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Multiple - Unit Floating Drug Delivery System for Gastric Retention of Weakly Acidic Drug

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ABSTRACT

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The objective of the work is to develop a multiple-unit-type of oral floating drug delivery system to prolong the gastric residence time and increase the bioavailability of weakly acidic drugs, which has absorption window in the gastric region. Floating alginate beads were formulated using Glipizide, an oral anti-diabetic drug as a model. The beads were prepared by dispersing Glipizide with various gas forming agent (Calcium Carbonate, Magnesium Carbonate, Sodium Bicarbonate, Sodium Carbonate, Potassium Bicarbonate and Potassium Carbonate) into sodium alginate solution and then dripping the dispersion into an acidified solution (10 % glacial acetic acid) of calcium chloride. The alginate beads were formed due to ionotropic gelation by calcium ions. The carbon dioxide developed from the reaction of carbonate salts with acid permeated through the alginate matrix, to form pores, which provided the beads buoyancy. The beads were evaluated for size, mechanical strength, floating lag time, total floating duration, *in-vitro* dissolution and release kinetics. The formulations were prepared with different gas forming agents and were optimized for different weight ratios of gas forming agent and sodium alginate. The beads containing higher amounts of Calcium carbonate showed good floating behavior with required release of the drug. The formulation was subjected to *In-vivo* X-ray studies in healthy male rabbits which showed the position of beads in the upper part of the stomach. The confirmation of *In-vivo* floating behavior made them as a suitable candidate for Multiple-Unit Floating Drug Delivery System.

Keywords: Glipizide, Floating Beads, Gas forming agents, Multiple-unit Floating Drug Delivery System

INTRODUCTION

The limited gastric residence time has complicated the oral sustained drug delivery system. Gastric emptying is a complex process that is highly variable and makes the *in-vivo* performance of drug delivery systems uncertain. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Among them, FDDS have been focused recently.[1]

Multiple-unit floating dosage form containing a wide variety of polyionic systems like alginates have been investigated, keeping in view about the "all or nothing" response of single-unit systems. The use of sodium alginate is supported by various literature reports for achieving sustained release of drugs and increasing its bioavailability, because of its ability to form stable and bio-adhesive gel. The preparative methodology of alginate beads involves the use of aqueous solvents, avoiding exposure of ingredients to high temperatures and toxic organic solvents. The preparation is non-immunogenic, with good bioadhesive properties that could serve as a potential advantage in stomach targeting.[2]

Glipizide is a second generation sulphonyl urea used as an oral anti diabetic medication in the treatment of type-II diabetes. It controls blood sugar level by stimulating the pancreas to secrete more insulin. Even though Glipizide is readily absorbed after oral administration, it is metabolized by hydroxylation to form a number of inactive metabolites and the plasma half life ($t_{1/2}$) is only 2 to 4 hours. Its short biological half life necessitates that it be administered in 2 or 3 doses of 2.5 – 10 mg / day. Thus the development of sustained release dosage form would be clearly advantageous.[3,4]

According to Bio-pharmaceutical Classification System (BCS), Glipizide is a class II drug (Low solubility and high permeability). Glipizide is having a dissociation constant pKa value of 5.9 i.e. it is weakly acidic drug, which is in unionized form in the acidic pH of the stomach region, and so the site of absorption of Glipizide is the stomach. The retention of Glipizide in gastric pH will increase its absorption and thereby enhance the bioavailability for the sustained release formulation.[5,6]

The present study involves the special emphasis on optimization of the formulation with different variables and also the *in-vitro* release profile methods.

MATERIALS AND METHODS

Materials

Glipizide was a gift sample from Micro Labs Pvt. Ltd., Hosur; Sodium Alginate was bought from Nice Chemicals, Mumbai;

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Sodium bicarbonate, Sodium carbonate, Potassium bicarbonate, Potassium carbonate, Calcium carbonate, Magnesium carbonate and all the other chemicals and reagents were pure and analytical grade, purchased from SD fine Chem., Mumbai.

Methods

Preparation of Multiple Unit Floating Delivery System (Floating Alginate Beads)

Floating alginate beads were prepared by drop wise addition of sodium alginate solution containing drug and different gas forming agents, into calcium chloride solution (0.5–2.0 % w/v) in glacial acetic acid (10 %). The solution containing suspended beads are stirred with magnetic stirrer for 10 min to improve the mechanical strength of beads and allowed to complete the reaction to produce CO_2 gas. The fully formed beads were collected, washed with ethanol and distilled water, and subsequently dried. [7, 8]

From various trial studies, it has been found that the 3 % w/v sodium alginate solution and 1 % w/v calcium chloride in 10 % acetic acid was able to form uniform rigid beads. Trial studies were done on different needle sizes also and finally 21 G was optimized to produce big size, rigid, uniform and porous beads. Hence these optimized variables were kept fixed and the floating beads were formulated with different gas forming agents such as Calcium Carbonate (FB-1), Magnesium Carbonate (FB-2), Sodium Bicarbonate (FB-3), Sodium Carbonate (FB-4), Potassium Bicarbonate (FB-5) and Potassium Carbonate (FB-6) at 1:1 ratio with sodium alginate**.** And the formulations FB-7 to FB-12 were prepared by varying the ratio of Sodium Alginate:$CaCO_3$ (Table 1).

Physical Characterization of Floating Beads

Size and Mechanical Strength Analysis

The average diameter of 100 wet and dry beads was determined using a Vernier Caliper (Mitutoyo Corporation, Mumbai). To precisely measure the mechanical strength of the alginate gel beads, large beads were prepared by replacing 21 G syringe needle with 1 ml pipette, and the hardness of the large beads (n=6) was tested by Monsanto hardness tester (Dolphin, Mumbai). [8]

Morphological Analysis

The morphology of the beads was examined using Scanning Electron Microscope [8, 9] (Jeol, JSM-6360, Japan). The beads were fixed on a screw shaped stubs sample holder with double-sided carbon adhesive tape. The samples were coated with platinum under an argon atmosphere under vacuum condition by using ion sputter chamber and they were examined at 15000V accelerating voltage.

Drug Content Analysis

To a quantity of the powdered beads containing 15 mg equivalent of Glipizide, 30 ml of methanol was added and heated gently on a water bath whilst shaking, cooled and sufficient methanol was added to produce 50 ml volume. It was filtered and 5 ml of the filtrate was diluted to 50 ml with methanol. The absorbance of the resulting solution was measured at the maximum of 274 nm, using methanol in the reference cell. The drug content was calculated taking 237 as value of A (1%, 1 cm) at the maximum at 274 nm. [10]

Table 1: Formulation of Floating Alginate Beads

Formulation Code	Sodium Alginate : Gas forming agent	Size Analysis (mm) *		Mechanical Strength * (kg/cm^2)	% Drug Content	Floating Efficiency *
		Wet diameter	Dry diameter			
FB-1	1:1 $CaCO_3$	3.3	2.1	1.0	100.51	> 24 hr
FB-2	1:1 $MgCO_3$	3.3	2.1	1.0	100.65	> 24 hr
FB-3	1:1 $NaHCO_3$	-	-	-	99.28	> 24 hr
FB-4	1:1 Na_2CO_3	3.3	1.9	1.0	98.89	> 24 hr
FB-5	1:1 $KHCO_3$	3.2	1.5	1.0	101.05	> 24 hr
FB-6	1:1 K_2CO_3	3.2	1.5	1.0	101.11	> 24 hr
FB-7	1:0.25 $CaCO_3$	2.8	1.1	1.0	101.25	> 24 hr
FB-8	1:0.50 $CaCO_3$	3.0	1.5	1.0	99.86	> 24 hr
FB-9	1:0.75 $CaCO_3$	3.1	1.6	1.0	99.66	> 24 hr
FB-10	1:1 $CaCO_3$	3.3	2.1	1.0	100.51	> 24 hr
FB-11	1:1.50 $CaCO_3$	3.4	2.3	1.0	99.21	> 24 hr
FB-12	1:2 $CaCO_3$	3.5	2.5	1.0	100.74	> 24 hr

* Average of three trials

In-vitro buoyancy study

The time interval between the introduction of the beads into the dissolution medium and its floatation to the top of the dissolution medium was termed as buoyancy lag time and the duration up to which the beads floats was known as duration of buoyancy.[11,12]

The buoyancy lag time and the duration of buoyancy were studied using USP XXIV type II dissolution apparatus (Disso 2000, Lab India) with 900 ml of hydrochloric acid buffer pH 1.2 at 37 $\pm$ 1°C at 50 rpm and also in Modified Beaker method with 70 ml of buffer medium at 37°C. The buoyancy lag time and total buoyancy duration were observed visually.

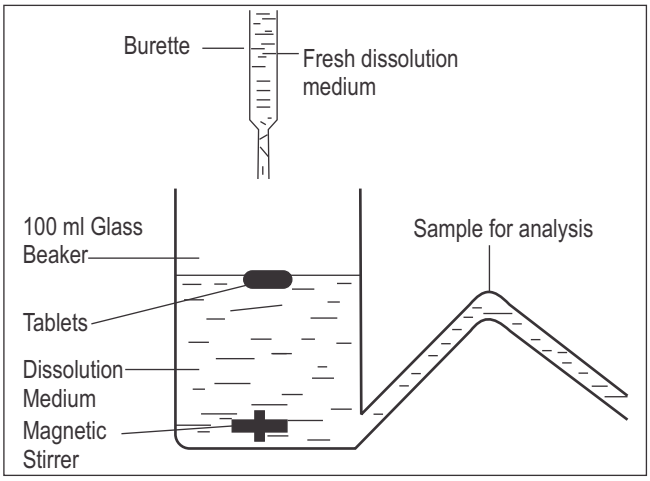
In-vitro drug release studies

USP Method

All the formulations were subjected to *in-vitro* release study using USP dissolution apparatus (Disso 2000, Lab India). [13] 900 ml of Hydrochloric acid buffer pH 1.2 was used as the dissolution medium at 50 rpm rotation speed and 37 $\pm$ 1°C ambient temperature. 10 ml of samples were withdrawn at periodic time intervals for up to 8 hours and replaced with fresh medium to maintain the sink conditions. The withdrawn samples were analyzed by UV-Visible spectrophotometer (Shimadzu) at 275 nm. The tests were done in triplicate for each formulation. The drug release data were analyzed to study the mechanism of release kinetics.

Modified Beaker Method

The formulations were also subjected to *in-vitro* release study using a Modified Beaker method.[14,15] The apparatus was designed to hold the dissolution medium of 70 ml capacity (gastric capacity) with a side tube to drain the excess volume and maintain the sink condition. The dissolution medium was continuously flowed through a burette at the rate of 2 ml/min to mimic the *in-vivo* gastric secretion flow condition. Hydrochloric acid buffer pH 1.2 was used as the dissolution medium at the temperature of 37 $\pm$ 1°C and a magnetic bead set at 50 rpm was maintained for stirring. The sink conditions are maintained by continuous replacement of fresh medium in the beaker and simultaneous drain out of the medium into another beaker. 10 ml of samples were withdrawn at predetermined time intervals for up to 8 hours. The withdrawn samples were analyzed by UV-Visible spectrophotometer (Shimadzu, Japan) at 275 nm. The tests were done in triplicate for each formulation. The drug release data were analyzed to study the mechanism of release kinetics.



Kinetics of Drug Release

The mechanism of drug release from the floating beads can be described by studying the release profile data, fitted to various kinetic models.[16,17,18,19] The data obtained from the cumulative percentage release of Glipizide from the floating beads at periodic intervals was fitted to zero order ($Q_t = Q_0 + K_0.t$), first order ($\ln Q_t = \ln Q_0 + K_0.t$), Higuchi ($Q = KH.\ t^{1/2}$), Hixon crowell ($Q_0^{1/3} - Q_t^{1/3} + K.t$), Korsemeyer and Peppas ($M_t / M_0 = a.t^n$) model kinetics. The following plots were made, Q vs. t (zero order), $\ln (Q_0 - Q_t)$ vs. t (first order), Q vs $t^{1/2}$ (Higuchi model), where Q is the percent of drug release at time t, Q_0 is the initial amount of drug present in the bead, K is the constant of the equations, n value is used to characterize different release mechanism and is calculated from slope of the plot of log of fraction of drug released (M_t / M_0) vs. log of time t.

In-Vivo X-Ray Studies

The in-vivo X-Ray studies were approved by the Institutional Ethical Committee (Ref. No: 15950/ E1(4)/2007) and performed on healthy male albino rabbits. X-Ray studies were conducted to find out the gastric retention of the beads in the rabbits. [20] Healthy rabbits weighing about 2 kg were selected and after over night fasting (water was available ad libitum) the beads containing Barium Sulphate (20 %) instead of Glipizide was administered orally. This amount of Barium Sulphate was determined experimentally to allow x-ray visibility but not to shun floatation of the formulation.[21] 60ml of 5 % Dextrose was administered to the animal through the stomach intubation tube (No: 12 French Catheter) periodically.[22] Gastric radiography was done at 2, 4, 8, 12 and 24 hours.

Stability studies

The formulation showing better dissolution profile and other

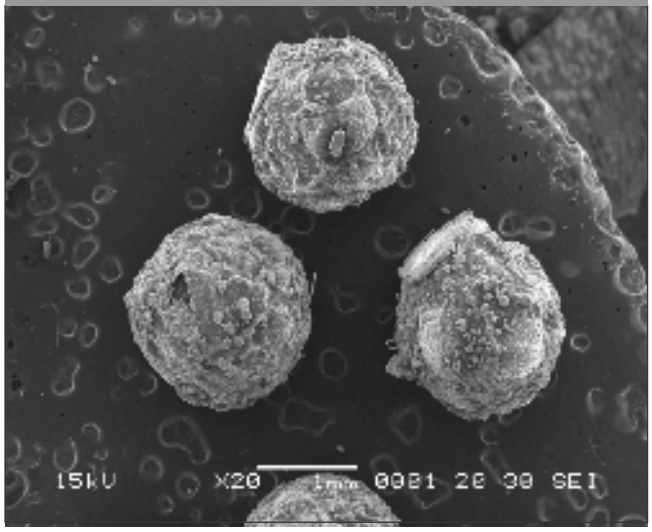
parameters was taken for the stability studies. [23, 24] The beads were filled in hard gelatin capsule shells and stored in tightly closed container. The accelerated stability studies were carried out at 40°C ± 2°C / 75% ± 5% RH for 3 months (as per ICH guidelines) to assess their stability. Control samples were kept at ambient room temperature and both were subjected to physical evaluation and assay at 15 days periodic time intervals.

RESULTS AND DISCUSSION

Physical characterization of Glipizide Floating Alginate Beads

The formulated floating beads were subjected to physical evaluation such as size analysis of wet and dry beads, morphological study, mechanical strength, percentage drug content and floating duration time. All the beads were formed within 10–20 sec., but beads containing $NaHCO_3$ as gas forming agents were formed within 5 sec, and burst immediately, before the walls are significantly hardened. Since the same needle size (21 G) is used for all the formulations, the beads produced have the same wet diameter. But they showed different diameter after drying. Except $NaHCO_3$, rest of the gas forming agents was able to produce spherical beads. The mechanical strength of the beads (n=6) was same for formulation (1.0 Kg/Cm^2), in spite of change in the gas forming agent and its concentration. The percentage drug content was within the prescribed limits of 90 % - 110 % for all the formulation. All the beads showed good floating behavior with no floating lag time (floated immediately) and the duration of total floating time was found to be more than 24 hours. The results are shown in the Table 1. The surface morphology of the beads was studied by Scanning Electron Microscopy, which showed spherical beads with pores and scales like structure, the photo graphs are shown in the Fig. 1

Fig. 1: SEM Photograph of $CaCO_3$ (1:1) Floating Beads



Effect of Gas forming agents on physical nature of beads

The SEM photo graphs of the beads shows that $CaCO_3$ produced uniform spherical and rigid beads compared to other gas forming agents. Beads produced using Na_2CO_3 and $KHCO_3$ were less rigid due to excess release of CO_2 during the beads formation. Hence $CaCO_3$ was taken for further studies. The order of size of the beads formed from different gas forming agents can be given as follows:

$$CaCO_3 = MgCO_3 > Na_2CO_3 > KHCO_3 = K_2CO_3$$

The beads having polyvalent (Ca^{2+}, Mg^{2+}) gas forming agents were able to produce rigid and large size beads than the beads having monovalent gas forming agents (Na^+, K^+), due to the internal ionotrophic gelation effect of Ca and Mg ions on alginate.

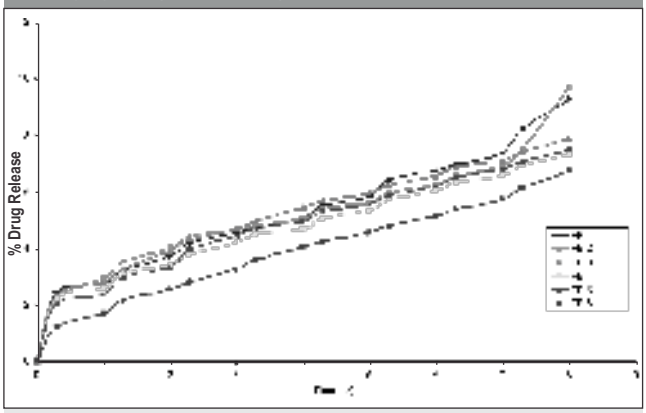
Effect of Concentration of Gas forming agents

On increasing the $CaCO_3$ ratio in the beads, the diameter of the beads was increased. $CaCO_3$ at 1:0.25 ratio produced smaller beads than at 1:2.00 ratio. The increase in concentration of $CaCO_3$ ratio had some impact in increasing the diameter of beads, due to high interaction of $CaCO_3$ with acetic acid during the bead formation.

In-vitro Release Profile

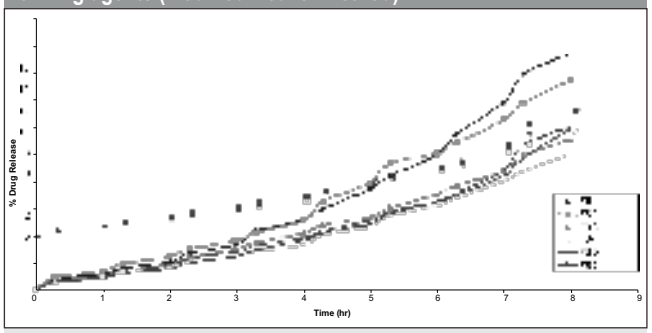
The formulations containing different gas forming agents (in the ratio of 1:1 with Sodium alginate) showed sustained release of the drug. Of all the formulations, beads containing $CaCO_3$ and $MgCO_3$ showed better release profile than the other carbonates and bicarbonates. In both USP dissolution method and Modified Beaker method, the cumulative percentage of drug release was more in these two batches compared to other gas forming agents (Fig. 2 and Fig. 3). Based on the morphology and release of drug, $CaCO_3$ was chosen for further formulations. The comparative release

Fig. 2: *In-vitro* release profile of Floating beads with different gas forming agents (USP Method)



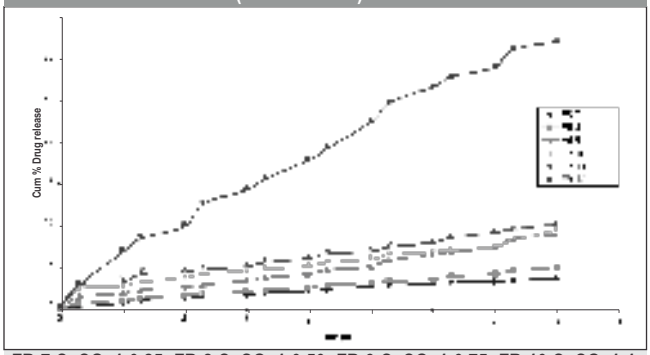
(FB-1 $CaCO_3$ 1:1; FB-2 $MgCO_3$ 1:1; FB-3 $NaHCO_3$ 1:1; FB-4 Na_2CO_3 1:1; FB-5 $KHCO_3$ 1:1; FB-6 K_2CO_3 1:1)

Fig. 3: *In-vitro* release profile of Floating beads with different gas forming agents (Modified Beaker Method)



FB-1 $CaCO_3$ 1:1; FB-2 $MgCO_3$ 1:1; FB-3 $NaHCO_3$ 1:1; FB-4 Na_2CO_3 1:1; FB-5 $KHCO_3$ 1:1; FB-6 K_2CO_3 1:1)

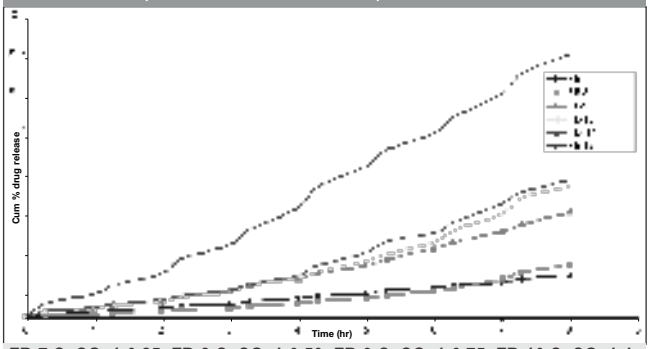
Fig. 4: *In-vitro* release profile of Floating beads of $CaCO_3$ at different concentration (USP Method)



FB-7 $CaCO_3$ 1:0.25; FB-8 $CaCO_3$ 1:0.50; FB-9 $CaCO_3$ 1:0.75; FB-10 $CaCO_3$ 1:1; FB-11 $CaCO_3$ 1:1.50; FB-12 $CaCO_3$ 1:2)

profile of the formulations with increasing concentration of $CaCO_3$ from 1:0.25 to 1:2.00 (FB-7 to FB-12) showed that as the concentration of gas forming agents increased, the release rate increased significantly (Fig. 4 and Fig. 5). This may be due to increase in size, floating property and the porous nature of the beads.

Fig. 5: *In-vitro* release profile of Floating beads of $CaCO_3$ at different concentration (Modified Beaker Method)



FB-7 $CaCO_3$ 1:0.25; FB-8 $CaCO_3$ 1:0.50; FB-9 $CaCO_3$ 1:0.75; FB-10 $CaCO_3$ 1:1; FB-11 $CaCO_3$ 1:1.50; FB-12 $CaCO_3$ 1:2)

Kinetics of drug release

All the bead formulations showed anamolous non-fickian release mechanism by USP dissolution method and Super case II transport mechanism by modified beaker method (Table 2). Based on the similarity factor f_2, the formulation containing 1:2 ratio of alginate : $CaCO_3$ was found to show

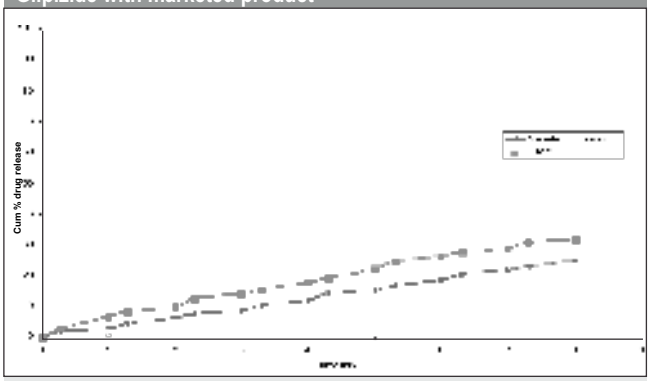
Table 2: R^2 Values for the Release Kinetics of the Floating Beads of Glipizide

Formulation code	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell
USP Dissolution Method					
FB-1	0.9547	0.9812	0.9608	0.9704	0.599
FB-2	0.9048	0.9218	0.9318	0.9299	0.5618
FB-3	0.9297	0.9883	0.9963	0.9975	0.5519
FB-4	0.9415	0.9972	0.9906	0.9909	0.5593
FB-5	0.9453	0.9887	0.9953	0.9974	0.5816
FB-6	0.9787	0.9948	0.9779	0.9947	0.6618
FB-7	0.9808	0.9838	0.9711	0.9943	0.7254
FB-8	0.9911	0.9938	0.9471	0.989	0.7298
FB-9	0.986	0.9831	0.9169	0.9643	0.74
FB-10	0.9547	0.9812	0.9608	0.9704	0.599
FB-11	0.9591	0.9944	0.9732	0.9685	0.5929
FB-12	0.9868	0.99	0.9541	0.9914	0.7529
Modified Beaker Method					
FB-1	0.9388	0.9312	0.7825	0.9756	0.9248
FB-2	0.9698	0.9648	0.8355	0.9784	0.8928
FB-3	0.9747	0.9693	0.85	0.9886	0.8749
FB-4	0.9643	0.9588	0.8303	0.9778	0.8827
FB-5	0.9469	0.9362	0.8121	0.981	0.8823
FB-6	0.9319	0.9237	0.7814	0.9734	0.909
FB-7	0.9954	0.9942	0.9019	0.9955	0.8383
FB-8	0.9146	0.9128	0.7548	0.9827	0.9324
FB-9	0.9753	0.9711	0.8447	0.99	0.8947
FB-10	0.9388	0.9312	0.7825	0.9756	0.9248
FB-11	0.953	0.9479	0.8014	0.9767	0.9232
FB-12	0.9782	0.9692	0.8734	0.9946	0.8838

better release, nearly similar to marketed sample (f_2 = 79, 85), as shown in Fig. 6. It was observed that this formulation follow first order kinetics with Korsmeyer Peppas mechanism.

The difference in the values of R^2, f_2 and also K, determined by USP dissolution apparatus and Modified Beaker apparatus was due to difference in the mechanism of the drug release in these two methods. Even the swelling and release property of the dosage form remains the same in both method, a perfect type of sink condition was maintained in the beaker method which correlates to the *in-vivo* conditions. So, variable results were obtained in release kinetics data.

Fig. 6: Comparison of *In-vitro* release profile of Floating Beads of Glipizide with marketed product

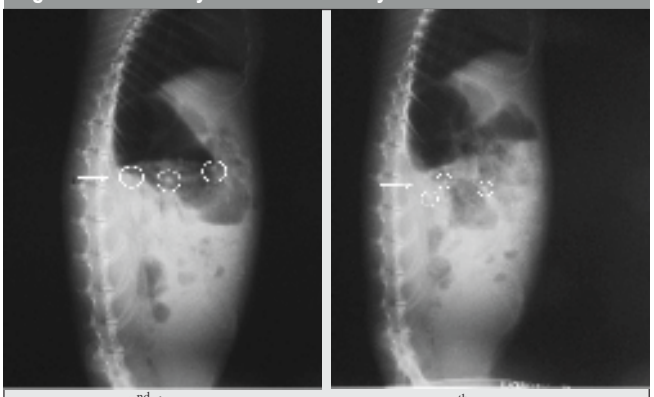


(Marketed Formulation – GLYNASE XL; FB-12 $CaCO_3$ 1:2)

In-Vivo X-ray studies

The appearance of the beads in the upper part of the stomach confirms its *in-vivo* floating behavior. The change in position of the beads in the 2nd hour x-ray and 4th hour x-ray proves that they does not adhere to the mucous and remained floating, as shown in Fig. 7.

Fig. 7: *In vivo* X- Ray Studies on healthy male rabbits



2nd hour | 4th hour

Stability Studies

As per ICH guidelines, stability studies were performed on the selected formulations as short time stability study at 40°C ± 2°C and 75% ± 5% RH for 3 months and compared with control samples kept at ambient room temperature. The insignificant change in the physical appearance, buoyancy and the drug content in the formulations showed that the formulations remain stable during the storage period of 3 months (Table 3).

Table 3: Stability Studies Report for Floating Alginate Beads of Glipizide FB – 12 (Sodium Alginate : $CaCO_3$ 1:2)

Intervals of Testing	Mechanical Strength (Limit 1-1.5 kg / cm^2)	Total Floating Time (Limit > 24 hr)	Drug Content (Limit 90- 110 %)
a) 40°C ± 2°C / 75% RH ± 5% RH			
0 day	1 kg / cm^2	> 24 hr	98.65
15 days	1 kg / cm^2	> 24 hr	100.21
30 days	1 kg / cm^2	> 24 hr	101.55
45 days	1 kg / cm^2	> 24 hr	100.69
60 days	1 kg / cm^2	> 24 hr	99.23
75 days	1 kg / cm^2	> 24 hr	101.60
90 days	1 kg / cm^2	> 24 hr	102.05
b) Ambient Room Temp. 25°C ± 2°C			
0 day	1 kg / cm^2	> 24 hr	101.62
15 days	1 kg / cm^2	> 24 hr	100.05
30 days	1 kg / cm^2	> 24 hr	99.83
45 days	1 kg / cm^2	> 24 hr	101.20
60 days	1 kg / cm^2	> 24 hr	98.75
75 days	1 kg / cm^2	> 24 hr	100.62
90 days	1 kg / cm^2	> 24 hr	99.98

CONCLUSION

The addition of gas forming agents, both type and concentration influences the formulation of floating alginate beads. The study has clearly shown that the gas forming agent has a profound effect on size, floating ability, morphology and release rate of the drug. In general $CaCO_3$ produced superior floating beads, which were smaller and stronger than other gas forming agents with extended drug release. The *in-vivo* floating behavior was also evident for its prolonged gastric residence time. The multiple unit floating drug delivery system formulated as Floating Alginate Beads can be employed as a successful tool for gastric retention of weakly acidic drugs.

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REFERENCES

1. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavi P. Development of sustained release gastroretentive drug delivery system for ofloxacin: *In vitro* and *in vivo* evaluation. Int J Pharm 2005;304(1-2):178-84.
2. Shishu, Gupta N, Aggarwal N. Stomach specific drug delivery of 5-fluorouracil using floating alginate beads. AAPS PharmSciTech 2007;8(2):E1-E7.
3. Moffat AC, Osselton MD, Widdop B. Clarke's Analysis of Drugs and Poisons. 3rd ed. Pharmaceutical Press 2003.
4. Current Index of Medical Specialities (CIMS). CMPMedica India Private Limited. Bangalore: Oct 2009 – Jan 2010.
5. Verma RK, Garg S. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. Eur J Pharm Biopharm 2004;57:513-5.
6. Patel JK, Patel RP. Formulation and evaluation of muco adhesive glipizide microspheres. AAPS PharmSciTech 2005;06(01):E49-E55.
7. Stops F, Fell JT, Collett JH, Martini LG. Floating dosage forms to prolong gastro-retention - The characterisation of calcium alginate beads. Int J Pharm 2008;350(1-2)301-11
8. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery system effects of CO_2 gas forming agents. Int J Pharm 2002;239:81-91.
9. Whitehead L, Collet JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. Int J Pharm 2000;210:45-9.
10. British Pharmacopoeia. Medicines and Health care products Regulatory Agency. Vol. I – IV: 2009.
11. Dave BS, Amin AF, Patel MM. Gastro retentive drug delivery system of ranitidine hydrochloride: Formulation and *in-vitro* evaluation. AAPS PharmSciTech 2004;5(2):1-6.
12. Patel DM, Patel NM, Pandya NN, Jogani PD. Gastro retentive drug delivery system of carbamazepine: Formulation optimization using simplex lattice design: A technical note. AAPS PharmSciTech 2007;8(1):E1-E5.
13. United States Pharmacopoeia (USP NF). USP 32 Revision and NF 27 edition. Vol. I – II: 2009.
14. Gohel MC, Mehta PR, Dave RK, Bariya NH. A more relevant dissolution method for evaluation of floating drug delivery system. Disso Tech 2004;11(4):22-5.
15. Karande AD, Yeole PG. Comparative assessment of different dissolution apparatus for floating drug delivery systems. Disso Tech 2006;13(1):20-3.
16. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: Formulation and *in-vitro* evaluation. AAPS PharmSciTech 2003;4(4):1-9.
17. Merchant HA, Shoaib HM, Tazeen J, Yousuf RI. Once-daily tablet formulation and *in-vitro* release evaluation of cefpodoxime using hydroxyl propyl methyl cellulose: A technical note. AAPS PharmSciTech 2006;7(3):E1-E6.
18. Narendra C, Srinath MS, Rao BP. Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique. Int J Pharm 2005;304:102-14.
19. Carla ML, Lobo JMS, Pinto JF, Costa P. Compressed mini tablets as a biphasic delivery system. Int J Pharm 2006;323:93-100.
20. Baumgartner S, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-35.
21. Molina, Gallo R. Process of making radiological contrast for gastro intestinal exploration comprising $BaSO_4$ and Sucralfate. US Patent No.5780011.
22. Gay WI. Methods of Animal Experimentation. Acadeic Press, New York, London; Vol.– I: 1965
23. Stability testing of new drug substances and products. European Medicines Agency, 2006; CPMP/ICH/2736/99.
24. Shah SS, Pandya SJ, Waghulade MK. Development and investigation of gastro retentive dosage form of weakly basic drug. Asian J Pharm 2010;4(1):11-6.

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