

Research Article

Formulation and Evaluation of Mucoadhesive Microbeads of Glimepiride

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Abstract: The main objective of this present research work is to achieve sustained release of Glimepiride and to enhance the gastrointestinal residence time, for this purpose mucoadhesive microbeads were formulated by employing Ionic gelation method with HPMC and NaCMC as coating polymers. Formulated mucoadhesive microbeads were properly evaluated for size distribution, tapped density entrapment efficiency, wall thickness, drug release studies, SEM and GI residence time. In this present research influence of polymer on rate of drug release and concentration of polymer coat on rate of drug release from the Glimepiride mucoadhesive microbeads were studied. The rate of drug release was found to be decreased by increasing the concentration of the coat polymer. The rate of drug release was found to be less for mucoadhesive microbeads formulated by NaCMC than compared to mucoadhesive microbeads formulated by HPMC. The mucoadhesive microbeads prepared with HPMC and Glimepiride in 1:9 ratio shown prolonged drug release up to 12 hours. The release follows first order kinetics and mechanism of drug release was found to be governed by diffusion mechanism.

Keywords: Glimepiride, HPMC, NaCMC, Sodium alginate, mucoadhesive microbeads, Ionic Gelation method

INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as Microbeads, Nanoparticles, Liposomes, etc. which modulates the release and absorption characteristics of the drug. mucoadhesive microbeads constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics. However, the success of these Novel DDS is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the DDS with absorbing membranes. It can be achieved by coupling mucoadhesion characteristics to mucoadhesive microbeads and developing novel delivery systems referred to as "microbeads" [1]. Glimepiride is the only third generation sulphonyl urea, which lowers the blood glucose level in the healthy subjects as well as in patients with type 2 diabetes [2]. Glimepiride belongs to biopharmaceutical classification- II with drug pKa: 6.2 showing small intestine as the major absorption site. To enhance the intestinal residence time and to achieve the oral controlled release of Glimepiride, mucoadhesive microbeads were formulated and evaluated.

MATERIAL USED

Glimepiride Gift sample Obtained from Orchid Pharma Pvt. Ltd., Chennai, Hydroxy Propyl Methyl Cellulose 3000-5600cps (S. D. Fine Chem Ltd., Mumbai.), Methyl Cellulose (Himedia Laboratories Pvt

Ltd., Mumbai.), Methanol (Qualigens Fine Chemicals, Mumbai.), Hydrochloric Acid (Qualigens Fine Chemicals, Mumbai.), Sodium Hydroxide (Qualigens Fine Chemicals, Mumbai.) Potassium Di Hydrogen Ortho Phosphate (Qualigens Fine Chemicals, Mumbai.) Calcium Chloride (Qualigens Fine Chemicals, Mumbai.) Sodium Alginate (Loba Chemie Pvt. Ltd., India)

METHOD

Mucoadhesive microbeads of Glimepiride were prepared with a coat consisting of alginate and a mucoadhesive polymer namely HPMC/NaCMC and prepared by an Ionic gelation process [3]. Sodium Alginate (1.0 g) and mucoadhesive polymer viz., HPMC/ NaCMC (1.0 g) were dissolved in purified water to form a homogeneous polymer dispersion. Core material, Glimepiride (containing equivalent to 1.0 g) was added to the polymer dispersion and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion was added drop wise in to 10 ml of 10% w/v solution of Calcium chloride for Ionic gelation (or curing) reaction. The resulting beads were separated and dried at 45°C for 12 hrs. In case of 1:3, 1:6 and 1:9 coat:core ratios, the corresponding polymer dispersion containing drug was transferred into 10 ml of 15%, 10 ml of 30%, 10 ml of 30% w/v Calcium chloride solutions respectively.

CHARACTERIZATION OF GLIMEPIRIDE MUCOADHESIVE MICROBEADS

Size Distribution and Size Analysis

For size distribution analysis, 250 mg of the microbeads 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 mucoadhesive microbeads was calculated by the formula [9].

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

Evaluation of Flow Properties

The flow properties of different microbeads were studied by measuring the angle of repose employing open tube method (2.3 cm diameter) method. The angle of repose was calculated by using the following formula [4].

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

Where h = height of the pile, cm ; r = radius of the base of the pile, cm

Tapped Density

Accurately weighed 10 g of the beads and transferred in to 25 ml measuring cylinder. It was subjected to tapping for 3 times and the volume occupied by the beads was noted. Tapped Density is estimated by using the following formula [5].

$$\text{Tapped Density} = \frac{\text{Weight of the Beads}}{\text{Bulk volume of the Beads}}$$

Estimation of Glimepiride

Accurately 100 mg mucoadhesive microbeads were weighed and transferred in to a mortar, powdered and dissolved in 100 ml of pH 7.8 phosphate buffer, suitably diluted the absorbance of the resulting solution was measured at 228 nm.

Entrapment Efficiency

Entrapment efficiency was calculated using the formula [6].

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

Estimated percent drug content was determined from the analysis of 100 mg mucoadhesive microbeads and the theoretical percent drug content was calculated from the employed coat:core ratio.

Wall Thickness

Wall thickness of mucoadhesive microbeads was determined by the method of Luu et al using the equation [7].

$$h = \frac{\bar{r}(1-p)d_1}{3[pd_2 + (1-p)d_1]}$$

Where h is the wall thickness

\bar{r} is the arithmetic mean radius of the mucoadhesive microbeads

d_1 is the density of the core material

d_2 is the density of the coat material

p is the proportion of the medicament in the mucoadhesive microbeads

Drug Release Studies

Release of Glimepiride from the mucoadhesive microbeads, was studied in phosphate buffer of pH 7.8 (900 ml) using Eight Station Dissolution Rate Test Apparatus (M/s. Electrolab) with a paddle stirrer at 75 rpm and at $37 \text{ OC} \pm 0.5 \text{ OC}$ [8]. A sample of mucoadhesive microbeads equivalent to 8 mg of Glimepiride were used in each test. Samples were withdrawn through a filter (0.45 μ) at different time intervals and were assayed at 228 nm for Glimepiride using Shimadzu double beam U V spectrophotometer. The drug release experiments were conducted in triplicate.

SEM Studies

The mucoadhesive microbeads prepared with HPMC by employing 1:9 ratio offered the required extended release, hence these formulations were subjected to SEM studies and the corresponding photograph was shown in figure 9. SEM photographs indicated that the alginate beads are discrete nearly spherical and covered with continuous coating of the polymer [10].

GI residence time studies

GI Residence Time associated with the administration of HPMC mucoadhesive microbeads containing barium sulphate (free from drug) was determined with *x-ray* photographs (figure 10 (A) and figure 10 (B)). These photographs indicated improvement in GI residence time [11] with the administration of HPMC beads prepared by employing 1:9 ratio.

IR Spectral Studies

The IR Spectra for the formulation, excipients and pure drug were recorded on BRUKER FT-Infra Red Spectrophotometer using KBr pellet technique (1:100) at the resolution rate of 4 cm^{-1} . Spectrum was integrated in transmittance mode at the wave number range 400 to 2000 cm^{-1} .

RESULTS AND DISCUSSIONS

Studies on HPMC mucoadhesive microbeads

Mucoadhesive microbeads were formulated by employing ionic gelation process. This process produced uniform beads. Glimepiride was coated with the mixture of HPMC and calcium alginate. Beads were developed with 1:1, 1:3, 1:6 and 1:9 ratio to determine the affect of coating material concentration on the release rate of Glimepiride. These beads were characterized for diameter, density, flow properties, drug content, wall thickness and entrapment efficacy. These results were reported in table 1. All the formulations offered good flow property. The method also showed good entrapment efficiency. Low coefficient variation in the percent drug content

indicated uniformity of drug content in each batch of beads. The beads were subjected to in vitro dissolution studies by using 7.8 pH phosphate buffer and the data was shown in figure 1. The release rate followed first order kinetics as the log % unrelease vs time graphs were found to be linear in figure 2. The mechanism of drug release was found to be diffusion controlled as the graphs drawn in between amount of drug release vs \sqrt{t} time were found to be linear in figure 3. The corresponding correlation coefficients and other dissolution parameters were shown in table 2. These results indicated that the release rate was found to

decrease with increase in concentration of coating material employed in the preparation of alginate beads. The wall thickness of beads was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant in figure 4. The formulations were also subjected to invitro wash off test in presence of 0.1 N HCl and pH 7.8 phosphate buffer. The wash off was relatively rapid in phosphate buffer than in acidic fluid. The results of wash-off test indicated in table 3 fairly good mucoadhesive property of the beads.

Table 1: Characterization of Glimepiride Microbeads prepared with HPMC

Coat:core Ratio	Mean diameter (mm)	Tapped Density	Angle of Repose	% drug Content	Entrapment Efficiency	Wall thickness (mm)
1:1	22.49	0.033	10.20	32.25	96.75	1.068
1:3	21.94	0.159	13.49	14.88	95.96	3.086
1:6	21.66	0.025	19.29	7.14	92.84	4.271
1:9	22.29	0.481	34.21	4.98	94.67	5.085

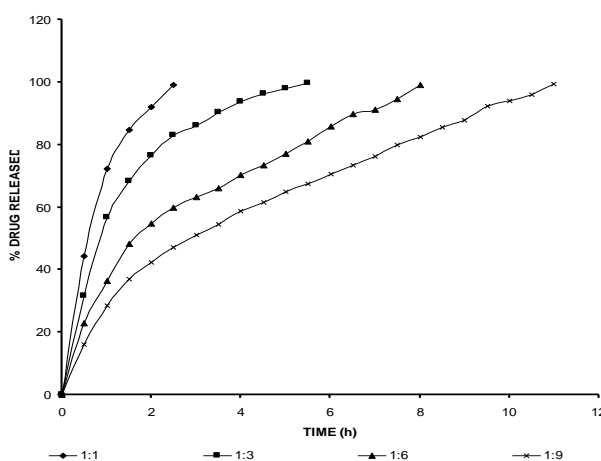


Fig. 1: Dissolution profiles of Glimepiride Microbeads prepared with HPMC

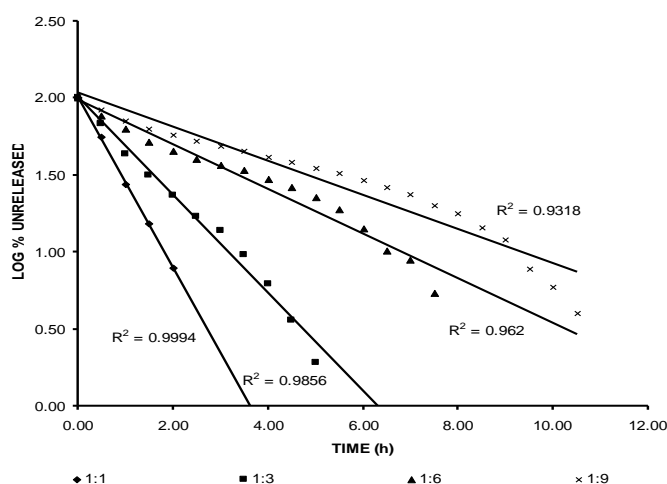


Fig. 2: First order plots of Glimepiride Microbeads prepared with HPMC

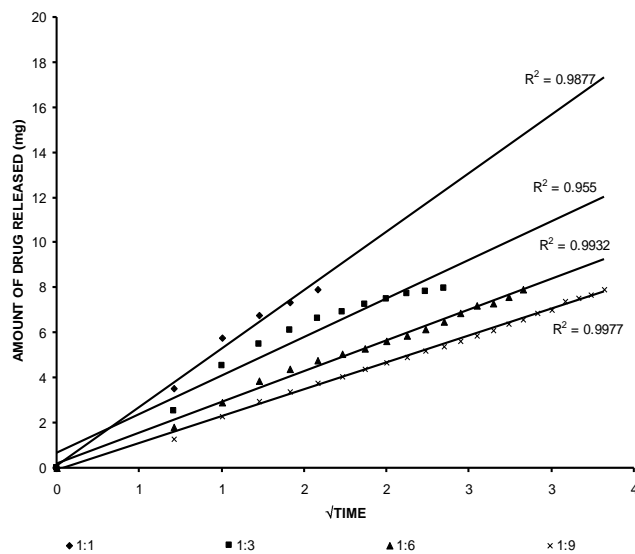


Fig. 3: Matrix plots of Glimepiride Microbeads prepared with HPMC

Table 2: Release kinetics of Glimepiride Microbeads prepared with HPMC

Coat: core Ratio	Correlation coefficient				Rate constant (h ⁻¹)	T ₅₀ (h)	T ₉₀ (h)
	Zero	First	Matrix	Peppas			
1:1	0.8766	0.9994	0.9936	0.9807	1.5604	0.4	1.5
1:3	0.6647	0.9856	0.9708	0.9637	0.7901	0.9	2.9
1:6	0.8008	0.9620	0.9959	0.9919	0.3821	1.8	6.0
1:9	0.8593	0.9318	0.9986	0.9950	0.2704	2.6	8.5

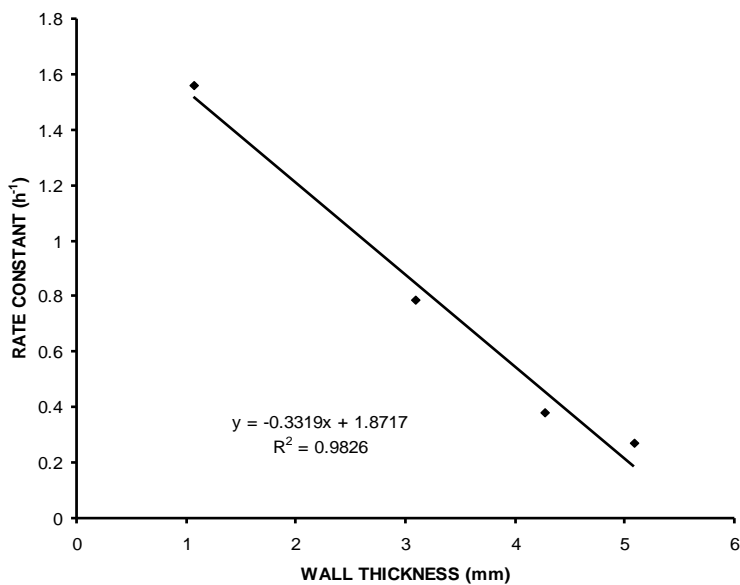


Fig. 4: Relationship between wall thickness and release rate constant of Glimepiride Microbeads prepared with HPMC

Table 3: Results of *In Vitro* wash-off test of Glimepiride Microbeads prepared with HPMC

Coat:Core Ratio	Percent of Microbeads adhering to tissue at 5 times (h)									
	0.1 N HCl, pH 1.2					Phosphate buffer, pH 7.8				
	1	2	4	6	8	1	2	4	6	8
1:1	40	33	27	20	06	38	29	20	13	---
1:3	42	35	30	24	12	40	33	23	18	07
1:6	45	39	35	29	16	43	37	27	21	15
1:9	47	43	40	35	22	45	40	32	24	17

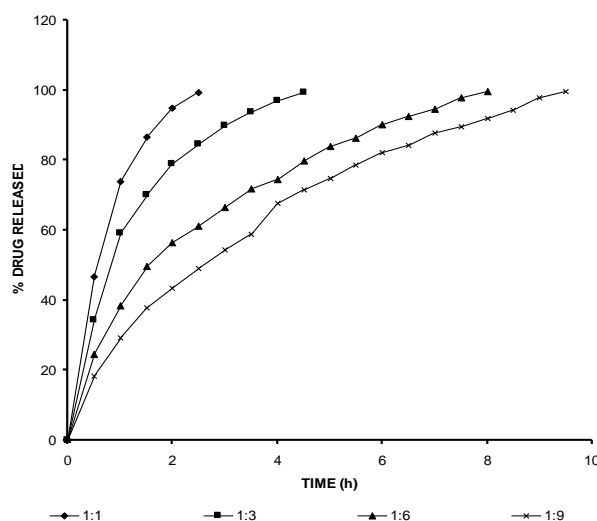
Studies on NaCMC mucoadhesive microbeads

Mucoadhesive microbeads were formulated by employing Ionic gelation process. This process produced uniform beads. Glimepiride was coated with the mixture of NaCMC and calcium alginate. Beads were developed with 1:1, 1:3, 1:6 and 1:9 ratio to determine the affect of coating material concentration on the release rate of Glimepiride. These beads were characterized for diameter, density, flow properties, drug content, wall thickness and entrapment efficacy. These results were reported in table 4. All the formulations offered good flow property. The method also showed good entrapment efficiency. Low coefficient variation in the percent drug content indicated uniformity of drug content in each batch of beads. The beads were subjected to in invitro dissolution studies by using 7.8 pH phosphate buffer and the data was shown in figure 5. The release rate followed first order kinetics as the log % unrelease vs time graphs were found to be linear in figure 6. The

mechanism of drug release was found to be diffusion controlled as the graphs drawn in between amount of drug release vs $\sqrt{\text{time}}$ were found to be linear in figure 7. The corresponding correlation coefficients and other dissolution parameters were shown in table 5. These results indicated that the release rate was found to decrease with increase in concentration of coating material employed in the preparation of alginate beads. The wall thickness of beads was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant in figure 8. The formulations were also subjected to *in vitro* wash off test in presence of 0.1 N HCl and pH 7.8 phosphate buffer. The wash off was relatively rapid in phosphate buffer than in acidic fluid. The results of wash-off test indicated in table 6 fairly good mucoadhesive property of the beads.

Table 4 : Charactarization of Glimepiride Microbeads prepared with NaCMC

Coat:core Ratio	Mean diameter (mm)	Tapped Density	Angle of Repose	% drug Content	Entrapment Efficiency	Wall thickness (mm)
1:1	21.65	0.180	6.50	31.68	95.04	1.616
1:3	21.65	0.035	15.05	13.84	93.01	4.774
1:6	21.67	0.035	14.03	7.28	94.67	5.853
1:9	21.21	0.829	32.61	5.04	95.82	6.030

**Fig. 5: Dissolution profiles of Glimepiride Microbeads prepared with NaCMC**

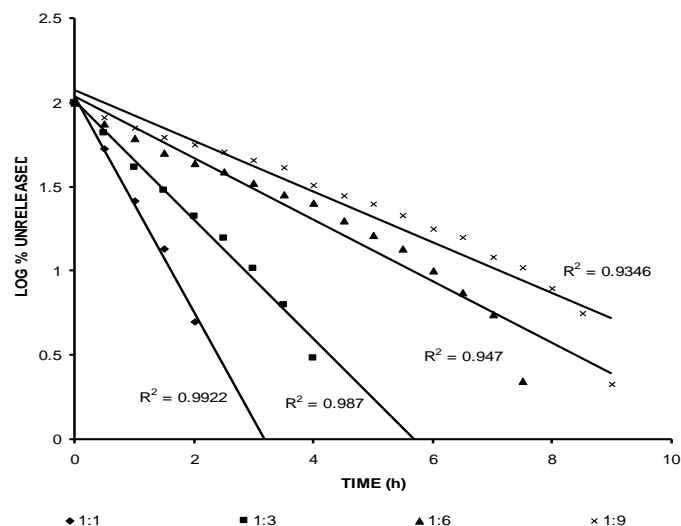


Fig. 6: First order plots of Glimepiride Microbeads prepared with NaCMC

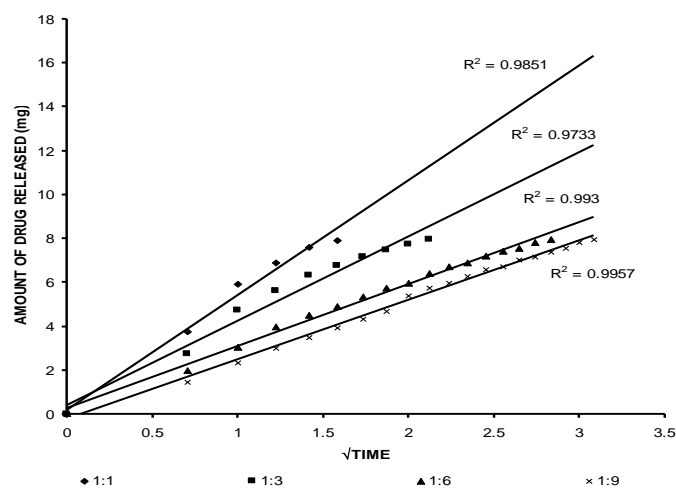


Fig. 7: Matrix plots of Glimepiride Microbeads prepared with NaCMC

Table 5: Release kinetics of Glimepiride Microbeads prepared with NaCMC

Coat:Core Ratio	Correlation coefficient				Rate constant (h ⁻¹)	T ₅₀ (h)	T ₉₀ (h)
	Zero	First	Matrix	Peppas			
1:1	0.8624	0.9922	0.9920	0.9804	1.6562	0.4	1.4
1:3	0.7582	0.9870	0.9839	0.9751	0.9016	0.8	2.6
1:6	0.7797	0.9470	0.9954	0.9943	0.4615	1.5	5.0
1:9	0.8740	0.9346	0.9974	0.9970	0.3682	1.9	6.3

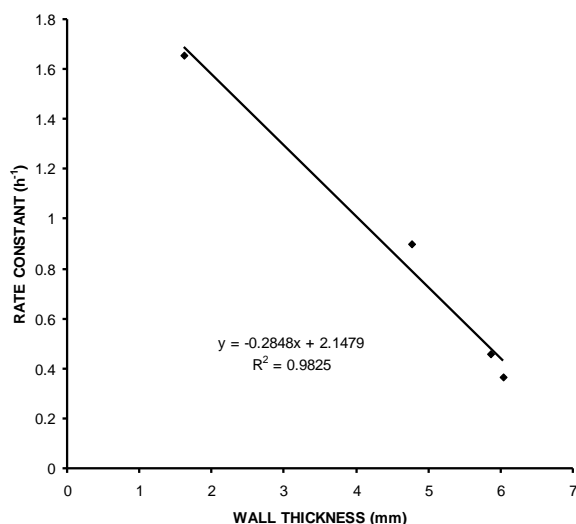


Figure 8: Relationship between wall thickness and release rate constant of Glimepiride Microbeads prepared with NaCMC

Table 6: Results of *In vitro* wash-off test of Glimepiride Microbeads prepared with NaCMC

Coat:Core Ratio	Percent of Microbeads adhering to tissue at 5 times (h)									
	0.1 N Hcl, pH 1.2					Phosphate buffer, pH 7.8				
	1	2	4	6	8	1	2	4	6	8
1:1	38	26	20	14	06	35	29	20	13	--
1:3	40	31	26	20	12	38	31	23	18	07
1:6	43	38	32	25	16	40	34	27	21	13
1:9	46	42	37	29	20	44	38	30	25	16

Comparison of HPMC and NaCMC mucoadhesive microbeads

To compare the efficacy of these polymers the formulations has to be prepared with the same method under similar set of conditions and having same thickness as it is not possible practically to obtain

mucoadhesive microbeads having same thickness linear regression analysis was applied to obtain the corresponding release rate constants from the beads produced with two different polymers and having a thickness of 5 mm.

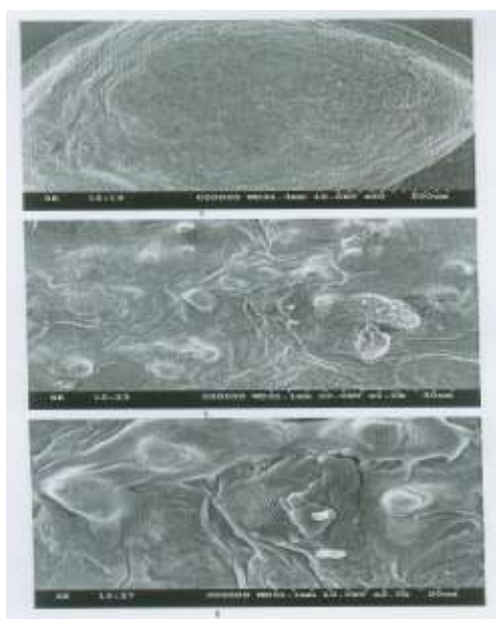


Fig. 9: SEM photographs of selected formulation

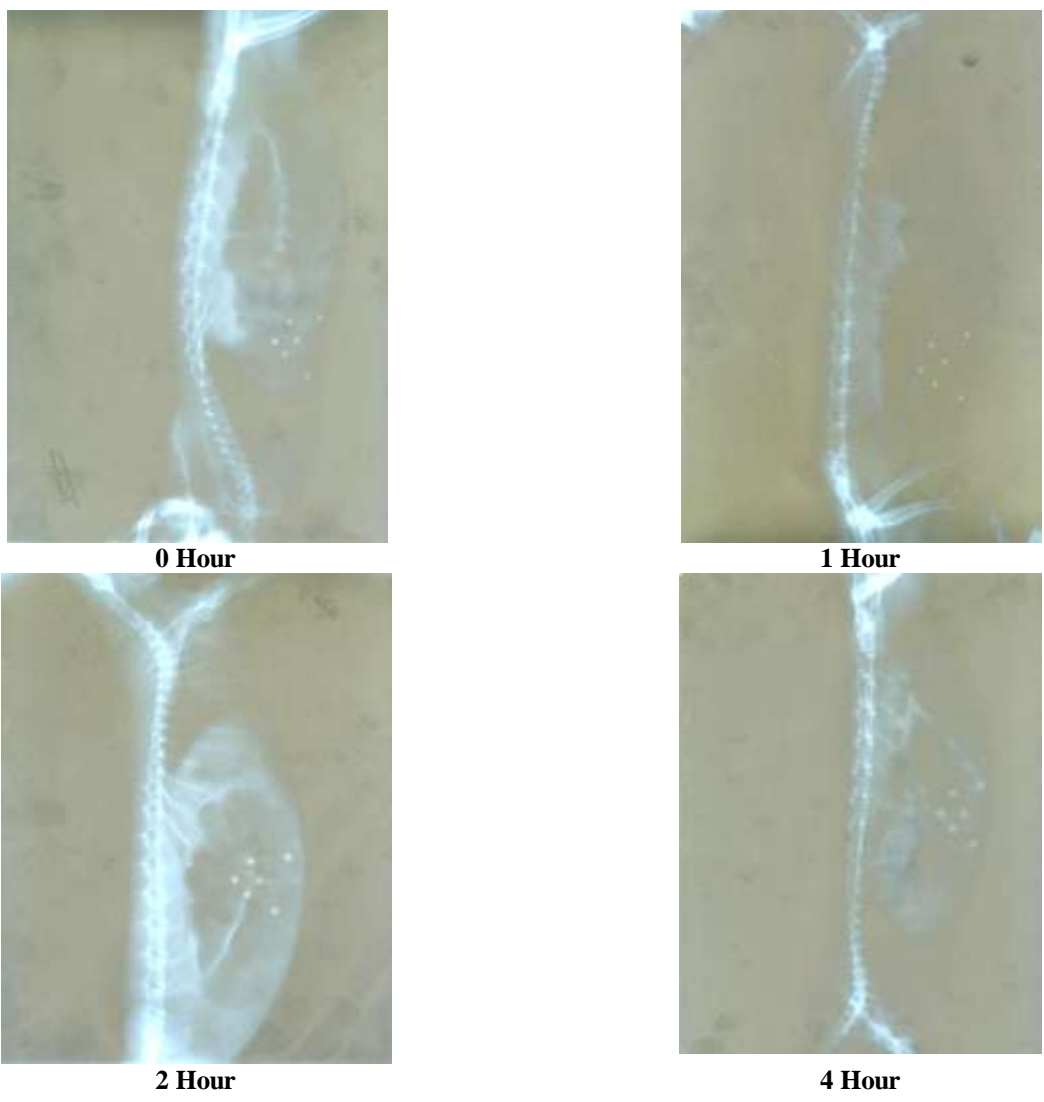


Fig 10 (A): GI Residence time studies of mucoadhesive Glimepiride Microbeads (x-ray studies)

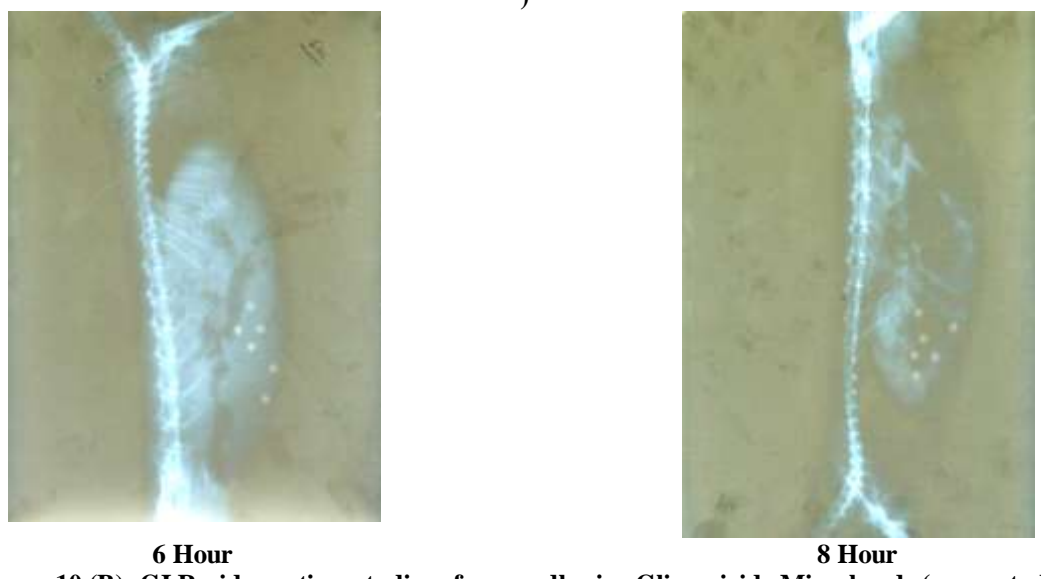


Figure.10 (B): GI Residence time studies of mucoadhesive Glimepiride Microbeads (x-ray studies)

CONCLUSION

Ionic gelation process was found to yield large, uniform sized spherical particles. Entrapment efficacy of Glimepiride was high with this method of preparation, Drug content was uniformly distributed in the beads. Wall thickness of the beads was found to be increased with the proportion of coating material employed in the preparation. The drug release rate followed first order kinetics and controlled by diffusion mechanism. Good correlation ship was observed in between wall thickness and release rate constant. The drug release rate was likely to be influenced by the coating material employed in the preparation of beads. HPMC offered much slower release when compared with the other two polymers. Alginate beads showed good mucoadhesion in 0.1 N HCl when compared with phosphate buffer. SEM studies showed that the beads are nearly spherical and covered with continuous coating shown in figure.9. The beads showed an elevation in GI residence time as shown in the figure 10(A) and figure 10(B). IR Spectral studies indicated compatibility in between drug & polymer. The drug release rate was found to be quite same as shown in figure 11(A), figure 11(B) and figure 11(C). Thus by changing the coating material, concentration of coating material and wall thickness, the required slow release could be readily obtained.

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