The Effect of *In Vivo* Dissolution, Gastric Emptying Rate, and Intestinal Transit Time on the Peak Concentration and Area-Under-the-Curve of Drugs with Different Gastrointestinal Permeabilities

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Purpose. To theoretically investigate the impact of gastric emptying half-time, intestinal transit time and the time for 85% *in vivo* dissolution on the peak concentration and area-under-the curve of model drugs.

Methods. Simulations were performed using mathematical models of gastrointestinal physiology and pharmacokinetics of model drugs with different gastrointestinal permeability. They were used to investigate the effect of different permutations of gastric emptying times, intestinal transit times, dissolution rates and effective permeabilities on the maximum plasma drug concentration and the area-under-the-curve of immediate release tablets relative to an oral solution (i.e., $Cmax_{tablet}/Cmax_{solution}$ and $AUC_{tablet}/AUC_{solution}$).

Results. The higher the permeability of the drug, the more sensitive the Cmax ratio is to dissolution rate and gastric emptying rate. As the intestinal transit time becomes more rapid, the sensitivity to T85% dissolution time and gastric emptying half-time increases. There is less dependence for the AUC ratio on the gastric emptying time and dissolution rate.

Conclusions. Under the assumptions of the models, the criterion of 85% dissolution in 15 minutes (T85%) for classifying a rapidly dissolving drug product is relatively conservative since the Cmax ratio exceeded 0.8 for a T85% dissolution time of one hour and a gastric emptying half-time faster than 0.2 hour over a wide range of permeabilities.

KEY WORDS: biopharmaceutic classification system; peak concentration; permeability.

INTRODUCTION

The effective permeability of drugs has been investigated using a variety of experimental approaches including human jejunal perfusion (1), *in situ* intestinal perfusion (2) and Caco-2 cell systems (3). There has also been an effort to correlate the permeability measurements obtained from these approaches to the fraction absorbed of a range of drugs. An empirical relationship exists between the fraction absorbed of a drug and its effective intestinal permeability. A theoretical basis for the relationship has been explored and various mathematical models have been proposed (4). A Biopharmaceutical Classification System (BCS) has been put forward for drugs based on this new understanding of the relationships between intestinal permeability and drug absorption and the relationships between *in vivo* bioavailability and *in vitro* dissolution (5). The BCS attempts to classify drugs according to their permeability and solubility.

The classification is already in effect in two regulatory guidances to the Pharmaceutical Industry (6,7). Drugs are grouped into classes and one such class defines a drug that is highly soluble and highly permeable and whose product rapidly dissolves *in vitro*. A highly soluble drug is a drug whose highest unit dose is soluble in 250 mL or less volume of buffer between pH 1.0 and 8.0. A rapidly dissolving drug product is one that shows 85% dissolution in 15 minutes in 900 mL of 0.1N hydrochloric acid using USP dissolution Apparatus I at 100 rpm or Apparatus II at 50 rpm. High permeability is defined in SUPAC-IR (scale-up and post-approval changes for immediate release dosage forms (6)) as those drugs that generally have an extent of absorption of greater than 90% in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally. The BCS dissolution specifications are based on average gastric emptying rates. Rapid dissolution of 85% in 15 minutes is close to the time it takes to empty 50% of about 200 mL of water from the stomach under fasting conditions (5).

Although these guidances did not recommend a waiver of *in vivo* bioavailability of bioequivalence studies, a further possible development of the BCS is to propose that *in vivo* bioequivalence might be waived for rapidly dissolving dosage forms of high permeability/high solubility drugs. Bioequivalence of one dosage form to another when tested *in vivo* most commonly involves a crossover pharmacokinetic study. The test dosage form is compared to a reference dosage form using the pharmacokinetic measures of the maximum plasma concentration (peak concentration) and the area-under-the-curve of the drug's plasma concentration-time profile. These pharmacokinetic measures are measures of a drug's bioavailability. The measure Cmax (or peak concentration) may be more sensitive to dissolution, solubility and permeability than AUC (area-under-the-curve). However, existing research related to the BCS has focussed almost entirely on the effects of permeability, solubility and dissolution rate on the extent of absorption and thus on AUC.

Previous publications have incorporated gastrointestinal absorption into models to assess drug plasma concentration-time profiles or fraction of dose absorbed (8–11). The present study was carried out to develop and apply a physiologically relevant pharmacokinetic model to investigate the impact of the gastric emptying half-time, the time for 85% dissolution of an immediate release tablet and the effective permeability on the peak plasma concentration and area-under-the-curve for model drug products.

METHODS

Mathematical models were constructed based on published physiological parameters such as gastric emptying time and

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intestinal transit time for pharmaceutical dosage forms (12). Pharmacokinetic parameters for atenolol hydrochloride, ranitidine hydrochloride and metoprolol tartrate were obtained from the literature and from in-house FDA submissions. The models simulated the handling of both dissolved and solid drug within the stomach and small intestinal tract. Schematics of the models used for, atenolol, ranitidine and metoprolol are shown in Fig. 1. Metoprolol has a high first-pass effect which is accounted for in the model by incorporating a liver compartment in Model C. The values used for the pharmacokinetic parameters and physiological parameters are shown in Table 1. The models were implemented using a combination of FORTRAN and Splus™ to explore different permutations of gastric emptying times, dissolution rates and effective permeabilities. The solid dosage form is assumed to immediately enter the stomach compartment where it immediately disintegrates and deaggregates. The models assume that there is no absorption from the stomach or from the colon. The simulations assume that the drug products have no influence on gastric emptying or intestinal motility. Also assumed, is that the dissolution rate is site-independent for each of the drugs.

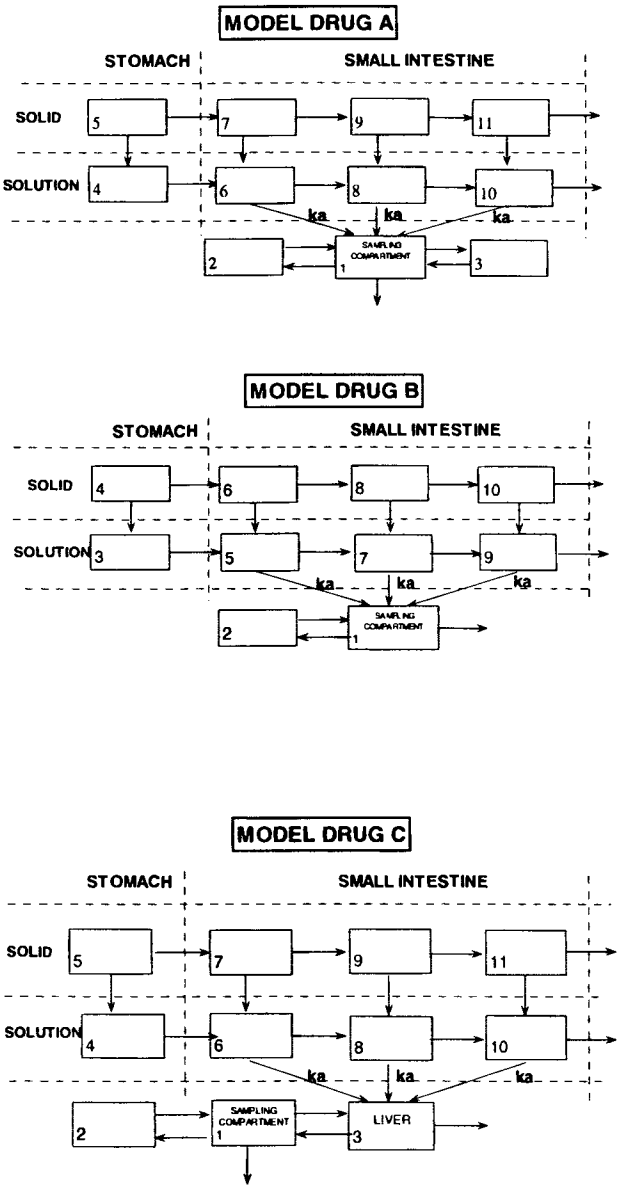

Fig. 1. Schematic of pharmacokinetic and physiologic models used for Model Drug A (based on atenolol hydrochloride), Model Drug B (based on ranitidine hydrochloride) and Model Drug C (based on metoprolol tartrate).

The theoretical explorations did not focus on the bioavailability of drugs but rather their bioequivalence. The BCS is being proposed as a means of deciding whether a formal bioequivalence study should be carried out or alternatively, if *in vitro* dissolution testing may serve as a surrogate for *in vivo* bioequivalence. A rapidly dissolving drug product that contains a highly soluble drug with high intestinal permeability is hypothesized to behave comparable to an oral solution. For such cases it is argued that gastric emptying controls the rate at which dissolved drug reaches the sites of absorption. Thus any two formulations with such properties should exhibit comparable bioavailability since the rate controlling processes are independent of the dosage form properties. Therefore, the drug as a solution was used as a reference in the present study to obtain the ratios of the maximum plasma drug concentration (i.e., $Cmax_{tablet}/Cmax_{solution}$). The rationale is that a dissolution criterion that assures bioequivalence to a solution would also assure bioequivalence to any immediate release oral solid dosage form that meets the same criterion for any particular high permeability and high solubility drug. This assumes that the excipients used in the immediate release dosage form do not affect gastrointestinal physiology such as transit time and permeability in comparison to the drug in solution.

The first order absorption constant for absorption from a solution, k_a can be considered to be directly proportional to permeability (5). Therefore for the purpose of the simulations, the first order absorption rate constant served as the measure of permeability in the disposition model.

Three model drugs were considered:

- Model Drug A - lowest permeability (k_a = 0.25 hr^{-1} comparable to atenolol)
- Model Drug B - low permeability (k_a = 0.8 hr^{-1} comparable to ranitidine)
- Model Drug C - highest permeability (k_a = 3 hr^{-1} comparable to metoprolol)

All intercompartmental transfers were modeled as first-order processes. Three compartments were chosen to represent the small intestine. In the simulations, the three rate constants which described the transfer between the compartments gave a total transit time of 3.3 hours. This is consistent with a mean total small intestinal transit time of about three hours found in gamma scintigraphy studies on pharmaceutical dosage forms (12). Additional simulations explored the effect of a faster small intestinal transit time of 1.67 hours on the Cmax ratio for each model drug. The gastric emptying half-time was varied from 0.01 to 0.5 hour for both the solid and solution component, and the time for 85% dissolution, was varied from 0.1 to 2 hours. All simulations were based on single dose administration.

The impact of permeability was further explored via simulations in which the absorption rate constant, k_a, was varied over 0.01 to 20 hr^{-1}. This was carried out using the disposition model for all three model drugs.

Table 1. Parameters Used for the Model Drugs in the Simulations

Drug	Model parameter	Value
Model drug A	Total Body Clearance (L/hr)	11
Dose = 50 mg	Compartment 1: Volume of Distribution (L)	23
	Distribution Clearance between Compartment 1 and 2 (L/hr)	41.5
	Compartment 2: Volume of Distribution (L)	14
	Distribution Clearance between Compartment 1 and 3 (L/hr)	12
	Compartment 3: Volume of distribution (L)	24
	Absorption rate constant (hr^{-1}), k_a	0.25
Model drug B	Total Body Clearance (L/hr)	43.7
Dose = 150 mg	Compartment 1: Volume of Distribution (L)	25.2
	Distribution Clearance between Compartment 1 and 2 (L/hr)	92
	Compartment 2: Volume of Distribution (L)	76.6
	Absorption rate constant (hr^{-1}), k_a	0.8
Model drug C	Non-hepatic Clearance (L/hr)	5
Dose = 100 mg	Compartment 1: Volume of distribution (L)	70
	Distribution Clearance between Compartment 1 and 2 (L/hr)	280
	Compartment 2: Volume of Distribution (L)	140
	Liver blood flow (L/hr)	81
	Fraction unbound	0.88
	Intrinsic clearance (L/hr)	112
	Absorption rate constant (hr^{-1}), k_a	3.0
Physiological parameters	Gastric emptying half-time (hr) for solid and solution	0.01–0.5
	Intestinal transit (hr^{-1})—across each compartment for solid and solution	0.9 or 1.8
Dissolution rate	T85% (time for 85% dissolution)	0.1–2.0

RESULTS

Figure 2 shows explorations on the effect of dissolution rate (T85% time) and gastric emptying rate (half-time) on the Cmax ratio (tablet/solution) for drugs with different effective permeabilities. As can be seen from the plots, comparing the different model drugs, the Cmax ratio is increasingly sensitive to dissolution rate and gastric emptying rate when comparing C to B or A. This increasing sensitivity is in order of increasing permeability. Other factors are changing for the three model drugs, however it is reasonable to hypothesize that the predominant influence is the degree of permeability. This is further tested and confirmed from the impact of changing the permeability whilst maintaining the same disposition model for each of the model drugs.

The impact of varying gastric emptying times and T85% dissolution times on the Cmax ratios of the three Model Drugs is further illustrated in Table 2. In this table, it can be seen that for an intestinal transit time of 3.33 hours, the Cmax ratio falls below the critical value of 0.8, only when that T85% dissolution time is prolonged to 1.5 and 2 hours and the gastric emptying half time is faster than 0.2 and 0.25 hour for Model Drugs A and B respectively. Model Drug C (with the highest permeability) is slightly more sensitive, with the Cmax ratio falling below the critical value of 0.8 at prolonged T85% dissolution times of 1 hour, when the gastric emptying half-time is faster than 0.2 hour. This is further illustrated in the contour plots, where the Cmax ratio is < 0.8 only when the dissolution T85% time is 0.95 hours and gastric emptying half-time is at the fast rate of 6 minutes even for the most sensitive of all three Model Drugs, i.e., C.

As the intestinal transit time becomes more rapid (1.67 hours in total), the sensitivity to T85% dissolution time and gastric emptying half-time increases, however the critical value for the Cmax ratio is still reached only at prolonged T85% dissolution times of one hour and fast gastric emptying times approaching 0.1 hour for all three models (see Table 2).

A different pattern is seen with the AUC ratio (Fig. 3); there are similar profiles in the AUC ratio vs. gastric emptying and dissolution T85% time plots between the three models. There is less dependence for the AUC ratio on the gastric emptying time and dissolution rate. The impact of varying gastric emptying times and T85% dissolution times on the AUC ratios of the three Model Drugs is further illustrated in Table 3. In this table, it can be seen that for an intestinal transit time of 3.33 hours, the AUC ratio falls below the critical value of 0.8, only when the T85% dissolution time is prolonged to 2 hours and the gastric emptying half time is faster than 0.2 hour for Model Drug A. The AUC ratios do not fall below the critical value of 0.8 for Model Drugs B and C within the range of values tested.

As the intestinal transit time becomes more rapid (1.67 hours in total), the sensitivity to T85% dissolution time and gastric emptying half-time increases, however the critical value for the AUC ratio is still reached only at prolonged T85% dissolution times of one hour and fast gastric emptying times of less than 0.2 hour for Model Drug A (see Table 3). Model Drug A with the lowest permeability of the three, now shows the greatest sensitivity in the AUC ratio to the faster intestinal transit time. The least sensitive to the faster intestinal transit time is shown by Model Drug C with the highest permeability.

Further explorations looked at theoretical drugs in which the permeability is varied (as reflected by k_a) and dissolution rate (T85% time) to see the effect on the Cmax ratio. In these explorations, the disposition model for all three model drugs

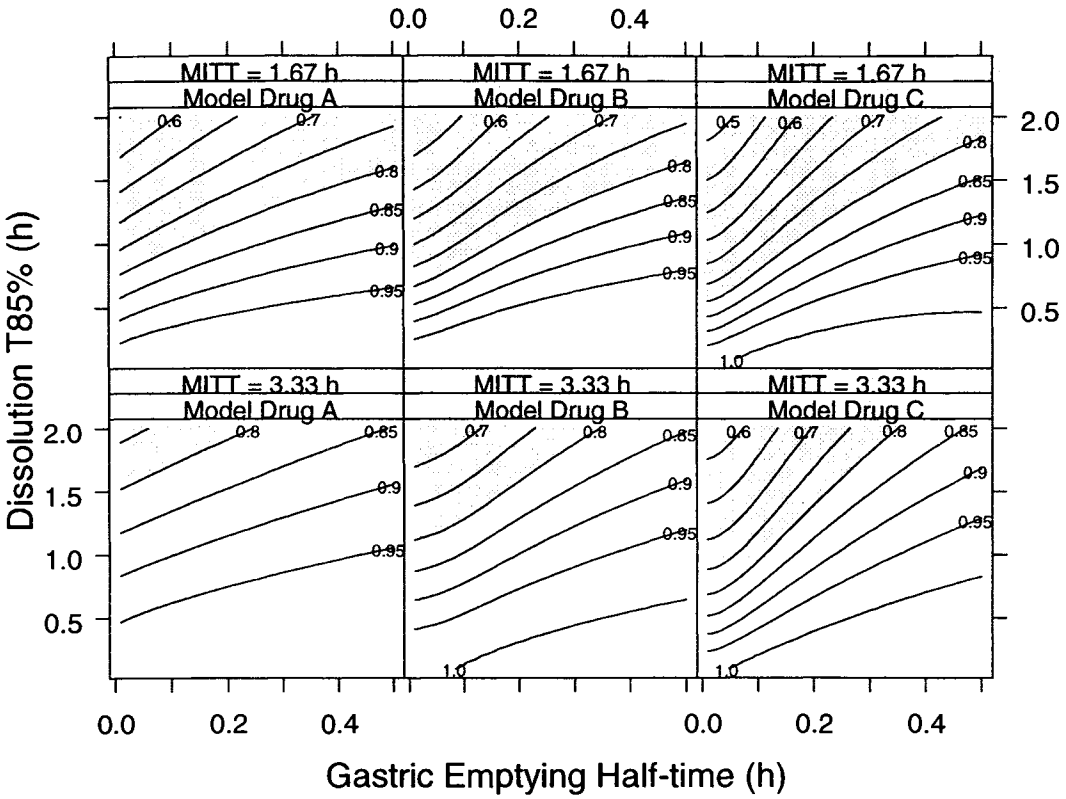

Fig. 2. Contour plots showing relationship between dissolution T85% time and gastric emptying half-time with contour lines for Cmax ratios ranging from 1.0 to 0.6 for all three Model Drugs. (The grey area shows the region falling below 0.80 Cmax ratio). The plots show Cmax ratios for the two different mean intestinal transit times (MITT) tested: 3.33 and 1.67 hours respectively.

was retained. Figure 4 illustrates that as permeability increases, the Cmax ratio becomes more dependent on dissolution T85%. However, the nearly parallel and horizontal curves for k_a greater than 3 hr^{-1}, suggests that the relationship between dissolution and the Cmax ratio is approximately independent of k_a for very highly permeable drugs. As the small intestinal transit time is reduced to 1.67 hours, there is a greater dependence on dissolution T85% time as the permeability increases. This is particularly notable where the k_a is less than 5 hr^{-1}.

Figure 5 illustrates that as permeability increases, the AUC ratio is less responsive to changes in dissolution T85% time. The AUC ratio shows values below the critical level of 0.8 when the small intestinal transit time is decreased to 1.67 hours. As the absorption rate constant is decreased to less than 3 hr^{-1}, the AUC ratio falls below the critical value at a prolonged dissolution time (T85% time) of 1.5 hour when the intestinal transit time is reduced to 1.67 hours.

DISCUSSION

The models used in the simulations were able to give insight into the impact of the gastric emptying half-time, the time for 85% dissolution of an immediate release tablet and the effective permeability on the peak plasma concentration and area-under-the-curve. The models used three compartments to represent the small intestine, essentially the physiological regions of the jejunum, duodenum and ileum. Previous authors have similarly compartmentalized the gastrointestinal tract for example, either to predict intestinal absorption (10) or to examine the occurrence of double peaks in plasma concentration-time profiles (11). The models in the present study went further by incorporating both the solid and solution components in order to investigate the effect of different dissolution times on the peak concentration of drugs and area-under-the-curve, important pharmacokinetic parameters used to determine bioequivalence.

These simulations suggest that the criterion of 85% dissolution time in 15 minutes for classifying a rapidly dissolving drug product is relatively conservative. The models assume that the *in vitro* dissolution of an immediate release dosage form is reflective of the *in vivo* dissolution. As illustrated by the tables and figures, the Cmax ratio fell below the critical value 0.8 for a T85% of greater than 1 hour for the three model drugs over a wide range of stomach emptying times and testing two different intestinal transit times. The dissolution times become less influential when addressing the impact on the AUC ratio for all three drugs and over the same range of gastric emptying times and an intestinal transit time of 3.33 hours. As the intestinal transit time was reduced to 1.67 hours, the AUC ratio fell below the critical value of 0.8 for a T85% of greater than 1 hour for the range of gastric emptying times tested. This sensitivity to T85% was greatest for the model drug with the lowest permeability suggesting that the opportunity for absorption was being influenced both by the shorter intestinal transit

Table 2. Cmax Ratios for Model Drugs A, B, and C with Varying Gastric Emptying Times and Dissolution T85% Times

	Total intestinal transit time of 3.33 hours					
	Cmax ratio for model drug A					
Dissolution T85% (hr)	0.125	0.25	0.5	1	1.5	2
0.10	0.996	0.988	0.964	0.899	0.828	0.762
0.20	0.998	0.993	0.975	0.919	0.853	0.789
GE half-time (hr) 0.25	0.998	0.994	0.979	0.927	0.864	0.801
0.30	0.999	0.995	0.981	0.935	0.874	0.813
0.40	0.999	0.996	0.986	0.946	0.892	0.834
0.50	0.999	0.997	0.989	0.955	0.906	0.852
	Cmax ratio for model drug B					
	0.125	0.25	0.5	1	1.5	2
0.10	1.000	0.995	0.957	0.854	0.762	0.685
0.20	1.001	1.002	0.984	0.901	0.813	0.736
GE half-time (hr) 0.25	1.001	1.002	0.992	0.920	0.836	0.760
0.30	1.001	1.003	0.997	0.935	0.856	0.782
0.40	1.001	1.003	1.002	0.957	0.888	0.818
0.50	1.001	1.003	1.004	0.972	0.911	0.846
	Cmax ratio for model drug C					
	0.125	0.25	0.5	1	1.5	2
0.10	1.005	0.993	0.924	0.788	0.692	0.620
0.20	1.005	1.011	0.982	0.876	0.780	0.703
GE half-time (hr) 0.25	1.004	1.011	0.997	0.907	0.816	0.740
0.30	1.003	1.011	1.005	0.931	0.847	0.772
0.40	1.002	1.008	1.013	0.964	0.892	0.823
0.50	1.001	1.006	1.014	0.983	0.923	0.860
	Total intestinal transit time of 1.67 hours					
	Cmax ratio for model drug A					
	0.125	0.25	0.5	1	1.5	2
0.10	0.991	0.970	0.914	0.790	0.682	0.596
0.20	0.996	0.985	0.948	0.847	0.748	0.663
GE half-time (hr) 0.25	0.995	0.982	0.940	0.831	0.728	0.643
0.30	0.997	0.987	0.954	0.861	0.765	0.682
0.40	0.997	0.990	0.964	0.882	0.793	0.713
0.50	0.998	0.992	0.970	0.898	0.815	0.738
	Cmax ratio for model drug B					
	0.125	0.25	0.5	1	1.5	2
0.10	0.997	0.982	0.913	0.760	0.641	0.553
0.20	1.000	0.995	0.954	0.826	0.711	0.620
GE half-time (hr) 0.25	1.000	0.997	0.965	0.850	0.738	0.648
0.30	1.000	0.998	0.973	0.868	0.761	0.672
0.40	1.000	0.999	0.982	0.896	0.798	0.711
0.50	1.000	0.999	0.987	0.915	0.824	0.741
	Cmax ratio for model drug C					
	0.125	0.25	0.5	1	1.5	2
0.10	1.003	0.985	0.901	0.738	0.622	0.538
0.20	1.004	1.005	0.962	0.829	0.715	0.625
GE half-time (hr) 0.25	1.003	1.006	0.977	0.860	0.750	0.661
0.30	1.002	1.006	0.987	0.884	0.779	0.691
0.40	1.001	1.004	0.996	0.917	0.823	0.739
0.50	1.000	1.002	0.998	0.937	0.853	0.774

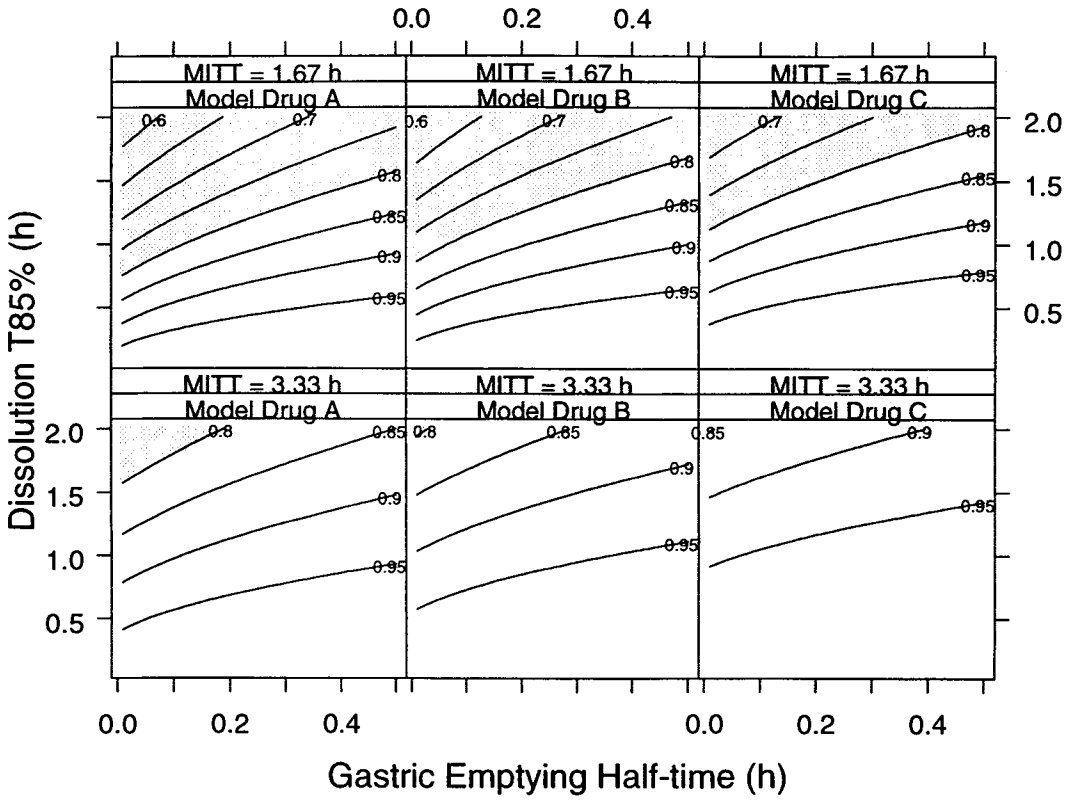

Fig. 3. Contour plots showing relationship between dissolution T85% time and gastric emptying half-time with contour lines for AUC ratios ranging from 1.0 to 0.6 for all three Model Drugs. (The grey area shows the region falling below 0.80 AUC ratio). The plots show AUC ratios for the two different mean intestinal transit times (MITT) tested: 3.33 and 1.67 hours respectively.

time and the time taken for dissolution particularly where the T85% was prolonged.

The models assume no absorption of the drug from the colon. This assumption results in simulations that overestimate the impact of decreasing the dissolution rate on the Cmax and AUC ratios compared to the situation where there is absorption from the colon. In other words, the simulations exaggerate the potential for bioinequivalence of drug products containing drugs that are absorbed in the colon.

An assumption in the models is that excipients in the formulation do not alter physiological factors such as intestinal transit time or the permeability of the drug. Koch *et al.* (13) reported a reduction in both the rate and extent of bioavailability of ranitidine when the excipient, sodium acid pyrophosphate was included both in an effervescent tablet formulation and with ranitidine as a powder. The excipient was shown to cause a decrease in the small intestinal transit time comparable to the decrease in bioavailability of ranitidine. It was assumed that the excipient was acting as an osmotic agent. If the gastrointestinal tract is thought of as a rigid system, increasing the amount of fluid in the system leads to an increase in flow rate and a decrease in the transit time. Using the model as set up for Model Drug B and incorporating the values for gastric emptying and intestinal transit times from the study by Koch *et al.*, it was found that the AUC and Cmax ratio of the solution to the tablet was about 0.7, which is much greater than a ratio of around 0.5 found by Koch *et al.* If the gastrointestinal tract is thought of as an elastic system, increasing the amount of fluid in the system leads to an increase in the volume in the gastrointestinal tract and a decrease in the absorption rate constant. (The absorption rate constant of a drug can be related inversely to the volume of fluid in the gastrointestinal tract and directly proportional to permeability (5)). By reducing the absorption constant in proportion to the reduction in transit time for Model Drug B, the resultant AUC and Cmax ratio of the solution to the tablet was closer to 0.6. This results in a change in bioavailability that is closer to the results from the study by Koch *et al.* Additional differences between the simulations and the experimental study may be due to assuming a well-stirred system, whereas influx of water from the gastrointestinal wall in the presence of an excipient with osmotic properties and the resulting increased flow rates may lead to changes in hydrodynamics that are not considered in the model.

The impact of varying the absorption rate constant on the Cmax ratio and AUC ratio was an extension of the simulations. As the absorption rate constant is increased, the influence of a slower dissolution on the Cmax ratio becomes more apparent, however the influence on the AUC ratio is much less.

The present simulations showed that the Cmax ratio is more sensitive to changes in gastric emptying and dissolution T85% time than AUC ratio as shown for three models of drugs with a range of permeabilities.

Table 3. AUC Ratios for Model Drugs A, B, and C with Varying Gastric Emptying Times and Dissolution T85% Times

	Total intestinal transit time of 3.33 hours					
	AUC ratio for model drug A					
DissolutionT85% (hr)	0.125	0.25	0.5	1	1.5	2
0.10	0.9951	0.9849	0.9581	0.8968	0.8353	0.7780
0.20	0.9971	0.9901	0.9691	0.9150	0.8573	0.8018
GE half-time (hr) 0.25	0.9976	0.9915	0.9726	0.9219	0.8662	0.8119
0.30	0.9979	0.9926	0.9754	0.9277	0.8741	0.8210
0.40	0.9984	0.9941	0.9796	0.9371	0.8873	0.8367
0.50	0.9987	0.9951	0.9826	0.9444	0.8980	0.8499
	AUC ratio for model drug B					
	0.125	0.25	0.5	1	1.5	2
0.10	0.9970	0.9903	0.9713	0.9226	0.8691	0.8165
0.20	0.9982	0.9936	0.9788	0.9363	0.8866	0.8362
GE half-time (hr) 0.25	0.9985	0.9945	0.9813	0.9415	0.8937	0.8446
0.30	0.9987	0.9952	0.9832	0.9459	0.9000	0.8521
0.40	0.9990	0.9962	0.9861	0.9529	0.9105	0.8652
0.50	0.9992	0.9969	0.9881	0.9584	0.9191	0.8761
	AUC ratio for model drug C					
	0.125	0.25	0.5	1	1.5	2
0.10	0.9990	0.9964	0.9868	0.9541	0.9111	0.8648
0.20	0.9994	0.9976	0.9903	0.9622	0.9230	0.8793
GE half-time (hr) 0.25	0.9995	0.9980	0.9914	0.9653	0.9278	0.8855
0.30	0.9996	0.9982	0.9923	0.9679	0.9321	0.8910
0.40	0.9997	0.9986	0.9936	0.9721	0.9392	0.9006
0.50	0.9997	0.9988	0.9945	0.9753	0.9450	0.9087
	Total intestinal transit time of 1.67 hours					
	AUC ratio for model drug A					
	0.125	0.25	0.5	1	1.5	2
0.10	0.9890	0.9661	0.9088	0.7922	0.6932	0.6131
0.20	0.9934	0.9777	0.9326	0.8289	0.7342	0.6546
GE half-time (hr) 0.25	0.9946	0.9810	0.9404	0.8427	0.7508	0.6722
0.30	0.9953	0.9834	0.9465	0.8545	0.7654	0.6880
0.40	0.9964	0.9868	0.9557	0.8735	0.7901	0.7155
0.50	0.9970	0.9890	0.9621	0.8880	0.8100	0.7385
	AUC ratio for model drug B					
	0.125	0.25	0.5	1	1.5	2
0.10	0.9914	0.9727	0.9229	0.8146	0.7184	0.6388
0.20	0.9949	0.9820	0.9430	0.8474	0.7561	0.6776
GE half-time (hr) 0.25	0.9957	0.9847	0.9496	0.8598	0.7714	0.6940
0.30	0.9964	0.9866	0.9548	0.8703	0.7848	0.7089
0.40	0.9972	0.9893	0.9626	0.8872	0.8075	0.7346
0.50	0.9977	0.9911	0.9681	0.9003	0.8259	0.7562
	AUC ratio for model drug C					
	0.125	0.25	0.5	1	1.5	2
0.10	0.9958	0.9849	0.9498	0.8584	0.7683	0.6898
0.20	0.9975	0.9901	0.9629	0.8834	0.7992	0.7231
GE half-time (hr) 0.25	0.9979	0.9915	0.9672	0.8929	0.8118	0.7372
0.30	0.9982	0.9926	0.9706	0.9009	0.8229	0.7499
0.40	0.9986	0.9941	0.9756	0.9139	0.8415	0.7720
0.50	0.9989	0.9951	0.9792	0.9238	0.8566	0.7905

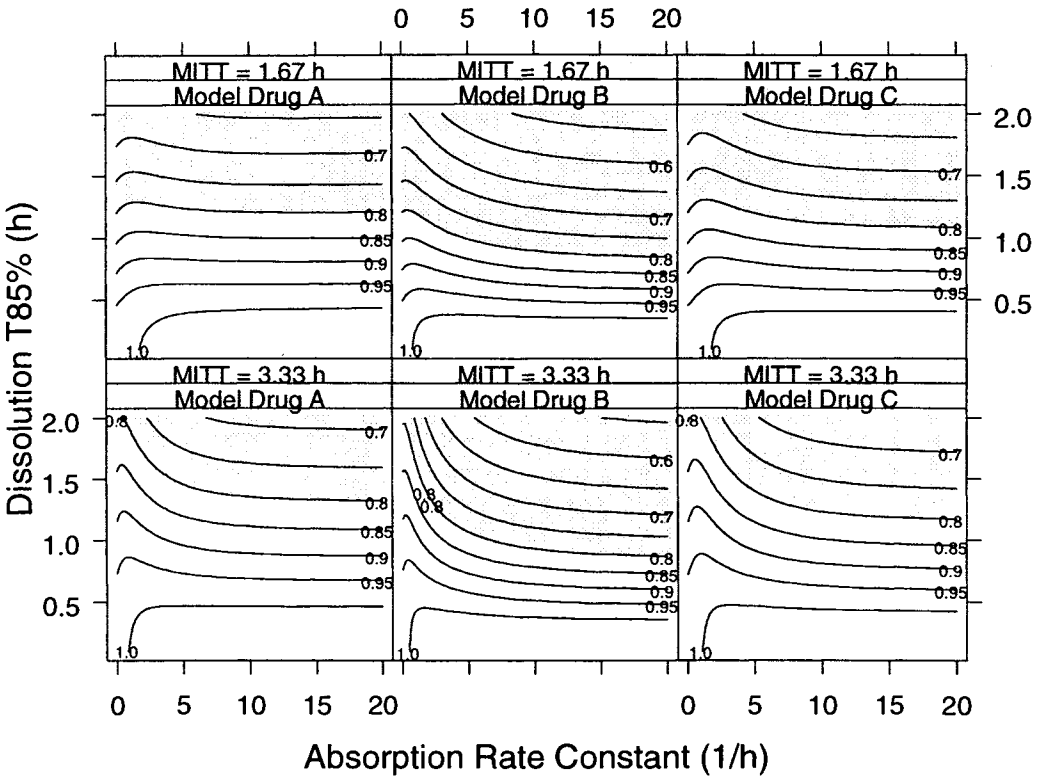

Fig. 4. Contour plots showing relationship between dissolution T85% time and absorption rate constant with contour lines for Cmax ratios ranging from 1.0 to 0.6 for all three Model Drugs. (The grey hatched area shows the region falling below 0.80 Cmax ratio). The plots show Cmax ratios for two different mean intestinal transit times (MITT) tested: 3.33 and 1.67 hours respectively.

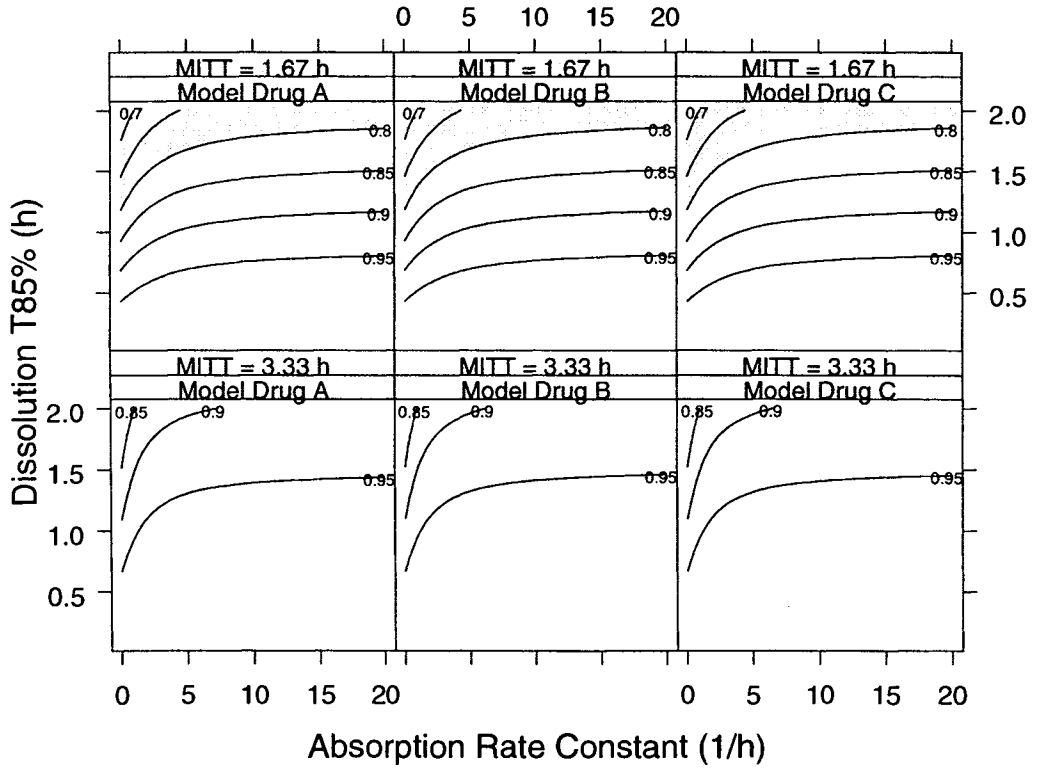

Fig. 5. Contour plots showing relationship between dissolution T85% time and absorption rate constant with contour lines for AUC ratios ranging from 1.0 to 0.6 for all three Model Drugs. (The grey area shows the region falling below 0.80 AUC ratio). The plots show AUC ratios for the two different mean intestinal transit times (MITT) tested: 3.33 and 1.67 hours respectively.

Results from the simulations indicated that the higher the permeability, the more susceptible is the Cmax ratio to changes in dissolution T85% time and gastric emptying, as shown by three model drugs classified as having high solubilities.

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