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Advanced Drug Delivery Reviews 19 (1996) 359–376

advanced
drug delivery
reviews

Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption

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Abstract

For almost a half century scientists have striven to develop a theoretical model capable of predicting oral drug absorption in humans. From the pH-partition hypothesis to the compartmental absorption and transit (CAT) model, various qualitative/quantitative approaches have been proposed, revised and extended. In this review, these models are classified into three categories; quasi-equilibrium models, steady-state models and dynamic models. The quasi-equilibrium models include the pH-partition hypothesis and the absorption potential concept, the steady-state models include the film model and the mass balance approaches, and the dynamic models include the dispersion, mixing tank and CAT models. The quasi-equilibrium models generally provide a basic guideline for understanding drug absorption trends. The steady-state models can be used to estimate the fraction of dose absorbed. The dynamic models predict both the fraction of dose absorbed and the rate of drug absorption and can be related to pharmacokinetic models to evaluate plasma concentration profiles.

Keywords: pH-partition hypothesis; absorption potential concept; mass balance approach; mixing tank; dispersion model; compartmental absorption and transit model

Contents

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0169-409X/96/$32.00
PII S0169-409X(96)00009-9

1. Introduction

The absorption of drugs from the gastrointestinal tract is very complex and often not well characterized. Many factors affect the extent and rate of drug absorption. These factors can be divided into three categories [1,2]. The first category represents physicochemical factors including pK_a, solubility, stability, diffusivity, lipophilicity, salts, surface area, particle size and crystal form. The second category comprises physiological factors including gastrointestinal blood flow, gastrointestinal pH, gastric emptying, small intestinal transit time, colonic transit time and absorption mechanisms. The third category contains dosage form factors, such as solution, capsule, tablet, suspension, emulsion and gel.

However, despite this complexity, progress has been made towards estimating oral drug absorption [3–5]. The pH partition hypothesis was proposed in the '50 and '60s. Over the years it has been employed as a basic guideline for predicting drug absorption trends. However, it is an oversimplification of a very complex process and often produces inconsistencies. In the '70s, the dispersion model was proposed to theoretically investigate simultaneous drug absorption and intestinal flow. Given its complexity, the dispersion model has not been widely utilized. However, the concept extracted from the dispersion model, namely, the anatomical reserve length concept, has often been used to explain absorption phenomena. In the '80s, the mixing tank model was proposed to simulate oral drug absorption. The advantages of the mixing tank model are its simplicity and intuition.

In recent years, a mass balance approach has been developed to estimate the fraction of dose absorbed [5]. This approach has resulted in simple expressions to correlate the extent of drug absorption with membrane permeability. The mass balance approach has been further extended to include chemical and enzymatic degradation and has been used to understand variation in bioavailability for water-insoluble drugs. Nevertheless, despite its success in predicting the fraction of dose absorbed, the mass balance approach is unlikely to be able to estimate the rate of drug absorption because of its steady-state assumption. More recently, a compartmental absorption and transit (CAT) model has been proposed. Using this CAT model, we are now not only able to predict the fraction of dose absorbed, but also the rate of drug absorption. Consequently, a quantitative and mechanistic absorption model can be accurately and easily related to pharmacokinetic models and used to evaluate plasma concentration profiles.

To distinguish the differences among various models, these models are classified into three categories based on their dependence on the spatial and temporal variables. The first category is referred to as quasi-equilibrium models. Such models, including the pH-partition hypothesis and the absorption potential concept, are independent of the spatial and temporal variables. The second category is referred to as steady-state models, which include the film model and the mass balance approaches. These models are independent of the temporal variable, but dependent on the spatial variable. The third category is referred to as dynamic models. Such models, including the dispersion models, the mixing tank and the CAT model, are dependent on the temporal variable. The complexity of the models generally increases from the quasi-equilibrium models to the dynamic models. However, this does not imply that the dynamic models are the best to describe the absorption phenomena. Each model has its own strengths and weaknesses. The quasi-equilibrium models generally provide a basic guideline for understanding drug absorption trends. The steady-state models can be employed to estimate the fraction of dose absorbed. The dynamic models can be used to predict the fraction of dose absorbed and to evaluate plasma concentration profiles. This report intends to briefly review the pH-partition hypothesis and discuss recent developments in detail.

2. Quasi-equilibrium models

2.1. pH-partition hypothesis

In 1940, Jacobs [6] described the theory of non-ionic membrane permeation of organic com-

pounds in quantitative terms. The influence of pH and pK_a on the drug absorption from the gastrointestinal tract was then extensively investigated in the '50s and '60s [7–11]. These studies resulted in the development of the pH-partition hypothesis. Based on this hypothesis, ionizable compounds diffuse through biological membranes primarily in their non-ionic forms. Therefore, the absorption extent of compounds across lipid membranes depends on the degree of ionization, that is, on the pK_a of compounds and the pH of the environment at both sides of the membranes.

The pH-partition hypothesis provides a basic guideline for understanding drug absorption. While correlations between absorption rate and pK_a were found to be consistent with the pH-partition hypothesis, often deviations from this hypothesis were reported [2]. Such deviations were explained by the existence of a mucosal unstirred layer [12,13] and/or a microclimate pH [14]. Although it is unlikely for the pH-partition hypothesis to predict the effect of pH on the extent of drug absorption accurately, it will probably remain a useful tool to forecast general trends in drug absorption.

2.2. Absorption potential concept

In reviewing the pH-partition hypothesis, it is apparent that the pH-partition hypothesis is an oversimplification of a very complex process. It does not consider one of the critical physicochemical factors, solubility. To address this issue, Dressman et al. [15] developed an absorption potential concept that takes into account not only the partition coefficient, but also the solubility and dose. Using a dimensionless analysis approach, the following simple equation was proposed

$$AP = \log\left(\frac{PF_{un}}{Do}\right) \tag{1}$$

where AP is the absorption potential as a predictor of the fraction of dose absorbed, P is the partition coefficient and F_{un} is the fraction in the unionized form at pH 6.5. The incorporation of F_{un} in the absorption potential concept implies the acceptance of the pH-partition hypothesis in this concept. Do in Eq. (1) is referred to as the dimensionless dose number and is defined as the ratio of dose concentration to solubility:

$$Do = \frac{C_0}{S} = \frac{D/V_0}{S} \tag{2}$$

where S is the physiological solubility, D is the dose, and V_0 is the volume of water taken with the dose that is generally set to be 250 ml [15].

Eq. (1) establishes a qualitative relationship to the fraction of dose absorbed. The quantitative absorption potential concept was proposed by Macheras and Symillides [16]:

$$F_a = \frac{(10^{AP})^2}{(10^{AP})^2 + F_{un}(1 - F_{un})} \tag{3}$$

with constraints that $AP = 1000$ when $AP > 1000$ and that $Do = 1$ when $Do > 1$.

Several drugs covering a wide range of absorption characteristics, from poorly absorbed compounds to those with virtually complete absorption, were selected to evaluate the ability of the absorption potential concept to predict the fraction of dose absorbed [15]. The drugs varied widely in their physicochemical characteristics. It was demonstrated that the absorption potential strongly correlated with the fraction of dose absorbed. The advantage of the absorption potential concept is its simplicity. It is solely based on the physicochemical properties of drugs. The absorption potential concept provides an alternative to the pH-partition hypothesis to forecast the absorption trends and to identify the critical limiting physicochemical properties, particularly for poorly soluble drugs. However, it should be noted that the absorption potential concept is based on the empirical dimensionless analysis. With more data available, the concept may need to be refined to incorporate other absorption variables.

3. Steady-state models

3.1. Macroscopic mass balance approach

Although the pH-partition hypothesis and the absorption potential concept are useful in-

dicators of oral drug absorption, physiologically based quantitative approaches need to be developed to estimate the fraction of dose absorbed in humans. Amidon et al. [17] employed a simplified film model to correlate the extent of absorption with membrane permeability. Sinko et al. [18] extended this approach by including the effect of solubility and proposed a macroscopic mass balance approach. The macroscopic mass balance approach has been further extended to include facilitated drug absorption and degradation [19]. Since the macroscopic mass balance approach includes the results of the film model, we will focus on the macroscopic mass balance approach.

The small intestine is assumed to be a cylindrical tube with the surface area of $2\pi RL$, where R is the radius and L is the length of the tube. The stomach is assumed to be an infinite reservoir with constant output rate with respect to concentration and volume. Therefore, from mass balance, we have

$$-\frac{dM}{dt} = Q(C_0 - C_{out}) = 2\pi RP_{eff}\int_0^L C\,dz \qquad (4)$$

where M is the amount of a drug, Q is the volumetric flow rate, C_0 and C_{out} are the inlet and outlet concentrations, respectively, and P_{eff} is the effective permeability. Under the steady-state assumption, the fraction of dose absorbed, F_a, is $1 - C_{out}/C_0$. So

$$F_a = 1 - \frac{C_{out}}{C_0} = 2An\int_0^1 C^*\,dz^* \qquad (5)$$

where C^* and z^* are dimensionless variables, $C^* = C/C_0$, $z^* = z/L$. An is the dimensionless absorption number and is defined as the ratio of the mean small intestinal transit time $\langle T_{si}\rangle$ to absorption time (R/P_{eff}):

$$An = \frac{<T_{si}>}{R/P_{eff}} = \frac{\pi RLP_{eff}}{Q} \qquad (6)$$

In order to integrate Eq. (5), we have to consider three cases separately according to the solubility of a drug:

Case I: $C_0 \le S$ and $C_{out} \le S$

Case II: $C_0 > S$ and $C_{out} < S$

Case III: $C_0 > S$ and $C_{out} > S$

Since derivation for case II requires results from cases I and III, we discuss cases I and III first and then we introduce the results of case II.

3.1.1. Case I

In this case, the drug is highly soluble. Assuming the complete radial mixing model, the drug concentration profile in the intestine is

$$C^* = e^{-2Anz^*} \qquad (7)$$

By substitution of Eq. (7) into Eq. (5) and integration of the resulting equation, we have

$$F_a = 1 - e^{-2An} \qquad (8)$$

Eq. (8) shows that the absorption number, and therefore the membrane permeability, is a fundamental parameter and that other parameters such as partition coefficient and pK_a are useful guides but are not fundamental parameters. For highly soluble drugs with linear absorption kinetics, dose and dissolution have no effect on the fraction of dose absorbed. In the case of drugs that are absorbed by a carrier-mediated process, a mean permeability is estimated from a concentration-dependent permeability and then used to estimate the fraction of dose absorbed.

The effective permeability in Eq. (8) is usually obtained by perfusion studies [20–22]. Considering the potential difference between perfusion and oral pharmacokinetics studies, Chiou [23] proposed the following equation

$$F_a = 1 - e^{-2fAn} \qquad (9)$$

where f is a proportional constant reflecting the possible difference between perfusion studies and oral pharmacokinetics and its value has not yet been determined.

3.1.2. Case III

In this case, solid drug exists at both the inlet and the outlet. If we assume that dissolution is relatively faster than drug absorption across the intestinal membrane, the concentration in the solution can be assumed to be the solubility of a drug:

$$C^* = \frac{S}{C_0} = \frac{1}{Do} \tag{10}$$

By substituting Eq. (10) into Eq. (5) and integrating the resulting equation, we have

$$F_a = \frac{2An}{Do} \tag{11}$$

3.1.3. Case II

In this case, the inlet drug concentration is above the solubility level. However, since the outlet concentration of the drug is below the solubility level, there exists a point where the concentration is equal to the solubility. Therefore, the whole intestine can be divided into two regions. The first region, where solid drug exists, is equivalent to Case III. The second region, where no solid drug exists, is equivalent to Case I. The fraction of dose absorbed in the first region is

$$F_a^1 = 1 - \frac{S}{C_0} = 1 - \frac{1}{Do} \tag{12}$$

The fraction of dose absorbed in the second region is

$$F_a^2 = \frac{1}{Do}(1 - e^{-2An+Do-1}) \tag{13}$$

The total fraction of dose absorbed is

$$F_a = F_a^1 + F_a^2 = 1 - \frac{1}{Do} e^{-2An+Do-1} \tag{14}$$

Eq. (11) and Eq. (14) show that, for poorly soluble drugs, the fraction of dose absorbed not only depends upon the absorption number, but also on the dose number. The estimation of the dose number requires physiological solubility information. Since the physiological solubility in vivo is usually difficult to measure, the aqueous solubility in vitro may be used. However, this may cause significant errors due to the potential differences between the in vivo and the in vitro estimations.

The mass balance approach has been used to correlate the fraction of dose absorbed and the rat intestinal permeability for nineteen drugs covering a wide range of physicochemical properties [24]. A good correlation was found by the macroscopic mass balance or film model. Since these drugs include acidic, basic and zwitterionic compounds, a simple relationship between absorption and partition coefficient is not expected. Furthermore, some of these drugs involve the facilitated drug absorption mechanism. They certainly will not follow the pH-partition hypothesis and the absorption potential concept.

More recently, Stewart et al. [25] measured intestinal permeabilities for a series of drugs using the rat in situ single-pass rat intestinal perfusion system, the rat everted intestinal ring uptake method and using monolayers of a human colon adenocarcinoma cell line (CACO-2). The fraction of dose absorbed ranged from 5% for D-mannitol to 100% for L-phenylalanine (at low concentration) and phenytoin. They confirmed the close agreement in the correlation between the fraction of dose absorbed and permeability, regardless of which of the three methods was used to determine the latter.

The mass balance approach was also applied to amoxicillin data. Amoxicillin is a broad spectrum, bacterial antibiotic administered orally for the treatment of various gram-positive and gram-negative infections. The dose ranged from 250 to 3000 mg with 200 ml of water. The corresponding dose concentration varied from 1.25 to 15 mg/ml. The low solubility (6 mg/ml) and non-passive absorption mechanism make estimation/prediction of absorption more difficult. However, Eq. (8) and Eq. (11) and Eq. (14) were able to predict the fraction of dose absorbed very well for doses from 250 to 4000 mg.

Sinko et al. [19] extended the macroscopic mass balance approach to include chemical and enzymatic degradation, where only highly soluble drugs were taken into account. Considering the effect of degradation, the total loss in the intestinal tube is due to absorption and degradation, therefore

$$F_{tot} = F_a + F_d = (2An + Da)\int_0^1 C^* \, dz^* \tag{15}$$

where F_d is the fraction of dose degraded and Da is the dimensionless Damkohler number defined as

$$Da = K_d \langle T_{si} \rangle \tag{16}$$

where K_d is the first-order degradation constant.

In the case of the complete radial mixing model, the drug concentration profile is

$$C^* = e^{(-2An + Da)z^*} \tag{17}$$

Therefore,

$$F_{tot} = 1 - e^{-(2An + Da)} \tag{18}$$

The fractions of dose absorbed and degraded are

$$F_a = \frac{2An}{2An + Da}(1 - e^{-(2An + Da)}) \tag{19}$$

$$F_d = \frac{Da}{2An + Da}(1 - e^{-(2An + Da)}) \tag{20}$$

Eq. (19) and Eq. (20) have been used to estimate the oral absorption of cefaclor, cefatrizine and insulin. The simulated results compare favorably to the reported literature values in humans. The macroscopic mass balance approach provides a quick approximation to the fraction of dose absorbed and degraded for both passively and non-passively absorbed drugs.

3.2. Microscopic mass balance approach

Sinko et al. [18] also used the microscopic approach to predict the fraction of dose absorbed for highly soluble drugs. The results from the microscopic approach are similar to those from the macroscopic approach. The macroscopic approach, therefore, is recommended for such a purpose, due to its simplicity. However, in a case where the dissolution is important, we may have to use the microscopic approach. Oh et al. [26] employed a microscopic mass balance approach to develop a mathematical model to estimate the fraction of dose absorbed from the suspensions of poorly soluble drugs. Again, the steady-state is assumed. Considering drug absorption from a cylinder tube, we have the following equation to describe the rate of change for the particle radius:

$$\frac{dr_p}{dz} = -\frac{D_i \pi R^2}{Q\rho} \cdot \frac{(S - C)}{r_p} \tag{21}$$

From mass balance for the solution phase, we have

$$\frac{dC}{dz} = \frac{4\pi^2 R^2 D_i \left(\frac{N_0}{V_0}\right)}{Q} r_p (S - C) - \frac{2\pi R P_{eff}}{Q} C \tag{22}$$

where r_p is the radius of particle, ρ is the density of particle, N_0/V_0 is the particle number density, and D_i is the diffusion coefficient. Although it has not been pointed out by the authors, Eq. (21) and Eq. (22) imply that the volume of particles is negligible when compared to the volume of the solution phase. This is usually true in most cases. Let

$$z^* = \frac{z}{L}, \quad r^* = \frac{r_p}{r_0}, \quad C^* = \frac{C}{S} \tag{23}$$

Eq. (21) and Eq. (22) become

$$\frac{dr^*}{dz^*} = -\frac{Dn}{3} \cdot \frac{1 - C^*}{r^*} \tag{24}$$

$$\frac{dC^*}{dz^*} = Dn.Do.r^*(1 - C) - 2AnC^* \tag{25}$$

where dose number Do and absorption number An have been defined by Eq. (2) and Eq. (6), respectively. Dn is the dimensionless dissolution number and is defined as the ratio of dissolution rate to flow rate:

$$Dn = \frac{(3D_i S/\rho r_0^2)(\pi R^2 L)}{Q} \tag{26}$$

Eq. (24) and Eq. (25) show that the dissolution number will also influence the drug absorption in addition to the absorption and dose numbers. Assuming that the initial amount of drug in solution is insignificant compared to the amount of solid drug, the fraction of dose absorbed can be estimated by

$$F_a = 1 - ((r^*)_{z^*=1})^3 - \left(\frac{C^*}{Do}\right)_{z^*=1} \tag{27}$$

Eq. (27) is valid only for monodisperse drugs. In the case of polydisperse drugs, the overall fraction of dose absorbed may be estimated based on the particle size distribution [27].

Fig. 1 gives a typical profile of the fraction of dose absorbed as a function of the dissolution number and the dose number for highly perme-

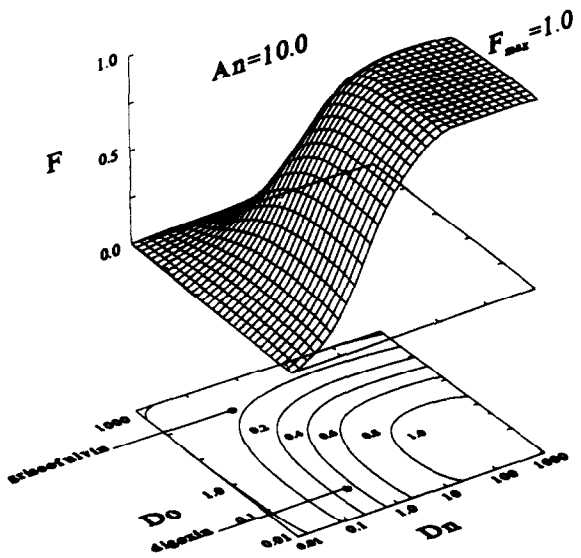

Fig. 1. Estimated fraction of dose absorbed vs dissolution number, *Dn*, and dose number, *Do*, for a high permeability drug. $An = 10$ corresponds to a drug with a permeability approximately that of glucose. *Dn* and *Do* for digoxin and griseofulvin were calculated from Eq. (26) and Eq. (2) and the following physicochemical/physiological parameters (from [5])

Drugs	S (mg/ml)	ρ (gm/ml)	D (mg)	V_0 (ml)	r_0 (μm)	D_i (cm^2/sec)
digoxin	0.024	1200	0.5	250	25	5×10^{-6}
griseofulvin	0.015	1200	500	250	25	5×10^{-6}

able (large absorption number) drugs. It shows that the fraction of dose absorbed sharply depends upon the dose and dissolution numbers when they are in critical ranges around one, for highly permeable drugs. Fig. 1 also shows the experimental results of griseofulvin and digoxin for further illustration of the significance of the dose and solubility of a drug. Griseofulvin and digoxin have similar solubilities, 15 and 24 mg/ml, respectively. Based on the solubility data, it can be assumed that both compounds should be equally absorbed. However, from the dose number of two compounds (133 for griseofulvin and 0.08 for digoxin), the fraction of a dose of digoxin that is absorbed is expected to be much greater than that of griseofulvin, as shown in Fig. 1. In fact, an increase in the dissolution number via micronization for digoxin causes it to be completely absorbed [28]. The relative bioavailability of griseofulvin can be improved by a factor of 1.7 via micronization, suggesting that incomplete absorption is due to its large dose number [29], where, unlike at low dose numbers, the dissolution number weakly influences the fraction of dose absorbed. It should be noted that the solubility and initial drug concentration, and therefore, the dissolution and dose numbers, are difficult to estimate precisely in vivo, due to physiological and physicochemical factors, such as aggregation and the unknown extent of solubilization. The actual absorption of a drug can only be estimated to be within a range. However, such analysis allows us to make comparisons between delivery systems and dosage forms for the same drug.

The above theoretical analysis of drug dissolution and absorption in the human gastrointestinal tract indicates that, for water-insoluble drugs, two independent variables will control drug absorption; dissolution number, *Dn* and dose number, *Do*. The variabilities in gastric and intestinal luminal contents, i.e. gastric emptying and intestinal transit rates, intestinal permeability characteristics of drugs in patients, as well as the solubility and dissolution characteristics of drugs are included in *Dn* and *Do*. Crison and Amidon [31,32] extended the microscopic mass balance approach to include intestinal transit rate variability and particle size distribution effects for predicted the expected variability in absorption of water-insoluble drugs. It is important to consider the variability due to intestinal transit time, since it is the expected that in vivo variability, even if a dosage form's dissolution characteristics are perfectly reproducible, sets a lower limit to the expected variance in bioequivalence studies for this class of drugs. For passively absorbed drugs, the effective permeability is given by the following equation; $P_{eff} = P_{aq}P_w/(P_{aq}+P_w)$. Due to the lipophilic properties of water-insoluble drugs, it is expected that transport across a lipid membrane will be fast. Therefore, when $P_w >> P_{aq}$, $P_{eff} = P_{aq}$. Based on the human intestinal permeability of glucose, an estimate of the upper limit of P_{eff} is 1×10^{-3} cm/s [32]. The mean residence time of pharmaceutical dosage forms in the small intestine is about 3 h and for the large intestine is about 30 h [33,34]. Examples of

absorption number for the small and large intestine calculated from these values are;

$An = P_{eff}\langle T_{si}\rangle / R = 10.8$ (Small Intestine)

$= 108$ (Whole Intestine)

The variability of the transit times of the small and large intestine are 3.2 ± 1.3 and 32 ± 18 h, respectively [33,34]. Therefore, the absorption number can vary significantly due to transit time variability alone, since An is directly proportional to the intestinal transit time. For example, in the small intestine, assuming $P_{eff} = 1 \times 10^{-3}$ cm/s, An could vary by up to 50%. Fig. 2 and Fig. 3 illustrate the expected variability in absorption due to transit time variability for griseofulvin and digoxin [30].

A second source of variability in the absorption of water-insoluble drugs is due to the variability of the particle size distribution [31]. Since the particle size of a milled drug is typically log normally distributed, the overall dissolution rate, and hence the extent of absorption, of the entire particle range is significantly effected by the spread of the distribution. This variability was included in the microscopic mass balance approach in the dissolution number which is inversely proportional to the square of the particle size; $Dn \propto 1/r_0^2$. For example, assuming a 200 mg dose of drug with aqueous solubility of 0.26 mg/ml, the fraction of dose absorbed (estimated for a monodispersed particle distribution) is 0.64 compared to 0.34 and 0.14 for distributions with the same mean particle size but geometric standard deviations of 1.5 and 2.0, respectively.

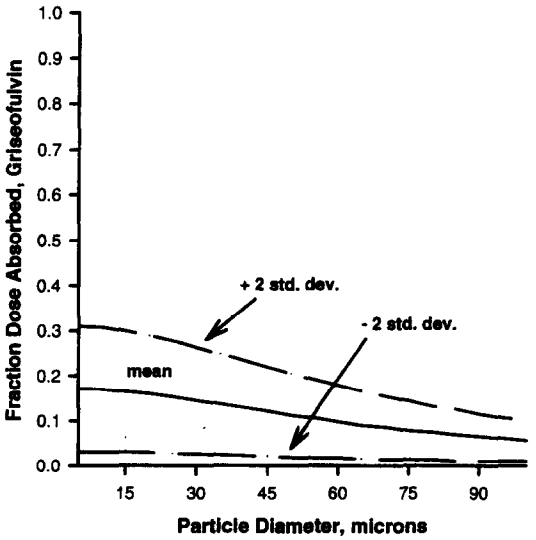

Fig. 2. Expected variability in fraction of dose absorbed due to small intestinal transit time variability (3.2 ± 1.3 h) for griseofulvin.

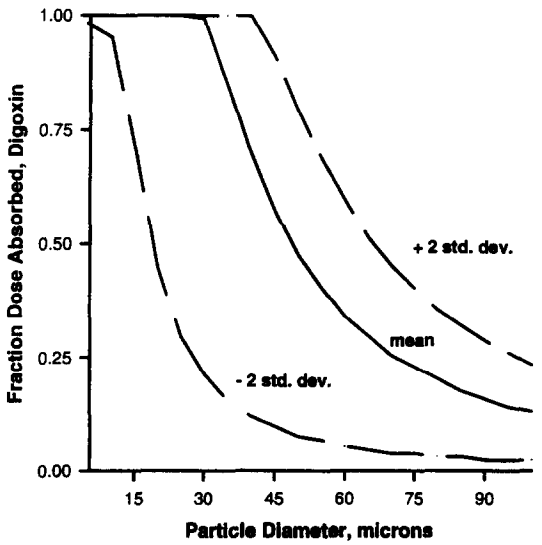

Fig. 3. Expected variability in fraction of dose absorbed due to small intestinal transit time variability (3.2 ± 1.3 h) for digoxin.

4. Dynamic models

4.1. Dispersion models

The dispersion model approach was first proposed to simulate dynamic absorption processes [35]. The dispersion model assumes that the small intestine can be considered as a uniform tube with constant axial velocity, constant dispersion behavior and a constant concentration profile across the tube diameter. Then, the absorption of highly soluble drugs in the small intestine can be delineated by the following dispersion model equation:

$$\frac{\partial C}{\partial t} = \alpha \frac{\partial^2 C}{\partial z^2} - v \frac{\partial C}{\partial z} - K_a C \qquad (28)$$

where C is the concentration of a drug, z is the axial distance from the stomach, K_a is the absorption rate constant, v is the velocity in the axial direction, and α is the longitudinal coefficient that accounts for mixing by both molecular diffusion and physiological effect, such as membrane surface solute binding, peristaltic and villous activities, and multi-S course of the small intestine [3]. Eq. (28) generally has to be solved numerically [36,37]. However, in some cases, analytical solutions may be possible. The initial condition for Eq. (28) is

$$\text{I.C.}, t = 0, \text{all } z, C = 0 \tag{29}$$

Two boundary conditions are required to solve Eq. (28). One boundary condition is obtained by assuming that the concentration of the drug is zero at infinite distance:

$$z = \infty, \quad \text{all } t, \quad C = 0 \tag{30}$$

Another boundary condition is at $z = 0$. While gastric emptying is with respect to volume, the boundary condition is with respect to concentration. Therefore, we have to transform volume into concentration. Unfortunately, a reasonable way to accomplish this transformation has not yet been established. Consequently, various conditions were used in the literature [3]. This results in correspondingly various analytical solutions. If, assuming that the stomach can be considered as an infinite reservoir with constant output rate with respect to concentration and volume, we have

$$z = 0, \quad \text{all } t, \quad C = C_0 \tag{31}$$

then the analytical solution is

$$\frac{C}{C_0} = \frac{e^{vz/2\alpha}}{2}\left(e^{-z\sqrt{\xi}/\alpha}\, erfc\left[\frac{z}{\sqrt{4\alpha t}} - \sqrt{\xi}t\right] + e^{z\sqrt{\xi}/\alpha}\, erfc\left[\frac{z}{\sqrt{4\alpha t}} + \sqrt{\xi}t\right]\right) \tag{32}$$

where

$$\xi = \frac{v^2}{4\alpha} + K_a \tag{33}$$

Obviously, even in the most simplified situation, the analytical solution is still very complex. The accurate calculation of Eq. (32) requires skillful numerical techniques because it involves the product of an infinite and a value close to zero.

Given its complexity, the dispersion model has not been widely used despite the fact that it provides a potential framework for oral drug absorption. However, a concept extracted from the dispersion model, i.e., the anatomical reserve length, has been used instead to explain absorption phenomena [38,39]. The reserve length for absorption is defined as the length of the intestine remaining after absorption is complete. If absorption from the stomach and colon is minor compared to that from the small intestine, the maximum reserve length is then the length of the small intestine. Thus, the reserve length is longer when absorption is efficient and, correspondingly, shorter for less efficient absorption. Mathematically, this can be represented by

$$RL = L - l \tag{34}$$

where RL is the anatomical reserve length, L is the small intestinal length, and l is the intestinal length at which absorption is complete.

When $l < L$, the reserve length is positive and absorption is complete within the small intestine. When $l > L$, the reserve length is negative and absorption is incomplete within the small intestine. If the fraction of dose absorbed above 95% is defined as the complete absorption, then l can be estimated by [38,39]

$$l = \frac{3Rv}{2P_{eff}} - \frac{3\alpha}{v} \tag{35}$$

and, in turn,

$$RL = L - \frac{3Rv}{2P_{eff}} - \frac{3\alpha}{v} \tag{36}$$

where R is the radius of the small intestine and P_{eff} is the effective membrane permeability. The third term in Eq. (36) is relatively small and Eq. (36) can be simplified into

$$RL = L - \frac{3Rv}{2P_{eff}} \tag{37}$$

R and v in Eq. (37) are physiologically related parameters and the reserve length depends on the effective permeability only. Essentially, the reserve length concept is equivalent to the

macroscopic mass balance approach. The reserve length concept provides qualitative information, while the macroscopic mass balance approach provides quantitative information.

4.2. Mixing tank model

The mixing tank model has been developed and utilized to simulate oral absorption phenomena [40]. This approach considers the gastrointestinal tract as one or more serial mixing tanks with linear transfer kinetics. Each tank is well mixed and has a uniform concentration. Dressman et al. [41,42] treated the gastrointestinal tract as one or two mixing tanks to investigate dose-dependent and dissolution rate control drug absorption. Hintz and Johnson [43] extended the approach of Dressman et al. [41,42] to include polydisperse drugs, in order to show the effect of particle size distribution on dissolution and absorption. Oberle and Amidon [44] employed four mixing tanks to explain plasma level double peak phenomena. Leesman et al. [45] proposed a physiological flow model and have demonstrated its utilization in the design and evaluation of dosage form. Recently, Luner and Amidon [46] employed a four mixing tank model to study the effect of bile sequestrants on bile salt excretion.

A single mixing tank model is reviewed here for illustration. The single mixing tank model was originally proposed by Dressman et al. [41] to investigate dissolution-controlled drug absorption. However, here we consider soluble drugs only. The rate of change in the mixing tank is

$$\frac{dM}{dt} = -\left(K_a + \frac{Q}{V_0}\right)M \tag{38}$$

The rate of drug absorption is

$$\frac{dA}{dt} = K_a M \tag{39}$$

where M is the amount of drug in the small intestine, A is the amount of drug absorbed, t is time, Q is flow-rate, V is the volume of the mixing tank and K_a is the absorption rate constant. Defining $Y = M/D$ and $Y_a = A/D$ and solving Eq. (38) and Eq. (39) yields

$$Y = e^{-(K_a + Q/V_0)t} \tag{40}$$

$$Y_a = \frac{K_a}{K_a + Q/Vo}\left(1 - e^{-(K_a + Q/Vo)t}\right) \tag{41}$$

The fraction of dose absorbed is then given by

$$F_a = \underset{t\to\infty}{Y_a} = \frac{K_a}{K_a + Q/Vo} \tag{42}$$

The absorption rate constant, K_a, can be estimated from the effective permeability

$$K_a = \frac{2P_{eff}}{R} \tag{43}$$

Rewriting Eq. (42) in terms of the absorption number according to Eq. (6) results in

$$F_a = \frac{2An}{1 + 2An} \tag{44}$$

Note that we define the fraction of dose absorbed as the upper limit of the percentage of dose absorbed. Therefore, the percentage of dose absorbed changes with time, but the fraction of the dose absorbed does not.

The advantage of the mixing tank model approach is its relative simplicity, intuition and easy correlation with pharmacokinetic models. However, there is no physical basis for assuming that one physiological segment of the small intestine can be considered as one or more serial mixing tanks, although such an assumption has been commonly and successfully utilized in physical and biological sciences.

4.3. Compartmental absorption and transit model

As reviewed in the previous section, different numbers of mixing tanks have been used to simulate and explain oral drug absorption in various publications. Obviously, the number of mixing tanks will affect the simulated results. Therefore, there is a need to define how many mixing tanks are most appropriate to characterize the flow and absorption process in the human small intestine. A mathematical model was developed in such a way that it best describes the transit flow of a drug in the human small intestine [47]. To emphasize the importance of the transit, the model was named compartmental transit and absorption (CAT). The CAT model

has been successfully utilized to estimate oral drug absorption and to evaluate oral plasma concentration profiles [48].

4.3.1. Compartmental transit model

The process of drug passing through the small intestine was viewed as flow through a series of segments. Each segment can be described as a single compartment with linear transfer kinetics. All compartments may have different volumes and flow-rates, but have the same transit rate constant K_t. It is assumed that a drug is neither absorbable nor degradable (absorption will be discussed in the Section 4.3). Therefore, the small intestinal transit flow can be depicted by

$$\frac{dY_n}{dt} = K_t Y_{n-1} - K_t Y_n, \quad n = 1, 2, \ldots, N \qquad (45)$$

where Y_n is the percent of dose at the nth compartment and N is the number of total compartments. The rate of the percent of dose exiting the small intestine or entering the colon is

$$\frac{dY_c}{dt} = K_t Y_n \qquad (46)$$

where Y_c is the percent of dose entering the colon. Coupling with Eq. (45), the analytical solution of Eq. (46) is

$$Y_c = 1 - \sum_{n=1}^{N} \frac{(K_t^* t)^{n-1}}{(n-1)!} e^{-K_t^* t} \qquad (47)$$

According to the definition, the transit rate constant, K_t, is

$$K_t = \frac{N}{< T_{si} >} \qquad (48)$$

In order to determine the optimal number of compartments, a total of over 400 human small intestinal transit time data were utilized. These data were collected and compiled from various publications, since the small intestinal transit time is independent of dosage forms, gender, age, body weight and the presence of food [33,49]. The data set was then analyzed by arranging these data into fourteen classes, each with a width of 40 min. Fig. 4 shows the small intestinal transit time cumulative distribution. Assuming the distribution of this data set is typical for the transit of a pharmaceutical dosage form through a human small intestine, the cumulative distribution of the small intestinal transit time represents the percentage of the drug that has entered the colon.

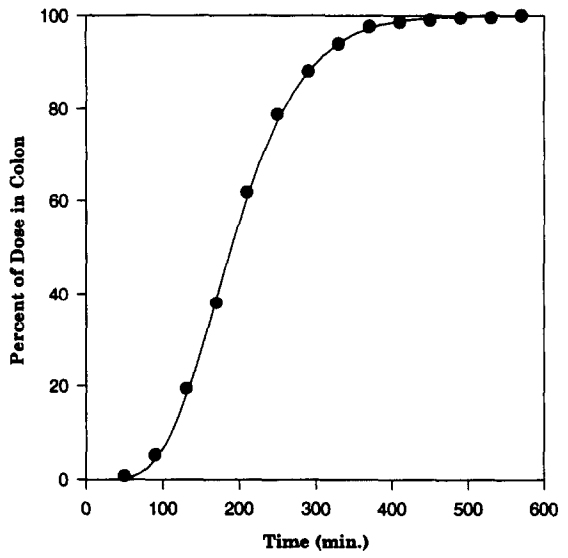

Fig. 4. Predicting human small intestinal transit flow by compartmental absorption and transit model, where (——) represents the compartmental absorption and transit model and (●) represents the cumulative percent of small intestine transit time.

The descriptive statistics showed that the mean small intestinal transit time was 199 min with a 95% confidence interval of 7 min. Based on this mean small intestinal transit time, the rate constant K_t was calculated by Eq. (48) and was used to predict the percent of dose in colon by Eq. (47). Different numbers of compartments were evaluated and it was found that seven compartments gave the smallest sums of the square of the errors (SSE) between the cumulative percentage of the small intestinal transit time and the predicted results. Therefore, seven compartments were determined to be the best compartmental model to depict the small intestinal transit process. The seven compartment model was referred to as the compartmental transit model thereafter.

The seven compartment transit model may also be physiologically sound. We may visualize that the first half of the first compartment represents the duodenum, the second half of the first compartment, along with the second and third

compartments, the jejunum, and the rest of the compartments, the ileum. The corresponding transit times in the duodenum, jejunum, and ileum are 14, 71 and 114 min, respectively. Considering the volumes and flow-rates in these three segments [50,51], such an assignment sounds reasonable.

4.3.2. Compartmental absorption model

The CAT model was proposed based on the transit model. The assumptions for the CAT model include minor absorption from the stomach and colon, linear small intestinal absorption and instantaneous dissolution. Therefore, for non-degradable and highly soluble drugs dosed in conventional dosage forms, the absorption and transit in the gastrointestinal tract can be depicted as follows:

$$\frac{dY_n}{dt} = K_t Y_{n-1} - K_t Y_n - K_a Y_n, \quad n = 1, 2, \ldots, 7 \tag{49}$$

The rate of drug absorption from the small intestine into the plasma is

$$\frac{dY_a}{dt} = K_a \sum_{n=1}^{7} Y_n \tag{50}$$

The fraction of dose absorbed, F_a, can be calculated by

$$F_a = K_a \int_0^{\infty} \sum_{n=1}^{7} Y_n \, dt \tag{51}$$

Coupling with Eq. (49) and Eq. (50), the analytical solution of Eq. (51) is

$$F_a = 1 - \frac{K_t^7}{(K_t + K_a)^7} \tag{52}$$

From Eq. (43) and Eq. (48), where N is equal to 7, we have

$$\frac{K_a}{K_t} = \frac{2P_{eff} < T_{si} >}{7R} = 0.29An \tag{53}$$

Substitution of Eq. (53) into Eq. (52) results in

$$F_a = 1 - (1 + 0.29An)^{-7} \tag{54}$$

Fig. 5 shows the correlation between the fraction of dose absorbed and the effective human intestinal permeability. The solid line represents the estimated curve from the CAT model and the symbols show the experimental data, respectively. Fig. 5 also shows the predicted fraction of dose absorbed as a function of the absorption number, by the mass balance approach and the single mixing tank. It can be seen from Fig. 5 that the single mixing tank gives underestimates of the fraction of dose absorbed, whereas the complete radial mixing model and the CAT model give a much closer fit to the data. The single mixing tank model assumes that the drug would leave the small intestine and enter the colon when $t>0$, contradicting the fact that none of the drug would leave the small intestine and enter the colon in the period of 0 to 30 min [47]. Consequently, the fraction of dose absorbed is underestimated.

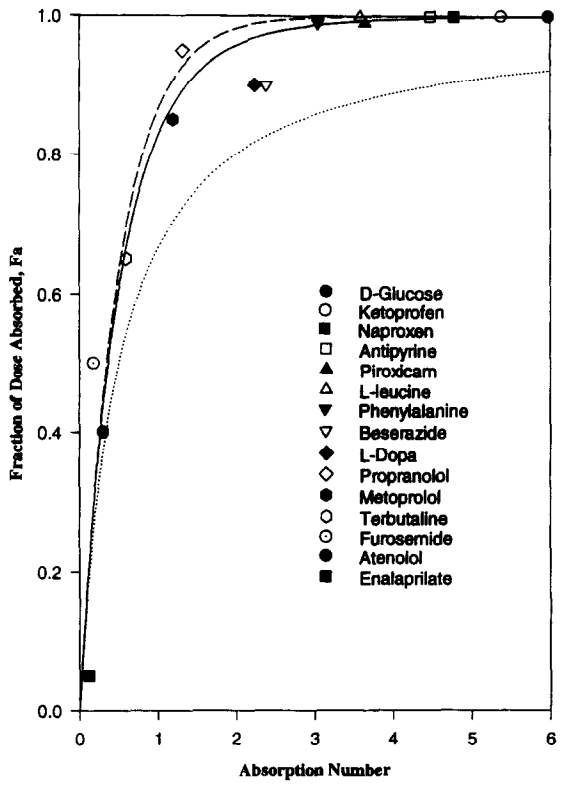

Fig. 5. The fraction of dose absorbed as a function of absorption number An, where (———) represents the compartmental absorption and transit model, (· · ·) the single mixing tank model, and (– – –) the complete radial mixing model and symbols represent experimental points.

In contrast, the complete radial mixing model assumes that the drug will not leave the small intestine and enter the colon until the mean small intestinal transit time has been reached. This is also contradicted by the fact that the drug could leave the small intestine and enter the colon in as short a time as 30 min, through rapid longitudinal dispersion [47]. However, since the effect of rapid longitudinal dispersion has been shown to be negligible in the estimation of the anatomical reserve length [39], it is not surprising that the complete radial mixing model gives a similar estimate of the fraction of dose absorbed to that of the CAT model. In addition, unlike the CAT model, since the mass balance approach is based on the assumption of steady-state, it is unlikely to be able estimate the rate of drug absorption.

5. Application

5.1. Pharmacokinetic modeling

The CAT model calculates the rate of percent of dose absorbed from the small intestine into the plasma, Eq. (50). It can be easily related to any compartmental pharmacokinetic model. In the case of a three compartment model with elimination from the central compartment, for example, we have the following pharmacokinetics model equations [52]:

$$\frac{dC_1}{dt} = -\frac{D}{V}\frac{dY_a}{dt} - (k12 + k13)C_1 + k21C_2 + k31C_3 - keC_1 \quad (55)$$

$$\frac{dC_2}{dt} = -k12C_1 - k21C_2 \quad (56)$$

$$\frac{dC_3}{dt} = -k13C_1 - k31C_3 \quad (57)$$

where C is the concentration and V is the compartmental volume. The model equations were solved using the ADAPT pharmacokinetic and pharmacodynamic modeling package [53].

Three antiarrhythmic drugs, atenolol, bretylium and sotalol, were chosen for model validation. These antiarrhythmic drugs cover a wide range of bioavailability from 22% for bretylium to 100% for sotalol, with 56% for atenolol being in the middle. They undergo essentially no first-pass metabolism [54,55] and, therefore, the fraction of dose absorbed can be interpreted as bioavailability. They also show dose-independent oral pharmacokinetics [56–59]. It was demonstrated that the CAT model, coupled with the intravenous kinetics, accurately estimated the fraction of dose absorbed and the oral plasma concentration profiles for these three drugs.

In addition to linear drug absorption, the CAT model has been applied also to saturable drug absorption where drug degradation in the small intestine was also considered [48]. In this case, Eq. (49) becomes

$$\frac{dY_n}{dt} = K_t Y_{n-1} - K_t Y_n - K_{an} Y_n - K_{dn} Y_n, n = 1, 2, \ldots 7 \quad (58)$$

where K_{an} accounts for the saturable and linear absorption and K_{dn} accounts for the degradation. Cefatrizine was chosen for model validation due to its saturable absorption characteristics and physicochemical properties. It was shown that the CAT-based pharmacokinetic model, along with the intravenous pharmacokinetic parameters, estimated dose-dependent oral plasma concentration profiles of cefatrizine in humans well at doses of 250, 500 and 1000 mg. The model predicted the regional specific absorption characteristics for cefatrizine, particularly at high dose. The predicted fractions of dose absorbed were 74% at 250 mg, 63% at 500 mg and 51% at 1000 mg, in good agreement with the reported experimental data [60].

The significant point of the use of the CAT-based pharmacokinetic model is that we may simultaneously estimate the fraction of dose absorbed while curve fitting pharmacokinetic data. The risk involved is that, we assume, no metabolism occurs. Otherwise, the bioavailability may be overestimated.

5.2. Design of oral controlled-release delivery systems

The CAT model has been extended to include a compartment representing the controlled-re-

lease dosage form. Such extension allows evaluation of formulation parameters and absorption characteristics of drugs [61]. Specifically, a dosage form with either a zero or a first order release rate moves down the intestine depending on the transit time parameters and the dissolved drug reaches the systemic circulation based on site-specific absorption parameters along the gut.

Initially, plasma profiles and fractions of the dose absorbed of two controlled-release compounds, metoprolol (Toprol XL®) and nifedipine (Procardia XL®), were simulated based on their standard pharmacokinetic parameters and known release rates, in order to validate the feasibility of the model. Varying absorption kinetics along the intestine were investigated to determine if significant colon permeability is necessary to obtain therapeutic plasma profiles and reported bioavailabilities. Plasma concentration–time profiles for metoprolol after administration of a bolus solution and a controlled zero order release dosage form were simulated under various permeability assumptions for the colon. In order to reach the therapeutic plasma levels, a colonic permeability of 1/10th of that of the jejunum is necessary, which results in the fraction of dose absorbed from the dosage form of 38%. Performing the same simulations for nifedipine, suggests that 1/5th of the jejunal permeability is required for the colon to obtain the desired plasma levels. This results in the fraction of dose absorbed being 52%.

Additionally, two other model compounds, propranolol and atenolol, were evaluated in order to define the minimum permeability necessary and the optimum release rate for a potential controlled-release dosage form, with estimated site-specific absorption rate constants from permeability studies. The performance of a model first-order release dosage form of propranolol and atenolol was also evaluated under various colonic permeabilities. As shown in Fig. 6, two conclusions might be drawn from these simulations. First, high permeability compounds, such as propranolol, are rapidly absorbed after bolus administration and variations in colonic permeability are without influence, since absorption is usually completed in the small intestine. Atenolol, on the other hand, which exhibits low jejunal permeability might potentially be com-

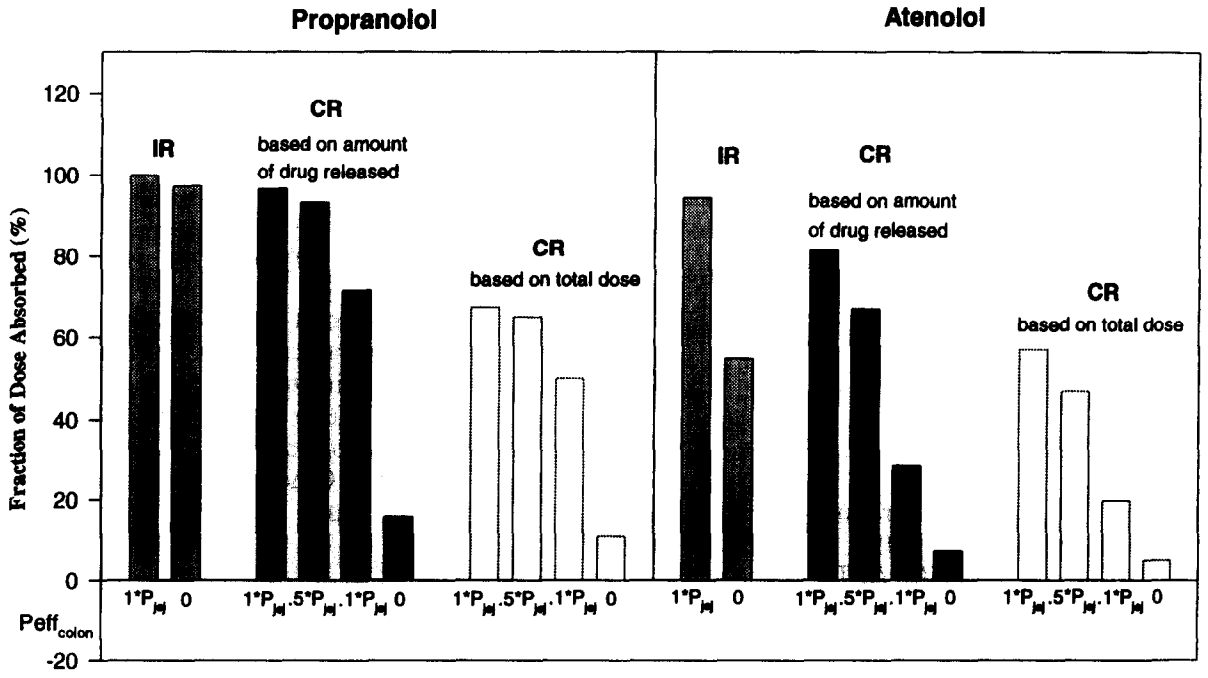

Fig. 6. Simulated fraction of dose absorbed for propranol and atenolol using the compartmental absorption and transit model.

pletely absorbed if colonic permeability is comparable to jejunal permeability. However, atenolol is not metabolized and its oral bioavailability amounts to only 50%, suggesting that colonic permeability is close to zero. Second, a drug that would be considered a promising controlled-release candidate should have a moderate-to-good jejunal permeability and permeability in the colon that is approximately 1/5–1/10 th that of the jejenum. Applying the CAT model to absorption data obtained in vivo as well as in vitro, release data has been shown to a be a useful tool to evaluate potential controlled-release drug candidates. This approach allows optimization of existing formulations as well as development of new dosage forms for therapeutic agents.

6. Conclusions

Throughout the last 50 years, numerous models have been developed ranging from the pH-partition hypothesis to the CAT model. The pH-partition hypothesis and absorption potential concept provide a basic guideline for understanding drug absorption. The advantage of the pH-partition hypothesis and the absorption potential concept is that they are entirely based on the physicochemical properties of drugs. Such approaches may be useful in the qualitative assessment of drug absorption for soluble and insoluble drugs. The dispersion model has the advantage of being more realistic on a physical basis. However, the dispersion model may be too complex to be used for quick assessment of the oral drug absorption.

Quantitative estimation of drug absorption requires the use of the mass balance approach or the CAT model. Both approaches employ the intestinal membrane permeability. The advantage of the CAT over the mass balance approach is that the former can be directly related to pharmacokinetic models and predict plasma concentration profiles. The CAT model is also useful in the design of the controlled-release delivery systems and has the potential to be used to investigate the effect of physicochemical, physiological and dosage form variables on the oral drug absorption. Nevertheless, considering the complexity of the oral drug absorption, it may be unrealistic to expect that a theoretical absorption model works well for any drugs and under any circumstances.

Very often we may find that a theoretical model inappropriately explains experimental results. This implies that either the model assumptions have not been met or that the model needs to be refined. After all, oral drug absorption is a very complex process. Many other factors, such as pK_a, solubility, crystal form, blood flow, gastrointestinal pH as well as dosage form factors, have not been completely considered. The incorporation of these factors requires further effort.

7. Notation

A	Amount of drug absorbed
An	Absorption number
AP	Absorption potential
C	Lumenal drug concentration or plasma concentration
C_i	Plasma concentration in the ith compartmental
C_0	Dose concentration
C_{out}	Drug concentration exiting the small intestine
D	Dose
Da	Damkohler number
D_i	Diffusivity
Dn	Dissolution number
Do	Dose number
F_a	Fraction of dose absorbed
F_d	Fraction of dose degraded
F_{tot}	Total drug loss in the intestine
F_{un}	Fraction in unionized form at pH 6.5
f	Proportional constant
ke	Elimination constant
K_a	Absorption rate constant
K_d	Degradation rate constant
K_t	First flow rate constant exiting each compartmental
k_{ij}	Microscopic rate constants from ith to jth compartmental
L	Length of the small intestine

l	Intestinal length at which absorption is complete
M	Amount of drug
N	Number of compartmental
No	Number of particles
P	Partition coefficient
P_{aq}	Aqueous permeability
P_{eff}	Effective permeability
P_w	Wall permeability
Q	Flow-rate
R	Radius of the small intestine
RL	Anatomical reserve length
r_o	Initial radius of particle
r_p	Radius of particle
S	Solubility
$<T_{si}>$	Mean small intestinal transit time
t	Time
V	Volume of distribution
V_{max}	Maximum rate of absorption
Vo	Volume of water taken with dose
Y	Percent of drug (dose)
Y_a	Percent of dose absorbed in the small intestine
Y_c	Percent of dose entering colon
Y_d	Percent of dose degraded in the small intestine
z	Axial distance
α	Longitudinal coefficient
ρ	Density of particles
ν	Velocity in the axial direction

Acknowledgments

L.X.Y. would like to thank the American Foundation for Pharmaceutical Education (AFPE) for their financial support.

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