- and intra-subject variability in their absorption (Horter and Dressman, 2001). This variability in absorption could result in the challenging drug development in terms of formulation design for such drugs.

2.3.4. Carrier mediated transport in the heterogeneous conditions of the GI tract

Carrier mediated transport is the only GI process which is nonlinear and is associated with the scientific-regulatory aspects of BDDCS (Wu and Benet, 2005). Invariably, the analysis of carrier mediated transport data relies on the Michaelian formalism. As far as the carrier mediated transport kinetics is concerned, the classical Michaelis-Menten theory is being questioned whenever an understirred water layer is considered in the analysis of drug-carrier interaction (Shibayama et al., 2015). The empirical approach proposed in 1977 by Winne (1977) is routinely used and assumes an association of the apparent Michaelis constant with the water layer thickness; however, there are other heterogeneous approaches for carrier mediated transport which are based on fractal kinetics (Macheras, 1995) or more recently on fractional kinetics (Damarla and Kundu, 2014) taking into account the topological constraints prevailing in the interface of the understirred water layer with the membrane.

3. Summary

Generally, classical diffusion principles still apply in most of the published work on GI drug absorption despite the inherent heterogeneity encountered both in vitro and in vivo. Besides, the exact origin and the implications of variability in GI drug lumen concentrations reported in numerous in vivo studies have not been elucidated so far. From the evidence presented in this work, it can be concluded that each one of the BCS classes contains compounds with a large variety of biopharmaceutical properties. This is the result of the continuous character of the properties and the absorption processes.

Drugs can be classified in two groups:

a) The homogeneous Class I (Fabs ≥ 90%) and
b) The heterogeneous Class II, III and IV (Fabs < 90%)

Gastric emptying controls the absorption of Class I drugs while time dependent coefficients control the absorption - e.g. dissolution and non-absorption e.g. precipitation processes for Class II, III and IV drugs. An explicit relationship between the F_{abs} and the biopharmaceutical drug properties cannot be developed since the absorption of Class I is controlled by the gastric emptying while the time dependency of absorption- and non-absorption processes for the heterogeneous group (Class II, III and IV) is "drug specific" and not "Class or Group specific". This fact may explain the enormous variability observed in studies dealing with in vivo dissolution, precipitation and composition of GI fluids.

Further to the above, time dependent approaches e.g. reaction limited dissolution or carrier mediated transport under topological conditions may be more suitable for the description of heterogeneous processes for Class II, III and IV drugs. Power laws, the Weibull function and fractional calculus are appropriate tools for the modeling of the heterogeneous processes.

Further research is needed on the investigation of these complex processes and their impact on drug classification.

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