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ScienceDirect
International Journal of Pharmaceutics 350 (2008) 291–300
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Sodium lauryl sulfate impedes drug release from zinc-crosslinked alginate beads: Switching from enteric coating release into biphasic profiles

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Received 17 June 2007; received in revised form 16 August 2007; accepted 5 September 2007
Available online 14 September 2007

Abstract

The aim of this research is to investigate the effects of sodium lauryl sulfate (SLS) on ionotropically cross-linked alginate beads. Different levels of SLS were mixed with sodium alginate and chlorpheniramine maleate (as loaded model drug). The resulting viscous solutions were dropped onto aqueous solutions of zinc or calcium ions for ionotropic curing. The generated beads were assessed by their drug releasing profiles, infrared and differential scanning colorimetery (DSC) traits.

SLS was found to exert profound concentration-dependent impacts on the characteristics of zinc-crosslinked alginate beads such that moderate modifications in the levels of SLS switched drug release from enteric coating-like behavior to a biphasic release modifiable to sustained-release by the addition of minute amounts of xanthan gum.

Calcium cross-linking failed to reproduce the same behavior, probably due to the mainly ionic nature of calcium–carboxylate bonds compared to the coordinate character of their zinc–carboxylate counterparts. Apparently, moderate levels of SLS repel water penetration into the beads, and therefore minimize chlorpheniramine release. However, higher SLS levels seem to discourage polymeric cross-linking and therefore allow biphasic drug release.

Keywords: Sodium alginate; Beads; Ionotropic cross-linking; Calcium; Zinc; Chlorpheniramine; SLS; Release profiles; Infrared; DSC

1. Introduction

Sodium alginate (algin) is the purified carbohydrate product isolated from brown seaweads. Algin consists chiefly of the sodium salt of alginic acid, which is a linear copolymer of 1,4-linked mannopyranosyluronic acid and 1,4- linked gulopyranosyluronic acid units as shown in Fig. 1. Alginic acid has received great interest as drug delivery matrix prompting the publication of several recent reviews in this area (George and Abraham, 2006; Raj and Sharma, 2003; Shilpa and Agrawal, 2003).

Alginate has been investigated as a carrier material in different controlled release systems (Coviello et al., 2006; Pillay et al., 2005; Pillay and Fassihi, 1999a,b). It was employed in the preparation of controlled release microspheres or minimatrices for a variety of medicinal agents including protein drugs (George and Abraham, 2006; Raj and Sharma, 2003), metoclopramide and cisapride (Al-Musa et al., 1999), diclofenac (Fernandez-Hervas et al., 1998), indomethacin (Pillay et al., 1998; Shiraishi et al., 1993), propranolol (Lim and Wan, 1997), and gentamicin (Iannuccelli et al., 1996). Furthermore, alginic acid was used to encapsulate chitosan bioadhesive microspheres, and *vice versa,* for intestinal drug delivery (George and Abraham, 2006; Ramdas et al., 1999; Gaserod et al., 1998). Recently, alginate was developed as a gene transfection agent (Patnaik et al., 2006).

Algin is characterized with useful gel-forming properties when mixed with different polyvalent cations (Takka and

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doi:10.1016/j.ijpharm.2007.09.010

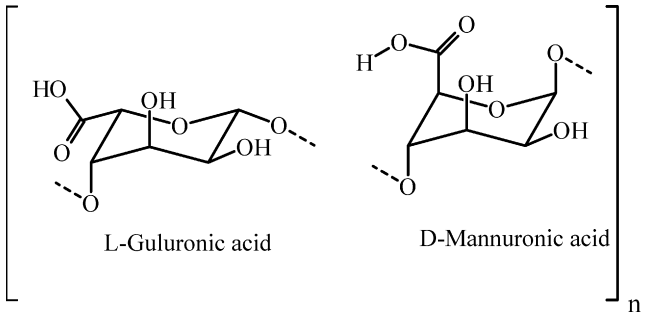


Fig. 1. Structure of alginic acid.

Acarturk, 1999a,b; Aslani and Kennedy, 1996). In particular, algin forms stable complexes with calcium ions that seem to assume the "egg box" model (Li et al., 2007). Calcium alginate has found applications in a number of gelation purposes including the formation of a firm gel for the preparation dental impressions (Steas, 1991), and in the preparation of matrices for drug delivery (Takka and Acarturk, 1999a,b; Aslani and Kennedy, 1996; Kamath and Park, 1993). The ratio of mannuronic acid to guluronic acid strongly influences the drug releasing properties of calcium alginate beads (Takka and Acarturk, 1999a,b; Shiraishi et al., 1993; Rousseau et al., 2004). A recent study has indicated that polymeric beads of calcium-alginate incorporating guluronic acid block (an alginate hydrolyzates) and chitosan yielded effective controlled release of hydrocortisone (Murata et al., 2004). In another study, albumin-crosslinked alginate hydrogel was evaluated as sustained drug release carrier (Tada et al., 2007). Chitosan–alginate-electrolyte matrices were found to be superior to their chitosan–carrageenan counterparts in providing prolonged drug release profiles (Tapia et al., 2004).

However, the drug releasing properties of calcium alginate matrices were reported to suffer from some serous problems: Their dissolution in phosphate buffered saline solution (pH 7.4) occurs completely within a short period after certain lag time (Aslani and Kennedy, 1996; Kikuchi et al., 1997; Ostberg et al., 1994). Additionally, these matrices were able to extend the release of theophylline and chloramphenicol only when pure water was applied as release medium (Ostberg et al., 1994). While in 0.1 M HC1, simulated gastric fluid (SGF), simulated intestinal fluid (SIF), and 0.1 M NaC1 drug release proceeded much more rapidly (Ostberg et al., 1994). The crosslinking calcium ions were rapidly discharged from the matrices in the presence of acid to yield the protonated alginic acid. This transformation reduced the degree of crosslinking within the matrix, and thus destroyed its ability to provide retarded drug release (Ostberg et al., 1994). In NaCI solutions and SIF, calcium ions were partly exchanged by the non-gelling sodium ions or sequestered by phosphate. This caused swelling and, in the latter case, dissolution of the matrices, thus inducing rapid release of the encapsulated drug. Accordingly, it was concluded that calcium alginate minimatrices do not seem applicable as an oral controlled release system, due to the pronounced sensitivity towards the composition of the release medium and the rapid drug release in media of physiological relevance (Ostberg et al., 1994).

These problems prompted several attempts to modify alginic acid in such a way to enhance the stability of its corresponding complexes with divalent cations under physiological conditions. For example, alginic acid was conjugated to hydroxamic acid moieties, which allowed excellent polymeric crosslinking by iron (III). The crosslinked polymeric matrices were explored as sustained delivery systems (Taha and Aiedeh, 2000; Aiedeh and Taha, 2001). Furthermore, conjugating alginic acid to cystein allowed access to thiolated forms of alginic acid of excellent affinities to zinc ions. These polymers were used to encapsulate folic acid via crosslinking with zinc. The resulting beads allowed selective release of the loaded drug in the simulated intestinal fluid only, while it retained the drug under gastric condition (Taha et al., 2005).

In line with our quest towards stable alginate/divalent cations complexes of enhanced drug releasing profiles (Taha and Aiedeh, 2000; Aiedeh and Taha, 2001; Taha et al., 2005), we decided to explore the possibility of introducing anionic surfactant molecules into ionotropically crosslinked alginate beads. Surfactant molecules can serve as dissolution enhancers to improve drug loading into the polymeric solution. However, upon ionotropic crosslinking, the surfactant molecules should lose the hydrophilicity of their heads as a result of coordination to the crosslinking cation, and therefore they are expected to switch into hydrophobic water repellents bound to the polymeric backbones and resistant to drug release from the beads. Up to our best knowledge, this concept is completely novel.

In this investigation, we explored the effect of sodium lauryl sulfate (SLS, Fig. 2), as a representative for anionic surfactants, on the drug-releasing profiles of ionotropically crosslinked alginate beads employing chlorpheniramine maleate as the model drug. chlorpheniramine (Fig. 3) is considered a suitable challenge for sustained release formulations due to its excellent water solubility.

SLS is an anionic surfactant of excellent wetting properties across wide pH range. It has several pharmaceutical and cosmetic applications (Hibbs, 2006). SLS is listed as Generally Regarded as Safe (GRAS) chemical and included in the FDA Inactive Ingredients Guide (dental preparations; oral capsules, suspensions, and tablets; topical and vaginal preparations), in nonparenteral medicines licensed in the UK, and in the Canadian List of Acceptable Non-medicinal Ingredients (Rowe et al., 2005).

2. Materials and methods

2.1. Materials

Reagent grade chemicals were purchased from the corresponding companies (in brackets): sodium alginate (Hipure,

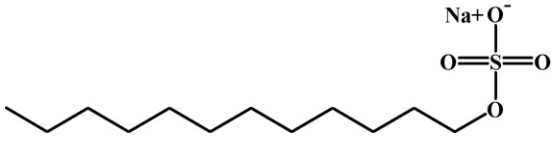


Fig. 2. Structural of sodium lauryl sulfate (SLS).

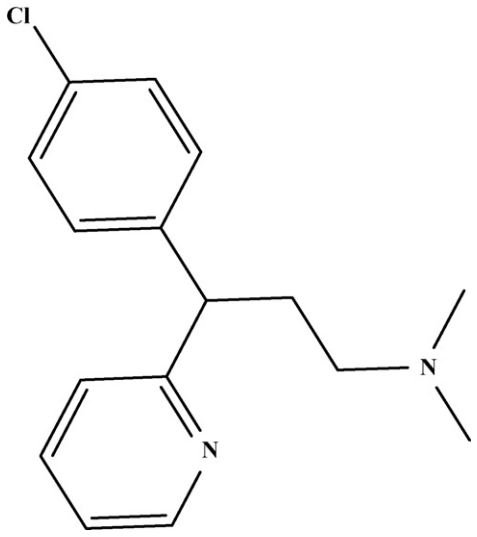


Fig. 3. The chemical structure of chlorpheniramine.

Fig. 4. Dry and wet beads prepared from formula **3** (Table 1).

Duchefa-Netherlands), Sodium lauryl sulfate (T.S.S.N.E, England), xanthan gum (Sigma, USA), chlorpheniramine (JPM-Jordan), zinc sulfate (Scharlau, European Union), calcium chloride (S.d. fine-chem. Ltd., India), sodium stearate (Riedel-De Haën, Germany), Tris buffer ultra-pure (Applichem, Germany), hydrochloric acid (GCC, U.K). All chemicals were used as obtained from the manufacturers without further purification.

2.2. Methods

2.2.1. General formulation procedure

Chlorpheniramine maleate (amounts are as in Table 1) was added gradually to a mechanically stirred solution (1500 rpm, propeller mixer) of sodium alginate (with or without xanthan gum, amounts are as in Table 1) in distilled water (50 mL) to yield viscous clear solution. Subsequently, a predetermined amount of SLS (amounts are as in Table 1) dissolved in distilled water (30 mL) was added to the polymer/drug solution under vigorous mechanical stirring to yield a creamy solution that was sonicated until clarity (over *ca.* 30 min). Thereafter, the resulting viscous solution was slowly dropped, from a 10-cm vertical distance, onto a mechanically stirred (150 rpm, orbital shaker) aqueous solution (100 mL) of the particular electrolyte curing agent (calcium chloride or zinc sulfate, the concentrations as in Table 1) to give spherical beads of around 2.0 mm diameter. The beads were left in the electrolyte solution over 20 min. Subsequently, they were filtered, washed with distilled water (3 × 50 mL), and dried at 50 °C. They underwent approximately 10-fold reduction in size upon drying. Fig. 4 shows some dry and wet beads.

2.2.2. Infrared and thermal characterization of polymer–surfactant-electrolyte composite matrices

Crosslinked polymer–surfactant composite matrices corresponding to formulas **1**, **2**, **3**, **6**, **7** and **8** (Table 1) were studied by infrared (IR) spectroscopy and differential scanning calorimetry (DSC). The matrices were prepared in a similar manner to their corresponding beads (Table 1) except that they were generated by adding the aqueous solution of the curing cation (zinc sulfate or calcium chloride) to vigorously stirred corresponding polymer–surfactant solution without chlorpheniramine maleate. The resulting white solid was filtered, washed with water until colorless filtrate was attained, and left to dry at 50 °C over few days.

The IR spectra were recorded on an Impact 400 Nicolet IR spectrophotometer using KBr discs. The dried matrices were

Table 1
Different formulations and their corresponding components

Formula	Polymer (g)		SLS (g)	Curing electrolyte		
	Sodium alginate	Xanthan gum		Calcium chloride (w/v%)	Zinc sulfate (w/v%)	Chlorphenir-amine maleate (g)
1	2.0	–	–	–	10.0	1.0
2	2.0	–	4.0	–	10.0	1.0
3	2.0	–	7.0	–	10.0	1.0
4	2.0	–	9.0	–	10.0	1.0
5	3.0	–	6.0	–	15.0	1.0
6	2.0	0.30	7.0	–	10.0	1.0
7	2.0	0.30	7.0	10.0	–	1.0
8	2.0	0.19	–	–	10.0	1.0
9	2.0	0.33	9.0	–	10.0	2.0
10	2.0	0.35	7.0	–	10.0	1.0

crushed and KBr discs were prepared from the resulting fine powder. Thermograms were recorded on Mettler TA3000 System. The dried matrices were placed in aluminum pans and heated at a rate of 10 °C/min.

2.2.3. Determination of drug loading in each formula

The total loaded drugs per gram polymer were calculated as in the following. Drug-containing beads were crushed, and an accurate weight of the finely crushed beads (*ca.* 0.15 g) was dispersed in hydrochloric acid (0.5 N, 50 mL) and stirred for 2 days at room temperature. Subsequently, the suspension was filtered, completed to 50.0 mL with HCl (0.5 N), then 5.0 mL of the solution was withdrawn and diluted to 50.0 mL with HCl (0.5 N). The concentration of the drug was calculated from appropriately drawn calibration plot at λ_{max} = 265 nm. Unloaded polymeric beads were used as blanks.

2.2.4. Dissolution profiles

A rotating basket apparatus (Hansen Research, USA) fitted with a 0.125-mm stainless steel basket was used. In each case, dried beads (1.0 g) from any particular formula were placed in the basket. Two dissolution media were used over two subsequent stages: 0.1 N HCl media (pH 1.0) for 2 h, then Tris buffer media (pH 6.8) for 4 h.

The dissolution media (500 mL) were maintained at 37 °C. The baskets were rotated at 100 rpm and samples (2.0 mL) were withdrawn at predetermined time intervals for the analysis of the released drug: Every 10 min for the first hour then every 30.0 min for the second hour (at pH 1.0), then every 60 min to the end of the dissolution (in Tris buffer). The withdrawn volume was immediately replaced with an equivalent volume of the fresh medium maintained at the same temperature. The absorbance values of the samples were reported at 265 nm for the acidic samples and at 262 nm for the Tris buffer samples (the λ_{max} values for chlorpheniramine maleate in the corresponding media) using a Milton Roy UV-visible spectrophotometer. Unloaded beads were utilized as blanks. The concentration of each drug was calculated from an appropriately drawn calibration plot (for each pH value).

3. Results and discussion

The inferior properties of calcium-crosslinked alginic acid matrices in simulated gastric and intestinal fluids (Aslani and Kennedy, 1996; Kikuchi et al., 1997; Ostberg et al., 1994) prompted us to replace calcium with zinc as cross-linking agent. Our choice of zinc is based on its recently reported excellent coordination qualities to polymeric carboxylate groups (Aiedeh et al., 2007). For example, zinc-crosslinked chitosan diacetate matrices succeeded in sustaining the release of caffeine contrary to calcium- or aluminum-crosslinked chitosan diacetate matrices which released their caffeine load rather quickly (Aiedeh et al., 2007).

We evaluated the effect of SLS on chlorpheniramine loading and release from cross-linked alginate beads by varying the amounts of SLS (formulas **1**–**4**, Table 1), alginate (formula **5**), and loaded chlorpheniramine (formula **9**). Furthermore, we incorporated xanthan gum in formulas **6**,**8**–**10** to probe the influence of increasing the polymeric viscosity on drug loading and release behavior.

3.1. Preparation of zinc-crosslinked chlorpheniramine-loaded polymeric composite beads

The zinc-crosslinked beads were prepared by dropping aqueous solutions of chlorpheniramine maleate, sodium alginate and varying levels of SLS (with or without xanthan gum, see Table 1) onto aqueous zinc sulfate solution. The resulting beads were generally white in color and oval in shape. Upon drying, they underwent approximately 10-fold reduction in their size to *ca*. 0.2 mm. Fig. 4 shows dry and wet beads prepared from formula **3**.

3.2. Chlorpheniramine loading

Fig. 5 shows drug loading in different bead formulas. As evident from the figure, chlorpheniramine loading is inversely proportional to SLS levels. In the absence of SLS (formula **1**, Table 1), zinc-crosslinked alginate beads loaded nearly 90 mg drug per 1.0 g matrix. However, drug loading decreased nearly three folds upon raising SLS to 75% (w/w) in formula **4**. The same trend can be seen in formulas **2** and **3**, i.e., increasing the amount of SLS is associated with proportional decrease in drug loading. This trend is probably explainable by the following: SLS has two negative effects on the cross-linking efficiency of alginic acid. Firstly, the sulfates of SLS compete with alginic carboxylates for coordination with zinc, thus reducing the degree of zinc-mediated carboxylate crosslinking across the polymer backbones. Secondly, bridging SLS with algin's carboxylates (via zinc) causes the lipophilic tails of SLS to be trapped between the polymeric backbones disallowing them from approaching each other for crosslinking. This combined effect should lead to significant leakage of the entrapped chlorpheniramine during ionotropic curing, and therefore reduce drug loading. Furthermore, by comparing drug loading in formulas **2** and **5** (Table 1), it appears that the effect of SLS on chlorpheniramine load was not reversed by increasing the amount of alginic acid and zinc,

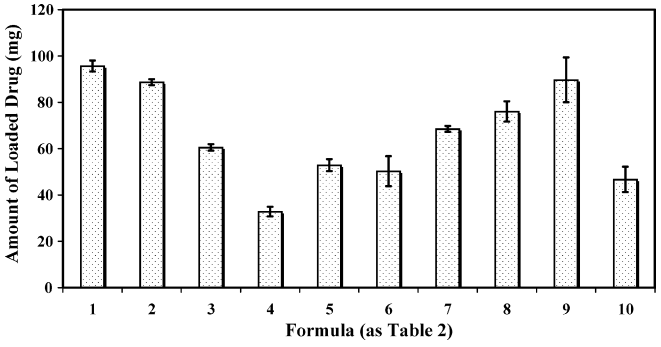


Fig. 5. Loading of chlorpheniramine in 1.0 g beads (each value represents the average loading in three separate preparations of the same formula, the error bars represent the standard deviation of the three measurements).

in fact increasing the amounts of alginic acid, SLS and zinc by one-third in formula **5** nearly halved the amount of loaded drug as compared to formula **2**.

A similar trend is seen upon introducing xanthan gum into the beads, i.e., formulas **6** and **10** (Table 1). The amount of loaded drug decreased from nearly 60 mg/1.0 g matrix in formula **3** to nearly 50 and 45 mg in formulas **6** and **10**, respectively. We believe that the decrease in drug loading is caused by the pronounced viscosity-enhancing effects of xanthan gum (Hardwaj et al., 2000). Increasing the viscosity of the gel core of the beads is expected to hinder the diffusion of zinc ions into the bead depth yielding thinner cross-linked crust, and therefore, more pronounced drug leakage during curing. However, this conclusion needs further experimental substantiation.

Unsurprisingly, the effects of SLS and xanthan gum on drug loading can be reversed by doubling the amount of chlorpheniramine: formula **9** accessed similar loading as formula **2** (Table 1).

Finally, to assess the effect of calcium cross-linking on drug loading, $CaCl_2$ was employed as cross-linking agent in formula **7** (Table 1). Interestingly, calcium cross-linking accessed higher drug loading levels compared to zinc cross-linking under identical formulation conditions, i.e., in formula **6**, as shown in Fig. 5. We believe this difference is related to the fact that calcium is a hard electrophile capable of forming quicker electrostatic attractive interactions with algin's carboxylates compared to the softer zinc ions, which tend to form slower covalent-like coordination bonds with carboxylates. This trend was previously observed in cross-linking carboxylic acid-containing polymers with ions of variable electrophilic hardness/softness profiles (Aiedeh et al., 2007).

It remains to be mentioned that the amount of SLS incorporated in any of the mentioned formulas should not exceed a maximum of 750 mg based on the facts that we were able to load from 30 to 95 mg chlorpheniramine maleate/1 g beads (see Table 1) and that the maximum therapeutic dose of chlorpheniramine maleate is 24 mg daily (Sweetman, 2004). This content is well within the safe levels of SLS intake knowing that the probable oral human lethal dose of SLS is 0.5–5.0 g/kg, while the oral LD50 for rat is 1.29 g/kg body weight (Rowe et al., 2005)

3.3. Chlorpheniramine release profiles

The dissolution profiles of chlorpheniramine from different bead formulas were studied under simulated gastric pH (1.0) followed by simulated intestinal pH (6.8). The dissolution media were maintained at 37 °C under sink conditions.

Fig. 6 shows the effect of SLS on chlorpheniramine release profiles from zinc cross-linked alginate beads. As evident from the figure, absence of SLS (formula **1**, Table 1) caused nearly immediate release of chlorpheniramine in the simulated gastric pH. However, raising the amount of SLS to 4.0 and 6.0 g, in formulas **2** and **5**, respectively (Table 1), caused dramatic reduction in the amount of released chlorpheniramine under the acidic pH. While on the other hand, the two formulas released their drug content nearly immediately in the simulated intestinal pH, reminiscent of enteric coating. This approach represents a novel alternative method for achieving enteric release by means other than coating, which may not be suitable for certain types of medications such as peptides and proteins that cannot withstand the harsher conditions of enteric coating processes.

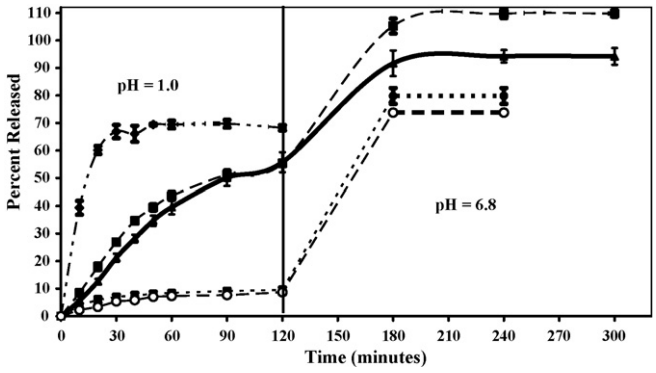


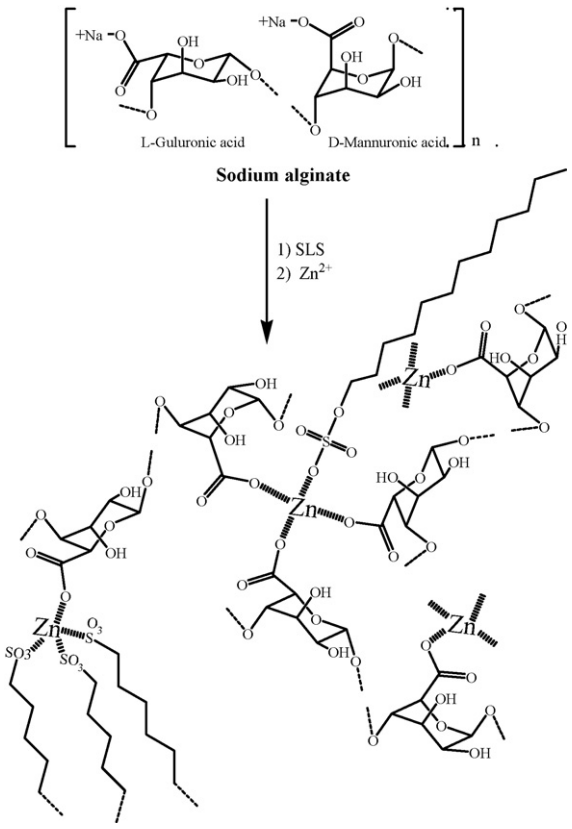
Fig. 6. The effect of varying amounts of SLS on the release profiles of chlorpheniramine from the zinc cross-linked microspheres. Formulas: **1** (♦), **2** (●), **3** (▲), **4** (■) and **5** (◯), see Table 1 for the components of different formulae. Each profile resembles the release measurements from three separate preparations from each formula. The error bars represent the standard deviation of the three measurements.

Intriguingly, further increases in the amounts of SLS to 7.0 and 9.0 g, in formulas **3** and **4** (Table 1), respectively, accessed biphasic release profiles in which nearly 50% of the drug was gradually released within the first 2.0 h in the acidic conditions, while the remaining drug was released within one hour in the simulated intestinal environment.

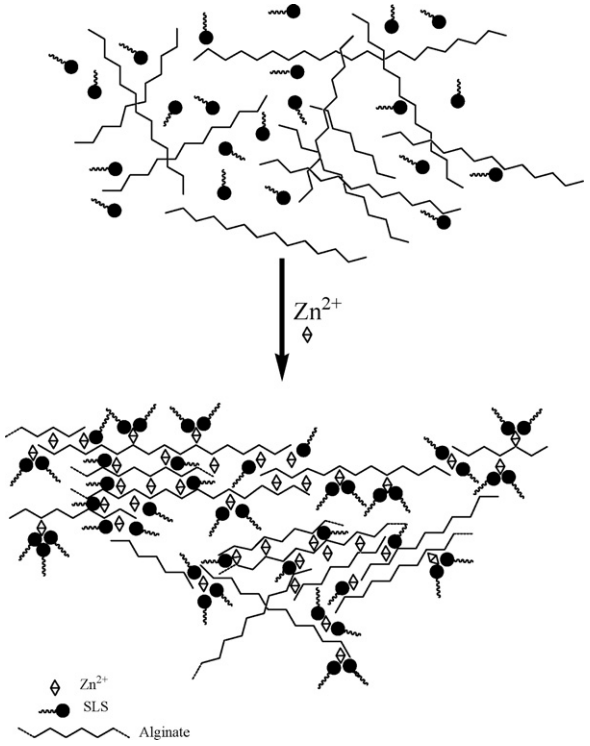
The most probable mechanism by which SLS modifies drug release can be clarified as follows: The coordination of moderate amounts of SLS to zinc ions in crosslinked alginate (formulas **2** and **5**) help in repelling water and therefore reduce the hydration rate of the polymeric matrix in acidic pH. On the other hand, increasing the amounts of SLS (in formulas **3**, **4**, **6** and **10**) seem to reduce the efficiency of polymeric cross-linking by saturating the coordination sites on zinc ions (Zn^{2+} can generally form four coordinate bonds (Fenton, 1995)) and by disallowing close approach between the polymeric backbones. This combined action reduces drug loading, as mentioned earlier, and allows certain degree of drug release in acidic pH. However, the acceleratory impact of high levels of SLS on the release profiles of chlorpheniramine is less than that resulting from the complete absence of the surfactant (i.e., formula **1**), probably due to the water repellant actions of the lipophilic tails of complexed SLS.

Upon fitting of the release profiles from formulas **3**, **6** and **10** against the Korsmeyer–Peppas equation (Korsmeyer et al., 1983), it was found that the release mechanism from formula **3** is anomalous (release exponent 0.82, $r^2 = 0.96$), while the release from formulas **6** and **10** conforms with a Super Case II release approaching a zero-order behavior (release exponents are 1.03 and 1.19, respectively, $r^2 = 0.98$).

It remains to be mentioned that all SLS-containing formulas exhibited quicker release profiles in the simulated intestinal pH,



Scheme 1. Representation of the formation of zinc-crosslinked alginate–SLS composite matrices.



Scheme 2. A schematic representation showing the effect of intermediate amounts of SLS on the cross-linking of zinc-alginate matrix. The figure shows how SLS (hydrophilic heads and lipophilic tails are represented by black spheres and wavy lines, respectively) is supposed to coordinate to zinc centers, and therefore repel water by the free lipophilic tails.

i.e., compared to the acidic pH, which is probably attributable to the ionization of uncomplexed polymeric carboxylates residing deep in the bead cores. Their ionization should lead to polymer swelling and cracking of the outer crosslinked crust and subsequent drug release. This effect is more pronounced in formulas **2** and **5** compared to formulas **3** and **4** because of the more effective water repellent actions associated with higher levels of complexed SLS in formulas **2** and **5**. The quicker intestinal phase in the cases of formulas **3** and **4** accessed an overall "biphasic profile".

Scheme 1 shows a representation of zinc-crosslinked alginate–SLS composite matrices, while Schemes 2 and 3 illustrate our explanations of the effects of varying levels of SLS on drug release from different bead formulas.

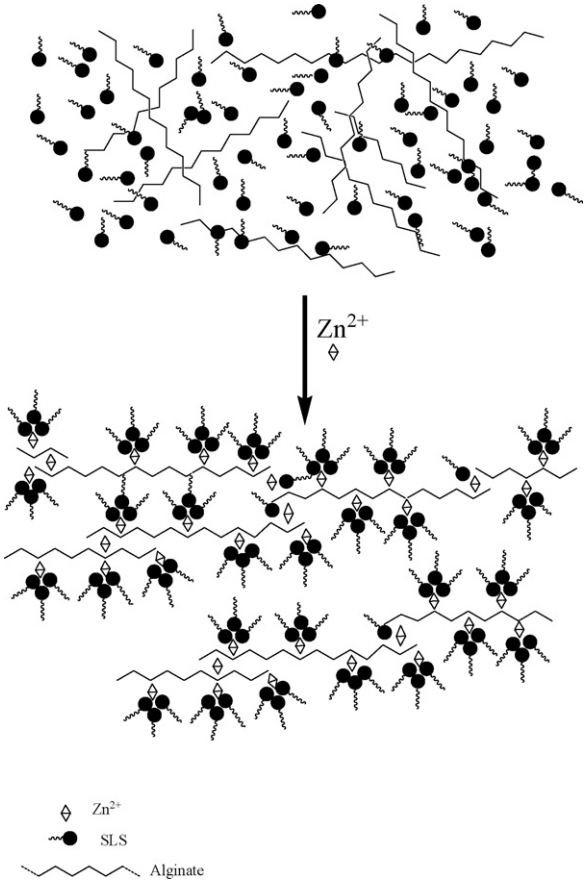
The influence of xanthan gum on chlorpheniramine release is shown in Fig. 7. Interestingly, only sub-gram levels of xanthan gum (*ca.* 0.30 g, Table 1) allowed access to smooth single-phase sustained-release curves. This trend is clearly evident in formula **10** (Table 1) whereby the incorporation of xanthan gum reduced the amount of released drug in the simulated gastric pH by *ca.* 10% compared to formula **3** (without xanthan gum, Table 1). Furthermore, formula **10** exhibited sustained drug release over nearly three hours in the simulated intestinal pH. The influence of xanthan appears to be proportional to its amount in the formula, e.g., formula **6** illustrated an intermediate release profile between those of formulas **3** and **10**.

The most probable explanation for the influence of xanthan gum is based on its viscosity-enhancing effects. Increasing the viscosity of the gel core of the beads hinders drug migration to the outer aqueous medium. This assumption is supported by the fact that higher levels of xanthan gum rendered the polymeric solution extremely viscous and of poor flowability in such a way that we failed to generate beads from formulas containing more than 0.35 g xanthan gum.

Nevertheless, in the absence of SLS, zinc-crosslinked xanthan/alginate beads failed in sustaining chlorpheniramine release, as evident from the behavior of formula **8** in Fig. 7 (apparent release rate constant = 0.19 $min^{0.38}$, r^2 = 0.91), which emphasizes the key role played by SLS in sustaining drug release.

The ability of the zinc-crosslinked SLS/xanthan/alginate beads to sustain chlorpheniramine release was greatly compromised upon doubling the amount of chlorpheniramine in the formula prior to cross-linking, i.e., formula **9**, as evident in Fig. 8. Apparently, increasing the amounts of chlorpheniramine, a highly hydrophilic drug, creates hydrophilic channels within the metal-crosslinked crust that draw water during dissolution allowing quicker drug release.

Replacing zinc with calcium as cross-linking agent in formula **7** (Fig. 8) caused immediate release of loaded chlorpheniramine. This conduct is probably related to the fact that calcium is a hard electrophile (Aiedeh et al., 2007; Fleming, 1996) and therefore, it interacts with carboxylates and sulfates via elec-



Scheme 3. A schematic representation showing the effect of high levels of SLS on the cross-linking of zinc–alginate matrix. The figure shows how SLS (hydrophilic heads and lipophilic tails are represented by black spheres and wavy lines, respectively) is supposed to reduce polymeric cross-linking by saturating zinc centers and hindering polymeric backbone approach due to the free lipophilic tails of complexed SLS.

trostatic (columbic) attraction interactions. Such interactions tend to be readily hydrated and thus broken under aqueous conditions. On the other hand, softer zinc ions tend to form covalent-like coordinate bonds with carboxylates and sulfates,

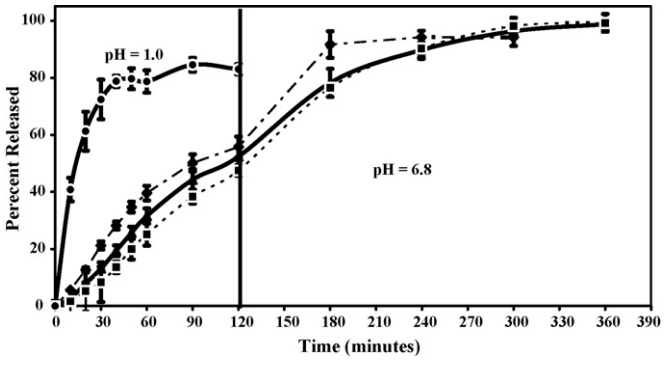


Fig. 7. The effect of xanthan gum on the release profiles of chlorpheniramine maleate from zinc-crosslinked alginate/SLS beads. Formulas: 3 (♦), 6 (▲), 8 (●) and 10 (■), see Table 1 for the components of different formulae. Each profile resembles the release measurements from three separate preparations from each formula. The error bars represent the standard deviation of the three measurements.

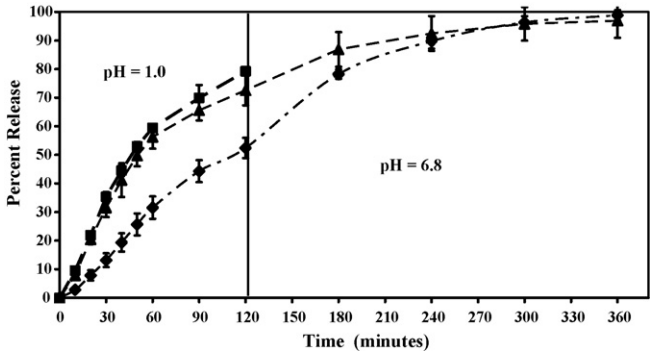


Fig. 8. The effect of the curing cation on the release profiles of chlorpheniramine maleate from the crosslinked alginate/SLS/xanthan beads. Formula 6 (♦), 7 (■) and 9 (▲), see Table 1 for the components of different formulae. Each profile resembles the release measurements from three separate preparations from each formula. The error bars represent the standard deviation of the three measurements.

which are normally more resistant to hydration (Aiedeh et al., 2007).

3.4. Thermal and infrared assessment

To further probe the molecular nature of the generated beads, we evaluated the thermal and vibrational profiles of their corresponding matrices. It was decided to avoid whole polymeric beads as probes in these investigations as the ionotropic cross-linking takes place only within the vicinity of the beads' surfaces, which comprise a small percentage of the generated beads. Therefore, if whole beads are to be used for infrared or thermal assessments they will yield weak complexation bands cluttered with stronger bands resulting from non-complexed core materials. Accordingly, we prepared composite matrices specifically for DSC and infrared investigation by adding the cross-linking metal (zinc or calcium) to vigorously stirred solution of the particular formula to maximize the degree of cross-linking and minimize any bands related to non-complexed components.

3.4.1. DSC profiles of selected formulas

Formulas **1**–**3** were selected to probe the thermal effects of SLS, while formulas **6** and **8** were selected to probe the effects of xanthan gum in the presence and absence of SLS, respectively. On the other hand, formula **7** was thermally profiled to assess the influence of replacing zinc with calcium as cross-linking agent.

Fig. 9 shows the DSC traits of selected formulas. As clear from Fig. 9, all cross-linked formulas illustrate broad endothermic bands ranging from 85 to 110 °C corresponding to the dehydration of the corresponding matrices.

The zinc-crosslinked alginate matrix corresponding to formula **1** exhibited shallow exothermic band at around 200 °C. This band is also apparent in the thermal profile of sodium alginate, albeit at higher temperature range (*ca.* 220 °C). Apparently, the shift to lower temperature in the case of formula **1** is related to zinc-induced degradation of alginate. Zn^{2+} is an effective Lewis acid capable of coordinating to hydroxyl groups and cleaving C-O bonds, particularly at high temperatures (March, 1992). This proposition is further supported by the fact that the

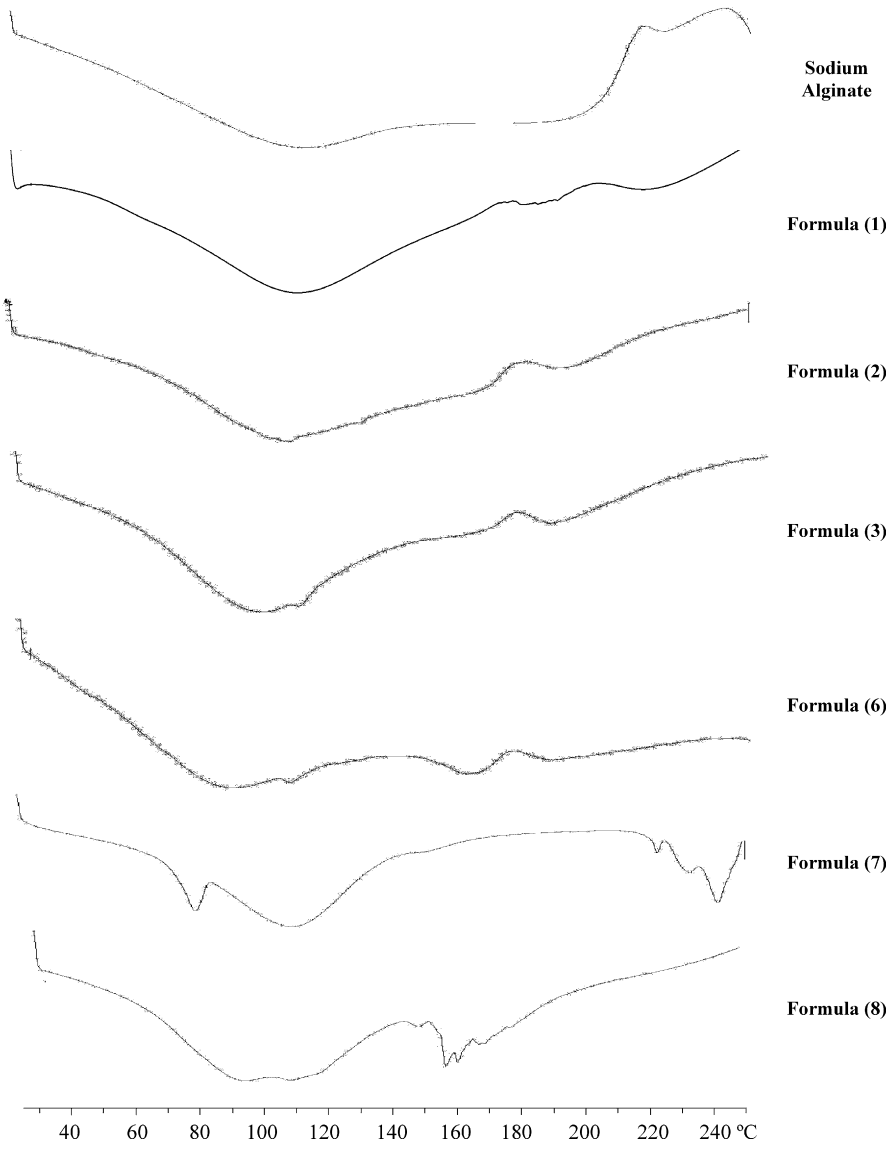


Fig. 9. DSC traits of selected formulas.

calcium-crosslinked formula **7** lacked any exothermic bands in this region, probably because calcium is a weaker Lewis acid compared to zinc (March, 1992). The same exothermic band appeared in SLS-containing formulas (i.e., formulas **2**,**3** and **6**), albeit more pronounced and at lower temperature (*ca.* 180 °C). This is probably related to zinc–SLS complexation, which is expected to promote facile exothermic cleavage of sulfate moieties in SLS molecules.

Emergence of endothermic bands at *ca.* 160 °C in the traits of formulas **6** and **8** is related to their xanthan gum contents. Alginate and xanthan gum are known to form significant hydrogen-bonding interactions (Pongjanyakul and Puttipipatkhachorn, 2007), which seem to break at around 160 °C causing these characteristic endothermic bands.

3.4.2. *Infrared spectroscopy of selected formulas*

Formulas **1** and **3** were selected to probe the vibrational effects of SLS complexation, while formulas **6** was selected to probe the effects of adding xanthan gum. Formula **7** was assessed to understand the vibrational influence of replacing zinc with calcium as cross-linking agent.

Fig. 10 shows the infrared profiles of the selected formulas. As clear from the figure, the major difference between the infrared spectra of zinc-crosslinked formulas and that of sodium alginate is the shift in the carbonyl stretching vibrations from 1610 to 1644 cm^{-1}. This shift is probably related to the formation of coordinate bonds between the carboxylate moieties of alginic acid (and/or xanthan gum) and zinc ions, which increases the double bond character of carboxylic carbonyls causing their shift to higher stretching energies (Williams and Fleming, 1997). On the other hand, calcium-crosslinking caused lesser shift in the carbonyl stretching, i.e., to 1636 cm^{-1}, which is probably due to the stronger ionic (and weaker coordinate) nature of the carboxylate–calcium interaction, which allow more free delocalization of the carboxylate electrons and reduce the double-bond character of the carboxylic carbonyls (Williams and Fleming,

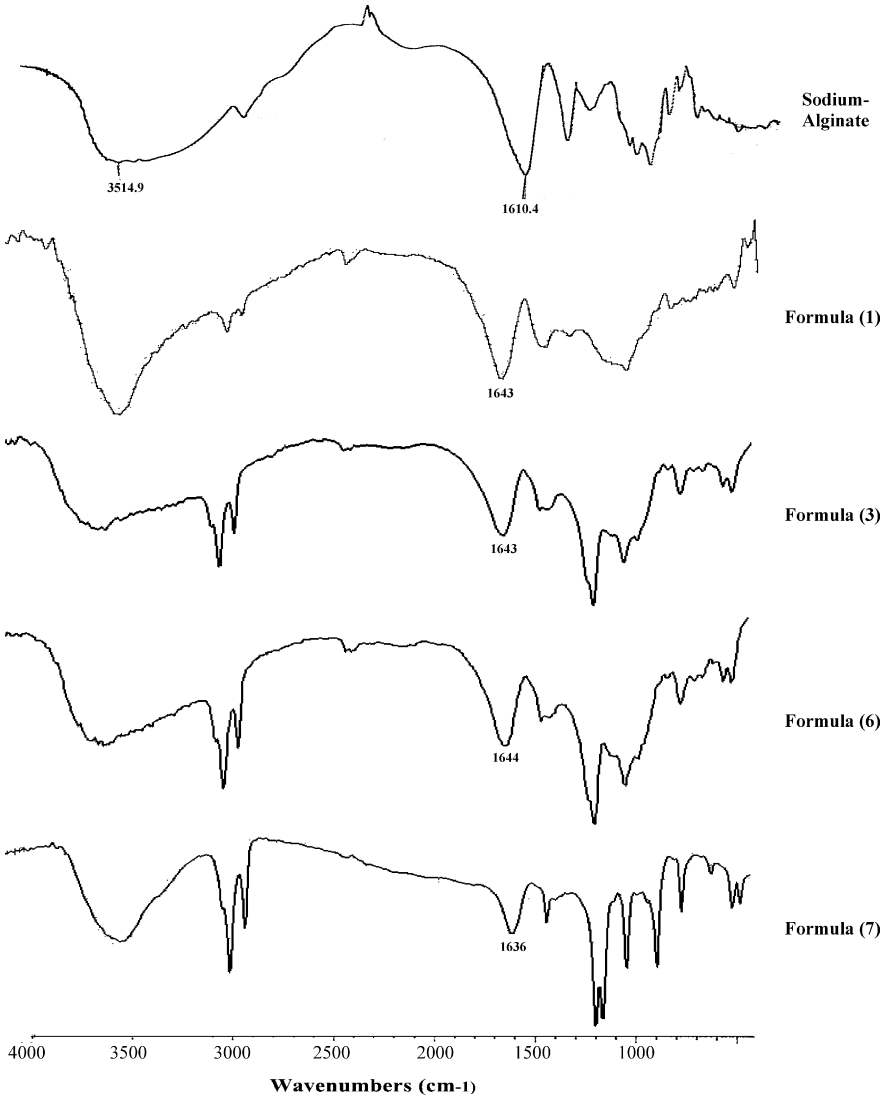


Fig. 10. Infrared spectra for some selected formulas.

1997). This behavior correlates well with the relative positions of zinc and calcium on the electrophilic hardness/softness scale mentioned earlier (Aiedeh et al., 2007).

Finally, it seems that neither SLS nor xanthan gum have any significant influences on the infrared spectra of their respective formulas (formulas **1**, **3** and **6**).

4. Conclusions

The effects of SLS on ionotropically cross-linked alginate beads were investigated. Zinc and calcium ions were separately employed as curing agents, while chlorpheniramine maleate was used as loaded model drug. Infrared spectroscopy and DSC were employed to probe the resulting beads.

SLS was found to exert profound impacts on the characteristics of zinc-cross-linked alginate beads allowing access to enteric coating-like behavior. However, higher levels of SLS allowed biphasic release. Xanthan gum modified the later profile into sustained-release.

Apparently, at moderate levels, complexed SLS molecules repel water penetration into the beads, and therefore minimizes chlorpheniramine release in simulated gastric pH. However, at higher levels SLS discourages polymeric cross-linking and therefore allow quicker chlorpheniramine release. Calcium crosslinking failed to reproduce the same behavior probably due to its harder electrophilic properties.

This study clearly illustrated that SLS can be used to finely tune drug release from zinc-crosslinked alginate matrices. Currently, we are evaluating the effects of other safer anionic surfactants on the drug-releasing profiles of ionotropically crosslinked alginate beads.

Acknowledgements

This project was funded by the Deanships of Scientific Research at the University of Jordan and The University of Applied Sciences, Amman, Jordan.

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