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## **Formulation and *invitro* evaluation of mucoadhesive microcapsules of Glipizide with gum Kondagogu**

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### **ABSTRACT**

*Mucoadhesive microcapsules are proposed for the antidiabetic drug glipizide, to obtain controlled release. Glipizide microcapsules with a coat consisting of alginate and gum kondagogu were prepared by employing ionic gelation process and emulsification ionotropic gelation process. The microcapsules were evaluated for flow properties, Carr's index, hausner ratio, micro encapsulation efficiency, drug release characteristics, surface characteristics; compatibility studies mucoadhesive properties and in-vivo hypoglycemic activity. As hausner ratio was less than 1.25 and Carr's index values were less than 16 from both the methods, hence they were found to be free flowing. Sharp endothermic peaks were noticed from the microcapsules formulated with two different techniques at 215°C indicating the compatibility between the drug and the polymer gum kondagogu. Glipizide release from the microcapsules was slow and followed zero order kinetics ( $r > 0.98$ ) and followed non-fickian ( $n$  value 0.5 to 1) release and depended on the coat: core ratio and the method employed in the preparation of microcapsules. Among the two methods emulsification ionotropic gelation method was found to be more suitable for slow and complete release of glipizide over a long period of time. These microcapsules exhibited good mucoadhesive property in the in-vitro wash-off test.*

**Key words:** Emulsification Gelation Technique, Glipizide, Gum kondagogu, Ionic Gelation Technique.

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### **INTRODUCTION**

Micro encapsulation by various polymers and its applications are described in standard textbooks [1, 2]. Micro encapsulation has been accepted as a process to achieve controlled release and drug targeting. Mucoadhesion has been a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or

absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve the bioavailability of drugs [3]. Several studies reported drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes. Amongst the polymers used for micro encapsulation alginate has gained much attention since it is nontoxic, biodegradable and can be prepared by a safe technique avoiding organic solvents [4]. Ionic gelation method is not practical because of the blockage of the spraying nozzle and the low yield of the product. Hence ionotropic gelation of sodium alginate by the emulsification technique was developed as an alternative approach [5]. Gum Kondagogu is natural gum exudates obtained from stems and branches of "*Cochlospermum gossypium*" and belongs to Bixaceae family [6]. Gum Kondagogu is a negative charged colloid and a high-molecular weight complex acidic polysaccharide. The general utility of Gum Kondagogu is based on its viscosity [6]. It was successfully evaluated for its suitability in the preparation of hydrophilic matrices [6], mini-matrices [6], microcapsules [6] and transdermal patches [6]. Glipizide, an effective antidiabetic that requires controlled release owing to its short biological half-life of  $3.4 \pm 0.7$  hours, [7] was used as the core in microencapsulation. The purpose of this research was to formulate and systemically evaluate *in-vitro* and *in-vivo* performance of mucoadhesive microcapsules of glipizide.

## EXPERIMENTAL SECTION

### **Materials:**

Glipizide U.S.P was kindly gifted by M/s Natco Fine Pharmaceuticals, Hyderabad. Girijan Co-operative Corporation Ltd (Visakhapatnam, India) supplied Gum Kondagogu (Grade1). Sodium alginate (having a viscosity of 5.5 cps in a 1% w/v aqueous solution at 25 OC), calcium chloride and heavy liquid paraffin were procured from s. d. Fine Chemicals Pvt. Ltd., Mumbai, India. All chemicals used were of analytical grade.

### **Preparations of Microcapsules:**

Sodium alginate (1.0 g) and gum kondagogu (1.0 g) were dissolved in purified water (32 mL) to form a homogeneous polymer solution. The active substance, Glipizide (2.0 g), was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (15% w/v) solution (40 mL) through a syringe with a needle of size no 18. The added droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce spherical rigid microcapsules having coat: core ratio 1:1 (MC1). Similarly microcapsules with coat:core ratio 1.5:1 (MC2) and 2:1 (MC 3) were also prepared. The microcapsules were collected by decantation and dried over night at room temperature.

In emulsion gelation technique polymer gum kondagogu (1 g) and sodium alginate (1 g) were dissolved in 32 ml of water. The drug (2 g) was added to the polymer solution and mixed thoroughly. The polymer dispersion was then added in a thin string to 50 ml of heavy liquid paraffin contained in a 250 ml beaker, while stirring at 500 rpm to emulsify the added dispersion as fine droplets. A Remi make medium duty stirrer with speedometer (RQ 121/D) was used for stirring. Then 20 ml of calcium chloride solution (15% w/v) was transferred into the emulsion while stirring at 500 rpm for 15 min to produce spherical microcapsules. The microcapsules were collected by decantation and washed repeatedly with petroleum ether. The product was then air dried to obtain discrete microcapsules. Different proportions of coat: core materials namely 1:1 (MC4), 1.5:1 (MC5) and 2:1 (MC6) were used to prepare microcapsules.

**Evaluation of Microcapsules:***Size Distribution and Size Analysis [8]:*

For size distribution analysis, 250 mg of the microcapsules of different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed. The mean particle size of the microcapsules was calculated by the formula.

$$\text{Mean Particle Size} = \frac{\sum(\text{Mean Particle Size of the Fraction} \times \text{Weight Fraction})}{\sum(\text{Weight Fraction})}$$

*Flowability of Microcapsules [9]:*

The static angle of repose was measured according to the fixed funnel and free standing cone method. The bulk density of the mixed microcapsules, the Hausner's ratio and Carr's index, were calculated from the poured and tapped bulk densities of a know weight of sample using a measuring cylinder. The following formulas were used for calculating

$$\text{Hausner ratio} = \frac{D_p}{D_t}$$

$$\text{Carr's index} = \frac{(D_p - D_t)}{D_p} \times 100$$

Where  $D_p$  (Poured density) = Weight of the microcapsules  $\div$   $V_p$  (Poured Volume),

$D_t$  (tapped density) = Weight of the microcapsules  $\div$   $V_t$  (tapped Volume).

*Drug Content Evaluation:*

Glipizide content in the microcapsules was estimated by a UV spectrophotometric (UV-1700, Shimadzu, Japan) method based on the measurement of absorbance at 223 nm in phosphate buffer of pH 7.4 [10]. Microcapsules containing equivalent to 100mg of glipizide were crushed to fine powder in a mortar and extracted with 50ml of methanol. It was filtered and made up to the volume of 100 ml with methanol. One ml of the sample was taken and made up the volume to 10ml with phosphate buffer pH 7.4 and the absorbance was measured at 223nm. The procedure was repeated with pure glipizide. The absorbance values from the pure drug and glipizide microcapsules were treated statistically by t-test. The absorbance values were not differed significantly ( $p > 0.1$ ) indicating non interference of gum kondagogu in the estimation of glipizide. The method was validated for linearity, accuracy, and precision. The method obeyed Beer's law in the concentration range 1 to 10 $\mu$ g/ml. When a standard drug solution was assayed repeatedly ( $n = 6$ ), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6% and 0.8%, respectively.

*Microencapsulation Efficiency:*

Microencapsulation efficiency was calculated using the following formula.

$$\text{Microencapsulation Efficiency} = \frac{\text{Estimated Percentage Drug Content}}{\text{Theoretical Percentage Drug Content}} \times 100$$

*Scanning Electron Microscopy (SEM):*

The samples for the SEM analysis were prepared by sprinkling the microcapsules on one side of the double adhesive stub. The stub was then coated with fine gold dust. The microcapsules were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 15kv.

*Differential Scanning Calorimetry:*

Differential scanning calorimetry (DSC) thermograms were obtained by a differential scanning calorimeter (DSC 220C, Seiko, Tokyo, Japan) at a heating rate of 10°C/min from 30 to 300°C in a nitrogen atmosphere 20ml/min with a sample weight of 3mg.

*Infrared Spectroscopic Studies:*

Fourier-transformed infrared (FT-IR) spectra were obtained on a Perkin Elmer 2000 FT-IR system (Perkin Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm<sup>-1</sup> and the resolution was 1 cm<sup>-1</sup>.

*In Vitro Release Studies:*

Microcapsules containing equivalent to 10mg of glipizide were packed in hard gelatin capsule and subjected to in-vitro drug release studies. Release of glipizide from the capsule was studied in phosphate buffer of pH 7.4 (900 mL) using a United States Pharmacopoeia (USP) XXIV 8-station dissolution rate test apparatus (Model TDT - 08L, M/s Electro lab, Mumbai, India) with a rotating paddle stirrer at 50 rpm and 37°C ± 1°C as prescribed for glipizide tablets in USP XXIV. A sample of microcapsules equivalent to 10 mg of glipizide was used in each test. Samples of dissolution fluid were withdrawn through a filter (0.45 µm) at different time intervals and were assayed at 223 nm for Glipizide content using a Shimadzu UV-1700 double beam spectrophotometer (Shimadzu Corporation, Japan). The drug release experiments were conducted in triplicate (n = 3). In-vitro drug release studies were also conducted for the marketed formulation (Glitop RPG Pharmaceuticals Mumbai INDIA). The release data obtained were fitted to zero order [11], first order [12], Higuchi [13] and Korsmeyer peppas [14-16] equations to determine the corresponding release rate and mechanism of drug release from the mucoadhesive microcapsules.

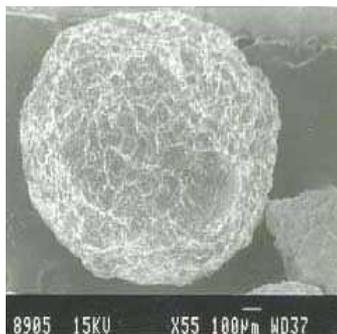
*Bioadhesive Evaluation:*

The mucoadhesive property of the microcapsules was evaluated by an in vitro adhesion testing method known as the wash-off test. The bioadhesiveness of these microcapsules was compared with that of non bioadhesive material, ethylene vinyl acetate microcapsules. Freshly excised pieces of intestinal mucosa (2×2 cm) from sheep were mounted onto glass slides (3×1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up-and-down movement in the test fluid at 37°C contained in a 1 L vessel of the machine. At the end of 30 minutes, at the end of 1 hour, and at hourly intervals up to 12 hours, the machine was stopped and the number of microcapsules still adhering to the tissue was counted [10]. The test was performed at both gastric pH (0.1N HCl, pH 1.2) and intestinal pH (phosphate buffer, pH 7.4).

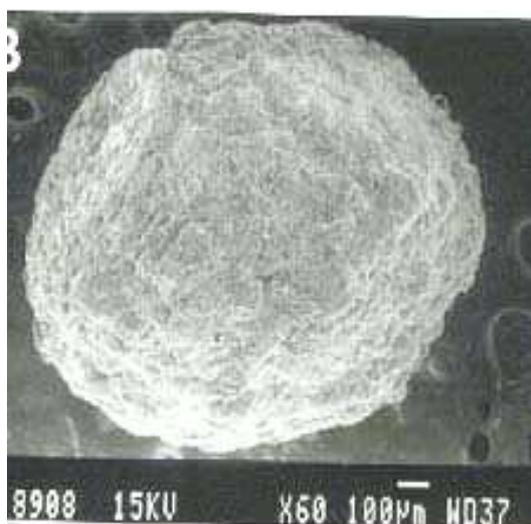
**RESULTS AND DISCUSSION**

Microcapsules of glipizide could be prepared by ionic gelation process and emulsification gelation process employing gum kondagogu as the polymer. The microcapsules were found to be discrete spherical and free flowing. The size analysis of different batches of microcapsules showed that about 70% of the prepared microcapsules were in the size range of 870 µm (-16 to +20). The size distribution of microcapsule was found to be normal in all the batches. The microcapsules imparted good flow ability as indicated by angle of repose (21.620 - 25.660), the Carr's index (12 g cm<sup>-3</sup> - 16 g cm<sup>-3</sup>) and the Hausner Ratio (1.1 -

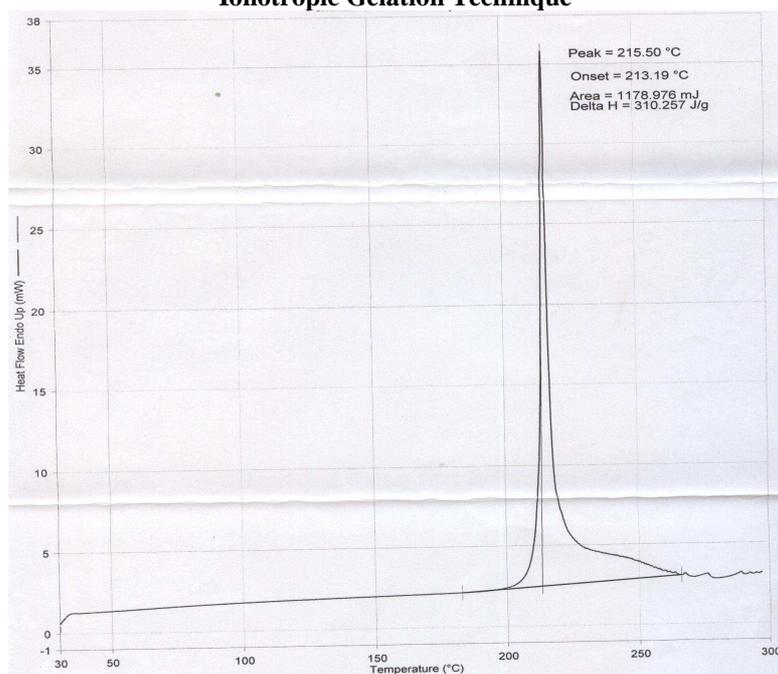
1.2). The SEM photographs indicated that the microcapsules were spherical and completely covered with the coat polymer (Fig 1 and 2).



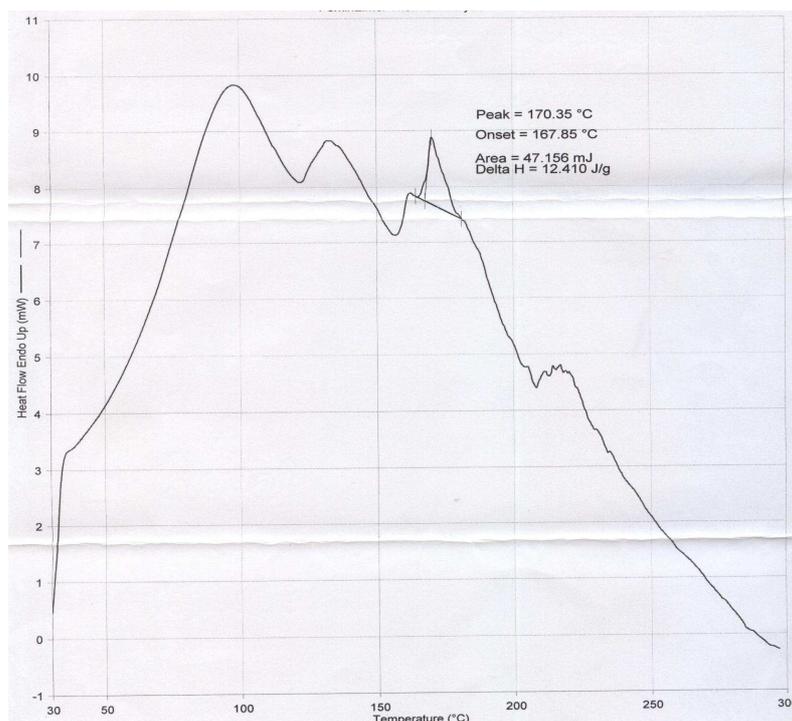
**Fig 1: SEM Photograph of Glipizide Microcapsules Formulated with Gum Kondagogu by Ionic Gelation Technique**



**Fig 2: SEM Photograph of Glipizide Microcapsules Formulated with Gum Kondagogu by Emulsification Ionotropic Gelation Technique**

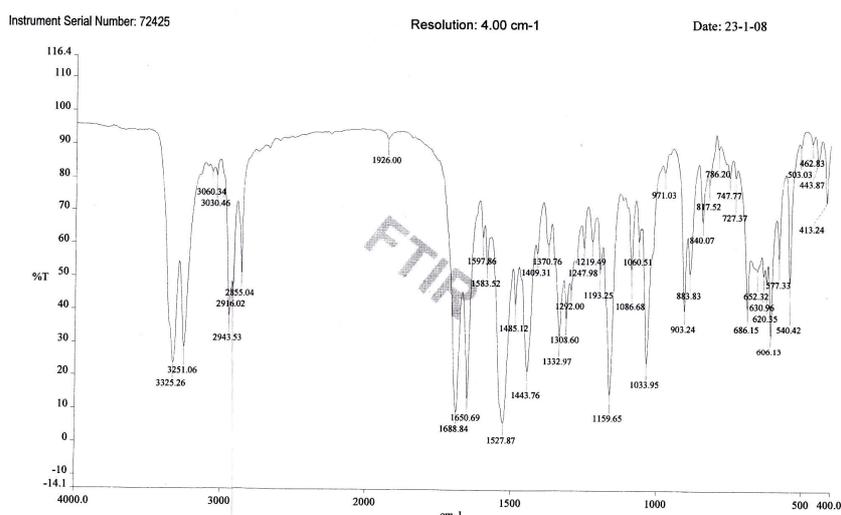


**Fig 3: DSC Thermogram of Glipizide**



**Fig-4: DSC Thermogram of Microcapsule (MC6)**

Low coefficient of variation (< 2.0%) in percent drug content indicated uniformity of drug content in each batch of microcapsules. The Microencapsulation efficiency was in the range of 89% to 95%, with various products. Selected DSC thermogram of the drug and microcapsule were shown in Fig 3 and Fig 4 respectively. The DSC thermogram of glipizide showed a short endothermic peak at 215.50°C the microcapsules showed an endothermic peak of drug at 170.35°C indicating a slight change in terms of shifting towards the lower temperature. It has been reported from the graphs that the quantity of material used affects the peak shape and enthalpy. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and excipients which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility.



**Fig 5: IR Spectra of Glipizide**

The IR spectrum of glipizide is shown in Fig 5 and the following characteristic bands were observed 1689 (- C=O, Amide), 1651 (- C=O, Urea), 1528 (Ar- CH, stretching), 1433 (Ar-

CH, bending), and 1333 and 1159 cm<sup>-1</sup> (- SO<sub>2</sub>NH). The IR spectrum of glipizide microcapsules (Fig 6) showed the presence of characteristic bands of glipizide. Thus, any change in the structure of glipizide was ruled out, and it was concluded that there is no chemical incompatibility between glipizide and gum kondagogu.

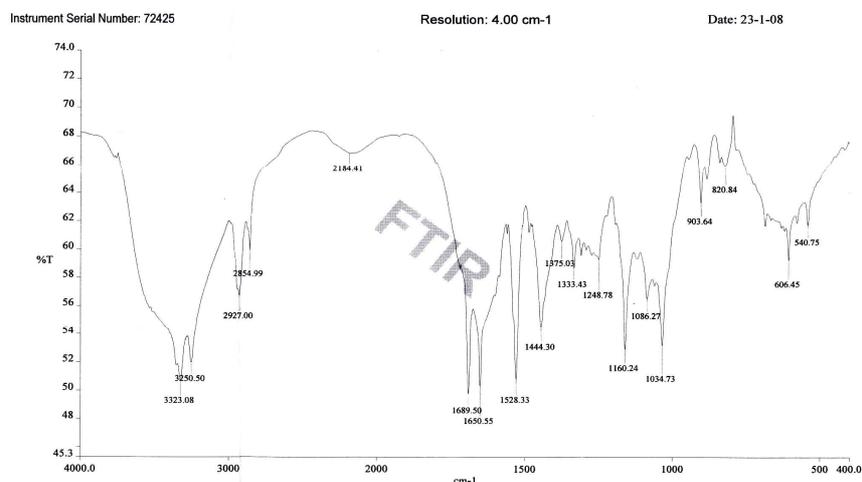


Fig 6: IR Spectra of Glipizide Microcapsules Prepared with Gum Kondagogu.

Glipizide release from the microcapsules was studied in phosphate buffer (pH 7.4) for 12 hours as prescribed for glipizide tablets in USP XXIV. Glipizide release from the microcapsules was slow, spread over extended period of time and depended on the composition of the coat and method employed for the preparation of microcapsules (Figure 7).

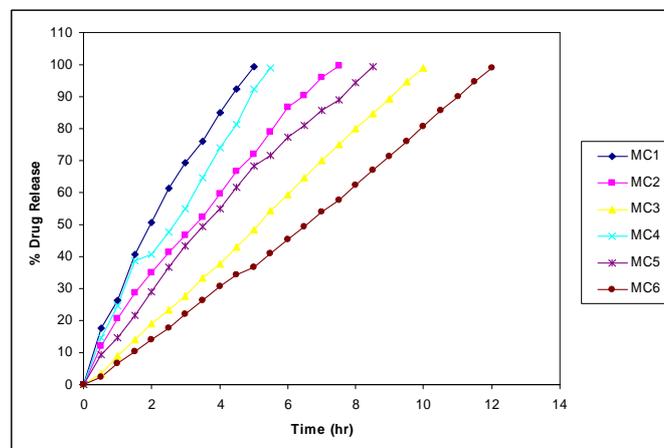


Fig 7: Dissolution Profiles of the drug release from the mucoadhesive microcapsules of glipizide.

Table 1: Correlation coefficient (R) values in various kinetic models tested to describe drug release from the mucoadhesive microcapsules of glipizide

Formulation	Correlation Coefficient Values				n
	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas Model	
MC <sub>1</sub>	0.9821	0.8455	0.9714	0.9974	0.7734
MC <sub>2</sub>	0.9893	0.8258	0.9601	0.9993	0.7877
MC <sub>3</sub>	0.9994	0.8203	0.9146	0.9987	1.0870
MC <sub>4</sub>	0.9897	0.8190	0.9558	0.9951	0.7827
MC <sub>5</sub>	0.9894	0.8444	0.9562	0.9982	0.8616
MC <sub>6</sub>	0.9978	0.8090	0.9031	0.9988	0.8359

n: Diffusional exponent derived from Peppas equation

The model that best fits the release data was evaluated by correlation coefficient (r). The correlation coefficient (r) value was used as criteria to choose the best model to describe the drug release from the microcapsules. The r value in various models is given in Table 1.

In most of the formulated microcapsules the r values were higher in zero order models than that of first order model indicating the drug release from the most of the microcapsules was according to zero order kinetics. To analyze the mechanism of release of drug from the microcapsules the equation,  $Q = Kt^n$  was used, where Q is the percentage of drug released; t is the release time; K is a constant incorporating structural and geometric characteristics of the release device, n is the release exponent indicative of mechanism of release. When n approximates to 0.5, a fickin/diffusion control release is implied, where  $0.5 < n < 1$  non fickin transport and  $n = 1$  for zero order release [17]. The drug release mechanism from the microcapsules was non fickin transport as n value is in between 0.77 to 1. The drug release from the marketed formulation followed zero order kinetics and controlled by Korsmeyer-Peppas mechanism. The release rate constants observed from the selected formulation (MC6) and marketed formulation were found to be 13.7614 mg/hr and 11.2183 mg/hr respectively. These two formulations were not differed in the in-vitro release rate ( $p > 0.1$ ).

Microcapsules with a coat consisting of alginate and gum kondagogu exhibited good mucoadhesive properties in the in vitro wash-off test when compared to non-mucoadhesive material, ethylene vinyl acetate microcapsules. The wash-off was slow in the case of microcapsules containing alginate-gum kondagogu as coat when compared to that of ethylene vinyl acetate microcapsules (Table 2). The wash-off was faster at gastric pH than at intestinal pH. The results of the wash-off test indicated that the microcapsules had fairly good mucoadhesive properties.

**Table 2: In vitro Wash-Off Test Data of Glipizide Microcapsules Formulated with Gum Kondagogu by Employing Different Techniques**

Formulation	Percent of Alginate Beads Adhering to Tissue at 5 Times (hr)									
	0.1 N HCl, pH 1.2					Phosphate Buffer, pH 7.4				
	1	2	4	6	8	1	2	4	6	8
MC <sub>1</sub>	90 (1.8)*	64 (1.2)	52 (1.0)	30 (1.6)	18 (1.5)	94 (0.5)	84 (1.0)	68 (1.3)	46 (1.4)	32 (1.5)
MC <sub>2</sub>	92 (0.7)	72 (1.2)	56 (1.8)	40 (1.4)	22 (2.0)	96 (0.5)	90 (0.8)	80 (1.2)	72 (1.0)	66 (1.5)
MC <sub>3</sub>	94 (1.0)	78 (1.8)	60 (1.1)	44 (1.5)	30 (1.0)	98 (0.5)	92 (1.0)	84 (1.2)	76 (1.8)	70 (1.2)
MC <sub>4</sub>	94 (1.5)	72 (1.8)	56 (1.5)	38 (1.2)	22 (1.8)	96 (0.5)	88 (1.0)	78 (1.2)	62 (1.8)	56 (1.5)
MC <sub>5</sub>	96 (1.8)	80 (1.2)	64 (1.8)	48 (2.0)	30 (1.8)	98 (0.5)	94 (1.0)	90 (1.5)	82 (1.5)	76 (2.0)
MC <sub>6</sub>	98 (1.5)	84 (1.8)	74 (1.2)	52 (1.8)	40 (2.0)	100 (0.5)	94 (1.0)	87 (1.0)	79 (1.0)	71 (1.0)
EVA	95 (1.8)	60 (2.0)	20 (1.0)	--	--	96 (2.0)	68 (2.5)	28 (2.0)	--	--

\*Figures in parentheses are coefficient of variation (CV) values.

## CONCLUSION

Thus, large spherical microcapsules with a coat consisting of alginate and a mucoadhesive polymer gum kondagogu could be prepared by an emulsion gelation process. The microcapsules exhibited good bioadhesive properties in an in vitro test. By comparing the

marketed glipizide tablets with glipizide release from the bioadhesive microcapsules was slow and extended over longer periods of time and depended on composition of the coat. Drug release was diffusion controlled and followed zero-order kinetics. These bioadhesive microcapsules are, thus, suitable for oral controlled release of glipizide.

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