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ORIGINAL ARTICLE

Evaluation the effect of cyclodextrin complexation on aqueous solubility of fluorometholone to achieve ophthalmic solution

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Abstract In this study, the effect of different CDs including α-CD, β-CD, γ-CD, hydroxypropyl β-CD (HP β-CD), sulphobutylether β-CD (SBE β-CD) and HP γ-CD on aqueous solubility of fluorometholone (Flu) was investigated. Also the phase solubility studies were performed in the presence of eye drop excipients such as benzalkonium chloride, hydroxypropyl methylcellulose (HPMC) and buffers. The aqueous solubility of Flu was increased by 8, 15, 5, 100, 65 and 135 folds in the presence of 20% w/v α-CD, β-CD, γ-CD, HP β-CD, HP γ-CD and SBE β-CD, respectively. Aqueous solubility of Flu was 0.43 ± 0.08 and 1.16 ± 0.04 mg/mL in systems containing 5% w/v HP γ-CD and SBE β-CD, respectively. The aqueous solubility of Flu in the presence of HP γ-CD was not influenced by buffer type while the phosphate buffer caused a reduction in the aqueous solubility in the presence of SBE-β-CD. Also, investigations on the solubility of Flu in water in the presence of 5% HP γ-CD and SBE-β-CD and the additives such as benzalkonium chloride and HPMC indicated that these components had no remarkable effect on the aqueous solubility of Flu. In conclusion, CD complexation is able to improve the aqueous solubility of Flu and it would be possible to prepare ophthalmic solution of Flu by this method.

Keywords Aqueous solubility · Cyclodextrin · Fluorometholone · Ophthalmic solution

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Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six (α-CD), seven (β-CD), eight (γ-CD) or more glucopyranose units linked by α-(1, 4) bonds [1–3]. Due to the chair conformation of the glucopyranose units, CDs take the shape of a truncated cone or torus rather than a perfect cylinder [3, 4]. Because of this structure CDs are able to solubilize many lipophilic drugs which previously were impossible to formulate in aqueous solutions [5–8]. Numerous CD derivatives with improved solubility, complexation power, and toxicological properties have been produced and studied; especially HP-β-CD and SBE-β-CD have proven highly useful [9–11].

Flourometholone (Flu) is a lipophilic compound that is only soluble to a limited extent in aqueous eye drop formulations and, thus, frequently is formulated as suspension, fluorometholone 0.1%. This topical corticosteroid is used for diseases of the outer eye and anterior segment of the eye [12, 13].

Complexation of drug molecule with CDs changes the physicochemical properties of the drug, such as its aqueous solubility and chemical stability. Since the CD molecule is hydrophilic on the outside, inclusion of lipophilic molecules inside the truncated cone of CDs will result in an increase in the aqueous solubility of lipophilic drug. Thus, it has been possible through CDs complexation to formulate water-insoluble steroids as aqueous eye drop solutions.

Furthermore, the chemical stability of the drug molecule is enhanced by inclusion complexation. This increases the shelf life of the aqueous eye drop formulation [14]. Moreover, improved bioavailability of CD-based steroid formulations has been demonstrated [9].

Eye drop solutions containing CD have already been registered in Europe [14]. Recent studies have shown that the addition of CDs to the ophthalmic formulations can improve the ophthalmic bioavailability of selected drugs [14–16]. It was reported that dexamethasone-CD complexes enhance the drug concentration level in the human aqueous humor compared to the commercial steroid eye drop [3, 11]. In the animal model, CDs increased the absorption of dexamethasone through the rabbit cornea by 40% [17]. Also it was reported a significant increase in the bioavailability of pilocarpine in HP-β-CD solution in comparison with pilocarpine alone [18]. It was also shown that formulation of methazolamide-CD complex as aqueous eye drop solution can lower the intraocular pressure [19].

The aim of the present study was to evaluate the effect of various CDs on the aqueous solubility of Flu. Also, the aqueous solubility was evaluated in the presence of some excipients such as benzalkonium chloride, HPMC and buffers to figure out the impact of these additives on drug-CD complexation for formulation of eye drop solution. Complementary studies was also undertaken to investigate Flu and CD interactions using differential scanning calorimetry (DSC).

Materials and methods

Materials

Flu was supplied by Sinadarou (Tehran, Iran). α-CD, β-CD, hydroxylpropyl β-CD (HP-β-CD), sulphobutylether β-CD (SBE-β-CD) and γ-CD were purchased from Seebio (China) and hydroxypropyl γ-CD (HP-γ-CD) was obtained from Aldrich (USA). Benzalkonium chloride and HPMC were from Merck (Germany) and Colorcon (UK), respectively. All materials were analytical grade unless otherwise stated.

Phase solubility studies

For phase solubility analysis, CD solutions with different concentrations (0–20% w/v) in water were prepared and excess amounts of Flu powder were added to each vial. The vials were placed on a rotator (Labinco, Netherlands) and rotated at room temperature (23–25 °C) for 24 h. Following this equilibration period, the systems were filtered through a 0.45 μm membrane filter and the concentration of Flu in the filtrate was analyzed using high-pressure liquid chromatography (HPLC). In all cases, solubility determinations were carried out in triplicate. An apparent stability constant was calculated from the initial straight line portion of phase-solubility diagrams. Solubility diagram type was determined according to the Higuchi and Connors (1965) [9, 10, 20].

In the next step, the effect of different ingredients of eye drop formulation including HPMC (0.1% w/v), benzalkonium chloride (0.05% w/v) and buffers (isotonic phosphate buffer, pH 7.2 or borate buffer, pH = 7) on aqueous solubility of Flu was determined in the presence of CDs. Also, the intrinsic solubility of Flu in water was determined for three samples.

HPLC assay

Quantitative determinations were performed by HPLC (Knauer, Germany) using a C18 column (Knauer, Germany) and measured at a detection wavelength of 254 nm. The mobile phase composed of 60% methanol and 40% water at a flow rate of 1 mL/min with the injection volume of 20 μL. The HPLC method was linear to a concentration of 0.008–5 mg/mL ($R^2 = 0.998$).

DSC analysis

DSC was carried out using a DSC apparatus equipped with STARE software (METTLER TOLEDO SW7.01, Switzerland). Thermograms of different samples (Flu, freeze dried SBE β-CD-Flu and HP γ-CD-Flu complexes) were plotted using 5–10 mg of samples placed in sealed aluminum crucibles and heated from 25 to 350 °C at 10 °C/min under a nitrogen atmosphere. Empty 40 μL crucibles were used as reference and the apparatus was calibrated with DSC calibration standard.

Result

Phase solubility studies

Phase-solubility diagrams of Flu with various CDs at room temperature were obtained according to the Higuchi and Connors [20] and demonstrated in Fig. 1. The intrinsic solubility of Flu was measured as 0.032 ± 0.006 mg/mL. All CDs increased the aqueous solubility of Flu. The Flu solubility was increased about 2–135 folds by adding of 5% w/v α-CD and 20% w/v SBE-β-CD, respectively.

The solubility of Flu in water increases almost linearly with increasing the concentration of all CDs except γ-CD and β-CD. HP-β-CD, HP-γ-CD and SBE-β-CD were increased aqueous solubility of Flu more effectively than

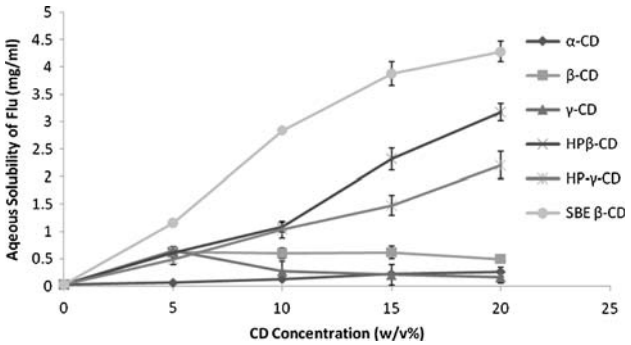

Fig. 1 Phase-solubility diagrams of Flu-CD complex in water at room temperature (mean ± SD, $n = 3$)

other CDs. α-CD, HP-γ-CD and SBE-β-CD exhibited A_L-type diagram in the chosen concentration range. β-CD and γ-CD showed B_S-type diagram displaying a linear increase in aqueous solubility of Flu after which a plateau was reached, indicating a limited solubility of the formed inclusion complex. HP-β-CD exhibited A_P-type diagram that increase linearly up to 1.08 mg/mL and than showed a positive deviates, indicating HP-β-CD was proportionally more effective at higher concentrations.

Because of the suitable effect of SBE-β-CD and HP-γ-CD on Flu solubility, they were chosen to analyze the aqueous solubility of Flu in the presence of eye drop ingredients. The aqueous solubility of Flu in the presence of SBE-β-CD and these ingredients was summarized in Table 1. When phosphate buffer was added to 5% w/v SBE-β-CD solution, the solubility of Flu was decreased from 1.16 ± 0.04 mg/mL to 0.70 ± 0.12 mg/mL, while adding of borate buffer caused to increase the solubility of Flu to 1.34 ± 0.05 mg/mL. The Flu solubility did not show any significant change when HPMC added to solution that contained SBE-β-CD and Flu complex. When Benzalkonium chloride was added to solution the solubility was reduced to 1.03 ± 0.05 mg/mL. Solubility of Flu was analyzed in the presence of all ingredients of eye drop formulation. The results showed that solubility of Flu in both formulations was almost equal and did not show any significant difference. In the case of HP-γ-CD, solubility of Flu was not improved by adding any ingredients, data shown in Table 2.

DSC studies

Thermograms of Flu and its complexes with SBE-β-CD and HP-γ-CD are reported in Fig. 2. Flu showed an endothermic peak at 297 °C and endothermic events at 260 and 270 °C were obtained for its complexes with SBE-β-CD and HP-γ-CD, respectively. Also the isolated SBE-β-CD-Flu and HP-γ-CD-Flu complexes were shown an endothermic peak at about 90 °C.

Discussion

The aqueous solubility of Flu was increased in the presence of different CDs. This result demonstrated the complexation of Flu with CDs. As it was reported by Vianna et al. [21], the interaction of drug and CD was related to different

Table 1 Aqueous solubility of Flu in the presence of 5% w/v SBE-β-CD and different ingredients of eye drop (mean ± SD, $n = 3$)

Formulations	Aqueous solubility of Flu (mg/mL)
5% w/v SBE-β-CD	1.16 ± 0.04
5% w/v SBE-β-CD + HPMC	1.17 ± 0.06
5% w/v SBE-β-CD + Benzalkonium	1.03 ± 0.05
5% w/v SBE-β-CD + Phosphate buffer	0.70 ± 0.12
5% w/v SBE-β-CD + Borate buffer	1.34 ± 0.05
5% w/v SBE-β-CD + HPMC + Benzalkonium + Phosphate buffer	1.48 ± 0.02
5% w/v SBE-β-CD + HPMC + Benzalkonium + Borate buffer	1.42 ± 0.02

Table 2 Aqueous solubility of Flu in the presence of 5% w/v HP-γ-CD and different ingredients of eye drop (mean ± SD, $n = 3$)

Formulations	Aqueous Solubility of Flu (mg/mL)
5% w/v HP-γ-CD	0.43 ± 0.08
5% w/v HP-γ-CD + HPMC	0.45 ± 0.07
5% w/v HP-γ-CD + Benzalkonium	0.45 ± 0.08
5% w/v HP-γ-CD + Phosphate buffer	0.42 ± 0.10
5% w/v HP-γ-CD + Borate buffer	0.42 ± 0.03
5% w/v HP-γ-CD + HPMC + Benzalkonium + Phosphate Buffer	0.41 ± 0.01
5% w/v HP-γ-CD + HPMC + Benzalkonium + Borate Buffer	0.39 ± 0.01

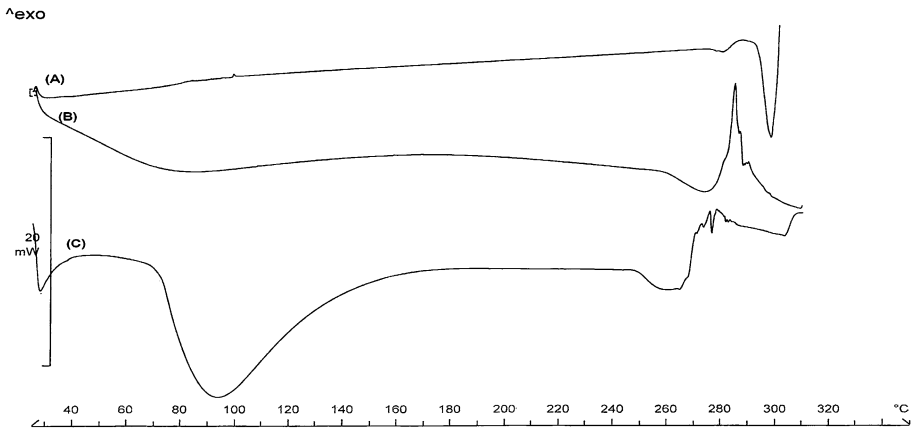

Fig. 2 DSC thermograms of (A) Flu, (B) HP-γ-CD-Flu complex and (C) SBE-β-CD-Flu complex

Table 3 Type of phase solubility diagram of Flu-CD inclusion complex, apparent inclusion complex stability constant and complexation efficiency (CE) value

Cyclodextrin	Diagram Type[a]	$K_{1:1}$ (M^{-1})[b]	R^2	Complexation efficiency (CE)[c]
α-CD	A_L	40.27	0.975	0.034
SBE-β-CD	A_L	2248.93[d]	0.991	1.911
HP-β-CD	A_L	786.66	0.971	0.668
HP-γ-CD	A_L	550.06	0.995	0.467
γ-CD	B_S	Not determined	Not determined	Not determined
β-CD	B_S	Not determined	Not determined	Not determined

[a] According to the Higuchi and Connors [20]

[b] Apparent stability constant

[c] Calculated according to the reference [3]

[d] Calculated from the linear range

parameters such as steric and hydrophobic relationship between host (CD) and guest (drug) molecules. Consequently, in the phase solubility study, different profiles were achieved in Flu-CD complexation. α-CD showed the least effect on the solubility of Flu (Table 3). Similar results were obtained by Larsen et al. [9], who showed that α-CD gave the weakest association constants with both prednisolone and 6α-methyl prednisolone. Also in the previous studies were showed that steroid with similar structure, hydrocortisone, can not penetrate the cavity of α-CD [22]. In the preliminary studies, phase solubility studies for some samples were done for 1 day and 1 week. Comparison of the solubility results showed that there were no significant differences between the results, so we considered the 24 h equilibrium time for the phase solubility studies (data not shown).

A linear phase solubility profile was observed for Flu and selected CDs such as HP β-CD, HP γ-CD, SBE β-CD and α-CD, suggesting the formation of 1:1 inclusion complex or at least complexes that are first order with respect to CD [10] but the association constant of each inclusion complex was different. Also the complexation efficiency (CE) proposed by Brewster and Loftsson [3] was presented in Table 3.

In the phase-solubility studies of β-CD and Flu, aqueous solubility increased with increase of CD concentration up to 5% w/v, after the plateau between 5 to 15% w/v, solubility declined. This profile could be related to restriction in β-CD solubility and precipitation of β-CD-Flu complex at higher concentration.

At the concentration of 5% w/v, γ-CD solubilized the Flu better than β-CD and the highest aqueous solubility among the non-substituted CDs was achieved by this CD at this concentration. This suggests that the larger cavity of γ-CD is more favorable for the complexation but in the case of γ-CD, aqueous solubility decreased by increasing the concentration of CD.

It was previously reported that the A-ring of hydrocortisone is able to enter inside the β-CD and γ-CD cavity, although γ-CD was shown to complex with this steroid more loosely compared to β-CD. Also, according to the reported association constants for β-CD- and γ-CD-prednisolone complexes by Laren et al. [9], β-CD displays a higher association constant compared to γ-CD.

The results of present study indicated that Flu solubility was increased more with cyclodextrin derivatives than native cyclodextrin. It is possible to relate this to high soluble structure of cyclodextrin derivatives. Also, derivatization of CDs may change the geometry of CD cavity, the properties and dimensions of the hydrophobic cavity and provide additional ionic, hydrogen and hydrophobic binding sites [9]. In the case of SBE β-CD, it was reported that derivatization of β-CD provides additional hydrophobic binding site for complexation [9, 23]. The phase solubility profile for SBE β-CD was observed to plateau out at concentrations of greater than 15% w/v CD. This represents the solubility limit of the SBE β-CD -Flu complex.

Among the CD derivatives, SBE β-CD showed the highest association constant. In the pervious studies, β-CD-prednisolone complex had the highest association constant while γ-CD-6α-methyl prednisolone complex showed the highest constant [9]. It was reported that the A-ring of steroids is the major site for drug-CDs complexation and modification in the D-ring only influenced the drug binding ability to a minor degree compared with the A-ring [9, 24]. The results of present study confirmed the previous results and also showed that the structural change in B-ring have the minor effect on CD complexation.

It was showed in the pervious studies that CDs increase solubility by inclusion [9, 10, 21] and non-inclusion complexation [25–28] through the formation of micellar structure. It has been shown that organic cations and anions can solubilize uncharged drug-cyclodextrin complexes that have limited aqueous solubility and it was confirmed that certain hydroxy acids and organic bases are able to enhance the complexation efficiency by formation of drug-cyclodextrin-acid or base complexes [10, 25, 26].

To evaluate the role of non-inclusion complexation on increasing solubility, in the previous studies water soluble polymers such as HPMC and anionic and cationic species such as sodium acetate and benzalkonium chloride were used [25, 27]. In the study of Loftsson and Frioriksdottir [29], the effect of β-CD on aqueous solubility of hydrocortisone was increased in the presence of HPMC (0.25% w/v) and sodium acetate (1% w/v) but in our previous study, aqueous solubility of CyA was decreased by increasing sodium acetate concentration [10]. However, in the present study, HPMC did not influence the Flu solubility but borate buffer improved the solubility. Phosphate buffer caused the dissociation of drug-CD complex and the solubility decreased. It can be due to medium effect such as increased ionic strength. Because it was reported that different mechanisms such as dilution, competitive displacement, protein binding, drug uptake by tissue, changing in ionic strength and temperature play important role in drug release from drug-CD complexes [30, 31].

DSC studies were used for characterization of Flu-CD complexes. The sharp endothermic transition at the DSC profile of Flu is corresponding to drug fusion peak. The board endothermic peak at about 90 °C in the thermogram of drug-CD complexes is due to CD structural water loss but movement of the endothermic peak of Flu may result from the formation of inclusion complexes between drug and two CDs tested.

Conclusion

The results of present study showed that it is possible to improve the aqueous solubility of Flu using CD complexation. Phase-solubility studies showed that SBE β-CD had a much greater effect on the solubility of Flu than other CDs. It was showed that in the formulation of lipophilic drug as ophthalmic solution using CD complexation, the impact different ingredients on aqueous solubility should be considered.

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