ISSN 2277-2685
IJPSL/July. 2022/ Vol-12/Issue-3/1-8
Venugopalaiah Penabaka ***et. al*** International Journal of Pharmacetical Sciences Letters

The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development

Venugopalaiah Penabaka, P Venkata Anudeep*, Yerikala Ramesh, D. VijayKumar, S. Ramesh
Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore

Dt.524001 A.P. India

Corresponding Author
Name: P Venkata Anudeep
Email id: anudeeppadavala9@gmail.com , Mobile Number: 73824 56321

ABSTRACT

A revised classification system for oral drugs was developed using the biopharmamaceutics classification system (BCS) as a starting point. The revised system is designed to have a greater focus on drug developability. Intestinal solubility, the compensatory nature of solubility and permeability in the small intestine and an estimate of the particle size needed to overcome dissolution rate limited absorption were all considered in the revised system. Thesystem was then validated by comparison with literature on the *in vivo* performance of a number of test compounds. Observations on the test compounds were consistent with the revised classification, termed the developability classification system (DCS), showing it to be of greater value in predicting what factors are critical to *invivo* performance than the widely used BCS.

INTRODUCTION

Following its introduction in the 1990s, the biopharmaceutics categorization system (BCS) had a significant impact on the creation of oral dosage forms with instant release (IR). This method replaced in vivo human trials with in vitro data to prove bioequivalence of low risk (BCS class I) chemicals. One, twoFurthermore, the BCS provides a framework for considering critical factors (dosage, solubility, permeability, and dissolution rate) that may impact a drug's efficacy in the body. Beyond identifying biowaiver-friendly medications, these factors likely also characterize the CQAs that affect in vivo effectiveness. When thinking about quality by design (QbD), it is very important to have a good understanding of these when developing oral pharmaceutical items.3Because of the heavy regulatory burden on the BCS, the classification scheme rightfully treads carefully when deciding which product properties, such solubility and/or dissolution rate, are most important for limiting oral absorption. Considering thatTo prioritize patient safety, it is vital to accurately categorize product modifications that cause changes to in vivo performance rather than misclassify those that do not. Permeability is a feature of the drug molecule that is not expected to vary with product and process changes, hence changes to the drug product typically have less of an impact on this attribute. This reduces the likelihood that permeability is associated with a drug's CQAs and makes it easier to identify a theoretical high/low permeability boundary (e.g., permeability equal to 90% fraction absorbed) that is useful for determining whether permeability is partially rate limiting to oral absorption.In rare cases, excipients may affect in vivo permeability by influencing the drug's active or passive transit across the intestinal wall, or indirectly by changing the GI transit/residence duration. While there have been documented cases of this happening, it is rather unusual and usually requires a substantial dose of certain high-risk excipients to cause any noticeable alteration in living organisms.

There have been proposals to expand the biowaiver classes of the BCS.6 Classes III compounds can be exempted from biowaivers as long as changes to excipients won't affect drug permeability.

Some classes II weak acids can also be exempted because these drugs often have enough solubility and permeability in the upper small intestine, so they don't need to meet the high solubility criteria at gastric pH.

THEDEVELOPABILITYCLASSIFICATIONSYSTEM

On living organisms. Most of the new guidelines from the World Health Organization include these expansions.For the purpose of simplifying the process of classifying compounds as having high or low permeability, Wu and Benetsuggested metabolic clearance as a suitable substitute for permeability. They also brought attention to the fact that the threshold for low/high permeability is very similar to the tendency of drugs to be cleared either unchanged (in the case of low permeability) or via metabolic pathways (in the case of high permeability). Theoretically, this overlap occurs because drugs' permeability determines how easily they may reach metabolic enzymes inside cells.

Rather than presenting the BCS as a regulatory classification to guarantee bio-equivalence, this article proposes an updated version of the system that better classifies medications according to the characteristics that restrict their oral absorption. Within the context of Quality by Design (QbD), this offers a better way to categorize the problems associated with the creation of oral products. Even though the BCS is no longer the primary emphasis, this system could still serve as a scientific basis for discussions with regulators regarding the potential for bio-inequivalence in relation to modifications to drugs that do not yet belong to the BCS I category. This is especially true for drugs in BCS class II, the most common category for orally active new chemical entities (NCEs).

THEORETICAL/BACKGROUND

Several seminal articles published in the previous ten years have focused on oral absorption modeling. In the early phases of drug research, one common and straightforward idea was the maximum absorbable dosage (MAD). There are several implementations of MAD, each with its own set of assumptions and permeability estimation methods. Another version by Sun et al. employs an estimate of the effective human jejunal permeability (Peff), while one by Curatolo11 uses an absorption rate constant (KA) for the derivation.

$$MAD = S * KA * V * T \quad (1)$$

S is the solubility, V is the fluid volume (250 mL), Tsi is the transit time for the absorption site (3.32 h for the small intestine), and A is the absorption surface area (7.54 104 cm2). In equation (2), MAD is equal to Peff when applied to humans.

High permeability may compensate for low solubility in determining the maximum dosage beyond which solubility in the GI tract becomes restrictive to absorption, according to one interpretation of the MAD equation. This means that permeability and solubility are compensatory. Assumption usefulness, at least for high permeability, is supported by further research.

Medications, as shown by Fagerholm et al.cause deuterium permeability in the human jejunum to be around the BCS high/low limit. On the assumption that deuterium and water have similar intestinal permeabilities, it follows that drugs with high permeability are absorbed more rapidly than small intestine fluid, increasing the dosage at which solubility becomes limiting, and drugs with low permeability are absorbed more slowly than small intestine water. The rate of drug disappearance from

the jejunum is a relevant measure of permeability, and Eq. utilizes this measure in this context.

Do, Dn, and an are three dimensionless numbers that are generated by another model that is often used in oral absorption modeling. These numbers are used to evaluate the likelihood that the dose-to-solubility ratio, dissolution rate, and permeability would restrict oral absorption in the gastrointestinal system. This paradigm articulates a number of crucial ideas:

(1) If the dissolving rate of a medicine is too slow to allow all of its particles to dissolve within the time it takes to pass the absorption site, we say that the drug is dissolution rate restricted. The model estimated the residence time at the absorption site using a modest intestinal transit time for simplicity's sake. Important product dependant factors include particle size and intestinal solubility.

(2) Inadequate fluid inside the GI system to dissolve the prescribed dosage will cause a medication to be solubility restricted. To keep things simple, the model employed a fluid volume of 250 mL, which is the same as the BCS, and the minimal aqueous solubility in the physiological pH range (1.2-7.5). The two most important product dependent factors are solubility and dose.

(3) When the rate of drug transfer from the gut lumen to the gut wall is insufficient, we say that the drug is permeability restricted. One important dependent variable of drugs is their permeability.

It is feasible to determine the proportion absorbed from the GI tract by combining these dimensionless quantities. Permeability and solubility are compensatory, a principle from the MAD equation that is also included into the estimation of percentage absorbed.

Part of the reasoning behind the commercially available modeling program Gastro-Plus comes from combining these ideas for oral absorption modeling with a compartmental model of the gastrointestinal system. There are various commercial models for oral absorption that are based on different principles, such as the one that is based on the modeling of gastrointestinal fluid flow.
PK-Sim in version.

BRIDAL COUTURE No.

Getting the Most Out of Solubility Data for Oral Absorption Models

The BCS utilizes the lowest solubility in 250 mL within the physiological pH range as their definition of solubility. Solubilizers in the gut, such as gastrointestinal secretions and food intake, contribute to drug solubilization, even for drugs with pH independent solubility in the physiologically relevant range, so this is likely to be an underestimate of the actual solubility experienced in vivo.

Dressman and colleagues advocated biorelevant dissolving medium including solubilizers such bile acids for the evaluation of drug developability and formulation performance of poorly soluble pharmaceuticals in order to enhance the prediction of GI dissolution. The acronyms FaSSIF, FeSSIF, FaSGF, and FeSSGF stand for fasting state simulated intestinal fluid, fed state simulator of gastric fluid, fasted state gastric fluid, and various fed state simulators of gastric fluid.

In addition to increasing the bio relevance of dissolution experiments, these media also allow for an improvement in the solubility estimate used in oral absorption models. To illustrate the in vivo performance of the weakly soluble medication halofantrine in both the fasting and fed states, Charman and colleagues used FaSSIF and FeSSIF solubility in conjunction with the Do, Dn, An, model that was previously discussed. Under fed state circumstances, there may be an improvement

in solubility and dissolution rate, which might explain the large food impact.

In a prior publication, we covered the prospect of replacing buffers with biorelevant media and of utilizing quantities that are more appropriate than the 250 mL used in the BCS or its derivatives.

Because there is more fluid volume and more opportunity for solubilization in the fed state, orally absorbed poorly soluble medicines are often better absorbed. That is why it is possible to avoid food-related solubility issues if full absorption can be accomplished during fasting. Since it is usually preferred for patient convenience to be able to administer a drug with or without food and get equivalent pharmacokinetic and therapeutic responses, it is especially important to use an estimate of intestinal solubility in the fasted state when predicting the extent of absorption (AUC).

Most medications with a rapid release are absorbed in the upper small intestine, where the fluid volumes for drug dissolution reach a maximum, hence it is crucial to get an estimate of jejunal solubility. If a drug doesn't have enough solubility and dissolving rate to ensure full extent of absorption, the upper small intestinal solubility is a better indicator than the gastric solubility, with the notable exception of weak bases, for which an estimate of the gastric solubility will also be highly significant.

For medications with poor solubility, the rate of in vivo absorption (Cmax, Tmax) may be significantly affected by gastric solubility and dissolution rate.
Several suggestions have been put forward to improve upon the media suggested by Dressman and Reppas. These include using more complicated mixtures of bile salts, adding components to mimic dietary lipids, adopting an intestinal buffer that is more relevant to the body, and using naturally occurring surface active agents in gastric media. While these synthetic media can be used to approximate intestinal solubility under simulated GI conditions, there is also support for using aspirates taken from the human or animal GI tract as a medium to estimate the actual GI solubility.You may also find a review of techniques that estimate solubility in the GI tract that covers a lot of these factors.

Making the Most of Oral Absorption Models with Permeability Data
During the process of developing a novel medicine, there are many methods that may be used to evaluate permeability. Using fraction absorbed as a cutoff for high and low permeability is both feasible and appropriate according to the BCS, but finding an easy-to-perform permeability measurement that correlates well with fraction absorbed is a hurdle. A number of methods have been documented in the literature for determining drug permeability. These include methods based on in silico drug properties (e.g., log D and hydrogen bonding potential), passive diffusion across an artificial membrane, in vitro permeability across cell lines, in situ perfusion techniques, and methods for excised human or animal tissue. In the early stages of product development and while evaluating therapeutic candidates, simpler approaches are recommended; later on, more complex measurements might be used. What constitutes an appropriate approach for evaluating permeability, in terms of both the method utilized and method validation, is defined specifically for formal BCS categorization.
As a qualitative (e.g., into high/medium/low bins) and quantitative (permeability given as a number) metric, simpler, higher-throughput approaches are especially valuable in early development, even if they are not commonly acknowledged in the BCS categorization guidelines. Correlating any quantitative value to a realistic measure of in situ human permeability or proportion absorbed may further increase its utility.
Permeability in humans as measured by jejunal perfusion is only partially documented in the literature.

System for Classifying Developmental Levels

the works published. This is especially useful since it allows for the correlation of measuring permeability to a relevant permeability for both weakly and well absorbed medications, unlike fraction absorbed data, which is only selective for substances with a poor absorption rate (<90% fraction absorbed). A qualitative estimate of permeability, for both low and high permeability chemicals, may be obtained by comparing other permeability data sets with the human jejunal permeability data set, regardless of how they are determined. A few examples of this kind of research in the literature include the association of the human jejunal permeability data set with log D-based in silico models, artificial membranes like PAMPA, in vitro cell lines, and in vivo rat perfusion.

METHOD:DEVISINGTHEMODIFIEDCLASSIFICATIONSYSTEM

The new categorization attempted to include the following ideas:

(1) A method to estimate the solubility in the human intestines while the subject is fasting (such as FaSSIF) since this is the main indicator of in vivo solubility that may be used to forecast the amount of absorption in humans.
(2) The SLAD approach, which holds that permeability and solubility are compensatory for class II medicines, is based on this principle.

(3) For medications with a restricted amount of absorption limited by the dissolution rate, the development risks and CQAs may be better assessed using the dissolution rate as a target drug particle size instead of the dose/solubility ratio.

Theincorporationofconcepts(1)and(2)isillustratedinFigure1.Notethesignificantdeviation

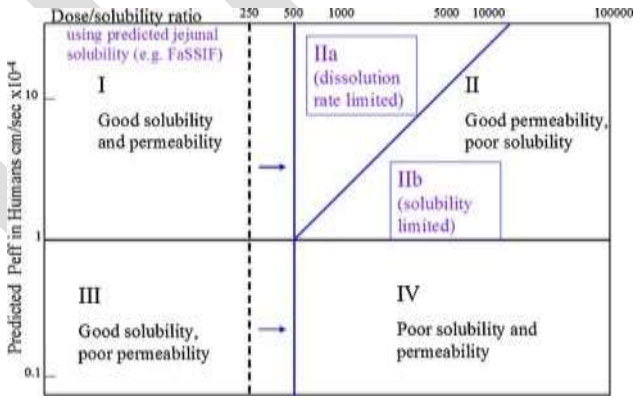

Figure 1. Modifying the BCS for more realistic volumesof fluid available in the GI tract and the compensatorynature of permeability on low solubility (modifications fromtheBCStoDCSareshowninblue).
by including two new subclasses for class II and shifting the focus from rate of oral absorption prediction to extent prediction, the redesigned system differs from the BCS.
For medications with high permeability, the border between classes IIa and IIb represents the solubility restricted absorbable dosage; for pharmaceuticals with poor permeability, the barrier between classes III and IV represents the same. I can say it this way:

Thirdly, SLAD = Ssi × V × MP

where Ssi is the estimated solubility in the small intestine, V is the amount of fluid (500 mL), and MP is the multiplier that depends on the permeability. MP is equal to the absorption number (An) for medications with high permeability, whereas it is maintained at unity for drugs with poor permeability.

Although various methods of determining intestinal solubility, such as aspirates obtained from animals or human volunteers by intubation, may be more suitable, the standard method is the saturation solubility in fasting condition simulated intestinal fluids.

Complete oral absorption from a normal solid oral dose form including crystalline medication may often be achieved without resorting to complicated solubilization methods, even when saturation solubility is reached in vivo for IIa drugs. This is because increased permeability has a compensating effect. To achieve total absorption, however, it will be crucial to manage parameters impacting drug release from a conventional formulation, such as particle size, surface area, and wettability. Class IIb compounds, on the other hand, provide a significant problem for drug formulators due to their inadequate absorption unless the drug is presented in an already solubilized form.

Keep in mind that the concept that solubility and permeability are compensatory is not carried over into class III, in contrast to what is implied by the MAD equation. This is due to the fact that both compounds with high and low permeability are still classified using the same starting volume accessible for dissolution in the gut, which is 500 mL, under the updated approach. This may be an oversimplification, but it is sufficient for evaluating developability, since fluid secretion into and out of the intestines is dynamic. Additionally, it is permissible to utilize the maximum dose instead of the maximum dose strength (as used for BCS classification) in the modified classification method. This is because clinical investigations during early product development sometimes include numerous dosage units.

To make it easier to remember, the revamped method is called the Developability Classification method (DCS).

CONCLUSION

In light of the presented examples, a revised BCS for evaluating the potential of oral immediate release drugs is a helpful tool for classifying compounds in a straightforward way to determine if a drug's oral absorption will be hindered by its dose/solubility ratio, dissolution rate, or permeability. To provide further insight into possible sensitivity to dissolving rate, a target particle size may be included by rearranging the dissolution number equation. Oral absorption is expected to be restricted by intestinal solubility beyond a certain dosage, which may be better estimated using the solubility limited absorbable dose (SLAD) approach.

Optimal formulation techniques and prospective key quality attributes (CQAs) may be better understood with the use of visualization tools that show which aspects are most likely to compromise a drug's in vivo performance.

ACKNOWLEDGEMENT

The authors are thankful to the Management and Principal from Ratnam Institute of Pharmacy, Pidathapolur, SPSR Nellore, for providing the necessary facilities to carry out this review work.

Funding Support

The Author declares that there is no funding.

Conflict of Interest

The Author declares that there is no conflict of interest.

REFERENCES

1. Sugano K, Nabuchi Y, Machida M, Aso Y. 2003. Prediction ofhuman intestinal permeability using artificial membranepermeability.IntJPharm257:245–251.
2. SunD,LennernasH,WelageL,BarnettJ,LandowskiC,Foster D, Fleisher D, Lee KD, Amidon GL. 2002. Comparisonof human duodenum and Caco-2 gene expression profiles for12,000 gene sequences tags and correlation with permeabilityof26drugs.PharmRes19:1400–1415.
3. Zakeri-Milani P, Valizadeh H, Tajerzadeh H, Azarmi Y, Islam-bolchilarZ,BarzegarS,Barzegar-JalaliM.2007.Predictinghuman intestinal permeability using single-pass intestinalperfusioninrat.JPharmPharmSci10:368–379.
4. FagerholmU,JohanssonM,LennernäsH.1996.Comparisonbetween coefficients in rat and human jejunum. Pharm Res13:1336–1342.
5. Salphati L, Childers K, Pan L, Tsutsui K, Takahashi L. 2001.Evaluationofasingleperfusionmethodinratforthepredic-tionofabsorptioninman.JPharmPharmacol53:1001–1013.
6. VanderMeerJWM,KeuningJJ,ScheijgrondHW,HeykantsJ,VanCutsemJ,BrugmansJ.1980.Theinfluenceofgastricacidityonthebioavailabilityofketoconazole.JAntimicrobialChemother6:552–554.
7. DerendorfH,VanderMaelenC, BricklR, MacGregor T, Eisert W.2005.Dipyridamolebioavailabilityinsubjectswithreducedgastricacidity.JClinPharmacol45:845–850.
8. Kostewicz ES, Wunderlich M, Brauns U, Becker R, Bock T,Dressman JB. 2004. Predicting the precipitation of poorlysoluble weak bases upon entry in the small intestine. J PharmPharmacol56:43–51.
9. GuCH,RaoD,GandhiR,HildenJ,RaghavanK.2004.Usinganovelmulticompartmentdissolutionsystemtopredicttheeffect of gastric pH on the oral absorption of weak bases withpoorintrinsicsolubility.JPharmSci94:199–208.
10. DressmanJ,FleisherD.1986.Mixing-tankmodelforpredict-ing dissolution rate control of oral absorption. J Pharm Sci75:109–116.
11. Rinaki E, Dokoumetzidis A, Macheras P. 2003. The meandissolutiontimedependsonthedose/solubilityratio.PharmRes20:406–408.
12. AlsenzJ,MeisterE,HaenelE.2007.Developmentofapar-tially automated solubility screening (pass) assay for earlydrugdevelopment. JPharm Sci 96:1748–1762.
13. HinderlingP,HartmannD.1991.Pharmacokineticsofdigoxin and main metabolites/derivatives in healthy humans.TherDrugMonit13:381–401.
14. GreenblattDJ,SmithTW,Koch-WeserJ.1976.Bioavailable-ity of drugs: The digoxin dilemma. Clin Pharmacokinetics 1:36–51.
15. Jounela AJ,SothmannA.1973. Bioavailabilityofdigoxin.Lancet1:202–203.
16. IgelS,DrescherS,MurdterT,HofmannU,HeinkeleG,TegudeH,GlaeserH,BronnerS,SomogyiA,Omori T,SchÄ- fer C,EichelbaumM,FrommM. 2007.Increasedabsorptionof digoxin from the human jejunum due to inhibition of intestinaltransporter-mediatedefflux.ClinPharmacokinetics46:777–785.
17. HunterJ,HirstB.1997.Intestinalsecretionofdrugs.Theroleof P-glycoprotein and related drug efflux systems in limitingoraldrugabsorption.AdvDrugDelivRev25:129–157.
18. Westphal K, Weinbrenner A, Giessmann T, Stuhr M, FrankeG, Zschiesche M, Oertel R, Terhaag B, Kroemer HK, Sieg-mundW.2000.Oralbioavailabilityofdigoxinisenhancedbytalinolol: Evidence for involvement of intestinal P-glycopro-tin.ClinPharmacolTher68:6–12.
19. Verstuyft C, Strabach S, El-Morabet H, Kerb R, BrinkmannU,DubertL,JailonP,Funck-BrentanoC,TrugnanG,BecquemontL.2003.Dipyridamoleenhances