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Regulatory perspectives on in vitro (dissolution)/in vivo (bioavailability) correlations[☆]

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Abstract

In vitro dissolution has been extensively used as a quality control tool for solid oral dosage forms. In several cases, however, it is not known whether one can predict the in vivo performance of these products from in vitro dissolution data. In an effort to minimize unnecessary human testing, investigations of in vitro/in vivo correlations (IVIVC) between in vitro dissolution and in vivo bioavailability are increasingly becoming an integral part of extended release (ER) drug product development. This increased activity in developing IVIVCs indicates the value of IVIVCs to the pharmaceutical industry. Because of the scientific interest and the associated utility of IVIVC as a valuable tool, the US Food and Drug Administration has published a Guidance in September 1997, entitled Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations. A predictive IVIVC enables in vitro dissolution to serve as a surrogate for in vivo bioequivalence testing. IVIVCs can be used in place of biostudies that may otherwise be required to demonstrate bioequivalence, when certain preapproval and postapproval changes are made in formulation, equipment, manufacturing process or in the manufacturing site. IVIVC development could lead to improved product quality (more meaningful dissolution specifications) and decreased regulatory burden (reduced biostudy requirements). This article will discuss in detail the FDA Guidance which deals with the development, evaluation methods and criteria, and applications of IVIVCs. From a regulatory point of view, the applications of IVIVC to grant biowaivers and to set dissolution specifications for ER oral dosage forms will be presented. Additionally, since the principles of IVIVC are considered to be similar for non-oral dosage forms, the guidance for oral extended release products may be applied for non-oral products as well. While the principles are likely to be the same, it is an interesting challenge to look at appropriate methods for dissolution testing and for development of in vitro/in vivo correlations for products such as injectable depot formulations. © 2001 Elsevier Science B.V. All rights reserved.

1. Introduction

In vitro/in vivo correlations (IVIVC) refer to

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relationships between in vitro dissolution and in vivo input rate. As is well known, in vitro dissolution testing is a powerful and useful method for determining product quality and sometimes to evaluate the clinical performance of dosage forms. The utility of in vitro dissolution as a surrogate for in vivo bioavailability is very attractive and has been demonstrated for several products. However, these general-

ly are achieved for controlled release dosage forms and not for immediate release dosage forms (for immediate release products, dissolution is generally not the rate-limiting step in absorption of the drug). In cases where a meaningful IVIVC could be developed, this can be used as a surrogate for bioequivalence and can minimize the number of the bioequivalence studies needed.

2. In vitro/in vivo correlations

2.1. Concepts

In the context of this article, IVIVCs are defined as correlations between in vitro dissolution and in vivo input rate. In order to successfully develop an IVIVC, in vitro dissolution has to be the rate-limiting step in the sequence of steps leading to absorption of the drug into systemic circulation. Furthermore, to utilize this dissolution test as a surrogate for bioequivalence (where a relatively simple in vitro test is used in place of human testing), the IVIVC must be predictive of in vivo performance of the product.

2.2. Levels of correlation

Four categories of IVIVCs have been described in the FDA guidance.

Level A: A level A correlation represents a point-to-point relationship between in vitro dissolution and the in vivo input rate (e.g. the in vivo dissolution of the drug from the dosage form). Generally these correlations are linear, however, non-linear correlations are also acceptable. A level A correlation is considered most informative and very useful from a regulatory viewpoint.

Level B: A level B correlation uses the principles of statistical moment analysis. The mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time. Although this type of correlation uses all of the in vitro and in vivo data, it is not considered a point-to-point correlation. Further, since it does not uniquely reflect the actual in vivo plasma level curve, this is not very useful from the regulatory point of view.

Level C: A level C correlation establishes a single

point relationship between a dissolution parameter (e.g. $t_{50\%}$ or percent dissolved in 4 h) and a pharmacokinetic parameter (e.g. AUC or C_{\max}). A level C correlation does not reflect the complete shape of the plasma concentration time curve, therefore is not the most useful correlation from a regulatory point of view. However, this type of correlation can be useful in early formulation development.

Multiple level C: A multiple level C correlation relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile. Multiple level C correlation can be as useful as level A IVIVC from a regulatory point of view. However, if one can develop a multiple level C correlation, it is likely that a level A correlation can be developed as well.

2.3. When is an IVIVC likely?

As stated previously, IVIVCs are generally seen when the in vitro dissolution is the rate-limiting step in the absorption and appearance of the drug in in vivo circulation. Therefore, if the drug is highly permeable [3] and in vitro dissolution is the rate-limiting step, it is very highly likely that a successful IVIVC can be developed.

2.4. FDA guidance, extended release oral dosage forms: development, evaluation and applications of in vitro/in vivo correlations

This guidance [1] has been developed (1) to reduce regulatory burden by decreasing the number of biostudies needed to approve and maintain an extended release product on the market and (2) to set clinically more meaningful dissolution specifications. It is anticipated that with a predictive IVIVC, the biostudies, that are generally required for major manufacturing changes are replaced by a simple in vitro dissolution test.

2.5. General principles in the development of a correlation

Generally, IVIVC should be developed using two or more formulations with different release rates (only one release rate is sufficient if dissolution is condition-independent). Data obtained from human

studies are required for regulatory consideration of the correlation. When two or more drug product formulations with different release rates are developed, their in vitro dissolution profiles should be generated using an appropriate dissolution methodology [1,4]. The dissolution method used should be the same for all the formulations. A bioavailability study should be conducted to determine the in vivo plasma concentration time profiles for each of the formulations. Preferably, this study should be of a crossover study design in adequate number of subjects. However, in certain cases, data from across studies can be used in the development of an IVIVC, if a common reference is included in these studies. One method to develop a level A correlation is to estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (using Wagner–Nelson method, numerical deconvolution, etc.). The in vivo absorption profile is plotted against the in vitro dissolution profile to obtain a correlation (Figs. 1 and 2). One could use alternative approaches other than that mentioned above to develop correlations. Also, if there is no one to one relationship, then dissolution conditions may be altered (prior to evaluation of predictability), or time scaling approaches used to develop the correlation. However, the time scaling factor should be the same for all the formulations. Different time scales for each of the formulations indicates absence of an IVIVC.

It is necessary to emphasize that the relationship

between in vitro dissolution and in vivo dissolution, or absorption, should be the same for all the formulations studied. If one out of the three formulations (only if this is the slowest or the fastest release rate formulation) shows a different relationship, then, such a formulation may be dropped from the IVIVC development.

2.6. Evaluation of predictability of IVIVC

An IVIVC should be evaluated to demonstrate that the predictability of the in vivo performance of a drug product, from the in vitro dissolution characteristics of the drug product formulations, is maintained over a range of in vitro release rates. The focus is on predictive performance of the model, and therefore, the prediction error is evaluated (Fig. 3). Depending on the intended application of an IVIVC and the therapeutic index of the drug, evaluation of predictability internally and/or externally may be appropriate. Evaluation of internal predictability is based on the initial data used to develop the IVIVC. Evaluation of external predictability is based on additional data sets. External predictability evaluation is not necessary unless the drug is a narrow therapeutic index drug, or only two release rates were used to develop the IVIVC, or, if the internal predictability criteria are not met (for criteria, see the FDA guidance on IVIVC, Ref. [1]). However, since the IVIVC will potentially be used to predict the in vivo performance for future changes, it is of value to

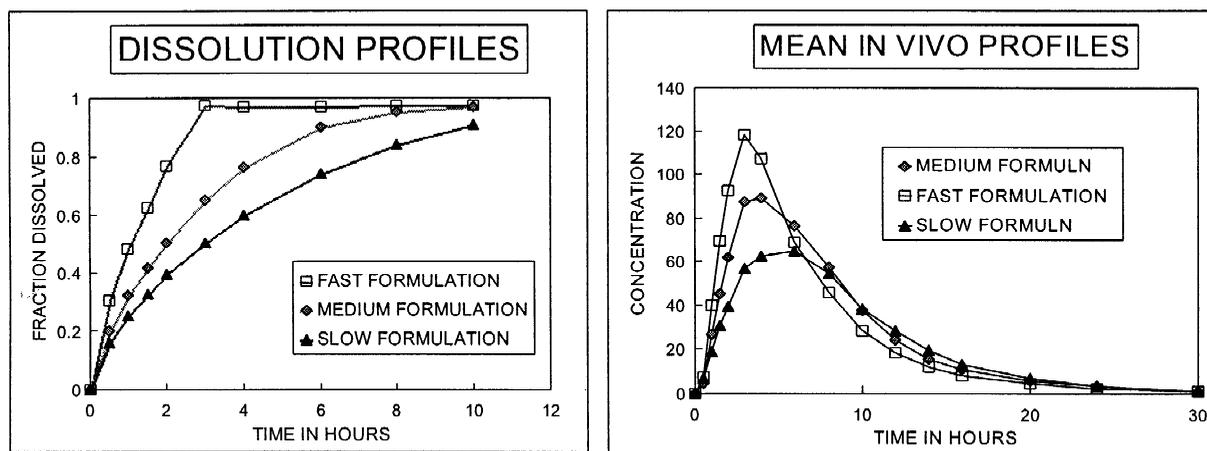


Fig. 1. (a) In vitro dissolution profiles and (b) in vivo plasma concentration profiles.

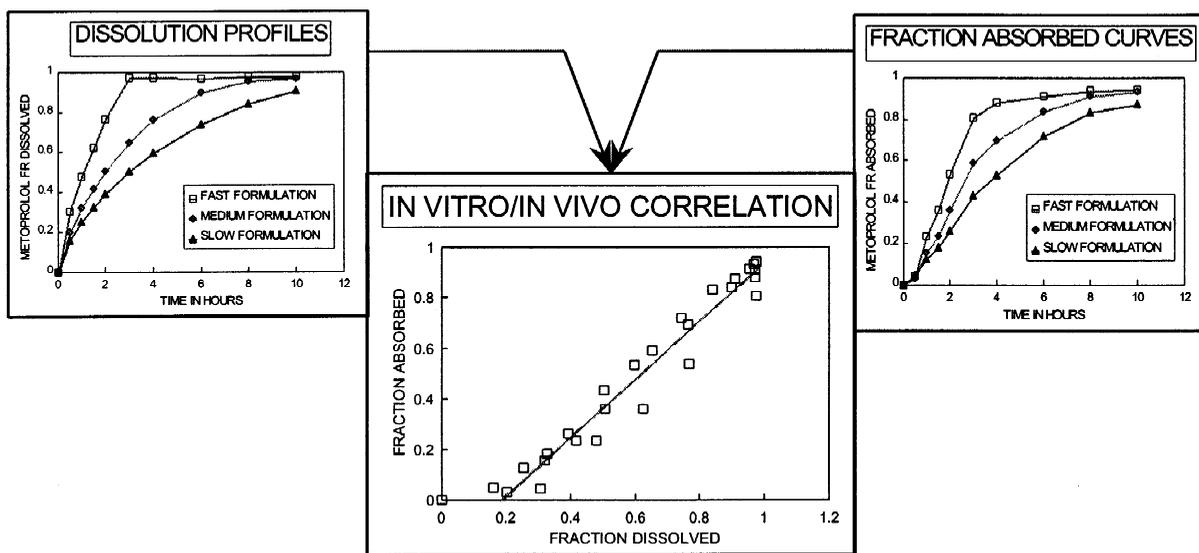


Fig. 2. Development of in vivo/in vitro correlation.

evaluate external predictability when additional data are available

Absolute % prediction error on C_{max} and AUC

$$[|obs - pred|]/obs \cdot 100$$

2.7. Applications of IVIVC

A predictive IVIVC can empower in vitro dissolution as a surrogate for in vivo bioavailability/bioequivalence. This can be used to

- grant biowaivers

- set meaningful dissolution specifications that take into account the clinical consequences.

2.7.1. Biowaivers

The guidance outlines five categories of biowaivers

1. Biowaivers without an IVIVC
2. Biowaivers using an IVIVC: non-narrow therapeutic index drugs
3. Biowaivers using an IVIVC: narrow therapeutic index drugs

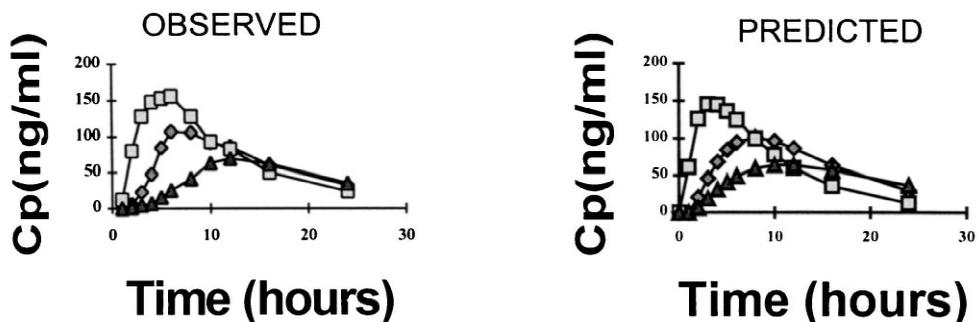


Fig. 3. Evaluation of predictability.

4. Biowaivers when in vitro dissolution is independent of dissolution test conditions
5. Situations for which an IVIVC is not recommended for biowaivers.

Ideally, one would like to be able to predict the in vivo performance of the drug product from its in vitro dissolution. Therefore, with a predictive IVIVC, waivers for in vivo bioavailability studies may be granted for manufacturing site changes, equipment changes, manufacturing process changes and formulation composition changes. The biowaivers section deals with changes ranging from situations such as minor changes that are insignificant for product performance to major changes for which an IVIVC is not sufficient to justify the change, for a regulatory decision. The IVIVC guidance in this area complements the SUPAC-MR guidance (scale up and post approval changes — modified release dosage forms [2]). An IVIVC can be used to support those drug product changes in SUPAC-MR that might have required a biostudy. However, there are situations such as those outlined under category 5, where an IVIVC cannot be used. One such example is, one sponsor's IVIVC cannot be used to justify in vivo performance of another sponsor's product.

The mechanism of drug release from the drug product should remain the same when changes are made to a formulation for an IVIVC to be applicable. If the release mechanism changes, a previously developed IVIVC is not applicable.

The two criteria for granting a biowaiver for a new formulation, where an IVIVC has been established are that the differences in predicted means of C_{\max} and AUC are no more than 20% from that of the reference product and, where applicable, the new formulation meets the application or compendial dissolution specifications.

2.7.2. Setting dissolution specifications

Once an IVIVC is developed, this should be used to set dissolution specifications for the product. The guidance describes procedures for setting dissolution specifications in cases where there is no IVIVC, where there is a level A IVIVC and where there is a level C IVIVC. When there is no IVIVC, specification ranges at each time point of 20% or less (of the label claim) are recommended. If justified, deviations

from this criteria can be acceptable up to a maximum range of 25%. Beyond this range, the specification should be supported by bioequivalence studies.

When an IVIVC has been established, IVIVC should be used to set specifications in such a way that the fastest and slowest release rates allowed by the upper and lower dissolution specifications result in a maximum difference of 20% in the predicted C_{\max} and AUC.

2.8. IVIVCs for non-oral dosage forms

While the FDA IVIVC guidance is applicable only to oral dosage forms, the principles of this guidance can be used to develop IVIVCs for non-oral products as well. For oral dosage forms, the dissolution methods are reasonably well understood and established. Guidances exist to develop appropriate test methods for these dosage forms (e.g. FDA immediate release dissolution guidance [4]). However, challenges exist with the dissolution method development for some of the non-oral products (such as parenteral depots). The volume of fluid needed, agitation conditions to be used etc. are not well defined. This is an active area of research to develop good dissolution methods for these types of products [5]. Further, for dosage forms such as depot injectables, in vivo factors, such as fluid volume, viscosity, tissue barriers, phagocytosis, inflammation etc. can also affect the in vivo release and absorption. Therefore, ongoing research is necessary in developing in vitro/in vivo correlations for these types of products.

2.9. Regulatory impact of IVIVCs

IVIVCs can decrease regulatory burden by decreasing the number of biostudies required in support of a drug product. As an additional benefit to the sponsors, IVIVC can support wider in vitro dissolution specifications, where justified.

3. Conclusion

IVIVC can impart in vivo meaning to the in vitro dissolution test and can be useful as surrogate for bioequivalence. Further, IVIVC can also allow set-

ting of more meaningful dissolution specifications. Both the regulatory agencies and industry sponsors have understood this value of IVIVCs. Therefore, the activity in the area of IVIVC for oral extended release dosage forms has increased in the last 5 years. The FDA Guidance on IVIVC provides general methods for the establishment of IVIVC. However, further research is necessary in the area of development of appropriate dissolution methods and IVIVCs for non-oral dosage forms.

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