Rate- and Extent-Limiting Factors of Oral Drug Absorption: Theory and Applications

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ABSTRACT: The oral absorption of drugs has been represented by various concepts such as the absorption potential, the maximum absorbable dose, the biopharmaceutics classification system, and *in vitro–in vivo* correlation. The aim of this article is to provide an overview of the theoretical relationships between these concepts. It shows how a simple analytical solution for the fraction of a dose absorbed (Fa equation) can offer a theoretical base to tie together the various concepts, and discusses how this solution relates to the rate-limiting cases of oral drug absorption. The article introduces the Fa classification system as a framework in which all the above concepts were included, and discusses its applications for food effect prediction, active pharmaceutical ingredient form selection, formulation design, and biowaiver strategy. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2777–2788, 2015

Keywords: intestinal absorption; salt selection; bioequivalence; biopharmaceutics classification system (BCS); *in silico* modeling; dissolution; food effects; formulation; gastrointestinal transit; oral absorption

INTRODUCTION

The theories of oral drug absorption have been actively investigated in the last three decades.[1] Various concepts have been introduced to represent the oral absorption of drugs, for example, the absorption potential (AP),[2] the maximum absorbable dose (MAD),[3] the biopharmaceutics classification system (BCS),[4] the developability classification system (DCS),[5] and *in vitro–in vivo* correlation (IVIVC).[6] These concepts originate from the same differential equations that describe the dissolution and intestinal membrane permeation of drugs. The aim of this article is to provide a comprehensive overview of theoretical relationships between these concepts. A brief history in this scientific area is shown in Table 1.

Abbreviations used: AP, absorption potential; API, active pharmaceutical ingredient; AUC, area under the curve; AUC BE, bioequivalence of AUC; BCS, biopharmaceutics classification system; BCS-BWS, BCS-based biowaiver scheme; BE, bioequivalence; COAS, computational oral absorption simulation; C_{max} BE, bioequivalence of C_{max}; $C_{dissolv}$, concentration of a dissolved drug; $C_{dissolv,ss}$, concentration of a dissolved drug at the steady state; DCS, developability classification system; DF, degree of flatness; DRL, dissolution rate limited; D_{eff}, effective diffusion coefficient; Dn, dissolution number; Dn_{crit}, critical dissolution number; Do, dose number; Do_{crit}, critical dose number; Dose, dose strength; EIE, equivalent-in-effect; EIP, equivalence of independent parameter; Fa, fraction of a dose absorbed; FaCS, Fa classification system; GI, gastrointestinal; IR, immediate release; IVIVC, *in vitro–in vivo* correlation; MAD, maximum absorbable dose; MDT, mean dissolution time; PBPK, physiologically based pharmacokinetics; PL, permeability limited; PL-E, epithelial membrane permeability limited; PL-U, unstirred water layer permeability limited; Pn_{crit}, critical permeation number; P_{UWL}, unstirred water layer permeability; P_{app}, apparent permeability; P_{eff}, effective intestinal membrane permeability; P_{ep}, epithelial membrane permeability of unbound drug molecules; PKs, pharmacokinetics; Pn, permeation number; S1I7, GI compartment model with one stomach compartment and seven intestinal compartments; SL, solubility–permeability limited; SL-E, solubility–epithelial membrane permeability limited; SL-U, solubility–unstirred water layer permeability limited; SMF, safe margin factor; S_{blank}, solubility in a blank buffer; $S_{dissolv}$, solubility in the GI tract (free and bile micelle bound drug molecules); Sn, saturation number; T_{abs}, transit time through the absorption site in the GI tract; UWL, unstirred water layer; V, fluid volume in the GI tract; VE, villi expansion factor; $X_{dissolv}$, dissolved amount; f_u, free fraction at the surface of the intestinal epithelial membrane; *in vitro* $T_{85\%}$, time to reach 85% dissolution in an *in vitro* dissolution test; k_{abs}, absorption rate coefficient; k_{diss}, dissolution rate coefficient; k_{el}, elimination rate coefficient; k_{perm}, permeation rate coefficient; r_p, particle radius of a drug; $T_{1/2}$, elimination half-life.

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DIFFERENTIAL EQUATIONS OF ORAL DRUG ABSORPTION

The oral absorption of a drug can be expressed by the two differential equations that describe the dissolution and intestinal membrane permeation of a drug (except for supersaturation). The dissolution of a drug is usually expressed by the Noyes–Whitney equation introduced in 1897 (Eq. (1)).[7,14] The intestinal membrane permeation of a drug is usually expressed by the first order equation (Eq. (2)). These are typically expressed as:

$$\frac{dX_{undissolv}}{dt} = -k_{diss}\,Dose^{\frac{2}{3}}X_{undissolv}^{\frac{1}{3}}\left(1-\frac{X_{dissolv}}{S_{dissolv}V}\right) \quad (1)$$

$$\frac{dX_{abs}}{dt} = k_{perm}X_{dissolv} \quad (2)$$

$$k_{diss} = \frac{3D_{eff}S_{dissolv}}{r_p^2\rho} \quad (3)$$

$$k_{perm} = \frac{2DF}{R}P_{eff} \quad (4)$$

where k_{diss} is the dissolution rate coefficient, k_{perm} is the permeation rate coefficient, Dose is the dose strength, $X_{undissolv}$ is the undissolved amount, $X_{dissolv}$ is the dissolved amount, X_{abs} is the absorbed amount, $S_{dissolv}$ is the solubility in the intestinal fluid (free and bile micelle bound drug molecules), D_{eff} is the effective diffusion coefficient, P_{eff} is the effective intestinal membrane permeability (free and bile micelle bound drug

Table 1. Brief History of Theoretical Biopharmaceutics

Year	Events	Reference
1897	Noyes–Whitney equation	7
1985	Absorption potential	2
1986	Mixed tank model	8
1993	Plug-low model	9
1995	Biopharmaceutics classification system	4
1996	Maximum absorbable dose	3
	Compartment absorption transit model	10
1999	Absorption-limiting step classification	11
2005	Biopharmaceutics drug disposition classification system	12
2009	Fa equation	13
2010	Developablility classification system	5

molecules), ρ is the true density, and r_p is the particle radius of a drug. R is the radius of the gastrointestinal (GI) tract, DF is the degree of flatness, and V is the fluid volume in the GI tract. Eq. (1) is for monodispersed spherical particles smaller than 60 μm. To calculate the fraction of a dose absorbed (Fa), Eqs. (1) and (2) have to be integrated simultaneously. However, the exact analytical solution for general cases has not been discovered. The quest for the answer(s) that leads to Fa is one of the main themes of theoretical biopharmaceutics.

QUEST FOR ANSWERS: A BRIEF HISTORY

A simple analytical solution can usually be derived from a differential equation(s) by applying the initial and boundary conditions for a special (limiting) case. Historically, this approach was first applied to the dissolution and permeation equations for the three absorption limiting cases, that is, the dissolution rate, permeability, and solubility–permeability limited (SL) cases. An illustrative explanation of these limiting cases is available elsewhere in the literature.[15]

Trivial Answers

Dissolution Rate-Limited Cases

In the case of dissolution rate-limited (DRL) absorption, Fa can be calculated by integrating the dissolution equation. By applying $X_{dissolv} = 0$ (perfect sink condition), we obtain

$$\mathrm{Fa} = 1 - \left(1 - \frac{2}{3}k_{diss}T_{abs}\right)^{\frac{3}{2}} = 1 - \left(1 - \frac{2}{3}\mathrm{Dn}\right)^{\frac{3}{2}} \quad (5)$$

where T_{abs} is the transit time through the absorption site in the GI tract. T_{abs} can be approximated as the small intestinal transit time for many cases. We can introduce a dimensionless parameter for dissolution [dissolution number (Dn) = $k_{diss} \times T_{abs}$]. This equation can be approximated as a first-order process,

$$\mathrm{Fa} = 1 - \exp\left(-k_{diss}T_{abs}\right) = 1 - \exp\left(-\mathrm{Dn}\right) \quad (6)$$

Permeability Limited Cases

When the whole amount of a drug instantly and completely dissolves after administration in the GI tract, the dissolution process will not become the rate-limiting step. In this case, the oral absorption of the drug becomes permeability limited (PL). The trivial answer for Eq. (2) is:

$$\mathrm{Fa} = 1 - \exp\left(-k_{perm}T_{abs}\right) = 1 - \exp\left(-\mathrm{Pn}\right) \quad (7)$$

This equation is often used to correlate *in vitro* membrane permeability values with Fa, for example, the Caco-2 cell assay,[16,17] the Madin–Darby canine kidney cell assay,[18] and the parallel artificial membrane permeation assay.[19–21] We can also introduce a dimensionless parameter for permeation (Pn = $k_{perm} \times T_{abs}$).

Sequential First-Order Approximation

When the oral absorption of a drug can be represented as the sequential first-order process of dissolution and permeation, the analytical solution becomes

$$\begin{aligned}\mathrm{Fa} = 1 &- \frac{k_{perm}}{k_{perm} - k_{diss}}\exp\left(-k_{diss}T_{abs}\right) \\ &- \frac{k_{diss}}{k_{diss} - k_{perm}}\exp\left(-k_{perm}T_{abs}\right) = 1 - \frac{\mathrm{Pn}}{\mathrm{Pn} - \mathrm{Dn}}\exp\left(-\mathrm{Dn}\right) \\ &- \frac{\mathrm{Dn}}{\mathrm{Dn} - \mathrm{Pn}}\exp\left(-\mathrm{Pn}\right)\end{aligned} \quad (8)$$

Solubility - Permeability Limited Case

The above three trivial answers were simply derived from the differential equations. However, the concentration gradient term [$1-X_{dissolv}/(S_{dissolv} \times V)$] makes it difficult to solve the equations for the cases of great interest in the pharmaceutical sciences. As no trivial answer is provided for this case, pharmaceutical insights are required to solve the equations. The concept of solubility - permeability limited absorption first emerged as the AP in 1985,[2] and then eventually developed to the concept of the MAD[3] and BCS.[4] When the dissolution rate of a drug is much faster than the permeation rate and the dose to solubility ratio (Dose/$S_{dissolv}$) exceeds the intestinal fluid volume (V), the concentration of a dissolved drug ($C_{dissolv} = X_{dissolv}/V$) in the GI tract reaches close to the equilibrium solubility of the drug ($S_{dissolv}$). In this case, Eq. (2) can be integrated by applying a constant value of $X_{dissolv} = S_{dissolv} \times V$ as:

$$\mathrm{Fa} = \frac{k_{perm}S_{dissolv}VT_{abs}}{\mathrm{Dose}} = \frac{\mathrm{MAD}}{\mathrm{Dose}} = \frac{\mathrm{Pn}}{\mathrm{Do}} \quad (9)$$

$$\mathrm{Do} = \frac{\mathrm{Dose}}{S_{dissolv}V} \quad (10)$$

where Do is the dose number. This oral absorption pattern is often referred as "solubility limited" in the literature. However, to explicitly recognize the role of permeability, we refer it as "solubility - permeability limited" in this article. In the AP, k_{perm} is represented by the lipophilicity of a drug. The maximum absorbable dose is defined as MAD = $k_{perm} \times S_{dissolv} \times V \times T_{abs}$. BCS categorizes a drug by Do and Pn. The classification boundary of DCS is based on Fa = Pn/Do (Fig. 1). Therefore, AP, MAD, BCS, and DCS are related to each other via Eq. (9).