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QUANTITATIVE, MECHANISTIC AND PHYSIOLOGICALLY REALISTIC APPROACH TO THE BIOPHARMACEUTICAL DESIGN OF ORAL DRUG DELIVERY SYSTEMS

Norman F.H. Ho*, Hans P. Merkle** and William I. Higuchi***

*College of Pharmacy, The University of Michigan
Ann Arbor, MI 48109
**Institute for Pharmaceutical Technology and Biopharmaceutics,
University of Heidelberg, Heidelberg, Germany
***College of Pharmacy, University of Utah
Salt Lake City, UT 84112

INTRODUCTION

The phenomenological and dynamic events that a drug and its dosage form (solution, emulsion, suspension, tablet, capsule and/or controlled-release system) undergo are complex. There exists a body of knowledge of adequate breadth and depth which recognizes a variety of factors affecting the oral bioavailability of drugs and points out the multivariable complexity of the overall situation[1,2,3]. These factors are commonly grouped into physiological, physicochemical and dosage form factors (Table 1). In the research and development of oral formulations, the pharmaceutical scientist employs various pathways in assessing bioavailability and/or bioequivalence as shown in Table 2. Despite the sophistication and rationale underlying each avenue in practice, the approaches, when considered as a whole, lack a programmatic strategy in defining delivery problems, sorting out the key variables, setting

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TABLE 1

Factors Influencing Bioavailability

Physiological Factors		
membrane transport mechanism		biliary and pancreatic secretions
GI motility		surface-bound enzymes
stomach emptying		intestinal pH gradient
disease state		surface pH
		pharmacological drug effects
Physicochemical Properties of the Drug		
lipophilicity	chemical stability	complexation & binding
molecular size	enzymic lability	particle size
pK_a	solubility	crystal form
Dosage Form Factors		
solutions	capsules and tablets	properties: disintegration time; dissolution rates; controlled-release rates
emulsions	controlled-release systems	
suspensions		manufacturing variables

quantitative boundaries and critical pathways within which optimization of oral formulations may be achieved, and pointing out strategies and options in drug formulation design on a physicochemical and biophysical basis. This underscores the need to put the factors into a comprehensive framework that the scientist can more fruitfully and rationally utilize in the course of designing and optimizing drug formulations. Significant developments along these lines are far more probable and efficient if they are approached from a basic standpoint and physically relevant information obtained from *in vitro* physicochemical, animal and human studies are judiciously interfaced.

This presentation is aimed at establishing the basic framework by which relevant physicochemical properties, dosage form

properties, gastrointestinal factors and mass transport kinetics are put into quantitative and mechanistic interrelationships. The anatomical reserve length concept for intestinal drug absorption provides the foundation on which the facts and relationships of rate-determining steps and factors are accommodated.

ANATOMICAL RESERVE LENGTH CONCEPT FOR INTESTINAL ABSORPTION

General Description

The anatomical reserve length is the length of the small intestine yet available for absorption, i.e., the difference between the small intestinal length and the length at which the drug is completely absorbed (Fig. 1). Thus,

$$RL = L - \ell^* \qquad \text{(Eq. 1)}$$

where

RL = anatomical reserve length, cm

L = maximum theoretical reserve length, i.e., the length of small intestine which is 300-350 cm in humans

ℓ^* = length at which absorption is completed, cm

The fraction of small intestine yet available for absorption is:

$$\frac{(R\ L)}{L} = 1 - \frac{\ell^*}{L} \qquad \text{(Eq. 2)}$$

Therefore, positive reserve lengths indicate complete absorption in the small intestine and negative reserve lengths signify incomplete absorption. Here, we have presumed that the small intestine is the principal absorption compartment of the gastrointestinal tract which is generally the case.

TABLE 2

To Date Scientific Approaches in Assessing the Bioavailability of Orally Administered Drugs

Approaches	Assessments	Advantages (A) / Limitations (L)
In vitro physicochemical studies to work out baselines for formulation of dosage form of high bioavailability, including solubility, melting point, crystal state, partition coefficient, physical and chemical and biological stability, etc.	Standard methods for physical and physicochemical characterization as prerequisites to biopharmaceutical evaluations	A: Necessary baseline for any rationale drug formulation L: Does not allow extrapolation of data to predict rate and completeness of drug dissolution, uptake and absorption in the GI tract
In vitro dissolution studies using beaker set-ups, flow-through cells, etc.; variables are pH, hydrodynamics, solvent, volume of solvent, etc.	In vitro availability of dosage form	A: Prerequisite for any successful formulation work L: Does not necessarily allow for extrapolation to in vivo dissolution profiles
Fitting of blood level data and urinary excretion data by means of classic compartment models	Evaluation of drug formulations and standards through relative and absolute bioavailability parameters using peak concentration, peak times, AUC, or Wagner-Nelson or Loo-Riegelman procedures	A: Blood level data are most accepted means to demonstrate clinical efficacy and bioavailability L: Mathematical modeling provides little insight into physiology and biophysics of drug transport and distribution within the intestinal wall; procedure is descriptive but non-predictive

Search for in vitro-in vivo correlation of disintegration/dissolution data vs blood level profiles after oral administration	Correlation based on stochastic approach	A: Aids in screening process and quality control L: Neither success nor failure of correlation provides insight into dissolution and absorption mechanisms of the GI tract
Evaluation of dissolution data and/or blood level profiles by numerical evolution and convolution procedures, assuming consistency of model	Numerical predictions of input data (dissolution) through output data (blood levels) and vice versa	A: Aids screening process and quality control L: Does not provide insight into real mechanisms of dissolution and absorption in GI tract; consistency of model cannot be assessed
Absorption studies using in vitro isolated gut segments (everted sac) and/or in situ methods with intact mesenteric blood flow (Doluisio method, perfusion, etc.) by applying appropriate animal models (rat, dog)	Determination of membrane transport mechanism of drug; determination of rate controlling factors	A: Aimed at mechanistic understanding of rate limiting factors in drug absorption and systemic uptake L: To date no advanced knowledge for direct extrapolation to humans due to constraints of species differences

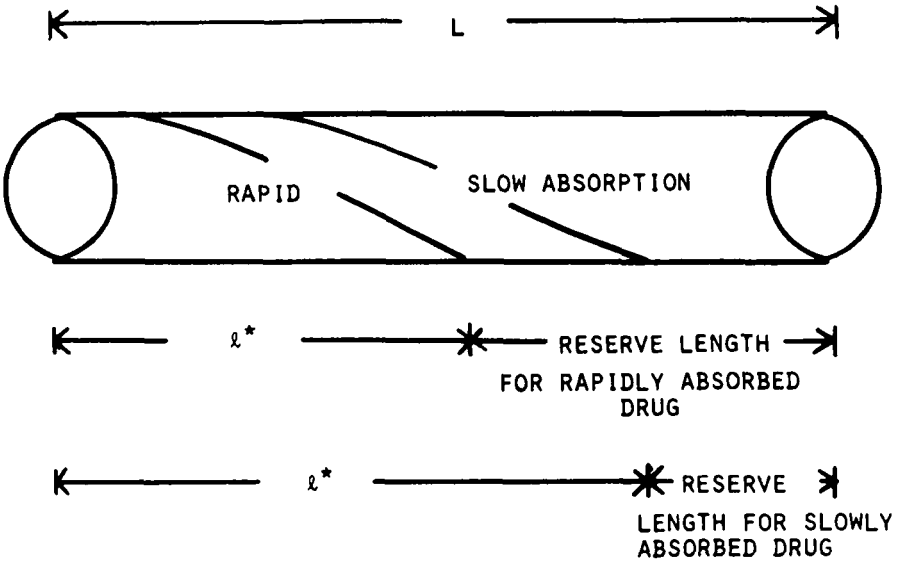


FIGURE 1
Schematic diagram of the anatomical reserve length.

Studies Supporting the Concept

The human intestinal digestion and absorption study by Borgstrom et al.[4] of a liquid mixture of homogenized oil, protein and glucose is, in our opinion, a classical example of the reserve length. Here, the principal constituents of the meal were completely absorbed in approximately 100 cm of the intestinal tract (Table 3). The concentrations of pancreatic enzymes (trypsin, chymotrypsin and amylase) and bile constituents (phospholipid and bile salts) were determined at different levels of the small intestine to correlate digestion with absorption. Taking 325 cm as the average length of the human small intestine, the reserve length is about 225 cm or 70% of the small intestine. From the viewpoint of the bioavailability of drugs, other human intubation studies which determined the extent of absorption of glucose, chenodeoxy-

cholic acid, highly lipophilic steroids and metoprolol tartrate solutions from samples retrieved at different lengths along the gastrointestinal tract are seen in Table 3 to be excellent additional examples of positive reserve length situations for solutes which are rapidly absorbed. It is also interesting that the compounds are representatives of a variety of mechanisms by which they are absorbed. Sugars and proteins must initially be digested by pancreatic and membrane-bound enzymes to glucose and amino acids which, in turn, are actively transported. Triglycerides are digested by pancreatic lipases to fatty acids, solubilized and carried to the membrane surface by biliary bile acid micelles and then permeate the intestinal membrane as free fatty acids. Chenodeoxycholic acid is absorbed passively in the duodenum and jejunum and actively in the ileum, whereas the steroids and metoprolol are passively absorbed.

Under the conditions of steady-state, through-and-through perfusion of an intestinal segment, the fraction of membrane permeable solutes remaining is given by[10]

$$\frac{C(\ell)}{C(0)} = \exp\left(-\frac{2\pi r \ell P_e}{Q}\right) \qquad \text{(Eq. 3)}$$

where

$C(\ell)$ = outflow concentration at intestinal length

$C(0)$ = inflow concentration from an infinite reservoir

r, ℓ = intestinal radius and length, cm, respectively

Q = bulk flow rate, cm^3/sec

P_e = effective permeability coefficient, cm/sec

TABLE 3

Intestinal Reserve Length

Reference	Description of Absorption Study	Approx. Intestinal Length of Complete Absorption, cm	Estimated Reserve Length, cm	Percent of Small Intestine Available for Absorption
Borgstrom et al[4] (1957)	Orally administered test meal mixture of corn oil, skim milk & sugars; normal bile secretions measured; healthy subjects intubated with multi-lumenal naso-jejunal tube; sample aspirated as function of distance beginning from the pyloric region			
	glucose	50	275	85%
	total fatty acids	100	225	69%
	^{131}I-human serum albumin	140	185	57%
Barreiro et al[5] (1968)	Steady-state perfusion of 5.4% glucose solution over 25 cm jejunal segment in intubated subjects; ave. linear-velocity about 1 cm/min	25	300	92%

van Berge-Henegouwen & Hofmann[6] (1977)	Micellar soln. of chenodeoxycholic acid (as the Na salt) as a bolus of 25, 200 & 400 mg doses into the distal duodenum from indwelling naso-jejunal tube; samples aspirated at end of 50 cm segment; healthy and gallstone subjects	50	275	85%
de Leon et al[7] (1980)	Aq. soln. of chenodeoxycholic acid (not as Na salt) infused as a bolus of 250, 500 & 750 mg doses into the duodenum; samples aspirated 60 & 120 cm from infusion port; healthy & gallstone subjects; chenic acid likely to precipitate in duodenum			
	chenic acid (250 and 500 mg)	between 60 & 120 cm	between 205 & 265 cm	63-82%
	chenic acid (750 mg dose)	120	205	63%

(continued)

TABLE 3 (cont.)

Reference	Description of Absorption Study	Approx. Intestinal Length of Complete Absorption, cm	Estimated Reserve Length, cm	Percent of Small Intestine Available for Absorption
Schedl[8] (1965)	Steady-state perfusion of solutions of ^{14}C-progesterone, dihydroprogesterone acetonide and norethisterone in Ringer's soln. over various segment lengths of intubated subjects	25 cm duodenum	300	92%
		<100cm jejunum	>235	>72%
		<100cm ileum	>235	>72%
Godbillon et al[9] (1981)	Metoprolol tartrate 100 mg in 400 ml homogenized meal introduced directly into stomach in intubated subjects; samples aspirated 30 & 90 cm from pylorus	90	235	72%

The permeability coefficient can be readily calculated by using

$$P_e = -\frac{Q}{2\pi r \ell} \ln \frac{C(\ell)}{C(0)} \qquad \text{(Eq. 4)}$$

and is further delineated by the following expression that takes into account the aqueous boundary layer barrier in series with the membrane:

$$P_e = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_m}} = \frac{P_{aq}}{1 + P_{aq}/P_m} \qquad \text{(Eq. 5)}$$

where

P_{aq}, P_m = permeability coefficients of the aqueous boundary layer and membrane, cm/sec, respectively

The bulk flow rate Q is related to the linear velocity, β cm/sec, and cross-sectional area:

$$Q = \pi r^2 \beta \qquad \text{(Eq. 6)}$$

The mean transit time, $\langle t \rangle$ secs, which is the time at which 50% of the drug leaves an intestinal segment, is:

$$\langle t \rangle = \frac{\ell}{\beta} = \frac{\pi r^2 \ell}{Q} \qquad \text{(Eq. 7)}$$

Finally, the steady-state fraction absorbed is expressed by

$$F.A. = 1 - \frac{C(\ell)}{C(0)} \qquad \text{(Eq. 8)}$$

These equations can be appropriately applied to many absorption studies carried out in intubated humans and animal models in which the test compound is constantly infused from an infinite reservoir. The physical model is predictive of the quantitative interplay of the fraction of drug absorbed, intestinal length, bulk flow rate, linear flow velocity, transit time, effective permeability coefficient of the aqueous boundary layer, membrane permeability

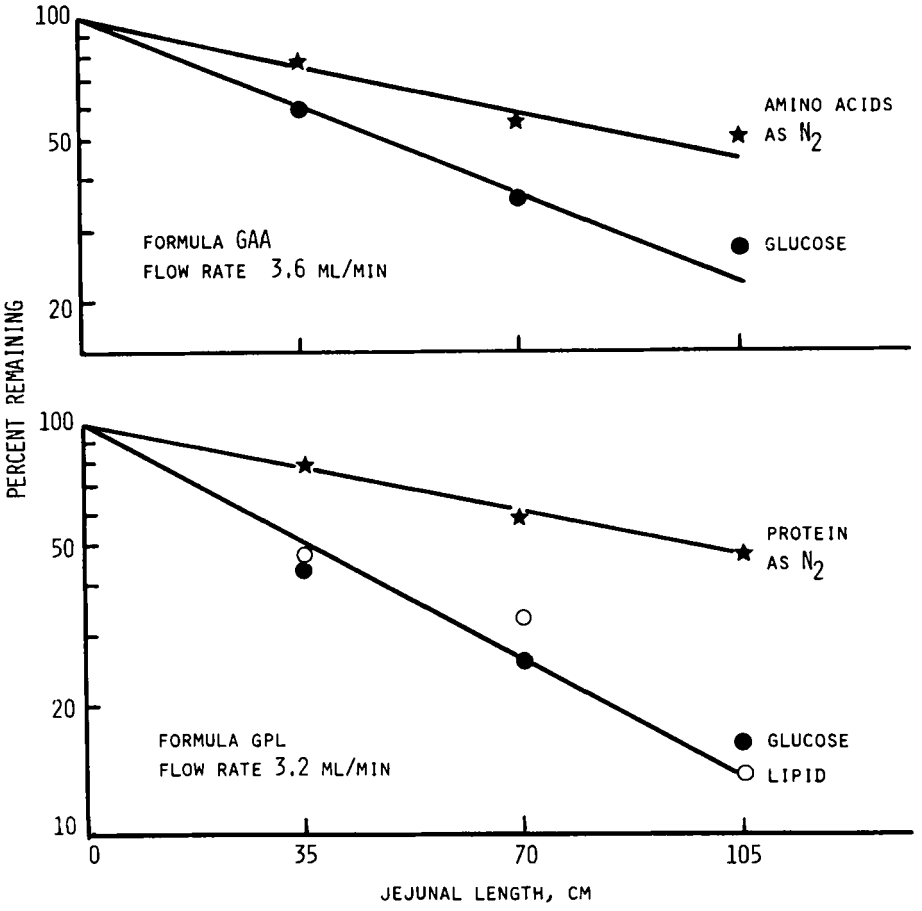


FIGURE 2

Human absorption of two nutrition formulations containing glucose, amino acids, proteins and lipids by steady-state perfusion and sampling at various intestinal lengths[11].

and solute lipophilicity. Considerations of ionic equilibria and transport mechanisms are also readily accommodated.

In Fig. 2 the fractions of glucose, aminoacids, proteins and lipids remaining in intubated human subjects are seen to be nearly semilogarithmically linear with intestinal length in accordance with Eq. 3[11]. As can be seen in Fig. 3, the semilogarithmic rela-

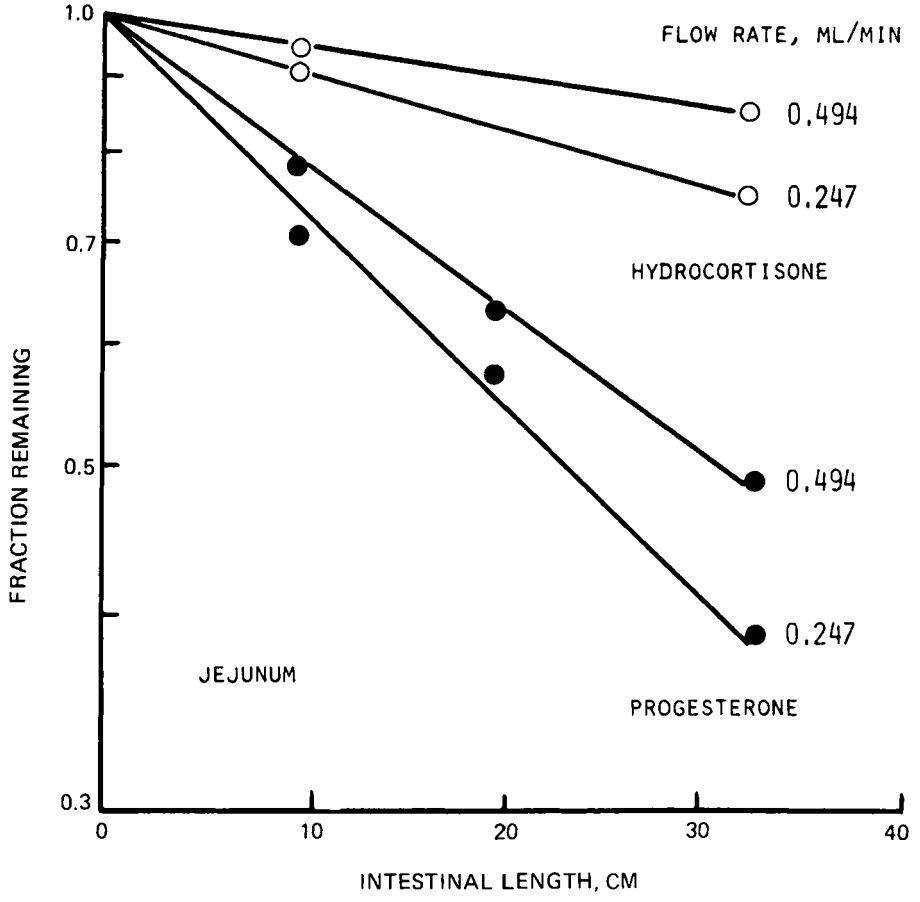


FIGURE 3

Semilogarithmic plot of the steady-state fraction of steroids remaining in various rat intestinal lengths as a function of fluid flow rates at pH 6[10].

tionship is also apparent for hydrocortisone and progesterone in the rat jejunum[10].

The results of the fraction absorbed for dilute solutions of steroids varying in lipophilicity, e.g., n-octanol/water partition coefficient, show sigmoidal shape profiles for various flow rates (Fig. 4). In these rat studies it is evident that the fraction absorbed is larger when the transit times are longer. Furthermore,

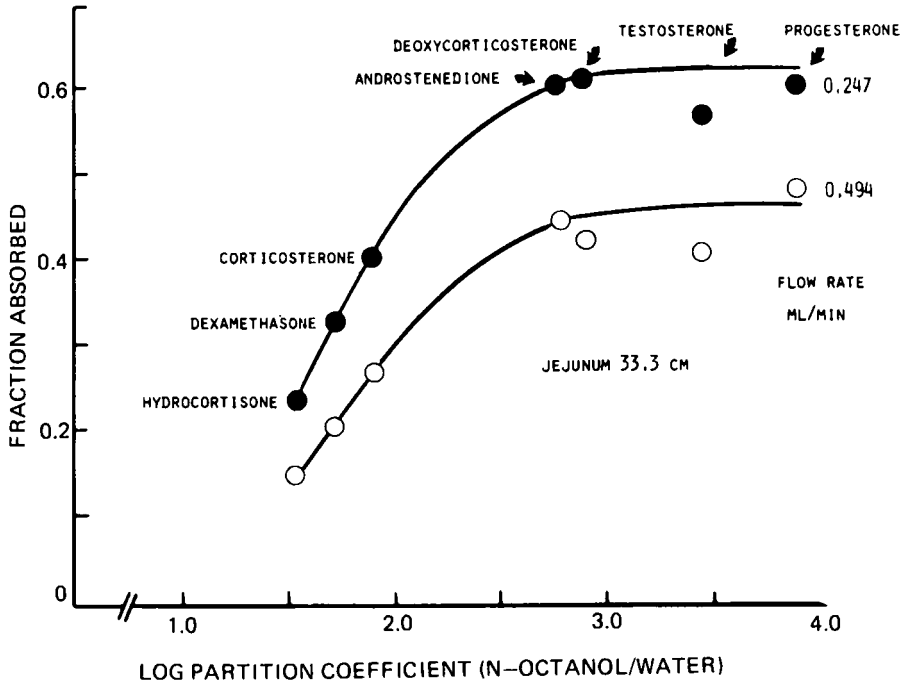


FIGURE 4

The influence of the lipophilicity of various steroids on the steady-state fraction absorption in the rat jejunum at pH 6.0.

effective permeability coefficient versus log partition coefficient plot in Fig. 5 provides insight to the mechanistic relationship of the permeability coefficients of the aqueous boundary layer and the membrane to the effective permeability coefficient (see Eq. 5). When the absorption process is essentially membrane-controlled as in the case of hydrocortisone ($P_m << P_{aq}$), the effective permeability is insensitive to flow rate; however, when diffusion across the aqueous boundary layer in front of the mucosal membrane is the rate-controlling step as for the case of deoxycorticosterone, testosterone and progesterone, the effective permeability is sensitive to flow rates. The higher the flow rate, the smaller

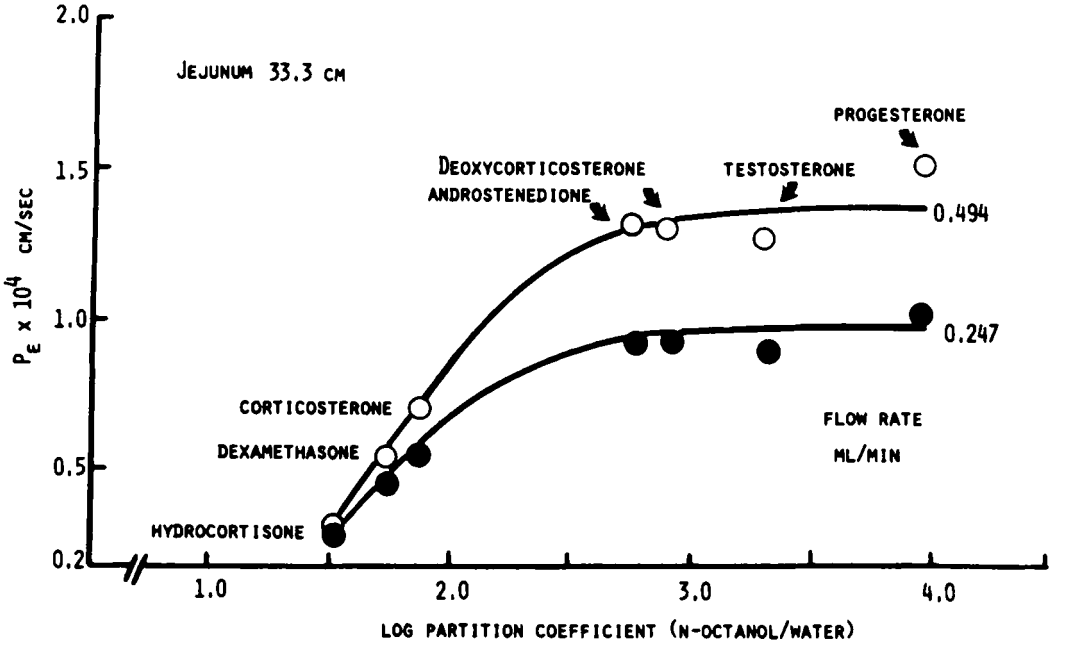


FIGURE 5

The influence of lipophilicity of various steroids on the effective permeability coefficient of the rat jejunal membrane.

the effective thickness of the aqueous boundary layer becomes. Thus, the fraction of steroids absorbed in the plateau regions in Fig. 4 is aqueous boundary layer-controlled.

Barreiro et al.[5] followed the intestinal motility pattern, peak transit time and steady-state absorption of xylose, a passively absorbed pentose sugar, concurrently in the human jejunum. Within the scatter of the data as shown in Fig. 6, rapid motility is accompanied by decreasing transit time and increasing fractions of xylose absorbed are related to longer transit times. With the use of Eqs. 4 and 7 and radius $r \simeq 1$ cm to calculate the effective permeability coefficient, it is found in Fig. 7 that P_e is influenced by the transit time through the effect of the flow

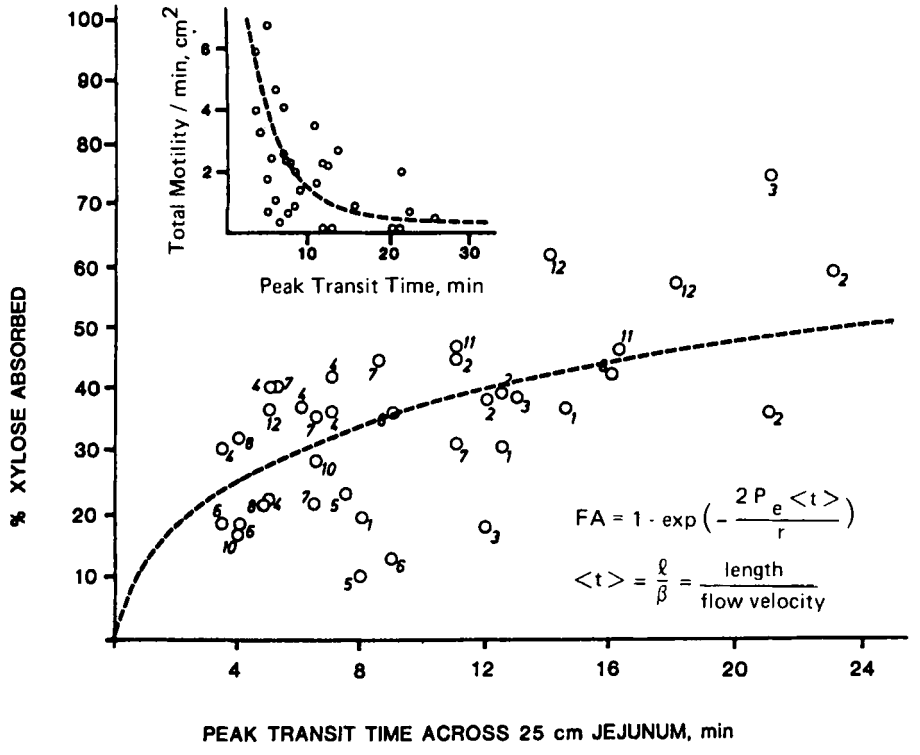


FIGURE 6

The effect of motility of the jejunum on the peak transit time of a solute marker and steady-state absorption of xylose[5]. The data shows inter- and intra-subject variations in 12 human volunteers each identified by a number. Each subject was fasted overnight and intubated for the steady-state perfusion and motility studies. The curve in the xylose plot is the theoretical curve obtained by computer fitting of the physical model described in the text.

velocity on the aqueous boundary layer thickness. The data in Fig. 7 are in reasonable agreement with the computer fitted curve obtained by nonlinear regression analysis of the following expression comparable to Eq. 5:

$$P_e = \frac{1}{\frac{k\,\beta^{-n}}{D} + \frac{1}{P_m}} \qquad \text{(Eq. 9)}$$

where

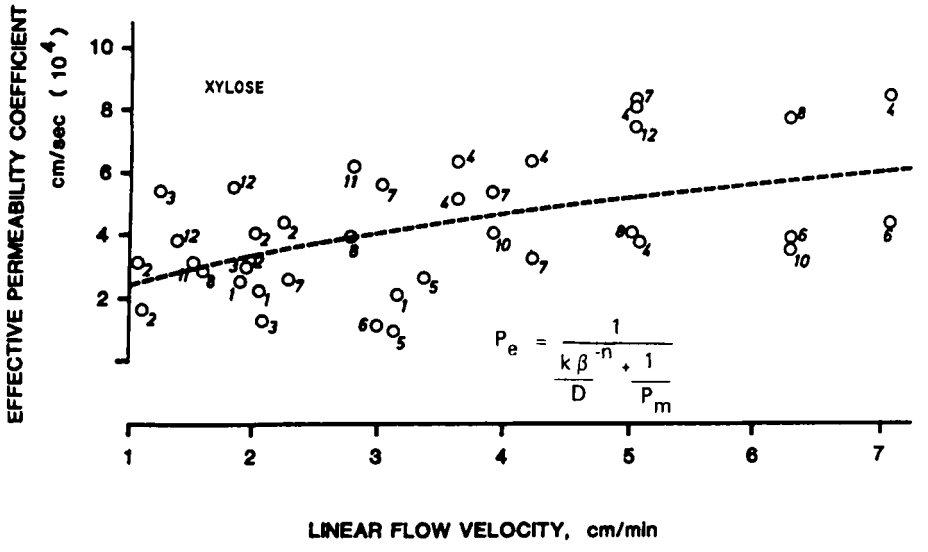


FIGURE 7

Change in the effective permeability coefficient of xylose in the human jejunum with flow velocity. The data were generated from Fig. 6 and the curve was obtained by nonlinear computer fit of Eq. 9.

P_m = membrane permeability coefficient which is 2.84×10^{-3} cm/sec for xylose

P_{aq} = permeability coefficient of the aqueous boundary layer $= D/k\,\beta^{-n}$, cm/sec

D = aqueous diffusion coefficient, which is 1.13×10^{-5} cm^2/sec for xylose at 37°C

k = a parameter descriptive of the geometry of the intestinal lumen and kinematic viscosity, which is 5×10^2 when the flow velocity β is expressed in cm/min

n = a constant which is 0.5

In turn, the P_e was used to generate the theoretical curve in the fraction absorbed versus $<t>$ plot in Fig. 6 using

$$F.A. = 1 - \exp\left(-\frac{2\,P_e\,<t>}{r}\right) \qquad \text{(Eq. 10)}$$

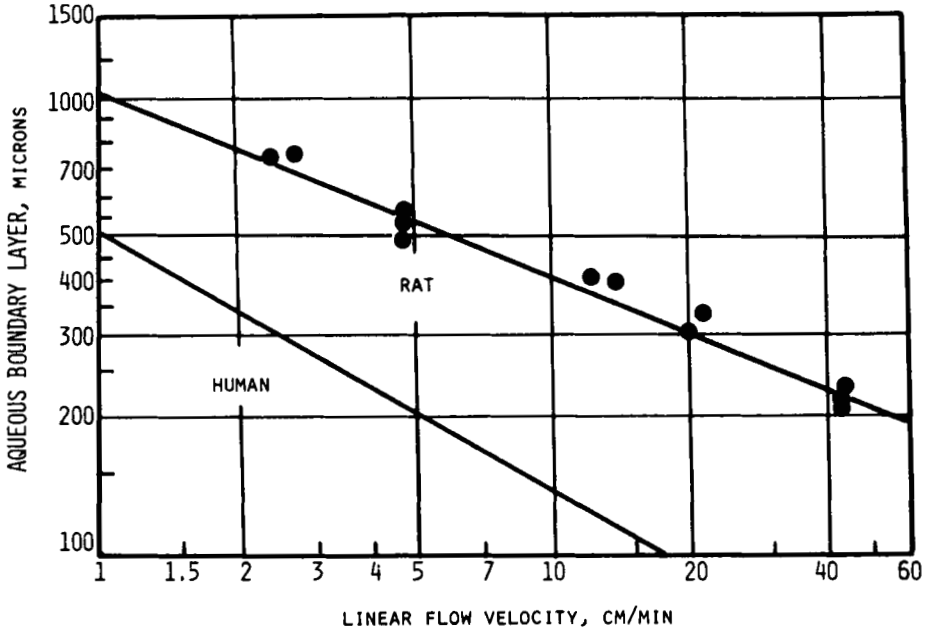


FIGURE 8

Relationship of the effective aqueous boundary layer thickness with flow velocity in the jejunum of anesthestized rats and human in vivo.

Figure 8 shows a comparison of the relationship of the boundary layer thickness and fluid flow velocity between the human and rat. When the effective thickness, δ, is expressed in microns and β in cm/min,

Human: $\delta = 500\ \beta^{-0.5}$

Rat: $\delta = 1000\ \beta^{-0.4}$

The values of δ and β should be viewed as useful quantities within the hydrodynamic conditions they were measured. The relationships were determined in intubated, motile jejunum in man[5] and perfused, distended, isolated jejunum segments in anesthesized rats[10].

Physical Model Description of the Reserve Length for Pharmaceutical Systems

In this section we describe the key physicochemical, physiological and dosage form factors and their mathematical relationships within the comprehensive framework of the anatomical reserve length. As we proceed, two major assumptions are made. The portion of the gastrointestinal tract, in which we strive to attain 90 to 95% drug absorption, is confined to the small intestines. This does not necessarily exclude the stomach and large intestine as potentially important compartments. Next, in this initial writing, we assume the small intestine to be homogeneous for simplification, although we are cognizant of various physiological elements that distinguishes the duodenum, jejunum and ileum from each other. However, accounting for heterogeniety is not an insurmountable problem for it could be overcome by integrating over the small intestine taken as piece-wise homogeneous segments.

A. Solutions. The reserve length at which 95% of the drug in solution is absorbed is given by[12,13,14]:

$$(R\,L)_{soln} = L - \ell^*_{soln} = L - \frac{3\beta r}{2P_e} - \frac{3\alpha}{\beta} \qquad \text{(Eq. 11)}$$

where

ℓ^*_{soln} = intestinal length at which 95% of the drug in solution is absorbed, cm

β = linear flow velocity, cm/sec

r = intestinal radius, cm

P_e = effective permeability coefficient, cm/sec

α = axial dispersion coefficient, cm^2/sec

Axial dispersion coefficients in the human intestine range from 0.1-0.5 cm^2/sec for linear velocities of 0.7-5 cm/min. In practice, $3\alpha/\beta$ is sufficiently small and could be ignored. Further descriptions of P_e are found in Table 4 for a variety of drug molecules and transport mechanisms.

B. Suspensions. The reserve length for essentially monodispersed suspensions undergoing concurrent fluid and particle flow, dissolution and absorption is expressed by[15]:

$$(RL)_{susp} = L - \left(\ell^*_{soln} + \ell^*_{particle} \right)$$

$$= L - \left[\frac{3\beta r}{2 P_e} + \frac{\rho \beta_p a_o^2}{2 D S} + \frac{\beta_p M}{\pi r^2 P_e S} \right] \qquad \text{(Eq. 12)}$$

where

ρ = density of the drug, gm/cm^3

a_o = initial particle radius, cm

D = aqueous diffusion coefficient, cm^2/sec

S = effective drug solubility, gm/cm^3

β, β_p = linear velocity of the fluid and particles, respectively, cm/sec

M = dose, gm

and the other parameters have been previously defined. The ℓ^*_{soln} is the same as Eq. 11 and $\ell^*_{particle}$, the length at which the particles are completely dissolved, is comprised of a dissolution

TABLE 4

Effective Permeability Coefficient Expressions[14]

Passive transport of weak electrolytes	$P_e = \dfrac{1}{\frac{1}{P_{aq}} + \frac{1}{P_o X_s + P_p}}$
Passive transport of non-electrolytes	$P_e = \dfrac{1}{\frac{1}{P_{aq}} + \frac{1}{P_o + P_p}}$
Passive transport of amphoteric drugs	$P_e = \dfrac{1}{\frac{1}{P_{aq}} + \frac{1}{P_o X_s^{\pm} + P_p (X_s^+ + X_s^-)}}$
Passive transport of micelle solubilized & reversibly bound drugs	$P_e = \dfrac{1}{\frac{1}{P_{aq} - P^*_{aq}} + \frac{1 + k^* (SAA)}{P_o}}$ $P^*_{aq} + \frac{}{1 + k^* (SAA)}$
Passive transport with membrane metabolism	$P_e = \dfrac{1}{\frac{1}{P_{aq}} + \frac{1}{\frac{K X_s \sqrt{kD}}{\tanh(L\sqrt{k/D})}} + P_p}$
Active transport of drugs (a) linear	$P_e = \dfrac{1}{\frac{1}{P_{aq}} + \frac{1}{J_{max}/K_M}}$
(b) concentration dependent	$P_e = \dfrac{1}{\frac{1}{J_{max}/K_M} + \frac{1}{2 P_{aq}} + \frac{C_b}{J_{max}}}$

Def. of permeability coefficients:

P_{aq}, aqueous boundary layer for solutes

P^*_{aq}, aqueous boundary layer for micelles

P_p, aqueous pores

P_o, membrane lipid pathway

Def. of other terms:

k^*, drug-micelle dissociation constant

(SAA), surfactant agent conc.

K, lipid membrane/water partition coefficient

D, membrane diffusion coefficient

L, membrane thickness

k, apparent 1st order enzyme reaction constant

J_{max}, maximum active transport flux per cm^2

K_M, Michaelis transport constant

rate-controlled term and a membrane-controlled, dose-dependent term. If the suspension slurry is very dilute and the effective permeability is large, one gets the reserve length for the dissolution rate-controlled case:

$$(RL)_{susp} \simeq L - \left[\frac{3 \beta r}{2 P_e} + \frac{\rho \beta_p a_o^2}{2 D S} \right] \qquad \text{(Eq. 13)}$$

It is readily seen in Eqs. 12 and 13 that

$$\lim_{\substack{a^2/S \to 0 \\ S \to \infty}} (RL)_{susp} = (RL)_{soln} \qquad \text{(Eq. 14)}$$

which, for example, is brought about by using submicron particles and highly soluble forms of the drug.

The velocities of the fluid and the particles may be very different. The particles can lag behind the faster moving liquid in a settling suspension to bring about longer mean transit times for particles in the flowing liquid[16]. More discussion will follow later. In the above equations, we have assumed that there is always fresh liquid in the intestinal tract to replace that flowing faster than the particles.

C. Bioavailability and Bioequivalence. The reserve length is an assessment of bioavailability, which may be defined as the rate and extent of absorption. A positive reserve length results in complete absorption of the dose while the effective permeability coefficient of the solute permeant and also the dissolution rate, in the case of suspensions, influence the absorption rate. Bioequivalence is then the comparison of the bioavailability of

drug products containing the same amounts of therapeutically active ingredients and administered in the same dosage regimen. Accordingly,

$$\text{Bioequivalence} = \frac{(RL)_x}{(RL)_{std}} = 1.0 \qquad \text{(Eq. 15)}$$

$$\text{Bioinequivalence} = \frac{(RL)_x}{(RL)_{std}} \gtrless 1.0 \qquad \text{(Eq. 16)}$$

where the reserve length may be appropriately expanded mathematically.

In striving to put bioavailability and improvement of drug formulations on a quantitative, predictive and mechanistic plane of understanding within the intestinal tract, the reserve length approach differs from the conventional approach taken to evaluate and optimize drug formulations which is based on (a) blood (or plasma) concentration of the drug versus time measurements in man or animals, (b) subsequent pharmacokinetic analysis to obtain pseudo-first-order absorption rate constants, and (c) seeking in vitro disintegration/dissolution rate correlations with in vivo absorption inferring that dissolution of solid dosage forms is the rate-determining step. Here, the pseudo-absorption rate constant is an ill-defined descriptor of a host of concurrent events, i.e., disintegration and dissolution, stomach emptying, fluid and particle flow, membrane transport, physicochemical interactions in the intestinal lumen, etc. Overall, the conventional approach leads to empirical strategies toward improving the bioavailability of drug formulations. The reserve length approach does not pre-

clude the use of appropriate in vitro dissolution and blood level measurements; however, it serves as a rational means in bridging the gap. It should be obvious that, unlike the assessment of bioavailability through blood level-time studies, considerations of stomach emptying rates, tissue distribution and elimination kinetics do not enter into the definition of bioavailability according to the reserve length concept since only those factors related to the intestinal length at which the drug is 90-95% absorbed are of concern.

THEORETICAL APPLICATION OF THE RESERVE LENGTH IN OPTIMIZING THE BIOPHARMACEUTICAL DESIGN OF ORAL FORMULATIONS

In this section we show simple applications of the reserve length concept to the biopharmaceutical design of oral formulations. We strive to use realistic examples and situations as much as possible. To set quantitative boundaries to many of the important physicochemical and physiologically based parameters in our calculations, we also review the pertinent literature for what is known about the permeability coefficients of drugs in the human intestine and flow rates and transit times of solute and particle markers. The effects of food and drugs on gastrointestinal motility are discussed within the context of the reserve length.

Solutions

One of the essential parameters of the reserve length is the effective permeability coefficient of the drug solute for

the aqueous boundary layer and membrane. This is readily calculated from experiments involving the steady-state perfusion of drug solutions within defined intestinal segments in intubated humans or large animals (dog and monkey). Table 5 lists permeability coefficients of a variety of solutes in the human intestines ranging from 0.1-9 x 10^{-4} cm/sec. These estimates should be considered from the viewpoint that the external pump flow rates were employed in the calculations by Eq. 4. As Barriero et al.[5] and Dillard et al.[17] have shown, the pump flow rates can be quite different from the average flow rates due to the peristaltic activity in the small intestines. In our judgment, the maximum P_e should be no more than 5 x 10^{-4} cm/sec under maximum *in vivo* flow conditions and this upper limit would correspond to the permeability coefficient of the aqueous boundary layer for highly membrane permeable molecules (for example, progesterone, glucose and amino acids).

To illustrate the interrelationship of the flow velocity and effective permeability coefficient on the reserve length, let us rearrange Eq. 11 as follows:

$$\beta^* = \frac{2\,P_e\left(L - (RL)_{soln}\right)}{3\,r} \qquad \text{(Eq. 17)}$$

Here, β^* is the critical flow velocity just above which the reserve length $(RL)_{soln}$ for a drug solute, having a permeability coefficient P_e, is smaller than stated. The term, $L-(RL)_{soln}$, is the length at which absorption is effectively completed. With the small intestinal length L = 325 cm and average radius r = 1 cm, the graph of β^* *versus* P_e for $(RL)_{soln}$ = 0, 100, 200 and 300 cm

TABLE 5.

Results of Steady-State Perfusion Studies in Human Small Intestines

Intestinal Segment	Permeant	Flow Rate ml/min	Fraction Absorbed	$P_e \times 10^4$ cm/sec[a]	References
Duodenum, 25 cm	Triamcinolone	15	4	0.6	Schedl[8] (1965)
	Triamcinolone acetonide	15	24	4.4	
	Cortisol	15	44	9.2	
	Cortisol-21-acetate	15	61	14.9	
	Progesterone	15	90	--	
Jejunum, 100 cm	Triamcinolone	15	2	0.1	Schedl[8] (1965)
	Triamcinolone acetonide	15	36	1.8	
	Cortisol	15	52	2.9	

Ileum, 100 cm	Triamcinolone	15	3	0.1	Schedl[8] (1965)
	Triamcinolone acetonide	15	43	2.2	
	Cortisol	15	27	1.3	
Duodenum and jejunum, 90 cm	Metoprolol	2	85	1.2	Godbillon et al.[9] (1981)
Jejunum, 70 cm	Glucose 1.25M	3.6	64	1.4	Heckelsweiler et al.[11] (1979)
	Glucose 0.74M	3.2	74	1.6	
Jejunum, 50 cm	Cholesterol in bile acid and 1-monoglyceride micelles	6.6	73	4.6	Simmonds, Hofmann and Theodor[18] (1967)
Jejunum, 25 cm	Oleic acid in taurocholate micelles	15	22	3.9	Hoffman & Hofmann[19] (1973)

[a]Effective permeability coefficient P_e is calculated by Eq. 4.

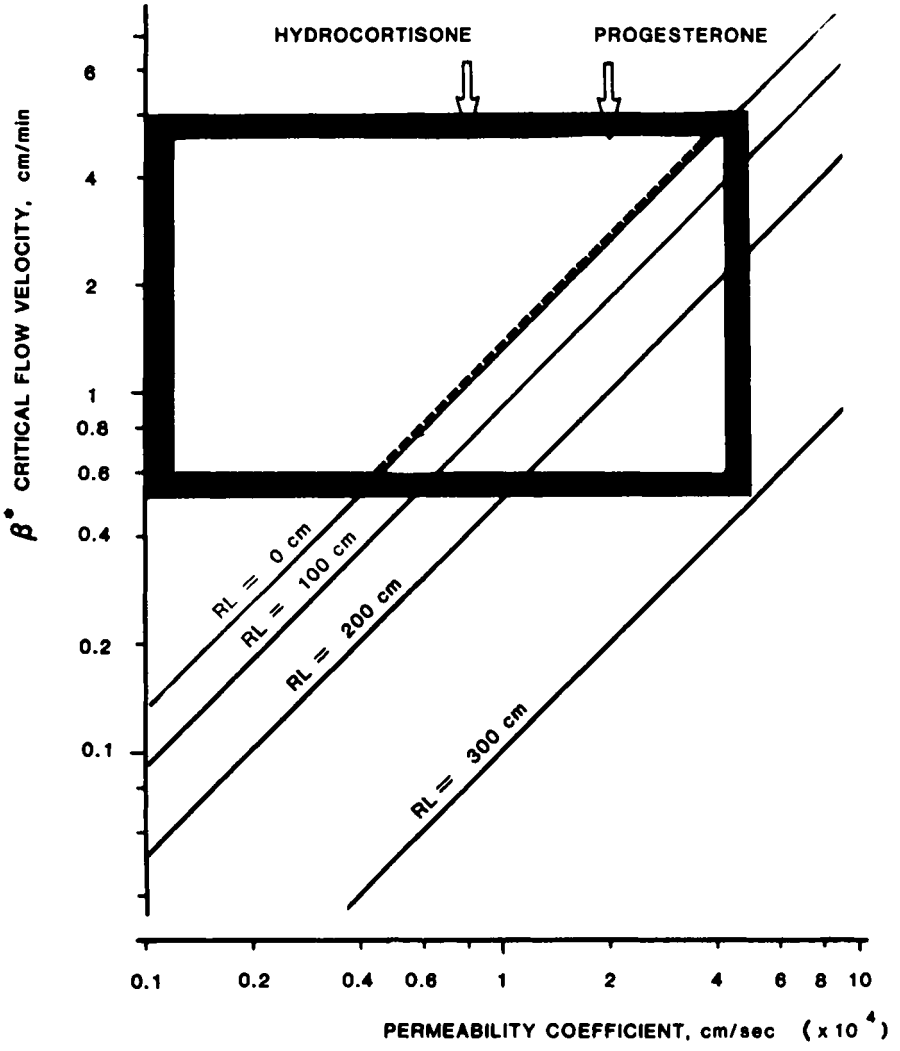


FIGURE 9

Interrelationship of fluid flow velocity and effective permeability coefficient on the reserve length of drugs in solution. The rectangular box defines the range of velocities and permeability coefficients found in man.

is displayed in Fig. 9. The shaded portion is the area of interest bounded by β* ranging from 0.5 to 5 cm/min and P_e from 1×10^{-5} to 5×10^{-4} cm/sec. These ranges of values are relevant to human situations. Complete absorption is predicted in that

part of the shaded area below the RL = 0 line, i.e., the zero reserve length line. Therefore, the shaded area above the zero reserve length line means incomplete absorption within the small intestine--a negative reserve length situation. Consequently, drugs having low permeability coefficients of $1 - 4 \times 10^{-5}$ cm/sec (for example, small hydrophilic molecules traversing the membrane via the aqueous pore pathway or drugs reversibly bound to polymers and micelles) may be completely absorbed only at low flow velocities; otherwise, at reasonably higher velocities absorption is complete somewhere beyond the ileoceacal junction. In contrast, drugs having higher $P_e \geq 1 \times 10^{-4}$ cm/sec remain within the predicted limits of complete absorption and, even at high flow velocities, there will still be excess gut length left for absorption.

In Fig. 9, predictions are made for hydrocortisone and progesterone in dilute solutions and supported by human absorption studies (Schedl, 1965)[8]. Their physicochemical and intestinal transport properties are found in Table 6. Hydrocortisone is less permeable than progesterone which is an aqueous boundary layer-controlled permeant.

Finally, inter- and intrasubject variations on $(RL)_{soln}$ should be discussed. Drug molecules flow exactly as the characteristics of the current of fluid flowing down the tract. From this perspective, the marked variations in flow velocities (1 to 7 cm/min) within and between human volunteers[5] (see Figs. 6 and 7) will have a substantial influence on the variability of $(RL)_{soln}$. The influence is largely through the transit time and less through the aqueous boundary layer effects on P_e.

TABLE 6

Values of Various Physical Constants Used in Theoretical Predictions

Physical Parameters	Progesterone	Hydrocortisone	Reference
Density, ρ	1.1 gm/ml	1.1 gm/ml	Merck Index[20]
Aqueous diffusion coefficient, D	8×10^{-6} cm^2/sec	8×10^{-6} cm^2/sec	Amidon et al[21] (1982)
Solubility in water, S	12 mcg/ml	280 mcg/ml	Flynn et al[22] (1976)
Partition coefficient n-octanol/water	3.99	1.5	Hansch & Leo[23] (1979)
Effective permeability coefficient, P_e	2×10^{-4} cm/sec	8×10^{-5} cm/sec	Schedl[8] (1965)
Average linear flow velocity in intestinal tract, β	0.5-1.0 cm/min	0.5-1.0 cm/min	Soergel[24] (1971)
Average intestinal radius, r	1 cm	1 cm	Soergel[24] (1971)
Average length of small intestines, L	325 cm	325 cm	Netter[25] (1962)

Suspensions

High slurry density suspensions. Let us consider the reserve length for suspensions which is expressed by Eq. 12 and repeated below.

$$(RL)_{susp} = L - \left[\frac{3\beta r}{2P_e} + \frac{\rho \beta_p a_o^2}{2DS} + \frac{\beta_p M}{\pi r^2 P_e S} \right] \qquad \text{(Eq. 12)}$$

Upon setting $(RL)_{susp} = 0$, we get

$$\beta_p^* \left(\frac{\rho a_o^2}{2DS} + \frac{M}{\pi r^2 P_e S} \right) = L - \frac{3\beta r}{2P_e} \qquad \text{(Eq. 18)}$$

where β_p^* is the critical flow velocity of the particles. At particle velocities greater than β_p^*, the reserve length is negative.

Because hydrocortisone is about 3-fold less membrane permeable and 20-fold more soluble than progesterone (see Table 6), these steroids of contrasting properties provide good examples for the reserve length discussions of suspensions. Log β^* versus log M plots were constructed for specified fluid flow velocities of 0.5 and 1.0 cm/min and particle sizes. In Fig. 10 the profiles for particle radii below 10 microns are essentially linear. Here, the particle size effect via the term, $\rho a_o^2/2DS$, is negligible so that the logarithmic form of Eq. 18 becomes

$$\log \beta_p^* = \log \left[\pi r^2 P_e S \left(L - \frac{3\beta r}{2P_e} \right) \right] - \log M \qquad \text{(Eq. 19)}$$

Thus, at relatively high doses the dissolution of particles flowing down the tract is controlled by the membrane permeability, and particle velocities much smaller than the fluid velocities are required to attain positive reserve lengths. On the other hand,

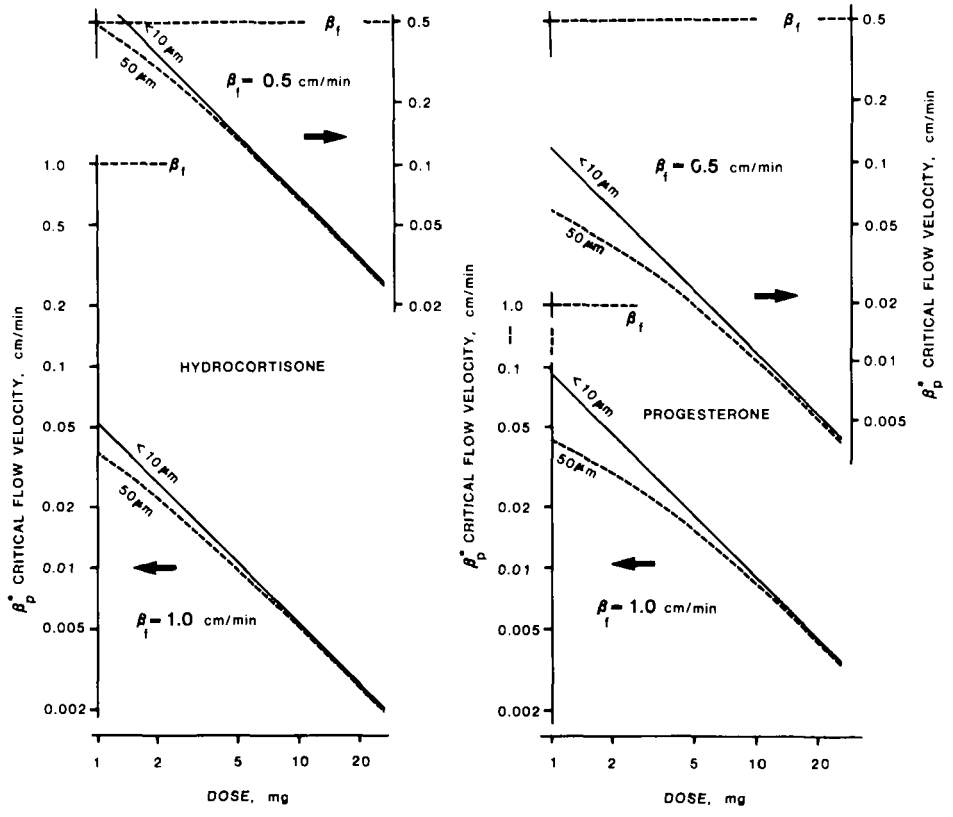


FIGURE 10

Illustration of the required flow velocities of progesterone and hydrocortisone particles at given fluid flow velocities in order to attain complete absorption within the small intestine for relatively concentrated suspensions varying in dose. The critical particle velocity is the velocity beyond which the reserve length is negative.

the profiles for particle radii greater than 50 microns and, particularly at low doses, deviate from linearity toward smaller β_p^*; the deviation reflects the increasing contribution of particle size on dissolution and concurrent absorption.

The interesting feature of the theoretical calculations is the influence of the dose on the reserve length. In blood level pharmacokinetics of orally administered suspensions, apparent

dose effects are usually attributed to nonlinear saturation absorption kinetics at the membrane level. The theory indicates that the effects of dose may be largely related to membrane-controlled dissolution of the particles and changes toward smaller reserve lengths. Furthermore, the maximum particle velocity β_p^* to achieve complete absorption in the small intestine dramatically decreases with increasing dose.

Between hydrocortisone and progesterone, their differences in the β_p^* at any corresponding dose lie in the interplay of P_e, S and β and could be readily understood with the aid of Eq. 19. For example, at the 1 mg dose of less than 10 micron radius particles and β = 1 cm/min case, β_p^* is about 0.1 cm/min for progesterone and 0.05 cm/min for hydrocortisone. Here, the high P_e of the progesterone solute sufficiently compensates for the low solubility as compared to that for hydrocortisone. Interestingly, the β_p^* for progesterone is about 0.1 cm/min for fluid velocities β of 0.5 and 1.0 cm/min, while β_p^* for hydrocortisone is about 0.7 cm/min for β = 0.5 cm/min,and 0.05 cm/min for β = 1 cm/min. Hence, the required particle flow velocity for complete absorption for the highly membrane permeable progesterone is somewhat insensitive to reasonable ranges of fluid flow velocities. In contrast, the less membrane permeable hydrocortisone requires particle velocities of about 10-to 20-fold smaller when the fluid velocities are only doubled.

As a result of our theoretical analyses, the phenomena of simultaneous particle flow in the fluid stream and plating out

of particles along the surface of the small intestinal tract have appealing features in solving a variety of problems associated with the bioavailability of oral suspensions of high doses and low water soluble drugs. We estimate that if the holdup of particles at the surface occurs to the extent that the effective particle velocity is 1% of the normal range of fluid velocities, we will have taken a significant step in overcoming the disadvantages of wide variations in fluid flow and, consequently, achieving predictable and uniform bioavailability in humans. How this could be achieved is a gap area for research.

Very dilute slurry density suspensions. We now turn to the very dilute suspension case in which there is no slurry concentration effects on the dissolution rate and absorption. The reserve length expression appropriate for this case is Eq. 13 which was previously described.

Using the examples of progesterone and hydrocortisone, Fig. 11 shows the reserve length versus particle radius for which the particle velocity, β_p, is taken to be equal to the fluid velocity, β. In general, the reserve length gets progressively smaller with increasing particle size at a much faster pace for progesterone as compared to hydrocortisone. This is attributed principally to the lower solubility and, hence, the lower dissolution rate of progesterone particles despite the fact that progesterone molecules are much more membrane permeable than that for hydrocortisone. The plateau regions indicate that the rate-determining step is the transport of the solute across the

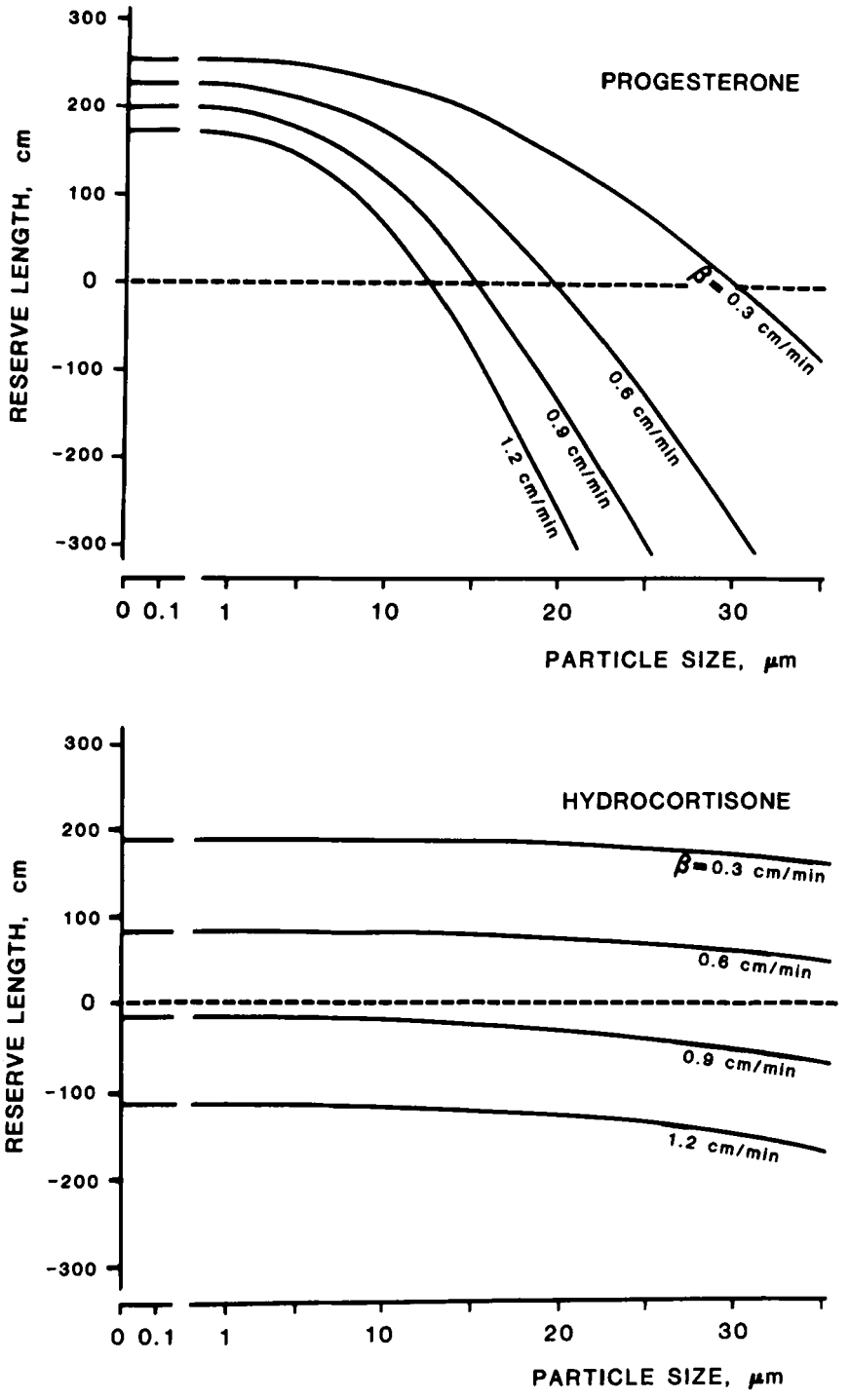


FIGURE 11

Illustration of the influence of particle radius and flow velocity on the reserve length of very dilute suspensions of progesterone and hydrocortisone. The particle and fluid velocities are taken to be equal.

aqueous boundary layer and membrane, while the decreasing regions reflect the increasing role of the dissolution step with increasing particle size. Since hydrocortisone is more soluble than progesterone, the plateau region extends over a larger particle size range. While an appreciable gain in progesterone solubility could be conceivably achieved through micelle solubilization, for instance, by the introduction of conjugated bile acids and lecithin from biliary secretions, there will be a decrease in the effective permeability coefficient[21,26]. Similarly, the gain in solubility and decrease in permeability for hydrocortisone should be less significant. One cannot comment enough on the marked influence of the fluid and particle velocities on the mean transit (or residence) times of the particle and the solute on the reserve length.

In summary, the question of "how small should micronized particles be such that dissolution is not the rate-determining step" depends upon the interrelationships of solubility, membrane permeability, flow velocity and particle size and, interestingly, could be quantitatively estimated.

Evaluation of a Case History. The availability of studies illustrating the reserve length of suspensions is scarce. This is because human intubation studies are not usually performed to systematically investigate the phenomenological events in the absorption of suspensions. In our estimation there is, however, a study that comes close as an example for examination in the light of the anatomical reserve length.

In the course of determining the oral bioavailability of chenodeoxycholic acid in man, vanBerge-Henegouwen and Hofmann[6] infused bolus doses of 25, 200 and 400 mg doses of micellar solutions of the bile acid as the sodium salt into the distal duodenum of fasted subjects from an indwelling nasojejunal tube. Measurements on intestinal aspirates showed rapid and complete passive absorption of the molecules within 50 cm indicating a large anatomical reserve length of 275 cm for an estimated 325 cm small intestine. The absorption was corroborated with areas under the blood level curve (AUC) over a 4-hour period. Thereafter, the absorption of ingested gelatin capsules containing 200 mg chenodeoxycholic acid as the weak acid and sodium salt was assessed by 4 hour AUC determinations. Both preparations were completely absorbed in which the more rapid absorption of the sodium salt was anticipated because it was previously found to dissolve much more rapidly than the protonated acid[27]. Commercial capsules containing small particles of 400 mg protonated bile acid were also found to be completely bioavailable. In terms of the reserve length concept, it appears that oral capsules of the weak acid form are well absorbed within the small intestine and the sodium salt preparation has a longer reserve length. The lone exception of a commercial preparation contained large crystals[27] (100 by 30 microns cubic or tetragonal crystals) which resulted in poor absorption and, possibly, negative reserve length. After the large particles were milled, complete absorption resulted. The bioavailability of chenodeoxycholic acid was not affected when taken with meals.

Small Intestinal Flow and Transit

In the preceding discussions the flow and transit time of solutes and particles are able to have dramatic effects on the reserve length of solutions and suspensions. Table 7 is a literature survey of transit time observed in humans and dogs.

One should be aware that the method by which the measurements are made will bring about different interpretation of the transit time. In the multi-lumen intubation method, the segment of small intestine is constantly perfused with the aid of a pump (generally 2 to 10 ml/min) and then, after the introduction of a bolus dose of a nonabsorbable dye or ^{14}C-PEG 4000, the solute marker flowing past a fixed distance of the tube is collected with time. Because of the rigthward skew of the nonsteady-state $C(\ell,t)$ versus time t curve, the peak transit time (PTT) is shorter than the mean transit time (MTT) and the difference does not seem to be very large. The presence of a flexible tube and the slow, steady pump flow of liquid are not considered to be serious artifacts to normal gastrointestinal activity. In other methods, the transit times are indicative of the first appearance of the marker at a distal location of the intestinal tract. For example, the pulmonary H_2 appearance time reflects the time of arrival of lactulose in the large intestine. Lactulose is a nondigestable sugar in the small intestine and is readily metabolized by microorganisms in the large intestine followed by absorption and pulmonary excretion of the anaerobically produced hydrogen. Roentgenography and gamma scintigraphy of the gastrointestinal passage of radiopaque sub-

stances, pellets, tablets, and colloids have the distinct advantage in being non-invasive and are generally used as qualitative tools to determine appearance transit times. Lately, quantitative gamma scintigraphy is made possible with the use of a sophisticated computer to focus at small areas of interest (observation window slits) simultaneously at many different, fixed locations of the gastrointestinal tract whereby the change in concentration of ^{99m}Tc-labeled markers with time at the various locations is followed (Fig. 12). Not only can the initial appearance and mean transit times of gamma-labeled solutes and particles be determined from segment to segment, but also the effective axial dispersion coefficients could be estimated to gain insights to the hydrodynamics in the intestine[13,45]. The flow velocities are not necessarily the same throughout the small intestine. Gamma scintigraphy has been used by a number of investigators to study gastric emptying and intestinal transit times[46,47].

As can be seen in Table 7, there seems to be remarkable variations in the flow of marker solutions in the human jejunum between and within normal subjects, ranging from 0.5 to 5 cm/min. Soergel's[24] studies indicate that the average velocity in the ileum is slower than in the jejunum. Although the flow of suspensions appear to be slower as compared to solutions, no real conclusions can be made. Although dogs are suitable animal models for general pharmacokinetic and bioavailability studies, intestinal flow studies are sparse. The flow is generally faster as compared to humans. However, this should not impair their use for dosage form evaluation when this factor is considered.

TABLE 7

Survey of Transit Times and Flow Velocities in Human Intestines and Dogs

Method/Reference	Description	Transit Time[a]	Flow Velocity[b] cm/min
Perfusion of Intubated Small Intestine			
BSP, indocyanine green Dillard et al[17] (1965)	Small intestine, 100 cm	21.4 ± 4.1 min (MTT) (range 17-28 min)	4.67 (3.57 - 5.88)
	Jejunum, 100 cm	30.7 min (MTT)	3.26
	Ileum, 100 cm	18.6 min (MTT)	5.38
PEG-4000, renografin, BSP Barreiro et al[5,28] (1968a,b)	Jejunum, 25 cm	10.9 ± 6.2 min (PTT) (range 3.5-30 min)	2.29 (0.83 - 7.14)
		11.8 ± 5.1 (MTT)	2.21
PEG-4000, BSP Mutachanski et al[29] (1969)	Jejunum, 25 cm	11.9 ± 5.7 min (PTT)	2.8
		11.4 ± 4.7 min (PTT)	2.19
		13.9 ± 5.9 min (MTT)	1.8
		16.0 ± 7.1 min (MTT)	1.56
BSP Brigham et al[30] (1970)	Jejunum, 30 cm, after cholera recovery	7.8 ± 0.9 min (MTT)	3.8
	Jejunum, 30 cm during cholera	10.3 ± 2.7 min (MTT)	2.9

PSP	Soergel[24] (1971)	Jejunum, 70 cm:		
		at fasting	87.5 min (MTT)	0.8
		after lunch	51.4 min (MTT)	1.36
		Ileum, 70 cm:		
		at fasting	175.0 min (MTT)	0.4
		after lunch	175.0 min (MTT)	0.4
PEG-4000	Cupello et al[31] (1976)	Small intestine, 100 cm in children	60 min (MTT)	1.67
PEG-4000	Hardison[32] (1979)	Jejunum, 50 cm	27.6 ± 2.46 (MTT)	1.81
Pulmonary H_2-Excretion				
Lactulose	Bond et al[33,34] (1975) Bond & Levitt[33,34] (1977)	Small intestine in normal human	72.6 ± min	4.13[c]
		Small intestine in gastroectomy patients		
		with diarrhea	35.2 ± 3 min	8.52[c]
		without diarrhea	74.6 ± 5 min	4.02[c]
Lactulose	Corbet et al[35] (1980)	Small intestine:		
		without diarrhea	93.0 ± 6.6 min	3.2[c]
		with diarrhea	54.1 ± 6.3 min	5.5[c]

[a] MTT = mean transit time; PTT = peak transit time; average ± s.d.

[b] Calculated by $\beta = \ell/\langle t \rangle$ or $\ell/t_{appearance}$

[c] Assuming 300 cm intestinal segment

(continued)

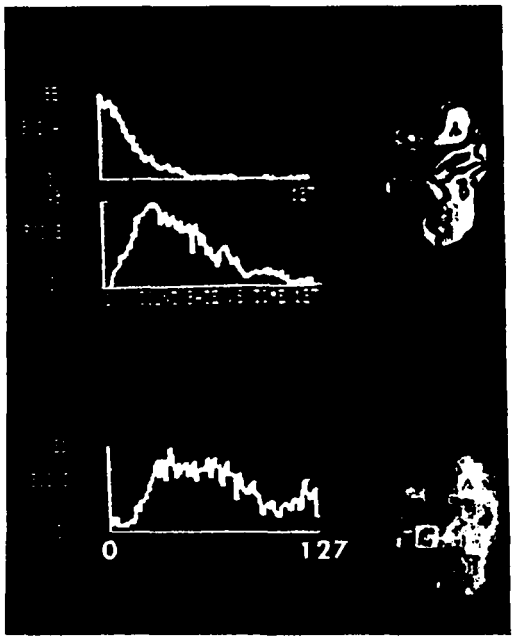
TABLE 7 (cont)

Method/Reference	Description	Transit Time[a]	Flow Velocity[b] cm/min
X-ray of Particles			
$BaSO_4$ viscous suspension Novak[36] (1976)	Small intestine:		
	normal control	126 min	2.38[c]
	lumenal gas distended	78 min	3.85[c]
$BaSO_4$, enteric coated Feinblatt & Ferguson[37] (1956)	Mouth to caecum	4-6 hrs in small intestine after ingestion	1.0 - 1.7[c,d]
Tablets, enteric coated, varying in density Stricker & Kulke[38](1981)	Stomach to caecum	15-60 min in duodenum & jejunum	2.1 - 8.3[e]
		~ 200 min in ileum	~ 0.9[e]
		No effects of density	
Gamma Scintigraphy			
Pellets varying in density Bogentoft et al[39] (1982)	Small intestine:		
	low density pellets	3.8 hrs	1.3[c]
	high density pellets	2.6 hrs	1.9[c]

[d]Assuming one hour in stomach

[e]Assuming length of duodenum & jejunum = 125 cm and length of ileum = 175 cm

Magnetic Transduction			
Mg-ferrite particles Benmair et al[40](1977)	Mouth to caecum	157.5 ± 63.9 min	--
Recovery in Ileostomy Bag			
Pellets, coated, varying in density Bechgaard & Ladefoged[41] (1978)	Mouth to ileostomy bag:		
	low density pellets	7 hr (MTT)	0.8[c,d]
	high density pellets	25 hr (MTT)	0.2[c,d]
Perfusion in Dogs			
PEG-4000 Barbezat[42] (1980)	Jejunum, 30 cm	6.2 min (MTT)	4.8
BSP Bueno et al[43] (1975)	Jejunum:		
	at fasting	--	4.3 ± 2.6
	after feeding	--	23.2 ± 8.6
PEG-4000 Sarr et al[44] (1980)	Jejunum, 75 cm	3 to 15 min	5 - 25



STOMACH, midportion
$t_{0.5}$ = 20 min

JEJUNUM, proximal ~ 25 cm
< t > = 46 min
β = 0.54 cm/min

JEJUNUM, distal ~100 cm
< t > = 64 min
β = 1.6 cm/min

FIGURE 12

Stomach emptying and intestinal flow profiles with time of ^{99m}Tc-diethyltriamine penta-acetic acid chelate marker in a human subject by quantitative gamma scintigraphy (courtesy of Dr. R. Caride of Yale University School of Medicine). Bolus dose of the marker solution was introduced directly into the stomach. The plots show scintigraphic output of count rate versus time over a period of 127 minutes.

In recognizing the wide intra- and inter-subject variations in the intestinal flow of water, we come to the conclusion that one should strive to "neutralize" this natural physiological phenomenon by utilizing biopharmaceutical approaches. This could be achieved by (a) the development of prodrugs and analogs with sufficiently high membrane permeabilities so that the absorption rate is aqueous boundary layer-controlled, (b) increased dissolution rates of particles through increased solubility and/or particle size reduction, and (c) delay of particle transit times.

In striving to prolong the transit of particles, Bechgaard and Lodefoged[41] studied the simultaneous flow of varying sizes of low and high density coated pellets in ileostomy patients utilizing an interesting experimental approach. After the subjects swallowed a gelatin capsule of the color-coded pellet preparation with water and normal activity, food and water were allowed and samples were collected from the ileostomy bags with time. The mean transit times from mouth to ileum for light density (ρ = 1.0) and high density (ρ = 1.6) particles were 7 hours (range 4.5 to 10.3 hrs) and 25 hours (range 23-26.5 hrs), respectively; the effect of particle size (0.3 to 1.7 mm diameter) was not significant (Table 8). However, Bogentoft et al[39] and Stricker and Kulke[38], who could not corroborate the same qualitative findings in normal subjects, questioned the general applicability of the conclusions derived from ileostomy subjects[41,48].

TABLE 8

Influence of Pellets on Transit Time (Mouth to Ileum) Exerted by Density and Size in Human Ileostomy Subjects[41,48]

Pellets	Density gm/cm^3	Diameter mm	Mean Transit Time, hr	
			Average	Range
Hard paraffin*	1.0	0.3 - 0.7	6.9	5 - 9
		1.2 - 1.7	7.3	5 - 8
Barium sulfate*	1.6	0.3 - 0.7	24.6	23 - 27
		1.2 - 1.7	25.4	23 - 28

*Methacrylate-coated

To put the understanding of the flow of suspension in the intestinal tract on a physicochemical basis, Najib and Amidon[49] studied the transit times of suspensions in a horizontal plastic tube. They related particle and fluid densities, particle size, fluid viscosity and fluid velocity to the transit times of a suspension and its liquid vehicle by a dimensional anaysis approach.

In connection with attempts to increase the transit time of particles, the strategy of promoting polymer binding to the surface of epithelial cells has been suggested[50].

Effects of Food, Fasting and Drug Activity

Food has long been recognized to influence the absorption and bioavailability of drugs. The reasons are many: (a) interference with tablet disintegration and dissolution, (b) delayed gastric emptying allowing for more time for complete dissolution of drug solids (nonelectrolytes and weak bases) but decreasing the apparent absorption rate, (c) increased intestinal motility and flow, (d) stimulated bile flow causing bile acid micelle solubilization of drugs, (e) binding of drugs to food substances, (f) stimulated pancreatic flow of enzymes, (g) drug uptake by emulsified oil droplets, and (h) hindered bulk diffusion of drugs. Gibaldi[51], Melander[52] and Beermann[53] have presented comprehensive reviews on this subject.

Table 9 gives a review of studies on food effects on the absorption and possible reasons given by the investigators for the observed bioavailability of drugs. It is seen that the

improved bioavailability of a large number of drugs has been ascribed principally to delayed gastric emptying giving rise to more complete dissolution of the drug solid, and micelle solubilization by bile acids. Most of the examples are drugs of low water solubility. In some cases, slow gastric emptying is seen to decrease the absorption rate as observed by blood level measurements; and, in other cases, no significant changes in bioavailability occurred. Thus, systematic studies are needed to understand the effects of food on drug absorption with the aid of test meals.

In the fasting state drug absorption should be viewed from the perspective of the interdigestive migrating motor complex (see Hofmann and Code in this symposium book). The complex is a cyclic band of motor activity which begins in the stomach and propagates in the small intestine. When one such complex reaches the ileum, another one begins in the stomach. The phenomenon occurs in dogs, other animals[61-63], and humans[64-67]. In dogs the cycle recurs every 1 to 2 hours and the calculated length of the band is about 30 cm in the proximal small intestine and about 10 cm in the distal portions. In the stomach and at each level of the small intestines, there are four phases in a cycle: phase I, low level motor activity; phase II, random increases in motor activity; phase III, continuous occurrence of intense motor activity; phase IV, rapid decrease in the intensity of motor activity. The motor complex is abolished by the ingestion of food.

The interdigestive motor complex is most likely responsible for the wide inter- and intrasubject variation in the peak transit

TABLE 9

Influence of Food on Absorption and Bioavailability of Drugs in Man

Drug	Food	Comments	Reference
Hydrochlorothiazide		Prolonged gastric stay leading to more complete drug dissolution	Melander[52] (1978) Beermann[53] (1981)
Spironolactone		Improved drug dissolution due to prolonged gastric stay; possible solubilization of drug by bile acids due to enhanced bile secretion	" "
Digoxin	Standardized breakfast	No change in bioavailability, but decreased absorption rate; delay of gastric emptying reduced absorption rate, but dissolution is complete	Greenblatt et al[54] (1974) Johnson et al[55] (1978)
Theophylline	High protein meal vs high fat and high carbohydrate meals	High protein meals led to faster absorption and higher bioavailability	Welling et al[56] (1975)
Isoniazid	Standardized breakfast	50% reduction of peak concentration and bioavailability due to delayed gastric emptying and change of gastrointestinal pH	Melander et al[57] (1976)

Tetracyclines	Calcium containing food, e.g., milk, cheese	Formation of stable chelates.	Melander[52] (1978) Beermann[53](1981)
Nitrofurantoin		Food induced delay of gastric emptying allows for better dissolution of drug in stomach and increase apparent solubility in small intestine; better bioavailability but reduced absorption rate	Bates et al[58] (1974)
Griseofulvin	High fat meal	Fat induced enhancement of drug dissolution	Melander[52] (1978) Beermann[53] (1981)
Dicoumarol		Delayed gastric emptying improves dissolution in the stomach and therefore higher apparent solubility in small intestine	" "
Phenytoin		Marked increase of bioavailability, possibly induced by slower gastric emptying and therefore better dissolution, or by increase in bile secretion and subsequent drug solubilization	" "
Riboflavin	Carbonate beverage containing phosphoric acid	Increased bioavailability due to delayed gastric emptying	Houston & Levy[59] (1975)

(continued)

TABLE 9 (cont.)

Drug	Food	Comments	Reference
Propoxyphene Norpropoxyphene	Various test meals and fluid	Delay of absorption due to delay of gastric emptying, but no effect on bioavailability; increased fluid intake decreased propoxyphene bioavailability	Welling et al[60] (1976)
Furosemide		No significant food effects	Kelly et al[61] (1974)
Propylthiouracil Oxazepam Metronidazole Melperone Sulfasomidine		No significant food effects	Melander[52] (1978) Beermann[53] (1981)

time, xylose absorption and motility of the proximal jejunal segment shown in Figs. 6 and 7. If it were not for the concurrent measurements of the peak transit time and motor activity, the wide variations in xylose absorption would not have made sense. Variability in absorption was related to variability in flow. This points out the importance of the simultaneous use of nonabsorbable and nonadsorbable dye solutes as flow markers, transport markers (such as glucose and amino acids in dilute solution) for the determination of the permeability of the aqueous boundary layer, and lastly a marker (such as PEG-4000) to correct for water fluxes, in addition to determining drug absorption in animals and humans by gastrointestinal intubation methods. The use of pressure tranducers to establish the phase(s) of motor activity within which the intubation studies are performed would also be desirable.

The interdigestive motor complex has been clearly shown to be responsible for the clinically recognized intraindividual variation in the results of repeated oral glucose tolerance tests. Thompson et al[68] showed that the variation in blood level glucose in intubated subjects could be produced by ingestion of the glucose solution during different phases of the normal fasting motor activity cycle of the stomach. The result is different stomach emptying rates of glucose to the absorptive surface of the small intestine. Such variation was not seen when glucose was administered intraduodenally during the same phases in activity; however, in our opinion, this may not be surprising in view of the fact that glucose is a rapidly absorbable, aqueous boundary layer-

TABLE 10

Effects of Drugs and Hormones on Gastrointestinal Motility and Transit and on the Absorption in Humans

Transit/Motility	Drug	Comments	Reference
Increased transit time and decreased motility	Propantheline	Increase of digoxin absorption and availability	Manninen et al[69] (1973)
	Propantheline	Increase of hydrochlorothiazide absorption by reduction of gastric emptying leading to complete dissolution	Beermann and Groschinsky-Grind[70] (1978)
	Atropine	Increase of transit time by 38% and and bile acid excretion by 38%	Hardison et al[32] (1979)
	Propantheline	Increase of riboflavin absorption due to prolonged residence in proximal small intestine	Levy et al[71] (1972)
	Propantheline	Delay in paracetamol absorption by decreased stomach emptying	Nimmo et al[72,73,74] (1971,1973,1979)

	Nifedipine Diltiazem Glucagon Epinephrine	Decrease of small intestinal motility	Walus and Jacobson[73] (1981)
Decreased transit time and increased motility	Metoclopramide	Decrease of digoxin absorption	Manninen et al[69] (1973)
Decreased transit time and increased motility	Methacholine Physostigmin Acetylcholine Morphine Bradykinin Serotonin Gastrin Prostaglandin $F_{2\alpha}$	Motility increase	Walus and Jacobson[75] (1981)
	Cholecystokinin	Shortening of transit time	Thompson and Amberg[76] (1978); Mutachanski et al[77] (1972)

controlled permeant. On the other hand, we would expect significant variations with membrane-controlled permeants, xylose and hydrocortisone for example.

As shown in Table 10, drugs can influence their own gastrointestinal absorption as well as other drugs through their pharmacological effects on gastrointestinal motility and, thereby, the residence time (or transit time) in the stomach and small intestine. Compounds having anticholinergic activity, such as atropine and propantheline, slows down gastric emptying and intestinal flow, while those possessing cholinergic activity (metoclopramide) have the opposite effects. Ordinarily, they are not employed as additives to affect drug absorption except for experimental purposes.

It is seen in Table 11 that drugs and other substances can affect blood flow. It is postulated that reduced blood flow reduces the absorption rate by (a) decreasing the effective concentration gradient across the epithelial cells for passively absorbed solutes by not rapidly carrying the solute away, (b) lowering oxygen supply to the absorption cells needed to maintain the active transport mechanism, and (c) affecting metabolic changes attending the integrity of the membrane. Since mesenteric blood flow influences the sink conditions on the blood side of the intestinal membrane, it plays a role in the reserve length concept via the effective permeability coefficients. Reduced blood flow will be significant when the membrane itself is not the rate-determining barrier in the absorption process[13]. Blood flow effects on drug absorption has been reviewed by Walus and Jacobson[75] and Boxenbaum[78].

TABLE 11

Effects of Selected Drugs on Blood Flow in the Gut[75]

Blood Flow	Drugs
Increase	Acetylcholine Gastrin and cholecystokinin Prostaglindin D_2 Nifedipine Diltiazem
Decrease	Physostigmine Prostaglandin $F_{2\alpha}$ Angiotensin II Vasopressin

Reserve Length Considerations of Controlled Release Systems

Having developed the reserve length for drugs in solution and suspension and the background information on intestinal flow of fluids and particles, we turn to controlled-release systems. There are many types and variations of controlled delivery systems but, from the general perspective of the reserve length concept, we will adopt the classification of single-unit and multiple-unit systems, used by Bechgaard and Nielsen[79] and explained in Table 12. Since these systems are intended to give sustained blood levels over a minimum 8-12 hour period, the transit time in the small intestine must be sufficiently long. It has been pointed out that the gastrointestinal transit time (includes gastric emptying and the small intestine) of single-unit tablets are prone to large variations, whereas stomach emptying of small pellets is zero-order or first-order and the pellets are scattered in the intes-

TABLE 12

Classification of Oral Controlled Release Systems

System	Definition	Example
Single-unit dosage form	Oral pharmaceutical formulation consisting of one undisintegrating unit	Enteric-coated tablets passing undisintegrated through the stomach
		Timed-release coated tablets, matrix tablets, sandwich and core-type tablets and osmotic pump tablets, passing through the entire alimentary canal.
Multiple-unit dosage form	Oral pharmaceutical formulation consisting of a unit which disintegrates in the stomach into a large number of sub-units.	Capsules containing hundreds of pellets or thousands of crystals individually coated (enteric or timed-release) being dispersed upon disintegration.
		Tablets containing thousands of individually coated crystals being dispersed upon disintegration.

tine and flow differently from a nondisintegrating tablet resulting in longer and less variable transit times[48,79,80].

The quasi-steady state rate of drug released from a matrix-controlled system is given by the well-known expression:

$$\frac{dQ}{dt} = \frac{S}{2}\left(\frac{D_e A C_s}{t}\right)^{1/2} \qquad \text{(Eq. 20)}$$

whereupon the amount released is related to the square root of time:

$$Q = S\left(D_e A C_s t\right)^{1/2} \qquad \text{(Eq. 21)}$$

where

Q = amount released at time t
S = surface area of the matrix system, cm^2
D_e = effective diffusion coefficient, cm^2/sec
A = amount of drug per unit volume of the matrix, $mass/cm^3$
C_s = solubility of the drug in the matrix

Here, the transport barriers of the aqueous boundary layer and intestinal membrane are insignificant, otherwise they must be taken into account[22,81]. As the nondisintegrating pellet flows down the intestinal tract, time t is related approximately to distance x and the flow velocity of the pellet, β_p, by

$$t = x/\beta_p \qquad \text{(Eq. 22)}$$

Thus, Eq. 21 becomes

$$Q = S\left(\frac{D_e\ A\ C_s\ x}{\beta_p}\right)^{1/2} \qquad \text{(Eq. 23)}$$

We now define the distance down the intestinal tract at which 95% of the drug has been released, i.e.,

$$Q = 0.95\ Q_\infty \text{ at } x = \ell^*_{\text{matrix pellet}}$$

where

Q_∞ = amount of drug released at infinite time
$= A \cdot V_m$
V_m = total volume of the pellet

It follows that

$$\ell^*_{\text{matrix}} = \left(\frac{0.95\ V_m}{S}\right)^2 \frac{A\ \beta_p}{D_e\ C_s} \qquad \text{(Eq. 24)}$$

Finally, the reserve length is

$$(RL)_{matrix} = L - \ell^*_{matrix}$$

$$= L - \left(\frac{0.95\ V_m}{S}\right)^2 \frac{A\ \beta_p}{D_e\ C_s} \qquad \text{(Eq. 25)}$$

For zero-order, controlled-release delivery systems, the amount released with time is

$$Q = S\ k_o\ t \qquad \text{(Eq. 26)}$$

where k_o is the zero-order rate per cm^2.

In terms of any distance x,

$$Q = \frac{S\ k_o\ x}{\beta_p} \qquad \text{(Eq. 27)}$$

The first approximation of the length at which 95% of the dose is released and absorbed is

$$\ell^*_{\substack{\text{zero-order}\\ \text{pellet}}} = \frac{0.95\ A\ V_m\ \beta}{k_o\ S} \qquad \text{(Eq. 28)}$$

and the reserve length is

$$(RL)_{zero\text{-}order} = L - \frac{0.95\ A\ V_m\ \beta_p}{k_o\ S} \qquad \text{(Eq. 29)}$$

The zero-order rate constant, mass/cm^2-sec, for various kinds of systems are:

Nonporous lipid-like polymer membrane encapsulated aqueous suspension reservoir[82]	$k_o = \frac{K\ D_m\ C_s}{h}$	(Eq. 30)
Porous nonlipid polymer membrane encapsulated solid drug particles reservoir[82]	$k_o = \frac{\varepsilon\ D\ C_s}{h}$	(Eq. 31)

Osmotic pump system[83] $$k_o = \frac{k}{h}\left(\pi_o - \pi_e\right) C_d \quad \text{(Eq. 32)}$$

where

D, D_m = diffusion coefficient in water and polymer membrane, respectively

h = membrane thickness

ε = volume fraction of aqueous pores

K = lipid membrane/water partition coefficient

C_s = aqueous solubility of the drug

C_d = drug concentration in the reservoir

k = membrane permeability to water

π_o,π_e = osmotic pressure of driving salt agents and drug compartment environment

At this time we would like to discuss the significance of the reserve length for matrix- and zero-order controlled release systems as expressed in Eqs. 25 and 29.

(a) Clearly, the concept provides the initial framework for the quantitative and mechanistic interplay of the small intestinal length, flow velocity of the pellet, drug content, and physicochemical parameters governing the release kinetics of the controlled delivery system.

(b) If β_p is very small or, equivalently, the transit time for the small intestine (i.e., $\langle t \rangle = L/\beta_p$) is long, (RL) will be positive and the controlled drug release will be accomplished within the small intestine. In view of the variability of fluid flow, β, it would then be advantageous to design features in the system to make β_p less prone to the influence of β.

(c) When (RL) is set equal to zero, we can estimate β_p^*, the critical pellet flow velocity at which the entire small intestinal length, $L \simeq 300$-350 cm, is utilized for complete bioavailability. Thus, flow velocities less than β_p^* will result in positive reserve lengths.

(d) If one has a multiple-unit system in which the pellets are designed to release its contents at different time intervals or different locations in the intestinal tract, then pellets for immediate release in the duodenum have the full advantage of the small intestinal length, while the distally located pellets have conceivably the disadvantage of less length to completely discharge its contents for absorption.

In the case of bio-erodable pellets, the reserve length can also be developed. Here, the amount released with time depends upon the shape of the pellet[84].

Spheres: $Q \propto t^3$ (Eq. 33a)

Cylinders: $Q \propto t^2$ (Eq. 33b)

Slabs: $Q \propto t$ (Eq. 33c)

Lastly, there are controlled release systems which are specially designed to remain in the stomach throughout its useful lifespan[85,86]. The released drug solute then empties into the small intestine for absorption. An example is the so-called hydrodynamically balanced system which has a density less than that for stomach contents (see Goldberg in this book) and are intended for drugs having poor solubility or an intestinal "absorption window". From a physical model standpoint, the phenomena involve the simultaneous flow, longitudinal dispersion and absorption of a drug in solution with drug input from a reservoir[13,45]. It follows that reserve length considerations are the same as that for solutions (see Eq. 11). Although the system encounters the variabilities in stomach emptying and intestinal flow of the drug solute because of the interdigestive motor complex in the fasted

state and the possibility of expulsion of the sustained delivery device, the system permits the drug solute to take advantage of the entire small intestinal length for absorption.

STRATEGIES AND OPTIONS

A summary of strategies and options relevant to the reserve length concept is given in Table 13 and is categorized by physicochemical/biophysical parameters and factors influencing the parameters. In practice one generally focuses upon strategies independent of others and is guided by qualitative principles. We believe that strategies and options should be considered from a wholistic point of view--a systems approach. For example, when one attempts to adjust the lipophilicity of the parent drug via molecular modification for improved intestinal absorption, one will also change the solubility, dissolution rate properties, and the requirements for particle size and transit time. In other words, the manipulation of one factor will invariably have physicochemical, but predictable, effects on other factors.

More often, the principal dilemma the scientist faces is knowing what the problems and their extent are. Next, the choice of one or more strategies over others requires knowledge of the framework by which strategies and options are interrelated. Then, when the choice(s) is made, the question is how much effort should be expended toward improving and optimizing the biopharmaceutical properties of the drug and its formulation. For example, how much more (or less) lipophilicity should be designed into the drug? How much more solubility is minimally required? How much

TABLE 13

Physicochemical and Biophysical Considerations of the Reserve Length

Physicochemical/Biophysical Parameters	Influencing Factors	Strategies and Options
A. Flow Dynamics (volume flow rate, flow velocity, flow regime)	Natural physiological flow influenced by peristalsis, geometry of intestinal tract and lumen Fasting, nonfasting & disease states Circadian cycle Individual differences Intrinsic effects of drugs on GI motility	No deliberate manipulation of physiologic functions governing GI motility and transit time
(1) Solutes	Same as above	No deliberate manipulation
(2) Suspensions, including suspensions following solid dosage form distintegration	Same as above Particle size, density and liquid viscosity effects on settling during passage of particles through GI tract Particle/particle interactions (flocculation, coalescence) Particle/membrane interactions (adsorption, adhesion) Mechanical entrapment in intestinal folds and intervillous spaces Slurry density	Manipulate particle density and size to enhance settling, thereby increasing transit time Enhance particle-membrane or particle-surface mucus interactions by change, adhesion, etc., to plate out particles during flow of suspension in GI tract

(3) Pellets, nondisintegrating granules and tablets	Same factors as above for solutes Same factors as for suspensions Shape of solid dosage form	Same as for suspensions
B. Permeability of Absorption Barriers		
(1) Aqueous boundary layer	Fluid velocity and viscosity effects on the thickness of the aqueous boundary layer Diffusion coefficient of the solute Mucus layer on the membrane	
(2) Membrane	Transport mechanism (passive, active, endocytosis, collision complex) Molecular size related to aqueous pore size and distribution along intestinal tract Lipid membrane/water partition coefficient (lipophilicity of solute) Effective thermodynamic activity affected by binding, ionic equilibria of weak electrolyte drugs, micellization by exogenous and endogenous surfactants Enzymic metabolism in gut lumen, mucosal surface and absorption cell	Increase lipophilicity through prodrugs & analogs Decrease enzyme lability through prodrugs and analogs Achieve high thermodynamic activity at membrane surface

(continued)

TABLE 13 (cont.)

Physicochemical/Biophysical Parameters	Influencing Factors	Strategies and Options
(3) Barrier on blood side	Mesenteric blood flow in normal and disease states Intrinsic effects of drugs on blood flow	
(4) Apparent (effective) permeability	Combination of (1), (2) and (3) in which the aqueous boundary layer, membrane and blood side barriers are in series: $\frac{1}{P_e} = \frac{1}{P_{aq}} + \frac{1}{P_m} + \frac{1}{P_{blood}}$	Make the aqueous boundary layer barrier the rate-determining barrier by improving the membrane permeability of the drug., i.e., achieve $P_e \simeq P_{aq}$
C. Small Intestinal pH	Natural secretions for gallbladder, pancreas and intestinal membrane bringing about a pH gradient from the duodenum through the ileum Buffer effects from weak electrolyte drugs and buffering agents which will cause a pH gradient across the aqueous boundary layer	No deliberate manipulation of natural physiological functions governing secretions

D. Drug Solubility	pH/pK_a relationship for weak electrolyte drugs Crystal forms and solvates Biliary micellar secretions and exogenous surfactants Binding agents such as proteins, mucopolysaccharides, excipient binders	Increase solubility through salt formation, micelle solubilization binding agents Increase solubility with use of selective crystal forms, solvates and molecular crystal packing Make high energy solids through coprecipitation with hydrophilic polymers Make solubility independent of intestinal pH gradient by (a) altering the pK_a through molecular modification or (b) formulating a granular mixture of drug & buffer agents to create a controlled local pH environment Take into account micelle solubilization by biliary secretions

(continued)

TABLE 13 (cont.)

Physicochemical/Biophysical Parameters	Influencing Factors	Strategies and Options
E. Particle Size	Manufacturing process Crystallization process	Micronize coarse particles Control precipitation kinetics to obtain submicron sizes Control particle size after manufacturing of solid dosage forms and during storage
F. Dissolution Kinetics	Flow dynamics (A) Permeability of the absorption barriers (B) determining whether dissolution occurs under sink conditions or is membrane-controlled Small intestinal pH particularly for weak electrolyte drugs (C) Drug solubility (D) Particle size (E) Slurry density (dose load) Meals	See strategies and options D and E

particle size reduction do we need to achieve? What kind of release rates (dissolution and/or sustained release) do we need when the transit times are short or long? Many more questions can be asked. In answering the questions, we need to be guided by quantitative principles and to know what strategic physicochemical/biophysical factors can be controlled and what cannot be controlled and, consequently, circumvented. Attempts to provide some of the answers and methods of approaches are found in this chapter and elsewhere[13,87,88].

SUMMARY

The anatomical reserve length for the intestinal absorption of drugs is presented as the framework by which many physicochemical, physiological and dosage form factors are put into quantitative interrelationships. The concept is a basic science approach to the optimization of oral drug formulations and provides a perspective in the selection of strategies and options within established boundaries. The framework, thus far described here, provides the base upon which refinements and other considerations can be added.

What is not covered here are considerations of absorption windows, which we have defined as that part of the small intestine where absorption occurs for special mechanistic reasons. The windows include the pH-absorption window, distribution of aqueous pore pathways along the intestinal tract, specialized membrane transport mechanisms, membrane distribution of enzyme systems and differences in transit times in the intestinal tract. We have

omitted this interesting topic from the reserve length treatment since this has been discussed previously[13]. In the course of the theoretical discussions of the reserve length, various gaps in research were highlighted. We leave this to be further discussed by Professor W.I. Higuchi in this symposium book.

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