

# Mucoadhesive beads of gliclazide: Design, development, and evaluation

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**ABSTRACT:** Novel mucoadhesive beads were developed and evaluated for oral controlled release of the hypoglycaemic agent gliclazide. Various formulations of mucoadhesive beads were prepared using two different natural polymers, alginate and ispaghula, in various stoichiometric proportions with CaCl<sub>2</sub> as a source of counter ions. The mucoadhesive beads were characterized for entrapment efficiency, particle size, surface morphology, and swelling index. The kinetics of drug release and their mucoadhesive nature in vitro using goat intestinal mucosa was also investigated at various physiological pH conditions. The effects of various proportions of the two polymers along with the effect of various percentages of counter ions on mucoadhesion property, size, entrapment efficiency, and drug release behaviour were studied. The effective mucoadhesion property with sustained release profile was observed from optimized mucoadhesive beads consisting of alginate and ispaghula husk (1:1) and polymer (2:1) with 5–10% w/v counter ions (CaCl<sub>2</sub>). These formulations showed optimum mucoadhesion behaviour having more than 70% w/v of drug entrapment and particle sizes of  $896.7 \pm 0.8$  and  $920.6 \pm 1.2$   $\mu\text{m}$ , respectively.

**KEYWORDS:** mucoadhesion, bioadhesion, alginate-ispaghula, cross-linking

## INTRODUCTION

Bioadhesion is defined as the attachment of macromolecules to any biological surface. When adhesion occurs with mucus lining the epithelial surface, it is referred to as mucoadhesion<sup>1,2</sup>. It is mostly achieved by using mucoadhesive polymers. Uses of mucoadhesive-based formulations include local action to treat the pathology of diseases<sup>3–5</sup>, protein and peptides delivery<sup>6</sup>, delivery of drug molecules intranasally<sup>7–9</sup>, delivery to the brain across the blood-brain barrier<sup>10</sup>, in ophthalmic formulations to increase the contact time with the mucus lining of ocular epithelium<sup>11</sup>, and drug delivery through inhalation<sup>12</sup>.

Formulations of mucoadhesive polymer-containing formulations is of interest in the design of delivery systems to prolong the residence time of drugs present in dosage form at the site of absorption and facilitate intimate contact with the underlying absorptive surface to enhance the bioavailability of drugs. The increased bioavailability may result from the higher flux generated due to intimate contact between two surfaces for a longer time which results

in a more sustained release profile of drug delivery than from conventional dosage forms<sup>13</sup>. The key factors governing the release of drug molecules from a mucoadhesive formulation include the type, molecular weight, concentration, hydrophilicity of polymers used, chemical functional groups present on its surface, degree of cross-linking produced, and degree of contact between the two surfaces. Several studies have been made using mucoadhesive polymers in oral drug delivery systems including clarithromycin against *H. pylori*<sup>14</sup>, glipizide<sup>15</sup>, amoxicillin<sup>16–18</sup>, cephadrine<sup>19</sup>, and timolol maleate<sup>20</sup>.

Gliclazide (GCD), 1-(3-azabicyclo-[3, 3, 0]-oct-3-yl)-3-(p-tolyl sulphonyl) urea, is one of the most frequently used oral hypoglycemics and belongs to the second generation sulphonylureas used for long-term treatment of non-insulin dependent diabetes mellitus<sup>21</sup>. Earlier study suggested that GCD possesses good general tolerability, low incidence of hypoglycemia, and a lower rate of secondary failure<sup>22,23</sup>. However, the absorption rate of GCD from the gastrointestinal tract is slow and varies among subjects<sup>24</sup>. It has been suggested that the slower

absorption is due to either its poor dissolution owing to its hydrophobic nature or poor permeability across the gastrointestinal membrane<sup>25,26</sup>. Incorporation of GCD in controlled release dosage forms such as cross-linked alginate beads may control its absorption from the gastrointestinal tract and overcome the variability.

Polymers used in mucoadhesive formulations include both natural and synthetic. Various mucoadhesive natural polymers used widely in drug delivery include agar, guar gum, chitosan, xanthan gum, alginates, and locust bean gum<sup>27</sup>. Among various natural polymers, alginates have been used as matrices to achieve controlled release drug delivery due to their hydrogel forming properties<sup>28</sup>. Alginate polysaccharides consisting of a monovalent form of alginic acid are obtained from the marine brown algae *Laminaria hyperborean*, *Ascophyllum nodosum*, and *Macrocystis pyrifera*. Alginates are composed of linear copolymers of two monomeric units, i.e.,  $\beta$ -D-mannuronic acid and  $\alpha$ -L-guluronic acid. These residues are arranged in homopolymeric and heteropolymeric blocks<sup>29</sup>. Similarly, ispaghula is a husk of seed obtained from *Plantago ovata* (Plantaginaceae). Husk consists of a xylan backbone with (1  $\rightarrow$  3) and (1  $\rightarrow$  4)  $\beta$ -D linkages and highly substituted with arabinose or aldobiouronic acid residue. The key reason behind its use in drug delivery may be its mucoadhesive property resulting from the high mucilage content (10–30%) of its husk. It swells and forms a mucilaginous gel by absorbing water and forming bonds with the mucus lining to get attached on its surface. It therefore provides a controlled release profile of drug delivery to improve bioavailability<sup>30,31</sup>.

Several investigations have been carried out to formulate alginate based mucoadhesive microcapsules or beads for controlled delivery of GCD. Biodegradable beads using alginate polymer by the ionotropic gelation method for controlling the systemic absorption of GCD have been prepared<sup>26</sup>. Mucoadhesive microcapsules of GCD using sodium alginate and mucoadhesive polymers such as sodium carboxymethyl cellulose, carbopol 934P, and hydroxy propylmethyl cellulose use the orifice-ionic gelation method<sup>32</sup>. Although the efficacy of alginate-ispaghula beads for delivery of metformin HCl has been investigated<sup>33</sup>, no attempt has been made to formulate a GCD loaded alginate based bead system using an ispaghula husk gel blend.

Although alginates are mucoadhesive, the cross-linked beads are usually fragile<sup>34,35</sup>. Incorporation of ispaghula husk strengthens the beads and enhances the mucoadhesive property as well. Therefore in the

present investigation, an attempt was made to prepare GCD loaded alginate-ispaghula mucoadhesive beads.

## MATERIALS AND METHODS

### Materials

GCD was donated by Lupin Ltd. (Mumbai). Ispaghula husk was purchased from a local market (Shree Baidyanath Ayurved Bhawan Pvt. Ltd., Kolkata). All chemicals and reagents used were of analytical grade.

### Preparation of alginate-ispaghula beads loaded with gliclazide

The GCD loaded alginate-ispaghula beads were prepared by the ionotropic gelation method using  $\text{CaCl}_2$  as a counter ion<sup>33</sup>. The dispersions of sodium alginate and ispaghula were prepared separately in deionized water. The active substance, GCD, was added to the ispaghula dispersion. Each dispersion was well mixed and homogenized (10 min at 1000 rpm) using a homogenizer (Remi Motors, Mumbai). The final alginate-ispaghula dispersion containing the polymer mixture (alginate and ispaghula husk) in water was kept at 2% w/v and the drug was ultrasonicated for 5 min for debubbling. The ratio of drug to polymer was maintained at 1:1 in all formulations. GCD loaded alginate-ispaghula beads were prepared by varying the ratio of sodium alginate to ispaghula husk (1:1, 2:1, and 2:3) The resulting dispersion was then added via a gauze needle (no. 23) into agitated  $\text{CaCl}_2$  solutions (2, 5, or 10% w/v concentration). The added droplets were retained in the  $\text{CaCl}_2$  solution for 20 min to complete the curing reaction and to produce spherical, rigid beads. The beads were collected by decantation, and washed repeatedly with deionized water. Collected beads were dried in a hot air oven at 40 °C for 48 h, and stored in a desiccator until used.

### Drug entrapment efficiency

Accurately weighed, 100 mg of beads were crushed using mortar and pestle. The crushed powders of drug-containing beads were placed in 500 ml of pH 7.4 phosphate buffer, and kept for 48 h at  $37 \pm 0.5$  °C with occasional shaking. The polymer debris formed after disintegration of the beads was removed by filtering through Whatman filter paper (No. 40). The drug content in the filtrate was determined using a UV-Vis spectrophotometer (Shimadzu) at 226.5 nm. The drug entrapment efficiency of the beads was calculated from the ratio of actual to theoretical drug content.

### Particle size measurement

To determine the particle size of GCD-loaded beads, 100 dry beads from each batch were measured using

an optical microscope (Olympus) with an ocular micrometer which was calibrated using a stage micrometer.

### Morphology analysis

The morphology of GCD-loaded alginate-ispaghula beads were examined under scanning electron microscopy (Hitachi S3400) after coating them with gold. The beads were mounted on a brass stub using double-sided adhesive tape and a thin layer of gold (3–5 nm) was applied for 75 s at 40 W under vacuum in an ion sputterer (Hitachi E1010).

### Evaluation of swelling behaviour

Swelling behaviour was studied by measuring the percentage water uptake by the beads. About 100 mg of beads were accurately weighed and placed in 100 ml of phosphate buffer (pH 7.4) and 0.1 N HCl (pH 1.2). Beads were removed from their respective swelling media after 8 h and weighed after drying the surface water using filter paper. The water uptake was calculated as the ratio of the increase in weight of beads after swelling to the dry weight.

### Mucoadhesion testing by in vitro wash-off method

The mucoadhesive properties of various formulations of GCD-loaded alginate-ispaghula beads were evaluated by the in vitro wash-off method<sup>20,30</sup>. Freshly excised pieces of goat intestinal mucosa (1 cm × 1 cm, collected from a slaughter house) were mounted on a glass slide (7.5 cm × 2.5 cm) using thread. About 50 beads were spread out on each piece of mucosa and then hung from the arm of the tablet disintegration test apparatus. The tissue specimen was given a regular up and down movement in a 1-l vessel containing 900 ml of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C. The adherence of beads was regularly observed. The beads that remained adhered to the mucosa were counted at regular intervals for up to 10 h.

### Ex vivo drug release study

The release of GCD from alginate-ispaghula beads adhered to fresh goat intestinal mucosa were performed in acidic (0.1 N HCl) as well as alkaline phosphate buffer (pH 7.4) media<sup>33</sup>. The GCD-loaded alginate-ispaghula beads were weighed accurately (100 mg) and spread out on the intestinal tissue specimen (goat intestinal mucosa) attached to a glass support. The beads were wetted by spraying the release medium. After hydration of the beads, the support was inserted in a 1-l beaker and kept inclined at an angle of

60° with the help of the beaker wall. The mucosa-containing beads were washed with freshly prepared release medium maintained at 37 ± 0.5 °C with a flow rate of 0.5 ml/min. The concentration of GCD in the washings was determined using a UV-Vis spectrophotometer (Shimadzu) at 227 nm.

### In vitro drug release study

The drug release studies from GCD-loaded alginate-ispaghula beads were carried out in vitro using a dissolution medium of HCl (0.1 N, pH 1.2) and phosphate buffer (pH 7.4) in USP Type-1 (basket) dissolution testing apparatus (Electro Lab India Limited, Mumbai) maintained at 37 ± 0.5 °C with a rotation rate of 50 rpm. An accurately weighed quantity of the microspheres (100 mg) was suspended in 900 ml of dissolution media. At preset time intervals, 5 ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution media, maintaining the sink condition throughout the experiment. The amount of drug released at different time intervals was found by using a UV-Vis spectrophotometer (Shimadzu) at 273 nm<sup>20</sup>.

## RESULTS AND DISCUSSION

The highest drug entrapment efficiency was observed in alginate-ispaghula beads at 10% w/v CaCl<sub>2</sub>. This may be due to the high degree of cross-linking by CaCl<sub>2</sub> upon increasing the amount of sodium alginate. When sodium alginate is placed into a solution of calcium chloride, sodium ions of the polymer are replaced by calcium ions to form calcium alginate which provides a cross-linking tendency to form the beads. The apparent gelation of calcium alginate matrices seemed to occur rapidly but the further rearrangement of the gel structure requires a long period<sup>10</sup>. The lowest drug entrapment efficiency of GCD was observed in alginate-ispaghula beads at low cross-linking agent concentration (2% w/v CaCl<sub>2</sub>). At lower concentrations of CaCl<sub>2</sub>, the beads showed larger pores due to insufficient cross-linking which results in lower drug entrapment<sup>7,18</sup>.

The incorporation of ispaghula husk gel with sodium alginate increased the particle size of the beads. This could be attributed to the increase in viscosity of the polymer solution with addition of ispaghula husk gel that in turn increased the droplet size during addition of the polymer solution to the cross-linking solution. It was observed that increasing the CaCl<sub>2</sub> concentration decreased the average particle size of the beads (Table 1). The higher cross-linking agent concentration may cause shrinkage of polymeric gel. Thereby the average particle size of the beads

**Table 1** Formulation charts of gliclazide-loaded alginate-ispaghula beads with drug entrapment efficiencies and particle sizes.

Formulation code <sup>a</sup>	S:I	CaCl <sub>2</sub> (% w/v)	Drug entrapment efficiency (%) <sup>b</sup>	Average particle size (µm) <sup>b</sup>
F1	2 : 3	2	50.5 ± 1.1	1249.8 ± 2.1
F2	2 : 3	5	61.7 ± 1.7	1122.6 ± 2.1
F3	2 : 3	10	68.1 ± 1.9	912.8 ± 1.2
F4	1 : 1	2	54.1 ± 0.7	1129.4 ± 1.4
F5	1 : 1	5	65.0 ± 1.6	1000.4 ± 1.0
F6	1 : 1	10	70.3 ± 2.0	896.7 ± 0.8
F7	2 : 1	2	60.1 ± 0.8	1098.4 ± 2.1
F8	2 : 1	5	70.6 ± 1.2	920.6 ± 1.2
F9	2 : 1	10	78.9 ± 1.7	833.4 ± 0.4

S:I = sodium alginate : ispaghula husk

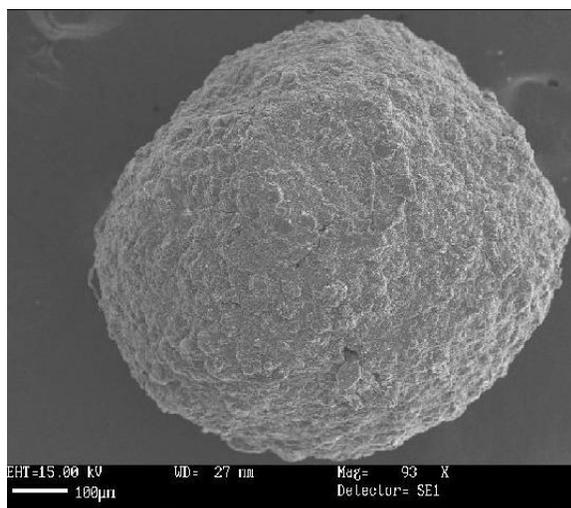
<sup>a</sup> The drug to polymer ratio of 1:1 was maintained in all formulations.

<sup>b</sup> (Mean ± SD, *n* = 3)

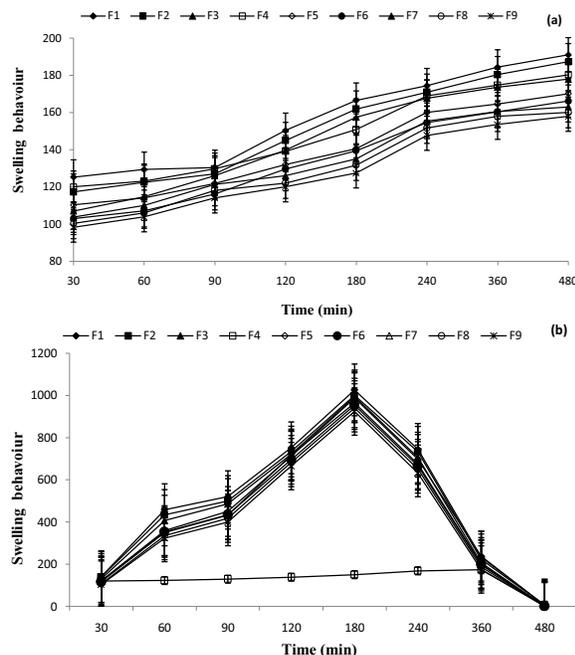
was decreased. Therefore, it is evident that the drug entrapment efficiencies of GCD-loaded alginate-ispaghula beads decreased with increasing size of the beads.

The negatively charged drops of alginate gel form beads by interaction with positively charged divalent calcium ions (Ca<sup>2+</sup>) in the CaCl<sub>2</sub> solution due to cross-linking between the carboxylate anions of alginate glucuronate and the calcium ions<sup>36</sup>. This results in the formation of spherical, stable alginate-ispaghula beads with rough surfaces when a mixture of sodium alginate gel, ispaghula husk gel, and GCD was dropped in solutions containing Ca<sup>2+</sup> ions in various concentrations<sup>23</sup> (Fig. 1).

Swelling behaviour of mucoadhesive polymeric



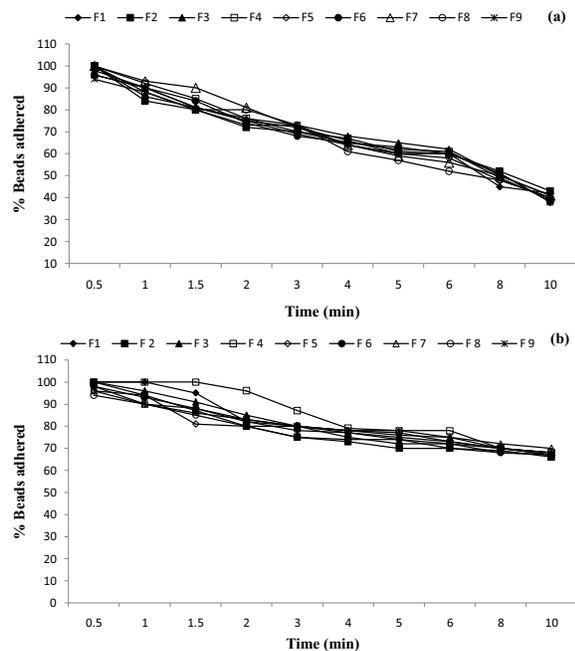
**Fig. 1** Scanning electron micrograph of gliclazide-loaded alginate-ispaghula beads.



**Fig. 2** Results of the swelling behaviour of alginate-ispaghula beads in (a) 0.1 N HCl (b) phosphate buffer. (Mean ± SD, *n* = 3).

beads is one of the major factors controlling the drug release from beads. For this reason, the swelling behaviour of GCD-loaded alginate-ispaghula was evaluated in phosphate buffer, pH 7.4 (intestinal pH) and 0.1 N HCl, pH 1.2 (gastric pH) (Fig. 2). The swelling index of alginate-ispaghula beads was lower in 0.1 N HCl than in phosphate buffer. Maximum swelling of beads was noticed at 2–3 h in phosphate buffer after which erosion and breakdown took place. Such behaviour may result from slow erosion of calcium cross-linked alginate microspheres due to slight degradation of alginate backbone into smaller fragments. In addition, the exchange of Ca<sup>2+</sup> ions in the microspheres with Na<sup>+</sup> ions of the phosphate buffer causes a sustained erosion of the microspheres which greatly increase the drug release rate in the phosphate buffer. These results clearly suggest that the desired gel particles will swell slightly in the stomach before they move to the upper intestine where the GCD is absorbed and the alginate-ispaghula beads begin to swell more and behave as matrices for the controlled release of the GCD in the intestine.

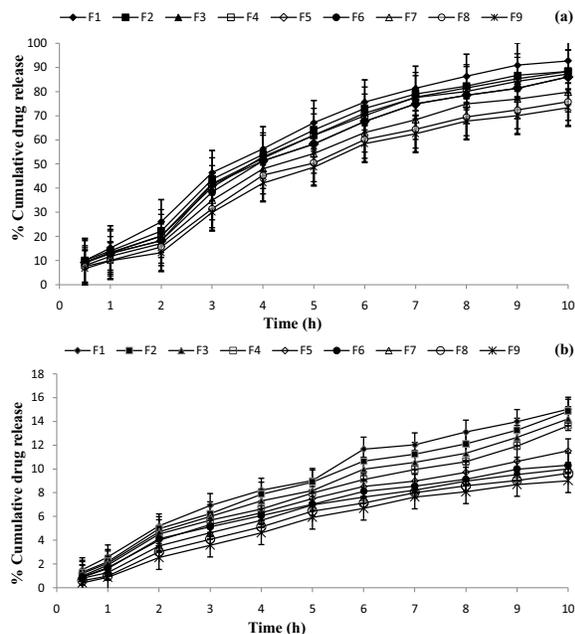
The beads exhibited good mucoadhesive properties in the ex vivo wash off test. In HCl and phosphate buffer, respectively, 66–70% and 38–43% of beads adhered to the goat intestinal mucosal tissue



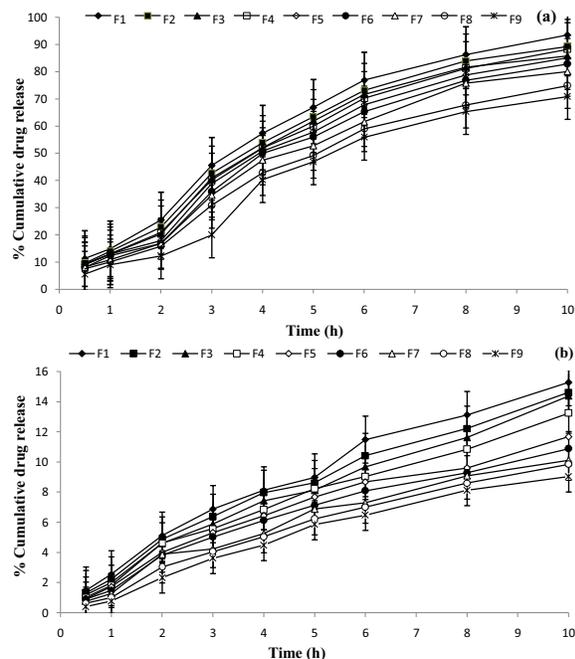
**Fig. 3** Mucoadhesivity of different formulations of beads in (a) phosphate buffer and (b) HCl (Mean  $\pm$  SD,  $n = 3$ ).

(Fig. 3). The ispaghula husk consists of hydrophilic residues like L-arabinofuranose or ionic residues like uronic acids which can bind with water at the surface or within the gel. The L-arabinofuranosyl groups may also bind non-specific water. The substituted flexible chains can diffuse into the mucosal layer and remain adhered for long periods<sup>33</sup>. The decreased mucoadhesion of beads in phosphate buffer may result from erosion of calcium ions which form a cross-linked structure<sup>7</sup>.

The release of GCD from beads was found to be in the range  $73.35 \pm 0.72\%$  to  $92.66 \pm 0.75\%$  in phosphate buffer, and  $9.01 \pm 0.54\%$  to  $15.03 \pm 0.60\%$  in HCl for 10 h (Fig. 4). However, the in vitro drug release studies were carried out in USP type-1 dissolution apparatus. The amount of GCD released from different beads was found to be  $70.86 \pm 0.92\%$  to  $93.4 \pm 1.1\%$  in phosphate buffer and  $9.03 \pm 0.09\%$  to  $15.28 \pm 0.10\%$  in HCl for 10 h (Fig. 5). The GCD release from beads was slow and dependent on both composition of the matrix (alginate and ispaghula husk gel) and the degree of cross-linking. The rate of GCD release from alginate-ispaghula beads formulated with a higher degree of cross-linking was more sustained than the beads formulated with a lower degree of cross-linking. Again, the release rate of GCD in acid was slower and more sustained. This may be due to the stability of alginate at lower pH<sup>37</sup> and the



**Fig. 4** Ex vivo release pattern of GCD from different formulations of beads adhered on fresh goat intestinal mucosa in (a) phosphate buffer (b) HCl. (Mean  $\pm$  SD,  $n = 3$ ).



**Fig. 5** In vitro release pattern of GCD from different formulations of alginate-ispaghula beads in (a) phosphate buffer (b) HCl. (Mean  $\pm$  SD,  $n = 3$ ).

conversion of calcium alginate to the insoluble, but swelling alginic acid<sup>38</sup>. The higher drug release in phosphate buffer may be due to the higher swelling rate of the alginate-ispaghula beads. In case of the beads with a alginate:ispaghula husk ratio of 2:3, the more hydrophilic property of the ispaghula husk gel containing residues like L-arabinofuranose, uronic acids binds better with water to form gel structure and swells more to produce a higher release profile of the drug.

## CONCLUSIONS

Based on swelling behaviour, mucoadhesivity and release studies, it can be concluded that the composition (2:3) of alginate-ispaghula mucoadhesive beads (F1) can be considered as an optimized formulation among the compositions studied. It can be recommended for further evaluation in suitable animal models for oral delivery of GCD for the treatment of non-insulin dependent diabetes mellitus.

## REFERENCES

1. Chowdary KPR, Srinivas L (2000) Mucoadhesive drug delivery systems: a status of current review. *Indian Drugs* **37**, 400–6.
2. Garg S, Vasir JK, Tambweker K (2003) Bioadhesive microspheres as a controlled drug delivery system. *Int J Pharm* **255**, 13–32.
3. Roldo M, Barbu E, Brown JF, Laight DW, Smart JD, Tsibouklis J (2006) Orally administered, colon-specific mucoadhesive azopolymer particles for the treatment of inflammatory bowel disease: An in vivo study. *J Biomed Mater Res A* **79**, 706–15.
4. Cashman J, Burt HM, Springate C, Gleave J, Jackson JK (2004) Camptothecin-loaded films for the prevention of postsurgical adhesions. *Inflamm Res* **53**, 355–62.
5. Chang JY, Oh YK, Kong HS, Kim EJ, Jang DD, Nam KT, Kim CK (2002) Prolonged antifungal effects of clotrimazole-containing mucoadhesive thermosensitive gels on vaginitis. *J Contr Release* **82**, 39–50.
6. Malaekheh-Nikouei B, Sajadi TSA, Jaafari MR (2008) Preparation, characterization, and mucoadhesive properties of chitosan-coated microspheres encapsulated with cyclosporine A. *Drug Dev Ind Pharm* **34**, 492–8.
7. Ikeda K, Murata K, Kobayashi M, Noda K (1992) Enhancement of bioavailability of dopamine via nasal route in beagle dogs. *Chem Pharmaceut Bull* **40**, 2155–8.
8. Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K (1984) Powder dosage form of insulin for nasal administration. *J Contr Release* **1**, 15–22.
9. Shinde JV, Mali KK, Dias RJ, Havaladar VD, Mahajan NS (2008) Insitu mucoadhesive nasal gels of metoclopramide hydrochloride: preformulation and formulation studies. *J Pharm Res* **1**, 88–96.
10. Kumar M, Misra A, Mishra AK, Mishra P, Pathak K (2008) Mucoadhesive nanoemulsion-based intranasal drug delivery system of olanzapine for brain targeting. *J Drug Target* **16**, 806–14.
11. Wu C, Qi H, Chen W, Huang C, Su C, Li W, Hou S (2007) Preparation and evaluation of a carbopol/HPMC-based in situ gelling ophthalmic system for puerarin. *Yakugaku Zasshi* **127**, 183–91.
12. Sakagami M, Kinoshita W, Sakon K, Sato JI, Makino Y (2002) Mucoadhesive beclomethasone microspheres for powder inhalation: their pharmacokinetics and pharmacodynamics evaluation. *J Contr Release* **80**, 207–18.
13. Jasti DB, Xiaoling LI, Cleary G (2003) Recent advances in mucoadhesive drug delivery system. *Business Briefing Pharmatech* 194-6.
14. Thorat YS, Modi VS, Dhavale SC (2009) Use of carbomers to design mucoadhesive microspheres for an anti- *H. pylori* drug, clarithromycin. *Int J PharmTech Res* **1**, 1421–8.
15. Chowdary KPR, Rao YS (2003) Design and in vitro and in vivo evaluation of mucoadhesive microcapsules of glipizide for oral controlled release: A technical note. *AAPS PharmSciTech* **4**, 87–92.
16. Cuna M, Alonso MJ, Torres D (2001) Preparation and in vivo evaluation of mucoadhesive microparticles containing amoxicillin-resin complexes for drug delivery to the gastric mucosa. *Eur J Pharm Biopharm* **51**, 199–205.
17. Nagahara N, Akiyama Y, Nakao M, Tada M, Kitano M, Ogawa Y (1998) Mucoadhesive microspheres containing amoxicillin for clearance of *H. pylori*. *Antimicrob Agents Chemother* **42**, 2492–4.
18. Liu Z, Lu W, Qian L (2005) In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin. *J Contr Release* **102**, 135–44.
19. Takishima J, Onishi H, Machida Y (2002) Prolonged intestinal absorption of Cephadrine with chitosan-coated ethylcellulose microparticles in rats. *Biol Pharmaceut Bull* **25**, 1498–502.
20. Sharma HK, Sarangi B, Pradhan SP (2009) Preparation and in-vitro evaluation of mucoadhesive microbeads containing Timolol Maleate using mucoadhesive substances of *Dillenia indica* L. *Arch Pharmaceut Sci Res* **1**, 181–8.
21. Harrower A (1994) Comparison of efficacy, secondary failure rate and complication of sulfonylureas. *J Diabetes Complications* **8**, 201–3.
22. Palmer K, Brogde R (1993) Gliclazide- an update of its pharmacological properties and therapeutic efficacy in non-insulin dependent diabetes mellitus. *Drugs* **46**, 92–125.
23. Mailhot J (1993) Efficacy and safety of gliclazide in the treatment of non-insulin dependent diabetes mellitus: a Canadian multicenter study. *Clin Therapeut* **15**, 1060–8.
24. Young JF, Wei GL, Lu R, Liu CX, Zheng BZ, Feng

- P (2006) Bioavailability of gliclazide sustained release tablet in healthy volunteers. *Asian J Pharmacodyn Pharmacokin* **2**, 150–60.
25. Hong S, Lee S, Lee Y, Chung S, Lee M, Shim C (1998) Accelerated oral absorption of gliclazide in human subjects from a soft gelatin capsule containing a PEG 400 suspension of gliclazide. *J Contr Release* **51**, 85–92.
  26. Al-Kassas RS, Al-Gohary OMN, Al-Faadhel MM (2007) Controlling of systemic absorption of gliclazide through incorporation into alginate beads. *Int J Pharm* **341**, 230–7.
  27. Bhardwaj TR, Kanwar M, Lal R, Gupta A (2000) Natural gums and modified natural gums as sustained-release carriers. *Drug Dev Ind Pharm* **26**, 1025–38.
  28. El-Kamel AH, Al-Gohary MN, Hosny EA (2003) Alginate-diltiazem hydrochloride beads: Optimization of formulation factors, in vitro and in vivo availability. *J Microencapsul* **20**, 211–25.
  29. Smidsrod O, Draget KI (1996) Chemistry and physical properties of alginates. *Carbohydr Eur* **14**, 6–13.
  30. Prajapati SK, Tripathi P, Ubaidulla U, Anand V (2008) Design and development of gliclazide mucoadhesive microcapsules: in vitro and in vivo evaluation. *AAPS PharmSciTech* **9**, 224–30.
  31. Sharma VK, Bhattacharya A (2008) Release of metformin hydrochloride from ispaghula-sodium alginate beads adhered on cock intestinal mucosa. *Indian J Pharmaceut Educ Res* **42**, 365–72.
  32. Kikuci A, Kawabuchi M, Sugihara M, Sakurai Y (1997) Pulsed dextran release from calcium-alginate beads. *J Contr Release* **47**, 21–9.
  33. Hudson A, Mitchell J, Davies M, Melia C (1995) Structure behavior of hydrophilic matrix sustained-release dosage form 3. The influence of pH on the sustained release performance and internal gel structure of sodium alginate matrices. *J Contr Release* **33**, 143–52.
  34. George M, Abraham TE (2006) Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan- a review. *J Contr Release* **114**, 1–14.
  35. Sandhu JS, Hudson J, Kennedy JF (1981) The gel nature and structure of the carbohydrate of Ispaghula husk (ex *Plantago ovata*) Forsk. *Carbohydr Res* **93**, 247–50.
  36. Yotsuyangi T, Ohkubo T, Ohaasi T, Kedak I (1987) Calcium-induced gelation of alginic acid and pH sensitive reswelling of dried gels. *Chem Pharmaceut Bull* **34**, 1555–63.
  37. Andreopoulos AG (1985) Stability of some soluble alginate solutions. *Biomaterials* **6**, 68–9.
  38. Sanap GS (2009) Formulation and evaluation of mucoadhesive beads of glipizide using 23 factorial design. *J Pharm Res* **2**, 934–8.