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Emerging Role Of Biopharmaceutical Classification And Biopharmaceutical Drug Disposition System In Dosage Form Development: A Systematic Review

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ABSTRACT
The biopharmaceutical classification system (BCS) is an advanced tool used for classifying medicines based on dissolution, water solubility, and intestinal permeability, which affect the absorption of active pharmaceutical ingredients (API) from immediate-release solid oral dosage forms. It is useful to formulation researchers to develop novel dosage forms based on modernistic rather than experimental approaches. The current review focuses on the fundamentals, objectives of BCS, their importance, and applications of BCS. Biowaiver extensions for drug or active pharmaceutical ingredient from different BCS classes with scientific basis are discussed as the current BCS guidelines by World Health Organization, Unites State Food and Drug Administration and European Medicines Agency allows for biowaivers based on conservative criteria. The potential applications of BCS in drug discovery, drug delivery, and drug research, as well as extensions for BCS, are discussed.

Keywords: *Bioavailability, biopharmaceutical classification system, drug solubility, dissolution, drug disposition.*

INTRODUCTION

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. This classification system was devised by Amidon et al. [1]. BCS has been endorsed by regulatory organizations and agencies and is incorporated in guidelines for biowaiver granting (European Medicines Agency, 2010, ICH M9 on, 2018, WHO biowaiver list, 2018; U.S. FDA, 2017; WHO, 2006). Based on aqueous solubility and intestinal permeability (Fig. 1), the four classes of the BCS represent four distinct expectations of *in vitro-in vivo* correlations (IVIVC). These expectations underscore the importance of drug dissolution for the biopharmaceutical classification of drugs. In fact, specific dissolution criteria have been incorporated in all regulatory biopharmaceutical guidelines [2].

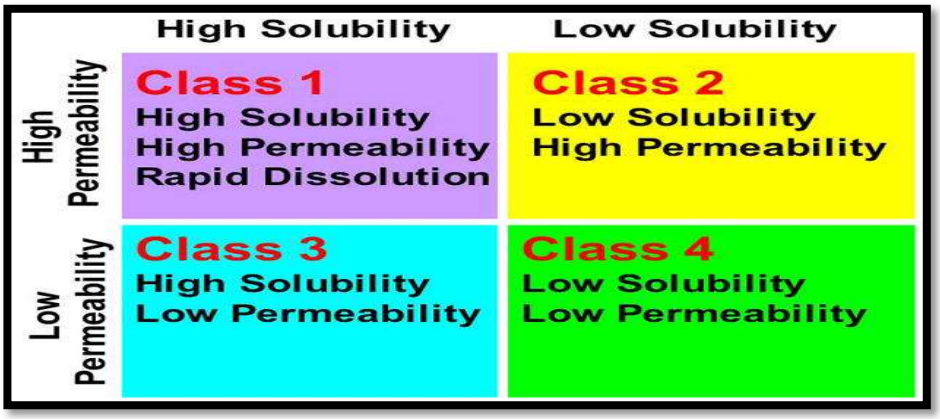

Figure 1: Biopharmaceutics Classification System

According to the guidelines of the FDA (U.S. FDA, 2017), a drug substance is considered to be "highly soluble" if the highest dose strength of the drug can be dissolved in ≤ 250 mL of aqueous media at a pH from 1 to 6.8 (including pH = pKa, pH = pKa + 1 and pH = pKa-1) and a temperature of 37 °C ± 1 °C. For a drug dose larger than the highest drug strength, additional data are required [3]. The chemical stability of the substance must be guaranteed for a period that includes the last dissolution time point plus the time required for the slowest analysis method.

"High permeability" is granted if the fraction absorbed reaches 85% or more of the dose administered, based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or compared to a reference I.V. dose [4]. When it comes to prodrugs, permeability is influenced by the anatomical site and the mechanism of the prodrug-to-drug reaction. If the reaction happens after intestinal permeation, then permeability must be measured for the prodrug. For a reaction prior to intestinal permeation, permeability must be determined for the drug itself.

Dissolution rate is the process by which a solute dissolves into a solvent and produces a solution,known as dissolution. When 85% of the labeled quantity of drug substance dissolves in 30 minutes using USP equipment 1 at 100 rpm or apparatus 2 at 50 rpm in a volume of 900 mL buffer solutions (0.1 N HCl/pH 4.5 buffer/pH 6.8 buffer without enzymes), the drug product is considered to have fast dissolution [5].

The main purposes of the BCS classification are to improve the efficiency of drug development and meet the challenges of formulation design, allow prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability (determined as the extent of oral absorption) and solubility, and for biowaiver status granting of *in vivo* bioequivalence studies [6].

This concept underlying the BCS published finally led to introducing the possibility of waiving in vivo bioequivalence (BE) studies in favor of specific comparative in vitro testing to conclude BE of oral immediate release (IR) products with systemic actions [7]. The BCS has found international recognition in industry, academic institutions, and public authorities [8]. The principle of the BCS is that if two drug products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same plasma profile after oral administration.

This concept can be summarized by the following equation:[3]

$$J = P_w C_w$$

where,

J is the flux across the gut wall,

P_w is the permeability of the gut wall to the drug, and

C_w is the concentration profile at the gut wall.

In terms of BE, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate BE of two drug products [9]. The BCS thus enables manufacturers to reduce the cost of approving scale-up and post-approval changes to certain oral drug

products without compromising public safety interests.

Objectives

- To evaluate the in vivo performance of a medicinal products based on its in vitro solubility and permeability data. The class of a medicinal products based on its aqueous solubility, intestinal permeability, and dissolution properties. The biopharmaceutics classification system (BCS) acts as a regulatory tool for replacing certain bioequivalence studies with accurate in vitro dissolution tests [10].
- The BCS will reduce the cost of the drug development process and unnecessary drug exposure in healthy subjects, and it will also increase the efficiency of medication drug development and evaluation [11].
- The biopharmaceutics classification system is an important tool for generic drug development because it provides a comparison between the test product and the reference product. It is used to recommend a class for immediate-release solid oral dosage forms [12].
- The biopharmaceutics classification system (BCS) based biowaiver approach reduces the necessity of in vivo bioequivalence studies, i.e., it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be eliminated if satisfactory in vitro data is obtained. The BCS is used to improve the efficiency of the drug development and review process.

Purpose

The BCS is applicable for both clinical and preclinical studies. The BCS acts as a guiding tool for the formulation and development of various new dosage forms. The biopharmaceutics classification system (BCS) distinguishes the medicinal drug products that are eligible for a biowaiver from those that require in vivo bioequivalence studies. The biopharmaceutics classification system (BCS) guidance expands the regulatory application of the BCS and the methods for the classification of drug categories [13]. Biowaiver bioequivalence studies are performed if the drug substance or active pharmaceutical ingredient (API) in the test and reference products is identical.

Scope

The biopharmaceutics (BCS) based biowaiver system is used to substitute in vivo bioequivalence studies [14]. The Biopharmaceutics Classification System (BCS) based biowaiver is only applicable for immediate-release drug products, solid orally administered dosage forms, or suspensions designed to deliver the drug to the systemic circulation. Narrow therapeutic index drug products are excluded from BCS-based biowaiver consideration.

Applications

- **Drug delivery technologies**

Class I systems: The Class I drugs are not those in which either solubility or permeability is limiting within the target regions of the GI tract. The drug release in such cases can be modulated using controlled release technology [15,16]. Controlled release technologies for Class I drugs include a number of products such as Macrocap, Micropump, MODAS (Multiporous oral drug absorption system), SCOT (Single composition osmotic tablet system), Microsphere, CONSURF (constant surface area drug delivery shuttle), Diamatrix (Diffusion controlled matrix system), DPHS (Delayed pulsatile hydrogel system), DUREDAS (Dual release drug absorption system), GMHS (Granulated modulating hydrogel system), IPDAS (Intestinal protective drug absorption system), Multipor, Pharmazone (Microparticle Drug Delivery Technology), PPDS (Pelletized pulsatile delivery system), BEODAS (Bioerodible enhanced oral drug absorption system), PRODAS (Programmable oral drug absorption system), SODAS (Spheroidal oral drug absorption system), SMHS (Solubility modulating hydrogel system) and SPDS (Stabilized pellet delivery system).

Class II systems: This class relates to the cases in which solubility or dissolution rate is limiting, and thus significantly affects absorption and bioavailability [17]. The technologies under this class include approaches such as classical micronization, stabilization of high-energy states (including lyophilized fast-melt systems), use of surfactants, emulsion or microemulsion systems, solid dispersion, and use of complexing agents such as cyclodextrins. The technologies under this class include: SoftGel (soft gelatin capsule formulation), Zer-Os

tablet technology (osmotic system), Triglas and nanosized carriers such as nanoemulsion, nanosuspension and nanocrystals, are treated as promising means of increasing solubility and BA of poorly water-soluble active ingredients.

Class III systems include manipulating the site or rate of exposure or incorporating functional agents into the dosage form to modify the metabolic activity of the enzyme systems, as described in Class III technologies [18]. The technologies under this class include the oral vaccine system, gastric retention system, high-frequency capsule, and telemetric capsule.

Extreme examples of Class IV compounds are exceptions rather than the rule and are rarely developed to reach the market. However, a number of examples of Class IV drugs do exist, such as Cyclosporin A, Furosemide, Ritonavir, Saquinavir, and Taxol [19].

- **Drug discovery and early development.**

BA and BE play a central role in pharmaceutical product development, and BE studies are presently being conducted for New Drug Applications (NDAs) of new compounds, in supplementary NDAs for new medical indications and product line extensions, in Abbreviated New Drug Applications of generic products, and in applications for scale-up and post-approval changes [20].

One of the starting problems with applying the BCS criteria to new drug substances is that, early in preformulation/formulation, the dose is not yet accurately known. Therefore, at this point, the Dose to Solubility ratio (D:S) can only be expressed as a likely range. Compounds with more than 100 mg/mL aqueous solubility seldom exhibit dissolution rate-limited absorption. Alternatively, one can estimate the maximum absorbable dose on the basis of the usual GI fluid volumes available under the anticipated dosing conditions and the drug solubility [21]. Regarding the solubility of the drug, it may be useful to consider the physicochemical properties of the drug when deciding which media to use for the solubility determinations. For example, measuring solubility at all pH values recommended by the BCS is unnecessary for neutral compounds in early development. Later, when formulations are compared, dissolution data for the drug product over the entire GI pH range will be useful in establishing the robustness of release from the formulation under GI conditions [22]. Lipophilic drugs may be very poorly soluble in water and in simple buffers, but in the GI fluids, the bile can often solubilize them to a significant extent. Increases in solubility of one to two orders of magnitude are possible for compounds with log P values of >4. For promising compounds that are both ionizable and lipophilic, extensive solubility experiments in biorelevant media will help to characterize the likely solubility behavior in vivo [23].

Another approach is to use aspirates from human volunteers, although the volumes aspirated are typically small and the choice of experiments and apparatus is therefore also limited. The next issue is the use of 250 mL as the volume in which a dose must be dissolved. This amount is a conservative estimate of the volume of fluid available in the gut under fasting-state conditions and is based on the volume usually ingested along with the dosage form in a pharmacokinetic study. Depending on whether drug administration is to be on an empty stomach or with meals, it is important and reasonable to adjust the volume used to assess the capacity of the gastrointestinal fluids to dissolve the dose. A suggested starting point would be to use a volume of about 300 mL for the fasted stomach, about 500 mL for the fasting small intestine, and up to 1 L for the postprandial stomach and small intestine. The choice of model for assessing the permeability is also a consideration [24]. The Caco-2 cells can be used to assess transcellular diffusion and can be standardized to ensure reproducible results, but they tend to underestimate paracellular and active mechanisms, cannot be employed to determine regional permeability within the gut, and tend to overestimate efflux via the P-glycoproteins. In situ perfusions in rats, although they are much better in terms of forecasting active transport and can be used to determine regional permeability, take more time and effort to produce a reliable permeability estimate,. Therefore, it is a good idea to have more than one permeability screen at the disposal of the laboratory in order to build confidence and robustness into the screening system. If solubility of the drug is the problem rather than its permeability, formulation efforts should target improving the dissolution profile. For example, the combined effects of formulating the drug as an amorphous solid dispersion and administering it in the fed state tend to shift the solubility-dissolution characteristics from those of a very poorly soluble drug (D:S .10,000 ml) to those of a

drug product with a D:S within the range of values encountered in the gut after meals. If permeability of the drug rather than solubility is the main problem, formulation approaches are less numerous and less reliable [25]. Even when allowance is made for the differences in solubility and permeability requirements for oral drug product development vis-à-vis biowaiver criteria according to the BCS, further factors still must be considered for new drugs. These factors include the possibility of decomposition under GI conditions and the assessment of first-pass metabolism both in the gut wall and the liver.

Pharmacokinetic optimization in drug research

The two parameters of biopharmaceutics, solubility and permeability, are of pivotal importance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics on these two properties. BCS provides drug designers an opportunity to manipulate structure or physicochemical properties of lead candidates so as to achieve better deliverability. With the enormous number of molecules being synthesized using combinatorial and parallel synthesis, high-throughput methodologies for screening solubility and permeability have gained significant interest in the pharmaceutical industry [26]. The ultimate objective of the drug discovery scientist in pharmacokinetic optimization is to tailor the molecules so that they exhibit the features of BCS Class I without compromising pharmacodynamics. Considerations to optimize drug delivery and pharmacokinetics from the initial stages of drug design have propelled the need for high-throughput pharmaceutics. In silico predictions and the development of theoretical profiles for solubility and lipophilicity provide structure-based biopharmaceutical optimization, while in vitro experimental models, microtitre plate assays, and cell cultures validate the predictions. Biopharmaceutical characterization during drug design and early development helps in the early withdrawal of new chemical entities with insurmountable developmental problems associated with pharmacokinetic optimization. Thus, BCS is helpful in optimizing the new chemical entity characteristics and minimize its chances of rejection.

Biowaivers based on the BCS

A biowaiver is a regulatory mechanism that in vivo bioequivalence studies for certain pharmaceutical products. A biowaiver is a regulatory mechanism that allows for the waiver of in vivo bioequivalence studies for certain pharmaceutical products. Bioequivalence studies are usually conducted to demonstrate that a generic drug performs in the same manner as the original branded drug in terms of pharmacokinetic and pharmacodynamic The Biopharmaceutics Classification System (BCS) is a scientific framework used to categorize drugs based on their solubility and intestinal permeability characteristics into four classes (Class 1 to Class 4) [27].

- Class 1 drugs are high solubility and high permeability. In this class, drugs have high bioavailability. Metformin and aspirin are examples of Class 1 drugs.
- Class 2 drugs are low solubility and high permeability. In this class, drugs have good permeability but limited solubility. Ketoconazole and griseofulvin are examples of Class 2 drugs.
- Class 3 drugs are high solubility and low permeability. In this class, drugs have good solubility but limited permeability, which can affect their absorption. Examples include drugs like cimetidine and atenolol.
- Class 4 drugs are low solubility and low permeability, which can result in low bioavailability. Examples include drugs like itraconazole and cyclosporine.

Types of Biowaiver

Biowaivers can be categorized into two major types.

1. The biopharmaceutics classification system (BCS) based biowaivers are granted primarily based on the classification of the drug according to its solubility and intestinal permeability characteristics [28]. Drugs that are highly soluble and highly permeable may be applicable for a BCS-based biowaiver if specific dissolution criteria are met.
2. Therapeutic equivalence-based biowaivers are granted primarily based on proof from comparative dissolution studies, pharmacokinetic modeling and simulation, or other scientific justifications that reveal therapeutic equivalence between the reference and generic drugs.

Biopharmaceutical Drug Disposition System

The significant route of elimination of drugs showing high intestinal permeability in humans is mainly by metabolism, and the drugs having weak intestinal permeability rates are mainly excreted as unchanged drugs in the urine and bile in humans [29].

In 2005 drug disposition was first observed by Wu and Benet, who proposed a system called Biopharmaceutics Drug Disposition Classification System (BDDCS): in case of class 1 and 2 drugs showing extensive metabolism, class 3 and 4 drugs showing a poor metabolism rate. The The BDDCS system estimates the effect of food, absorption, as well as efflux transporters, and the route of excretion on overall drug absorption. The permeability of immediate-release oral dose forms is less than bioavailability. The BDDCS system is an extension of the BCS [30]. Because BDDCS is a replacement for permeability, the researchers proposed that medications demonstrating metabolism as the main route of elimination be deemed highly permeable. Low permeable drugs are those whose primary route of excretion is renal and biliary excretion of unmodified medicine.

Conclusion

The BCS acts as a guiding tool for the development of various oral drug delivery technologies. The BCS provides drug designers an opportunity to manipulate the structure or physicochemical properties of the lead candidates. It is a controlling device for anticipating the in vivo performance of the medicinal substance and the improvement of the drug delivery system. The data generated from solubility and permeability in pipeline drug discovery or development can be used for early pipeline compound categorization. The BCS's advantageous circumstances include reduced medication exposure to a large panel of human participants and in some cases shorter drug product development time, in addition to significant cost savings. Substantial differences in biowaiver dossiers and respective assessments contribute to the impression that a common understanding is lacking on a successful use of the BCS concept to support.

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