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Review Article

Biopharmaceutics Classification System (BCS) and Biowaiver: in Drug Product Design

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ABSTRACT

The Biopharmaceutics classification system (BCS) represents a convenient way to look the solubility and intestinal permeability characteristics of a drug product. In 1995, the BCS was first developed by Amidon et al., and his colleagues. The biopharmaceutics classification system (BCS) reduce the need for in vivo bioequivalence studies by utilizing the in vitro dissolution tests. To Scale-up and Post Approval Changes (SUPAC) in drug(s) the biopharmaceutics classification system (BCS) principles can be applied to new drug application (NDA) and abbreviated new drug application (ANDA) approvals. The biopharmaceutics classification system (BCS) is a drug development tool, it estimate the three major factors: Dissolution, Solubility and Intestinal permeability. Knowledge of Biopharmaceutics Classification System (BCS) helps for the formulation scientist to develop a suitable dosage forms based on their mechanistic approaches. In 2000, the united states food and drug administration (FDA) was the first regulatory agency that publishes guidance for industry to describe how to meet criteria for waivers (i.e. Permission to skip in vivo bioequivalence studies) for highly soluble and highly permeable drugs (BCS Class I). The World health organization (WHO) and European medicines agency (EMA) published guidelines how to obtain Biophamaceutics classification system (BCS) biowaivers for BCS class 3 and class 1 drugs. Drug development is a very difficult and expensive process. Due to inadequate pharmacokinetic data of a drug candidate, there is a chance for failure during the clinical phases. In vitro in vivo correlation (IVIVC) studies have been used to select the appropriate excipients, optimize the manufacturing processes for quality control purposes and characterizing the release patterns of newly formulated modified release, extended release and immediate release products. Hence this literature review focuses on the BCS, covering the BCS based Biowaiver considerations and in vitro in vivo correlation (IVIVC) of drug product.

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INTRODUCTION:

The Biopharmaceutics classification system (BCS) is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). Amidon et al., in the year 1995 studied on the solubility and intestinal permeability characteristics of various drugs to obtain a biopharmaceutical drug classification. It is a theoretical basis for correlating *in vitro* dissolution and *in vivo* absorption [1]. The biopharmaceutics classification system is based on Fick's first law applied to a membrane:

$J_W = P_W C_W$

Where, J_W is the drug flux through the intestinal wall at any position & time (mass/area/time) , P_W is the permeability of the membrane , C_W is the drug concentration at the intestinal membrane surface [2].

Objectives of the biopharmaceutics classification system : To evaluate *in vivo* performance of medicinal product based on *in vitro* solubility and permeability data. Categorized the class of medicinal product based on aqueous solubility, intestinal permeability and dissolution properties. The biopharmaceutics classification system (BCS) act as a regulatory tool for replacing certain bioequivalence studies by accurate *in vitro* dissolution tests. It will reduce the cost of drug development process and unnecessary drug exposure in healthy objects; and also increase the efficiency of medication drug development and evaluation [3]. The biopharmaceutics classification system is an important tool for generic drug development because it gives a comparison between test product and reference product. To recommended a class for immediate release solid oral dosage forms [4,38].

The biopharmaceutics classification system (BCS) based biowaiver approach is reduced 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 we get the satisfactory *in vitro* data. To upgrade the efficiency of drug development and the review process [5,6].

Purposes of biopharmaceutics classification system : It is applicable for both clinical and preclinical studies. It acts as a guiding tool for formulation and development of various new dosage forms. Biopharmaceutics classification system (BCS) distinguishes the medicinal drug product which is eligible for a biowaiver *in vivo* bioequivalence studies or not. Biopharmaceutics classification system (BCS) guidance expands the regulatory application of BCS and methods for classification of drug categories [7,39].Biowaiver bioequivalence studies perform if the drug substance or active

pharmaceutical ingredient (API) in test and reference products is identical.

Scope of biopharmaceutics of classification system : The biopharmaceutics classification system (BCS) based biowaiver is used to substitute of *in vivo* bioequivalence studies. Biopharmaceutics cclassification system (BCS) based biowaiver is only applicable for immediate release drug product, solid orally administered dosage forms or suspensions designed product to deliver the drug to the systemic circulation. Narrow therapeutic index drug products are excluded from BCS based biowaivers consideration [8,9,40].

BCS CLASSIFICATION

In early drug development, the knowledge of the classes of a particular drug is an important factor that influences the decision to continue or stop the drug development processes. This system was developed by professor Amidon et al, that all drug molecules are classified into 4 classes based on their solubility and permeability properties in the aqueous medium [10]. A drug is called "Highly soluble" when the highest clinical dose strength is soluble in 250ml or less of aqueous media over a ph range of 1-7.5 at 37°C; if the drug not follow this condition then it is called "Low soluble". A drug is called "Highly permeable" when the extent of the absorption in humans is determined to be ≥90 % of an administered dose in comparison to an intravenous reference dose; if the drug not follow this condition then it is called "Low permeable".[42] These classes are as follows:

Class 1

Class 1 drugs belong to this class show high dissolution and high absorption rate. Drug dissolution is the rate limiting step if the dissolution rate is very high then the gastric emptying rate is rate determining step. Class I drug contain highly water soluble drugs that well absorbed through the intestinal membrane. It shows rapid therapeutic action. For the immediate release drug dosage forms the absorption rate controlled by the gastric emptying rate. If the dissolution rate is high then the bioavailability is also high , that over 85 % dissolution in 15 minutes. Bioavailability are very rapid for such products. These compounds are highly suitable for formulations and design of sustained release (SR) and controlled release (CR) drugs. *In vitro-In vivo* Correlation (IVIVC) can't be expected. Examples are:- propranolol, metoprolol, naproxen, diazepam, diphenhydramine, chlorpheniramine, carbamazepine, primaquine, levodopa, Midazolam, ketorolac, minocycline, lidocaine, chloroquine, doxepin, Paracetamol,

ketoprofen, diltiazem, verapamil, theophylline etc.

Class 2

Those drugs belong to this class show low dissolution and high absorption rate. So the rate of absorption of drug substance is primarily limited by drug dissolution in gastrointestinal tract or *in vivo* drug dissolution. So the dissolution rate is the rate limiting step. Class 2 drugs contain water-insoluble drugs that well absorbed from gastrointestinal tract when it dissolved. Bioavailability is controlled by the rate of release of drug and their dosage forms. Drugs in this class perform various absorption rates due to the numerous formulation effects and *in vivo* variables that affect the dissolution profile. Various formulation effects includes amorphous solid form, nanoparticles, surfactant addition, salt formation and complexation; that cause the insolubility of the drugs and show slow dissolution rate. These compounds are also suitable formulation and designing of controlled release (CR) and sustained release (SR) drug products. *In vitro-In vivo* Correlation (IVIVC) is usually expected for these types of drug products. Examples are: - azithromycin, phenytoin, dapsone, cyclosporine, glipizide, glibenclamide, ketoconazole, danazol, itraconazole, lansoprazole, lovastatin, troglitazone, mefenamic acid, atrovastatin, carbamazepine, nifedipine, nisoldipine, nicardipine, ritonavir, indinavir etc.

Class 3

Those drugs belongs to this class show high dissolution and low absorption rate. So the *in vivo* permeability of drug is the rate limiting step for drug absorption. Due to this drug show high variation in the rate and extent of drug absorption. Dissolution is rapid than the membrane permeability of dosage forms. Class 3 drugs contain water-soluble drugs that dissolve quickly but don't readily permeate biomembranes. These drugs shows low bioavailability rate; drug is not properly permeate through absorption window. For enhancing the drug absorption rate we added excipients in their formulations. For development of controlled released drugs this class of drug create problems. Examples are: - acyclovir, atenolol, captopril, insulin, enalaprilat, cimetidine, ranitidine, alendronate, metformin, neomycin B, cetirizine, furosemide, methotrexate, hydrochlorothiazide etc.

Class 4

Those drugs belongs to this class show low dissolution and low absorption rate. These low solubility and low permeability drugs are very difficult to formulate the orally effective drug. It shows low therapeutic action; so we need alternate route of administration. In early development to evaluate these types of drug *in vitro* models

are applied. These are not suitable for formulation of controlled release drug products. Examples are: - furosemide, cefixime trihydrate, ellagic acid, coenzyme Q_{10}, tobramycin, cefuroxime, cyclosporine A, ritonavir, saquinavir, taxol etc [11,12].

BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCES

The Biopharmaceutics classification system (BCS) based biowaivers are applicable for those drug products, where the drug substances exhibit either high solubility and high permeability (class 1) or high solubility and low permeability (class 3) [13,14]. A biowaiver is applicable if test of active pharmaceutical ingredients (API) and comparator products are identical; and also contain different salts provided that both belongs to BCS Class 1. But a biowaiver is not applicable when test product contain different ester, ether, and isomer, mixture of isomers, complex or derivative of an active pharmaceutical ingredient (API) from that comparator product. These differences leads to different bioavailabilities [15,16].

The Biopharmaceutical Classification System (BCS) as defined by the FDA after dissolution [17,18].

Solubility

If the highest single therapeutic dose of API is completely soluble in 250 ml or less aqueous media over the ph range of 1-8 at 37±1°C, then it is classified as highly soluble.

Permeability ↑ / Solubility →	
CLASS 1 High Solubility High Permeability	**CLASS 2** Low Solubility High Permeability
CLASS 3 High Solubility High Permeability	**CLASS 4** Low Solubility Low Permeability

Solubility is defined as what volume of an aqueous medium is required for the dissolve highest amount of dose strength under standard conditions of temperature, pressure and pH. For solubility determination the number of pH conditions can be based on the ionization characteristics of the test drug substance. Solubility should be evaluated by the properties of the active pharmaceutical ingredient (API). The pH for each test solution should be measured after the addition of active pharmaceutical ingredient (API) and at the end equilibrium solubility study is conducted to ensure the solubility measurement is under the specified ph. Equilibrium solubility experiments may be performed by using a traditional shake-flask technique or other alternative methods such as acid-base

titration method. The pH should be adjusted if it is necessary [19,43].

Permeability

Permeability should be based on the extent of absorption of drug substance derived from human pharmacokinetic studies. When the absolute bioavailability is ≥85 % of total therapeutic dose, then it can be concluded as High permeability. If ≥85 % of the administered dose is recovered in urine as unchanged form, then it can also be concluded as High permeability [20]. Permeability of the drug is determined which amount of drug pass through the biological membrane. If high permeability is not demonstrated, then the drug substance is considered to low permeability for BCS classification purposes. Drug should be represents a range of low (≤50 %), moderate (50 – 89 %) and high (≥85 %) absorption. Two different methods are used for the permeability classification:[21, 44]

1. Extent of absorption in humans:
a) Mass-balance pharmacokinetic studies
b) Absolute bioavailability studies.
2. Intestinal permeability methods:
a) *In vivo* intestinal perfusions studies in humans.
b) *In vivo* or *In situ* intestinal perfusion studies in animals.
c) *In vitro* permeation experiments with excised human or animal intestinal tissue
d) *In vitro* permeation experiments across epithelial cell monolayers; e.g. Caco-2 cells or TC-7 cells.

Mass balance studies

For document the extent of absorption of a drug pharmacokinetic mass balance studies using unlabeled, stable isotopes or a radio labeled can be used. To provide a reliable estimate of extent of absorption a sufficient number of subjects should be enrolled, it's depends on the variability of studies [22,23].

Absolute bioavailability studies

As a reference intravenous administered is used for Oral Bioavailability determination. A sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption, depending on the variability of the studies. Additional data for document the drug stability in the gastrointestinal fluid is not necessary, if the absolute bioavailability of a drug is shown to be 90 % or more [24,25].

Intestinal permeability methods

In vivo or *in situ* animal models and *in vitro* methods, those using cultured monolayers of animal or human epithelial cells, are considered to be appropriate for passively transported drugs. For low permeability of drug substances in human, caused by efflux of drugs via membrane transporters, such as P-glycoprotein (P-gp). If the efflux transporters are absent or their degree of

expression is low as compared to that in humans in these models, then there may be a chance of misclassification of permeability class. Functional expression of efflux systems can be demonstrated by bidirectional transport studies technique, such as a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system [26,27].

A rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs to demonstrate suitability of a permeability method intended for application of the BCS. For *in vivo* intestinal perfusion studies in humans, six model drugs are recommended; and for *in vivo* or *in situ* intestinal perfusion studies in animals and for *in vitro* cell culture methods, twenty model drugs are recommended. A sufficient number of subjects, animals, excised tissue samples or cell monolayers should be used in a study to provide a reliable estimate of drug permeability, depending on study variability. This relationship should be used to differentiation between drug substances of low and high intestinal permeability attributes [28,45].

Dissolution

It is a process in which solid substance solubilizes in given solvent i.e. Mass transfer from solid surface to liquid phase. It is a mass transfer phenomenon. Dissolution test should be carried out in USP Apparatus I (basket) at 100 rpm or Apparatus II (paddle) at 50 rpm using 900 ml of following dissolution media:

i. 0.1N hcl or Simulated Gastric Fluid (1.2) USP without enzymes.
ii. A ph 4.5 buffer and a ph 6.8 buffer.
iii. Simulated intestinal fluid without enzyme; but for capsules and tablets with gelatin coating, simulated gastric and intestinal fluids USP (with enzymes) can be used [29,46].

Dissolution testing apparatus should be based on a comparison of *in vitro* dissolution and *in vivo* pharmacokinetic data available for the drug product. To support a biowaiver minimum 12 dosage units of a drug product should be evaluated. Samples should be collected at intervals (e.g. 10, 15, 20 and 30 minutes) to characterize the dissolution profile of the drug products. Dissolution profiles should be compared using a similarity factor (f2), when comparing the test and reference products [30,47].

The similarity factor is a logarithmic reciprocal square root transformation of the sum squared error and is a measurement of

the similarity in the percentage of dissolution between the two curves [31].

$$F_2 = 50 \bullet \log \{[1 + (1/n) \Sigma=1^n (Rt - Tt)^2]^{-0.5} \bullet 100\}$$

Two dissolution profiles are considered similar when the F_2 value is >50.

The most of the oral solutions are developed by BCS Class 1 and BCS Class 3 apis, because the compounds are highly soluble in water or gastrointestinal ph media. There are a few BCS class 2 and class 4 compounds that are formulated as oral solutions or syrups. These products utilizes special techniques such as salt formation, micronization, and complexation with resins, cosolvents or surfactants for Solubilization to formulate homogeneous oral liquid dosage forms [32,47].

When ≥85 % amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of 900 ml buffer solutions is known to be rapidly dissolving.

Conditions that may affect drug dissolution and release: [33,48]

Drug substance

Particle size

Polymorph

Surface are

Chemical stability in dissolution media

Formulation of drug product

Excipients (lubricants, suspending agents etc.)

Medium

Volume

Ph

Molarity

Co-solvents, added enzymes/ surfactants

Temperature of medium

Apparatus

Hydrodynamics

Agitation rate

Shape of dissolution vessel

Placement of tablet in vessel

Sinkers (for floating products and products that stick to side of vessel)

IVIVC: - NEED FOR BCS

Correlation defines according to mathematically, "interdependence between qualitative and quantitative data, or relationship between measurable variable and rank. According to Biopharmaceutical point of view, it means relationship between observed parameters derived from *in vitro* and *in vivo* studies. In vitro in vivo correlation (IVIVC) means a mathematical model that can be describe the relationship between *in vitro* and *in vivo* properties of a drug product, so that the *in vivo* properties can be predicted from its *in vitro* behavior. It is a functional or qualitative relationship between *in vitro* dissolution and *in vivo* bioavailability parameters [34,49].

According to FDA, "in vitro in vivo correlation (IVIVC) is a predictive mathematical model describing relationship between *in vitro* properties of dosage form

and relevant *in vivo* response. Generally the *in vitro* property is rate or extent of drug dissolution or release while *in vivo* response is the plasma drug concentration or amount absorbed" [35,50].

The United States Pharmacopoeia (USP) also defines in vitro in vivo correlation (IVIVC) as "the establishment of a relationship between a biological property, and a parameter derived from a biological property produced from a dosage form and physiochemical property of the same dosage form" [36].

Food and drug administration (FDA) guidelines produce five categories of correlation; each level denotes its ability to predict *in vivo* response of dosage form from its *in vitro* properties:

1) Level A correlation
2) Level B correlation
3) Level C correlation
4) Multiple level C correlation
5) Level D correlation

The most important application for in vitro in vivo correlation (IVIVC) study is to use *in vitro* dissolution study as surrogate for human bioequivalence studies. The food and drug administration (FDA) guidance explain in vitro in vivo correlation (IVIVC) application as biowaivers for changes in manufacturing of a drug product [37].

The biopharmaceutics classification system (BCS) gives the fundamental guideline for determining the conditions under which in vitro in vivo correlation (IVIVC) are expected; also used as a tool for developing *in vitro* dissolution specification.

Table no. 1- Relationship between BCS and immediate release dosage form and its IVIVC expectation[51]

Class	Solubility	Permeability	Absorption rate control	IVIVC limitation for immediate release product	Possibility of predicting IVIVC from dissolution data
1	High	High	Gastric Emptying	IVIVC expected if dissolution rate is slower than gastric emptying rate otherwise limited or no correlation.	No
2	Low	High	Dissolution	IVIVC expected if *in vitro* dissolution rate is similar to *in vivo* rate, unless does it very high.	Yes
3	High	Low	Permeability	Absorption (permeability) is rate determining and limited or IVIVC with dissolution.	No
4	Low	Low	Case by case	Limited or no IVIVC expected	No

BIOWAIVERS BASED ON THE BCS

A biowaiver method that in vivo bioavailability or bioequivalence studies may be waived. 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 reveal that a generic drug performs inside 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) [37].

Class 1 drugs are high solubility and high permeability. In this class drugs are well and high bioavailability. Metformin and Aspirin are the 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 the examples of class 2 drugs.

Class 3 drugs are high solubility and low permeability. In this class drugs have good solubility and limited permeability, which can affect their absorption. Example include drugs like cimetidine and atenolol.

Class 4 drugs are low solubility and low permeability, which can result in low bioavailability. Example include drugs like itraconazole and cyclosporine [52].

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. Drugs which might be highly soluble and highly permeable can be applicable for a BCS based biowaiver if definite dissolution criteria are met.

2.Therapeutic equivalence based biowaivers are granted primarily based on proof from comparative dissolution studies , pharmacokinetic modeling and simulation , or different scientific justifications that reveal therapeutic equivalence between the reference and generic drugs [52].

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS) BASED BIOWAIVERS ELIGIBILITY

Class 1 drugs are generally eligible for biowaivers if the generic product meets certain dissolution criteria. If the dissolution profile of the generic drug matches that of the reference drug under specified conditions , it suggests similar *in vivo* behavior, and the need for *in vivo* bioequivalence studies may be waived.

Class 2 drugs are also eligible for biowaivers if certain dissolution criteria are

met, although the requirements may be more rigid compared to class 1 drugs.

Class 3 and class 4 drugs generally do not eligible for biowaivers due to their poor permeability and /or solubility characteristics , which can remarkably impact their absorption and bioavailability.

Prodrugs may be considered for a biopharmaceutics classification system (BCS) based biowaiver when absorbed as the prodrug.

Fixed dose combination (FDC) products

Are applicable for a biopharmaceutics classification system (BCS) based biowaiver when all drug substances contained in the combination drug product meet the criteria as of BCS Class 1 and Class 3 drugs.

The biopharmaceutics classification system (BCS) based biowaivers are not applicable for drug products have a narrow therapeutic index and drug product with buccal or sublingual absorption.

Dissolution testing

Dissolution testing is a key component of biopharmaceutics classification system (BCS) based biowaivers . It involves measuring the rate at which the drug substance dissolves from the dosage form into a surrounding medium under standardized conditions. For BCS Class 1 and Class 2 drugs , if the dissolution profiles of the generic and reference products are similar, it suggests comparable *in vivo* behavior and supports the granting of a biowaiver.

Regulatory consideration

The acceptance of biopharmaceutics classification system (BCS) based biowaivers varies between regulatory agencies, but many agencies , including the food and drug administration (FDA) and European medicines agency (EMA), provide guidelines outlining the criteria and requirements for granting such waivers . These guidelines specify dissolution testing conditions and other considerations to ensure the reliability and validity of biowaiver decisions.

Biowaiver consideration for active pharmaceutical ingredient (API)

Biowaiver consideration for active pharmaceutical ingredients (apis) involves a meticulous evaluation process aimed at expediting the approval of generic and reformulated drug products while maintaining stringent standards of safety and efficacy. At the core of biowaiver consideration lies the biopharmaceutics classification system (BCS) , which categorizes drugs based on their solubility and intestinal permeability characteristics into four classes . Active pharmaceutical ingredients (apis) that are highly soluble and highly permeable (BCS Class 1) are more likely to be eligible for biowaivers, as they exhibit predictable *in vivo* behavior

and are less likely to show differences in bioavailability between products.

In vitro dissolution testing plays a critical role in assessing the rate and extent of drug release from a dosage form . The generic product must demonstrate similar dissolution profiles to the reference product under specified test conditions , indicating comparable *in vivo* dissolution behavior.

The quality of excipients and manufacturing processes must be assured to maintain consistency and bioequivalence . Stability studies are conducted to assess the long term stability of the active pharmaceutical ingredient (API) and dosage form under various storage conditions , ensuring that the product maintains its quality and performance throughout its self life. Adherence to regulatory guidelines and requirements issued by agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) is essential. These guidelines provide detailed recommendations and criteria for biowaiver submissions , emphasizing the importance of robust scientific evidence in demonstrating equivalence and ensuring patient safety and efficacy [53].

PROTOCOL FOR BIOWAIVERS

For rapid and similar dissolution

To recognize the dissolution apparatus, such as USP Apparatus 1 (basket) or Apparatus 2 (paddle), and conditions (examples : temperature, rotation speed). Detail the selection of dissolution media based on ph and sink conditions applicable to the drug product. To provide instructions for sample collection at specific time points. Determine dissolution parameters such as dissolution efficiency, mean dissolution time and similarity factors (e.g.,f2). Outline the validation procedures, consisting of specificity, linearity, accuracy, and robustness.

For high Permeable drugs

Include details on *in vitro* permeability studies using validated methods such as parallel artificial membrane permeability assay (PAMPA) or the Caco-2 cell monolayer model. Include additional ingredients such as particle size distribution, and biopharmaceutical consideration.

For highly Soluble drugs

To provide data on the drug's solubility across a range of ph conditions, indicating high solubility. Details on chemical structure, molecular weight, dissociation constants, and nature of drug substance. Include results from solubility studies conducted in numerous dissolution media, such as simulated intestinal fluid (SIF) and simulated gastric fluid (SGF), to evaluate the impact of ph on solubility. To make sure that the highest dose strength is soluble in 250 ml or less of aqueous media

over the ph range of 1.2 to 6.8, as per regulatory guidelines [54].

Biopharmaceutics classification system (BCS) Based formulation strategy

The Biopharmaceutics classification system (BCS) based formulation strategies are designed to optimize drug delivery, bioavailability, and therapeutic efficacy. The biopharmaceutics classification system (BCS) is a regulatory structure used inside the pharmaceutical industry to categorize drugs based on their solubility and intestinal permeability characteristics into four classes.

Formulation strategies for class 1 drugs awareness on enhancing dissolution rate and improving bioavailability through techniques such as solid dispersion, nanoparticle formulations, or lipid based formulations. These strategies goal to enhance the drug's solubility and dissolution rate, thereby facilitating its absorption and improving therapeutic outcomes.

Formulation techniques for class 2 drugs to increase solubility and dissolution rate, which includes micronization, complexation, or formulation with surfactants or cosolvents. By improving drug solubility, these strategies goal to enhance drug absorption and bioavailability.

Formulation strategies for class 3 drugs purpose to enhance drug permeability across biological membranes. Techniques which includes prodrug formation, permeation enhancers, or formulation with absorption enhancers may be hired to enhance drug absorption and bioavailability by increasing permeability.

Formulation strategies for class 4 drugs regularly require a combination approaches targeting both solubility and permeability enhancement. Techniques such as solid dispersion, nanoparticle formulations, prodrug formation, or formulation with permeation enhancers to address the dual

Challenges of poor solubility and intestinal permeability [55].

CONCLUSIONS:

For identifying immediate release solid oral products for which in vivo bioequivalence tests may not always be necessary and for meaningful dissolution test specifications biopharmaceutics classification system (BCS) aids applications are used. Regulation of biopharmaceutics classification system (BCS) will be based on their intestinal permeability and solubility / dissolution characteristics. For providing novel treatment concepts as well as advanced data analysis methods in order to continue to increase our understanding of pharmaceutical drug product performance in humans and to facilitate the drug regulation process based on their Bioavailability (BA) and Bioequivalence

(BE) studies are presently being conducted for New Drug Applications (ndas) of new compounds. The biopharmaceutics classification system (BCS) is a simple tool in early drug development to determine the rate-limiting step in the oral absorption process and in the overall drug development process. It increases awareness of a proper biopharmaceutical characterization of new drugs in the future result in drug molecules with a sufficiently high permeability, solubility and dissolution rate. The biopharmaceutics classification system (BCS) principles provide a reasonable approach for testing and approving drug product quality and a method to predict drug disposition, transport, absorption and elimination. The current biopharmaceutics classification system (BCS) guidance issued by the food and drug administration (FDA) allows for biowaivers based on conservative criteria and class boundaries are proposed for additional biowaivers based on the underlying physiology of the gastrointestinal tract. It is necessary for avoiding costly and time consuming in vivo studies in order to produce safe, efficacious and quality generic product. In vitro in vivo correlation (IVIVC) gives more useful information on the relationship between in vitro release and in vivo absorption from dosage form, and evaluated for several purposes in formulation development, for example: to select the appropriate excipients and optimize the manufacturing processes, for quality control purposes and for characterizing the release patterns of newly formulated immediate release and modified release products. Biowaiver is needed to confirm the establishment of bioequivalence between generic and reference product. Biowaiver can be provided regulatory decision making and ensuring the integrity of the approval process.

DECLARATION

There is no conflict of interest in publishing this review article.

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