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Biopharmaceutical Classification System: A Review.

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ABSTRACT

Biopharmaceutical Classification System has provided information regarding the concept of drug solubility and then permeability. The biopharmaceutical classification system is valuable tool for selection and development of of the formulation to formulation scientists. Biopharmaceutical classification system and biopharmaceutics drug disposition classification system are complimentary, not competing classification systems that aim to simplify, improve and speed the development of drug. This article reviews the criteria for classifying drugs according to the BCS and discusses biopharmaceutics drug disposition classification system, including the development of new molecular entities and controlled release products.

Keywords: BCS, BDDS, solubility, new molecular entity, drug delivery.

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INTRODUCTION

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability across the biological membrans.The BCS serves as a guiding tool for formulation scientists for recommending a strategy to improve the effiency of drug development. According to the BCS, drugs are classified as high solubility or low solubility. Drugs exhibiting high intestinal permeability rates the major route of elimination in humans was through metabolism, while drugs exhibiting poor intestinal permeability rates were primarly eliminated in humans as unchanged drug in the bile and urine. The biopharmaceutics drug disposition classification system could serve as a basis for predicting the importance of transporters in determining drug disposition and in predicting drug-drug interactions.

BCS Class-1 drugs are well absorbed and their solubility and permibility also high such drugs are Diltiazem, Metoprolol and Propranolol. BCS Class-II drugs have variable absorption pattern and their solubility is low and permeability is high such drugs are Naproxen, Nifedipine, Carbamazepine. BCS Class-III drugs have variable in their absorption pattern and their absorption is high and permeabilityis low such drugs are Cimetidine, Insuline and Metformin. BCS Class-IV drugs are have low solubility and low permeability. Their absorption pattern is poor such drugs are Furosemide, Taxol and Chlorthizide.

Two drug products containing the same active substance are considered bioequivalent if their bioavailabilities(rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e., similarity in terms of safety and efficacy. In invivo bioequivalence studies, the pivotal pharmacokinetic parameters AUC (the area under the concentration time curve), and Cmax (the maximum concentration), are generally used to assess the rate and extent of drug absorption.

Solubility:

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at 37 ± 49 1°C. In cases where the highest single therapeutic dose does not meet this criterion but the highest strength of the reference product is soluble under the aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach.

The number of pH conditions for a solubility determination depends upon ionization characteristics of the test drug substance. A minimum of three replicate determinations of solubility in each pH condition should be carried out to predict accurate solubility. Standard buffer solutions described in pharmacopoeias are considered appropriate for use in solubility studies. The pH-solubility profile of the API should be determined at 37 6 1 8C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended. Initial recommendations in the BCS Guidance suggested that the solubility should be measured over a pH range of 1.2-7.5. But successive scientific discussions and publications suggest that a pH range of 1.2-6.8 is more appropriate. According to EMEA BCS guidance a drug substance is considered highly soluble if the highest single dose administered as IR formulation is completely dissolved in 250 ml of buffers within the range of pH 1-6.8 at 37 6 1 8C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. A minimum of three replicate determinations at each pH condition is recommended (e.g., shake-flask method or other justified method). Solution pH should be verified before and after addition of the drug substance to a buffer.

In addition, adequate stability of the drug substance in the solubility media 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 thus the drug substance cannot be classified. In this case a BCS-based biowaiver cannot be applied. In addition to experimental data, literature data may be provided to substantiate and support ICH M9 Guideline -3-solubility determinations, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.

Determination of solubility:

The solubilities are determined by exposing an excess of solid (drug) to the liquid in question (water/buffer) and assaying after equilibrium has been established. It usually takes 60 to 72 hours to establish equilibrium; sampling at earlier points is necessary. Solubilities cannot be determined by the precipitation method because of the so-called metastable (solubility) zone. The pH solubility profile of the drug is determined at 37 ± 10°C in the aqueous medium, with pH in the range of 1-7.5. A sufficient number of samples should be evaluated, to accurately define the pH solubility profile. A minimum of three replicate determinations of solubility in each pH condition should be carried out. Standard buffer solutions described in pharmacopoeia (B.P. 2003) are considered appropriate for use in solubility studies. The concentration of the drug substance in the selected buffer or pH condition should be determined using a validated solubility-indicating assay that can distinguish the drug substances from their degradation products.

Selection of dissolution medium:

The dissolution medium selected must be able to reflect the in-vivo conditions, to give a better in vitro - in vivo correlation (IVIVC). However the bile salts are present in the small intestine even in a fasted condition (average concentration @ 5 mM), standard buffer solutions have been used widely in the solubility analysis for BCS. In an attempt to duplicate the intestinal conditions in-vitro, two kinds of media have been designed, one to simulate the fasted state small intestine and the other to simulate fed state conditions in the small intestine. These two dissolution media can be used in drug discovery and development and are acceptable in regulatory aspects too. Hence for the drugs belonging to Class I and Class III (i.e., having high solubility), simple aqueous dissolution media such as simulated gastric fluid (SGF, without enzymes) or simulated intestinal fluid (SIF,without enzymes) are suggested. In contrast, for Class II and IV (i.e., drugs with low solubility), use of biorelevant media is recommended for dissolution testing. For example:

- To simulate fasting stomach condition - SGF plus surfactants
- To simulate fed state condition - Milk with 3.5% fat
- For fasted intestine - Low volume SIF. (For poorly soluble drugs)
- For fed intestine - High volume SIF. (For poorly soluble weak acid drugs). The intrinsic dissolution rate can also be used as an alternative in BCS, especially in a case when the solubility of a drug cannot be accurately determined. Addition of a surfactant like sodium lauryl sulfate (SLS) or other surfactants may be required to mimic the solubilization in-vitro. For example, the recommended USP dissolution media for medroxy progesterone acetate tablet, danazol capsule, carbamazepine tablet, and flutamide tablet contain 0.5%, 0.75%, 1.0% and 2.0% SLS (USP26-NF21S1). Further research is required to explore the proper selection of dissolution of media and to develop a uniform media reflecting the in-vivo dissolution condition.

Permeability:

The permeability class boundary is based indirectly on the extent of absorption of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro 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 a mass balance determination or in comparison to an intravenous reference dose. According to WHO guidance an API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. The initial recommendation in the BCS Guidance suggested an absorption value of 90% as a prerequisite for classification as highly permeable. However, successive scientific discussions and scientific publications have suggested relaxing the criterion to 85% absorption for classifying an API as highly permeable. An acceptable alternative test method for permeability determination of the API could be in vivo intestinal perfusion in humans. When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control. According to EMEA BCS guidance if a drug substance has linear and complete absorption then it is considered highly permeable.

Determination of permeability:

Permeability along with solubility forms the backbone of BCS that helps in accessing oral absorption of drug molecules.The various methods used for permeability screening are as mentioned below:

- Determination of o/w pH partition profile of the drug
- Studies of the extent of absorption inhumans - Pharmacokinetic mass balance and absolute bioavailability studies
- Intestinal permeability studies - The following tissues can be used: i) In-vivo intestinal perfusion studies in human ii) In-vivo or in-situ perfusion studies in animals
- Invitro permeation studies using excised human or animal intestinal tissue
- In-vitro permeation experiments across a monolayer of cultured human intestinal cells
- Caco2 cell lines are derived from human colon carcinoma and used widely for permeability determination. The technique is expensive and requires specialized skills. Caco2 cell lines are about 60% accurate in predicting human permeability/absorption
- Initial screening can also be carried out using parallel artificial membrane permeability analysis (PAMPA), which is carried out on microplates. It measures the permeation of compounds through a phospholipid-coated filter medium that mimics intestinal cell structures.

BDDCS:

The purpose of BDDCS is to predict drug disposition and potential drug-drug interactions in the intestine and the liver with an emphasis on defining which drugs would be amenable to enzymatic-only and transporter-only disposition and drug-drug interactions, as well as where transporter-enzyme interplay may be important. Recent reviews from the Benet Lab have defined these enzymatic, transporter and transporter-interplay characteristics with potential transporter effects following oral dosing. The recognition of the correlation between BCS intestinal permeability and BDDCS extent of metabolism by Wu and Benet preceded an explanation for these findings. We hypothesize now that high permeability rate compounds are readily reabsorbed from the kidney lumen and from the bile, facilitating multiple access to the metabolic enzymes. For example, consider the BCS/BDDCS Class 1 drug letrozole. This completely oral available drug is primarily eliminated by metabolism via CYP3A4 and CYP2A6 enzymatic processes with less than 4% of the dose excreted unchanged in the urine. However, letrozole is only 60% bound to plasma proteins and thus it might be expected, based on glomerular filtration rate and fraction unbound, that renal clearance could approach 48ml/ml. Yet the total clearance for letrozole is only 40.5 ml/min with less than 4% excreted unchanged. Thus, this high permeability compound is reabsorbed in the kidney tubules (and possibly from the bile) with the major route of elimination being metabolic processes. The rationale for the correlation between intestinal permeability rate and the extent of metabolism appears to be based on the fact that high permeability rate compounds are reabsorbed from potential unchanged drug excretion routes in the body and thus can only be eliminated through metabolism.

The Use of BDDCS for Drugs on the Market:

- Predict potential drug-drug interactions not tested in the drug approval process
- Predict the potential relevance of transporter-enzyme interplay
- Assist the prediction of when and when not transporter and/or enzyme pharmacogenetic variants may be clinically relevant
- Predict when transporter inhibition by uremic toxins may change hepatic elimination
- Predict the brain disposition
- Increase the eligibility of drugs for BCS Class 1 biowaivers using measures of metabolism

There is a marked difference in the BDDCS class distribution of drugs on the market as opposed to NMEs. We previously estimated the distribution for NMEs based on all recently synthesized medicinal compounds. we depict the distribution of oral immediate release drugs on the market versus small molecule NMEs, the latter percentages determined from a data set of Professor Oprea encompassing 28,912 medicinal chemistry compounds tested for at least one target and having affinities of µM or less concentrations. While 40% of oral immediate release marketed drugs are Class 1, only 18% of NMEs fall in this category. This

difference is primarily related to Class 2 drugs, where 33% of marketed oral immediate release products are found versus 54% of NMEs. As can be seen in quite similar numbers between marketed drugs and NMEs are found for Classes 3 and 4. That is, in essence, NMEs are becoming larger, more lipophilic and less soluble, with time in the drug discovery paradigm.

BDDCS classification may also allow predictions regarding food effects for orally dosed drugs. The area under the curve (AUC) and bioavailability of many drugs are greatly affected by concomitant food intake and the FDA recommends that high fat meals (800–1000 cal; 50–65% from fat, 25–30% from carbohydrates, 15–20% from protein) may be used in food effect studies in humans Many factors are believed to contribute to these food effects, including changes in gastric emptying time, bile flow, pH of the intestine, splanchnic blood flow, and gut wall metabolism. A variety of evidence exists supporting food effects on transporters as well, as described by Custodio et al. In general high fat meals have no effect on the extent of absorption of BDDCS Class 1 drugs, increase AUC for BDDCS Class 2 drugs, decrease AUC for BDDCS Class 3 drugs, with insufficient data to show a general trend for Class 4 drugs. However, the multiplicity of factors affecting absorption in the presence of food make it more difficult to have a uniform response, and I estimate that the accuracy of the food effect predictions above is only approximately 70%.

CONCLUSION

In conclusion, the in vivo pharmacokinetics of drugs depends largely on the solubility and permeability. The BCS has proven to be an extremely useful guiding tool for the prediction of the in vivo performance of drug substance and development of new drug delivery systems to suit the performance of the drug in the body, as also for the regulation of bioequivalence of the drug product during scale-up and post approval. In the future, the BCS concept will probably be used increasingly in the early development of new drugs, including for analog selection as well as for initial formulation approaches. BDDCS was developed with the purpose of predicting drug disposition and drug-drug interactions, both for drugs on the market and NMEs.

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