

## Development and Evaluation of Gastroretentive Floating Tablets of Glipizide Based on Effervescent Technology

Basavaraj K Nanjwade\*, Sagar A Adichwal, Veerendra K Nanjwade, Kishori R Gaikwad, Sachin A. Thakare and F V Manvi

Department of Pharmaceutics, KLE University College of Pharmacy, JN Medical College Campus, Belgaum- 590010, Karnataka, India

### Abstract

The purpose of this research was to develop a novel gastroretentive drug delivery system based on effervescent technology for controlled delivery of active agent. Glipizide, a poorly soluble drug has been used as a model drug and an attempt has been made to improve the solubility of drug by the incorporation of accelerating agents, such as dispersant, alkalisant agent in conjunction with hydrophilic swellable polymer such as hydroxypropylmethylcellulose and present it in the form of gastroretentive floating tablets, which are designed to provide the desired controlled and complete release of drug for prolonged period of time. Floating tablets were prepared by direct compression method. Hydroxypropylmethylcellulose (HPMC K15M, HPMC K100M), Carbopol 940P, were incorporated for gelforming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The optimized formulation (F7) exhibited 98.60% drug release in 24 hrs, while the buoyancy lag time was 140sec. In-vitro drug release kinetics was found to follow both the Zero order and the Korsmeyer and Peppas equation (Table 7). The release of glipizide from the formulations was found to be non-fickian type. Evaluation of Gastric Retention Using X-Ray Imaging studies were performed on rabbit to justify the increased gastric residence time of the dosage form in the stomach, based on the floating principle. Optimized formulation (F7) showed no significant change in physical appearance, drug content, total buoyancy time, or *in vitro* dissolution pattern after storage at 40°C/75% (Figure 5) relative humidity for 1 month.

**Keywords:** Glipizide; Gastroretentive; Intra-gastric Floating tablets; floating drug delivery; Controlled release

### Introduction

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action [1]. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation [2]. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that [1] are locally active in the stomach, [2] have narrow absorption window in gastrointestinal tract, [3] are primarily absorbed from stomach and upper part of GIT, [4] are unstable in the intestinal or colonic environment, [5] disturb normal colonic bacteria and [6] exhibit low solubility at high pH values [2,3]. The controlled gastric retention of solid dosage forms may be achieved by mucoadhesive systems that causes bioadhesion to stomach mucosa [2], floating systems, swelling and expanding systems, modified-shape systems, high density systems and other delayed gastric emptying devices [4]. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients [5]. Glipizide is selective second generation sulfonylureas used in the treatment of hyperglycemia. It is poorly soluble in acidic environment [6] and water, it is a weak acid (pKa = 5.9), and highly permeable (Class II drugs in accordance to Biopharmaceutics Classification System, BCS). The oral absorption is uniform, rapid, and complete; its bioavailability is nearly 100% and its elimination half-life is 2-4 hrs [7], thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance.

The present study was aimed towards the development of controlled release gastro retentive floating tablets of glipizide based on effervescent technology. In this study, an attempt has been made to enhance the solubility of glipizide by the incorporation of accelerating agents such as dispersants, alkalisant agents (hydrophilic electrolyte) in conjunction with hydrophilic swell able polymer such as hydroxypropylmethylcellulose and present it in the form of gastro retentive floating tablets to increase the efficacy and stability of the drug in the stomach, which will help to retain the dosage form in the stomach and to increase gastric residence time, resulting in prolonged drug delivery in stomach. The developed formulations were evaluated for various physico-chemical parameters. A formulation that combined excellent buoyancy and controlled release characteristics both were chosen for further evaluation of Gastric Retention Using X-Ray Imaging in rabbit for 5 hrs.

### Experimental

#### Materials

Glipizide was received as a gift sample from USV Ltd, Mumbai. Hydroxypropylmethylcellulose (HPMC K15M, HPMC K100M) were obtained as a gift samples from Colorcon Asia Pvt Ltd, Goa. Carbopol

\*Corresponding author: Dr. Basavaraj K. Nanjwade M.Pharm., Ph.D, Professor of Pharmaceutics, Department of Pharmaceutics, KLE University College of Pharmacy, JN Medical College Campus, Belgaum- 590010, Karnataka, India, Tel: 0091 9742431000; Fax: 0091 8312472387; E-mail: [bknanjwade@yahoo.co.in](mailto:bknanjwade@yahoo.co.in)

Received April 06, 2012; Accepted April 21, 2012; Published April 23, 2012

Citation: Nanjwade BK, Adichwal SA, Nanjwade VK, Gaikwad KR, Thakare SA, et al. (2012) Development and Evaluation of Gastroretentive Floating Tablets of Glipizide Based on Effervescent Technology. J Drug Metab Toxicol 3:121. doi:10.4172/2157-7609.1000121

Copyright: © 2012 Nanjwade BK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

940 procured from Corel Pharma Chem Ltd. Ahmedabad. sodium bicarbonate, PVP K30, anhydrous citric acid and all other ingredients used were of analytical grade.

## Method

**Preparation of glipizide floating tablets:** Floating tablets containing glipizide were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and citric acid.

All the powders were accurately weighed and passed through an 80 mesh sieve (180 micrometer size). Then, except magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The blend was compressed into tablets having average weight of 330 mg using a single punch tableting machine ( Cadmach, India) fitted with a 10 mm round flat punches. The Glipizide Floating Tablets were compressed at 3 N compression forces. The compositions of all formulations are given in (Table 1) [8-10].

## Evaluation Parameters

### Precompression parameters

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated. While the flow properties of the powder blend were accessed from the angle of repose.

### Evaluation of Floating Tablets

**Post compression parameters:** The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.

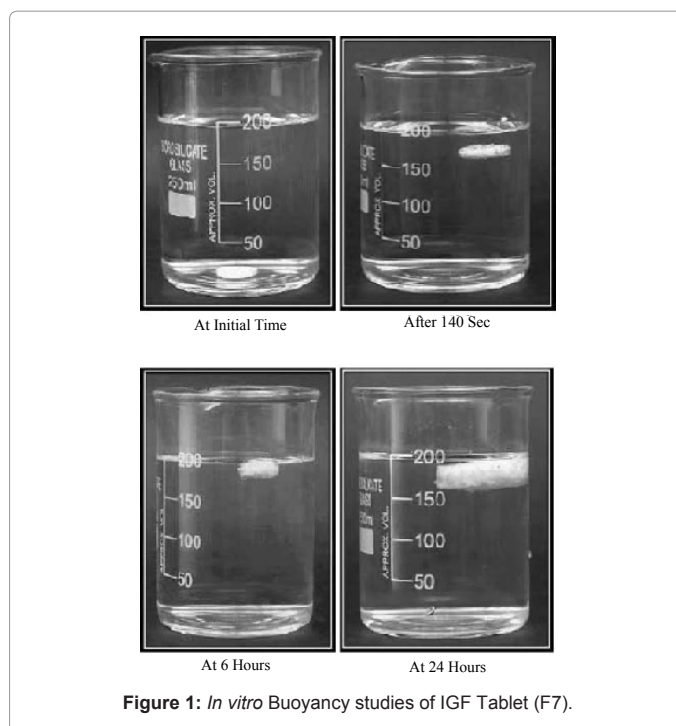
**Weight variation:** Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this; percentage weight difference was calculated and then checked for USP specifications.

**Hardness and friability:** Hardness of tablet was determined by Monsanto hardness Tester. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated. Friability test was done by Roche friabilator. Ten

Ingredients* (mg)	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Glipizide	15	15	15	15	15	15	15
HPMC K100M	65	115	60	90	95	105	115
HPMC K15M	115	65	90	60	45	35	35
Carbopol 940P	-	-	30	30	40	40	30
PVP K30	10	10	10	10	10	10	10
Sodium Bicarbonate	90	90	90	90	90	90	90
Citric Acid	20	20	20	20	20	20	20
Aerosil	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5
<b>Total Weight (mg)</b>	<b>330</b>	<b>330</b>	<b>330</b>	<b>330</b>	<b>330</b>	<b>330</b>	<b>330</b>

\*All the ingredients are in mg. per tablet

**Table 1:** Composition of Gastroretentive Floating Tablets of Glipizide (F1 to F7).



**Figure 1:** *In vitro* Buoyancy studies of IGF Tablet (F7).

tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de-dusted and reweighed. The percentage friability was calculated.

**Tablet Dimensions:** Thickness and diameter of tablets were measured using a calibrated dial calliper. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated [11].

**Content uniformity test:** The Glipizide floating tablets were tested for their drug content. Five tablets were finely powdered; quantities of the powder equivalent to 15 mg of Glipizide were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCL (pH 1.2 buffer) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 100 ml with 0.1N HCL and measure the absorbance of the resulting solution at 276 nm using a Shimadzu UV-visible spectrophotometer. The linearity equation obtained from calibration curve was used for estimation of Glipizide in the tablet formulations [6,11].

***In vitro* buoyancy studies:** The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 N HCL. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT) [12,13].

**Swelling study:** The floating tablets were weighed individually (designated as W0) and placed separately in glass beaker containing 200 ml of 0.1 N HCL and incubated at 37°C ± 1°C. At regular 1-hr time intervals until 24 hrs, the floating tablets were removed from beaker, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (Wt), and

% swelling index (SI) (Figure 2) was calculated using the following formula [13,14].

$$SI (\%) = (W_t - W_0 / W_0) \cdot 100$$

**In vitro Dissolution Studies:** The *In vitro* dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at  $37 \pm 0.5^\circ\text{C}$ . A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 hrs and the same volume was replaced with pre-warmed fresh dissolution media. The samples were filtered through a whatman filter paper and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 276 nm using a UV spectrophotometer [15].

**Curve fitting analysis:** The mechanism of Glipizide release from the floating tablets was studied by fitting the dissolution data of optimized formulation (F7) in following models

1. Zero order
2. First order
3. Higuchi model
4. Korsmeyer and Peppas equation

Based on the slope and the R2 values obtained from the above models the mechanism of drug release was decided [16].

**Evaluation of gastric retention using X-Ray imaging:** Before starting the study, permission was taken from the institutional ethical board. (Institutional ethics committee, JN Medical College, Belgaum) For X-Ray Imaging test, tablet prepared by incorporation of the X-ray opaque material BaSO<sub>4</sub> was necessary to ensure visibility by X-ray. The X-ray imaging was performed in one healthy female Albino rabbit weighing 2.5 kg. In each experiment, an unanaesthetized animal was fasted for 24 hrs and the first X-ray was made to ensure the absence of radiopaque material in the stomach (Figure 3). The tablet was administered by natural swallowing to rabbit followed by 50 ml of water. During the experiment the rabbit was not allowed to eat, but water was available. After the determined time intervals X-ray of the abdomen were taken using an X-ray machine from rabbit in a standing position. The distance between the source of X-rays and the object was the same for all imaging. This allowed us to see the tablet in the

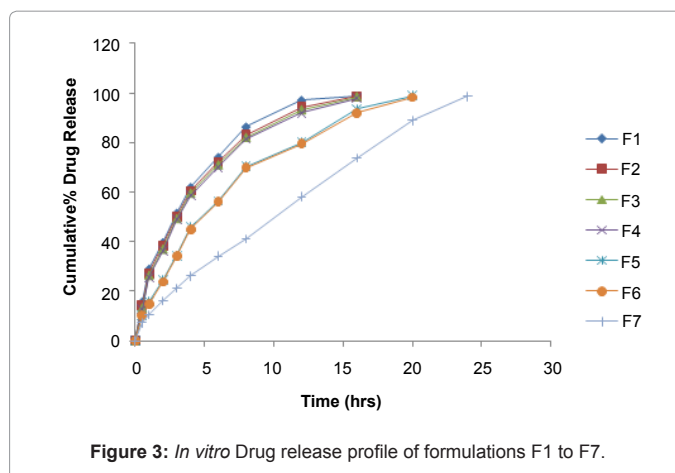


Figure 3: *In vitro* Drug release profile of formulations F1 to F7.

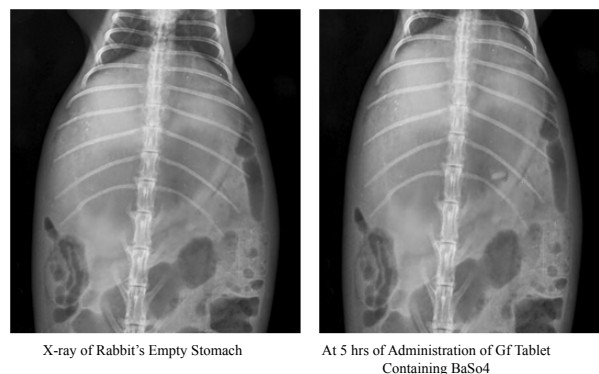


Figure 4: Evaluation of Gastric retention of IGF tablet (F7) using X-ray imaging.

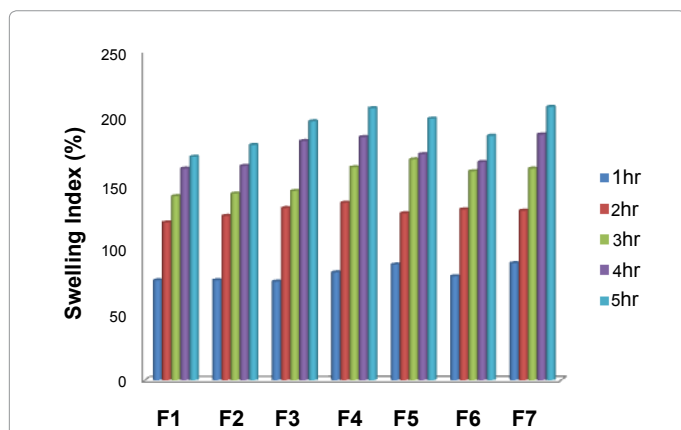


Figure 2: Swelling Index of Gastroretentive Floating Tablets of Glipizide (F1 to F7).

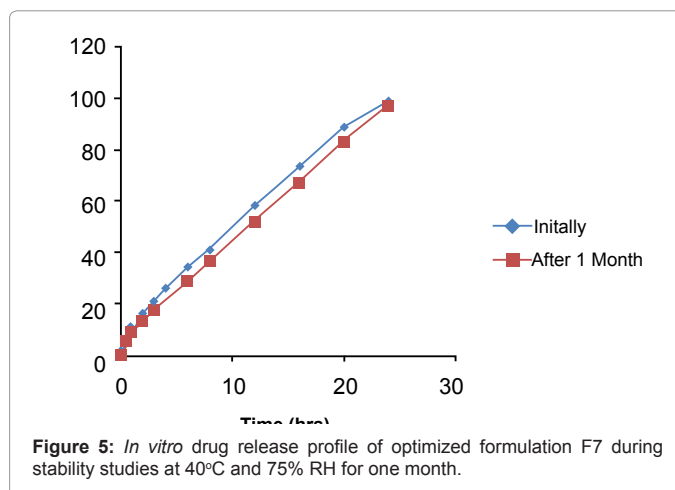


Figure 5: *In vitro* drug release profile of optimized formulation F7 during stability studies at  $40^\circ\text{C}$  and 75% RH for one month.

body of stomach, antrum and or pyloric part of the stomach so that observations of the tablet movements could be made. Gastric X-ray imaging was done at 30-min time intervals for a period of 5 hrs using an X-ray machine [13,17,18].

**Stability studies:** The optimized formulation of Glipizide were packed in strips of 0.04 mm thick aluminium foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai)

Formulation Code	Pre-compression Evaluation Parameters				
	Bulk Density (g/cc)	Tapped Density (g /cc)	Carr's Index (%)	Hausner Ratio	Angle of Repose (θ)
F1	0.3846	0.4545	15.37	1.1817	24° 30'
F2	0.4167	0.5000	16.66	1.1999	25° 77'
F3	0.4348	0.5263	17.38	1.2104	26° 54'
F4	0.4545	0.5556	18.16	1.2224	27° 68'
F5	0.5000	0.6250	20.00	1.2500	28° 56'
F6	0.3571	0.4545	21.43	1.2728	29° 65'
F7	0.4762	0.5882	19.04	1.2352	27° 29'

Table 2: Pre-compression Parameters of Designed Formulations (F1 to F7).

Formulation Code	Post-compression Evaluation Parameters					
	Diameter (mm.) (n=3) Mean±SD	Thickness (mm.) (n=3) Mean±SD	Hardness Kg/cm <sup>2</sup> (n=10) Mean±SD	Friability (%) (n=10)	Average weight (mg.) (n=10) Mean±SD	Drug content (%)
F1	10.0 ± 0.007	3.1 ± 0.130	4.5 ± 0.165	0.72	332.1 ± 0.117	97.17
F2	10.0 ± 0.004	3.1 ± 0.109	4.5 ± 0.170	0.79	329.5 ± 0.147	97.76
F3	10.0 ± 0.006	3.0 ± 0.192	5.0 ± 0.166	0.96	330.7 ± 0.273	98.35
F4	10.0 ± 0.005	3.0 ± 0.180	5.5 ± 0.172	0.91	332.4 ± 0.138	98.94
F5	10.0 ± 0.003	3.0 ± 0.168	5.5 ± 0.184	0.82	332.9 ± 0.178	100.12
F6	10.0 ± 0.006	3.0 ± 0.156	5.5 ± 0.196	0.97	331.6 ± 0.054	100.71
F7	10.0 ± 0.002	3.0 ± 0.198	5.0 ± 0.140	0.86	330.4 ± 0.096	99.53

Table 3: Physical Characterization of Gastroretentive Floating Tablets of Glipizide.

maintained at 40°C and 75% RH for 1 month (zone III conditions as per ICH Q1 guidelines). The samples were withdrawn periodically and evaluated for their hardness, content uniformity and for *in vitro* drug release (Figure 3) [19].

## Results and Discussion

In the present work, Glipizide an oral hypoglycemic agent used in the treatment of non insulin dependent diabetes mellitus (NIDDM: also called type 2), has been utilized as an active drug and considered to be good candidate for reducing dose frequency, for solid oral controlled release formulation as well as more compliance in diabetics. Glipizide is poorly soluble in water so an attempt has been made to improve the solubility of the drug by the incorporation of accelerating agents, such as dispersants, alkalising agents (hydrophilic electrolyte) in conjunction with hydrophilic swellable polymer such as hydroxypropylmethylcellulose and present it in the form of gastroretentive floating tablets to provide the desired controlled and complete release for prolonged period of time (Table 5).

Floating tablets of glipizide were prepared by dry blending of solubility modifier to modulate solubility of the active drug and varying concentrations of different grades of polymers with sodium bicarbonate and citric acid by direct compression technique.

### Precompression Parameters

The results of precompression evaluation parameters are shown in (Table 2). All the precompression evaluation parameters were within the USP Pharmacopoeia limits.

### Postcompression Parameters

The intragastric floating (IGF) glipizide tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in (Table 3). The thickness of IGF tablets was measured by calibrated dial calliper. Tablet mean diameter and thickness (n=3) were almost uniform in all the formulations and values for tablets ranged from 10.0 ± 0.002 to 10.0 ± 0.007 and 3.0 ± 0.156 to 3.1 ± 0.130 mm respectively. The standard deviation values indicated



Formulation Code	Floating lag time (Sec.)	Total Floating Time (hrs.)
F1	114 Sec.	> 16 hrs.
F2	120 Sec.	> 16 hrs.
F3	131 Sec.	> 16 hrs.
F4	137 Sec.	> 16 hrs.
F5	144 Sec.	> 20 hrs.
F6	150 Sec.	> 20 hrs.
F7	140 Sec.	> 24 hrs.

Table 4: Floating Lag Lime and Total Floating Time of Designed Formulations.

Time (hrs)	Swelling Index (%)						
	F1	F2	F3	F4	F5	F6	F7
1	76	76	75	82	88	79	89
2	120	125	131	135	127	130	129
3	140	142	144	162	168	159	161
4	161	163	182	185	172	166	187
5	170	179	197	207	199	186	208

Table 5: Swelling index of Gastroretentive Floating Tablets of Glipizide (F1 to F7).

Sampling Time(h)	F1	F2	F3	F4	F5	F6	F7
0.5	15.68	14.51	13.34	12.72	10.45	10.38	7.3
1	28.96	27.16	26.44	25.74	15.86	14.72	10.6
2	39.66	38.33	37.00	36.22	24.52	23.84	16.2
3	51.57	50.16	49.28	48.97	34.34	34.12	21.2
4	61.96	60.48	59.54	58.62	45.85	45.03	26.2
6	74.11	72.01	70.99	69.99	56.42	56.06	34.2
8	86.38	83.11	82.01	81.48	70.29	69.85	41.2
12	97.14	94.32	93.15	92.02	80.06	79.56	58.2
16	98.72	98.59	98.46	97.83	93.65	92.01	73.8
20	-	-	-	-	98.89	98.27	88.9
24	-	-	-	-	-	-	98.6

Table 6: Cumulative Percent Drug Releases of Formulations F1 to F7.

Formulation Code	Zero order	First order	Higuchi kinetics	Korsmeyer–Peppas	
	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	N	R <sup>2</sup>
F7	0.9899	0.8503	0.985	1.4317	0.997

Table 7: Kinetics of *In vitro* Release from Optimized Formulation F7.

that all the formulations were within the range and show uniform thickness.

The average weight of each formulation was recorded. The values were almost uniform and lie within the USP specifications. The values of tablets ranged from  $329.5 \pm 0.147$  to  $332.9 \pm 0.178$  mg. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of  $\pm 5\%$  of the weight.

The hardness of all formulations was in the range of  $4.5 \pm 0.165$  to  $5.5 \pm 0.196$  kg/cm<sup>2</sup>. The values of standard deviation indicate that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness.

The friability values of prepared tablets are given in (Table 3). The values ranged from 0.72 to 0.97%. All the values are below 1% indicating that the tablets of all formulations are having good compactness and showing enough resistance to the mechanical shock and abrasion.

The content uniformity was performed for all seven formulations. The percent drug content of tablets was found to be in between 97.17 to 100.71% of glipizide.

***In vitro* buoyancy studies:** All the intragastric floating (IGF) tablet formulations were prepared by effervescent approach. On immersion in 0.1 N HCl, pH 1.2 solution at  $37 \pm 0.5$  °C all floating effervescent tablets float immediately and remain buoyant up to 24 hrs without disintegration. The *in vitro* buoyancy of IGF tablets was induced by sodium bicarbonate and anhydrous citric acid in optimized ratio (9:2) without compromising the matrix integrity with the possible shortest buoyancy lag time and buoyancy duration of up to 24 hrs. It was observed that the gas generated was trapped in the tablet and protected within the gel formed by hydration of polymers, thus decreasing the density of the tablet below 1, and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. The IGF tablets F1 and F2 containing HPMC K15 and HPMC K100M respectively, without Carbopol 940, exhibited short buoyancy lag time of 114 sec and 120 sec but the total buoyancy time was less than 24 hrs. These might be due to rapid hydration of HPMC polymers which floated in short time as compared to IGF tablets containing Carbopol 940 polymer. The IGF tablets F3 and F4 containing Carbopol 940, HPMC K15 and HPMC K100M showed FLT of 131 sec and 137 sec respectively with TFT of 16 hrs. The Carbopol produces firm gel that entrapped the gas for longer time as compared to HPMC which has high rate of hydration.

As the concentration of Carbopol 940 increases the FLT also increases. The formulation F5 and F6 showed the FLT of 144 sec and 150 sec respectively with TFT of 20 hrs. Among IGF tablets F1 to F7 (Table 6), the formulation F7 showed shortest buoyancy lag time (140 sec) with more total buoyancy time (24 hrs). (Table 4) shows the results of buoyancy study and (Figure 1) shows buoyancy character of prepared tablets.

### Swelling study

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the matrix tablet. The IGF tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups.

### References

1. Patel SS, Ray S, Thakur RS (2006) Formulation and evaluation of floating drug delivery system containing clarithromycin for *Helicobacter pylori*. Acta Pol Pharm 63: 53-61.
2. Nayak AK, Maji R, Das B (2010) Gastroretentive drug delivery systems: a review. Asian J Pharm Clin Res 3: 2-10.
3. Khan FN, Dehghan MHG (2009) Gastroretentive drug delivery systems: a patent perspective. Int J Health Res 2: 23-44.
4. Singh BN, Kim KH (2000) Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 63: 235-259.
5. Garg R, Gupta GD (2008) Progress in controlled gastroretentive delivery systems. Tropical J Pharm Res 7: 1055-1066.
6. Prabhu P, Nayari HM, Ahmed GM, Yadav B, Charyulu NR, et al. (2008) Formulation and *in vitro* evaluation of gastric oral floating tablets of glipizide. Indian J Pharm Educ Res 42:174-183.
7. Jamzad S, Fassihi R (2006) Development of a controlled release low dose class II drug-Glipizide. Int J Pharm 312: 24-32.
8. Bomma R, Swamy Naidu RA, Yamsani MR, Veerabrahma K (2009) Development and evaluation of gastroretentive norfloxacin floating tablets. Acta Pharm 59: 211-221.
9. Streubel A, Siepmann J, Bodmeier R (2003) Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci 18: 37-45.
10. Pare A, Yadav SK, Patil UK (2008) Formulation and evaluation of effervescent floating tablet of amlodipine. Res J Pharm Tech 1:526-530.
11. Banker GS, Anderson NR (1991) Tablets. In: Lachman L, Liberman HA, Kang JL (Eds) The theory and practice of industrial pharmacy. (3<sup>rd</sup>edn), Varghese publication house 296-302.
12. Nama M, Gonugunta CS, Reddy Veerareddy P (2008) Formulation and evaluation of gastroretentive dosage forms of Clarithromycin. AAPS PharmSciTech 9: 231-237.
13. Patel A, Modasiya M, Shah D, Patel V (2009) Development and *in vivo* floating behavior of verapamil HCl intragastric floating tablets. AAPS PharmSciTech 10: 310-315.
14. Lodhiya DJ, Mukherjee DJ, Dholakiya RB, Akbari BV, Shiyani BG, et al. (2009) Gastroretentive system of atenolol using hpmc k15. Int J Pharm Tech Res 1:1616-1620.
15. Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR (2007) Development and *in vitro* evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. AAPS PharmSciTech 8: E73.
16. Garg R, Gupta GD (2009) Preparation and evaluation of gastroretentive floating tablets of Silymarin. Chem Pharm Bull (Tokyo) 57: 545-549.
17. Baumgartner S, Kristl J, Vrečer F, Vodopivec P, Zorko B (2000) Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 195: 125-135.
18. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, et al. (2007) Formulation and development of hydrodynamically balanced system for metformin: *in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 67: 196-201.
19. Natalie Mc Clure (1997) Stability studies in overview of ICH guidelines for drug products. Matrix Pharmaceutical Inc.