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A Regulatory Approach on BCS class 2 Drugs and their Solubility Enhancement

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ABSTRACT:

The Biopharmaceutical Classification Framework (BCS) organizes drugs into one of four biopharmaceutical categories based on their dissolvability in water and their capacity to pass through layers. This frame work successfully predicts the step that limits the rate of intestinal assimilation after drugs are taken orally. Regulatory bodies around the world have effectivelyestablished the BCS to set up bioavailability and bioequivalence measures for endorsing class-2 drug substances.The point of this article is to supply a outline of writing concerning changes in formulation details (such as scaling up or post approval changes). A few oral products have been allowed a biowaiver by Regulatory specialists. The criteria for accepting a biowaiver depend on the in vitro examination of both the drug substance and the formulation, utilizing the BCS as a establishment. Numerous administrative records have been distributed with respect to BCS-supported biowaivers, with the current FDA regulations.This article explores the recommendations and difficulties associated with categorizing medications in accordance with the BCS standards established by the European Medicines Agency (EMA), the US Food and Drug Administration (USFDA), and the World Health Organization (WHO).

Key words: class 2 drugs, solubility, regulatory applications, BCS classification, and SEDDS.

A Brief Overview:

By focusing on permeability and solubility, the Biopharmaceutics Classification System (BCS) offers a mechanistic framework that enhances our understanding of medication absorption (Amidon et al., 2000; Löbenberg et al., 2000). The BCS was first presented in 1995 as the outcome of comprehensive mathematical analyses designed to clarify the kinetics and dynamics of pharmacological interactions in the gastrointestinal (GIT) tract (Gordon L et al., 2000; Raimar et al., 2000). The BCS has served as a regulatory mechanism from its founding, enabling Specific in vitro dissolution testing should be used in place of some bioequivalence (BE) investigations (Chavda.H et al., 2010).This approach not only directly but also indirectly speeds up the medication development process. but also reduces the needless exposure of healthy volunteers, who usually make up the participant group in BE trials (C. Patel et al., 2010); (I. Anand et al., 2010).

GOALS AND THE BCS CONCEPT:

According to A. Karunakar et al. (2011), one of the objectives of the BCS is to increase the effectiveness of the drug development and review procedures by implementing a method to find clinical bioequivalence tests that are not required. A classification of immediate-release (IR) solid oral dose forms that can be evaluated for bioequivalence through in vitro dissolution tests is also suggested. Additionally, it describes methods for classifying dosage forms based on the drug products' solubility and permeability characteristics as well as their dissolution patterns.

Based on scientific principles, the BCS is a new methodology for assessing bioequivalence.

As stated by the BCS guidelines, certain drug products may qualify for biowaivers, permitting approval of the product based on the results of in vitro dissolution rather than BE tests involving human subjects. Originally used only for scale-up and post-approval adjustments (SUPAC), the concept of biowaivers has recently been expanded to cover the approval of new generic pharmaceutical goods. (Basanta Kumar et al., 2011). Consequently, this allows for the avoidance of unnecessary human trials, significantly reducing the costs associated with developing generic medications. It also provides drug developers with the opportunity to modify the structure or physicochemical properties of lead candidates to enhance their deliverability. (Reddy, B et al.,2011).

CLASSIFICATION:

The Biopharmaceutics Classification System (BCS) divides medicinal compounds, also known as active pharmaceutical ingredients (APIs), into the following classifications according to their permeability and solubility (Bajpai et al., 2022).

Class I: Excellent Solubility and Permeability

Class II: Low Solubility, High Permeability

Class III: High Solubility and Low Permeability

Class IV: Low Solubility-Low Permeability

BCS considers not just disintegration but also permeability, solubility, and dissolution—three important variables that affect bioavailability. The BCS framework is illustrated in a diagram and conforms to WHO rules (Sandeep Singh et al., 2022).

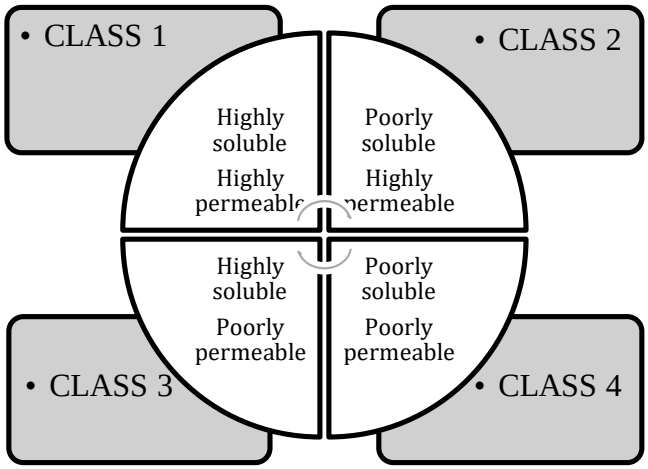

Figure: Biopharmaceutics classification system

This categorization pertains to drug absorption and dissolution models, which use a collection of dimensionless figures to identify crucial elements influencing medication absorption (VijaylaxmiBisht etal.,2022).
The absorption number (An) is equal to the mean residence time divided by the mean absorption time.
The dissolution number (Dn) is obtained by dividing the mean residency time by the mean dissolution time.
Solubility / maximal dose strength / 250 is the dose number (Do).

First-class

Both a high absorption number and a high dissolution number are typically present in this medication class. For these medications, the rate of absorption is limited by the drug's dissolution; if dissolution occurs rapidly, the gastric emptying rate becomes the primary limiting factor. The rapid rate of absorption of these drugs usually outpaces the rate of excretion. These medications' high solubility and absorption rate make them ideal for controlled release formulations. Examples include propranolol, verapamil, diltiazem, and metoprolol (Kanchan Butola et al., 2022).

Class II

Class II medications have a high absorption number but a low dissolving number. In this instance, in vivo drug dissolution is the rate-limiting factor for absorption. unless the dose number is really large. Generally speaking, Class II medications absorb more slowly and for an extended duration compared to Class I medications. In vitro–in vivo correlation, or IVIVC, is generally valid for both Class I and Class II drugs. The bioavailability of these drugs is limited by their solvation rates, suggesting a relationship between in vitro solvation and in vivo bioavailability. Some dosage adjustments are necessary for these medications, such as reducing the drug size (Micronization), using development of microemulsion methods, surfactants, etc. According to Abhishek Awasthi et al. (2022), such examples are trimipramine maleate, glibenclamide, phenytoin, mefenamic acid, nifedipine, ketoprofen, naproxen, carbamazepine, and ketoconazole.

Class III

In this class, the drug itself is quickly solvated, and the permeability of the drug is the limiting step for absorption. The rate and degree of absorption of these medications can vary significantly. This variability is typically caused by physiological changes and membrane permeability instead of the dosage form's characteristics because dissolution occurs rapidly. Class I requirements may be applicable if the formulation has no effect on permeability or the length of gastrointestinal transit. Due to their limited permeability, the dosage forms are created using high frequency capsules, gastric retention time permeability enhancers, etc.Cimetidine, ranitidine, neomycin B, acyclovir, atenolol, and captopril are a few examples (Sahil Kumar et al., 2022).

Class IV

Medications provide difficulties for efficient oral delivery. Significant variability results from their often low bioavailability and ineffective via the mucosa of the digestive tract. Because of their low permeability and poor solubility rate, these medications are altered using a variety of methods. Thankfully, extreme Class IV medication examples are rare and rarely manufactured and commercialized, but they do exist. Among these include furosemide, taxol, and hydrochlorothiazide (Yagesh Kumar et al.,2022), Reddy, B. et al. (2011), and Basanta Kumar et al. (2011).

Determination of solubility

The quantity of a material that has dissolved in a solution when equilibrium is reached is known as its solubility achieved between the dissolved particles and any remaining undissolved material at a particular pressure and temperature. If the maximal dosage of a medication or active pharmaceutical ingredient (API) dissolves in 250 milliliters or less of water, the drug is said to be very soluble. within a certain pH range (I. Anand et al., 2010). According to the standards established by the European Medicines Agency (EMEA), the World Health Organization (WHO), and the United States Food and Drug Administration (USFDA), a drug's solubility profile is assessed in an aqueous medium with a pH range of 1 to 7.5. The ionization properties of the material being studied determine how many pH levels are evaluated for solubility analysis. Pharmacopoeia-recommended standard buffer solutions are thought to be suitable for conducting solubility studies (Chavda.H et al., 2010). If the drug exhibits signs of degradation due to the buffer composition or its pH, this aspect must be taken into account. The concentration of the drug in the selected buffer solutions or pH levels should be quantified using a validated assay method capable of distinguishing the drug from the byproducts of its breakdown (C. Patel et al., 2010).

The following are some ways to calculate permeability:

Pharmacokinetic studies involving human subjects, which encompass mass balance evaluations and assessments of absolute bioavailability (BA) or techniques related to intestinal permeability.

- Intestinal perfusion in situ or in vivo utilizing appropriate animal models.
- In vitro techniques using intestinal tissues that have been removed.
- Relevant epithelial cell monolayers, like TC-7 or Caco-2 cells.

The degree of medication absorption is measured in mass balance evaluations using either radiolabeled drug molecules or stable isotopes without labels (I. Anand et al., 2010).

In absolute BA investigations, intravenous BA is used as a reference standard to evaluate oral BA. For medications that experience passive absorption, in vitro techniques and intestinal perfusion models are especially advised. Using in vitro systems made from the human adenocarcinoma cell line is a novel substitute for traditional intestinal tissue models. Caco-2 which effectively mimics small intestinal tissue (Chavda.H et al., 2010).

NOTE IN DETAIL ABOUT CLASS 2 DRUGS:

Significant differences in predicting the in vivo absorbability of drugs classified as BCS Class II is challenging due to absorption or dissolution kinetics and the absence of a suitable in vitro model for assessing dissolution behavior. AbrahamssonBertil et al. (2005).The underlying process and the precise anatomical location where the prodrug is transformed into the active drug substance will determine how permeable the prodrug will be. Once the prodrug has been transformed into the drug, often during intestinal entry, its permeability should be assessed. If medication conversion takes place prior to intestinal absorption, the permeability of the drug across intestinal tissue must be assessed. absorption.

The FDA should have either previously approved or currently approved the excipients in the dosage form. The dose form's inactive components should be proportionate. A straightforward aqueous solution can be used as the reference product , the regulatory authority may require further evidence to demonstrate that the addition of new excipients or unusually high concentrations of commonly used excipients to a solid dosage form has no effect on the drug's bioavailability in a relevant bachelor's degree research to supply information. Large quantities of some excipients, like sweeteners (like mannitol or sorbitol) and surfactants (like polysorbate 80), might cause issues. The medication must be stable in the gastrointestinal system, and the product must be designed to prevent absorption by the oral cavity (Lennernäs, Hans et al.,2005).

Applications for Regulation:

BCS-based biowaivers for INDs and NDAs apply to marketed formulations as the dosage forms exhibit quick and similar in vitro dissolution characteristics, the clinical trial formulation may involve modifications to its constituent parts, composition, or manufacturing procedures. Only when the drug substance is soluble and has a high permeability (BCS Class I) this method is acceptable if the formulations before and after the changes are deemed to be comparable to pharmaceuticals. Pharmacokinetic evaluations and food-effect bioavailability (BA) investigations should not employ these biowaivers; they are only intended for bioequivalence (BE) research.

Additionally, ANDAs may apply for biowaivers for immediate-release (IR) test products that dissolve quickly and are composed of highly soluble and permeable drug ingredients, provided that the reference listed drug (RLD) likewise dissolves quickly and that the test products show dissolution profiles similar to the RLD. When the reference and test dose forms are pharmaceutically equivalent, this approach is beneficial.

Changes Following for the Approval of Biowaivers may also be requested for major changes made after approval , as long as the post-change product keeps dissolving rapidly and the dissolution profiles of the pre- and post-change products are comparable, a dissolving, immediate-release (IR) product with a highly soluble and permeable drug material, such as Level 3 alterations in components and formulations, is acceptable. Pharmaceutical firms may lower costs associated with expanding and modifying certain oral medication products after approval. (quickly dissolving items of Class I) thanks to the BCS.

Application for Biowaivers Given the doubts around the biowaivers based on the BCS are applicable at both the pre-approval (IND/NDA and ANDA) and in vitro dissolution tests. post-approval stages. (A. Karunakar et al., 2011)

Information in Support of High Solubility

The data listed below should be included to back the high solubility of the test drug substance: (Basanta Kumar et al., 2011).

- A description of the test methods, including details on the buffer solutions and analytical methods used.
- Information on the drug substance's chemical makeup, molecular weight, dissociation constants, and whether it is basic, amphoteric, acidic, or neutral.
- Under solution pH, drug solubility (e.g., mg/ml), and the amount of media required to dissolve the maximum dose potency, a tabular summary of the test results (mean, standard deviation, and coefficient of variation) is provided.
- A picture showing the typical pH-solubility profile.

Evidence for High Permeability

To demonstrate that the test medication has a high permeability, the following details are required:

- An overview of the pharmacokinetic data collected, as well as the study design and methodology employed in human pharmacokinetic research.
- Details of the analytical technique and the method used to determine the extent of absorption or permeability; the drug concentrations in the donor fluid; the criteria for choosing human, animal, or epithelial cell lines; and information supporting the method chosen for direct permeability assessments.
- A list of model medications that include information on how well they are absorbed by people (mean, standard deviation, and coefficient of variation), which is used to validate the method, along with stability information and data that support the passive transport mechanism as needed.

Evidence for a Quick and Consistent Dissolution

To confirm the quick disintegration features of the reference and test items, the following details must to be provided:

- A succinct description of the products used in dissolution testing, including information on the weight, dimensions, strength, batch or lot number, and expiration date.
- Dissolution data was gathered from 12 different units of the test and reference items using predetermined test procedures. A graphic depicting the typical dissolution profiles of the test and reference goods in the three mediums should be included of this.
- Data demonstrating how the test and reference products' dissolving characteristics are comparable.

Due to significant heterogeneity in absorption or dissolution kinetics and the lack of an effective in vitro method, it is challenging to predict the in vivo absorption of drugs categorized as BCS Class II ,adequately assessing dissolution behavior (Reddy, B et al., 2011).

Various formulation techniques

The majority of newly identified chemical compounds have a high molecular weight and are classified as biopharmaceuticals under the Biopharmaceutical Classification System (BCS) II, which is characterized by strong membrane permeability and poor water solubility. These characteristics restrict the oral medication's bioavailability, low solubility limits absorption because it causes insufficient dissolution. In addition to lowering oral bioavailability, this also results in significant inter-individual variability and a lack of dose proportionality.

Lipid-based medication delivery systems (LBDDS)

Lipids have become more popular as delivery vehicles for medications that have recently become poorly soluble in water. The development of innovative lipid excipients has enabled the use of lipid-based formulations in medication administration that comply with safety and regulatory requirements, as well as by their capacity in order to enhance oral bioavailability.

Drug delivery systems that use nano emulsification (SMEDDS/SNEDDS).(Vinod P. Shah et al.,1995) & (John R. Crison et al.,1995) .Some of the common excepients used in the LBDDS are Triglycerides(TG) & vegetable oils ,Surfactants etc. When taken with food, lipids have a better function in increasing the bioavailability of certain medications. Nonetheless, food and many medication compounds interact (Kalepu. Sandeep et al., 2012). Food has no effect on BCS class 1 medications, but when food is consumed with class 2 medications, the absorption of the medication is changed.

(MohanvarmaManthina et al.,2012) . An aqueous When an insoluble medicine behaves like an oil, it can be made into a lipid-based formulation. or when the conventional formulation doesn't enhance the oral bioavailability (VeerabhadhraswamyPadavala et al., 2012).

Polymer nano carrier based approaches

The field of nanotechnology and the use of nanocarriers for drug delivery systems have revolutionized the biomedical landscape in recent years (Anindita et al.,2017). Numerous research organizations and industries worldwide are intensely investigating new formulations designed to effectively administer drugs (BalasubramanianSomasundaram et al.,2017) . Nanotechnology and nanocarrier-based treatments for chronic degenerative diseases allow for targeted drug delivery to specific cells using nanoparticles (Chowdhury et al.,2017). Drugs are typically encapsulated within a membrane or matrix system, where they may be adsorbed, dissolved, or dispersed. These systems also help protect drugs from first-pass metabolism and prolong their presence in the bloodstream. The small size of nanoparticles enables them to efficiently permeate tissues and potentially traverse biological barriers (SelvarajKunjiappan et al.,2017) . Nanoparticles suggest an exciting vision for enhanced personalized medicine, which aims to deliver the right drug at the correct dose and time to the right patient (ChiranjibBhattacharjee et al.,2017). The benefits of this strategy hinge on two critical factors: size and the use of biodegradable materials. This approach has led to the development of more precise, effective, safe, and rapid treatment methods (TheivendrenPanneerselvam et al,2017) .

Pharmaceutical crystal engineering

Crystal engineering methods, applicable to a variety of crystalline materials, present a viable alternative to improve the bioavailability of poorly soluble medications by increasing their solubility and rates of dissolution (Blagden et al., 2007). The ability to create materials with desired dissolving characteristics while maintaining chemical and physical stability is a strong argument for investigating both novel and well-established crystal engineering approaches in the design of drug delivery systems. (Nicholas et al.,2007). The challenge of low aqueous solubility creates an opportunity for employing crystal engineering to enhance bioavailability and establish stable, robust pharmaceutical products (Pauline T. Gavan et al.,2007).Thus, crystal engineering is seen as a valuable strategy for crafting effective dosage forms for poorly soluble drugs. It is defined as the exploitation of noncovalent interactions between molecular or ionic components for the rational design of solid-state structures that may exhibit intriguing electrical, magnetic, and optical properties (Marcel de Matas et al.,2007) ;& (Peter York et al.,2007).

Liquisolid technology

Liquisolid technology is utilized to convert water-insoluble medications into solid dosage forms that release quickly. In this method, the drug, although in a solid state, is contained within a powder substrate in a dissolved or nearly molecularly dispersed form, which enhances its dissolution characteristics. Through the Liquisolid technique, poorly soluble drugs by physically mixing non-volatile liquid vehicles, such as suspensions or solutions, with particular excipients known as the coating material and carrier, they can be converted into compressible, free-flowing powders. According to Sandeep Arora et al. (2013), this method has been successful in enhancing the release of low-dose medications that are poorly soluble.

How liquisolid compacts are formed: Through simple physical mixing with specific excipients known as the carrier and the coating material, a liquid can be transformed into a dry, readily compressible powder using Liquisolid technology (Kaur et al., 2013). The porous carrier material absorbs the liquid phase, which can include a liquid drug, a drug suspension, or a drug solution in an appropriate non-volatile liquid medium. Propylene glycol, liquid polyethylene glycols, or glycerin are examples of inert organic solvents with high boiling temperatures that are ideally water-miscible for this operation optimal as liquid vehicles (Manpreet et al.,2013). Once the carrier becomes saturated, a liquid layer forms on the surface of the particles, which is quickly adsorbed by fine coating particles. This results in a powder that appears dry, flows freely, and can be compacted easily. Generally, microcrystalline cellulose is used as the carrier material, while amorphous silicon dioxide (colloidal silica) serves as the coating agent (RajniBala et al.,2013) .

SEDDS

Self-emulsifying oil formulations (SEOF) or self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of solid or liquid surfactants, natural or synthetic oils, or a mix of one or more hydrophilic solvents and co-solvents/surfactants. These systems create fine oil-in-water (o/w) emulsions or microemulsions (SMEDDS) when they are diluted in aqueous environments, such as gastrointestinal (GI) fluids, after being gently shaken. Formulations that self-emulsify spread easily throughout the GI tract, aided by the stomach and intestinal movements that facilitate emulsification (Simon Benita et al.,2004) . SMEDDS usually generate emulsions with droplet sizes ranging from 100 to 300 nm, while SNEDDS create transparent microemulsions with droplets smaller than 50 nm. In contrast to emulsions, which can be sensitive and unstable, SEDDS are physically stable formulations that are simple to produce (Gursoy et al.,2004) . Therefore, for lipophilic drug compounds that face absorption limitations due to slow dissolution rates, these systems can enhance both the speed and magnitude of absorption, resulting in more consistent plasma concentration profiles (R. Neslihan et al., 2004) .

Regulatory status of excipients

Not every excipient is an inert substance; some may become harmful at higher concentrations. Substances deemed generally recognized as safe (GRAS) are listed by the FDA in the Code of Federal Regulations. The FDA also has an Inactive Ingredient Guide (IIG). which lists approved inactive ingredients that can be included into products that are advertised. The maximum permitted amounts for excipients based on specific administration routes are also

specified in this guidance. An inactive ingredient can be added to a medication once it has been authorized for use in a certain way. New drug formulations without requiring extensive reevaluation. Developers can reference both the GRAS list and the IIG while creating new formulations. Currently, the FDA lacks a dedicated process for assessing the safety of individual excipients. Instead, excipients are evaluated and authorized as parts of the application's total medication or biological product. Given that excipients are essential to formulation and cannot be evaluated independently of the medication, itself, this regulatory approach is scientifically valid.

CONCLUSION

A regulatory tool called the Biopharmaceutics Classification System (BCS) allows precise in vitro dissolution experiments to be used in place of certain bioequivalence studies in the creation of generic drugs. The future usage of BCS is expected to grow in importance, notably if the current framework is more widely recognized and the BCS boundaries for particular class II medications are extended. The impending modifications to BCS standards by regulatory agencies, in conjunction with professionals from academia and the industry, show promise and might result in increased applicability in the field of pharmaceutical development.

Additionally, we emphasize the BCS's usefulness as a simple method for identifying the rate-limiting variables in the oral absorption process in the initial phases of medication development. Gaining further insight into the proper biopharmaceutical characterisation of new medications could produce molecules with sufficient permeability, solubility, and dissolution rates, which will ultimately make the BCS more important as a regulatory tool.

APPLICATIONS FOR THE FUTURE

This includes Liquisolid technology, pharmaceutical crystal engineering, polymer nano carrier methods, lipid-based drug delivery systems (LBDDS), and self-emulsifying drug delivery systems (SEDDS) are some of the formulation techniques meant to improve the solubility of BCS class II medications.

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