Preparation, Characterization, and Drug Release Properties of Poly(2-hydroxyethyl methacrylate) Hydrogels having β-Cyclodextrin Functionality

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Received 8 May 2007; accepted 21 January 2008
DOI 10.1002/app.28284
Published online 17 April 2008 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: A new β-cyclodextrin urethane-methacrylate monomer was synthesized from the reaction of toluene-2,4-diisocyanate, 2-hydroxyethyl methacrylate (HEMA), and β-cyclodextrin (β-CD). Based on inclusion character of β-CD, a series of hydrogels were prepared by irradiating the mixtures of β-cyclodextrin urethane-methacrylate monomer (β-CD-UM), poly(ethylene glycol) diacrylate (PEG-DA), HEMA, and the photoinitator. Gel percentages and equilibrium swelling ratios (%) of hydrogels were investigated. It was observed that the equilibrium-swelling ratio increased with increasing β-CD-UM content in the hydrogel composition. SEM images demonstrated that β-CD-UM based hydrogel have porous fractured surface. In this study four different drug molecules, salicylic acid, sulfathiazole, rifampicin, and methyl orange as model drug, which are capable of forming inclusion complexes with β-CD were chosen. For sulfathiazole and rifampicin, the drug loadings are very low (0.04 and 0.008 mmol/g dry gel), whereas methyl orange and salicylic acid drug uptakes are found as 0.15 and 0.18 mmol/g dry gel, respectively. The incorporation of β-CD-UM comonomer into the gel slightly reduces the methyl orange and salicylic acid releases. However, a significant enhancement was achieved in the case of sulfathiazole delivery. It can be concluded that the inclusion complex formation capability of β-CD moiety increases the drug release by improving the aqueous solubility of hydrophobic drugs. On the other hand, in the case of hydrophilic drugs, the drug release retards by forming strong drug-β-CD complex and reducing the drug diffusivity. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 109: 1360–1368, 2008

Key words: β-cyclodextrin; photoinitiation; drug release; inclusion complex; hydrogel

INTRODUCTION

The hydrogels represent an important class of biomaterials in biotechnology and medicine. Their biocompatibility allows them to be considered for medical applications, whereas their hydrophilicity can import desirable release characteristics to controlled and sustained release formulations.[1]

Although hydrogels are available in various physical forms, such as discs, powders, or microspheres, they are generally glassy in the dehydrated state, but swell to become elastic gels upon water absorption. In drug delivery applications, the entrapped drug diffuses through the swollen network into the surrounding aqueous medium.[2–4] Various characteristics including gel structure, reactive sites, and crosslinking degree are considered for describing the overall performance of hydrogels in drug release applications. Moreover, some other factors, namely gel-drug interactions, still play an important role in determining release kinetics. In particular, the modification of the drug mobility through the swollen polymer can be used to modulate release.[5] One of the possible strategies is the introduction of a third component into the release device, which is able to decrease the effective mobility of the drug in a controlled way.

It is well-known that cyclodextrins (CDs) possess remarkable ability to include a wide range of guest molecules via noncovalent interactions into their hydrophobic cavities.[6–8] The ability to form inclusion complexes depends on the size and polarity of the host molecule. This unique behavior leads CDs to have wide spread applications in the biomedical and pharmaceutical fields.[9–12] It is found that the incorporation of the CDs into polymeric drug release systems could change the drug-polymer interactions and as a result, the mechanisms of drug release may be modified.[13–16]

Among CDs, β-CD and its derivatives are the first choices because of their suitable cavity sizes. It has 21 hydroxyl groups with 7 primary and 14 secondary hydroxyls. All of these hydroxyl groups are available as starting points for structural modifications. Previously Sreenivasan reported the coupling of β-CD to polyurethane using 2,4-toluene diisocya-

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Contract grant sponsor: Marmara University, Commission of Scientific Research Project; contract grant number: FEN-YLS-290506-0123.

nate as a coupling agent.[17] In various studies, β-CD conjugation to polymeric supports was also investigated by using hexamethylene isocyanate as coupling agent.[18] In recent years, many research efforts were made in bonding CD to polymerizable vinyl monomers as pendant groups. However arising from the presence of multiple hydroxyl moieties in the parent CD, mostly synthesis of multivinyl substituted CD monomers have been reported.[19,20] These multifunctionalized CDs may act as suitable crosslinkers for preparing hydrogels. Recently new monovinyl CD monomers were also reported that may be used in preparation of linear CD-containing polymers.[21] Complexation with CDs provides a way to increase the solubility, stability and bioavailability of drugs. Pinto et al. reported the Benzocaine-CD complex formation and its effects on Benzocaine solubility and its potential use in infiltrative anesthesia.[22] In another study, Liu and Zhu investigated inclusion complex of slightly water-soluble drug prazosin hydrochloride with CD. The phase solubility profiles indicated that a complex with 1 : 1 molar ratio was formed and also enhancement of the solubility of drug was observed.[23] Rodriguez-Tenreiro et al. demonstrated that because of the high loading ability of ethylene glycol diglycidyl ether-based hydrogels, the incorporation of a therapeutic dose of estradiol in a small piece of hydrogel was possible. The sustained release took place according to the affinity of the CD for the drug.[24]

UV curable hydrogels can be preferred when fast curing rate, temporal control over polymerization, and low heat production are demanded. In this study, a novel methacrylate functionalized β-CD monomer was synthesized and further used as a comonomer for the synthesis of novel UV-curable hydrogels composed of HEMA and PEG-DA. The influence of methacrylate functionalized β-CD monomer on the equilibrium swelling behavior was investigated. In addition, potential application of the novel hydrogels as drug carrier was evaluated using rifampicin, salicylic acid, sulfathiazole, and methyl orange as model drug with various solubilities and complexing abilities. Rifampicin was chosen because it is the most effective drug against bacteria called *Mycobacterium tuberculosis* and its poor solubility in water causes incomplete cure. Similarly sulfa drugs are used in the prevention and treatment of bacterial infections. On the contrary, hydrophilic drugs were chosen just for comparison.

EXPERIMENTAL

Materials

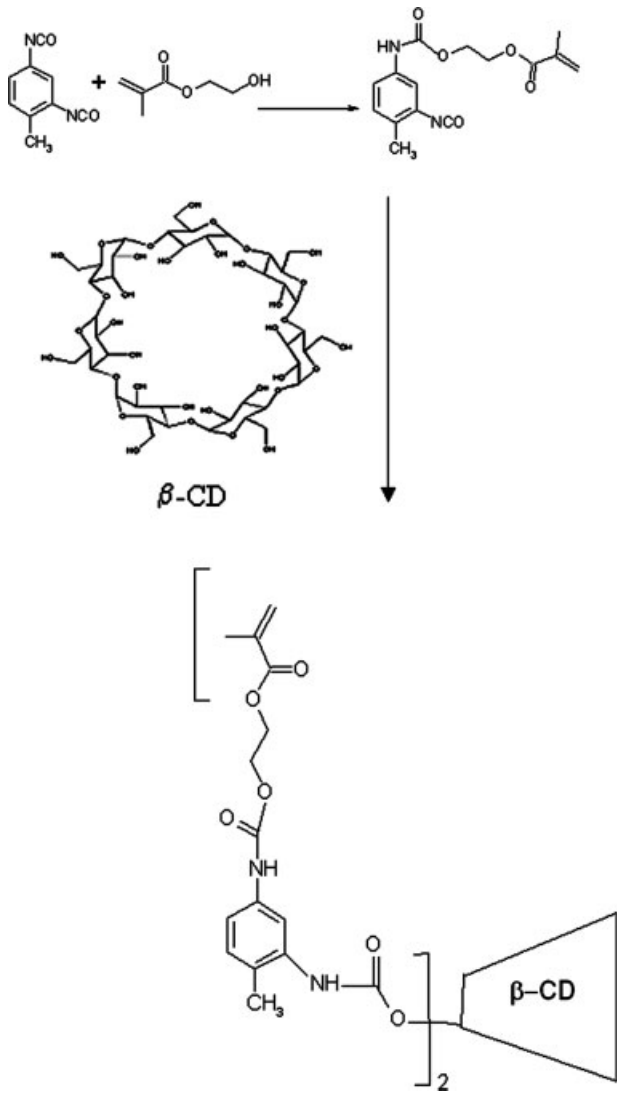
β-cyclodextrin, toluene-2,4-diisocyanate (TDI), 2-hydroxyethyl methacrylate (HEMA), and disodium phosphate ($Na_2HPO_4 \cdot H_2O$) were obtained from Fluka Chemie GmbH, Buchs, Switzerland. Triphenyl phosphine (PPh_3), monopotassium phosphate (KH_2PO_4), salicylic acid (SA), and methyl orange (MO) were purchased from Merck, Darmstadt, Germany. Poly (ethylene glycol) diacrylate (PEG-DA; MW: 258 g/mol) and sulfathiazole (ST) were obtained from Aldrich, Milwaukee, WI, USA. The photoinitiator Irgacure-184 (Irg-184) was kindly supplied by Ciba-Geigy Specialty Chemicals, Turkey. Dibutyltin dilaurate (Henkel Chemical Company) was used as a catalyst. Rifampicin (RIF) was a gift from Kocak Ilac, Turkey. All other chemicals were analytical reagent grade.

Characterization

FTIR spectrum was recorded on Shimadzu 8300 FTIR Spectrometer. ^{1}H-NMR spectrum was obtained by using a Bruker AC 200 L spectrometer operated at 200 MHz. ^{13}C CPMAS NMR was recorded on using a Varian Unity Inova spectrometer operated at 500 MHz. SEM imaging of the hydrogels was performed on a SEM JEOL JSM-5910 LV. The SEM specimens were prepared by lyophilization at −80°C and the dehydrated samples were freeze fractured in liquid nitrogen and applying a gold coating of ~ 300Å. Drug release was determined spectrophotometrically by using a Shimadzu 1601 model UV-spectrophotometer.

Synthesis of β-cyclodextrin urethane-methacrylate

The synthesis of methacrylate functional β-CD monomer (β-Cyclodextrin urethane-methacrylate) was carried out by two-step addition mechanism. A 250-mL three-neck flask equipped with a mechanical stirrer, nitrogen inlet, pressure equalized dropping funnel was immersed in an ice bath and charged with 1.93 g (0.011 mol) TDI and 0.00875 g triphenyl phosphine. Then HEMA (1.43 g, 0.011 mol) was added from a dropping funnel to the vigorously stirred TDI for 15 min. Then the mixture was stirred and allowed to react for additional 1 h. The obtained urethane-methacrylate was transferred into a dropping funnel for further reaction. In the second step, 12.5 g (0.011 mol) β-CD was dissolved in 42.5 mL dry DMF and placed into a three-neck flask. The urethane-methacrylate was introduced to the β-CD solution drop wise addition at room temperature under N_2 atmosphere. Three drops of dibutyltin dilaurate (T-12) were added as a catalyst. The reaction was carried out at room temperature for 1 h, 40°C for 2 h, respectively. Then the product was poured into the distilled water and the monomer was precipitated as a white solid. The synthesized monomer dried in vacuum at 35°C. Finally, the resulting monomer was



Scheme 1 Synthesis of urethane-methacrylate functionalized β-CD monomer.

analyzed by FTIR. Disappearance of the characteristic —NCO peak at 2275 cm^{-1} in the FTIR spectrum confirmed that the reaction was completed. A representation of this reaction is shown in Scheme 1.

^{1}H-NMR ($CDCl_3$): δ 7.15–8.2 ppm (aromatic protons), 4.3 ppm (—CH_2—O—), 5.6–6.2 ppm (CH_2=CCH_3—), 1.8–2.0 ppm (—CH_3), 3.5–3.9 ppm (β-CD protons), 3.0 ppm (—CH_2— β-CD).

^{13}C CPMAS-NMR: δ162–163 (C=O acrylate and carbamate), 143 (=CCH_3), 127 (=CH_2), β-CD signals (103(C-1), 81 (C-4), 73(C-2,3,5), 60 (C-6), 40 (—CH_2), 31 (—CH_3).

Preparation of β-cyclodextrin based hydrogels

The hydrogels based on β-cyclodextrin urethane-methacrylate, HEMA, and PEG diacrylate were prepared by free radical crosslinking copolymerization. The gels were prepared by UV-curing technique as follows. HEMA, β-cyclodextrin urethane-methacrylate, and PEG-diacrylate mixture were prepared with various compositions. The feed compositions are given in Table I.

Before UV-curing process, the monomer mixture was purged with nitrogen gas for 15 min to eliminate dissolved oxygen in the system. Then, the total mixture was transferred to silicone molds with 10 × 40 × 2 mm in size. To prevent the inhibiting effect of oxygen, mixture in the mold was covered by a transparent 25-μm thick Teflon® film. Finally, the formulations were irradiated 300 s under high pressure UV lamp (OSRAM 300 W, λ_{max} = 365 nm). The dry gel samples were weighed (W_i) before soaking into 25 mL of deionized water at room temperature for 1 day to wash out any unreacted monomers and initiators. The swollen hydrogel samples were dried in vacuum oven at 30°C for several days until reaching to constant weight.

All samples were reweighed (Wd). The percentage of gelation was calculated with the following formula;

$$\text{Gelation } (\%) = (W_d/W_i) \times 100 \quad (1)$$

Swelling measurements

The preweighed (M_d) dry hydrogels were placed in deionized water and kept there during 3 days to reach their equilibrium degree of swelling (Q). Equilibrated swollen hydrogels were then removed from water and tapped with filter paper for dry the gel surface and then reweighed (M_s). Equilibrium swelling ratio (%Q) was calculated from the following equation;

TABLE I
The Composition and Characteristic Properties of Hydrogels

Sample name	HEMA (mol %)	β-CD-UM (mol %)	PEG-DA (mol %)	Irgacure 184 (wt/wt %)	Gel percentage (wt %)	Equilibrium swelling ratio (%)
CD-0	90.0	0	10	3	97.9	34.2 ± 0.8
CD-05	89.5	0.5	10	3	94.8	44.8 ±1.1
CD-15	88.5	1.5	10	3	92.1	47.9 ±1.3
CD-25	87.5	2.5	10	3	90.3	50.2 ±1.5

$$\%Q = [(M_s - M_d)/M_d] \times 100 \quad (2)$$

Each swelling ratio reported in this article is an average of two separate measurements; standard deviations of the measured swelling ratios were less than 3% of the mean.

Phase solubility studies

Phase solubility isotherms were determined according to method described by Higuchi and Connors.[25] Briefly, excess drug was added to 10 mL of aqueous β-CD solutions with 0–10 m*M* concentrations. The suspensions were shaken at 25 ± 1°C for 2 days to reach to equilibrium and then excess drug was filtered off. The drug concentration in the remaining solution was determined spectrophotometrically. The apparent stability constants K_s were calculated from phase solubility diagrams with the assumption of 1 : 1 stochiometry according to the following equations:

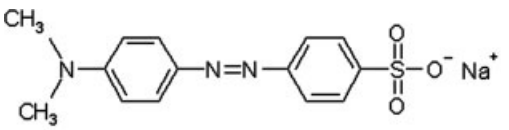
$$K_s = \text{slope}/\text{intercept}(1 - \text{slope}) \quad (3)$$

Drug loading and release experiments

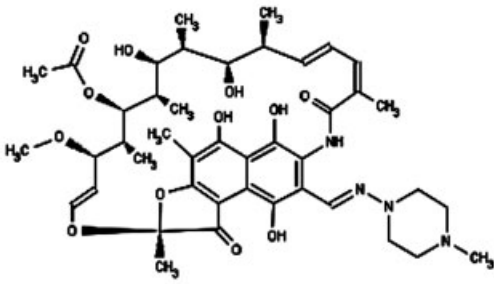
Salicylic acid (SA), sulfathiazole (ST), rifampicin (RIF), and methyl orange (MO) as model drug were used for drug loading and release experiments. The molecular formula of the drugs can be seen in Scheme 2. Solubilities of these drugs in water are in the order of MO > SA > ST > RIF. The dry hydrogels were equilibrated in vials filled with 100 mL of aqueous solution of the drugs [MO (200 ppm), SA (500 ppm), ST (500 ppm), and RIF (150 ppm)] at 25°C for 1 week. These initial drug concentrations were chosen to achieve the absorption readings with best accuracy in the range near 1 AU. After incubation, the samples were removed from the solution and rinsed twice in distilled water. The drug release experiments were carried out by transferring previously incubated drug loaded gels into 100 mL of phosphate buffered saline (8 g NaCl 0.2 g KCl 1.44 g Na_2HPO_4 0.24 g KH_2PO_4 in 800 mL of distilled H_2O), pH 7.4 at 37°C at a constant shaking rate. At various time intervals, 3 mL of sample was drawn from medium to follow drug release by using Shimadzu UV-spectrophotometer and an equal volume of phosphate buffer was added to the dissolution medium to maintain a constant volume. The percentage release of drug was calculated from the following equation;

$$\%\ \text{Release} = (W_t/W_{\text{total}}) \times 100 \quad (4)$$

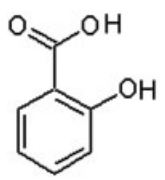
where W_t is the weight of released drug at time t and W_{total} is the total adsorbed drug in the gel structure. The absorbance of each released medium was read from the UV spectrum, than from the calibration curve the concentration of the drug was calculated. Hence the volume of the released medium was known exactly, the weight of released drug was found.



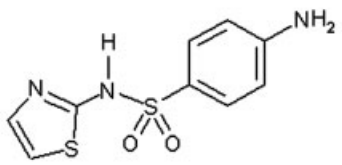
Methyl Orange



Rifampicin



Salicylic acid



Sulfathiazole

Scheme 2 Chemical structures of model drugs.

RESULTS AND DISCUSSION

In this work, a novel multifunctional β-CD urethane-methacrylate monomer (β-CD-UM) was synthesized from the reaction of TDI, HEMA, and β-CD. Scheme 1, illustrates the general synthetic procedure of β-CD-UM. The chemical structure of the resulting monomer was characterized by FTIR, ^{1}H-NMR, and ^{13}C-NMR. As it can be seen in Figure 1, the disappearance of the absorption band at 2275 cm^{-1}, assigned to the isocyanate group is indicative for the completion of the reaction. Moreover, the broad absorption band at 3335 cm^{-1} is ascribed to the —NH and —OH groups overlapping. It also shows the characteristic carbonyl-stretching band at 1725

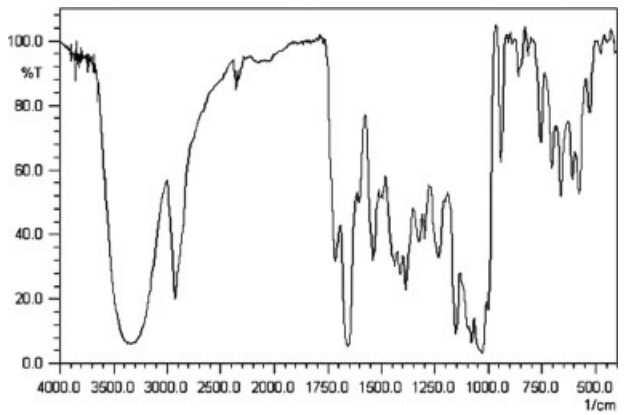


Figure 1 FTIR spectrum of urethane-methacrylate functionalized β-CD monomer.

cm^{-1}, amide I band at 1650 cm^{-1} (C=O stretching), and amide II band at 1550 cm^{-1} (*N*—H bending). The characteristic absorption peak of β-CD units can be seen at 1030 cm^{-1} due to the C—O stretching vibrations. In addition, OH in plane bending vibrations occurs at 1350 cm^{-1}. The ^{1}H-NMR and ^{13}C CPMAS-NMR spectra also confirm the formation of the monomer (spectra not given). In the ^{1}H-NMR, namely, the aromatic pattern produced by TDI appears at 7.15–8.2 ppm as three aromatic multiplets. Methylene protons adjacent to oxygen groups occur around 4.3 ppm. The absorption bands arising from acrylate groups appear at 5.6 and 6.2 ppm. The methyl protons attached to the ring and double bonds resonate at about 1.8–2.0 ppm. In addition, β-CD protons resonate around 3.5–3.9 ppm. The bands around 3.0 ppm probably represent methylene protons adjacent β-CD. The ^{13}C CPMAS-NMR analysis demonstrated that it contains an average value of 2 methacrylic double bonds per β-CD unit.

Hydrogel preparation

Hydrogel containing various amounts of β-CD were prepared from HEMA monomer and β-CD-UM by UV initiated photopolymerization. The feed compositions, the percentage of gelation, and equilibrium swelling ratios are collected in Table I. The gel percentages of hydrogels varied between 90 and 98 wt %. The hydrogels with 0.5–2.5 mol % of β-CD-UM content have slightly lower gel percentages. This is attributed to the fact that low polymerization conversion due to steric hindrance of β-CD molecules in the formulation. Table I also shows that the equilibrium-swelling ratio in water increased with increasing β-CD-UM content in the hydrogel composition. Notably, the hydrophilicity of poly(HEMA) hydrogels was effectively improved by the incorporation of β-CD-UM. It was previously reported that a decrease in the equilibrium-swelling ratio could be expectable since β-CD molecule occupies a large volume inside the pores of the hydrogel that restricts the penetration of water into the pores.[19] On the contrary, our results demonstrate that the effect of hydrophilic character of the β-CD molecule on the swelling is more pronounced.

To obtain successful delivery devices for drugs, the proper morphology of polymeric hydrogel is also required. It is believed that the drug release rate from nonporous polymeric hydrogel is much slower than that from porous biomaterials with large surface areas.[26] Figure 2(a,b) shows the SEM images of β-CD-UM based hydrogel (H15). For comparison, in Figure 2(c) the morphology of the hydrogel without β-CD can be seen. Secondary electron image technique was applied in SEMs. Figure 2 shows the fractured surface of dried hydrogel. It is known that the pore size is affected by the freezing rate. In this study, lyophilized hydrogels were first quickly dipped in liquid nitrogen to fix their natural structure then fractured. As seen in Figure 2(a), a cabbage-like surface morphology is seen. At higher magnification, the porous structure of hydrogel can be better detected. However without β-CD the hydrogel possesses lower porosity.

Phase solubility

The phase solubility profiles of SA-β-CD, RIF-β-CD, MO-β-CD, ST-β-CD are presented in Figure 3. The increase in solubility occurred as a linear function of β-CD concentration corresponding to A_L-type profile defined by Higuchi and Connors[25] up to 10 m*M*. This relationship indicates the formation of 1 : 1 molar ratio complex. The apparent stability constants, K_s, were obtained to be 35, 61, 173, and 354 M^{-1}, respectively, according to eq. 3. The K_s values showed that MO and ST formed more stable complex with β-CD than SA and RIF. In the case of SA and RIF, the solubility of drug in water changes very slightly by complexation with β-CD. This result indicates that the formation of complex is difficult.

Drug uptake

In this study four different drug molecules, which are capable of forming inclusion complexes with β-CD were chosen. The following order was given for solubility in water: MO > SA > ST > RIF. On the other hand, the molecular weight of these drugs are in the order of RIF = 823 g mol^{-1} > MO = 327 g mol^{-1} > ST = 255 g mol^{-1} > SA = 138 g mol^{-1}. Table II shows the effect of β-CD-UM monomer concentration on the drug uptake capacities of hydro-

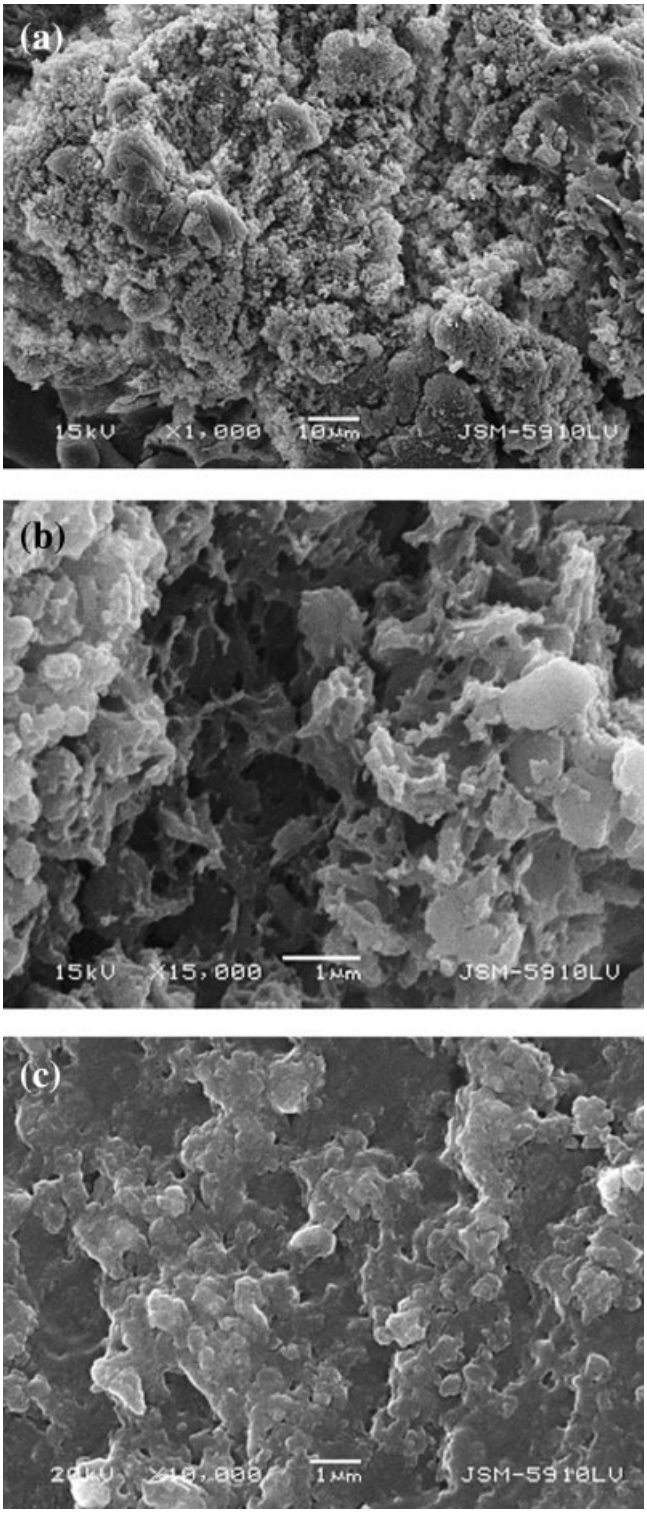


Figure 2 Scanning electron microscope image (SEM) of hydrogel with 2.5 mol % β-CD-UM content at two different magnification: (a) ×1000 and (b) ×15,000, and the control hydrogel without β-CD (c).

gels. As can be seen from this table, both the drug type and also β-CD-UM content affects the drug uptake. For all drugs, uptake into the hydrogel increases with increase in β-CD-UM content.

Lower limit of drug loading per unit mass of a polymer can be estimated from the following relation[27]:

$$\text{Loading (aqueousphase)} = \left(V_s/W_p\right) \times C_0 \quad (5)$$

where Versus is the volume of absorbed solvent, W_p is the dried hydrogel weight and C_0 is the drug concentration in solution.

For ST, lower limit of drug loading was calculated and the mean amounts are as follows: #CD-0 = 0.161 ± 0.02 mg/g dry gel; #CD-05 = 0.225 ± 0.03 mg/g dry gel; #CD-15 = 0.239 ± 0.03 mg/g dry gel; #CD-25 = 0.250 ± 0.04 mg/g dry gel. The actual ST loadings that are listed in Table II, were 25–40 times greater. This result demonstrates that the loading amounts largely depend on drug and network interaction rather than water absorption capacity of network.

The affinity of the drug for the network was estimated as the partition coefficient, K, between the polymeric network and the loading solution, as follows[28]

$$\text{Loading (total)} = \left[\left(V_s + KV_p\right)/W_p\right] \times C_0 \quad (6)$$

where V_p is the volume of dried polymer and other variables are defined as in eq. 5. The values of K (Table II) indicate that the hydrogel prepared with greatest β-CD-UM content has even greater affinity for drugs than the control hydrogel. As it is seen in Table II, highest drug uptake was achieved in the case of 2.5 wt % β-CD-UM containing HEMA gels. Besides the swelling capacity of hydrogel, the specific groups in the network play a significant role in drug uptake.

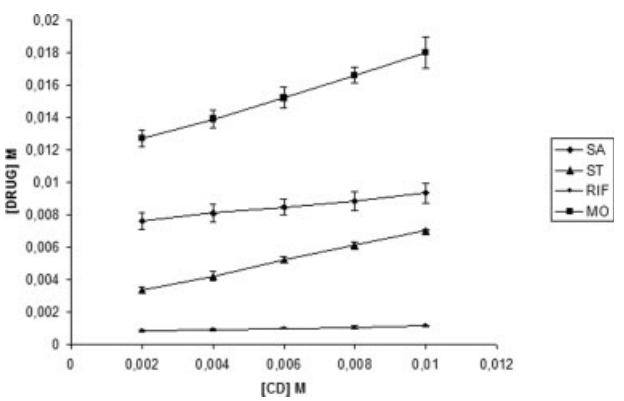


Figure 3 Phase solubility diagrams for methyl orange ■, salicylic acid ◆, sulfathizaole ▲, and rifampicin ●.

TABLE II
Variation of Drug Uptake with β-CD Content in the Gel Structure

	MO			ST			RIF			SA		
Sample name	mmol/g dry gel	mg/g dry gel	*K*	mmol/g dry gel	mg/g dry gel	*K*	mmol/g dry gel	mg/g dry gel	*K*	mmol/g dry gel	mg/g dry gel	*K*
CD-0	0.058	19	109	0.018	4.6	10	0.0048	4.0	30	0.095	13.2	30
CD-05	0.107	35	201	0.021	5.4	11	0.0056	4.6	34	0.134	18.5	42
CD-15	0.14	46	265	0.032	8.1	18	0.0057	4.7	35	0.149	20.6	46
CD-25	0.153	50	288	0.040	10.3	23	0.0077	6.4	48	0.208	28.8	65

Drug solubilities may also be responsible for the drug loading. In the case of ST and RIF the drug loadings are very low (0.04 and 0.008 mmol/g dry gel), whereas MO and SA drug uptakes are found as 0.15 and 0.21 mmol/g dry gel, respectively. As it is seen in Table II, the partition coefficient, *K*, values of MO are 10-fold greater than ST. In hydrophilic gels, the drug diffusion will be more difficult if the drug is hydrophobic. On the other hand, very low drug uptake values for RIF with respect to its moderate *K* values may be because of its higher molecular weight that reduces the diffusion of RIF though the hydrogel network.

Drug release

The release profile of each drug from hydrogels in phosphate buffered solution of pH 7.4 at 37°C was shown in Figure 4(a–d). As it can be seen in Figure 4(a), the MO release decreases with increasing β-CD content of hydrogels. It is well known that β-CD can form an inclusion complex with MO and its associa-

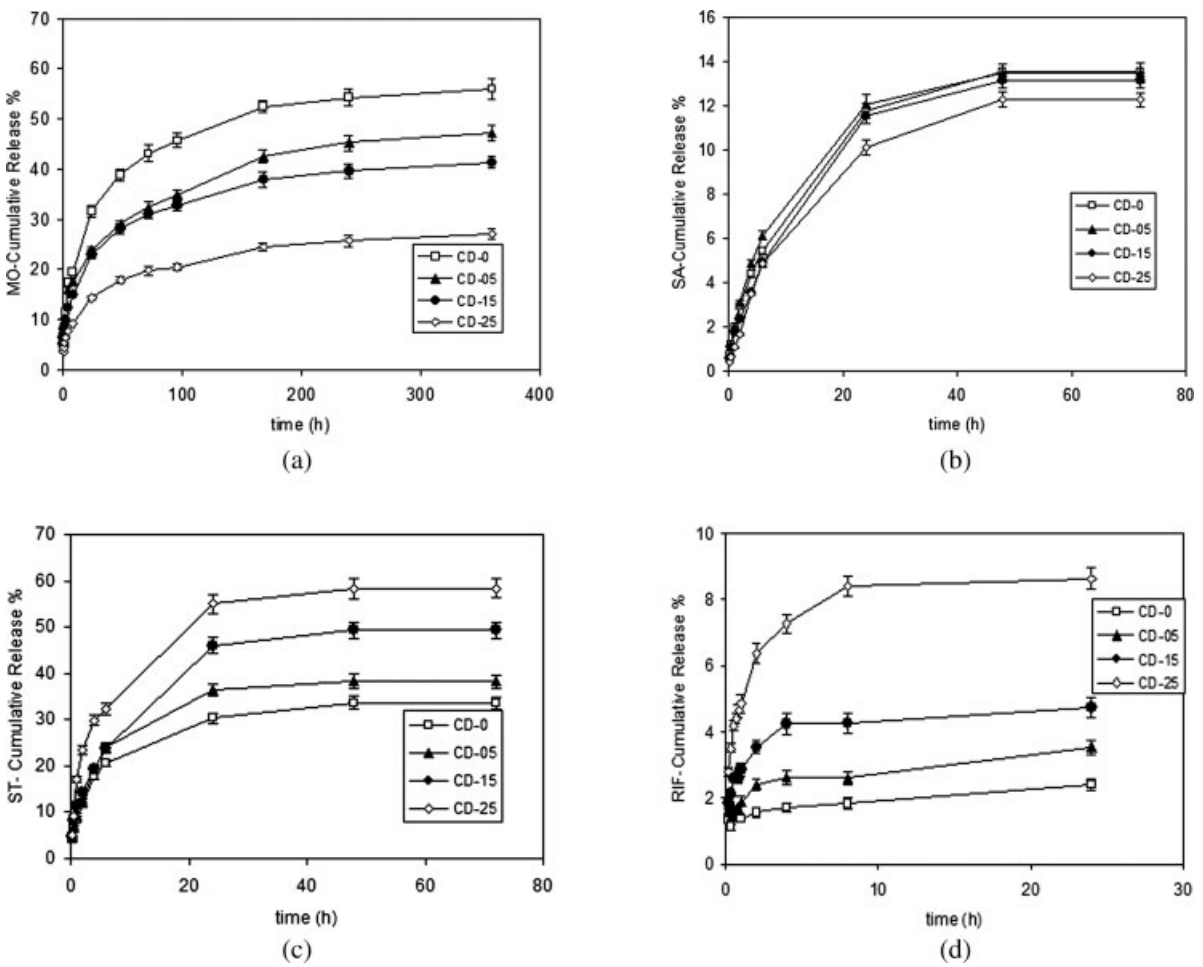


Figure 4 Cumulative drug release from β-CD-UM based hydrogels: (a) methyl orange, (b) salicylic acid, (c) sulfathizaole, and (d) rifampicin.

TABLE III
The Equilibrium Drug Release % from Hydrogels in Phosphate Buffer Solution of PH 7.4 at 37°C

Sample name	β-CD-UM (mol %)	MO	ST	RIF	SA
CD-0	0	55.9 ± 2.01	33.7 ± 1.28	2.4 ± 0.17	13.5 ± 0.43
CD-05	0.5	47.1 ± 1.46	38.2 ± 1.32	3.5 ± 0.22	13.5 ± 0.46
CD-15	1.5	41.2 ± 1.15	49.3 ± 1.79	4.7 ± 0.31	13.1 ± 0.37
CD-25	2.5	27.0 ± 0.94	58.4 ± 2.07	8.6 ± 0.33	12.3 ± 0.32

tion constant was found as 175 M^{-1}. The MO, during its migration through the hydrogel, could be included in β-CD cavity. In the first 24 h, the cumulative amounts of MO released from 0 and 2.5 wt % β-CD-UM containing hydrogels are 31.5% and 14.2% respectively. MO then presents a slow and sustained release. At equilibrium, although 56% of MO was released from nonmodified hydrogel, this value decreased to 27% of MO for 2.5 wt % β-CD-UM containing hydrogel (Table III). This indicates that the incorporation of β-CD into the gel structure leads to the specific interactions. At pH 7.4, there is a strong hydrophobic interaction between MO and the β-CD cavity.[12] The complex formation between MO and β-CD reduces the rate of MO diffusion through out the hydrogel.

As it is seen in Figure 4(b), SA release is slightly affected by β-CD incorporation into the gel structure. It is thought that SA makes strong H-bonding interaction with the hydroxyl and ether groups within the base hydrogel. Hence, introduction of β-CD-UM comonomer into the gel composition weakly reduces the drug release. Sreenivasan reported previously the formation of complex between β-CD and salicylic acid and the retardation of drug delivery due to this complex formation.[29]

ST and RIF showed different release patterns when they were loaded into the β-CD modified hydrogels [Fig. 4(c,d)]. For both drugs the cumulative release percentage increases with increasing the β-CD-UM comonomer ratio. As it is seen in Table II, the 2.5 wt % β-CD-UM comonomer containing hydrogel released 0.0413 mmol/g dry gel methyl orange. However, the released amounts of SA, ST and RIF were found as 0.026, 0.024, and 6.67×10^{-4} mmol/g dry gel, respectively. These results are in accordance with the solubility of the drugs. Furthermore, very good release percentage was obtained for ST that is relatively hydrophobic drug. It was reported previously that, PEG is one of the most widely used cosolvents for improving the aqueous solubilities of hydrophobic drugs.[30] PEG may assist to reduce the dipole moment of water and allows hydrophobic compounds to fit in[31] CDs also have been used to improve the solubility and the stability of drug compounds. Therefore, both the PEG chains and β-CD moiety in the hydrogel formulation may facilitate drug delivery. On the other hand, very low drug release percentage of RIF may be due to the unspecific absorption to hydrogel network.

Previously Siemoneit et al. reported the influence of the proportion of acrylamidomethyl-γ-CD on loading and release of the hydrophilic propranolol and hydrophobic triamcinoloneacetonide by acrylic acid hydrogels.[32] Hydrogels prepared with acrylamidomethyl-γ-CD showed remarkably higher capacity to load hydrophobic drug versus hydrogel without CD and made them potential drug delivery system for hydrophobic drugs. In this study, from Figure 4 one can see the effect of β-CD moiety in the release of drugs with various solubilities. A significant enhancement in release was achieved for ST delivery. The high affinity for the CD cavity controls the release of the hydrophobic drug. It can be concluded that β-CD can improve the release of a drug with low solubility while retarding the transport of soluble drugs.

CONCLUSIONS

This study has shown that the equilibrium-swelling ratio of the β-CD-UM based hydrogels in water increased from 34 to 50 as the mole % of β-CD-UM content increased from 0 to 2.5. Furthermore, it has been found that the drug uptake capacity of the hydrogels increases with increasing β-CD-UM content in the gel structure. The release studies showed that some basic parameters affects the drug-release behavior of β-CD-UM based hydrogels such as drug solubility in water, drug-network affinity, and drug-β-CD complex formation. As a conclusion, the inclusion complex formation capability of β-CD moiety increases the drug release by improving the aqueous solubility of hydrophobic drugs. On the other hand, in the case of hydrophilic drugs, the drug release retards by forming strong drug-β-CD complex and reducing the drug diffusivity.

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