Chapter 1
Introduction

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1.1 Introduction to Biopharmaceutical Classification System

With advancement in combinatorial chemistry and high throughput screening large number of drug molecules with required pharmacological activity have been developed (Alsenz and Kansy 546). These newly developed compounds have undesirable physicochemical properties like high lipophilicity, poor aqueous solubility and high molecular weight. The five key physicochemical parameters involved in early compound screening are dissociation constant, solubility, permeability, stability and lipophilicity. Amongst them poor aqueous solubility is ranked higher in the critical compound properties. Dissolution enhancement is thus one of the most important prerequisite in the field of dosage form designing.

The biopharmaceutical classification system (BCS) is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. The BCS was first devised in 1995, by Amidon et al. and has become a benchmark for regulating bioequivalence of oral drug products. The BCS serves as a guiding tool to formulation scientists. It recommends strategies to improve the drug development process by proper selection of dosage form and bioequivalence tests. It also recommends a class of immediate release (IR) solid dosage forms, for which bioequivalence can be assessed by *in vitro* dissolution tests (Sachan et al. 76). The influence of each of the three factors, dissolution, solubility and intestinal permeability on the oral absorption of drugs can be assessed by BCS. FDA has adopted it as a regulating tool in drug product development. The drug product dissolution standards can be set by BCS. This allows for *in vivo in vitro* correlation (IVIVC) and can significantly reduce *in vivo* studies. Thus, save time in product development.

**Class Boundaries Used in BCS** (Chavda, Patel, and Anand 62)

1. When the highest dose strength of a drug substance over a pH range of 1 to 7.5 is soluble in 250 ml water it is considered as highly soluble.
2. Based on the mass balance or in comparison to an intravenous dose when the extent of absorption in humans is determined to be 90% of an administered dose the drug is considered to be highly permeable.
3. When 85% of the labeled amount of drug substance dissolves within 30 minutes in a volume of 900 ml buffer solution, using USP apparatus I or II the drug product is considered to be rapidly dissolving.
The BCS defines three dimensionless numbers to characterize drug substances. They are dose number ($D_o$), dissolution number ($D_n$) and absorption number ($A_n$). The most fundamental view of GI drug absorption is represented by these numbers, which are combinations of physicochemical and physiological parameters.

First, the absorption number ($A_n$) is the ratio of permeability ($P_{\text{eff}}$) and the gut radius ($R$) times the residence time ($T_{\text{si}}$) in the small intestine, which can be written as the ratio of residence time and absorptive time ($T_{\text{abs}}$)

$$A_n = \frac{P_{\text{eff}}}{R} \times (T_{\text{si}}) = \frac{(T_{\text{si}})}{(T_{\text{abs}})}$$

Second, is the dissolution number ($D_n$) which is the ratio of the residence time to the dissolution time ($T_{\text{diss}}$), which includes solubility ($C_s$), diffusivity ($D$), density ($\rho$), and the initial particle radius ($r$) of a compound and the intestinal transit time ($T_{\text{si}}$).

$$D_n = \frac{(3D)}{r^2} \left( \frac{C_s}{\rho} \right) (T_{\text{si}}) = \frac{T_{\text{si}}}{T_{\text{diss}}}$$

Finally, there is the dose number, $D_o$, which is defined as the ratio of dose concentration to drug solubility

$$D_o = \frac{M/V_0}{C_s}$$

Where, $C_s$ is the solubility, $M$ is the dose, and $V_0$ is the volume of water taken with the dose, which is generally set to be 250 ml.

The fraction absorbed ($F$) of a solution follows an exponential function, and can be calculated by

$$F = 1 - e^{-2A_n}$$

Dissolution is an important parameter for BCS class II drugs as it changes the actual drug concentration in solution over time. Consequently, dissolution is brought into the
classification system since it affects the drug concentration at the membrane surface. The dissolution of a poorly soluble compound is normally low \((D_n < 1)\), while for many poorly soluble compounds \(A_n\) and \(D_o\) are usually high (class II) (Löbenberg and Amidon 3).

**Extension to BCS: (BCS Containing Six Classes)**

Bergstrom et al. devised a modified BCS and they categorized the drugs into six classes based on the solubility and permeability. The solubility was classified as "high" or "low" and the permeability were allotted as "low", "intermediate," or "high". This new classification was developed based on the calculated surface area descriptors on the one hand and solubility and permeability on the other side. Surface areas related to the non-polar part of the molecule resulted in good predictions of permeability. It was thus, proposed that these models would be useful for early detection of absorption profiles of the compound during the early stages of drug discovery so that the necessary modifications can be made to optimize the pharmacokinetic parameters.

Dissolution is a process by which a solid substance (drug) goes into the solution, that is, mass transfer of molecules from the solid surface to the liquid phase. The solubility is an intrinsic property of a drug substance by which it forms chemically and physically homogenous mixtures with other substances. The degree of solubility is the amount of the solute in a saturated solution at any given temperature. Dissolution and solubility are two different phenomena. In contrast to solubility, the dissolution is a dynamic process and better related to drug absorption and bioavailability. However, the rate of dissolution for a drug substance is directly proportional to its solubility in the dissolution medium. A compound should possess aqueous solubility in excess of 1% (10 mg/ml) over the pH range 1-7 at 37°C, to avoid any kind of bioabsorption problems. If the intrinsic dissolution rate is greater than 1 mg/cm²/min then the absorption remains unaffected (Yu et al. 921).

Thus, the oral absorption is particularly limited for BCS class II drugs by their (a) inefficiency of the whole dose to be dissolved in the GI aqueous fluid or (b) very slow dissolution rate. Thus, dissolution is a rate limiting step for BCS class II drugs and a large increase in bioavailability can result by even a small increase in dissolution rate. Therefore, an enhancement of the dissolution rate of BCS Class II drugs can be a key factor for improving their bioavailability.
Modification in BCS system: Developability Classification System (Butler and Dressman 4940)

A modification in BCS system was done in order to classify the drugs based on the factors affecting their oral absorption. According to the principles of Quality by Design (QbD), the modified system provides more appropriate classification system. The new method is based on following assumptions:

1. For the determination of the extent of human absorption the human fasted intestinal solubility parameter (e.g. by using FaSSIF) can be used as the primary measure of in vivo solubility.
2. For class II drugs, solubility limited absorbable dose (SLAD) concept, to be used assuming, their permeability and solubility are compensatory.
3. As a better means of evaluating the development risks and critical quality attributes (CQAs) for drugs with dissolution rate limited extent of absorption the dissolution rate can be expressed as a target drug particle size and not dose/solubility ratio.

Thus, this modified system is significantly deviated from the BCS mainly for Class II drugs with addition of two subclasses and giving emphasis on the prediction of extent rather than the rate of oral absorption. This modified system referred to as the Developability Classification System (DCS), is not simply a regulatory classification system but aims at issues in product development. One of the important advantage of this DCS is it gives an early signal to the formulator about poorly soluble drugs that can be adequately formulated via simple size control whereas others that need specialized solubilisation techniques in order to obtain complete oral absorption and avoid solubility related food effects.
1.2 Introduction to Dissolution Enhancement Techniques

The different methods available to enhance the dissolution and absorption rates of poorly soluble drugs are summarized in Table 1.1

<table>
<thead>
<tr>
<th>Methods which increase the solubility</th>
<th>Methods which increase the surface area</th>
<th>Newer technologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modifying the pH of microenvironment</td>
<td>Micronization</td>
<td>Lipid emulsions</td>
</tr>
<tr>
<td>Salt formation of weak acids and weak bases</td>
<td>Use of surfactants (to enhance effective surface area by improvement in wetting)</td>
<td>Microemulsions</td>
</tr>
<tr>
<td>Use of solvates and hydrates</td>
<td>Solvent deposition</td>
<td>Self emulsifying drug delivery systems</td>
</tr>
<tr>
<td>Use of selected polymorphic forms</td>
<td>Solid dispersion</td>
<td>Nanosizing by precipitation</td>
</tr>
<tr>
<td>Complexation</td>
<td>Liquid-solid compacts</td>
<td>Cryogenic and super critical fluid technologies</td>
</tr>
<tr>
<td>Prodrug approach</td>
<td></td>
<td>Melt-granulation</td>
</tr>
<tr>
<td>Use of surfactants</td>
<td></td>
<td>Melt-extrusion</td>
</tr>
<tr>
<td>Sublimation technique</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.2.1 Solid Dispersion System

Solid dispersion (SD) is the most widely used technique because of promises it offers in the bioavailability enhancement of poorly water-soluble drugs, low cost and industrial feasibility. Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared my melting, solvent or melting-solvent method (Chiou and Riegelman 1281).
Advantages of Solid Dispersions

1. Particle size reduction
In SD some drugs get molecularly dispersed in the carrier, which represent the last state on particle size reduction. This increases the effective surface area of the drug resulting in an increased dissolution rate and, hence, improved bioavailability (Leuner and Dressman 47).

2. Improvement in wettability
As the wettabillity of drug particles is increased the dissolution rate is also significantly increased (Karavas et al. 103). Carriers with surface activity like bile salts significantly increase the drug wettabillity. Moreover, it influences the drug dissolution profile by direct dissolution or co-solvent effects (Pouton 278).

3. Increasing the degree of porosity
Solid dispersion creates particles with highly porous structure. Carrier property influences the degree of porosity. Solid dispersions prepared from linear polymers have larger and more porous particles than reticular polymers and, so, have a high dissolution rate (Sharma and Jain 149). The increased porosity of SD particles enhances the drug dissolution rate.

4. Amorphization of drug
Amorphous forms of poorly water-soluble drugs have more aqueous solubility compared to its crystalline forms (Pokharkar et al. 20). In case of amorphous state no energy is needed to disrupt the crystal lattice during dissolution process (Taylor and Zografi 1691). Dissolution of SD results in supersaturated systems, where the drug is in metastable polymorphic form with higher solubility than the most stable crystal form. Amorphous compositions for drugs with low crystal energy (low melting temperature or heat of fusion), is detected by the difference in melting temperature between drug and carrier while for drugs with high crystal energy it can be obtained by selecting carriers, which exhibit specific interactions with them (Vippagunata et al. 111).
Properties of a Carrier for Solid Dispersions

Following criteria should be considered while selecting carriers for SD:

(i) It should be hydrophilic in nature so that it improves wettability and hence dissolution.
(ii) It must possess high glass transition temperature to improve stability.
(iii) It must have minimal water uptake capacity.
(iv) The drug and the carrier should be soluble in common solvent if solvent evaporation technique is used for its preparation.
(v) It should have a lower melting point if solid dispersions are to be prepared by melting method.
(vi) It must possess solid solution forming capacity with the drug having similar solubility parameters.

There are some problems that restrict the commercialization of SD. During the processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state of drug may revert back to crystalline state and decrease its dissolution rate and thus affects the physical stability. Moisture also plays an important role on the storage stability of amorphous dosage forms as it may promote drug mobility and cause drug crystallization. Moreover, phase separation, crystal growth, reversion of amorphous to the crystalline state or from a metastable crystalline form to a more stable form during storage is observed. This is because of the carriers used in SD which absorbs moisture (Tiwari et al. 1338). Solid dispersions are soft and tacky in nature, which results in poor flowability and compressibility. This may create trouble during the processing and the final product shows poor reproducibility of their physicochemical properties.

Table 1.2 summarizes the methods of preparation SD, advantages, disadvantages and the carriers commonly used for it (Tiwari et al. 1338)
<table>
<thead>
<tr>
<th>Method of preparation</th>
<th>Carriers used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td><strong>Solvent Evaporation</strong></td>
<td></td>
</tr>
<tr>
<td>Ease in Preparation</td>
<td>Toxicity</td>
</tr>
<tr>
<td>Feasible scale up</td>
<td>Residual amount</td>
</tr>
<tr>
<td><strong>Melting</strong></td>
<td></td>
</tr>
<tr>
<td>Ease in preparation</td>
<td>Drug degradation for thermosensitive drugs</td>
</tr>
<tr>
<td>Feasible scale up</td>
<td>Low solubility in molten carrier</td>
</tr>
<tr>
<td><strong>Antisolvent</strong></td>
<td></td>
</tr>
<tr>
<td>Solvent free</td>
<td>Low solubility in CO₂ Limited scale up</td>
</tr>
</tbody>
</table>

| Polymeric materials: | PVP, HPMC, HPMCAS, HPMCP, Eudragit systems (enteric acrylic acid based polymers) |
| Acids:              | Citric acid, succinic acid and tartaric acid |
| Sugars:             | Dextrose, sucrose, maltose, sorbitol, galactose, xylitol, inulin, chitosan, dextrin, cyclodextrin |
| Surfactants:        | Poloxamer, deoxycholic acid, tweens, spans, compritol 888 ATO, gelucire 44/14 and 50/13, sodium lauryl sulfate, phospholipid, polyoxyethylene stearate. |
| Miscellaneous:      | Urea, urethane, hydroxyalkyl xanthene, pentaerythritol. |

The third generation SD (solid dispersions with surfactant) may overcome problem like requirement of large amount of carrier. The problem of poor compressibility and scale up can be overcome by adsorbing the SD onto a porous free flowing carrier. This will help in commercialization of SD as tablet or capsule dosage form. Also, the stability problem can be also addressed by use of novel excipient like Neusilin® which along with improving the flow property also inhibits the conversion of amorphous form back to the crystalline form entrapping the molecularly dispersed drug into its porous network.
1.2.2 Marketed Products (Thayer 13)

Following is the list of drugs, which are available in market as SD or solid dispersion adsorbate (SDA).

<table>
<thead>
<tr>
<th>Product Name</th>
<th>BCS Class</th>
<th>Dispersion Polymer</th>
<th>Company</th>
<th>Dispersion Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afeditab (Nifedipine)</td>
<td>II</td>
<td>Poloxamer or PVP</td>
<td>Elan Cor. (Ireland)</td>
<td>Melt/adsorb on Carrier</td>
</tr>
<tr>
<td>Certican (Everolimus)</td>
<td>III</td>
<td>HPMC</td>
<td>Novartis (Switzerland)</td>
<td>Melt or spray drying</td>
</tr>
<tr>
<td>Cesamet (Nabilone)</td>
<td>II</td>
<td>Povidone</td>
<td>Lilly (U.S)</td>
<td>Process unknown</td>
</tr>
<tr>
<td>Fenoglide (Fenofibrate)</td>
<td>II</td>
<td>Polyethylene glycol (PEG)</td>
<td>Lifecycle Pharma (Denmark)</td>
<td>Spray melt</td>
</tr>
<tr>
<td>Gris-PEG (Griseofulvin)</td>
<td>II</td>
<td>Polyethylene glycol (PEG)</td>
<td>Novartis (Switzerland)</td>
<td>Melt Process</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>II</td>
<td>Various</td>
<td>Soliqs (Germany)</td>
<td>Melt Extrusion</td>
</tr>
<tr>
<td>Intelence (etravirine)</td>
<td>IV</td>
<td>HPMC</td>
<td>Tibotec (New Jersey)</td>
<td>Spray Drying</td>
</tr>
<tr>
<td>Isoptin SRE-240 (Verapamil)</td>
<td>II</td>
<td>Various</td>
<td>Soliqs (Germany)</td>
<td>Melt Extrusion</td>
</tr>
<tr>
<td>Kaletra (lopinavir and Ritonavir)</td>
<td>II and IV</td>
<td>PVP/Polyvinyl acetate</td>
<td>Abbott Laboratories (Illinois)</td>
<td>Melt extrusion</td>
</tr>
<tr>
<td>LCP-Tacro (Tacrolimus)</td>
<td>II</td>
<td>HPMC</td>
<td>Lifecycle Pharma (Denmark)</td>
<td>Melt granulation</td>
</tr>
<tr>
<td>Rezulin (troglitazone)</td>
<td>II</td>
<td>PVP</td>
<td>Pfizer (New York)</td>
<td>Melt extrusion</td>
</tr>
<tr>
<td>Sporanox (itraconazole)</td>
<td>II</td>
<td>HPMC</td>
<td>Janssen (Belgium)</td>
<td>Spray layering</td>
</tr>
<tr>
<td>Torcetrapibb</td>
<td>II</td>
<td>HPMC succinate</td>
<td>Pfizer (NY)</td>
<td>Spray drying</td>
</tr>
</tbody>
</table>
1.3 Introduction to Quality by Design Approach

There has been revolution in drug development process due to introduction of the concept of QbD in recent years. It has shifted the whole paradigm from a univariate empirical understanding to a systematic multivariate approach to build in the systemic quality of the final pharmaceutical product. Since January 2012, QbD has become mandatory for formulation development in the industry.

Quality by Design is a vast term that encompasses predefined target quality, along with predictable quality by fixing desired and predetermined specifications. Safe and effective products can be obtained by considering relevant physicochemical, physiological, pharmacological and clinical attributes (Zidan et al. 55). This can be done by thorough investigations of variables associated with raw materials, product design, process and scale-up. Design of experiments (DoE) is an important tool of the QbD which helps in identification of the factors and their interaction effects (Lionberger et al. 268). Quality by Design identifies CQA; critical material attributes (CMA) and critical process parameters (CPP) and helps in development of drug product with desired characteristics. Thus QbD, means designing and development of formulations and manufacturing processes to achieve predefined product quality (Lawrence 781). It identifies sources of variability in the manufacturing process and establishes a relationship between formulation and process. This knowledge is then utilized to implement a flexible and robust manufacturing process and products with the desired quality over a period of time (Cui et al. 312). The steps of QbD are outlined in the Fig.1.1.

Fig. 1.1: Overview of QbD (L Chaves et al. 253)
Quality Target Product Profile (QTPP) is defined as the desired quality characteristics of a product we want to achieve in order to have a safe and efficacious product. Before the publication of ICH Q8(R1), the QTPP was called as target product quality profile (TPQP). Once QTPP has been identified, the next step is to indentify relevant CQAs. A CQA has been defined as “a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. The CQAs and CPPs are the foundations of regulatory requirements. Process validation protocols typically stipulate what are the CQAs and CPPs and monitor and control their performance.

Once CQAs for a product have been identified, the next step is to find out the product design space (that is, specifications for in-process, drug substance and drug product attributes). ICH Q8(R2) defines design space as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.

The overall approach toward process characterization involves three key steps (Mire-Sluis et al. 1; Barrett et al. 938; Gupta et al. 1; Seely et al. 31). First is risk analysis to identify parameters for process characterization. Second are studies to be designed using DoE, such that the data are amenable for use in understanding and defining the design space. And third is the studies are performed and the results analyzed to determine the importance of the parameters as well as their role in establishing design space.

A control strategy should be adopted once a sufficient level of process understanding is achieved, to assure that the process will remain in control within the normal variation in material attributes and process operating ranges. Control strategy is a cornerstone of a modern quality system. It can be a combination of parametric and attribute-based controls. Generally, real-time monitoring and control of the process is more preferable over relying on end product testing.

The benefits to FDA with the implementation of QbD are tremendous. These includes enhancement of the scientific foundation of product review, better coordination across review,
compliance and inspection, improving information in regulatory submissions, more consistency of regulatory decision making, improving quality of review (establishing a quality management system for CMC), more flexibility in decision making, ensuring decisions are made on science and not on empirical information, involving various disciplines in decision making, and using resources to address higher risks (Rathore and Winkle 26).

Likewise, QbD also provides numerous advantages to industry. It ensures better design of products with less problems in manufacturing, reduces the number of manufacturing supplements required for post-market changes, relies more on process, and understanding and mitigation of risk, allows implementation of new technology to improve manufacturing without regulatory scrutiny, enables possible reduction in overall costs of manufacturing resulting in less waste, ensures efficient review and thus reduced deficiencies resulting in quicker approvals, enables continuous improvements in products and manufacturing, provides better understanding of how active pharmaceutical ingredients and excipients affect manufacturing and relates manufacturing processes to the clinic during design, thereby providing a better overall business model (Kozlowski and Swann 707).

Quality by Design is thus an evolution and not a revolution’’ – an evolution that is in response to the increasing cost pressures on both the regulatory agencies and industry to control the escalation of drug prices (Rathore and Devine 380). Quality by Design will continue to evolve for years to come as new tools and technologies advance to improve the way we mitigate risks and increase our understanding and control of the manufacturing processes. In addition to increasing quality, the pharmaceutical industry will reduce development and manufacturing cycle times as well as costs in the process.
1.4 References


Chapter 1


