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In vitro–in vivo correlation: Perspectives on model development☆

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ABSTRACT

In vitro–in vivo correlation (IVIVC) allows prediction of the in vivo performance of a drug based on the in vitro drug release profiles. To develop an effective IVIVC, the physicochemical and biopharmaceutical properties of the drug as well as the physiological environment in the body must be taken into consideration. Key factors include drug solubility, pK_a, drug permeability, octanol–water partition coefficient and pH of environment. In general, construction of an IVIVC involves three stages of mathematical manipulation: construct a functional relationship between input (in vitro dissolution) and output (in vivo dissolution); establish a structural relationship using data collected; parameterize the unknowns in the structural model. Some key mathematical relationships used in IVIVC development are presented. The establishment of an effective IVIVC has important implications in quality control and regulatory compliance.

1. Introduction

An in vitro–in vivo correlation (IVIVC) is defined by the U.S. Food and Drug Administration (FDA) as a predictive mathematical model describing the relationship between the in vitro property of an oral dosage form and relevant in vivo response. Generally the in vitro property is the rate or extent of drug dissolution or release, while the in vivo response is the plasma drug concentration or amount absorbed (The Food and Drug Administration, 1997). An important objective of pharmaceutical product development is to gain better understanding of the in vitro and in vivo drug performances. Through the successful development and application of an IVIVC, in vivo drug performance can be predicted from its in vitro behavior. The establishment of a meaningful IVIVC can provide a surrogate for bioequivalence studies, improve product quality, and reduce regulatory burden. Since the pioneering works of Edwards (1951) and Nelson (1957) in correlating aspirin and theophylline dissolution rates with their respective in vivo appearances following oral administration, IVIVC has gained increasingly more significance in the pharmaceutical product development field. In particular, the emergence of new lipophilic drug candidates with low aqueous solubility demands special considerations during IVIVC model development.

The objective of the present review is to examine the various factors that need to be considered in the development of an IVIVC, including physicochemical factors, biopharmaceutical factors, and physiological factors. We will discuss general approaches to developing an IVIVC. In particular, the steps associated with the construction of an IVIVC including modeling and data analysis will be addressed in detail. Lastly, the various applications of a meaningful IVIVC will be briefly described.

2. Considerations in IVIVC development

While it is widely recognized that correlations exist between in vitro drug dissolution and in vivo drug absorption, limited progress has been made towards the development of a comprehensive model capable of predicting in vivo drug absorption based on dissolution. This is due to the existence of a complex array of factors that contribute to the process of drug dissolution and absorption. In general, these factors can be classified into three groups; physicochemical factors, biopharmaceutical factors, and physiological factors. In order to develop a model that can demonstrate good correlation between in vitro drug dissolution and in vivo drug absorption, these factors have to be taken into consideration.

2.1. Physicochemical properties

Physicochemical properties play a major role in predicting the in vivo absorption of drug candidates. For almost all drugs admin-

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istered orally, dissolution is a prerequisite to drug absorption and clinical efficacy. Dissolution is dependent on several physicochemical properties, including solubility, pH dependency, salt forms, and particle size. A classical mechanistic equation that attempts to model dissolution is the Noyes–Whitney dissolution equation given by Eq. (1), which incorporates several of the physicochemical factors mentioned before:

$$\frac{dM}{dt} = \frac{DS(C_s - C_b)}{h} \quad (1)$$

In this equation, M is the amount of the drug dissolved, t is the time, D is the diffusion coefficient of the drug in the liquid, unstirred boundary layer surrounding the dissolving drug particle, S is the surface area of drug particle, h is the diffusion layer thickness, and C_s and C_b represent drug solubility and drug concentration in the bulk medium at time t, respectively. The Noyes–Whitney equation describes dissolution rate as a function of the change in drug concentration over time. If the sink condition is assumed, Eq. (1) can be transformed into the following form:

$$\frac{dM}{dt} = \frac{DSC_s}{h} \quad (2)$$

where C_s is approximated by the solubility of the drug substance. This concurs with our previous statement that the rate of dissolution is dependent on solubility. Although the Noyes–Whitney equation is a useful approach to model dissolution, it cannot be utilized to describe all types of dissolution data and may not apply in clinical settings (Dokoumetzidis et al., 2006). Another relatively simple model developed by Johnson and Swindell (1996) presents the concept of maximum absorbable dose (MAD) as an initial guide to determine dissolution characteristics. In this approach, the MAD is calculated by:

$$\text{MAD} = SK_a \times \text{SIWV} \times \text{SITT} \quad (3)$$

where S is the solubility at pH 6.5, K_a is the intestinal absorption rate constant, SIWV is the small intestinal water volume, and SITT is the residence time of the drug in the small intestines. In general, the SIWV is considered to be 250 mL and the SITT is assumed to be 3 h. This rather simplistic approach has many limitations and can only be utilized as an initial assessment of drug dissolution.

To develop a more comprehensive model, all relevant physicochemical properties must be considered. In addition to solubility, another important factor is the compound's ionization constant or its logarithmic equivalent, the pK_a value. The pK_a values determine the stability, solubility and absorption of compounds under different environmental pH conditions. This is highly relevant because the human body contains inherent pH gradients, especially in the gastrointestinal (GI) tract, which give rise to pH-dependent absorption profiles in vivo (Carlson et al., 1983). The salt form of the drug compound is yet another important factor to be considered. In general, a salt form has a higher dissolution rate than that of its free acid or base form. However, under certain pH conditions in the GI tract, the reverse may also be true (Serajuddin and Jarowski, 1985). Perhaps a more obvious source of effect on dissolution is the particle size. It is commonly recognized that a reduction in particle size would increase surface area and enhance rate of dissolution. It is, however, less well established how particle size reduction affects the dissolution rate. In the study conducted by Johnson and Swindell (1996), it was found that the effect of particle size on absorption is dependent on the drug dose and drug solubility. All these factors add to the complexity of the model building process.

2.2. Biopharmaceutical properties

Drug permeability plays a major role in drug absorption, particularly in orally administered dosage forms. The transcellular permeability (P_m) of a compound is defined as:

$$P_m = \frac{K_p D_m}{L_m} \quad (4)$$

where K_p is the membrane-water partition coefficient, D_m is the membrane diffusivity, and L_m is the membrane thickness (Li et al., 2005). Various models have been developed to estimate membrane permeability. One such model is based on the pH-partition theory, which states that the membrane uptake of unionized solutes is favored over the ionized solutes (Shore et al., 1957). For weakly acidic compounds, ionization is suppressed at low pH values, resulting in relatively high absorption rate. At high pH values, equilibrium is shifted towards the ionization of the compound, resulting in decreased membrane permeability. The opposite conclusions can be deduced for weakly basic compounds. It is also predicted that the pH value at which the half maximal absorption occurs is approximately equal to the compound's pK_a value (Winne, 1976). This particular model is not without limitations and deviations have been observed, possibly due to factors such as microenvironmental pH and solubility issues.

Another parameter that may be useful in model development is the oil–water partition coefficient. In particular, octanol–water partition coefficient (P or $\log P$) of neutral or unionized species is often used to provide insight into the ability of compounds to pass through membranes for absorption. Using computer and multiple linear regression, Hansch and Fugita (1964) were able to quantitate the structure activity relationships based on lipophilicity. They discovered that in general, a bell-shaped distribution exists between absorption and $\log P$ values. Kramer (1999) was able to further establish that compounds with $\log P$ between 0 and 3 generally had high permeability, and those with $\log P$ values less than −1.5 or greater than 4.5 had lower membrane permeability.

It is crucial to point out that although the octanol–water partition coefficient is a good indicator of membrane permeability, by itself it is not a sufficient parameter to predict in vivo absorption. Other measures of membrane permeability have been developed, such as absorption potential (AP) and polar surface area (PSA). The concept of absorption potential was developed by Dressman et al. (1985) and is defined as:

$$\text{AP} = \log\left(\frac{PF_{un}}{D_0}\right) \quad (5)$$

where P is the partition coefficient, F_{un} is the fraction of unionized drug at pH 6.5, and D_0 is the dose number equal to the ratio of dose concentration to solubility. Studies indicate that AP correlates well with the fraction of drug absorbed. PSA is the surface area of a drug molecule occupied by polar atoms. The PSA value has demonstrated good correlation with the passive transport of molecules through membranes, making it a candidate parameter to include in an in vivo absorption model.

2.3. Physiological properties

Besides physicochemical and biopharmaceutical considerations, physiological conditions are also important factors to consider for successful establishment of IVIVC, since physiological conditions can affect both drug dissolution as well as the rate and extent of drug absorption. In the previous sections, we have demonstrated the influence of pH on solubility, dissolution and membrane permeation. The effect of pH becomes particularly important in the human body, where there is an inherent pH gradient. The most well-known and commonly studied pH gradient is located throughout the GI tract, where it can range from values of 1–2 in the stomach to 7–8 in the colon. In the small intestine, where the vast majority of orally ingested substances are absorbed, the pH value ranges broadly from 5 to 8. These changes in GI pH profile can alter