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Review article

Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards

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Abstract

In the last decade, the regulatory bioequivalence (BE) requirements of drug products have undergone major changes. The introduction of the biopharmaceutics drug classification system (BCS) into the guidelines of the Food and Drug Administration (FDA) is a major step forward to classify the biopharmaceutical properties of drugs and drug products. Based on mechanistic approaches to the drug absorption and dissolution processes, the BCS enables the regulatory bodies to simplify and improve the drug approval process. The knowledge of the BCS characteristics of a drug in a formulation can also be utilized by the formulation scientist to develop a more optimized dosage form based on fundamental mechanistic, rather than empirical, information. This report gives a brief overview of the BCS and its implications.

Keywords: Bioequivalence; Biopharmaceutics drug classification system; Drug approval process

1. Introduction

During the last decade, biopharmaceutics has been undergoing a revolution from drug discovery to drug regulatory standards and harmonization. Biopharmaceutics is based on the chemical and physical properties of a drug substance, and the formulation and physiology of the route of administration. Today, many molecules are classified through screening processes, and promising candidates enter into drug pipelines for further in vitro and in vivo tests. At the end of the development process stands the approval by the regulatory agencies. From a strict economic point of view, this is the important step for moving from a drug candidate to a product which improves health and to cover the discovery costs. Many national and international societies and agencies are organizing workshops and conferences to harmonize the standards and documentation required for drug quality and safety [1], but there is still work ahead.

In this report, recent developments and future trends in bioavailability (BA) and bioequivalence (BE), based on the biopharmaceutics classification system (BCS) are discussed.

2. Historical view of biopharmaceutics

The biopharmaceutical quality of drug products was an important selling point even more than 100 years ago. Upjohn's friable pills (Upjohn, circa 1880) were advertised as: 'can be reduced to a powder under the thumb'. This emphasizes that drug delivery was recognized as being important even in the 1880s. In addition, the biopharmaceutical quality of some significant drug products on the US market protected them from generic competition. Examples include Dilantin®, digoxin, griseofulvin, Plendil®, extended-release Prilosec®, delayed-release Procardia-XL®, Sinemet® and the oral polio vaccine. The first three drugs, phenytoin, digoxins and griseofulvin, are considered water insoluble drugs [2] that have been on the market in the US for over 50 years with limited generic competition. The next two products are modified release dosage forms, with no immediate release dosage forms available in the US. Procardia XL® has a unique modified release claim that the immediate release product does not have in its labeling [3]. Sinemet® is a combination of two drugs, levodopa and carbidopa, an active therapeutic agent and a metabolic inhibitor. Finally, there is the oral polio vaccine a drug product with presumably very low oral BA. The long market half-life of these drug products is in no small measure due to the

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difficulty in meeting BE requirements, and therefore, in this sense, their biopharmaceutical properties and quality.

3. Regulatory changes

Biopharmaceutics and drug safety have played an important role in major regulatory changes in the US. First, the 1938 Food Drug and Cosmetic Act (FDCA) was a result of the use of ethylene glycol to solubilize a drug. With the subsequent deaths due to the ethylene glycol in the formulation, the FDCA of 1938 required drug products to be safe [4]. Because generics were required to meet essential safety, efficacy, and BE criteria, few were approved under these regulations. In 1984, the Drug Price Competition and Patent Term Restoration Act (Waxman–Hatch Act) [4] was passed, and established the abbreviated new drug application procedure (ANDA), permitted the FDA to approve generic products for drugs that had already been found safe and effective, and formalized the criteria for pharmaceutical equivalence and BE. The approval process for generic drugs was simplified. Many generics became available after this act changed the requirements for approval. Finally, there was the Generic Drug Enforcement Act in 1992 that included (among other additions) the inspection to the requirements in order to ensure the quality of generic drug products in the US. These two regulatory change periods were due to biopharmaceutics issues, and BE played a major role in the development of drug standards.

4. International definitions

Worldwide, a similar definition of BA is used in all relevant guidelines. According to the Code of Federal Regulations (CFR 21.320.1), in the US, BA means 'the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action'. This definition does not include much mechanistic information. On the other hand, rather than focusing on the 'rate and extent', focusing on the 'is absorbed' part of this definition, which technically may be taken as absorption into the intestinal cells or through the tight junctions of the gastrointestinal (GI) tract (Fig. 1), leads to a simplification of the regulatory requirements.

The 'Note for guidance on the investigation of bioavailability and bioequivalence' of the Committee for proprietary medicinal products (CPMP) of the European Medicines Evaluation Agency (EMEA) extends the above definition by adding the sentence 'BA is understood to be the extent and the rate to which a substance or its therapeutic moiety is delivered from a pharmaceutical form into the general circulation' [5]. This additional sentence, including systemic clearance variation in the definition, is more restrictive.

The mechanistic point of view in these definitions distinguishes between systemic availability and absorption. Systemic availability represents the amount of drug that arrives in the systemic circulation [6], and the test is based on C_{max} and AUC, which are usually measured values and can vary due to clearance, e.g. metabolic processes [7]. Absorption, on the other hand, represents permeation into the intestinal mucosa of the GI tract [8,9]. The availability of drug into the portal system or the fraction of dose absorbed into the portal system, or intestinal mucosa, represents an upper limit to the amount of drug that can reach the systemic circulation [8]. While it is difficult to make direct measurements in the GI tract to quantify the rate and extent of drug absorption [9], important conclusions can be drawn from this point of view that allow a simplification of drug regulatory standards based on this mechanistic approach.

A modern approach to BE has to consider, besides strictly empirical parameters like AUC and C_{max}, the mechanistic elements of the absorption process. There is little mechanistic information that can be obtained from C_{max} and AUC, and they can be insensitive to formulation changes [10].

The BE definitions of the BIO-international '94 conference was based on the empirical concentration time profile parameters 'two medical products are considered to be bioequivalent when their concentrations vs. time profiles, from the same molar dose, are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects' [11].

Most recently, the FDA has issued a guidance titled 'waiver of in vivo BA and BE studies for immediate release solid oral dosage forms containing certain active moieties/active ingredient based on a BCS' [12]. This new guidance is modifying the paradigm regarding BE regulations in the US. The BCS also relies on dissolution testing, and sets dissolution standards which can be used as the basis for requesting waivers from in vivo BE studies; emphasizing the position of being able to test in vitro mechanistically rather than in vivo empirically [13]. Both the mechanistic knowledge and a formulation based regulation of the drug absorption may allow one to predict and ensure BE. If two drug products have the same in vivo dissolution profile under all luminal conditions, they will present the same concentration time profile at the intestinal membrane

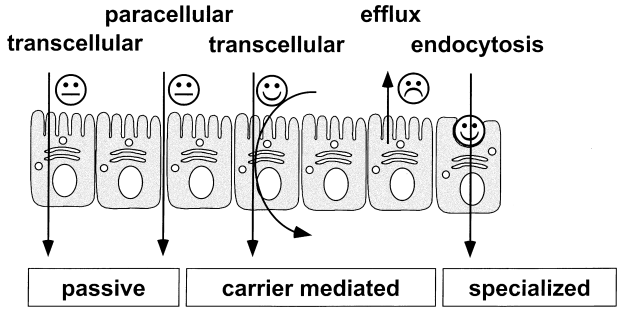

Fig. 1. GI membrane transport. The transport through the enteroyte barrier can be generally divided into active, passive and specialized transport; and into a paracellular and transcellular route.

Table 1
BCS classification of drugs and in vitro/in vivo correlation expectations for immediate release products based on the biopharmaceutics class[a]

Class	Solubility	Permeability	IVIVC expectation
I	High	High	IVIVC if the dissolution rate is slower than the gastric emptying rate, otherwise limited or no correlation
II	Low	High	IVIVC expected if the in vitro dissolution rate is similar to the in vivo dissolution rate, unless the dose is very high
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution rate
IV	Low	Low	Limited or no IVIVC expected

[a] Modified from [8].

surface and this will lead to the same rate and extent of absorption [8].

The introduction of the simplification of the BCS in FDA guidelines represents a major step forward in the regulation of oral drug products. The guidance classifies drug substances into four categories according to their permeability and solubility properties (Table 1) [12]. The FDA guideline suggests internal standards and marker substances to characterize the permeability of drug substances in vitro and in vivo (Table 2).

The BCS is used to set drug product dissolution standards to reduce the in vivo BE requirements [8,14]. Knowledge of the BCS can also help the formulation scientist to develop a dosage form based on mechanistic, rather than empirical, approaches [15]. This allows one to determine the potential for in vitro and in vivo correlations, and can significantly reduce in vivo studies.

Table 2
Suggested model drugs to classify permeability of new drug substances

Drug	Permeability class	Comments
Alpha-methyldopa	Low	Amino acid transporter
Antipyrine	High	Permeability marker
Atenolol	Low	Paracellular, internal standard
Caffeine	High	
Carbamazepine	High	
Hydrochlorothiazide	Low	Class IV
Furosemide	Low	Class IV
Ketoprofen	High	
Mannitol	High to low	Border marker
Metoprolol	High	High to low marker, internal standard
Naproxen	High	
Polyethylene glycol 400–4000	Low	PEG 4000 can be used as a non-absorbable marker for in vivo studies
Propanolol	High	
Ranitidine	Low	Internal standard
Theophylline	High	
Verapamil	High	Candidate for characterization of P-glycoprotein efflux in in-vitro systems

5. GI considerations

Principally, the rate of release of a drug from a dosage form within the GI tract has to be considered. Drug dissolution, especially for poorly soluble drugs, can be limited due to the volume of intestinal juices available in the gut and to the pH (Fig. 2). On the other hand, it is known that bile salts can increase the solubility of lipophilic substances [16–18], and the presence of food can have an additional impact on the solubilization and absorption of a drug [19,20].

Furthermore, gastric emptying [21,22] and GI transit time are important parameters for the onset and the degree of drug absorption [23,24].

For some controlled or extended-release dosage forms, the intestinal motility pattern may have an impact on the rate and extent of drug dissolution [25]. In addition, the drug amount in the gut lumen can be reduced due to hydrolytic, metabolic, or enzymatic degradation along the GI tract caused by the changing luminal environment or bacteria and enzymes [26,27]. Within the GI transit, the permeability of a drug can change due to physiological factors [13].

GI dissolution and membrane permeability of the drug into the mucosa are the key parameters in drug absorption. As shown in Fig. 1, there are different pathways and mechanisms for membrane transport [28,29]. There are many factors of obviously complex chemistry and physiology involved. However, the fraction absorbed represents an upper limit to the amount of drug that can reach the systemic circulation.

6. Drug absorption and the BCS

To follow the movement of a dosage form through the GI tract, the entire process has to be broken down into its component parts in order to see it mechanistically. Applying Fick's Fist Law to a membrane the absorption across the mucosal surface can be written as in Eq. (1)

$$J_w = P_w \times C_w = \frac{dM}{dt} \times \frac{1}{A} \quad (1)$$

where J_w is the mass transport across the gut wall, P_w can be assumed as the effective permeability, C_w is the concentration of the drug at the membrane, and A is the surface area. Eq. (1) shows that permeability and solubility are the fundamental variables to describe the mass transport through a membrane.

Based on a mass balance in the gut [30], different quantitative and mechanistic approaches have been developed to predict the GI uptake of drugs and are discussed by Yu et al. [31]. A general relationship between P_{eff} and the fraction dose absorbed (F) is shown in Fig. 3. Here, the assumption

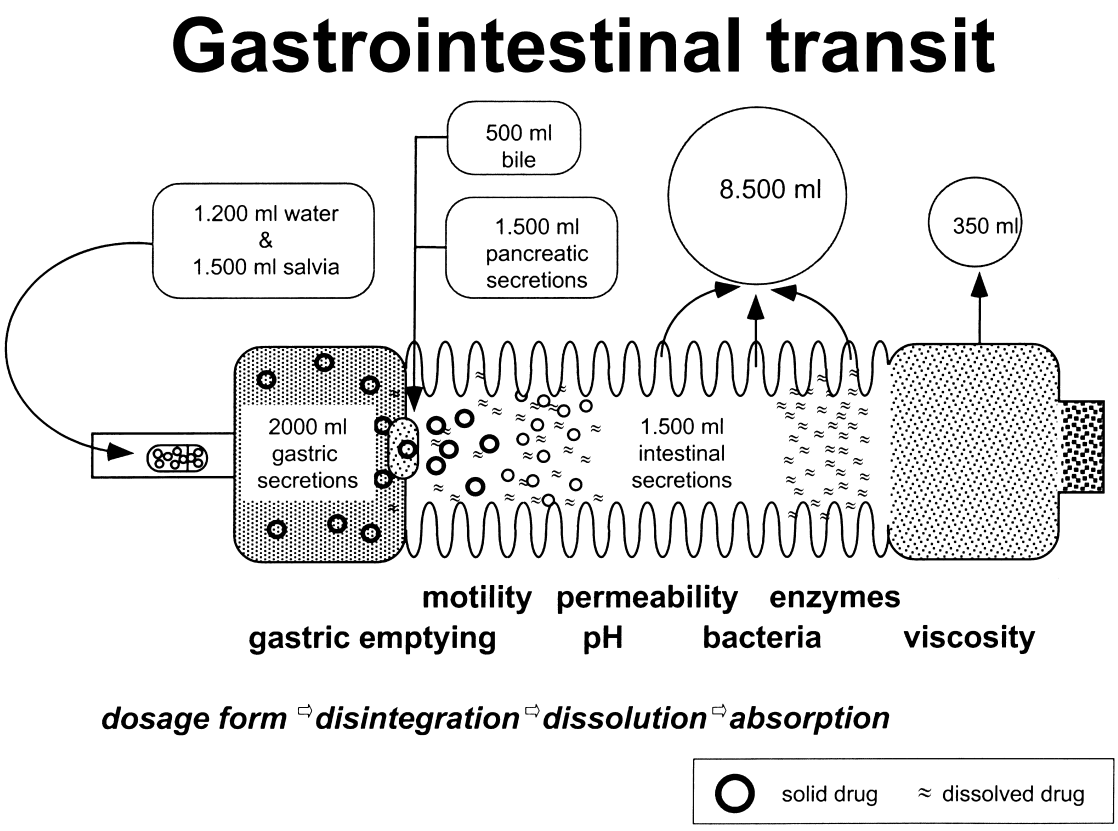

Fig. 2. Factors influencing the GI drug uptake. For poorly water soluble drugs, the volume of intestinal juices is important to estimate if a single dose can theoretically dissolve within the gut passage. Other factors influencing the pharmacokinetic pattern are gastric emptying, motility phase, pH changes, permeability, bacteria and enzymatic activities, and the luminal viscosity that is especially important for colon delivery or poorly soluble drugs if the administered dose will not dissolve and/or be absorbed within the small intestinal transit.

is made that drug solubility is not limited [32]. The important information that can be drawn from the shape of the graph is that if the P_{eff} value of a drug is below 2, then the drug absorption will be incomplete, while if P_{eff} has a value over 2, complete absorption can be expected [8].

The BCS defines three dimensionless numbers, dose number (Do), dissolution number (Dn) and absorption number (An), to characterize drug substances. These numbers are combinations of physicochemical and physiological parameters and represent the most fundamental view of GI drug absorption.

First, the absorption number is the ratio of permeability (P_{eff}) and the gut radius (R) times the residence time $\langle T_{\text{si}} \rangle$ in the small intestine, which can be written as the ratio of residence time and absorptive time $\langle T_{\text{abs}} \rangle$ (Eq. (2))

$$\text{An} = \frac{P_{\text{eff}}}{R} \times \langle T_{\text{si}} \rangle = \frac{\langle T_{\text{si}} \rangle}{\langle T_{\text{diss}} \rangle} \tag{2}$$

Second, is the dissolution number (Dn) which is the ratio of the residence time to the dissolution time $\langle T_{\text{diss}} \rangle$, which includes solubility (C_s), diffusivity (D), density (ρ), and the initial particle radius (r) of a compound and the intestinal transit time $\langle T_{\text{si}} \rangle$ (Eq. (3))

$$\text{Dn} = \left(\frac{3D}{r^2}\right)\left(\frac{C_s}{\rho}\right)\langle T_{\text{si}} \rangle = \frac{\langle T_{\text{si}} \rangle}{T_{\text{diss}}} \tag{3}$$

Finally, there is the dose number, Do, which is defined as the ratio of dose concentration to drug solubility (Eq. (4)).

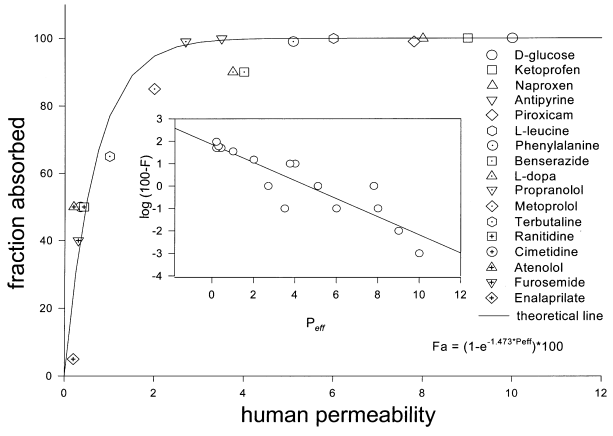

Fig. 3. The relationship between human permeability and fraction dose absorbed. Modified from [8].

$$\mathrm{Do} = \frac{M/V_0}{C_s} \tag{4}$$

where C_s is the solubility, M is the dose, and V_0 is the volume of water taken with the dose, which is generally set to be 250 ml.

As shown in Fig. 3, the fraction absorbed (F) of a solution follows an exponential function, and can be calculated by Eq. (5) [32]

$$F = 1 - e^{-2\mathrm{An}} \tag{5}$$

7. Class II drugs

Of particular interest are low solubility drugs, where the maximum flux due to absorption is equal to the solubility times the permeability [32]. For such drugs, dissolution is important because it changes the actual drug concentration in solution over time. Consequently, dissolution is brought into the classification system since it impacts the concentration of drug at the membrane surface. The dissolution of a poorly soluble compound is normally low ($\mathrm{Dn} < 1$), while for many poorly soluble compounds An and Do are usually high (class II). If An and Dn are low, then the drug will be considered as a class IV drug. Under the assumption that dissolution is not limited [32], the fraction dose absorbed of a suspension can be calculated as Eq. (6)

$$F = \frac{2\mathrm{An}}{\mathrm{Do}} \tag{6}$$

Two classical examples of poorly soluble drugs are digoxin and griseofulvin. They have about the same solubility of approximately 20 μg/ml. However, the normal administered single dose is different. Consequently, the volume required to dissolve a single oral dose of digoxin is approximately 20 ml, while the volume required to dissolve a single dose of griseofulvin is 33 l, a huge amount which can not be administered. In terms of the BCS, both drugs have different dose numbers, see Table 3.

Fig. 4. shows the relationship between the Do and Dn on the fraction dose absorbed (F) of the administered dose at a given An. The fraction absorbed in the graph reaches 1 (100% absorption) because in the example shown, the absorption time is shorter than the residence time [32]. The significant changes in the curve are occurring around the dose number of 1 and the dissolution number of 1. In this area, small changes in the value of Dn or Do can result in significant differences in the absorbed fraction. Consequently, to know where a drug is located in this graph can help to overcome BA problems at an early stage in formulation development. If it is possible, the formulation properties have to be changed so that the plateau of the graph can be reached.

The Do and Dn of digoxin and griseofulvin are marked in Fig. 4. According to Eq. (3), for digoxin, complete absorption can be expected if the particle size is small enough (high Dn). If the particle size of the drug powder gets too large (small Dn), then digoxin can be considered as a dissolution limited drug. In this case, the transit time will be too short for drug dissolution and absorption, while a micronized drug powder can dissolve faster due to its radius, and the absorption time can be sufficient for complete absorption [33,34].

In the case of griseofulvin, a micronization will not improve the fraction absorbed significantly. For this drug, besides a change of Dn, a change of Do is also required to move up to the plateau of complete absorption. A change in the value of Do is caused by a change in the ratio of dose/concentration and solubility. While the dose is usually set and the required volume to dissolve a single dose of griseofulvin is too high (33 l), and therefore limited to a much smaller amount, the only parameter which can be changed is the solubility. In the case of griseofulvin, a sufficient change of Do is due to a solubilization enhancement [34,35]. If such a solubility enhancement is not efficient, then griseofulvin can be considered as a solubility limited drug, due to the

Table 3
Calculated parameters for a single oral dose of digoxin and griseofulvin[a]

Drug	Dose (mg)	C_s (mg/ml)[b]	V_{sol} (ml)[c]	Do[d]	Dn[e]
Digoxin	0.5	0.024	20.8	0.08	0.52
Grisefulvin	500	0.015	33333	133	0.32

[a] Modified from [45].
[b] Minimum physiologic solubility in the pH range of 1–8 and at 37°C.
[c] Volume of solvent required to completely dissolve the dose at minimum physiologic solubility.
[d] Do, Dose/V_0/C_s; initial gastric volume, 250 ml.
[e] Assumptions: r, 25 μm; D, 5×10^{-6} cm^2/s; ρ, 1.2 mg/cm^3; $\langle T_{si} \rangle$, 180 min.

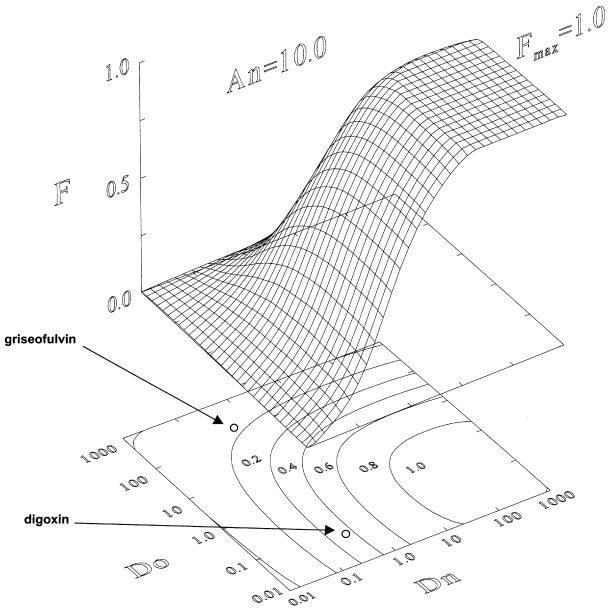

Fig. 4. The relationship between Do, Dn and An and the fraction dose absorbed. Modified from [8].

lack of available fluids. On the other hand, if ingredients of the formulation enable an efficient solubilization of the drug in gastric juices, a complete absorption can be expected.

8. In vitro/in vivo correlations (IVIVC) and dissolution test development

To establish IVIVC, several factors have to be considered. In Table 1, the IVIVC expectations for different BCS classes are given. However, if an IVIVC can be expected, the choice of a suitable medium, i.e. one that can simulate the in vivo dissolution, is critical. National pharmacopoeias describe different test media to cover the physiological pH range between 1.2 and 6.8. However, for many drugs which are poorly soluble within this pH range, these media are not very useful.

Aqueous solubility is a function of the lipophilic and hydrophilic properties of a molecule and can be increased by increasing the lipophilicity of the medium, or by increasing the hydrophilicity of the molecule itself, e.g. using its salt [36,37]. The easiest way to influence the solubility of a pH sensitive drug is to change the pH of the medium [14], or to introduce organic solvents. If the pH change is within the physiological range of pH 1–8, the obtained solubility and dissolution data may be used to establish an IVIVC [38].

A pH change outside this range makes a comparison between in vitro and the in vivo situation impossible. The same situation occurs if organic solvents are used, which is the less preferred way; because in the case of controlled release dosage forms, the release-controlling component can be influenced by the solvent and a correlation may not be obtained. The composition of modern dissolution media should provide a good predictability of the in vivo performance of a dosage form.

9. Micelle and emulsion systems

Another way to increase drug solubility besides pH changes, or the use of organic solvents, is the addition of surfactants to the medium or the use of emulsions [35,39–41]. Such media are preferable to non-physiological pH changes or organic solvents, because they may be able to simulate the in vivo environment of the gut lumen [16].

In the GI tract, bile salts and lecithin are physiologically present, and improve the wetting [42] and solubility of many lipophilic substances [17,18]. Furthermore, the interaction of intestinal juices with lipids or food components can increase the formation of emulsions [43].

In vitro, besides natural bile components, a number of synthetic surfactant is available for dissolution media [44,45]. In one study, several different surface active substances, including sodium lauryl sulfate (SLS), dodecyltrimethyl ammonium bromide (DTAB), Tween 20 (TW 20) and an emulsion containing Tween 20 and different oil/water rations, were used to investigate the impact of micelle and emulsion systems on the flux and the solubilization enhancement of griseofulvin [46].

$$\phi = J_{tot}/J_s = \left(D_{eff}^{2/3}/D_s^{2/3}\right)(C_{tot}/C_s) \quad (7)$$

$$k^* = C_{sm(0)}/C_{s(0)} \times C_{m(b)} \quad (8)$$

$$C_{tot} = C_{s(0)} + C_{sm} \quad (9)$$

In Eqs. (7–9), the dissolution rate enhancement model based on the flux enhancement factor [39] is shown, where J_{tot} is the total flux, J_s is the flux in the solvent, D_{eff} is the effective diffusivity, D_s the diffusivity in the solvent, C_{tot} is the total concentration, and C_s is the solubility. k^* is the equibrilium coefficient, $C_{sm(0)}$ is the concentration of the drug loaded micelle, the subscript (0) denotes the surface for the solid, and $C_{m(b)}$ is the concentration of surfactant in the bulk solution.

As shown in Table 4, the solubilization enhancement using surfactants can be up to 150-fold compared to simple water. The highest solubility enhancement was achieved in this experiment using 2% SLS, while DTAB showed a 42-fold enhancement and TW 20 showed only a seven-fold enhancement.

The bile salts used exhibit a moderate to poor solubilization compared to SLS and DTAB. Pharmaceutical surfactants can approximate the solubilization of the in vivo surfactants [41,47].

Compared to the high solubility enhancement, the flux enhancement of the micelle system was only increased by 40-fold, and the flux increase of the bile salts was about five-fold. The reason that the dissolution rate increased up to 40-fold while the solubility increased up to 150-fold, is due to a decrease of the diffusion coefficient of the micelle system of

Table 4
Calculated parameters for 500 mg griseofulvin in different media[a]

Medium content	C_s	σ	V_{sol}	Do	Dn
Water	0.015	1	33333	133	0.23
Micell systems					
2% SLS	2.205	150	227	0.9	7.62
2% DTAB	0.629	42	795	3.17	3.31
2% TW 20	0.11	7	4545	18.2	0.52
Emulsion					
2% TW 20 (10%)	0.222	15	2252	8.25	0.42
2% TW 20 (20%)	0.286	19	1746	7.58	0.28
2% TW 20 (30%)	0.345	23	1449	5.99	0.26
Bile salts					
2.15% NaTC (40 mM)	0.064	4.2	7874	22.5	0.54
1.72% NaC (40 mM)	0.064	4.2	7874	22.7	0.51
1.72% NaC (40 mM)[b]	0.049	3.3	10183	34.9	0.36
Pc/NaC (MR, 0.7)[c]	0.253	17	1976	7.64	0.32

[a] C_s, saturation solubility of drug compound in aqueous medium at 37°C; σ, solubility enhancement; V_{sol}, volume of medium required to completely dissolve the 500 mg dose; Do, dose number; Dn, dissolution number; NaTC, sodium taurocholate; NaC, sodium cholate.

[b] Containing 0.15 M sodium cholate.

[c] PC, phosphatidycholine; NaC concentration, 40 mM.

about one-third to one-fourth of the diffusion coefficient of the solution [36,39]. This phenomenon is due to the size of the micelles (Fig. 5). The much larger diameter of a micelle results in a slower diffusion compared to a dissolved molecule. At high surfactant concentrations, the solute is in the micelle, and the micelle, due to its size, diffuses more slowly. Therefore, a consequence of drug solubilization within micelles is a decrease in the apparent diffusion coefficient [44].

Due to the efficient solubilization of SLS, a decrease of the very high dose number of griseofulvin from 133 in water (Table 4) to about 1 in a medium containing 2% SLS can be observed. In addition to the change in Do, an increase in the dissolution number from 0.23 in water to 7.62 in 2% SLS occurs. However, the dose number approaches nearly 1 and the dissolution number increases between 1 and 10, providing evidence for the substantial solubilization of griseofulvin in SLS. According to Fig. 3, these values lead to the area of complete absorption of the administered dose. Of course, the in vivo solubilization is not really known, but these values can be used as references in a simulation and estimation of drug absorption. The potential of solubilization enhancement of pharmaceutical surfactants can be used to develop dissolution media which are able to simulate the in vivo environment to establish an IVIVIC.

Another factor to consider is that the micelle formation in vivo depends on several physiological factors, e.g. pH, bile concentration and lecithin content. Furthermore, the influence of food and lipids in the gut can increase the formation of emulsion. The next step to simulate the in vivo situation is to investigate O/W emulsion systems, and their micelle and emulsion facilitated dissolution and solubility enhancement on drugs.

A micelle system consists of relatively small vesicles of surfactants, while an O/W emulsion is characterized by the presence of micelles and much larger lipid vesicles surrounded by surfactants (Fig. 6). The drug can diffuse into the lipid phase of the emulsion, or can be solubilized by the micelles. To model this is complex, because, due to the surfactant and its structure at the interface between the water and lipid phases, diffusion within the vesicle and an interfacial barrier have to be considered as potential resistance barriers. Furthermore, the emulsion radius and the viscosity of the emulsion system could decrease the diffusivity, as shown before, for the aqueous solution and micelle system. Additionally, in an emulsion, a lower micelle concentration at the same surfactant concentration is expected in the medium because the lipid droplets will consume parts of the surfactant. An overall slower mass transport in an emulsion compared to a micelle system can be expected, due to bigger droplets and a lower micelle concentration.

Fig. 7 shows that an emulsion system is able to increase the flux and does not, as expected, decrease it. The contribution to the flux enhancement is due to the emulsion particle, as well as to the surfactant phase in the aqueous phase. A comparison of the surfactant system and the emulsion system shows that the micelle effect counts most for the increase in flux, and that the increase contributed by the emulsion is more moderate. Together, both effects counteract the expected decrease in flux.

In Table 4, the calculated dose number for griseofulvin in the emulsion system decreases significantly compared to the surfactant only. This can be explained by the high efficiency of the oil phase to solubilize the lipophilic drug and to the solubilization of the micelle system. From the changes in Do and Dn shown in Table 4, the conclusion can be drawn that an emulsion medium will have only a small effect on the dissolution rate, but offers a significant improvement in the solubilization of a lipophilic drug [44].

10. pH and solubilization

Many drugs are ionizable within the physiological pH

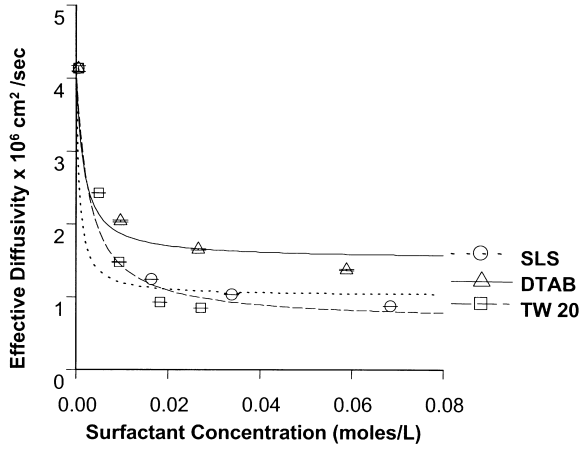

Fig. 5. Effective diffusivity as a function of surfactant concentration (total concentration − CMC, containing 0.15 M sodium chloride). Modified from [44].

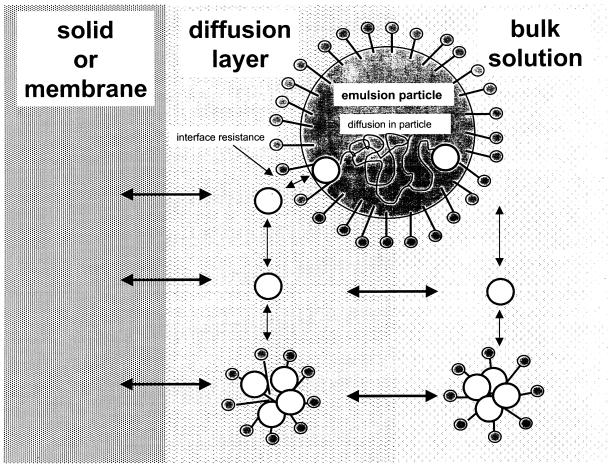

Fig. 6. A model for the solubilization of lipophilic drugs in a emulsion medium. The diffusion of the molecules can take place in the bulk solution, the micelles or the lipid droplets.

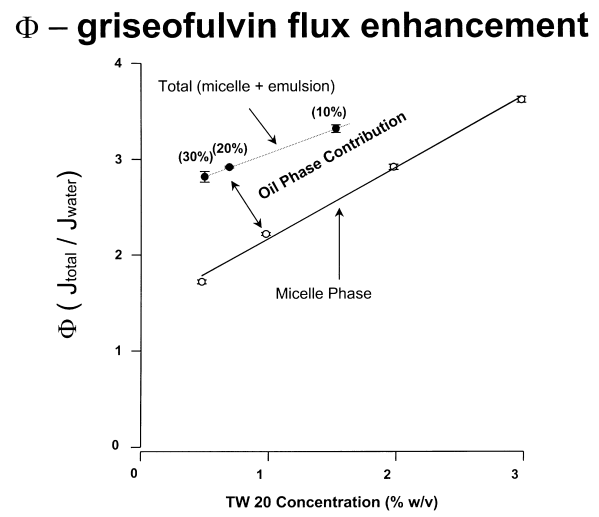

Fig. 7. Contribution of oil phase on the flux of griseofulvin at the same surfactant content as a micelle system without oil phase. Modified from [45].

range [48], which impacts their aqueous solubility [49]. Due to the pH, the solubility can increase, or an unfavorable pH change may even induce the precipitation of a dissolved drug. In vivo, the complexity is increased due to the varying pH with time and position in the intestine, as well as the varying of the surfactant concentration and time profile. Thus, predicting in vivo solubilization within these factors is fairly difficult. In vitro, a combination of pH and surfactant effects can lead to a better understanding of the in vivo situation.

A simple model, shown in Fig. 8, presents the solubilizations of both the ionized and unionized drug, as well as the ionization contribution to total solubilization for acetic drug substances [44]. Piroxicam was used as model drug to study the influence of solubility on changes in surfactant content and pH [50]. The drug is sparingly soluble in water, but it is slightly soluble in an aqueous alkaline solution due to its weakly acidic properties (pK_a, 6.1). One of the key points was to investigate the effect of micelle solubilization on the

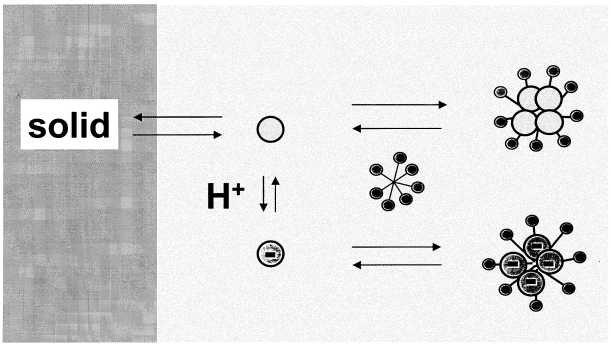

Fig. 8. A model for the contribution of ionized molecules on the total solubilization in a micelle containing medium.

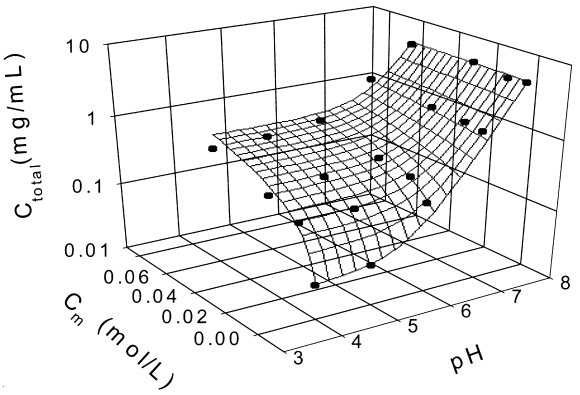

Fig. 9. The influence of pH and surfactant concentration (C_m) of SLS on the solubility (C_{total}) of piroxicam. From [50].

ionized species, and whether the contributions of surfactant and pH were additive.

In Fig. 9, the impact of both factors on the solubilization of piroxicam is shown. The shape of the graph indicates a combined effect of pH and surfactant. An approximate ten-fold increase in solubilization at a low pH is due to the surfactant concentration, while the 100-fold increase in solubilization is due to the pH. Furthermore, at high pH values, there is relatively little effect of the surfactant on the solubilization, showing that the surfactant mainly impacts the solubilization of unionized species at low pH values. Consequently, the influence of the surfactant on the solubility is most important at low pH values, and the maximum increase in solubility occurs at high pH values (170-fold) and is due to pH (150-fold), and additionally, due to the presence of the surfactant (20-fold).

Both factors enhanced the dissolution rate, similar to the solubility enhancement, but to a lesser degree (data not shown). The maximum surfactant effect on dissolution was ten-fold, while the maximum enhancement on solubility was 15-fold. This shows that dissolution enhancement is due to pH, rather than surfactant effects. Solubilization and dissolution of ionizable species in surfactant media can be concluded as an additive contribution from pH and solubilization.

The overall conclusions from the different experimental works are that pharmaceutical surfactants can be used to mimic in vivo solubilization of poorly soluble drugs in micelle and emulsion systems. The in vitro results may be used as surrogates to predict the in vivo performance of a dosage form for establishing IVIVCs. This allows a considerable simplification in dissolution media and methods.

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