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Dissolution Enhancement of Poorly Soluble Drugs by Using Complexation Technique – A Review

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Abstract
Orally administered drugs completely absorb only when they show fair solubility in gastric medium and shows good bioavailability. The solubility properties of drug play an important role in the process of formulation developments. Problem of solubility can be solved by different approaches. Each approach suffers with some limitations and advantages. Among all, complexation techinque has been employed to improve the solubility of poorly water soluble drugs. sophistication has to find its way in the area of excepients. One such versatile adjuvant , tailored with the help of advances in technology is cyclodextrin. Such cyclodextrin can interact with appropriate size drug molecules which lead to the formulation of inclusion complexes. A comprehensive literature survey was made collect the rightful utilization of cyclodextrins as complexing, solubility enhancing agents. In present review ,an attempt was made to discuss various complexation techinques and highlight the applications with these approaches.
Key Words: Cyclodextrins, solubility, dissolution, inclusion complexation, excipients.

INTRODUCTION

Various approaches of complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process, many physicochemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably enhanced. Cyclodextrins are being increasingly applied in various pharmaceutical formulations in recent years due to their approval by various regulatory agencies. Cyclodextrins are produced from starch by means of enzymatic conversion. [1,2]

Cyclodextrins (CDs) are cyclic oligosaccharides containing six (α-CD), seven (β-CD) or eight (γ-CD) α-1,4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center.

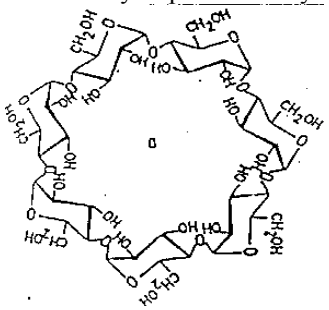

Figure 1 (a): The chemical structure

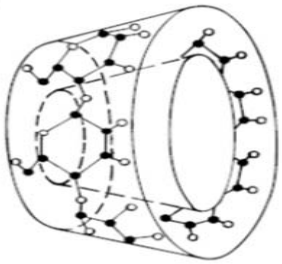

Figure 1 (b) the toroidal shape of the β-cyclodextrin molecule.

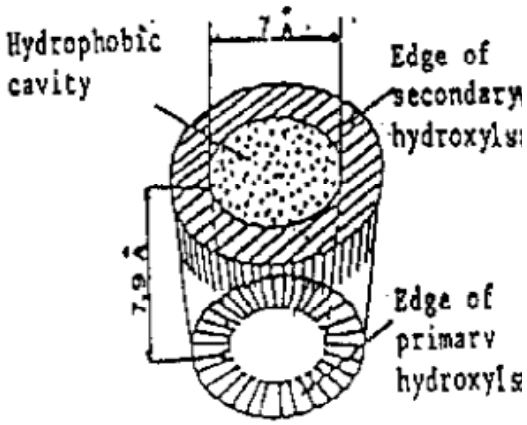

Figure 1 (c) Planner representation and the molecular shape of γ-CDs

Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped.Based on the architecture, the primary hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge were shown in (Figure 1). But due to stearic factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated δ-, ε-, ζ-, η- and θ-cyclodextrin, respectively have been reported. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution. Among the various approaches, preparation of inclusion complexes with cyclodextrin have proven to be successful in enhancing the solubility of poorly water soluble drugs[3,4,5]**.** Among the three types of CDs β - Cyclodextrin is known to be more suitable for practical use because of the following three reasons: [6,7,8] The main properties of those cyclodextrins are given in Table 1.[5]

Table 1. Important properties of cyclodextrins

Property	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
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 (Å3)	174	262	427

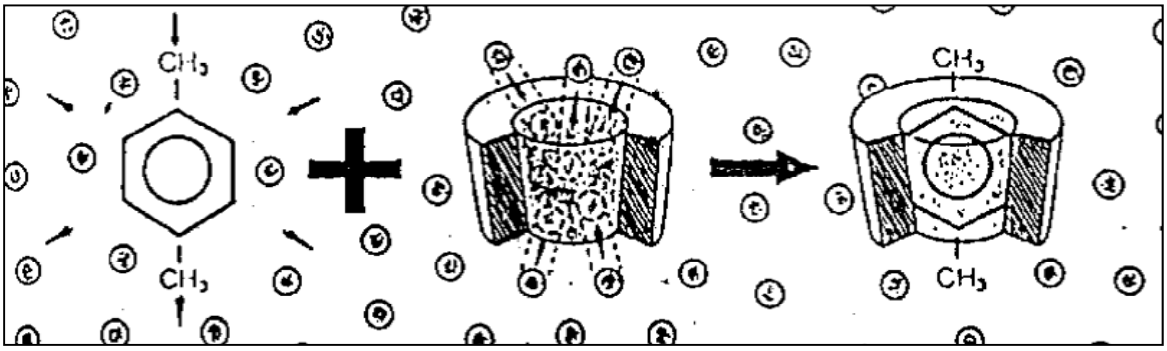

Fig 2: Schematic Illustration of the Complexation Process

- Its cavity diameter is the best one for guest molecules.
- Its production procedure does not require sophisticated technologies.
- It is cheaper.

The mechanism of complexation processes were discussed as CDs can be regarded as cylinders with hydrophilic outside and hydrophobic inside. The hydrophobic cavity forms an ideal harbour in which poorly water soluble molecules are to be protected from the surrounding atmosphere shelter their most hydrophobic parts or whole molecules. These hydrophobic molecules which can fit in the CD cavity are included in it in the presence of water. In aqueous solution the polar CD cavity is occupied by water molecules that are in an energetically unfavoured state (Polar – a polar repulsion) and are therefore, readily replaced by an appropriate guest molecules that is less polar than water and forms an inclusion complex [7,8]

The degree of complexation with CD depends upon the dimensions and lipophilicity of the guest molecules. The guest molecule or as part of it must fit into the CD cavity. For many drugs γ-CD offers the most interesting cavity size. Its dimensions are comparable to those of the substituted phenyl groups. Such groups are often most hydrophobic parts of drug and are therefore responsible for their poor solubility in water. Hiding these groups in CDs will markedly increase their overall aqueous solubility.

There are a few energetically favorable interactions that helps shift the equilibrium towards complex formation.

- Displacement of polar water molecule from the apolar cyclodextrin cavity.
- The increase number of hydrogen bond formed as the displaced water returns to the larger pool. A reduction of the repulsive interaction between hydrophobic guest and the aqueous environment.
- An increase in hydrophobic interaction as the guest insert itself into the a ploar cyclodextrin cavity [9]

PREPARATION TECHNIQUES

This is most widely used method to enhance water solubility and increase stability of hydrophobic drugs by using cyclodextrins. Solid inclusion complexes can be prepared by using following methods as follows,

Physical Blending Technique

A solid physical mixture of drug and CDs are prepared simply by mechanical trituration.[11,12] In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. In industry scale, the preparation of physical mixtures is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 minutes. These powdered physical mixtures are then stored in the room at controlled temperatures and humidity conditions.

Kneading Technique

This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required. [13]have reported the dissolution enhancement of nimesulide using complexation method. In laboratory scale kneading can be achieved by using a morter and pestle (14,15]In large scale the kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.

Co precipitation

Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.[13]

Solvent evaporation method

This method involves dissolving of the drug and CDs separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hours and evaporated undervaccum at 45 ºc. The dried mass was pulverized and passed through a 60-mess sieve. This method is quite simple and economic both on laboratory and large scale production and is considered alternative to the spray drying technique.

Neutralization

Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β-Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

Co-grinding

A solid binary inclusion compounds can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. This technique is superior to other approaches from economic as well as environmental stand point in that unlike similar methods it does not require any toxic organic solvents[16]This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impact effect on powder blend..

Spray-Drying Method

Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β-cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.[23]

Microwave Irradiation Method

Drug and cyclodextrins mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.[24]

Supercritical antisolvent technique

This method has been introduced in the late 1980s. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is 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. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow[17,18]

Freeze drying technique

In order to get a porous, amorphous powder with high degree of interaction between drug & CD, lyophilization/ freeze drying technique is considered as a suitable [19,20] In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent[21,22]

CARRIERS FOR DISSOLUTION ENHANCEMENT

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance dissolution of drugs. The carriers which have been reported in literature are presented in Table 2 [25,26,27]and are described in detail under different categories.

Table 2: Classification of carriers enhancing dissolution of drugs

Category	Example of carriers
Polymers	Polyvinylpyrrolidone, Polyvinylpolypyrrolidone, Polyvinyl alcohol, Polyethylene glycols, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Poly (2-hydroxyethylmethacrylate), Methacrylic copolymers (Eudragit® S100 sodium salts and Eudragit® L100 sodium salts)
Superdisintegrants	Sodium starch glycolate, Croscarmellose sodium, Cross-linked polyvinylpyrrolidone, Cross-linked alginic acid, Gellan gum, Xanthan gum, Calcium silicate
Cyclodextrins	_-Cyclodextrins, Hydroxypropyl-_-cyclodextrins
Carbohydrates	Lactose, Soluble starch, Sorbitol, Mannitol, _-(1-4)-2-amino-2-deoxy-D-glucose (Chitosan), Maltose, Galactose, Xylitol, Galactomannan, British gum, Amylodextrin
Surfactants	Poloxamers (Lutrol® F 127, Lutrol® F 68), Polyglycolized glyceride (Labrasol), Polyoxyethylene sorbitan monoesters (Tweens), Sorbitan esters (Spans), Polyoxyethylene stearates, Poly (beta-benzyl-L-aspartate) -b- poly (ethylene oxide), Poly (caprolactone) -b- poly (ethylene oxide)
Hydrotropes	Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxy benzoate, Sodium-p-hydroxy benzoate, Sodium citrate
Polyglycolized glycerides	Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
Acids	Citric acid, Succinic acid, Phosphoric acid
Dendrimers	Starburst® polyamidoamine (PAMAM)
Miscellaneous	Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk

Table No.3. Dissolution enhancement by various complexation techniques

Drug	Cyclodextrins	Technique	Mechanism	Reference
Piroxicam	βCD	Steam-Aided Granulation	Increased surface area	31
Glipizide	βCD&HPβCD	KG	Inclusion complexes	32
Ziprasidone Hydrochloride	βCD&HPβCD	KG, SE	Inclusion complexes	33
Gliclazide	βCD	Neutralization	Increased wettability	34
Glyburide	βCD,HPβCD & Chitosan	KG,SE	Inclusion complexes	35
Carbamazepine	βCD	KG	Increased solubility	36
Satranidazole	βCD	KG	Reduction in crystallinity	37
Nimesulide	βCD	KG	Inclusion complexes	38
Celecoxib	βCD	KG	Inclusion complexes	39
Piroxicam	βCD	FD	Inclusion complexes	40
Norfloxacin	βCD	KG	Inclusion complexes	41
Meloxicam	βCD&HPβCD	FD	Increased wettability	42
Nicardipine	βCD&HPβCD	KNG, SE, FD, SD	Improved wettability.	43
Gliclazide	βCD	RC	Inclusion complexes	44
Carbamazepine	βCD	SE	Inclusion complexes	45
Norfloxacin	βCD&HPβCD	FD	Reduction of particle size	46
Naproxen	βCD	KG, SE	Inclusion complexes	47
Efavirenz	βCD	KG, SE	IC	22

βCD: Beta Cyclodextrin; *HPβCD: Hydroxypropyl Beta Cyclodextrin; *KG: Kneding; *SE: Solvent Evaporation; *FD: Freeze Drying; *RC: Recrystallization.

APPLICATIONS OF CYCLODEXTRINS

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.[4] The various applications **[3]**of cyclodextrin derivatives were included below as,

- ✧ Stabilisation of light- or oxygen-sensitive substances.
  Eg: Curcumin and β cyclodextrins are used for improvement of water solubility and hydrolytic phytochemical stability of curcumin.
- ✧ Improvement of solubility of substances.
  Piroxicam is poorly soluble drug to increase the solubility β cyclodextrins are added . By using steam aided granulation techinque . Increased surface area of piroxicam and exposed to dissolution medium
- ✧ Cyclodextrins as permeation enhancers:
  In spite, the solubility enhancement application, CDs can also be used a membran permeability enhancer and stabilizing agents [4,10] The permeability through biological membrane is enhanced by the presence of cyclodextrins.
- ✧ Modification of liquid substances to powders.
  Inclusion complexes between the cinnamomum oil and cyclodextrins were prepared by co precipitation method in different ratios and converts the liquid substances into powders.
- ✧ Protection against degradation of substances by microorganisms.
  Photochemical stability of naproxen and niflumic acid in their liquid inclusion complexes with β-cyclodextrin.[28] Cyclodextrins are used to increase their stability and avoid degradation.
- ✧ Masking of ill smell and taste.
  Famotdine is complexed with cyclodextrin to impove the taste of the drug ,including polymer like hydroxy propyl cellulose.[29]
- ✧ Catalytic activity of cyclodextrins with guest molecules
  Water soluble palladium nanoparticles modified with covalently attached to cyclodextrins receptors. it decreases the catalytic activity of the pd nanoparticles.[30]
- ✧ Over the last few years, an application of Cyclodextrins is expanded into food, pharmaceutical, chemical, agricultural, and environmental engineering fields.

FUTURE ASPECTS

Among the emerging new chemical entites, most are poorly water soluble drugs putting impact on their bioavailability and therapeutic effect. Inclusion complex with cyclodextrins is the most attractive techinque to enhance solubility. Cyclodextrins and their derivatives have been of widespread attention in the pharmaceutical field because of their potentiallity to form complexes with a variety of drug molecules. CDs, are capable to modify the physicochemical properties of drugs such as solubility, particle size, crystal habbit and there by forming a highly water soluble amorphous form.

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