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IN VITRO-IN VIVO CORRELATION (IVIVC) OF DIFFERENT PARAMETERS OF DOSAGE FORM

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ABSTRACT

Researchers can achieve rapid drug production by discovering a mathematical link between bioavailability and dissolution testing that leads to the principle of in vitro - in vivo correlation (IVIVC). IVIVC is a mathematical model which from its in vitro output can be used to estimate in vivo action. Level A correlation is widely recognized by the regulatory agencies among all the five stages of correlation. IVIVC's suitability is demonstrated by the Biopharmaceutical Classification System (BCS). In the estimation of correlations, dissolution process design plays a central role. Other important parameters in the IVIVC analysis are the qualification of the apparatus and guidelines. During the production of IVIVC, several variables, such as first pass effect, stereochemistry, should be considered. Thus, the need for a method to compare in vitro and in vivo drug release data reliably has increased tremendously. Such an instrument shortens the time of drug growth, saves money and contributes to improved product quality. Increased IVIVC creation activity demonstrates the importance of IVIVCs to the pharmaceutical business. In the production of new pharmaceuticals, IVIVC can be used to minimize the number of human studies during the development of formulation, as the primary objective of IVIVC is to act as a replacement for bioavailability in vivo and to help bio waivers. The usage of dissolution encourages and/or validates methods and configurations for requirements. This is because in vivo importance of in vitro dissolution specifications is included in the IVIVC. Research is based on new oral dosage forms in the current scenario, where awareness of IVIVC is of vital importance. IVIVC implementations vary from drug and product production to improvements in their scale-up and post-approval. Therefore, in drug production, IVIVC should be used as an effective tool.

Keywords: IVIVC, In-vitro, In-vivo, Dosage forms.

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INTRODUCTION

The definition and application of in vitro-in vivo correlation (IVIVC) in pharmaceutical dosage forms has been a primary subject of interest in the pharmaceutical, academic and regulatory sectors in recent years. The term correlation is usually employed within the pharmaceutical and related sciences to explain the connection that exists between variables. Mathematically, the term correlation means interdependence between quantitative or qualitative data or relationship between measurable variables and ranks 2. From biopharmaceutical standpoint, correlation might be mentioned because the relationship between appropriate in vitro release characteristics and in vivo bioavailability parameters. Evolution formulation optimization is an important part of any therapeutic agent's manufacturing and marketing, which is also a time-consuming and expensive process. Changes to the formulation composition, production method, and equipment and batch sizes may be needed for the optimization process. If these kinds of changes are made to a formulation, experiments will be needed to show that in healthy human volunteers, the new formulation is bioequivalent to the old one **[1]**.

Certainly, enforcing these criteria not only prevents the new formulation from being sold, it also increases the expense of optimization processes. Therefore, it would be desirable to develop in vitro tests which represent bioavailability data **[2]**.

In general, IVIVC is defined as a mathematical model that describes the relationship between the drug product's in vitro and in vivo properties so that it's in vitro behavior can predict its in vivo properties. USP and FDA, however, have forwarded two concepts **[3]**. These are as follows: USP defines IVIVC as the relationship between a biological property or a parameter derived from a dosage form-produced

biological property, while FDA defines IVIVC as a predictive mathematical model which describes the relationship between the dosage form in vitro properties and the related in vivo response **[4]**.

A regulatory guideline for both immediate and updated dose releases the FDA has therefore built forms to eliminate the need for bioavailability studies as part of the design and optimization of formulations. The procedures of IVIVC are unique to some countries but may be adapted or used by other countries as the background for regulatory recommendations. In developing new pharmaceuticals, IVIVC can be used to minimize the number of clinical trials during the production of formulations **[6]**. This is because in vivo importance of in vitro dissolution specifications is included in the IVIVC. For some scale-up and post-approval adjustments, for example, to strengthen formulations or to adjust manufacturing processes, it may also assist in quality control. There must be some in vitro means of ensuring the same output of each batch of the same product in vivo **[7]**.

In a recent U.S. regulatory guidance, applications of IVIVC models were outlined. It may be possible to optimize the production of modified-release (MR) dosage forms by using IVIVC models or, alternatively, to predict the in vivo performance of MR dosage forms based on data from in vitro dissolution **[8]**.

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IVIVC SIGNIFICANCE

Pharmaceutical companies are hungry for the rapid production and approval of drugs, while regulatory agencies need product quality and performance assurance. There has been considerable interest in the in vivo and in vitro correlation of the oral dosage type over the last 25 years in the pharmaceutical, academic and regulatory sectors. In 1971, Wagner stated that "future dissolution rate research should primarily aim to establish a correlation between in vitro and in vivo data **[9]**." The in vivo output can be predicted by an accurate correlation between in vivo and in vitro results, indicating the usefulness of the method that can be used as a major instrument for development and production control. It is important to provide a valid method to generate both in vitro and in vivo correlation measurements to obtain a valid correlation **[10]**.

It was previously concluded that curvilinear or hockey stick plots for piroxicam and metoprolol were indicative of absorption-limited in vivo input. The current findings for metformin are similar and are consistent with earlier studies that have shown in vivo input limited absorption rate for Metformin **[5]**. The curvilinear relationship between percent in vivo input and percent in vitro dissolution, however, was not special, indicating the lack of a single IVIVC level A model that could cover all three formulations of MR. Consequently, a deconvolution-based level A IVIVC model could not be created **[11]**.

Previous research indicated that simple and extended-type convolution models were potential alternatives to a level A IVIVC model based on deconvolution. Whereas in vitro dissolution and IR plasma concentration data are used by the simple convolution model to predict plasma profiles of MR formulations, the extended convolution method specifically models the absorption mechanism prior to the prediction of MR plasma level. The extended convolution models were suggested to be ideal for drugs with incomplete or site-dependent absorption, in particular. In the present analysis, as shown by the discrepancies between observed and predicted plasma profiles and between measured and observed C_{max} and AUC (0±22) for metformin for all MR formulations, the internal predictability of the basic convolution model was low **[12]**.

TYPES OF IVIVC

Three types of IVIVC models have been defined by the FDA guidance: Level A, B, and C models, in particular. Based on these categories, multiple investigators have attempted to create IVIVC models. Since a level a correlation uses the entire time course of in vitro dissolution and in vivo input, it has been recognized for the purposes of obtaining setting dissolution requirements as the IVIVC model of choice **[7]**.

Nonetheless, models of levels B and C have been identified and may be used to analyze whether level A IVIVC models are feasible for particular drugs/formulations in the initial phases of formulation development or, alternatively, in vitro dissolution conditions may be changed **[9]**.

Level A

In general, a correlation of this form is linear and reflects a point-to-point association between in vitro dissolution and in vivo input rate (e.g. the dissolution of the drug in vivo from the dosage form). The in vitro dissolution and in vivo input curves can be directly related in a linear correlation. The use of a scaling factor may be super imposable or may be rendered super imposable **[10]**. Although rare, nonlinear correlations may also be suitable. Alternative methods are possible to build a Level A IVIVC Regardless of the method used to evaluate a Level A IVIVC, from the in vitro data, the model can predict the entire in vivo time course. In this context, the model refers to the relationship between an ER dosages forms in vitro dissolution and an in vivo response such as the

concentration of plasma drugs or the amount of drug absorbed **[15]**.

Level B

A Level B IVIVC uses statistical moment analysis concepts. A Level B correlation does not uniquely represent the real in vivo plasma level curve, since a variety of different in vivo curves can produce similar mean residence time values. The mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time **[16]**.

Level C

A Level C IVIVC defines a single point relationship between, for example, a dissolution parameter of t50 percent and a pharmacokinetic parameter dissolved in 4 hours (e.g., AUC, C_{max}, T_{max}). A Level C correlation does not reflect the full form of the time-time plasma concentration the curve, which is the essential factor that determines the quality of goods **[17]**.

Level D

This is a semi-quantitative or qualitative correlation and is not acceptable for regulatory purposes as it is not a formal correlation. However, it can be useful at a very preliminary level during product and process development **[18, 19].**

APPLICATIONS OF IVIVC

Biopharmaceutical Classification System

The biopharmaceutical arrangement (BCS) may be a way to categorize drug compounds Supported their solubility and permeability properties. Under the BCS, drug substances are often grouped into four classes: Class 1 compounds are highly soluble and highly permeable; Class 2 substances have high permeability but relatively low solubility; Class 3 compounds are highly soluble but not very permeable; and sophistication 4 drug substances have both low solubility and low permeability generally, It's recognized that the successful development and application of an IVIVC require dissolution to be the rate-limiting step within the process of drug administration and absorption. for sophistication 1 compounds, there are not any rate-limiting steps for drug absorption, with the possible exception of immediate release dosage forms, that gastric emptying could potentially become the rate-limiting step **[20]** for sophistication 2 compounds dissolution is that the rate-limiting step in absorption, therefore the establishment of IVIVC is predicted. for sophistication 3 compounds, IVIVC is usually considered unlikely but could also be possible counting on the relative rates of dissolution and intestinal transit. for sophistication 4 compounds IVIVC is very unlikely. Classification consistent with the BCS will enable early determination of whether IVIVC are often developed for a particular drug candidate.

Bio waivers

A bio waiver is an exemption granted by the FDA that permits in vivo bioavailability and/or bioequivalent studies to be avoided. A predictive and reliable IVIVC model can function a basis for bio waivers, allowing reductions in time and costs during pharmaceutical development. For immediate release dosage forms, the successful development of IVIVC models could also be limited to Class 2 and sophistication 3 compounds classified under the BCS, thereby restricting the appliance of biowaivers to those classes of drug compounds. However, consistent with FDA guidelines bio waivers also can be requested for sophistication 1 compounds provided the drugs are solubilized within the gastric fluid sufficiently rapidly that gastric emptying doesn't become the rate-limiting step. things for extended release (ER) dosage forms is more complex, since the factors considered within the BCS (i.e. solubility and intestinal permeability) are insufficient to predict the speed and extent of dissolution for ER drugs. Despite these limitations, the FDA has published important guidelines for establishing IVIVC for ER dosage forms. Readers should ask the document "FDA Guidance for Industry – ER oral dosage forms: development, evaluation, and application of IVIVCs **[21]** and "FDA Guidance for Industry – Waiver on in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms supported a Bio pharmaceutical classification system.

[22] for more detailed information.

Non-oral Dosage Forms

Currently, regulatory guidance for IVIVC is especially focused on oral dosage forms. However, similar principles of developing IVIVCs are often applied to non-oral dosage forms, with certain modifications to regulate for various modes and durations of drug delivery. Perhaps one among the foremost challenging aspects of developing IVIVCs non-oral drug delivery systems is the way to design in vitro studies such in vivo behavior is reflected the maximum amount as possible. for instance, it's difficult to use classical IVIVC to drug-eluting stents because it's an area delivery system, not a systemic delivery system like oral dosage forms. Several publications have attempted to correlate in vitro pharmacokinetics of paclitaxel **[23, 24]** loaded stents with in vivo delivery into the artery wall with limited success. Another difficulty which will hinder the planning of appropriate in vitro

studies is that the lack of suitable dissolution media that reflect the in vivo environment non-oral delivery systems are subjected to. this is often particularly the case for implanted drug delivery devices and liposomal products. Liposomal formulations have traditionally demonstrated poor correlation between *invitro* and *invivo* performance, possibly thanks to the physiological presence of a lipid membrane `sink' to which released drugs may bind **[25]** to bypass this problem, a completely unique drug release assay has been developed using excess multilamellar vesicles **[26].** This method demonstrated improved correlation between in vitro data and in vivo release of doxorubicin, verapamil and ceramide.

CONCLUSION

It is clear that there is a dynamic relationship between dissolution in vitro and bioavailability in vivo. Although it is desirable to use product dissolution to predict in vivo behavior, several years of research have shown that, with our current knowledge, this aim cannot be accomplished. Indeed, it may be potentially risky to presume such a relationship.

It is clear that there is a dynamic relationship between dissolution in vitro and bioavailability in vivo. Although it is desirable to use product dissolution to predict in vivo behavior, several years of research have shown that, with our current knowledge, this aim cannot be accomplished. Indeed, it may be potentially risky to presume such a relationship. As a quality control to ensure process and batch consistency in the production process, dissolution testing is important. However, it has failed to predict discrepancies between products that are poorly available in vivo or super bioavailable in relation to current standards. In addition, IVIVC may also allow more meaningful dissolution methods and requirements to be set up and validated. For some scale-up and post-approval adjustments, it may also assist in quality management. Therefore, both regulatory authorities and the pharmaceutical industry have recognized the importance of IVIVCs. Activity in the IVIVC region for oral extended release dosage forms has also increased. The FDA Guidance on IVIVC offers general guidance on the for the establishment of IVIVC, methods very small and further study is required to develop more meaningful methods of dissolution and permeation. and guidelines. The number of studies published in the field of the establishment of IVIVCs for non-oral dosage forms is very small and further study is required to develop more meaningful methods of dissolution and permeation.

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