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Citric acid crosslinked cyclodextrin/hydroxypropylmethylcellulose hydrogel films for hydrophobic drug delivery

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ABSTRACT

The present communication deals with preparation of β-cyclodextrin (βCD) grafted hydroxypropylmethylcellulose (HPMC) hydrogel films using citric acid as crosslinking agent with the aim of improving the loading and achieving controlled release of hydrophobic weak base (ketoconazole). The hydrogel films were characterized by attenuated total reflectance-fourier transform infrared (ATR-FTIR) spectroscopy, solid state ^{13}C-nuclear magnetic resonance (^{13}C NMR) spectroscopy, thermal analysis and scanning electron microscopy (SEM). The films were evaluated for βCD content, carboxyl content, swelling ratio, drug loading, drug release and hemolytic assay. ATR-FTIR spectra indicated crosslinking via ester formation whereas ^{13}C NMR, thermal analysis and SEM confirmed βCD grafting. The βCD grafted hydrogel films with high carboxyl content showed maximum swelling and high drug loading. The presence of grafted βCD helped to retard the release of ketoconazole from the hydrogel films. The hemolytic assay suggested the biocompatible nature of the hydrogel films. Altogether, βCD grafted HPMC hydrogel films were found to be suitable for delivery of poorly soluble weak bases.

1. Introduction

Hydrogels are cross-linked networks of water soluble polymers which have tendency to swell under physiological conditions. They are insoluble in aqueous solvents due to presence of physical and chemical cross-links in between the individual polymer chains, however they have huge tendency to absorb water [1]. The unique physical properties of hydrogels have created interest of pharmaceutical scientists in their drug delivery applications [2,3]. Their highly porous structure can be manipulated by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the molecules of different size through the gel network [4].

Hydrogels can be prepared from synthetic or natural polymers. Synthetic polymer based hydrogels have problem that they do not support cell adhesion and tissue formation due to their bio-inert nature [5]. On other hand, hydrogels made from natural polymers possess inherent biocompatibility, biodegradability and biologically recognizable moieties that support cellular activities [6,7]. Cellulose is the natural polymer which is abundant and readily available. The hydrogels prepared using cellulose and its derivatives offer additional advantages which includes transparency and low cost [8]. Amongst the cellulose derivatives, hydroxypropylmethylcellulose (HPMC) is widely used in the controlled release formulations due to its thickening, gelling and swelling properties. Also the previous reports indicate the successful application of the HPMC based hydrogels in controlled drug delivery [9,10]. The use of hydrogels for hydrophobic drug delivery poses difficult problem due to the inherent incompatibility in between hydrophilic hydrogel network and the hydrophobic drug. The problem arises during the loading of hydrophobic drug into the gel and its release into the aqueous gel environment. Incorporation of cyclodextrin inclusion complexes of hydrophobic drugs can solve this problem to a greater extent; however it may lead to diffusion of complex out of hydrogel further affecting the release kinetics [11]. Therefore, βCD grafted hydrogels have been prepared to improve the drug loading and control the release behavior of the hydrophobic drugs.

Various crosslinking agents used by the researchers for preparation of βCD grafted cellulose based hydrogels include, tetraethyl orthosilicate (TEOS) [12], ethyleneglycol diglycidylether (EDGE) [13–15], butylenediamine [16] and 1,4-butanediol diglycidylether (BDGE) [17]. These agents exhibit toxicity and therefore are unsuitable for pharmaceutical preparations [18,19]. In past few years,

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Table 1
β-CD modified HPMC hydrogel films.

Parameters	Batch								
	A	B	C	D	E	F	G	H	I
HPMC K100 M (%)	2	2	2	2	2	2	2	2	2
β-cyclodextrin (%)	0	0.2	0.4	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid (%*)	20	20	20	30	40	20	20	20	20
Sodium hypophosphite (%#)	20	20	20	20	20	30	40	20	20
Curing time (min)	20	20	20	20	20	20	20	30	40

%* indicates percent of HPMC amount; %# indicates percent of citric acid amount.

citric acid has gained recognition as a non-toxic crosslinking agent for grafting βCD on cellulose fibres [20,21]. It is also used in the preparation of cellulose based hydrogels where, at high temperatures, citric acid forms ester crosslinks between the polymer chains of cellulose derivatives by anhydride formation [9,22,23]. The presence of free carboxylic acid groups and hydroxyl groups within the citric acid crosslinks helps to balance hydrophilicity of the hydrogel network. These groups also provide hydrogen bonding and additional binding sites which may control the release of weakly basic drugs [24,25]. Besides, they may impart stability to the inclusion complex formed between βCD and poorly soluble basic drugs [26,27]. Therefore it is hypothesized that, βCD grafted cellulose based hydrogels prepared using citric acid as a crosslinking agent may improve the loading of the poorly soluble weak bases within the hydrogels as well as control their release.

In present study, βCD grafted hydroxypropylmethylcellulose (HPMC) hydrogel films were prepared using citric acid as a crosslinking agent. Ketoconazole was chosen as a model representative of hydrophobic weak bases. It is an imidazole antifungal drug which is administered topically as well as orally and shows poor solubility [28,29]. The main objective of the study was to increase the loading of ketoconazole within the hydrogel films and control its release. The biocompatibility of the hydrogel films was evaluated by hemolytic assay.

2. Materials and methods

Ketoconazole was obtained as a gift sample from Aarti Drugs Ltd., Tarapur, Maharashtra (India), HPMC K100 M (methyl content ~22%, hydroxypropyl content ~8.1%, degree of substitution: 1.4, average degree of polymerization: 750), β-cyclodextrin, citric acid (anhydrous) and sodium hypophosphite were supplied by Loba Chemie, Mumbai, Maharashtra (India). All other chemicals were purchased from Sigma Aldrich, Mumbai, Maharashtra (India).

2.1. Preparation of βCD grafted HPMC hydrogel films

βCD grafted HPMC hydrogel films were prepared according to the previously reported methods with certain modifications [9,20]. HPMC (2%) aqueous solutions containing βCD, citric acid and sodium hypophosphite (SHP) were prepared using magnetic stirrer at room temperature (see Table 1). SHP was used as a catalyst. The solutions were kept overnight to remove the air bubbles. The clear solutions were cast into petri dishes of uniform size (9 cm diameter) and dried in a hot air oven at 50 °C for 24 h. The dried films were cured at 160 °C for 20 min. The curing temperature and curing time was sufficient to achieve crosslinking. The cured hydrogel films were washed with distilled water and isopropyl alcohol for 1 h in order to remove the unreacted entities. Thereafter, the hydrogel films were dried in a hot air oven at 50 °C for 24 h and stored in a desiccator. The parameters such as concentrations of βCD, citric acid, SHP and curing time were varied individually to study their effect on hydrogel properties.

2.2. Determination of grafted βCD content

The percentage of βCD grafted to the HPMC in hydrogels was determined using phenolphthalein assay [30]. The standard solutions of βCD (0.1–0.5 mM/ml) were prepared in 0.05 M trisaminomethane hydrochloride (Tris HCl) buffer (pH = 7) for construction of calibration curve. One ml of these standard solutions was mixed with 4 ml of working phenolphthalein solution in the test tubes. Sample solutions containing hydrogel films (0.1 g) in the mixture of 1 ml of Tris HCl buffer and 4 ml of working phenolphthalein solution were prepared in separate test tubes. All the test tubes were vortexed and stored in dark for 2 h. The absorbance of the standard and sample solutions was measured at 550 nm using UV–vis spectrophotometer (UV-1800, Shimadzu, Japan). Percent decrease in the absorbance of solutions was calculated as given below.

$$\%\ \text{Decrease in absorbance} = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100 \quad (1)$$

The mixture of 1 ml Tris HCl buffer and 4 ml working phenolphthalein solution was used as control for standard solutions whereas, solutions containing non-grafted hydrogel films were used as control for sample solutions. The calibration curve (% decrease in absorbance vs βCD concentration) for standard solutions was plotted and concentration of grafted βCD was determined. The measurements were made in triplicate. The amount of βCD grafted to HPMC was calculated using following formula:

$$\beta CD \text{ grafted } \left(\text{mg/g of hydrogel}\right) = \frac{C_{\beta CD}}{W_{HG}} \times M_{\beta CD} \quad (2)$$

where, C_{mM} is the concentration of grafted βCD (mM), W_{HG} is the weight of hydrogel film (mg) and $M\beta_{CD}$ is the molecular weight of βCD (g/mol).

2.3. Determination of carboxyl content

Carboxyl content of the hydrogel films was determined using acid-base titration [31,32]. A known amount of hydrogel film was dissolved in excess of 0.1N NaOH and stirred on a magnetic stirrer for 2 h. Sodium hydroxide breaks down the ester linkages and reacts with the free carboxyl groups to form sodium carboxylate (citrate). The excess amount of 0.1N NaOH was titrated with 0.1N HCl using phenolphthalein as an indicator. The carboxyl content in milliequivalents per 100 g of hydrogel films was calculated as given below.

$$\text{Carboxyl content} = \frac{(V_b - V_a) \times N \times 100}{W} \quad (3)$$

where, N is the normality of HCl (eq/L), V_b and V_a are the volumes of HCl in absence and presence of sample, and W is the weight of sample (g).

2.4. Characterization of the hydrogel films

2.4.1. Attenuated total reflectance – Fourier transform infrared (ATR-FTIR) spectroscopy

The infrared spectra of HPMC, βCD, citric acid, and hydrogel films were obtained using ATR-FTIR spectrophotometer (Shimadzu, IR Affinity, Japan). The samples to be analyzed were transferred to the ATR compartment. The spectra were obtained for the range of 600–4000 cm^{-1} at an average of 25 scans and resolution of 4 cm^{-1}.

2.4.2. Solid state NMR spectroscopy

Solid state ^{13}C cross-polarization-magic angle spinning (^{13}C CP-MAS) NMR spectra of βCD, HPMC and βCD grafted hydrogel film (Batch B) was measured using JEOL-ECX400 spectrometer operating at 400 MHz (contact time of 3.5 ms, relaxation delay of 5s,