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FORMULATION AND *INVITRO* EVALUATION OF GLICLAZIDE MICROBEADS

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ABSTRACT

An attempt was made to formulate and evaluate alginate floating microspheres of gliclazide as a model drug by ion cross-linking technique or ion gelation method using cacl2 as cross-linking agent. The microspheres were formulated using sodium alginate (as release retardant agent) with a view to deliver drug at controlled/sustained manner in GIT and consequently into systemic circulation. The prepared microspheres were evaluated for particle size, angle of repose, % yield,% drug entrapment efficiency, degree of swelling and invitro drug release studies. The release rates were studied using dissolution apparatus. the percentage yield was decreased from F1-F4. This was found to be in the following order 89.755,87.56%,86.91% and 85.62%respectively. The drug entrapment efficiency of the microbeads prepared from sodium alginate alone were found to be in the range of 66.38-79.62% The average particle size of different formulations were 850,1050,1225,1155µ respectively. The percentage buoyancy of microbeads F1-F4 was increased from 55-86.3% . For F1 formulation the % drug release was 80% at the end of the 4th hour. For F2,F3,F4 formulation at the end of the 4th hour 77.2%,82.8%,84.8% was observed. Large particle size at greater polymer concencentration enhanced the polymer matrix density. The diffusional path length of the microbead increased which ultimately resulted in sustained drug release.

KEYWORDS: gliclazide, alginate beads, ion- crosslinking method, sodium alginate, diabetes mellitus, floating microspheres.

INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and most preferred method for administarting therapeutically agents for systemic effects because it is a natural, convenient and cost effective to manufacturing process. Oral route is the most commonly used for the drug administration.[1] Microspheres are small spherical particles, with diameters in the micrometer range (typically 1μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials.[2]

During the last decade, many studies have been performed concerning the sustain release dosage forms of drug, which have aimed at the prolongation of gastric emptying time (GET). The GET has been reported to be from 2 to 6 hours, in humans in fed state. Retention of drug delivery system in the stomach prolongs overall gastrointestinal transit time, there by resulting in bioavailability. Drugs that are required to be formulated into gastro retentive dosage forms include, drugs acting locally and primarily absorbed in stomach, drugs that are poorly soluble at an alkaline ph, those with a narrow window of absorption , drugs absorbed rapidly from GIT and drugs that degrade in colon scintigraphic studies determining gastric emptying rates revealed that orally administered to basically two complication; that of short residence time and unpredictable gastric empting rate.[3]

Controlled release or Extended-release dosage forms with prolonged residence times in the stomach is highly desirable for drugs which are.[9]

1. Has an absorption window in the stomach
2. Targeted at sites in the upper GI tract
3. Imbalancing, irritating, or unsafe in the lower GI region
4. More effective when plasma levels are more constant
5. Locally active in the stomach
6. Unstable in the intestinal or colonic environment
7. Low solubility at high pH values

Gliclazide is a second generation sulfonyl urea used in the treatment of diabetes. Gliclazide is selected as model drug for investigation because of its suitable properties like low dose (5 mg), half life of 10.4 hours and molecular weight (323.412 g/mol). In addition; it has the potential for slowing the progression of diabetic retinopathy. For these reasons, it appears to be a drug of choice in prolonged therapy for the control of NIDDM. However, the drawback

of this potentially useful hypoglycemic agent is that it belongs to BCS class 2 and therefore is highly hydrophobic and practically insoluble in water. Gliclazide exhibits slow GI absorption rate and inter individual variations of its bioavailability. The slow absorption rate of the drug usually originates from either poor dissolution of drug from the formulation or poor permeability of the drug across the GI membrane. The objective of this study is to formulate and evaluate alginate beads of gliclazide using different proportions of sodium alginate for controlled/sustained drug release. Gliclazide is a selective second generation sulphonylurea used in the treatment of hyperglycemia. It is poorly soluble in the acidic environment. When it is given orally in healthy people, it absorbs rapidly and completely. However, its absorption is erratic in diabetic patients due to reduced gastric motility. To over come these drawbacks, in the present study gastro retentive controlled release dosage form of gliclazide was formulated.

MATERIAL AND METHODS

Gliclazide was obtained as a gift sample from medrich, India. Sodium alginate was obtained from S.D. Fine Chemicals Ltd., India. Calcium chloride was obtained from qualigens chemicals mumbai., India. All other chemicals/reagents used were of analytical grade.

1. Determination of λ_{max} of gliclazide in 0.1N Hcl

Stock solution (100µg/ml) of gliclazide was prepared in 0.1N Hcl pH 1.2. This solution was appropriately diluted to obtain a concentration of 10µg/ml. The resultant solution was scanned in the range of 200nm to 360nm on Elico SL -159 UV- Visible spectrophotometer. The drug exhibited a λ_{max} at 227.0nm in 0.1N Hcl pH 1.2.

2. Preparation Of Beads Containing Gliclazide

The beads containing gliclazide was prepared by ionotropic -gelation method. Required amount of sodium alginate was dissolved in 50ml demineralised water with constant stirring. Accurately weighed quantity of gliclazide were added to sodium alginate solution. The final mixture containing sodium alginate was stirred at 5000 rpm continuously for 30 min until the homogeneous and stable suspension was formed. Then, the suspension was dropped through 21G needle into 10 % (w/v) calcium chloride chloride solution (100 ml), and the added droplets were retained for 15 min in the calcium chloride solution to complete the curing reaction. The prepared beads were filtered. The dried beads containing gliclazide were stored in desiccators until used.[4,6]

Table 1: Composition of various gliclazide beads

S.No	Ingridients	F1	F2	F3	F4
1	Gliclazide (mg)	80	80	80	80
2	Sodium alginate (mg)	80	160	240	320
3	Calcium chloride(10%w/v)(ml)	q.s	q.s	q.s	q.s

3. Percentage Yield

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[8]. The percentage yield was calculated using the following formula

$$\% \text{ yield} = \frac{\text{practical yield}}{\text{Theoretical yield}} \times 100$$

4. Determination Of Drug Entrapment Efficiency

Accurately weighed 100mg of prepared beads from each batch were taken separately and were crushed using pestle and mortar. The crushed powders were placed in 100ml of 0.1N HCl (pH 1.2) and kept for 24h with occasionally shaking at 37±0.5°C. After the stipulated time, the mixture was stirred at 500 rpm for 15min on a magnetic stirrer. The polymer debris formed after disintegration of bead was removed by filtering through Whatman filter paper (No. 40) [2]. Then, the drug content in the filtrate samples were determined using a UV–vis spectrophotometer (schimadzu 1800) by measuring absorbance at λ_{max} of 227nm.

The % DEE of beads was calculated using this following formula.

% DEE = (actual drug content in beads/ theoretical drug content in beads) × 100

5. Determination of bead size

Many methods are available for determining particle size, such as optical microscopy, sieving, sedimentation and particle volume measurement. Optical micro scopy is most commonly used for the particle size determination.[7]

Procedure

Particle size of the prepared microspheres was determined by optical microscopy. The optical microscope was fitted with an eye piece micrometer and a stage micrometer. The eyepiece micrometer was calibrated. The particle diameters of 200 microspheres were measured randomly by optical microscope.[3]

Calibration of Eyepiece Micrometer

One division of the stage micrometer = 0.01 mm = 10 µm

µ = (SM / EM) x 100

Where,

µ – Correction factor

SM – reading of stage micro meter, which coincides, with reading of

Eye piece micrometer (EM)

The average particle size was determined by using the Edmondson's equation:

$\frac{\sum nd}{\sum n}$

Where,

n – Number of microspheres observed

d – Mean size range

Each microsphere sizes were classified under different size range, the particle size data of the formulations is recorded in table 3 to 6 and particle size distribution is shown in the Figure 4 to 7.

6. Determination of buoyancy

Fifty milligrams of microballoons were placed in 100 ml simulated gastric fluid (SGF, pH 1.2). The mixture was stirred at 100 rpm on a magnetic stirrer.After 4 h, the floating and settled microballoons were collected separately, dried at 40^0C and weighed. The buoyancy was determined by the following formula.

$$\textbf{Buoyancy} = \frac{weight\ of\ floating\ microballoons \times 100}{weight\ of\ floating\ microballoons + weigth\ of\ settled\ microballoons}$$

7. 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.[8]

$$\textbf{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 &Wt are initial weight and Final weight of microspheres respectively.

8. In vitro drug release study

The release rate from different fractions of the formulation was determined using USP type II apparatus. Dissolution medium (SGF, pH 1.2, 900 ml) was filled in the dissolution vessel and stirred at 50 rpm. The temperature was maintained at 37 ± 0.5^0C. A weight of microballoons equivalent to 50 mg of gliclazide was placed in the dissolution vessel. Aliquots were withdrawn at every 15 min of the first hour and then at every hour till 4 hours. Samples were then analyzed by UV spectrophotometer at λ_{max} of 227nm.[10]

RESULTS

1.EVALUATION OF THE PREPARED MICROBEADS

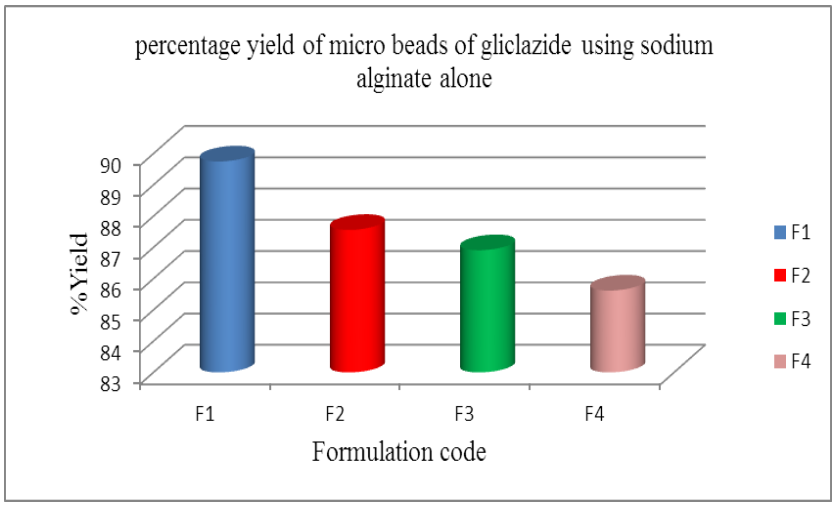

Fig.1.percentage yield of micro beads of gliclazide using sodium alginate alone

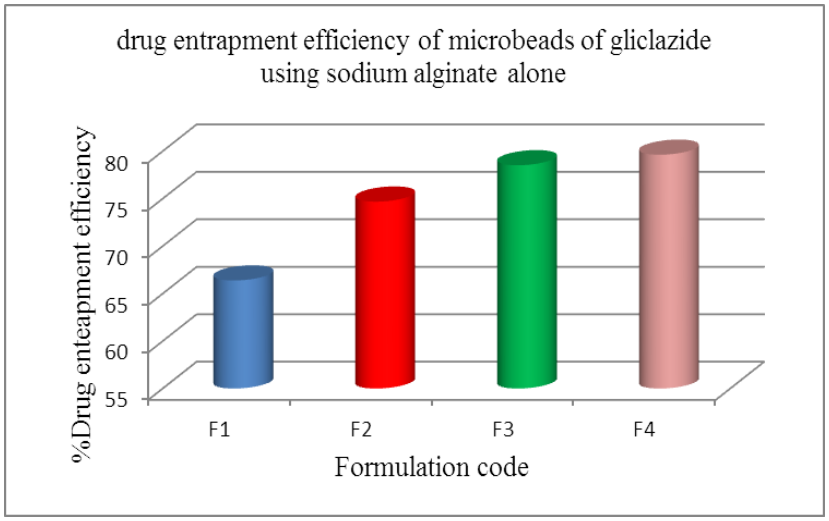

Fig.2.drug entrapment efficiency of microbeads of gliclazide using sodium alginate alone

Particle Size Analysis

Table 2. particle size data of F1

S.No	Particle size µm	Frequency(n)	Particle mid point(d)	nd	Average particle size
1.	500-600	1	550	550	850µ
2.	600-700	2	650	1300	
3.	700-800	6	750	4500	
4.	800-900	6	850	5100	
5.	900-1000	1	950	950	
6.	1000-1100	1	1050	1050	
7.	1100-1200	2	1150	2300	
8.	1200-1300	1	1250	1250	

∑n=20 ∑nd= 17000

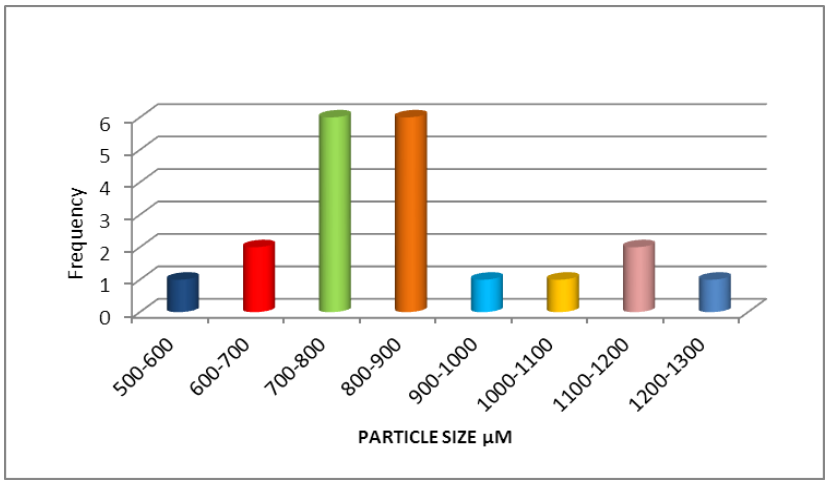

Fig.3.particle size data of F1

Table 3. particle size data of F2

S.No	Particle size µm	Frequency(n)	Particle mid point(d)	nd	Average particle size
1	800-900	3	850	2550	1050µ
2	900-1000	3	950	2850	
3	1000-1100	6	1050	6300	
4	1100-1200	2	1150	1300	
5	1200-1300	3	1250	3750	
6	1300-1400	3	1350	4050	

∑n=20 ∑nd= 20800

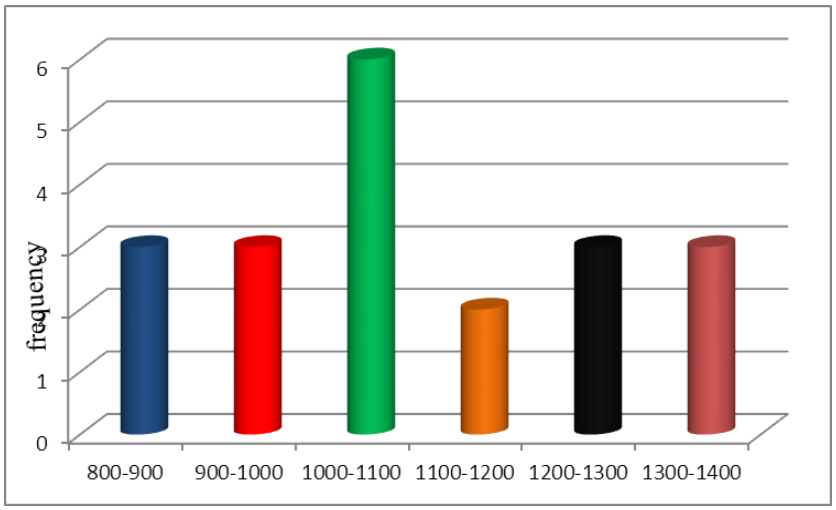

Fig.4.particle size data of F2

Table 4. particle size data of F3

S. N.	Particle size µm	Frequency(n)	Particle mid point(d)	nd	Average particle size
1	800-900	1	850	850	
2	900-1000	1	950	950	
3	1000-1100	2	1050	2100	
4	1100-1200	5	1150	5750	
5	1200-1300	5	1250	6250	1225µ
6	1300-1400	3	1350	4050	
7	1400-1500	1	1450	1450	
8	1500-1600	2	1550	3100	

∑n=20 ∑nd= 24500

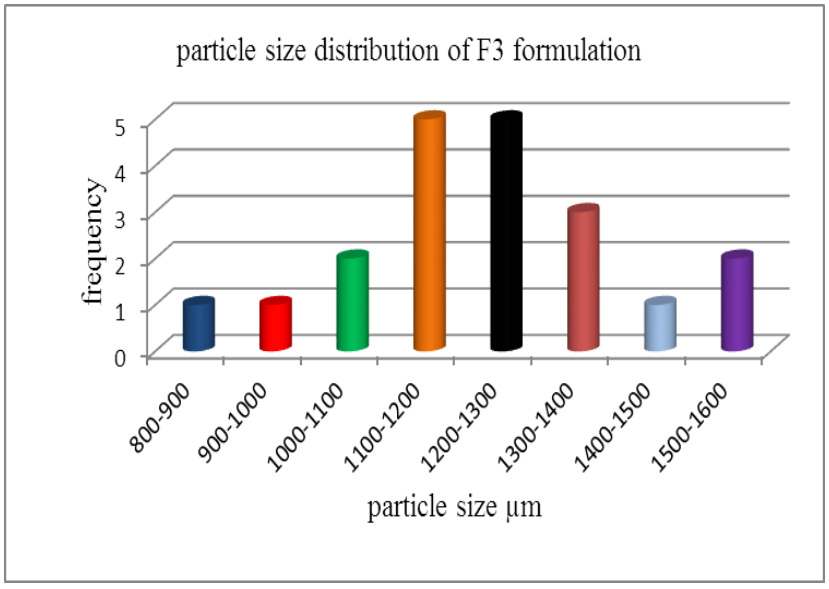

Fig.5.particle size data of F3

Table 5. particle size data of F4

S. No.	Particle size µm	Frequency(n)	Particle mid point(d)	nd	Average particle size
1.	800-900	1	850	850	
2.	900-1000	2	950	1900	
3.	1000-1100	2	1050	1050	
4.	1100-1200	7	1150	1150	
5.	1200-1300	6	1250	1250	1155µ
6.	1300-1400	2	1350	1350	

∑n=20 ∑nd= 23100

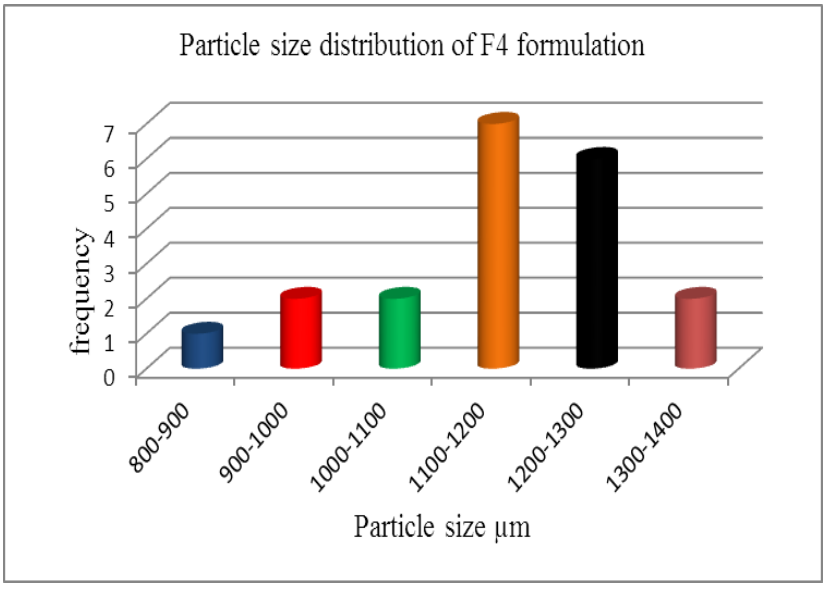

Fig.6.particle size data of F4

In Vitro Drug Release Studies

Table 6. Comparision Of Invitro Drug Release Of Microbeads Of Gliclazide Using Sodium Alginate

Time (minutes)	%cumulative drug release			
	F1	F2	F3	F4
30	70.8	43.6	50	50
60	71.6	69.6	75.6	57.6
120	74.4	70.8	76.4	80
180	78	76.4	77.2	82
240	80	81.2	82.8	84.8

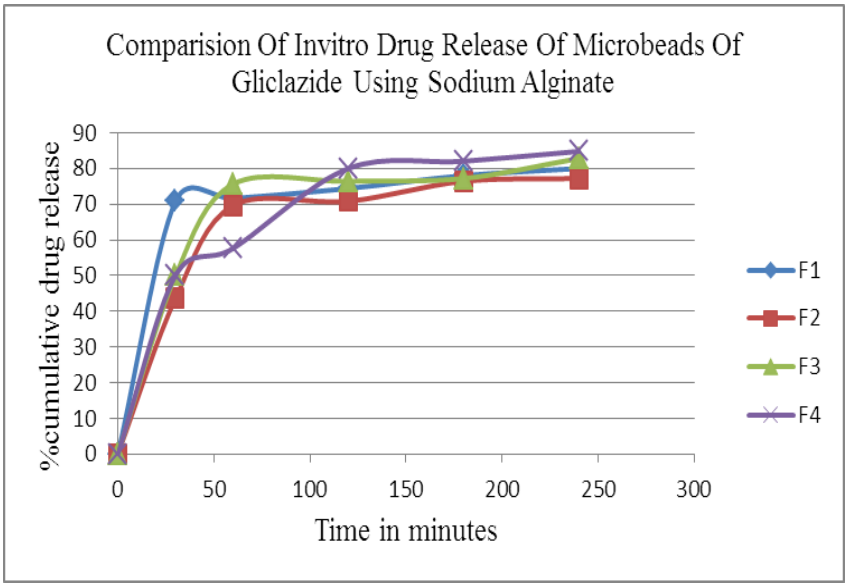

Fig.7.Comparision of Invitro Drug Release of Microbeads of Gliclazide Using Sodium Alginate

Table no 7. Evaluation of microbeads

Formulation code	% yield	Particle size (μ)	%Drug entrapment efficiency	% buoyancy	% swelling index	% drug release
F1	89.75	850	66.38	55	52.34	80
F2	87.56	1050	74.68	65	69.72	81.2
F3	86.91	1225	78.51	70	88.03	82.8
F4	85.62	1155	79.62	71	90.14	84.8

DISCUSSION

In the present investigation an attempt was made to prepare floating alginate microspheres of gliclazide using sodium alginate by ion cross-linking method or ion gelation method and various evaluation parameters were assessed , with a view to obtain sustained release for oral delivery.Water based ionic cross-linking technique can provide characterstic advantage over conventional microsphere which involves an "all-aqeous" system and avoids residual solvents in microsphers.Four formulations were prepared and the detailed composition is presented in table no.1. the prepared microspheres were then subjected to particle size analysis, drug entrapment efficiency,buoyancy study,swelling index and invitro drug release studies.

Preparation Of Alginate Microbeads

Totally four formulations of Floating micro beads were prepared using sodium alginate as polymer at different proportions .The present study was made inorder to evaluate the effect

of polymer concentration on the floating behavior, particle size , drug entrapment effficency, swelling index and invitro drug release from the polymer matrix .The prepared floating microbeads were physically observed for their shape and colour. The microbeads which were prepared with sodium alginate were light cream. all four formulations were regular in size with spherical shape.

Evaluation Of The Prepared Floating Microbeads

Percentage Yield

It was observed that as the polymer ratio increases the percentage yield was decreased . the probable reason behind this was due to increased viscosity and decreased syringibility of the polymer solution . the drug- polymer solution wastage occurred in the stirring of the mixture which adhered to the lab stirrer. the percentage yield was decreased from F1-F4. This was found to be in the following order 89.755,87.56%,86.91% and 85.62% respectively. The percentage yield was recorded in the table no.7 And figure no.1 respectively.

Drug Entrapment Efficiency

The drug entrapment efficiency of the microbeads prepared from sodium alginate alone were found to be in the range of 66.38-79.62%. increased polymer concentration increased the drug entrapment efficiency. this is due to the higher polymer concentration resulted in the greater viscosity which helps to higher drug loading. This property decreases the diffusion of the drug from the polymer matrix.

The drug entrapment efficiency of the floating microbeads were represented in the table no 7 and displayed in figure no.2.

Particle Size Analysis

The average particle size of different formulations were 850,1050,1225,1155µ respectively. The mean particle size was increased with increase in the polymer concentration upto formulation F3 and decreased for formulation F4. in the four formulations which are prepared with sodium alginate alone there is a linear relationship in the increasing order up to 1:3 ratio of drug and sodium alginate. Decreasing the viscosity of polymer solution caused the mean particle size to shift towards a lower particle size. Increasing the viscosity of polymer solution, formed larger droplets and consequently, microcapsules with large particle size.[11] The particle size distribution data was represented in the table no. 2 to 5 and displayed in figure no. 3 to 6.

% Buoyancy

The percentage buoyancy of microbeads was increased with increase in the polymer proportion. the higher water imbibition resulted in the formation of hydrogel. this imparts higher buoyancy of the micro beads. Here, the water imbibition capacity enhanced the buoyancy. The percentage buoyancy of microbeads F1-F4 was increased from 55-71%. it was represented in the table no. 7.

Invitro Drug Release Study

Dissolution studies of all formulations were carried out using dissolution apparatus USP-I. The dissolution studies were conducted using dissolution medium 0.1N Hcl.The results of the invitro dissolution studies of formulations from F1-F4 were represented in table no6,7. and displayed in fig no 7.The invitro drug release profiles were plotted between % cumulative drug release and time . formulations F1-F4 showed drug release at the end of the 4^{th} hour. For F1 formulation the % drug release was 80% at the end of the 4^{th} hour. For F 2,F3,F4 formulation at the end of the 4^{th} hour 77.2%,82.8%,84.8% was observed. With increase in the proportion of the polymer there was an increase in drug release except for F2 formulation. Large particle size at greater polymer concencentration enhanced the polymer matrix density. The diffusional path length of the microbead increased which ultimately resulted in sustained drug release. In sodium alginate micro bead formulations ,F4 microbeads showed enhanced drug release due to enhanced polymer density.

CONCLUSION

From the above experimental results it can be concluded that.

• Oral controlled release of *Gliclazide* can be achieved by ionotropic gelation technique using sodium alginate and aloe vera gel powder.

• From the study it is evident that a promising controlled release microparticulate drug delivery of *Gliclazide* can be developed. Further in-vivo investigation is required to establish efficacy of these formulations.

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