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Preparation of an extended-release matrix tablet using chitosan/Carbopol interpolymer complex

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Abstract

A chitosan and Carbopol interpolymer complex (IPC) was formed using a precipitation method in an acidic solution. The chitosan and Carbopol IPC was characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and turbidity measurements. FT-IR demonstrated that the IPC formed a complex through an electrostatic interaction between the protonated amine (NH_3^+) group of chitosan and the carboxylate (COO^-) group of Carbopol. DSC indicated the IPC to have different thermal characteristics from chitosan or Carbopol. The turbidity measurement revealed the complexation ratio of IPC between chitosan/Carbopol to be 1/4. A theophylline tablet was prepared using the IPC as a matrix material. The drug release profile from this tablet was similar to that from the HPMC tablet and showed a pH-independent release profile. The mechanisms for drug release from the IPC tablet were diffusional release at pH 6.8 and relaxational release at pH 1.2.

Keywords: Chitosan; Carbopol; Interpolymer complex; Extended release

1. Introduction

Hydrophilic gel-forming matrix tablets are widely used as oral extended-release dosage forms (Nellore et al., 1998; Kranz et al., 2005). Since the overall rate of drug release is regulated by the viscosity and thickness of the gel layer formed from the matrix tablets, selecting the appropriate hydrophilic polymer with the appropriate viscosity and disintegration rate is very important for designing a controlled release tablet.

Carbopol is a cross-linked polymer of acrylic acid with a high molecular weight that forms a hydrogel in aqueous solutions depending on the degree of hydration of the carboxyl group in Carbopol (Singlga et al., 2000). Although Carbopol has many advantages as a candidate for an extended-release tablet matrix, e.g. a good gel-forming ability and mucoadhesive property, there are few reports on the application of Carbopol to the extended-release dosage forms (Meshali et al., 1996; Betageri et al., 2001). This might be due to the ionic nature and high sensitivity of Carbopol to the pH of the medium. It is difficult to control the drug release rate from the Carbopol matrix and correlate the in vitro drug release with the in vivo drug absorption due to its pH sensitivity (Singlga et al., 2000). pH-dependent drug release can cause in vivo variability (Kranz et al., 2005).

Recently, an interpolymer complex (IPC) has attracted considerable interest by pharmaceutical researchers (Wang et al., 1997) on account of its unique characteristics due to a specific interaction between constituent polymers such as hydrogen bonds, electrostatic interaction, van der Waals force, or hydrophobic interactions (Zhong and Guo, 1996). Among them, the formation of an IPC between poly(acrylic acid) and chitosan has been previously reported (Chavasit et al., 1988). The complexation is due to an electrostatic interaction between the carboxylate group of poly(acrylic acid) as the polyanionic polymer and the protonated amine group of chitosan as the polycationic polymer (Mi et al., 1999). In a similar manner, the formation of an IPC between Carbopol and chitosan would be expected. This might solve the problem of the pH dependency of Carbopol because carboxyl groups, which are the main factors affecting the pH-dependant drug release, are complexed with chitosan. Moreover, chitosan possesses some favorable properties, such as non-toxicity, high biodegradability and biocompatibility (Cho and Choi, 2005a).

In this study, a Carbopol/chitosan complex powder was prepared and evaluated as an extended-release tablet matrix. The

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drug release pattern at lower and higher pH was also examined. Theophylline was selected as the model drug because it is water-soluble and has an almost constant solubility between pH 2 and 7.5 (Vendruscolo et al., 2005).

2. Materials and methods

2.1. Materials

Theophylline anhydrous and low (viscosity of 1% acetic acid solution: 20–200 cP), medium (viscosity of 1% acetic acid solution: 200–800 cP) and high (viscosity of 1% acetic acid solution: 800–2000 cP) molecular weight Chitosan were purchased from Sigma–Aldrich (St. Louis, MO, USA). Carbopol 971 was obtained by Noveon, Inc. (Cleveland, OH, USA). Hydroxypropylmethylcellulose (HPMC; Metolose® 60SH 4000cp) was obtained from Shin-Etsu (Tokyo, Japan). All the other chemicals were of reagent grade or above and used without further purification.

2.2. Preparation of Carbopol/chitosan complex

A Carbopol aqueous solution (1 mg/ml) and chitosan acetic acid solution (5 mg/ml) were mixed. The resulting precipitate (Carbopol/chitosan IPC) was washed with distilled water and dried under vacuum over a 24-h period. The dried complex was ground with a grinder and ball milled. The powder was passed through a 200-μm sieve and used for further study.

2.3. Fourier transform infrared (FT-IR) spectroscopy study

The infrared absorption spectra of Carbopol, chitosan and their IPC were analyzed using a FT-IR spectrophotometer (LX30-7012, Perkin Elmer, MA, USA). The pellets were prepared by pressing the sample with potassium bromide.

2.4. Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a differential scanning calorimeter (DSC 50, Shimadzu Scientific Instruments, MD, USA). The samples were placed in an aluminum-sealed pan and preheated to 200 °C. The sample was cooled to room temperature and then reheated from 40 to 450 °C at a scanning rate of 10 °C/min.

2.5. Turbidity measurements

The Carbopol/chitosan ratio in the complex was examined by monitoring the transmittance of the solution at a wavelength of 600 nm using a spectrophotometer (UV-1601, Shimadzu, Japan). An aqueous Carbopol solution (0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 mM) and a chitosan acetic acid solution (0.5, 1, and 2 mM) were used. The concentration was calculated by dividing the weight of chitosan and Carbopol by the formula weight of each monomer unit. Each Carbopol solution (3 ml) was mixed with the 0.5 mM chitosan solutions (3 ml), and each chitosan solution (3 ml) was mixed with a 0.5 mM Carbopol solution (3 ml). Each mixture was shaken vigorously. The mixtures were then left to stand for 10 min before measuring the transmittance as a function of the various mixing ratios (chitosan/Carbopol).

2.6. Preparation of extended-release matrix tablet

The extended-release matrix tablets with a total weight of 250 mg were prepared using a mixture of theophylline and an excipient at 1:1. The mixture was compressed using a hydraulic press with a 13-mm diameter. The compression force was 10 kN/cm^2 with a dwell time of 1 s. Carbopol, chitosan, HPMC and three types of Carbopol/chitosan complexes (three different molecular weight of chitosan) were used as the excipient.

2.7. Dissolution of theophylline from the tablet

A dissolution test was carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). The dissolution tester was calibrated using an USP Dissolution Calibrator, salicylic acid (Lot O) and prednisone (Lot O0C056) tablets. The rate of theophylline dissolution was measured using the USP paddle method at 50 rpm using 900 ml of a pH 1.2 or pH 6.8 medium at 37 °C. The samples were withdrawn at predetermined times and then analyzed using a HPLC system (Shimadzu Scientific Instrument, Kyoto, Japan) at a wavelength of 280 nm with a flow rate of 1.2 ml/min using an ODS column (Luna C8, 4.6 mm × 150 mm, 5 μm, Phenomenex, USA). The mobile phase used was pH 3.8 100 mM acetate buffer/acetonitrile = 93/7.

2.8. Determination of matrix erosion and water uptake

Matrix erosion and water uptake of a Carbopol/chitosan complex tablet were evaluated by measuring the amount of water uptake and weight loss in a dissolution tester. The tablets were placed in 900 ml of pH 1.2 or pH 6.8 medium at 37 °C using USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. The tablets were then pulled out of the vessel at predetermined times. The weight of the hydrated tablet (W_h) was measured after removing the surface medium with filter paper. The weight of the dried tablet was measured after drying the tablet under a vacuum for 24 h. The water uptake ratio and level of matrix erosion were calculated using the following equations:

$$\text{Water uptake } (\%) = \frac{W_h - W_d}{W_d} \times 100 \quad (1)$$

$$\text{Matrix erosion } (\%) = \frac{W_i - W_d}{W_i} \times 100 \quad (2)$$

where W_i is the initial weight of the tablet. W_d was corrected by subtracting the weight of the buffer components (KH_2PO_4, NaOH, NaCl) present in the absorbed medium from the measured weight after drying.

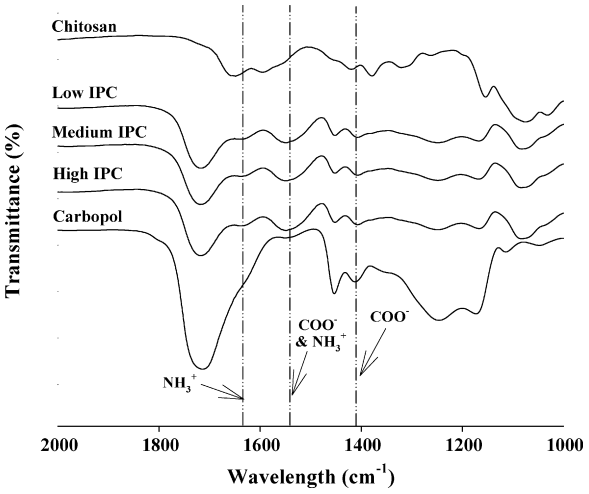

Fig. 1. FT-IR spectra of chitosan, Carbopol and Carbopol/chitosan IPC with chitosan at various molecular weights. Low, medium and high IPC indicate complex of low, medium and high molecular weight chitosan with Carbopol, respectively. The ratio of chitosan/Carbopol used was 1/4.

3. Results and discussion

3.1. Characterization of the Carbopol/chitosan IPC

The interaction between chitosan and Carbopol has been studied by several investigators (Shieh and Huang, 1997; de la Torre et al., 2003; Cho and Choi, 2005a). The results indicated that interpolymer complex could be formed by the electrostatic interaction between the COO^- group of Carbopol and NH_3^+ group of chitosan when pH of the solution was between pH 3 and 6 (Chavasit and Torres, 1990). To make protonated chitosan and dissociated Carbopol solutions, chitosan and Carbopol were dissolved in the acetic acid solution and water, respectively. Subsequently, the chitosan and Carbopol interpolymer complex was prepared with those solutions. Fig. 1 shows the IR spectra of chitosan, Carbopol and the Carbopol/chitosan IPC. Because the degree of deacetylation of chitosan is 85%, the amine group of the 2-aminoglucose unit and the carbonyl group of the 2-acetaminoglucose unit of chitosan showed absorption bands at 1595 and 1656 cm^{-1}, respectively (Tien et al., 2003). The peak at 1715 cm^{-1} in the IR spectrum of Carbopol was assigned to the carbonyl group of carboxylic acid. The IR spectrum of the IPC showed that the peak of 1595 cm^{-1} assigned to the amine band of chitosan was shifted to 1640 cm^{-1}, indicating that the amine group was protonated to a NH_3^+ group in IPC (de la Torre et al., 2003). The bands at 1550 and 1408 cm^{-1} were assigned to the symmetric and asymmetric stretching of the COO^- group (Nunthanid et al., 2004; de la Torre et al., 2003). In addition, the NH_3^+ peak was known to appear between 1600 and 1460 cm^{-1} (Pretsch et al., 2000). Moreover, the peak of NH_3^+ groups in the complex between chitosan and poly(acrylic acid) was known to appear at 1520 cm^{-1} (Chavasit et al., 1988). Therefore, the broad peak around 1550 cm^{-1} was believed to be the overlapped peak of COO^- and NH_3^+ peak. These results suggested that the Carbopol/chitosan IPC was formed by an electrostatic interaction between the COO^- group of Carbopol and NH_3^+ group of chitosan. No significant difference was observed in IR spectrum depending on different molecular weight of chitosan used to form the complex.

Fig. 2 shows the DSC thermograms of the chitosan, Carbopol and the Carbopol/chitosan IPC. An exothermic peak attributable to the decomposition of chitosan appeared at approximately 320 °C (Cho and Choi, 2005b; Neto et al., 2005). In the DSC thermogram of Carbopol, the glass transition temperature was observed near 135 °C and the decomposition of Carbopol was observed at approximately 280 °C at which the Carbopol had melted and decomposed sequentially (Koleng and McGinity, 2000; Gomez-Carracedo et al., 2004). The broad endothermic peak near 100 °C was attributed to the physically bound-water. The endothermic peak of the IPC due to bound water was smaller than that of chitosan. The water absorption ability of chitosan is expected on account of its amine group being reduced by the complexation of chitosan with Carbopol. Therefore, the water absorption capacity of the IPC may be lower than chitosan. The reduced water absorption capacity might result in the slow disintegration of the IPC matrix and the extension of drug release from the IPC matrix.

The change in transmittance as a function of the unit molar ratio of chitosan to Carbopol was measured to determine the composition of the IPC, as shown in Fig. 3. The chitosan acetic acid solution and the Carbopol aqueous solution were transparent regardless of their concentration prior to mixing. The transmittance of the IPC did not show a significant change with increasing Carbopol concentration up to a chitosan:Carbopol ratio of 1:1. However, the transmittance decreased as the ratio

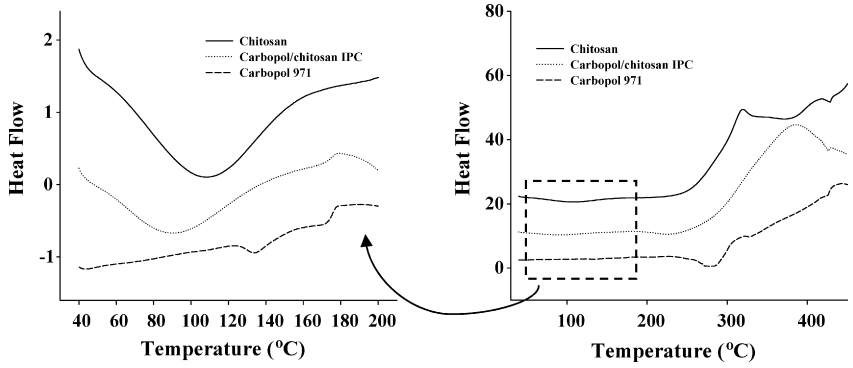

Fig. 2. Comparison of the DSC thermogram of the Carbopol/chitosan IPC with those of chitosan and Carbopol.

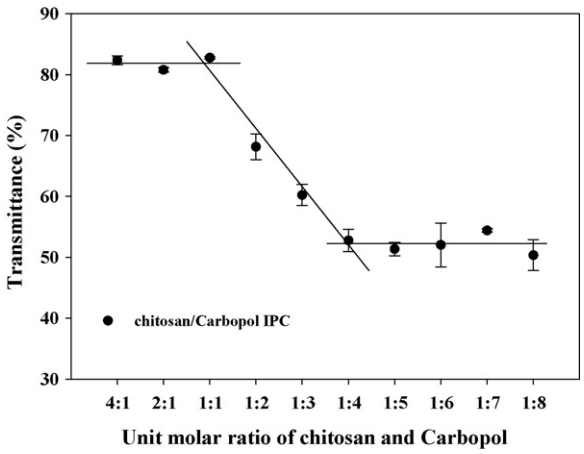

Fig. 3. Effect of the ratio of Carbopol 971 and chitosan on the transmittance of the solution.

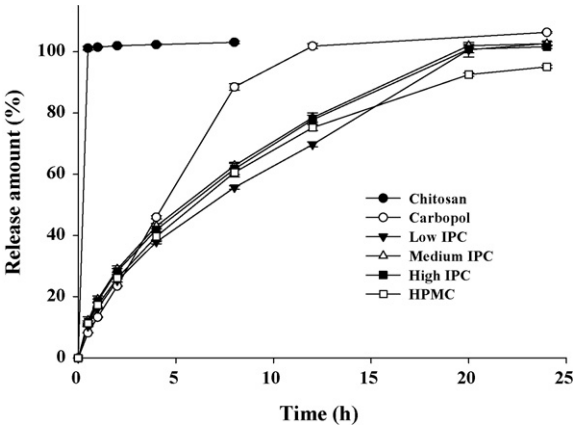

Fig. 4. Release profiles of theophylline from the tablets containing various excipients in pH 6.8. Low, medium and high IPC indicate complex of low, medium and high molecular weight chitosan with Carbopol, respectively. The ratio of chitosan/Carbopol used was 1/4.

was changed from 1:1 to 1:4. The change in transmittance was not significant at higher ratios. It appears that the excess chitosan (or Carbopol) did not react with Carbopol (or chitosan) because of the saturation of the electrostatic interaction sites of Carbopol (or chitosan) by that of chitosan (or Carbopol). As the chitosan:Carbopol ratio was changed from 4:1 to 1:1 (the amount of Carbopol was fixed at 0.5 mM), the amount of IPC formed was determined by the amount of Carbopol. As the chitosan:Carbopol ratio was changed from 1:1 to 1:4 (the amount of chitosan was fixed at 0.5 mM), the amount of IPC increased with increasing amount of Carbopol. At a chitosan:Carbopol ratio of 1:4, each interaction site of chitosan and Carbopol was saturated, and further increase in the amount of chitosan did not cause any change in turbidity. The transmittance results clearly show that the complexation unit molar ratio of chitosan with Carbopol was 1:4. Therefore, the chitosan and Carbopol IPC with the mixing ratio 1/4 was used to characterize the IPC and to study the release profile.

3.2. In vitro drug release study

Figs. 4 and 5 show the dissolution profiles of theophylline from the matrix tablets containing various excipients in pH 6.8 phosphate buffer and pH 1.2 HCl solutions, respectively. The rate of drug dissolution from the chitosan matrix tablet was faster than that from the other matrix tablets tested at pH 6.8. In addition, the rate of drug dissolution from the chitosan matrix tablet in pH 6.8 was faster than that at pH 1.2. This might be due to the gel forming ability of chitosan at a low pH, which retards the rate of drug release from the tablet. It was reported that the rapid rate of drug dissolution from the chitosan tablet was due to the poor gel formation ability and easy disintegration characteristics of chitosan at neutral pH (Betageri et al., 2001). In the case of the Carbopol matrix tablet, the rate of drug dissolution was influenced by the pH of the dissolution medium. Almost all the carboxyl groups will dissociate at pH 6.8 resulting in the formation of a swollen gel. However, the carboxyl groups of Carbopol will not dissociate at pH 1.2 resulting in a less viscous hydrogel (Bonacucina et al., 2004). Therefore, the rate of drug dissolution from the Carbopol matrix at pH 6.8 was slower than that of the drug at pH 1.2. The Carbopol/chitosan IPC matrix tablets showed much less pH dependency than the Carbopol tablets. The dissolution profile of theophylline from the Carbopol/chitosan IPC matrix tablet was compared with that from the HPMC matrix tablet because the matrix tablet with HPMC is widely used as an extended-release matrix tablet. The dissolution profile of the drug from the IPC matrix tablet at pH 1.2 and 6.8 was similar to that from the HPMC matrix tablet except that the release profile from the IPC at pH 6.8 was closer to zero-order kinetics than that from the HPMC.

The effect of the molecular weight (MW) of chitosan in IPC on the release profile of theophylline was examined in order to determine if the MW of chitosan could control the release rate. No significant difference was observed in the dissolution profiles at pH 1.2 and 6.8 (Figs. 4 and 5). This might be due to the fact that a similar portion of Carbopol interacted with chitosan regardless of the MW of chitosan.

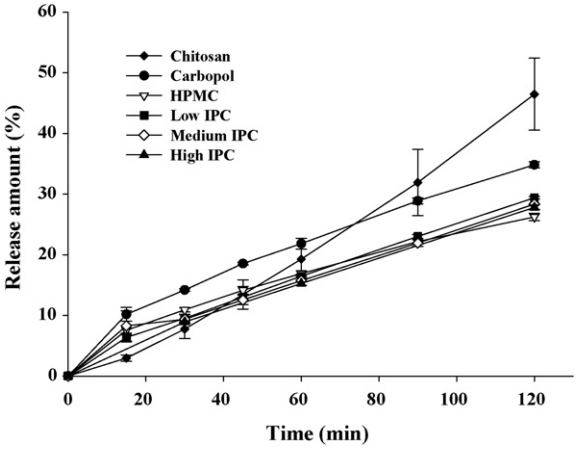

Fig. 5. Release profiles of theophylline from the tablets containing various excipients in pH 1.2. Low, medium and high IPC indicate complex of low, medium and high molecular weight chitosan with Carbopol, respectively. The ratio of chitosan/Carbopol used was 1/4.

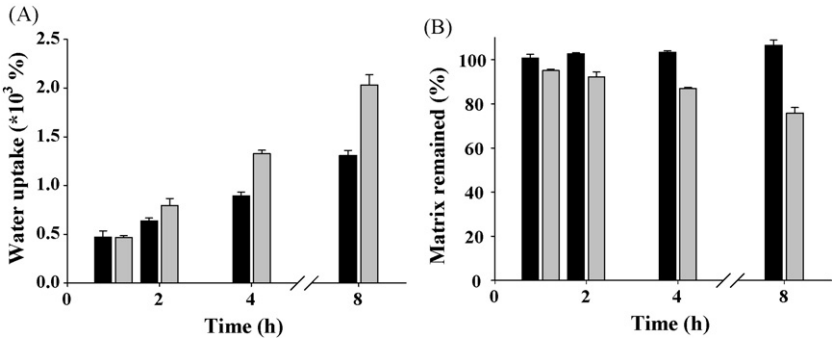

Fig. 6. Water uptake (A) and matrix erosion (B) of tablet containing 250 mg chitosan/Carbopol IPC (1/4) in pH 1.2 (gray column) and pH 6.8 medium (black column).

3.3. Evaluation of drug dissolution mechanism

The Peppas and Sahlin model was used to determine the drug dissolution kinetics (Peppas and Sahlin, 1989).

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$$

where M_t/M_∞ is the fractional drug dissolution at time t, t the drug dissolution time, m the purely Fickian diffusion exponent for a device of any geometry shape and k_1 and k_2 are the kinetic constants for the diffusional and relaxational drug dissolution, respectively. In order to obtain the Fickian diffusion exponent, the aspect ratio was calculated by dividing the diameter (13 mm) of the tablet by its thickness (1.61 mm). Based on the calculated aspect ratio (8.1), the Fickian diffusion exponent (0.47) was obtained from the correlation graph between the Fickian diffusion exponent and the aspect ratio reported in the literatures (Lee and Peppas, 1987; Ritger and Peppas, 1987). Table 1 shows the kinetic constants obtained by fitting the release data up to the first 60% of the drug release. The k_2/k_1 values represent the ratio of the relaxational to diffusional contribution. In the case of the IPC matrix tablets, the diffusional contribution was dominant at pH 6.8 and the relaxational contribution was dominant at pH 1.2. In the case of the Carbopol matrix tablet, the dissolution mechanism was reversed against the IPC matrix tablets.

Table 1
Parameter estimates derived from fitting Eq. (2) reported by Peppas and Sahlin (1989) to the experimental data

pH	Carrier	k_1	k_2	k_2/k_1	R^2
6.8	HPMC	0.185	0.012	0.0649	0.9977
	Carbopol	0.019	0.114	6.0000	0.9993
	Low IPC[a]	0.142	0.026	0.1831	0.9993
	Medium IPC[a]	0.169	0.026	0.1538	0.9995
	High IPC[a]	0.162	0.027	0.1667	0.9996
1.2	HPMC	0.114	0.056	0.4912	0.9999
	Carbopol	0.146	0.076	0.5202	0.9998
	Low IPC[a]	0.050	0.116	2.3200	0.9997
	Medium IPC[a]	0.043	0.156	3.6279	0.9999
	High IPC[a]	0.036	0.119	3.3056	0.9997

[a] Low, medium and high IPC indicate complex of low, medium and high molecular weight chitosan with Carbopol, respectively.

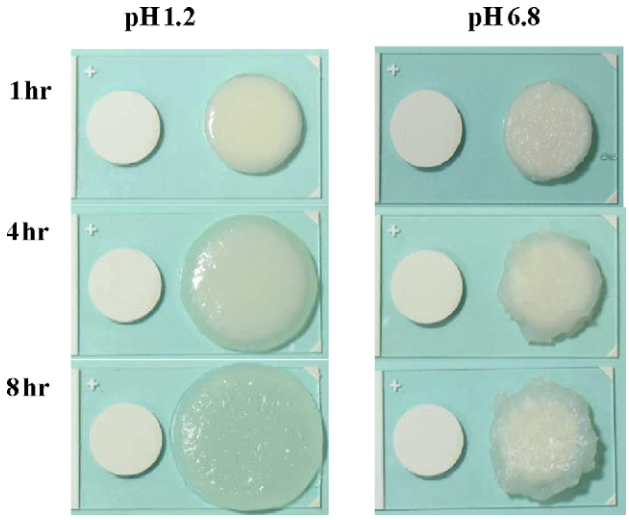

Fig. 7. Effect of the pH of the medium on the swelling and dissolution of the theophylline tablet containing Carbopol/chitosan IPC (1/4).

Fig. 6 shows the extent of water uptake and the erosion of the IPC matrix as a function of time. The erosion of IPC in the pH 6.8 medium was not significant, whereas approximately 25% of the IPC tablet matrix had eroded after 8 h in the pH 1.2 solution. The results are in accordance with the mechanism of drug release from the IPC matrix discussed previously. Swelling of the IPC was also observed at both pHs. Fig. 7 shows images of the theophylline IPC tablet during the dissolution test in the pHs 1.2 and 6.8 medium. In the pH 6.8 medium, the surface of the tablet gradually swelled with the core remaining intact. However, at pH 1.2, the tablet swelled quickly and formed a soft gel together with some erosion. The apparent zero-order release kinetics of theophylline from the IPC tablet in the pH 1.2 medium appeared to be due to synchronization between swelling and erosion of the polymer (Vendruscolo et al., 2005). An apparent first-order drug release profile was observed in pH 6.8, which might be caused by slow swelling, and there was no erosion of IPC observed at pH 6.8.

4. Conclusions

The chitosan/Carbopol IPC showed a similar release pattern to that of HPMC, which is widely used as a sustained- and extended-release matrix former, and showed pH-independent

release profile during the first 2 h of the dissolution study. The main release mechanisms of theophylline from the IPC tablet were diffusional release at pH 6.8 and relaxation of the polymer at pH 1.2. The pH dependency of Carbopol can be reduced by the formation of a complex with chitosan, and can be used as a pH independent extended-release tablet matrix.

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