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Zero-order release of aspirin, theophylline and atenolol in water from novel methylcellulose glutarate matrix tablets

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Abstract

A novel hydrocolloidal polymer, methylcellulose glutarate (MC-GA), was prepared by esterifying methylcellulose with glutaric anhydride. The formation of ester was confirmed by FTIR and NMR spectroscopy, DSC and elemental analysis. The physicochemical properties such as, rate of swelling in water, viscosity and hygroscopicity of MC-GA were determined and compared with those of methycellulose A (MC). Aspirin, theophylline and atenolol tablets were compacted on a Carver press using the wet granulation method. Each tablet contained: 200 mg active, 80 mg anhydrous lactose, 8 mg povidone, 4 mg magnesium stearate, 4 mg talc, 50 mg MC or MC-GA (drug-to-polymer ratio, 4:1). Contrary to the first-order release profile of all the drugs from the MC matrix tablets, a zero-order release was obtained from the MC-GA matrix tablets in water.
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Keywords: Methylcellulose; Methylcellulose glutarate; Hydrocolloid; Matrix bases; Matrix tablets; Zero-order release

1. Introduction

In the recent years of development in pharmaceutics, increasing attention is being given for administering drugs in a more challenging and controlled manner for better therapeutic end point (Langer, 1998; Venkatraman et al., 2005). To achieve this, various controlled release dosage forms have been developed or are still under development in treating diseases because of their advantages over other conventional dosage forms (Mohhammed et al., 2004; Torchilin, 2001; Kim, 2000; Freiberg and Zhu, 2004). A goal in the design of an oral controlled release drug delivery system includes maintaining relatively constant therapeutic blood levels of the drug for a desired period. The osmotic drug delivery system among others achieves this (Liu et al., 2000). Presently, hydrophilic matrix system is widely used for modified drug release because of its simplicity in manufacture. In such a system, the drug release is controlled by a combination of several physical processes which include but are not limited to diffusion, polymer swelling, erosion and dissolution (Nagai et al., 1989; Mahaguna et al., 2003; Siepmann et al., 1999). The penetration of water through the tablet and the resultant drug dissolution and diffusion primarily depends on the swellability of the polymer (Wan and Prasad, 1989). Polymer swellability, erosion control and the drug release rate, all depend on the polymer molecular weight (Kim, 1998), degree of substitution (Mitchell et al., 1993) and the polymer concentration (Shah et al., 1993).

To formulate a successful hydrophilic matrix system, one must select a polymer substance that will wet, hydrate and swell to form a gelatinous layer fast enough to prevent the disintegration of the tablet and to protect the interior of the tablet content from dissolving during the initial wetting and hydration phases. To achieve this, the use of different cellulosic derivatives or their combinations have been extensively used in the preparation of matrix tablets. Hydroxypropyl methylcellulose is the most widely studied hydrophilic swellable matrix forming material for preparation of modified drug release products (Streubel et al., 2000; Siepmann and Peppas, 2001; Li et al., 2005).

Modulation of the polymer swelling in controlling the drug release in a linear fashion is a novel concept (Dailey et al., 2005; Peppas et al., 1980; Morita et al., 2000; Lee and Lum, 1992). Here, the mode of expansion of swelling controlled drug release system is described by the introduction of a swelling dimensionality index (a characteristic number that can be determined from

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a logarithmic plot of the swelling ratio of a carrier versus time) (Peppas and Colombo, 1997; Colombo et al., 1996). The modulation of polymer swelling through interpolymer cross-linked hydrogels, has been reported (Kim and Lee, 1992). Modification of methylcellulose ethers has been utilized for extended drug release from matrix tablets. Kojima and Nakagami (2002) developed a sustained release theophylline system by extrusion spheronization of drug using hydroxypropyl methylcellulose acetate succinate. Several patents recite the utility of modified methylcellulose ethers to control the drug release from matrix tablet base (Hirakawa, 1995a,b; Gardener, 1997; Chen, 1998).

The objective of the study was to chemically substitute some of the hydroxyl groups of the MC with a hydrophobic acid derivative such as glutaric acid for the purpose of decreasing the swelling rate of the polymer matrix in aqueous medium. The reduced swelling rate of the polymer combined with the slower water penetration into the matrix should result in a reduction of drug release rate as compared to that from the MC matrix.

2. Materials and methods

2.1. Materials

Methylcellulose A (supplied as methylcellulose A4M, premium, a gift of the Dow Chemical Company, Midland, MI), theophylline (USP anhydrous grade, Knoll Pharma), aspirin USP 80 mesh powder and atenolol, USP powder grade (Gift of Rhodia, Inc., Cranbury, NJ), lactose anhydrous (60M NF, gift of Quest International, Irvine, CA), povidone (Kollidone 30, USP grade, gift of BASF, Germany), glutaric anhydride and all other chemicals were purchased from Sigma Chemicals Co. (St. Louis, MO).

2.2. Methods

2.2.1. Modification of methylcellulose with glutaric anhydride

An equimolar ratio of methylcellulose to glutaric anhydride was computed on the basis of molecular weight and the number of free hydroxyl group present in each monomer of methylcellulose. The polymer and glutaric anhydride were dissolved in tetrahydrofuran and allowed to react at ambient temperature for 12 h in a rotary evaporator (Buchi Rotovapor). After reaction, solvent was removed under reduced pressure. The product was washed several times with tetrahydrofuran to remove unreacted anhydride, air dried and passed through a #30 mesh screen.

2.2.2. FTIR spectroscopy

Thin films (0.03 mm) of both MC and MC-GA were prepared by casting an aqueous polymer solution (8%) on a clean glass plate, followed by drying for 12 h at ambient temperature. The film was pilled off and mounted on a sample holder for measurement. FTIR spectra were recorded using Mattson Gold Infinity FTIR at 4 cm^{-1} resolution for 32 scans between wavelengths of 400–4000 cm^{-1}. After first measurement, the film was treated with 0.1 N NaOH solution, followed by recording again to see if there was any shift of absorbance peaks.

2.2.3. NMR analysis

Nuclear magnetic resonance (NMR) analysis was done to characterize the esterified polymer, using a 400 MHz NMR and spectra were recorded on a Varian Inova 400 MHz spectrometer using deutorated chloroform as the solvent.

2.2.4. Elemental analysis

Elemental analysis of carbon, hydrogen and nitrogen was carried out at Galbraith Laboratories, Inc. (Knoxville, TN) using a Leco CHN-2000 determinator. A Perkin-Elmer Elemental Analyzer was used for the determination of oxygen.

2.2.5. Thermal analysis

Differential scanning calorimetric (DSC) studies were performed on MC, MC-GA, glutaric anhydride, and the physical mixture of MC and glutaric anhydride (sample size 2–5 mg) using a Tzero™ Q1000 (TA instruments, DE), at a heating rate of 10 °C per min under nitrogen purge.

2.2.6. Polymer swelling characterization

The polymer swelling study was performed as a function of water uptake by MC and MC-GA tablets. The tablets each weighing 0.365 g, were prepared by direct compression at 3000 psi using a Carver press. They were placed in separate petri dishes containing purified water. At 30 min intervals, swollen tablets were removed and weighed on an analytical balance. The amount of water uptake was computed from the weight difference. Photographs of the swollen tablets were captured using a *Nikon* Model F2 camera to obtain three-dimensional changes by recording both the top view and the side view of the tablets.

2.2.7. Moisture sorption–desorption study

Moisture sorption–desorption isotherms of MC and MC-GA were studied by gravimetric methods. Samples (3–5 mg) were dried at 60 °C for 1 h and sorption–desorption cycle was conducted at 25 °C at RH range from 10 to 90% using Symmetric Vapor Sorption SGA-100 (VTI Corporation, Inc., FL).

2.2.8. Viscosity study

The viscosity of varying concentration of aqueous MC and MC-GA polymer solutions was determined at 25 °C using AR 1000-N Rheometer (TA Instruments, DE), at a shear rate of 200. The data were plotted using Rheology Advantage 2.0 software.

2.2.9. Matrix tablet preparation

Each tablet contained: 200 mg active, 80 mg anhydrous lactose, 8 mg povidone, 4 mg magnesium stearate, 4 mg talc, and 50 mg MC or MC-GA. The drug to polymer ratio was kept at 4:1 (w/w). The tablets were prepared by the wet granulation method in a batch size of 40 tablets. Active, lactose and the polymer were passed through a #12 mesh screen and transferred to a bottle attached to a Turbula™ mixer and blended for 10 min. The blend was transferred to a glass mortar and granulated with 5 mL of 6% povidone in isopropyl alcohol by gentle trituration

with a pestle. The granules were transferred to a tray lined with a non-absorbent paper, air dried at ambient temperature for 1 h and passed through a #30 mesh screen. Magnesium stearate and talc were passed through a #60 mesh screen over the granules and blended for 2 min on the Turbula™ mixer. The tablets were compacted using a Carver press at 3000 psi with 0.95 cm standard flat faced tooling at a tablet weight and height of 0.346 g and 0.42 cm, respectively.

2.2.10. In vitro dissolution studies

Dissolution studies were conducted using Vankel 700 dissolution apparatus according to the USP method II in 900 mL of purified water at 37 ± 0.5 °C and agitated at 50 rpm with six tablets per study. Samples of 5 mL were withdrawn with media replacement at regular intervals, filtered through 0.45 m filters and assayed spectrophotometrically for aspirin, theophylline and atenolol at their respective λ_{max} of 265, 272 and 226 nm.

3. Results and discussion

Characterization of MC-GA was carried out using FTIR and NMR spectroscopy together with elemental and thermal analysis. The peaks at 3000–2700 and at 3600–3350 cm^{-1} in FTIR spectra of Fig. 1 represent the C–H symmetric and asymmetric stretching vibrations corresponding to the $-CH_2$ and $-CH_3$ groups of both polymers. The peak at 1727 cm^{-1} in Fig. 1A (b) is indicative of the formation of an ester of methylcellulose with glutaric anhydride. It represents the vibrational stretching of C=O bonds of the MC-GA. Treatment of the MC-GA with NaOH resulted in ester hydrolysis as indicated by the shift of the 1727 cm^{-1} peak to 1589 cm^{-1} (Fig. 1B (b′)). These results demonstrate esterification of methylcellulose with glutaric anhydride. As expected the FTIR of the physical mixture of MC and MC-GA did not show any ester formation in Fig. 2.

The peak at 7 ppm is attributed to deuterated chloroform (Fig. 3a and b). The peak representing CH_2 and CH_3 groups of MC is shifted downfield at 5.8 ppm due to their close proximity to the electronegative oxygen atom ($-CH_2$–O–CH_3). Two additional spectra around 5.6 ppm represent the proton peaks of hydrogen attached to the asymmetric carbon atom. The peaks around 4–5 ppm in Fig. 3b represent the protons from CH_2 groups of glutaric ester.

The C, H, O analysis of MC and the MC-GA are summarized in Table 1. It is to be noted that the empirical formula of both polymers can only be approximated due to their high polydispersity. For comparison between the theoretical and estimated values, the results are given as the ratios of elements in MC to MC-GA. The theoretical ratios for C, H and O are 0.932, 1.06 and 1.08, which correlates well with the estimated values of 0.977, 1.08 and 1.02 respectively. These values are in close agreement considering minor probable errors due to the moisture content of the samples. The chemical structure of the 1:1 modified polymer is delineated in Fig. 4.

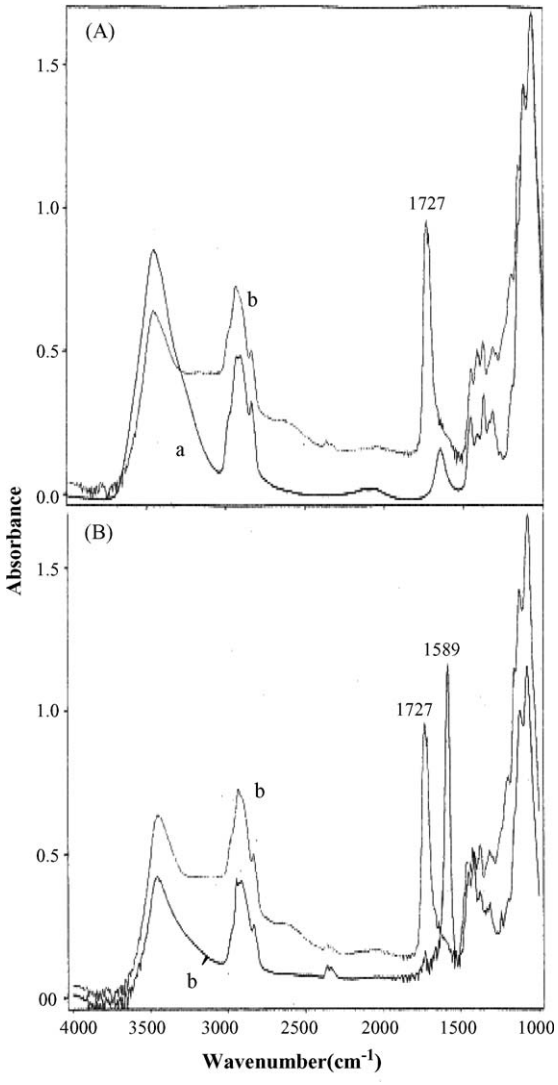

Fig. 1. FTIR Spectra: (A) MC (spectrum, a) and MC-GA (spectrum, b). (B) MC-GA (spectrum, b) and MC-GA treated with NaOH (spectrum b′).

Fig. 5a–d show the DSC thermograms of glutaric anhydride, MC, physical mixture of MC and glutaric anhydride and MC-GA, respectively. The endothermic peak at 55 °C in the Fig. 5a represents the melting point of glutaric anhydride. A broad

Table 1
Elemental analysis of MC and MC-GA

Polymer	Empirical formula	Theoretical (%)			Experimental (%)		
		C	H	O	C	H	O
MC	$C_8O_5H_{14}$	50.5	7.36	42.10	48.6	7.52	41.82
MC-GA	$C_{13}O_7H_{20}$	54.16	6.94	38.88	49.72	6.92	40.99
Ratio (MC:MC-GA)		0.932	1.061	1.083	0.977	1.08	1.02

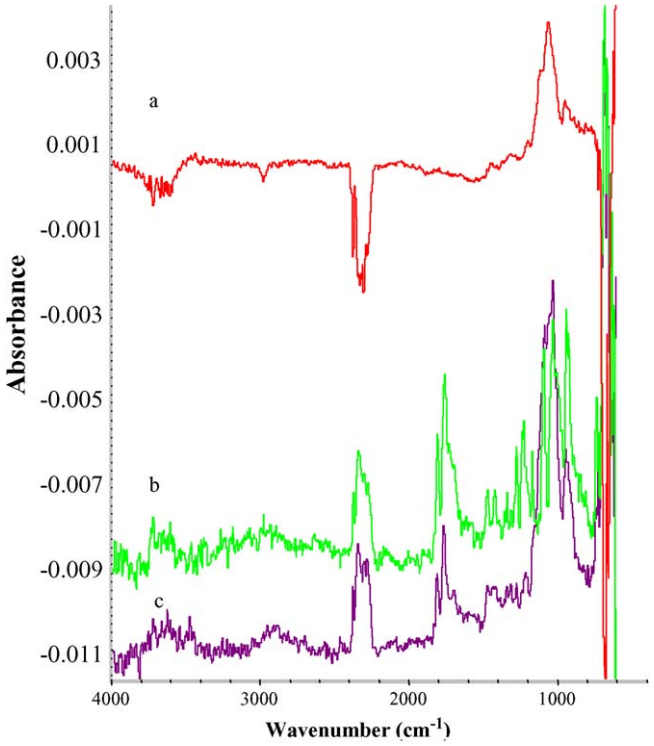

Fig. 2. FTIR spectra of MC (spectrum, a), glutaric anhydride (spectrum, b) and the physical mixer of MC and glutaric anhydride (spectrum, c).

endothermic bend in thermogram 5b from 70 to 150 °C for methylcellulose can plausibly be attributable to the glass transition of the polymer and the vaporization of moisture present in the sample. The presence of melting endotherm of glutaric anhydride in Fig. 5c at 51 °C from the physical mixture of MC and glutaric anhydride indicates the absence of any solid-state chemical reaction between them. This melting endotherm is absent in Fig. 5d of MC-GA which is indicative of the formation of ester with glutaric anhydride. The slight bend at 127 °C in Fig. 5d is a possible representation of glass transition of MC-GA.

The percent weight gain versus time profile depicted in Fig. 6 shows that at all times the percent water uptake by the MC-GA tablets was lower than that by MC tablets. Initially both the polymers showed a rapid hydration and swelling. After 30 min, they both showed a linear water uptake profile with the slope lower for the MC-GA compared to that for MC. Results suggest that esterification had significant diminutive effect on the swelling of MC in water.

The photographs of the swollen tablets portrayed in Fig. 7 demonstrate that the swelling of MC tablets at 6 h (Fig. 7(a)) and 12 h (Fig. 7(a′)) were higher than those of MC-GA tablets (Fig. 7(b) and (b′)), respectively. Surface erosion at the center of the MC tablet was also observed at 12 h only (Fig. 7(a′)). The results demonstrate that the esterification reduced the swelling expansion of the tablet (Fig. 7(b) and (b′)) due to reduction in the affinity of MC-GA for water.

Fig. 8 delineates the moisture sorption–desorption profiles of MC and MC-GA. In each case the lower and upper curve, represent the adsorption and desorption isotherms, respectively.

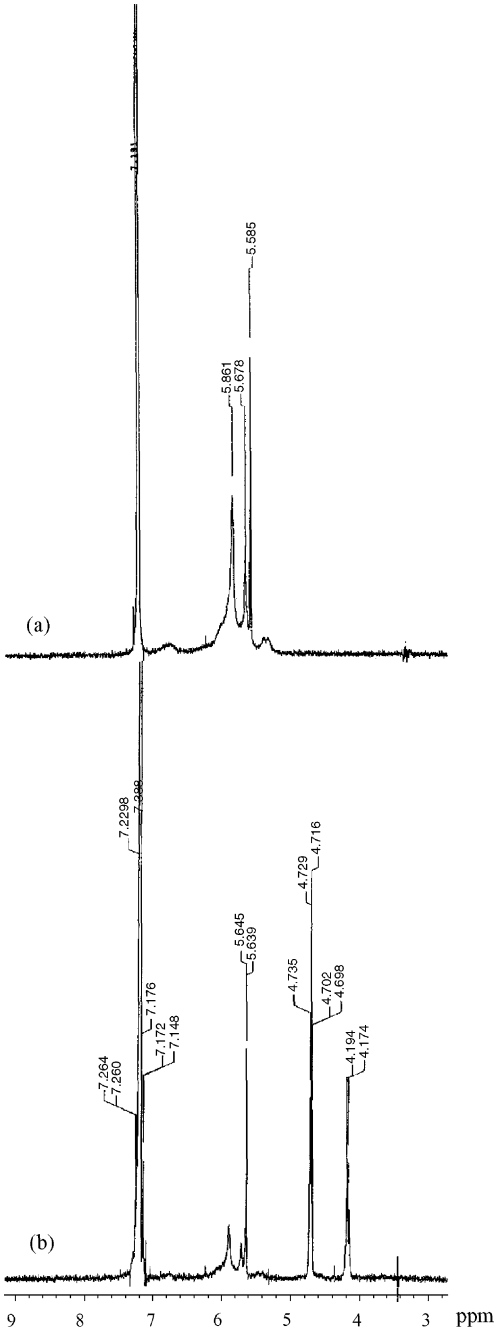

Fig. 3. NMR Spectrum of MC (a) and MC-GA (b).

As presented in the graph, MC has a higher moisture adsorption capability at all %RH compared to that of MC-GA. The moisture retention capacity during the desorption phase is also higher in MC compared to MC-GA. The results demonstrate that the esterification of MC has reduced its moisture uptake capacity.

The data of Fig. 9 demonstrate that viscosity of both the polymers increased as function of concentration (w/w). The viscosity of MC decreased after its esterification at all concentrations. This reduction in the viscosity of MC-GA is due to its decreased hydrophilicity.

Nonlinear fitting of the drug release data was performed in an iterative fashion using the Prostat™ (Poly Software

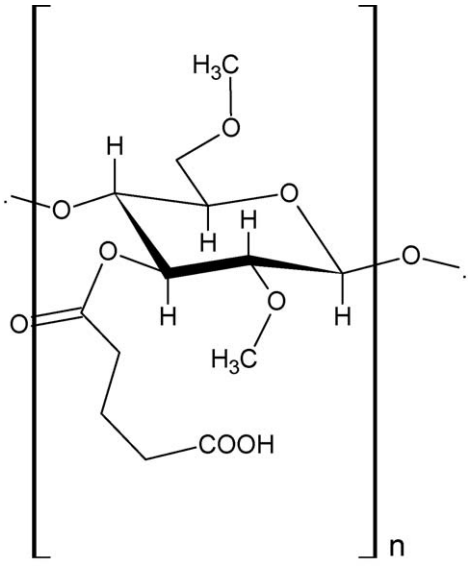

Fig. 4. Chemical structure of the MC-GA based on the elemental analysis of Table 1.

International, Version 3, NY). The best-fit equation was found to be $C = 100(1 - e^{-k \cdot t})$. Fig. 10a–c show the percent drug release versus time profiles of theophylline, aspirin and atenolol, respectively, from tablets compacted with MC and MC-GA. All the drug tablets containing MC yielded an approximately 80% drug release between 2.5 and 3 h, while those with MC-GA gave a zero-order drug release profile over 12 h with a correlation coefficient of ∼0.98. The fast release of the drugs from methylcellulose can be explained on the basis of the fairly rapid swelling of the matrix tablet due to polymer's high affinity with water creating channels in the diffusion layer of the matrix. On the contrary, the linear drug release profile of these drugs in water from MC-GA tablets may be explained on the basis of a reduction in the hydrophilicity of the polymer. The reduced swellability of the polymer may have contributed to the formation of a permeability

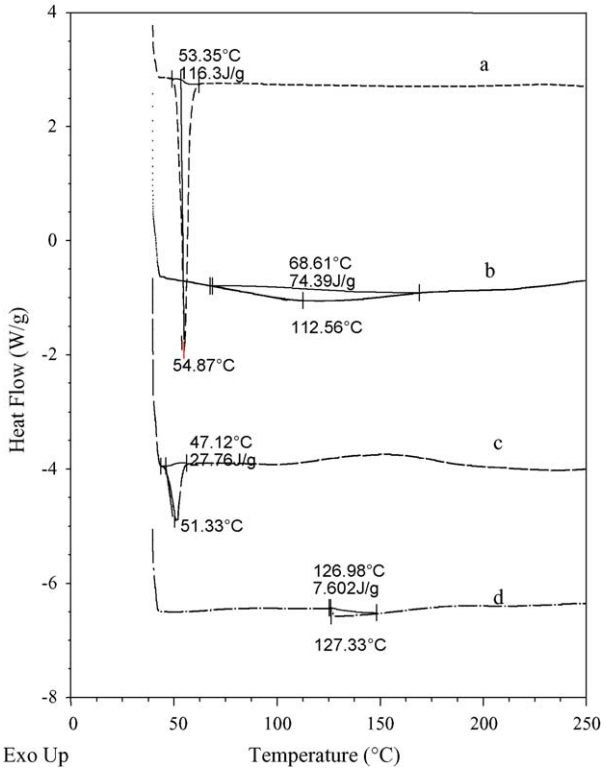

Fig. 5. DSC thermograms of (a) glutaric anhydride (b) MC (c) physical mixture of MC and glutaric anhydride (d) MC-GA.

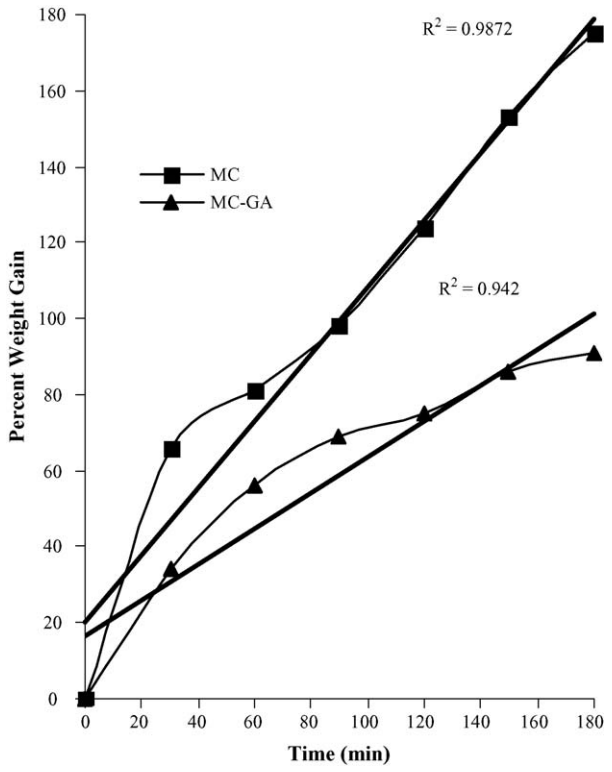

Fig. 6. Rate of water uptake indicating the swelling characteristics of MC and MC-GA tablets ($n = 1$), each weighing 0.346 g with a diameter and height of 0.95 and 0.42 cm, respectively.

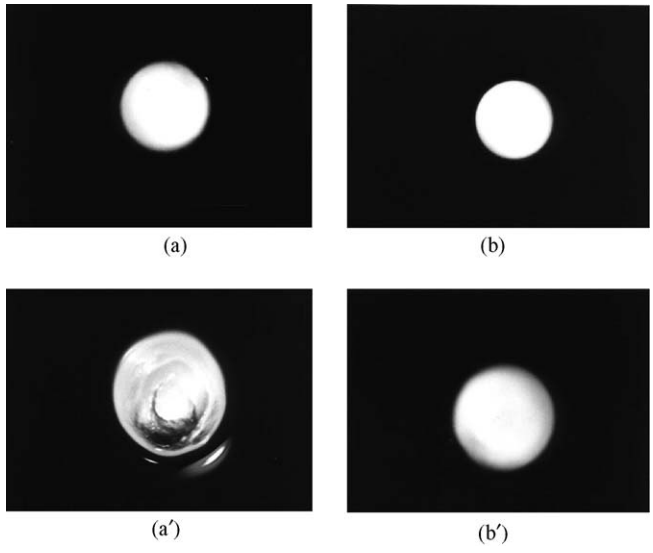

Fig. 7. Photographs a and b show the swollen MC and MC-GA tablets ($n = 1$) at 6 h in water, and a′ and b′ illustrate the respective swollen tablets at 12 h in water. Tablet dimensions are same as in Fig. 6.

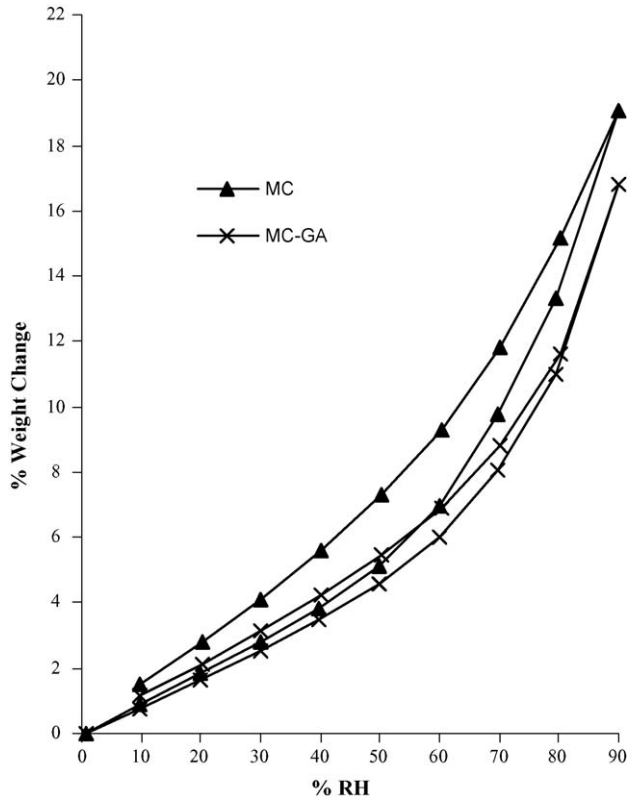

Fig. 8. Moisture sorption (lower), desorption (upper) curves of MC and MC-GA.

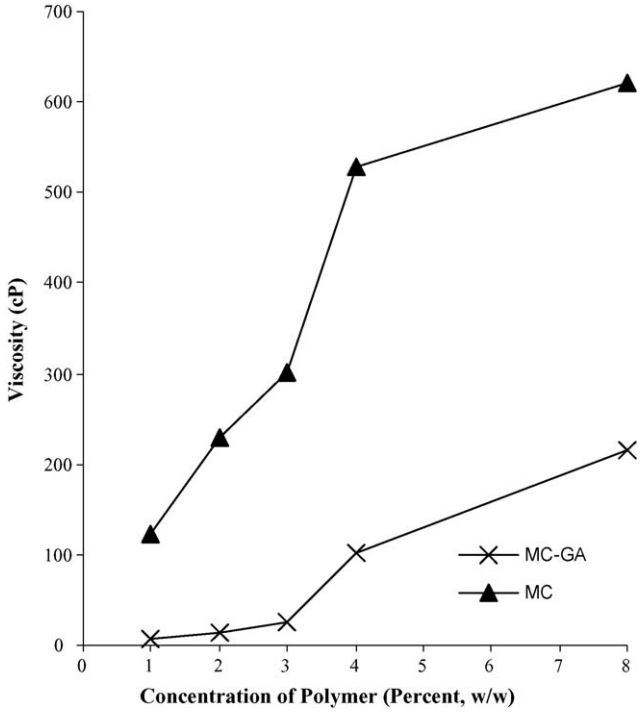

Fig. 9. Viscosity in water at varying concentrations of MC and MC-GA.

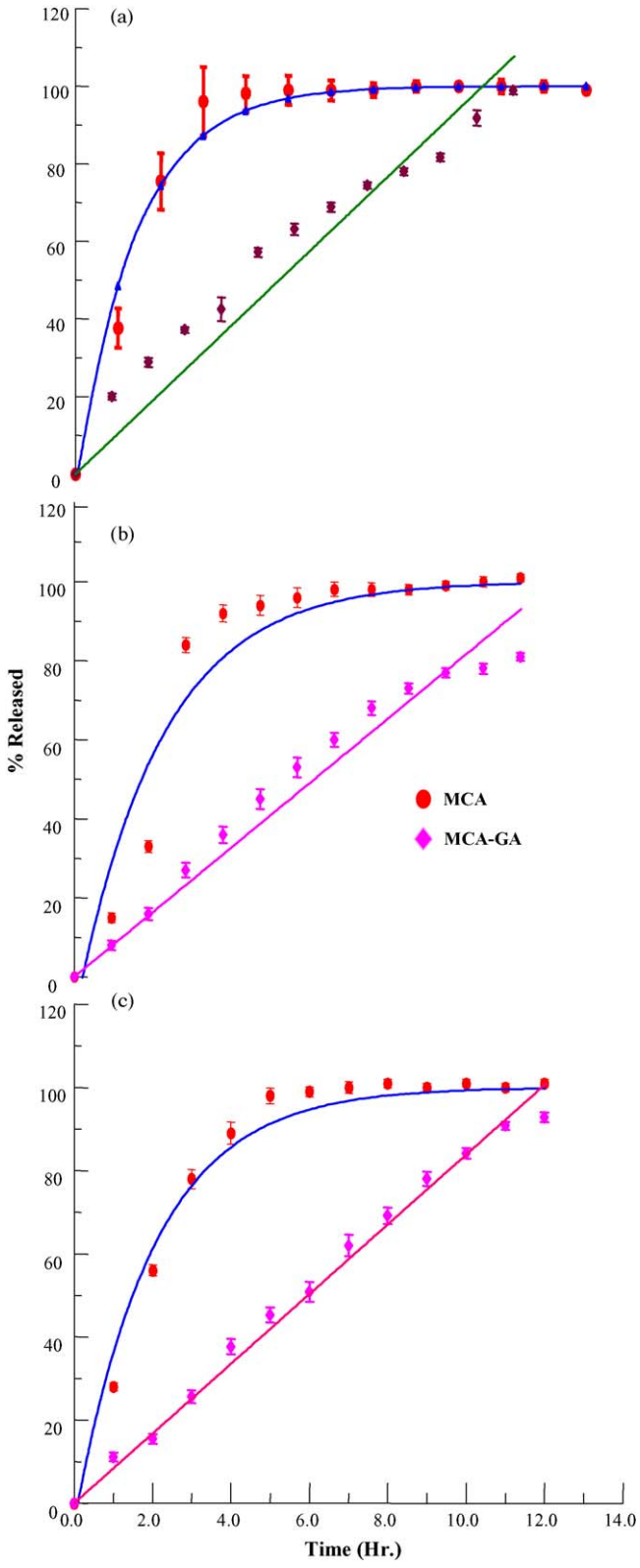

Fig. 10. Dissolution profile of (a) theophylline, (b) aspirin, (c) atenolol from MC and MC-GA tablets ($n = 6$), in water.

barrier controlling the drug release rate. It is to be noted that this system has not been investigated in different pH buffers.

4. Conclusions

In summary, drug release rate from methylcellulose can be prolonged with a 1:1 monomer-to-glutaric acid substitution of the polymer as can be inferred from this investigation. Substituting the free hydroxyl group with ester linkage would be expected to reduce the hydrogen bonding capacity of the polymer which in turn results in reduced water affinity (Fig. 6) and swelling (Fig. 7). The in vitro drug release rates of theophylline, aspirin and atenolol yielded a zero-order drug release profile in water from the MC-GA matrix tablet. Most importantly, the in vitro dissolution results in water demonstrate that the polymer matrix tablets of acidic and basic drugs with a linear drug release characteristics can be achieved at a high drug:polymer ratio (4/1).

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