DIFFERENT APPROACHES TOWARDS THE SOLUBILITY ENHANCEMENT OF DRUG: A REVIEW

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ABSTRACT
Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach market due to their poor aqueous solubility. Whereas only 8% of new drug candidates have shown both high solubility and permeability. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. For BCS class II drugs, enhancement of solubility is important parameter before formulation of dosage form. Solid dispersion, Solvent evaporation Complexation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drugs. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development.

Keywords: Solubility, BCS Class, Solid dispersion, cyclodextrin.

INTRODUCTION
Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. As a result, more than 40%...
of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties. Pharmaceutical companies have been primarily employing two strategies: rational drug design (RDD) and high throughput screening (HTS) for drug discovery. In both, lead compounds are identified according to screening in an environment in relation to biological system. RDD generally lead to compounds with higher molecular weight which ultimately result in to poorer permeability. On the other hand, HTS has led to compounds with increased lipophilicity and molecular weight; this consequently gives poorer solubility characteristics. Drugs have this property of lipophilicity too little or too much is a bad thing. When this property expressed as Log P gets above about 2, the drug is getting too lipophilic. The idea of permeability and solubility characteristics had been helpful to classify the drug under four classes prescribed by Biopharmaceutics Classification System (BCS). There are two parameters useful for identifying poorly soluble drugs. One is its aqueous solubility should be less than 100ug/ml and another is dose: solubility ratio. Dose to solubility ratio can be defined as volume of gastrointestinal fluids necessary to dissolve the administered dose. Recently, a quantitative BCS has highlighted the importance of transit flow, in addition to solubility and permeability, on the drug absorption process. The BCS defines three dimensionless numbers- dose number (Do), dissolution number (Dn), and absorption number (An) to characterize drug substances. These numbers are a combination of physicochemical properties of the drug and physiological parameters. The Do attaches a physiological relevance to dose by considering the volume of fluid required to dissolve the total dose. Drugs with Do < 1 are classified as highly soluble, whereas those with Do > 1 are termed poorly soluble. In a recent attempt to categorize WHO essential drugs based on BCS, 27.7% of drugs were reported to be poorly soluble. The BCS has not only transformed the way scientists today approach drug delivery, but it has also revolutionized the development of new drug molecules.

**Importance of Solubility**

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products.
The dissolution rate of a solid in a liquid may be described quantitatively by the Noyes-Whitney equation:

\[
\frac{dm}{dt} = ka (Cs - C)
\]

Where,

\(m\) = mass of solute that has passed into solution in time \(t\),
\(\frac{dm}{dt}\) = rate of dissolution,
\(A\) = surface area of undissolved solid in contact with the solvent,
\(Cs\) = concentration of solute required to saturate the solvent at the experimental temperature,
\(C\) = solute concentration at time \(t\) and
\(ka\) = intrinsic dissolution rate or simply the dissolution rate constant

However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role for other dosage forms like parenteral formulations as well.11

### Techniques to Improve Solubity of Poorly Water Soluble Drug

Classical and highly employed approaches to enhance the aqueous solubility and thus the bioavailability of poorly soluble drugs especially, BCS Class II drugs involve the solubilization by application of principles like pH adjustment, cosolvency, microemulsification, self-emulsification, micelles, liposomes and emulsions12, 13. Each method is

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Part of solvent required per part of solute</th>
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<tbody>
<tr>
<td>Very soluble</td>
<td>Less than 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1 to 10</td>
</tr>
<tr>
<td>Soluble From</td>
<td>10 to 30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>From 30 to 100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>From 1000 to 10,000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>10,000 and over</td>
</tr>
</tbody>
</table>
dealing with some merits and demerits. Hence the decision of the method is a crucial step in the formulation process.

**pH adjustments:** Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase water solubility of ionizable compounds. As per pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of drug. The change in the ionic milieu can also result to *in situ* salt formation. However, this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract.\(^1^4\)

**Co-Solvency:** Cosolvent system is a mixture of miscible solvents often used to solubilize lipophilic drugs. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. The water insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil.

**Polymeric Alteration:** Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability.\(^1^5\), \(^1^6\) Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy.\(^1^7\), \(^1^8\) With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

**Particle Size Reduction:** Micronization or nanonization is one of the most potential approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to sub-micron level.\(^1^9\) Particle size is a critical parameter which should be strictly controlled during the
preformulation studies of any formulation. Although the reduction in the particle size is a successful way to enhance the solubility, if uncontrolled and un-optimized, it can lead to re-crystallization and re-aggregation of drug on storage.²⁰

METHOD INCLUDES

✓ Co-grinding/Co-micronization
✓ Pearl Milling
✓ High-Pressure Homogenization
✓ Solution Enhanced Dispersion by the Supercritical Fluids (SEDS)
✓ Rapid expansion from Supercritical to Aqueous Solution (RESAS)
✓ Spray freezing into liquid (SFL)
✓ Evaporative precipitation into aqueous solution (EPAS)
✓ Ultra-Rapid Freezing

Co-evaporate System / Co-precipitation: Weak basic drugs like prochlorperazine maleate contain good solubility in acidic pH but in alkaline pH solubility is significantly reduced and when a conventional formulation containing weak base is given orally precipitation of poorly soluble free base occurs within formulation in intestinal fluid.

Solvent Deposition/Evaporation: In this technique drug is dissolved in a solvent like methylene chloride to produce a clear solution. The carrier is then dispersed in the solution by stirring and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The Increase in the dissolution rate is ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wetability of the particles brought about by the carrier.²¹

Lipid-Based Delivery Systems: Lipid-based delivery systems like emulsions, microemulsions, liposomes, microspheres, solid-lipid nanoparticles, etc. have ability to avoid resistant chemical and physical barriers to oral absorption and are most successful in enhancing the bioavailability of molecules that are poorly water-soluble but highly permeable drug molecules (BCS class II). Some proposed mechanisms of action of lipid-based systems to enhance oral bioavailability of compounds include:²²

i) Particle size reduction to molecular size yielding a solid-state solution within the carrier
ii) Enhanced wetting of hydrophobic solids resulting in enhanced dissolution
iii) Increased rate of dissolution into aqueous environment from oil droplets of high surface area
iv) Promotion of absorption via intrinsic lipid pathways
v) Enhanced thermodynamic activity via super-saturation of the aqueous environment of the gastrointestinal tract

a. Microemulsion
b. Self-Emulsification

**Hydrotropic Solubilization:** The peculiar solvent property of micelle forming surfactants is closely related to the peculiar nature of the self-association responsible for the formation of the micelles themselves. In the case of the flexible chain surfactants, if the rate of change of the solubility of a hydrophobic solubilizate with surfactant concentration is plotted against the concentration, the cooperative self-association that is responsible for the existence of the critical micellization concentration in such systems is clearly reflected in the plot. Formation of micelles is a prerequisite for micellarsolubilization in simple systems.

**Table no: - Various Agent Used For Hydrotropic Solubilization of Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Additive used to exhibit Hydrotropism</th>
</tr>
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<tbody>
<tr>
<td>Cefadroxil</td>
<td>Potassium acetate, potassium citrate, sodium acetate, urea</td>
</tr>
<tr>
<td>Paracetamol, Diclofinac Sodium</td>
<td>Sodium Acetate, Urea</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Sodium Salicylate</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Sodium Salicylate</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Urea, Sodium Citrate</td>
</tr>
</tbody>
</table>

**Cavitation & Melt Sono-Crystallization**

Cavitation can be in general defined as the generation, subsequent growth and collapse of cavities resulting in very high energy densities of the order of 1 to 1018kW/m3. Cavitation can occur at millions of locations in a reactor simultaneously and generate conditions of very high temperatures and pressures (few thousand atmospheres pressure and few thousand Kelvin temperature) locally, with the overall environment being that of ambient conditions. Thus, chemical reactions requiring stringent conditions can be effectively carried out using cavitation at ambient conditions. Moreover, free radicals are generated in the process due to the dissociation of vapors trapped in the cavitating bubbles, which results in either intensification of the chemical reactions or in the propagation of certain unexpected reactions. Cavitation also results in the generation of local turbulence and liquid micro-circulation (acoustic streaming) in the reactor, enhancing the rates of transport processes.
Melt Sono-Crystallization (MSC)

Application of ultrasound energy to modify the nucleation of a crystallization process is known as sono crystallization. The energy of ultrasound fashions consecutive compression and expansion. After several cycles a bubble forms and grows then collapses. The collapse of the bubble provides energy to promote the nucleation process. This results in a highly repeatable and predictable crystallization process. Applying Ultrasound to crystallization results in:

Nucleation at the lowest level of supersaturation where the crystallization overcomes the tendency of the compound to re-dissolve in the solution
- Narrowing of the metastable zone width
- Narrow particle size distribution
- Decrease in the level of cooling necessary to achieve crystallization
- Repeatable and predictable crystallization
- Polymorph control

Steam-Aided Granulation: Steam instead of water can be used in wet granulation because it provides a higher diffusion rate into the powder and a more favorable thermal balance during the drying step. After condensation of the steam, water forms a hot thin film, requiring only a small amount of extra energy for its elimination and evaporates more easily. The use of steam instead of liquid water in a wet granulation method can considerably decrease the amount of water used and as a result the whole operational time.26

Melt-Granulation: In this technique powdered drugs are efficiently agglomerated by the use of a meltable binder which can be a molten liquid, a solid or a solid that melts during the process usually in high shear mixers, where the product temperature is raised higher than the melting point of the binder either by a heating jacket or, when the impeller speed is high enough, by the heat of friction generated by the impeller blades. In this technique no water or organic solvents are needed and there is no drying step therefore the process is environmentally safe, less time consuming and uses less energy than conventional wet granulation. Polyethylene glycol is widely used as a molten binder due to its complimentary solution properties, low melting point, rapid solidification rate, low toxicity and little cost. The increase in dissolution rate can be ascribed to the hydrophilic character of the system due
to the presence of water-soluble carriers and the fact that the drug forms monotectic mixtures with PEG.\textsuperscript{27,28}

**Liquisolid Compacts:** Liquid Compacts are compressible powdered forms of liquid medications. The term “liquisolid medication” implies oily liquid drugs and solutions or suspensions of water insoluble drugs carried in suitable nonvolatile solvent systems. Using this technique, a liquid medication may be converted into a dry, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients such as the carrier and coating material. Surfactants like tweens are used to improve aqueous solubility of poorly soluble drugs.\textsuperscript{29}

**CATEGORIES OF SOLID DISPERSIONS**

1) **Simple eutectic mixtures**

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug.\textsuperscript{30,31} The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

2) **Continuous solid solutions**

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components.

3) **Discontinuous solid solutions**

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Below certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it\textsuperscript{32} only be applied when the mutual solubilities of the two components exceeds 5%. Whether or not the given solid solution can be utilized as a dosage form strategy will depend not only on the mutual
solubilities of the two components but also dose of the drug components the upper limit for tablet or capsule is about 1 g.

4) **Substitutional crystalline solid solutions**
   Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.  

5) **Interstitial Crystalline solid solutions**
   In interstitial solid solution, the dissolved molecules occupy the interstitial space between the solvent molecules in crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In case of the interstitial crystalline solid solutions, the solute molecule’s should have a molecular diameter that is no greater than 0.59 of the solvent molecule’s molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

6) **Amorphous solid solutions**
   In Amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using Greseofulvin in citric acid were the first to report the formation of an amorphous solid solution to improve a drug’s dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinyl pyrrolidone (PVP), Polyethylene glycol (PEG), and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in it’s glass transition temperature \( T_g \).

**MANUFACTURING METHODS**
Various methods used for the preparation of Solid dispersion are explained as follows.

**Melting Method**
Sekiguchi et al. were first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drugs incorporation.
common adaptation to the melting phase consist of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, reducing, therefore the process temperature. To cool and solidifying the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold drought, solidification on petri dishes at room temperature inside a desiccator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a desiccator were used. After cooling the mixture must be pulverized regarding its handling. However, the use high temperatures, and the fact that several drugs can be degraded by melting process, can be a limitation of this method. The incomplete miscibility between drug and carrier that may occur, because of the high viscosity of a polymeric carrier in molten state, is another limitation of this process. To avoid all these limitations several modifications like hot stage extrusion, Meltrex TM or melt agglomeration were introduced to the original method.

**Hot stage Extrusion**

Hot stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled. A reduction in processing temperature can be achieved by the association of hot stage extrusion with the use of carbon dioxide as a plasticizer which broaden the application of hot stage extrusion to thermally labile compounds. Solid dispersions of para amino salicylic acid/ethyl cellulose, Itraconazole/VP, Itraconazole/ethyl cellulose were successfully prepared by this technique. Moreover, it was observed that solid dispersions of Itraconazole/inutec SPI prepared by hot stage extrusion presented Itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying.

**Melt Agglomeration**

Melt Agglomeration allows the preparation of solid dispersions in in conventional high shear mixer. It is made by adding the molten carrier containing the drug to the heated excipients, by adding the molten carrier to a heated mixture of drug and excipients, or by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier. It is also possible to produce stable solid dispersion by melt agglomeration in a rotary processor.
Solvent evaporation method

The first step in the solvent method is the preparation of a solution containing both carrier material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges.

The first challenge is to mix both drug and carrier in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and carrier have to be dispersed in the solvent as fine as possible, preferably drug and carrier material are in the dissolved state in one solution.

Various strategies have been applied to dissolve the lipophilic drug and hydrophilic carrier material together in one solution. Low drug concentrations are used to dissolve both drug and carrier material in water, but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilisers like cyclodextrins or surfactants like Tween 80® increase the aqueous solubility of the drug substantially. Chloroform or dichloromethane have been used to dissolve both drug and PVP as carrier simultaneously.

The second challenge in the solvent method is to prevent phase separation e.g. crystalline of either drug or carrier, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for the molecular mobility of the drug and carrier remains high, favouring phase separation (e.g. crystallization). To dry the solutions, vacuum drying is often used.

Supercritical fluid method

Supercritical methods are mostly applied with the carbon dioxide (CO₂) which is used as either a solvent for drug and carrier or as anti-solvent when supercritical CO₂ is used as solvent, the carrier and drug are dissolved and sprayed through a nozzle, into expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in cooling. This technique does not require the use of organic solvents and since CO₂ is considered as environmentally friendly. This technique is referred to as ‘solvent free’. The technique is known as Rapid Expansion of Supercritical Solution (RESS).

Direct capsule filling

Direct filling of hard gelatine capsules with the liquid melt of solid dispersions avoids
grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.

**Electro spinning method**
The electro spinning technology used in the polymer industry combines solid dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameters are formed. As the solvent evaporates, the formed fibres can be collected on a screen to give an on woven fabric, or they can be collected on a spinning mandrel. The fibre diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest technique. This technique can be utilized for preparation of solid dispersions in future.

**Dropping solution method**
The dropping method facilitate the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.

**Coating on sugar beads using fluidized bed-coating system**
This method involves the fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipient or sugar sphere to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. The method can be applied for both controlled and immediate release solid dispersions. Itraconazole (Sporanox oral capsule, Janssen Pharmaceutical, Titusville, NJ) coated on sugar sphere, is made by layering
onto sugar beads a solution of a drug and hydroxyl propyl methyl cellulose (HPMC) in a mixture of suitable solvent system comprises a mixture of methylene chloride and preferably ethanol which may be denatured with butanone. As HPMC does not dissolve completely in methylene chloride, at least 10% alcohol has to be added. A solid solution of drug in HPMC is produced upon coating beads are done in a closed Wurster Apparatus. \(^{66, 67}\)

**Inclusion Complex**

**Formation-Based Techniques**

Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (Known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs). These are nonreducing, crystalline, water soluble, and cyclic oligosaccharides consisting of glucose monomers arranged in a donut shaped ring having hydrophobic cavity and hydrophilic outer surface as illustrated in Figure 1. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin. \(^{68}\)

**Derivatives of cyclodextrin**

<table>
<thead>
<tr>
<th>Derivative</th>
<th>Description</th>
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<tbody>
<tr>
<td>RMβCD</td>
<td>Randomly methylated β–CD</td>
</tr>
<tr>
<td>HPβCD</td>
<td>Hydroxy propyl β–CD</td>
</tr>
<tr>
<td>HP γ-CD</td>
<td>hydroxyl propyl γ-CD</td>
</tr>
<tr>
<td>DM β-CD</td>
<td>2,4-dimethyl β–CD</td>
</tr>
<tr>
<td>SBEβcd</td>
<td>Sulfobutylether β- CD</td>
</tr>
</tbody>
</table>

✓ Various technologies adapted to prepare the inclusion complexes of poorly water soluble drugs with cyclodextrins are briefly described below.

**A. Kneading Method:** This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to convert into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through a sieve if required. In laboratory scale, kneading can be achieved by using a mortar and pestle. In large scale, kneading can be done by utilizing the extruders and other machines.
This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.69

**B. Lyophilization/Freeze-Drying Technique:** In order to get a porous, amorphous powder with high degree of interaction between drug and CD, lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure.70 Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique is the use of specialized equipment, time consuming process, and yield poor flowing powdered product. Lyophilization/freeze drying technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent.71

**C. Microwave Irradiation Method:** This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a roundbottom flask.72 The mixture is reacted for short time of about one to two minutes at 60°C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40°C. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction times and higher yield of the product.73

**D. Co-precipitation:** Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.74

**E. Neutralization:** Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β- Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.75
F. Co-grinding: Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for suitable time.

G. Spray-Drying Method: Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β-cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried.  

Crystal Engineering
The surface area of drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. Hence, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy. By manipulating the crystallization conditions, it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs. A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. It was shown that the stable polymorph of chloramphenicol palmitate produced low serum levels, whereas the metastable polymorph yielded much higher serum levels when the same dose was administered. In another study, it was found that tablets prepared from the form Apolymorph of oxytetracycline dissolved significantly more slowly than the tablets with form Bpolymorph. The tablets with form a polymorph exhibited about 55% dissolution at 30 min, while the tablets with form Bpolymorph exhibited almost complete (95%) dissolution at the same time. Crystal engineering approach also involves the preparation of hydrates and solvates for enhancing the dissolution rate. During the crystallization process, it is possible to trap molecules of the solvent within the lattice. If the solvent used is water, the resultant crystal is a hydrate; if any other solvent is used, it is referred to as solvate. The dissolution rate and solubility of a drug can differ significantly for different solvates. For example, glibenclamide has been isolated as pentanol and toluene solvates, and these solvates exhibited higher solubility and dissolution rate than two non-solvated polymorphs.
REFERENCES


