DESIGN & DEVELOPMENT OF GLICLAZIDE FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The objective of this study is to formulate and evaluate alginate beads of Gliclazide using different proportions of sodium alginate and aloe vera gel powder for controlled/sustained drug release. Gliclazide is a second-generation sulfonyl urea used in the treatment of diabetes. The sulfonyl ureas drug class includes the effective oral antidiabetic medication Gliclazide, which is frequently used for the treatment of non-insulin dependent (Type II) diabetes mellitus. It is mainly absorbed from the stomach and is only moderately soluble in aqueous solutions. In order to improve the oral bioavailability of Gliclazide and to better control blood glucose levels to prevent hypoglycemia, which would improve clinical effectiveness and patient compliance, gastro retentive controlled release drug delivery systems are required. In the current study, floating microsphere tablets designed to increase bioavailability and achieve controlled release over 24 hours for once daily dosage. Alginate microspheres of Gliclazide were developed and tested as a model medication utilizing an ion cross-linking technique or ion gelation method with calcium chloride as the cross-linking agent. To deliver the medicament in the GIT in a controlled and sustained manner, as well as in combination with Aloe vera gel powder as a release retardant agent, the microspheres

were formulated using sodium alginate both alone and in copolymer form. Particle size, angle of repose, yield, drug entrapment efficiency, degree of swelling, and invitro drug release tests were assessed for the prepared microspheres. Dissolution apparatus was used to assess the release rates.

Key words: Gliclazide, Alginate beads, Ion- cross linking method, Aloe vera gel powder, Sodium alginate, Diabetes mellitus.

INTRODUCTION

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 and aloe vera gel powder for controlled/sustained drug release. An attempt was made to formulate and evaluate alginate microspheres of Gliclazide as a model drug by ion cross-linking technique or ion gelation method using Calcium chloride as cross-linking agent. The microspheres were formulated using sodium alginate alone and in combination with Aloe vera gel powder as copolymer (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.

In the present investigation an attempt was made to prepare floating alginate microspheres of gliclazide using sodium alginate alone and in combination with aloe gel powder as co polymer 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. Eight formulations were prepared and the detailed composition and the prepared microspheres were then subjected to particle size analysis, drug entrapment efficiency,

buoyancy study and invitro drug release studies.

MATERIALS AND METHODS

Materials

The API Gliclazide is received as gift sample. Sodium alginate Calcium chloride and Sodium bicarbonate are procured from local market.

Preparation of *Alovera* gel powder:

The leaves of Aloe vera plant were collected. Freshly cut *Aloe vera* leaves were washed with Millipore water and then cut open to collect the gel. The gel is then washed with Millipore distilled water and air dried for two days under ambient condition and then at 50ºC in a hot-air oven for four days to get a solid dry mass. This was then converted into fine powder by mechanical grinding and sieving. The *Aloe vera* gel powder is then stored under refrigeration.

Preparation of Beads Containing Gliclazide:

Inotropic- Gelation Method

The beads containing gliclazide was prepared by ionotropic -gelation method. Required amount of sodium alginate was dissolved in 50ml demineralized water with constant stirring. Accurately weighed quantity of drug(gliclazide) and sodium bicarbonate 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 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.

Table 1: Composition of various Gliclazide beads

SNO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1.	Gliclazide(mg)	80	80	80	80	80	80	80	80
2.	Sodium alginate(mg)	80	160	240	320	80	80	80	80
3.	Aloe gel powder(mg)	-	-	-	-	80	160	240	320
4.	Calcium chloride(10%w/v)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
5.	Sodium bicarbonate(mg)	80	80	80	80	80	80	80	80

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). Then, the drug content in the filtrate samples were determined using a UV–vis spectrophotometer (Shimadzu 1800) by measuring absorbance at λ max of 227nm.

Determination of buoyancy

Fifty milligrams of micro balloons 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 micro balloons were collected separately, dried at 400C and weighed.

Determination of bead size

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.

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 micro balloons 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.

RESULTS

Eight microsphere formulations were developed, and they were subsequently tested for particle size, drug entrapment effectiveness, buoyancy, and in vitro drug release.

FIG. No. 1: FTIR Spectrum of Pure Gliclazide

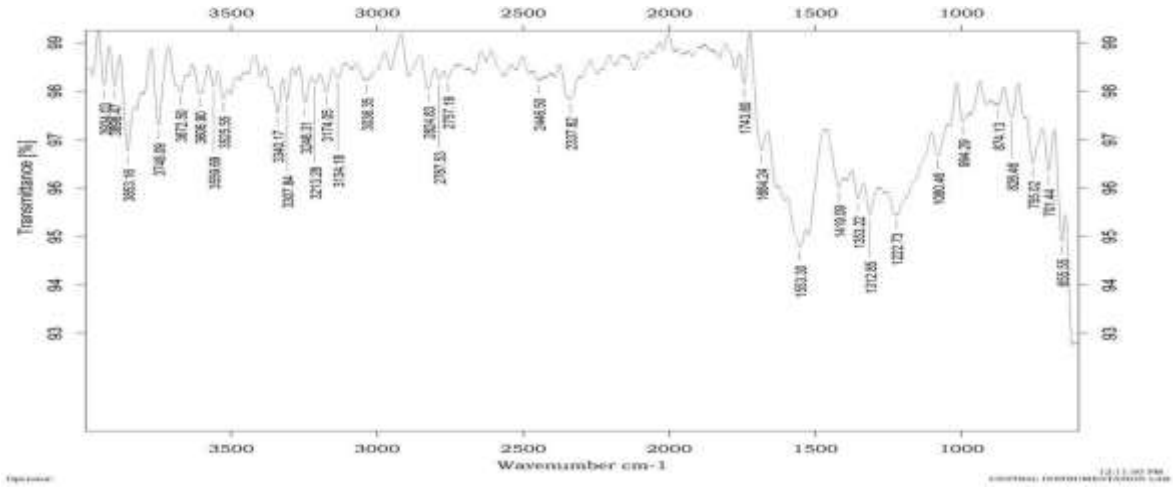
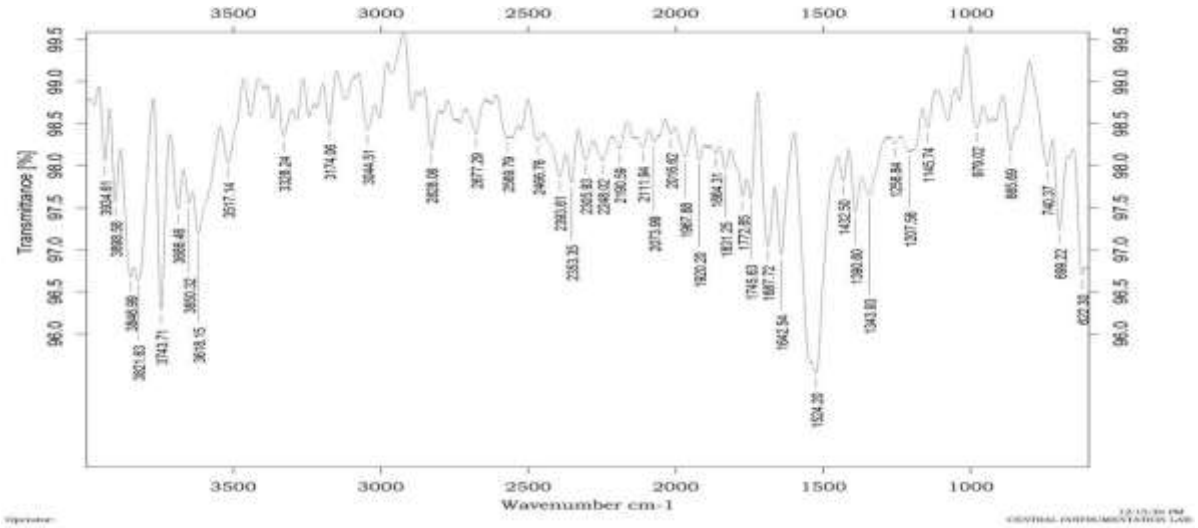


FIG. No. 2: FTIR Spectrum of Gliclazide Aloe- Sodium Alginate Beads



Evaluation of Floating Micro beads:

Percentage yield

Table 2: percentage yield of microbeads of Gliclazide using sodium alginate

Formulation code	F1	F2	F3	F4
% yield	89.75	87.56	86.91	85.62

Table 3: percentage yield of micro beads of gliclazide using aloe gel powder as Co-polymer

Formulation code	F5	F6	F7	F8
% yield	85.93	83.10	81.57	81.13

Drug Entrapment Efficiency

Table 4: Drug entrapment efficiency of microbeads of Gliclazide using sodium alginate alone

Formulation code	Drug content (mg)	% drug entrapment efficiency
F1	6.638	66.38
F2	**7.**468	74.68
F3	7.851	78.51
F4	7.962	79.62

Table 5: Drug entrapment efficiency of microbeads of gliclazide using Aloe vera gel as co-polymer

Formulation code	Drug content (mg)	% drug entrapment efficiency
F5	8.170	81.70
F6	8.659	86.59
F7	8.957	89.57
F8	9.035	90.35

Particle Size Analysis

The average particle size of different formulations was 850,1050,1225,1155,1325,1265,1140 and 1217.5µ respectively. The mean particle size was increased with increase in the polymer concentration up to formulation F3 and decreased for formulation F4, it was increased for formulation F5, and decreased up to F7. So, there is no relationship between polymer concentration and particle size. In the first set of 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 and further increase in the concentration from this drug: polymer ratio decreased the particle size. The second set of formulations which were prepared from sodium alginate and aloe gel by keeping the sodium alginate proportion at constant, the aloe vera gel concentration was increased but the particle size was decreased from 1325-1140µ. The particle size of formulation of F8 was increased to 1217.5µ

Table 6: Particle size data of F1

S.No	Particle size µm	Frequency(n)	Particle midpoint(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	

Table 7: 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	

Table 8: particle size data of F3

S.No	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	1225 µm
5.	1200-1300	5	1250	6250	
6.	1300-1400	3	1350	4050	
7.	1400-1500	1	1450	1450	
8.	1500-1600	2	1550	3100	

Table 9: Particle size data of F5

S.No	Particle size µm	Frequency(n)	Particle mid-point(d)	nd	Average particle size
1.	900-1000	1	950	950	1325µ
2.	1000-1100	1	1050	1050	
3.	1100-1200	2	1150	2300	
4.	1200-1300	5	1250	6250	
5.	1300-1400	2	1350	2700	
6.	1400-1500	7	1450	10150	
7.	1500-1600	2	1550	3100	

Table 10: Particle size data of F6

S.NO	Particle size µm	Frequency(n)	Particle mid-point(d)	nd	Average particle size
1.	700-800	2	750	1500	1265µ
2.	800-900	1	850	850	
3.	900-1000	0	950	0	
4.	1000-1100	1	1050	1050	
5.	1100-1200	2	1150	2300	
6.	1200-1300	4	1250	5000	
7.	1300-1400	3	1350	4050	
8.	1400-1500	3	1450	4350	
9.	1500-1600	4	1550	6320	

Table 11: particle size data of F7

S.No	Particle size µm	Frequency(n)	Particle mid-point(d)	nd	Average particle size
1.	700-800	1	750	750	1140µ
2.	800-900	2	850	1700	
3.	900-1000	5	950	4750	

4.	1000-1100	1	1050	1050	
5.	1100-1200	2	1150	2300	
6.	1200-1300	3	1250	3750	
7.	1300-1400	3	1350	4050	
8.	1400-1500	2	1450	2900	
9.	1500-1600	1	1550	1550	

Table 12: Particle size data of F8

S.No	Particle size µm	Frequency(n)	Particle mid point(d)	nd	Average particle size
1.	700-800	1	750	750	1217.5µ
2.	800-900	2	850	1700	
3.	900-1000	5	950	4750	
4.	1000-1100	1	1050	1050	
5.	1100-1200	2	1150	2300	
6.	1200-1300	3	1250	3750	
7.	1300-1400	3	1350	4050	
8.	1400-1500	2	1450	2900	
9.	1500-1600	2	1550	3100	

Determination of Buoyancy

The percentage buoyancy of microbeads was increased with increase in the polymer proportion. The higher water imbibition resulted in the formation of hydro gel. This imparts higher buoyancy of the micro beads. Here, the water imbibition capacity enhanced the buoyancy. The percentage buoyancy of microbeads F1-F8 was increased from 55-86.3%.

Table 13: Determination of Buoyancy

S.No	Formulation code	% Buoyancy
1.	F1	55
2.	F2	65
3.	F3	70
4.	F4	71
5.	F5	72.5
6.	F6	75.6
7.	F7	85.2
8.	F8	86.3

Invitro Drug Release Study

The invitro drug release profiles were plotted between % cumulative drug release and time. Formulations F1-F4 showed drug release at the end of the 4th hour. For F1 formulation the % drug release was 80% at the end of the 4th hour. For F 2, F3, F4 formulation atthe end of the 4th 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. The % cumulative drug release of F5-F8 was found to be 98.8%, 89.2%, 82% and 72.4% respectively. F5 formulation exhibited 98.8% drug release at the end of the 4th hour. For second set of formulations which are prepared from polymer blend 1:1 ratio of sodium alginate: aloe gel powder microbeads are good at invitro drug release. So, we selected this formulation as the optimized formulation. The higherand sustained drug release of the F5 formulation may be due to bead size which is 1325µ. Large particle size at greater polymer concentration enhanced the polymer matrix density. The diffusion path length of the microbeads increased which ultimately resulted in sustained drug release. When compared to sodium alginate formulations, polymer blend microbeads showed enhanced drug release due to enhanced polymer density.

Table 14: Comparison of Invitro Drug Release of Microbeads of Gliclazide UsingSodium 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	77.2	82.8	84.8

Table 15: Comparison of Invitro Drug Release of Micro beads Of Gliclazide UsingSodium Alginate +Aloe Gel Powder

Time (minutes)	%cumulative drug release			
	F5	F6	F7	F8
30	91.2	47.2	43.6	54
60	92	75.6	72.4	60.4
120	95.2	76.4	74.4	69.6
180	97.2	81.2	77.2	70.8

240	98.8	89.2	82	72.4

CONCLUSION

The authors found that the preparations were all within pharmacopoeia limitations and that they were the optimal dosage form for treating diabetes. To enhance bioavailability and achieve controlled release over 24 hours for a once daily dosage, the current study used floating microspheres. Using an ion cross-linking approach or ion gelation method with calcium chloride as the cross-linking agent, alginate microspheres of Gliclazide were developed and tested. The microspheres were developed utilizing sodium alginate both alone and in copolymer form to administer the medication in the GIT in a controlled and sustained way as well as in combination with Aloe vera gel powder as a release retardant agent. The produced microspheres particle size, angle of repose, yield, drug entrapment effectiveness, level of swelling, and invitro drug release tests and evaluated. Oral controlled release of *Gliclazide* can be achieved by ionotropic gelation technique using sodium alginate and aloe vera gel powder. The IR spectra revealed that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. Micro particles formulated with a combination of sodium alginate and aloe vera gel powder prolonged the release. These microspheres are used as a dosage form to maintain sustained drug delivery, which would increase patient compliance and maximize therapeutic efficacy.

REFERENCES

1. Yie W. Chien, 'Rate-controlled Drug Delivery Systems'. Ind. J. Pharm. Sci., 1988; Mar-April: 63-65.
2. Rajesh, K.S., Khanrah, A. and Biswanath SA, "Release of Ketoprofen from Alginate Microparticles Containing Film forming Polymer". J. Sci. Ind. Res., 2003, 62(10); 987.
3. Hardik Kumar Rajesh bhai and A. Senthil, et.al. Formulation and evaluation gastro retentive of floating tablets of gliclazide, IJRAP, 2011 2(4), 1368-13.
4. Raval Vishal, Sailor Girish, Seth A.K. and Chauhan Sachinkumar P. formulation and evaluation of gastro retentive drug delivery system of gliclazide, pharma science monitor, 2013; 4 (4): 214-230.
5. NP Sapkal, VA Kilor, KP Bhusari and AS Daud, Evaluation of some Methods

for Preparing Gliclazide- β-Cyclodextrin Inclusion Complexes, Tropical Journal of Pharmaceutical Research, 2007; 6 (4): 833-840.

6. Farzana S. Bandarkar, Ibrahim s. khattab, lyophilized liclazide-poloxamer solid dispersions for enhancement of invitro dissolution and in vivo bioavailability international journal of pharmacy and pharmaceutical sciences, 2011; 3; 122-127.
7. Formulation and Evaluation of Fast Dissolving Tablet of Gliclazide using Combination of Superdisintegrants. Webmed Central pharmaceutical sciences 2012; 3(2). 2-30.
8. Hitendra S. Mahajan**,** Ghanashyam A, Girnar Pankaj. P and Nerkar. Dissolution and Bioavailability Enhancement of Gliclazide by Surface Solid Dispersion Using Spray Drying Technique. Indian Journal of Novel Drug delivery, 2012; 4(2); 115-124.
9. Suseem S.R, Ojha khyati, Shenoy vranda, Gupta saumya, Formulation and evaluation of hydrogel with ascorbic acid using aloe vera gel powder as a drug carrier, Innovare journal of sciences, 2013; 1(1) 18-20.
10. Jyotsana Madan, Ramnik Singh, Formulation and evaluation of aloe vera topical gels: International journal of pharmaceutical sciences. 2010, 2 (2): 551- 555.
11. Nikunj B gurjar, bhavesh S barot, Pragana K Shelat. Development and evaluation ofcinnamon and aloe-vera containing herbal anti-acne gel. International journal of pharmacy and industrial research. 2012; 02(04).446-451.
12. Sailaja Dhanekula, Prathima Srinivas, Sadanandam Mamidi. Formulation and evaluation of herbal gels for antimicrobial and wound healing activity. Journal of Natural Pharmaceuticals, 2013; 4 (2); 141-148.
13. VM. Sherina, K. Santhi and C.I. Sajeeth. Formulation and Evaluation of Sodium Alginate microbeads as a carrier for the controlled release of nifedipine. International journal of pharmaceutical and chemical sciences, 2012; 1 (2); 699-710.
14. Arun Raj. Design and development of Aceclofenac alginate beads for sustained release drug delivery. International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5 (1), 82-85.
15. M L Soni, M Kumar and K P Namdeo. Sodium alginate microspheres for extending drug release: formulation and *in vitro* evaluation. International Journal of Drug Delivery, 2010; 2; 64-68.
16. Subramanian K, Narmadha S, Vishnupriya U, Vijayakumar V. Release characteristics of Aspirin and Paracetamol drugs from tablets with Aloe vera gelpowder as

a drug carrier. Drug Invention Today, 2010; 2(9): 424-428.

17. Jadupati Malakar,Sujit Karmakar, Amites Gangopadhyay Debajyoti Ghosh. Design Development and Evaluation of Multiple –Unit Beads of Gliclazide. Am.J. Pharm Tech Res.2012; 2(4):797-803.

18. Thakkar Hardik Kumar Rajeshbhai, A. Senthil, Chavda Gajendrasinh A, Patel Jyotindra N, Narayanswamy V.B. Formulation and Evaluation of Gastro Retentive Floating Tablets of Gliclazide. International Journal of Research in Ayurveda & Pharmacy, 2011, 2(4); 1368-1373.