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REVIEW

Emerging Role of Biopharmaceutical Classification and Biopharmaceutical Drug Disposition System in Dosage form Development: A Systematic Review

Ramu SAMINENI[1,2]*, Jithendra CHIMAKURTHY[2], Sathish KONIDALA[2]

[1]Vignan's Foundation for Science, Technology and Research, Department of Sciences and Humanities, Division of Chemistry, Andhra Pradesh, India
[2]Vignan's Foundation for Science, Technology and Research, Faculty of Pharmacy, Department of Pharmaceutical Sciences, Andhra Pradesh, India

ABSTRACT

Biopharmaceutical classification system (BCS) is an advanced tool used for classifying medicines based on dissolution, water solubility, and intestinal permeability, which affect the absorption of active pharmaceutical ingredients (API) from immediate-release solid oral forms. It is useful to the formulation researchers to develop novel dosage forms based on modernistic rather than experimental approaches. The current review focuses on the fundamentals, objectives, guidance of BCS, characteristics of BCS drugs, their importance and applications of BCS. This review explains the challenges in drug development in terms of solubility and *in vivo* disposition. In the current review, new strategies for improving BCS II drug solubility as well as biopharmaceutical drug disposition properties which are utilized throughout the early stages of drug development and commercialization are mainly discussed.

Key words: Bioavailability, biopharmaceutical classification system, drug solubility, dissolution, drug disposition, bioequivalence, new drug application

INTRODUCTION

Biopharmaceutical classification system (BCS) is an advanced tool used for classifying drug substances on dissolution, intestinal permeability and water solubility.[1] In 1995, a theoretical approach for comparing *in vitro* drug dissolution with *in vivo* bioavailability was first conducted by Amidon et al.[1] BCS is a pharmaceutical development tool that is used for basic management in the drug discovery and early development of novel medications.[1,2]

The criteria for BCS direction for biowaiver are given by the United States Food and Drug Administration (FDA or USFDA), World Health Organization (WHO) and European Medicines Agency.[3,4] The BCS data assist the particular researcher in constructing a dosage form based on intuition rather than experimental approaches (FDA rules, 2000).[5] The BCS conceptual structure requirements can be linked to New Drug Application and Abbreviated New Drug Application approvals as well as scale up and post-approval alterations in medication manufacturing.

BCS is a conceptual structure that discusses three rate-limiting phases in oral retention.

- Release of drugs from dosage form
- Gastrointestinal (GI) tract arrangement of disintegrated form
- Saturation through GI membrane into hepatic circulation[6]

The intestinal permeability arrangement is determined by a correlation with intravenous infusion and solubility characterization is determined according to United States Pharmacopeia (USP).[7]

BCS follows fick's first law utilized for membrane permeability

$$J_f = P_m C_i \quad \text{(equation 1)}$$

*Correspondence: samineni.ramu@gmail.com, Phone: 8142853086, ORCID-ID: orcid.org/https://orcid.org/0000-0002-8652-2883
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Where,

J_f = Drug flux rate (mass/area/time)

P_m = Membrane permeability

C_i = Concentration of the drug at the intestinal membrane surface

BCS acts as a regulatory tool and replaces certain bioequivalent studies, which are have been accurate *in vitro* dissolution tests and ensure avoiding unnecessary drug exposure to healthy volunteers.[8]

BCS classification

According to BCS system, drugs are classified into four types based on their intestinal permeability and solubility. BCS classification is based on key parameters like solubility, dissolution rate and permeability, which control absorption. In case of class I drugs, absorption is maximum, class II drugs are showing solubility limited, class III drugs have permeability limited, class IV drugs have poorly absorbed mentioned in Table 1.[6-8] Apparent permeability index (Papp) is the index used to assess the degree of permeability of drug substances. The permeability coefficient, which is a measure of flow to the drug concentration in the donor compartment. Papp of any drug substance can be calculated using *in vitro*, *ex vivo*, *in situ*, and *in vivo* techniques.[9]

Solubility

The amount of a substance that can be dissolved in a given amount of solvent is called solubility. A medicine that can be dissolved in 250 mL or less of water throughout a pH range of 1-8 is deemed an excellent dissolved pharmaceutical.[10]

Permeability

Permeability is the quality or state of being permeable. When a medicine has an absorption rate of more than 90% of the prescribed dosage and is stable in the stomach, it is termed an exception penetrable pharmaceutical.[11]

Dissolution rate

The process by which a solute dissolves into a solvent and produces a solution is known as dissolution. When 85% of the labeled quantity of drug substance dissolved in 30 min using USP equipment 1 at 100 rpm or apparatus 2 at 50 rpm in a volume of 900 mL buffer solutions (0.1 N HCl/pH 4.5 buffer/pH 6.8 buffer without enzymes), the drug product is regarded to have fast dissolution.[12-14]

Dimensionless parameter

BCS characterization is connected to medication dissolution and absorption display, which are essential factors for regulating medication absorption as a set of dimensionless numbers.[15,16] Drug properties and their corresponding dimensionless parameters and their significance related to them are highlighted in Table 2.

Absorption number (A_n) =
Average residence time/average absorption time (equation 2)

The dissolution number (DS_n) =
Average residence time/average dissolution time (equation 3)

Dose number (D_n) = Mass of drug/
uptake volume of 250 mL × drug solubility (equation 4)

Objectives

- The goal of BCS is to evaluate *in vivo* performance of medicinal products based on *in vitro* permeability and solubility data.[17]
- To provide techniques for categorizing medicinal products based on solubility and permeability properties as well as dosage form dissolution.
- We improved the efficiency of drug development and review processes by proposing a mechanism to perform clinical bioequivalence tests expandable.

Table 1. BCS classification system[6-8]

Class	Solubility	Permeability	*Papp (cm/sec)	*Q	Significance
I	High	High	P_{app} >10^{-5}	q ≤0.5	Well absorbed
II	Low	High	P_{app} >10^{-5}	q >1	Solubility limited
III	High	Low	P_{app} <2 C 10^{-6}	q ≤0.5	Permeability limited
IV	Low	Low	P_{app} <2 C 10^{-6}	q >1	Poorly absorbed

*P_{app}: Apparent permeability, *Q: Dose/solubility, BCS: Biopharmaceutical classification system

Table 2. Drug properties influencing absorption[6-8]

Drug property	Corresponding dimensionless parameter	Significance
Solubility	Dose number	Ideally, the dose ratio should be less than 1. Higher doses will increase the ratio and absorption less likely
Dissolution rate	Dissolution number	Ideally, dissolution number should exceed 1. In the case of solid dosage forms, a combination of inadequate solubility or excessive particle size or density can increase the time needed for full dissolution and reduce this ratio
Permeability rate	Absorption number	Ideally, absorption number should exceed 1. Longer absorption times resulting from lower permeability will reduce this ratio

Importance

To replace certain bioequivalent studies, BCS acts as a regulatory tool. It is applicable in both preclinical and clinical examinations. BCS can reduce the time and money for the immediate release orally administered drugs, which meet particular criteria; the FDA will allow a waiver for costly and tedious bioequivalence studies. It acts as a guiding tool for selecting the formulation of new dosage forms, development of various oral drug delivery systems.[18]

Class II drugs

BCS class II drugs have high permeability and low solubility. These medications have a high absorption number, but a small disintegration number. *In vivo* drug dissolution is then a rate limiting advanced step for absorption, except in very high dose numbers. These drugs have varied bioavailability and require improved solubility or dissolution to increase bioavailability. These compounds are suitable to outline the sustained release and controlled release formulations. *In vitro-in vivo* correlation applies normally to class II drugs. Based on solubility and permeability, drugs are classified into four types (class I to class IV) examples mentioned in Table 3.[18]

Biowaiver

Biowaiver is most commonly used in the administrative drug approval procedure, when the drug application is confirmed based on the proof of proportionality other than *in vivo* comparison testing. This waiver applies to both the pre- and post-approval stages. BCS-based biowaiver is applicable for immediate-release solid oral formulations containing the API approved by WHO.[19]

Biowaiver extension potential

BCS class II medicines are effective and completely absorbed, when taken orally. Class II drugs are weak acids with pKa values of ≤4.5 and intrinsic solubility (dissolvability of the unionized form) of ≥0.01 mg/mL, which are ineffectively dissolvable. At pH values typical of the fasted state in the jejunum (about pH 6.5), these medications will have a solubility of >1 mg/mL, produce about rapid and steady dissolution of the medication. Class II drugs are inadequately dissolvable at gastric pH, in which pH is considerably less than pKa because the small intestinal transit time is more consistent and when fasting longer than the gastric residence time (3 hr), drugs these physical characteristics will have enough time to dissolve. Class II drugs meet the permeability measure, biowaiver for products that break down quickly at the pH levels regularly in the small digestive tract, it has been suggested that BCS class II drugs have a biowaiver enhancement potential.[19]

Applications

Dissolution or solubility is the rate limiting factor in BCS II and it has a substantial impact on absorption and bioavailability. Lyophilization, micronization, microemulsion, inclusion of surfactants, solid dispersion, and use of complexing agents such as cyclodextrins; these are the methods used to improve solubility.[19-22] Zer-Os tablet innovation, soft gel, triglas, and nano-sized formulations are enhancement techniques, for example; nanocrystals, nanosuspension, and nanoemulsions are useful methods for increasing the solubility and bioavailability of low water soluble drugs[23-25] mentioned in Table 4.

Table 3. Examples of some model drugs as *per* BCS[10-14]

Class I	Class II	Class III	Class IV
Abacavir	Amiodarone	Acyclovir	Amphotericin
Acetaminophen	Atorvastatin	Amiloride	Chlorthalidone
Acyclovir	Azithromycin	Amoxicillin	Chlorothiazide
Amiloride	Carbamazepine	Atenolol	Colistin
Amitryptyline	Carvedilol	Bisphosphonates	Coenzyme Q10
Antipyrine	Chlorpromazine	Bidisomide	Ciprofloxacin
Atropine	Cisapride	Captopril	Ellagic acid
Buspironec	Ciprofloxacin	Cefazolin	Furosemide
Caffeine	Cyclosporine	Cetirizine	Hydrochlorothiazide
Captopril	Danazole	Cimetidine	Mebendazole
Chloroquine	Dapsone	Cipofloxacin	Methotrexate
Chlorpheniramine	Diclofenac	Cloxacillin	Neomycin
Cyclophosphamide	Diflunisal	Dicloxacillin	Ritonavir
Desipramine	Digoxin	Erythromycin	Saquinavir
Diazepam	Erythromycin	Famotidine	Taxol

BCS: Biopharmaceutical classification system

Techniques to enhance the solubility of BCS II drugs

Physical modifications

Micronization: Spray drying or use fluid energy or a jet mill to reduce the particle size to 1-10 microns. A reduced particle size will increase the surface area and improves bioavailability. Examples: Griseofulvin, sulfa, and certain steroidal drugs.[26]

Nanoionization: Powdered drug is converted to nanocrystals of size 200-600 nm using technologies such as pearl processing, homogenization in water, and homogenization using non-aqueous medium. Examples: estradiol, doxorubicin, cyclosporin, and paclitaxel.[27]

Sonocrystallization: Ultrasound in the range of 20 KHz-5 KHz is used to induce crystallization in sonocrystallization. Examples: This method increased the solubility of ketoconazole by 5.517 folds.[28]

Use of polymorphs, amorphous, solvates, and metastable form: Because the vitality required to transfer the crystal lattice is more than that necessary for amorphous solid, amorphous forms are more soluble than crystal structures. Metastable forms are more soluble than stable ones. Because hydrates are already associated with water, anhydrates are more soluble, so require less energy for crystal separation. Thus, the order of solubility of different solid forms of drugs is

Amorphous › Metastable › Stable › Anhydrates › Hydrates › Solvates › Non-solvates

Eutectic mixtures: The soluble carrier in the eutectic mixtures dissolves when exposed to water, leaving the drug in a microcrystalline state that solubilize rapidly. They are inexpensive and easily prepared. Examples: paracetamol with urea, griseofulvin with urea, griseofulvin with succinic acid.[29]

Table 4. Techniques employed for BCS II drugs

Drug name (category)	Polymers/co-formers	Method employed	Result	References
Meloxicam (NSAIDS)	PVP, PEG-6000	Solvent evaporation method	Increase the dissolution rate	26
Etoricoxib (NSAIDS)	Lactose, sucrose, mannitol	Solvent evaporation method	Improved solubility and dissolution of the poorly aqueous soluble drug	27
Ibuprofen (NSAIDS)	Starch 1500, PVP K30	Kneading method	Developed faster dissolution characteristics	28
Diacerein Antirheumatic	PVP K30, HPMC-E4	Solvent evaporation	Improved solubility of poorly soluble drug	29
Itraconazole Antifungal	Gelucire 50-13, compritol 888 ATO	Spray drying	Increased dissolution and *in vivo* bioavailability	30
Griseofulvin Antifungal	Britishgum, corn starch	Roll mixing method	Solubility and dissolution rate increases	31
	Beta-cyclodextrin	Complexation using co-precipitation method	Enhanced dissolution rate was observed	32
Carbamazepine Anticonvulsant	Croscarmellose, sodium starch glycolate	Modified solvent evaporation method	Improved solubility/dissolution profile of drug	33
Glipizide Antidiabetic	HPMC, croscarmellose	Solvent evaporation	Better phase solubility and *in vitro* dissolution rate	34
Olanzapine Antipsychotic	Pregelatinized starch, sodium starch glycolate	Dispersion method	Enhanced the aqueous solubility	35
Gliclazide Oral hypoglycemic agent	PEG 4000, PEG 6000, PVP K-30	Fusion and solvent evaporation method	Increased solubility and bioavailability rate of poorly soluble drug	36
Atorvastatin Antihyperlipidimic agent	Mannitol, PEG 4000, PVP K-30	Hot melt and solvent evaporation	Improved dissolution rate	37
Telmisartan Antihypertensive	Beta-cyclodextrin, MCC pH 102, polaxomer 188	Solid dispersion method	Increased solubility, dissolution and bioavailability	38
Mesalamine (antiulcerative)	SLS, urea	Kneading method	Improved saturation solubility and dissolution rate	39

NSAID: Non-steroidal anti-inflammatory agent, PVP: Polyvinylpyrrolidone, PEG: Polyethylene glycol, HPMC: Hydroxypropyl methylcellulose, BCS: Biopharmaceutical classification system, SLS: Sodium lauryl sulfate

Solid dispersions: A hydrophilic matrix (polyvinylpyrrolidone, povidone, polyethylene glycol, surfactant such as sodium lauryl sulfate, tween 80, pluronic F-68) and hydrophobic drug (fats, oils, waxes, alkanes, and other greasy substances) are used in preparing solid dispersions. Methods for preparing solid dispersions including.

Hot-melt method (fusion method): Drug and the carrier are heated directly until they melt and then rapidly cooled with ice by continuous stirring to solidify. After that, it is crushed, pulverized, sieved and compressed into tablets.[30]

Solvent evaporation method: Medication and the carrier were dissolved in a common solvent and the dissolved content was evaporated under vacuum to form an amorphous precipitate.[30] Examples: Meloxicam, naproxen, nimesulide.[31]

Hot melt extrusion: It is the same as the combination technique, except the extruder does the extreme mix. It is appropriate for large-scale preparations.[31] Examples: Ritonavir.[32]

Chemical modifications

Change in pH: The easiest approach to enhance solubility of organic ionized solutions is to change the pH of the formulation. A change in pH can be done by;

- Use of buffers
- *In situ* salt formation

Salt formation: When compared with pure API drugs, salt forms have better solubility. Example: Antacid metal salts of acidic medicines, such as penicillin, solid corrosive salts of vital pharmaceuticals, such as atropine.[33]

Prodrug: Solubility of the drugs can be increased by converting a pharmacologically inactive substance into a pharmacologically active drug. Examples: acyclovir, fluorouracil, cyclophosphamide, carbamazepine, captopril, and carisoprodol.

Atomic elucidation with cyclodextrins: The beta and gamma ray cyclodextrins can form sub-atomic consideration structures since they have a cavity to accommodate lipophilic medicines as guests and the exterior of the transporter is hydrophilic. As a result, there is a significant increase in dissolving rate and solubility. Thiazide diuretics, barbiturates, and benzodiazepines are examples of drugs with enhanced bioavailability due to this method.[34]

Derivatization: Conversion of a chemical compound into a product, which shows a similar chemical structure called derivative with different solubilities's that of the adduct.[35]

Miscellaneous modifications

Super critical fluid (SCF) recrystallization: These fluids have temperatures and pressures that are higher than their critical temperature and exhibit the characteristics of both gases and liquids. SCFs are profoundly compressible at close fundamental temperatures, modifying thickness and mass power by allowing weight modification. When the drug particles were dissolved in SCF, they crystallized with smaller molecule sizes.[36]

Use of surfactants: Surfactants increase the disintegration rate by advancing wetting and infiltration of disintegration liquid into the medication particles, when used in the focus beneath their basic micelle fixation because drug captured in the micelle structure failed to partition in the dissolution fluid above the critical micelle concentration. Example: a steroid-like spironolactone bioavailability has been enhanced by this technique.[36-38]

Solvent deposition: Poorly soluble medicines are dissolved and deposited on an inert, hydrophilic, and solid matrix by evaporation of the solvent using organic solvents such as alcohol. Example: Nifedipine.

Precipitation: Medication that is poorly water-soluble is first dissolved in a suitable organic solvent, then quickly mixed with a non-dissolvable to precipitate the medication in nanosize particles, and this result is known as a hydrosol.[39] Example: cyclosporine.

Co-solvents: Solubility is low for weak electrolytes and non-polar compounds. Solubility can be increased by altering the polarity of those molecules by adding organic co-solvents (mixing miscible or partially miscible solvents) to water, which drastically affects medication solubility.[40] Example: Etoricoxib, glipizide, glyburide, glimepiride and pioglitazone.

Hydrotrophy: The addition of a significant number of additives (hydrotropic agent) to the drug solution increases the medication's water solubility.[41] Example: Ethanol, resorcinol, pyrogallol, catechol and procaine hydrochloride.

Selective adsorption on insoluble carriers: Adsorbents can enhance solubility by forming weak physical bonding between the drug and adsorbent and can also by hydration and swelling of clay in aqueous media. Example: inorganic clay bentonite can improve the dissolution of drugs like griseofulvin, prednisone, and indomethacin.[42]

Drug disposition

The significant route of elimination of drugs showing high intestinal permeability in humans is mainly by metabolism and the drugs having weak intestinal permeability rates are mainly excreted as unchanged drugs in the urine and bile in humans. In 2005 drug disposition was first observed by Wu and Benet[43], who proposed a system called Biopharmaceutics Drug Disposition Classification System (BDDCS): in case of class 1 and 2 drugs showing extensive metabolism, class 3 and 4 drugs showing a poor metabolism rate shown in Table 5.[43-45]

BDDCS system estimates the effect of food, absorption as well as efflux transporters, route of excretion on overall drug absorption and the permeability of immediate-release oral dose forms is less than bioavailability. BDDCS system as an extension of BCS.[44]

Because BDDCS is a replacement for permeability, they proposed that medications that demonstrate metabolism as a main route of elimination be deemed highly permeable. Low permeable drugs are those, whose primary route of excretion is renal and biliary excretion of unmodified medicine.[45] Data on medication disposition for a few medicines from the WHO essential drug list are shown in Table 6.[46]

Table 5. Biopharmaceutics drug disposition classification system[43-45]

	High solubility	Low solubility
Extensive metabolism →	**Class 1** High solubility Extensive metabolism	**Class 2** Low solubility Extensive metabolism
Poor metabolism →	**Class 3** High solubility Poor metabolism	**Class 4** Low solubility Poor metabolism

Table 6. Drug disposition data from WHO essential medicines list[46]

Model drug	Dose (mg)	Formulation	Solubility (mg/mL)	Dose number	Bioavailability (%)	Excreted unchanged in urine (%)	Metabolism	BCS	BDDS
Aspirin	500	Tablets	10	0.2	Limited data	1.4	Extensive	3	1
Benznidazole	100	Tablets	0.4	1.0	96	NA	Extensive	3	1
Biperiden	2	Tablets	1.0	0.008	36	NA	Extensive	3	1
Clomiphene citrate	50	Tablets	1.11	0.2	90	8.0	Poor	1	3
Didanosine	25	Tablets	27.3	0.004	44	55	Poor	3	3
Ethambutol	400	Tablets	100	0.016	Not applicable	79	Poor	3	3
Ethosuximide	250	-	100	0.01	Not applicable	NA	Extensive	3	1
Folic acid	1	-	0.1	0.04	Not applicable	NA	Poor	3	3
Glibenclamide	5	-	0.01	16	Not applicable	NA	Extensive	2	2
Levothyroxine sodium	0.1	-	0.15	0.003	70	NA	Poor	1	3
Lumefantrine	120	-	1	0.48	Not applicable	NA	Poor	1	3
Methyldopa	250	Tablets	10	0.1	25	40	Extensive	3	1
Nicotinamide	50	-	100	0.002	High	NA	Extensive	3	1

NA: Not available, WHO: World Health Organization, BCS: Biopharmaceutical classification system, BDDS: Biopharmaceutical drug disposition system

CONCLUSION

BCS serves as a regulatory tool for the progress of various oral drug transport advancements. The BCS considers three major factors, dissolution, solubility and intestinal permeability, which govern the rate and degree of medication absorption from immediate solid dosage forms. It is a controlling device for anticipating *in vivo* execution of the medicinal substance and the improvement of the medication delivery system. The data generated from the solubility and permeability in pipeline drug discovery or development can be used for early pipeline compound categorization. The BCS's advantageous circumstances include reduced medication exposure to a large panel of human participants and in some cases shorter drug product development time, in addition to significant cost savings.

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Authorship Contributions

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