Review Article

In vitro–in vivo correlation and biopharmaceutical classification system

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 drug product development. Development, rapidity in drug development can be achieved by researchers on finding a mathematical link between bioavailability and dissolution testing, which leads to the concept of IVIVC. IVIVC is a mathematical model that can be used to estimate *in vivo* behavior from its *in vitro* performance. Among all the five levels of correlation, Level A correlation is widely accepted by the regulatory agencies. Biopharmaceutical classification system explains the suitability of IVIVC. Dissolution method design plays a pivotal role in the estimation of correlations. Applications of IVIVC ranges from drug and product development, their scale up and postapproval changes. Hence, IVIVC should be considered as an important tool in drug development.

Key words:
Applications of IVIVC, biowaiver, biopharmaceutical classification system, dissolution methodologies, fundamentals of IVIVC, IVIVC of novel dosage forms

Introduction

Correlations between *in vitro* and *in vivo* correlation data (IVIVC) are often used during pharmaceutical development in order to reduce development time and optimize the formulation. A good correlation is a tool for predicting *in vivo* results based on *in vitro* data. IVIVC allows dosage form optimization with the fewest possible trials in man, fixes dissolution acceptance criteria, and can be used as a surrogate for further bioequivalence studies; it is also recommended by regulatory authorities.[1-5] Many studies reported in the late 1970s and early 1980s established the basic concept of IVIVC.[6] Various definitions of IVIVC have been proposed by the International Pharmaceutical Federation, the working group, and regulatory authorities, such as the FDA or Europe, the Middle East and Africa (EMEA) (European Medicines Agency). The FDA[7] defines IVIVC as "a predictive mathematical model describing the relationship between an *in vitro* property of an extended release (ER) dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, for example, plasma drug concentration or amount of drug absorbed." As stressed in this definition, IVIVC is more an *in vitro–in vivo* relationship than a strict correlation. It should be kept in mind that a relationship does not imply a causality link between the *in vitro* data, in our case, and the *in vivo* data. Pharmaceutical companies are hungry for the rapid drug development and approval, while Regulatory agencies need assurance of the product quality and performances. During the last 25 years, there has been a considerable

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R. Tiwari, G. Tiwari, A. K. Rai, B. Srivastawa[1], P. Pandey, S. Pandey, Lokesh Bhati[2]

Department of Pharmaceutical Sciences, Pranveer Singh Institute of Technology, Kanpur, Uttar Pradesh, [1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, [2]Department of Pharmaceutical Sciences, Bhagwant University, Ajmer, Rajasthan, India

Address for correspondence:
Dr. Gaurav Tiwari
Department of Pharmaceutics,
Pranveer Singh Institute of Technology, Kalpi Road,
Bhauti, Kanpur – 208 020, Uttar Pradesh, India.
E-mail: tiwari_mpharm@rediffmail.com

interest within the pharmaceutical industry, academia, and regulatory sectors in *in vivo* and *in vitro* correlation[1] of oral dosage form. In 1971, Wagner stated that "future research in dissolution rates should be directed mainly towards establishing correlation between *in vitro* and *in vivo* data. An accurate correlation between *in vivo* and *in vitro* data can predict the *in vivo* performances indicating the usefulness of the method which can be used as a major tool for development and production control. To reach a valid correlation, it is necessary to have a valid method to yield measurements both *in vitro* and *in vivo* correlation. The completion of these criteria led to the publication[3] of "Stimuli" by U.S. pharmacopoeial convention's subcommittee on biopharmaceutics in pharmacopoeial Forum in 1988. *In vitro* specifications, such as physical and chemical properties, stability, water content, disintegration, solubility, and rate and extent of dissolution used as quality and process control in dosage form manufacturing. The merits of establishing such a relationship are to be measured in terms of cost, time, and safety. In general IVIVC is defined[8-11] as a mathematical model, which describes the relationship between *in vitro* and *in vivo* properties of a drug product, so that *in vivo* properties can be predicted from its *in vitro* behavior. However, two definitions have been forwarded by USP and FDA. These are as follows: USP defines IVIVC as the establishment of relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, while FDA defines IVIVC as a predictive mathematical model,[12] which describes relationship between *in vitro* properties of a dosage form and a relevant *in vivo* response.

Objectives of *In Vitro–In Vivo* Correlation

In vitro dissolution is one of the vital tools for characterization of biopharmaceutical quality of a dosage form at different stages of drug development. *In vitro* dissolution data helps in the evaluation and interpretation of possible risks, especially in the modified release dosage form and the food effects on bioavailability that influence the gastrointestinal conditions. It also plays a great role while assessing changes in the manufacturing process. However, none of these purposes will be fulfilled by *in vitro* dissolution testing without sufficient knowledge of its *in vivo* relevance. IVIVC have been defined in many ways and have been a subject to much controversy. A meaningful correlation must be quantitative[5] so as to allow interpolation between data, thus making the *in vitro* model predictive. IVIVC also ensures batch to batch consistency in the physiologic performance of a drug product.[13-15]

Development of Correlation

Two-step approach

Step 1: Estimate the *in vivo* absorption or dissolution time course using an appropriate technique for each formulation and subjects.

Step 2: Establish link model between *in vivo*

Predict plasma concentration from *in vitro* using link model.

One-step approach

Predict plasma concentration from an *in vitro* profile using a link model whose parameters are fitted in one step

- Do not involve deconvolution
- Link model is not determined separately
- Can be done without reference like IV bolus

Fundamentals of *In Vitro–In Vivo* Correlation

USP defined five levels of correlation each of which denotes the ability to predict *in vivo* response of a dosage form from its *in vitro* property. Higher the level better is the correlation. The level of correlation is categorized as given in the following sections.[16-20]

Level A correlation

A correlation of this type is generally linear and 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). In a linear correlation, the *in vitro* dissolution and *in vivo* input curves may be directly super imposable or may be made to be super imposable by the use of a scaling factor. Among all the levels of correlation defined, level A is of prime importance. It is defined as a hypothetical model describing the relationship between the fraction of drug absorbed and the fraction of drug dissolved. To develop a correlation between two parameters, one variable should be common between them. The data available is *in vitro* dissolution profile and *in vivo* plasma drug concentration profile whose direct comparison is not possible. To have a comparison between these two data, data transformation is required. The *in vivo* properties, such as the percentage drug dissolved or fraction of drug dissolved can be used while *in vivo* properties, such as the percentage drug absorbed or fraction of drug absorbed can be used, respectively. It is considered as a predictive model for relationship between the entire *in vitro* release time courses. Most commonly a linear correlation exists but sometimes nonlinear IVIVC correlation may prove appropriate. However, no formal guidance for nonlinear IVIVC has been established. When *in vitro* curve and *in vivo* curve are super imposable, it is said to be 1:1 relationship, while if scaling factor is required to make the curve super imposable, then the relationship is called point-to-point relationship. Level A correlation is the highest level of correlation and most preferred to achieve; since it allows biowaiver for changes in manufacturing site, raw material suppliers, and minor changes in formulation.

Level B correlation

A Level B IVIVC 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. A Level B correlation does not uniquely reflect the actual *in vivo* plasma level curve, because a number of different *in vivo* curves will produce similar mean residence time values. Here the mean *in vitro* dissolution time (MDT) is compared with either the mean *in vivo* residence time (MRT) or mean *in vivo* dissolution time derived by using the principle of statistical moment analysis. Although it utilizes all *in vitro* and *in vivo* data, it is not considered as point-to-point correlation since the number of *in vivo* curves can produce similar residence time value. Hence, it becomes least useful for regulatory purposes.

Level C correlation

A level C IVIVC establishes a single-point relationship between a dissolution parameter, for example, t50%, percent dissolved in 4 h and a pharmacokinetic parameter (eg, area under the curve [AUC], plasma concentration [C_{max}], and time curve [T_{max}]). A Level C correlation does not reflect the complete shape of the plasma concentration–time curve, which is the critical factor that defines the performance of ER products. In addition to these three levels, a combination of various levels of C is also described: 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. It is referred as single-point correlation, which is established in between one dissolution parameter (t50%) and one of the pharmacokinetic parameter (T_{max}, C_{max}, or AUC). However, it does not reflect the complete shape of plasma drug concentration–time curve, which is the critical factor that defines the performance of a drug product. Level C correlation is helpful in early stages of development when pilot formulations are being selected.

Multiple level C correlation

It refers to the relationship between one or several pharmacokinetic parameters of interest and the amount of drug dissolved at several time points of dissolution profile. It should be based on at least three dissolution time points that include early, middle, and late stages of the dissolution profile.[20,21]

Level D correlation

It is a semi-quantitative and rank order correlation and is not considered useful for regulatory purpose.

Predictability of Correlation

It can be calculated by prediction error (PE) that is the error in prediction of *in vivo* property from *in vitro* property of drug product. Based on therapeutic index of the drug and application of IVIVC, evaluation of PE internally or externally may be appropriate. Internal error provides a basis for acceptability of model while external validation is superior and affords greater confidence in model. The percentage PE can be calculated by the following equation:

$$\% PE = (C_{max} \text{ observed} - C_{max} \text{ predicted}) \times 100 / C_{max} \text{ observed}$$

Internal predictability

The bioavailability (C_{max}, T_{max}/AUC) of formulation that is used in the development of IVIVC is predicted from its *in vitro* property using IVIVC.[22-24] Comparison between predicted bioavailability and observed bioavailability is done and % PE is calculated. According to FDA guidelines, the average absolute %PE should be below 10% and % PE for individual formulation should be below 15% for establishment of IVIVC.[25-27]

External predictability

The predicted bioavailability is compared with known bioavailability and % PE is calculated. The PE for external validation should be below 10%, whereas PE between 10% and 20% indicates inconclusive predictability and need of further study using additional data set. Drugs with narrow therapeutic index, external validation is required.

Reasons for Poor *In Vitro–In Vivo* Correlation

Fundamentals

When *in vivo* dissolution is not the rate limiting pharmacokinetic stage, and when no *in vitro* test can simulate the drug dissolution along the gastrointestinal tract.

Study design

With inappropriate *in vitro* test conditions.

Dosage form

When the drug release is not controlled by the dosage form or is strongly affected by the stirring of synthetic liquid.

Drug substance

With a nonlinear pharmacokinetics, for example, first-pass hepatic effect, an absorption window, a chemical degradation, and a large inter- or intra-subject variability. All these factors are of vital concern and should be kept in mind, especially the intervariability of patients' response to a drug.[28-33]

Biopharmaceutics Classification System

Biopharmaceutics classification system (BCS) is based on solubility, intestinal permeability, and dissolution rate, all of which governs the rate and extent of oral absorption from immediate release solid oral dosage form. Based on solubility and permeability, there are four classes of BCS. Solubility criteria defined in present regulatory guidance for classifying an Active Pharmaceutical Ingredients as "highly soluble" requires the highest strength to be soluble in 250 ml of water over the pH range of 1–7.5 at 37°C, otherwise it is considered as poorly soluble. The FDA and also EMEA

guidelines define "highly permeable" as having a fraction dose absorbed of not less than 90%. The recently adopted world health organization (WHO) guidelines set a limit of not less than 85% of the fraction dose absorbed, otherwise it is considered to be poorly permeable.[34-36]

Biowaiver for BCS class I

On the basis of FDA guidelines, sponsor can request biowaiver for BCS Class I in immediate release solid oral dosage form, if the drug is stable in gastrointestinal tract (GIT) and having narrow therapeutic index with no excipient interaction affecting absorption of drug in the oral cavity. Once a drug enters in stomach; it gets solubilized in gastric fluid rapidly before gastric emptying and the rate and extent of absorption is independent of drug dissolution as in case of solution. Hence, the goal of biowaiver is achieved.

Biowaiver extension potential for BCS class II

The rate and extent of absorption of BCS Class II drug depends on *in vivo* dissolution behavior of immediate release products. If *in vivo* dissolution can be predicted from *in vitro* dissolution studies, *in vivo* bioequivalence study can be waived. *In vitro* dissolution methods can mimic *in vivo* dissolution behavior of BCS Class II drug and are appealing but experimental methods can be difficult to design and validate because of number of processes involved.

Biowaiver extension for BCS class III

If excipient used in two pharmaceutically equivalent solid oral immediate release product does not affect the drug absorption and the products dissolves very rapidly (>85% in 15 min) in all relevant pH ranges, there is no reason to believe that these products would not be bioequivalent.

Approaches for Development of Correlation

Basically, two methods are available for the development of correlations[36-38]

Two-stage deconvolution approach

This involves estimation of *in vivo* absorption profile from plasma drug concentration–time profile using Wagner–Nelson or Loo–Riegelman method, subsequently the relationship with *in vitro* data is evaluated.

One-stage convolution approach

It computes the *in vivo* absorption and simultaneously models the *in vitro–in vivo* data.

Two-stage method allows for systematic model development while one stage obviates the need for administration of an intravenous, oral solution, or IV bolus dose. Mostly IVIVC models developed are simple linear equations between *in vitro* drug released and *in vivo* drug absorbed. But sometimes these data can be better fitted by using nonlinear models, such as Sigmoid, Weibull, Higuchi, or Hixon–Crowell.

Dissolution Methodologies, Apparatus, and Classification

The principle applied to dissolution has stood the test of time. Basic understanding of these principles and their application are essential for the design and development of sound dissolution methodologies as well as for deriving complementary statistical and mathematical techniques for unbiased dissolution profile comparison. USP 27, NF22 (11) now recognized seven dissolution apparatus specifically and describes with allowable modifications in detail. The choice of dissolution apparatus should be considered during the development of the dissolution methods, since it can affect the results and duration of the test. The type of dosage form under investigation is the primary consideration in apparatus selection. The compendial apparatus for dissolution as per USP are: Apparatus 1 (rotating basket), Apparatus 2 (paddle assembly), Apparatus 3 (reciprocating cylinder), Apparatus 4 (flow-through cell), Apparatus 5 (paddle over disk), Apparatus 6 (cylinder), Apparatus 7 (reciprocating holder). The European Pharmacopoeia has also adopted some of the apparatus designs described in the USP, with some minor modifications in the specifications. Small but persistent differences between the two have their origin in the fact that the American metal processing industry, unlike the European, uses the imperial rather than the metric system. In the European Pharmacopoeia, official dissolution testing apparatus for special dosage forms (medicated chewing gum, transdermal patches) have also been incorporated.

Dissolution Medium

The most important parameters which are considered for simulating *in vivo* conditions are pH, buffer composition, buffer capacity, temperature, volume, hydrodynamics, and so on. Noncompendial media have shown better IVIVC as compared to compendial media, which is listed in the official monographs. Hence noncompendial media have been proved to have discriminating power and are widely used. Basically, pH increases from small intestine to large intestine (pH 6.7–8) due to which dissolution testing of ER drug product should be carried out throughout entire physiological pH range (6.7–8). Ionic strength of dissolution media also plays a vital role in dissolution testing. Ions present in the food and food-induced secretions in GIT causes changes in ionic strength of gastrointestinal (GI) fluid. Buffer capacity has importance in dissolution testing of formulation that contains acidic or basic excipients. Studies have shown that buffer capacity of a medium is an important criterion in design of dissolution media for IVIVC.

Qualification of Apparatus

Due to the nature of the test method, "quality by design"

is an important qualification for *in vitro* dissolution test equipment. The suitability of the apparatus for the dissolution/drug-release testing depends on both the physical and chemical calibrations which qualify the equipment for further analysis. Besides the geometrical and dimensional accuracy and precision, as described in USP 27 and European Pharmacopoeia, any irregularities, such as vibration or undesired agitation by mechanical imperfection, are to be avoided. Temperature of the test medium, rotation speed/flow rate, volume sampling probes, and procedures need to be monitored periodically. Another vital aspect of qualification and validation is the "apparatus suitability test." The use of USP calibrator tablets (for apparatus 1 and 2 disintegrating as well as nondisintegrating calibrator tablets) is the only standardized approach to establish apparatus suitability for conducting dissolution tests and has been able to identify or operator failures. Suitability tests have also been developed for Apparatus 3, using specific calibrators and the aim is to generate a set of calibrators for each and every compendia dissolution test apparatus.

Parameters to be Considered while Developing IVIVC

Metabolic factors

A drug must pass sequentially from the gastrointestinal lumen, through the gut wall, and the liver, before entering the systemic circulation. This sequence is an anatomic requirement because blood perfusion virtually all gastrointestinal tissues drain into the liver via the hepatic portal vein. Drug loss may occur in the GIT due to the instability of the drug in the GIT and/or due to complexation of drug with the components of the GI fluids, food, formulation excipients, or other coadministered drugs. In addition, the drug may undergo destruction within the walls of the GIT and/or liver.

Drug loss in GIT

Any reaction that completes with the absorption of a drug may reduce oral bioavailability of a drug. Reaction can be both enzymatic and nonenzymatic. Acid hydrolysis is a common nonenzymatic reaction. Enzymes in the intestinal epithelium and within the intestinal microflora, which normally reside in the large bowel, metabolize some drug. The reaction products are often inactive or less potent than the large molecule.

Stereochemistry

When one enantiomer has higher affinity toward receptors than other, the phenomenon is termed as stereo selectivity, which results in pharmacokinetics or pharmacodynamics. If such stereoisomers in the form of racemate are administered orally, one form may have higher bioavailability than the other.

Biopharmaceutical Classification System

BCS class permeability

- BCS Class I High
- BCS Class II High
- BCS Class III Low
- BCS Class IV Low

Parameters studied for *in vitro–in vivo* correlation

Earlier disintegration was considered as the most important pertinent *in vitro* parameter but recently, dissolution rate has been used as a manufacturing process standard and is generally considered to be the *in vitro* parameter most likely to correlate with *in vivo* bioavailability. *In vivo* bioavailability is described in terms of the rate and extent of drug absorption. Rate of absorption is reflected in peak drug concentrations in plasma (C_{max}) and the terms at which they occur (T_{max}). Other methods may be used to describe absorption rate profile, for example, deconvolution and statistical moment theory. However, use of these approaches does not detract from the basic relationships between absorption rate, C_{max}, and T_{max}. FDA guidance recommends these methods as a means of documenting bioavailability and bio inequivalence for topically acting solution formulations, because they can be performed reproducibly and are more discriminating among products.

Applications

The most vital application of IVIVC is to use *in vitro* dissolution study in lieu of human bioequivalence studies, which will reduce the number of human bioequivalence studies during initial approval process as well as certain scale up and postapproval changes.

Manufacturing control

The ER products are distinguished through their input rate to the absorption site. Therefore, the rate of drug release from these products is an important feature and should be carefully controlled and evaluated. The *in vitro* dissolution/release test is meaningful only when the test results are correlated to the products' *in vivo* performances.

Process change assurance

The manufacturing processes of approved products are regulated by the regulatory agencies. The manufacturers are required to demonstrate that kind of change, even an engineering improvement, does not cause changes in the finished product's *in vivo* performance.

Dissolution/Release Rate Specifications

Without a correlation, the specifications of an *in vitro* test can be established only empirically. This approach is data driven but is valid only if all the batches have been extensively evaluated in clinical trials; furthermore, it

probably can detect only relatively large differences between different batches. It is therefore more precise to set up the specification using the correlation to evaluate the *in vivo* consequences of the range. Clearly, the pharmacokinetic consequences alone are not sufficient to set up the specifications. The pharmacodynamic knowledge is the key to make the specification clinically meaningful. In the absence of the information, some scientists may be willing to rely on the empirical bioequivalence range of ±20% as the first guidance. In case of a one-to-one correlation, this automatically translates in a dissolution rate change of ±20%. It is empirically derived dissolution range is much wider than ±20%, and then the companies invariably believe that the products have been punished by the presence of one-to-one correlation.

Early Development of Drug Product and Optimization

In the early stages of drug product development drug products are characterized by some *in vitro* systems and some *in vivo* studies in animal models to find out toxicity and efficacy issues.

Biowaiver for Minor Formulation and Process Changes

After the evaluation of critical manufacturing variables and *in vitro* dissolution rate for controlled release formulation an IVIVC has been established. *In vitro* dissolution data is used to justify minor formulation and process changes. The changes may include minor change in shape, size, amount, and composition of materials, colors, flavors, procedure, and coating, source of inactive and active ingredients, equipment, or site of manufacturing.[36-42]

Comments

The products were bioequivalent despite difference in *in vitro* dissolution. Dissolution test modified to agree with *in vivo* data. *In vitro* dissolution rate not predictive of overall bioavailability. No IVIVC correlation slower absorption and reduced systemic bioavailability from slower dissolving SR capsule. All preparations were bioequivalent despite different dissolution rate of one preparation. Correlations obtained between *in vitro* and *in vivo* data had no discrimination. No significant differences among products in *in vitro* or *in vivo* data. Good IVIVC using specific sink condition dissolution method. Rank order correlation between dissolution rates and absorption rate constants, but no statistical significant difference in bioavailability of the three capsules products. Neither disintegration nor dissolution accurately reflected absorption. Two dissolution tests yielded different rank orders of dissolution rates. Neither test correlated with *in vivo* data. Products were bioequivalent despite different *in vitro* release rates. Close correlation between dissolution rate and bioavailability reflected in C_{max} and also the area under the plasma drug curve (AUC).[43-45]

IVIVC of Novel Dosage Forms

Enteric-coated multiple unit dosage form

Individual unit is emptied gradually and separately from the stomach to duodenum. Simulation of these conditions *in vitro* is troublesome and may be impossible. Takashi *et al*. developed a method to predict dissolution in GIT from *in vitro* data in consideration of gastric emptying process. Direct prediction of *in vivo* absorption profile from *in vitro* dissolution data in multiple unit system was difficult but convolution method overcame this problem. Good correlation (level A) was obtained for multiple unit enteric-coated granules by using convolution method.

Parenteral controlled or sustained release drug delivery system

Three methods for *in vitro* drug release study of microparticles system for parenteral administration have been established by far. These include sample and separate, flow through cell and dialysis technique.

Buccal tablets

Spiegeleer *et al*. have developed a useful correlation between *in vivo* residence time of mucoadhesive tablets in mouth and *in vitro* bending point of the same. Linear regression models permit optimization of buccal tablets to enhance the adhesion time using *in vitro* bending point as selection criteria.[46]

Transdermal drug delivery system

USP 29 gives methods for *in vitro* drug release testing of transdermal patches, such as paddle over disk, cylinder method, and reciprocating disk method. But Franz diffusion cell are highly used.

Suppositories

Modified basket or paddle methods are recommended for lipophilic suppositories, whereas conventional basket, paddle, or flow-through cells are recommended to be suitable for hydrophilic suppositories.

Nasal drug delivery system

A variety of methods on *in vitro* testing of nasal drug delivery system, such as emitted dose, droplet, or particle size distribution, spray pattern bioequivalence study. With the availability of an *in vitro* test with one-to-one correlation to the product's *in vivo* performance, a bioequivalence study should no longer be necessary. In such cases, the scientists and regulatory agencies may consider a pilot pharmacokinetic study as an assurance that the new excipient does not inadvertently affect the absorption.[47]

Conclusion

Level A IVIVCs define the relationship between an *in vitro* dissolution curve and an *in vivo* input (absorption) profile. A Level A correlation should always be tried *apriori* in order to have a tool that allows a complete *in vivo* prediction from an *in vitro* dissolution curve and thus accelerates the development and assists in some regulatory aspects (SUPAC). The correlation quality depends solely on the quality of the data. As *in vivo* data are now well standardized, the main effort must be directed to the *in vitro* data. Various apparatus and media should be tested and it is clear that a complex relationship exists between *in vitro* dissolution and *in vivo* bioavailability. While it is desirable to use product dissolution to predict *in vivo* behavior, many years of investigation have shown that this goal cannot be achieved with our current knowledge. Indeed, the assumption of such a relationship could be potentially dangerous. Dissolution testing is essential as a quality control to ensure process and batch consistency in the manufacturing process. It has failed, however, to predict differences among products that are poorly available *in vivo* or those that are super bioavailable relative to the existing standards.

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