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A Comprehensive Review: Cyclodextrin Complexation for Improved Drug Delivery of Poorly Soluble Drugs

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ABSTRACT

For a therapeutic application or to reach the target site, the drug should be dissolved in the body fluid. Solubility and bioavailability hold much importance for the therapeutic effectiveness of a drug. It is important for the desired concentration of drug in systematic circulation for pharmacological response. Factually stating only a few percent of new drug entities have high solubility and permeability. Many pharmaceutical drugs deal with poor water solubility or poor bioavailability. To overcome the solubility problems of the drugs, many techniques like co-solvency, complexations, micronization, etc. were used. This review focuses on cyclodextrin and its properties as well as the basics of controlling poorly water-soluble drug properties by preparing a drug cyclodextrin complexation and effects of hydrophilic excipients in cyclodextrin complex. This article also introduces the review of the main characteristics of the complexation and performance of cyclodextrin complex in drug delivery.

INTRODUCTION

Amongst the parameters affecting the desired concentration of drug in the systematic circulation, solubility is deemed of utmost importance. Solubility may be defined as the dissolution of solute into a solvent to provide a homogeneous system. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Its Units can be molarity, molality, mole fraction, mole ratio, concentration, etc. Solubility is often the greatest hurdle for formulation development. It could be observed by the fact that 40 % of the new chemical entities developed by pharmaceutical industries are insoluble in water[1].

Oral administration is typically employed route of drug delivery but the poor solubility stands as a hindrance in the path. Adoption of varying techniques like physical, chemical, and miscellaneous methods can be helpful. These may include particle size reduction like micronization and nanosuspension, modification of crystal habits like polymorphs and amorphous form of co-crystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions, and cryogenic techniques, pH adjustment, derivatization, complexation, salt formation, supercritical fluid process, use of adjuvants, solubilizers, co-solvency, hydrotrophy[2,34].

Process of solubilization[4,5]

The process of solubilization is as follows:

- Breakage of intermolecular bonds in solute.
- Separation of the molecules of the solvent to provide space in solvent for the solute, interaction between the solvent and solute molecules, or ion.

It happens in three steps:

- Holes open in solvent
- Molecules of the solid break away from the bulk.
- The free solid molecule is integrated into the hole in solvent.

The Indian Pharmacopoeia classifies solubility in terms of millimeters of solvent required to dissolve 1g of solute. If exact solubilities are not known the Pharmacopoeia provides general terms to describe a given rage. These terms are in Table No.1:

Table No. 1: Expression for approximate solubility

Descriptive term	**Relative amounts of solvents to dissolve 1 part of solute**
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

The BCS classification was introduced in the mid-1990s. BCS is the scientific method of classification of the drug based on aqueous solubility and intestinal permeability. According to the biopharmaceutics classification system, drug substances are classified as follows.

Table No. 2: BCS Classification

Class 1 – high permeability, high solubility Example: propranolol, verapamil, metoprolol Those compounds are well absorbed and their absorption rate is usually higher than excretion.	**Class 2 – high permeability, low solubility** Example: ketoprofen, naproxen, carbamazepine The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found.
Class 3 – low permeability, high solubility Example: ranitidine, cimetidine, atenolol The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastrointestinal duration time, then class 1 criteria can be applied.	**Class 4 – low permeability, low solubility** Example: furosemide, hydrochlorothiazide Those compounds have poor bioavailability. Usually, they are not well absorbed over the intestinal mucosa and a high variability is expected.

The drugs are classified in BCS based on the following parameters:

- Solubility
- Permeability
- dissolution

Need of solubility

Solubility and bioavailability hold much importance for the therapeutic effectiveness of a drug. It is important for the desired concentration of drug in systematic circulation for pharmacological response. Factually stating only a few percent of new drug entities have high solubility and permeability.

The knowledge of solubility allows the scientists to choose the best solvent in the preparation of a formulation which helps to outstrip the shortcoming surfacing in the preparation of a formulation. In the US Pharmacopoeia, more than one-third of the listed drugs are poorly water-soluble. Biopharmaceutical properties especially solubility is the main cause of the failure of approximately 41 % of the newly developed drugs. The lipophilic nature of the newly developed drugs stands as the biggest problem in the solubility of the newly developed drugs. Poor membrane permeability and poor aqueous solubility limit the absorption of the drug in the GIT. When administered orally an active agent must dissolve first in intestinal fluid before it reaches the systematic circulation by permeating the membrane of GIT. So, pharmaceutical research focuses on two main aspects that are improving the dissolution rate of poorly soluble drugs and enhancing solubility[6,7,8,9].

The poor drug-like properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of high clinical failure due to poor pharmacokinetics. To make the drug available at the intended site of action with optimum dose is the aim of the formulation and development section. For the *in-vivo* absorption of the drug, the deciding factors are solubility and permeability. These factors can be modified or altered by many techniques like.

Co- solvency

The addition of a water-miscible non-toxic solvent in a poorly soluble drug to increase the solubility is known as co-solvency. A mixture of one or more water-miscible solvents with water to create a solution with enhanced solubility is called co-solvents. Co-solvency is an important phenomenon especially for environmental scientists because of the way co-solvents can change the distribution and movement of hydrophobic contamination in the environment [10,11].

Co-solvency is the most largely used technique because of its simplicity in production and evaluation. The commonly used co-solvents are glycerin, glycol, glycofural and polyethylene glycols, PEG 300, or ethanol. Parenteral or oral route of administration can be used for co-solvent formulations. Solubility of poorly soluble drugs could be enhanced to several thousand times if co-solvents are used as compared to the other techniques [12].

Advantages

- Easy and quick to formulate and produce.

Disadvantages

- The toxicity of the solvent has to be taken into contemplation.
- The insoluble drug may have chemical stability which is worse than in a crystalline state which is the case with most solubilized forms.
- When dilution is done there is unconstrained precipitation. The precipitate may be amorphous or crystalline and may be different in size.

Cosolvent products: digoxin elixir pediatric and nimodipine intravenous injection are examples of the cosolvent products.

Particle size reduction

The drug particle size and bioavailability are related intrinsically. Reducing the particle size leads to the increment of the surface area which is helpful for improvement in the dissolution properties. Milling techniques may be used in the particle size reduction using a jet mill,

rotor-stator colloid mills, etc. micronization and nanosuspension can also be helpful in particle size reduction [12].

Particle size reduction is a viable, productive, and duplicable method. Typical methods of particle size reduction hinge on mechanical stress for the active compound's disaggregation however notable amount of stress on the drug product may actuate degradation[13]. The thermal stress caused by various methods of particle size reduction is also a reason for perturbing when thermosensitive or unstable active compounds may be in question[14, 15].

Micronization is a typically used technique for particle size reduction along with comminution and sprays drying. Micronization deals with the increment of the surface area by increasing the dissolution rate without increasing the equilibrium solubility. Jet mill, rotor station colloid mills, and other such milling techniques are essentially used for micronization. The process is not suitable for high-dose number drugs as the saturation solubility remains unchanged. When applied to various drugs like fenofibrate, progesterone, and griseofulvin their digestive absorption, bioavailability, and clinical efficacy were found to be increased[15,16].

Nanosuspension

A biphasic system consisting of nanosized drug particles stabilized by surfactants for oral, topical, parenteral, pulmonary administration is known as a nanosuspension. The average particle size of a nanosuspension is between 200 and 600 nm. Nanosuspension is mainly a technique used to increase the efficiency of hydrophobic drugs[17, 18]. Various techniques can be used in the preparation of nanosuspension such as precipitation technique, media milling, high-pressure homogenization in water, high-pressure homogenization in nanosuspension media, and a combination of precipitation and high-pressure homogenization[19, 20].

Complexation

The formation of a new complex drug with modified properties when various drugs interlink is known as the process of complexation. It can also be defined as the reversible linkage of the substrate and ligand leading to the formation of a new drug complex. The process of complexation has been of prime concern in pharmaceutical technology and pharmaceutical companies. This process is promising in ameliorating the existing drugs[21]. The

classification of complexes may be unpredictable but mostly depends upon types of interaction or the compounds involved metal complexes, inclusion complexes, and molecular complexes are some of the types. The result of the complexation process is a non-bonded entity that possesses well-defined stoichiometry [22]. The bonds that the complexation involves or depends upon are weak bonds like London forces, hydrogen bonding, and hydrophobic interactions. Drug dissolution is increased by a complex formation[23].

Cyclodextrins

Cyclodextrins are bucket-shaped cyclic oligosaccharides. They contain (a-1-4)-linked α-D glucopyranose units. Cyclodextrin contains a hydrophilic exterior and a lipophilic core. They are widely known as 'molecular cages' in pharmaceutical industries. The foundation of cyclodextrin dates back to almost 100 years, Villers discovered cyclodextrins in 1891 whereas their cyclic nature was discovered by Schardinger in 1903 [24]. Cyclodextrins were seen as a possible prospect for the last 40 years. The bacterial degradation (*bacillus macerans*) of starch by *CD glycosyltransferase* bacteria enzyme forms cyclic carbohydrates called cyclodextrins [25]. Other names for cyclodextrins are cycloamyloses, cyclomaltoses, and schadinger dextrin. Regulatory acceptance of CD is still a problem that hinders in development of cyclodextrin formulations. Commercially 20 products of CD are marketed two of which are marketed in the United States. Cyclodextrin is utilized in the reduction of gastrointestinal drug irritation, it holds the capability of conversion of liquid drugs to microcrystalline or amorphous powder, and prevents drug-drug and drug-excipient interactions[26].

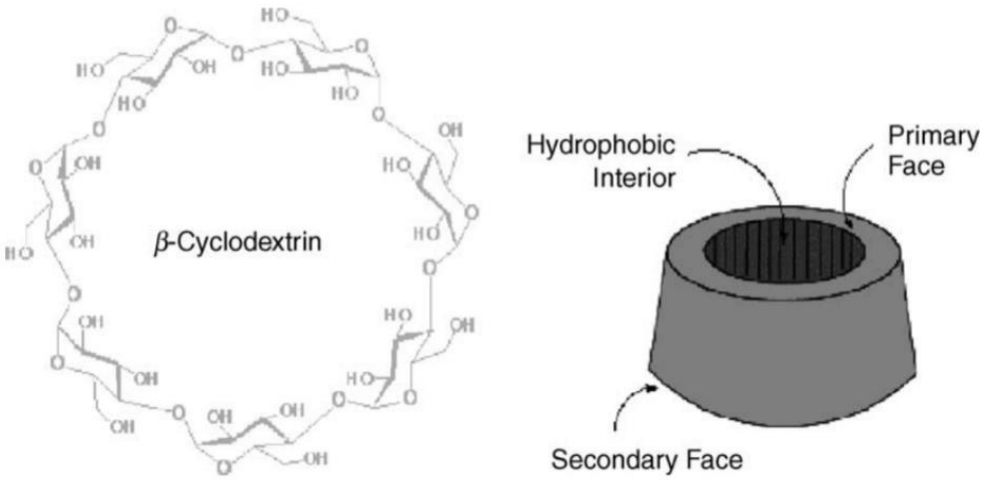


Figure No. 1: Chemical structure of cyclodextrin

Properties

There are three types of cyclodextrins: α, β, γ cyclodextrin. These are referred to as the first generation or parent cyclodextrin. Among these β-cyclodextrin is capital friendly and feasible and attainable. Depending on the type of cyclodextrin and guest compound there are two main types of crystal packing in which cyclodextrins crystallizes which are 'round' structures with glucopyranose units in the $^4C_1$ chain conformation and antiparallel double helix as indicated by linear maltohexaoses. There are other derivatives of cyclodextrin which are produced by aminations, esterification, or etherification. Solubility of derivative cyclodextrin may differ from their parent cyclodextrin depending on substituent[26]. All derivatives may have changed hydrophobic cavity volume which may help to improve solubility, stability against light or oxygen and help control the chemical activity of guest molecules. They are used as building blocks. There are up to 20 substituents having been linked to β-cyclodextrin in a regioselective manner [27]. Based on their properties to link covalently or non-covalently mainly to other cyclodextrins these are utilized as building blocks for the construction of the supramolecular complex. The opportunities to build supramolecular threads due to their capability to form an inclusion complex with host molecule is also an important property[28].

Table No. 3: Cyclodextrin properties

Properties	**α**	**β**	**γ**
Number of glucopyranose units	6	7	8
Molecular weight (g/mol)	972	1135	1297
Solubility in water at 25°C (%w/v)	14.5	1.85	23.2
Outer diameter(Å)	14.6	15.4	17.5
Cavity diameter(Å)	4.7-5.3	6.0-6.5	7.5-8.3
Height of torus(Å)	7.9	7.9	7.9
Cavity volume($Å^3$)	174	262	472

Inclusion complexation and cyclodextrin

CD's capability to form an inclusion complex is a very important property. The inclusion complex can be formed with solid, liquid, and gaseous compounds. The guest molecule is held in the cavity of the cyclodextrin host molecule. Formation of the complex is dimensional fit within host cavity and guest molecule. There is neither breakage nor the formation[29]. The main aspect is the release of enthalpy-rich water molecules from the cavity for inclusion complex formation. It is not permanent binding in host and guest molecule but dynamic equilibrium. The formation of complexes can be in solution and also in a crystalline state where water is a common solvent choice [30]. The inclusion complex provides the benefit of modification of guest molecules by enhancing their physicochemical properties when entrapped in the cavity[31]. The properties that are enhanced are solubility enhancement, stabilization, volatility and sublimation control, taste modification, unpleasant odor, and controlled release of drugs and flavors. Cyclodextrin applications are found in food, pharmaceuticals, cosmetics, environment protection, bioconversion, packing, and the textile industry. The compounds that can be used in inclusion complexes as guest molecules are: straight or branched chain aliphatic, aldehydes, ketones, alcohol, organic acids, fatty acids, aromatics, gases, polar compounds such as halogens, oxyacids, and amines. There are two factors on which inclusion complex depends firstly, steric which depend on both the host and guest molecules size and Secondly thermodynamic interaction among different component of the system. A favorable net energetic driving force to pull the guest in cyclodextrin is required for complex formation. Cyclodextrins cavity height is equal in all the parent cyclodextrin but the difference in glucose unit may affect the internal diameter [31]. CDs are cyclic oligosaccharides containing 6, 7, or 8 glucopyranose units, known as α-, β-, or γ-CD, respectively. At C-2 and C-3 every glucose units have two secondary alcohols and at C-6 they have primary alcohol with 18-24 sites for chemical modification and derivatization [32]. The improvement in solubility, stability the rate, and extent of dissolution of the drug are observed with the sequestration of hydrophobic drugs inside the cavity of the CD when solubility and dissolution are rate-limiting. The drugs which are insoluble and are hard to formulate using traditional excipients can be easily formulated as complex with CDs. Many derivatives of CDs are available with different properties. It is important to take into consideration their quantitative properties which are of major concern in evaluation[33, 34]. Formation of inclusion complex of CDs with the hydrophobic drug through an equilibrium process quantitatively described in (eq below) by an association or stability constant ($k_{a:b}$)

$$K_{a:b}=\frac{[drug_aCD_b]}{[Drug]^a[CD]^b}$$

Where a, b represents the molar ratio of the sequestered drug molecule to the CD. The associate constant can be helpful in the comparison of the binding effect of different CDs.

Evaluating CD complex

Phase solubility is one of the most typical methods for the determination of association constant. The graph of phase solubility is plotted by taking the molar concentration of dissolved solute on the Y-axis and concentration of the complexing agent on the X-axis [35]. There are two types of phase solubility profile type A and type B. In type, A soluble complexes are formed whereas the amount of the complexing agent was increased the solubility of the compound increases. Based on the nature of the complex the graph can be linear A_L or have a positive curvature A_P or have a negative curvature A_N. Linearity is observed in the graph which contained one molecule of complexing agent. In A_P more than one molecules are present, A_N was the result of self-association or high concentration causing alterations like the solvent. In type B limit solubility complex are formed where xy in the curve B_s shows that the complex increases the total solubility, point y show the solubility of the complex has reached, and with the additional compound, in solution, there is a precipitation of solid complex [36]. At z all the extra solid compounds had been consumed depletion of the compound from solution was shown at a point beyond z.

Other techniques which are used are: spectroscopy [UV, fluorescence, NMR, and ORD-CD], potentiometry, microcalorimetry, surface tension, membrane permeation, electrophoresis, freezing point depression, the chromatographic method includes HPLC, paper, and TLC techniques [37].

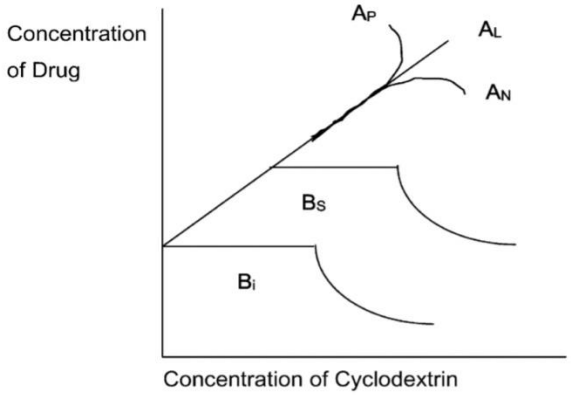


Figure No. 2: Graph of phase solubility

Toxicological studies

Studies show that orally administered cyclodextrins are non-toxic because of their lack of absorption from GIT. Since 1997 in the US β-cyclodextrin had been considered GRAS for some food. Further investigation proved γ-cyclodextrin, 2-hydroxypropyl-βcyclodextrin, sulphobutylether-β-cyclodextrin, sulfated-β-cyclodextrin, and mostly β-cyclodextrin are non-toxic when the parenteral route of administration was chosen but lipophilicity can cause irritation and hemolysis. α and β-cyclodextrin are not safe for administration parenterally, since the formation of insoluble complex leads to nephrotoxicity in the kidney[24].

Complexation techniques

- Co-precipitation
- Slurry complexation
- Paste complexation
- Damp mixing and heating
- Extrusion
- Dry mixing

Applications

- **Cosmetics, personal care, and toiletry:** Cosmetics, personal care, and toiletry is a booming industry where CD is needed in abundance due to its properties mostly in perfume for volatility suppression, room fresheners, detergents. Some of the important properties are stabilization, masking odour modification of liquid to solid. These properties are applied to toothpaste, skin creams, liquid, and solid fabric softener, paper towels, tissues, and underarm shields. Not only do CDs mask the odour but also are responsible for long-lasting fragrances. Inclusion complexes are responsible for stabilized fragrances even in bathing preparations, talcum powder. For odour control in diapers, menstrual products, paper towel CD powder of less than 12 mm are needed.

- **Food and flavors:** for flavor, colouring, texture improvement, stability in long-term storage CDs are used for the formation of inclusion complex. Natural and artificial flavors are typically volatile oils or liquids. CDs are also used as process aids to remove cholesterol from milk, butter, and eggs. In pastry and meat products CDs are used for texture improvement. CD is used for their different properties in different foods e.g. for elasticity in pizza, dough, cakes, noodles, and many others.

- **Pharmaceuticals:** CDs have the capacity of enhancing drug delivery through biological membranes. It is important because with limited solubility many drugs are not capable of permeating through a biological membrane. Cyclodextrin works as a penetration enhancer by increasing drug availability e.g. in dermal formulation aqueous mouth wash solution, nasal drug delivery system, eye drop solutions. Other uses in the pharmaceutical field are an increment in water solubility, improved bioavailability, the pharmacological effect which leads to reducing the dose of a drug, handling of volatile products.

- **Agricultural and chemical industries:** Herbicides, insecticides, fungicides, repellants, pheromones, and growth regulators are a few of the chemicals used in the agricultural industry that form complexes with cyclodextrin. Germination of seed can be delayed using cyclodextrins. Cyclodextrins are typically used for the separation of isomers and enantiomers, act as a catalyst to reactions, and aid in various processes of removing and detoxifying waste materials. In (HPLC) high-performance liquid chromatography or (GC) gas chromatography CDs are used for the separation enantiomers. Immobilized cyclodextrins or derived supramolecular architectures are used as stationary phases. In (NMR) nuclear magnetic

radiation CDs may act as chiral shift agents and in circular dichroism as selective agent altering spectra. With the removal of organic pollutants and heavy metals from the soil, water and atmosphere CDs have become an important part of agricultural and chemical industries[38, 39].

- **Adhesive, coatings, and other polymers:** Increment in adhesion and tackiness of some hot melts and adhesive are observed as the application of CDs. They are also responsible for enhancing compatibility with hot melts. The interaction between polymer molecule in associative thickening emulsion-type coatings such as paint tends to increase viscosity and CDs can be used to counteract this undesirable effect.

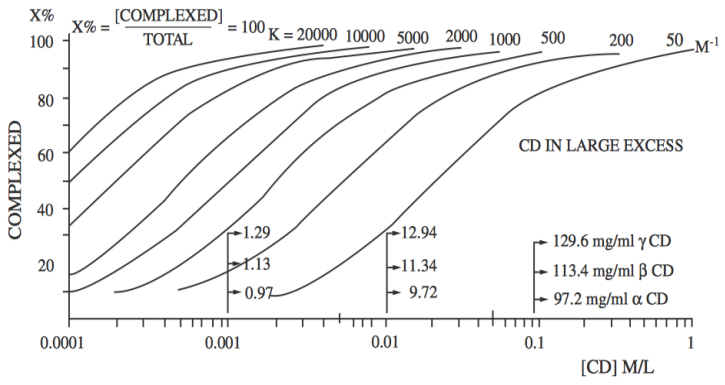
Advantages of cyclodextrin[24, 25]

- It improves the solubility.
- Enhancing of bioavailability
- Improvement in stabilization
- Reduces irritation
- Avoid incompatibility
- Mask the bad taste and odor
- Modification of chemical reactivity to the host molecule
- Very volatile substances are fixed
- Conversion of liquid substances to powder
- Colour pigmentation is taken care of.
- Act as a catalyst
- Prevent the degradation by microorganisms
- Improvement in the stabilization of light sensitive drugs or oxygen-sensitive drugs

Some factors affect complexation which has to be taken into consideration like steric effects, electronic effects (effects of the proximity of charge to CD cavity, the effect of charge density, the effect of the charge state of CD and drug, temperature, additives, and co-solvent effects among others.

Release from the complex

Complexation is a reversible process and hence the drug actions are not interfered with. The complexation of CD is continually formed and dissociates within milliseconds. In slower kinetics, it was observed dissociation happens with strong binding and the process is instantaneous. When diluted the drug leaves the complex effects of dilution are shown in the graph below:



Correlation between percentage of complexed drug and CD concentration at various *K* values. (Adapted from Ref.[62].)

Figure No. 3: The graph of complex effects of dilution

Evaluations [25, 26, 40]:

Dilution may depend on the route of administration as is observed minimal dilution in ophthalmic, transmucosal, and transdermal routes.

Evaluation:

1. **Physical characterization**

The physical characterization of the obtained sample was done by visual examination which included color, odor, and appearance.

- Color: on butter paper, a little amount of sample was taken and viewed in a well-lit up the place.

- Appearance: it was performed by visual examination.

- Odor: smelled a small quantity of drugs for the odor.

2. **Solubility:** In this preformulation study selection of a suitable solvent was done so the drug samples were dissolved in it and test its solubility. It was determined by the flask shake method. The weighed amount of drug was taken in a conical flask and added the required amount of water as a solvent and put on a flask shaker for the required time and analyzed the results by UV Spectrophotometer.

3. **Spectrophotometric study:** For the identification, evaluation of analytical characteristics of drug substances, formulations, and understanding drug's interaction with other constituent spectrophotometric study was used.

UV spectrophotometric analysis

A. Determination of absorbance maxima(λmax): By performing a wavelength scan and using a UV spectrophotometer determination of λmax was done.

Observation of absorbance: The above prepared standard solutions were measured in a UV spectrophotometer and noted the absorbance value. The absorbance obtained was plotted against the concentration in a graph where absorbance (nm) was taken on Y-axis and concentration on (µg/ml) X-axis.

Percentage yield: The weight of the complex obtained was divided by the total weight of the drug and excipients. The percentage yield of the complex was calculated according to the formula

$$\textbf{\% yield} = \frac{\text{total weight of complex} \times 100}{\text{Total weight of drug + total weight of excipients}}$$

Drug content: To determine the drug content in drug cyclodextrin complex,50 mg of the complex was taken and added to 100 ml of distilled water and measured for drug content at UV Spectrophotometrically.

Drug content =concentration of drug in final formulation × 100

Concentration of drug initially loaded in the formulation

FTIR analysis: Every sample was scanned in the wavelength range of 400-4000 cm^{-1} to check the compatibility of the drug with other excipients. The drug alone and in combination with other excipients was subjected to FTIR scanning. The fine powder sample (20 mg) was uniformly spread on ATR crystal and then the 'anvil' was positioned over the sample analyzed b.

X-Ray Diffractometry(X-RD): X-Ray powder diffractometry of drug and excipients was done using X-Ray diffractometry. The required amount of samples were taken and filled in the sample cuvettes, packed tightly to be scanned at 20 value ranging from 5-50° Diffractogram obtained for each sample was analyzed for crystallinity.

Scanning electron microscopy: SEM of the prepared complex was done using 20 kV strength by a gold coating method.

***In-vitro* study:** For *in-vitro* studies, permeation was carried out for the evaluation of the complex. This involves the study of penetration of permeate through a membrane. This study was carried out using a hollow tube that was clamped in place. The assembly consisted of a donor compartment consisting of the hollow tube through which the complex mixed in 20 ml water was passed and a receptor compartment consisting of a beaker containing 100 ml of pH 7.4 buffer mounted on a magnetic stirrer. The donor and receptor compartment was separated by a membrane which was attached to the hollow tube. Passed the complex mixed in water was passed through the donor compartment and received permeate in the receptor compartment. Pipetted out 1ml of permeate from a beaker at a regular time interval and made up their volume to 5ml and analyzed on UV-spectrophotometer.

CONCLUSION:

In this review, various solubility enhancing techniques line co-solvency, micronization, nanosuspension, and cyclodextrin complexation to improve the solubility of poorly soluble drugs have been discussed. The administration of cyclodextrin is nontoxic because of the lack of their absorption from GIT and cyclodextrin has many other fruitful properties which makes it suitable for enhancing the solubility of various drugs. The knowledge of solubility

allows the scientists to choose the best solvent in the preparation of a formulation which helps to outstrip the shortcoming surfacing in the preparation of a formulation. Poor membrane permeability and poor aqueous solubility limit the absorption of the drug in the GIT. When administered orally an active agent must dissolve first in intestinal fluid before it reaches the systemic circulation by permeating the membrane of GIT. So, this review also focuses on the main aspects that are improving the dissolution rate of poorly soluble drugs and enhancing solubility.

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