科技资料

Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis

Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis

Edited by
David Z. D'Argenio
University of Southern California
Los Angeles, California

Plenum Press • New York and London

Library of Congress Cataloging-in-Publication Data

Biomedical Simulations Resource Workshop on Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis (1990 : Marina del Rey, Calif.)
Advanced methods of pharmacokinetic and pharmacodynamic systems analysis / edited by David Z. D'Argenio.
p. cm.
"Proceedings of the 1990 Biomedical Simulations Resource Workshop on Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis, held May 18-19, 1990, in Marina del Rey, California"--T.p. verso.
Includes bibliographical references and index.
ISBN 0-306-44028-8
1. Pharmacokinetics--Congresses. 2. Drugs--Physiological effect--Congresses. I. D'Argenio, David Z. II. Title.
RM301.5.B56 1990
615'.7--dc20 91-22186
CIP

Proceedings of the 1990 Biomedical Simulations Resource Workshop on Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis, held May 18–19, 1990, in Marina del Rey, California

ISBN 0-306-44028-8

PREFACE

This volume records the proceedings of the Workshop on Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis, organized by the Biomedical Simulations Resource in May 1990. The meeting brought together over 120 investigators from a number of disciplines, including clinical pharmacology, clinical pharmacy, pharmaceutical science, biomathematics, statistics and biomedical engineering with the purpose of providing a high–level forum to facilitate the exchange of ideas between basic and clinical research scientists, experimentalists and modelers working on problems in pharmacokinetics and pharmacodynamics.

It has been my experience that in many areas of biomedical research, when a meeting of this type is held, the general attitude of those experimentalists willing to attend is one of extreme skepticism: as a group they feel that mathematical modeling has little to offer them in furthering their understanding of the particular biological processes they are studying. This is certainly *not* the prevailing view when the topic is pharmacokinetics and drug response. Quite the contrary, the use of mathematical modeling and associated data analysis and computational methods has been a central feature of pharmacokinetics almost from its beginnings. In fact, the field has borrowed techniques of modeling from other disciplines including applied mathematics, statistics and engineering, in an effort to better describe and understand the processes of drug disposition and drug response. This transfer of intellectual technology, however, has and continues to be done with a keen power of discrimination on the part of basic and clinical scientists in the field. What I have found to be especially significant, moreover, is that the general area of pharmacokinetics has also provided a return benefit to those disciplines from which it has borrowed, in that the difficult problems in pharmacokinetics have provided fertile ground for the development of new approaches and significant extensions to existing techniques of mathematical modeling, data analysis, and scientific computing.

The contributors to this volume are representative of those investigators who by addressing fundamentally important basic and clinical research problems have also provided a stimulus for development of new methodologies of modeling and data analysis in pharmacokinetics and pharmacodynamics. Other contributors are indicative of the biomathematicians, engineers and statisticians who have accepted the challenge of developing these new modeling, data analysis and computational techniques.

The book itself is divided into four sections. The first involves contributions on the physiological and biochemical basis of pharmacokinetics, including chapters on the mechanisms of oral drug absorbtion, reversible metabolic processes, novel drug delivery systems for anticancer and antiviral agents, and the significance of blood sampling site in pharmacokinetic studies. The second section addresses mea-

surement and modeling issues in pharmacodynamics as they relate to the study of corticosteroids, intravenous anesthetics and cardioactive drugs, as well as physiological approaches to pharmacodynamic modeling. Section three on pharmacometrics includes chapters on residence time distributions, estimation with model uncertainty, population analysis with intraindividual variability, and optimal design of dosage regimens. The last section addresses problems of measurement, control and drug delivery in pharmacotherapeutics, with chapters on fiber optic sensors for detecting general anesthetics, individualizing drug therapy in renal transplant and pediatric cancer patients, and drug delivery via a computer controlled infusion pump.

I wish to thank all the authors for their excellent contributions to this volume and for their generous and enthusiastic participation in the 1990 BMSR Workshop. It is with great pleasure that I acknowledge the many contributions of Mrs. Gabriele Larmon in both the efficient organization of the Workshop and in the professional preparation of this volume. Also, I would like to thank Nicolas Rouquette for his TEXnical expertise. Finally, I wish to acknowledge the support of the Biomedical Research Technology Program of the National Center for Research Resources of NIH for its support of the BMSR and its activities.

Los Angeles, California David Z. D'Argenio

CONTENTS

PHARMACOKINETICS: PHYSIOLOGICAL AND BIOCHEMICAL BASIS

PHARMACODYNAMICS: MEASUREMENTS AND MODELS

PHARMACOMETRICS: MODELING, ESTIMATION AND CONTROL

PHARMACOTHERAPEUTICS: MEASUREMENT, CONTROL AND DELIVERY

PHARMACOKINETICS:
PHYSIOLOGICAL AND BIOCHEMICAL BASIS

PREDICTING ORAL DRUG ABSORPTION IN HUMANS: A MACROSCOPIC MASS BALANCE APPROACH FOR PASSIVE AND CARRIER-MEDIATED COMPOUNDS

Doo-Man Oh, Patrick J. Sinko* and Gordon L. Amidon

College of Pharmacy
The University of Michigan, Ann Arbor
and
*Therapeutics Systems Research Laboratories, Inc.

INTRODUCTION

There are several models for estimating drug absorption in humans [1–8]. Both physicochemical properties of the drug and physiological/biochemical properties of the gastrointestinal tract affect the extent and/or rate of oral drug absorption. Some of these factors include: pKa, solubility and dissolution rate, aqueous diffusivity, partition coefficient, chemical and enzymatic stability, intestinal pH, transit time, gastrointestinal motility, endogenous substances such as bile salts, and exogenous substances such as nutrients (food). The systemic availability can be further reduced by first-pass hepatic metabolism. Consequently, prediction of absorption is semi-quantitative.

In this report, a recently developed theoretical approach will be discussed for drugs that are absorbed by passive and nonpassive (carrier-mediated) processes [9–13]. The chapter will focus on the prediction of fraction dose absorbed (portal system availability) rather than bioavailability (systemic availability) since factors such as first-pass hepatic metabolism will not be addressed. Drug loss in the intestine is further assumed to occur only from absorption and not from other factors such as chemical or enzymatic instability.

MACROSCOPIC MASS BALANCE APPROACH

The theoretical approach to estimating of the extent of oral absorption is based on a steady-state macroscopic mass balance on drug in the intestine [10,13]. This model does not include a stomach compartment even though a gastric emptying rate is an important consideration for some compounds. The physical model of the small intestine is taken to be a cylinder (tube) with surface area of $2\pi RL$ where R is the radius and L is the length of the tube (Fig. 1). Assuming the difference between the rate of mass flowing into and out of the tube is equal to the rate of mass absorbed, the rate of mass absorbed across the tube wall is

$$-\frac{dM}{dt} = \left(\frac{Q}{V_L}\right)(M_{in} - M_{out}) = \int\int_S J_w \, dA \qquad (1)$$

Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis
Edited by D'Argenio, Plenum Press, New York, 1991

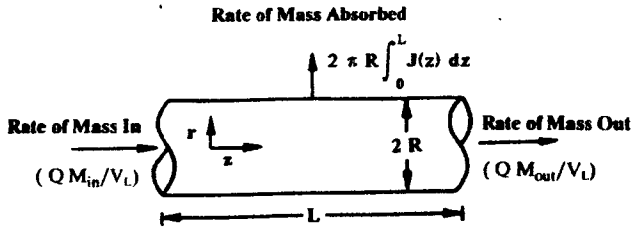

Fig. 1. Macroscopic mass balance on a tube. The rate of mass absorbed equals the difference between the rate of mass flow in and out of the tube.

where M is the mass in the tube, Q is the fluid flow rate, V_L is the luminal volume of the intestine, M_{in} and M_{out} are the mass at the inlet and outlet, respectively, J_w is the mass flux across the tube wall, and A is the absorptive surface area. The flux across the tube wall is generally expressed as:

$$J_w = P_{eff} \cdot C_L \tag{2}$$

where P_{eff} is the effective permeability [5], and C_L is the drug concentration in the tube.

With cylindrical geometry, Eq. (1) becomes:

$$-\frac{dM}{dt} = \left(\frac{Q}{V_L}\right)(M_{in} - M_{out}) = 2\pi R \int_0^L P_{eff} \cdot C_L \, dz \tag{3}$$

Further introducing the dimensionless variables,

$$z^* = \frac{z}{L} \quad \text{and} \quad C^* = \frac{C_L}{C_{in}} \tag{4}$$

where z is the axial coordinate and C_{in} is the initial concentration (M_{in}/V_L). From Eqs. (3) and (4), the fraction dose absorbed, F, is:

$$F = 1 - \frac{M_{in}}{M_{out}} = \left(\frac{2\pi RL}{Q}\right) \int_0^1 P_{eff} \, C^* \, dz^* \tag{5}$$

Eq. (5) is the basic equation for predicting drug absorption from the intestine. If the drug is passively absorbed from the intestine (constant wall permeability), Eq. (5) becomes:

$$F = \left(2 \, Gz \, P^*_{eff}\right) \int_0^1 C^* \, dz^* \tag{6}$$

where $P^*_{eff} = P_{eff}(R/\mathcal{D})$, $\mathcal{D}$ is diffusivity of drug, and $Gz = \pi \mathcal{D} L/Q$ for a complete radial mixing model. The Graetz number, Gz, is the ratio of axial convection to radial diffusion times in the tube. Since both Gz and P^*_{eff} are dimensionless, Eq. (6) suggests a definition of a new dimensionless variable, the absorption number (An) [10,12,13]:

$$An = Gz \cdot P^*_{eff} \tag{7}$$

Further Eq. (6) can be rewritten as:

$$F = 2\ An \int_0^1 C^*\, dz^* \tag{8}$$

Eq. (8) suggests that there are two factors that determine the fraction dose absorbed: absorption number (An) and concentration profile in the tube.

The absorption number is a physiological parameter which is obtained by experiments. The absorption number is the ratio of radial mass transfer rate to axial convective flow rate. It indicates that An is affected by not only the permeability of a drug but also by the bulk fluid flow in the intestine. An is calculated from the intrinsic wall permeability which is estimated from single-pass perfusion experiments [10,13]. Substituting $P^*_{eff} = P^*_w\ (1 - P^*_{eff}/P^*_{aq})$ into Eq. (7) and assuming $P^*_{aq} >> P^*_{eff}$ result in:

$$An = Gz\ P^*_w \left(1 - \frac{P^*_{eff}}{P^*_{aq}}\right) = Gz \cdot P^*_w \tag{9}$$

where P^*_w and P^*_{aq} are the dimensionless wall permeability and aqueous permeability of the compound, respectively. Eq. (9) is useful because P^*_w is independent of the fluid hydrodynamics in the intestine. The Graetz number may be considered as a scaling factor, when it is applied to predicting the fraction dose absorbed in humans from experimental data in rats [13].

The evaluation of the integral in Eq. (8) requires a knowledge of how the concentration of drug in the lumen varies down the length of the tube. The concentration profile in the tube is dependent on the P^*_w, as well as the actual flow (convection) pattern and the theoretical flow model that is chosen for analysis. Two limiting cases are a mixing tank (well-stirred) model and a complete radial mixing model [10,13]. The drug concentration is also dependent upon the initial drug concentration as well as other mass transfer processes (dissolution and absorption) and/or metabolism in the intestine. Three cases need to be considered with regard to inlet and outlet drug concentrations:

$$\text{Case I} \quad : \quad C_{in} < C_s \text{ and } C_{out} < C_s$$

$$\text{Case II} \quad : \quad C_{in} \geq C_s \text{ and } C_{out} < C_s$$

$$\text{Case III} \quad : \quad C_{in} > C_s \text{ and } C_{out} > C_s$$

where C_{in} and C_{out} are the inlet and outlet concentrations in the intestine, respectively, and C_s is the solubility of the compound.

A complete analysis of these models has been recently developed [10,13]. Case II is the intermediate of Case I and Case III. Case I and III are described in the following sections. Figure 2 shows a theoretical plot of fraction dose absorbed versus absorption number and dose number (see below) using mixing tank and complete radial mixing models [10,13]. If a drug is transported by a carrier-mediated system, the resultant wall permeability will demonstrate concentration dependent behavior. In this case Eq. (5) should be used to predict the fraction dose absorbed instead of Eq. (8). A microscopic mass balance approach can be used to predict the fraction dose absorbed. Using simultaneous differential equations and a mass balance on a

volume element of the tube, the concentration profile can be obtained to calculate the integral in Eq. (5) (Oh, unpublished results). An alternative approach to using Eq. (5) is to use a mean wall permeability [11].

CORRELATION OF F WITH An: CASE I

For the complete radial mixing model the concentration profile of a passively absorbed drug in the intestine is obtained from the mass balance at steady state:

$$C^* = e^{-2An \cdot z^*} \tag{10}$$

From Eqs. (8) and (10), the fraction dose absorbed for Case I is:

$$F_I = 1 - e^{-2An} \tag{11}$$

The fraction dose absorbed is exponentially related to absorption number. This result further supports that An is a primary parameter for predicting its absorption. The dependence of F on An is shown in Fig. 2 [11]. The Case I result is shown in Fig. 3 for the complete radial mixing model together with experimental results obtained for a number of drugs [11,12]. The correlation is excellent and can be used to estimate the extent of drug absorption for both passive and nonpassive (carrier-mediated) compounds (see below).

CORRELATION OF F WITH An AND Do: CASE III

In addition to nonpassive absorption, dose dependent absorption is also observed when a drug is dosed above its solubility. For Case III, it is assumed that

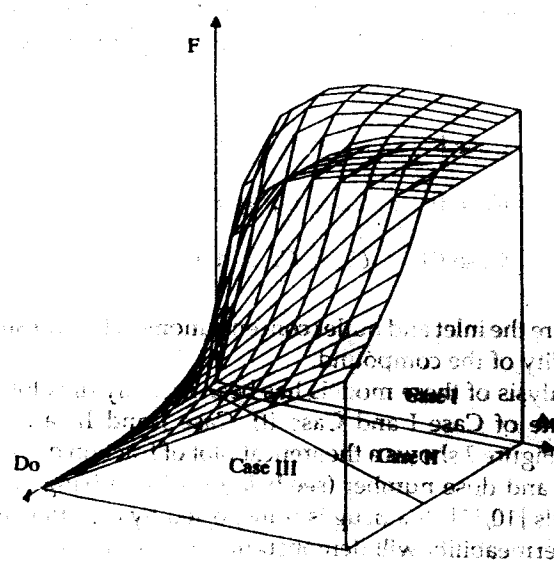

Fig. 2. Three dimensional plot of the absorption number (*An*) versus dose number (*Do*) versus the extent of absorption (*F*) for the complete radial mixing and mixing tank models.

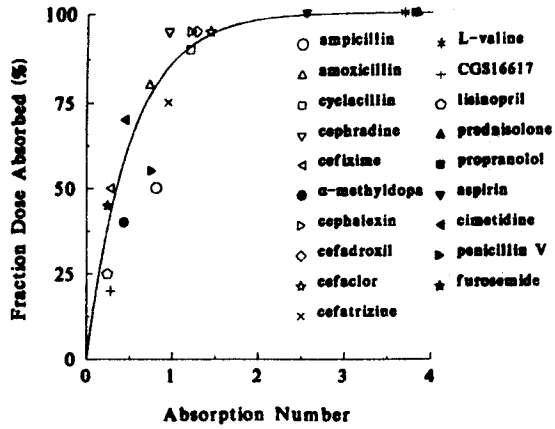

Fig. 3. Plot of fraction dose absorbed of Case I versus absorption number for several compounds whose absorption is passive or carrier-mediated. Complete radial mixing model is used for a theoretical line.

the drug concentration in the elemental volume of the tube is equal to the solubility of the drug. Substituting $C^* = C_s/C_{in}$ for the concentration profile in Eq. (8), the fraction dose absorbed for Case III is:

$$F_{III} = 2An \cdot \frac{C_s}{C_{in}} \tag{12}$$

Dose number (Do), another dimensionless parameter, is defined to be the ratio of initial concentration to the solubility of a compound:

$$Do = \frac{M_{in}/V_L}{C_s} = \frac{C_{in}}{C_s} \tag{13}$$

Therefore, the fraction dose absorbed of Case III is rewritten as:

$$F_{III} = \frac{2\,An}{Do} \tag{14}$$

From Eq. (14) the dependence of F on both An and Do is apparent. Dose number suggests that at a higher Do a lower fraction of dose is absorbed. Figure 4 shows the predicted curve for Case III illustrating the significant decrease in F as the dose number becomes larger. It suggests that dose dependency is mainly due to low solubility and the high dose taken. However, for low solubility compounds in the intestine, the luminal concentration may not be the same as their solubility due to slow dissolution and a microscopic mass balance approach for this case is being developed (Oh, unpublished results).

In both Case I and Case III, F is simply related to An, and for the intermediate case (Case II) the fraction dose absorbed can be predicted from the results of the two cases. An example of Case II is shown in Fig. 5 using the complete radial mixing model [14]. The dose dependency of amoxicillin is due to both a large dose number and a nonpassive absorption mechanism.

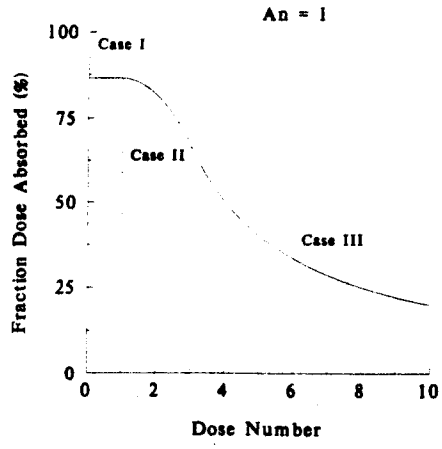

Fig. 4. Plot of fraction dose absorbed versus dose number. Complete radial mixing model is used for a theoretical line.

NONPASSIVE DRUG ABSORPTION

A modified boundary layer analysis has been developed by Johnson and Amidon [9] in order to calculate the intrinsic membrane absorption parameters from the perfused rat intestinal segment experiment. Drugs such as amino acids, dipeptides, several penicillins, cephalosporins, and ACE inhibitors are transported by a carrier-mediated (nonpassive) mechanism and have shown concentration-dependent permeabilities in rats [15–20] and absorption in humans [21]. The general expression for wall permeability is:

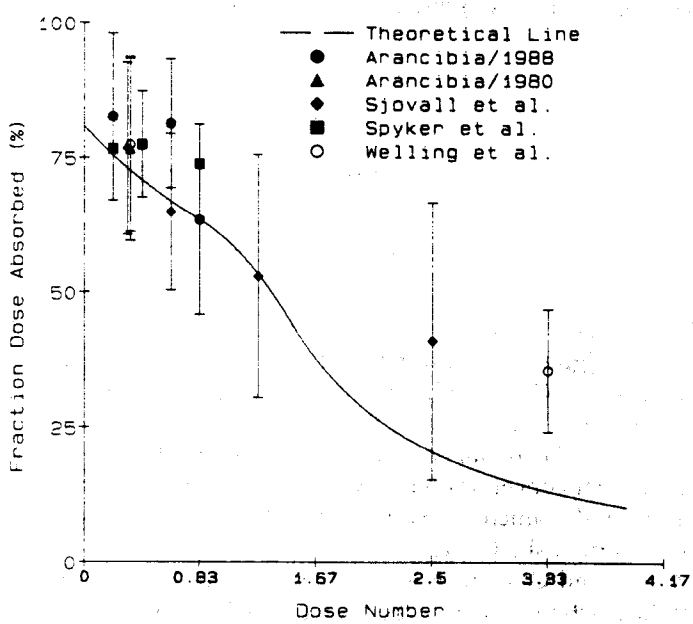

Fig. 5. Plot of the fraction dose absorbed for amoxicillin versus dose number. The curve represents the simulated curve generated using a complete radial mixing model.

$$P_w^* = \frac{P_c^*}{1 + (C_w/K_m)} + P_m^* \tag{15}$$

where P_w^*, P_c^*, and P_m^* are the dimensionless wall permeability, carrier permeability, and passive membrane permeability, respectively, K_m is a Michaelis constant for the transport system, and C_w is the wall concentration. Figure 6 shows an example of the wall permeability of ampicillin which is dependent on its concentration (Oh, unpublished results). A competitive inhibition study on the β-lactam antibiotics gives further evidence of a nonpassive absorption mechanism for these drugs [20].

To correlate F for a nonpassively absorbed drug with its wall permeability, a mean wall permeability $\overline{P_w^*}$ has been defined [11]:

$$\overline{P_w^*} = \frac{\int_{C_{in}}^{0} P_w^* \, dC_w}{\int_{C_{in}}^{0} dC_w} \tag{16}$$

where $C_{in} = M_{in}/V_L$, M_{in} is the dose administered, and V_L is the luminal volume. The absorption number is subsequently calculated from mean wall permeabilities for nonpassive compounds. Figure 3 includes compounds that are absorbed by both passive and carrier-mediated absorption pathways: nonpassively transported compounds include cephradine, cephalexin, cefatrizine, cefadroxil, cefaclor, ampicillin, amoxicillin, cyclacillin, L-valine, and α-methyl dopa.

Using a microscopic mass balance approach, the concentration profile in Eq. (6) can be obtained for estimating the fraction dose absorbed numerically. However, these results clearly indicate that the primary parameters for predicting the fraction dose absorbed are absorption number (An) and dose number (Do).

SUMMARY

Macroscopic mass balance approach has been developed and used for predicting the fraction dose absorbed in humans. The extent of drug absorption may be estimated from two dimensionless parameters: absorption number (An) and dose

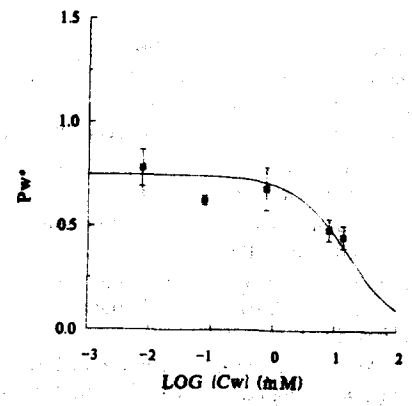

Fig. 6. Intrinsic wall permeability (P_w^*) versus wall concentrations (C_w) of ampicillin in the rat intestine: ■, experimental data (mean ± s.e.m.); ——, the best fit line.

number (*Do*). The absorption number is the ratio of absorption rate to convection in the intestine, whereas the dose number is the ratio of initial concentration to the solubility of a drug. The fraction dose absorbed is directly related to *An* and *Do*. Three cases with regard to inlet and outlet concentrations are discussed. This approach can be applied to compounds whose absorption mechanism is passive as well as carrier-mediated.

REFERENCES

1. N. F. H. Ho and W. I. Higuchi. Theoretical model studies of intestinal drug absorption IV: Bile acid transport at premicellar concentrations across diffusion layer-membrane barrier. *J. Pharm. Sci.* 63:686–690 (1974).
2. G. L. Amidon, J. Kou, R. L. Elliott, and E. N. Lightfoot. Analysis of models for determining intestinal wall permeabilities. *J. Pharm. Sci.* 69:1369–1373 (1980).
3. G. L. Amidon, G. D. Leesman, and R. L. Elliott. Improving intestinal absorption of water-insoluble compounds: A membrane metabolism strategy. *J. Pharm. Sci.* 69:1363–1368 (1980).
4. B. C. Goodacre and R. J. Murray. A mathematical model of drug absorption. *J. Clin. Hosp. Pharm.* 6:117–133 (1981).
5. G. L. Amidon. Determination of intestinal wall permeabilities. In W. Crouthamel and C. Sarapu (eds.), *Animal Models for Oral Drug Delivery in Man: In situ and in vivo Approaches*, American Pharmaceutical Association, Washington DC, 1983, pp.1–25.
6. J. B. Dressman, D. Fleisher, and G. L. Amidon. Physicochemical model for dose-dependent drug absorption. *J. Pharm. Sci.* 73:1274–1279 (1984).
7. J. B. Dressman, G. L. Amidon, and D. Fleisher. Absorption potential: Estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* 74:588–589 (1985).
8. J. B. Dressman and D. Fleisher. Mixing-tank model for predicting dissolution rate control of oral absorption. *J. Pharm. Sci.* 75:109–116 (1986).
9. D. A. Johnson and G. L. Amidon. Determination of intrinsic membrane transport parameters from perfused intestine experiments: A boundary layer approach to estimating the aqueous and unbiased membrane permeabilities. *J. Theor. Biol.* 131:93–106 (1988).
10. P. J. Sinko. Predicting oral drug absorption in man for compounds absorbed by carrier-mediated and passive absorption processes. Ph.D. dissertation, University of Michigan, Ann Arbor, 1988.
11. G. L. Amidon, P. J. Sinko, and D. Fleisher. Estimating human oral fraction dose absorbed: A correlation using rat intestinal membrane permeability for passive and carrier-mediated compounds. *Pharmaceut. Res.* 5:651–654 (1988).
12. G. L. Amidon, P. J. Sinko, M. Hu , and G. D. Leesman. Absorption of difficult drug molecules: carrier-mediated transport of peptides and peptide analogues. In L. F. Prescott and W. S. Nimmo (eds.), *Novel Drug Delivery and Its Therapeutic Application*, John Wiley & Sons Ltd., 1989, pp. 45–56.
13. P. J. Sinko, G. D. Leesman, and G. L. Amidon. Predicting fraction dose absorbed in humans: theoretical analysis based on a macroscopic mass balance. *Pharmaceut. Res.*, in press.
14. P. J. Sinko, G. D. Leesman and G. L. Amidon. Estimating the extent of amoxicillin absorption in humans: nonpassive absorption and solubility effects. *Pharmaceut. Res.*, in press.
15. P. J. Sinko, M. Hu, and G. L. Amidon. Carrier-mediated transport of amino acids, small peptides, and their drug analogs. *J. Control. Rel.* 6:115–121 (1987).
16. M. Hu and G. L. Amidon. Passive and carrier-mediated intestinal absorption components of captopril. *J. Pharm. Sci.* 77:1007–1011 (1988).
17. P. J. Sinko and G. L. Amidon. Characterization of the oral absorption of β-lactam antibiotics I. Cephalosporins:determination of intrinsic membrane absorption parameters in the rat intestine in situ. *Pharmaceut. Res.* 5:645–650 (1988).
18. D. I. Friedman and G. L. Amidon. Passive and carrier-mediated intestinal absorption components of two angiotensin converting enzyme (ACE) inhibitor prodrugs in rats: Enalapril and fosinopril. *Pharmaceut. Res.* 6:1043–1047 (1989).