

GELLAN MICRO-CARRIERS FOR pH-RESPONSIVE SUSTAINED ORAL DELIVERY OF GLIPIZIDE

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Abstract

The gellan gum (GG) micro-carriers were prepared by ionic and covalent crosslinking reactions for pH-sensitive delivery of glipizide. Fourier transformed infrared (FTIR) analysis confirmed the synthesis of particle carriers and chemical drug-polymer interaction. The particles ranged between 910 and 1050 μm and showed $\sim 82\text{-}95\%$ drug entrapment efficiency. Scanning electron microscopy (SEM) revealed spherical particle morphology. Ca^{+2} -GG particles swelled in simulated gastric fluid without enzymes (pH 1.2) less than in simulated intestinal fluids (pH 6.8) and therefore resulted in the release of small amounts of drugs in acidic fluid (8-12%). The swelling and surface erosion behaviours were accounted for drug release from the Ca^{+2} -GG particles. Glutaraldehyde (GA) treated Ca^{+2} -GG particles eventually swelled in highly acidic and weakly alkaline media with limited surface erosion. However, the amount of drug released did not corroborate with the degree of swelling of the particles. They released only 66% entrapped drug in simulated bio-fluids after 8 h. The relative contribution of simple diffusion and polymer relaxation phenomena in the anomalous transport of drug was evaluated by Peppas-Sahlin mathematical modelling. The pH-responsive GA-treated GG-micro-carriers had the potential to control the release of drug over a long period of time in simulated fluids.

Rezumat

Micro-carriers cu gumă gellan au fost preparați prin reacții de reticulare ionică și covalentă la pH-ul caracteristic glipizidei. Analiza FTIR a confirmat sinteza și interacțiunile polimer – compus chimic. Particule cu dimensiuni cuprinse între 910 și 1050 prezintă aproximativ 82-95% eficiență de încorporare a medicamentului. Microscopia de scanare electronică (SEM) a relevat morfologia sferică a particulelor. Particulele Ca^{+2} -GG și-au mărit volumul în fluidul gastric simulat fără enzime (pH = 1,2) mai puțin decât în fluidul intestinal simulat (pH = 6,8) și astfel a rezultat eliberarea unor cantități mici de medicament în fluidul acid (8-12%). Mărirea volumului și eroziunea suprafeței au fost puse pe seama eliberării substanțelor medicamentoase din particulele Ca^{+2} -GG. Glutaraldehida (GA) a fost tratată cu particule Ca^{+2} -GG, care și-au mărit volumul în mediu acid pronunțat și în mediu alcalin slab, cu eroziune de suprafață limitată. Cu toate acestea, cantitatea de medicament eliberată nu a putut fi coroborată cu gradul de mărire al volumului particulelor. Au fost eliberate doar 66% din particulele de medicament în fluidele biologice simulate în 8 ore. Contribuția relativă a difuziei simple și fenomenul de relaxare polimerică în transportul anormal al medicamentului au fost evaluate prin modelul matematic Peppas-Sahlin. *Micro-carriers* GG tratați cu GA la pH-ul optim au potențialul să controleze eliberarea medicamentului pentru o perioadă îndelungată în fluidele simulate.

Keywords: gellan gum, glutaraldehyde, Peppas-Sahlin modelling, release mechanism, hydrogel carriers, controlled release

Introduction

Natural polymers are often preferred to synthetic materials in drug delivery technology due to their non-toxicity and enzymatic degradation [1-4]. In addition, they have a number of reactive functional groups including hydroxyl and carboxyl, indicating their possibility for chemical modification [5]. Therefore, in the years to come, there is going to be increased interest in the natural gums and their modifications with the aim to have better materials for drug delivery.

Gellan gum (GG) is an anionic polysaccharide secreted by the bacterium *Sphingomonas elodea*. It is composed of tetrasaccharide repeating units of D-glucose, L-rhamnose, and D-glucuronic acid at the

ratio 2:1:1 with O-acetyl and L-glyceryl moieties as a side chain on D-glucosyl residue adjacent to D-glucuronyl residue [6]. According to Food and Drug Administration (FDA), GG can be safely used as direct food additive for human consumption [7]. Thus, numerous investigators have explored the potential of GG in oral drug delivery applications. GG finds its wide applications in food, cosmetic and pharmaceutical industries as thickening, binding and emulsifying agent. It has the ability to form gels in the presence of mono- or divalent cations. This property has enabled possible applications of GG in the field of drug delivery. GG alone or its modified form has been studied extensively as a vehicle for ophthalmic delivery of drugs [8-10] and as tablet binder [11], disintegrates [12-13], implantable

films [14], and oral hydrogel beads [15-19]. However, studies related to the elucidation of drug release mechanism from GG formulations in the prior art are very limited. In contact with simulated bio-fluids; the overall drug release mechanism may be influenced by either simple diffusion or polymer relaxation or both.

Glipizide is a BCS II sulfonyl urea class of drug, commonly used for the treatment of type 2 diabetes. It is absorbed throughout the gastro-intestinal tract and shows bioavailability of nearly 100%. Due to short biological half-life of 3.4 ± 0.7 h, it requires frequent dosing (2-3 times) per day [20].

Since the use of sustained release formulation offers many potential advantages like stable blood levels, attenuation of adverse effects, and improved patient compliance [21], it is indeed a real need to maintain the constant blood levels as otherwise hyperglycaemia may increase. Recalling the specific advantages of the particulate drug delivery systems, gellan gum particulate matrices of glipizide was formulated to improve therapeutic efficacy and patient compliance.

Ionic and covalent cross-linking is a suitable procedure to control swelling of hydrophilic matrices and regulate drug release rate in bio-fluids. In this work, the release of glipizide was modulated in simulated bio-fluids by chemical modification of GG matrices and the drug release mechanism was investigated.

Materials and Methods

Materials

Glipizide (Micro Labs Limited, Hyderabad, India), Gellan gum (GG) (SRL Pvt. Ltd., Mumbai, India), Glutaraldehyde aqueous solution (25%, v/v) (Merck Specialities Pvt. Ltd., Mumbai, India), Calcium chloride dihydrate (Qualigens Fine Chemicals, Mumbai, India). Other analytical reagents were purchased commercially from available sources.

Methods

Formulation of gellan particulate matrices. The gellan particles were developed by two processes: (a) ionic gelation; and (b) combined ionic gelation and covalent crosslinking. Ten millilitres of 1.2% (w/v) aqueous solution of GG were prepared by heating at 55°C and glipizide was loaded (30%, w/w) by uniform mixing. Sol dispersion was extruded through 21G flat-tipped needle into 50 mL calcium chloride (CaCl_2) solution (1-3%, w/v). The

sol droplets were incubated into salt solution for the formation of solid GG gelled particles. The gelation medium was decanted after 10 min. The solid particles were washed with distilled water (3×25 mL) and air-dried.

As soon as the GG droplets underwent ionotropic gelation with 3% CaCl_2 solution, the particles were incubated into 50 mL of 4.5% (v/v) glutaraldehyde (GA) solution (pH 2.0) at 50°C for 2 h. The covalently cross-linked particles were washed with distilled water to remove non-reacted GA. The absence of residual GA was ensured by Brady's (2,4-dinitrophenylhydrazine) qualitative test. The washings were added to Brady's reagent solution and the formation of a yellow precipitate indicated the presence of GA in the washings. The particles were washed with distilled water until no yellow precipitate was observed and thus confirming the absence of GA. The drug-free GG particles were produced by the same method.

Scanning electron microscopy. The particles were observed under a scanning electron microscope (JEOL-JSM-6360, JEOL Datum Ltd., Japan). The samples were coated with gold to increase the conductivity of the electron beam. Gold-coated samples were photographed at an acceleration voltage of 10 kV.

Size analysis of GG particles. The diameter of GG particles was measured by microscopic analysis (Olympus Model HB, India) using 10× eyepiece and 10× objective optical combinations. The optical micrometre was calibrated with a standard stage micrometre. The diameters of 100 particles were averaged.

Efficiency of drug entrapment. A known amount of particulate formulation (10 mg) was pulverized with a mortar/pestle and digested into 100 mL of phosphate buffer solution (pH 7.4) overnight for the extraction of drug. The digested fluid was passed through No.1 Whatman filter paper to remove digested insoluble polymer fragments and the filtrate was analysed spectrophotometrically (UV1, Thermo Spectronic, UK) at 276 nm. Then, the actual amount of drug present in the sample was estimated. Each sample was run in triplicate. The theoretical amount of drug was 30% of 10 mg sample; equal to 3 mg. The drug entrapment efficiency of GG particles was then determined by the following equation:

$$\text{Drug Entrapment Efficiency (\%)} = \frac{\text{actual drug content}}{\text{theoretical drug content}} \times 100$$

Drug release study. USP-II dissolution rate test apparatus (VDA-6D, Mumbai, India) was used for studying the *in vitro* drug release from GG particulate matrices into bio-fluids. Fifty milligrams

of the samples were put into 900 mL of enzyme-free simulated intestinal fluids (phosphate buffer solution, pH 6.8) at $37 \pm 0.5^\circ\text{C}$ and the paddle speed was set at 50 rpm. Ten millilitres of simulated

fluid were withdrawn from the dissolution medium at pre-set periods and replaced with the same volume of fluids. The samples were analysed using a spectrophotometer (UV1, Thermo Spectronic, UK) at 276 nm.

The drug release study in enzyme-free simulated gastric fluid (KCl/HCl buffer solution, pH 1.2) was carried out under similar conditions for 2 h. The samples were then filtered and simultaneously dipped into simulated intestinal fluid (phosphate buffer solution, pH 6.8) and the drug release study was continued further up to 6 h. The percentage of drug released into simulated fluids against time was

$$\text{Swelling Degree (\%)} = \frac{(\text{weight of sample at time } t - \text{weight of sample at time zero})}{\text{weight of sample at time zero}} \times 100$$

Statistical interpretation. The drug entrapment efficiency and release data of the formulations were analysed by one-way analysis of variance (ANOVA) at 95% confidence interval. Any statistical difference in drug entrapment efficiency of the GG particles as a function of type and strength of the cross-linker was analysed by the unpaired *t*-test. GraphPad Prism software (version 3.00) was used for finding differences of significant level at $p < 0.05$

Results and Discussion

The addition of aqueous GG sol droplets into calcium chloride solution led to the formation of insoluble gelled particles. This was accomplished by ionic interaction of free carboxylate groups in glucuronosyl residues of GG with divalent Ca^{2+} ions.

graphically demonstrated. Each sample was tested in triplicate.

Swelling study. The degree of swelling of GG matrices was investigated in simulated gastric fluids for a period of 2 h and thereafter in intestinal fluids. The swelling kinetics was also demonstrated in intestinal fluids without pre-exposure to gastric fluids. Pre-weighed samples were immersed into 50 mL of each fluid and the swollen samples were removed at definite periods, blotted with tissue paper and re-weighed (AB 204-S, Metler Toledo, Switzerland). The swelling degree was measured as a function of time as follows:

The mechanisms behind the formation of three-dimensional hydrogel network may involve the aggregation of double helical segments, complexation with metal ions followed by hydrogen-bonding with water [22].

In addition to ionic cross-linking, the calcium gellan particles were further reinforced with GA solution for inducing covalent acetal linkages in order to impart stability to the hydrogel particles [23]. Recalling the earlier reports [24-25], the aldehyde functional groups of glutaraldehyde was said to react with the hydroxyl group of GG under acidic condition, and formed acetal bridges.

The induction of ionic and covalent acetal cross-links in the GG particles was confirmed by FTIR analysis.

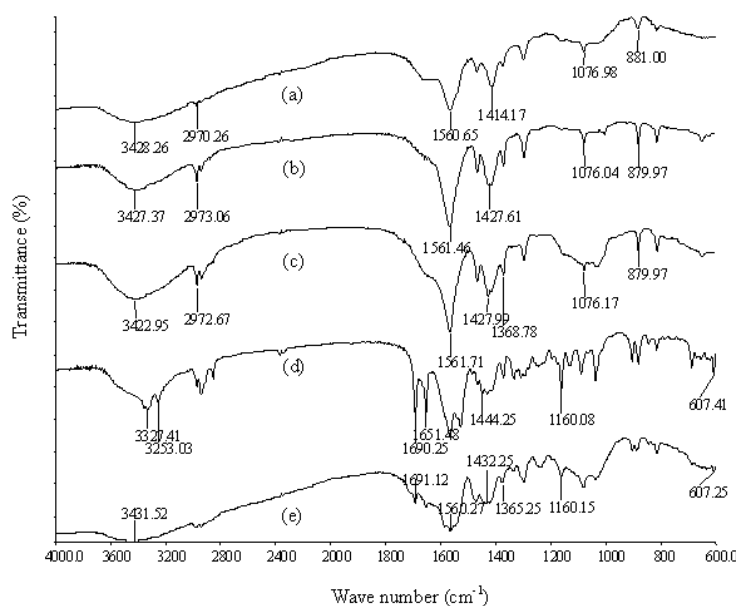


Figure 1.

FTIR scans of (a) GG; (b) Ca^{2+} -GG drug-free beads; (c) GA- Ca^{2+} drug-free GG beads; (d) pure glipizide and (e) glipizide-loaded GA- Ca^{2+} GG beads

In the FTIR spectrum (Figure 1a), GG showed characteristic peaks at 3428.26 cm^{-1} (O-H stretching), 2970.26 cm^{-1} (C-H stretching), 1560.65 cm^{-1} and 1414.17 cm^{-1} (asymmetric and symmetric COO^- stretching, respectively) and at 1076.98 cm^{-1} (C-O stretching of alkyl ethers) [26-27].

The peak at 881.00 cm^{-1} was assigned to C-O-C stretching of glycosidic linkage. The carboxyl stretching shifted to higher absorption frequencies (1561.46 cm^{-1} and 1427.61 cm^{-1}) (Figure 1b), and this indicated an ionic interaction between COO^- and Ca^{2+} ions. The hydroxyl groups may allow possible cross-linking of GG with GA. Here, the chemical reaction between hydroxyl groups of GG and aldehyde groups of GA was confirmed by FTIR measurements. A new peak appeared in the spectrum of GA-treated particles at 1368.78 cm^{-1} (Figure 1c) and this was attributed to C-H deformation of $-(\text{CH}_2)_3-$ groups of GA [28]. A broad ether absorption band (C-O-C groups of acetal groups) appeared in the region of $1050\text{--}1150\text{ cm}^{-1}$ [29]. Probably, the overlapping of C-O stretching of alkyl ethers with C-O-C acetal stretching led to broadening of the ethereal stretching. Recently, Distantina *et al.* reported the absence of C-O-C stretching of acetal groups in the spectrum of GA-crosslinked carrageenan hydrogels [30]. They stated that low concentrations of acetal groups in the sample could possibly be beyond the detection limit of spectroscopic analysis and hence, no characteristic peaks appeared in the carrageenan hydrogels. In addition to broad ethereal stretching of acetal linkages, a slight decrease of the absorption bands of hydroxyl groups in cross linked GG particles was noted at 3422.95 cm^{-1} . The hydroxyls were consumed during crosslinking reaction and thus, the reduction of hydroxyl absorption band indicated the successful reaction between GG and GA.

In Figure 1(d), the important peaks of pure glipizide were observed at 3327.41 cm^{-1} , 3253.03 cm^{-1} (N-H stretching), 1690.25 cm^{-1} (C=O), 1651.48 cm^{-1} ($-\text{CONH}$), 1444.25 cm^{-1} (substituted cyclohexane), 1160.08 cm^{-1} ($-\text{SO}_2$ group), 607.41 cm^{-1} (disubstituted benzene) [31]. In addition to stretching of carboxyl and acetal links, the drug absorption peaks were identified in the spectrum of GA- Ca^{2+} gellan particles (Figure 1e) without appreciable changes. However, N-H stretching peak shifted to a higher wave number (3431.52 cm^{-1}) and this could be attributed to overlapping of O-H and N-H stretching. Hence, it was understood that the drug did not interact chemically with the polymer and consequently, ionic interaction did not play an influential role in drug release mechanism in biological fluids.

The effect of salt concentration on the properties of gellan particulate matrices was studied. Irrespective of the variables, the shape of particles (CF1-CF3)

was found spherical. No visual difference was seen in morphological behaviours of the formulations (CF1-CF3). Henceforth, a representative photomicrograph of GG particles was displayed in Figure 2a.

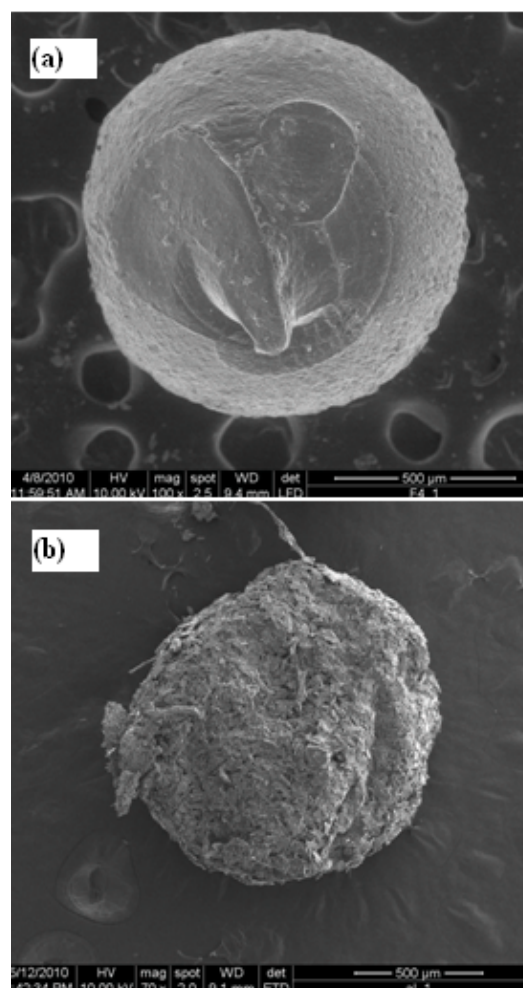


Figure 2.

Representative scanning electron micrographs of (a) Ca^{+2} -GG particles and (b) GA-treated Ca^{+2} -GG particles

It was worthy to note that the GG particles maintained their spherical shape both in wet and dry state. However, ionic and covalent cross-linking of GG particles (GF3) showed significant impact on their morphological structures. SEM photograph revealed their porous, spherical structures (Figure 2b). This could be due to a more rapid approach of divalent cations and consequent formation of a dense GG polymer matrix [32] in lieu of dual cross-linking in GF3 particles. It was apparent that the mean diameter of CF1 and CF3 particulate formulations decreased from $1090\text{ }\mu\text{m}$ to $1050\text{ }\mu\text{m}$ with increasing CaCl_2 concentration (Table I). An analogous result was reported by Babu *et al.* [19]. They observed that the size of GG particles became smaller (2.8 to 2.4 mm) with increasing CaCl_2 strength ($0.1\text{--}0.4\text{ M}$).

Table I

Results of drug entrapment efficiency and mean diameter of spherical gellan matrices prepared with different types of cross-linkers at different concentrations

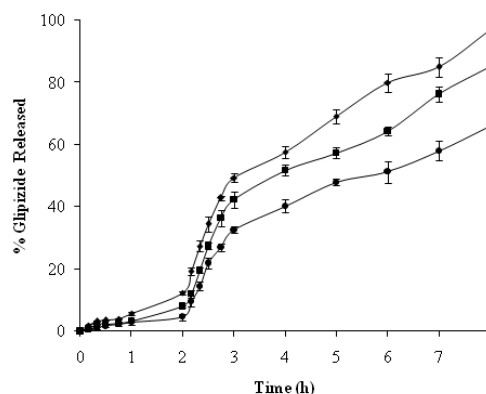
Code	GG (%)	GA (mL)	Gelation time (min)	CaCl ₂ (%w/v)	Drug Entrapment efficiency (%) $\pm$ SD, n = 3	Particle size ($\times 10^3 \mu\text{m}$) $\pm$ SD
CF1	1.2	0	10	1.0	94.88 $\pm$ 1.25	1.09 $\pm$ 0.03
CF3	1.2	0	10	3.0	91.61 $\pm$ 1.51	1.05 $\pm$ 0.04
GF3	1.2	1	10	3.0	82.22 $\pm$ 2.65	0.91 $\pm$ 0.05

Following the treatment with GA, the size of GF3 formulation dropped to 910 μm (Table I). Due to the possibility of a greater ion exchange between monovalent (H^+ , Na^+ , K^+) ions with divalent calcium ions, a higher degree of cross-linking was established in GG sol droplets at higher salt concentration, causing syneresis and consequent shrinkage of the GG particles [33]. Probably, this event in conjunction with reinforced acetal linkages resulted in further size reduction of GF3 particles.

The average drug entrapment efficiency dropped at higher salt concentrations (Table I). About 3% reduction in drug entrapment efficiency was envisaged as the salt strength was raised to 3% (w/v). Thus, variation in salt strength affected drug entrapment efficiency of the particles and a statistically significant difference in their mean values was recognized by unpaired t-test ($p < 0.05$). The treatment of the CF3 particles with GA cross-linker (GF3) reduced the drug entrapment efficiency further and the difference in their mean values was statistically significant ($p < 0.05$) when analysed by unpaired t-test. In the event of gelation process, water was squeezed out due to formation of cross links by the cations and GA. Therefore, a more cross-linked network may show a larger water loss. The dissolved quantity of drug could be lost from the GG particles by simple diffusion and the expulsion of water may cause convective loss of drug molecules [34]. Thus, low drug entrapment efficiency was achieved at higher salt strength and after GA treatment. Overall, differences in mean drug entrapment efficiency of the formulations (CF1, CF3 and GF3) were evident by ANOVA ($p < 0.05$). Since the calculated $F_{2,6}$ (35.67) was larger than the table value (5.14), the conclusion was that at least two of the means differed from each other at the 5% level. Tukey's multiple comparison tests revealed that the drug entrapment efficiency of the pairs CF1 vs. GF3 and CF2 vs. GF3 varied significantly ($p < 0.05$). However, no statistical difference in drug entrapment efficiency was indicated between CF1 and CF3 formulations ($p > 0.05$).

During its transit through the gastrointestinal tract, a dosage form has to face variable pH conditions in order to liberate its content before absorption into systemic circulation. To simulate *in vivo* situations, *in vitro* drug release study was initially performed at pH 1.2 KCl/HCl solution and then at pH 6.8

phosphate buffer solution. The drug release profiles of GG particulate matrices were illustrated in Figure 3.

**Figure 3.**

Release profiles of glipizide-loaded gellan particulate matrices in acidic medium for 2 h, followed by phosphate buffer solution (pH 6.8) in next 6 h as a function of the strength of calcium chloride (♦) 1%; (■) 3%; and (●) 3% with GA

Irrespective of metallic salt concentration, only ~ 8-12% drug released from CF1-CF3 formulations in acidic medium within a timeframe of 2 h. GA-treated formulation (GF3) liberated < 5% of entrapped drug in the same duration. Following a change in pH of the medium, the formulations (CF1-CF3) slowly released their content into pH 6.8 phosphate buffer solution. The drug release profile of CF1 formulation dominated over the profile of CF3 and that of CF3 over GF3. Compared to CF3, a slower drug release profile was achieved for GA-treated formulation (GF3). After 8 h, the percentage drug release was found in the order of 97.08%, 85.29%, and 66.05%, respectively for the CF1, CF3, and GF3 formulations. The mean values of $t_{50\%}$ (time required for the release of 50% entrapped drug) was determined from the drug release curves and were found in the order of 3.10 ± 0.05 , 3.80 ± 0.08 , and 5.65 ± 0.1 h, respectively for CF1, CF3 and GF3 formulations. The calculated $F_{2,6}$ (781.1) was much greater than the table $F_{2,6}$ (5.14) value and one-way ANOVA suggested significant differences in at least two of the mean values at 95% confidence level. The drug release behaviours of the gellan particles in phosphate buffer solution (pH 6.8) were demonstrated in Figure 4.

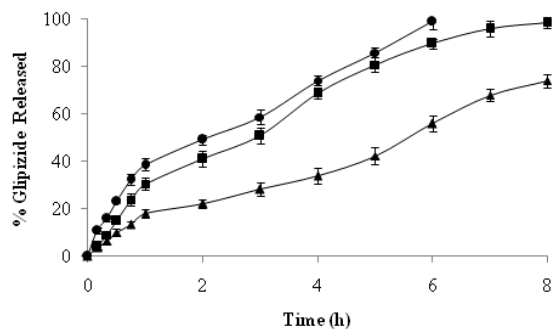


Figure 4.

Release profiles of glipizide-loaded gellan particulate matrices in phosphate buffer solution (pH 6.8) as a function of the strength of calcium chloride (●) 1%; (■) 3%; and (▲) 3% with GA

In phosphate buffer solution, the CF1 particles almost completed its drug release in 6h. However, the drug release extended up to 8 h in case of CF3 formulation. GA-treated particles (GF3) liberated its entrapped drug at a rate slower than CF1 and CF3 particles, releasing only 74.25% drug at the end of 8 h. In phosphate buffer solution, the $t_{50\%}$ values for CF1, CF3 and GF3 formulations were 2.13 ± 0.07 , 2.93 ± 0.18 , and 5.56 ± 0.16 h, respectively. The calculated $F_{2,6}$ value was about 84 times higher than tabulated value, which reflected statistical differences in the values of mean dissolution parameter ($p < 0.05$).

To correlate drug release data, the swelling kinetics of the GG matrices were assessed in simulated gastric fluids (pH 1.2) followed by intestinal fluids (pH 6.8) and was given in Figure 5.

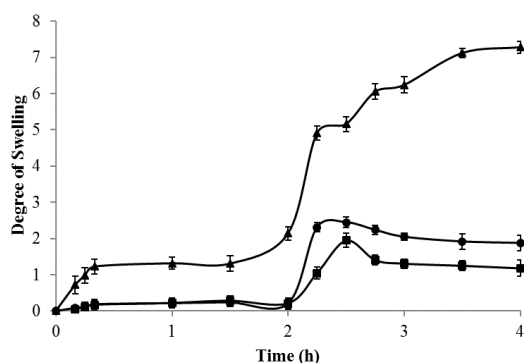


Figure 5.

Swelling kinetics of GG particulate devices in acidic release medium (2 h) followed by phosphate buffer solution (pH 6.8). Key: concentration of salt (●) 1%; (■) 3%; and (▲) 3% with GA

As was evident from swelling graphs (Figure 5), CF1 and CF3 matrices swelled to a very low extent (17.90-20.33%) up to 2 h in acidic medium. Thereafter, the degree of swelling of GG matrices suddenly increased to 210-266% in next half an

hour in phosphate buffer solution. Thereafter, the swelling ratio of particles gradually decreased and was associated with surface erosion of the polymer particles. Surface erosion caused mass loss and hence, swelling curves did not move upwards. On the other hand, GF3 particles did not show any sign of erosion. They swelled gradually in acidic medium for 2 h and the swelling continued in phosphate buffer solution for additional 2 h. Thus, higher percentage of drug release could be expected from GF3 formulation but the drug release data did not satisfy this expectation. Without pre-exposure of the particles in acidic medium, the swelling curves of GG particles were also studied in phosphate buffer solution and were illustrated in Figure 6.

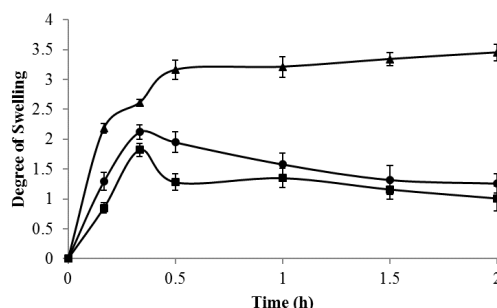


Figure 6.

Swelling kinetics of GG particulate devices in phosphate buffer solution (pH 6.8). Key: concentration of salt (●) 1%; (■) 3%; and (▲) 3% with GA

It was evident that the CF1 and CF3 particles swelled up to 20 min in phosphate buffer solution and then the swelling ratio reduced dramatically. This indicated the surface erosion of the calcium gellan matrices and subsequent dissolution of the polymer in the buffer solution. GF3 particles swelled freely in the buffer solution and the swelling curve switched upwards with time (Figure 6). The surface erosion of particulate matrices eliminated completely after GA treatment. In spite of higher propensity of swelling, the amount of drug release from GF3 particles was less than CF1 and CF3 formulations. This could be attributed to dissolution-controlled release of the drug due to its low aqueous solubility. Because the degree of cross-linking in CF1 particles was less than CF3 particles, the percentage of drug release was higher from CF1 particles. This could be attributed to the fact that at higher cross-linking, free volume of the matrix would be less, thereby hindering easy transport of drug molecules through the matrix. This also reduced the rate of swelling as well as the rate of drug release from the matrix [35]. Furthermore, the drug release was much faster in phosphate buffer solution than in acidic medium.

GG matrices did not ionize in acidic medium, thus caused insignificant swelling of the matrices [36] and consequently, resulted in release of small amount of drug in acidic medium. The equilibrium solubility of glipizide was reported to be $5.626 \pm 0.013 \mu\text{g/mL}$ and $9.458 \pm 0.083 \mu\text{g/mL}$ in 0.1 (N) HCl and phosphate buffer solution (pH 6.8), respectively [37]. Being a weak acid ($\text{pK}_a = 5.9$), glipizide is more soluble at relatively higher pH conditions (weakly alkaline phosphate buffer solution, pH 6.8). Therefore, the solubility of drug could also contribute to the differences in drug release rate depending upon the pH of the media.

The drug release data in phosphate buffer solution was modelled into Korsmeyer-Peppas equation [38] and the values of diffusion exponent (n) were defined to evaluate the drug release mechanism from GG particulate matrices.

$$\frac{M_t}{M_\infty} = kt^n$$

M_t/M_∞ was the fractional drug release at time t , k was a constant describing the structural and geometric characteristics of the device. The mechanism of drug release from spherical particulate matrices may be Fickian diffusion when $n = 0.43$ and that of non-Fickian when the criteria $0.43 < n < 0.85$ was met. The values of diffusion exponent (n) lied in the range of 0.43 and 0.85 (Table II). Hence, the drug release was said to follow an anomalous transport mechanism, meaning that the drug release was controlled by a combination of simple diffusion and polymer relaxation/erosion mechanisms.

Table II

The parameters for evaluating the drug release mechanism of the GG particles in phosphate buffer solution after fitting of drug release data into different mathematical models

Formulation code	Korsmeyer-Peppas model			Peppas-Sahlin model		
	n	k	r^2	k_1	k_2	r^2
CF1	0.595	0.3396	0.973	28.22	6.02	0.9685
CF3	0.829	0.2365	0.955	13.12	12.28	0.9722
GF3	0.683	0.1479	0.980	3.43	10.13	0.9679

The release data were further fitted into Peppas-Sahlin equation [39] to calculate the approximate contributions of the diffusional and relaxational mechanisms in an anomalous drug release process:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$$

The first and second component on right hand side of the equation indicated Fickian diffusion and relaxational contribution, respectively. The values of k_1 and k_2 were determined by non-linear regression analysis of the drug release data. The coefficient (m) was purely Fickian diffusion exponent and was 0.43 for a spherical device. In case of CF1 formulation, $k_1 \gg k_2$, and therefore Fickian diffusion was mostly operative in the event of drug release. On the other hand, the values of k_1 and k_2 did not differ significantly for CF3 formulation (Table II). Herein, Fickian diffusion and surface erosion mechanisms equally contributed to the drug transfer from GG matrices. Relative to simple diffusion, the swelling/relaxation of the polymer predominated over drug release from GA-treated particles because the criteria $k_2 \gg k_1$ was satisfied (Table II).

Conclusions

In this study, the chemically modified GG hydrogel particles were prepared by a combination of Ca^{2+} -induced ionotropic gelation and covalent cross-linking method. The duration of drug release

depended on the nature and concentration of the cross-linkers, which ultimately affected the degree of cross-linking. The drug release rate was slower in acidic medium than in weakly alkaline medium. Calcium GG particles swelled and eroded concentrically in different media and controlled the drug release. No such correlation was established in the event of drug release from GA-treated particles. Regardless of chemical treatment, anomalous drug transport process was elucidated for the GG particles. Surface erosion of calcium GG particles contributed to the drug release phenomenon in addition to simple diffusion. However, the surface erosion of the particles can be avoided by GA-treatment. Hence, GA-treated GG particles showed a great promise in controlling the release of glipizide in variable pH-environment of gastrointestinal tract over a longer duration.

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