CHAPTER II

2.1 LITERATURE ON BIOAVAILABILITY AND DISSOLUTION RATE

The most important property of a dosage form is its ability to deliver the active ingredients to its site of action in an amount sufficient to elicit the desired pharmacological response. This property of the dosage form has been variously referred to as its physiological availability, biologic availability or bioavailability. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly, the absorption of an intravenously administered drug is instantaneous and complete. However, for reasons of convenience and stability, most drugs are administered orally after first being formulated into dosage forms, usually tablets or capsules. The rate and extent of absorption from such dosage forms is usually not precisely known as it is affected by a number of factors related to the drug, dosage form and patient.

Dosage form related factors which can produce profound differences in drug bioavailability include formulation and manufacturing variables such as, particle size, the chemical form and solubility of the drug, the type and quantity of the excipients used, the compaction pressure etc. Among the patient related factors those over which the physician and/or the patient can exert some control include the time of administration of the drug relative to meals, co-administration of other drugs which may influence the absorption and compliance of the patient with the instructions of the physician, pharmacist or nurse. The patient related factors which
normally cannot be controlled but for which some allowance (or) adjustment can be made include age, disease state, abnormal genital characteristics and/or gastro-intestinal physiology. The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption in the gastro-intestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

Methods to enhance bioavailability can be related to one of two approaches. The first is pharmaceutically dependent and involves improvement of the absorption attributes by increasing the dissolution rate of the drug preparation. This usually is achieved by changing certain ingredients in the formulation, optimizing the manufacturing process or by altering the physico-chemical properties of the drug substance without altering its molecular structure. The second approach is pharmacokinetically dependent and deals with resolving specific bioavailability problems that are intrinsic mainly to the drug chemical entity which includes, using salt or ester form of the drug or prodrugs or by increasing the non-polar portion of a molecule by extending the length of the chain. In certain cases, however, significant enhancement of bioavailability can be obtained by modulating the drug metabolic fate, its distribution characteristics or its excretion profile.

**Dissolution and Absorption of Drugs from Solid Dosage Forms:**

Before being absorbed into systemic circulation, drugs must dissolve in body fluids existing at the site of absorption and the dissolved drug molecules from solution absorb or cross the biological barriers by various drug transport
mechanisms. Dissolution rate can be defined as the amount of solid substance that goes into solution per unit time under standard conditions of temperature, pH, solvent composition and constant solid surface area. It is a dynamic process and better related to drug absorption and bioavailability.

Wagner\textsuperscript{1} proposed the following scheme for the processes involved in the dissolution of solid dosage forms.

![Diagram of dissolution processes](image)

**Scheme -1**

Scheme -1 indicates the processes involved in the absorption of drugs after oral administration in the form of a tablet or capsule. Dissolution of the drug occurs not only from the fine particles of the drug that are ultimately produced, but also to a small degree from intact dosage form before its disintegration and from fragments and agglomerates produced after disintegration. \textit{In vitro}, process-4 (scheme - I) involves the absorption of the drugs. The drug dissolved in the gastro intestinal contents must diffuse through the aqueous fluids to the gastro intestinal barrier and then be transported through the barrier to the systemic circulation. When the
dissolution process is very much slower than the other processes, then the dissolution essentially and completely controls absorption rate. There is adequate evidence now available to conclude that the dissolution rate often partially or totally controls the rate of absorption. This is particularly true in the case of poorly soluble drugs. Examples of drugs for which dissolution rate limited absorption was observed include aspirin, tolbutamide, spiranolactone, prednisone, methyl prednisone, ampicillin, griseofulvin, sulphamethiazine, salicylamide, etc. The rates of the process of disintegration, deaggregation and dissolution are all dependent upon the composition and method of preparation of the dosage form. These rates are all largely dependent upon pharmaceutical factors, which the formulator can alter.

A more quantitative description of the dissolution rate is given by the Noyes-Whitney\(^2\) equation based on diffusion layer model:

\[
\frac{dc}{dt} = \frac{D}{h} S (C_s - C)
\]

Where

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>dc/dt</td>
<td>Rate of dissolution</td>
</tr>
<tr>
<td>S</td>
<td>Surface area</td>
</tr>
<tr>
<td>D</td>
<td>Diffusion coefficient</td>
</tr>
<tr>
<td>h</td>
<td>Thickness of the diffusion layer</td>
</tr>
<tr>
<td>Cs</td>
<td>Saturation solubility</td>
</tr>
<tr>
<td>C</td>
<td>Concentration of drug in solvent at time ‘t’</td>
</tr>
</tbody>
</table>
In dissolution rate limited absorption C is negligible compared to Cs. Under well defined conditions of use, D and h are relatively constant values that are not conveniently altered to any degree by product formulation. Hence,

\[
dc / dt = K \cdot S \cdot C_S
\]

i.e. Dissolution rate \(\alpha\) Surface area X Solubility

Thus, increasing either solubility or surface area or both can increase dissolution rate of poorly soluble drug. These two variables can be altered by the following techniques.

1. Controlling the solubility of weak acid or base by buffering either the entire dissolution medium or the microenvironment i.e. the diffusion layer surrounding a particle through the use of buffers and salts.

2. Controlling the solubility of the drug through the choice of physical state such as crystal form, its hydrates, its amorphous form and so on.

3. Controlling the surface area of the drug through control of particle size.

**Methods to Enhance the Dissolution Rate and Absorption of Poorly Soluble Drugs:**

The different methods available to enhance the dissolution and absorption rates of poorly soluble drugs are summarized in Table 2.1
### Table 2.1

Methods to Enhance the Dissolution of Poorly Soluble Drugs

<table>
<thead>
<tr>
<th>Method</th>
<th>Examples of drugs investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Methods which increase the solubility</strong></td>
<td></td>
</tr>
<tr>
<td>i. Buffering the pH of the microenvironment</td>
<td>Buffered aspirin (^3-^5), theophylline(^6), sulfamethoxazole(^7) and Cotrimoxazole(^8). Carvediol-hydroxypropyl-β-cyclodextrin(^61). Telmisartan - hydroxypropyl-β-cyclodextrin(^62).</td>
</tr>
<tr>
<td>ii. Use of salts of weak acids and weak bases</td>
<td>Na, K, Ca salts of p-aminosalicylic acid(^9), sod. tolbutamide(^10), tetracycline HCl(^11), Na and K salts of penicillin V(^12), sod. phenobarbitone(^13), theophylline isoprenoline(^14) and choline theophylline(^15).</td>
</tr>
<tr>
<td>iii. Use of solvates and hydrates</td>
<td>Ampicillin anhydrate(^16), caffeine and glutethimide anhydrous forms(^17), solvated forms of succinyl sulphathiazole and hydrocortisone(^17).</td>
</tr>
<tr>
<td>iv. Use of selected polymorphic forms</td>
<td>Novobiocin(^18), chloramphenicol palmitate(^19) and succinyl sulphathiazole(^20,21).</td>
</tr>
<tr>
<td>v. Complexation</td>
<td>Benzocaine-caffeine(^22), digitoxin-hydroquinone(^23), caffeine-ergot alkaloids(^24), PVP(^25). Etoricoxib-β-cyclodextrin(^58). Celecoxib-β and HPβ-cyclodextrin(^60).</td>
</tr>
<tr>
<td>vi. Prodrug approach</td>
<td>Pivampicillin(^25), hectacillin(^26), erythromycin-2'-N-alkylsuccinate(^27), 2'-N-alkyl glutaramate, prodrugs of carbenicillin(^28), lincomycin and clindamycin(^29).</td>
</tr>
</tbody>
</table>
vii. Use of surfactants
Hydrocortisone-Tween80\textsuperscript{30}, amphotercin-B-biosurfactants\textsuperscript{31} (sod.taurocholate and sod.cholate), tolbutamide-Tween 20 and Tween 80\textsuperscript{32}, sulphathiazole, prednisolone and chloramphenicol - polysorbate 80\textsuperscript{33}.

viii. Sublimation Technique
Etoricoxib-Menthol, Crospovidone\textsuperscript{55}, Etoricoxib- camphor, menthol, thymol, low substituted hydroxylpropyl methyl cellulose, low substituted hydroxyl-propyl cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate\textsuperscript{56}.

II. Methods which increase the surface area

1. Micronization (particle size reduction to increase the surface area)
Griseofulvin\textsuperscript{34,35}, digoxin\textsuperscript{36,37}, phenacetin\textsuperscript{38} and Sulphadiazine\textsuperscript{39}

2. Use of surfactants (to increase effective surface area by facilitating proper wetting)
Phenacetin\textsuperscript{40}, ethinamate\textsuperscript{41}, sulfisoxazole\textsuperscript{42}

3. Solvent deposition (deposition of poorly soluble drugs on inert materials)
Oxyphenbutazone\textsuperscript{43}, prednisolone\textsuperscript{44}, tolbutamide\textsuperscript{45}, indomethacin\textsuperscript{46}, phenylbutazone\textsuperscript{47,48} and hydrochlorothiazide\textsuperscript{46}.

4. Solid dispersions (dispersion of poorly soluble drug in a solid matrix of water soluble carrier)
Griseoflvin-PVP\textsuperscript{49}, reserpine-PVP\textsuperscript{50}, tolbutamide-PEG\textsuperscript{51} and chloramphenicolurea\textsuperscript{52}. Etoricoxib-croscarmellose sodium, crospovidone\textsuperscript{57}. Aceclofenac-crosspovidone, PVP-K 30\textsuperscript{59}.
NEWER TECHNOLOGIES$^{63}$

Newer and novel drug delivery technologies developed in recent years for bioavailability enhancement of insoluble drugs are listed below.

Lipid Based Delivery Systems:

Lipid Solutions,

Lipid Emulsions

Microemulsions

Self-Dispersing Lipid Formulations (SDLF)

Self-Emulsifying Drug Delivery Systems (SEDDS)

Self-Microemulsifying Drug Delivery Systems (SMEDDS)

Nanosizing by precipitation:

Evaporative Precipitation into Aqueous Solution (EPAS)

Controlled Precipitation

Cryogenic and Super critical fluid technologies.

Biopharmaceutical Classification System:

Biopharmaceutical Classification System$^{53}$ (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process. According to which drugs are grouped into four major classes basing on their solubility and permeability.
Class I: High Permeability and High Solubility
Propranolol, Metoprolol, Diltiazem, Verapamil

Class II: High Permeability and Low Solubility
Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam, Celecoxib

Class III: Low permeability and High solubility
Acyclovir, Neomycin B, Captopril, Enalaprilate, Alendronate

Class IV: Low permeability and Low solubility
Chlorthiazide, Furosemide, Tobramycin, Cefuroxime

A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5 and it is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose. A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

The rate limiting process for drug absorption and bioavailability (rate and extent of absorption) is either the release (or dissolution) of drug substances from the dosage form or its permeation through the intestinal membrane. If permeation through intestinal membrane is rate limiting, dissolution properties may be of negligible importance. Class I drugs behave in vivo like an oral solution. Dissolution and bioavailability is very rapid for these drugs. If the Class I drug substance is
released from the dosage form very rapidly in vivo, gastric emptying will become the rate limiting process for drug absorption. Whereas for drugs having high permeability and low solubility (Class II), dissolution or release from the dosage form occurs slowly and the dissolution rate will become the rate limiting factor for drug absorption. These drugs exhibit variable bioavailability and need enhancement in dissolution rate for increasing bioavailability. Permeation through the intestinal membrane forms the rate-limiting step for absorption of drugs of Class III and bioavailability is independent of drug release from the dosage form. These drugs generally exhibit low bioavailability and need enhancement in permeability. Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability, gastric emptying form rate limiting steps for absorption of these drugs.
REFERENCES


63. Chowdary KPR, Madhavi BLR. Indian Drugs. 2005; 42(9): 557.
2.2 LITERATURE ON CYCLODEXTRIN COMPLEXATION

Cyclodextrins (CDs), homologous cyclic oligosaccharides have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation\textsuperscript{1, 2}. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug\textsuperscript{3, 4}.

The α-, β- and γ- cyclodextrins are cyclic oligosaccharides consisting of six, seven and eight glucose units respectively. While it is thought that, due to steric factors, Cyclodextrins having fewer than six glucopyranose units cannot exist, Cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated δ-, ε-, ζ-, η, and δ-cyclodextrin, respectively, have been reported\textsuperscript{5, 6} of these large-ring Cyclodextrins only β-cyclodextrin has been well characterized\textsuperscript{7, 8}. Chemical and physical properties of the four most common Cyclodextrins are given in Table 2.2. The melting points of α-, β- and γ - cyclodextrins are between 240° and 265°C, consistent with their stable crystal lattice structure\textsuperscript{9}.
Table 2.2

Some Characteristics of α-, β-, γ- and δ-Cyclodextrins

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of glucopyranose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
<td>1459</td>
</tr>
<tr>
<td>Central cavity diameter (Å)</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>7.5-8.3</td>
<td>10.3-11.2</td>
</tr>
<tr>
<td>Water solubility at 25°C (g/100 ml)</td>
<td>14.5</td>
<td>1.85</td>
<td>23.2</td>
<td>8.19</td>
</tr>
</tbody>
</table>

They are enzymatic conversion products of starch. The enzyme cyclodextrin-glucosyl transferase produced by *B. macerans* acts on partially hydrolysed starch (a mixture of linear dextrins) and produces a mixture of cyclic and acyclic dextrins, from which pure cyclodextrins (CDs) are isolated. The structure of the most important CD, β-cyclodextrin is shown in Fig-2.1.

Fig. 2.1: The Structure of β-cyclodextrin

The 'torus' shaped macro-ring is built of α-l, 4-D-glucose units. As a
consequence of conformation of glucopyranose units, all secondary OH- groups are located on one edge (wider edge) of the 'torus' like CD molecule while all primary OH-groups are on the other side (narrow side of torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms, therefore, the inner surface is hydrophobic, but outer surface is hydrophilic.

**Absorption and Toxicity:**

Cyclodextrins are not absorbed orally and not hydrolyzed during their transit through the small intestine. They are totally resistant to α-amylases, but can be attacked by β-amylases. Hydrolysis occurs only in colon (partial hydrolysis occurs with α-CD). The oral administration of CDs does not result in acute toxicity. Long term administration leads to no significant change in organs or biological values. Natural CDs are highly toxic when given parenterally. α- and β-cyclodextrins induce haemolysis and nephrotoxicity upon i.v. injection γ CD is relatively less toxic parenterally11.

**Formation of Complexes:**

One of the most important characteristics of CDs are their ability to form inclusion complexes. Inclusion complexation involves entrapment of a guest molecule totally or partially in the cavity of host molecule without formation of any covalent bonds. CDs are typical host molecules and can entrap a wide variety of drug molecules resulting in the formation of monomolecular inclusion complexes12.

Inclusion complexation occurs when aqueous solution of CD is shaken with drug molecules or its solution. In aqueous solution the hydrophobic cavities of CD
are occupied by water molecules, which can be replaced by appropriate drug molecules that are less polar than water. The solubility of the complex is usually lesser than the solubility of CD and hence the complex may be precipitated from its saturated solution, as microcrystalline powder and this powder is subsequently separated by filtration. Usually 1:1 complexes are formed, but when a guest molecule is too long to find complete accommodation in one cavity, its other end is also amenable to complex formation leading to 2:1 (CD : drug) or sometimes 3:1 or 4:1 complexes. It may also be possible to form 1:2 and 1:3 (CD: drug) complexes.

The central cavity of the cyclodextrin molecule is linked with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic. The polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity. Measurements of stability or equilibrium constants ($K_c$) or the dissociation constants ($K_d$) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.

**Methods for Detection of Inclusion Complex Formation and Determination of Complex Stability Constant:**

One of the most interesting properties of CDs is their ability to form inclusion complexes with a wide variety of guest molecules. Molecular encapsulation may occur both in solution and solid state. In solution there is
equilibrium between complexed and non complexed guest molecules, in solid state
guest molecules can be enclosed within the cavity or may be aggregated to the
outside of CD molecule\textsuperscript{15}. Upon inclusion within the CD cavity a guest molecule
experiences changes in its physicochemical properties. These changes provide
methods to detect whether guest molecules are really included in the CD cavity.

**Detection of inclusion complexation in the solution state:**

Detection of inclusion complexation in solution state can be done by
spectroscopic methods like Ultraviolet/Visible (UV/VIS), Fluorescence, Circular
Dichroism, Electron Spin Resonance (ESR), and Nuclear Magnetic Resonance
(NMR) methods. The \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectroscopic studies can also be used
to determine the direction of penetration of guest molecules in to the CD cavity.
Other methods include Polarography, Conductivity measurement, Microcalorimetry
and Solubility methods\textsuperscript{2}.

Phase solubility technique\textsuperscript{16} is the one of the widely used methods to detect
the inclusion complexation in solution state.

The general experimental operation in studying molecular interactions by
means of phase solubility method entails the addition of an equal weight
(inconsiderable excess of its normal solubility) of a slightly soluble compound, S
(substrate or guest) into each of several vials containing increasing concentrations of
a relatively soluble compound, L (ligand or host or complex agent), which are closed
and brought to solubility equilibrium at constant temperature. The solution phases
are then analyzed, by any suitable means, for their total concentration of compound
S (guest), no matter what its molecular state may be.

A phase diagram is constructed by plotting, on the vertical axis, total molar concentration of S found in the solution phase against the molar concentration of L.

![Phase diagram](image)

The phase diagrams are observed to fall into two main classes, type A and type B with some variation within the classes.

The type A can be further classified in subtypes \(A_L\), \(A_P\) and \(A_N\), where the guest solubility of first type increases linearly with cyclodextrin concentration while those of the second and third types deviate positively and negatively, respectively from the straight line. The complex formation with a 1:1 stoichiometry gives the \(A_L\) type diagram, where as the higher order complex formation in which more than one cyclodextrin molecules are involved in the complexation gives the \(A_P\)-type. The interaction mechanism for the \(A_N\)-type is complicated, because of a significant contribution of solute-solvent interaction to the complexation. In the case of the Bs type, the initial ascending portion of the solubility change is followed by a plateau region and then a decrease in the solubility at higher cyclodextrin concentrations accompanying a microcrystalline precipitation of the complex. The \(B_1\)-type diagram
is indicative of the formation of insoluble complexes in water.

The stability constant \((K_s)\) and stoichiometry of complexes are determined by analyzing quantitatively the phase solubility diagram.

**Detection of inclusion complexation in the solid state:**

Detection of the inclusion complexation in solid state can be done by Powder X-ray diffractometry, Single crystal X-ray structure analysis, Thermo analytical, thin layer chromatography, Paper chromatography, Infrared spectroscopy, Scanning electron microscopy and Dissolution study methods\(^2\).

**Applications of Cyclodextrins:**

All the applications of CDs in drug formulations involve complexation\(^{11,17-19}\). When a drug becomes part of a CD complex, its physical and chemical properties are modified\(^20\). The solubility and dissolution rate of drugs are improved in CD complexes; poorly soluble drugs reach the blood more quickly and in higher concentration, suggesting the possibility of reducing the dose\(^21\).

\(\beta\)-CD is most widely used for complexation because of its unique cavity size and ease with which it can be obtained on industrial scale, leading to reasonably cheaper price of this compound\(^22\).

\(\beta\)-Cyclodextrin complex formation with lipophilic drugs and other compounds with limited aqueous solubility, frequently gives rise to B-type phase-solubility diagrams as defined by Higuchi\(^{16}\). \(\beta\)-and \(\delta\)-cyclodextrin form intramolecular hydrogen bonds between secondary OH groups, which detract from
hydrogen bond formation with surrounding water molecules, resulting in less negative heats of hydration\textsuperscript{8,14}. Thus, intramolecular hydrogen bonding can result in relatively unfavourable enthalpies of solution and low aqueous solubilities. For example, the aqueous solubility of $\beta$-cyclodextrin is only 1.85\% w/v at room temperature but increases with increasing degree of methylation. The highest solubility is obtained when two-thirds of the hydroxyl groups (i.e., 14 of 21) are methylated, but then falls upon more complete alkylation. The methylated derivative has a solubility that is lower than that of e.g., heptakis (2, 6-o-dimethyl)-$\beta$-cyclodextrin but that is still considerably higher than that of unsubstituted $\beta$-cyclodextrin\textsuperscript{23}.

**Recent Research Work on Cyclodextrin Complexation:**

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. A summary of recent research work on cyclodextrin complexation for enhancing the dissolution rate and bioavailability is given in Table 2.3.
Table 2.3

**Summary of Recent Research Work on Cyclodextrin Complexation**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Cyclodextrin (CD)</th>
<th>Purpose/Result</th>
<th>Ref.No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acetaminophen</td>
<td>α- and β -cyclodextrins</td>
<td>Effect of humidity on inclusion complex formation and their characterization by XRD, DSC and IR are reported</td>
<td>24</td>
</tr>
<tr>
<td>2.</td>
<td>Albendazole</td>
<td>α-, β- and HPβCD</td>
<td>Improved solubility and dissolution rate</td>
<td>25</td>
</tr>
<tr>
<td>3.</td>
<td>Amlodipine</td>
<td>β- and HPβCD</td>
<td>Improved solubility and characterization of inclusion complexes by DSC and thermogravimetric methods</td>
<td>26</td>
</tr>
<tr>
<td>4.</td>
<td>Benzthiazide</td>
<td>β-, γ- and Dimethyl βCD</td>
<td>Increased dissolution rate and inclusion complexes in solution and solid state were prepared and characterized by IR and DSC</td>
<td>27</td>
</tr>
<tr>
<td>5.</td>
<td>Bromozepam</td>
<td>Dimethyl βCD</td>
<td>Characterization of inclusion complexes by IR, XRD and DSC techniques</td>
<td>28</td>
</tr>
<tr>
<td>6.</td>
<td>Broperimine</td>
<td>β CD</td>
<td>Improved dissolution rate and stability studies</td>
<td>29</td>
</tr>
<tr>
<td>7.</td>
<td>Butyl methoxy dibenzoyl methane (Sunscreen agent)</td>
<td>α-, β-γ- and HPβCD</td>
<td>Characterization by phase solubility analysis, circular dichroism, DSC and XRD studies and improved solubility and photostability of complexes are reported</td>
<td>30</td>
</tr>
<tr>
<td>8.</td>
<td>Chenodeoxycholic acid</td>
<td>β-and Dimethyl- βCD</td>
<td>Improved aqueous solubility and dissolution rate</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Drug Name</td>
<td>Cyclodextrin Type</td>
<td>Effects</td>
<td>Page</td>
</tr>
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<td>-------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>9.</td>
<td>Clotrimazole</td>
<td>Dimethyl- βCD</td>
<td>Improved aqueous solubility, dissolution rate and antimycotic activity</td>
<td>32</td>
</tr>
<tr>
<td>10.</td>
<td>Danazol</td>
<td>HPβCD and sulfobutyl ether of β-cyclodextrin</td>
<td>Improved aqueous solubility and dissolution rate</td>
<td>33</td>
</tr>
<tr>
<td>11.</td>
<td>Diclobutrazol</td>
<td>α-, β-, Dimethyl β-and HPβCD</td>
<td>Improved aqueous solubility and dissolution rate</td>
<td>34</td>
</tr>
<tr>
<td>12.</td>
<td>Felodipine</td>
<td>β-and HPβCD</td>
<td>Improved solubility and characterization of inclusion complexes by DSC and thermogravimetric methods</td>
<td>26</td>
</tr>
<tr>
<td>13.</td>
<td>Fenabufen</td>
<td>α-, β - and γ-cyclodextrins</td>
<td>Improved dissolution rate and oral bioavailability of inclusion complexes</td>
<td>35</td>
</tr>
<tr>
<td>14.</td>
<td>Fucosterol</td>
<td>β-, Maltosyl- β- and Dimethyl- β CD</td>
<td>Improved solubility, dissolution rate and stoichiometry and stability constants were reported</td>
<td>36</td>
</tr>
<tr>
<td>15.</td>
<td>Furosemide</td>
<td>Cyclodextrins</td>
<td>Improved solubility and dissolution rate</td>
<td>37</td>
</tr>
<tr>
<td>16.</td>
<td>Glibenclamide</td>
<td>β - HP β and Dimethyl- βCD</td>
<td>Improved dissolution rate</td>
<td>38</td>
</tr>
<tr>
<td>17.</td>
<td>Glisentide</td>
<td>α-, β - and γCD</td>
<td>Complexation in aqueous solution and solid state is investigated</td>
<td>39</td>
</tr>
<tr>
<td>18.</td>
<td>Griseofulvin</td>
<td>β- and HPβCD</td>
<td>Improved dissolution rate</td>
<td>40</td>
</tr>
<tr>
<td>19.</td>
<td>Ibuprofen</td>
<td>β-Methyl, β-HP, and Hydroxyethyl β CD</td>
<td>Improved dissolution rate</td>
<td>41</td>
</tr>
<tr>
<td>20.</td>
<td>Indomethacin</td>
<td>β- and HPβCD</td>
<td>The methods of preparation of inclusion complexes and their characterization in liquid and solid phases were reported</td>
<td>42</td>
</tr>
<tr>
<td>21.</td>
<td>Indomethacin</td>
<td>β- and HPβCD</td>
<td>Decreased G.I irritation</td>
<td>43</td>
</tr>
<tr>
<td></td>
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2.3 SOLID DISPERSION TECHNOLOGIES

The term solid dispersion refers\(^1\) to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

**Advantages of solid dispersions**

1. **Particles with reduced particle size**

   Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers\(^2\). A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability\(^2,3\).

2. **Particles with improved wettability**

   A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions\(^4\). It was observed that even carriers without any surface activity, such as urea\(^5\) improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts when used, can significantly increase the wettability of drug particles. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.\(^6,3\)
3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity\(^7\). The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate\(^8\). The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility \(^9, 10\). The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process\(^11\). In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.\(^2, 4\) For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.\(^12\)

Properties of a Carrier for Solid Dispersions

Following criteria should be considered during selection of carriers: (a) High water solubility – improve wettability and enhance dissolution (b) High glass
transition point – improve stability (c) Minimal water uptake (reduces $T_g$) (d) Soluble in common solvent with drug – solvent evaporation (e) Relatively low melting point – melting process (f) Capable of forming a solid solution with the drug – similar solubility parameters.

**First generation carriers**

Crystalline carriers: Urea, Sugars, Organic acids

**Second generation carriers**

Amorphous carriers: Polyethylene glycol, Povidone, Polyvinylacetate, Polymethacrylate, cellulose derivatives

**Third generation carriers**

Surface active self emulsifying carriers: Poloxamer 408, Tween 80, Gelucire 44/14.

Solid dispersions of a number of poorly soluble drugs such as phenylbutazone$^{13}$, ketoprofen$^{14}$, sulphathiazole$^{15}$ etc. exhibited faster dissolution rates and improved bioavailability. For example, a marked increase (30 fold) in dissolution rate of indomethacin was observed with indomethacin-hydroxy propyl cellulose solid dispersions. Indomethacin was present in amorphous form in these dispersions. A significant increase in absorption rate and serum levels of indomethacin was also observed with these dispersions.

**Solvent Deposition Systems**

A solvent deposition (SD) system is defined as a solid preparation in which a drug is deposited from its solution in a volatile solvent on the surface of an excipient by evaporation of the solvent used for the distribution of the drug. Solvent deposition can be used for two purposes, (i) to improve the dissolution rate and
efficiency and (ii) to achieve content uniformity.

Solvent deposition technique achieves faster dissolution rates as the drug undergoes molecular micronization while depositing over the surface of the excipient. The form 'miniscular form' is used to describe this state. The choice of the support excipient has varied from very fine powder to granules, the former obviously allows for a large surface for deposition, ensuring faster dissolution rates. Solvent deposition may also lead to change in crystal type of the drug (polymorphism). The polymorph of significantly greater thermodynamic activity (i.e. solubility) can prove helpful in improving dissolution rate. Solvent deposition may also convert a crystalline drug into amorphous form, which produces faster dissolution and absorption rates.

Finely divided solids as well as granular support materials have been used for preparing the SD systems. Finely divided solids perform very well when increased dissolution rates are intended as they offer a large surface area, but content uniformity may suffer because of difficulties like poor flow properties and clumping which can lead to variable die-filling during capsule or tablet manufacturing. Granular support materials offer additional advantage of excellent control over the content uniformity and also they can be directly compressed after solvent deposition. Other factors to be considered in the selection of excipient include solubility in water and other solvents, compatibility with drugs, biologic inertness, hygroscopicity and cost.

Materials such as silicagel\textsuperscript{16, 17}, macrocrystalline cellulose\textsuperscript{16-18}, lactose\textsuperscript{16-19}, DCP\textsuperscript{16-17}, silicon dioxide\textsuperscript{20-21}, kaolin\textsuperscript{16}, potato starch\textsuperscript{16}, sucrose pellets\textsuperscript{22}, lactose-
starch granules\textsuperscript{23}, sodium starch glycolate\textsuperscript{24} and modified cellulose\textsuperscript{24} were reported as excipients for solvent deposition systems.

Solvent deposited systems of a number of poorly soluble drugs such as diazepam\textsuperscript{25}, phenylbutazone\textsuperscript{13}, piroxicam\textsuperscript{17}, ketoprofen\textsuperscript{16}, indomethacin\textsuperscript{26}, digoxin\textsuperscript{19} exhibited faster dissolution rates and efficiency. For example, solvent deposited systems of ketoprofen\textsuperscript{16} on silicagel, MCC, lactose, starch and DCP showed a marked increase in the dissolution rate of ketoprofen. In a study\textsuperscript{17}, it was noticed that water insoluble excipients (MCC, silicagel, kaolin) gave fast dissolution when compared to water soluble excipients (soluble starch, lactose) which themselves dissolved leaving aggregates of the drug. The relatively fast dissolution observed with water insoluble excipients may be due to the easy and rapid dispersible nature of these materials giving more surface area.
REFERENCES


