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Review on Inclusion Complexation: A Technique to Enhance the Solubility of Poorly Water Soluble Drug

Ms. Aishwarya Audumbar Karande*, Mr. Amol Sampat Deshmukh
Department of Pharmaceutics, S.M.B.T. College of Pharmacy, Dhamangaon, Nashik, Maharashtra, India.

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Corresponding Author:
Mr. Soham Mandal

Email ID:
aishwaryakarande742@gmail.com

Mob. No.
8421215468

Abstract:
The phenomenon of a solid dissolving into a liquid phase to create a homogeneous system is known as solubility. To acquire the required concentration of medication in the systemic circulation for the best pharmacological response solubility is a crucial factor. The main issue in developing formulations for new chemical compounds as well as for generic development is low water solubility. About 40% of all newly discovered chemical compounds are lipophilic, which prevents their use in therapeutic doses because of their poor water solubility. Solid dispersion, solvent deposition, micronization, and complexation are a few vital techniques frequently used to improve the solubility of medications that aren't very soluble in water. Poorly water soluble in pharmaceuticals their solubility increased by the use of complexation technology. Such cyclodextrin can interact with appropriate size drug molecules which lead to the formulation of inclusion complexes. In this review, brief information about improvement of aqueous solubility of drug and improve therapeutic efficacy by inclusion complexation method. The solubility, dissolution rate, and bioavailability of poorly soluble pharmaceuticals have been reported to be improved through complexation with CDs using a variety of techniques, including physical mixing, melting, kneading, spray drying, freeze drying, and co-evaporation.
Keywords: Cyclodextrin, Complex, Inclusion Complexation, Bioavailability

INTRODUCTION

In terms of quantity, solubility is defined as the amount of the solute present in a saturated solution at a particular temperature. In terms of quality, solubility is the spontaneous interaction of two or more substances to create a homogenous molecular dispersion(1). When the solute and solvent are in balance, a solution is said to be saturated. Parts, percentages, molarity, molality, volume fraction, and mole fraction are all acceptable ways to express a drug's solubility. The maximum amount of a drug's solute

that can be dissolved in a solvent under a given set of temperature, pH, and pressure conditions is known as the drug's solubility. Drug dissolving rate is a dynamic feature that is more closely related to bioavailability rate than drug solubility in saturated solution, which is a static attribute. Depending on how much of the drug dissolves in the solvent, different descriptive phrases are used to characterise a drug's solubility(2). The aqueous solubility is a key indicator for the solubility in intestinal fluids and its possible impact on bioavailability problems(3). In pharmaceutical industry almost 40% of newly developed drugs in the are practically insoluble in water(4). The limited aqueous solubility of these compounds results in a low absorption rate in the gut, leading to decreased bioavailability but increased side effects such as gastrointestinal tract irritation because of using high doses or high concentration of surfactants in emulsions(5). The solubility of bioactive compounds can be altered through particle engineering techniques and several formulation approaches. Particle engineering techniques are developed to produce defined particles to modify physiochemical properties of poorly soluble substances. Wet-milling, dry-milling, and high-pressure homogenization are examples of mechanical particle-size reduction techniques. Lyophilization and spray freezing are examples of cryogenic particle engineering techniques. Other techniques for preparing micro and nanoparticles include nano-precipitation and supercritical fluid processing(6). In a formulation strategy, the medicine or bioactive molecule is formulated in a solution that also contains various excipients, water or oil, and stabilisers. Solid formulations, lipid formulations (such as emulsion-based drug delivery systems), and amorphous formulations (such as amorphous solid dispersions) are examples of general formulations(7). These formulations are made utilising a variety of methods, including milling and spray drying(8).

Drug dissolution becomes the rate-limiting phase in the absorption process if the rate of dissolution is noticeably slower than the rate of absorption(9). Drug permeation becomes the rate-limiting phase in the absorption process if it takes longer for the drug to penetrate the gastro-intestinal tract than it does to dissolve. The medications were divided into four classes in biopharmaceutical terminology based on their solubility and permeability, as follows(10):

Table no:1 Biopharmaceutical classification system of drug(1)

Class	Solubility	Permeability	Examples
Class-I	High	High	Acyclovir, Diazepam Acetaminophen, Antipyrine, Buspirone
Class-II	Low	High	Glipizide, Indinavir, Amiodarone, Carvedilol, Dapsone, Flurbiprofen
Class-III	High	Low	Amoxycillin, Famotidine, Cetrizine, Cloxacillin, Dicloxacillin
Class-IV	Low	Low	Amphotericin B, Mebendazole, Neomycin, Colistin, Furosamide

Powder technology, one of mankind's oldest professions, has evolved into a science with its main applications in the food, chemical, and pharmaceutical industries(11). The majority of pharmaceutical

excipients and the active medicinal ingredient are available in powder form, making powder technology a necessary discipline in the pharmaceutical business and pharmaceutics. Pharmaceutical production techniques entail modifying powder and particle qualities in added to the fundamentally typical steps of grinding, mixing, and formulating in order to generate unique drug formulations with improved solubility and dissolving capabilities. Technology for pharmaceutical powder examines materials, formulations, additives, and procedures to produce particles or composites with the desired qualities or performance(12)(13). To improve the water solubility of poorly soluble medications, particle technology in pharmaceutics modifies the physicochemical, micrometric and biopharmaceutical aspects of the drugs(14).

Several concentration terminology, including quantity per quantity, percentage, parts, molarity, molality, mole fraction, milliequivalents, and normal solutions, are commonly used to express solubility. According to the US Pharmacopeia, it can alternatively be expressed in terms of the number of parts of solvent needed for every part of solute as follows:

Table no: 2 Examples of the drugs with their solubility as per USP

Term	Parts of solvent reqired for 1 part of solute	Examples of drug
Very soluble	Less than 1parts	Deltiazam, Metoprolol
Freely soluble	From 1-10 parts	Ipratropium bromide
Soluble	From 10-30 parts	Carmustine, Cyclophosphamide, Procainamide, Propananolol, Quinidine, Timolol
Sparingly soluble	From 30-100 parts	Fluorouracil, Labetolol, Quinidine Sulphate, Ramipril
Slightly soluble	From 100-1000 parts	Atenolol, Fludrabine, Valsartan
Very slightly soluble	From 1000-10,000 parts	Busulphan, Doxazocine, Flecainide, Lomustine
Practically Insoluble	More than 10,000 parts	Candesartan, Chlorambucil, Irbesartan, Lidocaine, Melphlan, Nifedipine

Modern drug discovery processes frequently produce poor water solubility drug candidates, which pose significant technical problems for formulators. Insufficient bioavailability is frequently brought on by poorly water soluble medicines' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids. The aqueous solubility of such compounds can be increased in a variety of ways, including.

A. Particle size reduction(1)

a. Micronization

b. Nanosuspension

B. Modification of the crystal habit

a. Polymorphs

b. Pseudo polymorphs

C. Drug dispersion in carriers

a. Eutectic mixtures

b. Solid

c. Solid solutions

D. Complexation(24)

a. Use of complexing agents

E. Solubilization by surfactants

a. Micro emulsions

b. Self-micro emulsifying drug delivery systems(25,26)

COMPLEXATION

When administering drugs with cyclodextrins, an increase in solubility is frequently credited with contributing to improved bioavailability along with an improvement in dissolution kinetics(15). In addition to affecting the concentration of the medication in solution in the intestinal lumen, solubility can also have an impact on penetration through the intestinal barrier. Inadequate bioavailability is thus frequently attributed to low solubility. To assess cyclodextrins' capacity to boost bioavailability, it is helpful to define what is meant by the "increase in solubility" brought about by these substances. The sum of the free drug and complex in solution constitutes the total amount of drug in solution when cyclodextrin is present(16). This total amount of drug in solution can have a maximum value equal to the product of the drug's own solubility and the volume of the complex that results when the free drug concentration in solution equals the drug solubility. Based on the binding constant with an ionised drug, similar expressions can be written for the total amount of an ionizable compound in solution in the presence of cyclodextrin(17). It is common to refer to this combined amount of free drug and complex as having "enhanced solubility." Prednisolone, for instance, dissolves in water at room temperature at a rate of 0.25 mg/ml while DM-CD and 15 mg/ml β-CD have solubilities of 3.4 mg/ml and 3.3 mg/ml, respectively(18). The amount of cyclodextrin needed in a formulation proposed is theoretically treated as a function of this improved solubility. It's vital to remember, nevertheless, that the value of the free drug concentration at equilibrium won't be greater than the free drug's solubility. This is important to note since the concentration of free drugs in the intestinal lumen determines the rate of penetration through the intestinal membrane. Some investigations have shown that cyclodextrins are transported

across the intestinal barrier(19)(20). When the complex is dosed, for instance, it will dissociate to a degree that depends on the binding constant and the quantities of the drug, cyclodextrin, and complex in the intestinal lumen. In contrast to the kinetics of dissolution and permeation through the intestinal membrane, association and disassociation are frequently assumed to occur instantly and free drug molecules can be thought of as being in pseudo equilibrium with molecules bound in the cyclodextrin cavity at all times(21,22). If the concentrations of the free medication and cyclodextrin in solution are greater than their equilibrium solubilities while dissolution and decomplexation is occurring, they will precipitate. However, dosing a complex can produce free drug concentrations for a while that are higher than the drug's solubility if dissolution and disassociation of the complex are sufficiently quick compared to precipitation(18). Increased medication absorption through the intestinal barrier may result from this. Hydroxypropyl cellulose (HPC) and PVP, for example, have been employed to extend the supersaturated state caused by complex dissolution. By delaying the precipitation of free drug, cyclodextrins may also increase free drug concentration. When some of the drug is bound by cyclodextrin, the precipitation kinetics, which are inversely proportional to the drug concentration, are lowered(23). In order to create a non-bonded entity with a clearly defined stoichiometry, two or more molecules must form complex(25). Hydrophobic interactions, hydrogen bonds, and other relatively weak forces, such as London forces, are the foundation of complexation. Chelates, EDTA, EGTA, polymeric molecular complexes, inclusion complexes and cyclodextrins are a few examples of complexing agents. There are two types of complexes:

Stacking complexes:

These are created when a drug's non-polar region joins forces with a complexing agent, preventing the non-polar region from coming into touch with water and lowering the system's overall energy. Whether the stacking is homogeneous or heterogeneous, the solution is always evident. Complexation is the term for the latter and self association for the former. Nicotinamide(27), Anthracene, Pyrene, Methylene Blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene are a few substances that are known to create staching complexes(28). substances that can stack can be divided into two kinds (classes A and B) depending on their structural characteristics. Class A compounds have a greater affinity for class B compounds than for class A compounds, and vice versa(29,30).

Inclusion Complexes:

When a compound can surround another component, inclusion complexes are created. Such complexes are also known as no-bond complexes since no force or bond is envolved(10).

INCLUSION COMPLEXATION

Inclusion complexes are made up of two or more molecules, one of which is the "host" molecule and the other of which is the "guest." The host cavity contains hydrophobic molecules or portions of molecules

that can fit there when there is water present. Due to their truncated cone structure, which has a hydrophobic interior cavity and a hydrophilic outer surface as a result of the presence of CH_2 and hydroxyl groups on the inner and outer sides of the cyclodextrin, respectively, cyclodextrins can accommodate the hydrophobic molecules. The CDs have enhanced water solubility due to their abundance of hydroxyl groups. In addition to increasing a compound's solubility, complexation with cyclodextrin also benefits chemical stability, shields bioactive molecules from the environment, changes flavour, and controls medication release(31). According to toxicology, CDs at low doses are well tolerated by people, but at high levels, side effects such diarrhoea and mushy stools may occur. Because of their lipophilic cavity and acceptable diameter for non-polar guest molecules, βcyclodextrins are frequently used in practical applications. α- and γ-CDs are more expensive to purify than β-CDs (32,33). By engulfing the drug molecule, or the lipophilic portion of the molecule, in the central cavity of the polar cyclodextrin, which is occupied by water molecules that are energetically unflavored and are therefore easily replaced by an appropriate guest molecule that is less polar than water, cyclodextrins are able to form inclusion complexes with drugs in aqueous solutions. Non-cyclic oligosaccharides and polysaccharides, create water-soluble complexes with lipophilic water-insoluble substances because the hydroxy groups on their outer surfaces can establish hydrogen bonds with other molecules(34). Fluorescence probes can bind to linear homologs of maltodextrins, such as α-1,4-linked linear glucose oligomers, but the binding constants are considerably smaller than those for their counter parts in cycles. It has been demonstrated that α-cyclodextrin can combine with dicarboxylic acids to create inclusion and non-inclusion complexes, and that aqueous solutions can accommodate both types of complexes(35). Guest/cyclodextrin complexes in saturated aqueous solutions typically combine inclusion and non-inclusion complexes(36). This may help to explain why the numerical value of the equilibrium constant for complex formation is frequently dependent on the method used and sometimes depends on concentration(37,38).

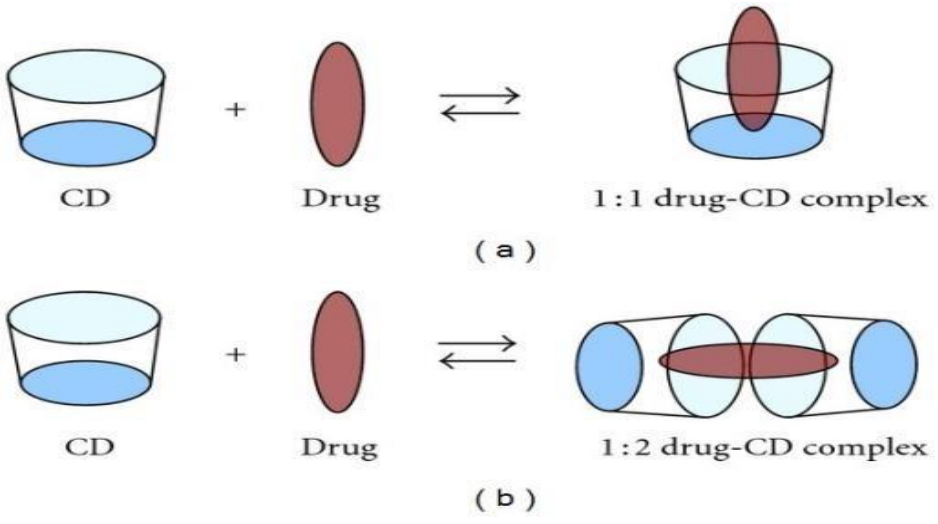

Fig:1 Formation of complex

Advantages of Complexation:

1. Enhance solubility.
2. Enhance bioavailability.
3. Enhance stability.
4. Simplest to formulate.
5. Convert liquids and oils to free-flowing powders.
6. Reduce evaporation and stabilize flavours.
7. Reduce odours and tastes.
8. Reduce haemolysis.
9. Prevent admixture incompatibilities.

Disadvantages of Complexation:

1. Laborious and expensive methods of preparation.
2. Difficulty in incorporating into formulation of dosage forms.
3. Scale-up of manufacturing process.
4. Stability issues.
5. Only small dose drugs are complexed(26).

To control the solubility and antioxidant activity of flavonoids, we looked at inclusion complexes of cyclodextrins with three distinct flavonoids: luteolin, kaempferol, and myricetin. A flavone called luteolin is present in numerous plants, including carrots, peppers, rosemary, tea, and chocolate. It possesses physiological properties such the ability to chemopreventive cancer, antibacterial, anti-oxidant, and anti-inflammatory activities both in vivo and in vitro. Myricetin and kaempferol are included in the flavonol subgroup. Antioxidant, depressive, and proven to lower the risk of heart disease, kaempferol extracted from plants and tea possesses these qualities. Fruits, herbs and vegetables all produce the antioxidant myricetin(39,40). These three flavonoids exhibit an antioxidant effect or free radical scavenging characteristics that have positive impacts on the management and prevention of a variety of oxidative stress-related diseases, such as cancer and heart disease. Despite these beneficial physiological traits, flavonoids have very limited solubility in water, unlike myricetin, which is soluble in alcohol or boiling water, while kaempferol and luteolin are soluble in organic solvents. Some flavonoids' solubility and antioxidant activity were increased by the use of cyclodextrin and sulfobutylether β-cyclodextrin. SBE-β-CD is a derivative of β-CD that has a negative charge because it has sulfobutylether added to it. One of the most well-liked β-CD derivatives, SBE-β-CD, has been employed to enhance the solubilization of several compounds that aren't very water soluble(41). At the 2, 3, and 6 positions of the hydroxyl group of β-CD, the SBE groups were variously substituted; the average degree of substitution is seven SBE groups per β-CD molecule. In contrast to

the original β-CD, we believe SBE groups connected to CD may favourably contribute to the more efficient complexation of several flavonoids used in this investigation(42).

Antioxidant defence is provided by CDs, which also improve their solubility, stability, and consequently their bioavailability and biological activity. As a result, antioxidant dosages can be utilised at lower levels, improving therapeutic index while costing less (43,44). Large quantities of antioxidants can be contained by CDs. For example, the loading capacity studies predicted that RES would be included to an extent of 80% in the methyl β-CD cavity(45). A successful and robust development of an antioxidant β-CDs inclusion complex is influenced by a number of variables. These include the pH, temperature, and mixing duration as well as the kind of solvent utilised in the formation of the inclusion complex. The optimal conditions that produced the best solubility improvement of the QCT β-CDs inclusion complex were pH

= 8.0 at 37 C with a 72-hour mixing period(46). The mixing speed has an impact on the effectiveness of antioxidants being trapped in CD cavities in addition to temperature and reaction time(47). The effects of mixing duration, temperature, and molar ratio on the incorporation of chrysin (5,7-dihydroxyflavone) inside the β-CD cavity were examined. According to one study, temperature has the biggest impact on inclusion rate, followed by molar ratio and mixing time(48).

The following substances are known to form staching complexes: Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, Naphthalene, Nicotinamide, Anthracene, Pyrene, Methylene Blue, etc. Substances that can stack can be divided into two kinds (classes A and B) depending on their structural characteristics. Class A compounds have a stronger affinity for class B compounds than for class A compounds, and vice versa(49).

The forces driving complexation were attributed to:

1. the exclusion of high energy water from the cavity.
2. the release of ring strain particularly in the case of β-CD.
3. Van der Wal's interactions.
4. Hydrogen and hydrophobic bindings.

Cyclodextrins, urea, caffeine, polyethylene glycol and N-methylglucamide are the most typical complexing ligands. The usage of cyclodextrins has significantly improved the drug's solubility and dissolution(50).The most effective way for establishing an IC between HA and β-CD was determined to be complexation utilising the FD method in a molar ratio of 1:2.

With animal models of orofacial pain, HA complexed in β-CD provided improved analgesic effects comparable to HA alone, but at a lower dose, indicating that β-CD contributed to boost solubility and bioavailability of this active component. This innovation aims to improve the biological and physical-chemical properties of compounds with low solubility(51).

In the binary systems of lamotrigine produced with various hydrophilic carriers, β-CD and PVP K30 outperformed PEG 6000 in terms of improving lamotrigine's water solubility and dissolution. The increased solubility brought on by complexation was the cause of the β-CD's better dissolving rate. PVP K30 is a suitable option among the employed carriers to improve the solubility and dissolution in water. Studies using XRD, FTIR, and DSC on the binary systems of lamotrigine with β-CD, PVP K30, and PEG 6000 revealed that the compound's crystallinity was significantly reduced in the complex and in solid dispersions. This resulted in a notably faster rate of lamotrigine dissolution. The findings suggest that solid dose formulations of lamotrigine for oral administration could be produced with β-CD, PVP K30, or PEG 6000, offering a faster start of action and better dissolving rate, enhancing bioavailability. To assess whether bioavailability is enhanced in vivo, more research is necessary.

CYCLODEXTRIN

Cyclodextrins (CDs) are cyclic oligosaccharides that fall under the group of carbohydrates and were very recently identified. When A. Villiers found them for the first time in 1891, they were known as "Cellulosine". The naturally occurring three cyclodextrins α, β and γ . Pringsheim is the top researcher in this field for 25 years between 1911 and 1935 in Germany, established that CDs could form stable aqueous complexes with a variety of different compounds. Enzymatic conversion of starch results in the creation of CDs. The CDs has use to increased recently in the domains of food, pharmaceuticals, chemicals, agriculture, and environmental engineering. The CDs were able to solubilize in aqueous media because of their orientation of their hydroxyl groups and unique structure, to encapsulate the lipophilic molecules into their interior cavity(52).

The major purpose of cyclodextrins is to speed up the pace at which medicines dissolve in water. α-CD, β-CD, and γ-CD are three parent cyclodextrins (CDs) containing six, seven, and eight glucopyranose units, respectively, each with a somewhat hydrophobic centre cavity and a hydrophilic outer surface(42). They are frequently pictured as hollow, truncated cones with the hydroxyl groups on the outside. As a result, CDs have a hydrophilic outside and an electron-rich, hydrophobic inside hollow. The development of reversible noncovalent inclusion complexes allows CDs to host a variety of nonpolar molecules thanks to this special cavity. The encapsulated molecule is shielded from the environment by CDs, which also enhance qualities like bioavailability, stability, and flavour masking. Additionally, cyclodextrins can be used to reduce volatility, lessen gastrointestinal or eye discomfort, minimise drug-drug and drug-additive interactions, turn liquid medications into microcrystalline powder, and cover the unfavourable taste or odour of medications. Threedimensional molecular configurations are present in cyclodextrin(38,53).

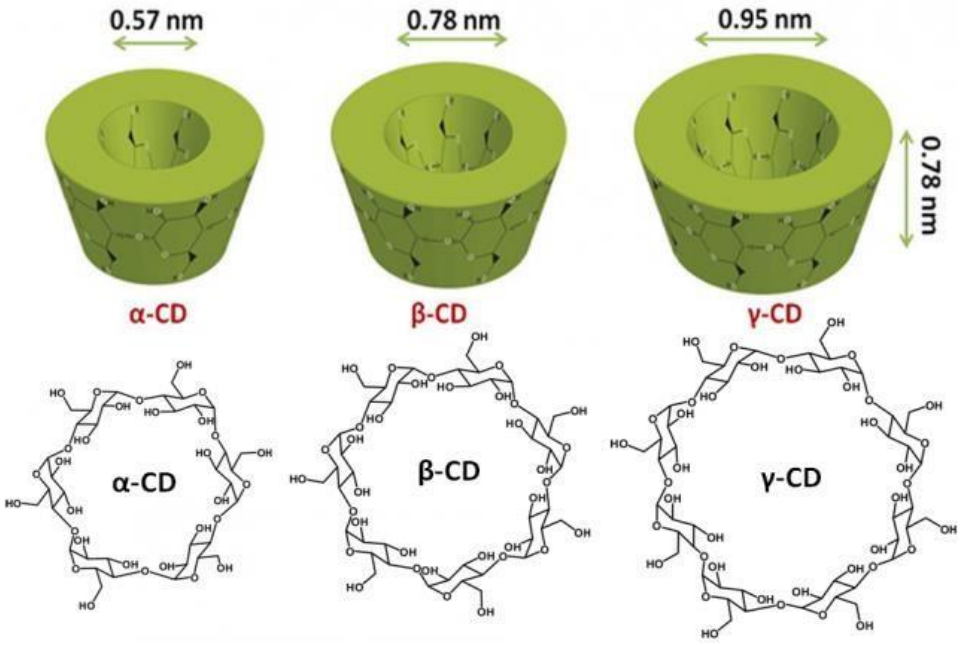

Fig:2 Structure α-cyclodextrine, β-cyclodextrine, γ-cyclodextrine respectively.

1. The higher, wider rim, which contains secondary hydroxyl groups.
2. The major hydroxyl groups are located on the bottom, thinner rim.

The ILs can construct a variety of self-assembly structures in aqueous solution, including host molecules, through the alkyl chain and other non-covalent interactions (α, β and γcyclodextrins) which have numerous uses in the industries of cosmetics, medicine delivery, and material science, among others. Both the form of the CD complexes and the nature of the interaction that occurs during host-guest complexation have garnered a great deal of attention. The molecular structure of ICs has frequently been determined using molecular modelling, simulation, X-ray crystallography, NMR, FTIR spectroscopy, optical spectroscopy (UV-Vis, fluorescence, circular dichroism) and thermal characterisation methods(54).

Class II and class IV substances absorb at different rates and to different degrees depending on their bioavailability, which ultimately depends on their solubility. The most popular technique for making hydrophobic medications more water soluble and stable is to use cyclodextrins(50). Cyclodextrin derivatives as well as natural cyclodextrins have both been employed to increase bioavailability. In addition to potentially having differing binding constants with a given substance, cyclodextrin derivatives frequently have higher solubilities than native cyclodextrins. Utilizing natural cyclodextrins as opposed to derivatives can lead to varying degrees of bioavailability increase(55,56). For instance, when rutin's β-CD and

HP-β-CD complexes were dosed, the β-CD complex had no effect on bioavailability while the HP-β-CD complex caused a rise in the AUC of 2.9 times(57). Similar to this, the AUC of salbutamol increased 4.6 times when administered as the perbutanoyl-β-CD (TB-β-CD) complex compared to dosing the drug alone, but only by 1.7 times when administered as the β-CD complex(23).

Table no:3 Derivatives of cyclodextrine:

Short form	Name
RM-β-CD	Randomly methylated β–CD
HP-β-CD	Hydroxy propyl β –CD
HP-γ-CD	hydroxyl propyl γ-CD
DM-β-CD	2,4-dimethyl β –CD
SBE-β-CD	Sulfobutylether β- CD

Cyclodextrins have grown in popularity as practical solubilizing excipients with a long list of advantageous qualities and functionalities. Although their usage in liquid dosage forms, such as parenteral and oral solutions is simple, their application to solids can be complicated by the formulation's extra weight. This aspect, which mostly concerns powerful pharmacological compounds has restricted the usage of cyclodextrin in tablets. A growing number of drug candidates and commercially available pharmaceuticals may benefit from this technology, and enhancing the capacity of cyclodextrins to complex with drugs by a manipulation of their complexation efficiency (CE) may increase the utilisation of these materials in these products. The relative weight of influencing drug solubility in relation to salt utilisation and drug ionisation, effects of polymers, charge interactions, and charge shielding, coincidental development of other complex types in the media and phase-solubility isotherm slope are examined. In the context of the underlying mechanisms, aggregation, inclusion, and noninclusion complex formation are examined together with the impact of drug form and supersaturation(58).

The inclusion complex creation technique has been used more accurately than any other solubility enhancement method to increase the aqueous solubility, bioavailability, dissolving rate and of medicines that are not very water soluble. The nonpolar molecule or nonpolar area of one molecule is inserted into the cavity of another molecule or group of molecules to produce inclusion complexes (known as host). The main structural prerequisite for inclusion complexation is that the guest must fit tightly inside the host molecule's cavity. In order to reduce the overall contact between water and the non-polar portions of the host and the guest, the cavity of the host must be both large enough to hold the guest and tiny enough to drain away water(59). Various techniques are used to prepare for making inclusion complexes of poor soluble drugs with an aim to improve their aqueous solubility are listed here:

APPROACHES FOR MAKING INCLUSION COMPLEXES:

1. **Physical Blending Method:** Simple mechanical trituration creates a solid physical mixture of drugs and CDs. To achieve the necessary particle size in the end product, CDs and drugs are completely

mixed together on a laboratory scale by trituration in a mortar and then passed through the proper sieve. When creating physical combinations on an industrial scale, the medicine and CDs are thoroughly blended in a quick mass granulator for typically 30 minutes. Then, under controlled humidity and temperature settings these powdered physical combinations are kept in the room(52).

2. Kneading Method: This method is based on turning CDs into a paste by impregnating them with a little amount of water or hydroalcoholic solutions. The medicine is subsequently mixed with the a forementioned paste for a predetermined amount of time. The kneaded dough is then dried and, if necessary, put through a sieve. The complexation approach has improved nimesulide's ability to dissolve using a mortar and pestle can help with kneading on a laboratory scale(60). Extruders and other machinery can be used for kneading on a huge scale. This is the most popular and straightforward technique for creating inclusion complexes, and it has a very cheap manufacturing cost. The method involves the formation of paste of cyclodextrin with guest molecules by using small quantity of either water or ethanol to form kneaded mass. Kneaded mass can be dried at 45°C and pulverized(61).

3. Co-Precipitation Technique: This technique entails the complex co-precipitation of a medication and CDs. This procedure involves adding the necessary amount of medication to the CDs solution. The system is maintained with controlled process parameters, magnetic agitation and the content is shielded from light. To prevent the loss of the structural water from the inclusion complex the produced precipitate is vacuum-filtered apart and dried at room temperature. The solid-state characterisation and dissolving properties of gliclazide-beta-cyclodextrin inclusion complexes have been investigated. With the inclusion of organic solvents and sudden temperature changes this method leaves a drug-CD solution extremely close to saturation. It is produced by the material precipitating and forming an inclusion complex. The solution is stirred while being rotated or filtered to produce the powders. However, this process is gaining little popularity on an industrial scale due to its low yield, risk of employing organic solvents and prolonged preparation time in bigger scales(62).

4. Melting-Solvent Method: Excessive amounts of guests are melted, combined with powdered cyclodextrin, after cooling and then washed with a weak solvent that forms a complex to remove them. The technique is only suitable for sublimable guests like menthol.

5. Solution-Enhanced Dispersion By The Supercritical Fluids (SEDS): SEDS is a brandnew, one-step technique that can create stable drug-cyclodextrin complexes. To achieve the best complexation efficiency and to compare with drug cyclodextrin complexation methods already described in the literature, it is imperative to optimise the processing conditions (e.g. kneading, freeze drying, spray drying etc).

a) Achieve high complexation efficiency are advantages over previous approaches (avoidance of excess cyclodextrine in powder).

b) The ability to create solid-cyclodextrin complexes in a single step.

c) The ability to reduce the amount of time that the drug comes into contact with the cyclodextrin.

d) Improvement of the drug's dissolution rate (which is comparable to the dissolution behaviour of micronized drug-cyclodextrin complex(52).

6. Co-Evaporation Or Solution/Solvent Evaporation Method: The aqueous solution of the host is added to the alcoholic solution of the guest, agitated for a short while and evaporated at room temperature till dried mass was formed. This mass was then ground and sieved and the fraction was collected. The drug and CDs must be separately dissolved in two solvents that are mutually miscible, combined to create a molecular dispersion of

the drug, complexing agents and then the solvent must be evaporated under vacuum to produce a solid powdered inclusion compound. In most cases, CDs' aqueous solution is simply added to medicines' alcoholic solution. The resultant mixture is agitated for 24 hours before being vacuum-evaporated at 45 degrees. The dried bulk was ground up and put through a sieve with a mesh size of 60. This procedure is both easy and affordable for laboratory use. This method is quite easy and economic both on laboratory and large scale production and is considered alternative to the spray drying technique(25).

7. Microwave Irradiation Method: This method uses a microwave oven to microwave irradiate the reaction between the medication and the complexing agent. In a precise proportion, the medication and CD are dissolved in a solution of water and an organic solvent before being added to with a circular bottom. The mixture is heated in the microwave for a brief period of one to two minutes at 60°C. A sufficient amount of solvent mixture is added to the aforesaid reaction mixture after the reaction is finished in order to eliminate the remaining, uncomplexed free drug and CD. The precipitate that results from this process is separated using Whatman filter paper and dried for 48 hours in a vacuum oven at 40°C. To create the fast-dissolving formulation employing several super disintegrants(63). Created inclusion complexes of ziprasidone hydrochloride with beta-cyclodextrin and hydroxypropyl beta-cyclodextrin. The microwave irradiation approach, which has the advantages of a quicker reaction time and a better yield of the product(64), is a revolutionary technique for industrial-scale preparation. This technique was created for quick organic synthesis and reactions that call for a higher end product and a quicker reaction time.

8. Lyophilization/ Freeze Drying Technique: Lyophilization/freeze drying is thought to be a promising method for producing a porous, amorphous powder with a high level of interaction between the medication and CD(65). In this method, the drug and CD are present in a solution that is first frozen and then dried at low pressure to remove the solvent system from the solution. By using this technique, thermolabile compounds can be successfully transformed into complex forms. The lengthy processing time and poorly flowing powdered product are its drawbacks. As an alternative to solvent

evaporation, the lyophilization/freeze drying process involves molecularly combining the medication and carrier in a shared solvent. Aqueous cyclodextrin solution was mixed with the necessary amount of host and guest, and this suspension was magnetically agitated for 24 hours and resulting mixture is freeze dried at 60°C for 24 hours(52).

9. Aromization/Spray Drying Method: In this approach, the host solution is typically made with a 50/50 ethanol and water ratio. Pharmaceutical companies frequently utilise spray-drying to convert a liquid phase into a dry powder. Another use is as a preservation technique, which increases storage stability by removing water. This technique is among the most popular ones for generating the inclusion complex strating from a solution. The mixture enters a rapid elimination system favouring solvent and demonstrates excellent efficiency in complex formation. Additionally the product made using this process produces particles in a controlled way improving the rate at which a medicine in a complicated form dissolves. Budesonide complexation in cyclodextrins and particle aerodynamic characterisation of the compound have been developed particle aerodynamic characterization of the complex solid form for dry powder Inhalation(59). This guest is then added, the resulting mixture is agitated for 24 hours at room temperature, and the solution is spray dried while keeping track of the following parameters: air flow rate, atomizing air pressure, intake temperature, outlet temperature, flow rate of solution, etc. produced after being filtered via a 63-160 micron granulometric sieve(2). The additional benefit of the atomization/spray drying approach is that the drug and CDs interact sufficiently and effectively to form a perfect complex, however the technique's drawbacks are heat stress and a poor yield of the finished product.

10. Supercritical Antisolvent Technique: This technique was first used in the 1980s. Numerous methods have been created and patented in the field of supercritical fluidassisted particle design. Carbon dioxide is employed in the supercritical fluid antisolvent method as an antisolvent for the solute but as an organic solvent's solvent. Due to its low critical temperature and pressure, supercritical carbon dioxide is helpful for processing medications that are heat-labile. When the process is finished it is also non-toxic, nonflammable, cheap, and much simpler to remove from the polymeric materials. Even though a little quantity of carbon dioxide is still trapped inside the polymer there is no risk to the customer. Processes for creating supercritical particles are a novel and effective way to increase the bioavailability of substances with medicinal activity(66). Supercritical fluid techniques have also recently been suggested as a fresh alternate technique for making drug-cyclodextrin complexes. Due to its enhanced mass transfer and higher solvating power, supercritical carbon dioxide is recommended as a new complexation medium. This technique is one of the most novel ways to manufacture the inclusion complex of a medication with CD in solid state. This technology is rapid, easy to maintain and non-toxic because it doesn't use any organic solvents. However, the initial investment is fairly significant. In this method, the medication and CD are first dissolved in a suitable solvent before the

solution is delivered through a nozzle into a pressure vessel under supercritical conditions (i.e. sprayed into supercritical fluid anti-solvent). The anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent when the solution is sprayed into supercritical fluid anti-solvent. The combination becomes supersaturated, causing the solute to precipitate and the solvent is transported away with the supercritical fluid flow because the expanded solvent in supercritical fluid has a lower solvent power than the pure solvent(64).

CONCLUSION

In this review conclude that, The most crucial physical property for a drug's formulation, oral bioavailability, development of various dosage forms, therapeutic efficacy, and quantitative analysis is its solubility. The essential to achieving the objectives of a good formulation, such as good oral bioavailability, decreased frequency of dose, and improved patient compliance, combined with a cheap production cost, is proper process selection for solubility improvement. A excellent method for increasing the solubility of weakly water soluble drugs is inclusion complexation. Inclusion complexation can be done using a variety of techniques, including kneading, melting, freezing, and spray drying. Enhancement in the solubility lending ample credence for better therapeutic efficacy and hence such complexation has great potential for product development.

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