1. INTRODUCTION

Oral route has been the major route of drug delivery for chronic treatment of number of diseases and is the simplest and easiest way of administering drugs. The greater stability, smaller bulk, accurate dosage and easy production of solid oral dosage forms have many advantages over other types of oral dosage forms\(^1\). It also offers convenient, cost-effective and non-invasive mode of drug administration. About 80% of the dosage forms in the worldwide market are administered orally. Most of the new chemical entities (NCE) under development are intended to be marketed as oral solid dosage forms\(^2\)\(^{-}\)\(^3\). Following oral administration of a solid dosage form, the drug must first dissolve in the gastrointestinal fluids before absorption across the intestinal mucosa to reach the systemic circulation and exert its pharmacological effect. Hence, the key parameters for successful oral product development include aqueous solubility and intestinal permeability\(^4\).

1.1 BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Biopharmaceutics Classification System (BCS) described by Amidon et al., is a scientific framework that classifies drug substances in four groups (Figure 1) according to their aqueous solubility and intestinal permeability properties\(^5\). BCS allows the prediction of \textit{in vivo} pharmacokinetics of immediate release (IR) dosage forms by considering three important factors; solubility, intestinal permeability and dissolution rate that governs the rate of drug absorption\(^6\). Extensive research and discussion exists on the validity and applicability of BCS\(^7\).

The classification is based on solubility of highest dose of drug and extent of its intestinal absorption. According to the US food and drug administration (FDA) guidance, a drug substance is considered highly soluble when the highest strength is soluble in 250 ml or less of aqueous media over the pH range of 1.0–7.5. The volume of media was decided based on bioequivalence protocols and to simulate \textit{in vivo} conditions. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be greater than 90%. The permeability studies are conducted using in-situ rat perfusion models and \textit{in vitro} epithelial cell culture models\(^8\)\(^{-}\)\(^9\).
The drug is said to produce rapid dissolution if the release from an immediate release (IR) dosage form is not less than 85% of the labelled amount within 30 min using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 ml or less of each of the following media: 1) 0.1 N HCl (pH 1.2) or USP simulated gastric fluid without enzymes; 2) pH 4.5 buffer; and 3) pH 6.8 buffer or USP simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be a slow dissolution product.

![Biopharmaceuticals classification system](image)

**Figure 1** Biopharmaceutics classification system

**Class I** drugs exhibit high absorption number and high dissolution number. The rate limiting step for drug absorption is gastric emptying rate if dissolution is rapid\(^6\). These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate\(^11\).

**Class II** drugs have high absorption number and low dissolution number. The absorption/bioavailability are limited by dissolution rate. These drugs exhibit varying bioavailability and small increment in dissolution may hence result in substantial improvement in bioavailability. Hence, dissolution enhancement is the key factor in formulating BCS class II drugs.

**Class III** drugs show permeability as the rate-limiting step for drug absorption. These drugs exhibit rapid dissolution and high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation in the rate and extent of drug
absorption is attributable to alteration of physiology and membrane permeability rather than the dosage form factors.

Class IV drugs exhibit challenging molecular properties such as low solubility and low permeability. Since both solubility and permeability are rate-limiting steps for absorption physiological factors like, gastric emptying time and gastrointestinal transit time, highly influence the absorption of BCS class IV drugs. These drugs exhibit large inter and intra subject variation in terms of absorption resulting difficulty in formulation development.

Recent developments in combinatorial chemistry and high-throughput screening used in drug discovery has resulted in increased number of drugs with poor aqueous solubility. Approximately 90 % of the NCEs are considered poorly soluble with either high or low permeability (BCS II and IV). These drugs also exhibit considerable interaction with food resulting in high fast/fed variability as shown in Figure 2. Hence, the delivery of these poorly soluble drugs through oral route results in low bioavailability and high inter subject variability.

![Bar chart showing occurrence of food effects (positive, negative, or no effect) in percent by BCS category](image)

**Figure 2** Occurrence of food effects (positive, negative, or no effect) in percent by BCS category

Due to the combination of low permeability and low solubility, BCS IV compounds are generally troublesome drug candidates and therefore, rarely developed and marketed. Currently, approximately 40 % of the drugs marketed as oral IR dosage
forms are categorized as BCS II drugs with solubility less than 100 μg/ml\textsuperscript{17-19}. These are usually more promising candidates since permeability through the gastro intestinal mucosa is not a problem. For poorly soluble, highly permeable (BCS class II) drugs, the rate of oral absorption is often controlled by the solubility and/or dissolution rate in the gastrointestinal tract\textsuperscript{20-22}.

Solubility is generally defined as the concentration of the compound in solution which is in contact with an excess amount of the solid compound\textsuperscript{23}. Solubility is closely related to dissolution which is a kinetic process in which, the drug molecules are detached from the solid surface and diffuses across the diffusion layer surrounding the solid surface. The drug administered orally can show therapeutic effect after entering into systemic circulation. The extent of the drug in the systemic circulation depends on the drug available for absorption in gastro intestinal tract (GIT). The drug available for GI absorption depends on the rate of dissolution and the aqueous solubility of the drug. For a drug to be absorbed into systemic circulation after oral administration the solid dosage form must disintegrate, dissolve, and diffuse to the surface of the intestinal epithelium (Figure 3). As the concentration of the compound increases when it dissolves, more drug molecules are present at the surface of the epithelial cells and a greater amount of drug is available for absorption. The maximum amount of drug available is determined by solubility and also dissolution rate\textsuperscript{24}.

The relationship of solubility and dissolution rate is described by the Nernst–Brunner/ Noyes–Whitney equation\textsuperscript{25}:

\[
\frac{dC}{dt} = D \cdot \frac{A(C_s - C_t)}{Vh} \quad (1)
\]

Where, \(\frac{dC}{dt}\) is the dissolution rate, ‘D’ the diffusion coefficient, ‘A’ the surface area, ‘h’ the diffusion layer thickness, ‘\(C_s\)’ the saturation solubility of the drug in the bulk medium and ‘\(C_t\)’ the amount of drug in solution at time ‘t’. If the concentration of the solute at the particle surface reaches its maximum value or solubility and the concentration in the bulk solvent is absorbed instantaneously, then

\[
\frac{dM}{dt} = D \cdot \frac{A}{h} C_s \quad (2)
\]
All the terms in above equation are constant under given conditions, and the dissolution rate depends on solubility ($C_s$). The low solubility ($C_s$) of the poorly soluble drug leads poor absorption and low oral bioavailability.

Figure 3 Schematic representation of the dissolution process of a solid dosage form

1.2 STRATEGIES TO IMPROVE BIOAVAILABILITY

The solubility problems of BCS class II drugs and methods for overcoming the solubility limitations are to be identified and applied commercially so that potential therapeutic benefits of these active ingredients can be realized. The increase in the amount of drug dissolved at the absorption site usually results in improvement in bioavailability. Two strategies are usually employed to achieve this; i) Improvement in solubility and ii) Enhancement in dissolution rate (Figure 4).
Over the years, a number of different strategies have been developed in order to overcome these limitations. Some of these efforts include salt formation\textsuperscript{26}, prodrugs\textsuperscript{27}, particle size reduction (Micronization)\textsuperscript{28}, co-solvency\textsuperscript{29}, hydrotropic solubilization\textsuperscript{30}, cyclodextrin complexation\textsuperscript{31}, micellar solubilization\textsuperscript{32}, pH modification\textsuperscript{33} and screening for more soluble analogues\textsuperscript{34}. However, there are some practical limitations to the few of above-mentioned techniques as mentioned in Table 1.

![Figure 4](representation_of_bcs_with_indication_of_improvements_inDifferent_class_to_obtain_good_in_vitro_in_vivo_correlation.jpg)

**Figure 4** Representation of BCS with indication of improvements in different class to obtain good *in vitro in vivo* correlation

The need of novel strategies has been the driving force for the development of technologies to improve the bioavailability-related problems of poorly water-soluble drugs. Liquisolid compaction and solid dispersion technologies shows promising potential in improving the dissolution and bioavailability of BCS class II drugs. Each of these techniques focuses on improving the extent or rate at which the drug enters solution in an effort to increase the bioavailability.
### Table 1 Techniques to improve bioavailability and their limitations

<table>
<thead>
<tr>
<th>Technique</th>
<th>Limitations</th>
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</table>
| Micronization              | Micronized powders tend to agglomerate  
|                            | Handling difficulties and poor wettability<sup>35</sup>                                                                                     |
| Cyclodextrin               | Toxicity problems  
|                            | Not suitable for large doses due to increase in bulk<sup>36</sup>                                                                           |
| Micellar Solubilization    | Liquid formulations are usually undesirable from patient acceptability and commercialization.  
|                            | High concentration of surfactants cannot be used<sup>37</sup>                                                                               |
| Soluble prodrugs           | Difficult to balance the properties of prodrug chemical stability and enzymatic liability in concert with prodrug solubility and parent drug or prodrug intestinal permeability |
| Salts                      | Salt formation is not possible for neutral compounds  
|                            | salts formed may convert back to their original acid or base forms and lead to aggregation in the GI tract<sup>38</sup>             |
| Co-solvency                | Toxicity and tolerability related with the level of solvent administered  
|                            | Precipitation occurs upon dilution with aqueous media<sup>37</sup>                                                                          |
| pH modification            | Chemical stability and precipitation of drug<sup>39</sup>                                                                                   |
1.2.1 LIQUISOLID COMPACTS

Liquisolid technology developed by Spireas\textsuperscript{40} is one of the most promising approaches to improve the aqueous solubility and drug dissolution. The concept of liquisolid compaction technology was developed from powdered solution technology used to formulate liquid medications\textsuperscript{41}. A liquisolid system is defined as dry, non-adherent, free-flowing and compressible powder mixture obtained from liquid drugs, drug suspension or drug solutions in non-volatile solvents\textsuperscript{40}.

In this technique, the poorly soluble drug is dissolved or dispersed in suitable non-volatile solvent and converted to dry, free flowing and readily compressible powder using selected excipients referred as carrier and coat materials (Figure 5).

\textbf{Figure 5} Schematic representation of manufacturing of liquisolid systems
Carrier material refers to porous materials possessing sufficient absorption properties like, micro crystalline cellulose (MCC). Coating material must possess high adsorption capacity with fine particle size. Amorphous silicon dioxide (Silica) can be used as coating material for adsorbing excess of liquid. Inert, non-volatile, and preferably water-miscible organic solvents with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine can be used as liquid vehicles. Since non-volatile solvents are used to prepare the drug solution/suspension, the liquid is not evaporated and the drug is carried in a liquid system and is dispersed throughout the final product. This will increase the surface area and wettability of the particles resulting in the increase in solubility and dissolution. The improved drug release may result in a higher drug absorption and improvement in oral bioavailability.

1.2.1.1 Theory of liquisolid systems

A powder can retain only limited volume of liquid while maintaining acceptable flow and compression properties. Spireas developed a mathematical approach to calculate the amounts of carrier and coating materials required for the formulation of liquisolid systems. This approach was based on the flowable and compressible liquid retention potential.

The flowable liquid-retention potential (Φ-value) of a powder represents the maximum amount of non-volatile liquid that can be retained by unit weight of powder inside its bulk (w/w) while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by of angle of repose measurements. The limit of acceptable flowability was set at an angle of slide equal to $33^\circ$.

The compressible liquid-retention potential (Ψ-number) of a powder is defined as the maximum weight of liquid that a powder can retain inside its bulk (w/w) while maintaining acceptable compactability resulting in compacts of sufficient hardness without presenting any liquid squeezing out during compression. The compactability may be determined by pactisity ($\Omega$) which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The plateau crushing force is the force required to achieve maximum powder cohesiveness which, in turn results in maximum tablet hardness.
The excipient ratio (R) can give the amount of liquid retained by the carrier and coating materials with acceptable flow and compression properties. The excipient ratio R of a powder is defined as the ratio between the weights of carrier (Q) and coating materials (q) present in the formulation.

\[ R = \frac{\text{Weight of carrier}}{\text{Weight of coating material}} = \frac{Q}{q} \quad (3) \]

Preparation of a liquisolid system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier is not exceeded. This characteristic amount of liquid is termed as liquid load factor \( (L_f) \). The liquid load factor \( (L_f) \) is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system.

\[ \text{Load factor } L_f = \frac{\text{Weight of liquid medication}}{\text{Weight of carrier}} = \frac{W}{Q} \quad (4) \]

Hence, the powder excipients ratio R and liquid load factor \( L_f \) of the formulations are related as follows:

\[ L_f = \varphi + \varphi \left( \frac{1}{R} \right) \quad (5) \]

The required ingredient quantities of carrier and coat material can be calculated from the flowable liquid retention potentials using equation (5). The optimum quantities of carrier \( (Q_0) \) and coating material \( (q_o) \) required to convert a given amount of liquid medication (W) into an acceptable free flowing and compressible powder was calculated using the equation (3) and (4).

**1.2.1.2 Classification of liquisolid systems**

Liquisolid systems are classified into three types based on the type of liquid medication.

- Powdered drug solutions (Drug dissolved in non-volatile solvent)
- Powdered drug suspensions (Drug dispersed in non-volatile solvent)
- Powdered liquid drugs (Liquid drugs)
Based on formulation techniques classified into two types

- Liquisolid compacts
- Liquisolid microsystems

Liquisolid compacts refer to immediate or sustained release tablets/capsules prepared by combining with the adjuvants required for tableting or encapsulation such as lubricants, disintegrants/super disintegrants and binders.

Liquisolid microsystems refer to capsules prepared by combining an additive, e.g., polyvinyl pyrrolidone (PVP) in the liquid medication. The resulting unit size may be as much as five times less than that of liquisolid compacts.

1.2.1.3 Advantage of liquisolid systems

- Increased wetting and rapid drug release compared to their commercial counterparts.
- Liquid drugs can be formulated with increased stability and ease of processing
- The production cost is lower than soft gelatin capsules
- Production is similar to that of conventional tablets
- Controlled drug delivery can be achieved using same principle
- It can be easily scaled up to industrial production

1.2.1.4 Limitations

- Requirement of high solubility of drug in non-volatile liquids used
- Not suitable for high dose drugs
- Low drug loading capacities

1.2.1.5 Mechanisms of enhanced drug release from liquisolid systems

The main suggested mechanisms include, increased surface area of drug available for release, increased aqueous solubility of the drug and improved wettability of the drug particles.

Many poorly soluble drugs have been formulated as liquisolid systems with improved solubility or dissolution rate. Different liquid vehicles, carrier and coating materials used to formulate these drug delivery systems are listed in Table 2.
**Table 2** List of poorly soluble drugs formulated as liquisolid systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Liquid vehicle</th>
<th>Carrier &amp; coating material</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam</td>
<td>Polyethylene glycol 400</td>
<td>MCC &amp; Colloidal Silica</td>
<td>45</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Capryol 90, Synperonic PE/L61, Solutol HS -15</td>
<td>MCC &amp; Colloidal Silica, Kollicoat SR 30 D</td>
<td>46</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Tween 80</td>
<td>MCC &amp; (Cabo-sil M-5)</td>
<td>47</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Cremophor EL</td>
<td>Lactose, (Cabo-sil M-5)</td>
<td>48</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Tween 80, Polyethylene glycol 400, Glycerin, propylene glycol</td>
<td>Avicel PH 200, Lactose monohydrate, (Cabo-sil M-5)</td>
<td>49</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Tween 80, Polyethylene glycol 400, Glycerin, propylene glycol</td>
<td>Avicel PH 200, Lactose monohydrate, (Cabo-sil M-5)</td>
<td>49</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Propylene glycol</td>
<td>Ceolus KG-802, Aerosil 200</td>
<td>50</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Propylene glycol</td>
<td>Avicel PH 102, Aerosil 200</td>
<td>51</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>Tween 80</td>
<td>Microcrystalline cellulose, Silica</td>
<td>52</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Poly ethylene glycol (PEG200) and Synperonic PE/L-61</td>
<td>Avicel PH 102, Aerosil 200</td>
<td>53</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>Polysorbate 20</td>
<td>Avicel PH 102, Aerosil 200</td>
<td>54</td>
</tr>
</tbody>
</table>
1.2.2 SOLID DISPERSIONS

Solid dispersion (SD) technique is a promising strategy to improve the solubility and dissolution of BCS class II drugs that show dissolution-rate-limited absorption. The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960. This technique was most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic and advantageous\textsuperscript{55}.

Solid dispersions are defined as, ‘a dispersion of one or more active ingredients in an inert carrier at the solid state, prepared by the fusion, the solvent or the melting solvent method’\textsuperscript{56}. The solid dispersions may also be called solid-state dispersions as first used by Mayersohn and Gibaldi\textsuperscript{57}. The improvement in the dissolution rate of drug from solid dispersion is due to particle size reduction, improved wetting, reduced agglomeration, change in the physical state of the drug and possibly dispersion of drug on a molecular level. The physical state of the solid dispersion will depend on the physicochemical properties of the carrier, drug, drug–carrier interactions and the preparation method\textsuperscript{10}. Hence, the selection of the carrier has an influence on the dissolution characteristics of the dispersed drug. A water-soluble carrier results in a fast release of the drug from the matrix and use of poorly soluble or insoluble carrier leads to a slower release of the drug from the matrix.

1.2.2.1 Classification of solid dispersions

First generation

First generation SDs include formulation of eutectic mixtures and use of crystalline carriers like urea and sugars\textsuperscript{58, 59}. Eutectic mixtures showed faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drugs were the main reasons for observed improvements in bioavailability. However, use of crystalline carriers hinders the release compared to amorphous carriers.
**Second generation**

Amorphous carriers like natural or synthetic polymers (Table 3) were used in the preparation of second generation SDs. The second generation solid dispersions show improved drug dissolution compared to first generation solid dispersions with crystalline carriers. The drugs are molecularly dispersed in an irregular form within the amorphous carrier. These are called as solid solutions.

**Figure 6** Schematic representation of classification of solid dispersions

**Solid solutions**: Drug and carrier are totally miscible with high soluble interaction energy resulting in a really true solution. The use of polymers produces a true solid solution (amorphous product) in which the crystalline drug is dissolved. This type of solid dispersion is homogeneous on a molecular level with only one phase. Solid solutions are again classified based on their miscibility and distribution in solvent. Based on miscibility they are divided into continuous and discontinuous solid solutions. According to the distribution of solute in the solvent, Substitutional and interstitial or amorphous solid solutions.
Table 3 Type of polymers used in the preparation of solid dispersion

<table>
<thead>
<tr>
<th>Polymer type</th>
<th>Polymer name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic</td>
<td>Povidone (PVP)</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycols (PEG)</td>
</tr>
<tr>
<td></td>
<td>Polymethacrylates</td>
</tr>
<tr>
<td></td>
<td>Hydroxy propyl methyl cellulose (HPMC)</td>
</tr>
<tr>
<td></td>
<td>Ethyl cellulose</td>
</tr>
<tr>
<td></td>
<td>Hydroxy propyl cellulose (HPC)</td>
</tr>
<tr>
<td></td>
<td>Starch derivatives</td>
</tr>
<tr>
<td>Natural</td>
<td></td>
</tr>
</tbody>
</table>

Continuous solid solutions: The components in this continuous solid solution are miscible or soluble at solid state in all proportions. The bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date\textsuperscript{56, 62}.

Discontinuous solid solutions: The solubility of each of the components in the other component is limited. The drug will present in supersaturated state because of forced solubilization or limited solubility in the carrier\textsuperscript{60}. These are composed of two phases. Drugs with a high melting point are candidates for producing discontinuous solid solutions.

Substitutional Solid Solution: The solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent as shown in Figure 7. It can form a continuous or discontinuous solid solution. The size and steric factors of the solute molecule plays a crucial role in the formation of solid solutions. According to the Hume-Ruthery rule, an extensive solid solution can be formed only when, the effective diameter of the solute differs less than 15 % from that of the solvent\textsuperscript{56}. 

Interstitial crystalline solid solutions: The dissolved molecules occupy the interstitial spaces between the solvent molecules (Figure 8) in the crystal lattice and usually form a discontinuous solid solution. The size of the solute is critical in order to fit into the interstices. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter less than 20 % (less than 0.59) of the solvent molecule's molecular diameter\(^{63}\).

Third generation:

The third generation SDs contains a surfactant carrier or a mixture of amorphous polymers and surfactants as carriers. These are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The surfactant that can be used in the preparation of solid dispersion was mentioned in Table 4.
Table 4 List of surfactants and lipids used in solid dispersion preparation

<table>
<thead>
<tr>
<th>Surfactants</th>
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</thead>
<tbody>
<tr>
<td>Compritol 888</td>
</tr>
<tr>
<td>Gelucire 40/14</td>
</tr>
<tr>
<td>Gelucire 50/13</td>
</tr>
</tbody>
</table>

1.2.2.2 Preparation methods

Different methods to prepare SD are shown in Figure 9.

Figure 9 Schematic representation of manufacturing procedure of solid dispersions

However, only few SD products are marketed currently. Recently use of polymers, polymeric surfactants in the preparation of solid dispersion gained much attention for the delivery of poorly soluble drugs. The use of polymers can overcome the certain problems related to solid dispersions and combining this technique with surface adsorption further provides advantages over conventional solid dispersion formulation and feasibility of large scale manufacturing.