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RESEARCH ARTICLE

Fabrication of chitosan–polyacrylic acid complexes as polymeric osmogents for swellable micro/nanoporous osmotic pumps

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Abstract

Aim: The aims of this study were to prepare and evaluate chitosan–polyacrylic acid complex (CS-PAA) as polymeric osmogents for swellable micro/nanoporous osmotic pump propranolol tablets.

Methods: The complexes were characterized and evaluated for their swelling characteristics. The selected complexes were incorporated into the core propranolol tablets as polymeric osmogents. The core tablets were formulated, compressed as monolithic and two-layered tablets, and finally coated with cellulose acetate containing PEG 400 and PVP K30 as plasticizers and pore formers, respectively. As a final point, the drug release was determined.

Results: A direct correlation was found between the CS content in the complex and the maximum swelling force and swelling ratio of the complex mixture. *In vitro* drug release revealed that the percent drug release increased with the amount of osmogent in the two-layered tablets. Drug release could be prolonged up to 12 h and conformed to the USP 31 criteria. In contrast, percent release decreased with the increasing amount of complexes in monolithic tablets. It was postulated that two opposing mechanisms were involved. Following water uptake, the complexes of polymers swelled and pushed the drug out of the tablets, and the drug bound to the polymer network and remained in the tablets.

Conclusions: The results indicated that the complex of CS-PAA at optimal proportion and amount was a promising polymeric osmogent for a zero-order controlled release from two-layered swellable micro/nanoporous osmotic pump tablets.

Keywords: Micro/nanoporous semipermeable membrane, osmotic agent, chitosan, polyacrylic acid, interpolymer complex

Introduction

Various devices have been developed based on principles of osmotically driven system[1] such as elementary osmotic pump (EOP)[2–4] or swellable elementary osmotic pump (SEOP)[5], push–pull osmotic pump (PPOP)[6–8], controlled porosity osmotic pump (CPOP)[9,10] or micro/nanoporous osmotic pump[11], asymmetric membrane osmotic pump[12–14], and system using swellable-core technology[15]. Osmotically controlled devices basically consist of an osmotic core containing drug and, as necessary, osmogent(s) surrounded by a semipermeable membrane with delivery orifice(s). When the osmotic system exposed to an aqueous environment, the osmotic pressure difference between inside of the device and environment draws water through the semipermeable membrane. The drug solution will be pumped out of the system through the opening(s) at a constant rate or zero-order release[1,2]. For controlling the drug release from osmotic pump systems, if the drug alone does not possess sufficient osmotic pressure, an osmogent can be

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added to the formulation. Generally, compounds that can be used as osmotic agents are water-soluble salts, for example, potassium chloride[10] and sodium chloride[16]; carbohydrates, for example, cyclodextrin derivatives[17]; water-soluble amino acids; and organic polymeric osmogents[18]. The swellable hydrophilic polymers commonly used as polymeric osmogents are chitosan (CS)[19], polyacrylic acid (PAA), hydroxypropyl methylcellulose (HPMC)[18], and polyethylene oxide[20].

Great attention has been focused on the application of polyelectrolyte complexes in biotechnology, pharmaceutics, and medicine[21]. Electrostatic polyelectrolyte complexes exhibiting unique physical and chemical properties with reasonable biocompatibility are formed by the reaction of a polyelectrolyte with an oppositely charged polyelectrolyte in an aqueous solution[21,22]. The electrostatic attraction between protonated amino groups on CS and carboxylate groups on PAA generates hydrogels. Noncovalent bonding complements the ionic bonding[21–33].

Freeze-dried interpolymer complexes based on CS-PAA were developed for amoxicillin delivery in an acidic environment[28,29]. Scanning electron microscopy has been used to show that electrostatic polymer–polymer interactions generate polyionic complexes with different porous structures[30]. In gastric simulated fluid (SGF), the presence of higher CS content in the complexes generated a higher repulsion between the polymeric chains; therefore, a further increase in its maximum swelling ratio and a more sustained erosion profile were obtained[28–30]. Moreover, the gastric residence time of the prolonged gastric antibiotic delivery formulations was evaluated by means of ^{13}C-octanoic acid breath test[30]. All the complexes showed extensive swelling; therefore, diffusion of the antibiotic was controlled by the degree of polymer–drug interaction.

CS is a natural biopolymer, partially N-deacetylated product from chitin, which is abundant in nature. It is inexpensive, safe, nontoxic, and biodegradable[34]. It was found that CS-PAA polyelectrolyte complex rapidly hydrated, swelled, and reached the desired equilibrium within 10–60 min[28–30]. This study proposed the hypothesis that the swellable CS-PAA complex could be successfully employed as a polymeric osmotic agent in a propranolol swellable micro/nanoporous osmotic pump system. The different mixtures were prepared by varying ratios of CS-PAA hydrogel and evaluated for their swelling behavior, which was the important factor in controlling drug release. Then, the selected polymer proportion was incorporated in propranolol swellable micro/nanoporous osmotic pump formulations and the drug releases based on criteria of USP 31 were determined.

Materials and methods

Chemicals

All chemicals were obtained from commercial suppliers and used as received. Propranolol HCl (Sinochem, Shanghai, China), pregelatinized starch (Colorcon, West Point, PA, USA), and lactose (Lactose of New Zealand, Taranaki New Zealand) were used in a core tablet as a model drug, binder, and filler, respectively. Cellulose acetate (39.8% acetyl content; Aldrich Chemical, St. Louis, MO, USA) and PVP K30 (ISP, Wayne, NJ, USA) were used in a micro/nanoporous membrane as coating materials and pore formers, respectively. CS (degree of deacetylation of 80%) was purchased from Fluka Chemie AG (Buchs, Switzerland). PAA (grade 934P) was obtained as a gift sample from Noveon (Cleveland, OH, USA). All other chemicals and reagents were of either analytical or pharmaceutical grade.

Preparation of interpolymer complexes of CS and PAA

To determine an appropriate molecular weight of CS and optimum ratio of CS:PAA for CS-PAA interpolymer complexes, three molecular weights of CS, that is, low (150,000; L-CS), medium (400,000; M-CS), and high (600,000; H-CS) were chosen to form the complex with PAA at the mass ratios of 1:2, 1:1, and 2:1. The polymer blends were prepared by separately dissolving CS and PAA in 1 M acetic acid (3.3% w/v) and then mixed together. The pH of the mixtures was adjusted to 5.0 with 3 M sodium hydroxide. The mixtures were kept at room temperature overnight to allow the complete precipitation of CS-PAA complexes. The complexes were collected on an 80-mesh sieve and washed with distilled water. The wet mass was dried at 50°C for 24 h and pulverized to fine powder by placing the dried mixtures on a 60-mesh sieve and forcing material through with a spatula.

Evaluation of swelling characteristics of CS-PAA complexes

Swelling properties of the powdered CS-PAA complexes were evaluated. Five hundred milligrams of the powder were directly compressed to flat-faced discs of 13 mm diameter × 3 mm thickness by hydraulic press at the pressure of 296 MPa for 1 min. The complex discs were further evaluated for their swelling characteristics, that is, swelling force and swelling ratio.

Swelling force

The swelling ability of the CS-PAA complex discs was determined in terms of swelling force using a self-built device as shown in Figure 1. Each disc was placed on a 20-mesh sieve attached to the lower end of the cylinder. A low-density polyethylene punch was placed on the top of the disc and connected to a texture analyzer-load cell (TA-XT plus; Stable Micro Systems, Surrey, UK) via a probe. Distilled water at room temperature was filled into the water chamber to the level of the sieve. As the medium moved through the sieve, the disc absorbed water and started to swell. The swollen disc pushed against the punch, which was kept at a fixed position. Thus, a swelling force was exerted on the probe and the force recorded as a function of time by the texture analyzer. The pretest speed, the test speed, and the posttest speed of the punch

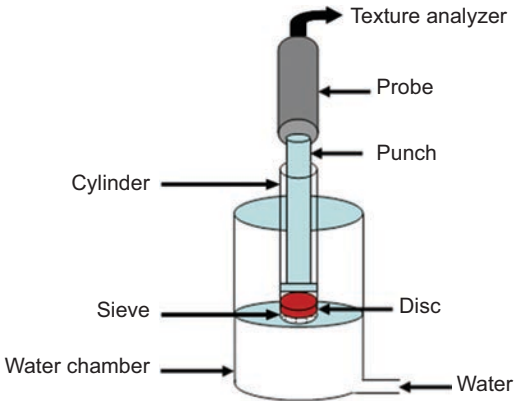

Figure 1. Swelling device for the measurement of the swelling force.

were set up at 0.5, 0.5, and 10 mm/sec, respectively, with an acquisition rate of 0.1 pps (point per second). The trigger force was 5 *g* and the distance was 0.1 mm. The swelling forces for each complex were monitored for 6 h and determined in triplicate.

Swelling ratio

The rate of water uptake was used to investigate the swelling characteristics of the CS-PAA complex discs. The water uptake was examined using a USP dissolution testing apparatus 2 (Model SR8-plus Q-Pak™; Hanson Research, Chatsworth, CA, USA). Each disc was accurately weighed and placed in a preweighed wire basket. The basket containing the disc was immersed in 500 mL distilled water at 37 ± 0.5°C. The paddle rotation speed was set at 25 rpm. At every 15-min interval for a period of 6 h, the basket was withdrawn from the medium and lightly blotted with filter paper to remove excess water prior to weighing. The water uptake was reported in terms of the swelling ratio (S_W), which was calculated according to the following expression:

$$S_W = W_S / W_D \quad (1)$$

where W_S is the weight of swollen disc and W_D is the initial weight of disc[28]. The determination was performed in triplicate and new discs were used for each time point.

FTIR spectrophotometry studies

To identify whether the new functional groups were introduced into the polymers, each sample was examined by Magna-IR 550 (Nicolet Instrument, Madison, WI, USA) using KBr pellets.

Preparation of swellable micro/nanoporous osmotic pump tablets

Swellable micro/nanoporous osmotic pump tablets were prepared by a wet granulation process. The composition of each formulation is shown in Table 1. Formulations A, B, and C were standard compressed tablets (homogeneous core), whereas formulations D and E were two-layered compressed tablets, as shown in Figure 2. For formulations A, B, and C, the drug was

Table 1. Compositions of core tablets.

Composition (mg)	Formulation A	B	C	D	E
				Drug layer	
Propanolol HCl	80	80	80	80	80
CS-PAA hydrogel	—	10	20	—	—
Lactose	80	80	80	48	48
Starch	132.5	122.5	112.5	53.1	53.1
PVP K30	2%	2%	2%	2%	2%
Mg stearate	0.5%	0.5%	0.5%	0.5%	0.5%
				Polymer layer	
CS-PAA hydrogel				10	20
Lactose				32	32
Starch				75.4	65.4
PVP K30				2%	2%
Mg stearate				0.5%	0.5%

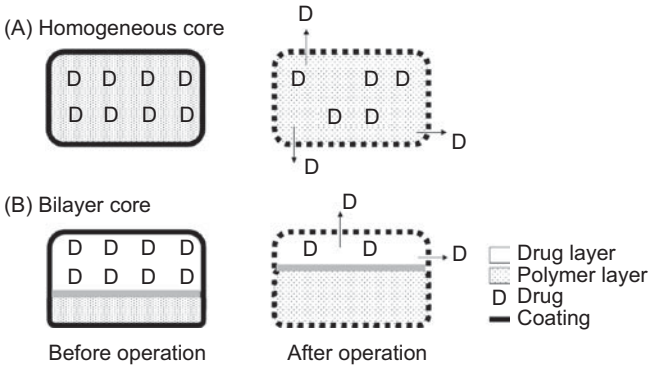

Figure 2. Schematic diagrams of swellable micro/nanoporous osmotic pump: (A) homogeneous core and (B) bilayer core.

blended with polymeric hydrogel, except formulation A, lactose and starch in a V-shaped solid–solid blender. The powder blend was transferred into a planetary mixer and mixed with 10% w/w povidone in ethanol solution. The damped mass was passed through a 16-mesh sieve and dried in a hot air oven. The dried granulation was screened through an 18-mesh sieve and dry-mixed with magnesium stearate. The mixture was compressed on a single punch tablet press using 9-mm tooling to the weight of 300 mg and the hardness of 80 N. For formulations D and E, the granulations for drug layer and polymer layer were prepared separately in a similar manner described above. The two-layered tablets were prepared manually by a double compression method. The polymer layer was compressed into a soft slug, then the drug layer was added and compressed again to form the two-layered tablet. The tablet weight and hardness were the same as the standard compressed tablets. Subsequently, the core tablets were coated with 3% w/v cellulose acetate in acetone:isopropyl alcohol (3:1, v/v) solution containing PEG 400 (10% w/v) as a plasticizer and PVP K30 (60% w/w based on cellulose acetate) as pore formers to obtain 8% additional weight. All coatings were performed in a perforated pan coater (Thai Coater®, Model 15" (L); Pharmaceuticals and Medical Supply, Bangkok, Thailand).

In vitro drug release studies

Propranolol osmotic pumps were evaluated for their release characteristics according to Propranolol Hydrochloride Extended Release Capsules USP 31, Dissolution Test 2, using a USP dissolution station (Model SR8-plus Q-Pak™; Hanson Research) and a UV/visible spectrophotometer equipped with six 1-cm flow cells and a six-channel peristaltic pump. The basket rotating speed was 50 rpm. The osmotic tablets were placed in 900 mL of pH 1.2 medium and maintained at 37 ± 0.5°C. After 1 h, the dissolution medium was changed to the pH 7.5 buffer and then run for another 11 h. The samples were analyzed at appropriate intervals at the wavelength of 318 nm. The dissolution profiles were constructed by plotting the average percent release of propranolol against time. Release profiles of various formulations were compared using a model-independent method, which is the calculation of "similarity factor" f_2 defined by US FDA[35]. The equation for calculating f_2 is as follows:

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5}\times 100\right\} \quad (2)$$

where R_t and T_t are percent drug dissolved at time t from the reference and test products, respectively. The two release profiles were considered to be similar, if the f_2 value (calculated from 0% to 80% drug release data) was between 50 and 100.

Results and discussion

CS-PAA interpolymer complex

Polymer blends of polyelectrolyte complexes comprised CS as a polycations polymer and PAA as a polyanions polymer were prepared at various ratios. The powdered polymers were dissolved in acetic acid and mixed together. When sodium hydroxide was added to adjust the pH to 5, the mixtures appeared as white gel-like precipitates and became more viscous after standing overnight. After drying at 50°C, a golden-yellow membrane was obtained. The color change after drying could be due to the oriented polymer chains of CS and PAA, which altered light reflection as reported previously[23]. The preparation of CS-PAA at the ratio of 1:2 provided the highest yield of 92.7%, whereas at the ratios of 1:1 and 2:1, the yields were 83.7% and 50.3%, respectively.

FTIR analysis

In this study, the FTIR spectrum of interest was in the range of 1400–1800 cm^{-1}. This range is a suitable region to investigate the influence of the vibration modes of carbonyl groups and carboxylate groups on possible hydrogen bonding interactions in the CS-PAA complexes[25]. Figure 3 shows FTIR spectra of CS, PAA, and CS-PAA complex. Characteristic peaks of amide I and amide II of CS were located at 1654 and 1596 cm^{-1}, respectively[21], whereas the absorption band of PAA at around 1714 cm^{-1} referred to

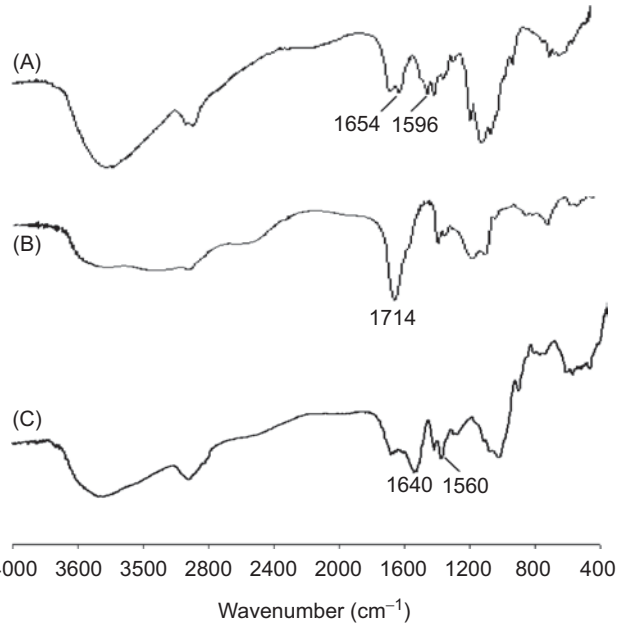

Figure 3. FTIR spectra of (A) CS; (B) PAA; and (C) CS-PAA complex.

C=O stretching vibrations of carboxylic groups[36]. In the spectrum of CS-PAA complex, two strong peaks at 1560 and 1412 cm^{-1} represented the asymmetrical and symmetrical stretching of COO^- groups, respectively, whereas one peak at 1655 cm^{-1} was attributed to the formation of protonated amino groups (NH_3^+). These results indicated that the carboxylic groups of PAA were dissociated to their ionized forms. These formed complexes with protonated amino groups of CS through electrostatic interaction. Similar electrostatic interactions have been reported[23,29,37].

Swelling study

Effects of molecular weight of CS and CS:PAA ratio

The swelling properties of CS-PAA complexes with different molecular weight of CS and with different CS:PAA ratio were evaluated. Swelling was characterized in terms of swelling force and swelling ratio. As the water was absorbed into a disc kept in a confined area, the disc swelled and expanded upward, pushing against the probe. The force exerted on the probe was monitored as a function of time. Figure 4 illustrates the effects of molecular weight of CS and CS:PAA ratio on the swelling force of the CS-PAA complex discs. The effect of molecular weight of CS was carried out only at 1:1 ratio of CS-PAA complexes. It was found that the swelling force increased with the molecular weight of CS. The CS-PAA complexes with low, medium, and high molecular weight of CS exhibited the swelling forces of 7.6, 16.3, and 20.8 N, respectively. The results indicated that the higher molecular weight of CS exhibited the greater swelling force. Thus, the high molecular weight of CS was chosen for further study of the effect of CS:PAA ratio on the swelling force. It was found that the swelling force increased with the increase in the CS proportion in CS-PAA complexes. At the end of

the observation, that is, 6 h, the swelling forces obtained with the 1:2, 1:1, and 2:1 ratios were 15.5, 20.8, and 27.6 N, respectively. It could be seen from the plot that the initial rate of swelling was rapid and then decreased as the swelling approached equilibrium.

The swelling ratios of the CS-PAA complexes reflected the amount of water uptake into the hydrogel discs. Upon immersion in the water, the hydrogel discs absorbed the water and swelled. As the swelling progressed, the disc mass loosened and erosion occurred. The effects of molecular weight of CS and CS:PAA ratio on the swelling ratio of the hydrogel discs are shown in Figure 5. As expected, at 1:1 CS:PAA ratio, the increase in molecular weight of CS resulted in the increase in water uptake and therefore the swelling ratio. It was evident

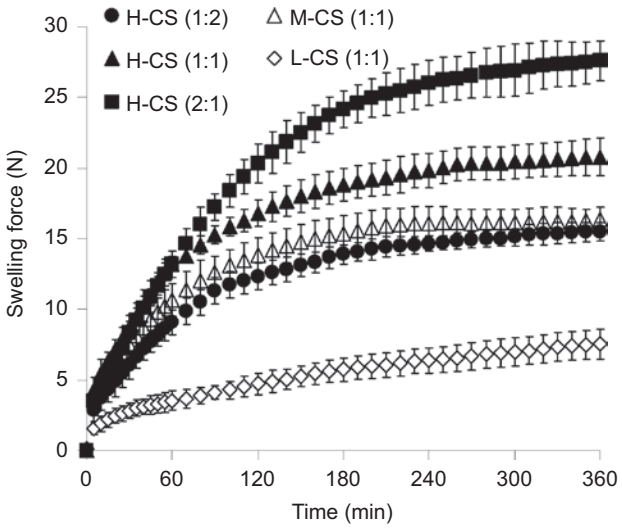

Figure 4. Effect of molecular weight of CS and CS:PAA ratio on swelling force of CS-PAA complex disc [three molecular weights of CS, i.e. low (L-CS), medium (M-CS), and high (H-CS). Error bars represent 1 SD].

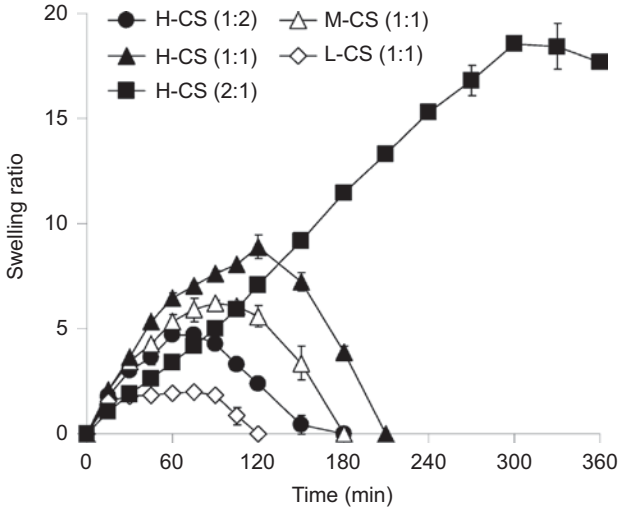

Figure 5. Effect of molecular weight of CS and CS:PAA ratio on swelling ratio of CS-PAA complex disc [three molecular weights of CS, i.e. low (L-CS), medium (M-CS), and high (H-CS). Error bars represent 1 SD].

that the swelling ratios increased to the maximum values and then declined. The descended swelling ratio was simply due to the erosion of the hydrogel disc mass. The CS-PAA complexes with low, medium, and high molecular weight of CS exhibited the maximum swelling ratios of 2.0, 6.2, and 8.9, respectively. Similarly, the CS-PAA complexes prepared from high molecular weight of CS at 1:2, 1:1, and 2:1 possessed the maximum swelling ratios of 4.9, 8.9, and 18.6, respectively. It was of interest that the CS-PAA complex containing high molecular weight of CS at 2:1 ratio exhibited a steadily increasing swelling ratio up to 18.6 at 5 h, although most of the CS-PAA complexes showed the maximum swelling ratio values within 2 h. These findings could be due to the stronger cohesion of the CS-PAA hydrogel mass with the 2:1 CS:PAA ratio, thus preventing the erosion of the swollen discs.

It was expected that an expansion of polymer chain would occur when ionic groups of CS in the formulation was increased[38]. As previously reported, the use of pure CS limited the maximum swelling force and swelling ratio; however, these properties were greatly improved in the presence of PAA[29]. PAA could enhance the protonation of the amine groups of CS, causing an electrostatic repulsion among polymeric chains[23,29,38]. The increase in CS content could result in the expansion of the polymer chains due to ionic repulsion of amino groups. Therefore, the greater swelling force and swelling ratio were observed. However, PAA could play a role in simultaneous swelling and eroding characteristics. In polyionic complexes with PAA, the erosion rate increased as the amount of this polymer increased in the hydrogel[39]. In the present study, the CS-PAA interpolymer complex at the ratio of 1:2 and 1:1 rapidly hydrated, swelled, and reached equilibrium within ~2 h (Figure 5). For further study of complexes, the CS:PAA complex containing high molecular weight of CS of 1:1 ratio was selected based on its appropriate percent yield and swelling properties.

Drug release study of propranolol osmotic pump tablets

The core tablets were prepared according to the formulations shown in Table 1. The physical properties of the tablets, that is, weight variation, hardness, and friability, were evaluated and found to be within the acceptable range, viz. 300 ± 5% mg, 80 ± 5% N, and <0.1% friability. The coating was performed in the perforated pan coater. The propranolol swellable micro/nanoporous osmotic pumps were aged 24 h prior to drug release testing. By visual observation, no bursting occurred during the dissolution period of 12 h. Figure 6 shows dissolution curves for different formulations at the same coating level. With the standard compressed tablets, the drug release markedly decreased with the increase in the CS-PAA hydrogel. Formulation A, without the hydrogel, released the drug as high as 73.8% at 12 h. The drug releases from formulations B and C at the end of the test were 52.1% and 24.9%, respectively. It appeared that the dissolution

profiles obtained with all three standard compressed tablet formulations did not meet the release criteria for the Propranolol Hydrochloride Extended Release Capsules USP 31. The reason that the drug release from the standard compressed tablets decreased with the increased hydrogel could be explained by the two opposing mechanisms proposed in this study. Upon immersion in the water, complexes of polymers absorb water, swell, and expand to push the drug out of the tablets, and, concomitantly, the drug is bound to the polymer network following water uptake. Interactions between positively charged propranolol, present as the hydrochloride salt, and anionic polymers, such as methacrylic acid copolymers, alginic acid, and acrylic–cyclodextrins have been reported previously[40–42]. It is likely that the ionic bonding between the propranolol amino group and the carboxylate groups of the polymers will contribute to these interactions. In this study, it could be explained that drug release from the monolithic tablets decreased with the increase in complexes due to the binding between the amino group of the drug and the COO^- group of the complexes of CS-PAA.

With the two-layered compressed tablets, the drug released as shown in Figure 6 increased with the amount of the CS-PAA hydrogel incorporated. At 12 h, the dissolution from both formulations D and E approached the limits and showed comparable dissolution values of 82.1% and 81.9%, respectively. Release profiles from multilayer systems clearly indicated a significant effect of polymer on the release of propranolol since the f_2 value between formulations A and E was found to be 41.7. It could be concluded that a CS-PAA content of 10–20 mg/300 mg tablet was sufficient to push the drug out of the tablets to accomplish the propranolol release criteria of USP 31. Preliminary study results corroborated that a higher proportion, that is, 30 mg in 300 mg tablet, bursting release was observed. It can be concluded that the two-layered system in which polymer can swell and directly push the drug out is more appropriate in order to control drug release, and hence conform to the USP criteria.

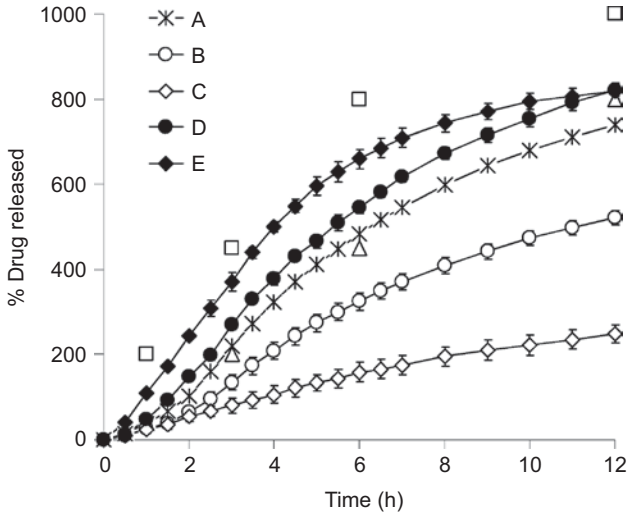

Figure 6. Drug release of propranolol from the micro/nanoporous tablets (USP 31 criteria: Δ, lower limits; □, upper limits; $n = 12$, error bars represent 1 SD).

A number of osmotic systems have been investigated and developed based on various principles. EOP[2–4] or SEOP[5] is a simple design requiring a laser or micro-drill to create an orifice. System using swellable-core technology[15] represents a broadly applicable osmotic pump. However, the processes for manufacturing are more complex. PPOP[6–8] needs to identify the drug layer side before making the delivery pore. CPOP[9,10] or micro/nanoporous osmotic pump[11] or asymmetric membrane osmotic pump[12–14] is an uncomplicated system, there is no need for any extra tool for producing the pores. In this study, the two-layered compressed tablets could be described as the PPOP system with micro/nanoporous membrane. In spite of the fact that the micro/nanopores distributed throughout the membrane, the CS-PAA hydrogel did not extrude though the pores due to the size of the hydrated complex was much larger than the micro/nanopores.

Various mathematical models (zero order, first order, and Higuchi) were fitted to the dissolution data of formulations D and E in order to establish the kinetics of drug release. The best goodness of fit (r^2), the smallest value of sum of squared residuals (SSR), and smallest Akaike information criterion (AIC) indicated the model suitability for a given dissolution data profile[43]. All mathematical parameters are tabulated and shown in Table 2. It was found that zero-order release best fitted drug release for up to 8 h from swellable micro/nanoporous osmotic pumps using CS-PAA as polymeric osmogents.

Conclusions

Homogeneous complexes of CS and PAA could be prepared by simple mixing of CS and PAA in 1 M acetic acid solution, and adjusting to pH 5. FTIR analysis revealed complex formation between CS and PAA due to ionic interactions. Hydrogels containing different ratios of CS-PAA as polymeric osmogents were evaluated to determine their utility in swellable micro/nanoporous osmotic pumps. These were examined for swelling behavior, an important factor for controlling

Table 2. Fitting of the drug release data based on mathematical models.

		Parameters used to assess the fit of model			
Formulations	Model	r^2	k*	SSR × 10^2	AIC
D	Zero order	0.9918	7.67	0.53	67.5
	First order	0.7815	0.479	37.6	123.3
	Higuchi	0.9103	27.4	172.1	153.3
E	Zero order	0.9953	9.66	0.25	46.5
	First order	0.8424	0.466	12.8	86.7
	Higuchi	0.9252	30.3	3.92	77.7

r^2, goodness of fit; SSR, sum of squared residuals; AIC, Akaike information criterion; and k*, release rate constant for respective model (k_0 in mg/h, k_1 in h^{-1}, k_H in $\%/h^{1/2}$ for zero-order, first-order, Higuchi equations, respectively).

drug release. The CS-PAA hydrogels rapidly hydrated, swelled, and reached equilibrium within 10–60 min. The swelling force and swelling ratio increased with the increased molecular weight of CS. Therefore, CS with high molecular weight was selected for the preparation of CS:PAA interpolymer complex due to its high swelling force and swelling ratio.

There was a direct correlation between the increased proportion of CS within the complex and the effect on the maximum swelling force and swelling ratio. Increasing CS content showed the greater swelling force and swelling ratio, which could be caused by the expansion of the polymer chains due to ionic repulsion of amino groups. The ratio of CS:PAA at 1:1 was selected for further development of the propranolol osmotically controlled release system based on its good percent yield and good swelling characteristics.

The swellable micro/nanoporous osmotic tablets used the complexes of CS-PAA as polymeric osmogents were successfully prepared; their drug releases were evaluated. The results were in good agreement with our hypothesis. They showed that a two-layered system in which polymer swelled and directly pushed the drug out was more appropriate than a monolithic system in order to control the drug release conforming to the USP criteria. The present study has demonstrated that the complexes of CS-PAA can be promising polymeric osmotic agents for controlling drug release in a zero-order release manner from osmotic pump systems.

Declaration of interest

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