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Commentary

The biopharmaceutics classification system (BCS): Class III drugs — better candidates for BA/BE waiver?

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Abstract

Current guidelines (CPMP Note for Guidance in Europe and FDA Guidance for Industry in the USA) consider a waiver of bioavailability/bioequivalence studies for immediate release dosage forms of highly soluble, highly permeable drug substances (Class I according to the BCS). In this paper, a waiver of BA/BE studies is being proposed also for Class III compounds (high solubility and low permeability) in fast dissolving products without excipients which may modify gastro-intestinal transit or membrane permeation. This type of drug substance may be an even better candidate for a waiver as, in this case, bioavailability will not so much depend on the formulation characteristics, as on drug substance properties (e.g. permeability). © 1999 Published by Elsevier Science B.V. All rights reserved.

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The discussion of the necessity of bioavailability/bioequivalence (BA/BE) studies in the regulatory process has been one of the major topics of the international debate on BA/BE issues during recent years. Two guidelines with new regulations in this respect were issued recently: the CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP, 1998) in Europe, and in the USA, the FDA Guidance for Industry ''Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System'' (FDA, 1999).

1. International regulatory requirements

1.1. European regulations

According to the CPMP Guideline, bioequivalence studies should be performed for all generic immediate release products intended for systemic action. However, exceptions are possible if the following catalogue of criteria are fulfilled:

- the drug substance has certain properties, e.g.
  is not a drug with a narrow therapeutic index,
  exhibits a linear pharmacokinetics and a first pass effect less than 70%,
  is highly water soluble over the entire physiological pH range (1–8) at 37°C,
  is highly permeable in the intestine (i.e. extent of absorption is greater than 80%)

and

- the drug product exhibits a particular quality pattern, e.g.
  excipients have no significant impact on the pharmacokinetics of the active substance(s),
  release of the active substance is fast in buffers over the entire physiological pH range (pH 1–8) at 37°C.

If all these requirements are met by a certain generic medicinal product, in vitro dissolution data are considered sufficient to ensure bioequivalence. For this purpose, dissolution profiles have to be ''similar'' to those of the reference product. Similarity has to be assessed over the entire physiological pH range (e.g. at pH 1.3, 4.6 and 6.8) by comparing the dissolution curves by means of the f_2 equation (FDA, 1997).

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1.2. US regulations

Similar, although more specific requirements are given by the FDA Guidance for Industry. This document is also only relevant for oral immediate release dosage forms intended for systemic use. According to this guideline ''drugs that are poorly permeable, poorly soluble and/or formulated in slowly dissolving dosage forms may be considered to be drugs with actual or potential bioequivalence problems''. As a consequence, in vivo studies are requested for such drug products.

In more specific terms, waiver of in vivo studies may be requested by the sponsor if

- the drug substance is highly soluble and highly permeable,
- the drug product dissolves rapidly, i.e. >85%/30 min over the entire physiological pH range (e.g. at pH 1.3, 4.6 and 6.8) and
- the drug is not a drug with a narrow therapeutic index.

Moreover, stability of the active substance in the medium of the gastrointestinal tract has to be assured (>95%/3 h). This supposition is important for the appropriate interpretation of experimental findings from solubility and permeability investigations or the mass balance analysis.

Special attention should be paid to the excipients. They should be ''well established'' (i.e. already used in approved IR forms) and ''unproblematic''. Excipients are considered critical in this respect if they significantly affect

- dissolution of the active drug ingredient from the dosage form (e.g. surfactants),
- permeation through the intestinal membrane (e.g. enhancers),
- gastro-intestinal transit time or
- drug metabolism in the mucosa.

2. The biopharmaceutics classification system

2.1. General concept

The regulations of both guidelines concerning a waiver of BA/BE studies are based on the Biopharmaceutics Classification System (BCS) which was developed over the last few years. The BCS classifies drug substances in four groups (Fig. 1) according to their solubility and permeability properties (Amidon et al., 1995).

The background of this classification is the understanding that dissolution from the dosage form depends considerably on the solubility of the drug ingredient and that absorption from the GI tract is dependent on permeability properties of the drug substance. However, dissolution is also affected by the biopharmaceutical characteristics of the formulation and absorption from the intestine may be influenced by certain ingredients (e.g. those modifying GI transit or membrane permeability).

Consequently, additional requirements on dissolution behaviour were introduced into the system. Thus, a waiver of bioavailability studies may only be granted for products whereby more than 85% of the drug ingredient is dissolved in 30 min in all physiological media. Moreover, in cases of generic products, waiver of bioequivalence investigations are only possible if both (test and reference) products exhibit similar dissolution profiles.

2.2. What is the rate limiting process for bioavailability?

The general understanding behind this concept is that differences in bioavailability (rate and extent) may only be observed between two essentially similar (generic) products if both dosage forms exhibit a different dissolution behaviour in vivo. However, this statement is only valid as long as the release from the dosage form represents the rate controlling process for drug absorption. On the other hand, if the permeation through the intestinal membrane is rate limiting, dissolution properties may be of negligible importance.

This interrelation is elucidated by the following examples (Figs. 2 and 3).

For glibenclamide generics from the German market, significant differences in dissolution were determined by use of an appropriately discriminating in vitro method (Fig. 2). This observation correlates with the in vivo findings. Products with a faster release of the active drug ingredient were also absorbed more rapidly in vivo. Thus,

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Fig. 1. Classification of drug substances according to the BCS.

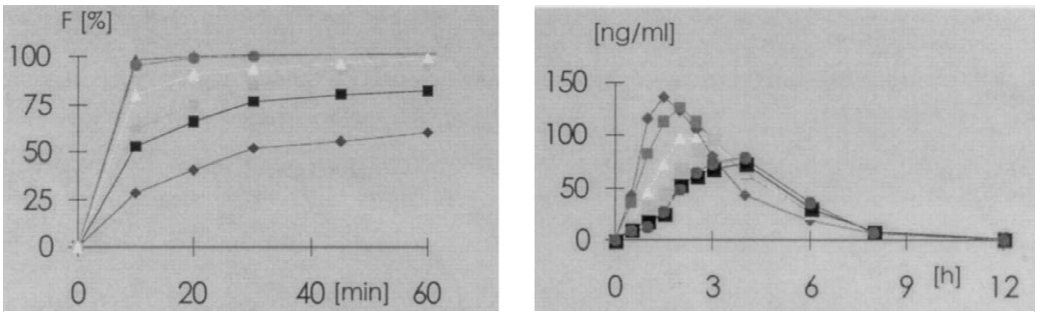

Fig. 2. In vitro dissolution (left graph, mean curves, $n=6$) and mean plasma profiles (right graph, $n=7$) of six glibenclamide generic products of the German market (Blume et al., 1984; Blume et al., 1985).

in this case, bioavailability is ''controlled'' by the release of the compound from the dosage form.

Significant deviations in rate and extent of dissolution were also detected by use of the USP method for two controlled/modified release (C/MR) indometacine products from the German market. However, such differences were not observed between these dosage forms when investigated in vivo. Bioavailability of both products was similar and thus, bioequivalence could be assessed. In this particular case, bioavailability was not greatly affected by the release of the active drug ingredient from the dosage form and consequently, rate and extent of absorption was dependent primarily on the permeation properties of the drug substance through the gut wall membrane.

2.3. BA/BE waiver for class I drugs?

Principally, both guidelines consider a waiver of BA or BE studies for rapidly dissolving drug products containing compounds of high solubility and high permeability (Class I). The motivation for such a regulation is the assumption that such products may behave in vivo like an oral solution for which bioavailability is considered self-evident. As a consequence, since dissolution of Class I drugs is expected to be very fast, BA/BE studies seem unnecessary for such products.

This general concept sounds conclusive. If the Class I drug substance is released from the dosage form very rapidly in vivo, gastric emptying will become the rate limiting process for drug absorption. In such cases, physiology, rather than the biopharmaceutical properties of the medicinal product, will be the decisive factor for bioavailability. Thus, bioavailability is not dependent on the product performance and consequently in vivo investigations may be waived.

2.4. Bioavailability of class III drugs

Compounds classified as Class III drugs are also characterised by high solubility. For IR products manufactured with these substances, a similar assumption should be acceptable as with Class I dosage forms: If their dissolution is rapid under all physiologic pH conditions, it can be expected that they will also behave like an oral solution in vivo.

Consequently, it seems appropriate to consider a waiver of BA/BE studies also for this type of IR products. Moreover, there are additional arguments which may underscore Class III drugs as even better candidates in this respect. For these compounds, permeation through the intestinal membrane will be the rate limiting process for drug absorption. Under such circumstances, rate and extent of bioavailability is not so much dependent on the release

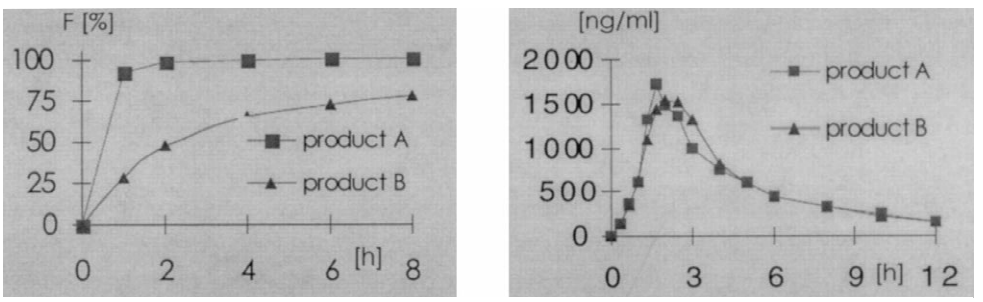

Fig. 3. In vitro dissolution (left graph, mean curves, $n=6$) and mean plasma profiles (right graph, $n=12$) of two indometacine C/MR generics of the German market (Steinigen, 1984; Blume et al., 1988).

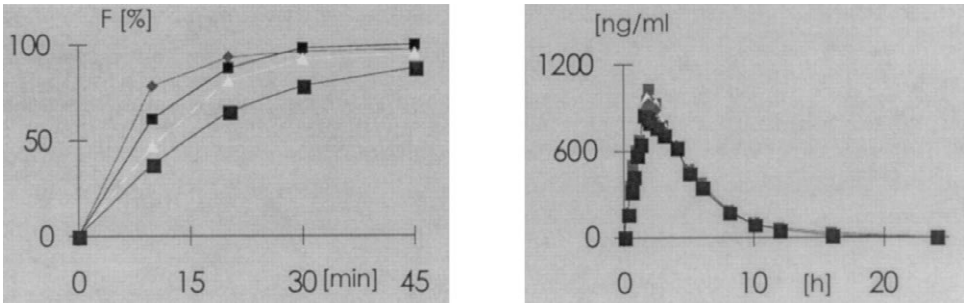

Fig. 4. In vitro dissolution (left graph, mean curves $n=6$) and mean plasma profiles (right graph, $n=14$) of four IR ranitidine dosage forms (Polli, 1997).

properties of the formulation but on the in vivo permeability pattern. This deduction is supported by the following example (Fig. 4).

For this study, several batches of an IR ranitidine product were manufactured exhibiting different biopharmaceutical properties. However, although the dosage forms showed obvious deviations in dissolution, superimposable plasma concentration vs. time profiles were observed in vivo. This behaviour may be explained by the BCS. As ranitidine is a Class III drug with high solubility and low permeability, the rate and extent of its bioavailability is ''controlled'' primarily by the permeation process and not so much by in vivo drug release.

Thus, in case of Class III compounds, bioavailability will be very much independent of the drug dissolution properties of the galenical form. Consequently, generic products of Class III drugs with differing in vitro dissolution will not necessarily exhibit also different in vivo performance. However, it has to be taken into consideration that low permeability compounds are often characterised by site dependent absorption properties. Consequently their bioavailabilities (rate and extent) will also depend on the transport velocity through the GI tract and thus, may be strongly affected by excipients which modify the GI transit time (e.g. mannitol (Adkin et al., 1995)).

3. Conclusions

BA/BE studies are requested in the regulatory process with different intentions:

- to investigate the impact of the dosage form properties on drug absorption (rate and extent) or
- to draw conclusions on clinical efficacy and safety from the measured plasma concentrations (correlation with pharmacodynamic and toxicological effects).

The BCS was primarily developed for a better understanding of the relationship of drug release (in vivo) from the product and the absorption process. In this respect, the question of the rate-limiting step is of primary relevance. According to current thinking in science and technology, bioavailability will be affected only by the in vivo performance of the dosage form if dissolution is rate-limiting for drug absorption. In contrast, as long as the permeation through the intestinal membrane is the slowest (and thus rate-limiting) process, bioavailability and consequently also bioequivalence are not so much dependent on the release properties of the dosage form.

As a consequence, solid oral medicinal products with very rapid dissolution in all physiological media (entire pH range) may be considered as minor problematic regarding bioavailability. For such preparations, it is reasonable to expect that they would behave in vivo like oral solutions and thus, that their bioavailability would be dependent more on gastric emptying than on the drug product properties. However, this general consideration does not necessarily imply that such (generic) products are per se bioequivalent to a given reference product (as this may exhibit different dissolution properties). Nevertheless, bioequivalence can be assessed in such cases by comparing in vitro dissolution profiles of test and reference under all physiological pH conditions and prove their sufficient similarity.

This concept is relevant not only for Class I drugs as mentioned by the current Guidelines, but principally also for Class III compounds. Moreover, the latter seem to be even better candidates for a waiver of BA/BE studies as their bioavailabilities are primarily dependent on permeability properties of the drug substance. As a consequence, also in cases of certain differences in dissolution between generic products of Class III compounds, their bioavailabilities should be similar due to the fact that drug absorption is not so much affected by the (in vivo) release from the dosage form but ''controlled'' by the (permeability) properties of the active drug ingredient.

On the other hand special attention should be paid to excipients which are known to modify GI transit (e.g. certain sugar alcohols) or drug absorption (e.g. enhancers). As some Class III drugs exhibit site dependent (low) permeabilities their absorption may be affected by such excipients. Consequently, for the decision process regarding bio-waivers a further specification of the BCS (as described in Fig. 1) is suggested by inclusion of dissolution properties and introduction of sub-classes for the Class

Class	Drug substance solubility	Drug substance permeability	Drug product: fast[1] dissolution/uncritical[2] excipients	Waiver of BA studies ?
I a	High	High	Yes	Yes
II	Low	High	./.	No
III a	High	Low	Yes	Yes
III b	High	Low	No	No
IV	Low	Low	./.	No

[1] ≥80 %/30 min [2] no relevant effects on GI transit, membrane permeation or gut wall metabolism

Fig. 5. Biopharmaceutical classification of drug substances and product characteristics as basis for a potential waiver of in vivo BA/BE studies.

III compounds depending on certain excipients used in their formulations (Fig. 5).

In conclusion, by extending the existing proposals mentioned in the current guidelines, a waiver of BA/BE studies should also be granted for rapidly dissolving oral IR products containing Class III drug substances with the supposition that the products do not contain excipients which may modify GI transit or the absorption process.

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