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RESEARCH PAPER

Dissolution and Absorption Modeling: Model Expansion to Simulate the Effects of Precipitation, Water Absorption, Longitudinally Changing Intestinal Permeability, and Controlled Release on Drug Absorption

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ABSTRACT

A previously described model for simulating drug dissolution, absorption, and pharmacokinetics has been expanded beyond the original application of simulating immediate-release dosage forms to include simulation of drug precipitation, water absorption from the gastrointestinal tract, changing gastrointestinal permeability, disintegration, and controlled-release and dissolution from a GITS-type dosage form. A mathematical description of the model is presented as well as a retrospective analysis of nifedipine to demonstrate the utility of the model. The fourth-order Runge-Kutta numerical method was used to solve the series of coupled differential equations used to simulate the process of dissolution, absorption, and drug disposition. The model was able to simulate the clinically demonstrated effect for drug particle size on nifedipine plasma concentrations for an immediate-release dosage form. Further simulations indicated that drug particle size was less important for a GITS-type dosage form at a release rate of 1.7 mg/hr compared to rate of 17 mg/hr. Hypothetical calculations simulated the potential effect of drug precipitation, water absorption, and changing permeability on drug plasma concentrations. The expanded model increases the utility of a previously described model in providing guidance in drug development and selection.

Key Words: Absorption; ADME; Controlled release; Dissolution; Modeling; Particle size; Permeability; Precipitation; Water absorption.

INTRODUCTION

Computer methods that predict plasma drug concentrations would be valuable tools in differentiating potential drug candidates as well as in guiding the development of commercial products. One early model provided a mechanistic approach to predict drug absorption as a function of dose,

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solubility, absorption rate constant, and drug particle size.[1] Important features included its ability to handle nonsink dissolution conditions and changing drug particle surface area to give a more realistic simulation of drug dissolution in vitro and in vivo. Subsequent research extended the model to handle polydisperse drug powders, particle size and time-dependent hydrodynamics, and nonspherical particle geometry.[2,3] When coupled with a standard pharmacokinetic model, drug plasma concentrations could be predicted if estimates of clearance and volume of distribution were available. This provided one of the earliest examples of an integrated ADME model (absorption, distribution, metabolism, and excretion) that utilized both drug physical properties and metabolic parameters to predict drug plasma concentrations. The intended utility of the approach was to provide guidance in formulation development and drug selection. Other reported applications included the study of drug particle aggregation[4] and the development of controlled-release dosage forms.[5]

The purpose of the current report is to describe several improvements in the dissolution/absorption/pharmacokinetic model discussed above that increase its scope in providing guidance in formulation development and drug selection. A retrospective analysis of some selected literature data on nifedipine is discussed to demonstrate that the model can predict the observed sensitivity of nifedipine plasma concentrations to drug particle size and to simulated plasma concentrations from a gastrointestinal therapeutic system (GITS)[6] controlled-release dosage form. Model improvements are discussed below.

The dissolution of drug particles can be tracked with respect to their release time by adding a release-time index to the appropriate variables. By varying the length of time chosen between the release of drug particles, the model will simulate immediate release, disintegration, controlled release, and multiple-dose dosing regimens. The amount of dissolved drug from all indexed particles is continuously totaled and corrected for absorbed drug. Depending on the combination of dose, solubility, absorption rate constant, and drug particle size, the dissolution of previously released drug particles can affect the dissolution of subsequently released drug particles. This occurs when dissolved drug reaches concentrations that significantly affect drug dissolution, commonly referred to as nonsink conditions. The treatment described in this report provides a mechanistically based simulation of drug dissolution and absorption from a variety of dosage forms.

Another improvement in the model allows the mass of drug particles released at any indexed time to change in either an increasing or decreasing manner. For disintegration of immediate-release dosage forms, the time interval between the release of particles would be short and the amount of particles released might be anticipated to decrease with time as the surface area of the rapidly disintegrating dosage form decreased. For a GITS push-pull osmotic pump dosage form, the mass of drug particles released from one time interval to the next would be fairly constant over most of the intended release period. This might not be true for a slowly eroding dosage form. The model described in this report would be able to handle any of the above situations.

The drug solubility term in the Noyes-Whitney expression can be made time dependent. This allows for either increasing solubility with time and a resulting increase in dissolution rate to simulate the behavior of an acidic drug as the pH increases from the stomach to the small intestine, or decreasing solubility with time to simulate the behavior of a basic drug. If the time-dependent solubility term falls below the concentration of dissolved drug, the overall sign of the Noyes-Whitney equation will reverse, and the model will simulate precipitation by transferring dissolved drug onto the remaining solid drug particles according to the Noyes-Whitney equation. Since the model does not currently simulate nucleation, precipitation will not occur on drug particles that have been calculated to be completely dissolved. This improvement in the model allows one to simulate the potential impact of precipitation, either due to a pH-dependent solubility change or the failure of an enhanced-solubility dosage form. Likewise, the effect of pH-dependent solubility enhancement on drug absorption can be simulated.

Two other model terms can also be made time dependent. By making the dissolution volume term in the Noyes-Whitney expression time dependent, water absorption or secretion can be simulated as well as the resulting effect on drug absorption. The absorption rate constant can also be made time dependent to simulate intestinal permeability changes along the length of the intestinal tract.

Nifedipine was chosen for demonstrating the ability of the model improvements to simulate its behavior for several reasons. First, nifedipine is a poorly soluble, highly permeable drug whose absorption becomes dose-limited by its solubility and is also sensitive to dissolution rate due to particle size in the clinically efficacious dose range.[7] Highly soluble drugs are less interesting to model in terms

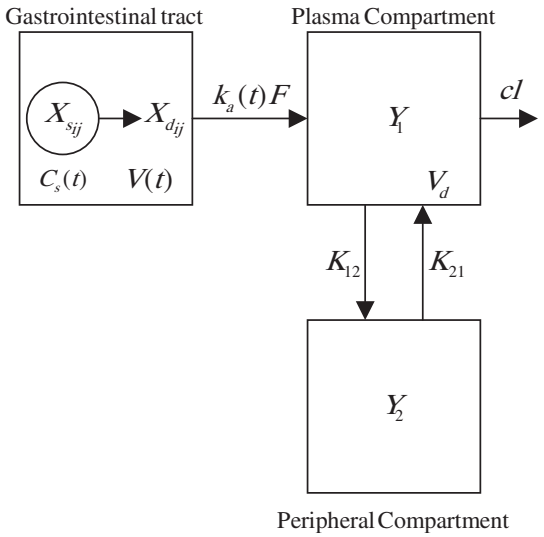

Figure 1. Schematic representation of the dissolution/absorption/pharmacokinetic model.

of dissolution, whether or not they are highly permeable, because their dissolution is rapid compared to the rate of absorption. Poorly soluble, low-permeable drugs rarely become commercial drugs, and usually would not be formulated as crystalline powders. Nifedipine has also been formulated into a controlled-release formulation[6] that releases crystalline drug particles over time that can be simulated by the expanded model.

THEORY

The general derivation of the Noyes-Whitney expression as applied to drug particles assuming spherical geometry has been discussed previously.[1,2] In the equations that follow, the subscript i refers to the particle size groups that make up the overall particle size mass distribution. Within any particle size group, all particles are the same size, but their size and mass will change as dissolution or precipitation occurs. However, their number remains unchanged unless their size becomes so small that numerical limitations are reached. At that time, their mass and number is set equal to zero. The subscript j refers to the time at which a distribution of particles is released. The time between the release of particles can vary as well as the mass associated with the index j. Figure 1 shows a schematic representation of the model, and the following series of coupled differential equations were used to simulate the process of drug dissolution, absorption, and pharmacokinetics:

$$\frac{dX_{s_{ij}}}{dt} = -\frac{3D(X_{o_{ij}}(t))^{1/3}X_{s_{ij}}^{2/3}}{\rho h_i r_{o_i}}\left(C_s(t) - \frac{X_{d_T}}{V(t)}\right) \quad (1)$$

$$\frac{dX_{d_{ij}}}{dt} = +\frac{3D(X_{o_{ij}}(t))^{1/3}X_{s_{ij}}^{2/3}}{\rho h_i r_{o_i}}\left(C_s(t) - \frac{X_{d_T}}{V(t)}\right) - k_a(t)X_{d_{ij}} \quad (2)$$

$$\frac{dX_{a_{ij}}}{dt} = k_a(t)X_{d_{ij}} \quad (3)$$

$$X_{s_T} = \sum_i^n \sum_j^t X_{s_{ij}} \quad (4)$$

$$X_{d_T} = \sum_i^n \sum_j^t X_{d_{ij}} \quad (5)$$

$$X_{a_T} = \sum_i^n \sum_j^t X_{a_{ij}} \quad (6)$$

$$\frac{dY_1}{dt} = k_a(t)FX_{d_T} - \left(\frac{cl}{V_d} + K_{12}\right)Y_1 + K_{21}Y_2 \quad (7)$$

$$\frac{dY_2}{dt} = K_{12}Y_1 - K_{21}Y_2 \quad (8)$$

where $X_{s_{ij}}$ is the mass of solid drug, $X_{d_{ij}}$ is the mass of dissolved drug, $X_{a_{ij}}$ is the mass of absorbed drug, t is time, D is the drug diffusivity, $X_{o_{ij}}(t)$ is the mass of drug released at any particular time and whose value may vary from one release index j to the next, $C_s(t)$ is the solubility of the drug whose value may vary with time, $V(t)$ is the dissolution volume whose value may vary with time, ρ is the drug density, h_i is the diffusion layer thickness, r_{o_i} is the initial drug particle size radius, $k_a(t)$ is the absorption rate constant whose value may vary with time, X_{s_T} is the summation of solid drug mass at any time from all particle size groups, X_{d_T} is the summation of dissolved drug mass at any time from all particle size groups, X_{a_T} is the summation of absorbed drug mass at any time from all particle size groups, Y_1 is the mass of drug in the central blood plasma compartment, Y_2 is the mass of drug in the peripheral compartment, F is the fraction of drug that enters the central blood plasma compartment, cl is drug clearance from the central blood plasma compartment, V_d is the volume of the central blood plasma compartment, K_{12} is the first order rate constant for drug leaving the central blood plasma

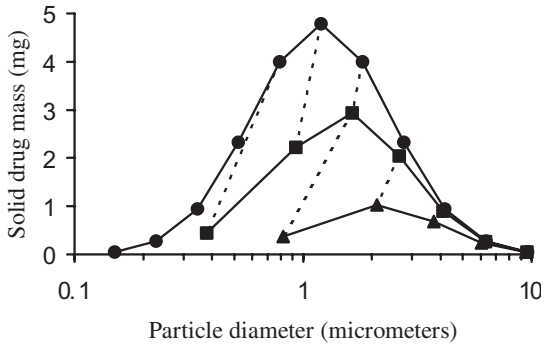

Figure 2. Simulated particle size distribution changes due to dissolution at time zero (●), at 50 min (■), and at 90 min (▲). Particles belonging to the same particle size group *i* are connected with dotted lines. Simulation parameters can be found in Table 1.

compartment into the peripheral compartment, and K_{21} is the first order rate constant for drug leaving the peripheral compartment into the central blood plasma compartment.

Figure 2 is an attempt to provide visual insight into the nature of powder dissolution by tracking the particle size distribution as a function of time. Several points are worth noting and instructive in understanding how drug dissolution was simulated. The four smallest particle size fractions are not connected to any later time particles as particles have completely dissolved by the 50 min time point. According to Eq. (1), there is no limit to how small particles may become as they dissolve, which could leave solid particles smaller than the dimensions of the molecule. The limit of the smallest number that can be used with the current software is approximately 5×10^{-324}. When particles within a given particle size group *i* reach this limit, a computer error will occur and the simulation will end unless an internal error handling routine is included. For simulations shown in this report, the error handling routine instructs the computer to set the mass of solid drug equal to zero for the offending particle size group and resumes calculations for remaining particle size groups. It should also be noted that the number of particles within a particle size group does not change with time until the mass is set equal to zero.

For the particle size groups connected by dotted lines in Fig. 2, it can be seen that dissolving particles are becoming smaller in terms of both size and mass. The particle size groups immediately to the left and right of the geometric mean contain the same mass initially. However, the particles to the left are smaller, greater in number, and have a greater surface area. As a result, it can be seen that at 50 min, the particle size group to the immediate left of the group that represented the geometric mean initially has dissolved to a greater extent than the particle size group to the immediate right of the initial geometric mean group.

All particle size groups are dissolving at a rate based on their own particular surface area at any given time. However, all particle size groups are dissolving against the same dynamic concentration gradient calculated from the sum of dissolved drug from all particle size groups.

The points covered above are also important in understanding how one might try to simulate drug precipitation due to a change in solubility. If solubility is allowed to change as a function of time, its value could fall below the total concentration of dissolved drug. If this were to happen, the overall signs of Eqs. (1) and (2) would reverse, and dissolved drug would be transferred back onto solid drug particles. However, the reverse rate may not be the mirror image of the initial dissolution rate because some of the dissolved drug has been absorbed and some of the drug particles have completely disappeared from being set equal to zero in the internal error handling routine discussed above. Because of this, it is possible that drug dissolved from smaller particle size groups will end up being transferred to different and larger particle size groups. Although no simulations in this report cover nucleation, it would be possible to define drug crystal nuclei of a certain mass distribution that could be introduced into the calculation that would increase the rate of drug precipitation by including new surface area beyond that available from existing drug particles. The nuclei could be either monodisperse or polydisperse and could be introduced at a single time point or over a period of time to simulate homogeneous or heterogeneous nucleation. Nucleation could also be trigger based on the degree of supersaturation.

METHODS

Development of Pharmacokinetic Model for Nifedipine

Blood plasma concentration data after intravenous dosing taken from Foster et al.[8] was fitted to a two-compartment pharmacokinetic model using WinNonlin® software (Pharsight Corporation,

Mountain View, CA). While holding the resulting intravenous-fitted pharmacokinetic parameters constant and using a value of 0.45 for F,[8] the blood plasma concentration data after oral dosing from the same reference was fitted by the method of least squares to determine the oral absorption rate constant. The oral dose was assumed to be in solution since the dosage form was a liquid-filled soft gelatin capsule. Parameters for all simulations contained in this report are listed in Table 1.

Simulations Showing the Effects of Dissolution, Precipitation, Water Absorption, Changing Permeability, and Controlled Release

Simulations using Eqs. (1–8) were generated numerically using the fourth-order Runge-Kutta method. For simulations involving changing solubility, dissolution volume, or absorption rate constant, a time-dependent exponential function was inserted within the framework of the numerical method:

$$Y = Y_1 e^{-(-\ln(Y_2/Y_1)/(t_2-t_1))(t-t_1)}$$

where Y is the value of solubility, dissolution volume, or absorption rate constant at any given time t, Y_1 is the respective value at the time when the exponential change begins, t_1, and Y_2 is the respective value at the end time of the exponential change, t_2. This allowed the respective values to be updated at each iterative step of the numerical simulation. Values for Y_1, Y_2, t_1, and t_2 appear in the figure captions when they are used in simulations.

Table 1. Simulation parameters.

Parameter	Value
Dose (mg)	20[a]
Solubility (mg/mL)	0.01[b]
Absorption rate constant (min^{-1})	0.07
Dissolution volume (mL)	250
Geometric mean particle size (μm)	1.5[c]
Particle size geometric standard deviation	2
Number of particle size groups	11[d]
Drug density (g/cc)	1.3
Diffusion coefficient (cm^2/min)	0.0003
Body weight (kg)	75.3[e]
Runge-Kutta step size (min)[f]	
F	0.45[e]
Plasma clearance (mL/min/kg)	4.0
Volume of distribution (mL/kg)	600
K_{12} (min^{-1})	0.028
K_{21} (min^{-1})	0.0088

[a]Except for Figs. 3, 4, and 7.
[b]From Ref. 6.
[c]Except for Figs. 6 and 7 that also include simulations using a geometric mean of 5.9 μm and Fig. 2 that uses a geometric mean of 1.2 μm.
[d]Except for Fig. 7 that uses 3 groups.
[e]From Ref. 8.
[f]0.0001 min for times < 0.1 min, 0.001 min for times < 1 min, and 0.01 for times > 1 min, except for Fig. 7 that uses a constant step size of 0.02 min.

Estimated Parameters for Simulating Dissolution

Log-normal drug particle size mass distributions used in the simulations were generated using previously described equations with an exponent of 3 on the geometric standard deviation.[9] The combination of geometric mean particle size with a geometric standard deviation of approximately 2 has been shown to simulate experimental particle size distribution over the range of mean particle sizes simulated in this report.[3,9] Crystalline powders characterized by surface area[7] were converted to particle size mass distributions of the same surface area using the aforementioned equations.

The diffusion layer thickness was set equal to the particle radius for all particles less than 30 μm in radius and equal to 30 μm for all particles with a radius greater than 30 μm. This treatment has been shown to be successful in simulating experimental dissolution data.[2]

The dissolution volume of 250 mL used in the simulations is approximately the volume of fluid that would be administered with a dosage form in a clinical setting and is also the value used in The Biopharmaceutics Classification System (BSC) Guidance issued by the U.S. Food and Drug Administration.[10]

Diffusion coefficients for drug molecules are in the approximate range of $2\text{–}4 \times 10^{-4}$ cm^2/min.[11,12] A value of 3×10^{-4} cm^2/min was selected for nifedipine simulations.

RESULTS AND DISCUSSION

Figure 3 shows the least-squares fit of the experimental intravenous nifedipine plasma concentration data[8] to a two-compartment model. The two

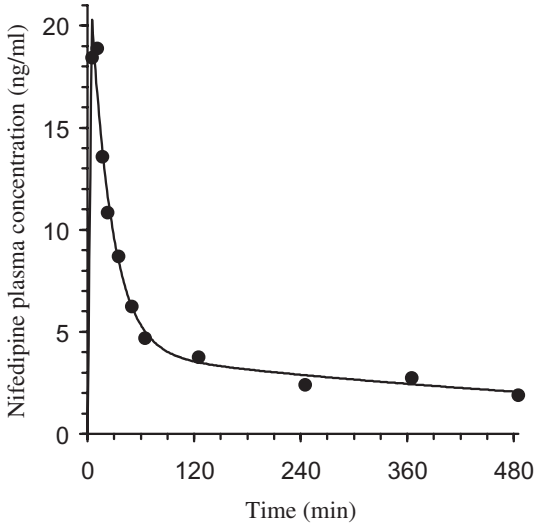

Figure 3. Nifedipine plasma concentrations after an intravenous dose of 1 mg given as an infusion over 5 min taken from Ref. 8. The data was fitted to a two-compartment model as represented by the curved line. Model parameters are reported in Table 1.

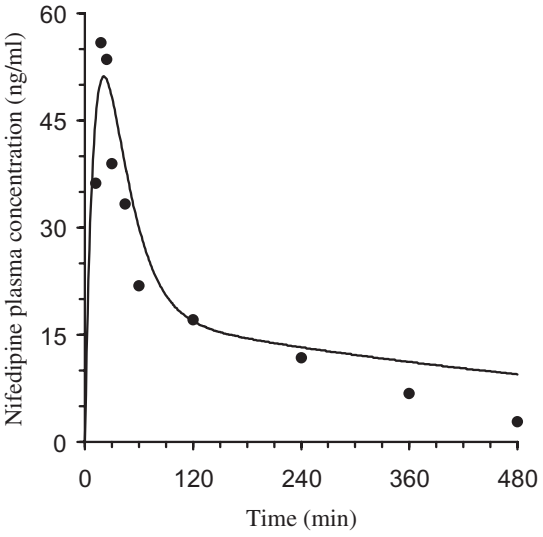

Figure 4. Nifedipine plasma concentrations after a 10 mg oral dose given as a liquid-filled soft gelatin capsule. Data was taken from Ref. 8. The solid line represents the least-squares fit of the data by varying the absorption rate constant while holding the pharmacokinetic parameters determined from the intravenous dose constant.

compartment model has been suggested by others as being appropriate.[13,14]

Figure 4 shows the least-squares fit of the experimental oral nifedipine plasma concentration data[8] assuming a first-order absorption rate constant while holding the pharmacokinetic parameters determined from the intravenous fit constant. The dose was treated as a solution and not as a crystalline powder because the dosage form used in this study was a soft gelatin capsule in which the nifedipine was dissolved in a nonaqueous vehicle.[15] The objective in analyzing the experimental data in Figs. 3 and 4 was to establish a reasonable pharmacokinetic model and an absorption rate constant that could be used in subsequent simulations involving dosage forms that were crystalline powders.

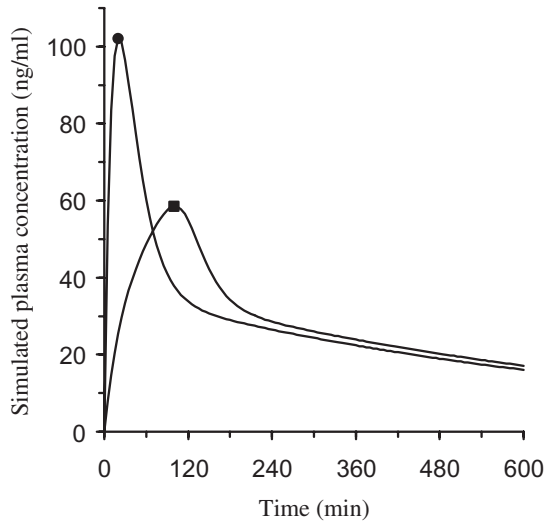

Figure 5. Simulated nifedipine plasma concentrations for a 20 mg solution dose (●, AUC = 18.4 μg min/mL) vs. a 20 mg crystalline powder dose (■, AUC = 15.4 μg min/mL) with a geometric mean particle size of 1.5 μm. Simulation parameters are listed in Table 1.

Figure 5 compares the simulated plasma concentration profiles for a solution dose of nifedipine with a crystalline powder with a geometric mean particle size of 1.5 μm. The simulations illustrate that the absorption profile of nifedipine can be affected by formulating the drug as a liquid-filled soft gelatin formulation resulting in a higher C_{max} than the same dose given as a crystalline powder.

The model was also able to simulate the effect of drug particle size on the plasma concentration profiles in the range of particle sizes demonstrated to affect actual human profiles[7] as shown in Fig. 6. The intention of the simulations is to show that the behavior of nifedipine could have been anticipated based on its physical–chemical properties and estimates of pharmacokinetic parameters in conjunction with a mechanistically based dissolution model. The discrepancy between the simulated data and actual data in

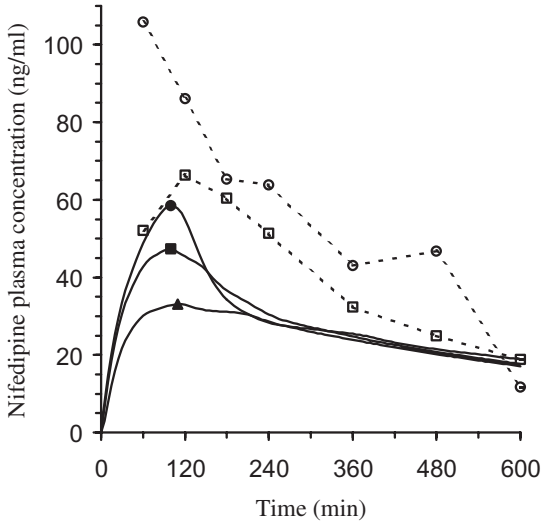

Figure 6. Actual plasma concentrations[7] for a 20 mg dose of nifedipine crystals with specific surface areas of 4 m^2/g (○) and 1 m^2/g (□) vs. simulated 20 doses with geometric mean particle sizes of 1.5 μm (●, AUC = 15.4 μg min/mL), 5.9 μm (■, AUC = 14.9 μg min/mL), and 15 μm (▲, AUC = 12.8 μg min/mL). The particle size distributions with geometric means of 1.5 and 5.9 μm have a specific surface area that approximate 4 and 1 m^2/g respectively. Simulation parameters are listed in Table 1.

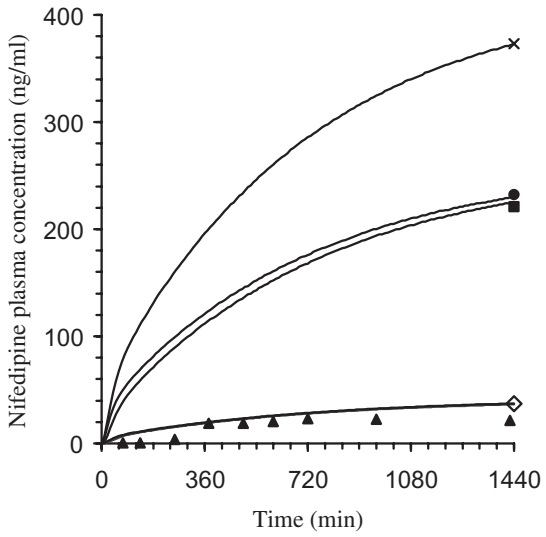

Figure 7. Nifedipine plasma concentrations simulated at a release rate of 17 mg/hr assuming the drug was released as a solution (×) or as crystalline powders with geometric means of 1.5 μm (●) or 5.9 μm (■). The lowest curve (◇) represents simulated nifedipine plasma concentrations for a release rate of 1.7 mg/hr for a solution and crystalline powders with geometric means of 1.5 and 5.9 μm: the 1.7 mg/hr simulations cannot be distinguished as they are essentially identical. Actual nifedipine plasma concentrations[14] for a GITS tablet with a nominal release rate of 1.7 mg/hr are also shown (▲). Simulation parameters are listed in Table 1.

Fig. 6 could be due to the high systematic difference in nifedipine plasma concentrations observed in separate studies using the same dose. This difference has been discussed by Hoyo-Vadillo et al.[13] In particular, Hoyo-Vadillo et al.[13] reported a C_{max} and area under the curve (AUC) for a 10 mg nifedipine capsule of 145 μg/mL and 23 μg min/mL respectively compared to a C_{max} and AUC of 73.5 μg/mL and 7.5 μg min/mL respectively, reported by Foster et al.[8] for the same dose. When comparing C_{max} and AUC, it should be remembered that Fig. 6 represents the dosing of 20 mg of crystalline nifedipine and that the studies of Hoyo-Vadillo et al.[13] and Foster et al.[8] represent the dosing of 10 mg soft gelatin capsules.

Although the simulations shown in Figs. 5 and 6 illustrate the logic in developing a liquid-filled soft gelatin capsule formulation by increasing C_{max} and eliminating the sensitivity to drug particle size, clinical experience with nifedipine has suggested that large variations between peak and trough concentrations may not be desirable.[14] The desire to flatten out nifedipine plasma concentrations and reduce the dosing frequency led to the development of the GITS controlled-release dosage form. Figure 7 shows the simulated plasma concentrations for release rates of 1.7 and 17 mg/hr, assuming the dose is released as either a solution or as a crystalline powder with a geometric mean particle size of 1.5 or 5.9 μm. Actual nifedipine plasma concentrations[14] for a GITS dosage form with a nominal release rate of 1.7 mg/hr are also shown for comparison. As shown in Fig. 7, drug particle size is less critical for a release rate of 1.7 mg/hr, as the solution, 1.5, and 5.9 μm powders are essentially identical. In this case, the simulated concentration of drug in the gastrointestinal tract never approached the solubility of nifedipine, and therefore, dissolution at this release rate did not control the rate of absorption. However, at a release rate of 17 mg/hr, the simulated concentration of drug in the gastrointestinal tract was essentially at the solubility of nifedipine. This limited the rate of absorption of crystalline powder compared to an equivalent solution dose. A slight sensitivity to particle size in the range of 1.5 and 5.9 μm was simulated.

Figure 8 shows the hypothetical effect that drug precipitation might have on plasma drug concentrations. The physical and pharmacokinetic parameters for nifedipine were used for illustrative purposes, although no applicability to nifedipine should be

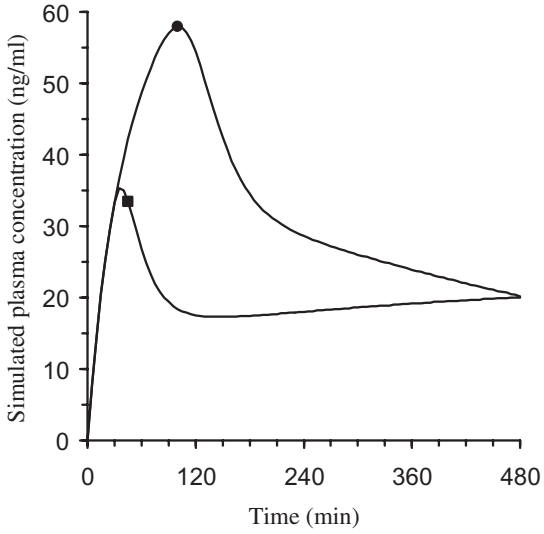

Figure 8. Simulated plasma concentrations comparing constant solubility of 0.01 mg/mL (●) to solubility changing exponentially from 0.01 mg/mL at 30 min to 0.001 mg/mL at 60 min to simulate drug precipitation (■). Simulation parameters can be found in Table 1.

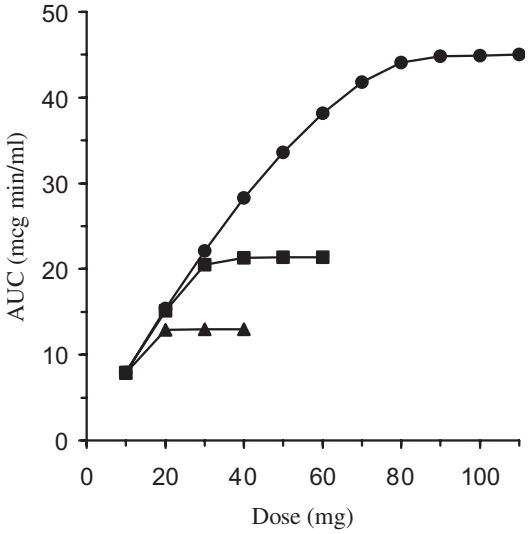

Figure 9. Simulated effect of water absorption on area under the drug plasma concentration vs. time profile for constant intestinal water volume of 250 mL (●), exponentially changing volume starting at 250 mL and ending at 25 mL at 480 min (■), and exponentially changing volume starting at 250 mL and ending at 2.5 mL at 480 min (▲). Simulation parameters can be found in Table 1.

implied since the solubility of nifedipine is not sensitive to pH changes in the gastrointestinal tract. The time-dependent solubility function can be selected to mirror the changes in pH taking place in the gastrointestinal tract or to mimic the effect of dilution on solubilized drug in a nonconventional vehicle or carrier. As the potential for precipitation is likely to increase with the degree of supersaturation, lack of dose proportionality for salts of basic drugs or solubilized drugs could be modeled in terms of precipitation to explain the observed results. The proposed method of modeling precipitation discussed in this report provides a tool for studying such precipitation that might lead to useful predictions.

Another poorly understood aspect of drug absorption is the effect of net water absorption on the absorption of drugs of low aqueous solubility. Figure 9 simulates the effect of water absorption on drug area under the curve (AUC) as a function of dose for three rates of water absorption. The simulations indicate that the maximum capacity of the gastrointestinal tract for absorbing drug is sensitive to the fluid volume residing there. The results suggest that information regarding the amount of fluid in the gastrointestinal tract can be obtained from single-dose escalation studies using a poorly soluble drug. The time-dependent fluid amount in the gastrointestinal tract could be estimated by finding a water absorption profile that is consistent with the plateau AUC. To the extent that water absorption profiles are similar from one drug to another, more accurate predictions can be made concerning the absorption of future drug candidates. Such predictions are useful in planning safety and efficacy studies to anticipate when nonconventional formulation approaches will be needed to overcome dose/solubility-limited exposure.

In a similar way that having a computational method to simulate continuously changing solubility and gastrointestinal fluid levels, the absorption rate constant can be made time dependent to simulate the effect of changing drug permeability as a function of time-dependent position in the gastrointestinal tract. Figure 10 compares plasma concentrations assuming a constant absorption rate constant to a situation where the absorption rate constant decreases with time. If regional-specific information about the absorption rate constant in the gastrointestinal tract is known, then more accurate simulations and better guidance can result.

CONCLUSIONS

Because any experiments are expensive and time-consuming to conduct, predicting outcomes

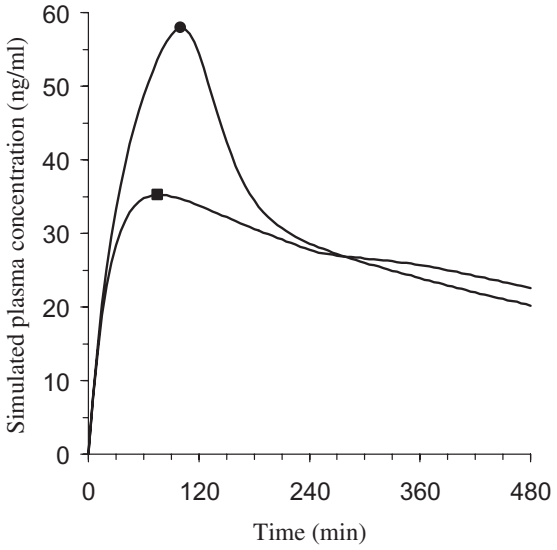

Figure 10. Simulated plasma concentrations comparing constant absorption rate constant of $0.07\,min^{-1}$ (●) to absorption rate constant changing exponentially from $0.07\,min^{-1}$ to $0.007\,min^{-1}$ at 240 min (■). Simulation parameters can be found in Table 1.

through mechanistically-based computer simulations can speed the process of drug selection and development by guiding the design of productive experiments. Using early clinical data on the i.v. and oral pharmacokinetics of nifedipine, the model described in this report was able to simulate the effect of drug particle size on nifedipine absorption from an immediate-release type dosage form. For a GITS-type controlled-release dosage form, the model simulated that drug particle size was less critical at a release rate of 1.7 mg/hr compared to a 10-fold higher release rate. If efficacious plasma concentrations can be projected, the model can simulate whether target concentrations can be achieved with an immediate-release dosage form, indicate whether drug particle size will affect absorption, and guide the selection of release rate and drug particle size for a GITS-type controlled-release dosage form. In terms of drug selection, the model can be used to gauge the degree of difficulty in developing a particular drug candidate as well as to compare it to other potential candidates.

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