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Review

A Review On Biopharmaceutics Classification System-Based Biowaivers

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Abstract

This review discusses the Biopharmaceutics Classification System (BCS) and its role in biowaivers for generic drug development. The BCS classifies drugs into four categories based on their solubility and permeability characteristics. The BCS classification system aids in determining regulatory requirements for generic drug development and guides formulation strategies to enhance drug solubility, permeability, and oral bioavailability. It primarily applies to immediate-release, orally administered dosage forms. Excipient effects on absorption are also considered, and specific criteria must be met for a drug product to qualify for a BCS-based biowaiver.

Keywords: Biowaiver, Biopharmaceutics classification, Solubility, Permeability

INTRODUCTION

Two drug products containing the same drug substance(s) are considered bioequivalent if their bioavailabilities (rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e., similarity in terms of safety and efficacy. In in vivo bioequivalence studies, the pivotal pharmacokinetic parameters AUC (area under the concentration time curve) and Cmax (maximum concentration), are generally used to assess the rate and extent of drug absorption.[1]

BCS (Biopharmaceutics Classification System) classification is a scientific framework used in the pharmaceutical industry to categorize drugs based on their solubility and permeability characteristics. The BCS classification system helps in predicting the in vivo performance of drug substances and supports the development of generic drug products. The BCS classification system classifies drugs into four different classes:

Class I: High solubility, high permeability

Drugs in this class have both high solubility (they readily dissolve in aqueous solutions) and high permeability (they can efficiently pass through biological membranes). These drugs generally exhibit excellent oral absorption and are most likely to have predictable and consistent bioavailability.Example:Metoprolol, Atenolol.

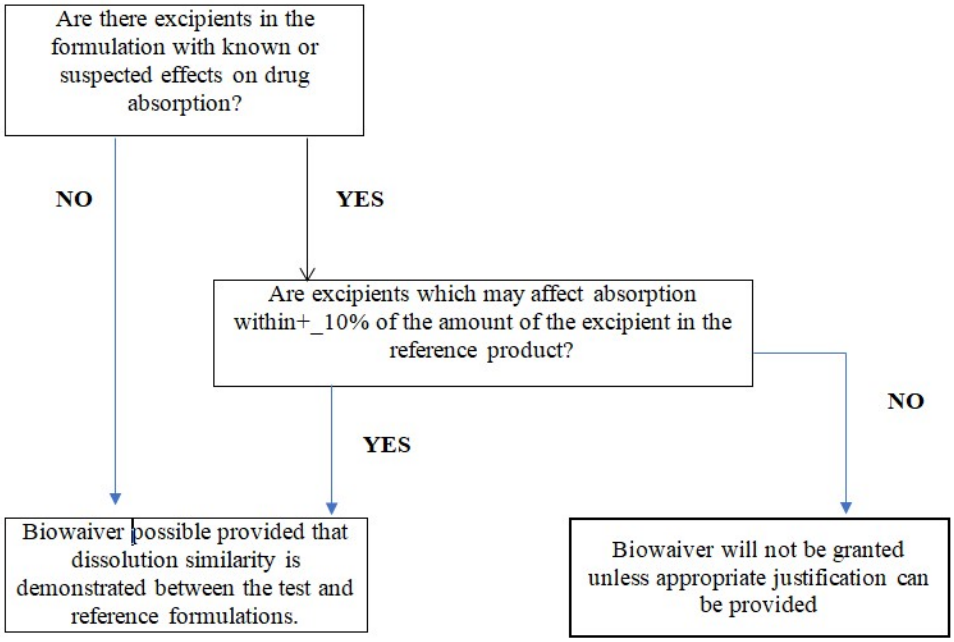

Fig 1: BCS class I drug substances

Class II: Low solubility, high permeability

Drugs in this class have low solubility (they do not readily dissolve in aqueous solutions) but high permeability (they can efficiently pass through biological membranes). The rate of dissolution may be the limiting factor for drug absorption. Formulation approaches, such as particle size reduction or amorphous solid dispersion, may be employed to improve drug solubility and bioavailability.Example: Ketoconazole, Griseofulvin.

Class III: High solubility, low permeability

Drugs in this class have high solubility (they readily dissolve in aqueous solutions) but low permeability (they have limited ability to pass through biological membranes).The rate of drug absorption is usually limited by permeability rather than solubility. Strategies like prodrug conversion or formulation modifications can be employed to enhance drug permeability. Example:Cimetidine, Ranitidine.

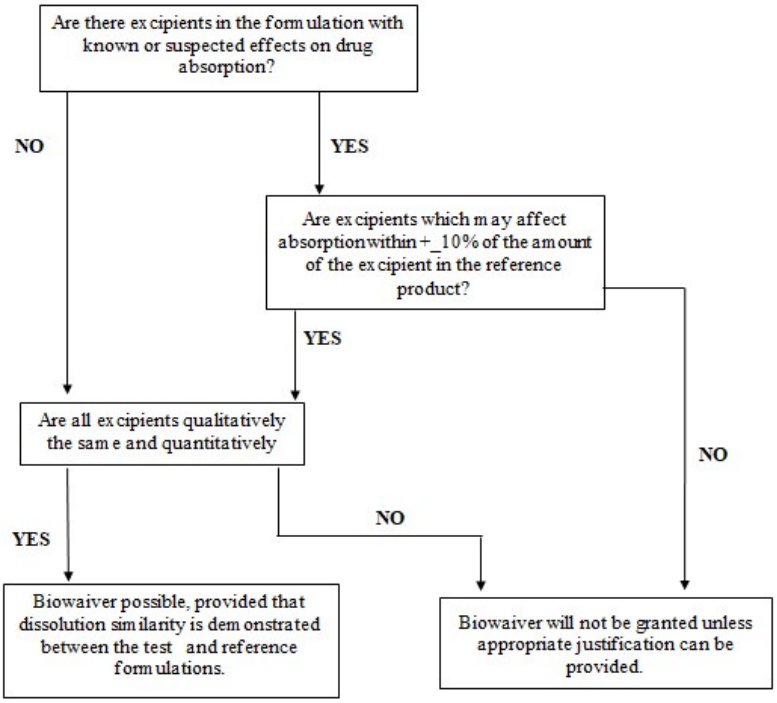

Fig 2: BCS Class III drug substances

Class IV: Low solubility, low permeability

Drugs in this class have low solubility (they do not readily dissolve in aqueous solutions) and low permeability (they have limited ability to pass through biological membranes). These drugs face challenges in both dissolution and permeability. Special formulation techniques may be required to enhance drug solubility and permeability for optimal absorption.Example: Carbamazepine, Danazol.

The BCS classification system aids in determining the regulatory requirements for generic drug development, including the need for bioequivalence studies. It helps in the design of drug formulations and supports the development of suitable strategies for improving drug solubility, permeability, and oral bioavailability.

The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation. Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination (FDC) products are eligible for a BCS-based biowaiver.

Biopharmaceutics classification of the drug substance

BCS-based biowaivers are applicable to drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III). A biowaiver is applicable when the drug substance(s) in test and reference products are identical. A biowaiver may also be applicable if test and reference products contain different salts provided that both belong to BCS Class I (high solubility and high permeability). A biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept. Prodrugs may be considered for a BCS-based biowaiver when absorbed as the pro-drug.[2]

SOLUBILITY

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37±1°C. experimentally the solubility of the drug substance over the pH range of 1.2–6.8 at 37±1ºC. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the drug substance should be evaluated if it is within the specified pH range. These experimentsshould demonstrate that solubility is maintained over relevant timeframes to accommodate the expected duration of absorption. Solubility should be evaluated by a method appropriate to the properties of the drug substance.[3]

Equilibrium solubility experiments may be performed, using a shake-flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental apparatus will permit it. The pH for each test solution should be measured after the addition of the drug substance and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The pH should be adjusted if necessary. The experiment should be conducted over a suitable timeframe to reach equilibrium. Alternatively, solubility experiments where the highest therapeutic single dose is examined in a 250 ml volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered. The lowest measured solubility over the pH range of 1.2–6.8 will be used to classify the drug substance. A minimum of three replicate determinations at each solubility condition/pH using appropriate compendial media is necessary to demonstrate solubility using a suitably validated method. In addition, adequate stability of the drug substance in the solubility media should be demonstrated. In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined and thus the drug substance cannot be classified. In addition to experimental data, literature data may be provided to substantiate and support solubility determinations, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.[4]

PERMIABILITY

- The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance.
- High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced prior to absorption, e.g., by microbial action within the gastrointestinal tract.
- Unchanged drug in feces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.
- If high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes.

Eligibility of a drug product for a BCS-based biowaiver

A drug product is eligible for a BCS-based biowaiver provided that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediaterelease oral dosage form with systemic action, and the drug product is the same dosage form and strength as the reference product. In cases where the highest single therapeutic dose does not meet the high solubility criterion but the highest strength of the reference product is soluble under the required conditions, BCS-based biowaivers can be supported based on demonstration of dose proportional pharmacokinetics (i.e., AUC and Cmax) over a dose range that includes the highest single therapeutic dose. Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. Furthermore, the BCS-based biowaiver approach is applicable only when the mode of administration includes water. If administration without water is also intended (e.g., orodispersible products), a bioequivalence study in which the product is dosed without water should be conducted. In order for a drug product to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and in vitro dissolution performance of the drug product should be satisfied.[5]

EXCIPIENTS

The possible effects of excipients on aspects of in vivo absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability including transporter mechanisms, should be considered. Excipients that may affect absorption include sugar-alcohols, e.g., mannitol, sorbitol, and surfactants, e.g., sodium lauryl sulfate. The risk that a given excipient will affect the absorption of a drug substance should be assessed mechanistically by considering:

- the amount of excipient used,
- the mechanism by which the excipient may affect absorption,
- absorption properties (rate, extent and mechanism of absorption) of the drug substance.

The amount of excipients that may affect absorption in the test and reference formulations should be addressed during product development, such that excipient changes are kept to a minimum. Small amounts included in the tablet coating, or levels below documented thresholds of effect for the specific drug substance, are of less concern.

Consideration of excipient effects for BCS Class I drug products should focus on potential changes in the rate or extent of absorption. For example, if it is known that the drug has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS Class I drugs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered. For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product. Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

For BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product, and the cumulative difference for these excipients should be within ± 10%.

BCS-based biowaivers are applicable to FDCs which are the same dosage form and strength. FDC formulations containing only BCS Class I drugs should meet criteria regarding excipients for a BCS Class I drug. FDC formulations containing only BCS Class III drugs, or BCS Class I and BCS Class III drugs, should meet criteria regarding excipients for a BCS Class III drug.

ADDITIONAL CONSIDERATIONS FOR REQUESTING BIOWAIVER

- Excipients used in the dosage form must have been used in a previously approved immediate release solid oral dosage form by the FDA.
- The quantity of excipients in the IR product should be consistent with their intended function.
- Large quantities of certain excipients such as surfactants (eg: sodium lauryl sulfate) or osmatic ingredients (eg: sorbital) may be problematic.
- Conversion site of prodrug to drug must be considered, if it occurs before intestinal absorptionthere permeability study of drug must be done otherwise permeability study of prodrug must be done.

EXCIPIENTS FOR BIOWAIVER APPLICATION

- Certain products are not applicable for application for waiver of bioavailability & bioequivalence study.
- Narrow therapeutic range drugs such as digoxin, phenytoin are notconsidered for biowaiver application due to safety point of view.
- Products designed to be absorbed in the oral cavity like buccal tablets and lozenges are also not applicable for biowaiver application.

CONCLUSION

The BCS-based biowaiver concept applies to immediate-release, solid orally administered dosage forms or suspensions designed to deliver drugs systemically. It can be used for generic drug products that meet specific criteria related to solubility, permeability, dosage form, and strength. Excipients used in formulations are also considered, especially those that may affect drug absorption.

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