Biorelevant Dissolution Testing to Predict the Plasma Profile of Lipophilic Drugs After Oral Administration

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Purpose. To quantitatively compare *in vitro* dissolution data in biorelevant and compendial media, to investigate whether *in vitro* differences are reflected in the simulated plasma profile and to specify under which circumstances prediction of the plasma profile of orally administered lipophilic drugs can be achieved.

Methods. Previously published dissolution data from seven products of four lipophilic drugs were compared using the first order model, the RRSBW distribution, and a model based on the Noyes-Whitney theory. Simulated plasma profiles were then obtained using a model-dependent approach. Simulated and observed plasma profiles were compared with the difference factor, f_1.

Results. No model consistently provided the best fit to the *in vitro* data, which varied significantly with medium composition. Prediction of the plasma profile was possible ($9.6 \leqslant f_1 \leqslant 34.2$) in seven out of eleven cases.

Conclusions. Although prediction of the plasma profile of lipophilic drugs solely on the basis of *in vitro* data remains an ambitious target, this study shows that the plasma profile of a lipophilic drug can be predicted with appropriate *in vitro* dissolution data, provided that the absolute bioavailability of the drug is known and the drug has dissolution limited absorption.

KEY WORDS: prediction; oral absorption; lipophilic drugs; troglitazone; atovaquone; sanfetrinem cilexetil; GV150013X.

INTRODUCTION

The absorption process of a lipophilic drug is often assumed to be determined mainly by its intralumenal dissolution process (1,2). The usefulness of *in vitro* dissolution data in the assessment of the overall absorption rate of drugs of this type depends on the relationship between gastric dissolution and gastric emptying rate, the drug solubility in the intestinal contents (2), and the relevance of the *in vitro* test conditions used to the actual intralumenal environment *in vivo* (3).

We have recently shown that biorelevant *in vitro* dissolution testing is useful for qualitative forecasts of formulation and food effects on the absorption of four orally administered lipophilic drugs with logP values ranging from 2.7 to 5.4, with a total of seven products studied (4). The objectives of the present study were threefold:

1. To evaluate the usefulness of various models for the description of the previously published *in vitro* dissolution data (4) and quantitatively assess differences among them.
2. To investigate whether these differences are reflected in the simulated plasma profile using a model-dependent approach.
3. To clarify prerequisites for prediction of the plasma profile of orally administered lipophilic drugs from *in vitro* dissolution data.

METHODS

Analysis of the *In Vitro* Dissolution Data

Four sets of previously published (4) *in vitro* tablet dissolution data from immediate release products were analysed, i.e., data from three troglitazone products (Romozin®, D157/155B and D157/155D), one atovaquone product (Wellvone®), two sanfetrinem cilexetil products (630/C078/49 and 630/C091/59), and one GV150013X (molecular formula: $C_{23}H_{27}N_3O_3.2HCL$) product. The physicochemical characteristics of these drugs have been summarized elsewhere (4). For each product, dissolution data were obtained in water, long-life cow's milk, USP simulated intestinal fluid without pancreatin (SIF_{sp}), fasted state simulating intestinal fluid (FaSSIF) and fed state simulating intestinal fluid (FeSSIF). Details of the composition of these media as well as other aspects of the *in vitro* dissolution test conditions have been previously published (4).

Two empirical models, and one model which is based on the theoretical physicochemical aspects of dissolution (5), were initially fitted to each individual data set (Minsq II, MicroMath Scientific Software, Salt Lake City, Utah).

First Order Model. For this model the cumulative amount dissolved is given by the following equation:

$$W_t = W_{\max}(1 - e^{-kt}) \tag{1}$$

where W_t and W_{max} is the amount dissolved at time t and the maximum amount dissolved, respectively, and k is a first order constant.

The RRSBW Distribution. This is commonly known as the Weibull distribution (6). Assuming no significant lag time prior to the initiation of the dissolution process, the cumulative amount dissolved is given by the following equation:

$$W_t = W_{\max}[1 - e^{-\left(\frac{t}{\tau_d}\right)^{\beta}}] \tag{2}$$

where τ_d is a time parameter providing information on the overall rate of the process and β is a parameter providing information on the shape of the cumulative curve.

A Model Based on the Noyes-Whitney Theory for Dissolution. This model assumes dissolution of isometric, similarly sized particles, occurring under continuously decreasing surface area conditions with the ratio D/δ (D is the diffusion coefficient and δ is the diffusion layer thickness) being constant during the dissolution process (eg., 7). Dissolution rate is given by the following equation:

$$\frac{dW_t}{dt} = \frac{D\Gamma N^{1/3}}{V\delta\rho^{2/3}} W^{2/3}(X_s - W_t) = zW^{2/3}(C_s - C) \tag{3}$$

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where X_s is the amount of drug which saturates the volume V, of the dissolution medium, W is the amount of drug remaining to be dissolved, C_s is the solubility of drug, C is the concentration of the dissolved drug at time t, ρ is the particle density, Γ is the shape factor, N is the number of particles to be dissolved and z is a constant equal to $D\Gamma N^{1/3}/\delta\rho^{2/3}$. The integrated form of Equation 3 was obtained with Mathematica® (Wolfram Research Europe Ltd., Oxfordshire, UK) and it has the following form:

$$y = (z/V)t \tag{4}$$

where y is a function of the initial amount brought to dissolution (*Dose*), the amount remaining to be dissolved (W) at time t, and the amount which saturates the volume of the dissolution medium (X_s). The z value from the *in vitro* data, z_{vitro}, was estimated by fitting Equation 4 to the data. In case of sink conditions, Equation 3 becomes

$$\frac{dW_t}{dt} = \frac{D\Gamma N^{1/3}}{V\delta\rho^{2/3}} W^{2/3} X_s = zW^{2/3}C_s \tag{5}$$

which is the differential form of the Hixson-Crowell equation (eg., 7).

In two cases, i.e., troglitazone products D157/155B and D157/155D, none of the three functions could be fitted to the data obtained in SIF_{sp} because the cumulative percent dissolved profile showed a substantial peak (4). In all other cases, the best fits were assessed on the basis of the value of the model selection criterion, MSC (8), for the data set [three repetitions per data set had been performed (4)].

Comparisons of cumulative percent dissolved profiles were made on a parametric confidence interval basis for the maximum percent dissolved data and with the multivariate model-dependent approach proposed by Sathe et al. (9) for the time and shape parameters of the RRSBW distribution.

Pharmacokinetic Data Available

Troglitazone. Only fed state data exist (GlaxoWellcome data on file) for the three dosage forms tested *in vitro* (4). These *in vivo* data come from two crossover studies. The first was performed in 36 subjects and had three phases, i.e., Romozin® vs. D157/155B vs. another troglitazone tablet formulation. The second study was performed in 24 subjects and had two phases, i.e. D157/155B vs. D157/155D. The caloric content of the meal administered 30 min. before drug administration was approximately 600 Kcal in all cases, and the dose was always 2 × 200 mg tablets. Although intravenous bolus data from 12 subjects exist, the administered dose was too low (Dose: 10 mg) to estimate the disposition phase, which in turn led to estimations of elimination half lives that were shorter than the values estimated from the oral data (10). Therefore, the disposition parameters of troglitazone were estimated by fitting an open two-compartment model to the median values of each data set. Values estimated from the best fit (coefficient of determination = 0.995) were used in all simulations. The absolute bioavailabilities of the three products in the fed state were estimated from the absolute bioavailability of Rezulin® in the fed state (GlaxoWellcome data on file) and the relative bioavailability of Rezulin® versus each of the tested products (4).

Atovaquone. For the product tested *in vitro* (4) there are data from a food study (11) in which the administered dose was 2 × 250 mg (GlaxoWellcome data on file). The caloric content of the meal administered 45 min prior to drug administration was approximately 667 Kcal. The absolute bioavailability of this product in the fasted and in the fed state was estimated from the mean AUC_{last} values of the oral data and the mean AUC_{last} value of intravenous data from 9 patients (GlaxoWellcome data on file). Although the dose administered in the intravenous infusion study (infusion time = 1 h) was small (36.9 mg) compared to the oral dose, the i.v. plasma profiles can be used to estimate disposition parameters because the absolute oral bioavailability of atovaquone is low. The disposition parameters of atovaquone were estimated by fitting an open two-compartment model to the mean intravenous data (coefficient of determination = 0.98). Fitting to either the mean or median oral data set was not possible.

Sanfetrinem Cilexetil. For the two products tested *in vitro* (4) there are comparative bioavailability data in the fasted state, and, for the 630/C091/59 product, data from a food study (GlaxoWellcome data on file). The former study was performed in 8 subjects on a crossover basis and had two phases. The latter study was performed in 16 subjects on a crossover basis, it had two phases, and the caloric content of the meal administered 30 min before drug administration was approximately 880Kcal. In all cases the dose was 400 mg sanfetrinem cilexetil which is equivalent to 250 mg sanfetrinem. Although there are data after intravenous infusion of 250 mg equivalent sanfetrinem (n = 12; infusion time = 30 min.), fitting of an open two-compartment model did not provide reliable estimations of the pharmacokinetic parameters. Fitting was only possible for the fasted state mean data of the 630/C078/49 product (coefficient of determination = 0.98) and the resulting pharmacokinetic parameters were used in all simulations. The absolute bioavailability of each product in each study was estimated from the median AUC_{last} of each oral data set and the median AUC_{last} of the intravenous data set (GlaxoWellcome data on file).

GV150013X. For the product tested *in vitro* (4) there are median data from a food study (GlaxoWellcome data on file) in which the dose was 1 mg. This study was performed in 12 subjects on a crossover basis and it had three phases, i.e., a tablet administered in the fasted state vs. a tablet administered in the fed state vs. an encapsulated solution. In the fed state, the drug was administered 30 min. after the beginning of a meal having a caloric content approximately 826 Kcal. The disposition parameters of GV150013X were estimated by fitting an open two-compartment model (coefficient of determination = 0.998) to median intravenous infusion data of GV150013X (n = 4; Dose = 0.5 mg; infusion time ~0.42h; GlaxoWellcome data on file). The absolute bioavailability of this product in the fasted and in the fed state was estimated from the median AUC_∞ values of the oral and the median AUC_∞ value of the intravenous data.

Simulation of Plasma Profiles

Simulated profiles were obtained using the software STELLA® 5.0 (Cognitus Ltd., North Yorkshire, UK). By assuming negligible gastric uptake, simultaneous solid and liquid emptying from the stomach, and no intestinal permeability restrictions, the scheme shown in Figure 1 can be applied. For all four drugs simulated, the initial volume of fluid in the

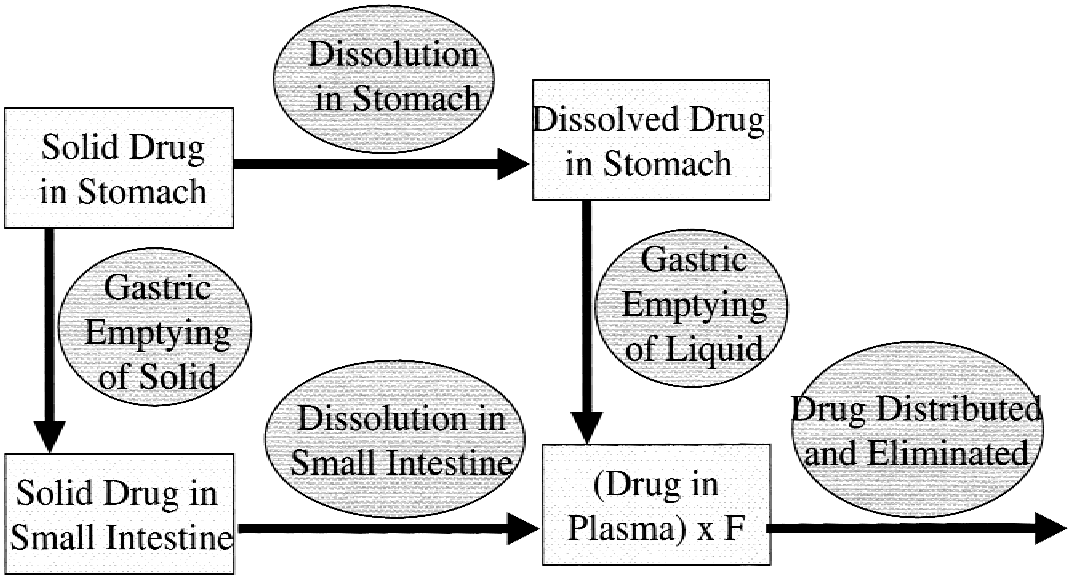

Fig. 1. Schematic of the model used to obtain the simulation profiles. F is the bioavailability coefficient.

stomach was assumed to be 250 ml in the fasted state and 500 ml in the fed state (12). Average population values for gastric emptying rates (eg., 1) were used, i.e. first order gastric emptying rate in the fasted state (rate constant = $2.8h^{-1}$) and zero-order gastric emptying rate in the fed state (rate constant = 4kcal/min). The amount of drug entering the plasma, i.e., dissolved drug emptied from the stomach and drug dissolved in the intestine, was multiplied by the bioavailability coefficient. In the case where a prodrug was administered (i.e. sanfetrinem cilexetil), the amount of drug entering the plasma was corrected by the molecular weight ratio.

Dissolution kinetics were introduced into the model by assuming that the process follows first order kinetics or takes place according to the model described with Equation 3. In the latter case, sink conditions were assumed for the dissolution in the intestine. When *in vitro* dissolution was considered to occur according to Equation 3 and the dose administered *in vivo* was the same as the dose tested *in vitro,* the z value for the *in vivo* dissolution process, z_{vivo}, was identical to z_{vitro}. However, if the administered dose *in vivo* differed from that tested *in vitro* (troglitazone and atovaquone), z_{vitro} differed from z_{vivo}, because z depends on N (Equation 3):

$$\frac{z_{vitro}}{z_{vivo}} = \frac{N_{vitro}^{1/3}}{N_{vivo}^{1/3}} = \frac{N_{vitro}^{1/3}}{(aN)_{vitro}^{1/3}} = \frac{1}{a^{1/3}} \quad (6)$$

where $a = Amount_{vivo}/Amount_{vitro}$.

Comparison of Observed with Simulated Oral Profiles

For each formulation, the average actual plasma profile was compared with the simulated profile using the difference factor, f_1 (13), and all the available experimental data points after each administration. The difference factor is a measure of the relative mean difference between two curves (13). Since observed and simulated plasma profiles are based on the same disposition parameters and absolute bioavailability for each compound, any differences between them can be attributed to failure of the dissolution test to accurately simulate conditions in the gastrointestinal tract, inappropriate selection of physiological parameters for construction of the simulated plasma profiles and/or failure of certain assumption(s) (e.g., high permeability) in the model.

RESULTS

Analysis of the *In Vitro* Dissolution Data

In cases where fitting of all three functions was possible, model selection criterion (MSC) values were $-3.0 \leqslant MSC \leqslant 6.7$, $1.0 \leqslant MSC \leqslant 6.6$, and $-2.8 \leqslant MSC \leqslant 6.4$ for the first-order model, the Weibull distribution, and the Noyes-Whitney based model, respectively.

With the exception of the troglitazone data in water, poor fits were obtained for data in water and SIF_{sp} with each of the three tested functions, with values of $-1.0 \leqslant MSC \leqslant 2.6$ for the water data and $-3.0 \leqslant MSC \leqslant 3.5$ for the SIF_{sp} data. Fitting of the Weibull distribution to most of the water data for Wellvone® and GV150013X tablets and the SIF_{sp} data for Wellvone® tablets was impossible because of the limited number of data points prior to the plateau level (4).

Estimated MSC values in milk, FaSSIF and FeSSIF ($0.4 \leqslant MSC \leqslant 6.7$) were higher than those estimated in water or SIF_{sp}. The Weibull distribution could not be reliably fitted to the milk data of D157/155D troglitazone tablets or to the FeSSIF data of Wellvone® tablets and a high dependence of the estimated parameters on each other was observed (the value of the second element of the first column of the correlation matrix was >0.985 in all three repetitions of each data set).

Table I shows that, for every product, maximum percent dissolved values are significantly different in the five tested media with the plateau levels being significantly higher in the biorelevant media. Furthermore, although the shape parameters look roughly similar in all media (their values were close to one in most cases), the time parameters are, in the vast majority of cases, higher in the biorelevant media than in water and SIF_{sp}, indicating a relatively slower approach to plateau in the biorelevant media. Additionally, the time parameter is higher in milk than in FeSSIF although differences in the shape parameter are inconclusive. No clearcut conclu-

Table I. 90% Confidence Intervals for the Difference of the $\%W_{max}$ Values (Upper Numbers), $\ln(\tau_d)$ Values (Middle Numbers) and the $\ln\beta$ Values (Lower Numbers) of the Weibull Distribution (Equation 2 in the text) for the *In Vitro* Dissolution Data Published Previously (4) to Assess Differences in Various Media[a]

	Romozin®	D157/155B	D157/155D	Wellvone®	630/C091/59	630/C078/49	GV150013X product
Water vs. milk	2.08/2.78 (92.5)[b]	2.04/2.49 (88.0)[b]	1.62/1.81 (64.8)[b]	0.08/0.10 (20.5)[b]	19.2/20.8 (81.2)[b]	−71.5/−49.8	7.43/8.52 (83.2)[b]
	−2.14/−1.69	−2.52/−2.01	—	—	−2.42/−1.26	−2.91/−1.52	—
	−0.24/0.22	−0.21/0.29	—	—	−1.28/−0.64	−1.42/−0.16	—
SIF_{sp} vs. FaSSIF	−8.58/−5.98	—	—	−0.60/−0.54	−15.5/−14.4	−17.8/−15.2	−72.7/−59.7
	−0.26/0.22	—	—	—	−0.47/−0.17	−0.70/−0.11	−2.37/−1.76
	−1.10/−0.88	—	—	—	−0.78/−0.07	−0.68/0.88	−0.68/−0.20
SIF_{sp} vs. FeSSIF	−66.8/−64.0	—	—	−2.02/−1.83	−41.3/−39.8	−38.3/−33.6	−65.6/−64.0
	−0.58/−0.12	—	—	—	−0.06/0.32	−0.66/−0.50	−0.75/−0.45
	−0.59/−0.38	—	—	—	−0.66/0.19	−0.32/0.14	−0.41/0.00
Water vs. FaSSIF	−15.1/−13.7	−6.49/−4.56	−14.6/−14.3	−0.56/−0.50	−10.54/−9.21	−12.6/−9.90	−68.9/−55.8
	−0.06/0.12	−0.01/0.52	−0.95/−0.66	—	−0.83/−0.38	−0.76/0.12	—
	−0.62/−0.41	−0.77/0.41	−0.03/0.16	—	−1.35/−0.82	−0.93/0.56	—
Milk vs. FeSSIF	73.8/76.1 (92.5)[c]	60.5/62.1 (88.0)[c]	61.3/65.0 (64.8)[c]	1.84/2.11 (20.5)[c]	54.7/56.2 (81.2)[c]	19.0/40.9	67.8/70.1 (83.2)[c]
	1.39/1.84	1.88/2.04	—[c]	—	1.22/2.14	1.12/2.32	2.04/2.51
	−0.24/0.24	−0.14/0.14	—[c]	—	−0.16/0.32	0.24/0.58	−0.54/−0.10
FaSSIF vs. FeSSIF	−59.2/−57.1	−54.6/−52.4	−48.3/−45.6	−1.46/−1.26	−26.2/−25.0	−21.8/−17.1	−5.19/7.92
	−0.41/−0.26	−0.61/−0.52	0.16/0.37	—	0.31/0.58	−0.32/−0.04	1.28/1.65
	0.38/0.62	0.08/0.36	−0.04/0.20	—	−0.07/0.46	−0.50/0.12	0.13/0.34

[a] Negative (positive) numbers for the $\%W_{max}$, $\ln(\tau_d)$ or the $\ln\beta$ difference indicate lower (higher) value of $\%W_{max}$, τ_d or β, respectively, in the medium which is written first in the far left cell of the same line of the Table. See text for more details.

[b] Since $\%W_{max}$ in milk was measured only once, numbers show the confidence interval of the mean $\%W_{max}$ in water. Value in parenthesis is the $\%W_{max}$ in milk.

[c] Since $\%W_{max}$ in milk was measured only once, numbers show the confidence interval of the mean $\%W_{max}$ in FeSSIF. Value in parenthesis is the $\%W_{max}$ in milk.

sions can be drawn for the differences in the time and shape parameters between FaSSIF and FeSSIF.

Table II shows that Romozin® has both a higher maximum percent dissolved and smaller time parameter (i.e., faster dissolution) in FeSSIF than either the D157/155B or the D157/155D formulation. This is in accordance with the *in vivo* data observed in the fed state (4). The two sanfetrinem cilexetil products have similar maximum percent dissolved values in FeSSIF and time parameters in water, milk and FeSSIF and only the FaSSIF data differ significantly. The similarity in the

Table II. 90% Confidence Intervals for the Difference of the $\%W_{max}$ Values (Upper Numbers), $\ln(\tau_d)$ Values (Middle numbers) and the $\ln\beta$ Values (Lower Numbers) of the Weibull Distribution (Equation 2 in the text) for the *In Vitro* Dissolution Data Published Previously to Assess Formulation Differences[a]

	Water	SIF_{sp}	Milk	FaSSIF	FeSSIF
Romozin® vs. D157/155B	−0.14/0.47	—	—	7.86/10.14	12.6/14.7
	−0.34/0.14	—	−0.68/−0.22	0.06/0.18	−0.16/−0.06
	−0.28/0.12	—	−0.29/0.23	0.03/0.48	−0.10/0.04
Romozin® vs. D157/155D	0.44/0.98	—	—	−0.04/1.26	10.2/13.4
	−0.20/0.08	—	—	−0.98/−0.82	−0.41/−0.20
	−0.26/−0.05	—	—	0.33/0.52	−0.14/0.13
D157/155B vs. D157/155D	0.37/0.72	—	—	−9.35/−7.44	−3.30/−0.37
	−0.21/0.29	—	—	−1.10/−0.96	−0.30/−0.10
	−0.26/0.12	—	—	−0.06/0.40	−0.10/0.14
630/C078/49 vs. 630/C091/59	3.20/5.48	3.11/5.20	70.2/99.8 (81.2)[b]	4.74/6.67	−2.62/1.81
	−0.69/0.12	−0.82/−0.49	−0.69/0.87	−0.83/−0.32	−0.08/0.17
	−0.37/0.70	−0.64/0.23	−0.24/0.20	−1.28/−0.18	−0.57/−0.13

[a] Negative (positive) numbers for the $\%W_{max}$, $\ln(\tau_d)$ or the $\ln\beta$ difference indicate lower (higher) value of $\%W_{max}$, τ_d or β, respectively, for the product which is written first in the far left cell of the same line of the Table. See text for more details. The $\%W_{max}$ values of all troglitazone products in milk was determined only once, i.e. no confidence intervals could be constructed for these products.

[b] The $\%W_{max}$ value of the 630/C091/59 product in milk was determined only once and the numbers are confidence intervals for the mean $\%W_{max}$ value of the 630/C078/49 product with the $\%W_{max}$ value for the 630/C091/59 product in parenthesis.

in vitro data agree with the minimal differences between the two products observed *in vivo* (4).

Simulated Profiles Versus Observed Data

Only the Noyes-Whitney equation and the first order model were used to obtain the simulated plasma profiles because the Weibull distribution could only be fitted to a limited number of the dissolution data sets (Tables I and II). Based on the estimated f_1 values for the difference between the average observed profile and simulated profile (Table III), the Noyes-Whitney based model performed better than the first order model. Moreover, with this model the simulated plasma profiles reflect better the *in vitro* differences between the dissolution profiles i.e. significant *in vitro* differences between compendial and biorelevant data correlate better with the differences between the corresponding simulated profiles. Therefore, the simulated profiles in Figures 2–6 have been constructed with dissolution data treated according to the Noyes-Whitney based model (Equations 3 and 5).

Figure 2 shows simulated profiles and median observed data in the fed state for the three troglitazone products. The observed data for the D157/155B product are from the three-way bio-study (see experimental). However, the data of D157/155B product from the second bio-study (not shown) were almost identical. When biorelevant dissolution data are used, the simulated profile is very close to the observed median data (Table III).

Figure 3 shows the median observed data and the simulated profiles of Wellvone® tablets in the fasted and in the fed state. When biorelevant dissolution data are used, simulated profiles are much closer to the observed median data (Table III). However, in the fasted state even the biorelevant data result in profiles that are different than the observed data (Table III). One reason may relate to the estimation of dissolution of this highly lipophilic compound in the fasted stomach. Wellvone® tablets contain the drug in a micronized form. Therefore, the z value (Equation 3) in water is expected to have been bigger if the surface tension of the medium had been lowered to physiologically relevant values (e.g., 14). An interesting observation for this compound is that, regardless of its high Dose/Solubility ratios in FaSSIF (80 liters) and in FeSSIF (25 liters) (4), dissolution under sink conditions (i.e., use of initial dissolution rates for the simulation) does not overestimate the plasma profile.

Figure 4 shows the mean observed and the simulated profiles of the two sanfetrinem cilexetil products administered in the fasted state. Although simulated profiles are close to the actual data (Table 3), the superiority of biorelevant media is not as clearcut as in the case of atovaquone. One reason for this may be that this compound is not as insoluble and lipophilic as atovaquone, resulting in less pronounced differences between the *in vitro* dissolution profiles in biorelevant and compendial media (e.g., Table 1, SIF_{sp} vs FaSSIF data). Figure 5 shows the mean observed data and the simulated profiles of 630/C091/59 tablets from the food study. Although prediction of the fasted state profile (Figure 5A) is similar to that from the previous study when the same product was used (Figure 4A), it is clear that in the fed state prediction of the profile was inadequate, irrespective of the *in vitro* dissolution medium used. The physicochemical properties of this drug indicate that it is a borderline-low solubility drug (4) and simulations in the fed state (Figure 5B) suggest the possibility of a zero-order absorption process, i.e. absorption is likely controlled by gastric emptying. It is worth mentioning that an alternative simulation model assuming first order gastric emptying in the fed state resulted in a profile similar to the observed profile (data not shown). In addition, although values of the pharmacokinetic microconstants estimated after intravenous administration exist, fits to any of the oral median or

Table III. Estimated f_1 Values for the Difference Between the Average Observed Plasma Data (Reference Data) and the Simulated Plasma Data (Test Data) of Seven Products. Simulated Profiles Were Obtained Assuming Dissolution to Take Place Either According to the Noyes-Whitney Theory or as a First Order Process[a]

	Noyes-Whitney based model		First-order model	
Product identifier-dosing conditions	Biorelevant dissolution data[b]	Compendial dissolution data[c]	Biorelevant dissolution data[b]	Compendial dissolution data[c]
Romozin®-fed state	15.5	46.4	16.6	17.6
D157/155B-fed state	15.2	ND	14.7	ND
D157/155D-fed state	34.2	ND	31.0	ND
Wellvone®-fasted state	49.5	78.0	166.1	162.7
Wellvone®-fed state	29.1	86.6	68.7	69.5
630/C091/59-fasted state-study 1	9.6	21.3	32.9	37.2
630/C078/49-fasted state	18.0	15.7	37.0	39.9
630/C091/59-fasted state-study 2	16.2	12.7	47.1	51.1
630/C091/59-fed state	42.3	53.2	42.6	44.8
GV150013X-fasted state	71.5	49.3	72.5	145.9
GV150013X-fed state	182.4	29.8	175.3	167.1

[a] ND: not determined due to inability to fit any function to the SIF_{sp} data of this product.
[b] Depending on the dosing conditions, dissolution in the stomach is simulated in water or in milk and in the intestine in FaSSIF or in FeSSIF.
[c] Regardless of the dosing conditions, dissolution in the stomach is simulated in water and in the intestine in SIF_s.

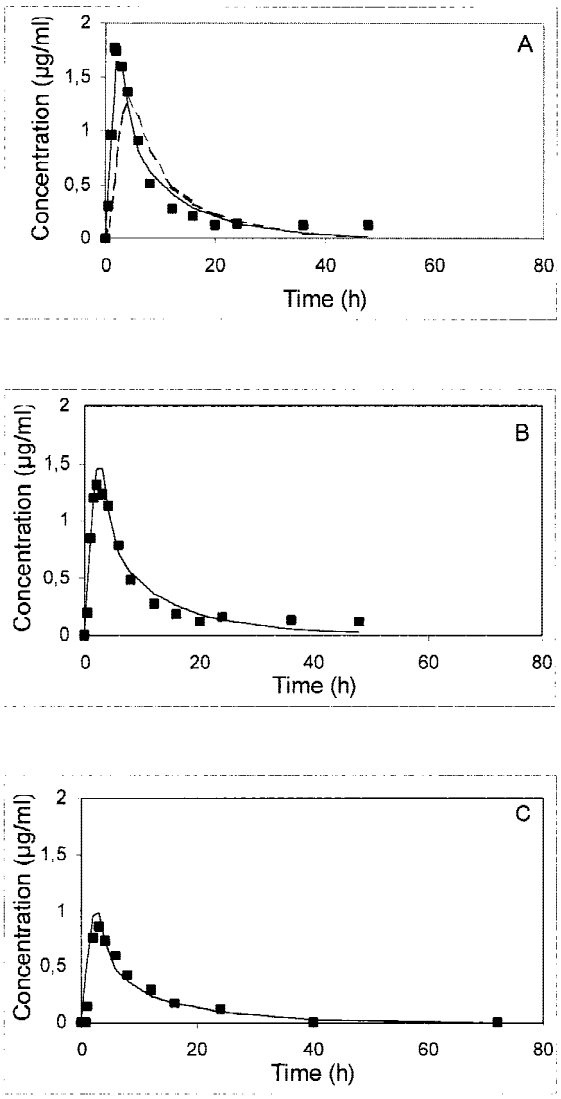

Fig. 2. Median observed plasma data in the fed state (■) and simulated profiles obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in milk and FeSSIF (—) after single oral administration of various troglitazone products (Dose: 2 × 200 mg) having absolute bioavailabilities of 41.6% (Romozin®, A), 37.0% (D157/155B, B), and 24.6% (D157/155D, C). For the D157/155B and the D157/155D products, none of the tested functions could be fitted to the dissolution data in SIF_{sp} (4) and, therefore, no simulated profiles are shown with water and SIF_{sp} data.

mean observed data were not possible using these values (see experimental section). Furthermore, the accuracy of the estimated disposition parameters used in our simulations is questionable, because they had to be estimated from oral data obtained in the fasted state. Possible food effects on disposition kinetics of this drug have not yet been studied.

Figure 6 shows the median observed data and the simulated profiles of a GV150013X product in the fasted and in the fed state. It is seen that simulated profiles vary from the observed data (Table III). Among the four compounds tested in this study, GV150013X is the most lipophilic, has the largest molecular weight (4), and reaches plasma levels 100 times lower than the other three compounds. Although some permeability data do exist (Caco-2 cells, GlaxoWellcome data on file), it is impossible to obtain a clearcut classification of this compound in terms of its permeability characteristics because of its extremely low solubility in the buffer solutions used in those studies. The possibility of this compound being low permeability (i.e., Class IV) is further supported by the overestimation of the plasma levels in the fed state with the biorelevant dissolution data (Figure 6B) and the possibility of an absorption window is raised by the unusual median data observed in the fasted state (C_{max} is very different from the remaining data points, Figure 6A). Our simulations show that after 6 hour residence in the small intestine the absorption process has been completed, with 29.5% of the drug absorbed in the fasted state and 40.7% in the fed state. Deconvolution of the median observed data (PCDCON, version 1.0, copyright 1991, W.R. Gillespie) revealed (data not shown) that 6 hours post-dosing only 8% has been absorbed in the fasted state and 8.9% has been absorbed in the fed state, and zero-order absorption in the fasted state. These data further suggest that this drug is a low permeability compound.

DISCUSSION

The Noyes-Whitney based model and the first order model proved to be the most generally applicable to describe the cumulative dissolution data of the four lipophilic compounds in this study. Although it is very useful for studying dissolution data obtained in media where 100% release is

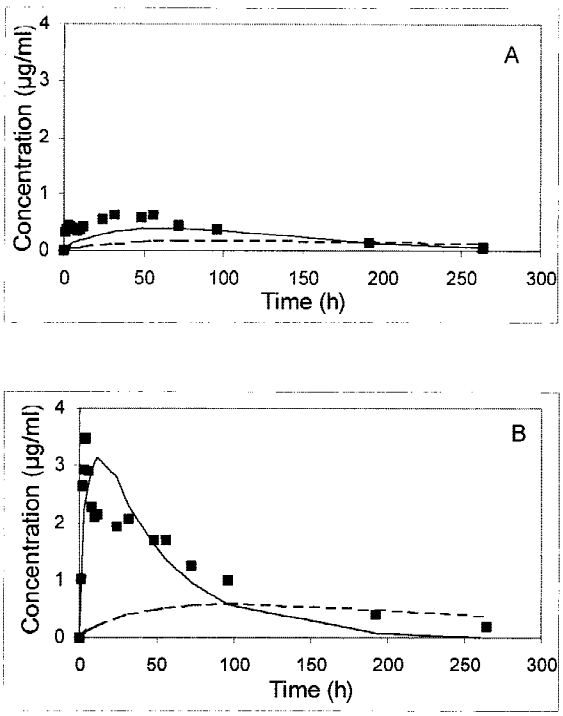

Fig. 3. (A) Median observed plasma data in the fasted state (■) and simulated profiles obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in water and FaSSIF (—) after single oral administration of one Wellvone® tablet (Dose: 2 × 250 mg) having an absolute bioavailability of 9.9%. (B) Median observed plasma data in the fed state (■) and simulated profiles obtained from *in vitro* dissolution data in water and SIF_{sp} (----) and in milk and FeSSIF (—) after single oral administration of one Wellvone® tablet (Dose: 2 × 250 mg) having an absolute bioavailability of 30.4%.

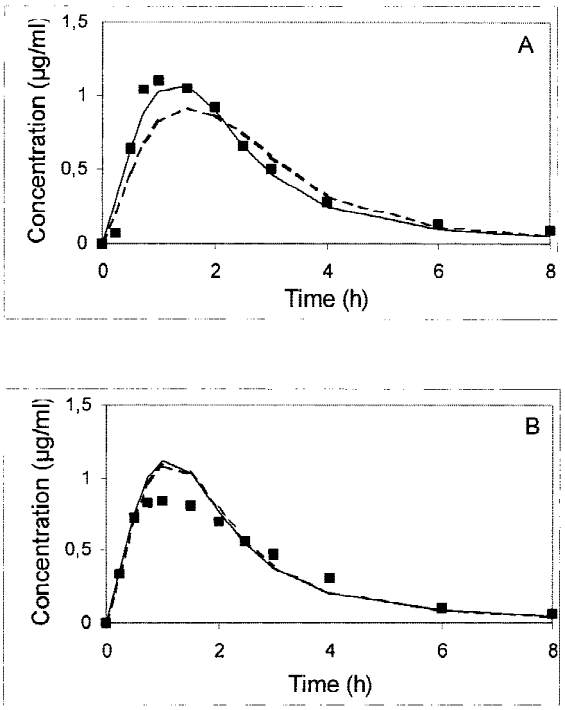

Fig. 4. Mean observed plasma data of sanfetrinem in the fasted state (■) and simulated profiles of sanfetrinem obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in water and FaSSIF (—) after single oral administration of one sanfetrinem cilexetil tablet (Dose: 400 mg). (A) batch #630/C091/59 with an absolute biovailability of 38.8%; (B) batch #630/C078/49 with an absolute bioavailability of 36.5%.

achieved (e.g., 9), the Weibull distribution may not be the most suitable to be fitted to cumulative dissolution data of lipophilic drugs in media where low percentages are dissolved, because fitting can be problematic either due the limited number of data points prior to plateau levels or because of the interdependence of the time and shape parameters. Furthermore, the *in vitro* dissolution data of lipophilic drugs in biorelevant media exhibited increased variability due to the low percent dissolved and/or the complexity of the medium (4). This makes the comparison of two mean profiles problematic. In particular, point estimates of various recently proposed indices (5) should be used cautiously with such data.

To date, prediction of the plasma profile after oral drug administration has been attempted using two approaches. The first, convolution, was initially proposed about twenty years ago (15,16). This approach requires the existence of the input profile (i.e., drug absorbed vs. time data) and the response profile of a weighting function (i.e., the plasma concentration vs. time data after intravenous administration). Experience over the years has confirmed that convolution may be applicable to products for which the limiting step to drug absorption is well defined and the absorption process takes place at a rate which is determined by the product, eg. some extended release dosage forms. It usually fails with immediate release dosage forms, partly because of the dependence of absorption with location in the GI tract, and partly because of the important role that gastric emptying can play in the absorption profile. Consequently, in the 1990s a second approach was considered, which differs from convolution in that the emphasis is given on the more precise estimation of the input profile. It considers the input phase as the result of processes taking place in various compartments (e.g., stomach, small intestine, colon) (17,18). However, despite the current general consensus that prediction of the *average* plasma profile of a drug orally administered in a solid form should be possible (19–22), only a limited number of papers have been published in this area (17,18,23) and, to date there are no published data with drugs that are highly extracted in the liver and only one with a lipophilic drug, glibenclamide (24). As for the drugs examined in the current work the authors of the glibenclamide article also found that the biorelevant media provided a more accurate simulation of pharmacokinetic profiles than SIF_{sp} (24). The major reason for the general lack of literature on lipophilic drugs is the high dependence of the dissolution process and/or permeability (the two most frequent limiting steps to absorption) on the intralumenal conditions and the location within the GI tract. Other reasons include the difficulty of measuring the permeability and/or intralumenal degradation kinetics of a compound with limited solubility, the possible substantial first-pass metabolism of these compounds, and the difficulty of estimating the disposition parameters of a lipophilic drug, since lipophilic compounds are often administered intravenously at doses much lower than those administered orally. Therefore, complete

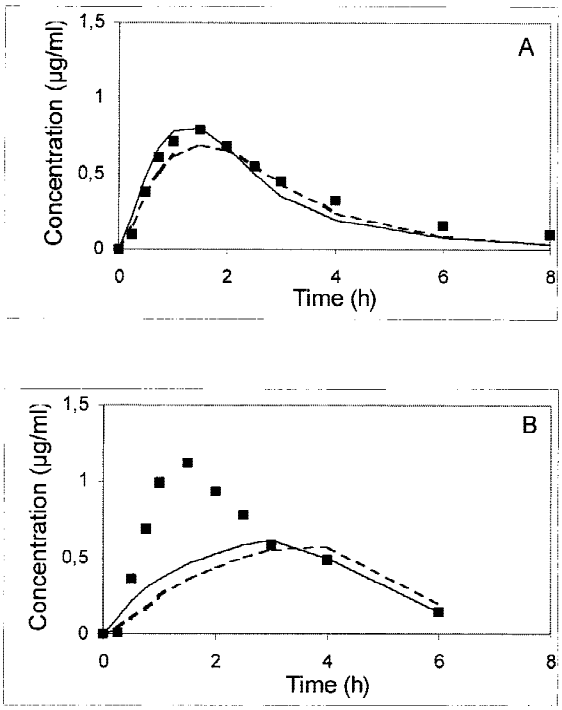

Fig. 5. (A) Mean observed plasma data of sanfetrinem in the fasted state (■) and simulated profiles obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in water and FaSSIF (—) after single oral administration of one sanfetrinem cilexetil tablet (batch #630/C091/59 Dose: 400 mg) having an absolute bioavailability of 29.1%. (B) Mean observed plasma data of sanfetrinem in the fed state (■) and simulated profiles obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in milk and FeSSIF (—) after single oral administration of one sanfetrinem cilexetil tablet (batch #630/C091/59; Dose 400 mg) having an absolute bioavailability of 33.1%.

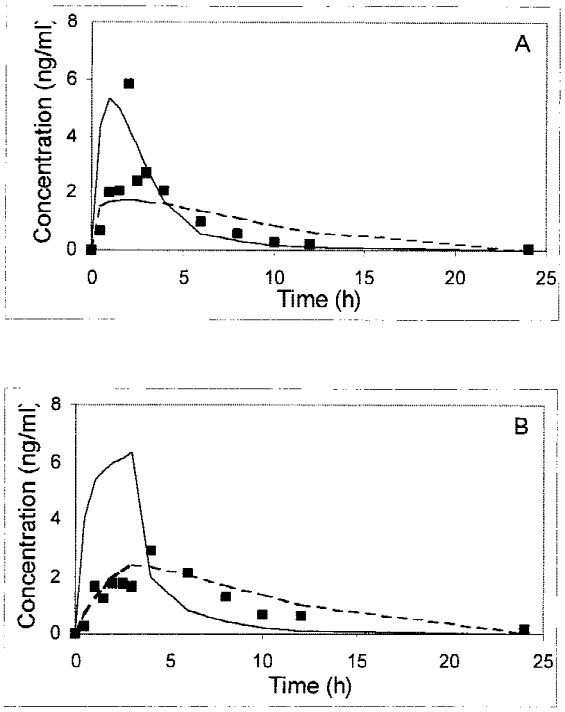

Fig. 6. (A) Median observed plasma data in the fasted state (■) and simulated data obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in water and FaSSIF (—) after single oral administration of one GV150013X tablet (Dose: 1mg) having an absolute bioavailability of 29.5 %. (B) Median observed plasma data in the fed state (■) and simulated data obtained using the estimated parameters of the Noyes-Whitney based model in water and SIF_{sp} (----) and in milk and FeSSIF (—) after single oral administration of one GV150013X tablet (Dose: 1 mg) having an absolute bioavailability of 40.7%.

characterization of the disposition phase may not be always possible.

In the present investigations we show that, although the lack of literature data suggests that the prediction of plasma profile after oral administration from *in vitro* data remains an ambitious target, prediction of the plasma profile of a lipophilic compound based on the *in vitro* dissolution data is achievable, provided that the absolute bioavailability of the drug is known. In cases where dissolution indeed limits absorption, use of *in vitro* dissolution profiles in biorelevant media led to better estimates of the plasma profile than those obtained with compendial media. Provided that further improvements in the *in vitro* dissolution test conditions can be made (in terms of both the hydrodynamics and media composition), this development will have a great impact on the number of pharmacokinetic studies that have to be performed to optimize dosing conditions and the product formulation during the development of new, lipophilic drugs. In addition, many post-approval changes in the formulation of lipophilic drugs could be assessed for bioequivalence on the basis of biorelevant dissolution testing (see reference 5 for a suggested procedure).

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