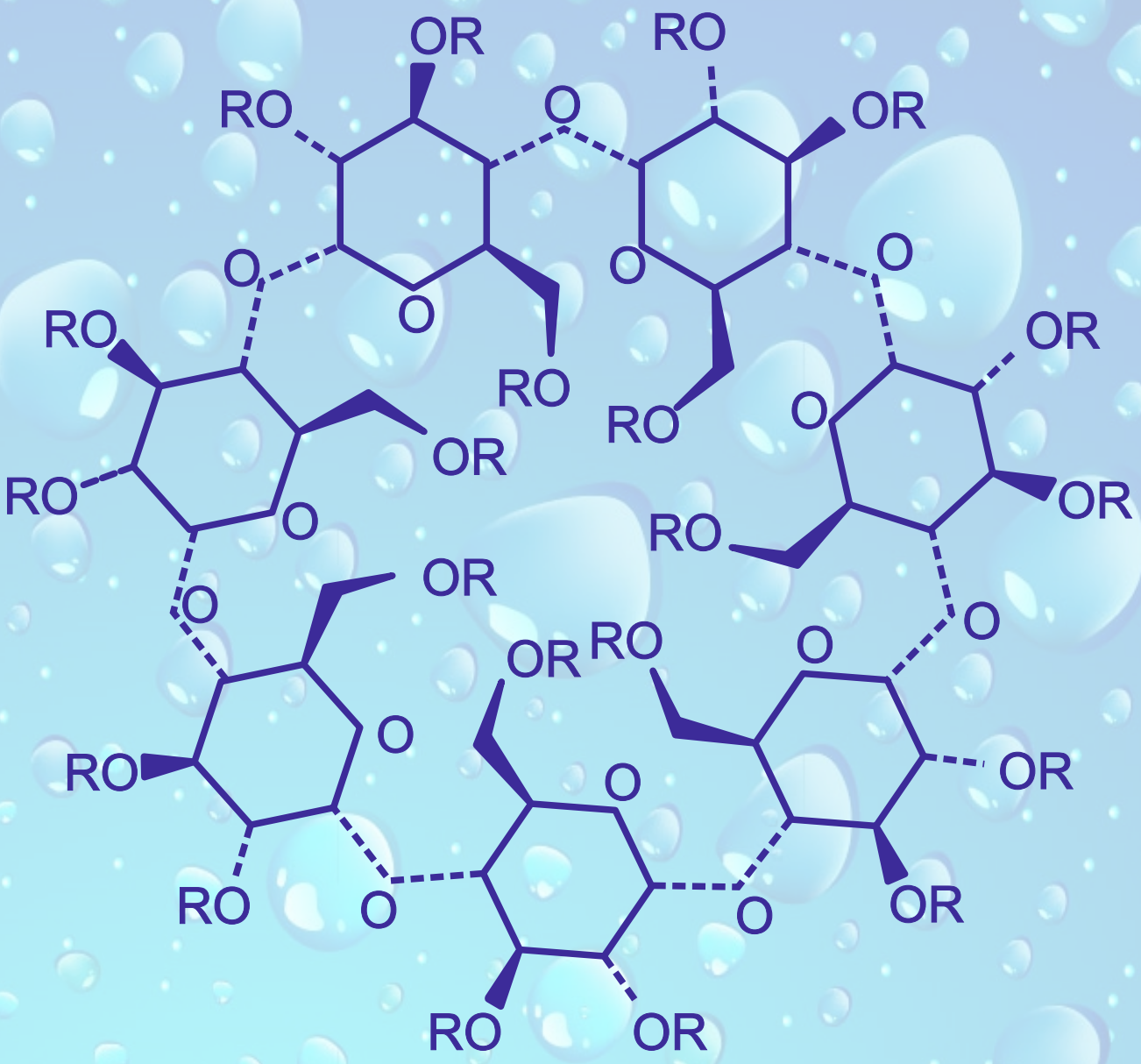
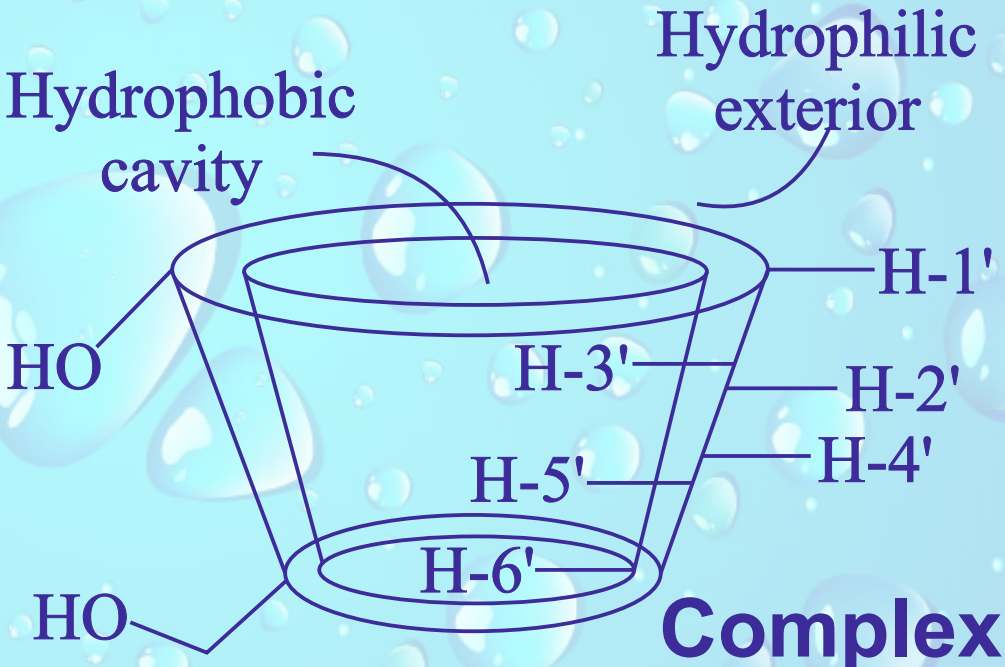
GANGWAL

Complexol-HP®

HYDROXYPROPYL BETADEX USP-NF / Ph. Eur. / BP





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Index

Introduction :

Cyclodextrins are natural cyclic oligosaccharides that were discovered just over 100 years ago, but only recently highly purified cyclodextrins became available as pharmaceutical excipients. Worldwide about 30 different pharmaceutical products containing hydroxypropyl beta cyclodextrin (HPBCD) are commercially available. Complexol-HP® has mainly been used as complexing agent to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability.

In addition, Complexol-HP® can be used to reduce gastrointestinal drug irritation, it converts liquid drugs into microcrystalline or amorphous powder, and prevents drug-drug and drug-excipient interactions. A number of books and review articles have been published on pharmaceutical applications of HPBCD.

Complexol-HP® is used in the formulation development of tablets, aqueous parenteral solutions, rectal, topical, nasal sprays and eye drop solutions.

Table 1: Use of cyclodextrins in different type of formulations

Application	HPBCD	BCD	α-CD	γ-CD	SBE-β-CD	RM-β-CD
Oral	✓	✓		✓	✓	
Nasal	✓					✓
Rectal	✓	✓				
Dermal	✓	✓		✓		
Ophthalmic	✓	✓				✓
Parenteral	✓		✓		✓	

Ref : Expert Opin. Drug Deliv. (2005) 2(2)

Among different types of cyclodextrin's available the Complexol-HP® demonstrated more stable complex formation. Complexol-HP® is preferred in formulation development due to its improved water solubility and safety profile compared to other cyclodextrins.

Complexol-HP® is a brand of **Gangwal Healthcare Pvt. Ltd.**, India; "foremost & sole manufacturers of cyclodextrins" in India as per BP, USP-NF, IP & Ph. Eur. compliance.

Synthesis of Complexol-HP(HPBCD) :

Complexol-HP is produced by reacting Beta-Cyclodextrin with Propylene Oxide. The original bucket structure and cavity volume of the Beta-Cyclodextrin remains intact.
The Propylene Oxide reacts randomly with Hydroxyl group of Beta-Cyclodextrin, resulting in mixture of compound with respective degree and position of substitution of hydroxyl group. By controlling the amount of propylene oxide use, the degree of substitution or average number of hydroxypropyl group per each cyclodextrin molecule can be controlled.

Properties of Cyclodextrins :

Cyclodextrins	Substitution	Molecular weight	Solubility in water (mg/mL)
Complexol-HP®	0.40- 1.50	**1400**	**>600**
α- Cyclodextirn	-	972	145
β - Cyclodextirn	-	1135	18.5
RM-BCD	1.8	1312	>500
SB-BCD	0.9	2163	>500
γ- Cyclodextrin	-	1297	232

Ref : Expert Opin. Drug Deliv. 2, 335-351 (2005)

Solubility of Complexol-HP® in Organic solvent :

Solvent	Solubility (g/100ml) DS 4.8	Solubility (g/100ml) DS 7.6
Octanol	0.179	N.D
Ethanol (95%)	200	225
Iso-propanol	N.D	152

Ref : Expert Opin. Drug Deliv. 2, 335-351 (2005)

Advantages of Complexol-HP®:

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 micro-organisms
7. Masking of malodour and taste
8. Masking pigments or the color of substances

Applications of Complexol-HP®:

There are many potential applications of Complexol-HP® in the pharmaceutical field:

- Improves the solubility of compounds with low water solubility, facilitating higher bioavailability of drugs (when the solubility or the rate of dissolution are the limiting factors of bioavailability)
- Increases shelf-life of expensive flavors and fragrances through encapsulation of volatile compounds
- Controls release of drugs, fragrances or flavors
- Improves organoleptic properties of drugs and obtain more palatable preparations
- Avoids incompatibilities between actives in the same formulation
- Stabilizes reactive ingredients against oxidation, hydrolysis
- Stabilizes against temperature degradation, hydrolysis, oxidation, photolysis
- Improves flowability and compression behavior of active compounds
- Transforms liquid actives into easily manipulated solid complexes

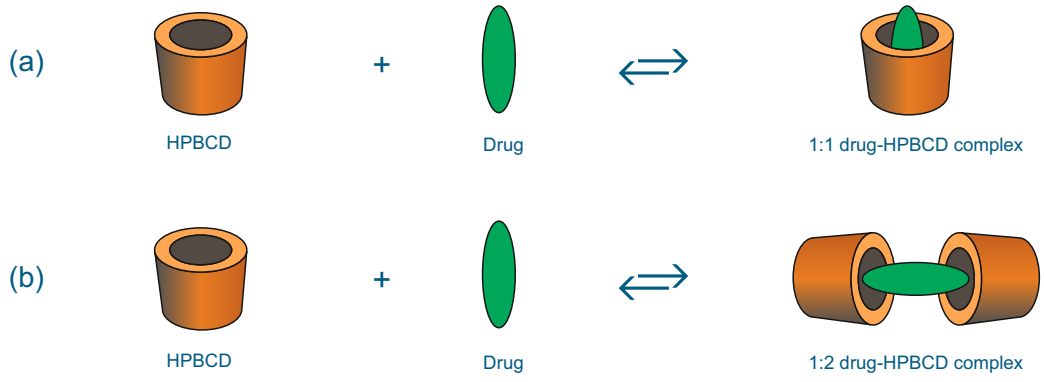
Application techniques :

A. Inclusion complex formation :

Complexation with Complexol-HP® is one of most frequently used methods for improving solubility of poorly soluble drugs. Due to chair configuration of the glucopyranose units, Complexol-HP® takes the shape of truncated cone, where hydroxyl groups are oriented to exterior giving it hydrophilic properties, while skeletal carbon and ethereal oxygen moieties are oriented to the central cavity, making it hydrophobic.

This unique structure enables formation of water-soluble inclusion complexes by taking up the whole molecule of poorly soluble drug, or more frequently only lipophilic moiety of drug molecule into hydrophobic Complexol-HP® cavity.

Complexol-HP® have an internal non-polar cavity and hydroxyl groups placed on the surface, the inclusion of hydrophobic compounds takes place mainly by hydrophobic interactions between guest molecules and the walls of Complexol-HP® cavity. However, other forces, such as Van Der Walls and Dipole–Dipole interactions, may be involved in the binding of guest.



B. Freeze-drying or lyophilization :

The freeze-drying technique is suitable for thermolabile or water-soluble molecules. The required proportion of cyclodextrin and the guest molecule are dissolved in water by stirring. The solution is freeze-dried and obtained powder is washed with organic solvent and then dried under vacuum.

This method can produce a very good yield of inclusion complex and it is possible to scale up. Comparing with other available techniques, freeze-drying technique has been widely applied for Cyclodextrin inclusion complex formation, especially water soluble HPBCD.
eg. Amylobarbitone, Several essential oils and their pure major active compounds have been encapsulated in hydroxyproply-β-cyclodextrin. These include cinnamon and clove, estragole (major component of basil and tarragon essential oils) [2, black pepper essential oil, thymol and thyme essential oil, kamebakaurin (kaurane diterpene), and chloramphenicol.]

C. Spray drying :

Cyclodextrin and guest molecule are dissolved in deionized water and then the solution is dried by the spray-dryer. The spray dryer is operated under the most appropriate condition such as inlet temperature and sample feeding speed; As temperatures of 50°–70°C are used, this technique is only used for thermostable molecules. Recently, the spray-drying technique has been used for encapsulation of folic acid in Complexol-HP® .

D. Kneading method :

Kneading technique is suitable for poorly water-soluble molecules, because molecule dissolves slowly during the formation of complex. It offers a very good yield of inclusion formation.

E. Co-precipitation method :

Co-precipitation technique is useful for insoluble in water substances. Poor yields are obtained by this method because of the competitive inhibition from organic solvents used as the precipitant. The guest gets dissolved in organic solvents (such as chloroform, benzene and diethyl ether, etc), and appropriate amount of Complexol-HP® dissolved in water is added with agitation. The solution gets cooled and complex crystals occur. The crystals are washed with organic solvent and then dried at 50°C. The co-precipitation technique has been previously applied for encapsulation of drugs such as Oxaprozin and trans-anethole (major component of Anise and Fennel essential oils). Heating in a sealed container After adsorbing a definite amount of water vapor, a physical mixture of active compound and the host molecule is sealed in a container and heated to a temperature ranging from 43°C to 142°C to obtain a crystalline inclusion compounds. This technique is also performed under nitrogen gas pressure and can be used for thermostable volatiles.

Application in pharmaceuticals :

The addition of Complexol-HP® increases the water solubility of several poorly water-soluble substances to improve bioavailability in pharmaceuticals. Complexol-HP® also have been used successfully to enhance organoleptic properties of bitter or unpleasant actives (taste-masking, odor-masking). Complexol-HP® is suitable for ophthalmic (Eye Drops), oral suspensions, aqueous dermal formulations, nasal drug delivery systems as well as for dry formulations (with possibility of in-situ encapsulation).

Ability of Complexol-HP® to form complexes with a wide variety of organic compounds, Helps to alter the apparent solubility of the molecule, to increase the stability of compound in the presence of light, heat and oxidizing conditions and to decrease volatility of compound.

Complexol-HP® can also be used as processing aid to isolate compound from natural sources and to remove unwanted compounds such as cholesterol from food products.

Name of API	Solubility (X fold) Without Complexol- HP	Solubility (X fold) with 10 % Solution of Complexol-HP
Alphaxalone	1	374
Betamethasone	1	118
Chlordiazepoxide	1	30
Cholesterol	1	225
Diazepam	1	21
Ibuprofen	1	55
Indomethacin	1	17
Hydrocortisone	1	67
Lorazepam	1	32
Methotrexate	1	56
Dipyridamole	1	12
Phenytoin	1	90
Nicardipine	1	58
Piroxicam	1	102
Retinoic Acid	1	5500
Rosoxacin	1	54
Tolmetine	1	79
Testosterone	1	176

Ref : Expert Opin. Drug Deliv. 2, 335-351 (2005)

Application in food and flavors :

Complexol-HP® is used in food formulations for flavor protection throughout many rigorous food-processing methods of freezing, thawing and microwaving, and used for flavor preservation to a greater extent and longer period, removal of bitter components from citrus fruit juices removal of phenolic compounds which cause enzymatic browning enhancement of flavor in alcoholic beverages such as whisky and beer

Application in cosmetics, personal care and toiletry :

- HPBCD (Complexol-HP®) can be used for controled release of fragrances from the inclusion compounds in perfumes, room fresheners or detergents used in silica-based toothpastes to increase the availability of triclosan, an antimicrobial agent.
- HPBCD (Complexol-HP®) is used in sunscreen lotions to reduce side effects of the formulation by limiting the interaction between the UV filter and the skin.

HPBCD (Complexol-HP®) have been used for controlled release of drugs such as Ciprofloxacin, Triclosan, Vancomycin and Chlorhexidine Digluconate.

Metabolism, safety and toxicity profile of Complexol-HP® :

A. Metabolism :

The cyclic structure of HPBCD (Complexol-HP®) resists enzymatic hydrolysis by ß-amylases and saliva -amylases and is poorly hydrolysed in the human small intestine but is fermented by the colonic microflora. Less than 1% of ingested HPBCD (Complexol-HP®) is absorbed intact by the small intestine and this is excreted in the urine.

B. Safety and toxicity :

A number of clinical studies are reported in the literature and have shown that HPBCD(Complexol-HP®) was well tolerated and safe in the majority of patients receiving HPBCD (Complexol-HP®) at daily oral doses of 4–8 g for at least 2 weeks. Higher oral daily doses of 16– 24 g when given for 14 days to volunteers, resulted in increased incidences of soft stools and diarrhoea. Therefore, based on these clinical data, HPBCD (Complexol-HP®) is considered to be non-toxic if the daily dose is <16 g.

In an intravenous dosing study, single dose up to 3 g were found to have no measurable effect on kidney function and were well-tolerated by all volunteers. Following a 1-week intravenous study at a single dose level of 1 g, no adverse effects were reported (Food and Chemical Toxicology 43 (2005) 1451–1459).

Approved pharmaceutical products containing HPBCD :

Drug	Trade Name	Dosage form	Company	Country
Diclofenac	Dyolect	I.V. and I.M.	Javelin Pharm.	Europe
Hydrocortisone	Dexacort	Mouth Wash	Actavis	Europe
Indomethacin	Indocid / Indocyllir	Eye drop	Chauvin/ Baush & Lomb	Europe
Itraconazole	Sporanox	Oral solution / I.V.	Janssen	Europe/USA
Mitomycin	MitoExtra	I.V. infusion	Novartis	Europe
Televancin	Vibativ	I.V. solution	Astellas Pharma	Europe
Perindopril Tert.butylamine	Perindopril Erbumine	Tablets	Sandoz	Europe
Voriconazole	Vorzu	Tablet	Ranbaxy	India
Cisapride	Prepulsid	Suppository	Janssen	Belgium
Diclofenac eye drop Solution		Eye drops	Ciba Vision	Switzerland
Ciprofloxacin and Dexamethasone	Ciplox- D	Eye/Ear drops	Cipla	India

Ref : Int. J. Pharm., 329, 1-11 (2007)

Recent development on HPBCD complexation for enhancing the dissolution rate and bioavailability :

Drug	Cyclodextrin	Results and Purpose
Naproxen	HPBCD	Increased effect of aqueous solubility of Naproxen
Carbamazepine	HPBCD	Increased oral absorption
Raloxifene	HPBCD	Enhancement of oral bioavailability
Methocarbamol	HPBCD	Two-fold increased in stability test
Ibuproxam	HPBCD	Increase in dissolution rate
Spironolactone	HPBCD	Increase in dissolution rate and bio-availability
Tadalafil	HPBCD	Increase in dissolution rate
Cefdinir	HPBCD	Enhance solubility and increased dissolution rate
Aceclofenac	HPBCD	Enhancement of dissolution with kneaded product
Glimepride	HPBCD	Increased dissolution rate
Gliquidone	HPBCD	Greater dissolution rate and enhance oral bioavailability
Furosemide	HPBCD	Increased solubility and dissolution rate

Ref : Expert Opin. Drug Deliv. 2, 335-351 (2005)

Regulatory status of Complexol-HP® :

- The American FDA has given market approval for solid oral, liquid oral, ophathalmic and intravenous formulations containing HPBCD derivatives
- Our manufacturing unit is approved by WHO-GMP and ISO 9001 : 2008
- **Complexol-HP® is having registered Type IV US DMF No. 23816**
- Pharmacopoeia conformity: the USP and EP have published draft monographs for hydroxypropyl betacyclodextrin
- HPBCD is also included in Inactive Ingredient database (IIG) of USFDA
- HPBCD is introduced into Generally Regarded As a Safe (GRAS) list of the USFDA

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