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RESEARCH ARTICLE

pH-sensitive hydrogels based on semi-interpenetrating network (semi-IPN) of chitosan and polyvinyl pyrrolidone for clarithromycin release

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Abstract

The aim of this study was to develop a pH-sensitive chitosan/polyvinyl pyrrolidone (PVP) based controlled drug release system for clarithromycin. The hydrogels were synthesized by cross-linking chitosan and PVP blend with glutaraldehyde to form a semi-interpenetrating polymer network (semi-IPN). These semi-IPNs were studied for their content uniformity, swelling index (SI), mucoadhesion, wettability, *in vitro* release and their release kinetics. The hydrogels showed more than 97% content of clarithromycin. These hydrogels showed high swelling and mucoadhesion under acidic conditions. The swelling may be due to the protonation of a primary amino group on chitosan. In acidic condition, chitosan would be ionized, and adhesion could have occurred between the positively charged chitosan and the negatively charged mucus. In the alkaline condition, less swelling and mucoadhesion was noticed. *In vitro* release study revealed that formulation containing chitosan (2% w/v) and PVP (4% w/v) in the ratio of 21:4 showed complete drug release after 12 h. Release profile showed that all the formulations followed non-Fickian diffusion mechanism. The cross-linking and compatibility of clarithromycin in the formulation was studied by Fourier transform infrared (FTIR) spectroscopic analysis, differential scanning calorimetry (DSC) and powder X-ray diffraction (p-XRD) study, which confirmed proper formation of semi-IPN and stability of clarithromycin in the formulations. The surface morphology of semi-IPN was studied before and after dissolution in simulated gastric fluid (SGF, pH 1.2) which revealed pores formation in membrane after dissolution. The results of study suggest that semi-IPNs of chitosan/PVP are potent candidates for delivery of clarithromycin in acidic environment.

Keywords: Chitosan, polyvinyl pyrrolidone, semi-IPN, hydrogel, controlled release, clarithromycin

Introduction

Hydrogels (networks of hydrophilic polymers) have the capability of absorbing large amounts of water, without losing their three dimensional structure[1]. Hydrogels are of special interest in controlled release applications that are capable of delivering drugs at a constant rate over an extended period of time[2,3] and in tissue engineering as scaffolds that can match the extracellular matrix properties because of their soft tissue biocompatibility[1,4], the ease with which the drugs are dispersed in the matrix and the high degree of control achieved by selecting the physical and chemical properties of the polymer network. Hydrogels consist of polymer chains cross-linked to each other to create a tangled mesh structure, providing a matrix for the entrapment of drugs[5]. pH-responsive microgels/nanogels are developed which offer unique advantages for polymer-based drug delivery systems: a tunable size from submicrons to tens of nanometers, large surface area for bioconjugation, interior network structure for the incorporation of therapeutics, low side effects of drugs, and controllable release at specific pH environment[6].

Over the past few decades, the study of polyelectrolyte hydrogels responsive to environmental stimuli such as pH, temperature, ionic strength, electric filed, solvent composition, light, pressure, and sound or a specific chemical trigger has been a very active field of research. Among them, polyelectrolyte gels based on polysaccharides and their derivatives have attracted much attention due to their unique properties. Recently, the blend

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polyelectrolyte gels of polysaccharides and synthetic polymers are investigated extensively because of their special properties and comparatively low cost[7].

Chitosan, [poly-β(1–4)-2-amino-2-deoxy-D-glucose], a polymer which derives from chitin deacetylation, is nontoxic, biocompatible and biodegradable[8]. It is one of the most abundant natural amino polysaccharide, and has been reported to have a variety of applications in pharmacy industry and biotechnology[9] and has been explored for the release of many drugs[2,4,6,10–13]. Chitosan is known to have various biological activities including immunoenhancing effects, antitumoral, antifungal and antimicrobial activities[14]. Furthermore, degradation products of chitosan have been shown to be nontoxic, non-immunogenic and non-carcinogenic[8]. Moreover, the presence of–NH_2 groups, whose amount is related to the chitin deacetylation degree, makes the polymer soluble in acid solutions. The solubilization pH lowers as the degree of acetylation increases.

Poly (N-vinyl pyrrolidone) (PVP), a synthetic polymer, has good biocompatibility and for many years has been applied as a biomaterial or additive to drug compositions and as vitreous humor substitute[2,7,15]. PVP hydrogel has excellent transparency and biocompatibility. The hydrogel of PVP itself is of limited applicability because of its inferior mechanical properties. So a series of PVP hydrogels prepared by PVP blends play a significant role as biomedical materials. The miscibility of chitosan and PVP in the films has been reported, and it is considered that carbonyl groups in the pyrrolidone rings of PVP interact with amino and hydroxyl groups in chitosan by forming hydrogen bonds and produce materials with novel characteristics[7].

PVP is a synthetic polymer, has good biocompatibility and is commonly used in the textiles and cosmetics industries[2] as well as in pharmaceuticals and medical applications[2,11,15] because of its outstanding absorption and complex formation abilities.

Chitosan and PVP blends have been prepared and investigated for their potential use as controlled release drug delivery systems, and for enhancing mucoadhesive properties[9]. Chitosan and PVP hydrogels have been extensively employed in biotechnical and biomedical fields[3,16].

Cationic hydrogels with pH-sensitive swelling properties have been proposed previously as candidates for stomach-targeted drug delivery systems[2,15]. Such matrices can be used to provide adequate drug release in gastric (low pH) environments[5].

Clarithromycin is a macrolide antibiotic widely prescribed in *Helicobacter pylori* mediated peptic ulcers and upper respiratory tract infections[17]. The recommended adult oral dosage of clarithromycin is 500 mg twice daily for the effective treatment of *H. pylori* caused peptic ulcer. It is stable in gastric acid and rapidly absorbed from the GIT[18]. As the drug is effective when the plasma fluctuations are minimized, sustained release dosage form of clarithromycin is desirable. The short biological half-life of drug (~3–5 h[19]) also favors development of sustained release formulation. A traditional oral sustained release formulation of clarithromycin may not be useful in the eradication of *H. pylori*, because the organism lives deep inside the gastric mucosa; also the oral bioavailability of clarithromycin is 55%.

One reason for the incomplete eradication of *H. pylori* is probably due to the short residence time of antimicrobial agents in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces where *H. pylori* exists[20].

Thus it is a logical way to improve the therapeutic efficacy of the antibiotic if the gastric residence time of the dosage form is increased in the ecological niche of bacterium. The high concentrations of clarithromycin in the stomach will ensure effective localized treatment for the pathogen[21]. This makes the necessity for the development of gastroretentive dosage forms of clarithromycin.

IPN hydrogels are very promising and versatile materials for biomedical applications due to their properties such as porosity, elasticity, degree of swelling and responsive behavior to a stimulus can be tuned by the appropriate choice of the network-forming polymers and suitable cross-linking agent and its proportion. They can be used in controlled release systems that are capable of delivering drugs at a constant rate over an extended period of time. Nevertheless, homopolymeric and copolymeric structures alone cannot meet such divergent demands in terms of both properties and performance. Therefore, IPN of two or three different polymers would be a better approach. Very commonly two or more polymers can be used to develop an acceptable product regarding the efficient control release of the active compound. Hence, in the present study, semi-IPNs of chitosan and PVP were developed and checked for their characteristics as a potential for pH-sensitive clarithromycin release

Experimental

Materials

Chitosan (M.W. ≈350,000, 85% deacetylated) was received as a gift sample from Central Marine Fisheries Research Institute (Cochin, India). PVP (M.W. 50,000) was obtained from S.D. Fine chem. Ltd. (Mumbai, India). Clarithromycin was received as a gift sample from Zydus Research Centre (Ahmedabad, India). Glutaraldehyde and *n*-octane were purchased from Rankem (New Delhi, India). All other chemicals and reagents were of analytical grades.

Methods

Synthesis of hydrogels

Chitosan solution (2%, w/v) was prepared in 0.1 M acetic acid. PVP solution (4%, w/v) was prepared in double distilled water. Six different ratios of these solutions were mixed to form a blend as shown in Table 1. Five hundred milligram of clarithromycin was added in each formula before cross-linking. Glutaraldehyde solution was used as a cross-linking agent and added at a concentration

Table 1. Formulae for hydrogel preparation.

Formula	Volume of chitosan solution (2%w/v) (ml)	Volume of PVP solution (4%w/v) (ml)
S1	3	17
S2	6	14
S3	10	10
S4	14	6
S5	17	3
S6	21	4

of 0.4% (v/v) to the chitosan-PVP mixture to form semi-IPNs. Hydrogels were cast in a casting apparatus and then air-dried. All hydrogels were stored in a vacuum until use. The dried hydrogels were crushed and passed through sieve # 60 and # 85. Those hydrogel particles passed through sieve # 60 and retained on sieve # 85 were used for further studies[22]. Semi-IPN without clarithromycin was also prepared to check the changes in polymer characteristics[5].

HPLC analysis

The amount of released clarithromycin was determined by HPLC. A Schimadzu LC 2010 AHT system equipped with a wavelength detector at 210 nm and a Kromasil C_{18} (250 × 4.6 mm ID, 5 µm pore size) column with auto integrator were used for HPLC assay. The mobile phase consisted of 65% methanol and 35% (v/v) 0.067 M monobasic potassium phosphate. The pH of the buffer component was adjusted to 4.0 using orthophosphoric acid. The flow rate was kept 1.2 ml/min at 50°C for 20 min run time with pressure of 1500 PSI. The retention time of clarithromycin was 8.5 min. The clarithromycin calibration curve at concentrations varying from 1.25 mg/ml to 3.75 mg/ml was used to evaluate all the samples with 10 µl injection volume[18].

Assay content

A sample of hydrogel, claimed to contain 500 mg of clarithromycin was transferred in a 100-ml volumetric flask. Then 70 ml of methanol was added and shaken for 30 min., diluted with methanol to volume, mixed and allowed any insoluble matter to settle. Thirty milliliter of supernant was transferred to 100-ml volumetric flask, diluted with mobile phase to volume and mixed. A portion of this solution was filtered through 0.45 µm membrane filter and assayed at 210 nm using HPLC.

Swelling study

Swelling of the hydrogels was determined by placing hydrogel in 100 ml of solutions with pH values of 1.2, 4.5 and 7.4 maintained at 37 ± 0.5°C. The hydrogels were collected at regular intervals of time; the excess of moisture was blotted off and weighed. The percentage weight change of the wet hydrogels and the dry hydrogels were noted using the following expression:

$$\%SI = [(W_t - W_0)/W_0] \times 100 \quad (1)$$

where, W_t and W_0 are the weight of the hydrogels at time "*t*" and dry state, respectively.

Mucoadhesion study

Mucoadhesion studies were conducted using a modification of the assembly described earlier[23]. All the experiments were conducted as per local licensing regulations. Rat stomach tissue was used to carry out mucoadhesion study[24,25]. The stomach tissue was used immediately after sacrificed the animal for this study. The stomach mucosal membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37 ± 1°C for 30 min in HCl buffer pH 1.2 before the mucoadhesion evaluation study[26]. The hydrogels films were lowered on mucosa under a constant weight of 5 gm for a total contact period of 1 min. Mucoadhesive strength was assessed in terms of weight (g) required to detach the film from the membrane. The detachment force, force required for separating the tablet from the tissue surface was determined.

Octane contact angle determination

Octane contact angle method was employed to determine the polar interactions across the polymer–water interface. Dried hydrogel membranes were mounted on microscope slides and supported in an inverted fashion in a container. The container was filled with double distilled water to immerse the slide. A goniometer was aligned and focused on the polymer–water interface. A microsyringe containing 99.99% *n*-octane was lowered into the water and a drop of around 0.1–0.2 µl was introduced on the polymer–water interface. The contact angle on both sides of the drop was measured immediately, assuming symmetry. Data represents the mean ± S.D. of at least 20 such angles on a membrane[5].

In vitro *drug release studies*

The *in vitro* dissolution study of clarithromycin from hydrogels was performed using USP XXIV apparatus II (model TDT 08L, Electrolab, Mumbai, India) fitted with paddles (100 rpm) at 37 ± 0.5°C using 900 ml simulated gastric fluid (SGF, pH 1.2), acetate buffer (pH 4.5) and phosphate buffer solution (PBS, pH 7.4) as dissolution mediums. It is known that gastric pH varies in fed and fasted states and also between genders as well as gastric pH is reported to go up to 4.5 after food intake hence, the *in vitro* release studies were performed at pH 1.2 and pH 4.5 to fully elucidate the behavior of this system in the gastric environment[27]. Weight equivalent to 500 mg of clarithromycin was taken for the dissolution. At the predetermined time interval, 10 ml samples were withdrawn, filtered through a 0.45-µm membrane filter, diluted, and assayed at 210 using HPLC. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Release kinetics

The drug release data were evaluated by the model-dependent (curve fitting) method. In the present study,

the Korsmeyer–Peppas model describing drug release from polymeric system was used. This model takes into account that the drug release mechanism often deviates from the Fick's law and follows anomalous behavior described by the following equation[24]:

$$M_t/M_\infty = k.\,t^n \quad (2)$$

where, M_t is the drug released at time t, M_∞ the quantity of drug released at infinite time, k the kinetic constant and n is the release exponent. The value of n is related to the geometrical shape of the delivery systems and determines the release mechanism.

The release data was further treated according to Higuchi equation:

$$Q = k.\,t^{1/2} \quad (3)$$

where, Q is the percent of drug released at time t and k is the kinetic constant. The value of n in Equation (2) determines the mechanism of drug release. When n approximates to 0.5, a Fickian/diffusion controlled release is implied, where $0.5 < n < 1.0$ non-Fickian transport and for $n = 1$ zero order (case II transport). When n approaches 1.0, phenomenologically, one may conclude that the release is approaching zero order[28].

Fourier transform infrared study

The changes in the polymer characteristic after formation of semi-IPN and drug-polymer interactions were studied by Fourier transform infrared (FTIR) spectroscopy. IR spectra for chitosan, PVP, Chiotosan-PVP semi-IPN, clarithromycin and formulation S6 recorded in a FTIR spectrophotometer (FTIR-8400 S, Shimadzu, Japan) with KBr pellets. The scanning range was 400–4000 cm^{-1}[27].

Differential scanning calorimetry

Differential scanning calorimetry (DSC) scans of about 10 mg, accurately weighed chitosan, PVP, Chiotosan-PVP semi-IPN, clarithromycin and formulation S4 were performed by using an automatic thermal analyzer system (DSC 60, Shimadzu, Japan) with TDS tread line software. Sealed aluminum-lead pans were used in the experiments for all the samples. All the samples were run at a scanning rate of 10°C/min from 50–300°C[27].

Powder X-ray diffractometry

The powder X-ray diffraction (p-XRD) study was carried out to characterize the polymorphic forms of chitosan, PVP, chiotosan-PVP semi-IPN, clarithromycin and formulation S6. A Philips X'Pert PW 3040/60 (Almelo, Netherlands) was used as an X-ray generator for CuKα radiation ($\lambda = 1.54178$Å). Data were collected in the continuous scan mode using step size of 0.01° 2θ. The scanned range was 5–50°[29].

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to examine the surface morphology of formulation S6 before and after dissolution. Dried films were mounted onto stubs by using double-sided adhesive tape. The films were coated with gold and observed under a SEM (Joel, JSM-5600 LV, Japan) for surface characteristics[29].

Results and discussion

Chitosan forms a gel at lower pH values and has antacid and antiulcer properties, which may prevent or lessen the drug irritation in the stomach[5]. However, chitosan matrices are known to be fragile and exhibit uncontrollable porosity. The use of pure chitosan formulations in oral administration is also limited due to their fast dissolution in the stomach and their limited capacity for controlling the release of drugs[5]. Therefore, systems with chitosan blended with other polymers have been examined[30]. PVP has been demonstrated to control the porous nature of the blend[31].

Assay content

All the formulations showed more than 97.26% ± 2.51% ($n = 3$, ± S.D.) content of clarithromycin. In the formulation of hydrogel no drug loss step was involved hence resulted in high assay content of the formulation.

Swelling kinetics

The pH-sensitive swelling patterns of hydrogels are shown in Figure 1. To determine their swelling behaviors, hydrogel formulations were immersed in solutions with different pH values (1.2, 4.5 and 7.4). As shown in Figure 1, hydrogels showed rapid swelling at pH 1.2 and reached a stable level of swelling by 5–6 h, whereas at pH 4.5 they showed slow swelling and reached a stable swelling state by 7–8 h. All the hydrogels showed no significant swelling at pH 7.4 and shown stable swelling state after 3–4 h. It was observed that an acidic environment had a pronounced effect on the swelling profiles of hydrogels as compared with alkaline medium. This was attributed to the protonation of–NH_2 group in hydrogels thus ensures chain relaxation, leading to faster hydrogen-bond dissociation and efficient solvent diffusion. In alkaline media the swelling was mainly driven by solvent diffusion, but the chain relaxation effect due to protonation of amino group was absent. In addition, the limited swelling could have been attributed to the inherent hydrophobicity of the hydrogels at higher pH value[5]. As the hydrogels showed significant swelling in acidic media mucoadhesion and *in vitro* release studies were studied at pH values of 1.2 and 4.5.

Mucoadhesion study

All the formulations showed good mucoadhesive property. As shown in Figure 2, all the formulations showed more than 18 gm mucoadhesive strength at pH values of 1.2 and 4.5. This resultant mucoadhesive strength was due to the mucoadhesive characteristic of chitosan[32]. Stagnation of the formulation was expected to take place in the stomach or in the upper small intestine,

where the pH is acidic or slightly acidic. In such an environment, the chitosan base would be expected to be ionized, and adhesion could have occurred between the positively charged chitosan and the negatively charged mucus[33].

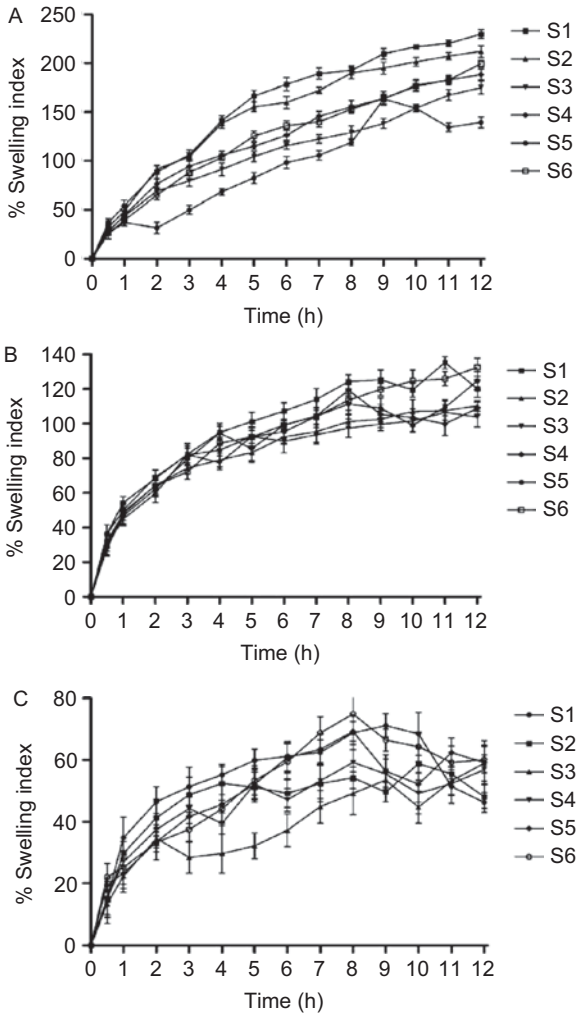

Figure 1. Percentage swelling index ($n = 3 \pm SD$) of formulations S1–S6 at pH 1.2 (A), pH 4.5 (B) and pH 7.4 (C).

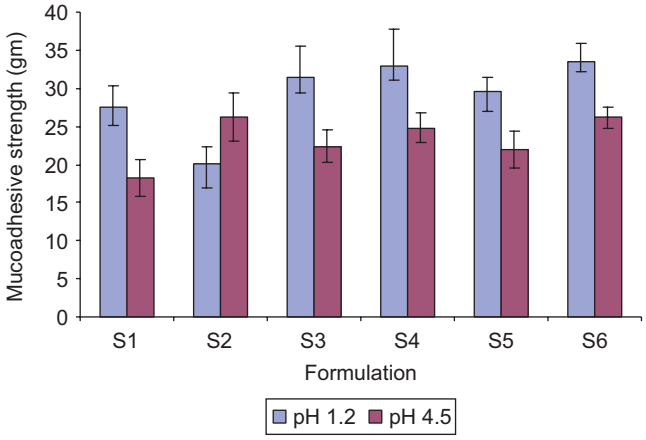

Figure 2. *Ex vivo* mucoadhesion study ($n = 3 \pm$ RSD) of formulations S1–S6 in pH 1.2 and 4.5 solutions.

In vitro release study

The release of clarithromycin was studied at pH values of 1.2, 4.5 and 7.4 (Figure 3). Formulations S1, S2, S3, S4 and S5 were failed to retard the drug release up to 12 h and complete release was observed after 5 h, 7 h, 9 h, 10 h and 10 h, respectively at pH 1.2, while S6 showed complete drug release at 12 h. Formulations S1–S4 were also failed to retard the drug release in pH 4.5 while only formulations S5 and S6 could sustained the drug release up to 12 h. The drug release profiles at pH 1.2 and pH 4.5 were found to be similar ($n > 0.1$). All the formulations showed less than 11% drug release at the end of 12 h in PBS (pH 7.4). Comparison of the *in vitro* data revealed the pH dependent drug release properties of prepared hydrogels attributed to pH dependent swelling. Direct correlation between the extent of swelling of hydrogel and drug release was observed[5]. Formulation S6 showed complete release at the end of 12 h in pH solutions 1.2 and 4.5. So S6 was considered as optimized formulation and used for further studies.

Release kinetics

The release kinetics of all the formulations were checked by fitting the release data to various kinetic models, and the release was best fitted to non-Fickian diffusion mechanism. It was further confirmed by fitting the data to the Korsmeyer–Peppas equation and the *n* value for all the formulations obtained between 0.5684 and 0.7658 for the dissolution in pH 1.2 and between 0.5985 and 0.7450 for the dissolution in pH 4.5, which revealed that release followed the non-Fickian diffusion mechanism (i.e. diffusion coupled with erosion[24]). The R^2 values for all the models in pH 1.2 and pH 4.5 are shown in Table 2.

Octane contact angle determination

Surface and interfacial behavior of hydrogels in the aqueous environment play a distinct role in evaluating their biocompatibility with living body. The surface free energy of a material is correlated to the contact angle, which is directly related to its wettability[34]. The prepared hydrogel formulations had octane contact angles in the range of 44.8° ± 0.64° to 49.01° ± 0.37°. These low octane contact angle values revealed high hydrophilicity of prepared hydrogels. The hydrophilicity is justified since chitosan and PVP are known to be hydrophilic polymers[5].

FTIR analysis

Figure 4 shows the FTIR spectra of chitosan, PVP, chitosan-PVP semi-IPN, clarithromycin and formulation S6. The spectrum of pure chitosan (Figure 4A) shows strong peaks in the range 3400–3200 cm^{-1} correspond to combined peaks of hydroxyl and intramolecular hydrogen bonding. Primary amines also show sharp absorption at 3500 and 3400 cm^{-1} arising from the asymmetric and symmetric stretching of 2 N–H bonds. The –C–H stretching vibration of the polymer backbone is manifested through strong peak at 2929.67 cm^{-1}[15,35]. The peak at 3420 cm^{-1} are attributed to free hydroxyl groups[36]. As

Table 2. Correlation coefficients of different pharmacokinetic models for repaglinide release in pH 1.2 and pH 4.5.

			Zero order	First order	Higuchi	Korsemeyer–Peppas	
Sl. No.	pH	Formulation	R^2	R^2	R^2	n	R^2
1	1.2	S1	0.9477	0.8769	0.9930	0.5967	0.9975
2		S2	0.9403	0.8731	0.9955	0.5684	0.9984
3		S3	0.9522	0.8300	0.9928	0.5685	0.9968
4		S4	0.9819	0.6387	0.9708	0.6646	0.9912
5		S5	0.9925	0.7571	0.9412	0.7658	0.9916
6		S6	0.9941	0.5807	0.9446	0.7516	0.9916
7	4.5	S1	0.9662	0.7155	0.9814	0.6631	0.9922
8		S2	0.9578	0.7811	0.9895	0.5985	0.9972
9		S3	0.9564	0.6955	0.9899	0.6274	0.9971
10		S4	0.9864	0.6513	0.9608	0.7067	0.9905
11		S5	0.9805	0.7627	0.9681	0.6970	0.9930
12		S6	0.9891	0.8106	0.9579	0.7450	0.9952

shown in Figure 4B, PVP shows the amide carbonyl band at 1681 cm^{-1}[136]. For cross-linked chitosan-PVP, an additional peak at 1661 cm^{-1} can be observed, which corresponds to stretching vibrations of C=N bond[15]. This strong peak indicates the formation of Schiff's base as a result of the reaction between carbonyl group of glutaraldehyde and amine group of chitosan chains ensuring the proper formation of semi-IPNs[5,35]. IR spectrum of pure clarithromycin shows characteristic peaks at 1690 cm^{-1} for Ketone carbonyl group, 1730 cm^{-1} for Lactone carbonyl group, 1420 cm^{-1} for N-CH_3, 2780–3000 cm^{-1} for Alkane stretching, 3450 cm^{-1} for hydrogen bond between OH group, 1000–1200 cm^{-1} for–C–O– stretching and 1340–1400 cm^{-1} for CH_2 group[18]. These all the peaks were maintained in formulation S6 also which confirm the stability of the drug in the formulation.

DSC study

The DSC analysis was used to characterize the thermal behavior of the polymer powders and the interactions between the polymers in the films, as well as thermal behavior of clarithromycin and its interaction with the polymer blend. Drug may have been dispersed in the crystalline or amorphous form or dissolved in the polymer matrix during formation of semi-IPN. There is no detectable endotherm if the drug is present in a molecular dispersion or solid solution state in the polymeric matrix. In the present investigation, DSC thermograms of chitosan, PVP, Chitoan-PVP hydrogel, clarithromycin and formulation S6 were taken. As shown in Figure 5A and 5B, the thermogram of pure chitosan and PVP shows broad melting endotherms at 88.56 °C and 104.02°C, respectively. While no sharp endothermic peak was observed in the chitosan-PVP semi-IPN hydrogel (Figure 5C), pure clarithromycin showed sharp melting endotherm at 217.81°C (Figure 5D), which corresponds to its melting point. Formulation S6 showed a sharp peak at 220.49°C as shown in Figure 6E, indicating the presence of drug in crystalline form. The results of DSC studies revealed no chemical change in clarithromycin was observed in hydrogel formulation.

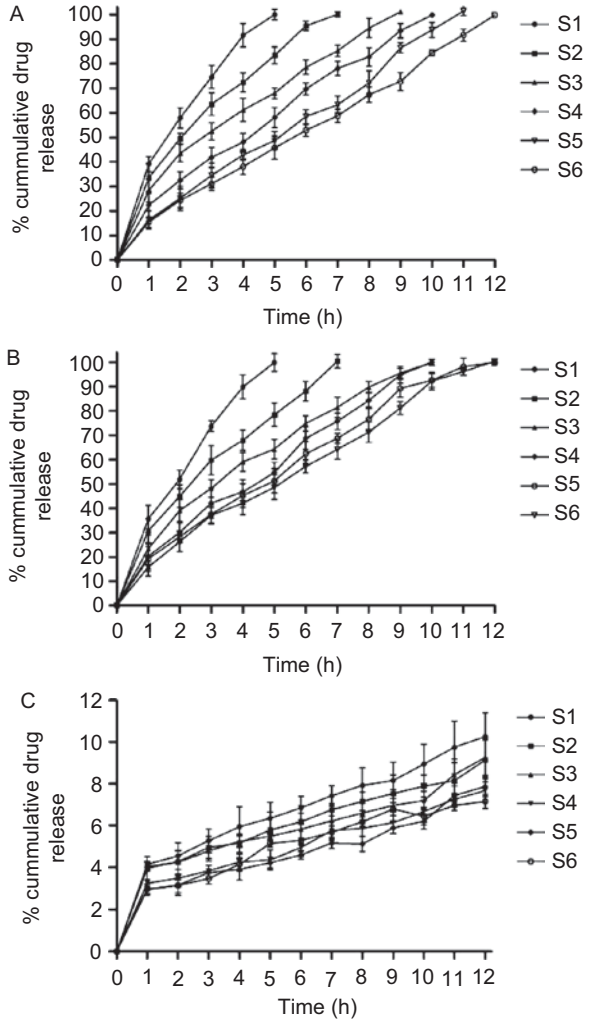

Figure 3. *In vitro* release profile of clarithromycin ($n = 3 \pm$ SD) from formulations S1–S6 in pH 1.2 (A), pH 4.5 (B) and pH 7.4 (C).

p-XRD analysis

Figure 6A shows the XRD patterns of the chitosan. It can be seen that the strongest diffraction intensity is the broad peak around $2\theta = 17–23°$ due to the substrate chitosan. It indicated semicrystalline nature of chitosan[37]. Figure 6B shows the XRD patterns of chitosan-PVP semi-IPN.

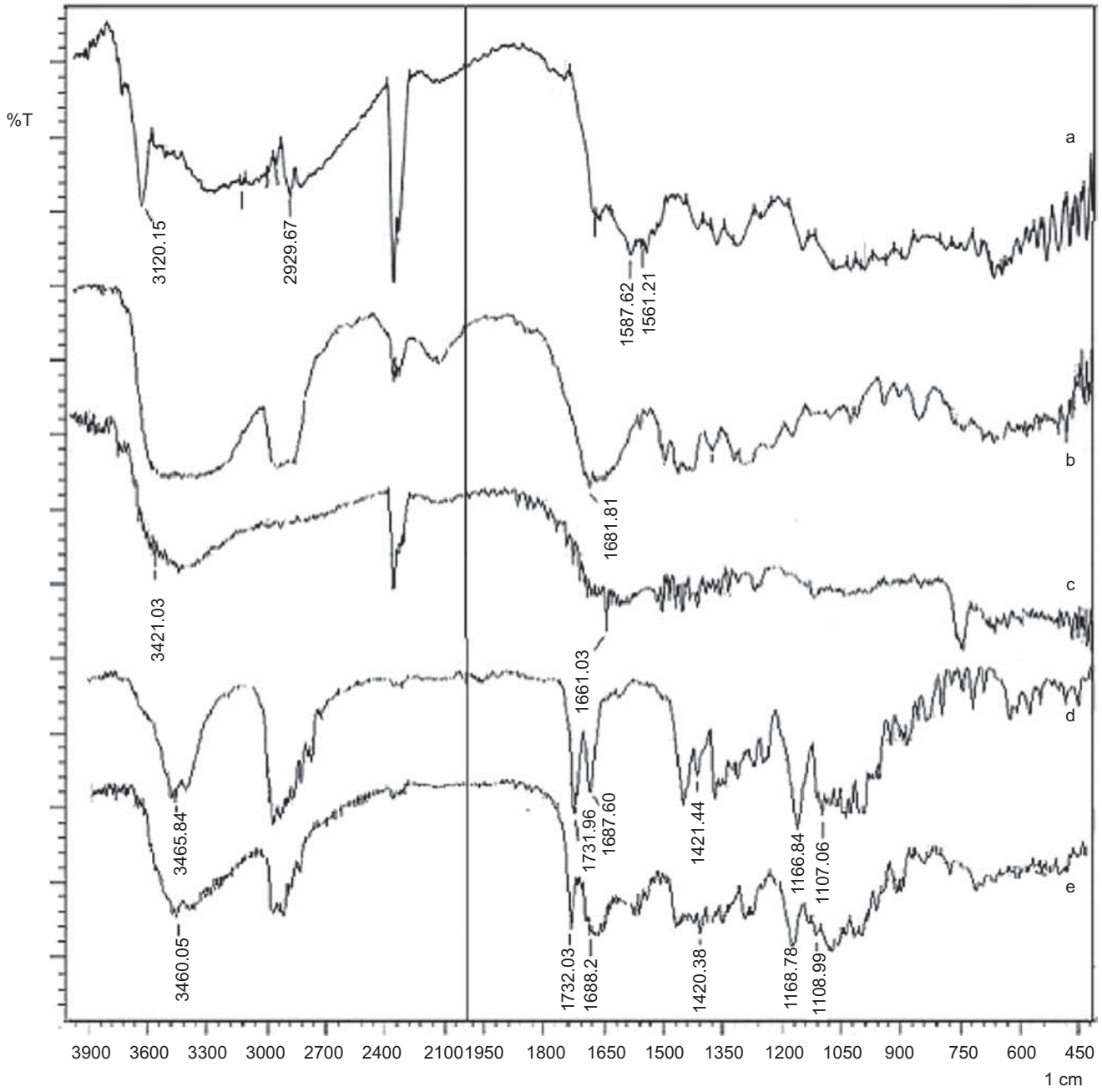

Figure 4. FTIR spectra of pure chitosan (A), PVP (B), chitosan-PVP semi-IPN (C), clarithromycin (D) and formulation S6 (E).

Some sharp peaks at $2\theta = 9°$, 9.3° and 26.6° were observed which indicated semicrystalline nature of hydrogel[38]. This indicates average intermolecular distance of the amorphous part. From the spectra of clarithromycin (Figure 6C) it was observed that it showed sharp peaks at 8.6°, 9.52°, 10.91°, 11.53°, 11.93°, 12.46°, 13.22°, 13.81°, 14.14°, 15.23°, 16.55°, 16.95°, 17.34°, 18.17°, 18.40°, 19.09°, 19.91°, 20.48°, 21.40°, 21.60°, 22.26°, 23.25° and 25.1°[18]. All these peaks were well maintained in the formulation S6 also (Figure 6D). This reveals that cross-linking of chitosan and PVP using gluteraldehyde did not affect crystalline nature of clarithromycin.

SEM

The semi-IPNs were optically clear to the naked eye. They showed neither separation into two layers nor any precipitation. The surface morphology of chitosan-PVP semi-IPN revealed non-porous translucent membrane at 1000× (Figure 7A) which indicates no phase separation while at 10,000× some pores were observed (Figure 7B). This indicates the positive reaction between chitosan and PVP[39]. The surface morphology was again checked after dissolution in pH 1.2. After dissoltion in pH 1.2, hydrogel exhibited open channel-like structure (Figure 7C) as compared to the hydrogels prior to dissolution.

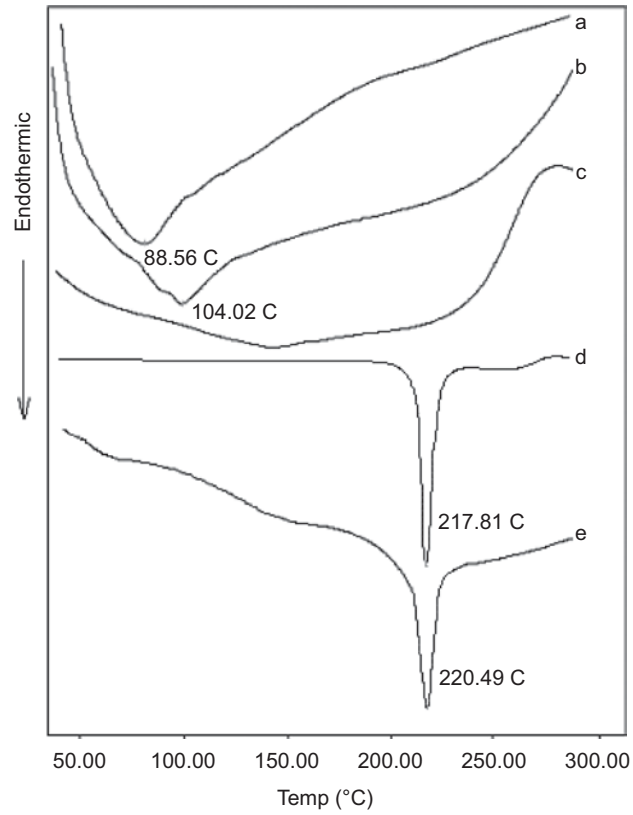

Figure 5. DSC thermograms of pure chitosan (A), PVP (B), chitosan-PVP semi-IPN (C), clarithromycin (D) and formulation S4 (E).

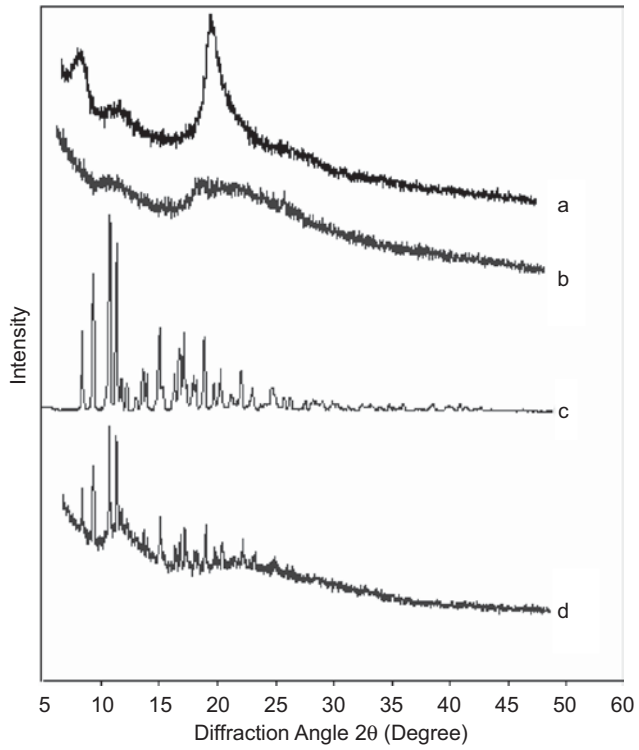

Figure 6. XRD thermograms of pure chitosan (A), chitosan-PVP semi-IPN (B), clarithromycin (C) and formulation S4 (D).

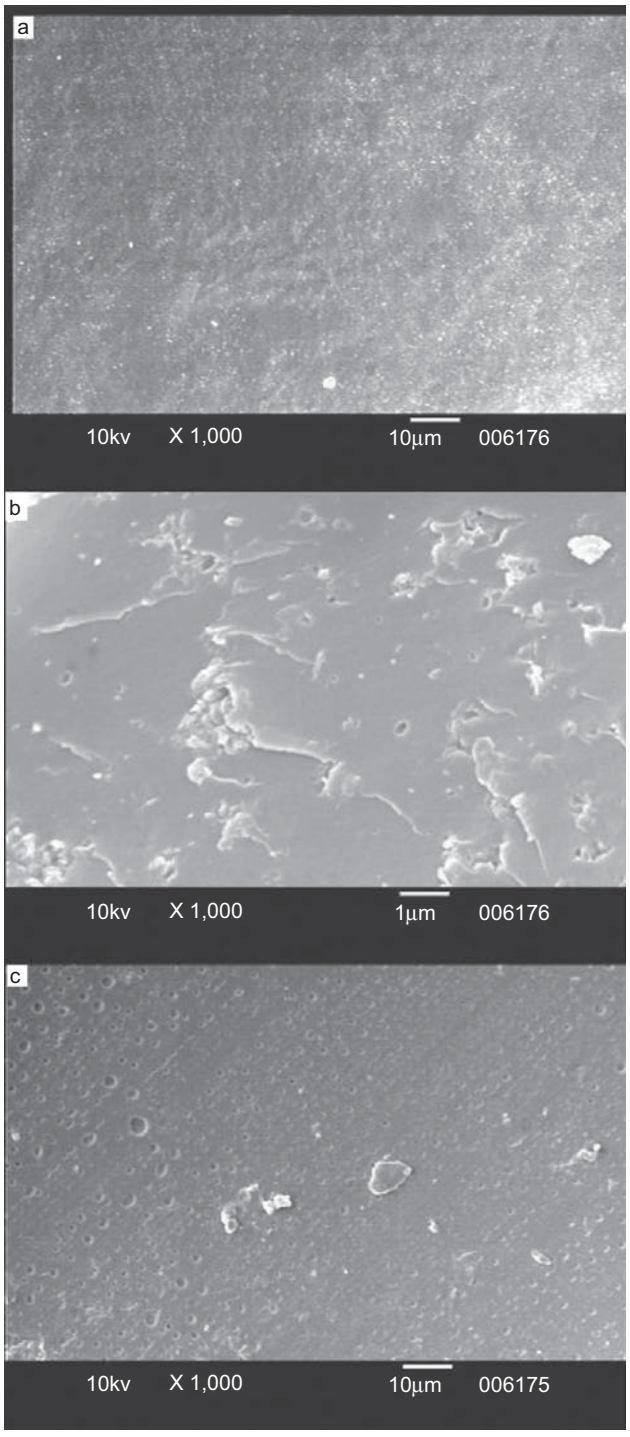

Figure 7. Scanning electron microscopy (SEM) of formulation S6 before dissolution at 1000× (A), at 10000× (B) and after dissolution (C).

Conclusion

In this investigation, it is demonstrated that blending of chitosan with PVP reduces crystallinity, which would help to improve the permeability and selectivity to water. The swelling of hydrogels under acidic condition was due to the protonation of the primary amino group on chitosan. FTIR, p-XRD and DSC study revealed the proper formation of hydrogels and the stability of clarithromycin

in semi-IPN matrices. SEM showed pore formation in formulations after dissolution. *In vitro* release of clarithromycin from the formulations followed the non-Fickian diffusion mechanism. So it has been concluded that the proposed chitosan-PVP semi-IPNs is a potential candidate for the release of clarithromycin in the acidic environment of the stomach.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

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