REVIEW

IV-IVC Considerations in the Development of Immediate-Release Oral Dosage Form

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ABSTRACT: Predictive scientific principles and methods to assess *in vivo* performance of pharmaceutical dosage forms based on *in vitro* studies are important in order to minimize costly animal and human experiments during drug development. Because of issues related to poor solubility and low permeability of newer drug candidates, there has in recent years been a special focus on *in vitro–in vivo* correlation (IV-IVC) of drug products, particularly those used orally. Various physicochemical, biopharmaceutical, and physiological factors that need to be considered in successful IV-IVC of immediate-release oral dosage forms are reviewed in this article. The physicochemical factors include drug solubility in water and physiologically relevant aqueous media, pK_a and drug ionization characteristics, salt formation, drug diffusion-layer pH, particle size, polymorphism of drug substance, and so forth. The biopharmaceutical factors that need to be considered include effects of drug ionization, partition coefficient, polar surface area, etc., on drug permeability, and some of the physiological factors are gastrointestinal (GI) content, GI pH, GI transit time, etc. Various *in silico*, *in vitro*, and *in vivo* methods of estimating drug permeability and absorption are discussed. Additionally, how IV-IVC may be applied to immediate-release oral dosage form design are presented. J Pharm Sci 94:1396–1417, 2005

Keywords: *in vitro in vivo* correlation; formulation; bioavailability; oral absorption; permeability; solubility; dissolution; particle size; *in silico* modeling; *in vitro* models; animal models

INTRODUCTION

The rate and extent of drug absorption after oral administration of a dosage form are dependent on various physicochemical and physiological factors.[1–3] The physicochemical factors include ionization constant, partition coefficient, solubi-

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lity, dissolution rate, crystal form, surface area, etc., of drug substances as well as the nature and properties of dosage forms. Some relevant physiological factors are: solubility of the drug substance in gastrointestinal (GI) environment, drug permeability through GI membrane, GI pH profile, GI transit time, presence of bile salts and other physiological surfactants, effect of food, and so forth. Since the pioneering works by Edwards[4] and Nelson[5,6] in the 1950s in correlating dissolution rates of aspirin and theophylline, respectively, with their *in vivo* appearance after oral administration, there have been a gradual increase in publications related to the influence of *in vitro* characteristics of drug substances and drug products on their *in vivo* performance. Early studies on *in vitro–in vivo* correlation (IV-IVC) were reviewed by Dakkuri and Shah[7] and by Abdou.[8]

IV-IVC has attained a much greater significance in pharmaceutical dosage form development and especially in immediate-release formulations during the past decade. As indicated by Serajuddin[9] in a commentary in 2002, widespread application of combinatorial chemistry and high throughput screening in recent years has dramatically increased the lipophilicity of new drug candidates and, as a consequence, the aqueous solubility decreased substantially. A look at drugs that were the subjects of intense scientific and regulatory scrutiny in 1970s and 1980s because of bioavailability issues show that most of them had aqueous solubility in the range of 20–100 μg/mL. In the present days, the situation has changed so much that drug candidates with intrinsic solubility of less than 1 μg/mL are very common. Special IV-IVC considerations are needed to cope with this situation during drug development. To address issues related to low drug solubility and drug permeability, there have also been various scientific and regulatory initiatives over the past few years to classify drug molecules in different categories based on their physicochemical properties[10] and then address their *in vivo* performance accordingly.[11,12]

The objective of the present review is to take a fresher look into various IV-IVC considerations necessary for the development of immediate release oral dosage forms. In particular, issues related to physicochemical properties and permeability of candidates will be discussed, and how such issues may be addressed by *in silico* modeling and *in vivo* experimentations will also be considered.

PHYSICOCHEMICAL PROPERTIES

Most of the models or tools utilized in predicting oral absorption during dosage form development are heavily dependent on physicochemical properties of drug candidates. Some of these models are: the pH-partition hypothesis[13] utilizing ionization and partition coefficient of drugs as a function of pH; absorption potential (AP)[14] based on physicochemical properties; mass balance[15,16] based on solubility and assuming that the small intestine as a tube; and compartmental absorption, such as mixing tank and compartmental absorption and transit (CAT) models.[17–19] The Rule of Five,[20] which provides experimental and computational approaches to estimate solubility and permeability in drug discovery and early development settings, is also dependent on chemical and physical properties of new drug molecules. Some of the physicochemical properties that influence rate and extent of drug absorption and relevant to oral dosage form development are discussed below.

Solubility

Solid drug substances must dissolve before absorption, and the rate of dissolution depends on drug solubility. However, the solubility of a compound must be considered together with its dose for an evaluation of its AP. Johnson and Swindell[21] proposed a relatively simple approach for estimating maximum absorbable dose (MAD):

$$\mathrm{MAD} = S \times K_a \times \mathrm{SIWV} \times \mathrm{SITT}$$

where S is solubility (mg/mL) at pH 6.5, K_a is intestinal absorption rate constant (min^{-1}) obtained from rat intestinal perfusion experiment that has been considered to be similar to human K_a, SIWV is small intestinal water volume (mL), which is considered to be 250 mL, and SITT is the residence time of drug in small intestine, generally assumed to be 3 h. The MAD concept serves as an initial guide to ascertain whether a compound might have potential dissolution and absorption issues and whether considerations for special dosage forms to overcome or minimize such issues have to be made.

In calculating MAD and, practically, for any other estimation of drug absorption, questions usually arise with respect to what drug solubility to use. In drug discovery settings, kinetic solubility based on the kinetics-driven turbidimetric light scattering method is generally used,[20] while

thermodynamic equilibrium solubility values are usually measured for dosage form development. Further, the "*in vivo* solubility" in the GI tract, which is a function of concentration of lipids, surfactants and mixed micelles present in intestinal fluids, might be more relevant to *in vivo* settings and for IV-IVC.[22–24] For compounds with log$P > 3$, it has been recommended that solubility and dissolution rate in simulated gastric and intestinal fluids or in human GI aspirates should be used for IV-IVC, since regular *in vitro* dissolution media used for quality assurance purposes do not contain bile salts, lecithin, lipid digestion products, etc.[25] For instance, when solubilities of danazol (log$P$ 4.5) were compared in simulated gastric fluid (SGF), simulated intestinal fluid (SIF), and human aspirates, the solubility in human aspirates was found to be much higher than that in buffers alone.[26] However, when different concentrations of bile salts, lecithin, and sodium lauryl sulfate were added to buffers, the solubility varied widely depending on nature and concentration of the added components. Therefore, in the determination of solubility for *in vivo* relevance, consideration must be given to thecomposition of solvents used.

pK_a

Solubility of a weak acid or a weak base is dependent on its ionization constant and intrinsic solubility (S_0; solubility of unionized or nonprotonated species) and, therefore, a function of pH of the dissolution medium. There are some excellent reports on the pH-dependence of drug solubility.[27–29] Both pK_a and S_0 are important in dictating what would be the drug solubility under gastrointestinal (GI) pH conditions; a relatively low pK_a of an acidic drug or a relatively high pK_a of a basic drug do not necessarily assure high drug solubility in the GI pH range unless the intrinsic solubility is also high. Figure 1A shows simulated pH-solubility profiles of four basic drugs where pK_a is kept constant at 8.0 and S_0 ranges from 0.1 to 100 μg/mL. For the compound with S_0 of 0.1 μg/mL, the solubility in the typical intestinal pH condition of 6 to 7 would be in the range of 1–10 μg/mL only, and the solubility must be lowered below 4 to obtain a solubility of 1 mg/mL and higher. One aspect of the pH-solubility profile that is not shown in Figure 1A is the solubility of the salt form. The pK_a does not keep on increasing with a decrease in pH, as shown in Figure 1A, indefinitely; at a certain pH, the total solubility exceeds the solubility of its salt form, preventing any further increase.[29] As expected, the solubility is also dependent on the pK_a value; Figure 1B shows the simulated pH-solubility profiles of four free bases as a function of pK_a values, where the S_0 value has been kept constant.

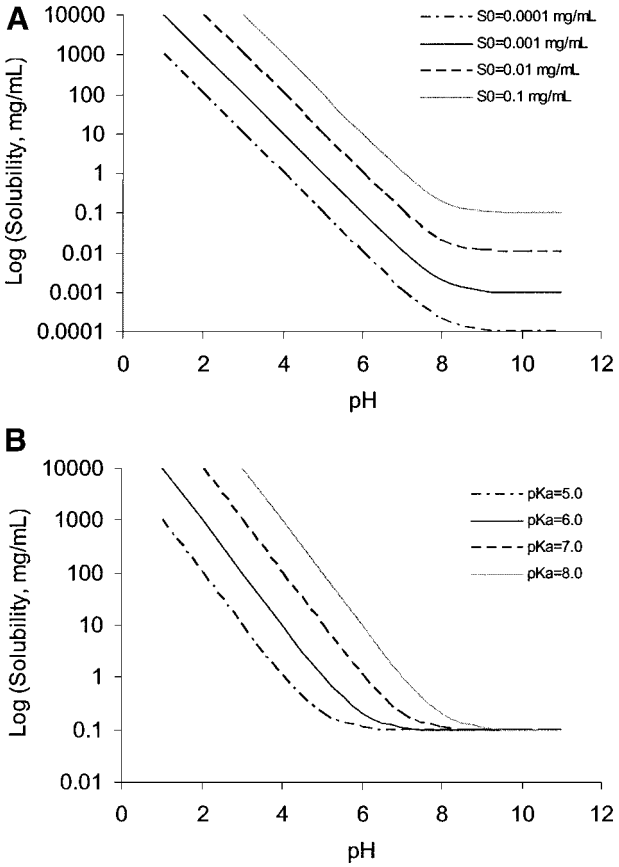

Figure 1. (A) Theoretical pH-solubility profile of a weak base with pK_a of 8.0 and different intrinsic solubility. (B) Theoretical pH-solubility profile of a weak base with S_o of 0.1 mg/mL and different pK_a values.

The pH gradient inherent to the GI tract influences and gives rise to areas of preferred absorption. Drugs with pK_a values in the range of 1 to 8 undergo considerable changes in the equilibrium between their ionized and unionized species as they transit through different regions of GI tract having different pH conditions. This effect, coupled with the solubility differences shown in Figure 1, gives rise to pH-dependent absorption. For example, the dissolution of a basic drug, ketoconazole, at pH 6 after 1 h is only 10%, while at pH < 3 more than 85% dissolves in less than 5 min.[30] This pH-dependence was evident *in vivo* when ranitidine was coadministered with

ketoconazole to raise the gastric pH to 6; the C_{max} of ketoconazole decreased from 8.2 to 0.6 μg/mL and the AUC decreased from 37.1 to 1.6 μg/h/mL.[31] Similarly, a decrease of almost 85% in C_{max} and AUC values of cinnarizine was observed in subjects with elevated gastric pH as compared to those exhibiting low gastric acidity.[32] Although it is often assumed that a basic drug dissolves well under the gastric environment, these examples illustrate that the actual amount dissolved could indeed be variable and depends on such factors as the pH and the gastric residence time. One way of improving the situation, as discussed under the next heading in this article, is to administer a base in its salt form, which usually has a higher dissolution rate.

Potential effects of pK_a on drug solubility, dissolution rate, and absorption need to be investigated at the early stage of drug development. When dissolution is the issue, appropriate formulation strategy to ensure the desired dissolution rate at the absorption site is necessary. Ho et al.[33] demonstrated the interplay of pH, pK_a, partition coefficient, concentrations of ionized versus unionized species, and permeability coefficients of aqueous boundary layers for a series of beta blockers by using cell culture monolayers. Structural modification of drug molecule can ensure optimal drug absorption. Derivatization into prodrugs or substitution of isosteres may also improve oral absorption of ionizable lipophilic molecules.[34]

Salt Formation

Since the early studies by Nelson,[5,6] there have been numerous reports on the effect of salt formation on drug dissolution[35–40] and its potential effect on bioavailability. A salt usually provides a higher dissolution rate than that of its free acid or base form by modifying pH and solubility in the diffusion layer at the surface of dissolving solid. Earlier work on physicochemical and biopharmaceutical aspects of pharmaceutical salts were reviewed by Berge et al.[35] It may also be pointed out here that, under certain GI pH conditions, a free base may have higher dissolution rate than that of its salt form. For example, Serajuddin and Jarowski[39] reported that the dissolution rate of the free base form of phenazopyridine at pH 1 is higher than that of the hydrochloride salt; however, if the full GI pH range (1–7) is considered, the salt still provides a superior pH-dissolution profile.

Because of pH-dependent solubility, there is a potential that free acid or base forms may precipitate out during the dissolution of salts under certain GI pH conditions. Depending on pK_a and solubilities of free forms, the precipitation of free acid occurs at a relatively lower pH, i.e., in the stomach, while the free base could precipitate at a relatively higher pH, i.e., in the intestine. This may be exemplified by the dissolution of phenytoin sodium under GI pH conditions. Phenytoin is an acidic compound with a pK_a of 8.4 and the solubility of ~37 μg/mL at 37°C between pH 1 and 6.[41] Therefore, it is expected that after oral administration as a sodium salt at a dose of 100 to 300 mg, it would precipitate out in its free acid form under the acidic environment of the stomach. It had been suggested that the precipitation of phenytoin acid in a very finely divided state would facilitate its rapid redissolution and faster absorption,[42] and later it was confirmed that it is indeed the case.[41] Figure 2 shows that when a 100-mg phenytoin sodium capsule was dissolved in 500 mL of a pH 2 medium, an equilibrium was established (~20% dissolved) in <10 min and the excess drug precipitated out as free acid. However, when an additional 500 mL of medium was added to the dissolution vessel, a new equilibrium was established in <5 min. Figure 2 also shows that there

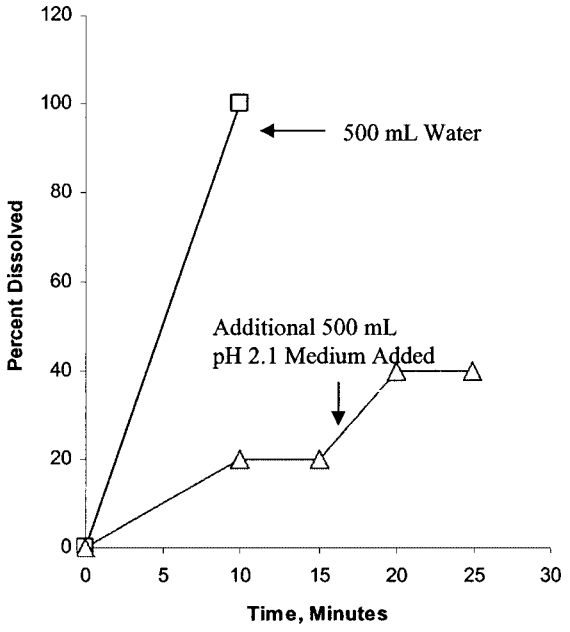

Figure 2. Dissolution profiles of fast-release phenytoin sodium formulation (100 mg) in (□) water and (△) pH 2.1 medium at 37°C. Each data point represents the average of three determinations. (Reproduced from Ref. 41 with permission of copyright owner.)

was no precipitation of phenytoin when water by itself was used as the dissolution medium, because the pH of the medium increased gradually with the dissolution of salt. This is, however, not the case in GI fluids where acidity, buffering action, etc., would keep pH relatively lower that could cause drug precipitation.

Despite the high dissolution rate of phenytoin sodium and the rapid redissolution rate of phenytoin acid that precipitated out in the stomach, phenytoin sodium dosage forms have been the subject of extensive IV-IVC studies. It was noted that there was a greater incidence of side effects if the innovator's product was substituted with an equivalent dose of products from other manufacturers,[43] which was due to 2–3 μg/mL higher steady state plasma level from the non-innovators' products.[44] To address this issue, the FDA classified the innovator's product as an "extended" or slow-release dosage form and the others as "prompt" or fast-release dosage form.[45,46] However, considering the long half life (22 ± 9 h) and Michaelis–Menten parameters of phenytoin, Sawchuk and Rector[47] determined that any variation in the release rate of phenytoin from dosage forms should not influence its steady state plasma level unless the extent of absorption is changed. They did not see any difference in plasma level when a situation assuming instantaneous absorption of phenytoin was compared with a situation in which a continuous constant rate of absorption occurred. Indeed, Arnold et al.[48] and, later Serajuddin and Jarowski,[41] demonstrated that there is a potential for incomplete release and, as a result, lower bioavailability of phenytoin from certain phenytoin sodium products. This example of phenytoin sodium highlights the importance of selecting not only a salt form but also of an appropriate dosage form for a drug to attain optimal plasma concentration and bioavailability. A similar situation may also arise for the salts of basic drugs, especially under intestinal pH conditions. If higher dissolution rate for a salt form cannot be ensured, a free base form may even be preferred.[49]

If other factors remain constant, the dissolution rate of a compound should determine the rate of build-up of blood levels with time and the maximum levels obtained. Nelson has reported that the rank order of dissolution rates correlated well with clinically determined blood levels.[5] Correlation of urinary excretion rates and dissolution rates of tetracycline and some of its acid salts was also demonstrated by Nelson.[6] Relative bioavailability of the vasodilator naftidrofuryl in oxalate and citrate salt forms has shown that the rate of absorption is higher for the citrate than for the clinically used oxalate form of the drug.[50] Lin et al.,[51] on the other hand, reported no enhancement in bioavailability when salts of a basic antihypertensive agent, having significantly different intrinsic dissolution rates, were compared.

Diffusion Layer pH

The effect of diffusion layer pH has been mentioned above in relation to the dissolution of free acids and bases versus their salts. Such an effect should also be considered in assessing the dissolution of one particular form of a compound (for example, free acid) under different pH conditions. It was reported that the diffusion layer pH on the dissolving surface of benzoic acid ($pH_{h=0}$) would remain practically constant around 3 while the pH of unbuffered bulk media may range from 3 to 11,[36,37] and, as a result, the dissolution rate within such a wide pH range would also remain practically unchanged. A self-buffering effect to maintain steady state pH in the diffusion layer may vary from compound to compound, depending on solubility and/or pK_a values. Figure 3 shows the effect of the pH of dissolution medium on the dissolution of three compounds having similar pK_a values, namely benzoic acid, 2-naphthoic acid, and indomethacin.[36] In this figure, the increase in dissolution rate (flux) relative to that of the unionized species (N/N_0) has been plotted. Despite pH-dependent solubility of all three compounds studied, pH of dissolution medium (bulk pH) had minimal effect on the

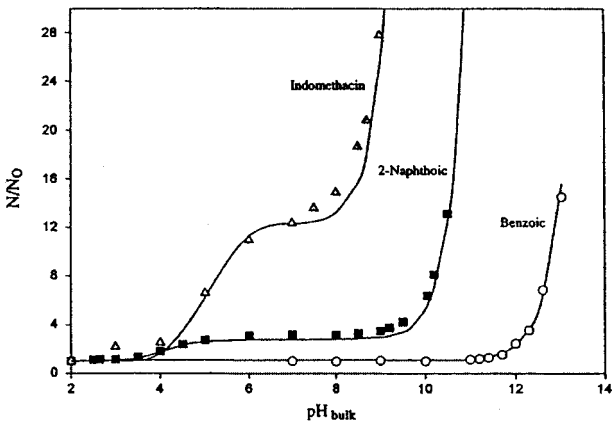

Figure 3. Relative flux (N/N_0) versus pH_{bulk} for several carboxylic acids at 25°C. N_0 is the respective flux at pH 2. (Reproduced from Ref. 36 with permission of copyright owner.)

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