Synthesis of pH Dependent Chitosan-EPI Hydrogel Films and Their Application for *In Vitro* Release of Promethazine Hydrochloride

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ABSTRACT: Chitosan-epichlorohydrin hydrogel films (ChitEPI) were synthesized by using chitosan in the presence of epichlorohydrin (EPI) as a crosslinking agent at various amounts. SEM, FTIR, TGA, and DSC analysis were conducted for the characterization of the hydrogels. The DSC measurements indicate that ChitEPI hydrogels did not exhibit better thermal stability when compared to chitosan. Swelling behavior of Chitosan-EPI hydrogel film is pH dependent and showed a reversible swelling behavior with a fast response. The hydrogels were used for *in vitro* release of promethazine hydrochloride (PHCl) in pH = 1.2 and pH = 7.4 phosphate buffer solutions (PBS). The release of PHCl synthesized from hydrogels at pH = 7.4 is quite low while at pH = 1.2, the highest value was observed as 49% for ChitEPI600. It has been also found that PHCl release from ChitEPI thin films is mainly controlled by diffusion control mechanism. ChitEPI hydrogels may be used for the delivery of drug in stomach and gastrointestinal tract. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 109: 683–690, 2008

Key words: chitosan; hydrogel; crosslinking; drug release

INTRODUCTION

Hydrogels are considered to be a polymeric material that has the ability to absorb >20% of its weight of water and still maintain a distinct 3D structure. The hydrophilicity of the polymer imparts waster attracting properties to the system.[1] Hydrogels can exhibit dramatic changes in their swelling behavior, network structure, permeability or mechanical strength in response to different stimuli, both internal and external to the body.[2] The response of hydrogels to environmental changes in biological systems such as pH, temperature, electric field, and ionic strength, is an active area of research.[3–10]

Chitosan, a copolymer of β-[1,4] linked 2 acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose is generally obtained by deacetylation of chitin, which is the main component of the exoskeleton of crustacean shells such as shrimps.[11] Chitosan has desirable biological properties, being biodegradable, biocompatible, nontoxic, bioabsorbable, and having gel-forming ability at low pH. Moreover, chitosan has antacid and antiulcer activities, which can prevent or weaken drug-induced irritation in the stomach.[10] The amino group, NH_2 in chitosan can be protonated to NH_3^+ in an acid environment, resulting in antifungal or antimicrobial activities, since cations can bind with anionic sites in protein.[12] These kinds of properties make the chitosan attractive for the application in controlled drug release formulations. However, chitosan has hydrophilic character, and consequently its poor mechanical properties in the presence of water and a humid environment limits its application.[13] Since chitosan dissolves in acidic conditions, this case creates some limitations for the release of drugs from chitosan.

A crosslinking step is required to overcome the solubility problem in acidic solutions. Some crosslinking reagents[14,15] have been used to stabilize chitosan in acid solutions but also have stronger mechanical properties.[16] The crosslinked chitosan is very stable and maintain their strength even in acidic and basic solutions.[17]

Attempts have been mostly made to produce bead forms of chitosan by crosslinking the surface of chitosan by crosslinking agent. The physical property of chitosan fiber crosslinked by epichlorohydrin (EPI) in a wet spinning system has been investigated.[16] A lot of researchers studied crosslinked chitosan bead by using ethylene glycol diglycidiyl ether (EGDE), glutaraldehyde and EPI as crosslinker.[17–21] On the other hand, crosslinked chitosan film is not common as crosslinked chitosan bead.

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In this study, pH dependent ChitEPI hydrogels which behaves reversible swelling have been developed. The aim of present study is to investigate the releasing of a model drug, promethazine hydrochloride from pH = 1.2 and 7.4 by using ChitEPI hydrogels. The main emphasis of the study is characterization of ChitEPI hydrogels and relation between swelling and releasing behavior of synthesized hydrogels.

MATERIALS AND METHODS

Materials

Chitosan (highly viscous) was purchased from Fluka (degree of deacetylation: 75–85%, average molecular weight: 500,000–700,000) as a flaked material. Crosslinking agent, EPI was supplied from Aldrich. KH_2PO_4, $Na_2HPO_4{\cdot}12H_2O$, HCl, NaOH were obtained from Riedel de Haen. KCl and NaCl were bought from Merck. The model drug, promethazine hydrochloride (PHCl) was supplied from Merck.

Synthesis of crosslinked chitosan film

One gram of chitosan flake was dissolved in 50 mL of 2% acetic acid in a beaker. It will take one night to dissolve completely. The solution was poured into a Petri dish which was placed in an oven at 60°C for 18 h. Chitosan was rinsed with phosphate buffer solution (PBS) to remove any residual acetic acid. To prepare 250 mL of PBS, 2 g of NaCl, 1.146 g of $Na_2HPO_4{\cdot}12\ H_2O$, 0.06 g of KH_2PO_4 and 0.05 g KCl were mixed with distilled water. Chitosan was put into 50 mL NaOH solution (pH = 10) and was subjected to stirring. Then the solution was centrifuged to remove the undissolved chitosan.

Different amounts of crosslinking agent; EPI 400, 600, and 800 μL was added to chitosan solution and stirred at 60°C for 3.5 h. The chitosan-epichlorohydrin hydrogel film (ChitEPI) was washed with deionized water to remove any unreacted EPI. The samples were freeze dried for 12 h.

Characterization of ChitEPI hydrogel film

pH sensitivity of hydrogel films

Freeze-dried hydrogels were immersed into the different buffer solutions (changing in the range pH = 2–8) for 3 h at 37°C. The pH values were precisely checked by a pH meter (WTW pH meter, with an accuracy of ±0.1). The swollen samples were taken out and dried with filter paper to remove surface water and weighted. The percent of swelling values for each pH were estimated by using the following equation.[10]

$$\text{Swelling ratio} = 100[(m_t - m_o)/m_o] \quad (1)$$

where m_o is the initial mass and m_t, is the final mass of the hydrogel, after incubation at time t. The experiments were conducted in triplicates and the results were given as averages. Besides, the reversible swelling behavior of ChitEPI hydrogels were also examined. For this purpose, the hydrogels that equilibrated at pH = 1.2 alternated between solutions at pH = 7.4 and pH = 1.2.

Swelling reversibility of ChitEPI hydrogels

The swelling reversibility of the ChitEPI hydrogels was alternately carried out at pH = 1.2 and 7.4 that are similar to that of gastric and intestinal fluids. After ChitEPI hydrogels equilibrated at pH = 1.2, the samples were immersed in pH 7.4 for about 250–300 min. Then, they were transferred into acidic medium (pH = 1.2) for another 250–300 min.

FTIR analysis

Freeze dried hydrogel films and chitosan were characterized by using FTIR (Perkin–Elmer Spectrum BX-II Model FTIR spectrophotometer in the range 400–4000 cm^{-1} with a resolution of 2 cm^{-1}).

SEM analysis

The morphologies of ChitEPI films were examined using SEM (Jeol JSM 60) equipped with energy dispersive X-Ray (EDX). Freeze dried samples were coated with gold before scanning. The micrographs were taken at various magnifications (2500× and 3000×) at 10 kV.

Thermal analysis

To investigate thermal stability and decomposition temperature of hydrogels, differential scanning calorimetric (DSC) analysis of ChitEPI films and chitosan in the temperature range of 5–500°C were performed at a heating rate of 10°C/min under Argon flow of 10 mL/min in SETARAM DSC Model 111 in Darmstadt Technical University, Ernst-Berl Institute, Department of Industrial Chemistry/Germany. Thermogravimetric analysis (TGA) was also performed with Perkin-Elmer Diamond TG/DTA Analyzer in Dokuz Eylül University/Turkey. The analyses were carried out in aluminum pans under a dynamic nitrogen atmosphere in temperature range 25–600°C at a heating rate of 25°C/min.

Drug loading and release

For the determination of loading amount, freeze-dried hydrogel films were immersed in an aqueous

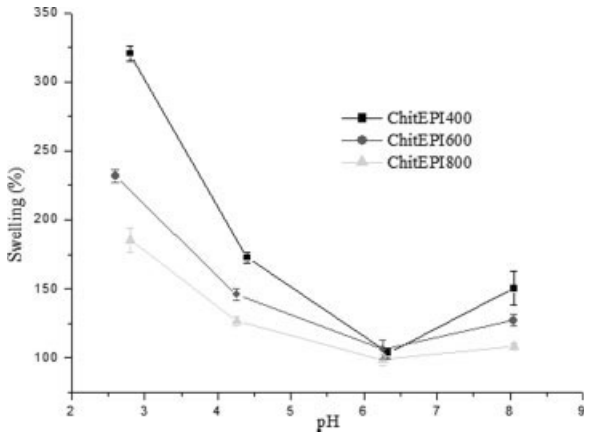

Figure 1 Effect of pH on the equilibrium swelling of ChitEPI hydrogels at 37°C.

solution of the drug (1.1 mg/100 mL) in the presence of BBS (borate buffer solution, pH = 8.9) at room temperature. After drug loading for 1 day, the amount of drug loaded was determined by measuring the absorbance values at 250 nm using UV spectrophotometer (90% of drug has been loaded).

The release of loaded drug *in vitro* was determined by immersing the drug loaded hydrogels in 10 mL of PBS (pH = 7.4) and HCl (pH = 1.2). The polyethylene bags were mixed end-over-end (50 rpm) in a shaker with water bath at (37 ± 0.1)°C. At regular intervals, 2 mL of solution was withdrawn and the release of drug was obtained by using UV spectrophotometer. The solutions were replenished with 2 mL fresh medium to keep the volume of drug release media constant. The mass released at time t (M_i) was calculated from the eq. (2).[22]

$$M_i = C_i V + \Sigma C_{i-1} V_s \quad (2)$$

where C_i is the concentration of drug in the release solution at time t, V is the total volume of drug release solution (10 mL) and V_s is the sample volume (2 mL). C_{i-1} is the concentration of the solution withdrawn (2 mL) from drug release solution.

Data points are the means of three determinations. The drug releases were given in terms of % drug release as a function of time.

RESULTS

pH-sensitivity of the hydrogels

The effect of pH on the equilibrium swelling ratio of ChitEPI hydrogels was shown in Figure 1. As shown in Figure 1, swelling values were significantly decreased with the rise of pH in the range from 2.5 to 6.5. In this pH range, the greatest swelling value belongs to ChitEPI400 when compared with the other produced hydrogels. The lowest swelling occurred almost at pH 6.3 for all hydrogels. According to Lin et al.,[23] if the chitosan is not crosslinked with an agent, swelling values with pH variations will follow that way. In the acidic pH regions, the swelling of chitosan decreased with a decrease of $—NH_3^+$ when raising the pH from 1.0 to 7.0. In alkaline environment, the amino groups were completely deprotonated. Namely, chitosan swelled hardly when pH > 7.0 due to the loss of solubility of the chain segments and also due the formation of new crosslink by hydrogen bonding. Chitosan is a weak base with a pK_a value of the D-glucosamine residue of about 6.2–7.0. When chitosan was crosslinked by EPI, the pH value of 7.0 for chitosan reduced to pH of 6.3. As mentioned earlier, this can be due to the fact that NH_2 groups may interact with EPI molecules. When some of the NH_2 groups are used in crosslinking, the amount of NH_2 groups gets lower. Moreover, swelling of the ChitEPI hydrogels in acidic medium are always greater than that in alkaline medium. As indicated above swelling increased with a decrease in the amount of crosslinker at the same pH range. It can be also added that the higher degree of crosslinking causing the compactness of the hydrogel network will prevent the permeation of water and result in lower swelling. As conclusion, it can be claimed that the swelling behavior of ChitEPI hydrogel film seems to be pH dependent.

At low pH values (acidic conditions) amine groups in the ChitEPI hydrogels are protonated. This causes an electrostatic repulsion in the ChitEPI hydrogel and swelling occurs. In other words, along with decreasing pH, the amount of $—NH_3^+$ increases inside the hydrogels resulting in an osmotic pressure and makes the ChitEPI hydrogels swell.

Beyond the pH value of 6.3, the swelling values are increasing with the increase of pH. At these pH values, while the amount of protonated amine groups reduces, the amount of neutral $—NH_2$ group increases. At higher pH values hydrogen bond may occur between amino groups of chitosan and OH^- groups.[23] On this consideration, following reaction can be offered

$$R—NH_2 + OH^- \longrightarrow R—NH_2 \text{ --- } OH^-$$

Swelling reversibility of ChitEPI hydrogels

As observed in Figure 2, the swelling reversibility of the ChitEPI hydrogels was alternately carried out at pH = 1.2 and 7.4 for ChitEPI hydrogels. After Chit EPI hydrogels equilibrated at pH = 1.2, the samples were immersed in pH 7.4 for about 250–300 min. A shrinking was measured at about 30–35%

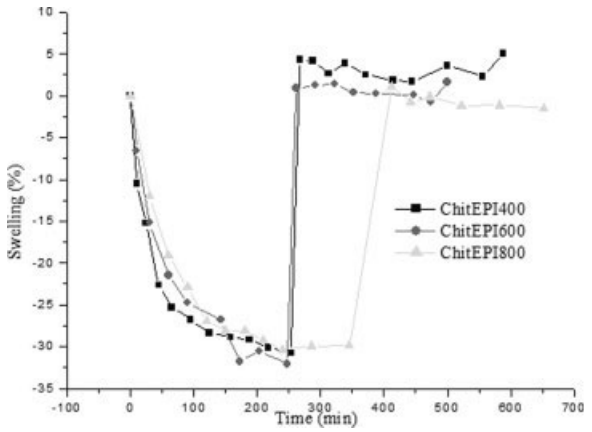

Figure 2 pH-dependent reversible swelling behavior of ChitEPI hydrogels (hydrogels equilibrated at pH 1.2, then alternated between solutions at pH = 7.4 and pH = 1.2).

for ChitEPI hydrogels at this pH. Then, those were transferred into acidic medium (pH = 1.2) for another 250–300 min and a swelling was observed to the equilibrium values of the hydrogels. When the pH values were varied repeatedly, ChitEPI hydrogel showed a reversible swelling behavior with a faster response than vinyl ether/acrylic acid terpolymer synthesized by Gumusderelioglu and Topal.[24] It could be concluded that reversible swell-shrink properties of produced hydrogels would be beneficial characteristics for pH sensitive controlled release system with controllable swelling ability, when used as a drug carrier.

The FTIR analysis

The FTIR spectra of chitosan, ChitEPI400, ChitEPI600, and ChitEPI800 were given in Figure 3. At 1651 cm^{-1} in the spectrum of chitosan can be assigned to amide I band, namely, C=O stretch of acetyl group. This is an indication of N-acetyl functional group of chitosan. This is an expected result, because degree of deacetylation for chitosan used in this study is changing from 75 to 85%. After modification of chitosan with EPI new bands at 1636 cm^{-1} for ChitEPI400 and ChitEPI600, and at 1637 cm^{-1} for ChitEPI800 can be attributed to an asymmetric NH_3^+ bending. C—N stretching vibration of chitosan was detected at 1318 cm^{-1}. This band was obtained at 1320 cm^{-1} for ChitEPI400, 1322 cm^{-1} for ChitEPI600 and 1312 cm^{-1} for ChitEPI800, respectively. There is not so much difference at the band of C—N, after EPI was crosslinked. Therefore, it can be claimed that EPI might not interact with chitosan at the position of amide group. The band at 1538 cm^{-1} corresponds to the NH_2 bending. This band shifted to 1550, 1555, and 1551 cm^{-1} for ChitEPI400, ChitEPI600, and ChitEPI800 indicating that amino group of chitosan may interact with EPI molecules. The strong band at 1089 cm^{-1} can be attributed to C—O stretching vibration. This band was lowered to 1084 cm^{-1} with the modification by EPI. The bands at 1030 cm^{-1} for synthesized hydrogels are due to C—O stretch primary hydroxyl group (characteristic peak of $—CH_2—OH$ in primary alcohols, C—O stretch).

C—H stretching vibration can be seen at 2922 cm^{-1} in the spectrum of chitosan. This band was appeared as a doublet (2935 and 2890 cm^{-1} for ChitEPI400, 2935 and 2889 cm^{-1} for ChitEPI600 and 2932 and 2888 cm^{-1} for ChitEPI800, respectively) when chitosan was crosslinked by EPI. Besides, C—H bending vibration of chitosan was observed at 1416 and 1379 cm^{-1}. In these bands, there was not so much difference after reaction with EPI, suggesting very weak interaction. The absorption band of 3363 cm^{-1} can be considered as OH stretching vibration. However, it may be added that this band may also contain N—H stretching vibrations. Because of the overlapping with OH stretching band, it cannot be seen exactly. The OH stretching vibration at 3363 cm^{-1} for chitosan shifted to 3338, 3350, and 3367 cm^{-1} for ChitEPI400, ChitEPI800, and ChitEPI600 respectively. As can be seen, ChitEPI600 when compared to the ChitEPI800 and ChitEPI400 increased slightly. Nevertheless, it can be claimed that the OH groups in chitosan may function as the recognition sites for the binding of EPI. The FTIR spectrum of chitosan exhibits the bands at 899 cm^{-1} and 1152 cm^{-1} which are owing to saccharide structure of chitosan. These bands did not change when the chitosan was crosslinked by EPI. As conclusion, NH_2 and OH groups in chitosan may function as the recognition sites for the binding of EPI.

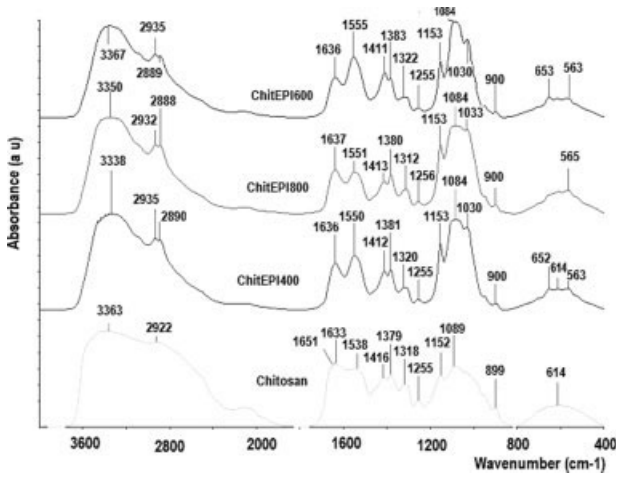

Figure 3 The FTIR spectra of chitosan and synthesized hydrogels.

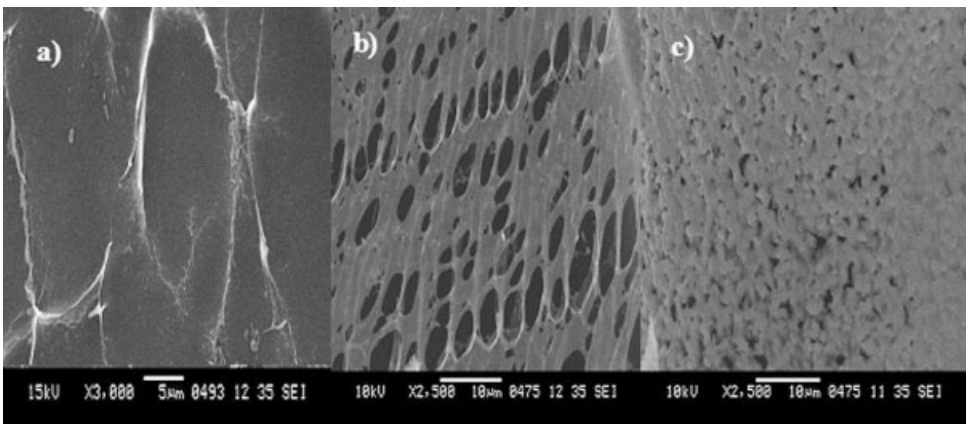

Figure 4 SEM micrographs of hydrogels: (a) ChitEPI400 (b) ChitEPI600 (c) ChitEPI800.

SEM analysis of hydrogels

SEM images of ChitEPI400, ChitEPI600, and ChitEPI800 were illustrated in Figure 4. Figure 4(a) shows micrograph of ChitEPI400. Macropores which are greater than 10 μm were observed at 3000× magnification. In addition to these, as seen from Figure 4(b) (SEM image of ChitEPI600) there are also large number of individual pores that are at about 5 μm and smaller than 5 μm. These pores are mostly circular and elliptical pores. Because of these pores, these hydrogels have also a macroporous structure. Namely, when the hydrogels are immersed in an aqueous solution, water molecules may diffuse easily into these gaps. As a consequence of this procedure, enhancement of swelling values occurs. From Figure 4(c) (ChitEPI800) as the same with the other hydrogels, a porous structure can be seen for ChitEPI800 at 2500× magnification. And the pores within this micrograph are quite small and it is difficult to determine the size of the pores. From SEM results it has been reached that when the amount of crosslinker increased, a more compact structure results in and the size of the pores decreases. SEM analysis demonstrated that the synthesized hydrogels have a porous structure. This is why the hydrogels swell in aqueous solutions.

Thermal properties of hydrogels

The thermal properties of ChitEPI hydrogel have been studied using DSC from 20 to 500°C. The DSC thermograms of chitosan, ChitEPI400, ChitEPI600, and ChitEPI800 were given in Figure 5. As shown by DSC analysis of chitosan in Figure 5, an endothermic peak at 103°C is caused by water evaporating from the sample. The endothermic peaks of ChitEPI hydrogels was observed at 85, 92, and 94°C for ChitEPI400, ChitEPI600, and ChitEPI800, respectively. As can be seen from these results, crosslinking of chitosan with EPI decreases the temperature which arises from water content. In addition to this, as the amount of crosslinker in chitosan was increased, that temperatures of hydrogels also increased. Heat flow values of hydrogels at melting temperatures were obtained to be −0.62, −1.45, −1.35, and −1.48 mW/g for chitosan, ChitEPI400, ChitEPI600, and ChitEPI800, respectively. The exothermic peaks in Figure 5 were observed due to thermal decomposition. For chitosan the exothermic peak was seen at 310°C. However, exothermic peaks representing thermal decomposition of ChitEPI hydrogels was appeared to be 236, 235, and 240°C for ChitEPI400, ChitEPI600, and ChitEPI800, respectively. It is clear that the temperature of the exothermic peak of chitosan was higher than those of ChitEPI hydrogels. From DSC analysis, it was realized that in terms of the thermal stability, there is not so much difference among synthesized ChitEPI hydrogels. Heat flow values at decomposition temperatures are found to be 1.59, 1.00, 0.45, and 1.17 mW/g for chitosan, ChitEPI400, ChitEPI600 and ChitEPI800, respectively.

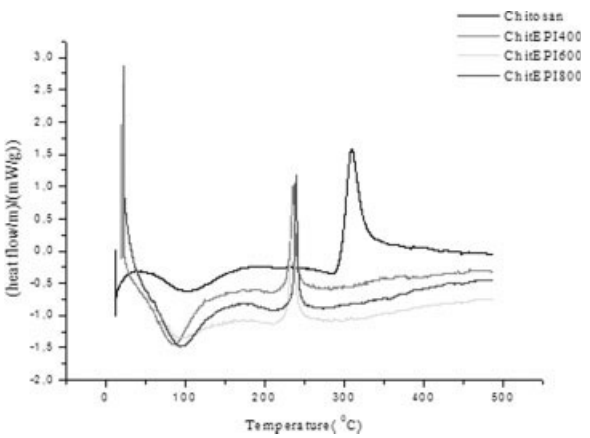

Figure 5 DSC thermograms for chitosan and ChitEPI hydrogels.

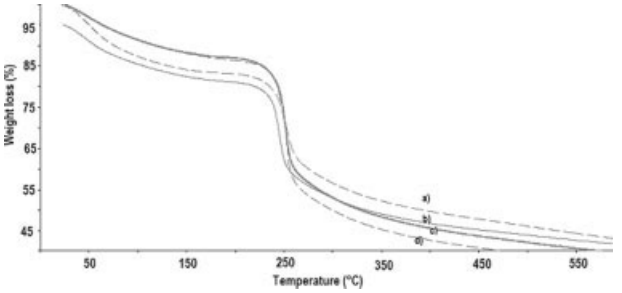

Figure 6 TGA Curves for the chitosan and ChitEPI hydrogels: (a) Chitosan (b) ChitEPI400 (c) ChitEPI600 (d) ChitEPI800.

Figure 6 shows TGA curves for chitosan, ChitEPI400, ChitEPI600 and ChitEPI800. Table I exhibits DTG maxima and weight losses of hydrogels used in this study. As can be seen from Table I, weight losses took place with two decomposition stages for both samples. One can realize from TGA curves that their shapes of the chitosan and ChitEPI hydrogels are almost similar. The first stage is owing to evaporation of bonded water. The DTG maxima of first stage are 55.8, 53.2, 59.6, and 55.2°C for chitosan, ChitEPI400, ChitEPI600, ChitEPI800, respectively. Considering the chitosan structure, it can be seen that water molecules can be bound by two polar groups, hydroxyl and amine, present in this macromolecule.[25,26] The second stage is assigned to thermal decomposition of the hydrogels. The second decomposition temperatures are 245.3, 251.0, and 253.0°C for ChitEPI400, ChitEPI600, and ChitEPI800 respectively. The content of EPI was increased, slightly higher decomposition temperatures were observed. Considering the second stage of decomposition, the weight losses are obtained to be 46.6, 47.0, and 46.5% for ChitEPI hydrogels.

Release of PHCl from ChitEPI hydrogels

The release of PHCl from ChitEPI hydrogels were performed by immersing PHCl loaded hydrogels in pH = 1.2 and 7.4. It can be noticed that Figures 7 and 8 show cumulative drug release profiles from ChitEPI for pH = 1.2 and 7.4, respectively. Considering the Figure 7, an initial burst was observed at pH 1.2 within 50 min. When the drug release at pH = 7.4 is concerned; only about 10% of the loaded drug is released during 600 min for all hydrogels. Besides taking into consideration PHCl release at pH = 1.2, about 28% for ChitEPI800, 36% for ChitEPI400, and 49% for ChitEPI600 was obtained, respectively, (during 600 min). It can be added that ~ 51% of the loaded drug was released during 720 min at pH = 1.2 for ChitEPI600 which can be considered as maximum value in this study in the time range of 720 min. The amount of drug released was much higher in acid medium than in PBS (pH = 7.4). This is an anticipated result. Since the release of PHCl may depend on swelling of the hydrogel, if drug release follows diffusion controlled mechanism through swollen gels. The hydrogels behaves as a diffusion barrier for drug, PHCl. Comparing the release of PHCl from ChitEPI400, ChitEPI600, and ChitEPI800

TABLE I
Thermogravimetric (TGA and DTG) Data of the Chitosan and ChitEPI hydrogels

Sample	Temperature range (°C)	DTG Maxima (°C)	% Weight losses
Chitosan	25–185	55.8	13.2
	185–580	249.7	43.3
ChitEPI400	21–185	53.2	12.8
	185–590	245.3	46.6
ChitEPI600	26–185	59.6	12.8
	185–578	251.0	47.0
ChitEPI800	22–185	55.2	16.7
	185–582	253.0	46.5

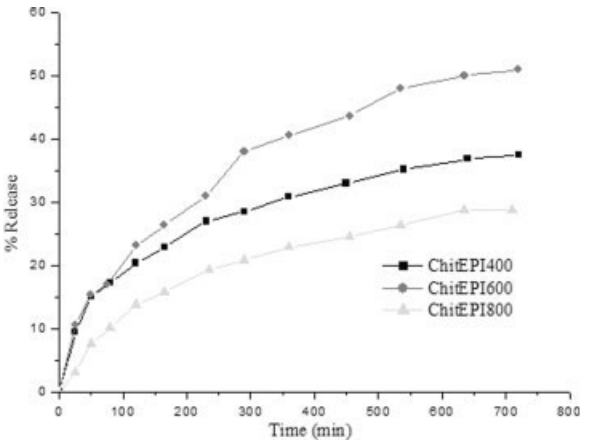

Figure 7 *In vitro* release measurement of PHCl from ChitEPI hydrogels at 37°C and pH = 1.2.

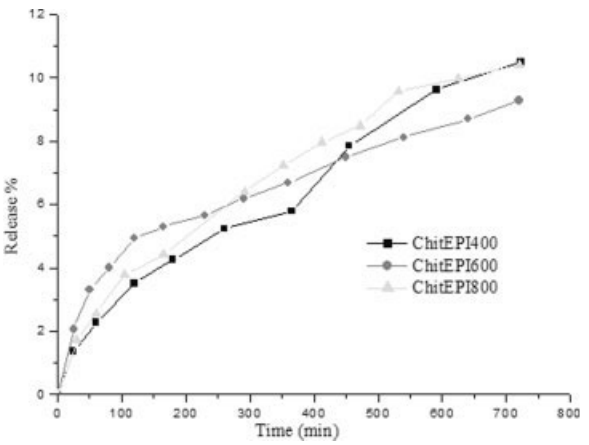

Figure 8 *In vitro* release measurement of PHCl from ChitEPI hydrogels at 37°C and pH = 7.4.

TABLE II
Release Kinetics of PHCl from ChitEPI Hydrogels

Hydrogel	Kinetic constant, k (min^{-1})	Release index, n
ChitEPI400	3.0	0.5
ChitEPI600	2.2	0.5
ChitEPI800	1.2	0.5

at pH 1.2, it can be put forward to that the lowest drug release belongs to ChitEPI800.

Drug release mechanism was investigated by using a semi-empirical equation is known as Power Law

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where M_t/M_∞, is the fractional release of the drug at time t, k the constant related to the structural and geometric characteristic of the device, and n is the swelling exponent, indicative of the drug release mechanism.[27]

For thin films, eq. (3) has two physical meanings in the two special cases of $n = 0.5$ (indicating diffusion-controlled drug release) and $n = 1.0$ (indicating swelling-controlled drug release). Once n value is 1.0, drug release rate is independent of time and corresponds to zero-order release kinetic model. For slabs the mechanism that creates the zero order release is known as case-II transport. If exponent n take place between 0.5 and 1.0, this can be indicator of both diffusion controlled drug release and swelling controlled drug release (Non-Fickian (anomalous) mechanisms).[28]

In the case of PHCl release from ChitEPI hydrogels, these parameters were calculated and given in Table II. As can be seen from Table II, exponent n takes a value of 0.5 for all ChitEPI hydrogels. It indicates that PHCl release from ChitEPI thin films is mainly controlled by diffusion control mechanism.

The pH dependent release of PHCl from ChitEPI hydrogels expresses that ChitEPI hydrogels can be used for the delivery of drug in stomach and gastrointestinal tract whose pH rises from 1.5 to 3.

CONCLUSIONS

The swelling values of ChitEPI hydrogels were significantly decreased with the raise of pH in the range 2.5–6.5. In this pH range, the greatest swelling value belongs to ChitEPI400 when compared the other hydrogels. Beyond the pH value of 6.3, the swelling values are increasing with the increase of pH. It is probable that the number of NH_3^+ were decreased with increasing of pH. The lowest swelling occurred almost at pH = 6.3 for all hydrogels. It is inferred that swelling behavior of chitosan-EPI hydrogel film is pH dependent. When the pH values were changed repeatedly, ChitEPI hydrogel showed a reversible swelling behavior with a fast response. The reversible swell-shrink properties of ChitEPI hydrogels would be beneficial characteristics for pH sensitive controlled release system with controllable swelling ability, when used as a drug carrier. SEM analysis demonstrated that the synthesized hydrogels have a porous structure. This is why the hydrogels swell in aqueous solutions. One can realize that when the amount of crosslinker increased, a more compact structure results in and the size of the pores decreases. The DSC results indicate that ChitEPI hydrogels do not exhibit better thermal stability as compared with chitosan. From FTIR analysis, it was inferred that NH_2 and OH groups in chitosan may function as the recognition sites for the binding of EPI. For the synthesized hydrogels, drug release (PHCl) in pH = 1.2, is greater than that in pH = 7.4. The release of PHCl from synthesized hydrogels at pH = 7.4 was quite low. PHCl release at pH = 1.2 for ChitEPI600 was about 49% within 600 min.

It could be concluded that reversible swell-shrink properties of ChitEPI hydrogels might be beneficial characteristics for pH sensitive controlled release system with controllable swelling ability, when used as a drug carrier in stomach and gastrointestinal tract whose pH rises from 1.5 to 3.

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