A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of *in Vitro* Drug Product Dissolution and *in Vivo* Bioavailability

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A biopharmaceutics drug classification scheme for correlating *in vitro* drug product dissolution and *in vivo* bioavailability is proposed based on recognizing that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption. This analysis uses a transport model and human permeability results for estimating *in vivo* drug absorption to illustrate the primary importance of solubility and permeability on drug absorption. The fundamental parameters which define oral drug absorption in humans resulting from this analysis are discussed and used as a basis for this classification scheme. These **Biopharmaceutic Drug Classes** are defined as: Case 1. High solubility-high permeability drugs, Case 2. Low solubility-high permeability drugs, Case 3. High solubility-low permeability drugs, and Case 4. Low solubility-low permeability drugs. Based on this classification scheme, suggestions are made for setting standards for *in vitro* drug dissolution testing methodology which will correlate with the *in vivo* process. This methodology must be based on the physiological and physical chemical properties controlling drug absorption. This analysis points out conditions under which **no** *in vitro-in vivo* correlation may be expected e.g. rapidly dissolving low permeability drugs. Furthermore, it is suggested for example that for *very rapidly* dissolving high solubility drugs, e.g. 85% dissolution in less than 15 minutes, a simple one point dissolution test, is all that may be needed to insure bioavailability. For slowly dissolving drugs a dissolution profile is required with multiple time points in systems which would include low pH, physiological pH, and surfactants and the *in vitro* conditions should mimic the *in vivo* processes. This classification scheme provides a basis for establishing *in vitro-in vivo* correlations and for estimating the absorption of drugs based on the fundamental dissolution and permeability properties of physiologic importance.

KEY WORDS: bioavailability; drug absorption; mathematical modeling; *in vitro–in vivo* correlation; intestinal permeability.

INTRODUCTION

Drug dissolution is a prerequisite to drug absorption and clinical response for almost all drugs given orally. Exceptions to this general requirement such as 'GI' drugs, e.g. resins, antidiarrials, adsorbants, some laxatives, etc. are not considered in this report. While this recognition is obvious and correlations between *in vitro* dissolution and *in vivo* bioavailability for oral products are extensive, comprehensive models for predicting oral drug absorption based on drug dissolution have been limited (1-5). This is due, in part, to the complexity of the processes occurring in the gastrointestinal tract and in part to the complex pharmacokinetics of drugs making it difficult to obtain accurate adsorption estimates from systemic availability. For example, any effort to model the gastrointestinal tract requires consideration of; fasted/fed state, cyclical fasted state motility, gastric emptying and intestinal transit, variable lumen contents; e.g. pH, enzymes, surfactants and dietary lipids, as well as drug absorption mechanism, permeability, and variation in drug physicochemical properties during gastrointestinal transit (6-13). Recently we have developed a simplified macroscopic approach to drug absorption and demonstrated a good correlation between the extent of drug absorption and the intestinal membrane permeability in an animal model that is mechanism of absorption independent (2). In addition we have developed a drug dissolution and absorption model for water insoluble drugs that limits to the previous macroscopic result under appropriate conditions (3,13). These models point out very clearly that the key parameters controlling drug absorption are three dimensionless numbers; an Absorption Number, An, a Dissolution Number, Dn and a Dose Number Do; representing the fundamental processes of membrane permeation, drug dissolution and dose, respectively. In this report we use this approach to set up a theoretical basis for correlating *in vitro* drug dissolution with *in vivo* bioavailability. This analysis has considerable significance for drug bioavailability and bioequivalence standards and *in vitro dissolution methodology* since it clarifies the 'regimes' of the drug absorption process and offers a basis for determining when and under what conditions *in vitro-in vivo* correlations are to be expected. Furthermore, this analysis leads to the suggestion that drug bioavailability standards should be set on the basis of a **Biopharmaceutics Drug Classification** scheme that follows from this analysis.

Theoretical Considerations

The fundamental starting point for this analysis is;

$$J_w = P_w \cdot C_w \qquad \text{equation 1}$$

where, $J_w(x,y,z,t)$ is the drug flux (mass/area/time) through the intestinal wall at any position and time, $P_w(x,y,x,t)$ is the permeability of this (complex) membrane, and $C_w(x,y,z,t)$ the drug concentration at the membrane (intestinal) surface. This is Fick's First Law applied to a membrane and applies at each point along the membrane (14) i.e. equation 1 is a local law pertaining to each point along the intestinal membrane. It is assumed that sink conditions (drug concentration equals zero) exist for the drug inside this complex membrane and that P_w is an effective permeability. The plasma *may be* assumed to be the physiological sink since concentrations in the plasma are generally more than several orders of magnitude below that in the intestinal lumen in humans (15). The drug absorption rate, i.e. the rate of loss of drug from

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the intestinal lumen, assuming no luminal reactions, at any time is;

$$\text{Absorption Rate} = dm / dt = \int\int_A P_w C_w dA \qquad \text{equation 2}$$

where the double integral is over the entire gastrointestinal surface. The total mass, M, of drug absorbed at time t is:

$$M(t) = \int_0^t \int\int_A P_W C_W dA dt \qquad \text{equation 3}$$

These mass balance relations are very general since the surface can be of arbitrary shape and the concentration at the membrane wall and permeability can have any dependence on position and time. For full generality the permeability, P_w, must be considered to be *position dependent* as well as *time dependent*. The time dependence may be due to a dependence on drug concentration as in the case of carrier mediated transport, through indirect effects on the membrane of other components of the dosage form, or due to other physiological or biochemical variations such as modulation of tight junction permeability, changes in luminal contents, up or down regulation of membrane transporters or changes in membrane structure or composition. The permeability is very often position dependent from duodenum, jejunum, ileum and colon due to the different morphology and mucosal cell differentiation down the intestine e.g. amino acid and di/tripeptide transport in the jejunum and ileum, but not colon.

Based on equations 1 and 2 above the following principle for bioavailability may be stated:

If two drug products, containing the same drug, have the same concentration time profile at the intestinal membrane surface then they will have the same rate and extent of absorption.

This statement furthermore implies that;

If two drug products have the same *in vivo* dissolution profile *under all luminal conditions*, they will have the same rate and extent of drug absorption.

These general principles assume that there are no other components in the formulation that affect the membrane permeability and/or intestinal transit. If that were the case then the dissolution standard would have to include specifications for the dissolution of those components as well. This second statement follows from equations 1 and 2 since the *in vivo* dissolution rate will determine $C_w(x,y,z,t)$. Due to variable gastrointestinal transit and lumen contents at time of dosing as well as differences in special populations, i.e. differences in the gastrointestinal state of an individual, intra individual, inter individual and special population gastrointestinal variation, variation in the rate and extent of absorption are to be expected.

Two aspects of this broad principle are considered in more detail below;

i.) The relationship between *in vivo* drug dissolution and the solution or intestinal wall concentration, C_w, and

ii.) The relationship between the *in vivo* dissolution and *in vitro* dissolution.

In Vivo Dissolution and Luminal/Surface Concentration

The relationship between drug dissolution *in vivo* and the concentration of drug at the absorbing surface of equation 2 or 3 is complex due to the complex hydrodynamics and contents of the gastrointestinal tract. Various approaches to modeling these processes have been taken. These include; mixing tank and plug flow models, mixing tanks in series and dispersed plug flow models (1-5,16-19). In virtually all models the wall permeability is treated as an effective wall permeability and includes an unknown aqueous resistance[6] That is:

$$P_e = P_a P_w / (P_a + P_w) \qquad \text{Equation 4}$$

P_w is the wall permeability discussed above. P_a is the apparent permeability to mass transport to the intestinal membrane. A lower limit to this permeability can be estimated using a laminar flow hydrodynamic model for the intestinal 'fluid' (20,21). Turbulence due to intestinal wall contractions and curvature would lead to large values of P_a. For laminar flow, P_a is estimated by:

$$P_a^{-1}(x) = 1.47(D / R)Gz^{1/3} (x / L)^{1/3} \qquad \text{Equation 5}$$

in a circular tube, under sink conditions in the diffusional entrance region (21,22). Assuming a mixing length in the human intestine of 10 cm P_a is estimated to be 2×10^{-5} cm/sec. ($\approx$ 0.072 cm/hr)[7] in an aqueous fluid (i.e. viscosity of water). This represents a lower limit of P_a in this simple fluid model.

An alternate line of reasoning however, suggests that P_a is much larger than the above estimate and *not a significant resistance to mass transport for most cases of drug absorption* at least in the upper gastrointestinal tract. For two organic molecules the aqueous permeability is principally a function of their aqueous diffusivity when the media is the same (eqn 5, (22)). Since, the extent of nutrient absorption is 100 % over less than half of the small intestine, P_a must be at least this large in the upper small intestine. The measured permeability of glucose (15) in humans is about 1×10^{-3} cm/sec (3.6cm/hr). This provides an experimental estimate of the lower limit of P_a *in vivo* in the jejunum. Since the aqueous diffusion coefficient of drugs such as α-methyldopa, cimetidine, or furosemide would be similar to that for nutrients such as glucose or the amino acids and their extent of absorption is less than 100% it can be concluded that the limitation to drug absorption is not usually the aqueous mass transport coefficient, P_a. The intestinal wall permeabilities for drugs that are less than 100% absorbed must be significantly less than that for a nutrient such as glucose or an amino acid and P_a cannot be rate limiting for drugs that are in solution i.e. high solubility drugs. This implies that P_w is the determining component in P_e, i.e.

[6] The major exception to this is for laminar flow models where defined hydrodynamics are assumed. This is appropriate for more controlled intestinal perfusion systems and allows for a more direct estimate of the intestinal membrane permeability.

[7] The values used to obtain this estimate: $D = 5\times10^{-6}$ cm/sec, L = 200 cm, R = 1 cm, Q = 0.5 ml/min.

$$P_e \cong P_w (< 100\% \text{ absorbed drugs})$$

This indicates that the intestine can be treated as well mixed radially i.e. locally and that the intestinal membrane is the dominant resistance to drug absorption.

Based on the above analysis, one would expect to obtain a good correlation between extent of drug absorption and intestinal membrane permeability for *high solubility* drugs that are dosed in solution or for high solubility drugs in dosage forms that dissolve very rapidly. Figure 1 shows a plot of fraction absorbed in humans vs. measured human jejunal membrane permeabilities (23-26). The insert in this plot is of Log(100-F) vs. P_w which is expected to be linear for a simple plug flow model of intestinal content movement (2). From this plot, a drug with a permeability greater than 2-4 $\times 10^{-4}$ cm/sec or about 1 cm/hr would be well absorbed with the expected fraction absorbed being greater than 95%. The correlation in Figure 1 is absorption mechanism independent since it is measuring the actual mass transfer resistance to drug absorption for high solubility drugs (2,11). This permeability can be used as a fundamental parameter for establishing drug properties that will lead to 'good' absorption rates.

The maximal absorption rate occurs when the drug concentration is at its solubility, C^s, and from equation 1 and 3,

$$J^{\max} = P_w C_w^s \qquad \text{equation 6}$$

and

$$M^{\max}(t) = \int_0^t \int \int_A P_e C_w dA dt$$

$$C_w = C_s, C \geq C_s$$

$$C_w = C, C \leq C_s \qquad \text{equation 7}$$

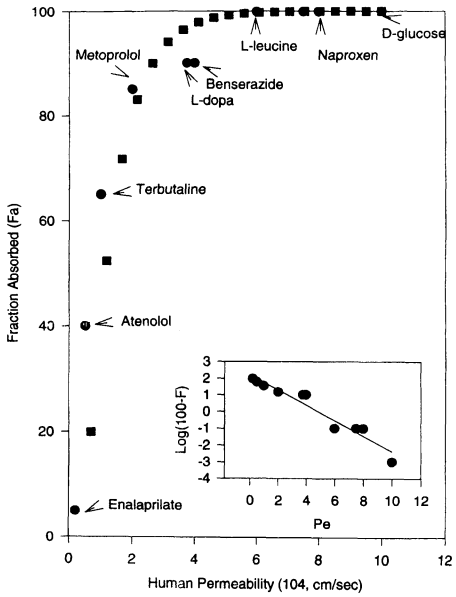

Fig. 1. Graph of the extent of absorption vs. human intestinal jejunal permeabilities.

This represents solubility limited absorption and assumes that the dissolution rate is sufficiently rapid to keep the solution concentration at saturation.

In Vitro–In Vivo Drug Dissolution and Absorption

In order to develop a more quantitative and predictive model for drug absorption rates, it is necessary to develop (microscopic) models of the flow, dissolution, absorption, and reaction processes occurring in the intestine. In general this is quite complex. However, a simple model that considers a segment of intestine over which the permeability may be considered constant, a plug flow fluid with the suspended particles moving with the fluid, no significant particle-particle interactions (i.e. aggregation) and dissolution in the small particle limit, leads to the following pair of differential equations in dimensionless form (3);

$$dr^* / dz^* = -(Dn / 3)(1 - C^*) / r^* \qquad \text{equation 8}$$

and

$$dC^* / dz^* = DoDnr^*(1 - C^*) - 2AnC^* \qquad \text{equation 9}$$

where

$$z^* = z / L = (v_z / L)t = t^*$$

$$t^* = t / (L / v_z) = t / (AL / Q) = t / (V / Q)$$

where: L = tube length, v_z = axial fluid velocity in the tube, A = tube surface area area $= 2\pi RL$, R = tube radius, Q = fluid flow rate $= Av_z$. The three important dimensionless groups are:

$$\text{Do} = \text{Dose Number} = \frac{M_o / V_o}{C_s}$$

$$\text{Dn} = \text{Dissolution Number} = \frac{DC_s}{r_o} \cdot \frac{4\pi r_o^2}{\frac{4}{3}\pi r_o^3 \rho} \cdot t_{res}$$

$$= t_{res} \cdot 3DC_s / \rho r_0^2 = t_{res} / t_{Diss}$$

$$\text{An} = \text{Absorption Number} = \frac{P_{eff}}{R} \cdot t_{res} = t_{abs}^{-1} \cdot t_{res}$$

$t_{res} = \pi R^2 L / Q$ = mean residence time.

$$t_{Diss} = \frac{r_0^2 \rho}{3DC_s} = \text{time required for a particle of the drug to dissolve.}$$

$$t_{abs}^{-1} = k_{abs} = (S / V)P_{eff} =$$

$$2 \cdot \frac{P_{eff}}{R} = \text{the effective absorption rate constant.}$$

Where, in addition to the symbols defined previously, S is surface area, V is volume, M_o is the dose, and r_o is the initial particle radius.

This analysis while simplified, emphasizes the three fundamental parameters controlling drug dissolution and ab-

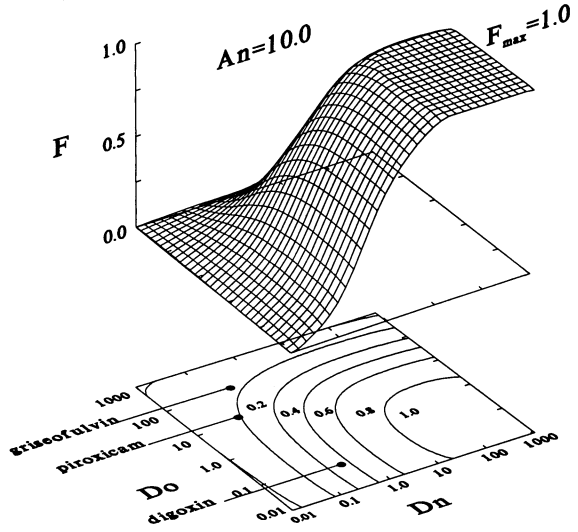

Fig. 2. Graph of estimated fraction dose absorbed vs Dissolution Number, Dn, and Dose Number, Do, for a high permeability drug. An = 10 corresponds to a drug with a permeability approximately that of glucose.

sorption. Figure 2 shows a typical profile for high permeability drug. This profile for a high permeability drug (An = 10)[8] illustrates the sharp dependence of extent of drug absorption on the Dose and Dissolution Numbers when they are in critical ranges around one for a well absorbed (high permeability) drug. It is also evident from the figure that at high dose numbers, the extent of absorption is only weakly dependent on the Dissolution Number. The limiting solution to equations 8 and 9 for this region is

$$F = 2An / Do$$

and is independent of dissolution rate (2,3). This is the *solubility limited* absorption region. Thus, in certain regions drug absorption is very dependent on drug dissolution rate and dose and in other ranges it is only weakly dependent.

[8] Values for An ≥ 6 represent sink conditions for drugs with low solubility, high permeability. Assuming conservative estimates for the parameters which make up An, ie, P_{eff} = 1 × 10^{-3} cm/sec, t_{res} = 180 min., and R = 1 cm, An = 10.

For estimating *in vivo* absorption, the extent of solubilization particularly in the small intestine is critical to making good estimates. Drugs with a high Dose Number must be effectively solubilized *in vivo* for good absorption. However, at the present time, a conservative estimate of the Dose Number is recommended, i.e., the *minimum* solubility of the drug should be determined in the physiological pH range (1-8) and temperature.

Table I presents some dose, solubility, Dose Number and estimated Dissolution Number data for a number of drugs. The drugs in Table I were chosen to illustrate the significance of the dose of a drug as well as its solubility. The drugs griseofulvin and digoxin are representative examples. Both compounds have similar solubilities (0.015 mg/ml and 0.024 mg/ml respectively) and it can be assumed that based on the solubility data, both drugs should be absorbed equally. However, based on the Dose Number of the two compounds (133 for griseofulvin and 0.08 for digoxin) the fraction of a dose of digoxin absorbed is expected to be much greater than that of griseofulvin (Figure 2). The absorption of digoxin is up to 100% for a solubilized form (27). While the relative bioavailability of griseofulvin can be improved by a factor of 1.7 via micronization, suggesting incomplete bioavailability (28). It is important to note that the solubility, and therefore the Dose and Dissolution Number, of a drug *in vivo* is difficult to estimate precisely due to potential aggregation and the unknown extent of solubilization, hence the actual absorption of a compound can only be estimated to be in a range depending on the assumed *in vivo* surface area and solubilization. However, this analysis allows for comparisons to be made among delivery systems and dosage forms for the same drug and estimates to be made based on assumed *in vivo* solubilization and surface area.

Permeability–Solubility Drug Classification

The above analysis suggests that correlations between drug dissolution and drug absorption are best done using the fundamental dimensionless groups, Do, Dn, and An. However, given the definition of these terms, it is clear that permeability and solubility are key underlying parameters controlling drug absorption. Thus, drugs can be divided into high/low solubility-permeability classes and the expectations regarding *in vitro-in vivo* correlations more clearly stated.

Table I. Calculated Parameters for Representative Drugs

Drug	Dose (mg)	C_S^{min} (mg/ml)[a]	V_{sol} (ml)[b]	Do[c]	Dn[d] (estimated intrinsic)
Piroxicam	20	0.007	2,857	11.4	0.15
Glyburide	20	<0.100	133	>0.80	0.78
Cimetidine	800	6.000	556	0.53	129
Chlorthiazide	500	0.786	636	2.54	17.0
Digoxin	0.5	0.024	20.8	0.08	0.52
Griseofulvin	500	0.015	33,333	133	0.32
Carbamazepine	200	0.260	769	3.08	5.61

[a] Minimum physiologic solubilities were determined in the physiological pH range (1–8) and temperature (31, 32).
[b] Volume of solvent required to completely dissolve the dose at minimum physiologic solubility.
[c] Do = Dose/V_O/C_S^{min}, initial gastric volume, V_o = 250 ml.
[d] Assumptions: r_o = 25 μm, D = 5 × 10^{-6} cm^2/sec, ρ = 1.2 gm/cm^3, ⟨t_{res}⟩ = 180 min. (33).

Table II. *In Vitro–in Vivo* (IVIV) Correlation Expectations for Immediate Release Products Based on Biopharmaceutics Class

Class	Solubility	Permeability	IVIV Correlation Expectation*
I	High	High	IVIV correlation if dissolution rate is slower that gastric emptying rate, otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high (see discussion).
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected

* A limited correlation means that the dissolution rate while not rate controlling may be similar to the absorption rate and the extent of correlation will depend on the relative rates.

These expectations are summarized in Table II and discussed in more detail below.

Case 1. High Solubility–High Permeability Drugs. This is the case where the drug is well absorbed (though its systemic availability may be low due to first pass extraction/metabolism) and the rate limiting step to drug absorption is drug dissolution or gastric emptying if dissolution is very rapid. In this case the dissolution profile must be well defined and reproducible to insure bioavailability. For immediate release dosage forms that dissolve very rapidly, the absorption rate will be controlled by the gastric emptying rate and no correlation with dissolution rate is expected. In the fasted state the gastric emptying rate is both volume and motility phase dependent with a gastric half emptying time of between 5 and 22 min., and an overall average of 12 and 22 min. for administered volumes of 50 and 200 ml respectively, Figure 3 (9). This suggests that a dissolution specification for immediate release (IR) dosage forms of perhaps 85% dissolved in less than 15 min. may insure bioequivalence[9].

Case 2. Low Solubility–High Permeability Drugs. This is the class of drugs for which the dissolution profile must be most clearly defined and reproducible. More precisely this is the case where Absorption Number, An, is high and Dissolution Number, Dn, is low. Drug dissolution *in vivo* is then the rate controlling step in drug absorption (except at very high Do) and absorption is usually slower than for Case 1. Since the intestinal luminal contents and the intestinal membrane change along the intestine, and much more of the intestine is exposed to the drug, the dissolution profile will determine the concentration profile along the intestine for a much greater time and absorption will occur over an extended period of time. Consequently, the dissolution profile must be determined for at least 4-6 time points and for at least 85% dissolution at several physiological pH's. In addition, media conditions reflective of the *in vivo* situation, such as addition of surfactants must be considered. Drugs in this class may be expected to have variable absorption due to the many formulation and *in vivo* variables that can effect the dissolution profile. Dissolution media and methods that reflect the *in vivo* controlling process are particularly important in this case if good *in vitro-in vivo* correlations are to be obtained.

[9] Stochastic simulations could be used to more precisely define these dissolution limits.

Case 3. High Solubility–Low Permeability Drugs. For this class of drugs, permeability is the rate controlling step in drug absorption. While the dissolution profile must be well defined, the simplification in dissolution specification as in Class 1 is applicable for immediate release dosage forms where drug input to the intestine is gastric emptying rate controlled. Both the rate and extent of drug absorption may be highly variable for this class of drugs, but if dissolution is fast i.e. 85% dissolved in less than 15 min., this variation will be due to the variable gastrointestinal transit, luminal contents, and membrane permeability rather than dosage form factors.

Case 4. Low Solubility–Low Permeability Drugs. This class of drugs present significant problems for effective oral delivery. The number of drugs that fall in this class will depend on the precise limits used for the permeability and solubility classification.

This classification of drugs follows naturally from the above theoretical analysis. While drug solubility and dose are readily available, and drug particle size often available, drug permeabilities are relatively less available, particularly in humans. Drug permeabilities in an animal model (rat) are more readily available and some human values are known. Recent methodological advances in the area of human intubation will undoubtedly provide more data in the future (15,23). Some of the available human permeability data were presented in Figure 1. More human data is necessary in

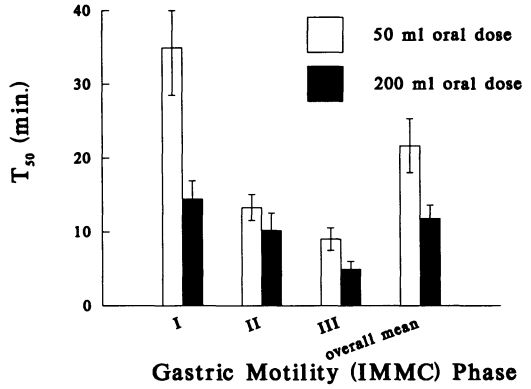

Fig. 3. Graph of measured gastric half emptying times, T50, in humans as a function of fasted state motility phase for administered volumes of 50 and 200 ml of water(9).

order to firmly establish the permeability classification criteria.

Dissolution Media and Methodology

The setting of *in vitro* standards must be done on the basis of reflecting the conditions existing *in vivo*. There is a large amount of literature on dissolution methodology and media (29). It is not the purpose of this report to suggest a methodology or media as being most appropriate. In fact the preceding analysis suggests that all that should be required is that the *in vitro* methodology/media reflect the *in vivo* situation when used to establish an IVIV correlation. There should be enough flexibility in the standards to allow for development of methods that truly reflect the *in vivo* rate controlling process for a given drug. This is particularly true for a methodology that might be used as a surrogate for an *in vivo* bioavailability test[10].

For water insoluble drugs, the relevant media for dissolution has been of considerable interest as a practical matter due to the large amount of media that may be required for a very water insoluble drug (30). The current approach that seems to be most appropriate is to use surfactants. The choice of surfactant can be important. While bile salts would be the logical choice based on physiological relevance, they are too expensive to be use on a routine basis. A surfactant such as sodium lauryl sulfate may be appropriate in many cases but the choice need not be limited to this surfactant. As noted above, the *in vivo* solubilization is a critical consideration and the dissolution media should be guided by reflecting the *in vivo* situation. If the drug is a case 2 drug (high permeability, low solubility) then absorption from solution is faster than dissolution and sink conditions are likely to prevail *in vivo*. As a general rule one should maintain sink conditions in the dissolution media if possible, such that the drug dissolves in less that 20-30% of the dissolution media.

Other factors which need to be considered, especially for case 2 drugs, are particle aggregation and the *effective* particle size *in vivo*. Quite often the first approach to increasing the dissolution rate of drugs in this class is micronization. This however, also increases the surface energy and hence potential for particle aggregation. When predicting *in vivo* bioavailability from *in vitro* dissolution profiles, it is critical that the particle size used in the model reflect the *in vivo* particle size. Therefore, it is important that the dissolution medium represent, as close as possible, the *in vivo* dissolution medium so that the apparent particle radius presented by the dosage form to the dissolution medium reflects *in vivo* conditions. Measuring the intrinsic dissolution rate, using for example rotating disk methodology, and then comparing the theoretical, measured particle(suspension), and dosage form dissolution rates can be a useful tool for determining when particle aggregation[11] is significant (22,29).

However, it must be emphasized that a strong argument for the physiological relevance of a particular surfactant containing dissolution media can not be made at this time. The dissolution media *in vivo* is a complex medium of bile salts, lecithin, cholesterol and its esters and a wide range of lipid materials that can vary considerably with meal type and diet. The physical chemistry of these systems is extremely complex. However, models for dissolution in less complex micelle systems have been developed, and it is clear that the drug solubility in the micelle phase and the effective diffusivity of the drug loaded micelle are the two most important parameters that are needed to estimate the drug dissolution rate enhancement factor (29). Further research is needed in order to establish correlations between *in vivo* representative media and the more readily available surfactant systems that could be used on a routine bases. The practical suggestion made above of using a dissolution media sufficient to dissolve the full dose of the drug in 20-30% of the media volume represents a starting point. The *in vitro* solubilization, however, should reflect the *in vivo* solubilization.

Further Consideration

Several factors will need further consideration; drugs with pH dependent solubility, drugs which exhibit complexation phenomena with gastrointestinal contents, and drugs that are unstable in the gastrointestinal tract. For drugs that exhibit pH dependent solubility, based on equations 1 and 2 governing drug absorption, it is the drug solubility at the pH of the local point in the intestine that is the most relevant pH. This pH of course varies down the intestine. The pH of the local region will influence the dissolution rate and possibility the drug permeability. This could be of importance if the dosage form altered the local pH, in which case it could alter the drug absorption rate as well as dissolution rate. In this case the dosage form dissolution specification may have to be extended to include these additional dosage form components[12].

For drugs that are unstable or interact with gastrointestinal contents in a manner so as to reduce their activity in solution e.g. complexation with ions or bile salts, dissolution rates can have a profound effect on drug absorption given the position dependence down the intestine of luminal composition. This can be the case even if the drug has high permeability (well absorbed from solution). For these drugs, where dissolution is not rapid, a multiple point dissolution profile at several pH's in addition to gastric pH should be required.

In general, the position dependence of drug absorption can be due to local pH and lumen content differences down the GI tract as well as a changing permeability. Since both of these factors can contribute to variation in rate as well as extent of absorption, it may be necessary to include in the permeability-solubility classification separate categories for drugs whose permeability, solubility, or stability varies significantly with position in the GI tract. The dissolution spec-

[10] A routine quality control dissolution methodology may be based on somewhat different considerations and it is not being suggested that this more elaborate methodology replace routine quality control methods. However, when used as a surrogate for bioavailability then the more elaborate methods may be required at least initially to establish the IVIV correlation.

[11] Particle size change can occur during processing of the dosage form, due to poor *in vivo* wetting or due to *in vivo* (re)precipitation.

[12] Drugs that may precipitate in the intestine present a particularly challenging problem due to the poorly understood and variable nucleation and crystal growth *in vivo*.

ification may need to be particularly well defined and controlled in order to insure bioequivalence for drugs with these properties.

Systemic Availability Considerations

It is clear from the above considerations that the drug absorption processes must be distinguished from the systemic bioavailability considerations. The systemic availability, F, is defined as the ratio of the dose corrected area under the plasma (blood) curves (AUC) following intravenous and oral administration;

$$F = (AUC)_{oral} * Dose_{iv} / (AUC)_{iv} * Dose_{oral}$$

and

$$F = f_a*(1-F_{TM})*(1-E_H)$$

where f_a is the fraction absorbed from the intestinal lumen. F_{TM} is the degree of metabolism by the intestinal mucosal tissue (or in the lumen) and E_H is the hepatic extraction ratio[13]. The fraction absorbed into the intestinal tissue is given by the dose normalized equation 3.

$$f_a = M(\infty) / Dose = (Dose)^{-1} \int_0^{\infty} \int\int_A P_w C_w dA dt$$

Clearly, the systemic availability will in general contain variation associated with the gastrointestinal metabolism and hepatic extraction/metabolism processes. The systemic availability will be less than that of intestinal tissue delivery, f_a, in general. For a drug with low hepatic extraction/metabolism and no GI luminal or tissue metabolism or instability, the systemic availability is equal to the fraction absorbed, f_a, from the intestinal lumen.

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