



Robert W. Lee, PhD

Comments On Biopharmaceutical Classification System And Formulation Development

Mark Mitchnick, MD, and Robert W. Lee, PhD

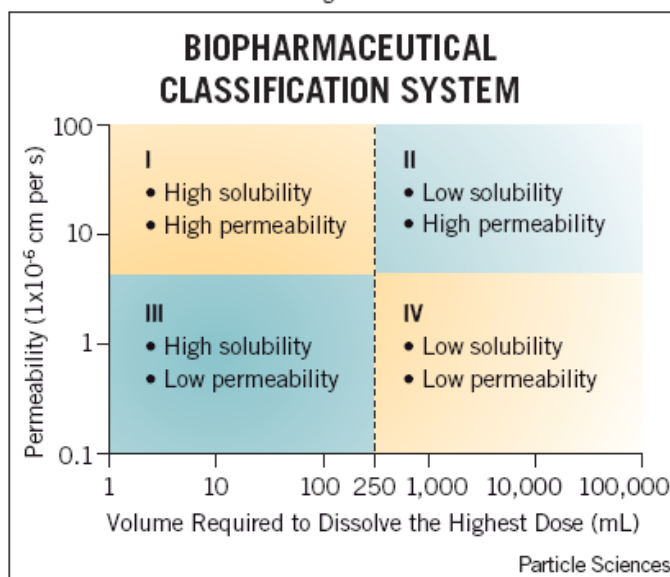
This is the first installment in a series of articles that will provide an overview of an area of potential interest to the readers of Pharmaceutical Online and Outsourced Pharma. Subsequent articles will cover analytical method development and validation, solid solutions, potent compound handling, CFR Title 21 Part 11 requirements, combination devices, encapsulation technologies, PAT, and in vitro dissolution testing of solid dosage forms.

Background

The Biopharmaceutical Classification System (BCS) is an experimental model that measures permeability and solubility under prescribed conditions. The original purpose of the system was to aid in the regulation of post-approval changes and generics, providing approvals based solely on in vitro data when appropriate. Importantly, the system was designed around oral drug delivery since the majority of drugs are, and remain, orally dosed. Waivers, permission to skip in vivo bioequivalence studies, are reserved for drug products that meet certain requirements around solubility and permeability and that are also rapidly dissolving.

More and more however, the industry is using the BCS as a tool in drug product development. As a simple example, BCS can be used to flag drugs that should not be tested clinically unless appropriate formulation strategies are employed (Figure 1). A BCS Class II compound for instance, permeable but relatively insoluble, would likely not be a good clinical candidate without the use of enhanced formulation techniques aimed at increasing solubility or rate of dissolution. This sort of data-informed formulation approach is a distinguishing feature of Particle Sciences and other leading groups. Various schemes exist that attempt to funnel a given API towards particular drug delivery techniques depending on, among other things, the API's BCS category. Still, most approaches remain fragmented in their methodology, ignoring commercially and biologically important factors. The BCS can however, when integrated with other information provide a tremendous tool for efficient drug development. One school of thought, very much endorsed by Particle Sciences, is that first in human (FIH) drug dosage forms should be designed to maximize bioavailability and that the FIH dosage form should be a logical step towards commercialization and not simply a stop gap to facilitate data acquisition. This makes sense both economically and ethically.

Figure 1



For BCS Class I molecules, FIH formulations are straightforward and may consist of essentially the neat API. However, for other compounds, effective dosage forms present greater challenges. Although designed originally to classify APIs as to their oral bioavailability, properly augmented, the BCS can be used as a key component of an algorithm to guide drug delivery system design for any route of administration. This notion has been elaborated on by a number of authors.

The Biopharmaceutical Classification System

Briefly, the BCS places a given API in one of four categories depending on its solubility and permeability as they pertain to oral dosing (Figure 1). A drug substance is considered "highly soluble" when the highest clinical dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1–7.5 at 37 °C. A drug substance is considered to be "highly permeable" when the extent of the absorption (parent drug plus metabolites) in humans is determined to be ≥90% of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose. Permeability can be determined a number of ways but is most often done using Caco-2 cell lines, an assay that lends itself to high

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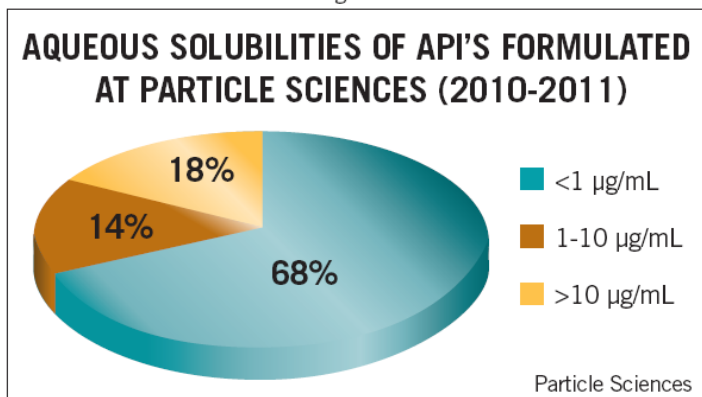
throughput automation. In this system, a monolayer of cells is grown and drug permeation from the drug donor (apical side) to the acceptor (basolateral side) compartments is assessed, usually by using a direct UV or LC-MS assay. Potential issues with Caco-2 based systems range from variation (from in vivo) in transport mechanisms to drug interactions with the apparatus itself. Commercial companies focused on this assay have developed multiple approaches to alleviate these issues but a review is beyond the scope of this paper and the reader is encouraged to contact the various suppliers. As a drug candidate moves up the development ladder, developers will often confirm and refine their BCS assessments with increasingly complex in vivo models.

An important subtlety here is that the BCS accounts for potency in that solubility and permeability are relative to clinical dose. Again, oral dosing is assumed in the testing design. So, for example, a compound that has poor absolute solubility might paradoxically be classified as “highly soluble” if it were a highly potent compound and the whole clinical dose was soluble in 250 mL.

BCS and Dosage Form Trends

It is commonly recognized that most new drugs present formulation challenges. In fact, older drugs as compared to newer ones have higher solubilities in general. One reference noted that BCS Class II compounds as a percentage of compounds under development had increased from 30% to 60%. BCS Class I compounds have fallen correspondingly from 40% to 20% over that same period. In practice, low solubility is the most common theme encountered. In our own experience the majority of compounds formulated at Particle Sciences on the behalf of our clients have low to no aqueous solubility (Figure 2). It should be noted that not every drug is classified the same by each investigator. The variability can be due to a number of things including the way permeability is measured. As above, in vivo permeability is impacted by, among other things, drug transporters. Both uptake and efflux transporters exist and can contribute to the differences seen by the various techniques.

Figure 2



For the majority of APIs a solid oral dosage form (SOD) is the preferred option. Sometimes the physicochemical and

physiologic mechanisms do not allow this and alternatives are pursued such as suspensions or oral solutions. Other times, the target and other factors dictate that a non-oral dosage form is most sensible. Examples include the local delivery of female hormones (i.e., gels and dissolving film strips), nasal allergy preparations (i.e., nasal aerosols or dry powders), ocular therapeutics (i.e., implants) and combination products (i.e., intravaginal rings, intrauterine devices, and stents) aimed at prolonged drug release. In all these cases, even though not orally dosed, the concepts inherent in the BCS can be important tools in dosage form design. Particle Sciences offers these and more delivery options.

Formulation Approach

Having a predefined system in which one can make decisions based on data is necessary for efficient drug development. Inputs into such a system include, in addition to BCS class, a detailed solubility profile, polymorph status, desired dosage form, target dose and dosing regimen, drug stability, excipient compatibility and knowledge of transporter and metabolic pathways. Non-technical factors that, as a practical matter, need to be considered are such things as cost, intellectual property and distribution chain limitations. Integration of these into a methodical systematic approach will maximize the chances of a successful outcome. As R&D dollars become ever scarcer, it becomes increasingly evident that early consideration of as many factors as possible is the most efficient way to proceed. This is true independent of the route of administration. In practice, this leads to the strategy of getting to FIH as quickly as possible with a formulation strategy that accounts for both physicochemical properties and physiologic influences.

A complete set of algorithms covering the four classes and all possible dosage forms is well beyond the scope of this article. However, a few fundamental principles can be covered. First, it is critical to characterize your compound. Understanding the basic behavior of a given compound in various solvents and across a range of pHs is fundamental to designing a dosage form. For instance, a compound soluble only at lower pHs will require a different formulation than one freely soluble at, for example, pH 7. Likewise, a soluble but impermeable compound will require yet another strategy. Very importantly, this is true whether one is administering the drug, for example, IV or orally. The implications to formulation are different for the different routes of administration but the fact that these properties need to be accounted for is universal. It is important that the drug developer or the CRO be equipped with a range of technologies to address the various patterns that emerge. Nothing wastes more time and money than trying to fit a drug to a specific preordained delivery technology.

Armed with the proper set of tools one can rapidly narrow down the potential approaches. For the most part, all drug delivery strategies are trying to control drug exposure. Most often, one is trying to maximize it over time and/or concentration but frequently goals also include extended release and/or site specific delivery. In addition to the

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delivery goals, other functions are often required such as API stabilization or taste masking as two examples. In short, no one formulation approach will ever satisfy all or even a substantial portion of drug delivery demands.

For oral drug delivery, a simplified summary of approaches based on properties might look like Table 1. Each approach must then be tailored to meet the other demands of that particular API and desired product profile.

Table 1

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	<ul style="list-style-type: none"> Techniques to increase surface area like particle size reduction, solid solution, solid dispersion Solutions using solvents and/or surfactants 	
3	High	Low	Incorporate permeability enhancers, maximize local luminal concentration	
4	Low	Low	Combine 2 and 3	

If formulation conditions dictate that a non-oral dosage form be used, similar charts exist for virtually all routes of administration. Each route of administration will of course have different options but they are all ruled by the interplay of the drug's physicochemical properties and the local and systemic physiology they encounter.

Concluding Remarks

Independent of the final dosage form, ideal drug development involves an iterative process of setting goals, performing formulation work and developmental stage appropriate testing. Early on, for example, after physicochemical evaluations are complete, screening BCS testing and early polymorph screens might be performed. After thorough preformulation including solubility and stability testing, early formulations might again be screened for their impact on dissolution or bioavailability. This approach is repeated such that at each inflection point data is gathered to support the development plan. In this way, FIH is achieved most efficiently and in such a way as to insure clinically relevant data is obtained.

¹ Chi-Yuan Wu and Leslie Z. Benet, Predicting Drug Disposition via Application of BCS: Transport/Absorption/Elimination Interplay and Development of a Biopharmaceutics Drug Disposition Classification System, *Pharmaceutical Research*, January 2005, 22(1), 11-23.

² <http://www.fda.gov/AboutFDA/CentersOffices/cder/ucm128219.htm>

³ M. Sherry Ku, Use of the Biopharmaceutical Classification System in Early Drug Development, *AAPS J.*, March 2008, 10(1), 208-212.

About The Authors

Mark Mitchnick, MD

Dr. Mitchnick is the CEO of Particle Sciences, Inc., a drug development CRO specializing in advanced drug-delivery technologies. He holds over 30 issued and pending patents related to drug delivery, surface chemistry and medical devices. Dr. Mitchnick has been extensively involved with both the formulation and clinical evaluation of pharmaceuticals, topics he has written extensively about and spoken on internationally. He has experience with the FDA, the EMEA and several developing world regulatory agencies. He serves a Director for several Life Sciences companies representing himself or institutional investors. Dr. Mitchnick received a B.Sc. in Animal Sciences from Purdue University and an M.D. from Georgetown University Medical School. He was trained in Pediatrics at The New York Hospital, Cornell Medical Center has practiced privately in the US and worked as a Pediatrician in a number of resource poor nations including Thailand and Nicaragua.

Robert W. Lee, PhD

Dr. Lee is Vice President of Pharmaceutical Development at Particle Sciences Inc. He is responsible for product development at Particle Sciences as well as providing support to clinical manufacturing operations and business development. His responsibilities include oversight of formulation development, drug delivery, analytical sciences, quality control, and quality assurance.

Before joining Particle Sciences, Dr. Lee held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Corp. Dr. Lee holds BS's in Biology and Chemistry from the University of Washington and a PhD in Physical Bioorganic Chemistry from the University of California-Santa Barbara.

Dr. Lee has published articles in numerous peer-reviewed journals and three book chapters plus holds 11 issued patents and 14 provisional or PCT patent applications. Dr. Lee has more than 22 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. He maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in 1992, and serving as a reviewer for both the *International Journal of Pharmaceutics* and *Journal of Pharmaceutical Sciences*.

