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Research Article

STUDIES ON DIFFERENT CHITOSAN POLYELECTROLYTE COMPLEX HYDROGELS FOR MODIFIED RELEASE OF DILTIAZEM HYDROCHLORID

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ABSTRACT

The aim of this work was to evaluate the possibility of using mixtures and/or polyelectrolyte complexe hydrogels from chitosan-alginate, chitosan-carboxymethylcellulose sodium and chitosan-carbopol as prolong drug release systems using Diltiazem HCl as model drug.The hydrogels were evaluated for swelling studies, invitro drug release, SEM(scanning electron microscopy), DSC(diffrencial scanning colorimetry) and FTIR analysis.The effect of chitosan concentration on swelling and invitro release was carried out.Regression analysis and correlation coefficient "r" values were calculated for all the formulation indicating non-fickian diffusion mechanism first order release. It is observed that swelling behavior of PEC hydrogels controlled the drug release.The PEC hydrogels with chitosan-carboxymethylcellulose sodium showed least rate of swelling with greator sustained drug release.

Keywords: Diltiazem HCl, Polyelectrolyte complex hydrogels, Sodium alginate, Carboxymethylcellulose sodium, Carbopol 940.

INTRODUCTION

Polyelectrolyte complexes (PECs) are the association complexes formed between oppositely charged particles (e.g polymer-polymer, polymer-drug and polymer-drug-polymer). These are formed due to electrostatic interaction between oppositely charged polyions. This avoids the use of chemical cross linking agents, thereby reducing the possible toxicity and other undesirable effects of the reagents[1].Chitosan[ά-(1,4)2-amino-2-deoxy-β-D-glucon] is a unique polysaccharide derived from chitin. Chitosan has a variety of promising pharmaceutical uses and is presently considered as a novel carrier material in drug delivery systems, as indicated by the large number of studies published over the last few years[2]. Chitosan is a poly cationic polysaccharide that forms polyelectrolyte complex with oppositely charged component like alginate, carboxymethylcellulose sodium, carbopol and pectin. Hydrogels are three dimensional, hydrophilic, polymeric networks capable of imbibing large amount of water or biological fluids. Hydrogels are of special interest in controlled release applications because of their soft tissue biocompatibility, the ease with which drugs are dispersed in matrix and the high degree of control achieved by selecting the physical and chemical properties of polymer network[3].The aim of this work was to evaluate the possibility to obtain different prolonged drug dissolution profiles by changing the polymer matrix system (chitosan-alginate, chitosan-carboxymethylcellulose sodium and chitosan-carbopol940) and the method used to include the polymers into the formulation (physical mixture or polyelectrolyte complex). Also we tried to explain the drug dissolution profile from the matrices considering the swelling behavior of the polymers used.

MATERIALS AND METHODS

Materials

Diltiazem HCl was received as gift sample from Enventia Health Care Pvt.Ltd, Mumbai. Chitosan was received from Tahira Chemicals Pvt.Ltd, Kerela. Sodium Alginate, Carboxymethylcellulose sodium and carbopol940 (SD fine-chem. Limited, Mumbai) were procured from commercial sources. All other chemicals and reagent used in this study were of analytical grade.

Methods[4,9]

The polyelectrolyte complexes were prepared from chitosan[12] solution at 4.0% w/v in 1% w/w acetic acid solution and sodium alginate/carboxymethyl cellulose sodium solution at 4.0% w/v in water. Each solution was heated at 70-80 C^0 counter ions such as $CaCl_2$ & $AlCl_3$ were added to chitosan solution. Both the solution were mixed at 75C^0 with agitation until the mixture reaches the room temperature. Then it was left to rest for 2hr. The polyelectrolyte complex was thoroughly washed with distill water then separated from water by centrifugation for 30 min at 8000 rpm. Thereafter the PEC was again submerged in distill water and left for over night. Finally the PEC was dried in hot air oven at 40C^0 for 8hrs. The dried hydrogels were crushed & passed through sieve #100. (chitosan and Alginate, Carboxymethylcellulose sodium & carbopol940 were used in the ratio of 0.5:1,1:1,1.5:1).

Characterization

DSC thermogram was obtained using an automatic thermal analyzer system (Perkin Elmer DSC Instrument, Japan). Temperature calibration was performed using indium as the standard. Samples were crimped in a standard aluminium pan and heated from 50 to 300ºC at a heating rate of 10ºC/ min under constant purging of dry nitrogen at 30 ml/ min. IR absorption of the prepared hydrogels were measured using the KBr pellet method at a compression pressure of 2500 Ib/m^2 on a FT-IR spectrophotometer type FT-IR 1600 Perkin Elmer Co Japan. SEM studies were carried out on hydrogel samples after coating with gold-palladium on a scanning electron microscope, model Joel LV 5600 USA.

Swelling and drug release studies[5,6]

Accurately weighed matrix tablets were immersed in 25 ml of pH 1.2 HCl buffer solutions after 2 hours, the tablets were transferred to 25 ml pH 7.4 phosphate buffer solutions. At fixed time intervals, the tablets were separated from the medium. Immediately, they were wiped gently with paper and weighed. The dynamic weight change of the tablets with respect to time was calculated according to the formula.

$$\text{Percent weight change} = \frac{W_s - W_i}{W_i} \times 100\%$$

Where, W_s is the weight of tablet in the swollen state and W_i is the initial weight of tablet.

The *in vitro* release of drug from PEC matrix tablets were carried out for 16 hours using paddle type Electrolab Tablet Dissolution Apparatus USP XXIII containing 900 ml of dissolution medium maintained at 37±0.5ºC and speed of agitation at 50 rpm. For the first 2 hours, pH 1.2 HCl buffer solution was used as dissolution medium, then the dissolution medium was changed by replacing with pH 7.4 phosphate buffer solution for further 14 hours. At prefixed time (every 1 hour), 5 ml of solution were withdrawn and

spectrophotometrically assayed for the drug content at 238 nm using Shimadzu-1700 UV-Visible spectrophotometer. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium[3,6,7].

RESULTS AND DISCUSSION

The DSC thermogram of diltiazem HCl (Fig 1) exhibited sharp endothermic peak at 214.63ºC. In case of diltizem HCl loaded chitosan- carboxymethylcellulose sodium PEC hydrogels, two endothermic peak was observed at 106.23 and 194.08ºC. For diltiazemHCl loaded chitosan carbopol PEC hydrogels, All results of DSC thermogram of formulations suggests that the polyelectrolyte complex formed between chitosan and sodium alginate, carboxymethylcellulose sodium and carbopol940 during formulation process. However, the peaks corresponds to diltiazem HCl is not observed or shifted in the DSC thermogram of formulations, which indicates that most of the drug was uniformly dispersed at the molecular level in the PEC hydrogels and might be due to the electrostatic interaction between charged diltiazem HCl and biopolymers.

The interactions and PEC complexation were further confirmed by Fourier-transform infrared (FTIR) spectroscopy. In the FTIR spectrum of diltiazem HCl loaded chitosan-sodium alginate PEC hydrogels (Fig 2), the peak at 1700 cm^{-1} (which was observed in sodium alginate spectra) was couple to form broad peak at nearby 3280.46cm^{-1} to 2884.50 cm^{-1}. In case of FTIR spectrum of diltiazem HCl loaded chitosan-carboxymethylcellulose sodium PEC hydrogels the peak observed at 1200 cm^{-1} in carboxymethylcellulose sodium FTIR spectra, was shifted to 3300-2894.78 cm^{-1}. In case of chitosan-carbopol940 PEC hydrogels the FTIR spectrum exhibited disappearance of peak at 1648.40cm^{-1}, which was observed in carbopol940 FTIR spectra. And it also showed an absorption peak around 1427.52-1319.92 cm^{-1} in FTIR spectrum of chitosan and carbopol940. This evidenced the formation of strong polyelectrolyte complex between chitosan and sodium alginate, carboxymethylcellulose sodium and carbopol940 during the formulation process. The surface morphology of prepared drug loaded PEC hydrogels was studied by scanning electron microscopy (SEM). The PEC hydrogels formed by chitosan and sodium alginate have rough texture and small gaps as shown in Fig 3. The PEC hydrogels formed by chitosan and carboxymethylcellulose sodium have less porous and smooth surfaces as shown in Fig 4. The PEC hydrogels formed by chitosan and carbopol 940 have sponge like surface with fibrilar structure as in shown in Fig 5.

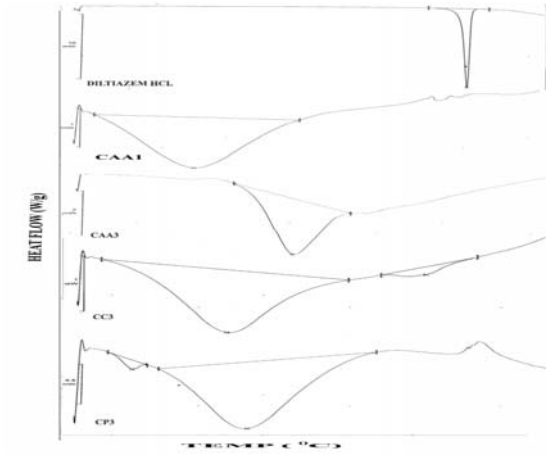

Fig. 1: DSC thermogram of diltiazem HCl, drug loaded chitosan-alginate with CaCl2 & AlCl3 (CAC3,CAA1&CAA3), chitosan-carboxymethylcellulose sodium(CC3) and chitosan-carbopol 940(CP3) polyelectrolyte complex hydrogels

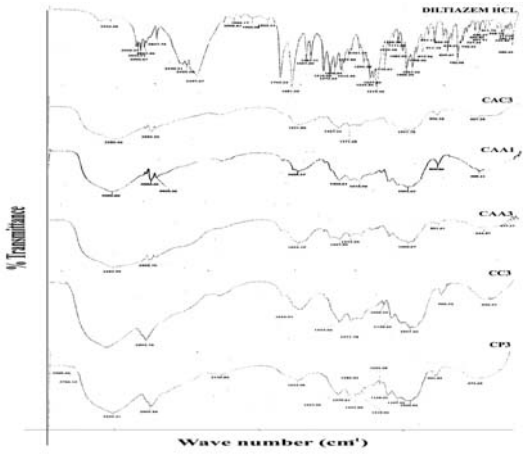

Fig. 2: FTIR spectra of diltiazem HCl, drug loaded chitosan-alginate with CaCl2 & AlCl3 (CAC3,CAA3), chitosan-carboxymethylcellulose sodium(CC3), chitosan-carbopol940(CP3) polyelectrolyte complex hydrogels.

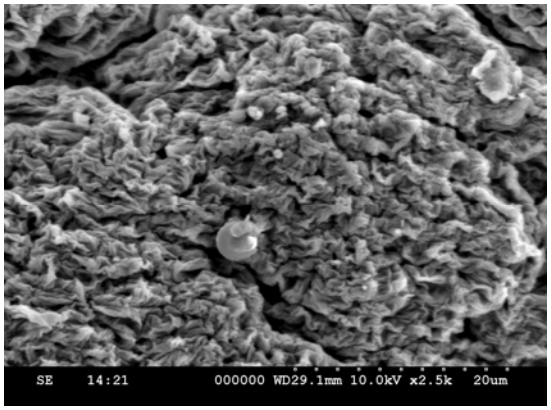

Fig. 3: Scanning electron micrograph of diltiazem HCl loaded chitosan-sodium alginate PEC hydrogels containing AlCl3.

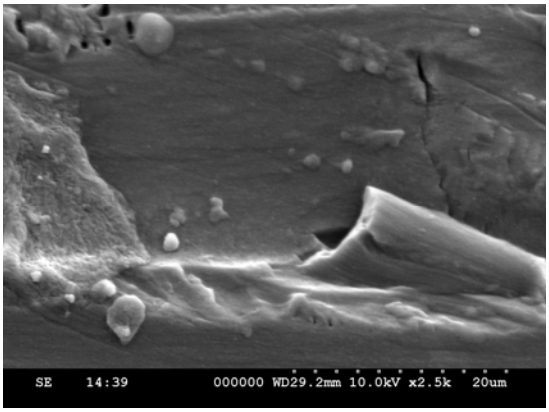

Fig. 4: Scanning electron micrograph of diltiazem HCl loaded chitosan-carboxymethylcellulose sodium PEC hydrogels.

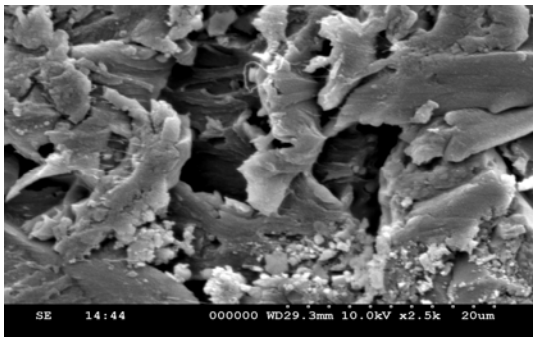

Fig. 5: Scanning electron micrograph of diltiazem HCl loaded chitosan-carbopol PEC hydrogels.

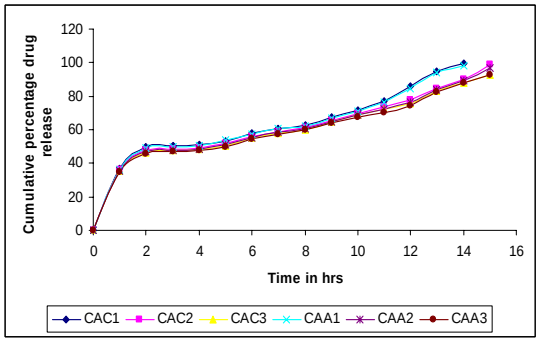

Fig. 6: In vitro release data of diltiazem HCl loaded matrix tablet formulated with chitosan-alginate PEC hydrogels containing $CaCl_2$ &$AlCl_3$

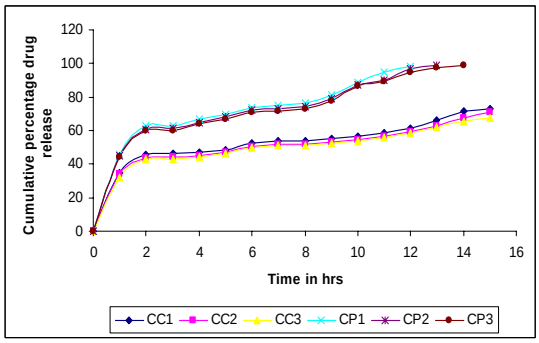

Fig. 7: In vitro release data of diltiazem HCl loaded matrix tablet formulated with chitosan-carboxymethylcellulose sodium and chitosan-carbopol PEC hydrogels.

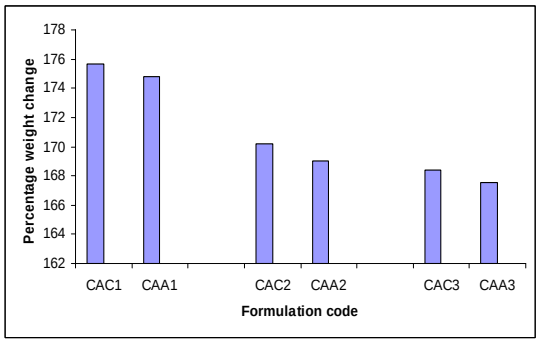

Fig. 8: Effect of chitosan concentration on swelling behavior of diltiazem HCl matrix tablet formulated with drug loaded chitosan-alginate PEC hydrogels containing $CaCl_2$ & $AlCl_3$ *Ratios(CAC1&CAA1,0.5:1 ,CAC2 &CAA2,1:1 ,CAC3& CAA3,1.5:1)

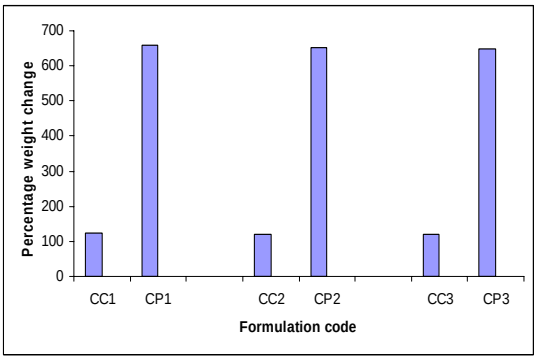

Fig. 9: Effect of chitosan concentration on swelling behavior of diltiazem HCl matrix tablet formulated with drug loaded chitosan-carboxymethylcellulose sodium and chitosan-carbopol PEC hydrogels. *Ratios(CC1&CP1,0.5:1 ,CC2&CP2,1:1 ,CC3&CP3,1.5:1)

The *in vitro* release of diltiazem HCl also depends on swelling behavior of the tablets. The *in vitro* release profile of diltiazem HCl is shown in Fig 6 & 7. The *in vitro* release study was performed in HCl buffer (pH 1.2) for initial first two hours, then the medium was replaced by phosphate buffer (pH 7.4) and study was continued for sixteen hours. The *in vitro* release of diltiazem HCl was very slow in first two hours in HCl buffer (pH 1.2). After 2 hours approximately 34.90% of diltiazem HCl, from chitosan-sodium alginate tablets, 44.47% from chitosan- carbopol and 32.33% from chitosan-carboxymethylcellulose sodium tablets has been released. At the acidic pH of the dissolution medium the charge density of chitosan was sufficiently high and the ionic interactions were increased resulting in the formation of much stronger network. Hence, the release mechanism was mainly due to diffusion. In the second phase of *in vitro* release study using phosphate buffer (pH 7.4), the release of diltiazem HCl, was rapid and a maximum of 87.783% from chitosan-sodium alginate, 99.061% from chitosan-carbopol 940 and 65.327% from chitosan- carboxymethylcellulose sodium was released within fifteen hours. The ionic interaction between chitosan and negatively charged polymers was greatly reduced at this pH of 7.4 and forms a loose network with increase porous surface which allows greater part of dissolution media along with counterions. Hence, at pH 7.4 of phosphate buffer, rapid dissociation of PEC membrane may observe and the release of diltiazem HCl was due to burst effect[8]. Tablets prepared with chitosan and carboxymethylcellulose sodium shows sustained release of diltiazem HCl, with a $\%DR_{15hr}$ value of 71.40 to 65.32% (formulations CC1 to CC3) due to formation of strong PEC membrane that restricts the easy entry of dissolution medium. The *in vitro* release of diltiazem HCl, from chitosan-sodium alginate containing $CaCl_2$ was more with a $\%DR_{15hr}$ value of 99.432 to 88.012 (formulations CAC1 to CAC3) as compared to PEC tablets containing $AlCl_3$ having $\%DR_{15hr}$ value of 98.423 to 87.783 (formulations CAA1 to CAA3). The reason was due to effect of counterions as explained previously. The overall *in vitro* release of diltiazem HCl, from all the formulations shows the following order with changing the negatively charged polymers carboxymethylcellulose sodium < sodium alginate< carbopol 940. The concentration of chitosan significantly affects the release of diltiazem HCl, (Fig. 8 & 9). As the concentration of chitosan increased (0.5, 1.0 and 1.5% w/v) in all formulations, interaction between the two polymers should have been increased forming a closer network, which showed decrease in the diffusion of drug outwards of the tablets. The *in vitro* release of diltiazem HCl, from the porous surfaces as in chitosan-sodium alginate tablets (formulated with $CaCl_2$) was more and rapid. The PEC with rough or smooth surfaces as in chitosan-sodium alginate tablets (formulated with $AlCl_3$) and chitosan-carboxymethylcellulose sodium tablets shows slow release of diltiazem HCl[13,14]. The *in vitro* drug release data obtained was subjected to zero order and first order. When the data was fitted to first order kinetic model, a linear relationship was

obtained with high 'r' value and small SSR value, suggesting that the drug release followed first order kinetics[11].

CONCLUSION

Hence it can be concluded that diltiazem HCl can be prepared as oral modified release systems effectively by using chitosan along with sodium alginate and carboxymethyl cellulose in the form of polyelectrolyte complex hydrogels.

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