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Prediction of dissolution–absorption relationships from a dissolution/Caco-2 system

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Abstract

While the analysis of in vitro dissolution–in vivo absorption relationships from oral solid dosage forms provides biopharmaceutical insight and regulatory benefit, no well developed method exists to predict dissolution–absorption relationships a priori to human studies. The objective was to develop an integrated dissolution/Caco-2 system to predict dissolution–absorption relationships, and hence the contributions of dissolution and intestinal permeation to overall drug absorption for fast and slow formulations of piroxicam, metoprolol, and ranitidine. Dissolution studies were conducted on fast and slow dissolving immediate-release formulations of piroxicam, metoprolol tartrate, and ranitidine HCl. Dissolution samples were treated with concentrated buffers to render them suitable (i.e. isotonic and neutral pH) for Caco-2 monolayer permeation studies. The dissolution/Caco-2 system yielded a predicted dissolution–absorption relationship for each formulation which matched the observed relationship from clinical studies. The dissolution/Caco-2 system's prediction of dissolution or permeation rate-limited absorption also agreed with the clinical results. For example, the dissolution/Caco-2 system successfully predicted the slow piroxicam formulation to be dissolution rate-limited, and the fast piroxicam formulation to be permeation rate-limited. Moreover, the system predicted this change from dissolution rate-limited absorption for slow piroxicam to permeation rate-limited absorption for fast piroxicam, in spite of piroxicam's high permeability and low solubility. The dissolution/Caco-2 system may prove to be a valuable tool in formulation development. Broader evaluation of such a system is warranted.

Keywords: Dissolution; Intestinal permeation; Oral drug absorption; Caco-2 cells; Human

1. Introduction

It is now generally recognized that in vitro dissolution can serve as a surrogate for in vivo bioequivalence. This is particularly evident in the

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context of addressing scale up and post-approval changes which previously required explicit and demonstrative bioequivalence between pre-change and post-change formulations. This requirement may now be waived, provided a validated 'in vitro–in vivo correlation' is established (Federal Register, 1995). This regulatory benefit of establishing an 'in vitro–in vivo correlation' has perhaps increased interest in linking dissolution performance with pharmacokinetic performance.

In addition to regulatory assistance, another potential benefit of evaluating the role of dissolution in pharmacokinetic performance is the biopharmaceutical insight gained from 'in vitro–in vivo correlation' analysis. For example, 'in vitro–in vivo correlation' analysis was performed on several oral formulations of piroxicam, metoprolol, and ranitidine (Polli and Ginski, 1998). This analysis utilized in vitro dissolution data and in vivo absorption data (derived from plasma data) to characterize the absolute and relative contributions of dissolution and intestinal permeation to overall absorption kinetics. The elucidation of dissolution and permeation contributions to overall drug absorption performance provides the formulation scientist with a basis for estimating the sensitivity of a product to formulation changes. For example, this analysis previously determined metoprolol absorption from tablets to be permeation and not dissolution rate-limited and rationalized wide dissolution specifications (Polli et al., 1995). Although this in vitro dissolution–in vivo absorption approach provides an efficient biopharmaceutical characterization of the dosage form, it is limited in that clinical data is required.

Unfortunately, no well-developed method exists to predict dissolution and permeation contributions to overall drug absorption. Well developed in vitro dissolution methodologies and in vitro intestinal permeation models such as Caco-2 monolayers exist. Additionally, a proposed Biopharmaceutics Classification System (BCS) aims to identify drug formulations whose bioavailability may be sensitive to formulation changes (Amidon et al., 1995). Nevertheless, an in vitro method which provides the formulation scientist with a single, integrated characterization of the anticipated in vivo biopharmaceutical performance of a prototype formulation would be beneficial. In vitro dissolution–in vivo absorption relationships and other 'in vitro–in vivo correlation' analysis have provided useful scientific insight and regulatory relief. The objective was to develop an integrated dissolution/Caco-2 system to predict dissolution–absorption relationships, and hence the contributions of dissolution and intestinal permeation to overall drug absorption. Fast and slow dissolving formulations of piroxicam, metoprolol, and ranitidine were investigated.

2. Materials and methods

2.1. Materials

Caco-2 cells were obtained from ATCC (Rockville, MD). Polycarbonate Transwell® filters were purchased from Corning-Costar (Cambridge, MA). Piroxicam, metoprolol tartrate, and ranitidine hydrochloride were USP grade. All organic solvents were HPLC grade. All other chemicals were reagent grade.

Fast and slow dissolving 'immediate release' formulations of piroxicam capsules, metoprolol tartrate tablets, and ranitidine HCl tablets were previously developed at the University of Maryland School of Pharmacy and evaluated in a cross-over bioequivalency study. The analysis of the critical manufacturing variables and clinical results (Augsburger et al., 1993; Piscitelli et al., 1994a,b, 1995; Rekhi et al., 1997) have been reported.

2.2. Methods

2.2.1. Dissolution studies

Dissolution studies on each fast and slow formulation of piroxicam, metoprolol, and ranitidine were conducted ($n = 6$) using compendial methods (United States Pharmacopeia, 1994) in a Van Kel dissolution apparatus (Cary, NC). For the fast dissolving formulations, dissolution samples were taken at 5, 10, 20, 30, 40 and 60 min. For the slow dissolving, samples were taken at 10, 20, 40, 60, 90 and 120 min. Samples were filtered through a 0.2-μm syringe filter and analyzed by HPLC. Dis-

Table 1
Description of dissolution samples following buffer treatment

Ingredients	HBSS (mM)	Piroxicam and metoprolol tartrate (mM)	Ranitidine HCl (mM)
Calcium	0.00126	0.00126	0.00126
Magnesium	0.000811	0.000811	0.000811
Sodium	0.138	0.0948	0.138
Potassium	0.00577	0.00536	0.00577
Chloride	0.145	0.0974	0.145
Sulfate	0.000811	0.000811	0.000811
Monobasic phosphate	0.000414	–	0.000414
Dibasic phosphate	0.000377	–	0.000377
Trizma base	–	0.79	–
D-Glucose	0.00555	0.00555	0.00555
Phenol red	0.000118	–	–
pH[a]	6.60 (0.30)	7.48 (0.10)	6.60 (0.10)
Osmolarity[b]	276.0 (13.8)	280.0 (1.1)	272.1 (1.0)

[a] Mean value ($n = 3$) $\pm$ S.E.M.
[b] Mean value ($n = 3$) determined using Osmotte S (Precision Instruments Inc.) in mOsm/kg H_2O ($\pm$ S.E.M.).

solution profiles obtained here were very similar to those previously reported.

2.2.2. Preparation of dissolution samples for Caco-2 monolayer permeation studies

Since Caco-2 permeation studies are typically conducted in isotonic and neutral pH transport medium, dissolution samples were treated with a concentrated buffer to render them suitable as donor solutions for Caco-2 permeation studies. The ionic content of the transport medium can significantly affect Caco-2 permeability. Low Ca^{2+} and Mg^{2+} concentrations alter Caco-2 monolayer tight junction morphology and increase paracellular diffusion (Arturrson and Magnusson, 1990; Callares-Buzato et al., 1994).

Dissolution samples were treated by adding 50 μl of concentrated buffer to 4.95 ml of each sample. Two different concentrated buffer systems were formulated to treat dissolution samples, one for ranitidine whose dissolution medium is water and one for piroxicam and metoprolol whose dissolution media is simulated gastric fluid. The ionic content, pH, and tonicity of each set of dissolution samples after treatment is listed in Table 1. The final compositions were similar to Hank's balanced salts solution (HBSS) and matched Ca^{2+} and Mg^{2+} concentrations in HBSS.

The use of treated dissolution samples for Caco-2 studies requires that drug solubility and permeability are not adversely affected by conversion from the dissolution medium to the final Caco-2 donor solution. A decrease in solubility may precipitate drug and reduce the donor concentration in the Caco-2 permeation studies. Piroxicam, metoprolol, and ranitidine solubility determinations in dissolution media and in treated dissolution media indicate this potential problem was not the case. Similarly, the use of this treatment procedure did not present methodological difficulties for Caco-2 permeation studies. The permeabilities of piroxicam, metoprolol, and ranitidine in treated dissolution media were the same as previously reported in HBSS (Polli and Ginski, 1998).

2.2.3. Caco-2 monolayer cell culture and permeation studies

Caco-2 cells were grown in T-75 flasks at 37°C in an atmosphere of 5% CO_2 and 95% RH using Delbecco's modified eagles media (DMEM) supplemented with 10% fetal bovine serum, 1% nonessential amino acids, and 0.05% penicillin/streptomycin. Media was changed approximately every 48 h. Cells were passaged at 80–90% confluency using a 0.20% EDTA/0.25% trypsin solution. Between passage numbers 35–

55, cells were seeded on polycarbonate Transwell® filters (0.4 μm mean pore size; 4.71 cm^2 area) at a density of 4×10^5 cells/cm^2. These cells were cultured for 21–28 days and subsequently used for permeation studies.

For each formulation, Caco-2 permeation studies ($n = 18$) were conducted on treated dissolution samples from three dissolution vessels. Permeation studies were conducted under sink conditions at 37°C and 50 oscillations per min, with 1.5 ml of the treated dissolution sample as the donor solution and 2.6 ml of treated dissolution medium as the receiver solution. The receiver compartment was sampled at 20, 40, 60, 90, 120, and 180 min. Samples from the receiver and donor compartment (at the end of the experiment) were analyzed by HPLC. Caco-2 monolayer permeability (P_m) was estimated by correcting the effective permeability (P_{eff}) for P_{filter} according to $P_{eff}^{-1} = P_m^{-1} + P_{filter}^{-1}$. At similar concentrations used in these studies, apical-to-basolateral and basolateral-to-apical permeabilities for these drugs were previously observed to be the same (Polli and Ginski, 1998). Mass balance ranged from 90 to 110% for all permeation studies. Monolayer integrity was evaluated using mannitol and transepithelial electrical resistance (TEER) in growth media (> 850 Ω cm^2 at ambient room temperature after subtracting a 'filter' resistance of 660 Ω cm^2).

2.2.4. Predicted dissolution–absorption relationships from dissolution/Caco-2 system

The objective of this study was to develop an integrated dissolution/Caco-2 system to predict dissolution–absorption relationships, and hence the contributions of dissolution and intestinal permeation to overall drug absorption for several oral formulations[1]. Prior to discussing the use of the dissolution/Caco-2 system to predict dissolution–absorption relationships, some comments regarding dissolution–absorption plots are provided here. A dissolution–absorption plot is typically constructed by plotting the fraction of drug absorbed (F_a) against the fraction of drug dissolved (F_d). F_a and F_d are paired according to identical times. The plot can be described as a phase plane (Polli et al., 1996), since it is a plot of two time-dependent variables. Generally, F_a and F_d each increase with time. Theoretical and example analyses of dissolution–absorption relationships have been presented previously (Polli et al., 1996; Polli and Ginski, 1998).

To construct a dissolution–absorption relationship from the dissolution/Caco-2 system, both the F_d vs time and F_a vs time profiles are required. These profiles need to be integrated into the same phase plane by pairing F_d and F_a data according to identical times. While dissolution directly provides an F_d vs time profile, a method to obtain an F_a vs time profile from the dissolution/Caco-2 system is not obvious. For example, consider a 60-min dissolution sample that is subjected to Caco-2 permeation for 40 min. F_a can easily be taken as the fraction of drug which has permeated across the monolayer relative to the amount which permeates after 180 min, which is approximately the mean residence time of drug in the small intestine (Davis et al., 1986). However, the time associated with this F_a is ambiguous. This sample has undergone 60 min of dissolution during which drug absorption may have occurred, followed by an additional 40 min of drug permeation in the Caco-2 study.

In the context of dissolution–absorption relationships, determination of the time for absorption must include time for dissolution and time for intestinal permeation. However, addition of the dissolution time and the Caco-2 permeation time would often be inappropriately long. The approach taken here employed mean dissolution time (MDT) in computing an absorption time. Eq. (1) was applied to the dissolution and Caco-2 permeation data:

$$t_a = t_d + t_p \quad (1)$$

where t_a is the absorption time (i.e. the time assigned to F_a data), t_p is permeation time, and t_d is the dissolution time. t_p is taken directly from

[1] A distinction between permeation and absorption is intended here. Permeation is the process of drug transversing the lumenal absorptive surface (i.e. results from Caco-2 studies alone). Absorption is the process of both drug dissolution and drug permeation (i.e. results from combined analysis of dissolution/Caco-2 system).

the Caco-2 monolayer permeation study. In the above example, $t_p = 40$ min. t_d is MDT up until the dissolution sample time and was calculated from:

$$\mathrm{MDT} = \frac{\sum_{i=1}^{n} t_{mid}\Delta M}{\sum_{i=1}^{n} \Delta M} \quad (2)$$

where i is the dissolution sample number (e.g. for fast formulations $i = 1$ for 5 min data, $i = 2$ for 10 min data, etc.), n is the number of dissolution sample times, t_{mid} is the time at the midpoint between i and $i-1$, and ΔM is the additional amount of drug dissolved between i and $i-1$.

By way of example, a 60-min dissolution sample from the piroxicam fast formulation was used in a Caco-2 study where permeation sampling was conducted at 20, 40, 60, 90, 120 and 180 min. The MDT through 60 min was 10.0 min, which was added to t_p values to yield t_a values of 30.0, 50.0, 70.0, 100.0, 130.0, and 190.0 min, respectively. These t_a values were paired with the corresponding F_a values. Note that in this example, a t_p of 40 min across Caco-2 monolayers is scaled to a t_a of 50.0 min to include both dissolution and permeation. Hence, this approach was able to utilize the dissolution/Caco-2 system to yield the requisite F_a vs t profile for dissolution–absorption analysis.

Finally, for the predicted dissolution–absorption relationship, F_d and F_a values must be for the same time point. Hence, F_a values were interpolated to 20, 40 min, etc. to match dissolution sample times. F_a were not included when t_p was too small relative to dissolution kinetics (i.e. when t_p less than three times MDT).

2.2.5. Comparison of predicted and observed dissolution–absorption relationships

The ability of this dissolution/Caco-2 system to predict the observed in vitro dissolution–in vivo absorption profile in humans was assessed by comparing the predicted relationship to those obtained from clinical studies (Polli and Ginski, 1998). As previously described (Polli et al., 1996), a 'straight line' relationship between F_a and F_d indicates dissolution rate-limited absorption, while a 'reverse L' appearing profile indicates permeation rate-limited absorption. An intermediate 'hockey stick' profile indicates both dissolution and permeation contribute roughly equally to overall drug absorption kinetics.

Although a benefit of this integrated dissolution/Caco-2 system is the minimal use of mathematical models, which typically require significant simplifying assumptions, the F_a vs. F_d plots from the dissolution/Caco-2 system were fit to Eq. (3) (Polli et al., 1996) to further evaluate the system's ability to predict biopharmaceutical properties of the oral solid dosage forms:

$$F_a = \frac{1}{f_a}\left(1 - \frac{\alpha}{\alpha - 1}(1 - F_d) + \frac{1}{\alpha - 1}(1 - F_d)^{\alpha}\right) \quad (3)$$

where F_a is the fraction of the total amount of drug absorbed at time t, f_a is the fraction of the dose absorbed at $t = \infty$, α is the ratio of the apparent first-order permeation rate constant to the first-order dissolution rate constant and F_d is the fraction of the dose dissolved at time t. Assumptions of this model include first-order dissolution, apparent first-order permeation, the equality of *in vitro* dissolution and *in vivo* dissolution profiles, and no physical or chemical degradation of the drug in the gastrointestinal lumen. α was determined from Eq. (3) and compared to previously reported α values from clinical studies (Polli and Ginski, 1998).

3. Results and discussion

3.1. Piroxicam

The predicted dissolution–absorption relationships (resulting from the dissolution/Caco-2 system) for the fast and slow dissolving formulations of piroxicam are plotted in Fig. 1a, b, respectively. The predicted dissolution–absorption relationship for fast shows a 'reverse L' appearance, characteristic of permeation rate-limited absorption. For this formulation, the dissolution/Caco-2 system predicts that dissolution is nearly complete before appreciable absorption takes place. On the other hand, the predicted relationship for slow has a 'straight line' appearance. Hence, the dissolution/Caco-2 system predicts piroxicam absorption from slow to be dissolution rate-limited.

Also plotted in Fig. 1a, b are the observed dissolution–absorption relationships from clinical studies of the fast and slow formulation, respectively. There appears to be general agreement between the predicted and observed dissolution–absorption profiles. The predicted and observed relationships for fast both result in a 'reverse L' appearance. The predicted and observed relationships for slow both result in a 'straight line' appearance. Hence, results suggest that the dissolution/Caco-2 system successfully predicts dissolution–absorption relationships.

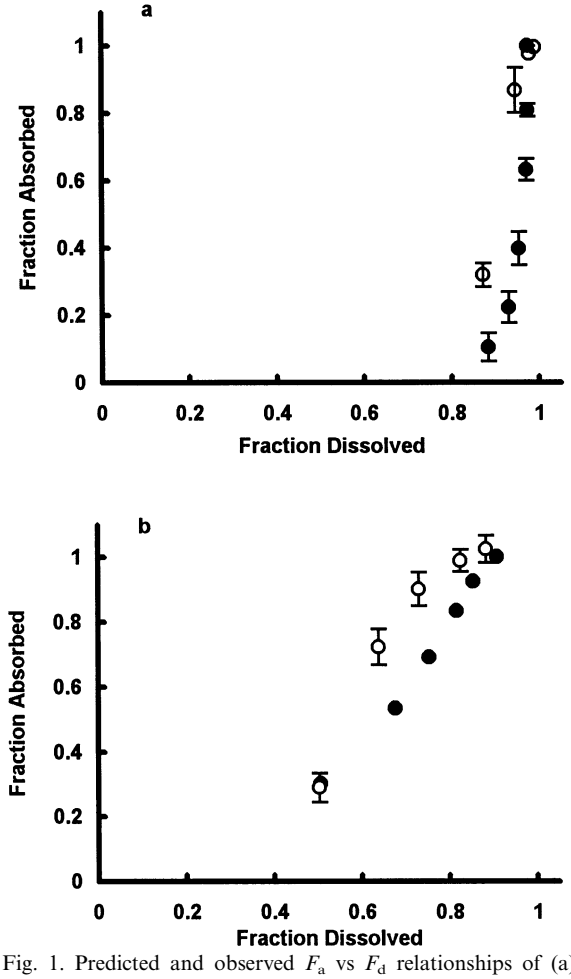

Fig. 1. Predicted and observed F_a vs F_d relationships of (a) fast- and (b) slow-dissolving formulations of piroxicam. The predicted relationship (closed circle) from the dissolution/Caco-2 system matched the observed relationship (open circle) for each formulation.

Table 2
Comparison of observed dissolution–absorption profile from clinical studies and predicted profile from dissolution/Caco-2 system

Drug	Formulation	Observed α	Predicted α
Piroxicam	Fast	0.896 (0.138)	0.394 (0.032)
	Slow	6.50 (2.17)	4.42 (0.08)
Metoprolol	Fast	0.0743 (0.0178)	0.260 (0.001)
	Slow	0.648 (0.103)	0.704 (0.06)
Ranitidine	Fast	0.0646 (0.010)	0.184 (0.003)
	Slow	0.156 (0.020)	0.196 (0.014)

This example of the dissolution/Caco-2 system's predictive capability is particularly significant in light of the change from dissolution rate-limited absorption for slow to permeation rate-limited absorption for fast. In the BCS, piroxicam (Class II) is a high permeable, low soluble drug. Therefore, overall piroxicam absorption from an oral solid dosage form is generally expected to be dissolution rate-limited. However, because the fast formulation employed micronized drug and the use of sodium lauryl sulfate (Augsburger et al., 1993), piroxicam absorption from fast was not dissolution rate-limited in vivo, but permeation rate-limited (Polli and Ginski, 1998). The dissolution/Caco-2 system was able to predict the fast formulation to be permeation rate-limiting, in spite of piroxicam's high permeability and low solubility.

In addition to evaluating the predictive capability of the dissolution/Caco-2 system by comparing F_a vs F_d profiles, the system was also evaluated by comparing α values from fits of Eq. (3) to the F_a vs. F_d profiles. α is a dimensionless parameter reflecting the degree to which dissolution limits overall drug absorption kinetics. An α value much greater than 1.0 indicates dissolution rate-limited absorption. An α value much less than 1.0 indicates permeation rate-limited absorption. An α value of 1.0 indicates perfectly mixed dissolution and permeation rate-limited absorption. Table 2 lists α values from the dissolution/Caco-2 system (predicted) and clinical studies (observed). For piroxicam, the dissolution/Caco-2 system predicts

dissolution rate-limited absorption from slow ($\alpha = 4.42$) and permeation rate-limited absorption from fast ($\alpha = 0.394$). These predictions are similar to the observed dissolution-absorption relationships of slow ($\alpha = 6.50$) and fast ($\alpha = 0.896$) from clinical studies.

3.2. Metoprolol tartrate

The predicted dissolution–absorption relationships for the fast and slow dissolving formulations of metoprolol are plotted in Fig. 2a, b, respectively. The predicted relationships for both fast and slow exhibit a 'reverse L' appearance, characteristic of permeation rate-limited absorption. For both formulations, the dissolution/Caco-2 system predicts nearly complete dissolution before appreciable absorption takes place, with the fast formulation more permeation rate-limited than the slow formulation.

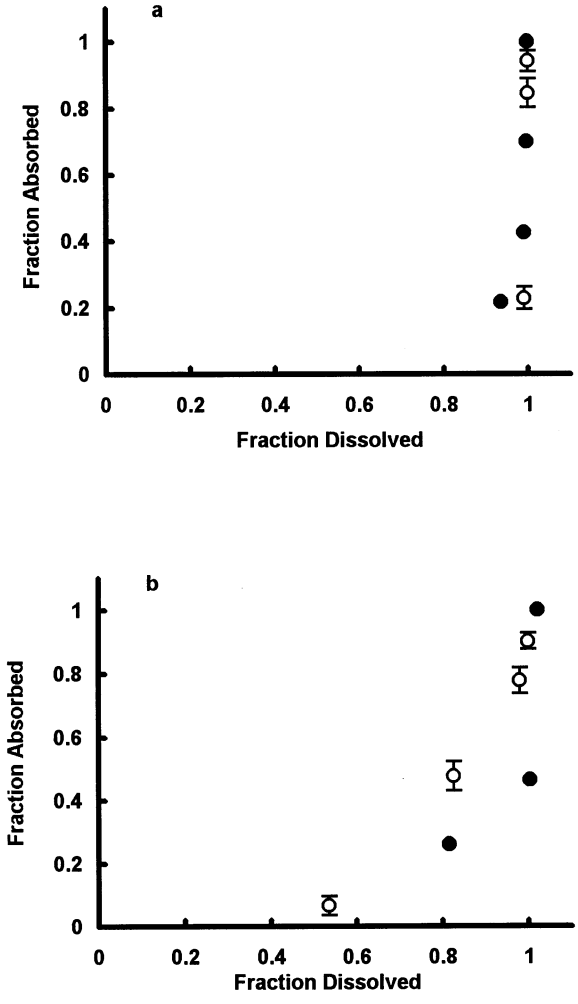

Fig. 2. Predicted and observed F_a vs F_d relationships of (a) fast- and (b) slow-dissolving formulations of metoprolol tartrate. The predicted relationship (closed circle) from the dissolution/Caco-2 system matched the observed relationship (open circle) for each formulation.

Also plotted in Fig. 2a, b are the observed dissolution–absorption relationships from clinical studies of fast and slow, respectively. There is general agreement between the dissolution/Caco-2 system predicted and observed dissolution–absorption profiles. For both fast and slow, the predicted and observed relationships exhibit a 'reverse L' appearance.

The dissolution/Caco-2 system was also evaluated by comparing α values from fits of Eq. (3) to the predicted and observed F_a vs F_d profiles. Table 2 lists α values from the dissolution/Caco-2 system and clinical studies. For metoprolol, the dissolution/Caco-2 system predicts permeation rate-limited absorption from slow ($\alpha = 0.704$) and fast ($\alpha = 0.260$). These predictions are similar to the observed dissolution–absorption relationship of slow ($\alpha = 0.648$) and fast ($\alpha = 0.0743$) from clinical studies.

In the BCS, metoprolol (Class I) is a high permeable, high soluble drug. From solubility and permeability, it is difficult to predict whether overall absorption is dissolution or permeation rate-limited because metoprolol both dissolves rapidly and permeates rapidly. Meanwhile, the dissolution/Caco-2 system successfully integrates dissolution and permeation into one study to allow for a prediction of the relative contributions of dissolution and intestinal permeation to overall absorption kinetics. The dissolution/Caco-2 system is able to make a prediction, in fact an accurate prediction, of the dissolution–absorption relationship.

3.3. Ranitidine HCl

The predicted dissolution–absorption relationships for fast and slow are plotted in Fig. 3a, b,

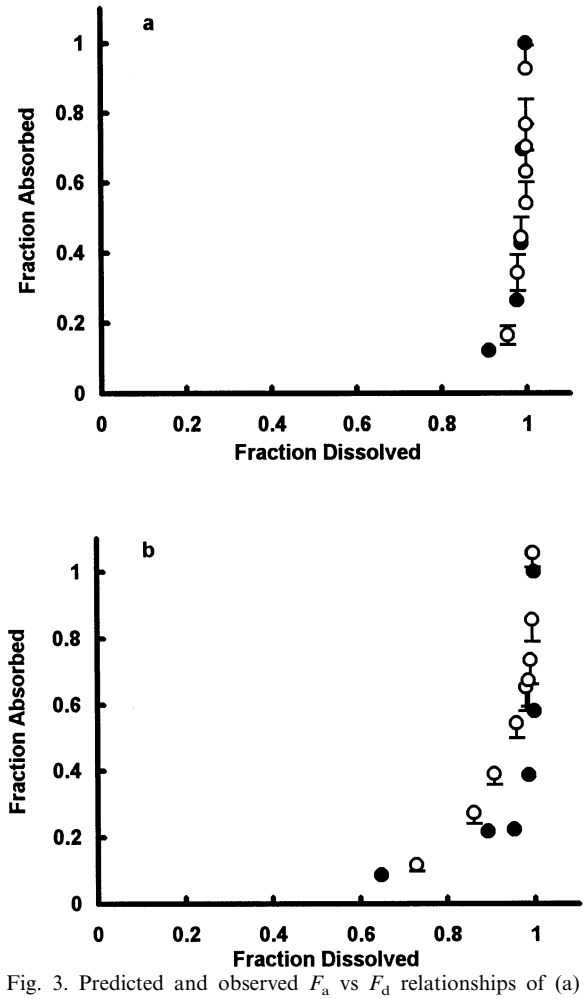

Fig. 3. Predicted and observed F_a vs F_d relationships of (a) fast- and (b) slow-dissolving formulations of ranitidine HCl. The predicted relationship (closed circle) from the dissolution/Caco-2 system matched the observed relationship (open circle) for each formulation.

respectively. The corresponding observed dissolution–absorption relationships are also shown. There is general agreement between the predicted and observed profiles for both fast and slow, with all profiles exhibiting a 'reverse L' appearance, characteristic of permeation rate-limited absorption. Hence, the dissolution/Caco-2 system successfully predicts ranitidine absorption from all formulations to be permeation rate-limited. Table 2 lists the predicted and observed α values. The dissolution/Caco-2 system predicts permeation rate-limited absorption from slow ($\alpha = 0.196$) and fast ($\alpha = 0.184$). These predictions are similar to the observed dissolution–absorption relationships for slow ($\alpha = 0.156$) and fast ($\alpha = 0.0646$).

Ranitidine is classified as a low permeable, high soluble drug (Class III) in the BCS. Therefore, overall ranitidine absorption from an oral solid dosage form is generally expected to be permeation rate-limited. For the piroxicam and metoprolol formulations, discrete evaluation of solubility and permeability were not able to predict the rate-limiting step in overall drug absorption. For these formulations, the utility of the dissolution/Caco-2 system was evident in that it was able to assess the relative contributions of dissolution and intestinal permeation to overall drug absorption. However, application of the dissolution/Caco-2 system to the ranitidine formulations does not provide information that could not be predicted from discrete solubility and permeability studies alone. Discrete solubility and permeability studies predicted permeation rate-limited absorption of ranitidine; the dissolution/Caco-2 system simply agrees with this correct prediction.

3.4. Benefits of dissolution/Caco-2 system

Bioequivalence study waivers for scale up and post approval changes and added biopharmaceutical insight from 'in vitro–in vivo correlation' analysis are two reasons for quantitatively linking dissolution performance with pharmacokinetic performance. Methods have been developed to perform 'in vitro–in vivo correlation' analysis on conventional dissolution and plasma profile data. Unfortunately, there is no well developed method to predict the F_a vs F_d relationship for a prototype formulation, and hence the relative contributions of dissolution and permeation to overall absorption kinetics, a priori to human clinical studies.

The objective was to address this need by developing an integrated dissolution/Caco-2 system and apply the system to formulations of piroxicam, metoprolol, and ranitidine. This system utilizes two well developed in vitro technologies: dissolution and Caco-2 monolayers. Formulation development has long relied on dissolution test-

ing. More recently, Caco-2 monolayers have been introduced as a model for intestinal drug permeability (Borchardt and Arturrson, 1997). Its utility in formulation development has perhaps been minimal, due in large part to the lack of an integration of Caco-2 permeability with dissolution.

The success reported here with the above described dissolution/Caco-2 system may facilitate the inclusion of dissolution and Caco-2 permeation considerations into formulation development. Such considerations will allow for, as performed above, the prediction of dissolution and permeation contributions to overall drug absorption performance, which provide the formulation scientist a basis to estimate the product sensitivity to formulation changes. For example, the dissolution/Caco-2 system predicts that metoprolol and ranitidine slow formulations are permeation rate-limited. In spite of slower release from slow compare to fast, overall absorption from the slow formulations is predicted not to be dissolution rate-limited. This type of predictive biopharmaceutical characterization of these metoprolol and ranitidine dosage forms suggests low potential for decreased bioavailability due to insufficient dissolution. Hence, a dissolution/Caco-2 system may prove to be a valuable tool in formulation development. Clearly, more experience is needed. Additionally, it should be noted that the dissolution/Caco-2 system predictions here were performed after the clinical studies. A prospective rather than retrospective challenge of a dissolution/Caco-2 system is preferable and is warranted.

In conclusion, an approach to integrate dissolution and Caco-2 permeation studies into a single dissolution/Caco-2 system was developed. The dissolution/Caco-2 system was applied to fast and slow formulations of piroxicam, metoprolol, and ranitidine, with the objective to predict dissolution-absorption relationships, and hence the contributions of dissolution and intestinal permeation to overall drug absorption. Predicted dissolution–absorption relationships matched the observed relationships from clinical studies.

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