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Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine

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Abstract

Solubility and dissolution relationships in the gastrointestinal tract can be critical for the oral bioavailability of poorly soluble drugs. In the case of poorly soluble weak bases, the possibility of drug precipitation upon entry into the small intestine may also affect the amount of drug available for uptake through the intestinal mucosa. To simulate the transfer out of the stomach into the intestine, a transfer model was devised, in which a solution of the drug in simulated gastric fluid is continuously pumped into a simulated intestinal fluid, and drug precipitation in the acceptor medium is examined via concentration–time measurements. The in-vitro precipitation of three poorly soluble weakly basic drugs, dipyridamole, BIBU 104 XX and BIMT 17 BS, was investigated. For all three, extensive supersaturation was achieved in the acceptor medium. Under simulated fasted-state conditions, precipitation occurred for all three compounds whereas under simulated fed-state conditions, the higher concentrations of bile components and the lower pH value in the acceptor medium inhibited precipitation at concentrations corresponding to usual doses in all cases. Comparison with pharmacokinetic data indicated that a combination of transfer model data with solubility and dissolution profiles should lead to better predictions of in-vivo behaviour of poorly soluble weak bases.

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Introduction

The rate at which a drug goes into solution is an important determinant of drug absorption from the gastrointestinal tract. Factors that are important to the kinetics of drug dissolution, as identified by the Nernst-Brunner and Levich modifications of the Noyes-Whitney model (Noyes & Whitney 1897; Nernst & Brunner 1904; Levich 1962), are the physicochemical properties of the compound itself such as pK_a, solubility, crystalline energy and specific surface area, as well as certain aspects of the prevailing conditions in the gastrointestinal tract. The physiological parameters that can play an important role include pH, surface tension, solubilisation, buffer capacity and the volume of the lumenal contents. These parameters not only vary widely with position in the gastrointestinal tract, but are also subject to change following the ingestion of food.

The pH of the gastrointestinal fluids is of vital importance to the solubility of ionisable drugs. For weak acids and bases the solubility is dependent on the compound's ionisation constant and the pH of the local environment. Reduction of the pH below the pK_a value for weak bases, for example, leads to an increase in solubility due to the contribution of the more soluble, ionised form of the drug. As the pH in the gastrointestinal tract varies widely with location, one can expect significant changes in solubility during gastrointestinal passage. Bile components, including bile salts and lecithin, have also been shown to increase the in-vitro dissolution rate for numerous poorly soluble compounds (Bates et al 1966; Mithani et al 1996). Enhancement of the dissolution rate in the presence of bile salts and lecithin can occur by an increase in solubility via micellar solubilization (at concentrations above the critical micellar concentration) or by the enhancement of the wettability of the compound. The greater concentrations of bile components in the intestine following meal intake (Fausa 1974;

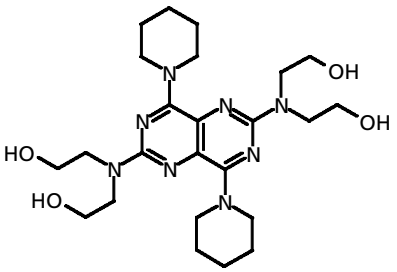
Tangerman et al 1986) can therefore lead to an increase in drug solubility and dissolution.

Biorelevant dissolution tests in media that simulate the conditions at specific sites in the gastrointestinal tract have been shown to be a useful tool to predict the absorption of poorly soluble drugs (Galia et al 1998; Nicolaides et al 1999; Löbenberg et al 2000). For example, dissolution test data in fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) were shown to correlate well with the oral bioavailability of poorly soluble drugs (Galia et al 1998; Nicolaides et al 1999).

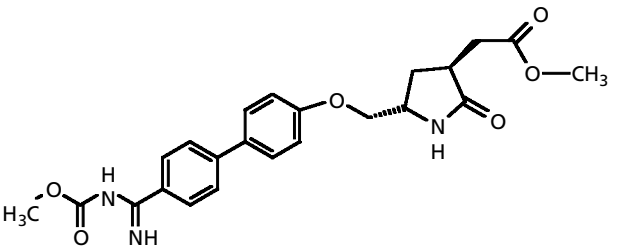
For the specific case of poorly soluble weak bases, one must not only consider solubility and dissolution but also the possibility of precipitation as the drug moves from the favourable pH conditions in the stomach to a less favourable pH environment in the small intestine. As the pH nears, or even exceeds, the pK_a of the base, its solubility undergoes a sharp decrease and the concentration of drug in the solution may, in fact, exceed the solubility. The question is, does the drug stay in (supersaturated) solution, or does it precipitate and therefore become no longer available for absorption.

To simulate the transfer out of the stomach into the intestine, which is the critical pH transition for poorly soluble weak bases, a new in-vitro model was developed (Kostewicz et al 1999, 2000, 2001). With this so-called transfer model, a solution of the drug in simulated gastric fluid is transferred into a simulated intestinal fluid, and drug precipitation is examined via concentration–time measurements. In this study, the in-vitro precipitation of three poorly soluble weakly basic model substances, dipyridamole, BIBU 104 XX and BIMT 17 BS, was investigated. By varying the experimental conditions in the transfer model, the influence of hydrodynamics, transfer rate and composition of the simulated intestinal media (fasted vs fed state) on the drug's precipitation behaviour could be investigated.

Dipyridamole:



BIBU 104 XX (INN Lefradafiban):



BIMT 17 BS (INN Flibanserin):

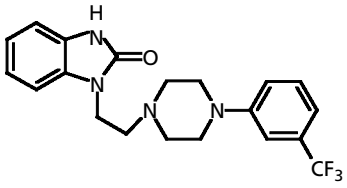


Figure 1 Structures of the compounds studied.

Materials and Methods

Materials

Dipyridamole, BIBU 104 XX and BIMT 17 BS (Figure 1) were chosen as model substances for poorly soluble weak bases, with aqueous solubilities of 0.008, 0.0028 and 0.0075 mg mL^{-1}, respectively (Kostewicz et al 2002). The pK_a values of the compounds, 6.4 (dipyridamole), 5.8 (BIBU 104 XX) and 6.03 (BIMT 17 BS), suggest that the solubility characteristics would vary considerably during transit through the gastrointestinal tract (Kostewicz et al 2002).

Dipyridamole powder (lot no. 170755), BIBU 104 XX powder (lot no. 740097) and BIMT 17 BS powder (lot no. 9701-P) were provided by Boehringer Ingelheim KG (Biberach an der Riss, Germany). Sodium taurocholate 98% pure (lot no. 15H5001 and 59H5225) was purchased from Sigma-Aldrich Chemie GmbH (Deisenhofen, Germany). Egg-phosphatidylcholine 99.1% pure (lot no. 12091-1 and 105013-1) was generously donated by Lipoid GmbH (Ludwigshafen, Germany). Potassium dihydrogen phosphate, sodium dihydrogen phosphate and potassium chloride, all analytical grade, were purchased from E. Merck (Darmstadt, Germany). All other chemicals were analytical grade (or equivalent) and purchased commercially.

Composition of the various media

SGF_{fast} dissolution medium, simulating gastric conditions in the fasted state, contains 34.2 mM NaCl in 0.01 M HCl. The medium has a pH of about 2.1.

Fasted state simulated intestinal fluid (FaSSIF) is a biorelevant dissolution medium containing 3 mM sodium taurocholate and 0.75 mM lecithin in a pH 6.5 phosphate buffer. It simulates the average conditions in the proximal intestine in the fasted state. It was prepared as described previously by Galia et al (1998).

Fed state simulated intestinal fluid (FeSSIF) is a biorelevant dissolution medium containing 15 mM sodium taurocholate and 3.75 mM lecithin in a pH 5 acetate buffer. It simulates the average conditions in the postprandial proximal intestine. It was prepared as described previously by Galia et al (1998).

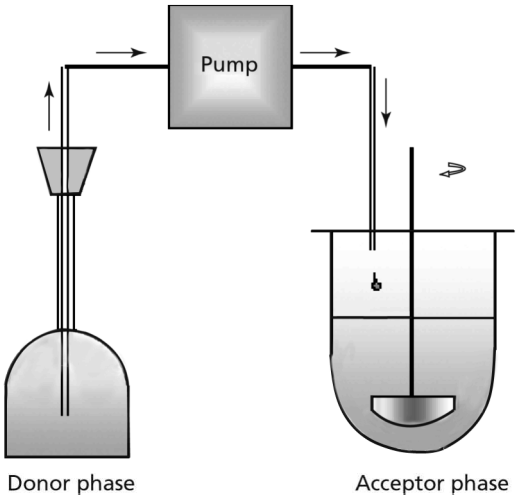


Figure 2 Experimental set-up to examine precipitation.

The transfer model

To simulate the drug transfer out of the stomach into the small intestine, an appropriate amount of drug powder was completely dissolved in SGF_{fast} (donor phase). Concentrations of $3\,mg\,mL^{-1}$ for dipyridamole, $0.2\,mg\,mL^{-1}$ for BIBU 104 XX and $2\,mg\,mL^{-1}$ for BIMT 17 BS were chosen. A peristaltic pump (Ismatec type IPC, Glattbrugg-Zuerich, Switzerland) was used to transfer the donor phase (SGF_{fast} containing dissolved drug) into a dissolution vessel containing 500 mL of either FaSSIF or FeSSIF as the acceptor phase. The transfer rates used ($0.5–9\,mL\,min^{-1}$) represent the range of flow rates out of the stomach that can be anticipated physiologically. The acceptor phase media was maintained at $37 \pm 0.5\,^{\circ}C$. To examine the influence of intestinal motility on drug precipitation, various paddle rotational speeds (50, 75, 150 $rev\,min^{-1}$) were used in the acceptor phase. The experimental set-up is illustrated in Figure 2.

An Erweka model DT80 dissolution tester (Erweka, Heusenstamm, Germany) was used for all of the dissolution and precipitation studies and was regularly calibrated according to the USP. Depending on the transfer rate, various transfer durations were chosen (see Table 1).

The final volume and pH in the acceptor phase vessel varied with the volume of donor phase transferred, which could potentially affect precipitation of the drug. Therefore, in separate experiments the pH was monitored in the acceptor phase. The pH after transfer of 125 mL of SGF_{fast} into 500 mL FaSSIF had decreased from 6.48 to 6.27 ($n = 3$), after addition of 250 mL the pH had decreased to 6.03 ($n = 3$). Using FeSSIF as the acceptor medium, a decrease in pH from 5.01 to 4.99 after 125 mL and, further, to 4.94 after 250 mL ($n = 3$ in each case) was observed. Comparing these pH changes to the pK_a values of the compounds studied, it appears that the solubility of dipyridamole in the acceptor phase would increase over the course of the transfer experiments in FaSSIF, but that the solubility of the other two compounds would be less affected. No solubility changes are expected for transfer into FeSSIF.

Sampling procedure

Samples were periodically withdrawn from the acceptor phase using a Fortuna Optima glass syringe (Fortuna Optima Luer Lock, Wertheim, Germany) fitted with a stainless-steel cannula. The tip of the cannula was fitted with a 10-μm frit to prevent undissolved material from being withdrawn from the vessel. The volume of medium withdrawn was replaced with the equivalent volume of blank medium from a separate vessel also held at $37 \pm 0.5\,^{\circ}C$. The samples were immediately filtered through a 0.45-μm PTFE filter (Schleicher & Schuell, Germany). The first 2 mL were discarded and a sample of the remainder was appropriately diluted with acceptor phase media to avoid precipitation in the sample vials before HPLC analysis. No significant loss of drug due to adsorption to the sampling device, filter or tubing used to transfer the donor solution was shown to occur for any of the drugs examined.

HPLC analysis

All assays were performed by HPLC using a UV detector. The HPLC system consisted of an autosampler (model ISS 101, Perkin Elmer, CT), a Merck Hitachi pump (model L-7110), a Spectroflow 757 absorbance detector (ABI/Westshore Technologies, MI) and a Shimadzu C-R5A integrator (Shimadzu, Kyoto, Japan). An injection volume of 100 μL was used for each analysis.

Table 1 Transfer duration at various transfer rates.

	Transfer duration (min)			
	at $0.5\,mL\,min^{-1}$	at $2\,mL\,min^{-1}$	at $4\,mL\,min^{-1}$	at $9\,mL\,min^{-1}$
Dipyridamole (FaSSIF)	120	60	30	6.66
Dipyridamole (FeSSIF)	240	120	90	30
BIBU 104 XX (FaSSIF)	500	125	62.5	27.78
BIBU 104 XX (FeSSIF)	500	125	—	—
BIMT 17 BS (FaSSIF)	270	50	30	15
BIMT 17 BS (FeSSIF)	360	120	80	40

The analysis of dipyridamole was performed on a LiChrospher 100 RP-8, 5-μm column (Merck, Darmstadt, Germany) using methanol–0.01 M HCl–diethylamine (64.9:34.9:0.2%) as mobile phase with a flow rate of 1.0 mL min^{-1}. The detection wavelength was set at 284.5 nm and the compound typically eluted at 4.5 min.

For BIBU 104 XX, the mobile phase used was acetonitrile–0.05 M ammonium formate (55:45%) and was also pumped at 1.0 mL min^{-1}. BIBU 104 XX had an approximate retention time of 3.6 min using a Prodigy ODS (3), 250 × 4.6 mm (i.d.) 5 μm (Phenomenex, Aschaffenburg, Germany) column and detection wavelength at 300 nm.

BIMT 17 BS was analysed using a LiChrospher 100 RP-8, 5 μm column (Merck, Darmstadt, Germany) and a mobile phase of methanol–0.01 M HCl–diethylamine (64.9:34.9:2%). The detection wavelength was set at 280 nm. With a flow rate of 1.0 mL min^{-1} the compound typically eluted at 4.5 min.

A 7-point calibration curve was prepared for each drug and linearity (r^2 not less than 0.999) observed in the 0.1–50 mg L^{-1} concentration range. The data obtained following the HPLC analysis were transferred to Excel (Microsoft, CO) for subsequent data analysis.

Data analysis

The concentration of dissolved drug (drug in solution) in the acceptor phase was determined as a function of time and compared against the theoretical concentration, which signifies the concentration in the acceptor phase assuming no precipitation. The theoretical concentration was calculated by taking into consideration the concentration of dissolved drug in the donor phase, the transfer rate and the subsequent dilution effect within the acceptor phase.

Precipitation was considered to occur when the profile for the measured concentration of drug in solution in the acceptor phase deviated significantly from the theoretical concentration. The time at which the two profiles deviated was also identified visually by the appearance of turbidity and subsequent formation of suspended particles that could be easily seen in the dissolution vessel. The maximum concentration (c_{max}), measured just before the rapid decline in drug concentration in the acceptor phase (due to precipitation), and its corresponding time of occurrence (t_{max}) were identified from the mean concentration–time profiles. The term supersaturation (σ) will be used in this context to signify $\sigma = c_{max}/c_s$, where c_{max} is the maximum measured drug concentration and c_s is the solubility of the drug in the acceptor phase media (using its composition at the start of the experiment).

Statistical methods

The number of replicates of each experiment is given in the figure legends. Where applicable, the mean value and the standard deviation were calculated using Microsoft Excel. The differences between treatments were examined using either Student's *t*-test or analysis of variance ($P < 0.05$ defining significance).

Results

Dipyridamole data

Influence of hydrodynamics on the in-vitro precipitation of dipyridamole

Various paddle speeds were used to determine whether differences in hydrodynamics in the acceptor phase would affect the precipitation process. No obvious change in the concentration–time profile due to varying the paddle speed was observed (Figure 3).

In-vitro dipyridamole precipitation under simulated fasted- vs fed-state conditions

Figure 4 shows the concentration–time profiles of dipyridamole in FaSSIF and FeSSIF at various flow rates. Table 2 lists the mean maximum concentration observed in FaSSIF during the experiment and its corresponding t_{max}.

With FaSSIF as acceptor phase media, supersaturation and then precipitation of dipyridamole could be observed at each flow rate. The maximum measured concentrations are similar (152.1–185.9 mg L^{-1}) indicating no clear dependence on the transfer rate. Maximum observed concentrations correspond to 6–7.4 fold supersaturation in the acceptor phase media. Once precipitation began, the decrease from the maximum measured dipyridamole concentration to the final equilibrium concentration occurred faster at higher transfer rates. Final equilibrium concentrations in the range of about 47–58 mg L^{-1} were observed and appeared to be independent of the transfer rate.

In FeSSIF, no dipyridamole precipitation occurred at any flow rate, even though final concentrations of up to 1000 mg L^{-1} were attained.

BIBU 104 XX data

In-vitro BIBU 104 XX precipitation under simulated fasted- vs fed-state conditions

Figure 5 shows the mean concentration–time profiles for BIBU 104 XX in both FaSSIF and FeSSIF at 0.5 and

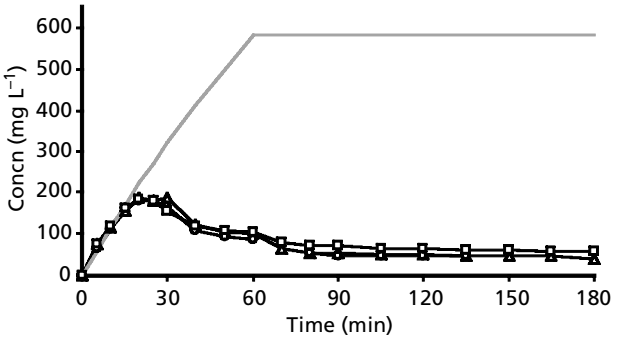


Figure 3 Influence of paddle speed in the acceptor phase on the precipitation of dipyridamole in FaSSIF (donor phase, dipyridamole dissolved in SGF_{fast} 3 mg mL^{-1}; acceptor phase, 500 mL FaSSIF; transfer rate, 2 mL min^{-1}; transfer time, 60 min). —, Theoretical concn; △, 50 rev min^{-1} (n = 1); □, 75 rev min^{-1} (n = 3); ○, 150 rev min^{-1} (n = 1).

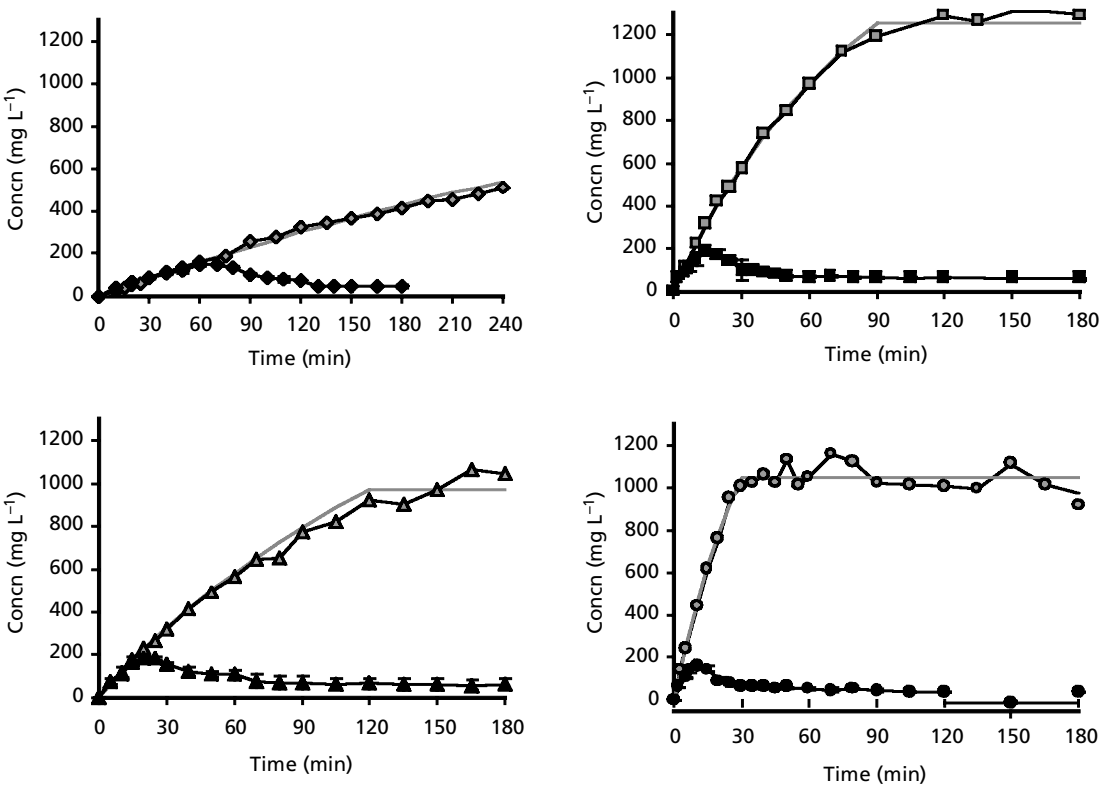


Figure 4 Measured (symbols) and theoretical dipyridamole concentration (solid lines) in FaSSIF (n = 3 ± s.d.) and FeSSIF (n = 1) using a paddle speed of 75 rev min^{-1} at various transfer rates (dipyridamole solubility in FaSSIF, 25 mg L^{-1}; in FeSSIF, 410 mg L^{-1}). —, Theoretical concn; ◆, 0.5 mL min^{-1} FaSSIF; ◇, 0.5 mL min^{-1} FeSSIF; ▲, 2 mL min^{-1} FaSSIF; △, 2 mL min^{-1} FeSSIF; ■, 4 mL min^{-1} FaSSIF; □, 4 mL min^{-1} FeSSIF; ●, 9 mL min^{-1} FaSSIF; ○, 9 mL min^{-1} FeSSIF.

2 mL min^{-1} and, additionally, the concentration–time profiles in FaSSIF at 4 and 9 mL min^{-1}. Mean maximum measured concentrations and corresponding t_{max} values are displayed in Table 3.

In FaSSIF, BIBU 104 XX precipitates after reaching maximum concentrations of 25.5–38.6 mg L^{-1}. The supersaturation in FaSSIF is 5.5–8.4 fold. The faster the rate of transfer, the faster was the rate of precipitation. Final concentrations varied between 7 and 22 mg L^{-1}, substantially higher than the solubility in FaSSIF, which might be explained by the formation of diverse polymorphic modifications of BIBU 104 XX.

No precipitation of the drug in FeSSIF was examined, even though the concentration at the end of the transfer clearly exceeded the drug's solubility in this medium.

BIMT 17 BS data

In-vitro BIMT 17 BS precipitation under simulated fasted- vs fed-state conditions

The concentration–time profiles for BIMT 17 BS in FaSSIF and FeSSIF at various transfer rates are given in Figure 6. Table 4 summarizes the mean maximum BIMT 17 BS concentrations observed in FaSSIF and the times at which they occurred.

Similarly to dipyridamole and BIBU 104 XX, BIMT 17 BS precipitated in FaSSIF at each flow rate. Mean maximum concentrations of 92.4–217 mg L^{-1} were reached, with maximum supersaturation ranging between 3 and 7 fold. The increase in rate of precipitation with increasing transfer rate is also similar to the behaviour of dipyridamole and BIBU 104 XX.

Table 2 Influence of donor transfer rate on the maximum dipyridamole concentration (c_{max}) and corresponding time of occurrence (t_{max}) following transfer of pre-dissolved drug into FaSSIF media.

	0.5 mL min^{-1}	2 mL min^{-1}	4 mL min^{-1}	9 mL min^{-1}	Solubility in FaSSIF (mg L^{-1})[a]
c_{max} (mg L^{-1})	152.1 ± 7.5	184.2 ± 7.5	185.9 ± 5.2	160.5 ± 2.7	25
t_{max} (min)	60	20	15	10	

[a]Kostewicz et al (2002).

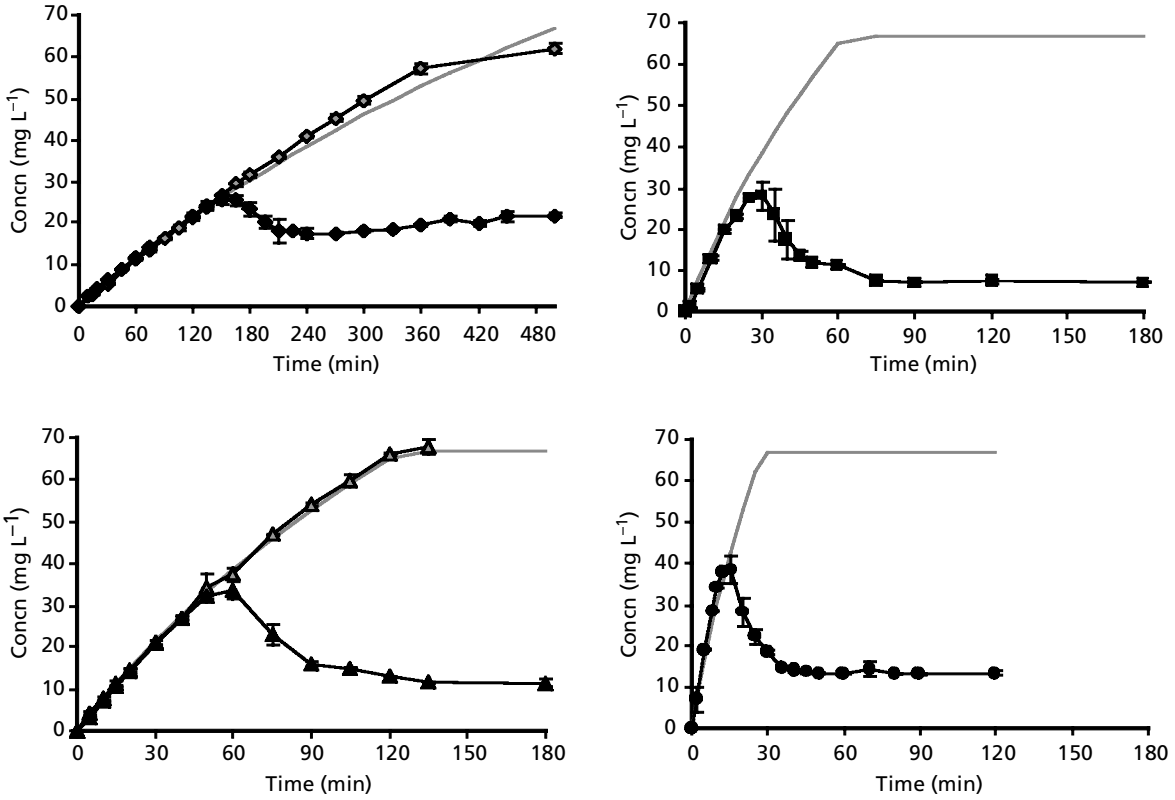


Figure 5 Measured (symbols, n = 3 ± s.d.) and theoretical BIBU 104 XX concentration (solid lines) in FaSSIF vs FeSSIF using a paddle speed of 75 rev min^{-1} at various transfer rates (BIBU XX 104 solubility in FaSSIF, 4.6 mg L^{-1}; in FeSSIF, 26 mg L^{-1}). —, Theoretical concn; ◆, 0.5 mL min^{-1} FaSSIF; ◇, 0.5 mL min^{-1} FeSSIF; ▲, 2 mL min^{-1} FaSSIF; △, 2 mL min^{-1} FeSSIF; ■, 4 mL min^{-1} FaSSIF; ●, 9 mL min^{-1} FeSSIF.

Unlike the other compounds, BIMT 17 BS precipitated after transfer to FeSSIF. Maximum concentrations ranged from 290 to 565 mg L^{-1}, which corresponds to a 1.4- to 2.7-fold supersaturation in FeSSIF. In FeSSIF, as well as FaSSIF, the maximum concentration increased with higher transfer rate.

Discussion

Supersaturation phenomenon

The results with the transfer model clearly demonstrate that poorly soluble, weakly basic drugs can precipitate in the small intestine, even if they are fully dissolved in the stomach. This is predictable on the basis of pH–solubility behaviour of the compounds studied. However, the high degree of supersaturation achieved before precipitation started is a phenomenon that cannot be predicted with either solubility or dissolution experiments. In all three case studies, supersaturation by a factor of at least 3 fold was observed in FaSSIF, indicating that concentrations considerably higher than those predicted from solubility in biorelevant media (and well over an order of magnitude higher than the aqueous solubility) can be achieved in the small intestine. Since the concentration in solution at the sites of absorption is the key driving force for drug absorption, it is obvious that the rate of absorption of poorly soluble weakly basic compounds from the intestine can be much higher than one would predict based on aqueous solubility data or even solubility in media simulating the small intestine.

Table 3 Influence of donor transfer rate on the maximum BIBU 104 XX concentration and corresponding time of occurrence (t_{max}) following transfer of pre-dissolved drug into FaSSIF media.

	0.5 mL min^{-1}	2 mL min^{-1}	4 mL min^{-1}	9 mL min^{-1}	Solubility in FaSSIF (mg L^{-1})[a]
c_{max} (mg L^{-1})	25.5 ± 0.9	33.8 ± 2.1	28 ± 3.5	38.6 ± 3.2	4.6
t_{max} (min)	150	60	30	15	

[a] Kostewicz et al (2002).

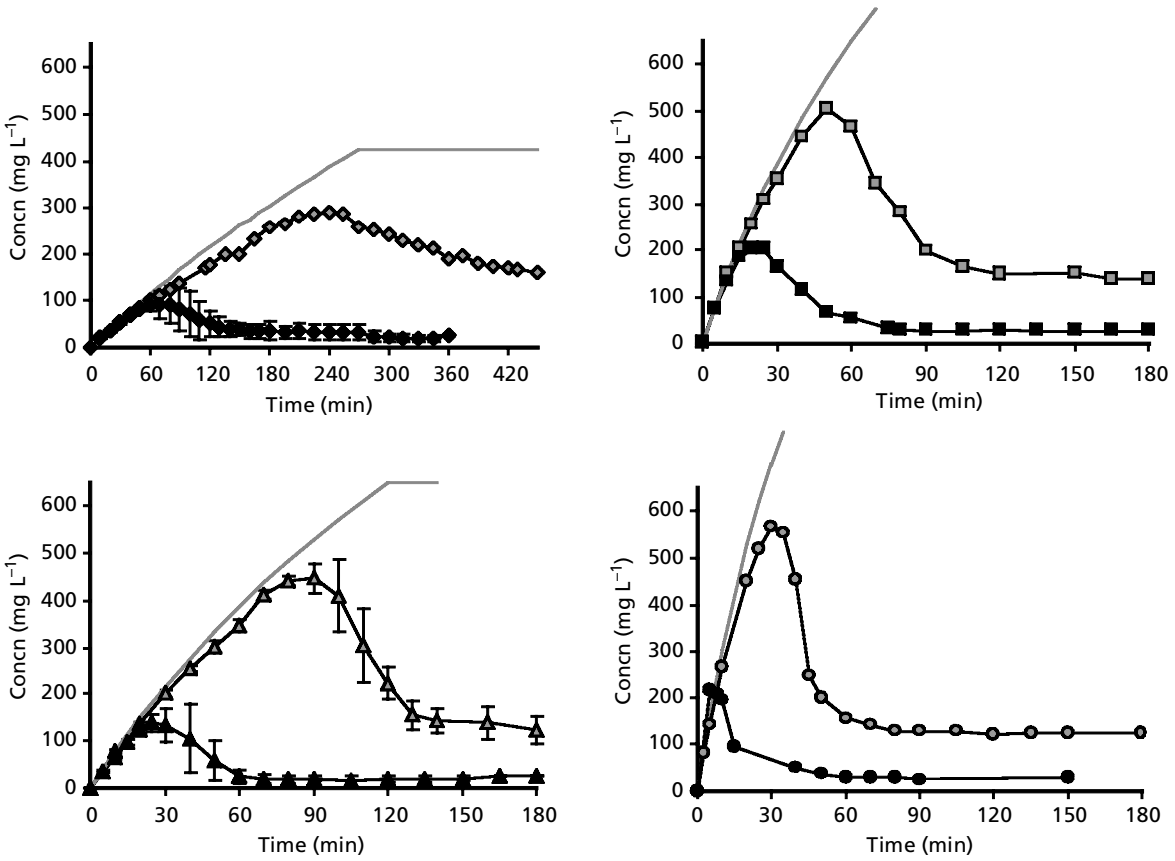


Figure 6 Measured (symbols) and theoretical BIMT 17 BS concentration (solid lines) in FaSSIF (0.5 and 2 mL min^{-1} n = 3 ± s.d.; 4 and 9 mL min^{-1} n = 1) vs FeSSIF (2 mL min^{-1} n = 3 ± s.d.; 0.5, 4 and 9 mL min^{-1} n = 1) using a paddle speed of 75 rev min^{-1} at various transfer rates (BIMT 17 BS solubility in FaSSIF, 32 mg L^{-1}; in FeSSIF, 208 mg L^{-1}).). —, Theoretical concn; ◆, 0.5 mL min^{-1} FaSSIF; ◇, 0.5 mL min^{-1} FeSSIF; ▲, 2 mL min^{-1} FaSSIF; △, 2 mL min^{-1} FeSSIF; ■, 4 mL min^{-1} FaSSIF; □, 4 mL min^{-1} FeSSIF; ●, 9 mL min^{-1} FaSSIF; ○, 9 mL min^{-1} FeSSIF.

Hydrodynamic effects on supersaturation and precipitation

In the fasted state, gastric emptying, and therefore the drug arrival into the intestine, varies significantly depending on the motility pattern at the time of drug administration. For our in-vitro experiments, transfer rates from 0.5 to 9 mL min^{-1}, corresponding to the varying gastric emptying rates in the fasted and fed state (Theodorakis et al 1980; Jonsson et al 1983; Meyer et al 1988), were chosen to investigate the influence of gastric emptying on drug precipitation. All tested drugs showed the lowest c_{max} values at the slowest transfer rate (0.5 mL min^{-1}) in FaSSIF. At higher transfer rates, no trend in maximum concentration with rate of transfer was seen with either dipyridamole or BIBU 104 XX. For BIMT 17 BS, c_{max} increased as a function of transfer rate. As a result, no general conclusions can be drawn about the effect of transfer rate on the maximum supersaturation achieved.

In contrast, the precipitation kinetics were found to be clearly dependent on the flow rate. Once precipitation started, the drug concentration decreased noticeably faster at higher transfer rates. Crystal growth can be described in an idealized way by equation 1 (Martin et al 1987):

$$dM/dt = k_{cg}(c - c_s)A \quad (1)$$

Table 4 Influence of donor transfer rate on the maximum BIMT 17 BS concentration in solution (c_{max}) and corresponding time of occurrence (t_{max}) following transfer of pre-dissolved drug into FaSSIF media.

	0.5 mL min^{-1}	2 mL min^{-1}	4 mL min^{-1}	9 mL min^{-1}	Solubility in FaSSIF (mg L^{-1})[a]
c_{max} (mg L^{-1})	92.4 ± 13	138.8 ± 18	201	217	32
t_{max} (min)	60	25	25	5	

[a] Kostewicz et al (2002).

where M is crystallized mass, k_{cg} is crystal growth coefficient, c is actual concentration, c_s is concentration at saturation and A is crystal surface area.

Given the lack of dependency of the $(c-c_s)$ term on the transfer rate for two of the three compounds, one has to look at the developing crystal surface area as an alternative explanation for the faster precipitation rate in these cases. It is plausible that at higher transfer rates, the number of seed crystals generated (and hence the developing crystal surface area) is greater. For BIMT 17 BS both the $(c-c_s)$ and A terms may play a role.

The results at the various transfer rates indicate that a fast gastric emptying rate tends to lead not only to a higher maximum drug concentration in the intestine, but also to an earlier onset of precipitation combined with a faster decrease of drug concentration. Therefore, in-vivo drug precipitation is assumed to be more likely when the drug is quickly delivered from the stomach. In contrast, slow gastric emptying rates lead to a slow drug arrival in the intestine. Because of concurrent drug absorption into the gastrointestinal membrane, precipitation may be less likely to occur in this case. To quantitate these predictions, it would be necessary to couple the concentration profiles observed in the transfer model with permeability data in a mathematical model.

In addition to the variability in gastric emptying, we also attempted to model the effects of changes in motility within the small intestine on the precipitation kinetics. The approach was to vary the paddle speed in the acceptor phase. No dependency of precipitation on the stirring rate in the acceptor phase was observed in experiments with dipyridamole transfer into FaSSIF. Comparable results were observed for BIMT 17 BS precipitation in FeSSIF at various transfer rates (data not shown). Based on these limited results, it is assumed that intestinal hydrodynamics play a minor role in precipitation compared with other factors like gastric emptying rate, intestinal pH and levels of bile components.

Precipitation under usual dosing conditions

As might be expected for poorly soluble weak bases in general, the composition of the acceptor phase media (fasted or fed state simulated intestinal fluid) had the strongest influence on drug precipitation. The intestinal environment and therefore the conditions for drug dissolution and precipitation are altered substantially by the ingestion of food. Assuming a small intestinal volume of approximately 500 mL in the fasted-state small intestine, the maximum anticipated concentrations after usual doses would be 400 mg L^{-1} for dipyridamole, 60 mg L^{-1} for BIBU 104 XX and 100 mg L^{-1} for BIMT 17 BS. In-vitro, all three drugs precipitated when FaSSIF was used as the acceptor phase. Dipyridamole precipitated after reaching maximum concentrations of 152.1–185.9 mg L^{-1}, indicating that precipitation in the fasted state upon entry in the small intestine is likely to occur. This could, in turn, limit the oral availability of the drug. The anticipated intestinal BIBU 104 XX concentration (60 mg L^{-1}) is about twice as high as the in-vitro c_{max} values observed for this drug in FaSSIF (25.5–38.6 mg L^{-1}). Therefore, in-vivo precipitation of BIBU 104 XX would also be anticipated when the dose is administered in the fasted state. Interestingly, the BIBU 104 XX plateau concentrations were substantially higher than its solubility in the acceptor phase, which might be an indication that it precipitates in polymorphic forms other than that in the material used for the experiments. The maximum measured BIMT 17 BS concentrations in FaSSIF (92.4–217 mg L^{-1}) indicate that precipitation of this drug might also occur during the transfer into the small intestine.

The fed-state intestinal pH is slightly lower than that in the fasted state (Dressman et al 1990) and the volume of the lumenal contents increases to about 1–1.5 L (Fordtran & Locklear 1966). Furthermore, bile is secreted in response to food arrival in the small intestine, so the concentrations of amphiphilic bile salts and of phosphatidylcholine are elevated. The decrease in pH, the increased volume and the bile input would all be favourable to solubility and dissolution of weak bases. All of these changes were taken into consideration in the model and interpretation of results. No precipitation in FeSSIF could be observed for dipyridamole or BIBU 104 XX, with final concentrations of about 1000 mg L^{-1} and about 60 mg L^{-1}, respectively. Different behaviour was observed for BIMT 17 BS, which precipitated in FeSSIF after achieving maximum concentrations of 290–565 mg L^{-1}. Assuming a postprandial volume of 1000 mL, the maximum anticipated small intestinal concentration after administering a single dose is 200 mg L^{-1} for dipyridamole, 30 mg L^{-1} for BIBU 104 XX and 50 mg L^{-1} for BIMT 17 BS. Therefore, in-vivo precipitation seems to be unlikely for any of the three drugs when administering the dose after a meal.

Comparison with pharmacokinetic data

Results from pharmacokinetic studies of food effects for all three drugs were provided by BI Pharma KG (Kostewicz et al 2002). The administration of a 100-mg dipyridamole dose as a suspension in 9 healthy subjects 30 min after meal intake resulted in an approximately 12% increase in the area under the plasma concentration curve (AUC) values (0–24 h) compared with administration of a 100-mg dose of dipyridamole in the fasted state (4.6 ± 2.2 fasted vs 5.2 ± 1.6 μg·h mL^{-1} fed). A further interesting point for dipyridamole is the bimodal pharmacokinetics in the fasted state (Russell et al 1994). A partial explanation for the prolonged tail in the plasma curve could be slow re-dissolution and subsequent absorption of the precipitated drug.

For BIBU 104 XX, a food effect study was performed in 12 healthy subjects examining the influence of meal intake following the administration of a 30-mg dose of BIBU 104 XX formulated as a simple tablet. In this case, concurrent administration with food reduced the AUC values by approximately 33% (1326 ± 357.2 fasted vs 883.3 ± 245.5 ng·h mL^{-1} fed), whereas from the in-vitro

transfer data the opposite was predicted. SGF_{fast} with a pH of about 2 is currently being used for the simulation of both the fasted- and fed-state stomach. With ingestion of food, the gastric pH is buffered to a less acidic pH (typically pH 3–7). Thus, it is quite possible that in the pharmacokinetic study, BIBU 104 XX was not fully dissolved before it left the stomach, accounting for the lower overall bioavailability in the fed state.

The importance of simulating the fed-state conditions in the stomach for the prediction of plasma profiles of lipophilic drugs after oral administration has recently been demonstrated by Nicolaides et al (2001). Obviously, there is a need to evolve the transfer model to better account for variations in gastric conditions, not only with respect to fed-state administration but also to simulate absorption in individuals with elevated gastric pH (achlorhydria, those receiving gastric acid blockers and some pathological conditions).

BIMT 17 BS was given in a 50-mg dose as a simple tablet or capsule formulation to 22 subjects either in the fasted state or following a high-fat breakfast. Postprandial administration led to a significant increase in the mean AUC levels (0–∞) of 36% for the capsule (1006 ± 603 fasted vs 1376 ± 645 ng·h mL^{-1} fed) and up to 40% for the tablet formulation (1009 ± 475 fasted vs 1417 ± 757 ng·h mL^{-1} fed). Dipyridamole and BIMT 17 BS in-vivo data, therefore, correspond to the predictions from the in-vitro transfer results in FaSSIF versus FeSSIF media.

The results highlight the need to consider all three aspects – solubility, dissolution and precipitation – in both the stomach and small intestine, when trying to predict in-vivo performance of poorly soluble weak bases.

Conclusion

Results with the transfer model demonstrate its utility for predicting supersaturation and precipitation of poorly soluble, weakly basic drugs as they move from the stomach into the small intestine. Modifications of the model to study concomitant dissolution and transfer out of the stomach, as well as to better simulate gastric contents in the fed state, should result in better prediction of the in-vivo behaviour of poorly soluble, weakly basic drugs.

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