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PREPARATION AND EVALUATION OF GLIPIZIDE MICROSPHERES USING MUCOADHESIVE POLYMERS

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ABSTRACT: Microspheres are the carrier linked drug delivery system in which particle size ranges from 1-1000 μm . Microspheres constitute an important part of drug delivery systems by virtue of their small size and reliable means to deliver the drug to the target site with specificity. However, the advantages of microspheres are limited due to their short residence time at site of absorption. This can be achieved by coupling bioadhesion characteristics to microspheres and developing “mucoadhesive microspheres”. Glipizide is an oral hypoglycemic drug with short half-life. So to provide prolonged action glipizide microspheres were prepared by ionic gelation technique using different concentration of mucoadhesive polymers. The prepared microspheres were characterized for various physicochemical parameters such as particle size, percentage yield, encapsulation efficiency, scanning electron microscopy, *in-vitro* drug release and kinetics study. The *in-vitro* drug release studies were performed in buffer media and shown the controlled release pattern of drug up to 10 hours. Drug release from the microspheres was found following zero order release kinetics with non-fickian release mechanism. The satisfactory results were obtained in all prepared formulations and based on the results F6 was best one when compared to other formulations.

INTRODUCTION: Glipizide is an oral hypoglycemic agent used in management of non-insulin dependent diabetes mellitus. Among people who are suffering from long term disorders, the major were categorized under diabetes so a dosage form is required to provide continuous therapy with high margin of safety and such dosage form can be achieved by microencapsulation.

Glipizide is rapidly eliminated from the blood, its plasma elimination half-life is 2-5 hours, and so frequent administration was required to maintain therapeutic plasma level. To overcome these problem mucoadhesive microspheres were found to be the effective dosage form. The primary objective using mucoadhesive microspheres is to achieve a substntial increase in the length of stay of drug in the GI tract ¹.

The aim of this present work was to develop prolonged release dosage form to be used for targeted and controlled release drug delivery. Preparation of mucoadhesive microspheres of Glipizide helps in releasing drug in a controlled manner for the treatment of diabetes mellitus.

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Glipizide whose physicochemical properties and short half-life make it a suitable candidate for colonic drug delivery. Thus an attempt was made to develop microspheres by ionic orifice gelation technique using synthetic mucoadhesive polymers like Sodium alginate, HPMC K4 M, PEG4000 and Ethyl cellulose and to study effect of polymer composition on various physicochemical parameters and release pattern².

MATERIALS AND METHOD: Glipizide was obtained as a gift sample from Natco Pharmaceuticals Ltd, (Hyderabad, India). Sodium alginate, HPMC K 4 M, PEG 4000, Ethyl cellulose and calcium chloride were procured from S.D Fine chemicals, India. All other reagents used were of analytical grade.

TABLE1. COMPOSITION OF MICROSPHERES

Ingredients	Formulation					
	F1	F2	F3	F4	F5	F6
Glipizide	500	500	500	500	500	500
Sodium Alginate	500	250	250	250	250	250
PEG 4000	-	250	-	-	125	-
Ethyl Cellulose	-	-	250	-	125	125
HPMC K4M	-	-	-	250	-	125
TOTAL(mg)	1000	1000	1000	1000	1000	1000

EVALUATION:

Particle size analysis: Particle sizes of different batches of microspheres were determined by optical microscopy. A minute quantity of microspheres was spread on a lean glass slide and average particle size was determined.

Percentage yield: The batch was weighed after drying and the yield % was calculated using the formula given below

$$\text{Yield\%} = W/W_t \times 100$$

Where, W=Practical Weight of prepared microspheres, W_t=Original weight of drug+polymer

Determination of Micromeritic Properties: To measure the flow property angle of repose of the drug mixture and prepared microspheres was determined by fixed funnel method and bulk density and tapped density was measured by the tapping method⁵. The formulas were given below;

$$\theta = \tan^{-1} h/r$$

Preparation of Microspheres: Glipizide microspheres were prepared by ionic orifice gelation technique³⁻⁴ using sodium alginate as the controlled release material and calcium chloride dehydrate as the cross-linking agent. The pure drug was dispersed in the solution of sodium alginate and water and to this PEG 4000 and HPMC K 4 M and Ethyl cellulose (Table 1) was added and stirred to get a viscous aqueous dispersion. Drop wise the dispersion was extruded through 18# syringe needle and poured in 7.5% CaCl₂ solution by stirring at 50 rpm using a magnetic stirrer. The microspheres thus formed were allowed 1 hour for curing in calcium chloride solution then were decanted and washed with petroleum ether and air dried over night at room temperature.

Where h- height of the heap in cm, r- radius of the pile in cm

$$\text{Bulk density} = W/V_0, \text{ Tapped density} = W/V_t$$

Where W-Weight of the formulation, V₀-Bulk volume, V_t-Tapped volume

Carr's index=

$$\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio=Tapped density/ Bulk density

Drug Encapsulation Efficiency: The assay of Glipizide was estimated by (UV/VIS) spectrometric method. Drug solution was prepared in phosphate buffer (pH- 6.8) and absorbance was measured on UV /Vis spectrometer at 220nm

It is calculated by formula;

$$\left[\frac{\text{Actual drug content}}{\text{Theoretical drug content}} \right] \times 100 = \% \text{ drug entrapped}$$

TABLE 2: MEASUREMENT OF PHYSICO-CHEMICAL PROPERTIES

Formulation	Angle of repose	% Carr's Index	Hausner's Ratio	% Yield	% Drug Encapsulated	Average particle size(μ m)
F1	13.4±.96	5.3±1.1	1.05±1.01	91±1.2	98.6±.88	510±2.3
F2	12.5±.84	5.3±.8	.946±.89	93.8±1.3	97.1±.84	518±2.5
F3	13.2±1.02	5.5±.98	.944±.98	86.3±1.35	98.7±.94	520±1.9
F4	12.2±1.26	5.6±.93	.943±.96	90.8±1.5	98.9±.92	498±1.7
F5	13.6±1.65	5.8±.95	.941±.97	71.4±1.6	89±.8	505±1.4
F6	13.4±.87	5.4±.99	.946±.94	90±1.41	88.3±.9	511±1.3

Scanning Electron Microscopy: Scanning Electron Microscopy (SEM) is an electron optical imaging technique that gives elemental information. The shape and surface characterization of microspheres were observed under scanning electron microscope. The microspheres were mounted directly on the SEM sample stud, using double sided sticking tape and coated with gold film and Photographed. SEM photographs were shown in **Fig. 1**.

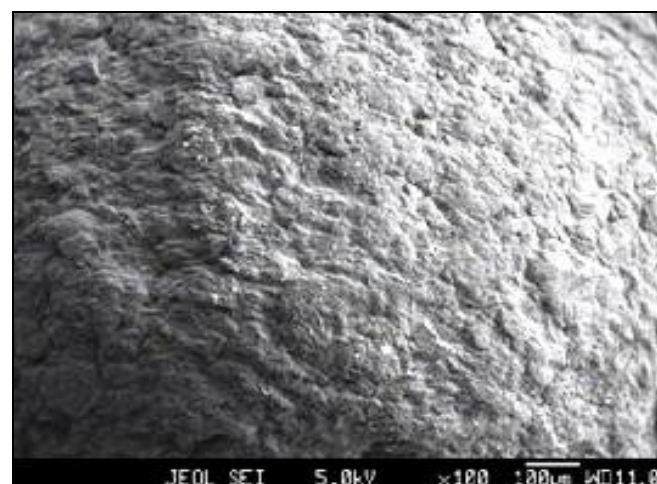
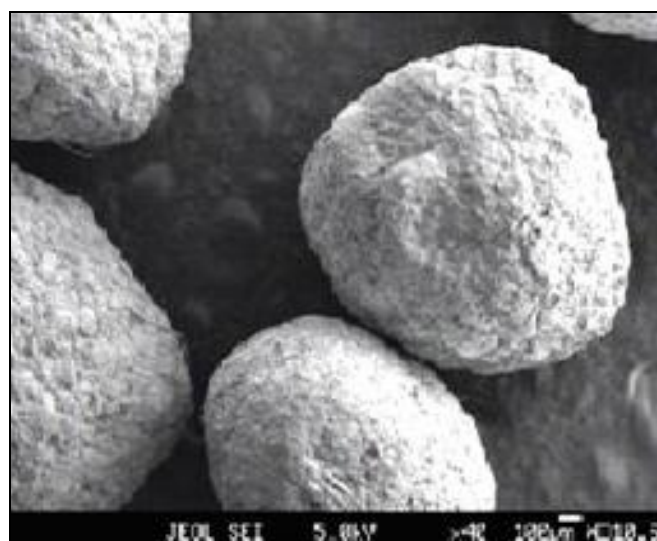


FIG. 1: SEM PHOTOGRAPHS OF GLIPIZIDE MICROSPHERE

In vitro drug release study: Dissolution studies was carried out for all the formulations employing USP XXIII apparatus (paddle method) at 37 ± 0.5°C rotated at constant speed of 100rpm using 900ml pH6.8phosphate buffer for10 hours. An aliquot of the sample was periodically withdrawn at suitable time interval and the volume was replaced with fresh dissolution medium in order to maintain the sink condition. The samples were filtered through 0.45μm membrane filter, suitably diluted and analyzed at 220nm using double beam UV/Vis spectrophotometer (**Fig. 2**).

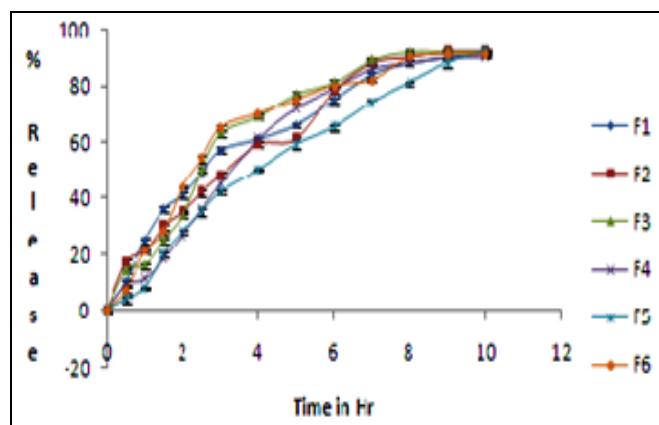


FIG. 2: COMPARATIVE IN VITRO RELEASE PROFILE

Kinetic modeling and mechanism of drug Release: The release data obtained were fitted to zero order, first order, Higuchi and Hixon Crowel equation to determine the corresponding release rate and mechanism of drug release from the mucoadhesive microspheres (**Table 3**).

RESULT AND DISSCUSSION: The present study was an attempt to develop and evaluate drug delivery system containing mucoadhesive polymers⁶. Microspheres were prepared by ionic gelation method as shown in Table 1. All formulations were found spherical having particle size in the range of

498- 520 μm and free flowing with Carr's index, Hausner's ratio values were within the limit.

TABLE 3: REGRESSION ANALYSIS DATA

Formulation	Zero order	First Order	Higuchi	Hixon Crowel
F1	.969	.912	.921	.935
F2	.991	.898	.965	.944
F3	.990	.960	.955	.974
F4	.983	.993	.981	.991
F5	.921	.988	.969	.975
F6	.979	.961	.968	.976

The Microencapsulation efficiency was found around 88.3 ± 9 to $98.9 \pm 9.2\%$ indicating uniformity in drug content. The physicochemical datas are shown in Table 2. Scanning electron microscopy was performed to characterize the surface morphology of the formed microspheres and shown in Fig.1. The microspheres showed some porous structure. Release of the active constituents is an important consideration in case of mucoadhesive microspheres. The *in-vitro* release studies of glipizide from prepared microspheres were carried in the buffers for a period of 10 hrs.

The overall cumulative % releases for F1 to F6 were found to be about 90 % at the end of 10 hrs and shown in Fig.2. The 'r' values for zero order kinetics of F-1 to F6 were 0.921 to 0.991 respectively. The 'r' values shown in Table 3 indicate the drug release follows zero order. To ascertain the drug release mechanism, the *in-vitro* data were also subjected to first order, Higuchi and Hixon-Crowel diffusion model. Basing on the release characteristic F6 is found to be the optimized formulation.

CONCLUSION: The Glipizide mucoadhesive microspheres were prepared by ionic gelation method using polymers like Sodium alginate, HPMC K4M, PEG 4000, Ethyl cellulose. The satisfactory results were obtained in all prepared

formulations and based on the results F6 was best one when compared to other formulations. Hence Glipizide oral mucoadhesive microspheres could be promising one as they increase bioavailability, minimize the dosing frequency, reduces the side effects and improve patient compliance.

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