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Biopharmaceutical Classification System: A Brief Account

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ABSTRACT

The Biopharmaceutical Classification System (BCS) was introduced to reduce the need for *in vivo* bioequivalence studies, utilization of *in vitro* dissolution tests as a surrogate for *in vivo* bioequivalence studies. Biopharmaceutical classification system is a method for classifying drug substances based on their solubility ratio, dissolution and intestinal permeability. It allows predicting the *in vivo* pharmacokinetic performance of drug products. The principles of the BCS classification system can be applied to NDA and ANDA approvals as well as to scale up, and post approval changes in drug manufacturing. Therefore, can save significant amount of product development time of pharmaceutical companies and reduces its costs. 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. Knowledge of BCS helps to the formulation scientist to develop a suitable dosage forms based on mechanistic rather than empirical approaches.

INTRODUCTION

The Biopharmaceutical classification system (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [1]. The BCS is a useful tool for decision making in the discovery and early development of new drug.

It allows for the prediction of *in vivo* pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form [2]. Biopharmaceutical Classification System (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process [3]. The Biopharmaceutical Classification System (BCS) is a system to differentiate the drugs on the basis of their solubility and permeability. It is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration.

BCS is based on scientific framework describing three rate limiting steps in oral absorption.

The three necessary steps for a drug to be absorbed are:
(1) Release of drug from dosage forms;
(2) Maintenance of dissolved state through Gastro-intestinal (G.I) tract;
(3) Permeation through G.I. membrane into hepatic circulation.

The solubility classification is based on a United States Pharmacopoeia (USP) aperture 2. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important, since 85% of the most sold drugs in the USA and Europe are orally administered [4].

Until now, application of BCS has been partially hindered by the lack of a freely available and accurate database summarising solubility and permeability characteristics of drug substances. Thus the knowledge of BCS help the formulation scientist to develop a dosage form based on mechanistic rather than empirical approaches (FDA Guidelines, 2000) [5].

Concept behind BCS

The *in-vivo* performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. The release rate or solubility of the drug substance will not be a parameter if the absorption of the drug is permeation rate limited and in such cases the *in vitro* dissolution study can be used to demonstrate the bioavailability (BA) or bioequivalence (BE) of the drug product through *in vitro* - *in vivo* correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed *in-vivo* study will be required in such a case, to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. Such a drug substance is a good candidate for controlled delivery provided they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development. Also if a drug itself is having low solubility and a slow dissolution rate, the release will automatically get slower and the dosage form need not have an in-built release retardation mechanism, rather the absorption will now be governed by the gastric emptying rate. Therefore, the dosage form must be able to restrain within the absorption window for a sufficient time so that absorption can take place. In such case, a hydro-dynamically balanced (floating) system or a mucoadhesive dosage form will serve the purpose. Hence the BCS can work as guiding tool for the development of various oral drug delivery technologies [6].

Purpose of the BCS Guidance [1]

1. Expands the regulatory application of the BCS and recommends methods for classifying drugs.

2. Explains when a waiver for *in vivo* bioavailability and bioequivalence studies may be requested based on the approach of BCS.

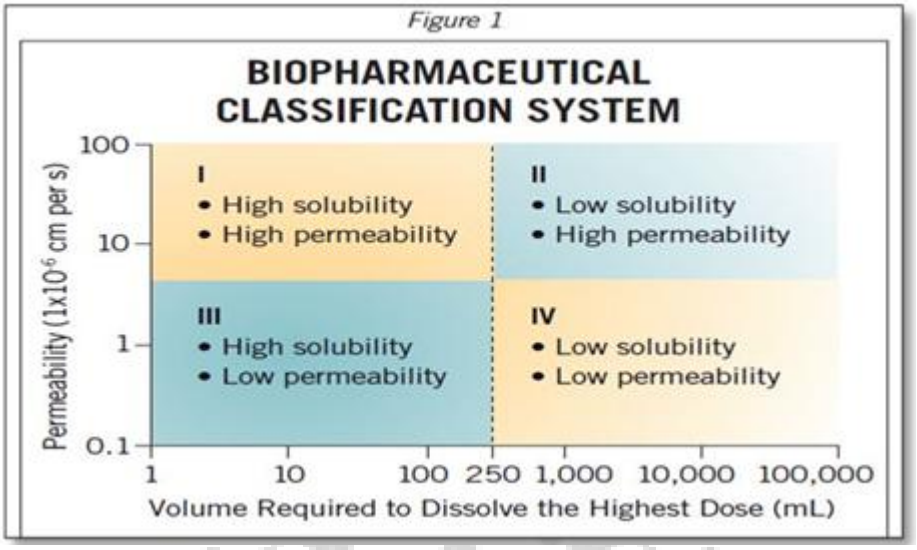
Objective of BCS [2]

1. To improve the efficiency of the drug development and review process by recommending a strategy for identifying expendable clinical bioequivalence test.

2. To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on *in vitro* dissolution tests.

3. To recommend methods for classification according to dosage form dissolution along with the solubility–permeability characteristics of the drug product.

Classes of Biopharmaceutical Classification System [1][2][4][8]



Class I - High Permeability, High Solubility: Those compounds are well absorbed and their absorption rate is usually higher than excretion. The drugs of this class exhibit high absorption number and high dissolution number. The rate-limiting step is drug dissolution, and if dissolution is very rapid, then the gastric-emptying rate becomes the rate-determining step. They dissolve rapidly when presented in immediate release form, and are also transported across the gut wall.

Class II – High Permeability, Low Solubility: These drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number. These drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. *In vitro- in vivo* correlation (IVIVC) is usually expected for class II drugs.

Class III - Low Permeability, High Solubility: The absorption is limited by the permeation rate but the drug is solvated very fast. Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These drugs exhibit a high variation in the rate and extent

of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors.

Class IV - Low Permeability, Low Solubility: Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected. The drugs of this class are problematic for effective oral administration. Fortunately, extreme examples of Class IV compounds are the exception rather than the rule, and these are rarely developed and marketed.

Extension to BCS (BCS Containing Six Classes): Bergstrom devised a modified Biopharmaceutical Classification System, in which they categorized the drugs into six classes based on the solubility and permeability. The solubility was classified as "high" or "low" and the permeability was allotted as "low", "intermediate," or "high". This new classification was developed based on the calculated surface area descriptors on the one hand and solubility and permeability on the other. Surface areas related to the non-polar part of the molecule resulted in good predictions of permeability. It was tentatively concluded that these models would be useful for early indication with regard to the absorption profiles of the compound during the early stages of drug discovery so that the necessary modifications can be made to optimize the pharmacokinetic parameters [6].

Examples of Drugs belonging to different Classes of BCS [1][2][6]

Class I: Chloroquine, Diltiazem, Metoprolol, Paracetamol, Propranolol, Theophylline
Class II: Carbamezapine, Danazol, Glibenclamide, Ketoconazole, Nifedipine, Phenytoin
Class III: Acyclovir, Atenolol, Captopril, Cimetidine, Metformin, Ranitidine
Class IV: Cyclosporin A, Furosemide, Ritonavir, Saquinavir, Taxol, Ellagic acid

Parameters of BCS

The drugs are classified in BCS on the basis of following parameters:

1. Solubility
2. Permeability
3. Dissolution

The class boundaries for the parameters are:

Solubility class boundaries- It is based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

Permeability class boundaries- It is based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of predicting drug absorption in humans can be used (such as *in-vitro* culture methods). A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90 % or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose.

Dissolution class boundaries- An immediate release product is considered rapidly dissolving when no less than 85 % of the labelled amount of the drug substance dissolves within 15 minutes using USP Dissolution Apparatus - I at 100 RPM or Apparatus - II at 50 RPM in a volume of 900 ml or less in the following media: 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid [5].

Drug Properties that determine BCS classification [7]

Drug property influencing absorption	Corresponding dimensionless parameter	Significance
Solubility: a drug with high solubility is the one whose largest dosage strength is soluble in 250 ml or less water over a pH range of 1-7.5.	Dose number: it is the mass of drug divided by an uptake volume of 250 ml and drugs solubility.	Ideally, dose ratio should be below 1 if full dissolution is to be possible in principle. Higher doses will raise the ratio and absorption less likely.
Dissolution rate: a drug product with rapid dissolution is the one when ≥ 85 % of the labelled amount of drug substance dissolves within 30 minutes using USP apparatus I and II in a volume of ≤ 900 ml buffer solutions.	Dissolution number: it is a ratio of mean residence time to mean dissolution time.	Ideally, dissolution number should exceed 1. In the case of solid dosage forms, a combination of inadequate solubility or diffusivity, or excessive particle size or density can increase the time needed for full dissolution and reduce this ratio.
Permeability: a drug with high permeability is the one having extent of absorption greater than 90 % of the administered dose given that the drug is stable in the gastrointestinal environment.	Absorption number: it is the ratio of the mean residence time of the drug in the GIT to the absorption time.	Ideally, absorption number should exceed 1. Longer absorption times resulting from lower permeability will reduce this ratio.

Determination of Solubility

Solubility is the amount of a substance that has passed into solution when equilibrium is attained between the solution and excess (i.e., undissolved) substance at a given temperature and pressure.

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. A drug substance is considered

highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous medium over the pH range of 1- 7.5 (per FDA guidelines) or 1.2–6.8 (per WHO guidelines). The pH-solubility profile of the test drug substance should be determined at 37 ± 1°C. A sufficient number of samples should be evaluated to accurately define the pH–solubility profile. A minimum of three replicate solubility determinations in each pH condition should be carried out. Depending on study variability, additional replicates may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions may be used. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous medium over the pH range of 1– 7.5. The volume estimate of 250 ml is derived from the typical volume of water consumed during the oral administration of a dosage form. This boundary value is a reflection of the minimum fluid volume anticipated in the stomach at the time of drug administration. A sufficient number of pH conditions should be evaluated to accurately define the pH–solubility profile. The number of pH conditions for a solubility determination depends upon the ionization characteristics of the test drug substance. A minimum of three replicate determinations of solubility at each pH condition should be carried out. Standard buffer solutions described in pharmacopoeias are considered appropriate for use in solubility studies. If these are not suitable for physical or chemical reasons, other buffer solutions can also be used provided the solution pH is verified. The concentration of drug substance in selected buffers or pH conditions should be determined using a validated stability-indicating assay that can determine the drug substance in the presence of its degradation products. If degradation of drug is observed as a function of buffer composition or pH, it should be taken into consideration. Solubility can be measured as either a kinetic or a thermodynamic value. Kinetic solubility measurements start from dissolved compound and represent the maximum (kinetic) solubility of the fastest precipitating species of a compound. Kinetic solubility values are strongly time-dependent. Due to the degree of supersaturation that may occur, values are likely to over-predict the thermodynamic solubility and are not expected to be reproducible between different kinetic methods, such as a

turbidimetric – nephelometric method and UV absorption. In thermodynamics, solubility can predict drug properties during lead optimization. These methods include a scaled-down shake-flask method and a solvent evaporation method [2][4][6].

Determination of Permeability

The permeability is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane. To understand the nature of gastrointestinal permeability limitations, there are methods and techniques to both screen and grade these characteristics. These methods range from a simple oil/water (O/W) partition coefficient to absolute bioavailability studies. A drug substance is considered highly permeable when the extent of absorption in humans is 90 % or more of an administered dose, based on mass-balance or compared with an intravenous reference dose. The methods that are routinely used for the determination of permeability include:

• Human studies: Mass balance pharmacokinetic studies Absolute bioavailability studies, intestinal perfusion method

• Intestinal permeability methods: *In vivo* intestinal perfusions studies in humans *in vivo* or *in situ* intestinal perfusion studies in animals *in vitro* permeation experiments with excised human or animal intestinal tissue.

• *In vitro* permeation experiments across epithelial cell monolayer's (e.g., Caco-2 cells or TC-7 cells): In mass-balance studies, unlabelled, stable isotopes or radiolabel drug substances are used to determine the extent of drug absorption. However, this method gives highly variable estimates, and hence other methods are carried out. In absolute bioavailability studies, oral bioavailability is determined and compared with the intravenous bioavailability as a reference. Intestinal perfusion models and *in vitro* methods are recommended for passively transported drugs. The observed low permeability of some drug substances in humans could be attributed to the efflux of drug by various membrane transporters like P-glycoprotein. This leads to misinterpretation of drug substance permeability. An interesting alternative to intestinal tissue models is the use of well-established *in vitro* systems based on the human adenocarcinoma cell line Caco-2. These cells serve as a model of small intestinal tissue. The differentiated cells

exhibit the microvilli typical of the small intestinal mucosa and the integral membrane proteins of the brush-border enzyme. In addition, they form the fluid filled domes typical of a permeable epithelium. Recent investigations of Caco-2 cell lines have indicated their ability to transport ions, sugars, and peptides. The directed transport of bile acids and vitamin B-12 across Caco-2 cell lines has also been observed. These properties have established the Caco-2 cell line as a reliable *in vitro* model of the small intestine [2][4].

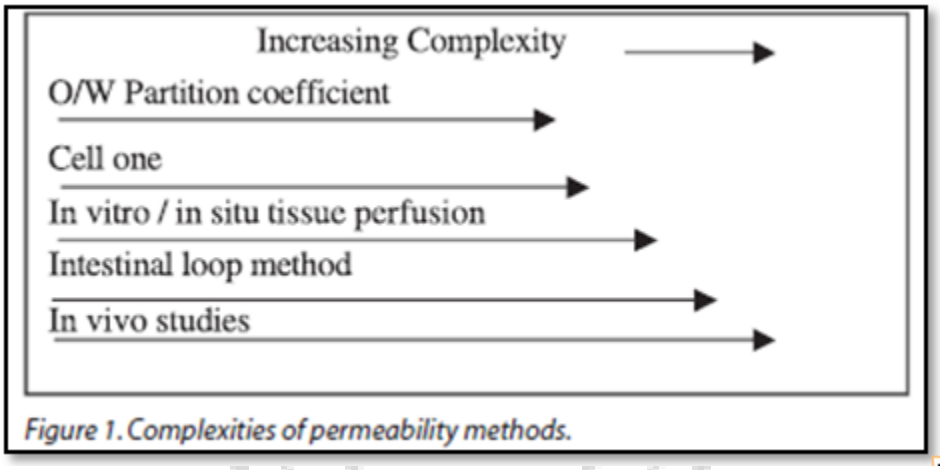


Figure 1. Complexities of permeability methods.

Determination of Dissolution

Formulation composition and the manufacturing process generally influence *in vitro* drug dissolution. The BCS classifies a drug product as rapidly dissolving when no less than 85 % of the labelled amount of the drug substance dissolves in 30 min using the following:

• USP Apparatus 1 (basket) at 100 RPM or USP Apparatus 2 (paddle) at 50 RPM.

• Dissolution medium volume of 900 ml or less in each of the following:

1. 0.1 N HCI or simulated gastric fluid (SGF) USP without enzymes

2. A pH 4.5 buffer

3. A pH 6.8 buffer or simulated intestinal fluid (SIF) USP without enzymes.

$$f_2 = 50 \cdot \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

The similarity factor (*f*2) for test versus reference profile comparisons should be greater than 50 (i.e., *f*2 value between 50 and 100 suggests the two dissolution profiles are similar) where *Rt* and *Tt* are the cumulative percentage dissolved at time point *t* for reference and test products, respectively, and *n* is the number of pool points. According to the BCS guidance, the test and reference dissolution profiles are considered similar if both products have at least 85 % dissolution in 15 min or if comparison of profiles by the *f*2 test results in an *f*2 value of at least 50. To allow for the use of mean data, the coefficient of variation should not be more than 20% at earlier time points (e.g., 10 min) and should not be more than 10% at other times. Dissolution performance is influenced by both the physicochemical properties of the substance and the prevailing physiological conditions in the GI tract, which varies between the fasted- and fed-states as well as within and among subjects. There was consensus that the *f*2 test is not necessary when the two products each provide at least 85% dissolution in 30 min. A profile comparison test (e.g., *f*2 or a single time point comparison) would be necessary when at least one product has 85% dissolution between 30 and 60 min. The number of time points sampled need not be extraordinary; sampling can be as infrequent as every 30 min (i.e., two samples over 60 min). The *f*2 acceptance criterion ($f2 \geq 50$) can be lowered with justification that considers underlying biopharmaceutical characteristics and risk based factors (e.g., dissolution results from the most relevant pH) [2][17].

Table 2. Physicochemical and Physiological Parameters Important to Drug Dissolution in the Gastrointestinal Tract

Factor	Physicochemical Properties	Physiological Properties
Surface area of drug	Particle size, wettability	Surfactants in gastric juice and bile
Diffusivity of drugs	Molecular size	Viscosity of luminal contents
Boundary layer thickness	Concentration of the drug	Motility patterns and flow rate
Solubility	Hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile and food composition
Amount of drug already dissolved	Hydrophilic, lipophilic nature of the drug	Permeability
Volume of solvent available	Depends upon type of body fluid	Secretion, coadministered fluids

BCS Biowaiver

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through *in vivo* equivalence testing. Biowaiver means to obtain waive off for carrying out expensive and time-consuming BA and BE studies.

A biowaiver has been regarded as an official approval of the waiver for conducting a bioequivalence study in the context of an application for drug approval process. The BCS-based biowaivers apply during pre- (IND/ NDA and ANDA) and post approval phases.

BCS-based biowaivers are applicable for immediate-release solid oral dosage formulations containing one or more of the API(s) mentioned above if the required data ensure the similarity of the submitted pharmaceutical product and the appropriate pharmaceutically equivalent comparator product. BCS-based biowaiver has become an important and cost-saving tool in approval of generic drugs [2][9][10][12].

Criteria for BCS based biowaiver

Biowaiver are based on the Biopharmaceutics (BCS) classification of the active ingredient. Currently BCS class I and some class III compounds are eligible for biowaivers.

• The drug substance should be highly soluble and highly permeable.

• An IR drug product should be rapidly dissolving.

• The drug should not be a narrow therapeutic index drug.

• Excipients used in the dosage form should have been used previously in FDA approved IR solid dosage forms.

• For waivers of an *in vivo* relative bioavailability study, dissolution should be greater than 85% in 30 min in the three recommended dissolution media (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).

• For waivers of *in vivo* bioequivalence, test and reference products should exhibit similar dissolution profiles under the dissolution test conditions defined for rapidly dissolving products. Two dissolution profiles may be considered similar when compared using the f2 metric (f2 > 50) .When both the test and the reference products dissolve 85 % or more of the label amount in < 15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary [4].

Exceptions

BCS-based biowaivers are not applicable for the following:

1) Narrow Therapeutic index: This guidance defines narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labelling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, applicant should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

2) Products Designed to be Absorbed in the Oral Cavity: A request for a waiver of *in-vivo* BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets) [11].

Request for Biowaivers [2]

Data Supporting Rapid and Similar Dissolution

- A brief description of the IR products used for dissolution testing.
- Dissolution data obtained with 12 individual units of the test and reference products at each specified testing interval for each individual dosage unit. A graphic representation of the mean dissolution profiles for the test and reference products in the three media.
- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f_2 metric.

Data supporting High Permeability

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data.

- For direct permeability methods, information supporting method suitability with a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations, description of the analytical method, method to calculate extent of absorption or permeability, and information on efflux potential (if appropriate).
- A list of selected model drugs along with data on the extent of absorption in humans used to establish method suitability, permeability values and class for each model drug, and a plot of the extent of absorption as a function of permeability with identification of the low/high permeability class boundary and selected internal standard.
- Permeability data on the test drug substance, the internal standards, stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

Data supporting High Solubility

- Description of test methods (analytical method, buffer composition).
- Information on chemical structure, molecular weight, nature of drug substance, dissociation constants.
- Test results summarized in a table with solution pH, drug solubility, volume to dissolve highest dose strength.
- Graphical representation of mean pH-solubility profile.

Biowaiver Extension Potential

Biowaiver extension potential for solubility and permeability class boundaries

As the solubility class boundary requires that the highest strength of drug substance is soluble in 250 ml or less volume in aqueous media over the pH range of 1 - 7.5 as per USFDA BCS guidance. The pH range of 1 - 7.5 may be stringent requirement. Under fasting condition, the pH range in the GI tract varies from 1.4 - 2.1 in the stomach, 4.9 - 6.4 in the duodenum, 4.4 -6.6 in the jejunum, and 6.5 - 7.4 in the ileum. In addition, it generally takes approximately 85 min for a drug to reach the ileum. By the time the drug reaches the ileum, the dissolution of drug product is likely to be complete if it meets the rapid dissolution criterion, i.e., not less than 85% dissolved within 30 min. The researchers redefined the pH range for BCS solubility class boundary from 1.0 - 7.5 to 1.0 - 6.8 in alignment with dissolution pH ranges, which are pH 1, 4, 5, and 6.8

buffers. The volume 250 ml seems a conservative estimate of what actually is available *in vivo* for solubilisation and dissolution. The physiological volume of small intestine varies from 50 - 1100 ml, with an average of 500 ml under fasted conditions. When administered with a glass of water, the drug is immersed in approximately 250 ml of liquid in the stomach. If the drug is not in solution in the stomach, gastric emptying would then expose it to small intestinal fluid, and the solid drug would dissolve under the effect of additional small intestine fluid. Because of the large variability of small intestinal volume an appropriate definition of volume for solubility class boundary is difficult to set. Another factor influencing *in vivo* solubility is bile salt micelle solubilisation. The intestine is the absorbing region for most of the drug. Many acidic drugs, which have low solubility at low pH, are well absorbed. For example, most nonsteroidal anti-inflammatory drugs are poorly soluble in stomach but are highly soluble in distal intestine and their absolute human BA are 90% or higher, thus exhibiting behaviour similar to those of BCS Class I drugs. The criterion of 90% for the fraction of dose absorbed can be considered conservative because the experimentally determined fraction of dose absorbed is seen to be less than 90 % for many drugs that are generally considered completely or well absorbed.

Therefore, it has been suggested, that there is a potential of redefining BCS permeability class boundary such that a class boundary of 85% might be more appropriate in defining high permeability. Revision of interchangeably and specific BCS guideline by WHO implemented the pH range of from 1 - 7.5 to 1.2 - 6.8 for solubility class boundary and permeability class boundary of 85% absorption from 90%. The implementation is sensible only in regulatory environments in which pharmaceutical products and respective manufacturing and control processes are defined.

Biowaiver extension potential for class II drugs

Some Class II drugs are consistently and completely absorbed after oral administration. These are typically poorly soluble weak acids with pKa values of $\leq$ 4.5 and intrinsic solubility (solubility of the unionized form) is of $\geq$ 0.01 mg/ml. At pH values typical of the fasted state in the jejunum (about pH 6.5), these drugs will have solubility of > 1 mg/ml, resulting in fast and reliable dissolution of the drug. Currently, these drugs are classified as Class II drugs because they are poorly soluble at gastric pH, in which pH is much less than pKa. Because the small-

intestinal transit time is more reliable, and in the fasted state, longer than the gastric residence time (3 hr), drugs with these physical characteristics will have sufficient time to be dissolved. As long as these drugs meet the permeability criterion, biowaivers for products that dissolve rapidly at pH values typical of the small intestine could be considered. Therefore, it has been suggested that it is possible to have a biowaiver extension potential to BCS Class II drugs.

Biowaiver extension potential for class III drugs

If the dissolution of Class III products is rapid under all physiological pH conditions, it can be expected that they will behave like an oral solution *in vivo*. Because the absorption of Class III drugs is essentially controlled by the gut wall permeability of the drug and not by the drug's solubility, biowaiver for rapidly dissolving products of Class III drugs also could be justified. The Class III compounds often exhibit site dependent absorption properties, and thus the transit time through the specific region of upper intestine may be critical for BE.

Biowaiver for modified release products

Following administration in the fasted (to abstain from food) condition, a modified release product will have left the stomach within about 1 hr and can be expected to arrive in the colon about 3 hr later. If we have to extend the BCS model to oral MR products, we need to recognize the role of intestinal metabolism in the absorption process; a simple measure of permeability is not adequate. It has been found that the drug absorption was diminished in distal intestine and in some cases, so much so that drug as an IR product was terminated following the regional absorption study. It has also been shown that absorption will not always be reduced following delivery to the ileum and colon. In some of the studies it has been shown that BA of drug delivered to the distal small bowel was higher than the reference (solution) formulations. If we are considering a simple mechanistic model of absorption in which permeability and concentration are the key parameter, then this will only be correct if the metabolism rate is constant over the region of intestine to which the drug is delivered. The role of gut wall metabolism and, particularly cytochrome P450 3A4 iso enzyme activity, has recently become the focus of attention. It has been recently shown that 3A4 activity in man diminishes significantly from the jejunum to ileum. So, if we compare the ratio of parent drug to metabolite following

delivery to the different intestinal regions, then the influence of gut wall metabolism can be clearly demonstrated [9].

Applications of BCS

BCS is widely used in design and development of innovation drugs, new dosage forms (Permeability amplifiers), in clinical pharmacology (drug-drug, drug-food interaction) and also by regulation agencies of several countries as the scientific approach, for testing of waivers on bioavailability.

Given below the application of BCS in different fields:

1. Application of BCS in Oral Drug Delivery

Drug Delivery Technology: Once the solubility and permeability characteristics of the drug are known it becomes an easy task for the research scientist to decide upon which drug delivery technology to follow or develop.

For Class I drugs: To achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile is the main fight. The Class I drugs are not those in which either solubility or permeability is limiting within the target regions of the GI tract. The drug release in such cases can be modulated using controlled release technology. Controlled release technologies for Class I drugs includes number of products such as Macrocap, Micropump, MODAS (Multiporous oral drug absorption system), SCOT (Single composition osmotic tablet system), Microsphere, CONSURF (constant surface area drug delivery shuttle), Diamatrix (Diffusion controlled matrix system), DPHS (Delayed pulsatile hydrogel system), DUREDAS (Dual release drug absorption system), GMHS (Granulated modulating hydrogel system), IPDAS (Intestinal protective drug absorption system), Multipor, Pharmazone (Microparticle Drug Delivery Technology), PPDS (Pelletized pulsatile delivery system), BEODAS (Bioerodible enhanced oral drug absorption system), PRODAS (Programmable oral drug absorption system), SODAS (Spheroidal oral drug absorption system), SMHS (Solubility modulating hydrogel system) and SPDS (Stabilized pellet delivery system).

For class II drugs: This class relates to the cases in which solubility or dissolution rate is limiting, and thus significantly affects absorption and BA. The technologies under this class include the approaches such as classical micronization, stabilization of high-energy states (including lyophilized fastmelt systems), use of surfactants, emulsion or microemulsion systems, solid dispersion and use of complexing agent such as cyclodextrins. The technologies under this class include: SoftGel (soft gelatin capsule formulation), Zer-Os tablet technology (osmotic system), Triglas and nanosized carriers such as nanoemulsion, nanosuspension and nanocrystals are treated as hopeful means of increasing solubility and BA of poorly water-soluble active ingredients.

For class III drugs: Manipulating the site or rate of exposure or perhaps by incorporating functional agents into the dosage form to modify the metabolic activity of the enzyme systems are included in Class III technologies. The technologies under this class include Oral vaccine system, Gastric retention system, High-Frequency Capsule and Telemetric Capsule, Proteins and peptide drug delivery system.

For Class IV drugs: The manufacturers have the challenge for the development of the drug delivery system with the parenteral route of administration by employing the best excipients as a solubility enhancer [9].

Drug discovery and early development: BA and BE play a central role in pharmaceutical product development and BE studies are presently being conducted for New Drug Applications (NDAs) of new compounds, in supplementary NDAs for new medical indications and product line extensions, in Abbreviated New Drug Applications of generic products and in applications for scale-up and post approval changes. One of the starting problems with applying the BCS criteria to new drug substances is that, early in preformulation / formulation, the dose is not yet accurately known. Therefore, at this point, the Dose to Solubility ratio (D: S) can only be expressed as a likely range. Compounds with more than 100 mg/ml aqueous solubility seldom exhibit dissolution rate-limited absorption. In concern with the solubility of the drug, it may be useful to consider the physicochemical properties of the drug when deciding which media to use for the solubility determinations. For example, measuring solubility at all pH values recommended by the BCS is unnecessary for neutral compounds in early development. Later,

when formulations are compared, dissolution data for the drug product over the entire GI pH range will be useful in establishing the robustness of release from the formulation under GI conditions. Lipophilic drugs may be very poorly soluble in water and in simple buffers, but in the GI fluids the bile to a significant extent can often solubilize them. Another approach is to use aspirates from human volunteers, although volumes aspirated typically are small and the choice of experiments and apparatus therefore is also limited. Next issue is the use of 250 ml as the volume in which a dose must be dissolved. This amount is a conservative estimate of the volume of fluid available in the gut under fasting-state conditions and is based on the volume usually ingested along with the dosage form in a pharmacokinetic study. A suggested starting point would be to use a volume of about 300 ml for the fasted stomach, about 500 ml for the fasting small intestine, and up to 1 l for the postprandial stomach and small intestine. If permeability of the drug rather than solubility is the main problem, formulation approaches are less numerous and less reliable. Even when allowance is made for the differences in solubility and permeability requirements for oral drug product development vis-à-vis biowaiver criteria according to the BCS, further factors still must be considered for new drugs. The enzymes that can be suitable are pepsin and gastric lipases for the stomach, pancreatic enzymes for the jejunum, and bacterial enzymes for the colon. In the case of first-pass metabolism in the gut wall, it may be possible to screen for metabolites in the permeability model depending on how the model is set up [9].

Pharmacokinetic optimization in drug research: The two parameters of biopharmaceutics, solubility and permeability, are of pivotal importance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics on these two properties. BCS provides drug designer an opportunity to manipulate structure or physicochemical properties of lead candidates so as to achieve better deliverability. With the enormous number of molecules being synthesized using combinatorial and parallel synthesis, high throughput methodologies for screening solubility and permeability have gained significant interest in pharmaceutical industry. Ultimate objective of the drug discovery scientist in pharmacokinetic optimization is to tailor the molecules so that they show the features of BCS Class I without compromising on pharmacodynamics. Considerations to optimize drug delivery and pharmacokinetics right from the initial stages of drug design propelled need for high throughput pharmaceutics. In silico predictions and development of theoretical profiles for

solubility and lipophilicity provides structure-based biopharmaceutical optimization, while *in vitro* experimental models, microtitre plate assays and cell cultures, validate the predictions. And so, biopharmaceutical characterization during drug design and early development helps in early withdrawal of new chemical entities with insurmountable developmental problems associated with pharmacokinetic optimization. Thus, BCS is helpful in optimizing the new chemical entity characteristics and minimize its chances of rejection [9][14].

2. Application of BCS in New Drug Application (NDA) and Abbreviated New Drug Application (ANDA):

The principles of the BCS classification system can be applied to NDA and ANDA approvals as well as to scale-up and post approval changes in drug manufacturing. This has resulted in the following outcomes:

INDs and NDAs: BCS based biowaivers are applicable to the formulations intended to be marketed where changes in composition, components of the formulation, or method of preparation occurs to the clinical trial formulation, as long as the formulation has a rapid and similar *in vitro* dissolution profile. This approach is useful if the drug is highly soluble and highly permeable (BCS class I drugs) and both the pre and post change formulations are pharmaceutically equivalent.

ANDA: For a highly soluble highly permeable drug substance formulated whose dissolution is rapid as defined in section III, US FDA guidelines, an *in- vivo* bioequivalence study can be waived, provided that the reference listed drug product is also highly soluble and both the test product and the reference product have similar dissolution profile, i.e., this approach is suitable only when the test and the reference products are pharmaceutically equivalent. Where feasible the choice of dissolution apparatus (USP I or II) is should be limited to that established for the reference product.

Post-approval Changes: BCS based biowaivers can be requested for significant post approval changes, *e.g.*, level 3 changes in components and composition, to a rapidly dissolving immediate release product intended for oral use. Further the drug substance should be highly soluble and highly permeable provided that the dissolution remains rapid for pre and post

change product and both pre and post change products exhibit similar dissolution profile.

Approval of Generics: Because generics were required to meet essential safety, efficacy, and BE criteria, few were approved under these regulations till 1984. In 1984, the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Act) was passed, and established the abbreviated new drug application procedure (ANDA), permitted the FDA to approve generic products for drugs that had already been found safe and effective, and formalized the criteria for pharmaceutical equivalence and Bioequivalance. Provisions for post approval changes for BCS Class I rapid release oral dosage form has made it possible for generic pharmaceutical companies to obtain approval without necessarily conducting their bioequivalent studies.

Cost Savings: After the introduction of the biopharmaceutical classification system in 1995 a considerable increase in NDA and ANDA filing of drugs has been noticed. The total number of NDAs filed in 2010 was 86. According to the FDA, about 80% of all filed applications will eventually be approved. Recently, DiMasi noted an approval rate of approximately 90% for NDAs. It was estimated that about 25% of the total products approved were classified as highly soluble and highly permeable which could request for a biowaiver for the bioequivalence studies. Using the 25% estimated above, there is the potential to save one quarter the annual expenditures on bioequivalence studies estimated as $22 to $38 million dollars/year. Additional indirect savings can occur if bioequivalence studies are rate limiting to drug development. For example, let us suppose the results of a bioequivalence study are needed before proceeding with development of a compound with eventual peak sales of one billion dollars/year. It can be easily assumed that results of *in vitro* dissolution can be obtained 6 weeks earlier than results from an *in vivo* bioequivalence trial which translates into a potential additional $110 million dollars in sales from a 6 week earlier approval. Further, by not having to run a human bioequivalence trial, clinical resources are freed to be applied elsewhere which is an asset to the industry[13].

3. BCS as a Framework for Optimization of a New Chemical Entity

The BCS provides a clue about the pharmacokinetics of the drug (NCE), which is already synthesized or identified chemical molecule that is proved to be therapeutically active, but is still

under investigation for formulation development and final approval, which provides an opportunity to the synthetic chemist or the drug designer to manipulate in the chemical structure of the drug entity so as to optimize the physicochemical parameters of the lead molecule for desired drug delivery and targeting characteristics. The synthetic chemist and formulation scientists act together to achieve better 'deliverability' directed toward the desired pharmacokinetics and therapeutic efficiency right from the initial stages of drug design, to fulfil the propelled need for "High Throughput Pharmaceutics (HTP)". Compounds that are substrates for the biological transporters are an exception to the rule. Pharmaceutical drug discovery and delivery groups and companies are increasingly using Human Drug Absorption (HDA) Studies to better understand the biopharmaceutical properties of early drug candidates and establish Life Cycle Management (LCM) strategies for marketed drugs. The proactive adoption of HDA studies provides a significant guidance to pharmaceutical formulation scientists when planning and selecting a route of experimentation, out of a wide array of possibilities, that is, having a higher probability for successful formulation development. In addition, results from the HDA studies undertaken early in the clinical development give an indication of problem compounds and provide a reliable "route-map" for subsequent developments. If the drug is absorbed from the selective area of the intestine, an appropriate bioadhesive system may be developed to improve bioavailability [15].

4. Application of BCS for Pharmacological Screening

Pharmaceutical drug discovery and delivery groups are using Human Drug Absorption (HDA) studies for understanding the biopharmaceutical properties of early drug candidates.

HDA provides significant guidance to a pharmaceutical formulation scientist in:

- Selecting a route of experimentation.
- Clinical development.
- Improvement of Bioadhesive system if the drug is absorbed from the selective area of the intestine.

According to Lipinski et al. (1997), 'a rule of 5' is widely adopted for screening of compounds that are likely to have poor absorption profiles. According to this rule the poor absorption or permeation is more likely when:

- There are more than five H-bond donors (expressed as a sum of hydroxyl and N-H linkage).
- The molecular weight of the drug moiety is more than 500
- The log P is over %.
- There are more than 10 H-bond acceptors

Compounds that are substrate for the biological transporters are an exception to the rule.

5. BCS in Regulatory Practice

Throughout the past decade, the BCS has become an increasingly important tool in drug product regulation worldwide, by presenting a new paradigm in bioequivalence. Bioequivalence (BE) is the critical step that connects the physical drug product with the clinical properties claimed on its label, ensuring continuing quality of the innovative products and the generic products. Before the presentation of the BCS, the BE standard was solely empirical, depending on *in vivo* bioavailability (BA) studies, i.e., plasma levels, AUC, and C_{max}. By revealing the fundamental parameters dictating the *in vivo* oral drug absorption process, the BCS is able to ensure BE by mechanistic tools, rather than empirical observation; if two drug products that contain the same active pharmaceutical ingredient (API) have a similar GI concentration– time profile under all luminal conditions, than a similar rate, and extent of absorption is ensured for these products, i.e., they are bioequivalent. Thus, BE can be guaranteed based on *in vitro* dissolution tests that provide the mechanistic proof for similar bioavailability, rather than empirical *in vivo* human studies. This is the regulatory waiver of *in vivo* BE, based on the scientific and mechanistic rationale provided by the BCS. Initially, waivers of *in vivo* BE were accepted only for Scale-Up and Post Approval Changes (SUPAC), but later, the biowaiver principle was extended to the approval of new generic drug products, thus avoiding unnecessary human experiments and reducing cost and time of developing generic IR oral drug products. The solubility classification of a given drug is based on the highest dose strength in an IR product. According to the current FDA guidance, drug substance is considered highly soluble if the highest strength is soluble in 250 ml or less of aqueous media throughout the pH range of 1.2 – 6.8 (the volume of 250 ml is

derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 oz) of water. Otherwise, the drug substance is considered poorly soluble. A drug substance is considered highly permeable if the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered poorly permeable. The permeability classification is based either directly on the extent of intestinal absorption of a drug substance in humans determined by mass balance or in comparison to an intravenous reference dose, or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane. Alternatively, animal or *in vitro* models that predict human intestinal absorption, e.g., intestinal rat perfusion models or epithelial cell culture models, can be used. An IR product is characterized as rapidly dissolved if not less than 85% of the labelled drug amount is dissolved within 30 min using USP Apparatus I at 100 rpm or USP Apparatus II at 50 RPM in a volume of 900 ml or less of each of the following media: (1) acidic media, such as USP simulated gastric fluid without enzymes; (2) pH 4.5 buffer; and (3) pH 6.8 buffer or USP- simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be slow dissolving. Up to now, The FDA has implemented the BCS system to allow waiver of *in vivo* BA/BE testing of IR solid dosage forms for class I, high-solubility, high-permeability drugs. As for class III (high-solubility low-permeability) drugs, as long as the drug product does not contain agents and/or excipients that may modify intestinal membrane permeability, *in vitro* dissolution test can ensure BE. The absorption of a class III drug is likely limited by its permeability, less dependent upon its formulation, and its bioavailability may be determined by its *in vivo* permeability pattern. If the *in vitro* dissolution of a class III drug product is rapid under all physiological pH conditions, it's *in vivo* behaviour will essentially be similar to oral solution (controlled by gastric emptying), and as long as the drug product does not contain permeability modifying agents (this potential effect is largely mitigated by the large gastric dilution), *in vitro* dissolution test can ensure BE. Hence, biowaivers for BCS class III drugs are scientifically justified and have been recommended.

Future Prospect of BCS

The future application of the BCS is most likely increasingly important when the present framework gains increased recognition, which will probably be the case if the BCS borders for certain class II and III drugs are extended. The future revision of the BCS guidelines by the

regulatory agencies in communication with academic and industrial scientists is exciting and will hopefully result in an increased applicability in drug development. Finally, we emphasize the great use of the BCS as a simple tool in early drug development to determine the rate limiting step in the oral absorption process, which has facilitated the information between different experts involved in the overall drug development process. This increased awareness of a proper biopharmaceutical characterization of new drugs may in the future result in drug molecules with a sufficiently high permeability, solubility and dissolution rate, and that will automatically increase the importance of the BCS as a regulatory tool over time.

CONCLUSION

The Biopharmaceutical Classification System is not only a tool for obtaining waivers for *in vivo* bioequivalence studies but also for decision making in the discovery and early development of new drugs and formulations. The Biopharmaceutical Classification System provides a regulatory tool for replacing certain bioequivalence studies with accurate *in vitro* dissolution tests during the process of generic drug development. The data obtained through solubility and permeability in the discovery/ development can be utilized for preliminary classification of pipeline compounds.

Considering the uncertainties associated with *in vitro* dissolution tests, the BCS proposed biowaivers for rapidly dissolving drug products (i.e., a drug must be stable in the gastrointestinal tract), non-narrow therapeutic index drugs, and other application commitments should be met during drug development. As our knowledge of GI compounds becomes more sophisticated, we will be able to design *in vitro* tests that would better simulate the *in vivo* conditions of GI tract. This in turn would result in more powerful predictions *in vivo* parameters of drugs and ultimately to a significant reduction in human and animal studies required to optimize the formulation.

Poor solubility and poor permeability account for many pharmacokinetic failures and about thirty percent of drug molecules are rejected due to pharmacokinetic failures. When poor pharmaceutical properties are discovered in development, the cost of bringing a potent, but poorly absorbable molecule to the product stage by formulation can become very high. Fast and reliable *in vitro* prediction strategies are needed to filter out problematic molecules at the earliest stage of discovery. This communication will consider recent developments in physiochemical

profiles used to identify molecules with physical properties related to good oral absorption. FDA's biopharmaceutical classification system (BCS) is an attempt to rationalize the critical components related to oral absorption and utilization of these principles for selection of a suitable technology to serve the interests of the early stages of drug discovery.

Although BCS has brought a revolution in drug approval and development process, there is always scope for amendments in its principles. Efforts should be constantly done to utilize the concepts of BCS beyond the immediate release solid oral dosage forms.

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REFERENCES

1. Mohd Y. , Mohd A., Kumar A., Aggarval A.; Biopharmaceutical Classification System: An Account; International Journal of Pharm Tech Research; July-Sept 2010; Volume 2(3); pp. 1681-1690.
2. Reddy B.B. and Karunakar A.; Biopharmaceutics Classification System: A Regulatory Approach; Dissolution Technologies; Febraury 2011; pp. 31-37.
3. Chowdary K. P. R. and Pavan Kumar A., Recent Research on Formulation Development of BCS class II drugs – A Review; International Research Journal of Pharmaceutical and Applied Sciences; 25/02/2013; Volume 3(1); pp. 173-181.
4. Wagh M. P and Patel J. S.; Biopharmaceutical Classification System: Scientific Basis for Biowaiver Extensions; Volume 2(1); 2010; pp. 12-19.
5. U.S. Food and Drug Administration, 04/01/2009, Available from: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128219.htm
6. Rohilla S., Rohilla A, Marwaha R.K., Nanda A.; Biopharmaceutical Classification System: A Strategic Tool for Classifying Drug Substances; International Research journal of pharmacy; 06/07/2011; Volume 2(7); pp. 53-59.
7. Brahmankar D. M., Jaiswal S. B.; Biopharmaceutics and Pharmacokinetics A Treatise; Second Edition; Vallabh Prakashan; pp. 345-347.
8. Aulton M. E.; Aulton's Pharmaceutics: The Design and Manufacture of Medicines; Tthird edition, Churchill livingstone Elsevier; pp. 22.
9. Patel R. C., Keraliya R., Jansari J., Patel M. M.; Application of Biopharmaceutics Classification System in Formulation Development; PhTechMed; 02/09/2013; Volume 2(4); July-Aug 2013; pp. 334-340.
10. WHO Prequalification of Medicines Programme; General notes on Biopharmaceutics Classification System (BCS)- Based Biowaiver Applications; Guidance Document November 2011; pp. 1-5.
11. Saudi food and drug authority; Guidelines for Biowaiver Based on Biopharmaceutics Classification System (BCS) For Immediate-Release (IR) Solid Oral Dosage Forms; Version 1.1, 17/09/2012.
12. Rohilla S., Rohilla A., Nanda A.; Biowaivers: Criteria and Requirements; International Journal of Pharmaceutical & Biological Archives 2012; 17/07/2012; Volume 3(4); pp. 727-731.

13. Budhwaar V, Nanda A., The biopharmaceutical classification system(BCS): present status and future prospective, international research journal of pharmacy, 12/09/2012, Volume 3(9), 7-11.
14. Chavda H.V., Patel C.N., Anand I. S.; Biopharmceutical Classification System; Systemic Reviews in Pharmacy 2010; Volume 1(1), pp. 62-69.
15. Dash V., Kesari A.; Role of Biopharmaceutical Classification System In
Drug Development Program; Journal of Current Pharmaceutical Research 2011; Volume 5(1); pp. 28-31.
16. Dahan A., Miller J. M., Amidon G. L.; Prediction of Solubility and Permeability Class Membership: Provisional BCS; Classification of the World's Top Oral Drugs; 30/10/2009; Volume 11(4); December 2009; pp. 740-746.
17. Hans L., Bertil A.; The Use of Biopharmaceutical Classification of Drugs in Drug Discovery and Development: Current Status and Future Extension; Journal of Pharmacy and Pharmacology; 2005; 57; pp. 273–285.