REVIEW
DOI: 10.4274/tjps.galenos.2021.73554

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

Ramu Samineni[1], Jithendra Chimakurthy[2], SATHISH KONIDALA[2]
[1]Division of Chemistry, Department of Sciences and Humanities, Vignan's Foundation for Science, Technology and Research, Vadlamudi, Guntur, AP-522213
[2]Faculty of Pharmacy, Vignan's Foundation for Science, Technology and Research, Vadlamudi, Guntur, AP-522213

Corresponding Author Information
Ramu Samineni
8142853086
samineni.ramu@gmail.com
https://orcid.org/0000-0002-8652-2883
27.03.2021
09.11.2021

ABSTRACT
Biopharmaceutical Classification System (BCS) is an advanced tool utilised for classifying medicines based on dissolution, water solubility, and intestinal permeability, which affect the absorption of active pharmaceutical ingredients from immediate release solid oral forms. It is useful to the formulation researcher 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 utilised throughout the early stages of drug development and commercialisation are mainly discussed.

Keywords: Bioavailability, Biopharmaceutical Classification System, Drug Solubility, Dissolution, Drug Disposition, Bioequivalence, New Drug Application.

1. INTRODUCTION:

Biopharmaceutical Classification System (BCS) is an advanced tool used for classifying drug substances on dissolution, intestinal permeability and water solubility[1]. In the year 1995, a theoretical approach for comparing *in vitro* drug dissolution with *in vivo* bioavailability was first conducted by Gordon Amidon et al. 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 United States Food and Drug Administration (FDA or USFDA), World Health Organization (WHO) and European Medicines Agency (EMEA)[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 (NDA) and Abbreviated New Drug Application (ANDA) 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 a dosage form
- Gastrointestinal (G.I) tract arrangement of disintegrated form
- Saturation through G.I. membrane into hepatic circulation

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

BCS follows fick's first law utilised to membrane permeability

$$J_f = P_m C_i \quad \textbf{(Equation 1)}$$

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 having accurate in vitro dissolution tests and also ensures avoiding unnecessary drug exposure to healthy volunteers[8].

1.1. BCS Classification

According to BCS system drugs are classified into four types based on their intestinal permeability and solubility. BCS classification based on key parameters like solubility, dissolution rate and permeability, which controls absorption. In case of class I drugs absorption is maximum, class II drugs are showing solubility limited, class III drugs are having permeability limited, Class IV drugs are having poorly absorbed mentioned in the 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]

1.1.1. 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[6].

1.1.2. 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[7].

1.1.3. Dissolution rate

The process by which a solute dissolves into a solvent and produces a solution is known as dissolution. When 85 percent of the labelled quantity of drug substance dissolve in 30 min using USP equipment 1 at 100 rpm or apparatus 2 at 50 rpm in a volume of 900 mL. buffer solutions (0.1N HCl/pH 4.5 buffer/pH 6.8 buffer without enzymes), the drug product are regarded to have fast dissolution[8].

1.1.4. Dimensionless parameter

BCS characterisation 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 parameter and significance related to them is 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)**

1.2. Objectives

- The goal of BCS is to evaluate in vivo performance of medicinal products based on in vitro permeability and solubility data.
- To provide techniques for categorising medicinal products based on solubility and permeability properties, as well as dosage form dissolution.
- Improving the efficiency of drug development and review processes by proposing a mechanism to find clinical bioequivalence tests expandable.[18]

1.3. 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]

1.4. 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 had varied bioavailability and require improved solubility or dissolution to increase bioavailability. These compounds are suitable for outline the Sustained Release (SR) and Controlled Release (CR) formulations. *In vitro- in vivo* correlation (IVIVC) applies normally to class II drugs. Based on solubility and permeability drugs are classified as four types (Class I to Class IV) examples mentioned in table 3.[18].

2. 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 Active Pharmaceutical Ingredient (API) approved by WHO [10].

2.1. 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 with 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 esteems regularly in the small digestive tract, it has been suggested that BCS Class II drugs have a biowaiver enhancement potential.

2.2. Applications

Dissolution or solubility is the rate limiting factor in BCS II, and it has a substantial impact on absorption and bioavailability. Lyophilisation, Micronization, Microemulsion, inclusion of surfactants, solid dispersion, and use of complexing agents such as Cyclodextrins. This 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

3. Techniques to enhance the solubility of BCS II drugs

3.1. Physical modifications

3.1.1. Micronization: Spray drying or utilising fluid energy or a jet mill to reduce particle size to 1–10 microns. Reduced particle size will increase the surface area and improve bioavailability. Examples: griseofulvin, Sulpha, and certain steroidal drugs[41]

3.1.2. Nanoionization: powdered drug is converted to nanocrystals of size 200–600 nm[22] using technologies such as pearl processing, homogenisation in water, and homogenisation using non aqueous medium. Examples: estradiol, doxorubicin, cyclosporin, and paclitaxel

3.1.3. Sonocrystallization: Ultrasound in the range of 20 KHz – 5 KHz is used to induce crystallisation in sonocrystallization. Examples: This method increased the solubility of ketoconazole by 5.517 folds [21]

3.1.4. 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 for solubility of different solid forms of drug is[18]

Amorphous > Metastable>Stable> Anhydrates > Hydrates> Solvates > nonsolvates

3.1.5. Eutectic Mixtures: The soluble carrier in the eutectic mixtures dissolves when exposed to water, leaving the drug in a microcrystalline state that solubilises rapidly. Because they are inexpensive and easily prepared. Examples: Paracetamol with Urea, Griseofulvin with Urea, Griseofulvin with Succinic acid[18].

3.1.6. Solid Dispersions: A hydrophilic matrix (PVP, Povidone, PEGs, surfactant such as SLS, Tween80, 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

3.1.6.1 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 get solidify. After that, it is crushed, pulverised, sieved and compressed into tablets[37].

3.1.6.2 Solvent Evaporation Method: Medication and the carrier were dissolved in a common solvent and the dissolved content was evaporated under vacuum to form amorphous precipitation [30]. Examples: Meloxicam, Naproxen, Nimesulide[38]

3.1.6.3 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[40]

3.2. Chemical modifications [18-20]

3.2.1. Change in pH: The easiest approach to enhance solubility for organic ionised solutions is to change the pH of the formulation[18]. Change in pH can be done by

- Use of Buffers
- *in situ* salt formation

3.2.2. 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[19]

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

3.2.4. Atomic elucidation with Cyclodextrins: The beta and gamma rays 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 because of this method.

3.2.5. Derivatization: Conversion of a chemical compound into a product, which shows a similar chemical structure called derivative with different solubility's that of the adduct[18].

3.3. Miscellaneous modifications

3.3.1. Super Critical Fluid (SCF) recrystallisation: 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 crystallised with smaller molecule sizes[18].

3.3.2. 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 (CMC). Example: A steroid like Spironolactone bioavailability has been enhanced by this technique[18-20].

3.3.3. 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[18]. Example: Nifedipine

3.3.4. 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[19]. Example: Cyclosporine

3.3.5. 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.[31]. Example: Etoricoxib, Glipizide, Glyburide, Glimepiride, Pioglitazone[20].

3.3.6. Hydrotrophy: The addition of a significant number of additives (hydrotropic agent) to the drug solution increases the medication's water solubility[18]. Example: Ethanol, Resorcinol, Pyrogallol, Catechol, Procaine Hydrochloride

3.3.7. 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].

4. 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 drug in the urine and bile in humans. In the year 2005 Drug disposition was first observed by Chi Yuan Wu and Leslie Z. Benet, and proposed a system called Biopharmaceutics Drug Disposition Classification System (BDDCS) in case of class 1and 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, absorptions 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[43].

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[36]. Data on medication disposition for a few medicines from the WHO essential drug list are shown in table 6[46]

5. 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 categorisation. The BCS's advantageous circumstances include reduced medication exposure to a large panel of human participants and some cases shorter drug product development time, in addition to significant cost savings

.**6. Acknowledgement**
The authors are thankful to the management of Vignan's Foundation for Science, Technology and Research (VFSTR) for providing the necessary facilities and infrastructure to complete this work.
Declarations of interest: None

7. REFERENCES

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413-420.
2. B. K. K. Reddy and A. Karunakar. Biopharmaceutics Classification System: A Regulatory Approach. Dissolution Technologies. 2011;18:31-37.
3. Guidance for Industry. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Rockville, MD, Department of Health and Human Services, US Food and Drug Administration, 2000. (http://www.fda.gov/cder/guidance/index.htm)
4. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, Forty-ninth report. Geneva, World Health Organization, 2015;992(7):134-184.
5. Committee for Medicinal Products for Human Use. Guideline on the Investigation of Bioequivalence. European Medicines Agency. 2008. (CPMP/EWP/QWP/1401/98 Rev.1)

6. Siya D. Sinai Kunde, Shilpa Bhilegaonkar, Ajeet M. Godbole, Pankaj Gajre. Biopharmaceutical Classification System: A Brief Account. Ijrm.Human.2015;1(1): 20-46.
7. Wagh M. P and Patel J. S. Biopharmaceutical Classification System: Scientific Basis for Bio waiver Extensions. IJPPS. 2010;2(1):12-19.
8. Chavda HV, Patel CN, and Anand IS. Biopharmaceutics classification system. Sys Rev Pharm. 2010;1(1):62-69.
9. Dokoumetzidis A, Valsami G, Macheras P. Modelling and Simulation in Drug Absorption Processes. Xenobiotica. 2007;37(10–11):1052–1065
10. Verbeeck RK, Junginger HE, Midha KK, Shah VP, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms based on Biopharmaceutics Classification System (BCS) literature data: Chloroquine phosphate, chloroquine sulfate, and chloroquine hydrochloride. J Pharm Pharm Sci.2005;94:1389-1395.
11. Nagesh XB, Murti V. BCS Class IV Drugs: Develop or Discard? AAPS annual meeting and Exposition. San Diego Convention Centres, San Diego, CA. 2007; 11-15;
12. Bala I, Bhardwaj V, Hariharan S, Sitterberg J, Bakowsky U, Ravi Kumar MN. Design of biodegradable nanoparticles: A novel approach to encapsulating poorly soluble phytochemical ellagic acid. Nanotechnology.2005;16:2819-2822.
13. Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying Drug Delivery Systems (SEDDS) of Coenzyme Q10: Formulation development and bioavailability assessment. Int J Pharm.2001;212:233-246.
14. Sharma P, Varma MV, Chawla HP, Panchagnula R. In situ and in vivo efficacy of peroral absorption enhancers in rats and correlation to in vitro mechanistic studies. II Farmaco 2005;60:874-883

15. Sumit Kumar, Deepak Bhargava, Arti Thakkar, Saahil Arora. Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review. Crit Rev Ther Drug Carrier Syst. 2013;30(3):217-256.
16. Brahmankar, D.M. and Jaiswal, S.B. Biopharmaceutics and Pharmacokinetics. Vallabh Prakashan, 1 st Edn. 1995:347-352.
17. Mohd Yasir, Mohd Asif, Ashwani Kumar, Abhinav Aggarval. Biopharmaceutical Classification System. Int.J. PharmTech Res.2010;2(3):1681-1690.
18. V. Ramesh, S. Meenakshi, N. Jyothirmayee, M. Bullebbai, SK. Noorjahan, G. Rajeswari, G. Nagesh Babu and D. Madhavi. Enhancement of Solubility, Dissolution rate and Bioavailability of BCS Class II Drugs. International Journal of Pharma And Chemical Research. 2016;2(2):80-95.
19.Devane J. Oral drug delivery technology: Addressing the solubility/permeability paradigm. Pharm Technol. 1998;22:68-80.
20.Sruti Sunder and Reshmi Nair. Methods of nanonization of drugs for enhancing their dissolution. Euro. J. Adv. Engg. Tech. 2016;3(8):101-110
21.M. Sunitha Reddy, Yama Narendra, and S.Md. Fazal-Ul-Haq. Solubility Enhancement of Poorly Soluble Drug Ketoconazole by Self-Emulsifying Drug Delivery System. Int J Pharm Biol Sci. 2018;8(1):111-127
22. Kushal Shah, Sheetal Borhade, Vaishali Londhe. Utilization of Co-Crystallization For Solubility Enhancement of A Poorly Soluble Antiretroviral Drug – Ritonavir. Int J Pharm Pharm Sci. 2014;6(2):556-558
23. Amit kumarnayak and Prachi Prava Panigrahi. Solubility Enhancement of Etoricoxib by Cosolvency approach. ISRN Physical Chemistry.2012;1-5
24. Neelam seedher and Mamta kanojia. Co solvent solubilization of poorly soluble antidiabetic drugs. Pharmaceutical Development and Technology. 2009;14(2):185-192.
25. Ketan T. Savjani, Anuradha K. Gajjar, Jignasa K. Savjani. Drug Solubility: Importance and Enhancement Techniques. International Scholarly Research Notices. 2012:10 [https://doi.org/10.5402/2012/195727]
26. Mohammed Jafar ,Dehghan Mhg, Adil Shareef; Enhancement of Dissolution and Antiinflammatory Effect of Meloxicam Using Solid Dispersions. International Journal of Applied Pharmaceutics.2010; 2(1):22-27.
27. Abhisekh Das, Amit Kumar Nayak, Biswaranjan mohanty, and Satyabrata Panda. Solubility And Dissolution Enhancement of Etoricoxib By Solid Dispersion Technique Using Sugar Carriers; International Scholarly Research Network. 2011;8
28. K. P. R. Chowdary, D. Udaya Chandra, V. Parimala and M. Indira. A Factorial Study on Formulation Development of Ibuprofen Tablets Employing Starch 1500 and P PVP K 30. International Journal of Pharmaceutical Sciences and Research. 2012; 3(1):189-193.
29. D.B. Deshmukh, P.D. Gaikwad, V.H. Bankar, S.P. Pawar. Dissolution Enhancement of Poorly Water Soluble Diacerein By Solid Dispersion Technique. Journal of Pharmaceutical Sciences and Research. 2010;2(11):734-739.
30. R.S.Prasad, Sarath K.Yandrapu ,R Manavalan. Preparation and Characterization of Itraconazole Solid Dispersions For Improved Oral Bioavailability. International Journal of Chemtech Research Coden(Usa). 2010;2(1):133-142.
31. Masataka Saito, Takashi Ugajin, Yasuo Nozawa,Yasuyuki Sadzuka, Atsuo Miyagishima, Takashi Sonobe. Preparation and dissolution characteristics of griseofulvin solid dispersions with saccharides. International Journal of Pharmaceutics. 2002;249(1):71-79

32. Samia M.Omara,Fares Ibrahim, Aliaa Ismail. Formulation and evaluation of cyclodextrin-based nanosponges of griseofulvin as pediatric oral liquid dosage form for enhancing bioavailability and masking bitter taste. Saudi Pharmaceutical Journal. 2020;28(3):349-361
33. Renu Kalyanwat, Stuti Gupta, Rajendra Kr Songara, Dolly Jain and Sushma Patel. Study of Enhancement of Dissolution Rate of Carbamazepine By Solid Dispersion; International Journal of Comprehensive Pharmacy; 2011; 5(09):1-4
34. M.R.Shivalingam, T.Jyothibasu, Y.V.Kishore Reddy, Apparao.B, V.Tejaswi, D.Nagaanusha; Formulation and Evaluation of Solid Dispersions of Glipizide for Dissolution Rate Enhancement. International Journal of Pharma Research and Development. 2011;3(23):231-239
35. Venkateskumar Krishnamoorthya, Arunkumar Nagalingama, Verma Priya Ranjan Prasad, Siva Parameshwarana, Neema Georgea and Punitha Kaliyan. Characterization of Olanzapine-Solid Dispersions. Iranian Journal of Pharmaceutical Research 2011;10 (1):13-24.
36. Gopal Venkatesh Shavi, Averineni Ranjith Kumar, Yogendra Nayak Usha, Karthik Armugam, Om Prakash Ranjan, Kishore Ginjupalli, Sureshwar Pandey, Nayababhirama Udupa; Enhanced Dissolution and Bioavailability of Gliclazide Using Solid Dispersion Techniques. International Journal of Drug Delivery. 2010;2:49-57.
37. K R Bobe, C R Subrahmanya, Sarasija Suresh, D T Gaikwad, M D Patil, T S Khade, B Gavitre, V S Kulkarni And U T Gaikwad. Formulation and Evaluation of Solid Dispersion of Atorvatstatin with Various Carriers. International Journal of Comprehensive Pharmacy Pharmacie Globale. 2011;1(02):1-6.
38. V. Ramesh, Rukesh Kumar Jat and K.P R Chowdary. Formulation of Telmisartan tablets employing solid dispersions in MCC PH102 and Poloxamer188 as per 2^2 factorial design. World Journal of Pharmaceutical Research. 2015;4(12):1397-1405.
39. Lalit Jejurkar and K. K. Tapar. Preparation and Characterization of Mesalamine Solid Dispersions by Kneading Method. International Journal of Pharmaceutical Sciences and Research. 2011;2(10): 2623-2628.
40. Jia Liu, Feng Cao, Chan Zhang, Qineng Ping. Use of Polymer Combinations in the Preparation of Solid Dispersions of a thermally unstable drug by hot melt extrusion. Acta Pharmaceutica Sinica B. 2013;3(4):263-272
41. Marvania Akshay, and Deshpande Ashwini. Griseofulvin: BCS classification and solubility enhancement techniques. Int. J. Res. Dev. Pharm. L. Sci. 2012;1(3):112-121.
42. Sumit Kumar, Deepak Bhargava, Arti Thakkar, Saahil Arora. Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review. Crit Rev Ther Drug Carrier Syst. 2013;30(3):217-256.
43. Wu C-Y, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a Biopharmaceutics drug disposition classification system. Pharm Res. 2005;22(1):11-23.
44. Leslie Z Benet , Gordon L Amidon, Dirk M Barends, Hans Lennernäs, James E Polli, Vinod P Shah, Salomon A Stavchansky, Lawrence X Yu. The use of BDDCS in classifying the permeability of marketed drugs. Pharm Res. 2008;25(3):483-488.
45. Leslie Z. Benet. The role of BCS (Biopharmaceutics classification system) and BDDCS (Biopharmaceutics drug disposition classification system) in drug development. J.Pharm.Sci. 2013;102(1):34-42.
46. Akash Khandelwal, Praveen M. Bahadduri, Cheng Chang, James E. Polli, Peter W. Swaan, and Sean Ekins. Computational Model to assign Biopharmaceutics Drug disposition classification from Molecular Structure. Pharmaceutical Research. 2007; 24(12):2249-2262.

Table.1 BCS classification system[6-8]

Class	Solubility	Permeability	P_{app}*(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

Papp- apparent permeability and Q*- Dose/solubility

Table.2 Drug properties influencing absorption[17,18]

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.

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

Table.4 Techniques employed for BCS II drugs[26-39]

Drug Name (Category)	Polymers/Co-formers	Method Employed	Result	Reference
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,	Solid dispersion method	Increased solubility, dissolution and bioavailability	38

	Polaxomer 188			
Mesalamine (Antiulcerative)	SLS, Urea	Kneading method	Improved saturation solubility and dissolution rate	39

NSAID-Nonsteroidal anti-inflammatory agent, PVP–Polyvinylpyrrolidone, PEG-Polyethylene glycol, HPMC-Hydroxypropyl methylcellulose

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