IJPSR (2013), Vol. 4, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 July, 2012; received in revised form, 28 November, 2012; accepted, 16 December, 2012

CYCLODEXTRIN INCLUSION COMPLEX TO ENHANCE SOLUBILITY OF POORLY WATER SOLUBLE DRUGS: A REVIEW

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Keywords:
Complexation, Cyclodextrins, Bioavailability, DSC, FTIR, XRD, SEM

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ABSTRACT

Low solubility compounds show dissolution rate limited absorption and hence poor absorption, distribution and target organ delivery. Improvement of aqueous solubility in such a case is valuable goal to improve therapeutic efficacy. Complexation with CDs by different methods like physical mixing, melting, kneding, spray drying, freeze drying, co-evaporation has been reported to enhance the solubility, dissolution rate and bioavability of poorly water soluble drugs. The formation of inclusion complex can be confirmed by DSC, FTIR, XRD and SEM study. This review aims to assess the use of cyclodextrines as complexing agents to enhance the solubility of poorly soluble drugs and hence to resolve the many issues associated with developing and commercializing poorly water soluble drugs.

INTRODUCTION: To be pharmacologically active, all drugs must possess some degree of aqueous solubility, and most drugs should be lipophilic to permeate the biological membranes via passive diffusion. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability [1].

Poorly water-soluble compounds with dissolution rate-limited low oral bioavailability present one of the major challenges in pharmaceutical formulation development [2]. To be pharmacologically active, all drugs must possess some degree of aqueous solubility, and most drugs should be lipophilic to permeate the biological membranes via passive diffusion [3]. The water solubility of any drug is determined by its potency and its type of formulation [4, 5, 6].

For pharmacological response to be shown the solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation.

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the *in vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption [7, 8, 9].

Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability.

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There are many ways to increase the aqueous solubility of such compounds, including

Physical Modifications:

A. Particle size reduction
   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 dispersions
   c. Solid solutions
D. Complexation
   a. Use of complexing agents
E. Solubilization by surfactants:
   a. Micro emulsions
   b. Self-micro emulsifying drug delivery systems

Chemical Modifications: The CD complexes generally show favorable changes of the characteristics of the guest molecule, such as increased solubility, enhanced stability, reduced side effects, and moreover, a general improvement in the bioavailability

Inclusion Complexes: Inclusion complexes are entities comprising two or more molecules in which one of the molecule, the "host" molecule and the second one is a “guest” molecule. Molecules or part of molecules which are hydrophobic and can fit into the cavity of host in the presence of water are included into the host cavity.

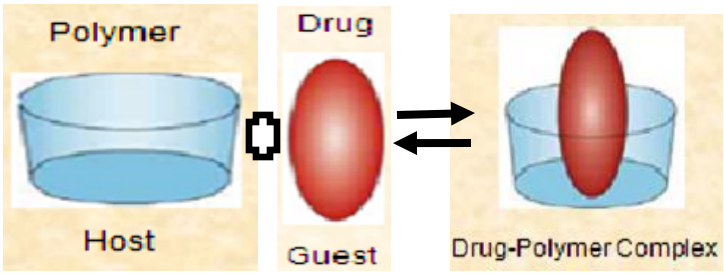

FIG. 1: CYCLODEXTRIN/POLYMER-DRUG COMPLEX

In aqueous solutions, cyclodextrins are able to form inclusion complexes with drugs by taking up the drug molecule or lipophilic moiety of the molecule, into the central cavity in which the polar cyclodextrin cavity is occupied by water molecules that are in an energetically unflavored state and are therefore readily replaced by an appropriate guest molecule that is less polar than water as shown in **Fig. 1**.

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. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms
4. Scale-up of manufacturing process and
5. Stability issues
6. Only small dose drugs are complexed

Cyclodextrin: Cyclodextrins (CD) are crystalline, homogeneous nonhygroscopic substance, which have a torus like macro ring shape, built up from glucopyranose units. They are cyclic oligosaccharides consisting of six α-cyclodextrin, Seven β-cyclodextrin, eight γ-cyclodextrin or more glucopyranose units linked by α- (1.4) bonds [9]. Each glucose unit contains two secondary alcohols and a primary alcohol, providing 18-24 sites for chemical modification and derivatization. When the glucosyltransferase enzyme degrades starch, the primary product of chain splitting undergoes an intramolecular reaction without the participation of water molecule and α-l→4-linked cyclic product known as cyclodextrins are formed [10, 11, 12]. They are also known as cycloamyloses, cyclomaltoses and Schardinger dextrins [13]. The chemical structure of cyclodextrin is shown in **Fig. 2**.

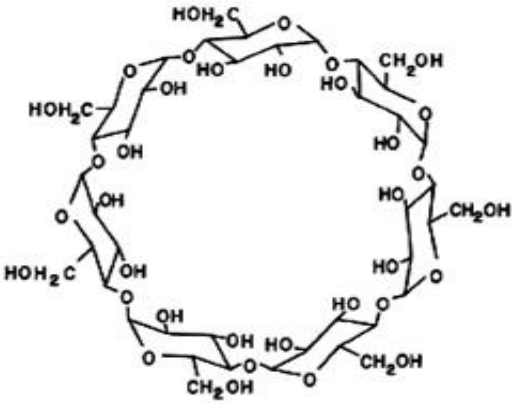

FIG. 2: STRUCTURE OF CYCLODEXTRIN

Properties of Cyclodextrins: Cyclodextrins are of three types: α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, referred to as first generation or parent cyclodextrins. α-, β- and γ-cyclodextrins are composed of six, seven and eight α-(1, 4)-linked glycosyl units, respectively [14]. Among the all β-Cyclodextrin is the most accessible, the lowest-priced and generally the most useful as shown in **Fig. 3**.

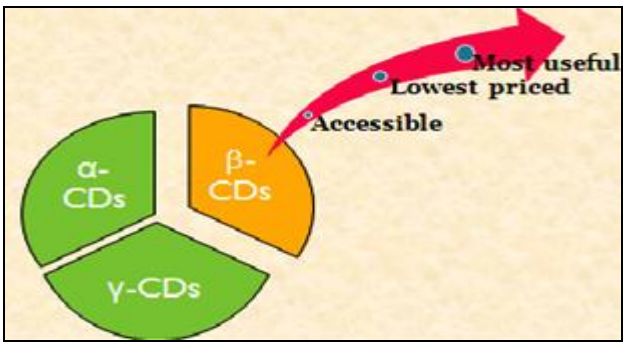

FIG. 3: TYPES OF CYCLODEXTRIN

The main properties of these cydodextrins are given in **Table 1**.

TABLE 1: SOME CHARACTERISTICS OF α, β, γ –CD

Type of cyclodextrins	α	β	γ
No of glucopyranose units	6	7	8
Molecular weight	972	1135	1297
Central cavity diameter (A°)	4.7-5.3	6-6.5	7.5-8.3
Water solubility at 25°C (g/l00ml)	14.5	1.85	23.2

Cyclodextrins are typical host molecules and may tarp a great variety of molecules having a size of one or two benzene ring or even large ones carrying a side chain of comparable size, to form crystalline inclusion complexes. Molecules or parts of molecules that are hydrophobic and can fit into the cyclodextrin cavity are, in the presence of water, included into the cyclodextrin cavity.

In aqueous solution, the polar cyclodextrin cavity is occupied by water molecules that are in an energetically unfavoured state and are therefore readily replaced by an appropriate guest molecule that is less polar than water [15].

In general, there are four energetically favourable interactions that help inclusion complex formation.

- The displacement of polar water molecules from the apolar cyclodextrin cavity.
- The increased number of hydrogen bonds formed as the displaced water returns to the large pool.
- A reduction of the repulsive interaction between the hydrophobic guest and theaqueous environment.
- An increase in the hydrophobic interactions as the guest inserts itself into the apolar cyclodextrin cavity.

While the initial equilibrium to form the complex is very rapid (often within minutes), the final equilibrium can take much longer to reach. Once inside the CD cavity, the guest molecule makes conformational adjustments to take maximum advantage of the week van der Waals forces that exist.

The ability of a cyclodextrin to form an inclusion complex with a guest molecule is a function of two key factors. The first is *stearic* and depends on the relative size of the cyclodextrin to the size of the guest molecule or certain key functional groups within the guest. If the guest is the wrong size, it will not fit properly into the cyclodextrin cavity. The second critical factor is the thermodynamic interactions between the different components of the system (cyclodextrin, guest, solvent). For a complex to form, there must be a favourable net energetic driving force that pulls the guest into the cyclodextrin.

The structures of crystalline cyclodextrin complexes are not necessarily identical with structure of complexes in solution. In a dissolved state, the guest molecule or its parts is located within the cavity of the cyclodextrin and the whole complex is surrounded by a multilayer of water molecules. In the crystalline state, guest molecule may be located not only inside the CD cavity but also between the cyclodextrin rings and thus form a crystal lattice inclusion complex. At the same time, some of the CD molecules that contain only water molecule may be present.

Therefore, the crystalline complexes of CD with drugs are rarely of strictly stoichiometric composition. Since there are no covalent bonds between the host and guest molecules, the complexes of cyclodextrins under physiological condition are easily dissociated. **Fig. 4** illustrates equilibrium binding of drug and CD to form a 1:1 and 1:2 complexes.

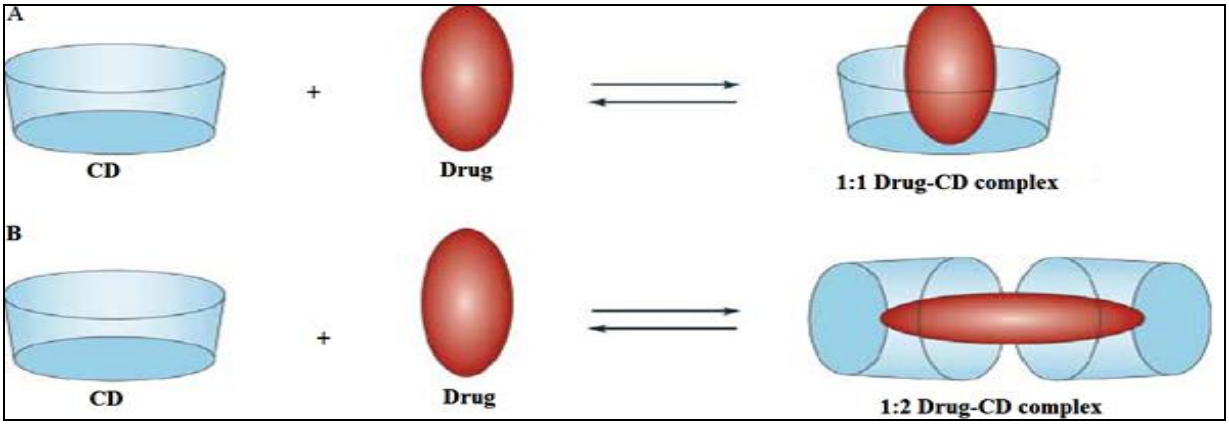

FIG.4 EQUILIBRIUM BINDING OF DRUG AND CD TO FORM A (A) 1:1 COMPLEX AND (B) 1:2 COMPLEX

The potential guest list for molecular encapsulation in cyclodextrins is quite varied and includes such compounds as straight or branched chain aliphatic, aldehydes, ketones, alcohols, organic acids, fatty acids, aromatics, gases, and polar compounds such as halogens, oxyacids and amines. Due to the availability of multiple reactive hydroxyl groups, the functionality of cyclodextrins is greatly increased by chemical modification.

Through modification, the applications of cyclodextrins are expanded. CDs are modified through substituting various functional compounds on the primary and/or secondary face of the molecule. Modified CDs are useful as enzyme mimics because the substituted functional groups act in molecular recognition. The same property is used for targeted drug delivery and analytical chemistry as modified CDs show increased enantioselectivity over native CDs [13].

Complexes can be formed by a variety of techniques that depend on the properties of the active material, the equilibrium kinetics, the other formulation ingredients and processes and the final dosage form desired. However, each of these processes depends on a small amount of water to help drive the thermodynamics. Among the methods used are simple dry mixing, mixing in solutions and suspensions followed by a suitable separation, the preparation of pastes and several thermo-mechanical techniques.

Dissociation of the inclusion complex is relatively rapid process usually driven by a large increase in the number of water molecules in the surrounding environment. The resulting concentration gradient shifts the equilibrium to the left. In highly dilute and dynamic systems like the body, the guest has difficulty finding another cyclodextrin to reform the complex and is left free in solution.

Phase Solubility: One of the most useful and widely applied analytical approaches in this context is the Phase-solubility method described by Higuchi and Connors [16]. Phase-solubility analysis involves an examination of the effect of a solubilizer, i.e. cyclodextrin or ligand on the drug being solubilizer, i.e., the substrate (S) a constant volume of water containing successively larger concentrations of the cyclodextrin or ligand (L) is added. The vials are mixed at constant temperature until equilibrium is established. The solid drug is then removed and the solution assayed for the total concentration of S. A Phase –solubility diagram is constructed by plotting the total molar concentration of S on the y-axis and the total molar concentration of L added on *x* –axis.

A detailed phase-solubility diagrams curve is shown in fig 5. Phase-solubiliy diagrams prepared in this way fall in two main categories, A-and B- type curves are indicated for the formation of soluble inclusion complexes while B-type behaviour are suggestive of the formation of inclusion complexes of poor solubility. Abs-type response denotes complexes of limited solubility and a B_1-curve are indicative of insoluble complexes. The A-curves are subdivided into A_L (linear increases of drug solubility as a function of cyclodextrin concentration), Ap (positively deviating isotherm) and A_N (negatively deviating isotherms) subtypes.

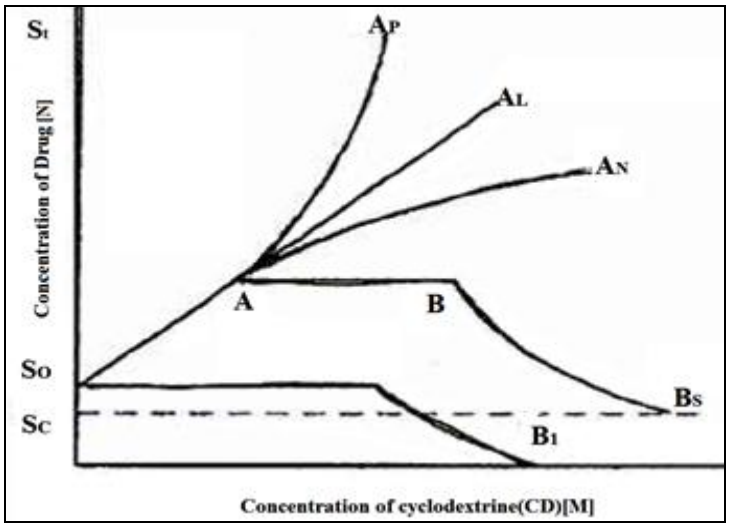

FIG. 5: PHASE SOLUBILITY DIAGRAM

While β-cyclodextrin often gives rise to B-type curves due to the poor water solubility of the ligand itself, the chemically modified CDs including usually produce soluble complexes (i.e. A-type systems). A_L-type diagrams are first order with respect to the cyclodextrin (L) and may be first or higher order with respect to the drug (S). i.e. SL, S_2L, S_3L. . . .. S*m*L. If the slope of an A_L-type system is greater than one, higher order complexes are indicated. A slope of less than one does not necessarily exclude higher order complexation but 1:1 complexation is usually assumed in the absence of other information. Ap-type systems suggest the formation of higher order complexes with respect to the ligand at higher ligand concentrations, i.e. SL_2, SL_3,……SL*n*. The stoichiometry of Ap-type systems can be evaluated by curve fitting. A_N-type systems are problematic and difficult to interpret.

The negative deviation from linearity may be associated with ligand-induced changes in the dielectric constant of the solvent or self-association of the ligands at high cyclodextrin concentrations.

These Phase-solubility systems not only allow a qualitative assessment of the complexes formed but may also be used to derive equilibrium constants. The equilibrium constant *(K)* can be represented by:

$$Ks = \frac{Slope}{S_o\,(1 - Slope)}$$

Where, S_o is the equilibrium solubility of S (*i.e.*in absence of solubilizer)

Continuous variation method (Job's plot): A Job plot is used to determine the stoichiometry of a binding event. In this method, the total molar concentration of the two binding partners (e.g. a protein and ligand) is held constant, but their mole fractions are varied.

A measurable parameter that is proportional to complex formation (such as absorption signal) is plotted against the mole fractions of these two components. The maximum on the plot corresponds to the stoichiometry of the two species [17]. This method is named after P. Job, who first introduced this methodology in 1928 [18].

Applications of Cyclodextrins: The reasons for the inclusion of CDs in a particular formulation can vary widely, and are specific to the circumstance - that is, the specific physicochemical issues that have to be overcome and the administration route [15, 19, 20]. Cyclodextrins (CDs) can be used to achieve the following:

Enhance solubility, Enhance bioavailability, Enhance stability, convert liquids and oils to free-flowing powders, reduce evaporation and stabilize flavours, reduce odours and tastes, reduce haemolysis, prevent admixture incompatibilities.

Since each guest molecule is individually surrounded by a cyclodextrin (derivative), the molecule is micro-encapsulated from a microscopical point of view. This can lead to advantageous changes in the chemical and physical properties of the guest molecules.

1. Stabilization of light- or oxygen-sensitive substances.
2. Modification of the chemical reactivity of guest molecules.
3. Fixation of very volatile substances.
4. Improvement of solubility of substances.
5. Modification of liquid substances to powders.
6. Protection against degradation of substances by microorganisms.
7. Masking of ill smell and taste.
8. Masking pigments or the color of substances.

These characteristics of cyclodextrins or their derivatives make them suitable for applications in analytical chemistry, agriculture, the pharmaceutical field, in food and toilet articles [22].

Other Non-Pharmaceutical Applications [23, 24 ,25, 26]:

a) Cosmetics, personal care and toiletry

b) Foods and flavours

c) Agricultural and chemical industries

d) Adhesives, Coatings and other polymers

Complexation Techniques: Several techniques are used to form cyclodextrin complexes [6, 19, 21].

Grinding: CD inclusion complexes can be prepared by simply grinding the guest with CD. This works best with oils or liquid guests. This is the very slow process for masking inclusion complex and degree of complexation achieved is also very low.

Solid Dispersion/Co-Evaporated Dispersion: The drug is dissolved in ethanol and CD is either dissolved in alcoholic solution or dissolved separately in water, or other suitable medium. The CD solution is then added to the drug solution or vice versa, and stirred to attain equilibrium. The resulting solution is evaporated to dryness preferably under vacuum.

Neutralization Method: In this method equimolar concentration of drug and CD are separately dissolved in 0.1 N NaOH, mixed and stirred for about half an hour. pH is recorded and 0.1 N HCl is added drop wise with stirring until pH reaches 7.5, where upon complexes precipitates. The residue is filtered and washed until free from chlorine, it is dried at 250^{o}C for 24 h and stored in a desiccators.

Slurry Complexation: It is not necessary to dissolve the cyclodextrin completely to form a complex. Cyclodextrin can be added to water as high as 50-60% solids and stirred. The aqueous phase will be saturated with cyclodextrin in solution. Guest molecules will complex with the cyclodextrin in solution and, as the cyclodextrin complex saturates the water phase, the complex will crystallize or precipitate out of the aqueous phase. The cyclodextrin crystals will dissolve and continue to saturate the aqueous phase to form the complex and precipitate or crystallize out of the aqueous phase, and the complex can be collected in the same manner as with the co-precipitation method.

The amount of time required to complete the complexation is variable, and depends on the guest. Assays must be done to determine the amount of time required.

Generally slurry complexation is performed at ambient temperatures. With many guests, some heat may be applied to increase the rate of complexation, but care must be applied since too much heat can destabilize the complex and the complexation reaction may not be able to take place completely. The main advantage of this method is the reduction of the amount of water needed and the size of the reactor.

Extrusion: Extrusion is a variation of the heating and mixing method and is a continuous system. Cyclodextrin, guest and water can be premixed or mixed as added to the extruder. Degree of mixing, amount of heating and time can be controlled in the barrel of the extruder. Depending upon the amount of water, the extruded complex may dry as it cools or the complex may be placed in an oven to dry. Extrusion has the advantages of being a continuous process and using very little water. Because of the heat generated, some heat-labile guests decompose using this method.

Kneading Method: In this method CD is not dissolved but kneading like a paste with small amount of water to which the guest component has been added, guest component can be added without a solvent or in a small amount of ethanol in which guest has been suspended. After grinding paste solvent get evaporated & powder like complex formed.

Precipitation Method: In this method drug & CD are dispersed in water & solution is heated to obtain concentrate, viscous and translucent liquid. The solution is left to give precipitate of inclusion complex. The precipitate can be collected by decanting, centrifugation or filtration. The precipitate may be washed with a small amount of water or other water-miscible solvent such as ethyl alcohol, methanol or acetone. Solvent washing may be detrimental with some complexes, so this should be tested before scaling up.

On the other hand, additives such as ethanol can promote complex formation in the solid or semisolid state [27]. Un-ionised drugs usually form a more stable cyclodextrin complex than their ionic counterparts and, thus, complexation efficiency of basic drugs can be enhanced by addition of ammonia to the aqueous complexation media.

For example, solubilisation of pancratistatin with hydroxypropyl-cyclodextrins was optimized upon addition of ammonium hydroxide [28].

Spray Drying: In this first monophasic solution of drug and CD is prepared using a suitable solvent. The solution is then stirred to attain equilibrium following which the solvent is removed by spray drying.

Freeze-Drying: Freeze drying method is similar to spray drying except that in this after attaining equilibrium, the solvent is removed by freeze drying.

Melting: Complexes can be prepared by simply melting the guest, mixed with finely powdered CD. In such cases there should be a large excess of guest, and after cooling this excess is remove by careful washing with a weak complex, forming solvent or by vacuum sublimation. The later is preferred method and is used to sublimate guests such as menthol.

Characterization of Complex:

1. **Determination of Guest Content:** Quantitative determination can be performed by analytical methods such as Ultraviolet Spectroscopy, Gas Liquid Chromatography (GLC) and High Pressure Liquid Chromatography (HPLC). Complexation of a guest may often result in a small shift of U.V. absorption maximum and molar extinction coefficient.

2. **Thermo Analytical methods:** Thermal analysis of complexes has been first used to differentiate between inclusion complexes and adsorbates and secondly to characterize the special thermal affects due to molecular entrapment. Frequently used methods are Thermo derivatography (TG, DTG) Thermal Evolution Analysis (TEA) Differential Scanning Calorimetry (DSC) Pyrolysis - Thin layer Chromatography (TLC) Pyrolysis- Gas Chromatography (GC) Vacuum Sublimation and Mass Spectrometry (MS).

   DSC is the measurement of the rate of heat evolved or absorbed by the sample during a temperature programme e.g. DSC thermograph of Paracetamol shows that Paracetamol melts at 168°C and decomposition begins. The DSC curves of the simple mixture resemble the sum of the cure of two pure substances. After melting, a small exothermic peak is recorded, suggesting complex formation. The complex did not shows the melting peak of guest substance and the decomposition of Paracetamol only started at about 220°C. This behavior is characteristic of many guests, which melt or recrystallize before reaching the decomposition temperature of β-CD.

3. **Infra Red Spectroscopy:** The characteristic bands of CD, representing the overwhelming part of the complex, are scarcely influenced by the complex formation. Bands due to the included part of the guest molecule are generally shifted or their intensities are altered, but since the mass of the guest molecule does not exceed 5-15% of the mass of the complex, these alterations are usually obscured by the spectrum of the host.

   In literature, most often the IR spectroscopic studies of such CD complexes are reported which have a carbonyl group-bearing guest. This is due to the adequate and well-separated bands of the carbonyls (about 1680-1700cm^{-1}), which is significantly covered and shifted by complexation with CD.

4. **X-ray Powder Diffraction:** Liquid guest molecules do not produce diffraction pattern. When guest molecule is a solid substance, a comparison of the diffractogram of the supposed complex with a mechanical mixture of the guest and cyclodextrin has to be made.

   When the diffractograms are different, i.e. the characteristic peaks of one or other components disappear and new ones appear as a result of the complex experiments, complex formation is very probable.

5. **Scanning Electron Microscopy:** The scanning electron microscope (SEM) is a type of electron microscope that images the sample surface by scanning it with a high-energy beam of electrons in a raster scan pattern. The surface morphology of raw materials such as drug and cyclodextrin and binary systems was examined by means of a scanning electron microscope.

   The samples were fixed on a brass stub using double-sided tape and then made electrically conductive by coating in a vacuum with thin layer of copper and the photographs were taken. Nevertheless, the SEM technique is inadequate to conclude in genuine complex formation, the obtained microphotographs support the idea of the consecution of a new single component [29].

Morphological and Mechanical Properties:

1. **Particle Size Distribution:** Particle size distribution depends on the complex preparation method. A general observation is that β-CD complexes of a guest, when prepared by kneading or cocrystallization and washed with some solvent to remove the uncomplexed fraction of the guest, possess the smallest particle size (several μm). Complexation by heterogeneous "slurry method' result in larger particle size (e.g. 6-20μm). These characteristics of the solid complexes may play a significant role in their dissolution properties, particularly in their tabletting.

2. **Characterization of Flow properties and Hygroscopicity of CD Complexes:** Using an appropriate complexation technology, the solid inclusion a complex shows very favorable free flowing properties, clumping tendency, and remarkably low moisture sorption.

3. **Wettability and Dissolution Properties:** Cyclodextrin complexation of lipophilic drugs, pesticides and flavors considerably improve their wettability in water. The results of the dissolution studies reveal not only improvement of the water solubility of a guest due to molecular encapsulation but also enhanced rate of dissolution.

4. **Formulation Studies:** The complexes prepared by different methods can studied for physical properties to judge its tabletting ability. Formulation of tablets of eq. to actual dose of pure drug, it's PMs and complexes can done.

5. **Stastical Analysis:** Prepared complexes and tablets of them are tested for dissolution and f_1 and f_2 values are calculated to study the dissolution behavior.

CONCLUSION: Cyclodextrins have been used in recent years as drug delivery vehicles, improving the bioavailability and therapeutic efficacy of many poorly water-soluble drugs. To enhance the availability of the poorly water-soluble drugs by inclusion complex formation with cyclodextrine have been reported to achieve enhanced solubility and hence, bioavaibility

and target specificity and reduce toxicity. These findings indicate synergistic effects of combination of drug in cyclodextrine for better pharmacological response of many classes of poorly water soluble drugs.

ABBREVIATIONS:

- **CD:** Cyclodextrin
- **β-CD:** β-Cyclodextrin
- **UV:** Ultraviolet Spectroscopy
- **GLC:** Gas Liquid Chromatography
- **HPLC:** High Pressure Liquid Chromatography
- **SEM:** Scanning Electron Microscope
- **IR:** Infrared Spectroscopy
- **DTG:** Thermo Derivatography
- **TEA:** Thermal Evolution Analysis
- **DSC:** Differential Scanning Calorimetry

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How to cite this article:
Chaudhary VB: Cyclodextrin Inclusion Complex to Enhance Solubility of Poorly Water Soluble Drugs: A Review. *Int J Pharm Sci Res*. 2013,4(1); 68-76.