

# Development of natural gum based glipizide mucoadhesive microsphere

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## ABSTRACT

The objective of this study was to develop glipizide microsphere with natural gums. Guar gum and xanthan gum were used separately in different ratios as natural polymers. The microspheres were prepared by orifice ionic gelation method and they were characterized by scanning electron microscopy and particle size analysis. Among six formulations, microspheres of four formulations (F1-F4) were discrete, spherical and free flowing. There was an inverse relationship found between the amount of gum and surface smoothness in case of guar gum-containing microspheres while a forward relationship was found between amount of gum and surface smoothness in case of the microspheres containing xanthan gum. The size of the particles increased with increasing amounts of gum. It can be concluded that guar gum and natural gum at a ratio of 1:0.25 and 1:0.5 can be ideal for formulating natural gum based glipizide mucoadhesive microsphere.

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## INTRODUCTION

Recently, dosage forms that can target a specific body site have been the area of interest in formulation and development of the novel drug delivery systems (Parmar *et al.*, 2010). Microsphere is the carrier linked drug delivery system having particle size that ranges from 1-1000  $\mu\text{m}$  where a core of drug is dispersed in polymeric matrix and the core is surrounded by an outer layer of polymers (Prajapati *et al.*, 2008). The use of microspheres spread from simple oral dosage form to as far as cancer drug delivery (Rajput and Agrawal, 2010). Microspheres can be engineered in many ways to target the body sites accurately. In case of oral drug delivery, the success of these microspheres is limited due to their short residence time at the site of absorption (Patel *et al.*, 2005; Amin *et al.*, 2013). Therefore, it would be desirable to have them make an intimate contact with the absorbing membranes resulting in numerous advantages. This can be approached by combining mucoadhesion property to the microspheres. Mucoadhesion has been a topic of interest in

designing drug delivery systems to prolong the residence time of a dosage form at the site of absorption (Mathiowitz *et al.*, 1997; Harsha *et al.*, 2013). This mechanism of drug delivery offers efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs. Other advantages include rapid absorption due to enormous blood supply and good blood flow rates and protection of drug from degradation in the acidic environment of the gut (Patel *et al.*, 2005; Asane *et al.*, 2007). Type 2 diabetes mellitus (non-insulin dependent diabetes mellitus) is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency (Chiasson *et al.*, 2002). Despite the availability of new agents for treatment, oral sulfonylureas remain a cornerstone of therapy which is associated with triggering insulin release by inhibiting the  $K_{ATP}$  channel of the pancreatic beta cells (Gaba *et al.*, 2011). Sulfonylureas are appealing in the treatment because they are relatively inexpensive and are well tolerated. Glipizide is a second-generation sulfonylurea that can lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and typically prescribed to treat type II diabetes. Its biological half-life is short (2-5 h) and it possesses low gastric residence time (Verma and Garg, 2004;

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Patel *et al.*, 2005; Jamzad and Fassihi, 2006). Absorption of oral glipizide is potentially affected by food intake, delaying the absorption (Ismail, 2009). Keeping in close contact with the mucosal layer (the unstirred layer) can facilitate its faster absorption. Natural gums are cheap, biodegradable, have good sticky property and do not require any organic solvents (Jani *et al.*, 2009). Microspheres of glipizide have been prepared with synthetic polymers in recent researches (Behera *et al.*, 2008; Phutane *et al.*, 2010).

In this study, we attempted to develop formulations of glipizide microspheres with natural gums by orifice ionic gelation method which is simple and cost effective. We used two different natural gums separately in different amounts to formulate mucoadhesive microsphere of glipizide. Guar gum and xanthan gum were used as mucoadhesive polymers. Guar gum is extracted from the seed of the leguminous shrub *Cyamopsis tetragonoloba*. It is a reverse polysaccharide consisting of monosaccharide mannose and galactose units. Guar gum is hydrophilic and soluble both in cold and hot water (Soppirnath *et al.*, 2002; Gaba *et al.*, 2011). Xanthan gum is a polysaccharide secreted by the bacterium *Xanthomonas campestris*.

It is soluble in water and its solutions are neutral (Garcia-Ochoa *et al.*, 2000). Both the gums have good mucoadhesive and biodegradable properties and require low concentration to become sticky very quickly, making them ideal for mucoadhesive carriers (Jani *et al.*, 2009).

## MATERIALS AND METHODS

### Materials

Glipizide and Sodium alginate were purchased from Technodrugs & Intermediates (P) Ltd., India and Merck KGaA, Germany, respectively. Guar gum and xanthan gum were purchased from Koster Keunen Inc., U.S.A. Calcium chloride was procured from Wilfrid Smith Ltd., UK.

### Preparation of mucoadhesive microsphere

Glipizide Microspheres were prepared according to the method used by Mankala *et al.* (2011) by using different ratios of drug, sodium alginate, guar gum and xanthan gum (Table 1). Sodium alginate was dissolved in deionized water to form a homogeneous solution (2% w/v). Guar gum and xanthan gum were dissolved separately with deionized water to get viscous and sticky solutions.

The pure drug was dispersed in the solution of gum and then sodium alginate solution was added to it with vigorous stirring until formation of an even dispersion. The resulting dispersion was then extruded drop wise into the calcium chloride solution (10% w/v) through a 23G syringe. The formed beads were retained in the calcium chloride solution for 15 minutes to complete the formation of spherical rigid microspheres. They were collected by decantation, washed with petroleum ether and dried at 45°C for 12 hours.

### Particle size

Particle size of the prepared microspheres was determined by standard sieving method. Microspheres were weighed and spread on the upper sieve of an automatic sieve shaker (AS 200, Germany). The amount passed and retained on each sieve was weighed. The average particle size of each formulation was calculated using the following formula,

$$\text{Mean particle size} = \frac{\sum(\text{mean particle size of the fraction} \times \text{weight fraction})}{\sum(\text{weight fraction})}$$

### Shape and surface morphology

Shape and surface morphology of the microspheres were observed under electron scanning microscopy (SEM). Small amount of microspheres was spread on the glass stub and the stub containing the sample was placed in the scanning electron microscope (JEOL JSM – 6490 LA, Japan). Then SEM photographs were taken at an acceleration voltage of 20 kV. The drug-loaded microspheres were evaluated for their sphericity and surface smoothness.

## RESULTS

Microspheres were formulated successfully with good sphericity except formula F5 and F6, which contained the highest amount of gum. They were very irregular in shape and their sizes were over 1000 µm. The performed tests indicated that formulations, containing lower amount of gum, had smaller particle size than the formulations that contained higher amount of gum (Table 1).

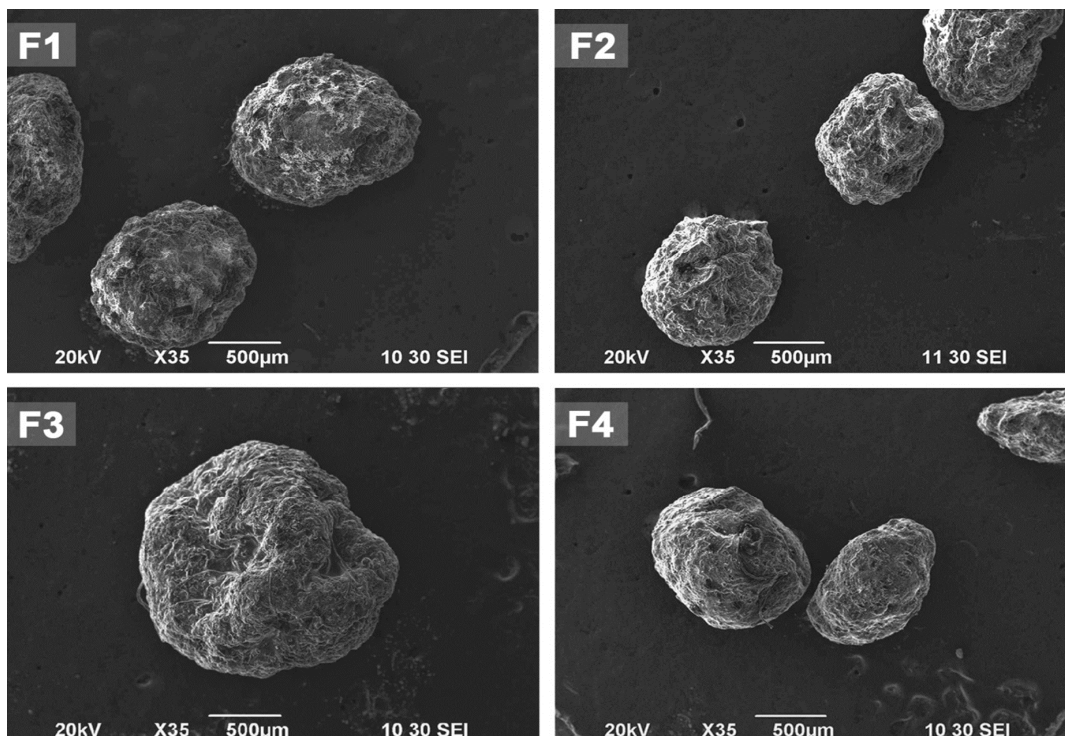
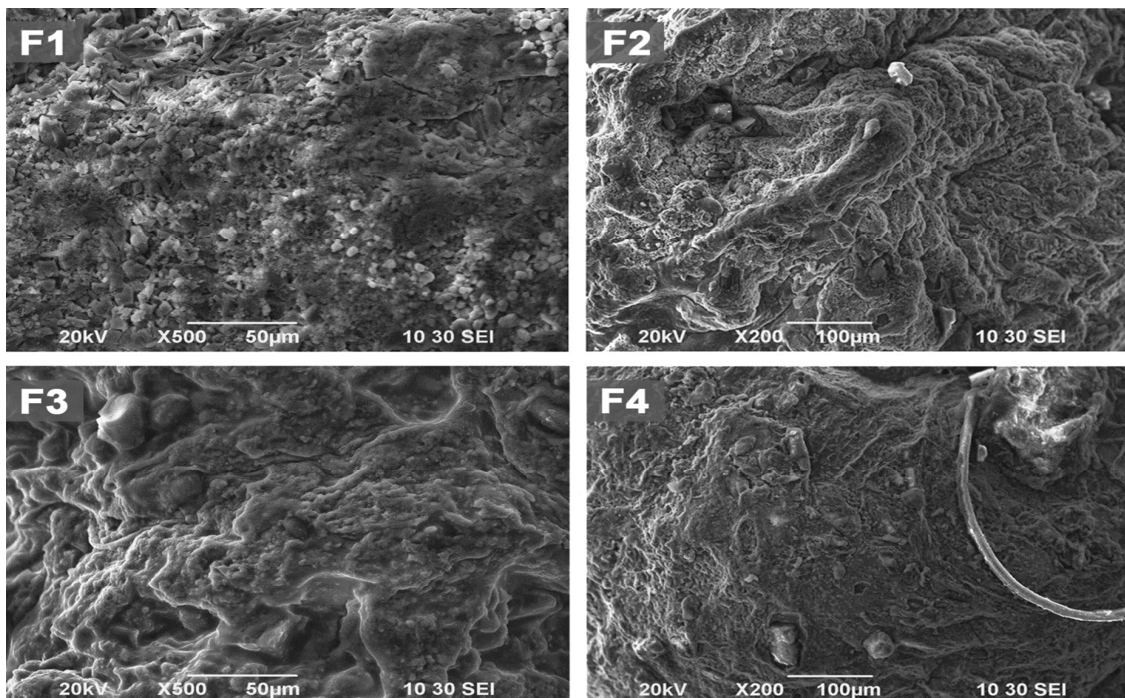
The SEM images illustrated that guar gum-containing microspheres were slightly more spherical than xanthan gum-containing microspheres. Sphericity decreased with increasing amount of gum (Figure 1). In case of guar gum, microspheres had smoother surface with lower amount of gum. On the other hand, xanthan gum-containing formulations showed better smoothness in increased amount of gum (Figure 2).

## DISCUSSIONS

Increased amount of gum might have interfered with the crosslinking process between sodium alginate molecules by calcium ions. Crosslinking of alginate molecules by divalent calcium ions of calcium chloride solution results in the formation of a closer network (calcium alginate coat) surrounding the beads. As we increased the amount of gum, extent of crosslinking decreased because the amount of sodium alginate remained same and additional amount of gum interfered with the crosslinking process between alginates molecules by calcium ions, being present on the surface. It might cause the irregular shape of the formulations that contained an increased amount of gum. As additional amount of gum increased the viscosity of the solution, so the drops became larger resulting in increased particle size.

**Table. 1:** Composition and characteristics of the natural gum based glipizide mucoadhesive microspheres.

Formulations	Glipizide (mg)	Sodium alginate (mg)	Guar gum (mg)	Xanthan gum (mg)	Crosslinking agent (CaCl <sub>2</sub> ) w/v	Coat composition (alginate-gum ratio)	Sphericity	Particle size (μm)
F1	50	50	12.5	-	10%	1:0.25	Spherical	675.21
F2	50	50	-	12.5	10%	1:0.25	Spherical	828.87
F3	50	50	25	-	10%	1:0.5	Spherical	753.23
F4	50	50	-	25	10%	1:0.5	Spherical	894.72
F5	50	50	37.5	-	10%	1:0.75	Very irregular	1002.08
F6	50	50	-	37.5	10%	1:0.75	Very irregular	1042.11

**Fig. 1:** SEM images of the prepared microspheres showing their shapes (F1-F4).**Fig. 2:** Surface morphology of the microspheres from different batches (F1-F4).

## CONCLUSION

Mucoadhesive microspheres of glipizide with natural gums were successfully prepared by orifice ionic gelation method. Among six formulations, four formulations were found to be spherical and free flowing. The ratio of sodium alginate and gum at 1:0.25 and 1:0.5, were found to be optimum for the formulation of mucoadhesive microsphere. F1 and F4 possessed the best results among all the formulations in terms of surface smoothness and shape. Therefore, guar gum and xanthan gum can be considered as promising materials for designing glipizide mucoadhesive microspheres and further studies can be carried out.

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