Trends In Carbohydrate Research, Vol.2, No.3 (2010) 45-51 0975-0304/09

Trends in Carbohydrate Research

website: www.trendscarbo.com

Pectin-based hydrogels as colon-specific delivery carriers for mebeverine hydrochloride

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Abstract

Mebeverine hydrochloride is a spasmolytic agent with local anesthetic effect. Its controlled-release behavior was investigated from a series of environment-sensitive and biodegradable pectin-based hydrogels. The hydrogels were prepared by crosslinking 'pectin only' or separately in the presence of three monomers, i.e., acrylic acid, *N*-vinyl pyrrolidone and 2-acrylamidomethylpropane sulphonic acid (AAmPSA) using glutaraldehyde as crosslinker. The candidate hydrogels were loaded with mebeverine hydrochloride. The release behavior of the drug was observed to be affected both by the structural and the environmental factors. The maximum drug was loaded on the poly(AAmPSA)-based hydrogel series, and the maximum drug release was observed at pH 8.1 from all the hydrogels. The pattern of the release behavior was observed to be uniform irrespective of the structure of the hydrogels, as the mechanism of the drug release changed from 'diffusion-controlled' to 'chain relaxation-controlled' with the change of the pH from 2.0 to 8.1.

Keywords. Colon-specific drug; Diffusion controlled, Mebeverine hydrochloride, pH sensitive hydrogels; Polymer-drug interactions.

Introduction

It is necessary to design effective colon-specific delivery carriers for the slow or controlled-release of a drug since the chronic inflammatory diseases such as ulcerative colitis requires daily treatment with aminosalicylates or even corticosteroids such as prednisolone[1]. The colon-specific drug delivery carriers have to be designed to minimize *en route* drug losses and side effects, and to ensure the maximum bioavailability of the drug where it is required[2]. The polysaccharide-based hydrogels are the materials of choice as site-specific drug delivery carriers. These can be synthesized with structure control to enable their responsiveness to the external stimuli under the physiological conditions. The hydrogel characteristics such as pH sensitivity, biodegradability and the swelling behavior can be tuned by the proper selection of crosslinker and by using the other suitable polymer component[3]. Recently, researchers are showing keen interest in the use of modified polysaccharides as drug carriers[4,5]. One of the key features of these drug carriers is their inherent biodegradability due to the presence of polysaccharide. The enzymes released by colonic microflora include polysaccharidases such as glucosidases, glycosidases, etc.; those degrade the polysaccharide component of the hydrogel[6]. Hence, by designing the hydrogel structure, most of the drug release can be targeted to reach the colon.

Pectin is an attractive hydrogel material. It has many of the desired properties a hydrogel is expected to encompass as a colon-specific drug carrier. It has carboxylic groups along the macromolecule chain that imparts it pH sensitivity in a slightly alkaline pH, and result is the extensive swelling and subsequent release of the encapsulated drug from its hydrogels. Pectin-derived hydrogels swell in solutions at high pH and shrink at low pH[7,8]. The combination of pectin with another polymer can create unique properties and extend practical applications of the hydrogels than those present in either of the component[9]. There are many reports on the use of modified pectin as carrier of the colon-specific drugs[10-14]. However, it follows from the literature survey that there is scanty information on the site-specific delivery of mebeverine hydrochloride by using drug carrier and delivery devices.

Mebeverine is *N*-substituted ethylamphetamine derivative, 4-{ethyl- [2-(4-methoxyphenyl)-1-methylethyl]-amino}-butan-1-ol, and is available as hydrochloride. It is an effective anti-plasmodic and is used for the treatment of gastrointestinal (GI) spasm, especially in the case of irritable bowel syndrome. It is very effective in relaxing the spasm of the gut, helps in relieving pain and restores and maintains bowel regularity. A pharamacokinetic comparison of the modified release capsule and a plain tablet formulation of mebeverine[15], local anesthetic activity in gel formualtion[16], and *in vitro* release and *ex vivo* spasmolytic effects of mebeverine hydrochloride have been reported[17].

In this article we report the loading and release

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mechanism of mebeverine hydrochloride from four series of environmentally sensitive pectin-based hydrogels. The hydrogels were prepared by crosslinking 'pectin only', or pectin and acrylic acid, *N*-vinyl pyrrolidone (*N*-VP) or 2-acrylamidomethylpropane sulphonic acid (AAmPSA) as the other component, using different concentrations of glutaraldehyde (GA). The drug-polymer interaction was studied to understand the loading and release behavior of the drug. An attempt was made to understand the mechanism of the drug release, and correlate the structure and properties of the hydrogels with their drug loading and release behavior.

Experimental

Materials

Acrylic acid, glutaraldehyde (S.D. Fine, Mumbai, India), 2-acrylamido-2-methylpropanesulphonic acid (E. Merck, Mumbai, India), ammonium persulphate (Sarabhai Chemicals, India), pectin (Loba Chemie, Mumbai, India), *N*-vinyl pyrrolidone (Merck, Schuchardt, Germany), were used as received. Mebeverine hydrochloride was kindly provided by M/s. Solvay Pharma India Ltd., Mumbai, India.

Synthesis of hydrogels

The hydrogels were synthesized by crosslinking pectin as such or separately in 2.5:1 weight ratio separately with three monomers and using different concentrations (5-25%) of glutaraldehyde following an earlier described method[18,19]. Three monomers used were: AAc, AAmPSA and *N*-vinyl pyrrolidone. The self-insolublized product were separated and lyophilized by stirring thoroughly with acetone and dried under vacuum. The xerogels thus obtained were refluxed separately with water by stirring for 1 h. The % network efficiencies were calculated as follows:

$$\%\ \text{Efficiency}\ (\%\,E) = (W_d/W_r) \times 100$$

Where W_d is the weight of the dried hydrogel (xerogel) and W_r is the weight of all reacting species including pectin, GA and monomer in the feed. Thus, four series of hydrogels, pectin-*cl*-GA, pectin/poly(AAc)-*cl*-GA, pectin/poly(AAmPSA)-*cl*-GA, pectin/poly(*N*-VP)-GA, where -*cl*- stands for crosslinked, were prepared. The feed amount of the crosslinker in the designated hydrogels is shown by the number as exemplified for pectin-*cl*-GA5 or pectin-*cl*-GA25 prepared with 5 or 25% feed concentrations of GA, respectively.

Characterization of hydrogels

The hydrogels were characterized by scanning electron micrography (Joel Stereoscan-150 microscope), Fourier transform infrared spectra (Nicollet 5700) and nitrogen analysis (Carlo Erba Instrument 1150). The swelling behavior of the hydrogels was studied at 37 ºC and over a range of pH following an earlier reported procedure[19]. The % swelling (P_s) of each hydrogel was calculated from the following relation:

$$P_s = (M_t M_o)/M_o) \times 100$$

Where M_t is the mass of swollen gel at time *t*, and M_o is the initial mass of the dry gel.

Drug loading and release studies

Hydrogels (2.0 g) were separately immersed in 50.0 mL of 10.0 mM mebeverine hydrochloride solution prepared in water. The solution was stirred continuously for 24 h at 30 ºC. Subsequently the hydrogels were removed and dried under vacuum. The drug loading was evaluated spectrophotometrically from the rejected drug in the solution from the standard curve (Table 1). *In vitro* drug release was studied by the immersion of hydrogels in solutions of different pH at 37 ºC for different time intervals. The amounts of mebeverine hydrochloride released were measured from the corresponding OD values of the standard curve. The cumulative values were plotted against time scale from 30 min to 240 min. The release behavior of the mebeverine hydrochloride was studied using the modified Fick's equation:

$$P_t/P_i = k.t^n, \text{ for } 0 < P_t/P_i < 0.60$$

Where P_t is the percent release of drug at time `*t*' and P_i is percent release at infinite time. The log-log form of the above equation was used to calculate diffusion exponent (*n*) and gel characteristic constant (*k*). The release kinetics from the swellable systems, zero order, anomalous kinetics and fickian release behavior are represented by $0.8 < n < 1.0$, $0.5 < n < 0.8$ and $n = 0.40.5$, respectively. The amounts of the drug released for different hydrogels was plotted by taking $\ln P_t/P_i$ along x-axis and lnT along y-axis. From the slopes and intercepts of the above plots so obtained, diffusion exponent (*n*) and gel characteristic constant (*k*) have been calculated (Table 1). The release behavior of each hydrogels was explained from the values of the diffusion exponents.

Results and Discussion

Characterization of hydrogels

Four series of pectin-based hydrogels were synthesized. The biodegradability of these or analogous hydrogels was demonstrated in an earlier study[18]. %E increased with an increase of %GA in the feed in a narrow range from 81.23 at 2.5 mM to 85.34 at 12.5

mM. Thus, it is implied that high network yields with minimum loss of the reacting species is obtained even at the low crosslinker concentrations. %N from the nitrogen analysis of the pectin/poly(AAmPSA)-*cl*-GA and pectin/poly(*N*-VP)-*cl*-GA was also found to increase with the %GA in the feed. SEMs revealed porous nature of the hydrogels**.** The surface morphology, pore size and their distribution is affected by the nature of monomers and feed concentration of the crosslinker, as the pore size of the hydrogels decreased with an increase of %GA in the feed[19]. In the FTIR spectra of pectin-*cl*-GA5 important absorption peaks appear at 1742.0 and 1728.6, 1041.1 cm^{-1} due to the stretching of -C=O (acid and ester) and -COC- between the anhydrogalacturonic units. Apart from the characteristic peaks of pectin, in the FTIR spectrum of pectin/poly(*N*-VP)-*cl*-GA5 has important peaks at 1754.9 cm^{-1} due to -C=O stretching of cyclic amide poly(*N*-VP), and in the spectrum of pectin/poly(AAmPSA)-*cl*-GA5 peaks at 1654.1 cm^{-1} and at 1300 cm^{-1} appear due to the -C=O and -S-OH stretching poly(AAmPSA). The swelling behavior of the different hydrogels was studied as a function of the variation of feed concentration of GA at 37 ºC for 120 min and at four different pH. The swelling was affected by pH or with an increase of %GA in the feed with the low pH and high feed concentration of crosslinker affecting it adversely. The hydrophilic nature of the other polymer component of the hydrogel contributed in the enhancement of the water uptake. The swelling of hydrogels follows the order: pectin/poly(AAmPSA)-*cl*-GA > pectin/poly(AAc)-*cl*-GA > pectin/poly(*N*-VP)-*cl*-GA > pectin-*cl*-GA.

Loading and release behavior of mebeverine hydrochloride

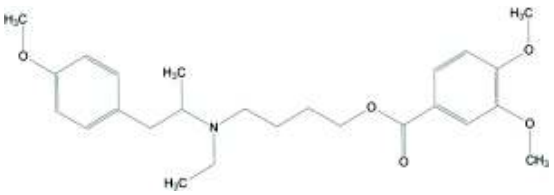
Effect of hydrogel structure on the drug-polymer loading

Table 1. Loading of mebeverine hydrochloride on hydrogels.

Hydrogel	Mebeverine Loaded (mM)*
Pectin-*cl* –GA5	5.858
Pectin-*cl* –GA15	4.392
Pectin- *cl* –GA25	4.117
Pectin/poly(AAc)-*cl*-GA5	6.660
Pectin/poly(AAc)-*cl*-GA15	5.294
Pectin/poly(AAc))-*cl*-GA25	5.039
Pectin/poly(AAmPSA))-*cl*-GA5	7.120
Pectin/poly(AAmPSA)-*cl*-GA15	6.382
Pectin/poly(AAmPSA)-*cl*-GA25	6.019
Pectin/poly(N-VP))-*cl*-GA5	4.089
Pectin/poly(N-VP))-*cl*-GA15	3.785
Pectin/poly(N-VP))-*cl*-GA25	3.024

*Feed =10.0 mM/L.

Mebeverine has the following structure:



To understand its interactions with the hydrogels, mebeverine hydrochloride was complexed separately with pectin, poly(AAc), poly(*N*-VP) and poly(AAmPSA) and the absorbances (λ_{max}) in the UV region were studied. It shows λ_{max} at 310 nm in water, but with pectin the λ_{max} shifts to 272 nm due to the interaction. Similar red shifts were observed in the presence of poly(AAc), poly(AAmPSA) and poly(*N*-VP) with the λ_{max} at 262 nm, 260 nm and 290 nm, respectively (Table 1). Thus, the strongest interactions took place with poly(AAmPSA) which means that in this case most of the drug got partitioned from the solution phase to the hydrogel phase, which got reflected in the highest drug loading in this hydrogel series. This argument is also reaffirmed as the drug loading trends are in conformity with the swelling of these hydrogels, as higher the swelling more is the amount of the drug effectively partitioned from solution phase to the hydrogels phase. An order for the mebeverine hydrochloride loading on different hydrogels can be put as: pectin/poly(AAmPSA)-*cl-GA* > pectin/poly(AAc)-*cl-GA* > pectin-*cl-GA* > pectin/poly(N-VP)-*cl-GA* (Table 1). The drug release behaviour has been found to be directly proportional to the amount of the drug loaded on the hydrogels.

Release mechanism of mebeverine hydrochloride

Results of the mebeverine hydrochloride release in different pH media from different hydrogels are presented in Figure 1-4. Release behavior of pectin-*cl*-GA5 is presented in Figure 1. At pH 1.0 ($n = 0.473$) and at pH 4.0 ($n = 0.473$), the release behavior is Fickian-type as no deviation was observed from the linearity. As expected at higher pH ($n > 0.5$ at 0.635 at pH 7.0 and $n < 0.5$ [(0.344) at pH 8.1], the release behavior exhibited deviation from the fickian behavior, and it was more pronounced at pH 8.1. It follows there from that at low pH, drug release behavior was diffusion-controlled, but as the pH of the media increased it became chain relaxation-controlled as well as diffusion-controlled. Such mechanism of drug release from these hydrogels was expected as these swell less in the medium of low pH due to the suppression of the ionization of the -

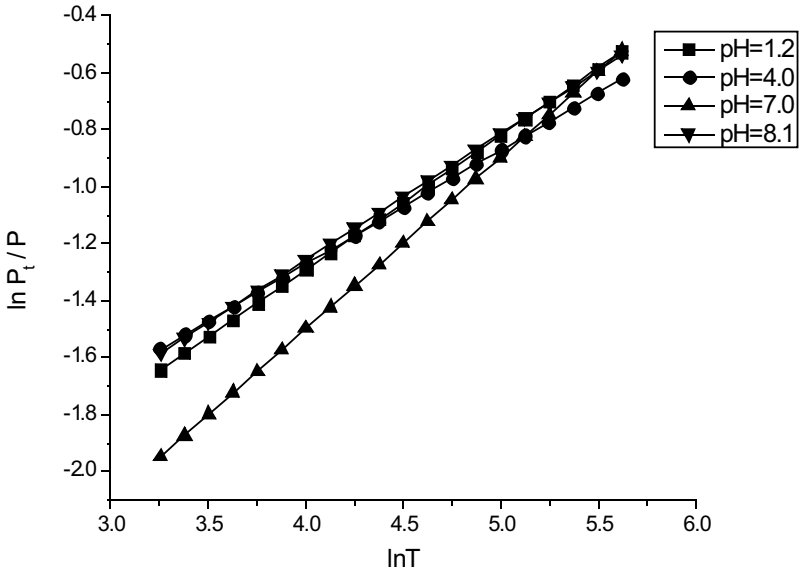


Figure 1: Plots of $\ln P_t / P_i$ versus lnT for the evaluation of diffusion exponent (n) and gel characteristic constant (k) for the release of mebeverine hydrochloride from pectin-*cl*-GA5 in different pH media at 37 °C.

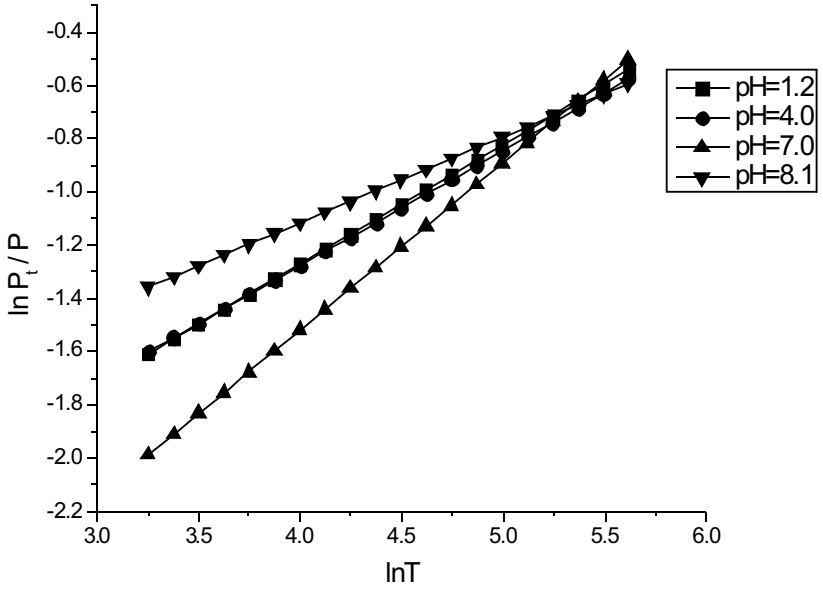


Figure 2: Plots of $\ln P_t / P_i$ versus lnT for the evaluation of diffusion exponent (n) and gel characteristic constant (k) for the release of mebeverine hydrochloride from pectin/poly(AAc)-*cl*-GA5 in different pH media at 37 °C.

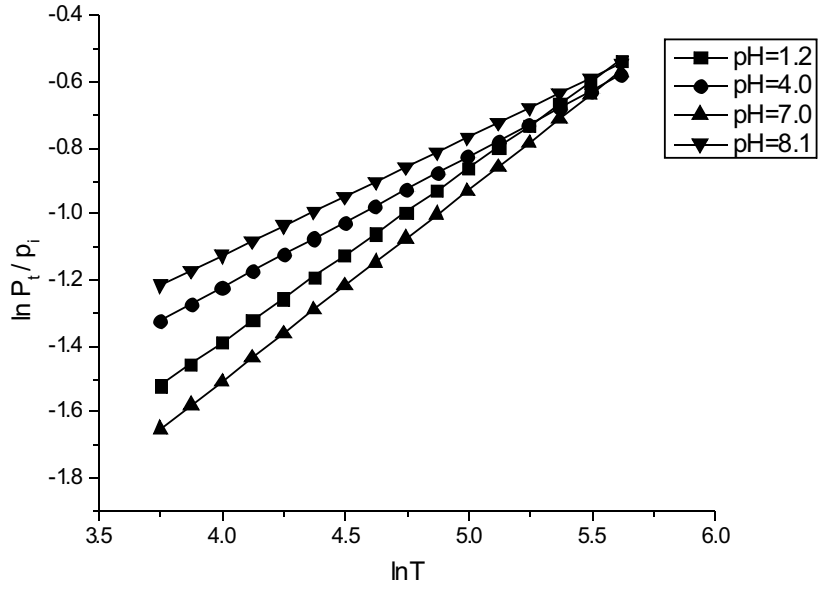


Figure 3: Plots of $\ln P_t / P_i$ versus lnT for the evaluation of diffusion exponent (n) and gel characteristic constant (k) for the release of mebeverine hydrochloride from pectin/poly(AAmPSA)-*cl*-GA5 in different pH media at 37 °C.

CO_2H, and on the contrary these swell more at the neutral and the alkaline pH. Since, with an increase in swelling, the polymer chains become relaxed, more drug release took place at the higher pH, and deviation from the fickian behavior was evident. The more deviation of the release behavior from the 'Fickian only' at the higher pH is also related to the onset of the the biodegradability of these hydrogels[18]. The hydrogel structure-property relationship was more evident from the release behavior of pectin-*cl*-GA15 and pectin-*cl*-GA25 as these released less amount of drug as compared to pectin-*cl*-GA5. In all the cases, the amount of the drug released corresponded to the drug loaded. However, the drug release behavior remained the same at different pH as observed for pectin-*cl*-GA5. Hence, at low pH the release behaviour was only diffusion-controlled while at high pH, relaxation of polymeric chains takes place, and release mechanism became diffusion-controlled as well as chain relaxation-controlled.

The effect of the other polymer component of hydrogel on mebeverine hydrochloride release behavior is more of quantitative nature, as these hydrogels absorbed larger amounts of the drug than the pectin-*cl*-GA hydrogel series, hence the drug release

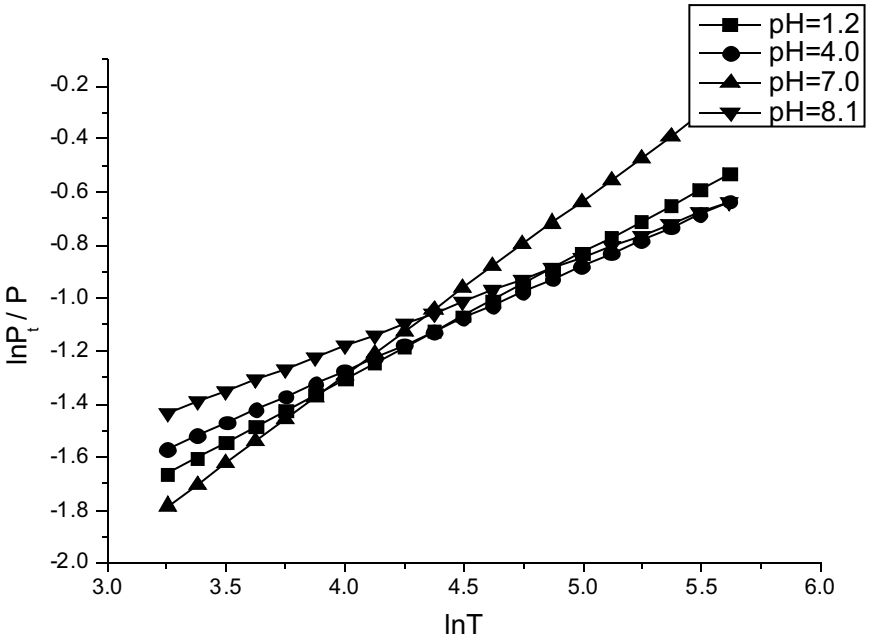


Figure 4: Plots of $\ln P_t / P_i$ versus lnT for the evaluation of diffusion exponent (n) and gel characteristic constant (k) for the release of mebeverine hydrochloride from pectin/poly(N-VP)-*cl*-GA5 in different pH media at 37 °C.

from a particular hydrogel at a particular pH corresponded to the amount of the drug loaded (Figures 1-4). Otherwise for the candidate hydrogels studied from the three series of pectin-poly(AAc)-*cl*-GA, pectin-poly(AAmPSA)-*cl*-GA and pectin-poly(*N*-VP)-*cl*-GA hydrogels, the drug release behavior remained the same as observed for the hydrogel series discussed earlier. Pectin-poly(AAmPSA)-*cl*-GA5 showed the maximum release of the drug. In all the hydrogels studied, the extent of the drug release was observed to decrease for the hydrogels prepared with the higher feed concentrations of GA.

Conclusions

Pectin-based four series of the cost-effective, biocompatible, biodegradable and environmentally-sensitive hydrogels were synthesized. The structural and environmental factors affected the drug loading and release profile of these hydrogels. Pectin-based hydrogels are good candidates as the carriers and delivery devices of mebeverine hydrochloride since these have exhibited desirable high drug loading and site-specific drug release. The hydrogels exhibited differences mainly in the extent of drug release and

loading. The release mechanism remained the same over a range of pH for all the hydrogel series studied with the 'diffusion-only' at the low pH to the 'diffusion and chain relaxation-controlled' at the higher pH. The candidate hydrogels those exhibited the high level of drug-uptake with controlled-release mechanism are good candidates in the targeted applications.

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