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Review article

Biopharmaceutical Classification System (BCS): Concept and Development Strategies in Drug Delivery System

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Abstract

In this article, viable formulation options are reviewed on the basis of the biopharmaceutics classification system of drug substances. The introduction of the biopharmaceutics drug classification system (BCS) into the guidelines of the Food and Drug Administration (FDA) is a major step forward to classify the biopharmaceutical properties of drugs and drug products. Based on mechanistic approaches to the drug absorption and dissolution processes, the BCS enables the regulatory bodies to simplify and improve the drug approval process. The relationships between the solubility/dose ratio and the fractions of dose dissolved and absorbed were also examined. Mean time calculations for drug dissolution (MDT) and permeation (MPT) of the GI wall were analyzed in respect to the mean intestinal transit time (MITT) to identify a cutoff point for drug dissolution and GI wall permeation. The knowledge of the BCS characteristics of a drug in a formulation can also be utilized by the formulation scientist to develop a more optimized dosage form based on fundamental mechanistic, rather than empirical approaches, and information.

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INTRODUCTION

Combinatorial chemistry and high-throughput screening used in drug discovery have resulted in an increase of poorly water soluble drug candidates[1, 2]. In drug discovery, the number of drug candidates defined as having low solubility has increased, and 70% of new drug candidates have shown poor aqueous solubility in recent years[3]. Currently, approximately 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble (<100µg/mL)[4]. There are many problems arising from the poor solubility of drug candidates in drug research and development.

Various approaches to overcome the poor aqueous solubility of drug candidates have been investigated in drug research and development. Changing the chemical structure in the lead optimization phase is considered to be an option to increase the solubility of drug candidates. Prodrug approaches might also enhance the aqueous solubility of drug candidates by introducing a polar functional group into the structure of a molecule[5].

The concept of BCS has been used for the biowaiver as well as for the formulation design from biopharmaceutical point of view. For BCS Class II or IV drugs, formulation designs are based on both the physicochemical and biopharmaceutical properties of the drugs which to obtained sufficient and reproducible bioavailability after oral administration. When combined with the dissolution of the drug product, the BCS depend on rate and extent of the drug absorption from immediate release solid dosage forms viz: dissolution rate, solubility and permeability[6, 7].

Solubility

The solubility classification of a drug in the BCS is based on the highest dose strength in an immediate release (IR) product. The drug substance is considered to be highly soluble when the highest dose strength is soluble in 250 ml or less of the aqueous media over pH range of 1.0-7.5.The volume estimate of 250 ml is derived from BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water[7].

Permeability

The permeability classification 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. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable[8].

Bioequivalence

The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Biowaiver

A biowaiver is an exemption granted by the US FDA from conducting human bioequivalence studies when the active ingredient(s) meet certain solubility and permeability criteria in vitro and when the dissolution profile of the dose form meets the requirements for an "immediate" release dose form.

Comparator product

Product Containing similar amounts of the same excipients as the test product, sameness of the manufacturing method and quality of the test product. The difference in drug content or potency between the test and comparator products should be less than 5%.

Very rapidly dissolving product

At least 85 % of the labelled amount is released within 15 minutes or less from the test and the comparator product. In this case profile comparison is not needed.

Rapidly dissolving product

At least 85 % of the labelled amount is released within 30 minutes or less from the test and the comparator product. Profiles are superimposable or profile comparisontest and the comparator product.

PRINCIPLE CONCEPT BEHIND BCS

Principle concept behind BCS is that if two drugs products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same plasma profile after oral administration. This concept can be summarized by application of Fick's first in the following equation

$$J = (Pw)(Cw)$$

Where J is the flux across the gut wall, Pw is the permeability of the gut wall to the drug, and Cw is the concentration profile at the gut wall[8].

PURPOSE OF THE BCS GUIDANCE [8]

Explains when a waiver for bioequivalence studies and in-vivo bioavailability may be requested based on the approach of BCS.
Expands the regulatory application of the BCS and recommends methods for classifying drugs.

GOALS OF THE BCS GUIDANCE [8]

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

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

To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability characteristics of the drug substance.

BCS classification is based on the 3 parameters

1. Absorption number defined as the ratio of the mean residence time (Tres) to mean absorption time (Tabs).

$$An = \left(\frac{Tres}{Tabs}\right) = \left(\frac{3.14R^2L}{Q}\right)\left(\frac{R}{Peff}\right)$$

2. Dissolution number defined as the ratio of the mean residence time to mean dissolution time.

$$Dn = \left(\frac{Tres}{Tdiss}\right) = \left(\frac{\frac{3.14R^2L}{Q}}{\frac{\rho r^2}{3DCs\,\min}}\right)$$

3. Dose number defined as the mass divided by the product of uptake volume (250 ml) and solubility of drug.

$$D_O = \frac{Dose}{V_O x C^{\min} S}$$

CHARACTERISTICS OF DRUGS OF VARIOUS BCS CLASSES

Class I

The drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. Bioavailability and dissolution is very rapid. So bioavailability and bioequivalency studies are unecessory for such product. IVIVC can nte be expected. Thes compounds are highly suitable for design the SR and CR formulations. Examples include Ketoprofen,Naproxen, Carbamazepine, Propanolol, Metoprolol, Diltiazem, Verapamil etc[9, 10, 11, 12].

Class II

The drugs of this class 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. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time. In-vitro in-vivo correlation (IVIVC) is usually accepted for Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the in-vivo bioavailability and the in-vitro solvation can be found[13,14,15]. Examples include naproxen, carbamezapine,ketoconazole.glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine and ketoprofen,

Class III

For Class III drugs, permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption[16]. Absorption is permeability-rate limited but dissolution will most likely occur very rapidly. For this reason, there has been some suggestion that as long as the test and reference formulations do

not contain agents that can modify drug permeability or GI transit time, waiver criteria similar to those associated with Class I compounds may be appropriate. Permeability, High Solubilitye.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

Class IV

Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected[16] with very poor oral bioavailability. These compounds are not only difficult to dissolve but once dissolved, often exhibit limited permeability across the GI mucosa. These drugs tend to be very difficult to formulate and can exhibit very large inter subject and intra subject variability.

Low Permeability, Low Solubility e.g. taxol, hydroclorthiaziade, furosemide.

Tab 1. BCS classification of drugs and in-vitro/in- vivo correlation expectations for immediate release products based on the Biopharmaceutics class

Class	Solubility	Permeability	Absorption rate control step	IVIVC expectation
I	High	High	Gastric emptying	IVIVC if the dissolution rate is slower than the gastric emptying rate, otherwise limited or no correlation
II	Low	High	Dissolution	IVIVC expected if the in vitro dissolution rate is similar to the in vivo dissolution rate, unless the dose is very high
III	High	Low	Permeability	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution rate
IV	Low	Low	Case by case	Limited or no IVIVC expected

BCS Class boundaries

Highly Soluble

A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5[17].

Highly Permeable

A drug substance is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose[16].

Rapidly Dissolving

A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions[16].

Determination of drugs solubility class

The solubility class boundary[18] is based on the highest dose strength of an IR product that is the subject of a biowaiver request. The volume estimate 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 ounces) of water. An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37 ± 1°C in aqueous media with a pH in the range of 1-7.5. 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 can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3-5, solubility should be determined at pH = pKa, pH = pKa +1, pH = pKa-1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication 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 can 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.

Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability indicating assay that can distinguish the drug substance from its degradation products. If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported along with other stability data.

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[19].

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[13]

Human studies

- Mass balance pharmacokinetic studies
- Absolute bioavailability studies,
- Intestinal perfusion methods

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

- monolayers (e.g., Caco-2 cells or TC-7 cells)

In mass-balance studies, unlabelled, stable isotopes or radio-labelled 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.

Determining Drug Product Dissolution Characteristics

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm using 900 ml of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. For capsules and tablets with gelatin coating, Simulated

Gastric and Intestinal Fluids USP (with enzymes) can be used.

Selection of the dissolution testing apparatus (USP Apparatus I or II) during drug development should be based on a comparison of in vitro dissolution and in vivo pharmacokinetic data available for the product.

A minimum of 12 dosage units of a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product (e.g., 10, 15, 20, and 30 minutes). When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

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

Two dissolution profiles are considered similar when the f_2 value is > 50.

Tab 2.Dissolution Apparatus Used for Novel/Special Dosage Forms [20]

Type of the dosage form	Related apparatus
1.solid oral dosage forms (Conventional)	Basket. Paddle, Reciprocating cylinder or Flow through cell
2. Oral suspensions	Paddle
3. Orally disintegrating tablets	Paddle
4. Chewable tablets	Basket. Paddle, Reciprocating cylinder with glass beads
5. Transdermal-patches	Paddle over disk
6. Topical semisolids	Franz diffusion cell
7. Suppositories	Modified basket. Paddle, Dual chamber Flow through cell
8. Chewable gum	Special apparatus (PhEur)
9. Powders and granules	Flow through cell (Powders/ granules sample cell)
10.Micro particulate formulations	Modified flow through cell
11. Implants	Modified flow through cell

Tab 3. 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
Solubility	Hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile and food composition
Volume of solvent available	Depends upon type of body fluid	Secretion, coadministered fluids
Amount of drug already dissolved	Hydrophilic, lipophilic nature of the drug	Permeability
Boundary layer thickness	Concentration of the drug	Motility patterns and flow rate

Applications of BCS in oral 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.

1. BCS in the drug development

In early drug development, knowledge of the class of a particular drug is an important factor influencing the decision to continue or stops it development. BCS classification can be utilized in drug candidate selection at an early phase in drug development, during formulation development, and in regulatory applications[21].

The BCS class of a drug indicates the rate-limiting step for oral absorption: gastric emptying, dissolution or intestinal permeability. In the early development phase, the permeability and solubility boundaries can be set as selection criteria for new drug candidates[22]. In vitro methods are utilized to measure solubility and permeability. Solubility is typically measured by the shake-flask method and permeability by Caco-2 cells.

Gastric emptying of the dissolved drug is the rate limiting step for oral absorption of class I drugs with rapid dissolution. Class I drugs have favourable absorption properties, leading to rapid and complete absorption. Drug absorption can be mediated either by passive transcellular diffusion or by active transport.

Even simple, conventional IR formulation assures rapid and complete absorption for this class of drugs. Therefore, formulation development is fast and cheap unless other issues, such as stability or production problems exist. IVIVCs cannot be found for IR formulations of class I drugs if dissolution is faster than gastric emptying. Thus, the dissolution method can be a simple and cheap quality control tool. However, if a BCS biowaiver is utilized in a regulatory application, dissolution should be tested in three different media representing the pH range of the gastrointestinal tract.

Dissolution controls absorption of class II drugs and a point-to-point relationship, i.e., level A *IVIVC*, can be found between in vitro dissolution and in vivo dissolution or absorption. Like BCS I drugs, class II drugs have high permeability, and transport may be active or occur by passive transcellular diffusion. If absorption is limited by solubility or dissolution, it may be incomplete. Formulation development may be more challenging than for BCS I drugs if special techniques and skills are utilized to enhance drug solubility or dissolution. For example, nanoparticles, microemulsion, cyclodextrins or lipid formulations can be used. In-vitro dissolution method development also requires more time and a high level of knowledge if in-vitro conditions are to mimic drug release and dissolution in vivo. Several pH values, agitation speeds, and different apparatuses should be tested. An appropriate method should discriminate critical formulation or manufacturing variables of the product affecting drug dissolution in-vivo.

If successful, a level A *IVIVC* may be proven and in-vitro dissolution tests can be used as surrogates for in-vivo bioavailability and bioequivalence studies.

BCS III drugs have permeability limited absorption. Incomplete absorption due to limited permeability can rarely be solved by formulation factors, because specific and non-toxic permeability enhancers are difficult to develop. Instead, bioavailability may be increased by prodrug derivatization of the parent compound, improving drug distribution to the target tissue[23]. The prodrug can be more lipophilic than the parent drug, facilitating transcellular passive diffusion or, alternatively, the prodrug can be designed to be a substrate for a transporter[24, 25]. In many cases, permeability is high enough to achieve therapeutic drug concentrations in plasma. Then conventional immediate-release formulation is a good choice. For example, the BCS III drugs ranitidine and cimetidine in immediate-release tablets have bioavailability of 50- 60%[26]. In many cases, the prodrug approach is not needed if therapeutic drug concentrations are achieved with the parent drug and with simple and cheap conventional formulations. An IVIVC cannot be found for BCS III drugs when permeability is the rate-limiting step for absorption[27]. The role of the dissolution method is to act as a quality control tool to ensure batch-to-batch consistency. Dissolution method development is thus easier for such class III drugs than for class II drugs or controlled-release products. BCS IV drugs have low solubility and permeability.

The rate-limiting step in drug absorption can be solubility, dissolution or permeability. The fraction of absorbed drug dose may be low and highly variable because class IV drugs have problems in solubility and permeability. Formulation and dissolution methods may be similar to those for class II drugs if dissolution is the rate-limiting factor. For permeability-limited absorption, class IV drugs may be developed like class III drugs. Some class IV drugs may be unsuitable for oral administration if the fraction absorbed is too low and oral absorption is highly variable. However, the tolerated level of

variability depends on the indication and therapeutic index of the drug.

2. Approval of the generics

BCS is done in accordance with the FDA guidelines when the potential class I drug candidate enters in human testing. If the compound meets all the criteria a petition is send to FDA asking for the agreement with the compound classification. The goal is to send to the FDA prior to initiation of phase II.

The BCS is used to set drug product dissolution standard to reduce the in-vivo bioequivalence requirement. As subsequent R & D proceeds, dissolution studies are done on a new formulation in accordance with the FDA guidance and petition is submitted to FDA requesting waivers of in-vivo bioequivalence studies.

The knowledge of BCS can also help the formulation scientist to develop a dosage form based on mechanistic approach rather than empirical approach. This allows determining the potential for in-vitro in-vivo correlation and significantly reducing the in-vivo studies.

Exception for BCS

1. Narrow Therapeutic Range Drugs

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, drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, and 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 or buccal tablets).

CONCLUSION

The biopharmaceutics classification system (BCS) is not only a useful tool for obtaining waivers for in-vivo bioequivalence studies but also for decision making in the discovery and early development of new drugs and formulation thereof. BCS applications for Class 2 and 3 are challenging, but at the same time provides opportunities for lowering regulatory burden with scientific rational. BCS also provides an avenue to predict drug disposition, transport, absorption, elimination. The in-vivo performance of the drug depends upon its solubility and permeability. The biopharmaceutical classification system is the guiding tool for the prediction of in-vivo performance of the drug substance and development of drug delivery system to suit that performance. In conclusion, the role of biopharmaceutics is an indispensable part in accomplishing the goals of drug development, i.e. getting safe and more efficacious drugs with reduced development time and cost.

References

1. Lipinski, C.A., Drug-like properties and the causes of poor solubility and poor permeability. Journal of Pharmacological and Toxicological Methods. 2000; 44: 235–249.

2. Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews. 2001; 46:3–26.

3. Ku, M.S., Dulin, W., A biopharmaceutical classification-based Right-First-Time formulation approach to reduce human pharmacokinetic variability and project cycle time from First-In-Human to clinical Proof-Of-Concept. Pharmaceutical Development & Technology. 2010; 1–18.

4. Takagi, T., Ramachandran, C., Bermejo, M., Yamashita, S., Yu, L.X., Amidon, G.L., A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Molecular Pharmaceutics. 2006; 3: 631–643.

5. Stella, V.J., Nti-Addae, K.W., Prodrug strategies to overcome poor water solubility. Advance Drug Delivery Review. 2007; 59: 677–694.

6. Kawabata Y, Wada K, Naktani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on Biopharmaceutics classification system: Basic approaches and practical applications. Int. J. Pharm. 2011; 420: 1– 10.

7. Puranik PK, Kasar SA, Gadade DD, Mali PR, Biopharmaceutics Classification System and Biowaiver: A overviews. Int. Res. J. Pharm. 2011; 2 (5): 66-71.

8. BiopharmaceuticsClassification System Guidance Office of Pharmaceutical Science, CDER/FDA, August 2006.

9. Guidance for Industry, "Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on biopharmaceutics classification system," FDA, August 1999 .

10. Swarbrick J , "Encyclopedia of pharmaceutical technology", Vol III, 3rd Edition, Pharmaceu tech inc,Informa Healthcare USA , 2007; 2049-2062.

11. Chowdary KPR, Vijayasrinivas S, "Biopharmaceutical classification system," The Indian Pharmacist, 2004; 7- 10.

12. Khar RK, Pandita D, "Biopharmaceutical classification system and its importance," The

Indian Pharmacist. March 2005; 25- 30.

13. Gothoskar, A. V. Biopharmaceuticalclassification of drugs.Pharm. Rev. [Online] 2005;3(1):http://www.pharmainfo .net/reviews/biopharmaceutical-classification-drugs (accessed 18, 2011).

14. Devane, J. Oral drug delivery technology: Addressing the solubility/permeability paradigm. Pharm. Technol. 1998; 22: 68–74.

15. Lipka, E.; Amidon, G. L. Setting bioequivalence requirements for drug development based on preclinical data: Optimizing oral drug delivery systems. J. Controlled Release. 1999; 62: 41–49.

16. Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System, FDA 2000.

17. Yazdanian M, Briggs K, Jankovsky C, Hawi A. The "high solubility" definition of the current FDA Guidance on Biopharmaceutical Classification System may be too strict for acidic drugs. Pharm. Res. 2004; 21: 293–9.

18. Kasim NA, Whitehouse M, Ramachandran C. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Mol Pharm 2004; 1: 85–96.

19. Yu, L. X.; Amidon, G. L.; Polli, J. E.; Zhao, H.; Mehta, M. U.; Conner, D. P.; Shah, V. P.; Lesko, L. J.; Chen, M. L.; Lee, V. H. L. Biopharmaceutics classification system: The scientific basis for biowaiver extensions. Pharm. Res. 2002; 19 (7): 921–925.

20. L Shargel, ABC Yu, "Applied biopharmaceutics and pharmacokinetics," 3rd ed, Appleton and Lange, Stamford, Connecticut, 1999; 365-376.

21. Lennernäs H and Abrahamsson B, "The use of biopharmaceutics classification of drugs in drug discovery and development: current status and future extensions," J. Pharm. Pharmacol. 2005; 57: 273-285.

22. Aungst BJ, Intestinal permeation enhancers. J. Pharm. Sci. 2000; 89(4): 429-442.

23. Steffansen B, Nielsen CU, Brodin B, Eriksson AH, Andersen R and Frokjaer S, "Intestinal solute carriers: an overview of trends and strategies for improving oral drug absorption," Eur. J. Pharm. Sci. 2004; 21: 3-16.

24. Todd PA and Heel RC, "Enalapril a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension and congestive heart failure. Drugs, 1986; 31(3): 198-248.

25. Beaumont K, Webster R, Gardner I and Dack K, "Design of ester prodrugs to enhance oral absorption of poorly permeable

compounds: Challenges to the discovery scientist. Curr. Drug Metab. 2003; 4: 461- 485.

26. Bogues K, Dixon GT, Fowler P, Jenner WN, Maconochie JG, Martin LE and Willoughby BA, "Pharmacokinetics and bioavailability of ranitidine in humans," Br. J. Clin. Pharmacol. 1980; 73: 275-276.

27. The European Agency for the Evaluation of Medicinal Products (EMEA), Note for Guidance on the Investigation of Bioavailability and Bioequivalence. Committee for Proprietary Medicinal Products, 2002.

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