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2-Hydroxypropyl- β -cyclodextrin: Properties and Usage in Pharmaceutical Formulations

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The solubility of drugs is an important factor with respect to drug administration and drug delivery. Many physical and chemical approaches have been used to improve the solubility of poorly water-soluble compounds. Recently various water soluble cyclodextrin-drug complexes have been investigated and shown to be an attractive alternative to existing methods. However, a serious drawback in their therapeutic use is their toxicity. 2-Hydroxypropyl- β -cyclodextrin (HP β CD) has been shown to lack these toxic side effects. It has been used to increase the solubility of a variety of drugs dramatically. An overview is given over the effects of HP β CD on drug solubility and drug stability. Some examples of applications in animal and human studies are reviewed.

2-Hydroxypropyl- β -cyclodextrin (HP β CD): Eigenschaften und Verwendung in pharmazeutischen Zubereitungen

Die Löslichkeit von Arzneistoffen ist ein wichtiger Faktor in bezug auf die Arzneimittelanwendung und Bioverfügbarkeit. Es gibt eine Vielzahl physikalischer und chemischer Ansätze zur Verbesserung der Löslichkeit schlecht wasserlöslicher Substanzen. In den letzten Jahren ist gezeigt worden, daß der Einsatz von Cyclodextrin-Derivaten eine attraktive Alternative zu diesen Methoden darstellt. Allerdings ist die Anwendung einiger dieser Derivate als Arzneistoffvehikel häufig mit erheblicher Toxizität verbunden. Versuche mit 2-Hydroxypropyl- β -cyclodextrin (HP β CD) haben dagegen keine Toxizität nachweisen können. Diese Substanz kann die Wasserlöslichkeit schwer löslicher Verbindungen signifikant erhöhen. Der vorliegende Artikel gibt einen Überblick über den Einfluß von HP β CD auf die Löslichkeit und Stabilität einer Vielzahl von Arzneistoffen. Einige Beispiele von tierexperimentellen und klinischen Anwendungen von HP β CD-Komplexen werden vorgestellt.

Keywords: 2-Hydroxypropyl- β -cyclodextrin, drugs, solubility, stability, toxicity, review

Introduction

Formulation of pharmaceutical dosage forms is frequently hampered by poor aqueous solubility of the drugs which again can severely limit their therapeutical application. Also, slow dissolution of a solid state drug formulation and side effects of some drugs are the results of their poor aqueous solubility.

Increasing the drug solubility through appropriate formulation can, thus, lead to increased therapeutic efficiency of the drug. Various methods have been used to increase the solubility of drugs, such as the use of organic solvents, emulsions, liposomes and micells, adjustments of pH and the dielectric constant of the solvent system, chemical modifications, and complexation of the drugs with appropriate inorganic or organic complexing agent. Unfortunately all of the above mentioned techniques have their limitations and pharmaceutical formulators are constantly searching for new methods to increase the solubility of drugs and ways to improve the old ones. Recently various

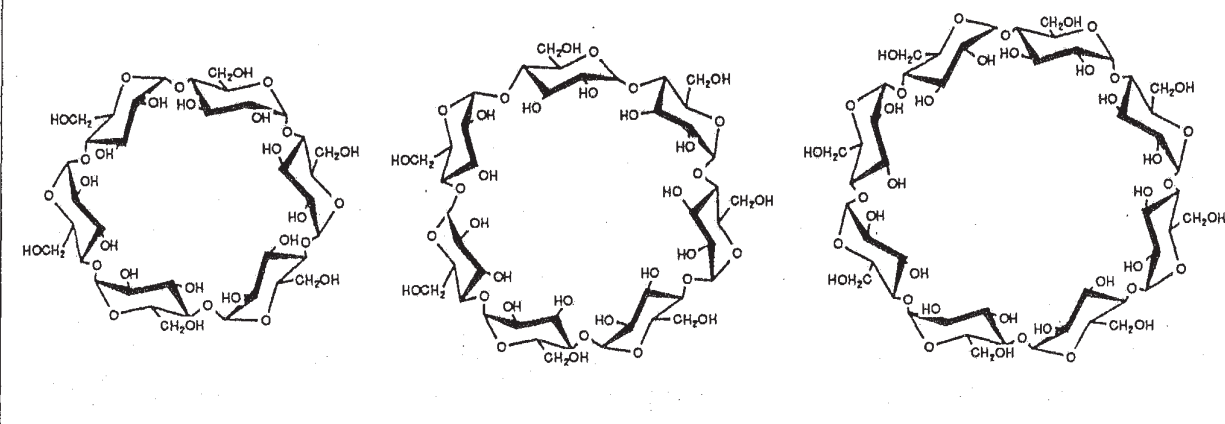
water soluble cyclodextrin-drug complexes have been investigated and shown to be an attractive alternative to the existing methods.

Cyclodextrins were first isolated by Villiers in 1891 as digests of *Bacillus amylobacter* on potato starch (1), but the foundations of the cyclodextrin chemistry were laid down by Schardinger in the period 1903–1911 (2,3) and many of the older literature refers to cyclodextrins as Schardinger's dextrins. Cyclodextrins are formed by enzymatic cyclization of starch. Until 1970, only small amounts of cyclodextrins could be produced in the laboratory and the high production cost prevented the usage of cyclodextrins in the pharmaceutical industry. In recent years, dramatic improvements in the cyclodextrin production and purification have been achieved and the cyclodextrins have become cheaper. This has made industrial applications of cyclodextrins possible.

Cyclodextrins and their Derivates

Cyclodextrins are cyclic oligosaccharides with hydroxyl groups on the outer surface and a void cavity in the center. Their outer surface is hydrophilic, and therefore they are usually soluble in

Table 1: Structure and Physical Properties of Various Cyclodextrins^a

			
	Alpha (α)	Beta (β)	Gamma (γ)
Molecular weight	972	1135	1297
Glucose monomers	6	7	8
Internal cavity diameter (nm)	0.5	0.6	0.8
Water solubility (g/100 mL; 25 °C)	14.5	1.85	23.3
Surface tension (mN/m)	71	71	71
Melting range (°C)	255–260	255–265	240–245
Water of crystallization (%)	10.2	13–15	8–18
Molecules of water in cavity	6	11	17

^a Modified from References (4) and (5)

water, but the cavity has lipophilic character. The most common cyclodextrins are α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin, consisting of 6, 7 and 8 α -1,4-linked glucose units, respectively (Table 1). The number of these units determines the size of the cavity. Cyclodextrins are capable of forming inclusion complexes with a wide variety of hydrophobic drug molecules by taking up a whole molecule, or some part of it, into the cavity. The stability of the complex formed depends on how well the guest molecule fits into the cyclodextrin cavity (6, 7, 8, 9).

Unfortunately, the cyclodextrin which is the most useful for incorporating a number of drugs, β -cyclodextrin, is poorly water soluble (only 1.85 g/100 ml) compared with α - and γ -cyclodextrin (14.5 and 23.3 g/100 ml, respectively). This low solubility of β -cyclodextrin is believed to be associated with strong intermolecular hydrogen bonding in the cyclodextrin crystal. Alkylation (methyl- and ethyl- β -cyclodextrin) or hydroxyalkylation (hydroxypropyl- β -cyclodextrin and hydroxyethyl- β -cyclodextrin) of the hydroxyl groups or substitution of the primary hydroxyl groups by saccharides (glucosyl- β -cyclodextrin and maltosyl- β -cyclodextrin) of the cyclic oligomer disrupts this hydrogen bonding which destabilizes the crystal lattice (10). In addition, these manipulations can transform the crystalline material into amorphous mixtures of isomeric cyclodextrins (11). The amorphous nature of modified β -cyclodextrin as well as the derivation contribute to increasing the aqueous solubility of the preparations. The β -cyclodextrin derivatives, including 2-hydroxypropyl- β -cyclodextrin (HP β CD), have been shown to possess similar solubilizing and stabilizing effects on drugs in aqueous solutions as the parent β -cyclodextrin (12, 13).

HP β CD is obtained by treating a base-solubilized solution of β -cyclodextrin with propylene oxide. The resulting mixture of isomers is then purified to give HP β CD of various mean degrees of substitution (14). The average number of 2-hydroxypropyl groups substituted on the β -cyclodextrin nucleus is determined by the amount of propylene oxide used.

Toxicity Studies

One of the most serious drawbacks in the use of β -cyclodextrin or alkylated β -cyclodextrins such as methyl- β -cyclodextrin is their toxicity (11, 15). Systemic administration of β -cyclodextrin associated with severe nephrosis. This toxicity is apparently related to the poor water solubility of β -cyclodextrin and after i.p. or i.v. administration, the material collects, crystallizes and precipitates in the kidney. The LD₅₀ of β -cyclodextrin is, therefore, unfortunately low, in the range of 300–700 mg/kg (i.v. in rats) (7, 15, 16). The toxicity of methylated β -cyclodextrins is related to a distinct physical property namely their surface activity. Methylated β -cyclodextrins are relatively lipophilic and act to destabilize biological membranes even at low concentration. This property causes methyl- β -cyclodextrin to be hemolytic and also imports a low i.v. LD₅₀ (200 mg/kg) (16).

The hydroxyalkylated- β -cyclodextrins and in particular HP β CD lack these untoward biological effects as indicated by extensive animal and human testing (17, 18, 19, 20, 21). Animal studies using a variety of model systems have failed to identify any significant toxicological potential. Intravenous evaluations have included subacute and subchronic administration of HP β CD to rats and monkeys (200 mg/kg every second day) and subchronic administration to rats and dogs (doses as high as 400

mg/kg daily) (17). In addition, i.v. doses as large as 10 g/kg were shown not to be acutely lethal or toxic to monkeys (17). High dose oral administration was also innocuous. In all animal testing, there were no significant changes in kidney function and HP β CD was readily and completely excreted by renal elimination. The mean plasma half-life of HP β CD was 0.9 hrs in dogs (19).

Human clinical studies on HP β CD have been similarly encouraging. This excipient was used in doses as high as 5 g as a vehicle for an estrogen derivative with no adverse effects in a group (n=10) of post-menopausal women (20). In a separate study, a rising dose tolerance paradigm was used to evaluate HP β CD (0.5 g to 3.0 g) in two groups (n=8) of healthy volunteers (21). There were no adverse effects and no alteration in any of the reno-specific parameters examined. In humans, HP β CD is cleared from the plasma with a half-life of 1.4-1.8 hrs and is almost totally eliminated by the kidneys. This favorable profile has led several pharmaceutical companies to exploit this potential excipient with several drug combinations in advanced clinical tests.

Effects of HP β CD on Drug Solubility

Table 2 shows the effects of HP β CD on the aqueous solubility of a number of drugs possessing different physicochemical properties, such as molecular size, lipophilicity, aqueous solubility and chemical structure. The largest solubility enhancement appears to be obtained when the drug shows low aqueous solubility, e.g., norethindrone acetate. HP β CD has little or no effect on the aqueous solubility of hydrophilic and water soluble drugs, e.g., propranolol hydrochloride and trifluorothymidine. Also, it appears that only some lipophilic part of the drug molecule has to fit into the lipophilic HP β CD cavity and not the entire molecule. Thus, steroids with a flat unsaturated and unhindered A-ring, like dexamethasone and 17 β -estradiol, or accessible phenyl or benzyl rings, like chloridazepoxide, generally have good solubility in aqueous HP β CD solutions. Steroids with a hindered A-ring, like ethynylestradiol 3-methyl ether, and benzodiazepines with hindered phenyl or benzyl rings have less solubility. The aqueous solubility of the drugs generally shows linear dependency on the HP β CD concentration and the phase-solubility diagrams are of Higuchi's A₁-type (24, 25). Figure 1 shows, for example, this linear type of phase-solubility diagrams for six steroids. There are, however, examples of both positive (A_P-type) and negative (A_N-type) deviations from linearity (12, 26).

The enthalpy change for the HP β CD complex formation, like for other cyclodextrin complexation, is negative and the free energy decreases through the complexation process (12, 26, 27). Thus, the HP β CD complexes will dissociate when the temperature is increased. Since increase in the free energy is generally observed when drugs are dissolved in pure water, the solubility enhancement is larger at low temperature than at high temperature (22).

The solubility enhancement of drugs in water obtained through HP β CD complexation has been shown to be very advantageous in a number of pharmaceutical formulations. For example, due to their low aqueous solubility the anti-cancer drugs chlorambucil and melphalan have only been marketed as tablets. It has now been shown that it is possible to formulate both chlorambucil and melphalan in an aqueous i.v. solution through HP β CD complexation (26). The daily dosage of both drugs could be dissolved in 1 to 2 ml of isotonic HP β CD

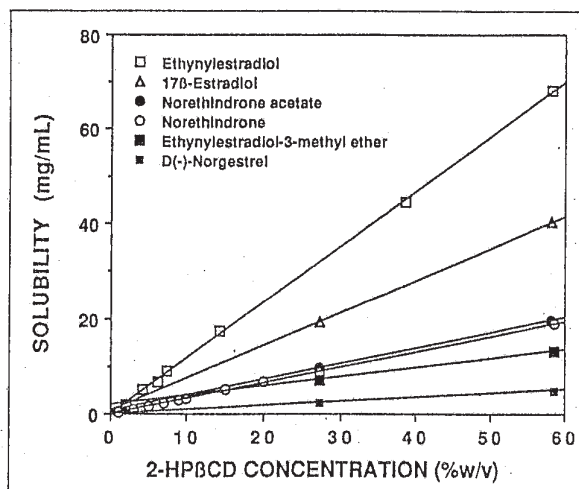


Figure 1: Phase-solubility diagrams for various steroids at neutral pH and 25°C (from Reference 22)

solution. Also, replacing chlorambucil with the solid HP β CD-chlorambucil complex in tablets significantly improves the dissolution of the drug.

An example in which HP β CD has been shown to be useful in obviating the need for water-soluble prodrugs is the case of dexamethasone. Dexamethasone is a widely used glucocorticoid which is used in the treatment of shock, trauma and asthma. In many instances, i.v. administration is necessary but the poor aqueous solubility of dexamethasone prevents simple aqueous formulation. Currently, a water-soluble prodrug of the steroid, dexamethasone-21-phosphate sodium salt, is used. This compound reverts to the parent compound subsequent to i.v. dosing but is associated with various unpleasant side effects not associated with dexamethasone itself. Administration of a HP β CD complex of dexamethasone may, therefore, provide an advantage over the currently used therapy. Intravenous administration of the dexamethasone-HP β CD complex to dogs resulted in higher initial plasma levels of dexamethasone than those obtained after dexamethasone phosphate dosing. The area under the dexamethasone plasma concentration-time curve during the therapeutically important first hour after the injection was more than 50% higher than after the administration of an equivalent dose of the phosphate prodrug (Fig. 2). At later time points there was no significant difference in the pharmacokinetics of dexamethasone generated from the prodrug vs. the HP β CD. Although the utilized HPLC-assay does not differentiate between free and complexed dexamethasone, the administered dose of cyclodextrins of approximately 2g should be sufficiently diluted in the blood stream to result in rapid complex dissociation (28).

Another application of HP β CD has been to sublingual administration of gonadal steroids. Due to their low aqueous solubility and a large first-pass effect, oral administration of these steroids frequently results in a low and variable bioavailability. Pitha has shown that when testosterone is complexed with HP β CD, it is readily absorbed from under the tongue resulting in rapid increase in plasma levels (29). Similar findings were observed for estradiol and progesterone (29).

Many transdermal delivery systems and topical semi-solid preparations cause side effects in the skin due to long term

Table 2: Solubility of some drugs in water and aqueous HP β CD solutions at room temperature

Drug	Solubility in water (mg/ml)	HP β CD concent. (% w/v)	Solubility in the aqueous HP β CD solution (mg/ml)	Increase in solubility (HP β CD/water)	Ref.
Acetaminophen	11	58	67.0	6	14
Acetylsalicylic acid	3.3	45	13.4	4	23
Acyclovir (at pH 7.2)	1.7	58	3.9	2	22
Apomorphine	20	58	116.0	6	14
Carbamazepine	—	45	16.8	—	23
Chlorambucil	0.3	58	30.0	100	23
Chlordiazepoxide	0.01 ^a	58	147.8	15,000	22
Chlortetracycline	0.5	45	30.1	60	23
Chlorthalidone	0.12	58	10.5	90	14
Cholecalciferol	0.02	25	0.65	33	23
Dexamethasone	0.008	58	44.3	5,500	22
Diazepam	0.05 ^a	58	7.4	150	22
Dicumarol	<0.15	58	1.3	—	14
Digoxin	0.07 ^a	58	68.0	1,000	14
17 β -estradiol	0.004 ^a	58	40.5	10,000	22
Estriol	0.003 ^a	58	41.0	14,000	14
17 α -Ethinylestradiol	0.008	58	68.2	8,500	22
Ethinylestradiol 3-methyl ether	0.001	58	13.3	13,000	22
Hydrocortisone	0.28 ^a	45	41.8	150	23
Hydrocortisone acetate	0.01 ^a	45	8.0	800	23
Hydroflumethiazide	0.3	58	9.3	30	14
Indomethacin	0.02 ^a	58	4.2	210	14
Iproniazid phosphate	30	58	95.0	3	14
Lomustine	0.1	58	12.0	120	23
Medazepam (at pH 7.5)	0.01	58	8.3	850	22
Melphalan	2.1	58	21.9	10	23
Methotrexate (at pH 7.6)	0.045	58	10.0	200	22
17-Methyltestosterone	<0.17	58	39.0	—	14
Nitrofurantoin (at pH 7)	0.2	25	0.2	1	22
Nitroglycerin	1.25 ^a	45	10.4	8	14
Norethindrone	0.005	58	19.0	4,000	22
Norethindrone acetate	0.0002	58	19.5	97,500	22
D(-)-Norgestrel	0.002	58	4.9	2,500	22
Ouabain	13	58	80.0	6	14
Oxazepam	0.03	58	4.2	150	22
Oxperolol	127	58	238.0	2	14
Oxytetracycline	1.1	45	2.4	2	23
Phenytoin	0.02	58	9.3	450	22
Progesterone	0.015	45	34.0	2,300	14
Propranolol HCl	107	58	124	1	22
Retinal	<0.07	45	2.6	—	14
All-trans-Retinoic acid	<0.07	45	0.8	—	14
All-trans-Retinol	0.001	58	4.6	4,600	22
Spironolactone	0.03 ^a	45	42.0	1,400	14
Sulfadiazine	0.2 ^a	45	2.9	15	23
Sulfamerazine	0.17 ^a	45	4.7	30	23
Sulfamethiazine	0.15 ^a	45	4.4	30	23
Sulpiride	<0.21	58	10.0	—	14
Testosterone	0.026	50	38.0	1,500	14
Tetracycline	1.7 ^a	45	3.9	2	23
Theophylline	8.3	58	11.0	1	14
Trifluorothymidine	58.4	58	72.6	1	22
Trimethoprim	0.4 ^a	45	6.9	15	23

^a Literature values

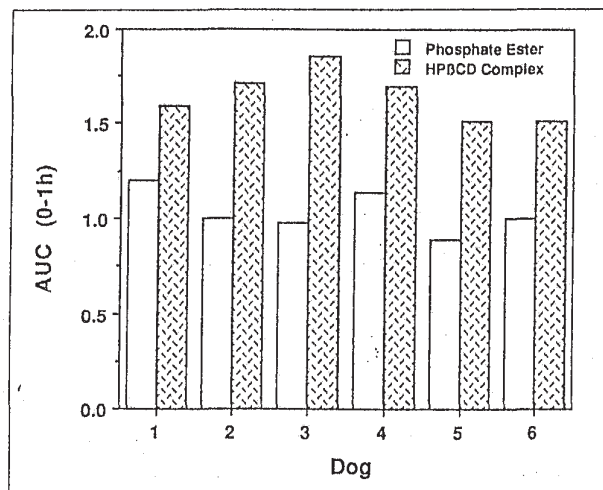


Figure 2: Area under the dexamethasone plasma concentration-time curve for six different dogs after intravenous administration of 5 mg/kg dexamethasone in form of its phosphate ester or HPβCD-complex

occlusion. It is possible that these side effects can be avoided by using nonocclusive aqueous vehicle systems. Many lipophilic drugs, such as steroid, have very low aqueous solubility and cannot be used in aqueous vehicle systems without effective solubilization. HPβCD forms water soluble complexes with a number of steroids and aqueous HPβCD solutions have been shown to be effective vehicle systems for the transdermal delivery of 17β-estradiol, hydrocortisone and testosterone (30). Although the concentration of the free drug in the vehicle was low, the drug molecules within the complex were in a fast equilibrium with the free drug molecules out in the solution resulting in an effective delivery of the drug to the skin surface.

Other formulations where HPβCD has been used to increase aqueous solubility of drugs include parenteral formulations of alfaxalone (31), nimodipine (18), testosterone (32) and of chemical delivery systems containing various drugs (33, 34, 35). Also, HPβCD has been used to solubilize proteins (36).

Effects of HPβCD on Drug Stability

Frequently the rate of degradation of a drug within the inclusion complex is slower than out in the solution and addition of HPβCD to aqueous solution of the drug results in increased stability and, thus, longer shelf-life (Table 3). There are, however, some examples of cyclodextrin destabilization of drugs such as of prostaglandin E₁ (37).

The recent developments in biotechnology have made biologically active peptides and proteins available in sufficient quantities to be used as drugs. Many of these peptides and proteins are very unstable in aqueous solutions and their formulations have brought a new challenge to the pharmaceutical scientists. One of the main problems of injectable protein solutions is the aggregation of the proteins and changes in their three-dimensional structure which leads to denaturation and, consequently, deactivation. HPβCD has been shown to stabilize aqueous buffer solutions of insulin and interleukin-2 (36, 38).

Conclusion

In conclusion, HPβCD is a non-toxic cyclic oligosaccharide capable of forming hydrophilic inclusion complexes with a large number of lipophilic drugs. The complexation can improve the clinical usage of the drugs by increasing their aqueous solubility, rate of dissolution and pharmaceutical availability. The complexation can also improve the stability of many drugs in aqueous solutions and increase their shelf-life. HPβCD is a new pharmaceutical excipient with numerous potential uses in the pharmaceutical industry.

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Table 3: The effect of HPβCD on the rate of degradation of some drugs in aqueous solutions

$D + \text{HP}\beta\text{CD} \rightleftharpoons D\text{-HP}\beta\text{CD}$ $\downarrow$ k_o Degradation products $\downarrow$ k_c Degradation products							
k_o is the rate constant for the degradation of the drug out in the solution, i.e., outside the complex, and k_c is the rate constant for the degradation of the drug within the inclusion complex.							
Drug	Buffer	pH	T(°C)	$k_o(\text{min}^{-1})$	$k_c(\text{min}^{-1})$	k_o/k_c	Ref.
Acetylsalicylic acid	Hydrochloric acid	1.0	70	8.6×10^{-3}	3.6×10^{-3}	2.4	12
Chlorambucil	Nitric acid	1.3	50	2.0×10^{-2}	1.0×10^{-2}	2.0	26
	Mellvaine buffer	7.3	50	0.21	9.5×10^{-3}	22	26
Lomustine	Formate	2.6	55	2.3×10^{-2}	9.7×10^{-3}	2.4	13
	Acetate	5.9	55	3.0×10^{-2}	1.3×10^{-2}	2.3	13
	Phosphate	7.0	55	6.9×10^{-2}	3.4×10^{-2}	2.0	13
Melphalan	Nitric acid	1.3	60	8.6×10^{-2}	5.0×10^{-3}	17	26
	Mellvaine buffer	7.0	60	0.22	7.5×10^{-3}	29	26
	Sodium hydroxide	11.7	60	0.43	1.1×10^{-2}	39	26

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