ISSN: 2230-7346

Venkateswara Reddy et al. / JGTPS / 6(1)-(2015) 2379 – 2387

(Research Article)

Journal of Global Trends in Pharmaceutical Sciences

Journal home page: www.jgtps.com

COMPARATIVE ASSESSMENT OF POTENTIAL OF VARIOUS POLYMERS IN THE FORMULATION DEVELOPMENT AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF GLIPIZIDE

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ABSTRACT

In the present work, bioadhesive microspheres of Glipizide using Sodium alginate along with Carbopol 934, Carbopol 940, HPMC K15M as copolymers were formulated to deliver Glipizide via oral route. The results of this investigation indicate that ionic cross linking technique of Ionotropic gelation method can be successfully employed to fabricate Glipizide microspheres. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used. Micromeritic studies revealed that microspheres have good flow properties. The mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration. Varoius parameters such as drug entrapment efficiency, % yield, swelling nature, in-vitro mucoadhesion strength were determined for the prepared formulations. The *invitro* drug release decreased with increase in the polymer and copolymer concentration. Analysis of drug release mechanism showed that the drug release from the formulations followed non-Fickian diffusion and the best fit model was found to be Korsmeyer-Peppas. Based on the results of evaluation tests formulation coded T_4 was concluded as best formulation.

Key words : Glipizide, Carbopol, Microspheres, Sodium alginate, Ionotropic gelation

INTRODUCTION:

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials that are biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin. The synthetic polymers include polylactic acid and polyglycolic acid. Microspheres are small and have large surface to volume ratios[1]. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity[2].

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Microspheres have varied applications and are prepared using assorted polymers. However the success of these microspheres is limited owing to their short residence time at the site of absorption[3]. So, various attempt have been made to increase the bioavailability as well as prolong the gastric residence time of dosage form in the stomach resulted in development of bio adhesive drug delivery system which will provide an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Mucoadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[4]. Mucoadhesive drug delivery system are the systems which utilizes the property of bio adhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time. Gastric mucoadhesive drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability[5, 6].

Glipizide is an oral hypoglycemic agent, a second-generation sulfonylurea which is a commonly prescribed drug for the treatment of type II diabetes[7]. It belongs to BCS class-II drug and has uniform, rapid and complete oral absorption with bioavailability of nearly 100%. It has a short half- life of 2-4 hours, thus there is a need to administer in 2-3 doses which leads to patient non-compliance. This short half life of the drug makes it a suitable candidate for the development of control release dosage form[8, 9]. In the present work Glipizide mucoadhesive microspheres were prepared using different polymers by ionotropic gelation method, where by the drug is retained in the stomach for longer period of time and releasing the drug in a controlled fashion.

MATERIALS AND METHODS:

Materials: Glipizide was obtained as a gift sample from Sura labs hyderabd. Sodium alginate, carbopol 934, carbopol 940, HPMC K 15 M,calcium chloride dehydrate were procured from merck specialiities Pvt Limited, Mumbai.

Methods:

Compatibility studies:

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable,efficacious, attractive and safe product hence before proceding to actual formulations compatibity of glipizide woth different polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique.

Fourier transform infrared spectroscopy(FTIR): In order to check the integrity of the drug in the formulation, FTIR spectra of the formulations along with the drug and other excipients were obtained and compared using Shimadzu FT-IR 8400 spectrophotometer. In the present study, Potassium bromide(KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug and the polymers.

Method of preparation

Ionotropic Gelation Method:

Microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer (as mentioned in table-1) were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. Glipizide (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 300rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried[10-12].

CHARACTERIZATION OF MICROSPHERES

Micromeritic properties

The microspheres were characterized by micromeritic properties such as particle size, bulk density, tapped density, compressibility index, Hausners ratio and angle of repose[13].

Bulk density

In this method microspheres are transferred to a measuring cylinder and are tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

$$Bulk\ density = \frac{Mass\ of\ microspheres}{bulk\ volume}$$

Tapped density

In this method microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density of microspheres.

Percent Compressibility index was determined by using the formula,

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

Hausners ratio

Hausners ratio of microspheres was determined by comparing tapped density to bulk density using the equation

$$\text{Hausners ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

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

Here, θ - Angle of repose; h - Height of granules above the flat surface; r - Radius of the circle formed by the microspheres heap. The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formu la:

$$\%\text{Yield} = \frac{\text{Practical mass (microspheres)}}{\text{Theoretical mass (Polymer + Drug)}}$$

Drug entrapment efficiency:

Microspheres equivalent to 15 mg of the drug Glipizide were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 1.2. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 269 nm[14, 15]. The amount of drug entrapped in the microspheres was calculated by the following formula,

$$\%\text{Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Particle size analysis:

Samples of the microspheres were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 microparticles sizes were calculated under 45 x magnifications. The average particle size was determined by using the Ed mondson's equation:

$$D_{mean} - \frac{nd}{n}$$

Where, n – Number of microspheres observed; d – Mean size range.

Swelling study:

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2 .The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$Swelling\ ratio = \frac{W_t - W_0}{W_0} \times 100$$

Where W_0 & W_t are initial weight and Final weight of microspheres respectively.

Evaluation of mucoadhesive property:

The mucoadhesive property of microspheres was evaluated by an *in-vitro* adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in simulated gastric fluid pH 1.2 at 37ºC contained in a 1-litre vessel of the apparatus. At an interval of 1 hour up to 8 hours the machine is stopped and number of microspheres still adhering to mucosal surface was counted[16].

$$\%\ \text{Mucoadhesion} = \frac{\text{Number of microspheres adhered}}{\text{Number of microspheres applied}} \times 100$$

***In vitro* drug release study:**

The dissolution studies were performed in a fully calibrated eight basket dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type–I rotating basket method in simulated gastric fluid pH 1.2 (900ml). A quantity of accurately weighed microspheres equivalent to 15mg Glipizide each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 269nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment[17,18].

***In-vitro* drug release kinetics:**.

To examine the release mechanism of Glipizide from the microspheres, the release data was fitted into different kinetic models such as zero order, first order, higuchi and peppas model.

RESULTS AND DISCUSSION

Drus excipient compatibility studies:

The FTIR spectras of the drug and drug along with polymers are given in the figures 1-5. The IR spectrum of all the combinations containing drug and drug with polymer shows same or slightly shift in peak values when compared with the characteristic peak values of the pure drug. Thus, from the above it is concluded that there is no interaction between glipizide and polymers used.

Evaluation and characterization of microspheres:

Micrometric properties

The data's were shown in Table 3.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index fall in the range of 13.06% to 18.18%. The Hausner ratio values are in the range of 1.14 to 1.22. From the result it was concluded that the microspheres had good flow properties.

Percentage yield:

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 80 to 88% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 62.22 to 87% for microspheres containing sodium alginate along with carbopol 940 as copolymer and 80 to 87.5% for microspheres containing sodium alginate along with HPMC K 15 M as copolymer. The percentage yield of the prepared microspheres is recorded in Table 4.

Drug entrapment efficiency:

Percentage Drug entrapment efficiency of Glipizide ranged from 82.66 to 88.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 53.2 to 76.66% for microspheres containing sodium alginate along with carbopol 940 as copolymer and 66.73 to 79.2% for microspheres containing sodium alginate along with HPMC K 15 M as copolymer. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer

concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is given in Table 4.

Particle size analysis:

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally microspheres size. Microspheres containing sodium alginate along with carbopol 934 as copolymer had a size range of 512µm to 826µm, microspheres containing sodium alginate along with carbopol 940 as copolymer exhibited a size range between 517µm to 834µm and microspheres containing sodium alginate along with HPMC K 15 M as copolymer had a size range of 664µm to 903µm. The particle size data is represented in table 4. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in polymer concentration.

Swelling study:

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swellability is an important characteristic as it affects drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in table 4 that with an increase in polymer concentration, the percentage of swelling also increases. Thus we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 28 to 85% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 24 to 64% for microspheres containing sodium alginate along with carbopol 940 as copolymer and 31 to 85% for microspheres containing sodium alginate along with HPMC K 15 M as copolymer.

***In-vitro* mucoadhesion test**

As the polymer to drug ratio increased, microspheres containing sodium alginate along with carbopol 934 as copolymer exhibited % mucoadhesion ranging from 65 to 85%, microspheres containing sodium alginate along with carbopol 940 as copolymer exhibited % mucoadhesion ranging from 60 to 75% and microspheres containing sodium alginate along with HPMC K 15 M as copolymer exhibited % mucoadhesion ranging from 60 to 80%. The results of *in-vitro* mucoadhesion test are complied in table 4. The rank of order of mucoadhesion is carbopol 934 > HPMC K 15M > carbopol 940.

***In-vitro* Drug release studies:**

The results of the in-vitro dissolution studies T_1 to T_4, T_5 to T_8 and T_9 to T_{12} are shown in table 5 and 6 and the compartitive profiles are given in figure 6 and 7. The formulations T_1, T_2, T_3 and T_4 containing Sodium alginate along with Carbopol 934 as copolymer showed a maximum release of 92.66% after 9 hours, 90.66% after 10 hours, 90.6% after 11 hours and 94.66% after 12 hours respectively. The formulations T_5, T_6, T_7 and T_8 containing Sodium alginate along with Carbopol 940 as copolymer showed a maximum release of 92.22% after 9 hours, 91.33% after 10 hours, 89.55% after 11 hours and 90.66% after 12 hours respectively. The formulations T_9, T_{10}, T_{11} and T_{12} containing Sodium alginate along with HPMC K 15 M as copolymer showed a maximum release of 92.6% after 9 hours, 91.3% after 10 hours, 90% after 11 hours and 92.44% after 12 hours respectively. This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

Table. 1: Prepared formulation of Bio adhesive microspheres.

Formulation Code	Drug: Polymer Ratio	Polymers	Polymer Ratio
T_1	1:2.5	Na alginate: Carbopol 934	1.5:1
T_2	1:3	Na alginate: Carbopol 934	2:1
T_3	1:3.5	Na alginate: Carbopol 934	2.5:1
T_4	1:4	Na alginate: Carbopol 934	3:1
T_5	1:2.5	Na alginate: Carbopol 940	1.5:1
T_6	1:3	Na alginate: Carbopol 940	2:1
T_7	1:3.5	Na alginate: Carbopol 940	2.5:1
T_8	1:4	Na alginate: Carbopol 940	3:1
T_9	1:2.5	Na alginate: HPMC K 15M	1.5:1
T_{10}	1:3	Na alginate: HPMC K 15 M	2:1
T_{11}	1:3.5	Na alginate: HPMC K 15 M	2.5:1
T_{12}	1:4	Na alginate: HPMC K 15 M	3:1

Table.2: Type of release mechanism

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport or non-Fickian	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Table.3: Micromeritic properties of microspheres

Formulations	Bulk Density (gm/cc)	Tap Density (gm/cc)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
T_1	0.45	0.55	18.18	1.22	27.91
T_2	0.47	0.55	14.54	1.17	28.23
T_3	0.50	0.58	13.79	1.16	29.34
T_4	0.46	0.55	16.36	1.19	26.71
T_5	0.50	0.58	13.79	1.16	29.34
T_6	0.47	0.55	14.54	1.17	28.23
T_7	0.50	0.58	13.79	1.16	29.34
T_8	0.41	0.50	18	1.21	26.78
T_9	0.43	0.50	14	1.16	26.78
T_{10}	0.42	0.51	18.24	1.20	26.68
T_{11}	0.48	0.56	18.12	1.21	26.70
T_{12}	0.41	0.54	18.11	1.22	26.71

Table.4: Characterization of microspheres

Formulation code	% yield	Particle size (µm)	% Drug entrapment efficiency	Percentage Swelling	Percentage mucoadhesion
T_1	80	512	82.66	28	65
T_2	83.33	617	84.4	42	70
T_3	85	711	84.66	62	75
T_4	88	826	88.66	85	85
T_5	62.22	517	53.2	24	60
T_6	80	642	55	39	65
T_7	80	792	68.86	55	70
T_8	87	834	76.66	64	75
T_9	80	664	66.73	31	60
T_{10}	86	774	70	53	70
T_{11}	86.66	814	75	67	75
T_{12}	87.5	903	79.2	85	80

Table.5: In-vito dissolution profile of the formulations T1-T6

Time (h)	Cumulative percentage of drug released					
	T_1	T_2	T_3	T_4	T_5	T_6
0	0	0	0	0	0	0
1	24.88	21.11	18.66	15.88	27.77	22.44
2	31.55	31.55	25.11	24.22	36.44	32.22
3	42.44	39.77	35.44	32.66	43.77	40.88
4	53.55	47.77	40.66	39.33	54.66	48.66
5	62	56.66	52	47.55	64.01	57.55
6	74.66	62.44	57.33	55.77	75.77	63.55
7	83.55	69.55	63.11	61.77	84.65	70.44
8	89.33	75.33	69.11	69.55	90	76.55
9	92.66	84.66	75.33	77.55	92.22	85.55
10	85.55	90.66	82.66	85.55	84.88	91.33
11	80.22	84.22	90.66	90.66	79.55	85.77
12	78.88	80.88	89.55	94.66	77.55	81.11

Table.6: *In-vito* dissolution profile of the formulations T7-T12

Time (h)	Cumulative percentage of drug released					
	T_7	T_8	T_9	T_{10}	T_{11}	T_{12}
0	0	0	0	0	0	0
1	18.44	17.11	25.77	21.55	18.66	16.44
2	29.33	26.44	35.33	31.77	26.55	27.11
3	39.55	37.55	43.55	40.44	36.55	36.44
4	45.55	46.88	54	48.44	43.66	45.55
5	57.33	55.77	63.55	57.11	54.55	55.33
6	65.33	63.55	75.33	63.11	62.33	63.11
7	71.55	71.33	84	70.22	67.68	71.55
8	77.56	75.77	89.77	76	73.55	76.44
9	81.55	79.77	92.66	85.11	78.55	80.66
10	83.33	82.44	85.11	91.33	83	85.55
11	89.55	86.88	80.66	85.33	90	89.55
12	87.55	90.66	78	81.11	87.55	92.44

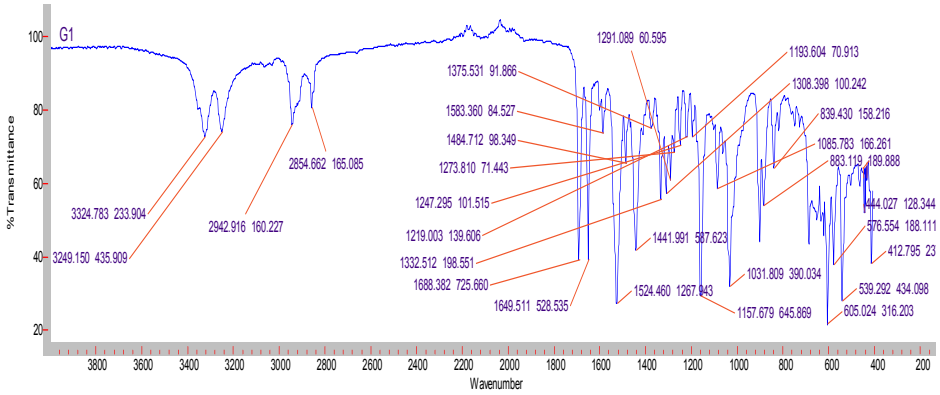

Figure.1: FTIR spectra of pure drug

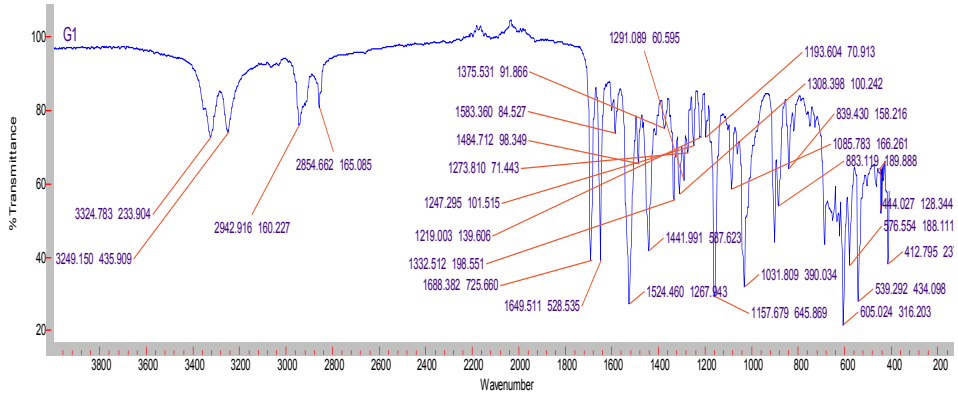

Figure.2: FTIR spectra of drug with sodium alginate

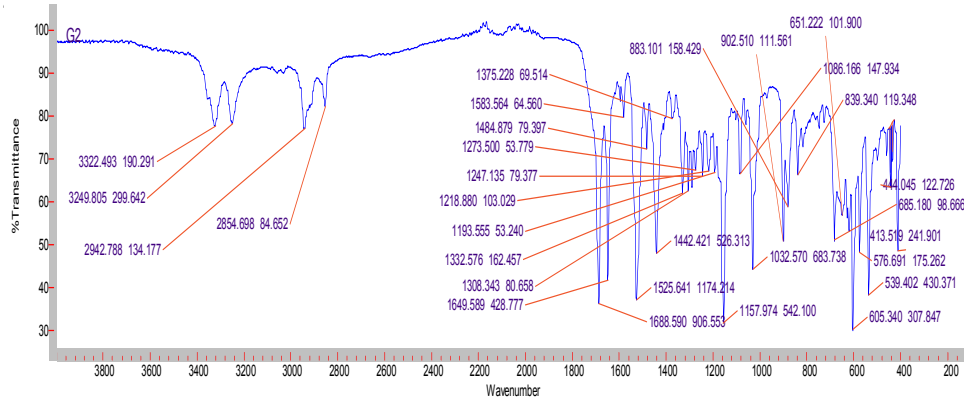

Figure.3: FTIR spectra of drug with carbapol 934

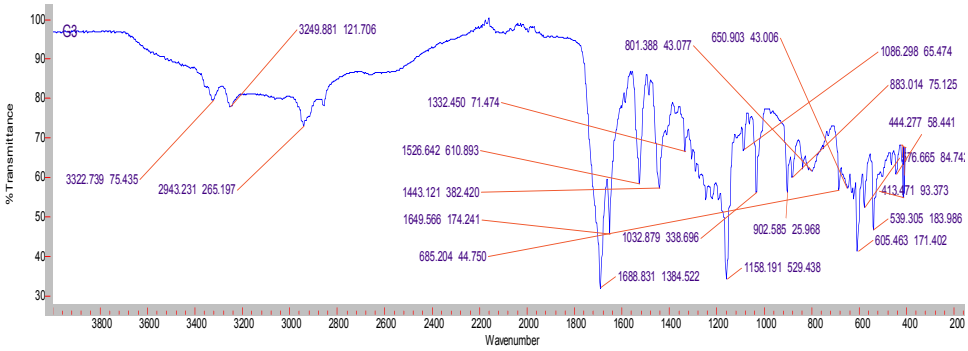

Figure.4: FTIR spectra of drug with carbapol 940

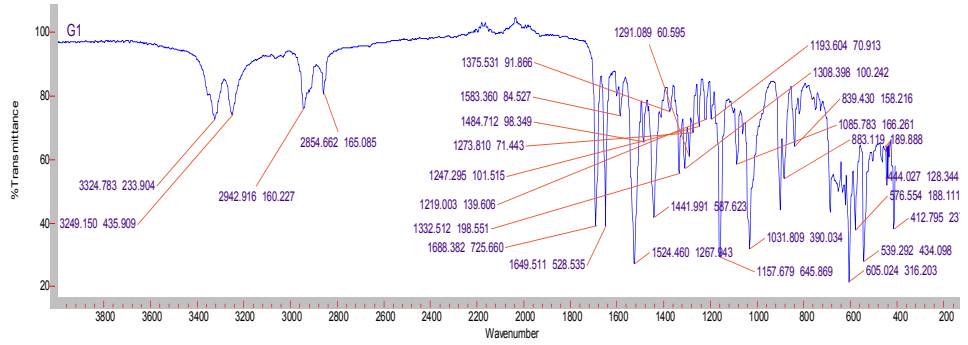

Figure.5: FTIR spectra of drug with HPMC K15M

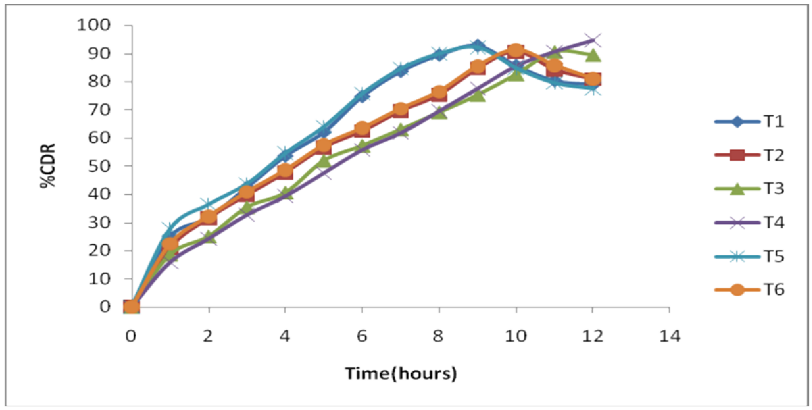

Figure.6: Compartive dissolution profile of formulations T1-T6

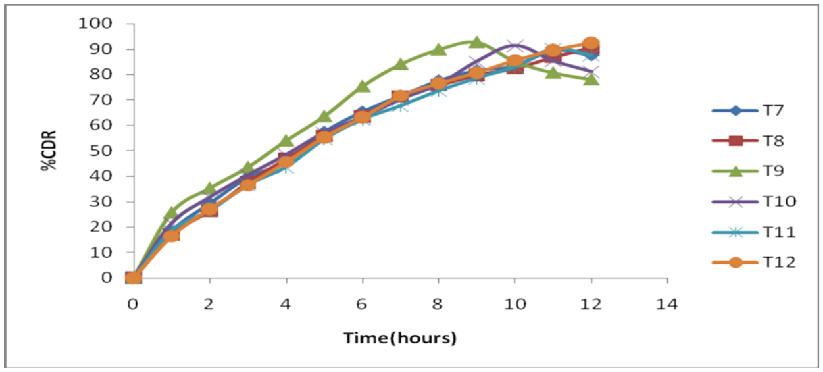

Figure.7: Compartive dissolution profile of formulations T7-T12

CONCLUSION:

The results of this investigation indicate that ionic cross linking technique of Ionotropic gelation method can be successfully employed to fabricate Glipizide microspheres. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion.The *in-vitro* mucoadhesive study demonstrated that microspheres of Glipizide using sodium alginate along with Carbopol934 as copolymer adhered to the mucus to a greater extent than the microspheres of Glipizide using sodium alginate along with Carbopol 940 and HPMC K15M as copolymers. The *invitro* drug release decreased with increase in the polymer and copolymer concentration. Out of all the formulations prepared formulation T4 has shown maximum drug release at the end of 12^{th} hour. The drug release is found to follow non-fickian diffusion. From the results it is conclued that the formulation T4 containing Na alginate and Carbopol 934 in 3:1 ratio have shown to be promising one with desired properties for the delivery of glipizide via oral route.

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How to cite this article:
B.Venkateswara reddy, K.Navaneetha*: Comparative assessment of potential of various polymers in the formulation development and evaluation of mucoadhesive microspheres of glipizide, 6(1): 2379 - 2387. (2015)*