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A Review on Biopharmaceutical Classification of Drug from Orally Administered Drug Product

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Abstract: ***Through the biopharmaceutics classification system (BCS), a mechanistic framework for understanding the concept of drug absorption in terms of permeability and solubility has been made available. This article reviews the BCS categorisation standards and challenges. The current BCS guidelines from the world health organisation state that biowaiver extensions for medications or active pharmaceutical components from different BCS classes that have scientific support are taken into consideration. The US food and drug administration and the european medicines agency both allow biowaivers under very specific conditions. The study explains possible new criteria and class boundaries proposed for additional biowaivers based on the underlying physiology of the gastrointestinal system under required conditions. The potential applications of BCS in drug delivery, drug discovery, and drug research are discussed, along with BCS extension. The biopharmaceutical classification system (BCS) is an advanced technique for classifying drugs based on intestinal permeability, water solubility, and dissolution all of which affect the absorption of active pharmaceutical ingredients (API) from immediate - release solid oral forms. It is more advantageous for formulation researchers to use modernistic techniques rather than experimental ones when developing new dosage forms.***

Keywords: drug absorption, biopharmaceutics classification system, permeability and solubility, biowaiver guidelines, drug formulation

1. Introduction

A sensible method for classifying pharmacological substances according to their intestinal penetrability and aqueous solvency is the biopharmaceutics classification system (BCS). The authors of this classification system are *amidon et al*. Presenting the probability sparing in - vivo bioequivalence examination for explicit near in - vitro testing to close bioequivalence of oral fast discharge item with essential activity was the final push for this concept behind the BCS. The BCS has gained international recognition as an open expert and academic foundation. According to BCS, if two medicine items have a comparable focus profile and gastrointestinal tract profile, they will also produce a similar plasma profile following oral administration. Pharmacological substances are categorised using a scientific framework called the BCS based on their water solubility and intestinal permeability. In addition to the medicinal product's dissolution, the BCS takes into account three important factors that affect the rate and extent of drug absorption from ir solid oral dosage forms. The main objectives of the BCS classification are to improve the efficiency of drug development, solve formulation design issues, and make it possible to predict the in vivo pharmacokinetic performance of drug products using measurements of permeability and solubility, which are markers of the extent of oral absorption.

BCS classification types

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability
- Class 4: Low Solubility – Low Permeability

Table 1: Examples of some drugs as per biopharmaceutical classification system

Class I	Class II	Class III	Class IV
Chloroquine	Carbamazepine	Acyclovir	Coenzyme Q10
Diltiazem	Danazol	Atenolol	Cyclosporin A
Metoprolol	Glibenclamide	Captopril	Ellagic Acid
Paracetamol	Ketoconazole	Cimetidine	Furosemide
Propranolol	Nifedipine	Metformin	Ritonavir
Theophylline	Phenytoin	Neomycin B	Saquinavir
Verapamil	Troglitazone	Ranitidine	Taxol

It is a scientific framework for grouping pharmacological compounds according to intestinal permeability and water solubility. The three main parameters that affect oral drug absorption from ir solid oral dosage forms—dissolution, solubility, and intestinal permeability—can be estimated using this drug - development method. It was initially incorporated into the process of regulatory decision - making.

Class boundries

Solubility: the maximum dose strength of a medication under biowaiver (approval of a medication without a pharmacokinetic be research) is the basis for the solubility class border. A drug substance is deemed very soluble, according usfda BCS guidelines, if its maximum dose strength dissolves in 250 millilitres or less of aqueous media with a ph range of 1 to 7.5.

In accordance with who guidelines, an api is deemed highly soluble if it dissolves in 250 millilitres or less of aqueous media with a ph range of 1.2 to 6.8 at the highest dose (if the api is listed on the who model list of essential medicines) or the highest dose strength that is commercially available as an oral solid dosage form. In aqueous conditions, the api's ph - solubility profile should be assessed at 37 6 1 8c.

It is advised to do at least three replicate solubility tests at every pH level. The BCS guidance's original recommendations recommended measuring solubility across a ph range of 1.2 - 7.5. However, subsequent research and

publications indicate that a pH range of 1.2–6.8 is better suitable. A drug ingredient is deemed very soluble, according emea BCS guidelines, if the maximum single dose given as an ir formulation or formulations is fully dissolved in 250 millilitres of buffers with a pH range of 1 - 6.8 at 37 6 1 8c.

For this demonstration, the study must be conducted in a minimum of three buffers within this range (ideally at pH 1.2, 4.5, and 6.8) and, if the pH range is within it, at the pka as well. It is advised to perform at least three replicate measurements for every pH condition (e. G., shake - flask method or other justifiable approach). Prior to and following the addition of the medicinal material to a buffer, the pH of the solution should be checked.

Permeability

Measurements of the rate of mass transfer across the human intestinal membrane and the degree of pharmacological substance absorption in humans serve as the direct and indirect bases for the permeability class border. As an alternative, nonhuman systems (such as in vitro epithelial cell culture procedures) that can forecast the degree of drug absorption in humans can be employed. According to usfda BCS guidelines, a drug substance is deemed highly permeable when the extent of absorption in humans is 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose, provided that there is no evidence of gi tract instability.

When an api's extent of absorption in humans is 85% or above, as determined by a mass balance analysis or when compared to an intravenous comparator dose, it is deemed extremely permeable, per who guidelines. The BCS guidance's original recommendation required an absorption rating of 90% in order to be classified as extremely permeable. However, a number of scholarly articles and conversations have proposed lowering the criteria for identifying an api as highly permeable to 85% absorption. In vivo intestinal perfusion in humans may be a suitable substitute test method for determining the permeability of the api. When applying this strategy to permeation research, the methodology's applicability should be demonstrated. This entails utilising a negative control and assessing the permeability in comparison to a reference material whose dose absorption percentage has been demonstrated to be at least 85%. According to emea BCS criteria, a pharmaceutical substance is considered highly permeable if its absorption is full and linear.

Dissolution

According to usfda BCS guidelines, an ir drug product is considered swiftly dissolving if at least 85% of the indicated amount of the drug component dissolves in 30 minutes while using usp apparatus i at 100 rpm (or apparatus ii at 50 rpm) in a volume of 900 ml or less in each medium [5]: pH 4.5 buffer, pH 6.8 buffer, or enzyme - free simulated gastric juice usp, 0.1 n hcl, and free intestine fluid simulation usp according to who BCS guidelines, a multisource product (pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent) is considered to be very rapidly dissolving if at least 85% of the labelled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each medium: phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and hcl solution (pH 1.2).

When at least 85% of the prescribed dosage of a multisource product dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket device at 100 rpm in a volume of 900 ml or less in each of the media, the product is said to be fast dissolving: phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and hcl solution (pH 1.2).

When more than 85% of the labelled amount dissolves in 15 minutes using usp apparatus i at 100 rpm (or apparatus ii at 50 rpm) in a volume of 500 ml in each of the media, drug items are deemed to be very fast dissolving, under emea BCS guidance: it should be shown that the dissolving profiles of 0.1 n hcl or simulated gastric fluid without enzymes, buffer (pH 4.5), and buffer (pH 6.8) or simulated intestinal fluid without enzymes are similar.

Biowaivers

A regulatory drug approval process is referred to as a "biowaiver" when the dossier (application) is accepted on the basis of equivalency evidence other than in vivo equivalency testing. Biowaiver refers to obtaining a waiver for conducting time - consuming and costly ba and be studies. For class i, ii, and iii drugs, BCS offers biowaivers with certain requirements.

Both the preapproval and postapproval stages are covered by this waiver. If the necessary information guarantees that the submitted pharmaceutical product is similar to the relevant comparator product, then BCS - based biowaivers are applicable for immediate - release solid oral dosage formulations that contain one or more of the api (s) that the who prequalification of medicines program (pqp) has determined to be eligible. He who pqp's current list of recommended comparator products, which includes the suitable fixed - dose combination product, should be utilised to choose comparator goods for BCS - biowaiver applications.

The following standards are suggested for biowaiver by who BCS guidance:

1) Based on the given BCS, dosage forms of apis that are highly soluble, highly permeable (BCS class i), and rapidly dissolving are eligible for a biowaiver:
   a) Using the paddle method at 75 rpm or the basket method at 100 rpm, the dosage form dissolves quickly, and the multisource product's dissolution profile satisfies the dissolution profile similarity criterion of f2 $50 (or an equivalent statistical criterion) at pH 1.2, 4.5, and 6.8 buffer.
   b) The two items are considered equivalent and no profile comparison is required if the comparator and the multisource dosage forms dissolve extremely quickly.

2) According to who BCS guidelines, dosage forms of apis with low permeability and high solubility (BCS class iii) are eligible for biowaivers as long as all the following requirements are satisfied and the risk - benefit analysis

is further examined in terms of the extent, site, and mechanism of absorption.

a) The solubility and permeability of the api
b) How well the multisource and comparator products dissolved in media with pH values of 1.2, 4.5, and 6.8.
c) The formulation's excipients; and d) the dangers of making a poor biowaiver choice concerning the api's therapeutic index and clinical indications.

3) API dosage forms with high permeability and high solubility at pH 6.8 but not at pH 1.2 or 4.5 (by definition, some but not all BCS class ii substances with weak acidic characteristics) are eligible for a BCS - based biowaiver as long as the requirements are met.

Applications of biopharmaceutics classification system

Class i medications are not those whose penetrability or dissolvability limits their ibility to reach the target areas of the git tract. In these situations, controlled discharge innovation and advancement can be used to modify the pharmaceutical discharge. Class i drugs include a variety of things, such as macro caps and lower scale sphion. Modas (multiporus oral meication ingestion framework), scot microsphere duredus, gmhs, ipds, multipore, ppds, beods, and spds.

Such as the following: multipor, pharmazone (micro particle drug delivery technology), PPDS (Pelletised 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 Hydro Gel System), SCOT (Single Composition Osmotic Tablet System), CONSURF (Constant Surface Area Drug Delivery Shuttle), DIAMATRIX (Diffusion Controlled Matrix System), DPHS (Delayed Pulsatile Hydro Gel System), DUREDAS (Dual Release Drug Absorption System), IPDAS (Intestinal Protective Drug Absorption System), PPDS (Intestinal Protective Drug Absorption System), PPDS (Intestinal Protective Drug Absorption System), PPDS (Pelletised Pulsatile Delivery System), PRODAS (Programmable Oral Drug Absorption System), SODAS (Spheroidal Oral Drug Absorption System), SMHS (Solubility Modulating Hydro Gel System), and SPDS (Stabilised Pellet Delivery System).

Class ii this class relates to situations when the rate of disintegration or solvency is limiting, which fundamentally affects ingestion and ba. The class's advancements include strong scattering, the use of complexing operators, such as cyclodextrin, the use of surfactant emulsion or miniaturised size emulsion frameworks micronization adjustment of high - vitality states, and old - style technique. Softgel (soft gelatin capsule formulation), zer - os tablet technology (osmotic system), triglas, and nanosized carriers like nano emulsion, nano suspension, and nano crystals are considered as promising ways to improve the solubility and ba of active ingredients that are not very water soluble.

Class iii progress includes this systems framework that regulates the site or rate of introduction or perhaps combines a utilitarian operator into the measurement structure to modify the metabolic movement of the catalyst framework. These advances include the telemetric case, the high - recurrence container, the gastric maintenance framework, and the oral antibody framework.

Class iv frameworks are exceptional examples of class iv mixes; they are not the norm and are occasionally developed to meet market demands. However, there are several examples of class iv drugs, such as taxol, cyclosporine a, furosemide, ritonavir, and saquinavir.

BCS on oral drug product administration

One of the most important methods for controlling medications for fundamental effects is the oral course of medication organisation. One of the main questions was discovered during another mediation. A pharmaceutical company enquires as to whether the drug can be sufficiently managed by oral therapy for its intended effects. Given the various factors governing the assimilation of the medication from the gastrointestinal tract and the focus goal, which is a movie created to improve on a target or set of designations, the development of measurement frames, especially for the prolonged discharge reason, has been a test to define researchers. This could corrupt another goal or set of targets.

For example, altering the medication's solvent to delay its release in the gastrointestinal tract may result in a reduction in the overall payload of the plan. The formulator cannot determine how close a particular definition is to the optimum arrangement using experimentation approaches for plans, and determining the appropriate trade - off does not make the fundamentals evident. Since the drug ingredients are divided into four classes based on their solvency parameter and porusness to biofilm, a quick screen is now necessary to enable them to define astutely. This order framework is known as the biopharmaceutical characterisation framework (BCS).

Amidon et al. Initially developed the BCS in 1995, and since then, it has become a standard in the guidelines for the bioequivalence of oral medicine products. The BCS serves as a guiding tool for researchers who define medications in order to prescribe a system to enhance the efficiency of drug development by properly determining the measurement and bioequivalence structures and tests to propose a class of strong dose frames with rapid discharge for which bioequivalence may be evaluated based on the invitro disintegration test and to determine the effect of the excipient on prediction penetrability.

The BCS provides a more thorough understanding of the relationship between medication discharge from the item and the retention process by directing medication ingestion from quick for discharge strong measurement. The bioavailability will be significantly impacted by the in - vivo display of the dose structure in this regard, and if disintegration medication discharge is not entirely dependent on the medication discharge conduct of the measurement structure, then the rate constricting advance is crucial.

Every BCS class has its assigned rate districted advance and possible methods for its modification, which enable the formulator to select and advance measurement structure the drug substance that belongs to a particular BCS class. The link

between drug release from the product and the absorption process is better understood thanks to the BCS concept. The rate - limiting phase is the most important step in this regard.

If drug release or dissolution is the dosage form's rate limiting factor, then the bioavailability will solely be impacted by the dosage form's in vivo performance. On the other hand, bioavailability and bioequivalence are less reliant on the dosage form's drug release behaviour as long as the process of permeation via bio - membranes is rate - limiting
The formulator can choose and optimise a dosage form for the drug ingredient that belongs to a specific class of BCS since each class has a designated ratelimiting step and potential strategies for modifying it. Additionally, the BCS has appeared in a number f regulatoryly significant advice publications.

2. Conclusion

The BCS concept will probably be used more and more in the early development of new medications, including for simple choice and introductory definition approaches. It has proven to be an incredibly useful management tool for predicting the in - vivo display of medication substance and improving new medication conveyance frameworks to suit the presentation of the medication in the body, as well as for guidelines of bioequivalence of the medication item during scale - up and post endorsement later on the BCS serves as a guiding tool for enhancing various improvements in oral medicine delivery.

Three central point disintegration, dissolvability, and intestinal porosity are taken into account by the BCS, which monitors the rate and extent of drug absorption from ir strong measurement morphologies. The structure or physicochemical characteristics of the lead candidate can be controlled by the product designer thanks to BCS. The benefits provided by the BCS include reducing the amount of medication that is introduced to massive board of human subjects and occasionally shortened the time needed to develop a medication item, which also requires a significant amount of reserve dollars. Setting solid oral pharmaceutical items makes sense because BCS focusses on ingestion, dissolvability, and penetrability. The be administrative decision - making process also benefits from biopharmaceutics, medication air order frameworks, and metabolic data reliant on human research.

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