Int. J. Pharm. Investigation, 2022; 12(4) : 475-478

Original Article

Ionically Cross-linked Pectin-alginate Hydrogel Beads for Prolonged Release of Glibenclamide

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ABSTRACT

Background: Glibenclamide is a second-generation sulfonylurea extensively associated with the therapy of diabetes mellitus. A sustained release of the drug in the gastrointestinal tract may aid in maintaining therapeutic range for an extended period of time. Alginate and pectin are two commonly used biopolymers in the field of drug delivery with favourable biodegradation and biocompatibility. **Materials and Methods:** In the present study, pectin-alginate hydrogel beads were developed for intestinal delivery of glibenclamide. A barium ion (Ba^{+2}) induced ionic gelation technique was employed for synthesising pH sensitive beads by varying the ratio of sodium alginate and pectin. The FTIR study confirmed the compatibility between drugs and polymers. The developed beads were evaluated for scanning electron microscopic study, drug entrapment efficiency (DEE), bead size, swelling ratio, and *in-vitro* dissolution study. **Results:** The microscopic images exhibited hemispherical shaped beads with cracked and rough surfaces. The DEE study reported to vary between 78.38 ± 1.17 % and 92.08 ± 0.64 %. The mean size of the bead was found to be 668.81 ± 2.10 µm to 984.62 ± 2.84 µm. A pH dependent swelling was observed, which indicated a restricted water uptake in an acidic medium and an increased water uptake in alkaline pH. The *in-vitro* dissolution study demonstrated a sustained release of drug with increasing pectin concentration up to 12 h. **Conclusion:** The study findings reported the successful development of Ba^{+2} ions cross-linked pectin-alginate hydrogel beads for sustained delivery of glibenclamide.

Keywords: Barium ion, Ionic gelation, pH sensitive bead, Alginate, Pectin..

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DOI: 10.5530/ijpi.2022.4.81

INTRODUCTION

Hydrogels have been reported for extensive applications as drug carriers and also in the biomedical field. The three-dimensional cross-linked polymeric network can entrap the drug molecules within it and is able to release them at a controlled rate. The physical behaviour of hydrogels has also encouraged researchers to employ them in the area of tissue engineering.[1] Being a particulate and multiple-unit delivery system, beads offer many advantages, including gastric clearance, adjustable release of drugs, and avoiding the risk of local irritation.[2,3] The easy synthesis process and flexible nature as a drug carrier have made beads an emerging drug delivery tool. In the recent past, several polysaccharide-based hydrogel formulations have been reported for drug delivery applications. Sodium alginate is one such naturally occurring polymer that can undergo ionotropic gelation in the presence of multivalent cations. Alginate is one of the widely occurring polysaccharides. It is derived from marine and bacterial sources. This linear, high molecular weight polysaccharide contains β-D mannuronic acid (M) and α-L guluronic acid (G) units. The carboxyl group present in alginate can interact with the multivalent metal ions, which causes the cationic ions to be entrapped in the cavities of guluronic acids following an "egg box" model.[4]

Pectin is considered one of the most widely used polysaccharides in the pharmaceutical and food industries for its versatile applications as emulsifying agents, thickeners, and gelling agents.[5,6] Pectin is safe, stable, renewable, and low in cost due to its abundance and availability. It can be easily extracted from various citrus fruits.[2] The swellable nature of pectin depends on the water absorbing ability based on the presence of –COOH groups in the polymeric chains. The hydrogel forming ability of pectin in the presence of aqueous medium has encouraged pharmaceutical researchers to investigate it as a drug carrier for gastrointestinal targeting. The controlled release ability can be attributed to maintaining a desired prolonged release of therapeutic agents, facilitating maximum drug absorption and maintaining the required concentration of drugs in systemic circulation.[7]

Glibenclamide is a second-generation sulfonylurea widely used for the treatment of diabetes mellitus. It is known chemically as 5-chloro-N-[2-[4-(cyclohexylcarbamoylsulfamoyl) phenyl] ethyl]-2-methoxybenzamide. It can stimulate the secretion of insulin by inhibiting the ATP-responsive ion channels that can increase the calcium and potassium ion concentration in the intracellular region of beta cells. The enhanced calcium ion concentration can trigger insulin secretion.[8,9] Here, we have reported the development and characterization of pectin-alginate hydrogel beads for achieving prolonged release of glibenclamide.

MATERIALS AND METHODS

Materials

Glibenclamide was procured from TCI Chemicals India Pvt., Ltd. Pectin was purchased from Fisher Scientific India Pvt. Ltd., Mumbai. Sodium alginate was commercially procured from Aldrich Chemistry. Barium

chloride was procured from Qualigens Fine Chemicals, Mumbai, India. The materials were analytical grade.

Preparation of glibenclamide loaded pectin-alginate hydrogel beads

Glibenclamide loaded pectin-alginate beads were prepared by the ionotropic gelation technique using the composition specified in Table 1. A homogeneous polymer (alginate and pectin) solution in water (25 ml) was prepared by using a mechanical stirrer (REMI RM 4000). Glibenclamide was added to the polymeric mixture of pectin-alginate complex and mixed homogeneously with a stirrer. The drug-polymer mixture was then introduced dropwise into a solution of barium chloride (2.5% w/v) with continuous stirring. The formed droplets were kept in the barium chloride solution for 30 min to complete the Ba^{+2} ion induced cross-linking reaction for rigid spherical hydrogel beads. The formed beads were separated by decantation and filtration. The unbound barium chloride present on the surface of the beads was removed by washing with water. The collected beads were kept in a petri dish and dried in a hot air oven incubator at 40°C.[10]

Fourier transform infrared spectroscopy (FT-IR)

FTIR spectroscopy was carried out to check the compatibility between drugs and polymers. The IR spectra of pure glibenclamide, alginate, pectin, and formulation were carried out. Potassium bromide was mixed in an appropriate ratio with the drug, polymer, and formulation before being compressed as pellets and scanned by an FTIR spectrophotometer (Bruker, Alpha T, Germany) between 4000 and 550 cm^{-1} wavenumber range while maintaining a scanning speed of 2 mm/s.[9]

Bead size analysis

Digital slide callipers (CD-6" CS, Mitutoyo Corporation, Japan) were used to measure the size of glibenclamide-loaded pectin-alginate beads. 50 beads were randomly selected and tested between the metallic plates of the slide calipers. The diameters of each bead were displayed digitally, which was recorded.[11]

Drug entrapment efficiency

10 mg of drug equivalent beads were crushed and mixed with 100 mL of phosphate buffer (pH 6.8). It was kept for 24 hr, and then the filtration wad made. The filtrate was analysed for drug content by a UV-visible spectrophotometer (SHIMADZU, UV-1900i) at 228 nm.[12]

$$\text{Percentage of drug entrapped} = \frac{\text{Actual glibenclamide content}}{\text{Theoretical glibenclamide content in beads}} \times 100$$

Table 1: Composition of glibenclamide loaded pectin- alginate hydrogel beads.

Formulation	Drug (mg)	Sodium Alginate (mg)	Pectin (mg)	Polymers ratio	Crosslinker $BaCl_2$ (%w/v)
F1	50	1000	0	10:0	2.5%
F2	50	900	100	9:1	2.5%
F3	50	800	200	8:2	2.5%
F4	50	700	300	7:3	2.5%
F5	50	600	400	6:4	2.5%
F6	50	500	500	5:5	2.5%
F7	50	400	600	4:6	2.5%
F8	50	250	750	1:3	2.5%

Swelling ratio

The swelling ratio for the developed pectin-alginate hydrogel bead was determined by placing 10 mg of beads into 100 ml of pH 1.2 acidic medium followed by a pH 6.8 phosphate buffer solution and allowing them to swell for 2 hr. The swollen beads were removed from the buffer solution and blotted carefully with tissue paper.[13,14] The weight of the beads was noted and the swelling ratio was calculated.

$$\% \text{ Swelling ratio} = \frac{\text{Final wt of beads} - \text{Initial wt of beads}}{\text{Initial weight of beads}} \times 100$$

Shape and surface morphology

A scanning electron microscope (JEOL-JSM-840A, Japan) was employed for the shape and surface characteristics studies of the formed beads. The dried glibenclamide-loaded beads were placed on an adhesive paper. It was further coated by a sputter coater (JEOL Fine Coat JFC 1100E) to attain a 30 nm film thickness. The sample was then subjected to imaging under a 20 kV electron beam.[15]

In-vitro drug release studies

The *in-vitro* release profile for glibenclamide incorporated pectin-alginate beads was evaluated by using a USP type II dissolution test apparatus (LABINDIA DS 8000) containing 900 ml of pH 1.2 HCl buffer solution. The dissolution in acidic medium was carried out for 2 hr at a controlled temperature of 37±0.5°C. The speed of rotation was fixed at 50 rpm. After completion of 2 hr of dissolution in acidic medium, the beads were collected and subjected to further dissolution in a 6.8 phosphate buffer solution. At the prefixed time intervals of 1 hr, starting from 0.5 hr, 5 ml of aliquots were collected and replenished with suitable buffer solution. The collected aliquots were analyzed by a UV-Visible spectrophotometer (SHIMADZU, UV-1900i) at 228 nm.[16]

In vitro drug release kinetics

The drug release mechanism was determined by fitting dissolution data of all formulations into several mathematical models, including zero-order kinetics, first-order kinetics, Higuchi kinetics, and Korsemeyer-Peppas kinetics. Depending upon R^2 and release exponent "n" values obtained from different models, the best-fit model for glibenclamide release was determined.[17]

RESULTS

Fourier transforms infrared spectroscopy (FT-IR)

The FTIR spectrum of glibenclamide, sodium alginate, pectin and selected formulations is represented in Figure 1. The broadening of the peak at 3200 to 3500 cm^{-1} indicates hydrogen bond formation in the formulation. The presence of a carbonyl group (C=O) in the drug and formulation is designated by the distinct peaks at 1701.64 cm^{-1} and 1704.76 cm^{-1} respectively. Peaks for aromatic ring C-O stretching, aromatic amine N-H bending, alkyl halide C-Cl stretching, aromatic ring C-C stretching, and aromatic ring C-N stretching were observed at 1265.81 cm^{-1}, 1621.67 cm^{-1}, and 803.94 cm^{-1}, 1446.00 cm^{-1}, and 1023.69 cm^{-1}, respectively. The FTIR spectrum of the formulation shows peaks at 1266.46 cm^{-1}, 1622.18 cm^{-1}, 804.16 cm^{-1}, 1447.02 cm^{-1}, and 1023.65 cm^{-1} for C-O stretching for the aromatic ring, N-H stretching for aromatic amines, C-Cl stretching for alkyl halides, C-C stretching in the aromatic ring, and C-N stretching, respectively.

Drug entrapment efficiency (%DEE)

The percentage of drug entrapment was calculated for all the developed glibenclamide loaded pectin-alginate beads and was found to be

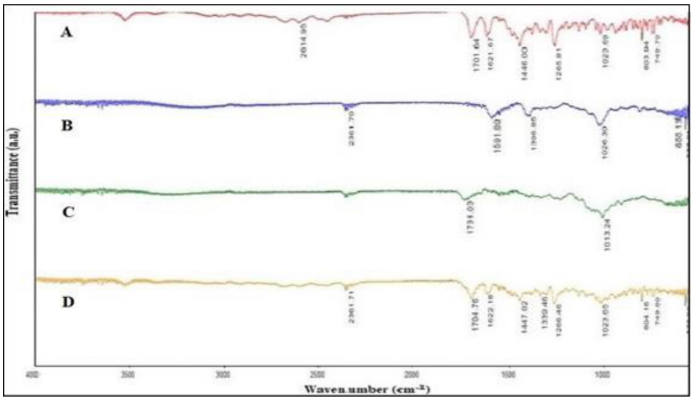

Figure 1: FTIR spectra of (A) pure glibenclamide; (B) sodium alginate; (C) pectin and (D) formulation.

Table 2: Characterization of pectin- alginate hydrogel beads of glibenclamide (*n*=3).

Formulation	Drug entrapment efficiency (%) (Mean ± SD)	Average bead size (µm) (Mean ± SD)	Swelling ratio after 2 h (Mean ± SD)	
			pH 1.2	pH 6.8
F1	85.18 ± 0.43	668.81 ± 2.10	1.60 ± 0.17	4.49 ± 0.31
F2	92.08 ± 0.64	734.34 ± 3.28	1.51 ± 0.13	4.28 ± 0.33
F3	78.38 ± 1.17	783.75 ± 2.37	1.42 ± 0.12	4.40 ± 0.20
F4	80.70 ± 0.40	853.16 ± 3.46	1.65 ± 0.09	3.39 ± 0.27
F5	85.59 ± 0.67	968.80 ± 2.59	1.37 ± 0.13	3.17 ± 0.21
F6	91.07 ± 0.84	928.44 ± 4.64	1.04 ± 0.09	2.84 ± 0.19
F7	88.01 ± 0.35	885.05 ± 2.76	0.89 ± 0.14	2.26 ± 0.23
F8	91.60 ± 0.54	984.62 ± 2.84	0.82 ± 0.15	1.82 ± 0.19

78.38 ± 1.17 % to 92.08 ± 0.64 % as shown in Table 2. Except F3, all the formulations exhibited more than 80% drug entrapment.

Particle size analysis

The size of the beads was analysed by digital slide callipers from which the mean size was calculated as reflected in Table 2. The obtained data indicated the average size of beads varied within a range of 668.81 ± 2.10 µm to 984.62 ± 2.84 µm.

Swelling ratio

The swelling study for all formulations was carried out in acidic (pH 1.2) and alkaline media (pH 6.8). The data shown in Table 2. The maximum swelling ratio from all the formulations in acidic media and alkaline media was found to be 1.65 and 4.49 percent, respectively.

Shape and surface morphology

The morphological evaluation of beads was done by scanning electron microscopy (SEM), as shown in Figure 2. A hemispherical shape of beads was observed with the presence of cracks and wrinkles.

In vitro drug release study

The *in vitro* drug release performance of the developed beads in 0.1N HCl for 2 hr and followed by in a phosphate buffer of pH 6.8 has been illustrated in Figure 3. Nearly 88% of drug release was observed after 5 hr of study from the formulation F1, which was prepared with sodium alginate alone. The drug release from all the developed formulations was found to be 41-88% after 5 hr.

Furthermore, the release performance was analysed by fitting the data into the Zero Order, First Order, and Higuchi's kinetic models and Korsemeyer-Peppas equation as shown in Table 3. The kinetic study indicates that the drug release from F1, F6-F8 was best fitted with Zero-Order and Higuchi's kinetic for F2-F5 based on the highest linearity observed ($R2$>0.963).

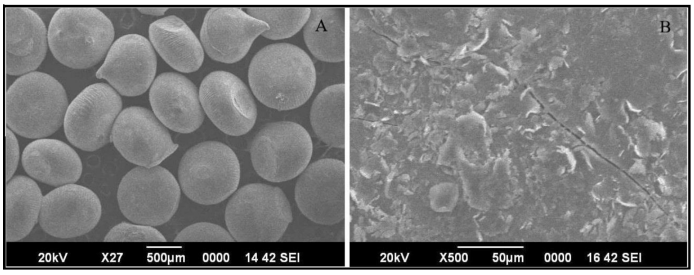

Figure 2: Scanning electron microscopic images of developed bead formulation at different magnification (A) indicating the hemispherical shape of beads and (B) exhibiting the surface morphology of hydrogel beads.

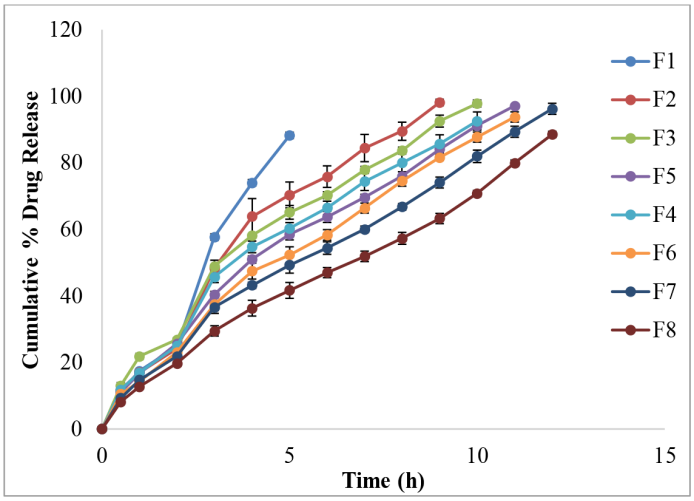

Figure 3: *In vitro* release profile of glibenclamide loaded pectin-alginate hydrogel beads in pH 1.2 for 2h followed by pH 6.8. The values are mean ± SEM (n = 3)

Table 3: Kinetic analysis of *in-vitro* release data of different formulations.

Formulation	Zero order	First order	Higuchi model	Korsmeyer- Peppas model		
	R^2	R^2	R^2	R^2	n (pH 1.2)	n (pH 6.8)
F1	0.978	0.923	0.882	0.950	0.57	1.38
F2	0.963	0.871	0.963	0.973	0.51	0.84
F3	0.961	0.878	0.981	0.983	0.52	0.72
F4	0.963	0.960	0.978	0.984	0.54	0.73
F5	0.976	0.939	0.982	0.994	0.60	0.73
F6	0.984	0.928	0.973	0.991	0.57	0.78
F7	0.986	0.859	0.970	0.994	0.61	0.76
F8	0.990	0.904	0.956	0.995	0.63	0.78

DISCUSSION

The characteristic peaks that appeared in the FTIR spectrum of the drug were also seen in the formulation without substantial changes in peaks. This indicates the nonappearance of any physical or chemical incompatibility in the formulation during and after preparation.[9] The drug entrapment efficiency of the formulated beads was found to be satisfactory. The observed bead size is within the µm range. The size gradually increased as more pectin was introduced, taking the place of the alginate. According to the swelling data observed, the proportion of water uptake steadily reduces as the amount of alginate in the matrix decreases. The experimental results showed that swelling was restricted in an acidic environment and that the swelling ratio was substantially higher in simulated intestinal fluid. With lower sodium alginate concentrations, a progressive decline in swelling ratio was seen in both media. The SEM study exhibited slightly rough surfaces with slight depressions and elevations. It may be due to the deposition of some drug particles on the beads' outer surface. The slight deformation of the spherical shape could be the result of uneven contraction due to water evaporation.[12] Initially, a bursting drug release was observed from all the formulations. It may be due to the entrapment of the drug at the surface of the beads and/ or the solubility of the drug. It was also found that the rate of drug release in an acidic medium was lower than in the alkaline medium due to the restricted swelling of the polymers in an acidic medium. The release performances indicate that it was gradually reduced when pectin was added without changing the total polymer concentration as a replenisher with sodium alginate. This may be due to the mechanical strength of the swelled surface gel formed and the degree of cross-linking.[18] The Korsemeyer-Peppas equation was used to analyse all of the release kinetics data. The release exponent "n" value was found to be 0.51-0.63 up to 2 hr in pH 1.2, indicating Fickian diffusion was more pronounced in an acidic medium with less erosion. But in an alkaline medium (pH 6.8), erosion was gradually increased with diffusion as the observed release exponent tended to 1 from 0.72, which appeared to indicate anomalous drug transport where erosion is coupled with the diffusion mechanisms of drug release.[19] In the case of F1, release was followed by super case-II transport as n exceeded 1.

CONCLUSION

This investigation has demonstrated the development and characterization of pectin-alginate hydrogel beads for the oral controlled delivery of glibenclamide. An ionotropic gelation technique was employed to synthesise Ba^{+2} ion cross-linked beads. The FTIR study confirmed the absence of any drug-polymer interactions. The entrapment efficiency for all the formulations was found to be satisfactory. The swelling study performed in acidic and alkaline media revealed the pH dependent behaviour of the developed beads. The *in-vitro* dissolution study of the glibenclamide loaded bead formulations showed sustained release ability with increasing pectin concentration. The release exponent values demonstrated both Fickian diffusion and anomalous drug transport. The study concluded that the Ba^{+2} ion cross-linked micro-beads can sustain the release of glibenclamide depending on the ratio of pectin and alginate.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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Article History: Submission Date : 19-06-2022; Revised Date : 20-07-2022; Acceptance Date : 12-08-2022.
Cite this article: Manna S, Aziz A, Das S, Bhowmik M. Ionically Cross-linked Pectin-alginate Hydrogel Beads for Prolonged Release of Glibenclamide. Int. J. Pharm. Investigation. 2022;12(4):475-8.