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In Vitro-In Vivo Correlation for Complex Non-Oral Drug Products: Where Do We Stand?

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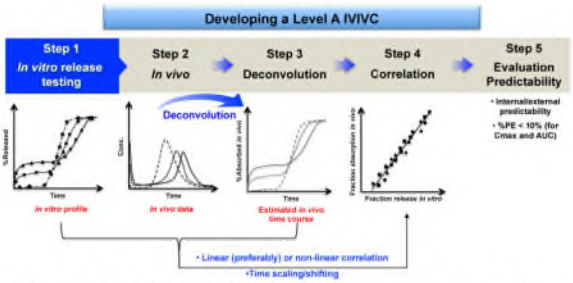
Abstract

In vitro -in vivo correlation (IVIVC) is a predictive mathematical model describing the relationship between an *in vitro* property and a relevant *in vivo* response of drug products. Since the U.S. Food and Drug Administration (FDA) published a regulatory guidance on the development, evaluation, and applications of IVIVC for extended release (ER) oral dosage forms in 1997, IVIVC has been one of the most important issues in the field of pharmaceutics. However, even with the aid of the FDA IVIVC Guidance, only very limited Abbreviated New Drug Application (ANDA) submission for ER oral drug products included adequate IVIVC data to enable the completion of bioequivalence (BE) review within first review cycle. Establishing an IVIVC for non-oral dosage forms has remained extremely challenging due to their complex nature and the lack of *in vitro* release methods that are capable of mimicking *in vivo* drug release conditions. This review presents a general overview of recent advances in the development of IVIVC for complex non-oral dosage forms (such as parenteral polymeric microspheres/implants, and transdermal formulations), and briefly summarizes the knowledge gained over the past two decades. Lastly this review discusses possible directions for future development of IVIVC for complex non-oral dosage forms.

Graphical abstract



Procedures of developing a Level A IVIVC. Example in vitro release profiles of three complex parenteral formulations with different release characteristics (i.e. slow, medium, and fast).

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Keywords

In vitro-in vivo correlation (IVIVC); non-oral; parenteral; prediction; *in vitro* release testing; modeling

1. Introduction

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 an *in vitro* property of a dosage form and a relevant *in vivo* response" [1]. 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. In the case of non-oral drug products (*e.g.* transdermal and ophthalmic dosage forms), an *in vitro* property could be *in vitro* drug permeation across the membrane of interest, while an *in vivo* property could be *in vivo* drug permeation. The history of IVIVC can be traced back to as early as 1950s, when pharmaceutical scientists attempted to correlate *in vitro* drug dissolution profiles of oral formulations with their respective *in vivo* pharmacokinetic profiles by means of mathematical modeling [2, 3]. In 1997, the U.S. FDA published a regulatory guidance related to the development, evaluation, and applications of IVIVC for extended release oral dosage forms. Since then, the establishment and application of IVIVC has increasingly gained more significance in the field of pharmaceutics. Generally, IVIVC can be categorized into five different levels: Levels A, B, C, D, and multiple Level C (Figure 1).

- Level A represents a point-to-point relationship between *in vitro* and *in vivo* profiles. Generally the correlations are linear. However, non-linear correlations are also acceptable [4]. A Level A correlation is considered the most informative and is recommended by the U.S. FDA. It is also the only level of IVIVC that can be used to obtain biowaiver.
- Level B correlation utilizes the principles of statistical moment analysis. A mean *in vitro* dissolution time ($MDT_{in\ vitro}$) is compared to either a mean *in vivo* residence ($MRT_{in\ vivo}$) or dissolution time ($MDT_{in\ vivo}$). Similar to a Level A IVIVC, a Level B correlation compares all *in vitro* and *in vivo* data available. However, since various *in vivo* release profiles may result in the same $MRT_{in\ vivo}$ or $MDT_{in\ vivo}$, a Level B correlation is not considered to be a point-to-point correlation, and does not necessarily reflect the actual *in vivo* plasma profile and hence may lack sufficient predictability.
- Level C correlation establishes a single point relationship between a dissolution parameter (*e.g.* the time required for 50% dissolution, $T_{50\%}$) and a pharmacokinetic parameter such as C_{max}, T_{max} or AUC. Since it is based on a single point analysis, it is does not reflect the complete shape of the plasma concentration time curve, which is critical to define *in vivo* performance of a drug product. Accordingly, a Level C IVIVC is limited in predicting *in vivo* drug performance. Nevertheless, Level C correlations may be useful in the early stages of formulation development when pilot formulations are being selected.

- Multiple Level C correlation relates multiple dissolution time points to one or more pharmacokinetic parameter(s) (*e.g.* C_{max}, T_{max} or AUC). A multiple Level C correlation should be based on at least three dissolution time points covering the early, middle, and late stages of the dissolution profile. A multiple Level C correlation can be as useful as a Level A correlation. However, if a multiple Level C correlation is obtainable, then the development of a Level A correlation should also be feasible and is more preferable.
- Level D correlation is a rank order correlation comparing *in vitro* and *in vivo* release profiles. A level D correlation is only qualitative and is not adopted in the U.S. FDA IVIVC Guidance.

A meaningful IVIVC can be used to guide formulation and/or process development changes in the various stages of drug product development. In addition, an IVIVC can be used to support and/or validate the use of an *in vitro* dissolution method and can help set clinically relevant dissolution specifications to ensure product quality [5]. Most importantly, when a Level A IVIVC is established and validated, the *in vitro* release method can be used as a surrogate for bioequivalence studies when pre-approval and post-approval changes are required (*e.g.* formulation composition, as well as manufacturing process, equipment and site) [6–8]. Through the successful development and application of a meaningful IVIVC, the *in vivo* performance may be accurately predicted from the *in vitro* performance of drug products and therefore, human or animal studies can be minimized and the regulatory burden can be reduced [9, 10].

Despite the publication of the FDA IVIVC guidance on ER oral dosage forms nearly two decades ago, only 14 ANDA submissions had IVIVC data, most of which were deficient and thereby, not acceptable [11]. Compared to the ER oral dosage forms, the establishment of an IVIVC for non-oral drug products (*e.g.* parenteral microspheres and implants, as well as transdermal and ophthalmic products) has been even more challenging due to their complex characteristics as well as the lack of standardized, compendial *in vitro* release testing methods [10]. In recent years, there has been significant interest within the pharmaceutical industry, academia, and regulatory agencies in developing suitable *in vitro* release testing methods as well as establishing IVIVCs for complex non-oral drug products. Notably, the U.S. FDA has funded over 20 research grants to advance *in vitro* equivalence methods for complex non-oral drug products and drug-device combinations in the past two years. Through collective and collaborative efforts in the field of pharmaceutics and drug delivery, some “ground-breaking” progress has been achieved. This review highlights recent advances in the development of IVIVC for complex non-oral dosage forms and briefly summarizes the knowledge gained over the past two decades. Lastly this review discusses possible directions for future development of IVIVC for these complex dosage forms.

2. Current State-of-the-Art

To date, there is no regulatory IVIVC guidance available for complex non-oral drug products. The same principles of developing IVIVC for ER oral dosage forms as detailed in the FDA IVIVC Guidance have been applied to develop IVIVC for various complex non-

oral dosage forms such as parenteral polymeric microspheres and implants [12–17], transdermal patches/gels [18, 19], as well as ocular inserts [20].

2.1. Approaches to develop IVIVCs

A Level A IVIVC is generally considered the highest level of correlation and is desirable from a regulatory point of view. Typically, developing a Level A IVIVC involves the following procedures (Figure 2): *1)* obtaining formulations (preferably, three or more) with different release rates (*e.g.* slow, medium, and fast) or using one formulation if its *in vitro* dissolution is independent of dissolution testing conditions (*e.g.* pH, media, and agitation); *2)* obtaining *in vivo* plasma concentration profiles or *in vivo* dissolution profiles of the selected formulations; *3)* estimating *in vivo* absorption or dissolution time course of each formulation using an appropriate deconvolution technique (*e.g.* model-dependent, and model-independent numerical) (Table 1); *4)* establishing a correlation/relationship between the estimated fraction *in vivo* release/absorption and the faction *in vitro* release, using a linear (preferably) or non-linear model (*e.g.* Sigmoid, Hixon-Crowell, Weibull, Higuchi, and Logistic) [21]; and *5)* evaluating the predictability of the developed IVIVC internally and/or externally. Based on the FDA IVIVC Guidance, an average percentage prediction error (%, PE) of 10% or less for pharmacokinetic parameters of interest (*e.g.* C_{max} or AUC) establishes the predictability of a developed IVIVC. When developing a Level A IVIVC, there may be disparity between deconvoluted *in vivo* and *in vitro* dissolution profiles due to the intrinsic difference between *in vitro* and *in vivo* dissolution conditions. Accordingly, time shifting/scaling may be utilized to allow the deconvoluted *in vivo* data to be on the same time scale as the *in vitro* dissolution data, which in turn makes it possible to establish a correlation/relationship between *in vitro* and *in vivo* release data.

Although a Level A IVIVC is most informative and recommended by the U.S. FDA, other levels of IVIVC (*e.g.* multiple Level C, and Level B) can be helpful to assure product quality, and to assist in formulation development. When developing a Level B IVIVC, at least three formulations are required. Based on the principles of statistical moment analysis, a mean residence time ($MRT_{in\ vivo}$), mean absorption time ($MAT_{in\ vivo}$), or mean *in vivo* dissolution time ($MDT_{in\ vivo}$) is calculated and related to a mean *in vitro* dissolution time ($MDT_{in\ vitro}$) (Figure 3A). All parameters determined are model-independent. In the case of developing a multiple Level C correlation, one or more pharmacokinetic parameters (*e.g.* C_{max}, T_{max} or AUC) are correlated with at least three dissolution time points covering the early, middle, and late stages of the dissolution profile. Based on the U.S. FDA IVIVC Guidance, the recommendations for assessing the predictability of Level C correlations depend on the type of application for which the correlation is to be used. The methods and criteria for assessing the predictability are the same as that for Level A correlations described above.

The development of IVIVCs for non-oral drug products is a complicated process, due to not only their complex characteristics (*e.g.* multi-phasic release) but also the lack of suitable *in vitro* release testing methods. Despite that extensive efforts have been devoted in this area, there are only a few literature reports on the establishment of IVIVCs for these drug products based on multiple formulations, albeit with different *in vitro* release testing

methods such as USP apparatus 4 methods [15, 16], dialysis membrane methods [14, 22], and Franz diffusion cells [18–20] (Table 2).

2.2. IVIVCs for parenteral polymeric microspheres/implants

Parenteral polymeric microspheres/implants, particularly poly(lactic-co-glycolic acid) (PLGA)/poly(lactic acid) (PLA)-based microsphere/implant drug products have been one of the most successful complex non-oral polymeric drug products on the market. The PLGA/PLGA-based microsphere/implant drug products are biodegradable, biocompatible, and possess the capability of delivering a variety of therapeutics (*e.g.* small molecules and biologics) in a controlled manner over periods of days to several months [33–36]. These ER parenteral drug products normally contain substantial amounts of potent therapeutics. Therefore, it is critical to assure consistent product performance and safety through *in vitro* quality control tools such as discriminatory *in vitro* release testing methods, as well as reliable IVIVCs or *in vitro-in vivo* relationship (IVIVR) in the event that an IVIVC is not feasible. Over the past two decades, the development of IVIVCs for polymeric microspheres/implants has received the most attention, as a result of which considerable progress has been achieved (Table 2). However, most reported literature are "proof-of-concept" research that only demonstrated the possibility of developing point-to-point linear correlations or Level B correlations based on one formulation. Encouragingly, Level A IVIVCs established using two or more microsphere formulations with different release characteristics have recently be presented [14, 16, 22, 23]. It should be noted that multiple formulations with different release characteristics are essential to develop a reliable IVIVC.

One of the most challenging aspects of developing IVIVCs for complex microsphere/implant drug products is to design *in vitro* release studies in such a way that the *in vivo* behavior of these products is reflected as much as possible. PLGA/PLA-based polymeric microspheres/implants are normally administrated into subcutaneous or muscular tissues or directly injected into local areas (*e.g.* knee joints). Following injection/implantation, therapeutics are slowly released from microspheres/implants into the tissue fluids *via* complex release mechanisms (*e.g.* diffusion, polymer erosion or a combination thereof) [37, 38], and are subsequently transported into the systemic blood circulation system *via* diffusion and/or convective processes [39–41]. Due to the lack of compendial *in vitro* release methods, various *in vitro* release methods (*e.g.* sample-and-separate [23, 26, 27], membrane dialysis [14, 22], and flow through [15, 16]) have been utilized to determine *in vitro* drug release characteristics and to develop IVIVCs. Although it is feasible to develop IVIVCs for parenteral microspheres/implants based on a simple sample-and-separate method [17, 23–25], there are limitations associated with this method such as poor hydrodynamic conditions, loss of product (*e.g.* microspheres) during sampling as well as inability to mimic different *in vivo* drug release conditions. For example, the presence of the *in vivo* boundary layers as well as the small interstitial fluid volume available for drug release at the administration sites. It has been reported that the correlation/relationship between the *in vitro* and *in vivo* data of huperzine microspheres was sensitive to the route of administration. Additionally, the sample-and-separate method appeared to better reflect drug release from PLGA microspheres in muscular tissues compared to that in subcutaneous tissues, thus a better correlation was obtained for the intramuscular route [23]. Compared to

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