



A REVIEW ON: BIOPHARMACEUTICS CLASSIFICATION SYSTEM

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ABSTRACT

The Biopharmaceutical Classification System (BCS) was created to minimise the need for in vivo bioequivalence studies and to enable in vitro dissolution experiments to be used as a proxy for in vivo bioequivalence studies. The biopharmaceutical classification system classifies pharmacological compounds based on their solubility ratio, dissolution, and intestinal permeability. It enables drug products' in vivo pharmacokinetic performance to be predicted. The BCS categorization system's concepts may be used to NDA and ANDA approvals, as well as scale-up and post-approval drug manufacturing adjustments. As a result, pharmaceutical businesses may save a substantial amount of time and money on product development. The drug can be classified into four classes of the BCS namely, high solubility high permeability, low solubility high permeability, high solubility low permeability, low solubility low permeability. The formulation scientist can use BCS knowledge to produce appropriate dose forms based on mechanistic rather than empirical methodologies.

1) INTRODUCTION

The oral route of medication administration is preferred by formulators and is also preferred by patients, hence oral drug delivery systems continue to dominate. The solubility and permeability of the medication are two major obstacles to oral medication administration. The amount of medication solubility and permeability determines medication oral absorption and hence bioavailability. Since the inception of the Biopharmaceutics Classification System (BCS), its application and validity have been the topic of much research and debate. The solubility and permeability of the medication determine bioavailability and bioequivalence, and it is a helpful tool for the drug development process supplied by U. Food and Drug Administration of the United States. During the early stages of drug development, the Biopharmaceutical classification system (BCS) is a critical tool for determining bioavailability decisions. The BCS was initially developed in 1995 and has since become a standard in the regulation of oral dosage form bioequivalence. The BCS is a biopharmaceutics classification system for drugs based on two factors: water solubility and intestinal permeability. The BCS evaluates three primary aspects that determine bioavailability from Immediate Release (IR) solid oral-drug products: solubility, intestinal permeability, and dissolution rate, based on a combination of these parameters and the drug product's in vitro dissolution properties. Each class of BCS includes a specifically specified rate-limiting step with options for modification, allowing the formulator to select and optimise a specific dosage form for the drug ingredient belonging to that class.^[1]

The BCS system is based on a scientific framework that describes three rate-limiting phases in oral absorption. The following are the three processes that must be followed in order for a medicine to be absorbed:

- (1) Drugs are released from their dose forms;
- (2) Gastro-intestinal (G.I.) tract maintenance of dissolved state;
- (3) Hepatic circulation by permeation through the G.I. membrane.^[2]

2) SOME IMPORTANT DEFINITIONS:^[3, 4]

2.1. Absorption number (An): The ratio of mean absorption time to mean residence time.

2.2. Dissolution number (Dn): Mean residence time divided by mean dissolution time is the ratio.

2.3. Biowaiver: When the active pharmaceutical components fulfil specified solubility and permeability criteria in vitro and the dissolution profile of the dosage form fulfils the standards for immediate release dosage forms, the US FDA grants a biowaiver, which exempts the company from completing human bioequivalence studies.

2.4. High aqueous solubility: According to the US FDA BCS criteria, a drug substance's aqueous solubility is high if the ratio of the maximum orally given dosage (in mg) to the solubility (mg/ml) is less than 250 ml. At 37°C, this requirement is satisfied across the pH range of 1-7.5. If the dose/solubility ratio is less than 250 ml at 37°C and a pH range of 1.2-6.8, an active pharmacological component is classified as "highly soluble" by WHO.

2.5. Active Pharmaceutical Ingredient (API): Any substance or mixture of substances that, when used to make a pharmacological dosage form, becomes an active component in that dosage form. Such compounds are designed to provide pharmacological action or have another direct influence on the diagnosis, cure, mitigation, treatment, or prevention of disease, or to influence the body's structure and function.

2.6. Generic Pharmaceutical Products: Product that is either a pharmaceutical equivalent or a pharmaceutically alternative product, depending on whether or not it is therapeutically equal. Interchangeability exists between multisource pharmaceutical medicines that are therapeutically similar.

2.7. Rapidly Dissolving Product: The test or comparative product from which at least 85 percent of the declared quantity of active ingredient is released within 30 minutes or less.

2.8. High Permeability: When more than 90% of an orally delivered dosage is absorbed in the small intestine, the medication is deemed extremely permeable. According to WHO criteria, an API is termed "highly permeable" if it is absorbed to a degree of 85 percent or more. In the WHO multisource publication, the permeability criteria was lowered from 90% in the FDA advice to 85%.

2.9. Bioequivalence: When supplied at the same molar dose under identical conditions in a suitably planned research, there is no substantial difference in the pace and degree to which the active ingredient or active moiety in pharmaceutical counterparts or pharmaceutical alternatives becomes accessible at the site of therapeutic action.

2.10. Comparator product: Product that has identical levels of the same excipients as the test product, as well as the same production technique and quality. The difference between the test and comparative goods in terms of drug content or potency should be less than 5%.

2.11. Very rapidly dissolving product: The test and comparative products both release at least 85% of the labelled quantity after 15 minutes or less. There is no need to compare profiles in this scenario.

3) CONCEPT BEHIND BCS

Orally given medicines' pharmacotherapeutic response is largely determined by their solubility and tissue permeability properties. Drug compounds are divided into four types based on their solubility and permeability, according to BCS. Which are stated in the table below: ^[1]

Classes/ Parameters	Solubility	Permeability	Rate Limiting step for Bio-availability
Class-1	High	High	None
Class-2	Low	High	Solubility
Class-3	High	Low	Permeability
Class-4	Low	Low	Both

Table 1. Biopharmaceutical Classification System

The basic idea underpinning BCS is that if two medications produce the same concentration profile in the GI tract, they will also produce the same plasma profile following oral delivery. The following equation may be used to describe this notion by using Fick's first.

$$J = (P_w)(C_w)$$

Where J is the flux across the gutwall,

P_w is the permeability of the gutwall to the drug, and

C_w is the concentration profile at the gut wall.^[3]

4) PURPOSE OF THE BCS: ^[3]

- Based on the BCS methodology, when a waiver for bioequivalence studies and in-vivobioavailability may be obtained.
- The BCS is expanded in terms of regulatory use, and techniques for categorising drugs are recommended.

5) GOALS OF THE BCS: ^[3]

- To propose a family of immediate-release (IR) solid oral dosage formulations for which in vitro dissolution testing may be used to demonstrate bioequivalence.
- By providing an approach for selecting disposable clinicalbioequivalence testing, we want to increase the efficiency of medication development and evaluation.
- To provide categorization techniques based on dosage form dissolving, as well as the drug substance's solubility and permeability properties.

6) CLASSES OF BCS: [5, 6]

Drug compounds are classified as follows by BCS into high/low solubility and permeability classes:

Solubility	
Class I	Class II
Highly Soluble	Poorly Soluble
Highly Permeable Eligible for Biowaiver	Highly Permeable Eligible for Biowaiver only if weak acids, highly soluble at pH 6.8, +Dissolution
Permeability	
Class III	Class IV
Highly Soluble	Poorly Soluble
Poorly Permeable Eligible for Biowaiver if very rapidly dissolving	Poorly Permeable Not Eligible for Biowaiver

Fig. 1-Classes of BCS

6.1. Class I-High Permeability, High Solubility

e.g. Metoprolol, Diltiazem, Verapamil, Propranolol

Class I medicines have a high absorption rate as well as a high dissolution rate. In general, these chemicals are well absorbed. The dissolving rate of Class I drugs designed as instant release products usually surpasses stomach emptying. As a consequence, nearly 100 percent absorption may be expected if at least % of a material dissolves within 30 minutes of in vitro dissolution studies at a variety of pH levels. In vivo bioequivalence studies are thus not required to ensure product comparability.

6.2. Class II -High Permeability, Low Solubility

e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine

Drugs in the Class II category have a high absorption rate but a low disintegration rate. Except at extremely large dosage numbers, in vivo drug dissolution is a rate limiting step for absorption. Products containing these chemicals are likely to have dissolution rate restricted in terms of bioavailability. As a result, there may be a link between in vivo bioavailability and in vitro dissolution rate (an IVIVC).

6.3. Class III- Low Permeability, High Solubility

e.g. Cimetidine, Acyclovir, Neomycin B, Captopril

Permeability is the rate-limiting stage in medication absorption for Class III medicines. The pace and breadth of medication absorption vary greatly with these medicines. Absorption is restricted by permeability rate, although disintegration will most likely happen quickly. As a result, some have argued that waiver criteria similar to those used for Class I medications would be appropriate as long as the test and reference formulations don't contain any agents that may affect drug permeability or GI transit time.

6.4. Class IV - Low Permeability, Low Solubility

e.g. Taxol, Hydrochlorothiazide, Furosemide.

Those chemicals have a low bioavailability; they are typically poorly absorbed by the intestinal mucosa, and a considerable degree of variability is predicted due to their poor oral bioavailability. These chemicals are not only difficult to dissolve, but they also have low permeability across the GI mucosa once dissolved. These medications are notoriously difficult to synthesise and can have significant inter- and intra-subject variability.

7) BCS CLASS BOUNDARIES:-[4]

7.1. Highly Soluble: When the greatest dosage strength of a pharmacological ingredient is soluble in 250 mL water over a pH range of 1 to 7.5, it is termed very soluble.

7.2. Highly Permeable: When the amount of absorption in humans is proven to be > 90% of a given dosage, either on mass-balance or in comparison to an intravenous reference dosage, a drug substance is deemed extremely permeable.

7.3. Rapidly Dissolving : When more than 85 percent of the labelled amount of drug material dissolves in 30 minutes using USP equipment I or II in a volume of 900 ml buffer solutions, the drug product is said to be quickly dissolving.

8) APPLICATIONS OF BCS[1]

The concepts of BCS are frequently used in the development of novel dosage forms, in clinical pharmacology, and as a scientific methodology for assessing bioavailability waivers and regulatory clearances in the pharmaceutical industry.

8.1 BCS in Early Drug Development:

BCS can play a crucial role in drug candidate selection throughout the early stages of development. The understanding of a drug's BCS class has an influence on development decisions. The BCS class of a medication indicates the rate-limiting stage, which can be dissolution, permeability, or stomach emptying, and solubility and permeability can be used as selection criteria. Gastric emptying is the rate limiting step for Class I medicines with favourable absorption and quick dissolving qualities. As a result, formulation development for this class of medications is quick and inexpensive, as long as there are no challenges with stability or manufacturing. For IR formulations of class I medicines, no in vitro-in vivo correlations (IVIVCs) have been identified.

Because class II medicines have a high permeability, drug solubility augmentation technologies such as nanoparticles, microemulsions, and others can be used to increase absorption. Time and expertise are also required to design an effective dissolve method that can distinguish crucial product formulation or manufacturing factors that impact in vivo medication dissolving.

Because it's difficult to produce particular permeability enhancers, permeability is the rate-limiting phase in BCS III drug absorption, and it's tough to fix it using formulation parameters. To boost medication availability to the target tissue, a pro drug strategy may be used to promote bioavailability. The pro drug idea may not be necessary if the requisite drug concentrations for therapeutic impact can be attained using the parent drug and cost-effective traditional formulations. For BCS III medicines, there is no IVIVC. In compared to class II medications, developing a dissolving mechanism for class III medications is simple.

Solubility, dissolution, or permeability can be the rate-limiting stage in drug absorption for class IV medicines, resulting in dosage variability. The amount of variability that may be tolerated is determined by the drug's therapeutic index and indication.

8.2 Generics Approval

During the early stages of clinical investigations, the categorization of drugs according to the BCS is done in accordance with FDA rules. The BCS can be a valuable technique for developing a standard for product dissolution and reducing the need for in vivo bioequivalence. The formulation scientist can use BCS information to estimate the possibility for in vitro-in vivo correlation (IVIVC) and drastically minimise the number of in vivo trials.

8.3 BCS in Oral Drug Delivery Technology

The BCS gives information about the drug's solubility and permeability properties, making it easier to decide whether to design a certain drug delivery system. The key problem for class I medicines is to achieve a set release rate while maintaining an adequate pharmacokinetic and/or pharmacodynamic profile. Controlling the rate of release and certain physicochemical aspects of pharmaceuticals, such as the pH-solubility profile of the medication, are examples of formulation techniques. Micronization, the use of surfactants and complexing agents such as cyclodextrins, lyophilization, emulsions and microemulsion systems, and other techniques are used to produce systems for class II pharmaceuticals. Class III medications necessitate technology that aid in overcoming permeability's inherent constraints. Class IV medications provide a significant difficulty for the development of drug delivery systems. Solubility enhancers are included in the formulation, and the parenteral route is the preferred mode of drug delivery.

8.4 BCS in Biowaiver

Biowaiver is a word that refers to getting rid of the need for expensive and time-consuming bioavailability and bioequivalence studies. Biowaivers are available from BCS for medications in classes I, II, and III, with some restrictions. Biowaiver is recommended by the USFDA BCS guidelines for class I medicines or immediate release pharmacological products. In the absence of an in vivo relative bioavailability investigation, dissolution in the three specified dissolving medium should be more than 85% in 30 minutes. A profile comparison is not necessary if both the reference and test items dissolve 85 percent or more of the indicated quantity in less than 15 minutes in all three specified dissolving media. Medications having a weak acidic nature and medications with a weak basic nature may be eligible for biowaivers for BCS class II drugs. Weakly basic medicines, such as Diclofenac Sodium and Diclofenac Potassium, have a high solubility at the higher pH of the gut, allowing for full absorption. Weakly basic medicines have a high solubility in lower pH in the stomach, allowing for absorption. If the requisite data support the similarity of the pharmaceutical product and reference product, the biowaiver based on BCS is applicable for IR oral solid dosage forms that contain one or more of the API(s). Biowaivers are applicable for IR medicinal products of BCS class I with very fast (> 85 percent within 15 minutes) in vitro dissolution characteristics, according to BCS recommendations for Europe, the Middle East, and Africa (EMEA). If there is no influence of excipients on membrane transporters, the biowaiver is also applicable to BCS Class III drug substances with very fast (> 85 percent within 15 minutes) in vitro dissolution of the test.

9) REGULATORY APPLICATIONS^[3]

Request for Biowaivers:

Based on the Biopharmaceutical Classification System, the US Food and Drug Administration (US FDA) issued guidelines for industry in 2000 on in-vivo bioequivalence and bioavailability research waivers (biowaivers) (BCS). Given the risks inherent with in vitro dissolution testing, both the US FDA and the European agency EMEA have published rules under which pharmaceutical firms can obtain a waiver from in vitro bioequivalence studies. The FDA does not consider quickly dissolving compounds of highly soluble and highly permeable pharmaceuticals (BCS class I medicines) to be "Narrow Therapeutic Index Drugs," according to the draught guideline.

The following grounds should be used to substantiate a request for an exemption from in vivo bio studies:

- The drug material, which is described as a Class I drug above, should be extremely soluble and permeable.
- A rapid-dissolving medication product should be used for immediate release.
- For authorization of an in vivo relative bioavailability study, the dissolution rate in the three specified dissolving medium must be greater than 85% in 30 minutes (acidic media, such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, a pH 4.5 buffer; and a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes). Under the dissolution test parameters established for quickly dissolving products, test and reference goods should have comparable dissolution characteristics for waivers of in vivo bioequivalence.
- The medicine should have a broad therapeutic index rather than a limited therapeutic index. This restriction is intended to apply mostly to bioequivalence studies presented in New Medication Applications (NDA) and Abbreviated New

Medication Applications (ANDA) following approval, as well as bioequivalence studies submitted in an ANDA, because an experimental drug may not be clearly defined as a narrow therapeutic index drug during the IND phase.

- The dosage form's excipients should have previously been utilised in FDA-approved IR solid dosage forms. The amount of excipients in the IR product should be proportional to their function. Surfactants (e.g., sodium lauryl sulphate) and osmotic substances (e.g., sorbitol) in large concentrations might be troublesome.
- All other application deadlines should be adhered to.

The solubility and permeability of BCS class I products are both high. Permeation through the intestines often surpasses gastric emptying time for immediate release products of these substances designed for oral absorption. As a result, if at least 85 percent of the indicated quantity is released within 30 minutes of in vitro dissolution tests, one should assume 100 percent absorption. Drug absorption is limited for class III medications due to permeability, but drug breakdown happens quickly in the GIT. As a result, unless the test and reference items contain ingredients that modify drug permeability, waiver criteria may be suitable for these goods. The 2010 European Medicines Agency Bioequivalence Guideline expands on biowaivers to include class III medicines (low permeability, high solubility). As a result, biowaivers are now available for all Class I and certain Class III substances. Because of their poor solubility profiles, both Class II and Class IV chemicals do not fulfil the biowaivers requirements. In scientific literature, more acidic BCS II medicines have been suggested as potential biowaivers.

Biowaiver requests based on the BCS classification system's principles can be used for NDA and ANDA approvals, as well as scale-up and post-approval adjustments in drug production. As a result, the following outcomes have occurred:

- **Investigational New Drugs and New Drug Applications (INDs and NDAs):** As long as the formulation has a quick and comparable in vitro dissolution profile, BCS-based biowaivers are applicable to marketed formulations when changes in composition, formulation components, or technique of preparation occur to the clinical trial formulation. If the medication is highly soluble and permeable (BCS class I medicines), and the pre- and post-change formulations are pharmaceutically identical, this method can be used.
- **Abbreviated New Drug Applications (ANDA):** For a highly soluble, highly permeable pharmacological material that has been produced with fast dissolving, as stated in section III of the US FDA guidelines, an in-vivo bioequivalence research can be skipped if the reference listed drug product is similarly highly soluble and both the test and reference products have comparable dissolving profiles, i.e., this method is only appropriate when the test and reference products are pharmaceutically equal. Wherever possible, the dissolving apparatus (USP I or II) used should be the same as the one used for the reference product.
- **Post-approval Changes:** Significant post-approval adjustments, such as level 3 modifications in components and composition, to a fast dissolving instant release product designed for oral use can be sought via BCS-based biowaivers. Furthermore, the pharmacological material should be highly soluble and permeable, with quick dissolution for both prior and post change products and a comparable dissolution profile for both pre and post change products.
- **Approval of Generics:** Few generics were allowed under these restrictions until 1984, since they had to fulfil critical safety, effectiveness, and BE requirements. The Waxman-Hatch Act introduced the abbreviated new drug application procedure (ANDA), which allowed the FDA to approve generic goods for medications that had already been determined safe and effective, and standardised the standards for pharmaceutical equivalence and bioequivalence. In 1995, Amidon et al. introduced the biopharmaceutical categorization system (BCS), which made generic approval even easier. The provision for post-approved adjustments in the BCS Class I quick release oral dosage form has allowed generic pharmaceutical companies to acquire clearance without having to complete bioequivalent studies.
- **Cost Savings:** Since the inception of the biopharmaceutical categorization system in 1995, there has been a significant increase in drug NDA and ANDA filings. In 2010, a total of 86 NDAs were signed. According to the FDA, approximately 80% of all completed applications will be granted. DiMasi recently stated that NDAs are approved at a rate of about 90%. It was predicted that around 25% of all authorised products were classed as highly soluble and highly permeable, allowing for a biowaiver for bioequivalence investigations. Using the 25% estimate above, it is possible to save one-quarter of the yearly bioequivalence study costs, which are expected to be between \$22 and \$38 million dollars per year. If bioequivalence tests represent a bottleneck in medication development, additional indirect savings may be possible. Let's say you require the findings of a bioequivalence research before moving further with the development of a chemical with a one-billion-dollar annual peak sales potential. It is easy to imagine that in vitro dissolution data may be acquired 6 weeks earlier than results from an in vivo bioequivalence experiment, resulting in an additional \$110 million in sales from a 6 week earlier clearance. Furthermore, because a human bioequivalence trial is not required, clinical resources can be used elsewhere, which is a benefit to the company.

10) INDUSTRIAL IMPLEMENTATION OF THE BCS^[7]

Amidon et al. developed the bio-pharmaceutics classification system (BCS) in 1995 to classify medications according to their water solubility and intestinal permeability. It was established that when the dissolution rate of highly soluble and highly permeable (BCS Class I) drugs is fast enough, the rate has no influence on bioavailability. As a result, numerous regulatory bodies, including the US Food and Medication Administration (FDA), now allow in vitro dissolving to be used to establish bioequivalence of BCS Class I drug formulations (often called a bio-waiver).

10.1 Potential Cost Savings

- The potential savings are based on the number and cost of bioequivalence studies that may be avoided (not performed).
- The number of bioequivalence studies undertaken by the pharmaceutical industry each year was studied to determine the possible savings. Bioequivalence studies are anticipated to cost the pharmaceutical industry between 90 and 150 million dollars each year.
- Approximately 25% of all chemicals were identified as extremely soluble and permeable, with the other 41% lacking enough information to be categorised.

- Using the 25% estimated, there is the potential to save one quarter the annual expenditures on bioequivalence studies, \$22 to \$38 million dollars/year. If bioequivalence studies represent a bottleneck in medication development, there may be further indirect savings.
- Assume that the findings of a bioequivalence research are required before moving on with the development of a chemical with a one-billion-dollar annual peak sales potential. It is acceptable to expect that in vitro dissolution findings can be acquired 6 weeks before in vivo bioequivalence experiment findings. This time savings corresponds to an additional \$110 million in potential sales from a six-week earlier approval. Furthermore, because a human bioequivalence investigation is not required, clinical resources can be used elsewhere.

10.2 BCS -Implications for drug development

Application in the early stages of medication development and later in the management of product modification throughout the product life cycle.

- Aids in the basic comprehension of the drug's biological and physical characteristics.
- Assists in the development of selective dissolution methods
- Can aid in the creation of in vitro/in vivo correlations.
- It's possible to get a biowaiver using this method.
- Drugs that are poorly soluble are being developed.

This categorization is linked to the drug dissolution and absorption model, which defines the essential factors that affect drug absorption as a collection of dimensionless numbers, such as

BCS defines 3 numbers (no units)

- ❖ Absorption number(A_n)
- ❖ Dose number(D_o)
- ❖ Dissolution number(D_n)

Absorption Number: A function of GI Permeability to Drug Substance

$$A_n = \left\{ \frac{P_{eff}}{R} \right\} (TGI) = \frac{TGI}{TABS}$$

Where P_{eff} is effective permeability, R is radius of GI, TGI is residence time in GI, $TABS$ time required for complete absorption.

Dose Number: A function of solubility of drug substance

$$D_o = \frac{D/V_{water}}{C_s}$$

D is Highest dose unit, V is Volume (250ml), C_s is Solubility.

Dissolution Number: A function of drug release from formulation

$$D_n = (3D/r^2)(C_s/\rho)(T_{GI}) = (T_{GI}/T_{DISS})$$

Where, $3D$ is Diffusivity $5 \times 10^{-6} \text{ cm}^2/\text{s}$, r^2 is Particle Radius 25 mm , C_s is Solubility mg/mL , ρ is Density 1.2 mg/cm^3 , T_{GI} Residence time in GI 180 min , T_{DISS} Time required for complete dissolution.

CONCLUSION

Solubility and permeability characteristics have an impact on drug pharmacokinetics in vivo. The BCS idea is a valuable guideline for predicting in vivo performance of pharmacological substances, developing innovative drug delivery methods to match the drug's performance in the body, and ensuring bioequivalence of medicinal products throughout scale-up and after approval. BCS also allows for drug disposition, transport, absorption, and elimination to be predicted. The BCS theory may be employed more frequently in the beginning creation of novel medications in the future, including for analogue selection and early formulation techniques.

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