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BIOPHARMACEUTICS CLASSIFICATION SYSTEM: AN OVERVIEW

J. Adlin Jino Nesalin *1, Bhavana AG, Ranjith TN *2, Deekshitha A*3, Rajesh J*4, Shashikiran YH*5 ,Anu PA*6 , RajiRaju*7, Nisarga BK*8, Rosbin MJ*9, Harshitha S*11

**1(Lecturer, Department Of Pharmaceutics, Bharathi College Of Pharmacy, India)*

**2-11(Student, Department Of Pharmaceutics, Bharathi College Of Pharmacy, India)*

adlinjino@gmail.com*1

ABSTRACT

In 1995,Amidonet al devised Biopharmaceutics classification system to classify drug based on the aqueous solubility and intestinal permeability. This method to identify situation that might allow in vitro dissolution testing to be used to ensure bioequivalence in the absence of actual clinical bioequivalence studies of oral immediate release product with systemic actions. This approach is meant to reduce unnecessary in vivo bioequivalence studies. It has been used as the regulatory tool for the replacement of certain BE studies with accurate in vitro dissolution tests. The biowaivers extension for drug or active pharmaceutical ingredient from different BCS classes with scientific basis is discussed as the current BCS guideline by the world health organization. Substantial differences of biowaiver dossiers and respective assessments contribute to the impression that a common understanding is lacking on successful use of the BCS concept to support the biowaivers. The drug discovery, drug delivery and drug research as well as extension for BCS are discussed.

Key words: *Biopharmaceutical classification system, Bioequivalence, Solubility, Permeability, Biowaivers.*

INTRODUCTION

The Biopharmaceutical classification system(BCS) isa scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is now well clear that drug absorption dependent on bioavailability and bioequivalence during the drug development process provided by Food and Drug Administration. Two drug products containing the same drug substance are considered bioequivalent or their bioavailability after administration in the same molar dose lie within the acceptable predetermined limits. These limits are set to ensure comparable in vivo performance that is similarity in terms of safety and efficacy. In in vivo bioequivalence studies the pivotal pharmacokinetic parameters AUC (Area under the curve) and C_{max}(Maximum concentration) are generally used to access the rate and extend of drug absorption.

SOLUBILITY

The solubility of a substance refers to the amount of substance that passes into solution to achieve a saturated solution at constant temperature and pressure. Solubility should be measured at two

temperature 40°C and 37°C.40°C to ensure physical stability,37°C to support biopharmaceutical evaluation

SOLUBILITY DETERMINATION[1]

A drug substance or an Active pharmaceutical ingredient (API) is considered highly soluble when the highest dose strength is soluble in 250ml or less of aqueous medium over a specific pH range. An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH condition. The pH solubility profile of the drug substance is determined at 37°± 1°C in the pH range of 1-7.5 as per united-state food and drug administration [USFDA] guidance.1.2-6.8 as per WHO guidance.1.8 as per European medicines academy [EMEA]. A sufficient number of pH conditions should be evaluated to accurately define the pH solubility profile. Equilibrium solubility experiments may be performed using 2 shake flask technique or alternative method, if justified. The pH for each test solution should be measured after the addition of the drug substance and end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH.The experiment should be conducted over a suitable time frame to reach equilibrium. A minimum of three replicate determinations at each solubility condition or pH using appropriate compendia media is necessary to demonstrate solubility using a suitably validated method. Adequate stability of the drug substance in solubility should be demonstrated in cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined and the drug substance cannot be classified. The following points should be considered in the determination of solubility's;

- The solvent and solute should be considered.
- A saturated solution must be obtained before any solution is removed for analysis.
- The method of analyzing solution must be reliable.
- Temperature must be adequately controlled.
- The method of separating a sample of saturated solution from undisclosed solute must be satisfactory.

PERMEABILITY[2]

It is the ratio of rate of drug transport in receiver compartment [dm/dt] to the product of area of the membrane.[A] and apical chamber of drug concentration [C].The permeability class bounding is based indirectly on the extent of absorption of a drug substance in humans and directly on measurement of rate of mass transfer across human intestinal membrane.

- Alternatively non-human systems capable of predicting the extend of drug absorption in humans can be used.(eg: invitro epithelial cell culture methods).
- According to USFDA, BCS guidance in the absence of evidence suggesting instability in the GI tract. A drug substance is considered to be highly permeable when the extent of absorption

in humans is determined to be 90% or more of an administered dose, based on mass balance determination or in comparison to an intravenous reference code.

- According to WHO an API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination.

DATA SUPPORTING HIGH PERMEABILITY[3]

1. For human pharmacokinetic studies information on study design and methods along with the pharmacokinetic data.
2. For direct permeability methods information supporting method suitability with a description of the study method criteria for selection of human subject's, animals or epithelial cell line, drug concentration.
3. A list of selected model drugs alongwith data and extent of absorption in human used to establish method suitability, permeability values and class for each model drug.
4. Permeability data on the test drug substance the internal standards, stability, information, data supporting passive transport mechanism.

DETERMINATION OF PERMEABILITY CLASS

Effective Permeability[4]

It is generally desired in terms of units of molecular movement distance per unit time (e.g: 10cm/s)

1. Extend of absorption in humans.

- Mass balance pharmacokinetic studies.
- Absolute bioavailability studies.

2. Intestinal permeability methods.

- Invitro intestinal perfusion studies in humans.
- In vivo or In situ intestinal perfusion studies in animals.

PERMEABILITY DETERMINATION

The methods that are routinely used for determination permeability include the following.

a)Pharmacokinetic studies in human substances including mass balance studies and absolute bioavailability studies or Intestinal permeability methods.

b)In vivo or In situ intestinal perfusion in a suitable animal model.

c)In vitro permeability methods using excised intestinal tissue.

d)Mono layers of suitable epithelial cells.

DISSOLUTION TEST METHODS[5]

In this guidance an IR drug product is considered rapidly dissolving when number less than 85% of the labeled amount of the drug substance dissolved within 30 minutes using U.S Pharmacopoeia (USP). Apparatus 1 at 100rpm or apparatus 2 at 50rpm in a volume of 900ml or less in each of the

media like 0.1N Hcl or simulated gastric fluid USP without enzyme pH 4.5 buffer, pH 6.8 buffer or simulated intestinal fluid USP without enzymes.

CLASSIFICATION OF ORALLY ADMINISTERD DRUGS ACCORDING TO THE BCS.

Drug	Solubility (mg/ml)	Permeability (10^{-4})	Dose (mg)	BCS class
Atenolol	26.5	0.20	100	3
Carbamazepine	0.01	4.30	200	2
Cimetidine	1.00	0.26	200	3
Furosemide	0.01	0.05	40	4
Hydrochlorthiazide	1.00	0.04	50	3
Propranolol	33	2.91	40	1
Verapamil	83	6.80	80	1

EXAMPLES

Drug	Permeability Class
Antipyrine	High (Potential IS Candidate)
Ketoprofen	High (Potential IS Candidate)
Verapamil	High (Potential ES Candidate)
Poly ethylene glycol [400]	Low (Zero Permeability Marker)

BIOPHARMACEUTICS CLASSIFICATION STYSEM[6,7]

Biopharmaceutics classification system is a scientific framework for classifying drug substances. In 1995, Amidon and coworkers introduced to biopharmaceutical classification system, to reduce the need for in vivo bioequivalence studies, utilization of in vitro dissolution tests as a surrogate for in vivo bioequivalence studies. BCS is a drug development tool that allows estimation of contributions of 3 major factors dissolution, solubility and intestinal permeability. These are the key parameters for the BCS classification of a drug.

CLASSIFICATION

According to BCS drug substance or API are divided into high/low solubility and permeability.

Class I: High solubility –High permeability

Class II: Low solubility –High permeability

Class III: High solubility –Low permeability

Class IV: Low solubility –Low permeability

Class V: Chemically or metabolically unstable drugs.

Class	Solubility	Permeability	Absorption Pattern	Examples
I	High	High	Well absorbed	Diltiazem, Propranolol Metoprolol
II	Low	High	Variable	Nifedipine, Carbamazepine
III	High	Low	Variable	Insulin, Metformin
IV	Low	Low	Poorly absorbed	Cimetidine,Taxol

Thisclassificationisassociatedwithdrugdissolutionandabsorptionmodel,whichindicates the key parameters controlling drug absorption as a set of dimensionless numbers.

Absorption number, An = Mean resistance time/Mean absorption time

Dissolution number, Dn = Mean resistance time/Mean dissolution time

Dose number, Do = Maximum dose strength (250) solubility.

BIOWAIVERS[6]

The term biowaiver is applied to a regulatory drug approval process when the dossier 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. BCS provides biowaiver for class I,II,III drug with some specifications. This waiver is for both pre and post-approval phases.

The criteria recommended by USFDA BCS guidance for Biowaiver

1. The drug substance should be highly soluble and highly permeable.
2. An immediate release drug product.
3. The drug should not be a narrow therapeutic index drug.
4. Excipients used in the dosage form should have been previously used in a FDA approved IR solid dosage forms.
5. The drug must be stable in gastrointestinal tract and the product is designed not to be absorbed in oral cavity.

The criteria recommended by WHO BCS guidance for Biowaiver.

1. Dosage forms of APIs which are highly soluble, highly permeable (BCS class I) and are rapidly dissolving are eligible for a biowaiver based on the BCS.
2. Dosage forms of APIs that are highly soluble and have low permeability (BCS class III) areeligibleforbiowaiversprovidedallthecriteriamentionedbelowaremetinaccordance with WHO
3.

BCS guidance and the risk benefit is additionally addressed in terms of extent, site and mechanism of absorption;

i. The solubility and permeability of API;
ii. The excipients used in the formulation;
iii. The risks of an incorrect biowaiver decision in terms of the therapeutic index of, and clinical indications for, the API.

3. Dosage forms of APIs with high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeabilityareeligibleforabiowaiverbasedonBCSprovidedthatcriteria(b),(c)and(d) described in the above section 2 are met, that the API has high permeability (i.e., the fractionabsorbedis85%or greater)andadose:solubilityratio250mlorlessatpH6.8and that the multisource product;

i. Is rapidly dissolving (85% in 30 minutes or less) in pH 6.8buffer.
ii. The multisource product exhibits similar dissolution profiles, as determined with the f2 value or equivalent statistical evaluation, to those of the comparator product at the three pH value (pH 1.2, 4.5 and6.8).

APPLICATION OF BIOPHARMACEUTICAL CLASSIFICATIONS[5]

Drug Delivery Technologies

Class I systems

The class I drugs are not those in which either solubility or permeability is rate limiting withinthetargetregionsoftheGItract.Thedrugreleaseinsuchcasescanbemodulatedusing controlled release technology. Controlled release technologies for class I drugs includes number of products such as Macrocap, Micropump, MODAS (Multiporous oral drug absorption system), Diamatrix (Diffusion controlled matrix system), DPHS (Delayedpulsatile hydrogel system), GMHS (Granulated modulating hydrogel system).

Class II systems

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, use of surfactant, emulsion or micro emulsion systems, solid dispersion and use of complexing agent such as cyclodextrins.

Class III systems

Manipulatingthesiteorrateofexposureorperhapsbyincorporatingfunctionalagentsinto 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.

Class IV systems

Extreme examples of class IV compounds are exceptions rather than the rule and arerarely developed to reach the market. But a number of examples of class IV drugs to exist, for example, Cyclosporin A, Furosemide, Ritonavir, Saquinavir andTaxol.

CONCLUSION

BCS principles provide a reasonable approach for testing and approving drug product quality. BCS also provide an avenue to predict drug deposition, transport, absorption and elimination. BCS is the guiding tool for the in vivo performance of the drug delivery technologies.Theinvivoperformanceofthedrugdependsuponitssolubilityandpermeability.

BCSapplicationforclassIIandIIIarechallenging,butatthesametimeprovidesopportunities for lowering regulator burden with scientific rational. The BCS was developed for the better understanding of the relationship of drug release from the product and the absorption process. Based on data from literature, it is evident that current IVIVC studies have focused more on the development and validation of level of IVIVC. Also it is possible that the IVIVC can still be explored to provide a greater understanding about the factors influencing Clinical Quality.

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