Using chitosan and xanthan gum mixtures as excipients in controlled release formulations of ambroxol HCl - *in vitro* drug release and swelling behavior.

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ABSTRACT

Directly compressed matrices were produced using a binary mixture of different chitosan (CH) and xanthan gum (XG) ratios. These hydrophilic excipients were used to control the release of ambroxol HCl. CH and XG were investigated at three ratios of 1:1, 1:4 and 4:1. Mucosolvan LA® was used as a commercially available reference product. The optimal CH to XG ratio was 1:1 and the optimal drug to polymer ratio was 1:3. Matrix erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method). The release mechanism is also discussed.

KEY WORDS: Ambroxol HCl, xanthan gum, chitosan, controlled release, swelling

INTRODUCTION

Naturally occurring hydrophilic polymers are increasingly used as excipients in controlled release (CR) formulations due to their nontoxic, biocompatible, biodegradable and swelling properties (1-5). Polymer properties, however, have a large impact on drug release from their matrices. In order to optimize drug release from polymeric matrices, different chemical modifications must be carried out, for example, through depolymerization, deriveatization or cross linking. However, using a suitable binary or ternary polymer mixture could be an alternative method to achieve this goal. Such mixtures can make them versatile for use in CR formulations of a wide range of drugs providing varying solubility and dose (6-10).

Mixtures of chitosan (CH) and xanthan gum (XG) have been studied and their compression properties have been characterized previously (11-13). However, their hydration and swelling properties require additional research. The rationale for using this mixture is based on mixing a branched polymer i.e., XG with a non-branched one, i.e., CH. Such a mixture may provide a hydrated layer where the release could be controlled in a more predictable manner.

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XG is a high molecular weight anionic polysaccharide produced by the bacteria *Xanthomonas*. Its backbone structure consists of β-glucose rings and the side chains include substituted α-mannose, β-glucose and β-mannose rings (14). Although XG solutions are able to produce high intrinsic viscosity and weak gel-like properties at low shear rates, they do not form true gels at any concentration or temperature. Nevertheless, XG is an effective excipient in formulations intended for controlled drug delivery. The release-controlling ability of XG matrices have been improved through interactions with various proteins and polysaccharides such as gelatin, galactomannans, glucomannan, starch and chitosan i.e., polymers that themselves are capable of forming gels (15-20).

Chitosan, a polymer of N-glucosamine produced by alkaline deacetylation of chitin, is biocompatible, biodegradable, non toxic, and mucoadhesive (21). The free amine groups of CH become protonated in an acidic environment. The positively charged polymer is soluble at low pH. The net positive charge of CH in acidic environments allows the formation of a polyelectrolyte complex (PEC) with polyanionic species such as XG. The hydrogel network formation due to this ionic interaction shows pH-sensitive swelling characteristics (22-25). Recently, this combination was used as a platform to produce various CR preparations. In the present study ambroxol HCl was used as a referenec drug. Ambroxol HCl is the active metabolite of the mucolytic agent bromhexine and is used for the treatment of bronchitis to improve expectoration. The drug is rapidly absorbed after oral administration with an elimination half-life of 3 to 4 hours requiring three doses per day for optimum therapeutic efficacy (26, 27). Such properties make Ambroxol HCl an ideal candidate for incorporation into a CR formulation.

Based on this rationale matrices were prepared from a mixture of CH and XG polymers. The controlled release and the swelling behavior of the matrix containing ambroxol HCl was compared *in vitro* with that of Mucosolvan LA® capsules, a commercially available product.

MATERIALS AND METHODS

Materials

The chitosan had a degree of deacetylation of 93%, low molecular weight, a moisture content <10%, viscosity (1.0%, in 1.0% acetic acid) <20 mPa.s, particle size pass through a 80/100 mesh, pharmaceutical grade obtained from Xiamen Xing DA Import and Export Trading Co. Ltd. (Batch No. F000802), , China. The xanthan gum had a viscosity of 1% in a 1% KCl solution (spindle 3, 60 RPM) of 1492 mPa.s, particle size pass through a 80/200 mesh, was of food and pharmaceutical grade from Jungbenzlauer Ges. M.B.H. Handelsgericht Wien, Germany (Lot No. 1949/ 01.05). Ambroxol HCl (particle size pass through 80/100 mesh was purchased from Sifavitor Company, (Italy). All other materials used were obtained from the Jordanian Pharmaceutical Manufacturing Co. Ltd. (JPM), Naor, Jordan.

Methods

Tablet Preparation

Tablets containing 75 mg ambroxol HCl and polymer(s) were prepared by mixing the components of each tablet geometrically in a mortar using a spatula. The required weight was filled in a die of 13 mm diameter and compressed before applying pressure at approximately 443 MPa for 15 seconds using a hydraulic press (C-30 Research and Industrial Instruments, London).

Three tablet groups were prepared as shown in Table 1. In the first group the drug was compressed with CH or XG in a drug to polymer ratio (D:P) of 1: 3 and labeled F01 and F02, respectively. In the second group the drug was compressed using different binary mixtures of CH and XG (1:1, 1:4 and 4:1 and labeled F03, F04 and F05, respectively with a D:P ratio of 1:3). In the third group a 1:1 CH:XG ratio was

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used to prepare tablets with a 1:1 and 1:2 D:P

Table 1 Matrix composition of Ambroxol HCl, Chitosan and/or xanthan gum

TABLET FORMULATION	F01	F02	F03	F04	F05	F06	F07
Ambroxol HCl (mg)	75	75	75	75	75	75	75
CH (mg)	225	—	112.5	45	180	37.5	75
XG (mg)	—	225	112.5	180	45	37.5	75
Total weight (mg)	300	300	300	300	300	150	225
CH:XG ratio	—	—	1:1	1:4	4:1	1:1	1:1
D:P ratio	1:3	1:3	1:3	1:3	1:3	1:1	1:2

ratio (labeled F06 and F07 respectively). All the prepared matrices contained 75 mg of ambroxol HCl.

Swelling, erosion, floation and drug release properties of the polymer mixture

Swelling, erosion and drug release were studied using the USP apparatus I (model DT 80, Erweka, Germany) fitted with six rotating baskets at 75 RPM. In order to simulate the gastrointestinal (GI) tract, the tablets were exposed to 500 ml of 0.1 M HCl for 2 hours, and then transferred to a 500 ml phosphate buffer with a pH of 6.8. For drug release studies 5 ml samples were withdrawn at specified time intervals and replaced with an equal pre-warmed volume. Amounts of ambroxol HCl released from the matrix tablets were assayed spectrophotometrically (PDA Multi-spec UV-1501, Shimadzu, Japan) at 306 nm with respect to calibration curves. For swelling and erosion studies each basket was thoroughly cleaned and then accurately weighed before and after placing the matrix tablet in the basket. This allowed for an accurate calculation of the weight of each tablet. The baskets containing the tablets were then rotated in the dissolution medium at regular time intervals. The baskets were detached, blotted with absorbent tissue to remove any excess medium on the basket surface and accurately weighed using a Mettler AE50 analytical balance (Mettler Instrument Corp., Hightstown, NJ). After weighing, the hydrated matrices were dried in an oven at 60°C until a constant weight was achieved. All studies were carried out in triplicate. The swelling (% weight gain) was calculated using Equation 1.

$$\text{Water uptake } (\%) = \frac{\text{Final weight} - \text{initial weight}}{\text{Initial weight}} \times 100 \qquad \text{Eq. 1}$$

Swelling and changes in tablets dimensions were recorded by taking photographs using the camera of a Samsung Galaxy Y (2 mega pixels). The dried samples were also analyzed using FT-IR and DSC. For the floation experiment, tablets without the drug were prepared from the ratios shown in F01- F07 in Table 1. The test was carried out by dropping each tablet separately in a glass test tube containing 15 ml of 0.1 M HCl (pH 1.2), distilled water or a phosphate buffer at pH 6.8. Photographs were taken at different time intervals for 4 hours.

Fourier transform infrared (FT-IR)

Fourier transform infrared (FT-IR) spectral studies were carried out using a Nicolet Magna-IR® system 560 FTIR Spectrophotometer (Nicolet Instrument Corporation Inc., Madison, WI) instrument using KBr discs. Samples weighing 2 mg were mixed with 300 mg potassium bromide. The powders were compressed using a hydraulic press (Fred S. Carver Inc., Menomonee Falls, WI) at approximately 20,000 pounds under vacuum for 3 minutes. The samples were scanned from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of CH, XG and dried hydrogels formed after heating the hydrogels in the dissolution media using a TA Instruments model 2920 (New Castle, DE). Approximately 10 mg of powder was placed into aluminium pans and sealed. The temperature ramp speed and range for the measurement of samples were 5°C/min and 25–180°C, respectively. The temperature ramp speed and range on crosslinking studies were 10°C/min and 0–400°C, respectively.

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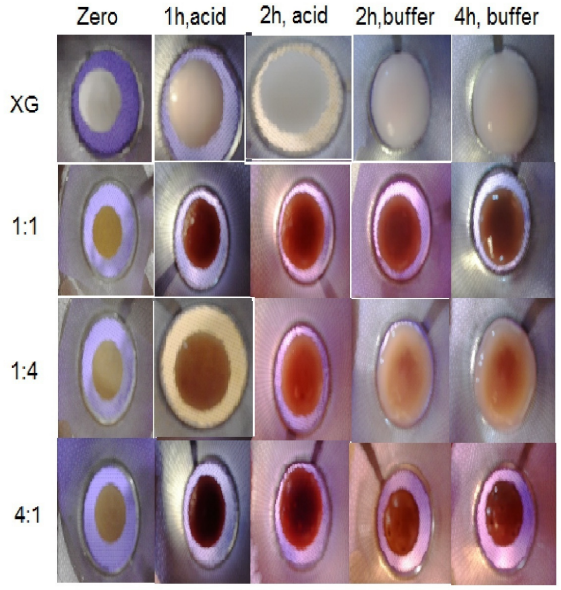

Figure 1 Photo micrographs of the different formulations in acid and buffer media for 4 hours.

RESULTS AND DISCUSSION

Characterization of CH and XG hydro gel layer

Tablet matrices made using only CH dissolved completely in the acidic medium (pH 1.2) during within 2 hours. However, those made using only XG showed great swelling properties in acidic, as well as, in buffer media as shown in Figure 1.

The swelling behavior of the different CH/XG matrices showed that the matrix with maximum XG content i.e., 1:4 CH/XG ratio (F04) showed the highest swelling ability in both acidic and basic media. It is anticipated that the nonionic polymer, XG plays a major role in the swelling process. For the three matrices, F03, F04 and F05, water was absorbed to a limited extent in F03 without gel disintegration. This may be related to the optimum electrostatic interaction between the two polymers at the 1:1 CH/XG ratio with consequent suppression of electrostatic repulsion between the XG side chains and the reduction in immobilisation of counterion in the gel. The matrix tablet with a high CH content, F05, showed a lower swelling ability compared to F03 due to the higher CH dissolution.

In acidic media, XG remains in the unionized form (−COOH) and CH ionizes ($-NH_3^+$), while in basic medium, the (−COOH) groups of XG converts to the ionized form ($-COO^-$), and CH remained in the unionized form ($-NH_3$). The mutual repulsion between positive (in acidic media) or negative (in basic media) charges inside the gel and the transport of water containing the counter ions cause swelling and the formation of hydrogels.

Figure 2 shows the IR spectra of the CH, XG, CH: XG hydrogel layer in 0.1N HCl and CH:XG hydro gel layer in a buffer at pH 6.8. The peak at 1710 cm^{-1} in the IR spectrum of XG was assigned to the carbonyl group of carboxylic acid. The IR spectrum of the (dried) hydrogel formed in 0.1N HCl showed peaks at 1730, 1632 and 1522 cm^{-1} that correspond to C=O stretching, asymmetric NH_3^+ (N−H bend) and symmetric NH_3^+ (N−H bend), respectively. The peak at 1595 cm^{-1} assigned to the amine band of CH had shifted to 1640 cm^{-1}, indicating that the amine group was protonated to a NH^{3+} group in IPC (21-23). However, the NH_3^+ peak was known to appear between 1600 and 1460 cm^{-1}. Therefore, the broad peak around 1550 cm^{-1} was assumed to be the overlapped peak of the COO^- and $NH3^+$

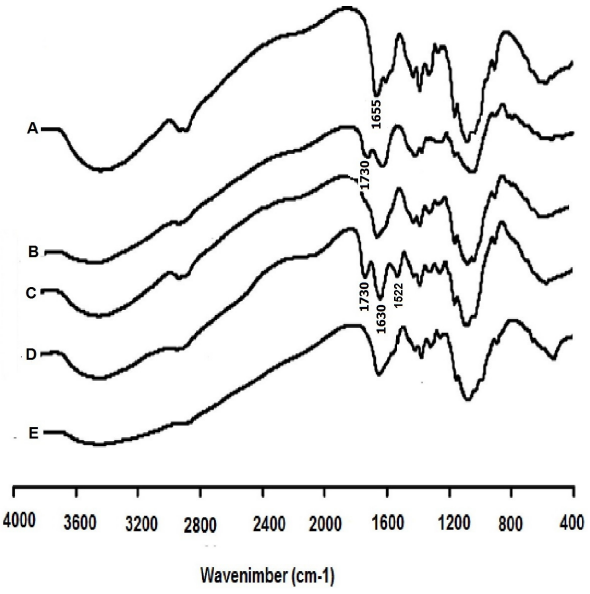

Figure 2 FTIR spectra of CH (A), XG (B), CH: XG physical mixture (C), CH: XG, 0.1 N HCl (D), CH: XG, Buffer pH 6.8 (E).

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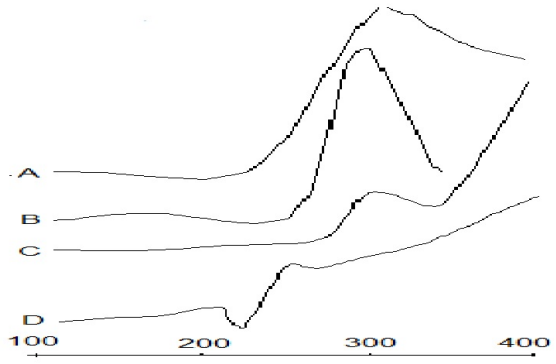

Figure 3 DSC thermogram of CH (A), XG (B), CH:XG 1:1 exposed physical mixture (C), and gel layer exposed to 0.1 M HCl for 2 hours then to a phosphate buffer at pH 6.8 for the rest of the dissolution process of the same matrix (D).

peak, indicating that the CH/XG ionic polyelectrolyte complex (IPC) was formed by an electrostatic interaction between the COO^- group of XG and the $NH3^+$ group of CH (21, 22).

The DSC thermograms of both CH and XG polymers decompose by heating as shown in Figure 2. The gel layer of CH: XG at a 1:1 ratio, compared with their physical mixture, suggested the presence of the reaction as shown in Figure 2 (C, D). The hydro gel layer showed a melting endotherm which could be due to a complex formation between XG and CH.

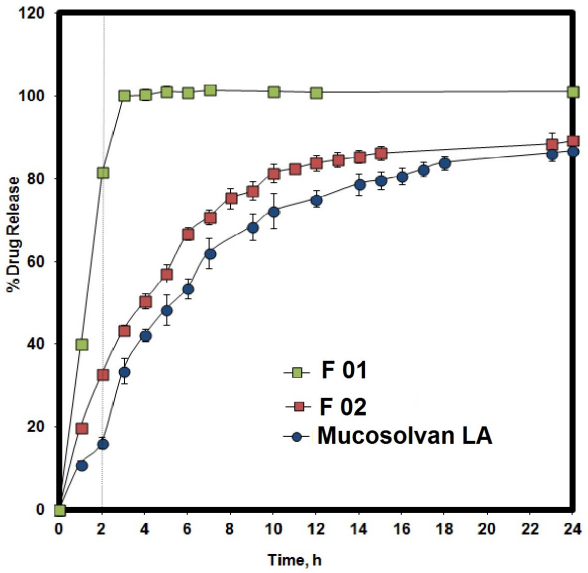

Figure 4 Dissolution profiles of 75 mg ambroxol HCl from CH and XG matrices compared with Mucosolvan LA® capsules.

The degree of interaction can be determined from the resulting heat of fusion (ΔH_f). The greatest degree of interaction should result in the greatest heat of fusion. The value of ΔH_f (J/g) of F03 was greatest compared to F04 and F05 (3.969 ± 0.325, 2.095±0.132 and 3.095 ± 0.035, respectively) indicating the greatest degree of interaction in formulation F03.

Analysis of matrix tablets

The finished tablets were 13 mm in diameter and 4.5 mm in height. The amount of drug in each tablet was within the range of 99.8–100.4% and the standard deviation (SD) was less than 6.0% as specified by the United States Pharmacopeia.

In vitro drug release

The release profiles of ambroxol HCl for the matrix tablets made with CH or XG as a single component and their different binary mixtures are shown in Figure 4 and Figure 5, respectively. From their release profiles, based on using Mucosolvan LA® as a commercially available reference product, the single component matrix tablets resulted in faster drug release where 82% and 33 % of the drug was released after 2 hours in acidic media from the tablets containing CH and XG, F01 and F02 respectively. The fast drug release from the CH tablets could be attributed to the high solubility and poor swelling properties of CH in acidic media compared to that of XG. Matrix tablet F03, showed a lesser release rate compared with the other formulations i.e., F04 and F05 (Figure 5).

The differences in release profiles could be due to the hydration behavior and the molecular interactions of the hydrophilic polymers in the matrices.

Greater gum hydration with simultaneous swelling is expected to result in the lengthening

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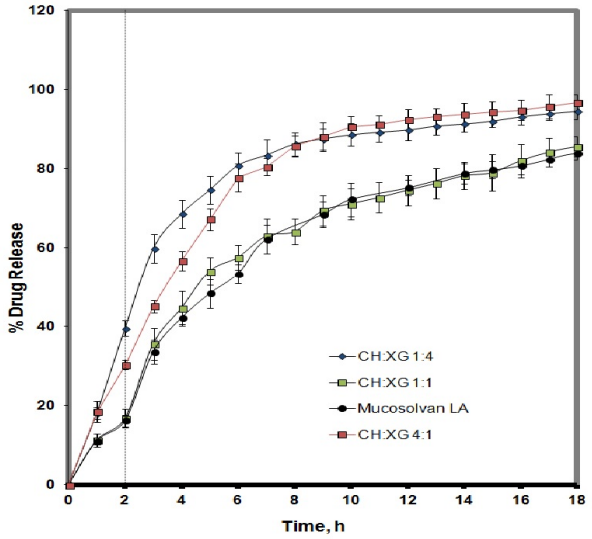

Figure 5 Dissolution profiles of 75 mg ambroxol HCl in polymer mixtures of CH to XG at ratios of 1:4, 1:1 & 4:1 compared with Mucosolvan LA capsules.

of the drug diffusion pathway a consequent reduction of drug release rate. The strong synergistic interactions between polymers resulted in the formation of a network with decreased porosity able to retard the dissolution of the drug. Ambroxol HCl is soluble within the pH range tested, thus its release from the hydrogel matrix is dependent on the swelling and the dissolution/erosion of the matrix.

Figure 5 shows that F03 exhibits a slower release rate compared with F06 and F07.

Drug release kinetic mechanisms

In vitro release data of ambroxol HCl from the matrix tablets were modeled using various kinetic models to determine a putative drug release mechanism. First, the Korsmeyer–Peppas equation (28, 29) Equation 2:

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{Eq. 2}$$

where, M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant correlated with the structural and geometrical properties of the dosage form. The diffusion exponent n indicating the type of drug release mechanism depends on the polymer swelling characteristics and the relaxation rate at the swelling front.

Formulations with an n value of 0.5 are usually taken to be indicative of a Fickian diffusional release whereas values of $0.5<n<1.0$ indicate an anomalous transport or non-Fickian release. For $n=1.0$ the release mechanism is a case-II or zero-order relaxational release associated with stresses and state-transition in hydrophilic glassy polymers which swell or erode. Formulations with $n>1.0$ indicate super case-II transport due to the combination of diffusion and polymer relaxation/dissolution.

The drug release in swellable matrices depends on two processes (i) drug diffusion into the swollen polymer, and (ii) matrix swelling due to the diffusion and relaxation mechanisms (30, 31). In order to estimate the diffusion and relaxation contributions during the anomalous transport process, the Peppas–Sahlin model, Equation 3, was used:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad \text{Eq. 3}$$

where, k_1 and k_2 are kinetic constants related to diffusional and relaxational release, respectively. The first term on the right side of Equation 3 represents the Fickian diffusional contribution (F), whereas the second term represents the case-II relaxation contribution (R). The coefficient m is the purely Fickian diffusion exponent for a device of any geometrical shape exhibiting controlled release. In this study, the value for m is a constant of 0.45 for the formulations with a cylindrical shape.

The Korsmeyer–Peppas and Peppas–Sahlin models are valid only for the early stages of drug release ($M_t/M_\infty \leq 60\%$).

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The percent of drug release due to the Fickian mechanism, F, was determined using Equation 4 (15):

$$F = \frac{1}{1+\frac{k_2}{k_1}t^m} \quad \text{Eq. 4}$$

Drug release from the XG matrix showed an anomalous transport in both acidic and neutral solutions $n = 0.73$ and 0.58, respectively ($0.5 < n < 1.0$). In contrast, drug release from the CH matrix showed super-Case II, ($n > 1.0$), in the acidic medium where the drug was almost completely released. The CH:XG 1:1 (F03) release order (n) was approximately 0.5 in both the acidic and neutral media. Consequently, at this ratio the drug release was controlled mainly by Fickian diffusion. The deviation of the release profiles from square root of time kinetics ($n = 0.5$) is due to polymer relaxation (32, 33). From this it can be inferred that the ratio of CH:XG at 1:1 involves the maximum contribution of drug diffusion and the least contribution of polymer relaxation.

Changing the ratio of drug to polymer mixture to D:P 1:1, 1:2 and 1:3 (F06, F07 and F03, respectively) whilst maintaining the CH: XG ratio at 1:1, showed changes in the drug release mechanism. The release parameters (m, k_1 and k_2) in both acidic and neutral phases determined using Equation 2 are shown in Table 2. The percentage Fickian transport, F, in the acidic and in the neutral phase was determined using Equation 3. Drug release from the F03 matrix resulted in the highest percentage Fickian transport compared to the other ratios in both the acidic and neutral phases. Thus, F03 resulted in the lowest polymer relaxation among all combinations.

The D:P ratio is a critical factor in the formation of the gel layer. For each matrix (D:P 1:1, 1:2, or 1:3) the mechanism of release in the acidic phase shifted showing, with time, an increase in polymer relaxation, and a decrease of pure Fickian diffusion. This indicated that the Fickian diffusion was a time-dependent process. As swelling was succeeded by relaxation the contribution of pure diffusion from such a gel layer decreases with time. In the neutral medium all matrices showed larger F values indicating an increase in the Fickian diffusion compared to that observed in acidic medium. However, in the neutral medium the Fickian contribution to dissolution did not decrease with time.

Table 2 Release parameters of ambroxol HCl from binary mixtures of CH and XG 1:1, using drug to polymer ratios at 1:1, 1:2 and 1:3

MEDIUM	PARAMETER	DRUG POLYMER RATIO 1:1	1:2	1:3
Acid medium	k_1	0.047	0.047	0.061
	k_2	0.160	0.088	0.044
	m*	0.470	0.460	0.457
	$\frac{\sum \mathrm{Res}d^2}{n-2}$	1.009E-05	2.293E-06	8.635E-06
Neutral medium	k_1	0.519	0.220	0.205
	k_2	0.110	0.050	0.025
	m*	0.455	0.440	0.430
	$\frac{\sum \mathrm{Res}d^2}{n-2}$	3.305E-03	1.585E-03	6.360E-04

* Pure Fickian diffusion exponent determined based on the aspect ratio (2a/l), where, a is the observed tablet radius and l is the thickness. This ratio (2a/l) was used to determine m according to the Peppas and Sahlin method k_1 and k_2 are the proportionality constant of the Fickian diffusion and stress relaxation of Equation 3, respectively.

Swelling and/or erosion behavior of CH:XG 1:1 matrix

The release of ambroxol HCl from CH to XG 1:1 matrix occurred largely because of a swelling mechanism rather than by an erosion mechanism. This was further determined by performing a swelling/erosion study of a drug unloaded polymer matrix (CH:XG 1:1) an ambroxol HCl loaded matrix of the same polymer mixture with a drug to polymer ratio of 1:3. The drug unloaded matrix showed nearly no decrease in tablet weight during the *in vitro* dissolution experiment while the drug loaded matrix showed a decrease in the dry weight of the tablet that correlated to the amount of drug present in the tablet. These results indicated that the erosion mechanism had

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no significant effect on drug release from such matrix systems.

CONCLUSION

In conclusion, the present work showed that a binary mixture of naturally hydrophilic polymers, i.e., xanthan gum and chitosan could be used to produce controlled release formulations. Such a mixture could be directly compressed thereby providing a simple, fast and reliable method of manufacturing. It was shown that the mixture of excipients chosen in this work could be used to control the release of ambroxol HCl equivalent to the commercially available medicinal product.

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