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RESEARCH ARTICLE

Preparation and *in vitro* characterization of glibenclamide-loaded alginate hexyl-amide beads: a novel drug delivery system to improve the dissolution rate

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Abstract

Objective: This investigation aimed to synthesize amphiphilic hexyl amidic derivative of alginate to be used in the preparation of glibenclamide-loaded release system of improved dissolution rate.

Materials and methods: Hexyl amine was associated to the activated carboxylic acid moieties of alginate to synthesize alginate hexyl amide polymer (AHAP). This polymer in comparison to alginate was used in different concentrations for preparing beads containing glibenclamide by an ionic gelation using Ca^{++} as gelling ion. The prepared beads were characterized by DSC, FTIR and scanning electron microscope. The swelling behavior, drug loading capacity and release behavior were studied.

Results and discussion: The results showed that the prepared AHAP beads were smaller in size and more spherical. The surface was highly corrugated with much and wider pore size. The beads showed a high drug loading capacity and efficacy that was affected by the polymer concentration. The drug release rate from AHAP beads reached 100% after 4, 8 and 12 hours in comparison to 75.3%, 73.2% and 69.2% from alginate beads at 3%, 2% and 1% polymer concentrations, respectively.

Conclusion: It can thus be concluded that the amphiphilic AHAP-based bead is a simple and efficient delivery system of promising industrial significance for the improvement of the dissolution rate.

Keywords

Amphiphilic polymer, dissolution rate, glibenclamide, hexyl alginate, ionotropic gelation

History

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Introduction

Polymeric surface active agents have a great importance in the pharmaceutical and biomedical area, and exploring renewable resources for their production have attracted a growing research interest. Polysaccharides represent optimizing raw materials for the preparation of amphiphilic macromolecules through chemical modification[1]. This modification affects their chemical characteristics and, thus, their surface active properties. Hydrophobically modified polysaccharides were applied as rheology modifiers[2,3], emulsion stabilizers[4–6], or polymeric surfactants for miniemulsion polymerization[7].

Alginate is a polyanionic linear polysaccharide obtained from marine brown algae. Chemically, it is 1, 4-linked-R-L-guluronic acid (G) and β-D-mannuronic acid (M)[8]. In the presence of metal cations like calcium, Barium, Aluminum, etc., it undergoes ionotropic gelation by forming an egg-box junction due to the interaction between these cations and carboxylic acid groups of alginate and the formation of electrostatic binding between guluronic residues[9,10].

Being biocompatible, nontoxic and easily eliminated from the body, the hydrogel-forming properties of alginate and its sodium salt have been used in drug delivery to prepare a matrix for controlling the release and to encapsulate a wide variety of proteins such as hemoglobin[11], albumin[12] and DNA[13]. The gelation of alginate to prepare a matrix or bead is an optimally economic process because it is inexpensive, simple and easy to carry out under mild conditions that potentiate its industrial application[14]. High drug leakage, low mechanical strength and large pore size are the main disadvantages of alginate gel matrix[15], and many efforts were exerted to optimize its encapsulation efficiency and controlled release properties[16–18].

Recently, amphiphilic alginate derivatives are strongly recommended for investigation as a promising tool for more application in the pharmaceutical and biomedical areas[19]. Leonard et al.,[20,21] used the amphiphilic covalently associated alkyl alginate derivatives to prepare microparticles as protein carriers with remarkable controlled release properties. Broderick et al.,[22] also studied the encapsulation properties of amphiphilic butylated alginate derivative hydrogels with calcium for both hydrophobic and hydrophilic materials. In other work, Octyl-grafted amphiphilic

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alginate-amide derivative was prepared and used to encapsulate λ-cyhalothrin in microcapsules of controlled release[23].

Glibenclamide (glyburide) is one of the most prescribed long-acting hypoglycemic drugs. It is an oral second-generation sulfonylurea hypoglycemic agent that is used in the management of type 2 diabetes. It acts by stimulating the insulin release from pancreatic β-cells on binding high-affinity receptors that are present in the K/ATP channels in β-cells of plasma membranes, it also increases the sensitivity of peripheral tissue to insulin. Glibenclamide is a poorly water-soluble drug[24]. It is classified as a BCS class II drug (it has high permeability and poor water solubility). Drug absorption from GIT is controlled by its dissolution rate and water solubility; and this ultimately affects the bioavailability[25,26].

In this work, amphiphilic alginate-hexyl amide polymer (AHAP) of expected surface active properties were synthesized by integrating the short-chain hexyl group onto the activated carboxylate group of alginate molecules through an amide linkage. Glibenclamide-loaded AHAP beads were prepared by ionotropic gelation in calcium solution and the prepared beads were characterized. The effect of this chemical modification on the drug solubility, entrapment efficiency and release rate from the prepared beads were investigated and the kinetics of drug release were also discussed.

Materials and methods

Materials

Glibenclamide (received as a gift from E.P.C.I. Company, Beni Suef Gov., Egypt), sodium alginate (Hipure, Genzyme-England), nitric acid (Frtaron Ltd., UK), calcium chloride (C-13 H Lab. Chemicals, Nottingham, UK), N,N′-Diisopropylcarbodiimide (DIC, Fluka-Switzerland), hexyl amine (Sigma-Aldrich, St. Louis, MO) and sodium hydroxide (S.D. Fine-Chem. Ltd., Boisar, India). All chemicals are of reagent grade and were used as obtained from the manufacturers without further purification.

Methodology

Synthesis of Alginate-Hexyl amide Polymer (AHAP)

A solution of sodium alginate (10.40 g, 0.05 Mol) in distilled water (500 ml) was neutralized with nitric acid (1.5 M, 100 ml) while stirring. Subsequently, N,N′-Diisopropylcarbodiimide, DIC (4.41 g, 0.035 Mol) was added to the reaction mixture. Two hours later, the hexyl amine (7.07 g, 0.07 Mol) was added and the pH of the reaction mixture was raised to 6 using sodium hydroxide solution (2.0 M). Two hours later, the pH was further raised to 9 using the same sodium hydroxide solution and the reaction was left overnight. The reaction was terminated by precipitation with nitric acid (100 ml, 1.5 M) and acetone (1000 ml) and the generated precipitate was filtered and thoroughly washed with acetone (3×250 ml) and ethanol (3×250 ml). The resulting white polymer was stored in a desiccator for drying. The generated semi-synthetic polymer was characterized using IR Spectrophotometer (Bruker Alpha-P, Germany).

Preparation of glibenclamide-loaded beads

Sodium alginate and the prepared AHAP solutions in different concentrations namely 1%, 2% and 3% were prepared by separately adding preweighed amounts of each polymer to 25 ml of deionized water under gentle mixing while heating until complete solubility of the polymer. To each solution, 250 mg of glibenclamide was added portion wise while stirring and the stirring was continued for further 10 minutes at 1000 rpm using an overhead stirrer (Remi Instruments, Mumbai, India) until a homogenous dispersion is obtained, and the resultant drug/polymer dispersions were treated in an ultrasonic bath for 10 minutes. The prepared drug/polymer dispersions were extruded dropwise into 50 ml of 2% (w/v) gently agitated calcium chloride solution through the 18-gauge 1-mm needle, where the formed droplets were instantaneously gelled into discrete glibenclamide calcium alginate and calcium AHAP beads. The formed gel beads were allowed to cure in the $CaCl_2$ solution for three hours, then filtered, washed with deionized water and dried at 45 °C for 12 h.

Equilibrium solubility study

Solubility measurements of glibenclamide were performed according to Higuchi and Connors method[27]. An excess amount of glibenclamide, the prepared glibenclamide-loaded ca-alginate beads, and the prepared glibenclamide-loaded Ca-AHAP beads were added to 25 ml of phosphate USP buffer (pH 7.4) in screw-capped bottles. Samples were shaken for 48 h at room temperature. After equilibrium, the suspensions were filtered through a Wattman filter paper no. 40 and spectrophotometrically analyzed at 240 nm using a Shimadzu UV/Vis double beam spectrophotometer (Tokyo, Japan) after suitable dilution with buffer.

Characterization of the prepared beads

The prepared glibenclamide-loaded alginate and AHAP beads were characterized as follows:

Differential scanning calorimetry (DSC) studies. Samples of plain glibenclamide, alginate, AHAP, glibenclamide-alginate beads and glibenclamide-AHAP beads for thermal analysis were weighed ($5.00–8.00 \pm 0.5$ mg) into an aluminum pan, covered with an aluminum lid and crimped into position. The pan was placed in the oven together with a blank (prepared exactly the same way but without the sample). The sample and blank were continuously purged with nitrogen gas and thermograms were recorded over a temperature range of (25–300 °C) with a programmed heating rate of 10 °C/min. Temperature calibration was made with an indium standard. The DSC thermograms for the tested samples were recorded and analyzed (DSC 8500 PerkinElmer, Inc., Waltham, MA).

Infrared spectoropectroscopy (FTIR) studies. Samples of plain glibenclamide, alginate, AHAP, glibenclamide-alginate beads and glibenclamide-AHAP beads were mixed with about 400 mg of dry potassium bromide powder compressed into the transparent disc under pressure of 10.000 to 15.000 psi. The IR spectra were recorded and analyzed (IR Spectrophotometer, Bruker Alpha-P, Germany).

Scanning electron microscope (SEM) Studies. The surface morphology of the prepared glibenclamide-containing beads of both alginate and AHAP was examined by SEM (model JEOL JSM-6360, Tokyo, Japan). A small sample of each batch was manually dispersed onto a double adhesive carbon coated tape adhered to an aluminum stub. These sample stubs were coated with a thin layer (30 Å) of gold by employing POLARON-E 3000 sputter coater. The samples were examined by SEM operated at 20 KV and photographed under various magnifications with direct data capture of the images onto a computer.

Particle size distribution. The particle size determination of the prepared glibenclamide-loaded beads of both alginate and AHAP was carried out using an optical microscope fitted with a stage micrometer having an accuracy of 0.01 mm. The beads were suspended in liquid paraffin and then one drop of this suspension was added onto a clean glass slide surface and optically examined.

The average sizes of 100 beads were determined for each formulation using the calibration factor. The average diameter of the beads was calculated using the following formula:

$$X = \sum(Xi)/N$$

X = Average particle diameter, Xi = Individual diameter of beads, N = Number of beads.

Determination of drug loading capacity[25]. A preweighed quantity (10 mg) of the prepared glibenclamide-containing alginate and AHAP beads was grounded and separately extracted in 50 ml hydrochloric acid 0.1 M and sonicated for 15 min. Samples were filtered through 0.45 µ filter paper to obtain clear solutions and the glibenclamide content was determined by measuring the absorbance at 240 nm (using Shimadzu UV/Vis double beam spectrophotometer, Tokyo, Japan). The drug concentration was determined using standard calibration curve. The mean of three determinations was considered. The percentage of drug loading and incorporation efficiency were calculated using the following equations:

$$\text{Drug loading } \% = \left(\frac{\text{Total amount of drug in the particle}}{\text{Weight of the particle taken}}\right) \times 100$$

$$\text{Percent incorporation efficiency} = \%\text{ drug loading}/\%\text{ theoretical loading} \times 100$$

Swelling studies[28]. The extent of swelling was measured in terms of percentage weight gain. Swelling properties of the beads were studied by soaking the beads at $37 \pm 1\,^{\circ}C$ in phosphate buffer pH 6.8 in a glass beaker. The beads were removed at different time intervals and weighed after drying the surface water on tissue paper. The ratio of water uptake was calculated as:

$$\text{The ratio of water uptake (Swelling index)} = \frac{(\text{Wet weight} - \text{Dry weight})}{(\text{Dry weight})} \times 100$$

All mass measurements of the swollen beads were taken on a single pan balance (Mettler AE 240S, Switzerland), having an accuracy up to the fifth decimal.

In vitro *release studies.* Dissolution studies of glibenclamide from the prepared alginate and AHAP beads were conducted using USP apparatus 2 (Hanson G2 Vision Classic 6, Chatsworth, CA) (paddle method). The dissolution medium was 500 ml phosphate USP buffer (pH 7.4) at $37 \pm 0.5\,^{\circ}C$, stirred at 50 rpm. Five milliliter sample aliquots were withdrawn at a prespecified time intervals of 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 12.0 hours and replaced with an equal volume of the fresh medium. Absorbance of the drug in each sample was measured spectrophotometrically at 240 nm using Shimadzu UV/Vis double beam spectrophotometer (Tokyo, Japan) after filtration (0.45 µ membrane filter) and the cumulative percentage of drug release was calculated using an equation obtained from a standard curve. The mean of six determinations was considered.

Kinetic analysis of dissolution data. To study the mechanism of glibenclamide release from the prepared Ca-alginate and Ca-AHAP beads, KinetDS 3.0 (Aleksander Mendyk, GNU GPLv3 license, 2007, Krakow, Poland) software was used to kinetically analyze the release data.

Results and discussion

Enhancement of solubility and dissolution rate of poorly soluble drugs is a very challenging task in drug development to affect reasonable and acceptable bioavailability. In this work, attempt was made to develop a new, simple, economical and efficient delivery system to improve the drug dissolution rate.

In this work, a relatively short-chain alkyl group (hexyl) was associated with the alginate polysaccharide backbone through a polar amidic linkage and the degree of substitution was limited to 70%.

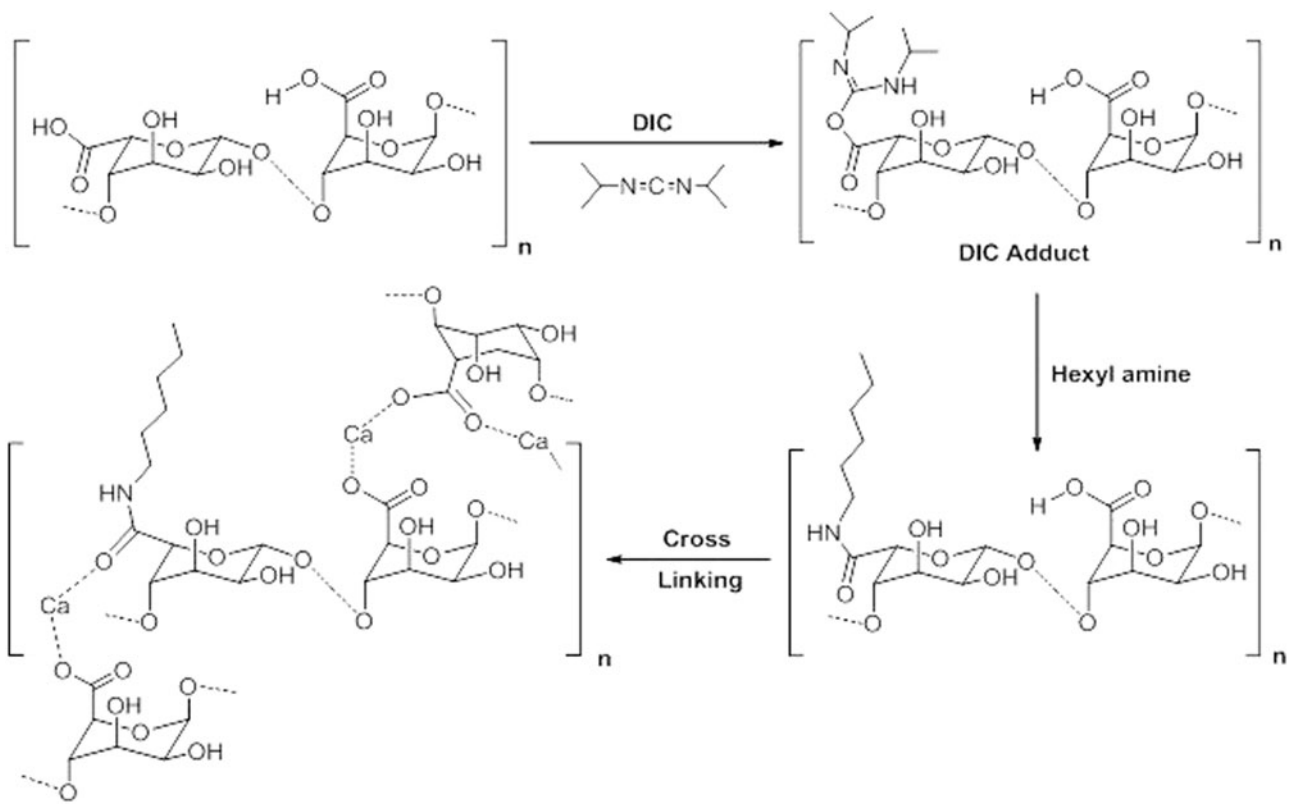

Figure 1. Scheme of the synthesis of hexyl-alginate polymer and formation of Ca^{+2} beads.

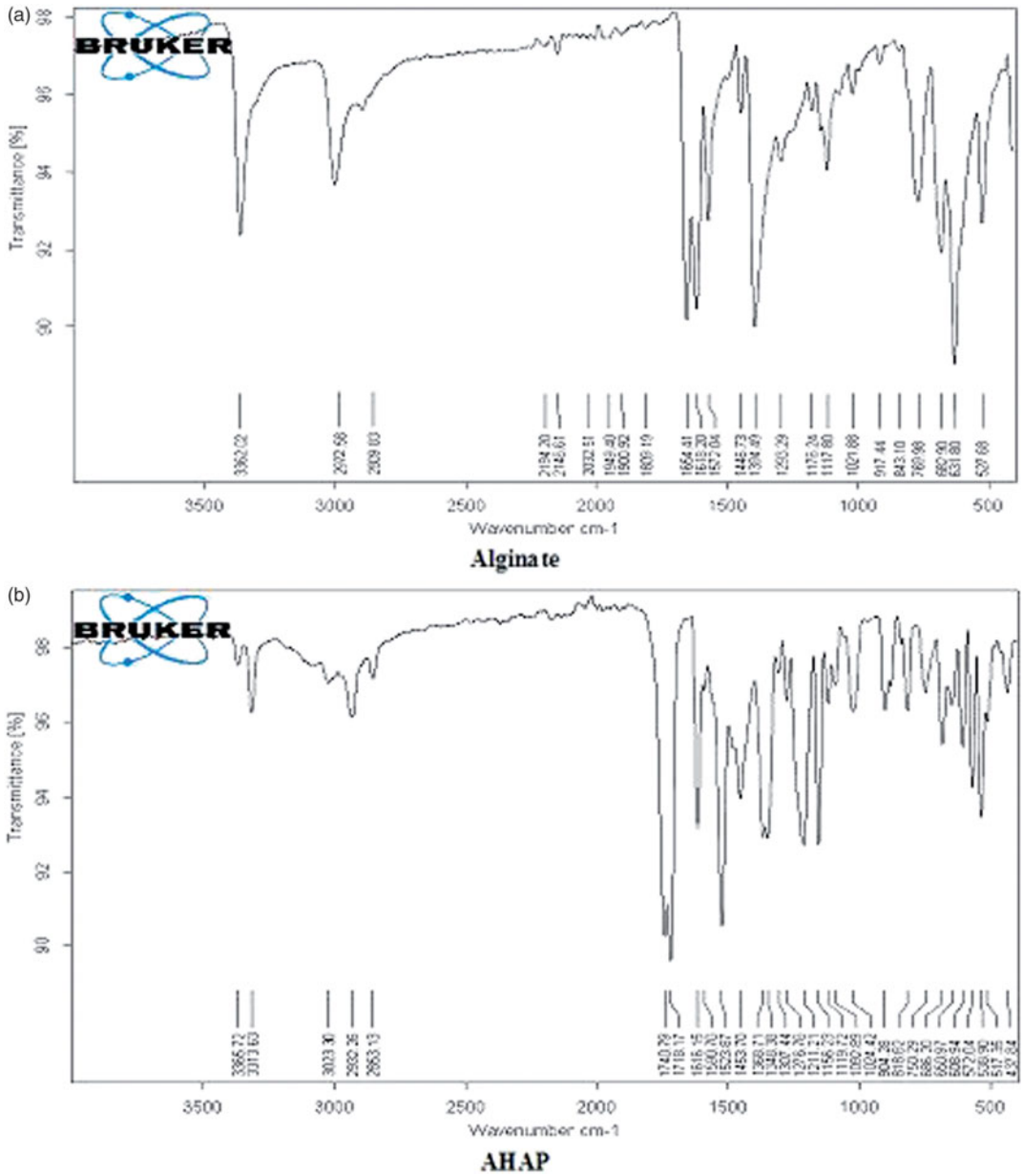

Figure 2. Infrared spectra of sodium alginate and the synthesized Hexyl-alginate polymer.

Chemistry

The reaction of sodium alginate with hexyl amine was performed through the activation of carboxylic acid moieties with N,N′-Diisopropylcarbodiimide (DIC) followed by quenching the reaction mixture with hexyl amine under basic conditions as shown in Figure 1[29]. Theoretically, DIC was calculated to activate 100% of the available carboxylic acid groups in alginic acid to produce alginate-hexyl complex. Due to the sterically hindering environment of the polysaccharide polymer, hexyl amine was added in twofold excess (compared to DIC) to force the forwardness of the reaction.

Characterization of the prepared semi-synthetic AHAP

The IR spectrum of sodium alginate (Figure 2a) revealed that there is a broad peak starting from 2600–3250 cm^{-1} which was attributed to the stretching vibrations of the carboxylate group, and a small peak at 2970.58 cm^{-1} was attributed to the aliphatic C-H stretching vibrations of methyne groups. The bands at 1740.79 cm^{-1} were assigned to the carbonyl group stretching vibration.

On the other hand, it was clearly evident from the IR spectra of AHAP (Figure 2b) that the appearance of intense carbonyl stretching peak at 1654.41 cm^{-1} was the most observed change that occurred upon hexyl amine incorporation which undoubtedly corresponds to the newly introduced amide bond[30]. Moreover, the new band that appeared at 3362.02 cm^{-1} was assigned to the N-H stretching vibration of the amino group that confirms the incorporation of the hexyl amine into the alginate polymer. Finally, the peaks of 2972.58 and 2809.83 cm^{-1} were assigned to methylene groups of hexyl amine.

Investigation of the chemical structure of the prepared amphiphilic AHAP declares that it contains a significant balance between both hydrophilic and hydrophobic moieties linked through the incorporated amidic group and hence a surface active properties of this molecule is expected and this explains the obtained results.

Solubility studies

Solubility of glibenclamide was markedly increased from both the prepared alginate and AHAP beads. The solubility of glibenclamide was increased from 16.3 µg/ml to 20.1, 24.6 and

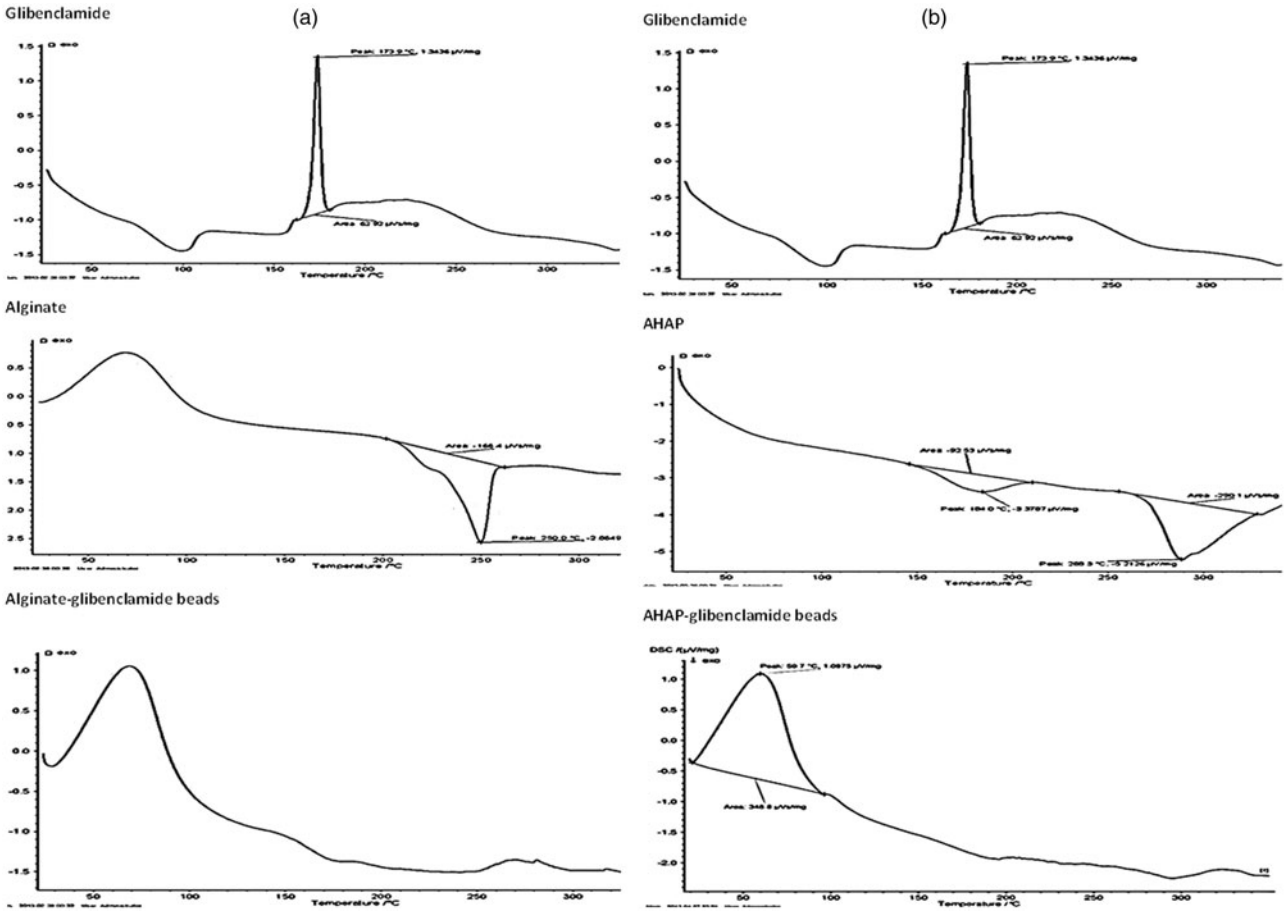

Figure 3. DSC thermograms of glibenclamide, alginate and AHAP in comparison to the prepared drug-loaded beads.

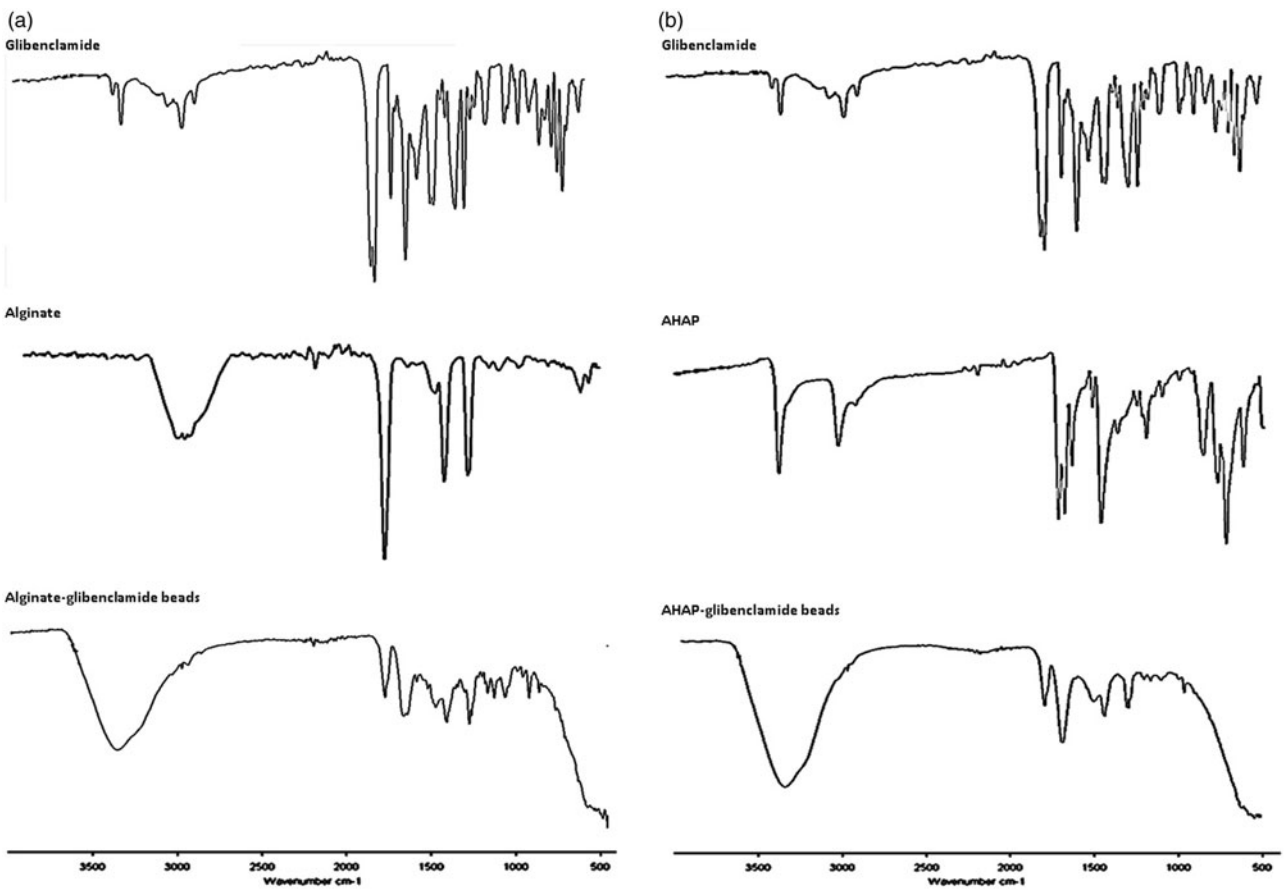

Figure 4. Infrared spectra of glibenclamide, alginate and AHAP in comparison to the prepared drug-loaded beads.

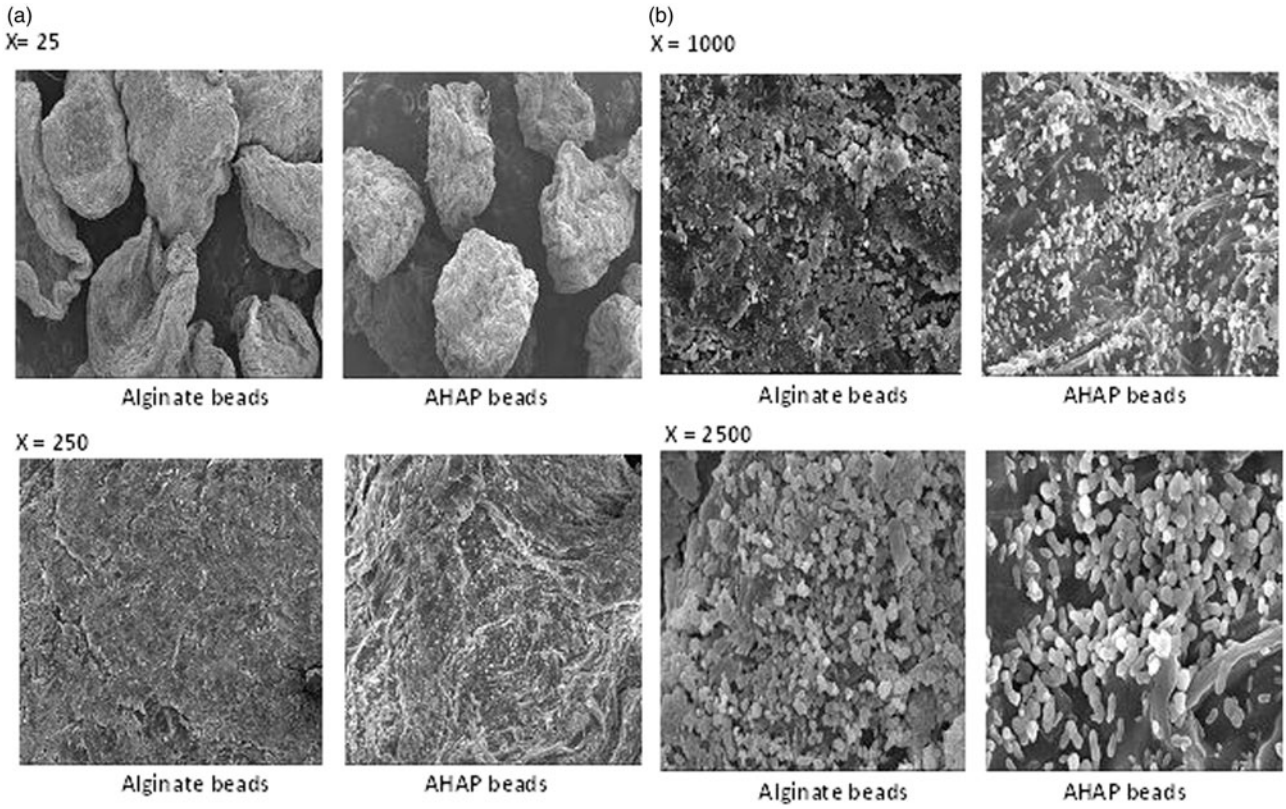

Figure 5. SEM of the glibenclamide-loaded Ca-alginate and Ca-AHAP beads at different magnifications.

Table 1. Characterization of the prepared glibenclamide-loaded Ca-alginate and Ca-AHAP beads.

Code	Polymer ratio (%)	Percentage yield (%)	Drug content (mg)	Entrapment efficacy (%)	Particle size range (μ)
Alginate beads	1	90.24	7.241	69.57	680–750
Alginate beads	2	89.43	7.913	81.98	720–800
Alginate beads	3	89.21	8.342	87.31	760–830
AHAP beads	1	91.18	9.683	89.46	510–560
AHAP beads	2	90.57	10.108	95.88	490–530
AHAP beads	3	88.99	10.582	97.82	475–510

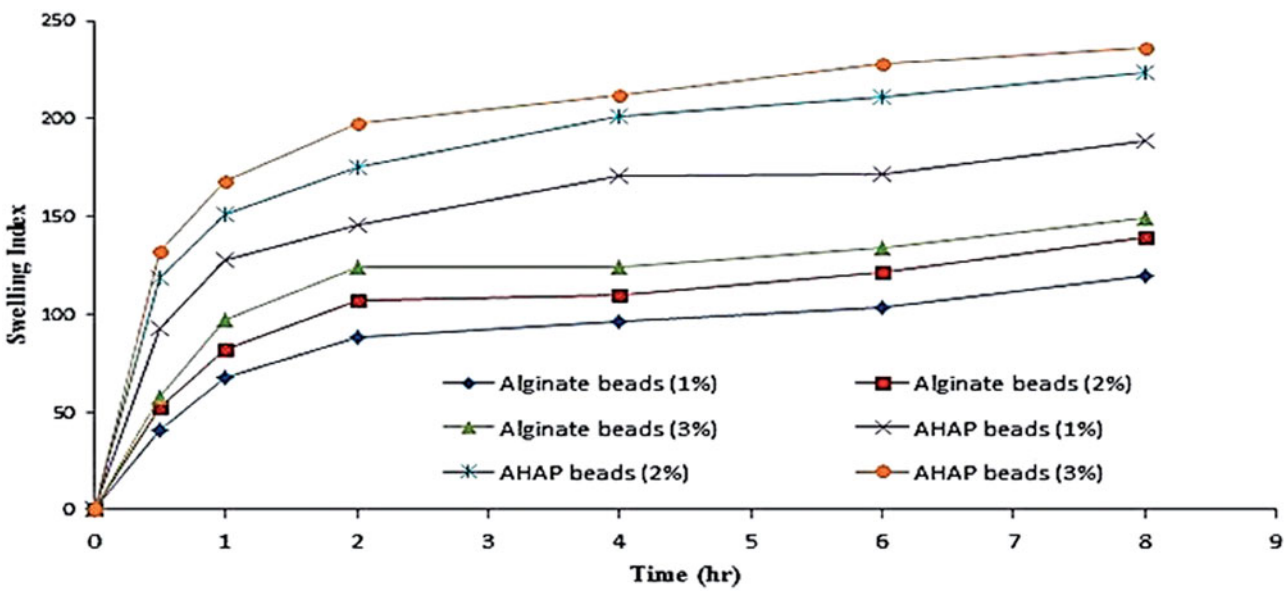

Figure 6. Swelling behavior of the prepared drug-loaded Ca-alginate and Ca-AHAP beads in buffer 6.8.

24.6 µg/ml in aqueous solution of alginate beads prepared at polymer concentration of 1%, 2% and 3%. Alginate is a natural water-soluble polymer and contains hydroxyl and carboxyl groups, which imparts hydrophilicity to the molecule and this explains the improved solubility of the drug[31]. Higher drug solubility was observed in the aqueous solution of AHAP beads where the solubility reached 41.6, 48.9 and 52.9 µg/ml in the bead solution prepared at polymer concentration of 1%, 2% and 3%, respectively. This could be explained by the surface active action of the prepared amphiphilic AHAP that affects the degree of subdivision of the drug in the polymer matrix and increases the drug wettability.

Characterization of the prepared beads

Results of the characterization tests can be discussed under the following headings:

Differential scanning calorimetry studies

Figure 3 shows the DSC thermograms of glibenclamide, alginate, AHAP and the prepared beads. The drug thermogram shows a sharp endothermic melting peak at 173.9°C that was disappearing in thermograms of the prepared beads and this indicates the conversion of the drug from crystalline to amorphous state, where the drug was uniformly dispersed at the molecular level.

Infrared spectroscopy studies

The drug compatibility with alginate and the prepared AHAP was investigated (Figure 4). The IR spectrum of Glibenclamide shows the main characteristic peaks at 3365.72, 3313.63 cm^{-1} (2 N-H stretching), 3023.30, 2932.26 cm^{-1} (C-H aromatic, C-H aliphatic, respectively), 1740.79, 1718.17 (2 C = O), 1156.23 cm^{-1} (S = O) and 818.62 cm^{-1} (C-Cl). Comparing with the IR spectra of the prepared alginate and AHAP beads, it is noteworthy that all peaks of the drug were retained excluding any chemical interaction between the drug and the polymer and indicating good compatibility in the prepared beads.

Scanning electron microscopy

Figure 5 shows the SEM image of the prepared alginate and AHAP beads under dry state at different magnification (x) values. AHAP beads are more spherical and smaller in size (Figure 5a). Further investigation at higher *x*-values of the surface (Figure 5b) shows that alginate and AHAP beads have irregular or ruptured spherical morphology. The surfaces of AHAP beads showed a significant number of relatively larger pores of irregular size that deeply penetrates into the surface layer. On the other hand, the surface of alginate beads was covered with smaller pores that are closely packed.

Particle size distribution

Results of particle size distribution are shown in Table 1. The prepared alginate beads had a particle size range of 680–750 µm, 720–800 µm and 760–830 µm, while the AHAP beads had a particle size range of 510–560 µm, 490–530 µm and 475–510 µm at polymer concentration of 1%, 2% and 3%, respectively. It can

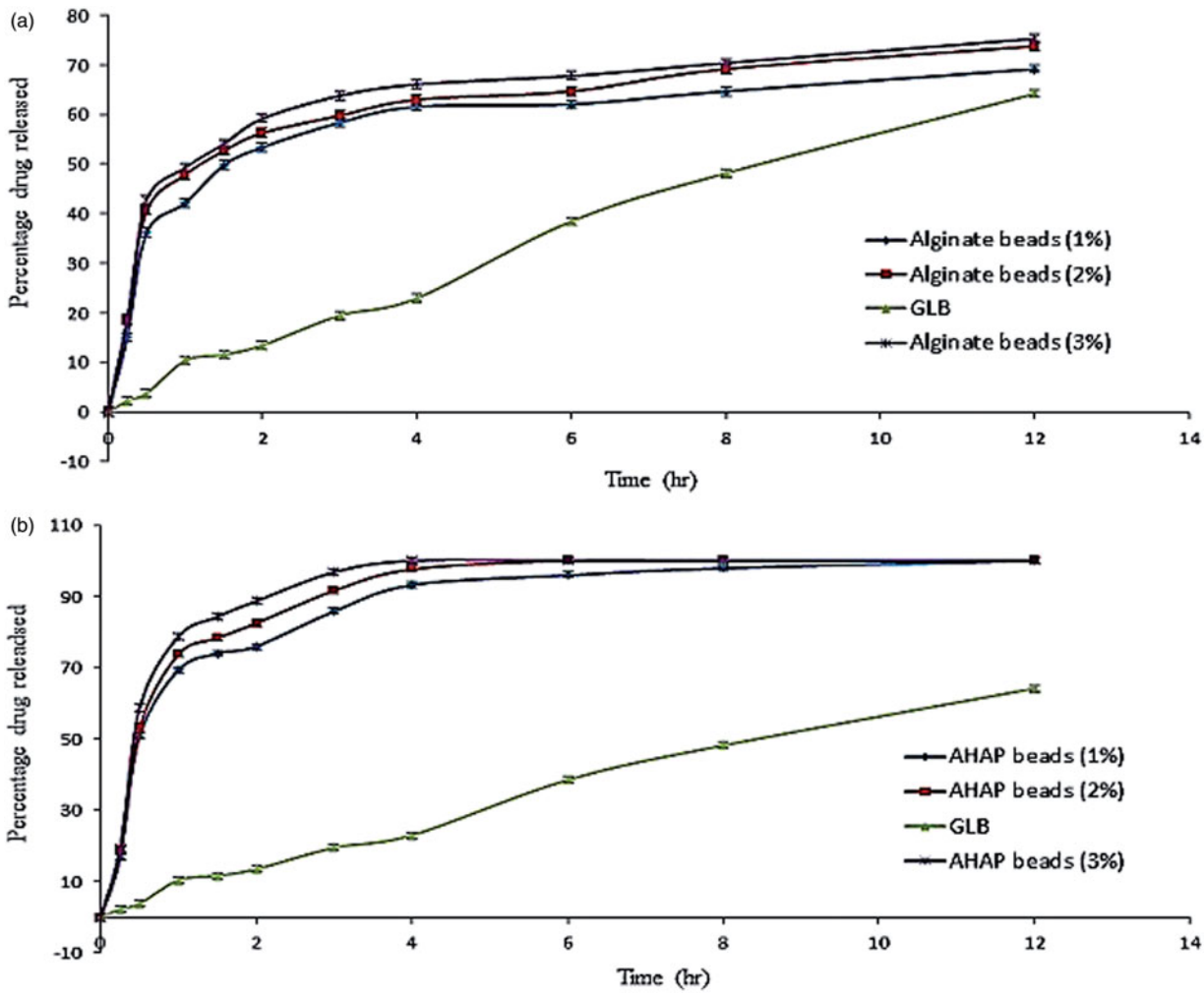

Figure 7. Release profiles of glibenclamide from Ca-alginate and Ca-AHAP beads prepared at different polymer concentrations.

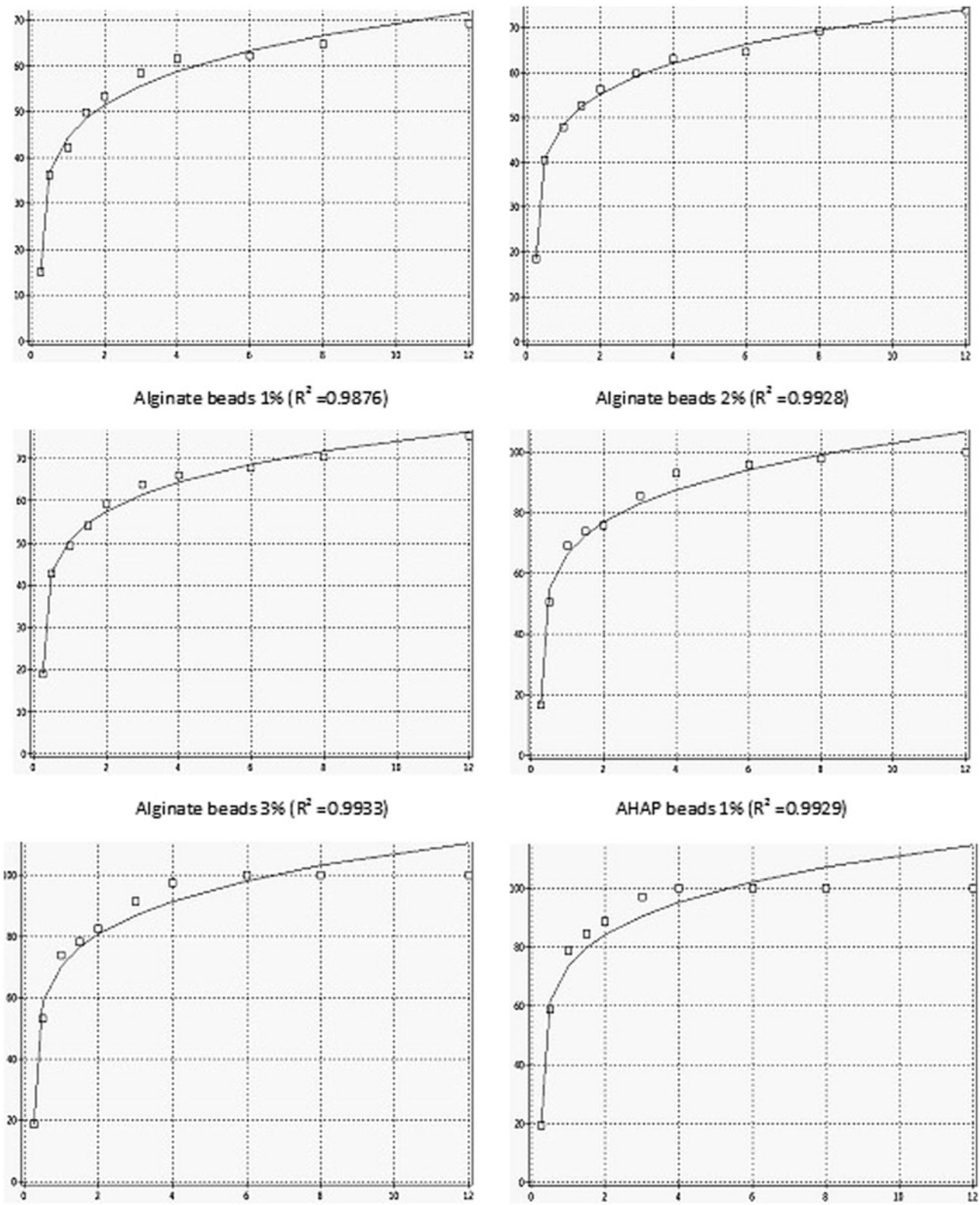

Figure 8. Fitting curves of the release date to Korsmeyer–Peppas diffusion model with a correlation coefficient.

be noted that the particle size of the alginate beads increase as alginate concentration increase and this could be attributed to the rise of the viscosity of the drug polymer solution[32]. On the other hand, the size of AHAP beads decreases with increasing polymer concentration and this could be attributed to the surface active action of the hexyl alginate derivative where the higher the polymer concentration the lower the surface tension of the prepared drug polymer solution and hence the smaller the particle size[33].

Drug loading capacity

Results of drug content and entrapment efficacy are listed in Table 1. The percentage of drug entrapment within the prepared beads was 69.5, 81.98 and 87.31 in the prepared alginate beads, while the percentage reached 89.46, 95.88 and 97.82 in AHAP beads at polymer concentration of 1%, 2% and 3%, respectively. The drug loading capacity of the prepared beads was proportional to the polymer concentration and this can be explained by

different mechanisms, the bead size increases with alginate concentration due to viscosity rise as discussed before and hence the amount of loaded drug in the bead increase. On the other hand, increasing the drug loading as the AHAP concentration increases can be attributed to the higher wettability and solubility of the drug in the polymer solution due to the surface active action of the amphiphilic polymer.

Swelling studies

Swelling is a function of the hydrophilicity of the beads[34], and this explains why the prepared AHAP beads showed higher swelling indices than that of alginate beads and that the swelling was proportional to the polymer concentration in both bead types. The initial swelling of AHAP beads within the first hour was faster than the alginate beads, and this could be attributed to large pore size of the surface as indicated by SEM images, the water could be easily diffused through the surface pores deeply into the bead matrix, Figure 6.

Release studies

Percentage of glibenclamide released from the prepared alginate and AHAP beads in 7.4 phosphate buffer solution was studied and the release profile, Figure 7, showed that the percentage of drug released was 69.2, 73.8 and 75.3 after 12 hours from alginate beads prepared at polymer concentration of 1%, 2% and 3%, respectively, in comparison to 64.2% for the non-formulated drug. The drug release rate from the prepared AHAP beads was higher and faster where the percentage of glibenclamide released reached 100% after 4, 6 and 12 hours from the beads prepared at polymer concentration of 3%, 2% and 1%, respectively. These results support the proposed surface active action of the prepared AHAP and comply with the results of solubility, where the prepared polymer increased the degree of subdivision of the drug within the bead and decreased the contact angle between the drug particles and the dissolution medium leading to increased drug wettability. The initial release occurred with a higher rate due to the dissolution of the drug from the surface and outermost layers of the bead and by the time the release rate became slower due to the slow diffusion of the dissolution medium within the inner matrix of the bead. The percentage of drug released after one hour was 42.2, 47.9 and 49.3 from alginate beads, while the percentage drug release reached 69.4, 73.8 and 78.8 from AHAP beads and this could be attributed to the larger surface pore size of the AHAP as indicated by SEM images.

Kinetic analysis of the data, Figure 8, showed that glibenclamide release from either the prepared alginate or AHAP beads followed Korsmeyer–Peppas diffusion model with correlation coefficient (R^2) equals 0.9876, 0.9928 and 0.9933 for drug-alginate beads in comparison to 0.9929, 0.9871 and 0.9808 for drug-AHAP beads at polymer ratio of 1%, 2% and 3%, respectively, and these results are in accordance with the proposed structure of the bead where the drug is uniformly distributed through the polymer matrix rather than formation of core/coat bead type.

Conclusion

In this study, the amphiphilic hexyl amidic derivative of alginate was synthesized and used to prepare glibenclamide-loaded calcium beads by ionic gelation technique. The prepared AHAP beads showed a spherical shape with smaller particle size than conventional Ca-alginate beads. The surface of AHAP bead was more porous that result in a higher swelling rate of the beads in contact with aqueous medium. A high drug loading and entrapment efficiency of glibenclamide was achieved and was affected by the percentage of polymer used. The drug release rate was highly improved to reach 100% and the release rate was affected by the polymer ratio in the prepared bead matrix, where the percentage glibenclamide release was 100 after 4%, 8% and 12% at the AHAP percentage of 3%, 2% and 1%, respectively. Depending on these results, it can be strongly recommended that the prepared semi-synthetic AHAP has a surface active properties that affects drug wettability, solubility and release rate, and the amphiphilic AHAP-based bead delivery system is a simple, and efficient technique of promising industrial significance for improvement of release rate of poorly water-soluble drugs and can help to overcome their bioavailability problems.

Declaration of interest

The authors are all declaring no conflict of interest in relation to this investigation and the preparation of this manuscript was prepared without receiving any financial support.

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