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Review Article

SOLUBILITY ENHANCING METHODS FOR POORLY SOLUBLE DRUGS: A REVIEW

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Abstract: Orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, 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 solubility behavior of drugs remains one of the most challenging aspects in formulation development. 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.

Key**words:** pharmaceutical product, enhancing drug solubility, technological approaches, Solid dispersion

Introduction:
In dealing with new drug substances, it is extremely important to know something about their solubility characteristics, especially in aqueous systems since they must possess some limited aqueous solubility to elicit a therapeutic response. When a drug substance has an aqueous solubility less than 1mg/ml in the physiologic PH range (1-7) a potential bioavailability problem may exist. If the solubility of drug substance is less than the required concentration necessary for the recommended dose, step must be taken to improve its solubility.The approach taken will usually depend on the chemical nature of the drug substance and the type of drug product desired. Solubility analysis is one of the criteria for the preformulation study.

Preformulation research:
Preformulation may be described as a phase of the research and development process where the preformulation scientist characterizes the physical, chemical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage forms. Preformulation testing is the first step in the rational development of dosage forms of a drug substance. other principle areas of preformulation research are as follows[1,4].

Bulk Characterization:
- crystallinity and polymorphism
- hygroscopocity
- fine particle characterization
- bulk density
- powder flow properties

Solubility Analysis :
- ionization constant-pKa
- pH solubility profile
- common ion effect-Ksp
- solubilization
- partition coefficient
- dissolution

Stability Analysis:
- solution stability
  pH rate profile
- solid state stability
  Bulk stability
  Compatibility

Bulk Characterization:
a. Crystallinity and polymorphism:
Different polymorphic forms of a given solid differ from each other with respect to many physical properties, such as solubility and dissolution, true density, crystal shape, flow properties and solid state stability[2]. There are various methods for the characterization of solid forms (i.e. to study polymorphs) as differential scanning calorimetry (DSC/DTA), infrared spectroscopy X-ray powder diffraction, scanning electron microscopy, or thermo gravimetric analysis[1].

b. Hygroscopocity:
Hygroscopocity is the ability of solids to adsorb water onto their surfaces microscopically adsorption and adsorption isotherms may be determined by monitoring equilibrium moisture uptake or loss in samples stored in desicators with different relative humidity's the amount of

water present is determined by loss on drying, ,Karl fisher titration ,the calorimetric method, or near IR spectroscopy[3].

c. Fine Particle Characterization:

In general, each new drug candidate should be tested during preformulation with smallest particle size as is practical to facilitate preparation of homogenous samples and maximize the drug surface area for interactions[5].

d. Bulk Density:

Knowledge of the absolute and bulk densities of drug substances is very useful in forming some idea as to the size of the final dosage form [5].

e. Powder Flow Properties:

The initial characterization of the flow properties of solids was conducted in the seminal works of Carr and Jenike.Carr evaluated interparticulate cohesive properties with angle of repose measurements and studied the effect of packaging geometry of solids with bulk and tap density measurements.[5]

Solubility Analysis:

a. Ionization Constant,pKa:

For ionizable substances such as acids or bases, the solubility at a given pH may be estimated if the pKa is known. On the other hand, the solubility of a nonionizable substance is not affected by pH. Common methods of determination of pKa are: UV spectrometry determination, titration determination, & solubility determination[3].

b. pH Solubility Profile:

The degree of ionization and therefore, the solubility of acidic and basic compounds depend on the pH of the medium. The saturation solubility for such compounds at particular pH is the sum total of solubility of ionized and unionized forms[3].

c. Common Ion Effect (Ksp) :

In a saturated solution of a salt with some undissolved solid, there exists equilibrium between the excess solid and the ions resulting from the dissociation of the salt in the solution[2].

d. Effect Of Temperature:

The heat of solution, Δ Hs, represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent, most commonly, the solution process is endothermic, or ΔHs is positive, and thus increasing the solution temperature increases the drug solubility[7].

e. Solubilization:

A general means of increasing solubility is the addition of cosolvents to the aqueous system. The solubility of poorly soluble non electrolytes can often improved by orders of magnitude with suitable cosolvents such as ethanol, polyethylene glycol, and glycerin[7].

f. Partition Coefficient:

A measurement of drug's lipophilicity and an indication of its ability to cross the cell membranes is the oil/water partition coefficient in the systems such as octanol/ water and chloroform/water[6] .The partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium.

$P_{o/w}$= (C_{oil}/C_{water}).

For drug delivery, the lipophillic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption[7].

g. Dissolution:

Dissolution of a drug particle is controlled by several physicochemical properties, including chemical form, crystal habit, particle size, solubility, surface area, and wetting properties.When coupled with equilibrium solubility data, dissolution experiments can help to identify potential bioavailability problem areas[8].

Stability Analysis:

a. Solution Stability:

The primary objective of this phase of preformulation research is identification of condition necessary to form a stable solution. These studies should include the effects of pH, ionic strength, cosolvents, light, temperature and oxygen[9].

b. Solid State Stability:

The primary objectives of the investigation are identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation[9].

Table: 1. A solubility of compound has classically been defined as fallows[10]:

Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Need to Improve Solubility :

- Poorly water soluble drugs present significant challenges during dosage form designing due to their inadequate solubilization in digestive fluids.
- Drugs with poor water solubility can show performance limitation such as incomplete or erratic absorption, poor bioavailability, and slow onset of action.
- Effectiveness can vary from patient to patient and there can be a strong effect of food on drug absorption.
- Poor bioavailability leads to high dose.
- Inter and intra individual variability leads to inadequate therapy and or safety concern.

- In order to overcome problem associated with poorly water soluble drugs there is need to improve solubility, for which various solubilization techniques have been used.
- While selecting different solubilization technologies following factor should be considered.
- Bioavailability and dissolution rate: the technology must demonstrate to enhance dissolution and or bioavailability.
- It should not add substantial time or complexicity to the development of poorly water soluble drugs and should be applicable to wide range of compounds with varying physical and chemical properties.
- Stability: The enhance material produced by the technology should be stable in terms of physical characteristics (particle size, morphology) and chemical properties (degradation) and consistent in regards to in vitro dissolution and in vivo bioavailability performance.
- Drug loading (ratio of drug to excipients) should be maximized for high dose drugs to minimize the size of the dosage form.
- Other considerations for the selection of an appropriate technology include the physical and chemical properties of the drug itself, along with its end use characteristics, such as dose and route of administration, and therapeutic considerations[11].

Factors affecting solubility:-

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system[6].

Particle Size:

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by[12]

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

S is the solubility of infinitely large particles
S is the solubility of fine particles
V is molar volume
g is the surface tension of the solid
r is the radius of the fine particle

Temperature :

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature[7]. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases[13].

Pressure:

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility[13].

Nature of the solute and solvent :

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their natures[13].

Molecular size:

Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent[14].

Polarity:

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules[14].

Polymorphs:

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy[15].

Rate of solution:-

The rate of solution is a measure of how fast substances dissolve in solvents[13].

Techniques Of Solubility Enhancement:-

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are[16]:

Physical Modifications:

Particle size reduction

a. Micronization
b. Nanosuspension

Modification of the crystal habit

a. Polymorphs
b. Pseudopolymorphs

Drug dispersion in carriers

a. Eutectic mixtures
b. Solid dispersions
c. Solid solutions

Complexation

a. Use of complexing agents

Solubilization by surfactants:

a. Microemulsions
b. Self microemulsifying drug delivery systems

Chemical Modifications

a. Prodrug:
b. Salt Formation:

Physical Modifications:-

Particle size reduction:

For drugs whose GI absorption is rate limited by dissolution, reduction of particle size generally increases the rate of dissolution, rate of absorption and /or bioavailability. Particle size reduction is usually achieved by.

Conventional trituration and grinding.
Ball milling
Fluid energy micronisation
Controlled precipitation by change of solvent or temperature, application of ultrasonic waves,[17] and spray drying [18].

a. Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improve the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution[19].

Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility[17]. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

b. Nanosuspension:

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants[18]. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed.

Techniques for the production of nanosuspensions[18]:

a. Homogenization:

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles.

Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors[20].

b. Wet milling:

Active drug in the presence of surfactant is defragmented by milling. Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.

The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one [16]. Drying of nanosuspensions can be done by lyophilisation or spray drying.

c. Sonocrystallisation:

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size[21]. The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation.

Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API). Most applications use ultrasound in the range 20 kHz-5 MHz[21].

RESS involves solubilising a drug or a drug-polymer mixture in SCF and subsequently spraying the SCF solution into a lower pressure environment via a conventional nozzle or recrystallisation capillary tube. The rapid expansion undergone by the solution reduces the density of the CO_2, correspondingly reducing its solvent power and supersaturating the lower pressure solution. This supersaturation results in the and precipitation of pure drug or drug-polymer particles of greatly reduced size, narrow size distribution and high purity. The solubility of nifedipine has been improved by RESS[22].

GAS processing requires the drug or drug-polymer mixture be solubilised via conventional means into a solvent that is then sprayed into an SCF; the drug should be insoluble in the SCF, while the SCF should be miscible with the organic solvent. The SCF diffuses into the spray droplets, causing expansion of the solvent present and precipitation of the drug particles.

The low solubility of poorly water-soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry[23]

d. Spray Drying:

Spray drying is a commonly used method of drying a liquid feed through a hot gas. Typically, this hot gas is air but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used instead. The liquid feed varies depending on the material being dried and is not limited to food or pharmaceutical products and may be a solution, colloid or a suspension. This process of drying is a one step rapid process and eliminates additional processing[22]. Spray drying of the acid dispersed in acacia solutions resulted in as much as a 50% improvement in the solubility of poorly water soluble salicylic acid[23].s

Modification of the crystal habit: [Polymorphs And Pseudopolymorphs]

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point,density, texture,stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area[15].

Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent.

Amorphous >Metastable polymorph >Stable polymorph

Melting followed by a rapid cooling or recrystallization from different solvents can be produce metastable forms of a drug[14].

Drug dispersion in carriers :

a. 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 component starts to crystallize out before theother[24].

Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two components 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[12]. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

b. Solid dispersion (SD):

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion

1. Hot Melt method

Sekiguchi and Obi used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process[25]. An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form.

2. Solvent Evaporation Method

In this method first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent[26]. The solvent can be removed by various methods like by spray-drying or by freeze-drying[27]. Temperatures used for solvent evaporation generally lie in the range 23-65 C.

3. Hot-melt Extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient[28]. The process has been useful in the preparation of solid dispersions in a single step.

4. Melting –solvent method :

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70^0C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

5. Fusion method :

The fusion is technically the less difficult of the process of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath. spray congealing from a modified one Polyvinyl pyrolidone (PVP) k 30 have been prepared by closed melting point method. This method involves controlled mixing of water content to physical mixtures of troglitazone PVP k30 by storing at various equilibrium relative humidity levels (adsorption method)or by adding water directly (charging method) and then mixer is heated. This method is reported to produce solid dispersion (SD) with 0% apparent crystallinity[28].

On the other hand, the fusion process does not require an organic solvent but since the melting of sparingly water-soluble drug and water-metal surface. Decomposition should be avoided and is affected by fusion time and rate of cooling[29]. Another soluble polymer entails a cooling step and solid pulverizing step, a time consuming multiple stage operation is required. To overcome this problem Nakano et al [30] have described a method conceptualizing the formation of a SD as the solid-to-solid interaction between a sparingly water soluble drug, nilvadipine and water soluble polymer which, unlike conventional production method, comprises mixing a sparingly water soluble drug and water soluble polymer together under no more than the usual agitation force with heating within the temperature region not melting them, instead of heating the system to the extent that the two materials are melted , the sparingly water soluble drug can be amorphous to have never been achived by any dry process.

6. Spray drying :

The manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process, resulting solid particles. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications [31]. SD(s) of loperamide and peg 6000 were prepared by this technique, wherein solutions containing different concentrations of loperamide relative to the total amount of solid were spray dried. After spray drying, the dispersions were dried at 400C under vacuum until constant weight. Solvent used was dichloromethane[32].

The prepared SD(s) exhibited higher dissolution rates than that of pure crystalline loperamide. the suitability of this technique for preparation of SD(s) of glibenclamide polyglcolized glycerides. This study revealed the improvement in solubility and dissolution rates, also improvement in the therapeutics efficacy of amorphous glibenclamide in SD(s) was observed. Some other investigators [33] also reported improvement in solubility and dissolution rate. The frequent use of the organic solvent in spray drying pose problems such as residues in products, environmental pollution and operational safety as well as corporate problems such as capital investment.

A process for producing the SD(s) of poorly water-soluble drugs using water-soluble polymer dispers and/ or water-soluble polymer solution and the plasticizer solution by using 4-nozzle spray gun. The spray drying technique is a useful method to obtain spherical particle and narrow distribution. The role of porous materials such as calcium silicate, controlled pore glass and porous cellulose is appreciated to formulate solid dosages forms because they confer special characteristics such as decrease of melting point and a decrease in the crystallinity of drug entrapped in pores. In addition, porous materials control polymorphs and stabilizes meta-stable crystals in SD(s) under sever storage conditions. Moreover, porous silica has been reported to improve solubility and dissolution rates of indomethacin and tolbutamide[34] .

Selection of Suitable Carrier:-[35]

The following criteria are required for carrier.

- It should be non toxic.
- It should have intrinsic rapid dissolution property.
- It should be freely water soluble
- The carrier chosen for fusion processes should be chemically, physically and thermally stable and should have low melting point.
- It should solidify rapidly into stable dispersion by rapid and complete crystallization. The carrier and drug should be miscible in liquid state.
- The carrier should increase the aqueous solubility of drug.
- The chosen carrier should be chemically compatible with the drug and in the solid state should not form strongly bonded complex with high association constant.
- It should be pharmacologically inert.

Table.2 Materials Used as a Carriers for Solid Dispersions[36]

Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol, Mannitol, Lactose.
Acids	Citric acid, Tartaric acid, Succinic acid, Bile acid
Polymeric materials	Polyvinylpyrrolidone, Polyethylene glycol, Hydroxypropyl methyl-cellulose, methyl cellulose, Pectin, hydroxyethyl cellulose, Cyclodextrins, Gallactomannan
Surfactants	Polyoxyethylene Stearate, Renex 650, Poloxamer 188, Texafor ATP, Deoxycholic acid, Tweens, Spans
Miscellaneous	Urea, Urethane, Hydroxyalkyl xanthenes, Sterols and related compounds

C. Solid solution: -

A solid solution compared to liquid solution is made up of a solid solute dissolved in a solid solvent. It is often called mixed crystal because the two components crystallize together in a homogeneous one-phase system[21]. In solid solution of poorly soluble drug in a rapidly soluble carrier achieves faster dissolution rate than a eutectic mixture because the particle size of drug[12]. In the solid solution is reduced to minimum state i.e. its molecular size.

Complexation

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions[37].

There are many types of complexing agents and a partial list can be found in below table.

Table. 3 : List of Complexing Agent [37]

Sr.No.	Types	Examples
1	Inorganic	I_B^-
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA, EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular	Polymers

The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility[38]. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule.

Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules[39].

Factors affecting complexation[40]:

1. Steric effects
2. Electronic effects
3. Temperature, additives and cosolvent effects

Solubilisation by surfactant :

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic[41]. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent[21].

a. Microemulsion:

The term microemulsion was first used by Jack H. Shulman in 1959. A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion[42]. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions[21].

b. Self-emulsifying drug delivery systems (SEDDS) :

Self-emulsifying drug delivery systems (SEDDS) can be defined as mixtures of oils and surfactants, ideally isotropic, which emulsify under gentle agitation in the gastro-intestinal tract[21.] Sometimes SEDDS formulated by including cosolvents. Characteristic of SEDDS provides potential to increase bioavailability of poorly water soluble drugs.

Chemical Modifications :

All approaches are targeted to increase surface area and the saturation solubility of poorly soluble drugs

a.Prodrug:

Many pharmaceutical new chemical entities (NCE) were synthesized as prodrug e.g. metronidazole N, N-dimethyl glycinate, to increase the solubility of

metronidazole. For the formation of prodrug it is essential to have NCE with favorable functional group(s) for salt formation. So that, one can synthesizes prodrug with the help of promoiety. The second important thing is that human body should have biochemical mechanism to cleave this molecule into the active entity once it is absorbed int the blood. But alteration in chemical structure may lead change in toxicological properties[43].

b. Salt Formation:

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. For the salt formation drug should have ionisable groups that will assist salt formation forces.

The use of salt forms is a well known technique to enhanced dissolution profiles[44]. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs.An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates)[45]

Other techniques:-

Co-crystallisation:

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystal, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex)[17]. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces[46].

Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature

Cosolvency:

The solubilisation of drugs in co-solvents is an another technique for improving the solubility of poorly soluble drug. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs[47].

Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending[48] .

Hydrotrophy:

Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute[49].

Example: Solubilisation of Theophylline with sodium acetate and sodium alginate.

Solubilizing agents:

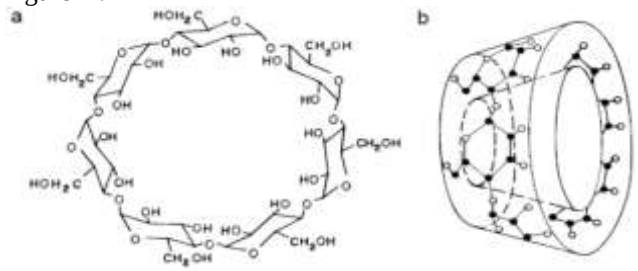
The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazid. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide[50].

Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary[49]. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned.

Introduction to Cyclodextrin :

Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes .Chemically they are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds.[51]. The 3 natural CDs, α-, β-, and γ-CDs (with 6, 7, or 8 glucose units respectively), differ in their ring size and solubility (Table 1) CDs with fewer than 6 units cannot be formed due to steric hindrances while the higher homologs with 9 or more glucose units are very difficult to purify. However, recently Endo et al established an isolation and purification method for several kinds of large ring CDs and also obtained a relatively large amount of δ-CD (Cyclomaltonose) with 9 glucose units[52].

Figure 2 :



(a) The toroidal shape of a cyclodextrin[53]

(b) The chemical structure of a cyclodextrin molecule[53].

Complexation of molecules to CDs occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the guest molecule associates and dissociates from the host CD. CDs are insoluble in most organic solvents; they are soluble in some polar, aprotic solvents. Although the solubility of CDs is higher in some organic solvents than in water,

complexation may not occur readily in non-aqueous solvents because of the increased affinity of the guest for the solvent compared to its affinity for water. Also CDs form complexes with lipophilic solvents, even with ethanol and methanol, and these complexes become contaminants in the final product. CDs glass transition occurs at about 225 to 250 °C[53].

Table 4. Some characteristics of α-, β-, γ-, and δ-CD [51,53] :

Type of CD	Cavity Diameter Å	Molecular Weight	Solubility (g/100 mL)
α-CD	4.7–5.3	972	14.5
β-CD	6.0–6.5	1135	1.85
γ-CD	7.5–8.3	1297	23.2
δ-CD	10.3–11.2	1459	8.19

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a solubilizer, ie, CD or ligand, on the drug being solubilized, ie, the substrate. Phase solubility diagrams are categorized into A and B types[54].

A type curves indicate the formation of soluble inclusion complexes while B type suggest the formation of inclusion complexes with poor solubility. A B_S type response denotes complexes of limited solubility and a B_I curve indicates insoluble complexes. A-type curves are subdivided into A_L (linear increases of drug solubility as a function of CD concentration), A_P (positively deviating isotherms), and A_N (negatively deviating isotherms) subtypes. β-CD often gives rise to B-type curves due to their poor water solubility whereas the chemically modified CDs like HP-β-CD and SBE-β-CD usually produce soluble complexes and thus give A-type systems. In the case of a 1:1 complex, using the following equation one can determine the equilibrium binding or association constant, K, from the slope of the linear portion of the curve[55].

$$Ka : b = \text{slope } S_0 \ (1 - \text{slope})$$

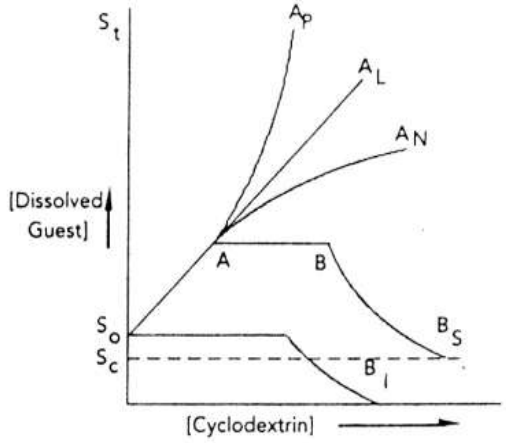


Figure 3. Theoretical phase solubility diagram[54,55].

Where S_o is the intrinsic solubility of the drug studied under the conditions.

Cyclodextrin (CD) Use as Excipients in Drug Formulation:

In the formulation and processing of drugs:

As excipients, CDs have been finding different applications in the formulation and processing of drugs. β-CD, due to its excellent compactability (varied with source) and minimal lubrication requirements, showed considerable promise as a filler binder in tablet manufacturing but its fluidity was insufficient for routine direct compression. β-CD was also found to be useful as a solubility enhancer in tablets[56,51]. The ability of β-CD to complex progesterone by wet granulation was found to be dependent on both binder solution and mixture type. Complexation can cause suitable changes in the tabletting properties of drugs or CDs that can substantially affect the stability and tabletting performance of tablet formulations containing drug/CD complexes. Complexation of tolbutamide with HP-β-CD (freeze-dried or spray-dried) altered the water sorption-desorption and tabletting properties of the CD, and the resultant complex showed worse compactability than the pure CD or the drug/CD physical mixture[56]. CDs also affect the tabletting properties of other excipients, eg, microcrystalline cellulose codried with β-CD showed improved flowability, compactability, and disintegration properties suitable for direct compression. In the case of high-swelling wheat starches, β-CD (1%) increased the peak viscosity (PV) but decreased the cool paste viscosity (CPV) and in the case of low-swelling starches, the same CD slightly decreased the PV but increased the CPV. However, β-CD reduced the heat paste viscosity of both the starches. Avicel/β-CD co-dried product showed improved flowability and disintegration properties but its rounder particles, because of their sensitivity to lubrication, gave tablets weaker than those with avicel. But on addition of magnesium stearate, the codried excipient with improved powder flowability served as a better excipient in wet granulation[57].

To mask the taste of drugs in solutions:

CDs can be used to mask the taste of drugs in solutions, eg, suppression of bitter taste of 4 mm oxyphenonium bromide by CDs. With the assumption that only the free drug molecule exhibits bitter taste regardless of the kind and concentration of CD, the suppression of drug bitter taste by CDs was reported to be in the order of α-CD < γ-CD < β-CD, reflecting the stability constants of the complexes[58].

Interaction of CDs with the preservatives:

Interaction of CDs with the preservatives in the formulation is an important factor and should be investigated. It was reported that such interaction can result in reduction of both the solubilizing effect of CD and the antimicrobial activity of preservatives, eg, interaction of HP-β-CD with preservatives like benzalkonium chloride, chlorhexidine gluconate, chlorambutanol, methylparaben, and propylparaben[58].

Complexation :

The internal cavity, hydrophobic in nature, is a key feature of the CDs providing the ability to form complexes, which include a variety of guest molecules. CD inclusion is

astoichiometric molecular phenomenon in which usually only one molecule interacts with the cavity of the CD molecule to become entrapped. A variety of non-covalent forces, such as van der Waals forces, hydrophobic interactions and other forces are responsible for the formation of the stable complex[59]. Inclusion complex formation can be regarded as'encapsulation' of the drug molecule, or at least the labile part of the molecule. The encapsulation protects the drug molecule against attack by various reactive molecules and in this way reduces the rate of hydrolysis, oxidation, stearic rearrangement, racemization and even enzymatic decomposition . In addition, CDs can decrease the photodegradation of various light sensitive drugs .Many techniques are used to form CD complexes, like co-precipitation, slurry complexation, paste complexation, damp mixing, heating method, extrusion and dry mixing. The name itself describes the process of complex formation[60].

Co-precipitation:- CD is dissolved in water and the guest is added while stirring the CD solution. By heating, more CD can be dissolved (20%) if the guest can tolerate the higher temperature. The CD and guest solution must be cooled under stirring before a precipitate is formed[57]. The precipitate can be collected by decanting, centrifugation or filtration nand washed. The main disadvantage of this method lies in the scale-up[58].

Slurry comlexation:- CD can be added to water, as much as 50–60% solids, and stirred. The aqueous phase will be saturated with CD in solution. Guest molecule will complex with the CD in solution and, as the CD complex saturates the water phase, the complex will crystallize or precipitate[61].

Paste complexation :- A small amount of water is added to the guest to form a paste, which is mixed with the CD using a mortar and pestle. The resulting complex can be dried directly, and milled if hard mass forms[62].

Damp mixing: - The guest and CD are thoroughly mixed and placed in a sealed container with a small amount of water. The contents are heated to about 100 °C and then removed and dried[63].

Extrusion: - CD, guest and water can be premixed or mixed as added to the extruder. The extruded complex may dry as it cools or the complex may be placed in an ovento dry. Heat-labile guests can get decomposed[28].

Dry mixing :- Some guests can be complexed by simply adding the guest to the CDand mixing them together. This works best with oils or liquid guests[62].

In all methods, optimization of the amount of water, degree and time of mixing, temperature and heating time is necessary for each guest. Different mechanisms play an important role in drug release from the drug-CD complex. Complexation of the drug (D) to CD occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the drug molecule continuously associates and dissociates from the host CD[61].

Dilution: – Dissociation due to dilution appears to be a major release mechanism Dilution is minimal when a drug-CD complex is administered ophthalmically. Efficient corneal absorption is further exacerbated by contact time[26].

Competitive displacement :– Competitive displacement of drugs from their CD complexes probably plays a significant role in vivo. Addition of parabens to parenterals notely leads to decreased antimicrobial activities of the parabens, due to complexation, but also decreases the drug solubility due to its displacement from complexes showed that alcohol displaces 2-napthol from CD complexes reported that the CD complex of a poorly water-soluble drug, cinnarizine, wasmore soluble in vitro than cinnarizine alone. Oral administration of the complex showed less bioavailability than expected, based on the in vitro dissolution experiments. It was suggested that cinnarizine was too strongly bound to the CD so that complex dissociation was limiting oral bioavailability. Co-administration of phenylalanine, a displacing agent, improved the bioavailability of cinnarizine from the complex but not from conventional cinnarizine tablets[64].

Protein binding :- Drug binding to plasma proteins may be an important mechanism By which the drug may be released from a drug-CD complex. It is evident that proteins may effectively compete with CDs for drug binding and thus facilitate the in vivo release of drugs from drug-CD complexes. Dilution alone may be effective in releasing free drugs from weak drug-CD complexes but when the strength of the binding between the drug and CD is increased, a mechanism such as competitive displacement is at work. Plasma and tissue protein binding may also play a significant role[58]. The effect of HPCD on the displacement of both naproxen and flurbiprofen from plasma binding sites in vivo. They found that tissue distribution of flurbiprofen and naproxen was higher when HPCD-drug solution was administered compare to drug solution in plasma, 10 minutes after parenteral dose, meaning that more drug was free from CD solution to distribute to the tissues than from the plasma solution[63].

Drug uptake by tissue: - A potential contributing mechanism for drug release from CD is preferential drug uptake by tissues. When the drug is lipophilic and has access to tissue, and is not available to the CD or the complex, the tissue then acts as a sink, causing dissociation of the complex based on simple mass action principles[60]. This mechanism is more relevant for strongly bound drugs or when the complex is administered at a site where dilution is minimal, e.g. ocular, nasal, sublingual, pulmonary, dermal or rectal sites. For example, CD has been used in ophthalmic delivery of poorly water-soluble drugs to increase their solubility and/or stability in the tear fluid, and in some cases to decrease irritation [60].

Change in ionic strength and temprature :- In the case of a weak electrolyte, the strength of binding to CD is dependent on the charged state of the drug, which is dependent on dissociation constant(s) of the drug and the pH of environment. For most molecules, the ionized or charged form of the molecule has poorer binding to CD compared to

the non--ionized or neutral form of the drug, especially when bound to a neutral CD [13]. any increase in temperature results in a weakening of these complex and thus increases the free fraction of substrate. Drug-CD complexes are usually prepared and stored at/or below room temperature. Since the normal body tissue temperature can be as high as 37 °C, this difference in temperature may be another contributing factor to drug dissociation in vivo[28].

Cyclodextrin Inclusion Complexes:

Cyclodextrins (CDs) are cyclic macromolecules obtained by degradation of starch by glycosyl transferases. Depending on the specific character of the respective transferases, different CDs results, consisting of 6 (alpha-CD), 7 (beta-CD) of 8 (gamma-CD) glucose units. The molecular shape of CDs resembles that of cones. They build up a hydrophobic cavity, where small or medium sized molecules can be included. Stability and properties of these host-guest complexes are dependent on the size of the CDs rim, but also on the molecular properties of the guest molecules. Biological active substances interact, in most cases[65], with biomolecules, triggering specific molecular mechanisms like activation of an enzyme cascade or opening of an ion channel, which finally leads to distinct biological response. Quantitative structure-activity relationships correlate this response with molecular properties of the compounds of interest. Due to the fact that the response depends on the concentration of the active substance as well as on the strength of interaction with the macromolecule, both of these aspects have to be modelled quantitatively. The most general relationship connecting structure and molecular properties to biological activities is given by the equation[65]

$\log(1/D)=A+\log B -\Delta G/RT$

where A is a constant, log B summarizes transport properties and the ability to cross biological membranes of the considered compounds, and ΔG describes the free energy of interaction with the biomolecules. Log (1/D) is a quantitative measure of the biological response. A broad variety of methods is available to obtain correlations of a biological effect with molecule properties, reaching from classical statistical methods to more sophisticated three dimensional methods and artificial neural methods. The quality of the calculated correlations and prediction models mainly depends on these parameters, which describe the structure and the properties of a molecule as accurate as possible. Therefore, methodological developments have been performed by our group reaching from alignment-independent procedures to calculations of new molecular descriptors, e.g. taking into account the chirality of the investigated compounds[66].

The complexation of various molecules with CDs is of high industrial importance as many application possibilities exist in pharmacy, chemistry and environmental research. Therefore, many physicochemical and theoretical investigations have been performed on the reaction mechanisms of host-guest inclusion processes, to get some information about the forces, which lead to the association of a molecule into the cavity of CDs. The interactions between the included molecules and the interior of various CDs can be also studied by molecular calculations, particularly by accurate calculations as well as by empirical Monte Carlo (MC) simulations. Moreover, Molecular Dynamics(MD) simulations give some insight into the structure and the mobility of the complexes and enable to find the most favourable geometries of the association complexes[67].

Other simulations concern the dynamical behaviour of cyclodextrins in water environment and the effects of ligand binding. One of compounds with a very large association constant is spironolactone. This compound shows a large reaction enthalpy, caused by the strong interaction between the molecular surface of the molecule and the glucose units of the CDs[66]. As the contribution of the entropic term is positive for this system, a very high association constant is the consequence.

Hydroxy propyl beta cyclodextrin (HPBCD):

CD inclusion has concentrated its efforts on the hydroxy propyl derivative of B-cyclodextrin believing it to be the most likely candidate of all the chemically modified cyclodextrins for incorporation into formulations used by humans and animals. HPBCD has the best balance of enhanced aqueous solubility, a wide range of drugs with which it forms stable complexes, and the most extensive collection of safety data in the technical literature with no adverse reactions reported. HPBCD is itself very soluble in water (greater than 500 mg/ml at room temperature compared to 18 mg/ml for B-cyclodextrin) More importantly, HPB forms soluble complexes of the AL type that is, the concentration of drug complexed increases linearly as the concentration of HPBCD increases[57] .

HPB is non-hygroscopic with inherently excellent tabletting properties. It does not change the surface tension of water as much as other cyclodextrins such as dimethyl Beta-Cyclodextrin, which exerts a detergent-like effect on biological membranes. This property of dimethyl Beta-Cyclodextrin makes it much more hemolytic and irritating when administered intramuscularly or topically to mucous membranes[68].

Application of Cyclodextrin to improve solubility of poorly soluble drugs :

CDs reduce the reactivity of drugs in the solid state, enhance their dissolution rate and solubility, and reduce unpleasant mouth taste[56].

Often one would like to combine multiple ingredients or drug actives within a single formulation because of the potential for synergistic benefits. However, different drugs are often incompatible with each other or with other inactive ingredients in a formulation. Encapsulating one of the incompatible ingredients within the cyclodextrin molecule stabilizes the formulation by physically separating the components to prevent chemical interaction[69]; e.g., complexing phenobarbital with ß-CD improved its compatibility with papaverine hydrochloride.

- CD-complexed forms of drug having no own crystal structure, and the problems associated with polymorphism are eliminated, e.g., spiranolactone-containing tablets contain a thermodynamically more stable crystal form, produced by long storage at elevated temperature and humidity, result in lower

bioavailability. On complexing, spiranolactone with y-CD, the dissolution and bioavailability properties can be guaranteed for a long time[58].

- In suspension, CD can act as a crystal form stabilizer[18].
- Crosslinked CD is an interesting product for the preparation of sustained release formulations, e.g., local anesthetic effect of pilocaine and lidocaine can be elongated with ß-CD[70].
- Active ingredients that are either oils/liquids or volatile materials can be difficult to handle and formulate into stable solid dosage forms. Encapsulating these types of substances in a cyclodextrin converts them to a solid powder that has good flow properties and can be formulated into a tablet by conventional production processes and equipment. CD complexes of complexable liquids are microcrystalline, easily tablatable powders with a good storage life[71], e.g., clofibrate, garlic oil.
- The physical properties of the tablet can be improved. CDs are nonhygroscopic; therefore, mixing with hygroscopic substances reduces the deliquescence, e.g., sodium valproate reported with ß-CD. Decrease in crystallinity increased tablet hardness and disintegration time[58].
- Transdermal absorption and stability is better than when the drug is complexed with CD, e.g., nitroglycerin complexed with ß-CD[72].
- CD complexes can be homogenized with all kinds of suppositorial bases. Complexes will not decrease their melting point, mechanical strength, and distribution of drugs. No separation occurs during solidification. Complexation with CD in ophthalmological preparations improves stability and solubility and strongly reduces eye irritating effect[20], e.g., preparation of CD-containing eye drops were reported with various drugs such as indomethacin, flurbiprofen, diclofenac sodium, steroids.
- Volatile components form stable complexes with CD. Sprinkling the powdery complex onto hot water, it submerges, dissolving slowly; uniform release of volatile component can thus be ensured[72].

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