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Ca^{2+} ion cross-linked interpenetrating network matrix tablets of polyacrylamide-grafted-sodium alginate and sodium alginate for sustained release of diltiazem hydrochloride

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ABSTRACT

Interpenetrating network (IPN) matrix tablets of diltiazem-HCl (DTZ) was prepared by wet granulation method using polyacrylamide-grafted-sodium alginate (PAam-g-SAL) co-polymer and sodium alginate (SAL) for sustained release of the drug. Formulation of IPN structure was examined using FTIR spectroscopy, and compatibility of the drug with the polymers was evaluated through FTIR, DSC, and XRD analyses. The effect of co-polymer/SAL ratios, drug load, and total polymer/calcium gluconate (CG) ratios on drug release in acidic and phosphate buffer solutions was investigated. The release of drug was controlled by the relative magnitude of swelling capacity of IPN matrix and viscosity of the gel formed following dissolution of the polymers. The swelling capacity of the matrix was governed by the formation of calcium alginate gel structure and the rigidity imparted by the co-polymer. The results indicated that IPN matrix tablets of PAam-g-SAL and SAL could be used for sustained release of DTZ.

1. Introduction

Development of oral sustained release drug delivery systems is of much interest to the pharmaceutical scientists as these systems provide prolonged duration of action of drugs having short biological half-life, and reduce dose-related toxicity, dosing frequency, and patient non-compliance (Chien, 1997; Uhrich, Cannizzaro, Langer, & Shakesheff, 1999). Among the various sustained release drug delivery systems, pharmaceutical industries prefer sustained release tablet dosage form because of the ease of production using the existing tablet manufacturing infrastructure (Bayomi, Al-Suwayeh, & El-Heiw, 2001; Giunchedi, Gavini, Moretti, & Pirisino, 2000; Liew, Chan, Ching, & Heng, 2006). Biopolymers have received increased attention to formulate tablets for controlled release of drugs (Bhardwaj, Kanwar, Lal, & Gupta, 2000; Billa & Yuen, 2000).

Carbohydrate comprises more than 90% of the dry weight of all biomass, and more than 90% of the carbohydrate mass is available in the form of polysaccharides (Zohuriaan-Mehr & Pourjavadi, 2003). Traditionally, polysaccharides have been widely used as excipients such as suspending agents, emulsifying agents, jelling agents, and tablet binders in pharmaceutical formulations. With the advancement of macromolecular chemistry, the use of polysaccharides has been extended to newer applications in pharmaceutical, biomedical and agricultural fields. The biodegradability and biocompatibility of these materials would reduce or eliminate side effects in biomedical applications (Klouda & Mikos, 2008). In addition, native polysaccharides are amenable to various chemical modifications (Vyas & Khar, 2002) and thus, many important functional properties can be imparted to these materials (Tapia et al., 2002). Sodium alginate (SAL), a natural polysaccharide obtained from marine brown algae and composed of 1,4-linked β-D-mannuronic acid and α-L-guluronic acid residues, has been used to formulate matrix tablets of various drugs. However, easy solubility in water, substantial swelling and rapid erosion of SAL matrix tablet are some of the limitations to make it an ideal matrix material (Laurienzo et al., 2006; Sutar, Mishra, Pal, & Banthia, 2008). One approach to overcome these limitations is to physically crosslink SAL with Ca^{2+} ions through ionotropic gelation process. When alginate matrix tablets containing a calcium salt such as CG come in contact with acidic aqueous solution, in situ gelation takes place between SAL and Ca^{2+} ions generated from the calcium salt, and leads to the formation of calcium alginate gel matrix which, in turn, controls the release of the embedded drug. It has been reported that matrix tablets containing SAL and CG, as a source of Ca^{2+} ions, could provide 100% release of DTZ in 12 h (Mandal, Basu, & Sa, 2009). Another approach involves chemical modification of SAL to form stable network and to modify the physico-chemical properties of

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SAL (Holte, Onsøyen, Myrvold, & Karlsen, 2003; Tønnesen & Karlsen, 2002).

One of the powerful methods to modify the various physical and chemical properties of polysaccharides is graft co-polymerization in which polymers are grafted onto polysaccharides backbone. Graft co-polymerization introduces hydrophobicity and steric bulkiness which considerably protect the matrix and carbohydrate backbone from rapid dissolution and erosion, and provides extended release of drugs (Mundargi, Patil, & Aminabhavi, 2007). Polyacrylamide-grafted polysaccharides like guar gum (Toti & Aminabhavi, 2004) and xanthan gum (Mundargi et al., 2007) have been used to prepare matrix tablets for controlled release of various drugs. However, Ca^{2+} ion cross-linked PAam-g-SAL (having 418% grafting) matrix tablets containing co-polymer and CG in weight ratio of 1:1.5 released 100% of DTZ in only 5.5 h (Sa et al., 2009).

In addition to graft co-polymerization, further development in this area involves the formulation of interpenetrating network (IPN) structure to impart additional rigidity to the matrix (Lee & Chen, 2001). IPN hydrogels are three dimensional networks formed from homogeneous or heterogeneous polymers cross-linked in presence of one another (Ekici & Saraydin, 2004), and hence, combine the properties of each network (Hsieh, Hsieh, Simon, & Till, 1990; Kosmala, Henthorn, & Peppas, 2000). IPN are thus emerging as a rapidly developing branch of polymer blended technology and are finding applications in artificial implants, dialysis membrane, drug delivery, and burn dressings (Bajpai, Bajpai, & Shukla, 2001). IPN hydrogel beads have been developed using SAL and gelatin or egg albumin (Kulkarni, Soppimath, Aminabhavi, & Rudzinski, 2001), SAL and polyvinylalcohol-grafted–poly acrylamide (Kumber & Aminabhavi, 2002), and SAL and carboxymethyl cellulose (polyacryl-amide-grafted-alginate) (Kulkarni & Sa, 2008) for controlled release of drugs.

The present investigation was envisaged to prepare sustained release IPN matrix tablets by wet granulation method using varying ratios of PAam-g-SAL and SAL, and cross-linked with Ca^{2+} ions. In vitro release studies were conducted initially for 2 h in acidic medium followed by in phosphate buffer (PB) solution of pH 6.8. The tablets were subjected to FTIR, DSC, and XRD studies to detect any drug polymer interaction. DTZ, a highly water soluble drug, has been selected as a model drug in this study. DTZ, a calcium channel blocker, is widely used for the treatment of angina pectoris (Barnhart, 1991; Satoskar, Bhandarkar, & Rege, 2005), arrhythmias and hypertension. Its short biological half-life and, thus, frequent administration (3–4 times a day) make it a potential candidate for sustained release preparation.

2. Experimental

2.1. Materials

Diltiazem hydrochloride (DTZ) USP was obtained as a gift sample from Sun Pharmaceutical Pvt. Ltd. Gujarat, India. Sodium alginate (SAL, mol wt-240 kDa), acrylamide (Aam), ammonium persulphate (APS), calcium gluconate (CG), methanol, and all other materials of reagent grade were purchased from S.D. Fine-chem, Mumbai, India and used as received. Double distilled water was used throughout the study.

2.2. Preparation of PAam-g-SAL co-polymer

PAam-g-SAL co-polymer having 418% grafting (98.5% grafting efficiency) was prepared following the method reported elsewhere (Sa et al., 2009). Briefly, SAL (2 g) was slowly dispersed in 100 ml water in a three-necked round bottom flask and allowed to hydrate for 4 h with continuous purging of nitrogen gas. Aam (4.8 g) and APS (0.4564 g) were added to SAL solution at 75 °C under nitrogen gas. After 1 h, the resulting co-polymer was cooled to ambient temperature and poured into 400 ml methanol. The product was filtered, washed with excess aqueous methanol (30%, v/v) to remove any homopolymer of Aam, and dried at 50 °C to constant weight. The product was stored in vacuum desiccator until used.

2.3. Preparation of IPN matrix tablet

The principle involved in the formulation of IPN matrix tablet was to cross-link both co-polymer and SAL with Ca^{2+} ion in presence of water. Drug-free IPN matrix tablets were prepared by wet granulation method. Required amounts of co-polymer, SAL and CG were blended manually for 15 min, appropriate amount of water was added to prepare a cohesive mass which was then granulated through # 18 mesh screen. The granules were dried in a tray drier at 60 °C for sufficient period of time so that the moisture content of the granules reached 2–4%. The dried granules were passed through #22 mesh screen, mixed with magnesium stearate, and compressed into tablet using a flat face 10 mm punch in a 10 station rotary mini-press tablet machine (RIMEK, Karnavati Engineering Ltd., Gujarat, India).

DTZ-loaded matrix tablets were prepared in the same way under the following conditions:

1) Keeping the amount of DTZ (90 mg) and total polymer to CG weight ratio (1:2) constant, the weight ratios of co-polymer to SAL were varied from 1:0.33 to 1:3.
2) Amount of DTZ was varied from 60 to 120 mg, keeping the weight ratio of co-polymer to SAL (1:0.33) and weight ratio of total polymer to CG (1:2) constant.
3) Keeping the amount of DTZ (90 mg) and co-polymer to SAL weight ratio (1:0.33) constant, total polymer/CG weight ratios were varied from 1:0.5 to 1:2.

Duplicate batches of each tablet formulation having a batch size of about 100 tablets were prepared. The composition of the tablets each having 395 mg weight is shown in Table 1.

2.4. Fourier-transform infrared (FTIR) spectroscopy

FTIR spectra of SAL, PAam-g-SAL, and drug-free IPN matrix tablet were recorded in a FTIR spectrometer (Perkin-Elmer, model Spectrum RX-1, UK). Each sample was mixed with KBr and converted into pellets at 600 kg pressure using a hydraulic press. The spectra were recorded within 4000–400 cm^{-1} wave numbers.

FTIR spectra of DTZ and drug-loaded IPN matrix tablet were recorded in the same way.

2.5. Differential scanning calorimetry (DSC) study

DSC thermograms of DTZ, powdered drug-free and drug-loaded IPN matrix tablets were obtained in an atmosphere of nitrogen in the following way: weighed amount (4.8–6.2 mg) of samples were kept in hermetically sealed aluminum pans and heated at a scan speed of 10 °C/min over a temperature range of 30–300 °C in a differential scanning calorimeter (Perkin Elmer, model Pyris Diamond TG/DTA, UK) which was calibrated against indium. The chart speed was 10 mm/min.

2.6. X-ray diffraction (XRD) study

The qualitative XRD analyses were performed using an X-ray diffractometer (Miniflex Gonimeter, Japan). Pure DTZ and powdered drug-free and drug-loaded IPN matrix tablets were scanned

Table 1
Composition of interpenetrating network matrix tablet.

Tablet code	PAam-g-SAL co-polymer (mg)	SAL (mg)	CG (mg)	Drug (mg)	Magnesium stearate (mg)	Ratio of co-polymer/SAL	Ratio of SAL:CG	Ratio of total polymer/CG
F1	25	75	200	90	5	1:3	1:2.7	1:2
F2	50	50	200	90	5	1:1	1:4	1:2
F3	75	25	200	90	5	1:0.33	1:8	1:2
F4	82.5	27.5	220	60	5	1:0.33	1:8	1:2
F5	67.5	22.5	180	120	5	1:0.33	1:8	1:2
F6	150	50	100	90	5	1:0.33	1:2	1:0.5
F7	112.5	37.5	150	90	5	1:0.33	1:4	1:1
F8	90	30	180	90	5	1:0.33	1:6	1:1.5

from 0° to 60° diffraction angle (2θ) range under the following measurement conditions: Kb-filtered Cu-kα radiation; voltage, 30 kV; current, 15 mA; scan speed 1 °C/min.

2.7. Determination of drug content of tablet

Five tablets were finely powdered; a quantity equivalent to 25 mg of DTZ was accurately weighed and transferred into 50 ml volumetric flask containing USP phosphate buffer solution (PB) of pH 6.8. The mixture was allowed to stand for 12 h with an intermittent shaking. The mixture was filtered and the filtrate following suitable dilution was analyzed for DTZ content at 237 nm using a UV–Visible spectrophotometer (Varian Bio-spectrophotometer; model CARRY 50, Australia). The reliability of the above analytical method was judged by conducting recovery analyses at three levels of spiked drug solution and for three consecutive days in the absence or presence of the polymers. The recovery averaged 99.23 ± 1.72%.

2.8. In vitro drug release study

In vitro drug release study was carried out in acidic solution (0.1 N HCl, pH 1.2) for an initial 2 h followed by in USP PB solution (pH 6.8) using USP II dissolution rate test apparatus (model TDP-06P, Electro Lab, Mumbai, India). One tablet was placed in 900 ml acidic solution (37 ± 1 °C) and rotated at 100 rpm with a paddle. After 2 h, the acidic solution was removed carefully and replaced with 900 ml PB solution (37 ± 1 °C). Aliquot was withdrawn at different times and replenished immediately with the same volume of fresh solution. The withdrawn samples following suitable dilution were analyzed spectrophotometrically at 236 nm for acidic solution and 237 nm for PB solution. The amounts of drug released in acidic medium and PB solution were calculated from the calibration curves drawn, respectively, in 0.1N HCl and PB solution (pH 6.8). Each release study was duplicated.

2.9. Swelling study

Drug free IPN matrix tablets having different co-polymer/SAL ratios (1:0.33 to 1:3) and total polymer/CG ratio of 1:2 were weighed and placed in wire baskets and immersed in 200 ml acidic medium (0.1 N HCl pH 1.2) at 37 °C for 4 h. The baskets were periodically removed from the solution and weighed after removing the surface water with tissue paper in an electronic balance (Precisa Electronic Balance, model XB 600 M/C Switzerland). Swelling ratios of the tablets were determined from the following relationship (Mundargi et al., 2007):

$$\text{Swelling ratio} = \frac{\text{Wt} - \text{Wo}}{\text{Wtab}}$$

where Wo is the initial weight of the tablet and basket and Wt is the weight of tablet plus basket at time t, and Wtab is the weight of the dry tablet.

The swelling ratios of the above tablets were also determined in PB solution (of pH 6.8) for 8 h.

2.10. Viscosity measurement

Viscosity of the blended polymers having weight ratios of co-polymer to SAL (1:0.33, 1:1 and 1:3) were measured in a Brookfield viscometer using spindle no. M1 (Toki Sangyo viscometer, model no. TV-10, Japan).

3. Result and discussion

3.1. Physical characterization of tablets

The physical testing of the tablets revealed the following information: the weight of the tablets was confined within ± 5% of the average weight, thickness varied from 3.59 to 3.70 mm with MSD 0.20% (n = 10), the maximum friability found was 0.38% and the drug content varied within ± 5% of the labeled amount. All these variation were found to comply with the requirements of official compendium.

3.2. Formation of IPN structure

The mechanism of graft co-polymerization and the formation of IPN structure have been represented schematically in Fig. 1. Formation of IPN structure was examined by FTIR spectroscopy of drug-free IPN matrix tablet. The spectrum of SAL (Fig. 2A) showed the presence of peaks of two important functional groups: one at 3447 cm^{-1} for O—H stretching vibration and the other at 1610 cm^{-1} for carboxylate (COO^-) anion. The spectrum (Fig. 2B) of PAam-g-SAL exhibited a doublet peak at 3447 cm^{-1} for N—H stretching vibration, a peak at 1655 cm^{-1} which represented the overlapping of COO^- anion and primary amide C=O absorption bands, and a peak at 1323 cm^{-1} due to C—N vibration. The spectrum (Fig. 2C) of drug-free IPN matrix tablets showed a peak at 3404 cm^{-1} due to overlapping of O—H stretching vibration of SAL and N—H streaching vibration of PAam-g-SAL, a peak at 1650 cm^{-1} due to overlapping of COO^- and primary amide C=O. The result confirmed the formation of IPN structure.

3.3. Compatibility between drug and polymers forming IPN

The compatibility of DTZ with the polymers forming IPN was studied using FTIR. The spectrum of DTZ (Fig. 2D) exhibited the characteristics bands of)C=O lactum,)C=O acetate, and N—H respectively at 1680, 1741, and 2363 cm^{-1}. The peaks of the drug were also present almost at the same wave numbers in the spectrum (Fig. 2E) of drug-loaded IPN matrix tablet.

DSC thermogram of DTZ, powdered drug-free IPN matrix tablet and drug-loaded tablet obtained under nitrogen atmosphere are shown in Fig. 3. A sharp endothermic peak corresponding to the

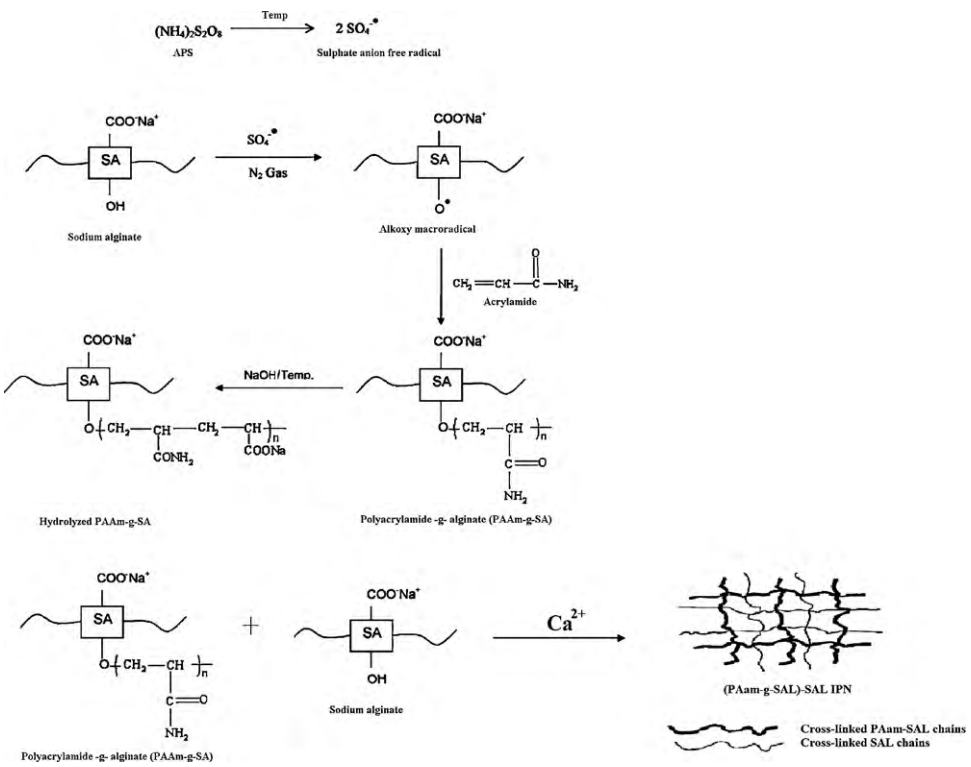

Fig. 1. Schematic diagram representing the formation of IPN structure.

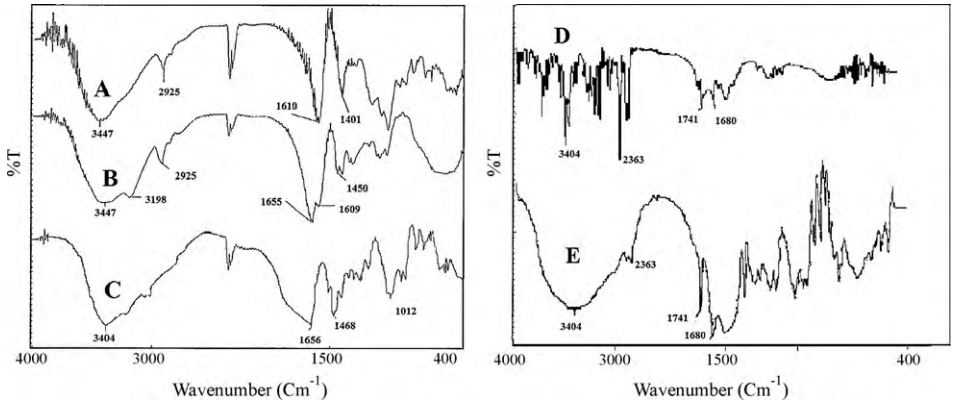

Fig. 2. FTIR spectra of (A) sodium alginate, (B) PAam-g-SAL, (C) drug-free IPN matrix tablet, (D) pure diltiazem, and (E) drug-loaded IPN matrix tablet.

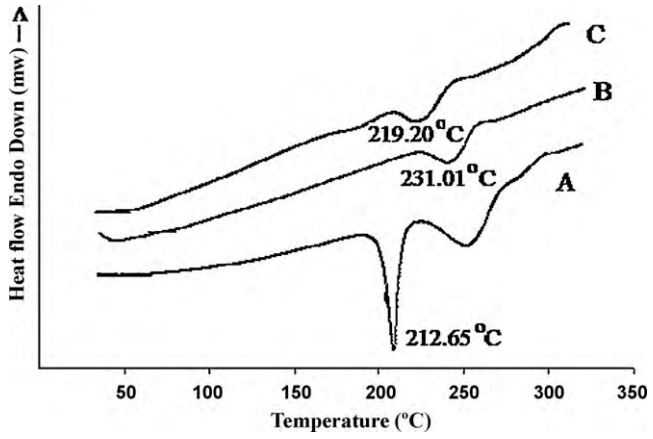

Fig. 3. DSC thermograms of (A) pure diltiazem, (B) drug free IPN matrix tablet, and (C) drug-loaded IPN matrix tablet.

melting point of DTZ was found at 212 °C (Fig. 3A). The DSC curve of drug-free IPN matrix tablet (Fig. 3B) exhibited a broad endothermic peak at 231 °C. However drug-loaded matrix tablet (Fig. 3C) did not show sharp endothermic peak; instead a broad endothermic peak at 219 °C appeared in the DSC thermogram. The disappearance of the melting endothermic peak of the drug indicates that the drug might have been molecularly dispersed or converted into amorphous form during the preparation of matrix tablet. Many research reports are available in literature which state that many drugs become molecularly dispersed or undergo amorphization during the preparation of cross-linked SAL beads (Kulkarni, Soppimath, Aminabhavi, & Dave, 2002; Kulkarni et al., 2001) and chitosan–polyethylene glycol–g-acrylamide hydrogel microsphere (Agnihotri & Aminabhavi, 2006). On the other hand, reports are also available stating that the endothermic peak of DTZ did not disappear and no solid state transformation took place during the preparation of cross-linked SAL (Mandal et al., 2009) or PAam–g-SAL (Sa et al., 2009) matrix tablets by wet granulation method.

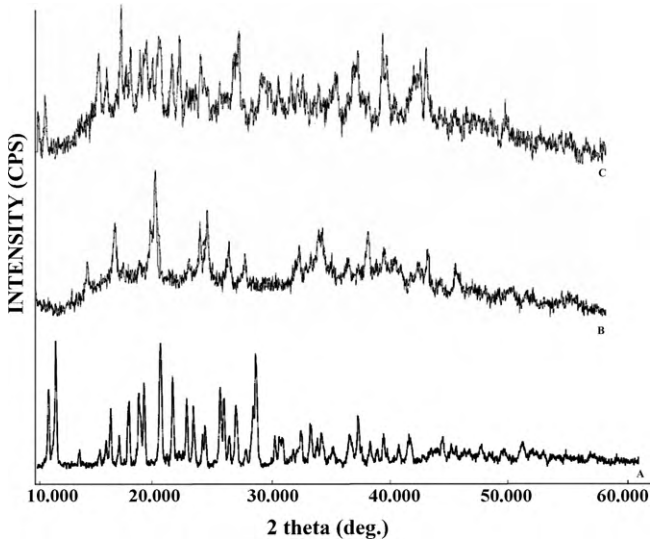

Fig. 4. X-ray diffractograms of (a) pure diltiazem, (b) drug-free IPN matrix tablet, and (c) drug-loaded IPN matrix tablet.

To further ascertain whether solid state transformation of DTZ took place, X-ray diffraction study was conducted. The XRD diffractograms of DTZ, powdered drug-free IPN matrix tablet and drug-loaded tablet are shown in Fig. 4. XRD trace of DTZ showed reflection to the interplanner distances of 8.38, 5.83, 5.02, 4.91, 4.56, 4.33, 4.10, 3.63 and 3.23 Å respectively at 10.54, 15.16, 17.62, 18.04, 19.42, 20.47, 21.64, 24.49 and 27.55 2θ. The peakscharacteristics of the drug were not observed in drug free IPN matrix tablet. However, drug loaded IPN matrix tablet showed reflection to the interplanner distances of 8.19, 5.73, 5.08, 4.85, 4.51, 4.24, 4.05 and 3.20 Å respectively at 10.78, 15.43, 17.41, 18.25, 19.63, 20.89, 21.91 and 27.79 2θ. The results demonstrated that the characteristic peaks of the drug appeared almost at the same 2θ values in the XRD chart of drug loaded IPN matrix tablet, although the intensity of the peaks was considerably reduced. It clearly indicated that the crystallinity of the drug was retained in the IPN tablet. Although inconclusive without further experimentation, it may be stated that without being transformed into amorphous form, DTZ might have been entrapped into the network of IPN structure formed by PAam-g-SAL co-polymer and SAL.

3.4. Release of drug

3.4.1. Effect of co-polymer/SAL ratio

Release profiles of DTZ from IPN matrix tablets, which were prepared using different weight ratios of co-polymer/SAL while keeping the amount of DTZ (90 mg) and total polymer/CG weight ratio (1:2) constant, are shown in Fig. 5. The release of the drug in acidic medium was faster from the tablet (F1) which was prepared with the lowest ratio of co-polymer/SAL. As the ratios of co-polymer/SAL were increased in the tablets (F2 and F3), the drug release decreased.

Following the dissolution study in acidic medium for 2 h, the tablet were placed in PB solution of pH 6.8, and the drug release was found to follow the same trend and extended for different periods depending upon the co-polymer/SAL ratios in the tablets. While F1 tablet released 97.5% of the loaded drug in 12 h, F3 tablet released 88.5% drug during the same period.

SAL is a polysaccharide composed of varying proportions of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues which are arranged in MM or GG blocks interspersed with MG blocks (Aslani & Kennedy, 1996). The —COOH groups of guluronic acid of SAL interact with Ca^{2+} ions to form calcium alginate gel through ionotropic

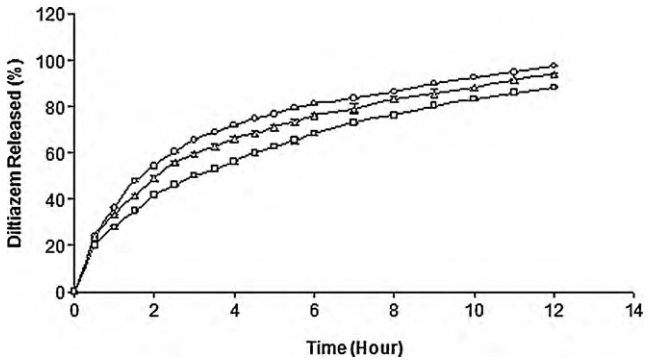

Fig. 5. Effect of co-polymer/SAL ratio on the release of diltiazem from IPN matrix tablet. Co-polymer/SAL ratio: (○) 1:3, (△) 1:1, (□) 1:0.33. (Maximum SD ± 1.82, $n = 4$.)

gelation process. SAL fraction of PAam-g-SAL may also undergo ionotropic gelation in the same way. The extent of gel formation depends on the ratio of SAL/Ca^{2+} ions. When the co-polymer/SAL ratio is less, the amount of SAL in the IPN matrix tablet will be more and hence the ratio of SAL/CG will increase as the amount of CG is fixed (Table 1). The available Ca^{2+} ions convert the proportionate amount of SAL to calcium alginate and the residual amount of SAL remains as such in the matrix. Thus the amount of free SAL and that of calcium alginate formed during wet massing stage of tablet preparation were, respectively, the highest and the lowest in F1 tablets. When F1 tablet was placed in acidic solution, free SAL was converted into alginic acid which, although water insoluble, swells in water. Since calcium alginate does not swell appreciably in acidic solution, a large amount of alginic acid made the tablet swell. In addition, the hydrophilic free amide groups increase the swelling of co-polymer (Şanle, Ay, & Işiklan, 2007) and may add to the swelling of the tablet. On the other hand, increase in the ratio of co-polymer/SAL decreases the amount of free SAL and increases the amount of calcium alginate and PAam-g-SAL in the tablets. As a result, the swelling of the tablets decreases. Swelling studies of drug-free IPN tablets prepared using various co-polymer/SAL ratios revealed that as the ratio of co-polymer/SAL increased the swelling ratios of the tablet decreased (Fig. 6). Release of a drug from a swellable polymeric matrix is not only dependent on the swelling capacity of the polymers but also on the viscosity of the polymer solution. When a tablet comes in contact with aqueous fluid, the tablet begins to swell and gel layer is formed around and inside the tablet as the polymer dissolves. While increase in swelling will facilitate the diffusion of drug through the gel layer, increase in viscosity will offer resistance to the same. Determination of viscosity of 1% (w/v) solution in acidic medium (pH 1.2) revealed that as the co-polymer/SAL ratio was increased from 1:3 to 1:0.33, the viscosity increased from 123.5 to 334.8 cp. Decrease in swelling

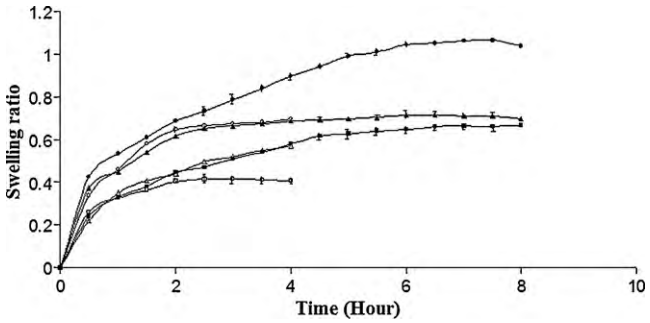

Fig. 6. Swelling ratios of drug-free IPN matrix tablets in acid solution (open symbol) and in PB solution (closed symbol). Co-polymer/SAL ratio: (○) 1:3, (△) 1:1, (□) 1:0.33, and (●) 1:3, (▲) 1:1, (■) 1:0.33.

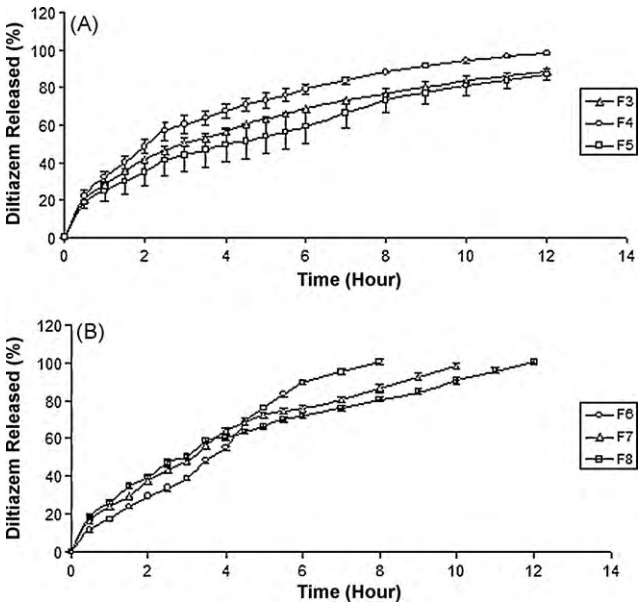

Fig. 7. Effect of (A) drug load and (B) total polymer/CG ratio on the release of diltiazem from IPN matrix tablets. Drug load: (○) 60 mg, (△) 90 mg, (□) 120 mg. (Maximum SD ± 3.11, $n = 4$.) Total polymer/CG ratio: (○) 1:0.5, (△) 1:1, (□) 1:1.5. (Maximum SD ± 1.80, $n = 4$.)

and increase in viscosity were responsible for the decrease in drug release.

Subsequent placement of the IPN matrix tablets in PB solution of pH 6.8 may lead to reconversion of alginic acid to SAL that forms gel in presence of water (Liew et al., 2006). In addition, calcium alginate, which is insensitive to acidic medium, swells in aqueous medium having higher pH and then undergoes erosion due to break-down of gel structure. At higher pH, ion exchange takes place between the gel forming Ca^{2+} ions and Na^{+} ions of the dissolution medium (Tomida, Mizuo, Nakamura, & Kiryu, 1993). As the Ca^{2+} ions are exchanged, electrostatic repulsion between the ionized carboxylate anions of alginic acid accelerates the swelling and erosion of alginate gel (Kikuchi, Kawabuchi, Sugihara, Sakurai, & Okano, 1997). Moreover, upon ionization, the counter-ion concentration inside the polymeric network increases, and an osmotic pressure difference exists between the internal and external solutions of the tablets. The increased osmotic pressure is balanced by the swelling of the tablets (Soppimath, Kulkarni, & Aminabhavi, 2001). As the weight ratios of co-polymer to SAL increases, the amount of PAam-g-SAL increases and the ratio of SAL/CG decrease. Thus more Ca^{2+} ions become available for ionotropic gelation. Increase in Ca^{2+} ions increases the gel strength of calcium alginate matrix and increase in PAam-g-SAL increases the rigidity of the gel structure. The combined effect decreases the swelling of the tablets in PB solution (Fig. 6) and consequently decreases the drug release from IPN matrix tablets. Moreover, the viscosity of 1% solution in PB (pH 6.8) increased from 84.6 to 240.8 cp as the ratio of co-polymer/SAL increased. Consequently, the release of drug from the IPN matrix tablet decreased.

3.4.2. Effect of drug load

The effect of drug load on its release was studied by varying the amount of DTZ from 60 to 120 mg in the tablet prepared using co-polymer/SAL weight ratio 1:0.33 and total polymer/CG weight ratio 1:2. The tablets were designated as F4, F3 and F5. Increase in the amount of drug in the tablets decreased the drug release (Fig. 7A). Generally, a tablet containing lower amount of drug should release its content slowly. As the drug load is increased, the concentration gradient between the drug in the dosage form and the external dissolution medium is increased. This favors faster release of drug. However, the release of a drug from a polymeric matrix is governed not only by drug diffusion through the polymeric network, but also by the relaxational process of the polymer on solvent penetration. Low drug load in IPN matrix tablet forms loose matrix structure and formation of large pore fraction which causes higher swelling of the matrix and consequently easier influx of liquid and efflux of the dissolved drug from the tablets. As the drug load is increased, the matrix becomes more rigid causing shrinkage of the pores and thereby, less absorption of dissolution fluid. This results in a fall in drug release. Decrease in drug release with increase in drug load has been reported to occur from various microgel and beads (Kumbar & Aminabhavi, 2003; Kumbar, Soppimath, & Aminabhavi, 2003; Soppimath et al., 2001; Soppimath, Kulkarni, & Aminabhavi, 2002).

3.4.3. Effect of CG

The effect of CG on the release of DTZ was studied from the tablets (F6-F8) prepared using co-polymer/SAL weight ratio 1:0.33, 90 mg of DTZ and varying weight ratios of total polymer/CG (1:0.5 to 1:1.5) and the results are shown in Fig. 7B. Although the initial drug release appeared to be less from the tablet (F6) prepared using less amount of CG, the overall release was higher than that from the tablets (F7 and F8) prepared using larger amounts of CG. To ascertain this, the area under the curves (AUCs) was calculated from the release profiles using the trapezoidal rule. It was found that as the amount of CG was increased, the values of AUCs increased from 455.68 to 799.59% mg h/ml, and hence the release of the drug from the IPN matrix tablets decreased. Increasing in the amount of CG provides larger amount of Ca^{2+} ions for ionotropic gelation with SAL available from both polymers and results in the formation of a more rigid gel structure and consequently decreases the release of drug.

3.5. Kinetics of drug release

The release of a drug from a swellable matrix is dependent on the degree of gelation, hydration, chain relaxation, and polymer erosion, The mechanism of drug transport through IPN matrix tablets was evaluated by fitting the drug release data (up to 60%) to the classical power law expression (Ritger & Peppas, 1987):

$$\frac{Mt}{M\alpha} = kt^n$$

where Mt and Mα are, respectively the amounts of drug released at time t and at infinite time; k represents a constant incorporating structural and geometrical characteristic of the dosage forms; n denotes the diffusion exponent indicative of the mechanism of drug release. Values of n ranging from 0.45 to 0.5 indicate Fickian or diffusion controlled release, values of n ranging from 0.89 to 1.0 indicate Case II transport mechanisms. Values of n intermediate between the above limits indicate anomalous or non-Fickian transport. By applying least square method to release data, the values of n were estimated. The values of n were confined within 0.41–0.5 when co-polymer/SAL ratios and drug loads in the tablets were varied. This indicates that the release of drug followed Fickian transport. When the ratios of total polymer to SAL were varied from 1:0.5 to 1:1.5, the values of n were found to vary within 0.76–0.52 indicating that the release deviated from Fickian to anomalous transport.

4. Conclusion

PAam-g-SAL and SAL in various ratios and CG in different amounts were used as matrix materials for the preparation of IPN matrix tablets by wet granulation method. While FTIR study demonstrated the formation of IPN structure, FTIR, DSC and XRD analyses apparently indicated the absence of any interaction of the

drug with the polymers. In vitro drug release study, which was conducted in acidic solution (pH 1.2) for the initial 2 h and followed by in PB solution (pH 6.8) for the rest of the study, indicated that the release of drug in both the dissolution media decreased as the co-polymer/SAL ratio in the tablet increased. Decrease in swelling of the matrix and increase in viscosity of gel formed on hydration of the tablets was responsible for slow drug diffusion and hence, sustained release of the drug from the tablets. Moreover, increase in both the drug load and the amount of CG decreased the drug release. The findings of the study indicate that a blend of PAAm-g-SAL and SAL and cross-linked with Ca^{2+} ions could be a suitable matrix material for the preparation of IPN matrix tablet for sustained release of DTZ.

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