BCS CLASSIFICATION SYSTEM: BENCHMARK FOR SOLUBILITY AND PERMEABILITY

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ABSTRACT
Solubility and permeability plays an important role in development of dosage form. Benchmark for solubility and permeability is the Biopharmaceutics Classification System (BCS) which demonstrates four classes based on solubility and permeability. It enables the scientist to modify chemical structure of active pharmaceutical ingredient so as to optimize chemical properties. Oral dosage form have the rate limiting steps as dissolution and permeability for which BCS plays an important role. Biowaver can be given for some dosage forms based upon its BCS classification system. Dissolution number, dose number and absorption number are the fundamental basis for BCS classification. It is also a guideline for determining the conditions under which in vitro-in vivo correlations are expected. Solubility, permeability and dissolution are the class boundaries of the BCS. As per regulatory aspects during the process of generic drug development in vitro dissolution can replace bioequivalence studies.
INTRODUCTION [1-3] 
Oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. Limited drug absorption due to poor solubility of drugs results in poor bioavailability which is paramount amongst the potential problems that are encountered during delivery of an active agent via the oral route. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability. The solubility of a solute can be defined as maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Bioavailability as per FDA CDER 2004 is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS) 
The introduction of the Biopharmaceutics Classification System (BCS) in 1995 was the result of continuous efforts on mathematical analysis for the elucidation of the kinetics and dynamics of the drug process in the gastrointestinal (GI) tract [2]. Since the BCS was introduced, it has been used as a regulatory tool for the replacement of certain BE studies with accurate in vitro dissolution tests. The fundamental basis of BCS was established by Dr. Gordon Amidon. [4]. Fundamentals are as follows. [5]

OBJECTIVES AND CONCEPT OF BCS [2] 
The objectives of the BCS are as follows

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

CLASSIFICATIONS [1, 5-7]
A. Class I [8] 
Dissolution is very rapid, then the gastric-emptying rate becomes the rate-determining step. These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate. Examples include Metoprolol, Diltiazem, Verapamil, and Propranolol.

Media selection [8] 
Substances that belong to class I possess good aqueous solubility and are transported through the GI mucosa. Their bioavailability after oral administration is usually close to 100%, provided they are not decomposed in GIT and do not undergo extensive first pass metabolism. After administration, the dosage form quickly passes into stomach and, usually disintegrates there, so it is logical to use a dissolution medium that reflects the gastric conditions. Simulated gastrointestinal fluid (SGF) without enzymes is suitable for many immediate release dosage forms of this class. For some capsules, an enzyme (pepsin) may have to be added to the medium to ensure the timely dissolution of the shell. In case of weak acids drugs simulated intestinal fluid without enzyme may be used due to hampered dissolution of this drug by the SGF medium. Water is less suitable medium than the aforementioned buffers, because it has a nominal buffer capacity zero; therefore, the pH may vary during the test. [9] Ensure and Milk as dissolution media can improve the drug solubility includes the solubilization of drugs in the fatty part of the fluid. Of these media contains similar ratio of protein-fat-carbohydrate. Use of Ensure and Milk have been vigorously suggested as a media suitable for simulating fed state in the stomach.

B. Class II drugs [8,9] 
These drugs exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the sustained release and controlled release formulations. In vitro- In vivo correlation (IVIVC) is usually expected for class II drugs. Examples include Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine, Felodipine, Nicardipine, Nisoldipine etc.

Media selection [5,10] 
Substances that belong to class II possess poor aqueous solubility but are easily transported across the GI mucosa. Suitable biorelevant media for class II drugs are:

- Simulated gastric fluid plus surfactant (e.g., Triton X- 100), to simulate the fasted state in the stomach. This medium is specifically useful for weak basic drugs, because these are most soluble under acidic condition. Presence of surfactant in the gastric may play a role in the wetting and solubilization of poorly soluble acids in the stomach.
- Ensure and Milk as dissolution media can improve the drug solubility include the solubilization of drugs in the fatty part of the fluid. Both of these media contains similar ratio of protein/ fat/ carbohydrate.
- Fasted state simulated intestinal fluid (FaSSIF) and Fed state simulated intestinal fluid (FeSSIF) are the recently developed to simulate the intestinal condition. The two media are particularly useful for forecasting the in vivo dissolution of the poorly soluble drugs from different formulations and for assessing potential for foods effects on the in vivo dissolution. The dissolution rate of the poorly soluble drug is often better in FaSSIF and FeSSIF than in the simple aqueous buffers because of the increased wetting of the drug surface and micellar solubilization of the drug by the bile components of these media.
- Hydroalcoholic mixtures as dissolution media were popular for the dissolution of poorly soluble drugs. Particular significance of these media over the surfactant containing media is that they do not tend to foam, which makes deaeration and volume adjustment somewhat less frustrating.
C. **Class III drugs** [11,12]
These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement in permeability. Examples include Acyclovir, Alendronate, Captopril, Enalaprilat Neomycin B etc.

**Following permeation enhancers can be used** [13]
- **Synthetics surfactants:** Sodium lauryl sulphate, Polysorbate 20 & 80, Sorbitan Laurate, Glycerol monolaurate
- **Bile Salts:** Sodium deoxycholate, Sodium glycocholate, Sodium fusidate
- **Fatty acids:** Oleic acid, Caprylic acid, Lauric acid
- **Chelators:** Sodium EDTA, Citric acid, Salicylates
- **Inclusion complexes:** Cyclodextrins and derivatives
- **Mucoadhesive polymers:** Chitosan, Polycarbophil

**Media selection** [13]
Despite their good aqueous solubility, class III substances fail to achieve complete bioavailability after oral dosing because of their poor membrane permeability. A simple aqueous media can be used.

D. **Class IV** [13,14]
The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Nevertheless, several Class IV drugs do exist. These are unsuitable for controlled release. Examples include Chlorothiazide, Furosemide, Tobramycin etc.

**Media selection**
Class IV drugs combine poor solubility with poor permeability. Therefore, similar to class III drugs, they usually do not approach complete bioavailability. Two compendial media i.e. Simulated gastric fluid and Simulated intestinal fluid with addition of a surfactant to ensure the complete release of drug from formulation can be used.

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**BIOWAVER**
The BCS, which is based on scientific principles, presents a new paradigm in bioequivalence. According to the tenets of the BCS, certain drug products can be considered for biowaivers (i.e., product approval based on in vitro dissolution tests rather than bioequivalence studies in human subjects). At first, biowaivers were only applied to scale-up and post approval changes (SUPAC), but later the biowaiver principle was extended to the approval of new generic drug products. It provides drug designers an opportunity to manipulate the structure or physicochemical properties of lead candidates to achieve better “deliverability” [6].

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 governing 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 pharmacodynamic 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 inbuilt 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 hydrodynamically balanced system or a mucoadhesive dosage form will serve the purpose. Hence the BCS can work as a guiding tool for the development of various oral drug delivery technologies. [12]

EXCEPTION FOR BCS
1. Narrow Therapeutic Range Drugs
Narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and where product labeling 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, sponsors 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 tablets).

APPLICATIONS OF BCS IN ORAL DRUG DELIVERY TECHNOLOGY [5]

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:

- **BCS in the drug development**
  The pharmacokinetic idea of a new chemical entity which is already synthesized or identified and has therapeutic value but still under investigation for formulation development and final approval can be provided by BCS. The BCS provide an opportunity to the synthetic chemist to manipulate in the chemical structure in the chemical entity in order to optimize the physicochemical properties of lead molecule for desired delivery and targeting.

Table No. 1 Review of various category of drugs as per their BCS classification

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>NAME OF DRUG</th>
<th>BCS CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Steroidal anti-inflammatory Drugs</td>
<td>Paracetamol (12)</td>
<td>Class 3</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen (13)</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td>Diclofenac Sodium (15)</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td>Aspirin (17)</td>
<td>Class 1</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen (18)</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td>Etoricoxib (19)</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td>Nimesulide (20)</td>
<td>Class 2</td>
</tr>
<tr>
<td>Antiviral Drugs</td>
<td>Acyclovir (20)</td>
<td>Class 3</td>
</tr>
<tr>
<td></td>
<td>Amantadine (21)</td>
<td>Class 3</td>
</tr>
<tr>
<td></td>
<td>Zidovudine (22)</td>
<td>Class 3</td>
</tr>
<tr>
<td></td>
<td>Tenofovir (23)</td>
<td>Class 2</td>
</tr>
<tr>
<td>ANTIDIABETIC</td>
<td>Metformin (24)</td>
<td>Class 1</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone (25)</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td>Glimepiride (26)</td>
<td>Class 2</td>
</tr>
<tr>
<td></td>
<td>Glipizide (27)</td>
<td>Class 2</td>
</tr>
<tr>
<td>TETRACYCLINES</td>
<td>Doxycycline (28)</td>
<td>Class 1</td>
</tr>
<tr>
<td></td>
<td>Oxytetracycline (29)</td>
<td>Class 2</td>
</tr>
<tr>
<td>ANTITUBERCULAR</td>
<td>Isoniazid (30)</td>
<td>Border line of Class 1 and class 3</td>
</tr>
<tr>
<td></td>
<td>Ethambutol (31)</td>
<td>Class 3</td>
</tr>
<tr>
<td></td>
<td>Rifampicin (32)</td>
<td>Borderline class 2</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin (33)</td>
<td>Class 4</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide (34)</td>
<td>Class 3</td>
</tr>
</tbody>
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CONCLUSION:
BCS classification is used to replace BE studies by accurate in-vitro dissolution tests. This is used to increase the biopharmaceutical characterization of new drugs which results in high permeability, high solubility and increase in the dissolution rate.

REFERENCES:
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