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Research paper

Estradiol sustained release from high affinity cyclodextrin hydrogels ☆

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Abstract

Hydrogels for loading estradiol and controlling its release were prepared cross-linking various cyclodextrins with ethyleneglycol diglycidylether. To select the more adequate cyclodextrins, estradiol solubility diagrams in water with β-cyclodextrin (βCD), methyl-β-cyclodextrin (MβCD), hydroxypropyl-β-cyclodextrin (HPβCD), and sulfobutyl-β-cyclodextrin (SBβCD) were made in absence and presence of hydroxypropyl methylcellulose (HPMC) applying or not autoclaving. Although all cyclodextrins showed enough complexation capability, the low solubility of βCD and the high anionic character of SBβCD hindered the cross-linking process, and these cyclodextrins were discarded for preparing hydrogels. Hydrogels prepared with MβCD (20%, 25%) or HPβCD (20%, 25%, and 30%), with or without HPMC 0.25%, absorbed 4–10 times their weight in water and loaded up to 24 mg estradiol per gram, which is 500 times greater than the amount of drug that can be dissolved in their aqueous phase. Positive linear correlation was found between the stability constant and the network/water partition coefficients of drug. The hydrogels sustained the release up to one week; the affinity of estradiol for the cyclodextrin units controlling the process, as shown by the negative correlation with the release rate constants. These results highlight the potential of cyclodextrin complexation for the development of hydrogels useful in loading hydrophobic drugs and controlling their release.

Keywords: Hydroxypropyl-β-cyclodextrin; Methyl-β-cyclodextrin; Sulfobutyl-β-cyclodextrin; Inclusion complexes; Hydrophobic drugs; Chemically cross-linked hydrogels; Controlled release

1. Introduction

Estradiol is the most potent natural estrogenic hormone and its main clinical use is in post-climacteric replacement therapy. For this purpose, a variety of oral, transdermal, subcutaneous, and intravaginal dosage forms have been developed [1,2]. Oral therapy is limited by the poor water solubility of this drug, its low stability in the upper part of the gastrointestinal tract, and its intensive first pass hepatic metabolism [3]. Therefore, in order to maintain a long term effective blood concentration, the delivered doses of estradiol must exceed several times those administered by other routes, which enhances the risks of adverse reactions and non-compliance by the patients [4]. Transdermal formulations, such as matricial or reservoir patches, can avoid these drawbacks, but usually require an oily or alcoholic medium to dissolve the drug [5–7]. Buccal and vaginal mucosa are also adequate for the absorption of steroids when administered as inserts, films or rings [1,4,8,9].

Aqueous physical gels containing drug-loaded vesicles (liposomes, niosomes, micelles, and microemulsions) have been extensively evaluated as topical and transdermal estradiol delivery systems [1,10–12]. Chemically cross-linked hydrogels may also offer interesting possibilities as estradiol dosage forms, administered by almost any route [13], if their limited ability for the direct loading of this poorly water-soluble drug is overcome. Attempts to load hydrogels involved a synthesis in the presence of estradiol, previously dissolved in ethanol [14], or its incorporation to

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hydrophobic regions of amphiphilic networks [15]. Cross-linked cyclodextrins that enable the combination of the hydrogel versatility with the complexation capability of cyclodextrins could be particularly useful [16–19]. Polymerized cyclodextrins maintain, or even promote, the complexation ability of the free cyclodextrins in solution [19,20].

In general, the stronger the binding constant of the drug–cyclodextrin complexes is, the slower the dissociation kinetics is. However, when solutions of drug–cyclodextrin complexes are diluted in the physiological fluids, the release of the drug is practically instantaneous. As a consequence, cyclodextrin solutions do not provide a sustained release and even a precipitation of drug can occur [21–23]. By contrast, in the case of the cyclodextrin hydrogels, the dilution phenomena are minimal since the cyclodextrin units are covalently attached to each other and the volume of water which can enter the hydrogel is limited by the own network. This should provide a microenvironment rich in cavities available to interact with the surrounding drug molecules. Consequently, delivery systems comprising chemically linked cyclodextrins offer considerable possibilities of achieving sustained release [17,18,24].

Cyclodextrin hydrogels are usually obtained by copolymerization of cyclodextrin monomeric derivatives with other acrylic or vinyl monomers [17–19,24]. In order to avoid the important drawbacks of the chemical modification of cyclodextrins (low reproducibility of the synthesis or residual toxic monomers), we previously developed a direct procedure to obtain HPβCD hydrogels using diglycidylethers as cross-linking agents. This type of cross-linkers is able to react directly with the hydroxyl groups of cyclodextrin under mild conditions. The resultant hydrogels have been shown to be able to efficiently load and control the release of an amphiphilic drug, such as diclofenac [25].

The aim of this work was to prepare hydrogels of different cyclodextrin varieties, cross-linked with ethyleneglycol diglycidylether (EGDE), and to evaluate their loading capability and their potential as estradiol aqueous-based sustained delivery systems. The ability of some cyclodextrins to complexate estradiol and increase its solubility in physiological environments [26–29] suggests that cyclodextrin hydrogels may present a high affinity for this drug. First, the complexation of estradiol with various natural and semi-synthetic cyclodextrins was evaluated in water, in the presence and absence of hydroxypropyl methylcellulose (HPMC), which was chosen as the potential promoter of the affinity. Several hydrogels were prepared and their behavior is discussed on the basis of the cyclodextrin affinity for the drug.

2. Materials and methods

2.1. Materials

β-Cyclodextrin (βCD) and methyl-β-cyclodextrin (MβCD; KLEPTOSE® CRYSMEB; 4 methyl groups per native cyclodextrin molecule, M.S. 0.57) were provided by Laisa-Roquette (Barcelona, Spain); hydroxypropyl-β-cyclodextrin (HPβCD; D.S. 4.6) by Janssen Pharmaceutica Products (Belgium); and sulfobutyl-β-cyclodextrin (SBβCD; hepta-substituted, M.S. 1) by CyDex (Kansas, USA). Hydroxypropyl methylcellulose Methocel® K4M (HPMC, batch MM87050902K) was provided by Dow Stade GmbH (Germany); 17β-estradiol and sodium dodecyl sulfate (SDS) were from Sigma–Aldrich (Spain); ethyleneglycol diglycidylether (EGDE) (50% w/w in water) was from Fluka Chemie GmbH (Germany). Purified water with a resistivity above 18.2 MΩ cm^{-1} was obtained by reverse osmosis (MilliQ®, Millipore Spain). All other reagents were of analytical grade.

2.2. Solubility studies

Suspensions of estradiol were prepared (in quadruplicate) by adding an excess of drug to cyclodextrin or cyclodextrin/0.25% w/v HPMC aqueous solutions. The βCD concentration ranged from 0% to 0.9% (w/v). The concentration of the βCD derivatives was up to 5%. Some of these suspensions (two replicates) were autoclaved (Raypa AES-1219, Spain) at 121 °C for 20 min. The autoclaved and non-autoclaved suspensions were shaken at 25 °C and 50 rpm for 5 days, and then filtered through 0.22 μm cellulose acetate membranes (Millipore®, Ireland). Drug concentration was determined by UV spectrophotometry (Agilent 8453, Germany) at 280 nm ($E_{1\%\ 1\ cm} = 67.59$).

The apparent stability constants of the drug–cyclodextrin 1:1 complexes were estimated from the A_L-type diagrams using the following expression [30]:

$$K_{1:1} = \frac{m}{S_0(1-m)} \quad (1)$$

where m is the slope of the plot and S_0 is estradiol solubility in water [31]. The apparent stability constants from the B_S and A_N type diagrams were also estimated using Eq. (1) by considering only the initial linear section of the plots. The ratio between free and complexated cyclodextrin molecules in solution was directly estimated from the solubility diagrams assuming that the stoichiometry of the complexes is 1:1.

2.3. Synthesis of cyclodextrin hydrogels

HPβCD (20, 25 or 30% w/v) and MβCD (20 or 25% w/v) were dissolved in freshly prepared 0.2 M NaOH solutions. The solutions were divided in 5 ml portions and HPMC was added to some, up to a final concentration of 0.25% w/v. Once homogenized, EGDE (2 ml of 50% w/w water solution) was added to each dispersion and stirred for 2 min at 20 °C. The systems were immediately transferred to test tubes (8.6 mm internal diameter), which were hermetically closed and kept at 50 °C for 12 h. After cooling down, the HPβCD, MβCD, HPβCD-co-HPMC, and MβCD-co-HPMC hydrogels were carefully removed from the moulds and immersed in ultrapure water for

12 h to swell. After, they were transferred to a 10 mM HCl solution for 12 h to neutralize the alkaline medium and, then, immersed in water once again. Finally, cylindrical pieces of each gel (4–5 mm thickness) were cut and maintained in water.

2.4. Characterization of the hydrogels

2.4.1. Swelling studies

Dry samples of each hydrogel (about 58 mg, 5 mm diameter and 1.5 mm thickness) were immersed in 10 ml of water and weighed after pre-established time periods. The total amount of water absorbed was estimated using the expression:

$$Q = (W_\infty - W_0)/W_0 \quad (2)$$

where W_0 is the weight of the hydrogel after being dried at 40 °C and W_∞ is the weight of the fully swollen hydrogel.

The kinetics of water uptake was characterized by fitting the data obtained up to 60% of the final content in water to the following empirical equation [32]:

$$W_t/W_\infty = K_w t^{0.5} \quad (3)$$

where W_t is the amount of water absorbed at time t and K_w is a rate constant.

2.4.2. Estradiol loading

Cylindrical pieces of each hydrogel (4–5 mm thickness) were placed in vials containing aqueous suspensions of estradiol (15 mg in 10 ml), which were put in a bath at 25 °C and subjected to 50 oscillations per minute for 1 week; some being firstly autoclaved for 20 min at 121 °C. To determine the amount loaded, hydrogels were immersed in 15 ml of 0.3% w/v SDS solutions that were replaced every second day, for approximately 1 week, and the estradiol concentration in the washing medium was determined spectrophotometrically ($\lambda = 280$ nm; Agilent, Germany). The amount of estradiol loaded was estimated as the total estradiol released to the washing medium. Experiments were carried out in quadruplicate.

2.4.3. Estradiol release

Estradiol-loaded hydrogels were rinsed with water and immersed in 15 ml SDS (0.3% w/v) solution at room temperature, under sink conditions. The amount of estradiol released was measured spectrophotometrically ($\lambda = 280$ nm) in periodically taken samples and again placed in the same vessel so that the liquid volume was kept constant. The release profiles in the first 8-h period were characterized by fitting the Higuchi equation [33]:

$$M_t/M_\infty = K_H t^{0.5} \quad (4)$$

where M_t and M_∞ represent the amounts of estradiol released at time t and after infinite time, respectively. The experiments were carried out in quadruplicate.

3. Results and discussion

In order to carry out the study, βCD and its derivatives were chosen since dimensions of the cavity of this cyclodextrin enable effective complexation of estradiol [29]. Using different derivatives, the influence of the substitution characteristics on the estradiol complexation in solution and, thus, on the loading/controlled release performance of the hydrogels can be analyzed. Compared to βCD the main advantage of the derivatives is their greater aqueous solubility, which enables highly soluble complexes to be obtained [23,26]. This is an important issue since the preparation of cyclodextrin concentrated solutions is required to allow the cross-linking agent to efficiently promote intermolecular bonds during hydrogel formation. In addition to the most common hydroxypropylated derivative (HPβCD), the polyanionic SBβCD and a methylated derivative MβCD were used. SBβCD presents sodium sulfonate substituents separated from the hydrophobic cavity by a butyl ether spacer group. This cyclodextrin can form strong complexes with poorly water soluble drugs owing to an extended hydrophobic cavity and an extremely hydrophilic exterior surface [28]. MβCD is a low substituted non-ionic cyclodextrin that shows enhanced water solubility despite its deeper and more hydrophobic cavity compared to βCD. Therefore, it is also particularly adequate to host hydrophobic molecules [34,35]. All these βCD derivatives have been shown to be safe when orally and some parenterally administered, and exhibit a significantly lower nephrotoxicity compared to the parent cyclodextrin [19].

3.1. Cyclodextrin–estradiol complexes in solution

Phase-solubility diagrams obtained in the presence of βCD were Bs type [30] which is indicative of the formation of inclusion complexes with limited water solubility. The 0.2% βCD solutions enhanced estradiol solubility 34-fold. Further increases in the βCD concentration did not significantly enhance the solubility. By contrast, phase solubility diagrams obtained with MβCD, HPβCD and SBβCD were A_L type with a slope lower than 1, which is characteristic of the formation of 1:1 mol–mol complexes (Fig. 1). Estradiol solubility ranked as follows: MβCD > HPβCD > SBβCD; with increments of 158-, 100- and 76-fold, respectively, when cyclodextrin concentration in solution was 1% (Table 1). The stability constants of the complexes (Table 2) were calculated according to Eq. (1) from values of the slope of the phase-solubility diagrams. The close values of the stability constants obtained with βCD, SBβCD and MβCD indicate the similarity of their complexation capacity at low cyclodextrin concentrations.

The complex stability constants also provide information about the proportion of cyclodextrin molecules that remain free in the drug/cyclodextrin solution, which is of great practical interest [31,36]. We found that one out of three molecules of βCD, MβCD or SBβCD in solution forms a water-soluble complex with estradiol; this relation

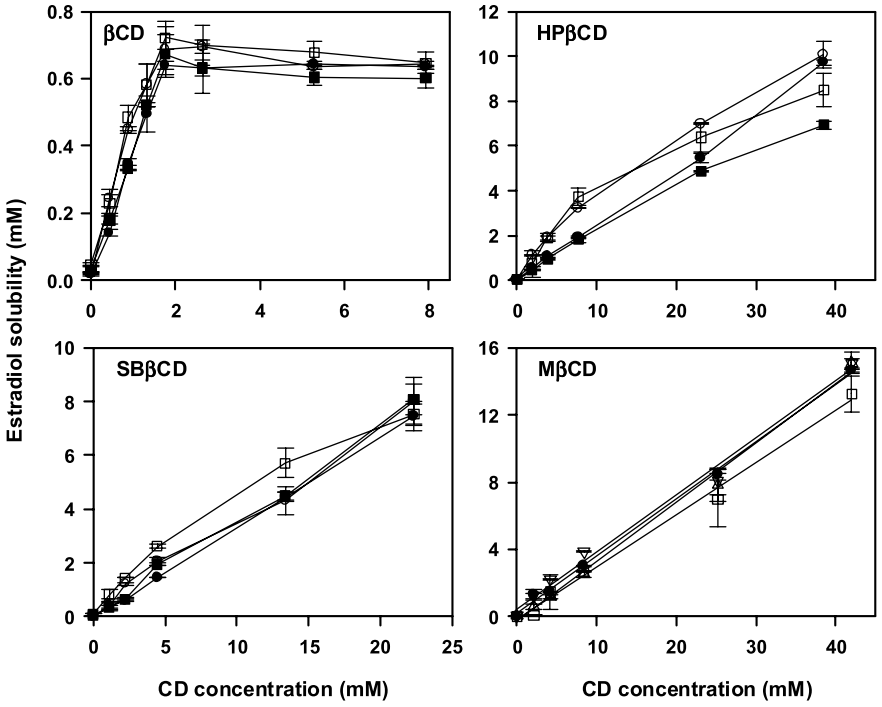

Fig. 1. Solubility diagrams of estradiol in cyclodextrin solutions before (●) and after autoclaving (○), or in cyclodextrin/HPMC (0.25%) solutions before (■) and after autoclaving (□).

Table 1
Solubility of estradiol in cyclodextrin (Sc) or cyclodextrin/0.25% HPMC solutions (Sc-p) at 25 °C

Cyclodextrin	Sc (mM)	Sc* (mM)	Sc-p (mM)	Sc-p* (mM)	Sc*/Sc	Sc-p/Sc	Sc-p*/Sc
βCD (0.2%)	0.64	0.69	0.67	0.72	1.07	1.05	1.13
HPβCD (1%)	1.91	3.23	1.81	3.72	1.69	0.94	1.95
MβCD (1%)	3.01	2.67	2.51	3.86	0.89	0.84	1.28
SBβCD (1%)	1.45	2.07	1.95	2.62	1.43	1.34	1.81

Estradiol solubility in water was determined to be 0.019 mM.
* Autoclaved samples.

Table 2
Apparent stability constants, $K_{1:1}$ (mM^{-1}), of estradiol–cyclodextrin inclusion complexes in solution prepared under different thermal treatments

System	Non-autoclaved	Autoclaved
βCD	32.5 (4.2)	32.2 (7.8)
βCD + HPMC	31.7 (4.5)	31.8 (0.7)
HPβCD	17.4 (0.1)	36.4 (0.1)
HPβCD + HPMC	11.7 (0.4)	50.2 (4.5)
MβCD	27.2 (0.9)	23.1 (0.9)
MβCD + HPMC	28.9 (2.3)	27.9 (0.1)
SBβCD	26.6 (2.0)	27.0 (2.1)
SBβCD + HPMC	29.2 (3.4)	66.2 (2.5)

Mean values and, in brackets, standard deviations ($n = 3$).

decreasing to one out of four cyclodextrins in the case of HPβCD. Therefore, MβCD and SBβCD appear as the most effective estradiol solubilizers and are, *a priori*, more suitable to prepare liquid formulations with a low cyclodextrin proportion.

The enhancement of the complexation capability by the incorporation of hydrophilic polymers and the application of thermal treatments, which has received a great attention over last few years [36], can be particularly relevant for the optimization of the hydrogels. Thus, the effects of adding HPMC (0.25%) and/or applying autoclaving on estradiol solubility were evaluated. Neither the complexation efficiency nor the solubility of estradiol was significantly modified in the βCD or MβCD systems (Table 2). By contrast, complexation with SBβCD was quite susceptible to the combination of both factors; the enhancement in complexation efficiency resulted in an increase in estradiol solubility, with more than half of the total cyclodextrins in solution forming complexes with estradiol. Autoclaving was particularly effective at increasing both the complexation efficiency and the solubility of estradiol in HPβCD solutions, in particular when HPMC was present. In the latter case nearly as many molecules of cyclodextrin as those complexed with estradiol were free.

3.2. Cyclodextrin hydrogels

3.2.1. Preparation and water sorption

The influence of different variables on the synthesis and properties of EDGE cross-linked HPβCD hydrogels has been previously evaluated in detail [25]. According to those studies, alkaline pH and mild temperature are required to form systems with the consistency required for easy handling, but also with enough elasticity to avoid damage to surrounding biological tissues once administered. Similarly to HPβCD hydrogels, the MβCD hydrogels with or without HPMC were formed in less than six hours, but attempts to prepare SBβCD hydrogels following the same protocol failed. This can be explained by the high degree of substitution of this hepta-substituted derivative (few OH groups remain in the cyclodextrin structure available to interact with EDGE) and by the repulsions among the cyclodextrin units owing to the ionized sulfonate groups. Therefore, SBβCD had to be discarded for the following studies.

Once immersed in water, the MβCD, HPβCD, HPβCD-co-HPMC and MβCD-co-HPMC hydrogels swelled from 8.6 up to around 12 mm in diameter, showing a smooth and continuous surface. This behavior is characteristic of a homogeneously cross-linked network which does not lose material by disentanglement of the polymer chains. This was expected taking into account the proportion of EGDE used in the synthesis, which leads to 60% of the hydroxyl groups of the cyclodextrins to participate in the cross-linking bridges [25].

The dried hydrogels behaved as superabsorbing systems, being able to uptake in few hours 6–10 times its weight in water (Fig. 2). The final degree of swelling was slightly lower for HPβCD hydrogels than for those made of MβCD. The lower swelling degree and the brittle character of HPβCD(30%)-co-HPMC(0.25%) hydrogels are explained by the attainment of a higher cross-linking density.

The amount of sorbed water depended linearly on $t^{1/2}$ ($r^2 > 0.99$) for all the hydrogels studied; i.e. Fickian behavior was maintained in spite of the swelling of the network [32]. The swelling rate constants (Table 3) indicate that water molecules, as well as other small size molecules, can easily penetrate the structure of the cyclodextrin network.

3.2.2. Estradiol loading

Table 4 shows the results of the loading experiments. HPβCD hydrogels that underwent autoclaving loaded twice the estradiol that the corresponding non-autoclaved ones did. This effect is in agreement with the results of the solubility study (Fig. 1). As it could be also expected, hydrogels containing MβCD showed, in general, greater complexation capacity, and the autoclaving had modest and random influence (loading only slightly decreased for MβCD hydrogels but increased for MβCD-co-HPMC ones). Considering the high potency of the drug, which is orally administered in doses of 1–2 mg/day or as patches

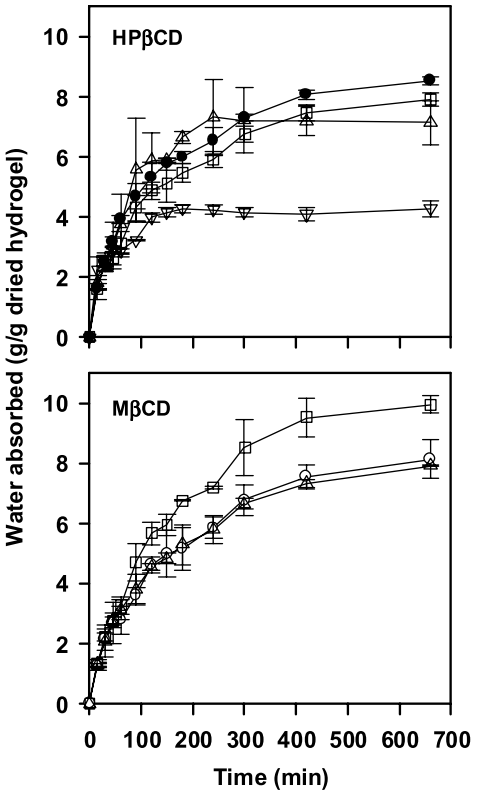

Fig. 2. Swelling profiles in water of dry HPβCD or MβCD hydrogels prepared with 20% cyclodextrin (●), 20% cyclodextrin–0.25% HPMC (□), 25% cyclodextrin–0.25% HPMC (△), and 30% cyclodextrin–0.25% HPMC (▽).

Table 3
Mean values of water sorption constants (K_w) of the hydrogels at 25 °C

Hydrogel		K_w ($min^{-1/2}$)	r
MβCD	20%	0.042	0.989
	20% +HPMC 0.25%	0.043	0.983
	25% +HPMC 0.25%	0.046	0.995
HPβCD	20%	0.050	0.995
	20% +HPMC 0.25%	0.047	0.988
	25% +HPMC 0.25%	0.064	0.995
	30% +HPMC 0.25%	0.093	0.958

The variation coefficients were below 5%, ($n = 3$).

of 2–5 mg/week [4], the weight of a suitable formulation once estradiol is included in the cyclodextrin hydrogel would be in the range of 50–200 mg. The lowest loading yield of the HPβCD(30%)-co-HPMC(0.25%) hydrogel is probably related to its lowest degree of swelling; the low mesh size of this hydrogel hindering drug diffusion through the network.

The amount loaded just by a simple equilibrium between the aqueous phase of the network and the loading solution can be estimated using the following equation [37]:

$$\text{Loading (aqueous phase)} = (V_s/W_p) \times C_0 \quad (5)$$

where V_s is the volume of water sorbed by the hydrogel, W_p is the dried hydrogel weight, and C_0 is the concentration of

Table 4
Estradiol load (mg/g of dry hydrogel) and hydrogel/water partition coefficient ($K_{N/W}$) obtained when hydrogels were loaded in a drug suspension, and release rate constant (K_H) values in 0.3% SDS solution

Hydrogel	Non-autoclaved				Autoclaved			
	Load (mg/g)	$K_{N/W}$	CD unit: estradiol (molar ratio)	K_H (% $h^{-1/2}$)	Load (mg/g)	$K_{N/W}$	CD unit: estradiol (molar ratio)	K_H (% $h^{-1/2}$)
20% MβCD	17.03 (0.01)	3285	6.7	6.70 (0.25)	13.43 (0.01)	2590	8.6	11.39 (0.29)
20% MβCD + HPMC	18.73 (0.01)	3612	6.1	9.12 (0.60)	18.22 (0.01)	3514	6.4	14.23 (0.12)
25% MβCD + HPMC	16.31 (0.01)	3146	7.1	10.15 (0.33)	24.70 (0.02)	4769	4.7	8.28 (0.12)
20% HPβCD	7.71 (0.01)	1482	13.6	9.89 (0.39)	19.31 (0.01)	3726	5.5	6.24 (0.12)
20% HPβCD + HPMC	10.29 (0.01)	1982	10.2	11.37 (0.42)	22.04 (0.01)	4255	4.8	6.64 (0.16)
25% HPβCD + HPMC	9.61 (0.01)	1852	10.9	11.20 (0.54)	13.37 (0.01)	2579	7.9	8.22 (0.32)
30% HPβCD + HPMC	3.21 (0.01)	616	32.6	16.01 (1.85)	6.33 (0.01)	1220	16.5	9.50 (0.37)

Mean values and, in parentheses, standard deviations ($n = 4$).

drug in the loading solution. Since estradiol solubility is 5.17 mg/l (obviously in the suspension this concentration should remain constant) and the hydrogels can uptake 6–10 times its weight in water (6–10 ml/g), the maximum amount of estradiol that could be loaded in the aqueous phase of the hydrogel should be in the range 0.031–0.051 mg/g. This value is of a mean of 500 times lower than that presented by the hydrogels. Therefore, most drug has to be hosted by the cyclodextrin units. In the hydrogels, cyclodextrin unit–estradiol molar ratio ranged between 4.7 and 13.6, except for HPβCD(30%)-co-HPMC(0.25%) hydrogel (Table 4).

To estimate the affinity of the drug for the network, the partition coefficient, $K_{N/W}$, between the polymer network and the drug loading solution was calculated as follows [37]:

$$\text{Loading (total)} = [(V_s + K_{N/W}V_p)/W_p] \times C_0 \quad (6)$$

where V_p is the volume of dried polymer and the other symbols maintain the meaning of Eq. (5). The values of $K_{N/W}$ (Table 4) clearly prove that all MβCD hydrogels and the autoclaved HPβCD hydrogels present a remarkably high affinity for estradiol. A strong correlation between the $K_{N/W}$ values and the $K_{1:1}$ stability constant was observed (Fig. 3). This finding clearly proves the essential role of the cyclodextrins in the uptake of estradiol.

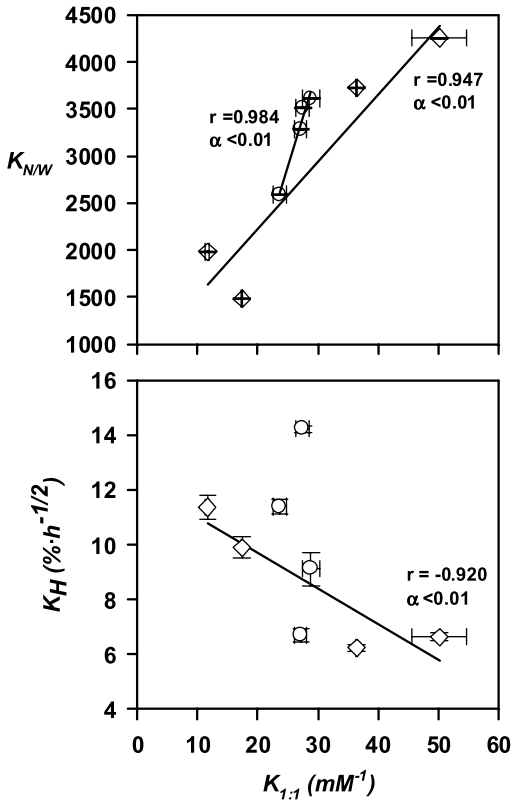

Fig. 3. Dependence of network/water partition coefficient ($K_{N/W}$) and of the release rate constant (K_H) of estradiol for HPβCD- (open diamonds) and MβCD-based hydrogels (open circles) on the estradiol–cyclodextrin stability constants ($K_{1:1}$).

3.2.3. Estradiol release

Fig. 4 shows the estradiol release profiles in SDS 0.3% solution, which is the medium recommended in USP27 for low solubility drugs. Although all hydrogels were able to sustain the release for several days, remarkable differences in the kinetics were observed. In general, hydrogels containing HPMC released the drug faster; the highest release rates being observed for HPβCD hydrogels loaded without applying autoclaving. The release rate constants obtained by fitting Eq. (4) ($r^2 > 0.99$) to the HPβCD hydrogels data showed a strong negative correlation with the estradiol–cyclodextrin stability constants estimated from the solubility diagrams (Fig. 3). That is to say, the greater the affinity, the lower the release rate. MβCD hydrogels showed a lag time of 45–60 min, which is in agreement with the high stability constant values obtained for this cyclodextrin variety. Once the release started, no correlation between the release rate constants and the stability constants was found, because under all conditions tested the stability constant values were similar. The faster estradiol release observed for the autoclaved hydrogel consisting of MβCD(20%)-co-HPMC(0.25%), compared to the hydrogel prepared without HPMC or to the hydrogel consisting of MβCD(25%)-co-HPMC(0.25%), can be explained by its lowest proportion in cyclodextrin by weight unit of dry hydrogel. In summary, these findings highlight that the drug-cyclodextrin complexation determines the affinity of

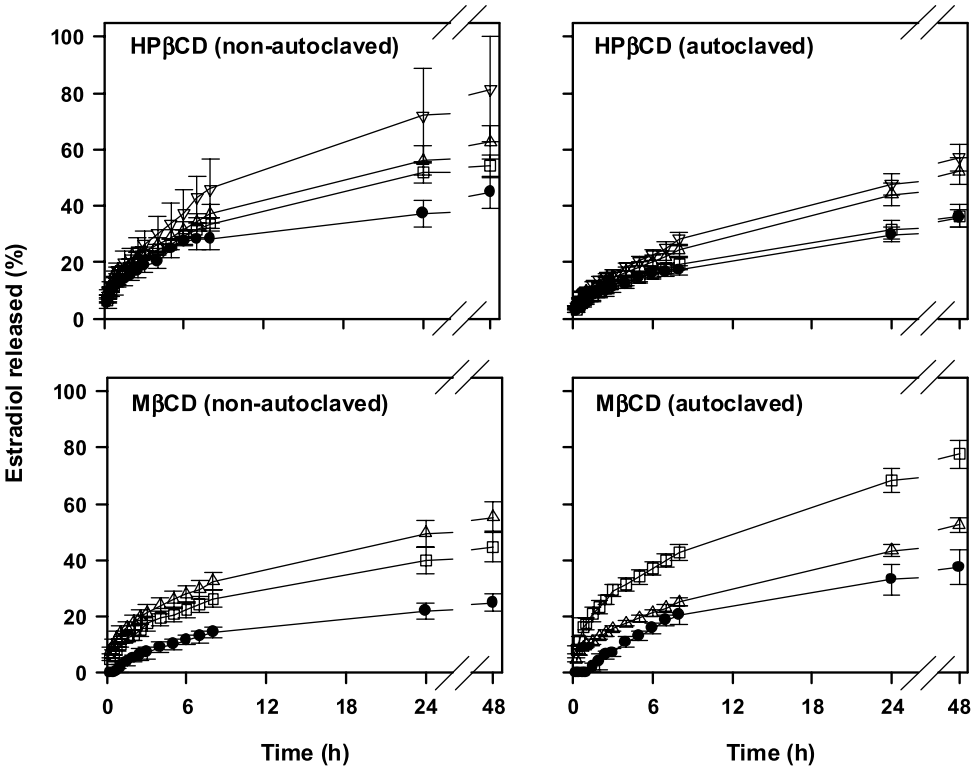

Fig. 4. Estradiol release profiles from HPβCD or MβCD hydrogels prepared with 20% cyclodextrin (●), 20% cyclodextrin–0.25% HPMC (□), 25% cyclodextrin–0.25% HPMC (Δ), and 30% cyclodextrin–0.25% HPMC (▽), which were previously loaded in aqueous suspensions of estradiol.

the drug for the hydrogel and plays the main role in the control of the release.

4. Conclusions

Estradiol presents a higher affinity for βCD, MβCD and SBβCD than for HPβCD. The affinity for this last cyclodextrin is greatly enhanced when HPMC (0.25%) is added to the medium and the system is autoclaved. The application of a one-step cross-linking with EGDE, under mild conditions, enabled the formation of MβCD and HPβCD hydrogels. By contrast, the low solubility of βCD and the high anionic character of SBβCD hindered obtaining hydrogels. Hydrogels can absorb 4–10 times their weight in water, depending on their cyclodextrin content and hydrophilicity. The estradiol loading was driven by the interaction of the drug with the cyclodextrin network, and a positive correlation was found between the stability constant, estimated from the phase solubility diagrams, and the network/water partition coefficients of estradiol. The high loading ability of the hydrogels may make the incorporation of a therapeutic dose of estradiol in a small piece of hydrogel possible, the release being sustained for several days owing to the affinity of the cyclodextrin for the drug.

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