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FORMULATION AND EVALUATION OF GLICLAZIDE LOADED ALGINATE BEADS FOR CONTROLLED RELEASE

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Abstract- Microencapsulation by emulsification-ionic gelation technique is an approach to achieve controlled release of drug, gliclazide beads were designed to improve the absorption and bioavailability of the drug. Gliclazide beads were formulated with sodium alginate and by combination of sodium alginate with hydrophilic polymer such as Na CMC in the ratio of (core:coat) 1:1,1:2, 1:3, 2:1 and 3:1. The prepared beads were characterized such as particle size of beads, angle of repose by fixed funnel method, compressibility index, Hausner's ratios, wall thickness, drug content,entrapment efficiency. The shape of beads were found to be spherical by SEM analysis. In-vitro dissolution data revealed that formulations exhibited the zero order kinetics and followed peppas transport mechanism.

Keywords- Gliclazide, Na CMC- Sodium Carboxy Methyl Cellulose,SEM-scanning electron microscopy, Alginata beads

Introduction

Controlled release drug delivery systems[1-4] are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. Controlled drug delivery systems are designed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible [5,6].

Gliclazide is an oral hypo glycemic second generation sulfonyl urea drug which Is useful for a long term treatment of non insulin dependent diabetes mellitus (NIDDM). Previous studies showed that gliclazide possesses good general tolerability, low incidence of hypoglycemia and low rate of secondary failure. Rapid absorption from the GIT is required for the oral hypoglycemic drug for effective therapy. However, the absorption rate of Gliclazide from the GIT is slow and varied among the subjects. Slow absorption has been suggested to be due to either poor dissolution of Gliclazide due to hydrophobic nature of drug and poor permeability of drug across the GI membrane [7, 8]. By incorporation of Gliclazide in the alginate beads may control its absorption from GI tract and overcome the variability problems. Thus this study was undertaken to develop controlled formulations of Gliclazide using sodium alginate and Na CMC as release retardant polymers.

Materials and Methods

Gliclazide was received from hetro drugs, Hyderabad as gift sample, sodium alginate was procured from S.D fine chem., Na CMC from yarrow chem. Products and all other chemicals and solvents used in this study were LR grade.

Preparation of Gliclazide Alginate Beads

Gliclazide beads were prepared by emulsification- ionic gelation method with sodium alginate alone and combination of sodium alginate with Na. CMC in the core: coat ratio of 1:1, 1:2, 1:3, 2:1 and 3:1 as shown in [Table-1] and [Table-2]. Sodium alginate powder is mixed with 30 ml of purified water and allowed to stirring for 30 mins. The required amount of drug gliclazide was thoroughly mixed in sodium alginate at 400 rpm. The resulting dispersion was added drop wise into beaker containing 400ml of liquid paraffin through a syringe with a needle size no.18 and the solution was stirred at 400 rpm. A Remi medium duty stirrer was used for stirring and the stirring was continued for 5 mins to emulsify the added droplets. Then finally 20 ml of 10% w/v calcium chloride solution was added slowly while stirring for ionic gelation reaction. Stirring was continued for 30 mins to complete the curing reaction and the product was separated, washed with petroleum ether. The collected beads were dried at 45°C for 12 hrs. Similarly glicazide alginate beads were also prepared by the combination of sodium alginate with hydrophilic polymer such as Na CMC in the core: coat (1:1, 1:2, 1:3, 2:1, and 3:1).

Table 1- Formulations of Gliclazide Beads with Sodium Alginate

Formulation	Core: Coat	Coat Composition
EG1	01:01	Sodium Alginate
EG2	01:02	Sodium Alginate
EG3	01:03	Sodium Alginate
EG4	02:01	Sodium Alginate
EG5	03:01	Sodium Alginate

Table 2- Formulations of Gliclazide Beads with NaCMC Prepared by using Emulsification Gelation Method

Formulation	Core: Coat	Coat Composition
EG6	01:01	Sodium Alginate+ NaCMC
EG7	01:02	Sodium Alginate+ NaCMC
EG8	01:03	Sodium Alginate+ NaCMC
EG9	02:01	Sodium Alginate+ NaCMC
EG10	03:01	Sodium Alginate+ NaCMC

Infrared Spectroscopy

Compatibility studies between drug and polymers were studied by FTIR. Infrared (IR) spectroscopy was conducted using a Shimadzu FTIR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) and the spectrum was recorded in the wavelength region of 4000 to 400 cm -1, in which the sample was dispersed (drug alone or mixture of drug and excipients) in KBr and compressing into discs and the pellets was placed in the light path and the spectrum was obtained

Materials and Methods

The following evaluation studies are conducted on prepared gliclazide beads [9-11].

Size Analysis

Particle size distribution and the mean diameter of the beads were determined by sieving method. The beads were sieved by taking the standard IP set of sieves of 10, 12, 16, 22, 44, 60, and 100. The average particle size of the beads was calculated by using the following equation.

$$d_{average} = \frac{\sum nd}{\sum n}$$

where n = frequency weight; d = mean size.

Evaluation of Flow Properties

The flow properties of different beads were studied by measuring the angle of repose employing open tube method (2.3 cm diameter). The angle of repose was calculated by using the following formula

$$Tan\ \alpha = \frac{h}{r}\ or\ \alpha = Tan^{-1}\frac{h}{r}$$

where h = height of the pile in cms; r = radius of the base of the pile in cms

Bulk Density

Bulk density is the ratio of the beads to the bulk volume it occupies, expressed in gm/ml. 5 gm of the beads were weighed and poured into a 100ml- measuring cylinder and the volume was measured, it can be measurd by the following equation.

$$\text{Bulk density} = \frac{\text{Mass of beads}}{\text{Volume of packing}}$$

Tapped Density

Tapped density of beads determined by weighed accurately 5 gm of the beads were weighed and poured into a 100ml-measuring cylinder and the volume was measured. It was tapped mechanically for 100 times till a constant volume bulk volume obtained, which includes the true volume of beads and void space among the beads.

$$\text{Tapped density} = \frac{\text{Mass of beads}}{\text{Tapped volume of packing}}$$

Carr's Index

The percentage of compressibility of beads was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = \frac{\text{(Tapped density - Bulk density)}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

Hausner ratio of beads determined by comparing the tapped density to the bulk density by using the equation

Hausner's ratio = Tapped density / Bulk density

Wall Thickness

Wall thickness of beads were determined by the method of Luu et al using the equation

$$h = \frac{\bar{r}(1-p)d1}{3[pd2 + (1-p)d1]}$$

where h is the wall thickness

$\bar{r}$ = Arithmetic mean radius of the microcapsules

d_1 = Density of the core material

d_2 = Density of the coat material

p = Proportion of the medicament in the microcapsules.

Drug Content

Gliclazide content in the alginate beads was estimated by an UV Spectrophotometric method based on the measurement of absorbance at 226 nm in pH 7.4 of phosphate buffer. The method was validated for linearity, accuracy and precision.

Entrapment Efficiency

Entrapment efficiency was calculated using the formula.

$$Entrapment\ \ efficiency = \frac{Estimated\ percent\ drug\ content}{Theoretical\ percent\ drug\ content}\ X\ 100$$

In- Vitro Drug Dissolution Study

The *in vitro* dissolution study was carried out using USP Type 1 Dissolution apparatus. The study was carried out in 900 ml of phosphate buffer pH 7.4 for 12h. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5°C. The basket was lowered so that the lower end of the stirrer was 25 mm above from the base of the beaker. The pre-weighed beads were then introduced into the dissolution basket and rotated at 100 rpm. Five ml of sample were withdrawn at different time intevels and filtered through 0.45 µm milli pore filter unit and analyzed spectrophotometrically at 226 nm for the drug release. At each time of withdrawal, 5 ml of fresh dissolution medium was replaced into the dissolution flask.

In- Vitro Wash-off Test

The Mucoadhesive property of the alginate beads was evaluated by an *in-vitro* adhesion testing method known as wash-off method. In this method Pieces of intestinal mucosa (2x2 cm) were mounted on to glass slides (3x1 inch) with cellophane tape. Two glass slides were connected with a suitable support. About 50 beads were spread on to each wet rinsed tissue specimen and immediately there after the support was hung on to the arm of a USP tablet disintegrating test machine and machine was switched on up and down in a test fluids at 37 ^{O}C taken in a one lit vessel of the machine. At the end of every 1 h the machine was stopped and the number of microcapsules still adher-ing on to the tissue was counted for 8h the test was performed at both gastric pH 1.2 and intestinal pH7.4.

SEM Analysis

SEM was performed for morphological characterization of microcapsules using scanning electron microscope (SEM-LEICA, 5430, London, U.K). They were mounted directly on to the SEM sample stub using double - sided sticking tape and coated with gold. Im (thickness, 200 nm) under reduced pressure (0.001 mmHg).

Results and Discussion

The drug-excepient compatibility studies were conducted by FT-IR spectroscopy, results revealed that no chemical interaction's were observed between the drug - polymers, the spectras given as [Fig-1], [Fig-2], [Fig-3] and [Fig-4].

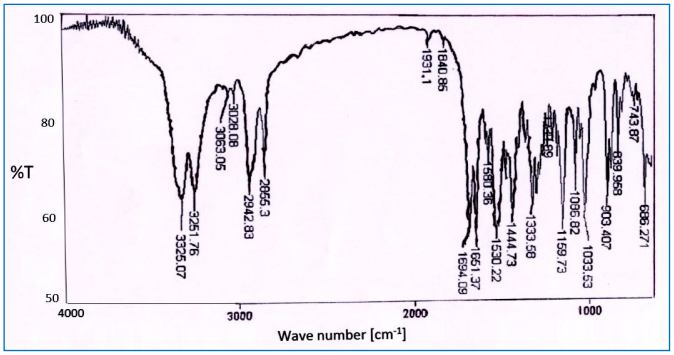

Fig. 1- IR Spectra of Gliclazide

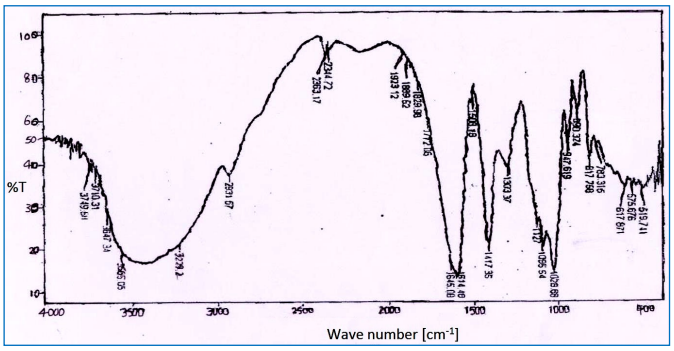

Fig. 2- IR Spectra of Sodium Alginate

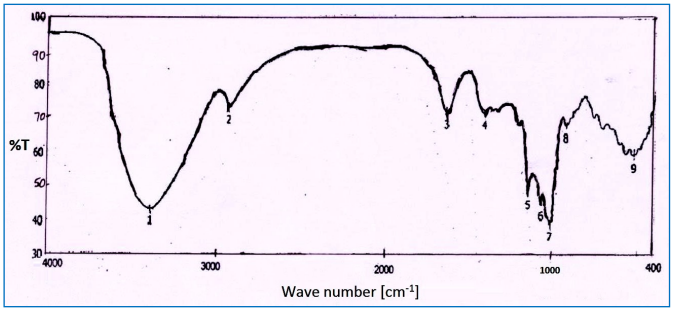

Fig. 3- IR Spectra of NaCMC

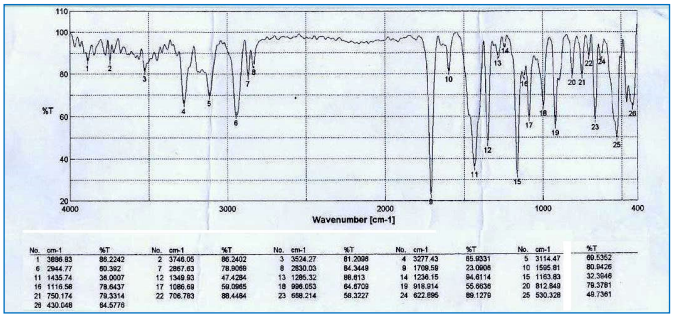

Fig. 4- IR Spectra of Gliclazide Beads

The results of physical characteristics of formulated gliclazide beads were shown in the [Table-3]. The particle size of the gliclazide were found in the range of 769.46 to 1174.98 µm. Results of the angle of repose for the formulations indicates that formulations exhibited good flow properties, further supported by corr's index and hausner's ratio. From the observation the particle size increased while increasing the concentration of polymer coat and flow properties.

Table 3- Evaluation of Gliclazide Beads Prepared with NaCMC

FC	PS (mm)	AR (q)	CI (%)	HR	WT (mm)	DC (%)	EE (%)
EG1	769.46	180.08	5.9	1.06	35.44	98.86	91.72
EG2	1084.89	160.22	5.8	1.05	37.98	97.12	87.39
EG3	1165.5	140.8	7.1	1.04	42.36	98.87	83.48
EG4	1107.98	190.5	5.4	1.03	34.29	93.22	94.38
EG5	1131.26	210.8	6.2	1.07	30.82	95.56	98.08
EG6	790.02	220.89	4.9	1.06	36.81	92.12	92.24
EG7	1062.43	180.12	5.2	1.04	43.72	98.48	85.47
EG8	1174.98	120.86	6.2	1.04	47.3	93.42	80.96
EG9	1131.28	230.04	5.5	1.03	34.83	95.24	93.36
EG10	1145.66	250.72	5.6	1.07	33.42	98.26	97.68

FC: Formulation Code; PS: Particle size (mm); AR: Angle of repose; CI: Compressibility index; HR: Hausner's ratios; WT: Wall thickness; DC: Drug content; EE: Entrapment efficiency.

Topographical studies were conducted by SEM analysis as given in [Fig-5], which indicates surface of the coat have smooth surface and completely covers with a coat material, found to be spherical in shape.

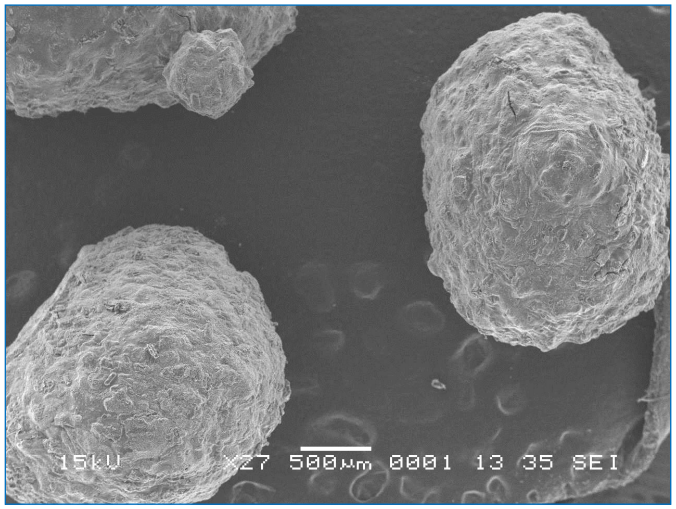

Fig. 5- SEM Photographs of Selected Formulation

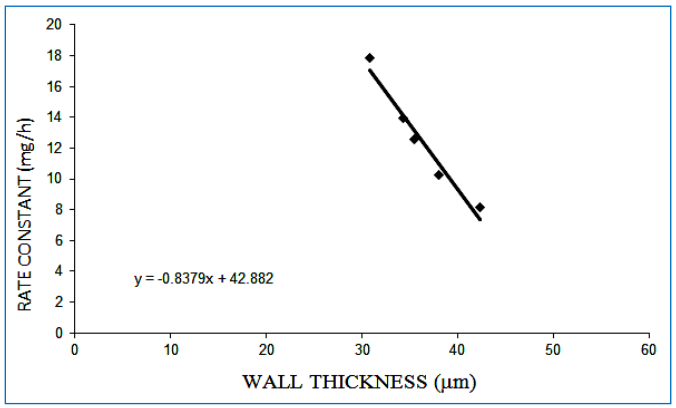

Fig. 6- Relationship Between Wall Thickness and Release Rate Constant Wall Thickness (mM)

The wall thickness of gliclazide beads found to be increased while increasing the coat thickness that is concentration of polymer that

exists good correlation ship between wall thickness and release rate constant as shown [Fig-6]. All formulations have maximum percentage of drug content and good entrapment efficiency due to ionic gelation process.

The formulations were also subjected to *In-vitro* wash off test in presence of 0.1N HCl and pH 7.4 phosphate buffers. The wash off was relatively rapid in phosphate buffer pH 7.4 than in acid buffer pH 1.2. From the results of *in-vitro* wash off test indicated that beads have fairly good mucoadhesive property prepared by emulsification gelation process the results were shown in [Table-4] and [Table-5].

Table 4- Results of *In vitro* Wash of Test of Gliclazide Beads Prepared with Sodium Alginate

FC	Percent of Alginate Beads Adhering to Tissue After (h)									
	0.1N HCl					Phosphate Buffer PH 7.4				
	1	2	4	6	8	1	2	4	6	8
EG 1	68	57	42	32	22	62	56	44	17	-
EG 2	75	62	68	31	28	64	52	34	16	-
EG 3	80	76	56	33	29	72	58	40	38	-
EG 4	62	50	37	24	11	60	50	22	5	-
EG 5	59	48	32	18	10	56	25	6	-	-

FC: Formulation Code;

Table 5- Results of *In vitro* Wash Off Test of Gliclazide Beads Prepared with Sodium Alginate with NaCMC

FC	Percent of Alginate Beads Adhering to Tissue After (h)									
	0.1N HCl					Phosphate Buffer PH 7.4				
	1	2	4	6	8	1	2	4	6	8
EG 6	78	67	52	32	24	72	56	34	17	02
EG 7	85	72	58	41	28	74	62	44	26	11
EG 8	92	84	66	54	36	82	68	52	38	29
EG 9	72	60	47	24	17	70	38	22	08	-
EG 10	69	58	42	18	11	66	30	06	-	-

FC: Formulation Code;

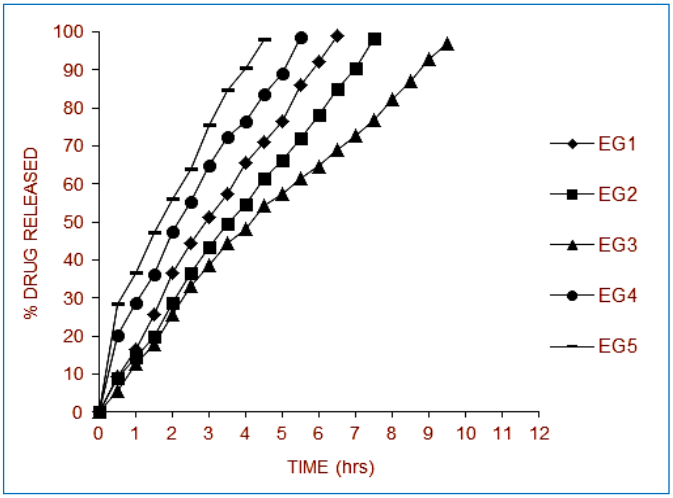

Fig. 7- Dissolution Profile of Gliclazide Beads Prepared with Sodium Alginate by Emulsification Gelation Method

Gliclazide release from the beads were studied (*In-vitro* dissolution studies) in phosphate buffer of pH 7.4, release profiles were shown in [Fig-7] and [Fig-8]. The *in vitro* release data fitted into zero order, first order, matrix and peppas equations. Drug release from the formulations EG3 and EG8 controlled the release for the period of 9 and 12 hrs. among all the prepared formulations. The rate of drug release form the formulations followed zero order kinetics exhibited peppas transport mechanism results given in [Table-6] and [Table-7]. The exponential coefficient values were found > 0.8 indicating the non fickian diffusion mechanism. Gliclazide alginate beads formulates with NaCMC have good mucoadhesive property than the formulations formulated with the sodium alginate alone and mucoadhesive property confirmed by the *in vitro* wash off test.

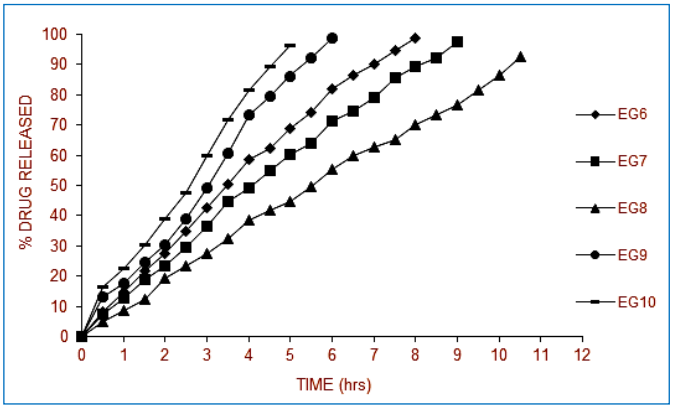

Fig. 8- Dissolution Profile of Gliclazide Beads Prepared with NaCMC by Emulsification Gelation Method

Table 6- Release Kinetics of Gliclazide Beads Prepared with Sodium Alginate by Emulsification Gelation Method

FC	Correlation Coefficient				Rate Constant (K mg/hr)	n	P_m (mm.mg) /h
	Zero	First	Matrix	Peppas			
EG1	0.9957	0.8174	0.9063	0.9878	12.602	1.11	0.446
EG2	0.997	0.9354	0.9133	0.9953	10.263	1.29	0.389
EG3	0.9925	0.8972	0.928	0.9878	8.184	1.129	0.346
EG4	0.9887	0.8804	0.8879	0.9798	13.961	1.117	0.478
EG5	0.9913	0.8443	0.8908	0.982	17.854	1.034	0.55

FC: Formulation Code.

Table 7- Release Kinetics of Gliclazide Beads Prepared with Sodium Alginate by Emulsification Gelation Method

FC	Correlation Coefficient				Rate Constant (K mg/hr)	n	P_m (mm.mg) /h
	Zero	First	Matrix	Peppas			
EG6	0.9817	0.8069	0.8644	0.9685	11.092	0.939	0.408
EG7	0.9828	0.8308	0.9616	0.9953	8.784	0.863	0.384
EG8	0.9984	0.7829	0.9261	0.9983	7.324	0.979	0.346
EG9	0.9925	0.8205	0.8996	0.9709	13.586	0.952	0.473
EG10	0.9926	0.8940	0.9164	0.9605	15.653	0.887	0.523

FC: Formulation Code.

Conclusion

Gliclazide beads formulated by emulsification - ionic gelation method employing sodium alginate and alone and sodium alginate with sodium CMC. In-vitro wash off test results indicates the beads formulated with Na CMC have good mucoadhesive property, which inturn helps to control the drug release for longer period of time. Drug release from the formulations followed zero order kinetics and exhibited peppas transport mechanism, hence the bioavailability of the drug were enhanced by this technique, this effects results in maintaining tight blood glucose levels and improved patient compliance.

Conflicts of Interest: None Declared.

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