IJPSR (2022), Volume 13, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 December 2021; received in revised form, 03 February 2022; accepted, 02 May 2022; published 01 August 2022

ASSESSING THE FLOATING DRUG DELIVERY SYSTEM USING THE MODEL ANTI-DIABETIC DRUG GLIMEPIRIDE

Bhargab Jyoti Sahariah [1], Ibadahun Lyne Gatphoh [2], Apurba Talukdar [1], Manoj Kumar Deka [1], Ripunjoy Bordoloi [1] and Chanam Melody Devi [*1]

NETES Institute of Pharmaceutical Science [1], NEMCARE Group of Institutions, Mirza - 781125, Assam, India.
Faculty of Pharmaceutical Science [2], Assam Down Town University, Panikhaiti - 781026, Assam, India.

Keywords:

Glimepiride, Floating drug delivery systems (FDDS), Floating tablets, sustain release, Gastric Retention Time (GRT)

Correspondence to Author:
Chanam Melody Devi

Assistant Professor,
NETES Institute of Pharmaceutical Science, Under Nemcare Group of Institutions, Mirza - 781125, Assam, India.

E-mail: melodykhr90@gmail.com

ABSTRACT: Floating drug delivery systems can increase the gastric retention time by manufacturing the systems with a density less than the gastric contents of the stomach. This causes the system to float over the gastric contents in the stomach without affecting the gastric emptying rate for a prolonged period. Glimepiride was selected as a model drug to increase oral bioavailability and efficacy. Hydroxypropyl methylcellulose (HPMC) and Carbopol, which are hydrophilic swellable polymers, govern the drug release from the prepared floating tablets. Buoyancy was achieved by using sodium bicarbonate as a gas-generating agent. The optimized formulation F5 showed a drug release of 42.14% within 12 hrs, whereas the floating lag time was found to be 50 seconds. The formulation variations were made in HPMC and Carbopol concentrations. The dissolution study revealed that sustain release profile can be achieved by increasing polymers concentrations in the formulation. The current study confirms that HPMC and Carbopol with sodium bicarbonate as a gas generating agent can develop floating systems that can provide controlled drug release for an extended duration, thereby achieving prolonged action of drug, enhancing oral absorption bioavailability.

INTRODUCTION: Floating drug delivery systems (FDDS) are one of the novel carriers that are developed to extend the gastric retention time of dosage forms. Having a bulk density lesser than the gastric fluids, FDDS remains buoyant over the stomach contents, the unaffected gastric emptying rate for a longer duration, and slower drug release can be achieved at a predetermined rate [1, 2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(8).3343-49

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(8).3343-49

Extending the gastric retention time can increase the solubility of poorly soluble drugs, thereby improving their bioavailability [3]. The ideal candidates for gastro retentive systems include drugs that exert localized action, are well absorbed in the stomach, have low water solubility, are unstable at alkaline pH, and have a narrow absorption window [4].

Rosiglitazone, Repaglinide, Pioglitazone, Nateglinide, Metformin, Glipizide, Glimepiride are the anti-diabetic drugs that can be formulated in this type of delivery system [5]. Glimepiride is a potent anti-diabetic drug belonging to the 3rd generation sulfonylurea, commonly prescribed in managing Type II Diabetes mellitus. The major

drawbacks of this drug include its poor solubility in the physiological fluids, the short biological half-life of 3-5 h, and rapid elimination reaching before the systemic circulation [6, 7]. However, it is mostly absorbed from the stomach. Therefore, a significant therapeutic effect of glimepiride can be achieved by increasing the gastric residence time with controlled release kinetics. In recent times, numerous approaches are available to enhance the solubility and absorption of the drug from the stomach, such as hydrogels, bioadhesives, size-increasing dosage forms, high-density and floating systems, *etc.* [8]. Among these approaches, enhanced solubility and absorption of low water-soluble drugs for improving its bioavailability can be achieved through the development of floating systems. Therefore, the goal of the study is to design a novel carrier of glimepiride based on gastro retentive floating tablets for controlled and prolonged release in the stomach. This will reduce frequent dosing of the drug as well as fluctuations in plasma concentrations, thereby increasing patient compliance and decreasing the incidence of adverse effects.

EXPERIMENTAL:

MATERIALS: The chemicals used in the formulations were of analytical grade. Glimepiride, Hydroxypropyl methylcellulose (HPMC K15M), Carbopol 940 were procured from BS Trading, Kolkata, India. Sodium bicarbonate and magnesium stearate were purchased from SRFCL, New Delhi, India. Lactose was procured from Fisher Scientific, Mumbai, India.

METHODS:

Preparation of Glimepiride Floating Tablets: The glimepiride floating tablets were prepared by direct compression method using the formula as shown in **Table 1**. All the ingredients, *i.e.*, Glimepiride, HPMC K15M, Carbopol 940, Sodium bicarbonate, Magnesium stearate, and Lactose monohydrate, were weighed out accurately and mixed to form a homogenous blend.

It was then compressed into tablets with an average weight of 250 mg on a single punch tablet press on a die having a diameter of 6.5 mm.

TABLE 1: COMPOSITION FOR GLIMEPIRIDE FLOATING TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5
Glimepiride	5	5	5	5	5
HPMCK15M	10	15	20	25	30
Carbopol 940	10	15	20	25	30
Sodium Bicarbonate	80	80	80	80	80
Magnesium Stearate	5	5	5	5	5
Lactose Monohydrate	140	130	120	110	100

Evaluation Parameters:

Characterization of Powder Blend: The powder blend's bulk density and tapped density were determined by using the bulk density apparatus. From the obtained result, the Compressibility index and Hausner ratio were calculated.

The flow properties of the powder blend were determined from the angle of repose value obtained by the funnel method.

Characterization of Glimepiride Tablets:

Weight Variation: A weight variation test was performed by selecting 20 tablets randomly from each formulation, and individual weight was measured from which the average weight was calculated. The obtained average weight was compared with the individual weight; further % weight variation was calculated and checked for the IP limits [9].

Hardness and Friability: The hardness test was performed using Pfizer tablet hardness tester and expressed in Kg/cm^2. Triplicate readings were taken, and the average was calculated. % Friability was determined using Roche friabilator. 20 tablets were weighed accurately (initial weight) and were kept in to the tumbling chamber of the friabilator. The rotational speed of the friabilator was maintained at 25 rpm for 4 min. After completing100 revolutions, the tablets were reweighed (final weight) and the percentage friability was computed [9].

$$\% \text{ Friability} = (\text{Initial weight} - \text{Final weight} / \text{Initial weight}) \times 100$$

Tablet Dimensions: The tablets' thickness and diameter were determined using a calibrated vernier caliper by randomly picking 3 tablets from each formulation [10].

***In-vitro* Buoyancy Studies:** The prepared glimepiride tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to one-third of the surface of the dissolution medium was recorded as Floating Lag Time (FLT), and the period up to which the tablet remained floating on the surface of the dissolution medium was determined as Total Floating Time (TFT) [3, 11].

Swelling Index: The individual weight of each tablet from every batch of formulations was measured (designated as W_0) and kept in separate beakers that contained 100 ml of 0.1 N HCl, maintaining the temperature at 37°C ± 0.5°C. The tablets were reweighed (W_t) in every 1 hr interval for a period of 5 h and % Swelling Index (SI) was computed in the following expression [12].

$$\%S_I = W_t W_0 / W_0 \times 100$$

Where, SI is swelling index, W_t is the tablet's weight at time t, Wo is the weight of the dry tablet before placing in the glass.

Drug Content: The drug content of the prepared glimepiride floating tablets was determined by grinding 10 tablets into a fine powder. The quantities of the powder equivalent to 15 mg of glimepiride were weighed out and transferred it into a 100 ml volumetric flask.

It was then filled with methanol and mixed thoroughly. 10 ml of the resulting solution was then diluted to 100 ml using 0.1 N HCl with 0.5% w/v sodium lauryl sulphate.

The solution was kept for continuous stirring up to 5 min and filtered through a 0.45µ membrane filter. The absorbance of the resulting solution was measured at 226 nm using UV spectrophotometer [3, 13].

***In-vitro* Dissolution Study:** The *in-vitro* dissolution study was performed in a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 50 rpm. The tablet was placed inside the dissolution vessel containing 900 ml of 0.1N HCl as the dissolution media with 0.5% w/v sodium lauryl sulphate, maintaining the temperature at 37±0.5°C. 5ml of sample were withdrawn at a specified time interval for 12 hrs, filtered through 0.45µ, and replaced the same volume with fresh dissolution media. The absorbance of the samples were measured at 226 nm using a UV spectrophotometer [3, 13].

***In-vitro* Drug Release Kinetics:** The following plots were made to find out the mechanism of drug release from the prepared tablets-

a. Zero-order kinetic model - % Qt Vs t

b. First-order kinetic model - log (100 - % Qt) Vs t

c. Higuchi's model - % Qt Vs $t^{1/2}$

d. Korsmeyer-peppas equation - log % Qt Vs log t.

Different kinetic models such as zero-order (percentage cumulative drug release Vs. time), first-order (log cumulative percentage of drug Vs. time), Higuchi model (percentage cumulative drug release Vs. square root of time), and Korsmeyer-Peppas model (log percentage cumulative drug release Vs. log t) were applied to explain the drug release kinetics from the prepared glimepiride floating tablets.

The best fit model was decided based on the highest regression values for correlation coefficients for all the formulations [3, 14].

RESULTS AND DISCUSSION:

Pre-compression parameters: The results of the pre-compression study parameters are shown in **Table 2**. All the pre-compression study parameters were within the specified standard limits.

TABLE 2: PRECOMPRESSION PARAMETERS

Formulation no.	Angle of repose	Carr's index	Hausner ratio
F1	27.13	14.09	1.08
F2	28.62	14.45	1.16
F3	28.81	14.11	1.17
F4	28.70	15.12	1.16
F5	28.75	15.12	1.16

Post Compression Parameters:

Weight Variation: The average weight of each formulation was recorded. The values were almost uniform and lie within the specifications. The values of tablets ranged from 248.5±1.1 to 250.12±1.12 mg. The prepared glimepiride floating tablets passed the weight variation test since the % weight variation was within the specified limits of ±5% of its weight.

Hardness and Friability: The hardness of all formulations was in the range of 5.4 to 7.4 kg/cm^{2,} which indicates that the hardness of all the formulations was almost uniform and possessed good mechanical strength. The friability values of prepared glimepiride floating tablets were less than 1%, indicating that the tablets of all formulations have good compactness and show enough resistance to mechanical shock and abrasion.

Tablet Dimensions: The thickness of the glimepiride floating tablets was measured by calibrated vernier caliper. Tablets diameters were found to be in the range of 0.81 to 0.82 mm and thickness was uniform for all the formulations with a value of 0.49 mm.

TABLE 3: THE RESULTS OF PHYSICAL CHARACTERIZATIONS

Formulation no.	Thickness (mm)	Diameter (mm)	Weight Variation	Friability (% Wt loss)	Hardness (kg/cm^2)
F1	0.49	0.81	248.5±1.1	0.8	5.4
F2	0.49	0.82	248.51±1.2	0.76	5.6
F3	0.49	0.82	249.3±1.05	0.83	6.4
F4	0.49	0.81	250.12±1.12	0.61	7.4
F5	0.49	0.81	250.12±1.12	0.40	6.6

***In-vitro* Buoyancy Studies:** All the prepared floating tablets float immediately after placing it into 0.1 N HCl solutions maintaining the temperature at 37±0.5 °C and remaining buoyant over 12 hrs without disintegration **Table 4**. The reaction between Sodium bicarbonate and the acidic environment produces carbon dioxide, which induced buoyancy of the glimepiride floating tablets without compromising the integrity of the polymer matrix. The hydration of the polymers leads to the formation of gel responsible for entrapping and protecting the gas generated within the tablet, thus reducing the tablet's density to less than 1 and starting floating. The prepared glimepiride floating tablets F5 exhibited the shortest floating lag time of 50 secs compared to other formulations F1, F2, F3, and F4, but the total buoyancy time was the same for all the formulations. A decrease in floating lag time of the formulation F5 could be due to an increase in the polymer concentration that produces a firm gel that entrapped carbon dioxide into, giving rapid buoyancy of the tablets [15].

TABLE 4: *IN-VITRO* BUOYANCY TEST

Formulation No.	FLT	TFT
F1	60 secs	> 12 h
F2	68 secs	>12 h
F3	68 secs	> 12 h
F4	57 secs	> 12 h
F5	50 secs	> 12 h

Swelling Index: Swelling is an essential factor in establishing buoyancy and dissolution of the drug from the tablet matrix. The results of the swelling index study of all the formulations were mentioned in **Fig. 1**.

The formulation F5 with the highest percentage of polymers shows the maximum swelling, i.e., 196.8% at 5 hrs compared to that of the formulations F1, F2, F3, and F4 containing lower polymer concentration than F5.

The swelling index was increased with the concentration of polymers since this polymer gradually absorbs buffer due to its hydrophilic nature, thereby building up a gel layer. The formed gel layer regulates the drug release from the tablet matrix [16, 17].

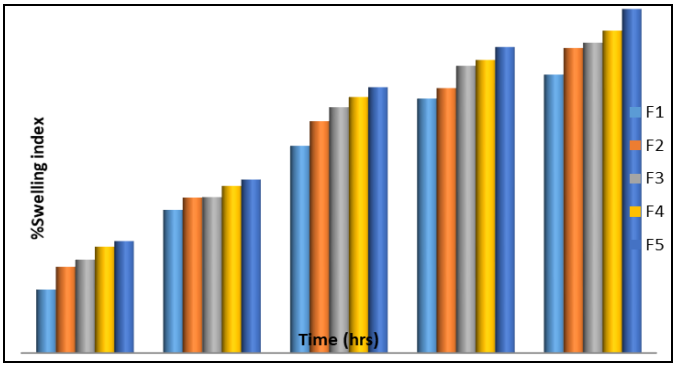

FIG. 1: SWELLING INDICES OF GLIMEPIRIDE FLOATING TABLETS (F1TO F5)

***In-vitro* Drug Release Studies:** The dissolution studies of all the formulations of glimepiride were carried out in 0.1 N HCl with 0.5% w/v sodium lauryl sulphate and the percentage drug release was calculated. The release profiles are shown in **Fig. 2.**

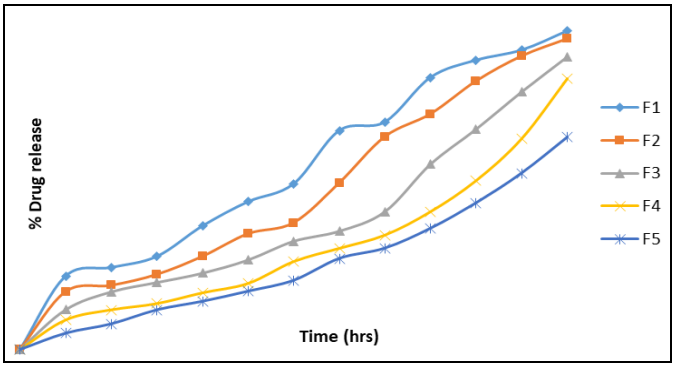

FIG. 2: *IN-VITRO* RELEASE PROFILE OF GLIMEPIRIDE FROM FORMULATIONS F1, F2, F3, F4, AND F5, RESPECTIVELY

By increasing the amount of polymers (HPMC K15M and Carbopol 940) the drug release was decreased proportionately in the following order F5<F4<F3<F2<F1.

In-vitro drug release studies show that the drug release is higher in case of F1 *i.e.*, 63.31%, and least in case of F5 *i.e.*, 42.14%, respectively, in 12 hrs [18, 19].

Drug Release Kinetics: The comparison between different kinetic models found that the zero-order kinetics model showed a higher degree of correlation coefficient (R^2) for all the prepared glimepiride floating tablets than other models **Table 5**.

This shows that the drug release rate is independent of the concentration, meaning the same amount of the drug will be released per unit of time. The model Korsmeyer-Peppas indicates that the type of diffusion evaluated by value of n between 0.45 and 0.89 implies non-fickian diffusion, and more than 0.89 indicates non fickian Super case II transport.

The n values of formulations F1 to F4 indicates non-fickian diffusion (anomalous diffusion) *i.e.*, coupling of diffusion and erosion mechanism. Whereas the n value of formulation F5 indicates that the drug release from the system follows Super case II transport [20, 21].

TABLE 5: RELEASE KINETIC DATA OF FORMULATIONS

Kinetic Models	Zero order	First order	Korsemeyer Peppas	Higuchi
F1	R^2=0.981 K0=5.117	R^2=0.978 K1= -0.035	R^2 = 0.931 n = 0.677	R^2 =0.936 KH = 19.33
F2	R^2=0.977 K_0= 5.052	R^2 = 0.949 K1= -0.034	R^2 = 0.903 n = 0.764	R^2 = 0.879 KH = 18.54
F3	R^2=0.943 K_0= 4.373	R^2 = 0.889 K1= -0.027	R^2 = 0.908 n = 0.792	R^2 = 0.820 KH = 15.77
F4	R^2=0.909 K_0= 3.744	R^2 = 0.838 K1 = -0.022	R^2 = 0.902 n = 0.863	R^2 = 0.763 KH = 13.32
F5	R^2=0.946 K_0= 4.032	R^2 = 0.905 K1= -0.023	R^2 = 0.955 n = 1.131	R^2 = 0.790 KH = 14.25

*R^2 = correlation coefficient, K_0 = Zero order rate constant, K_1= First order rate constant, KH= Higuchi dissolution constant, n = release exponent.

CONCLUSION: Glimepiride is a third-generation new sulfonyl urea oral hypoglycemic drug that is poorly soluble in an acidic environment. On oral administration in healthy people, it gets absorbed rapidly and completely. However, the absorption pattern in diabetic patients is erratic due to impaired gastric motility or gastric emptying.

This erratic absorption of glimepiride becomes clinically significant since the efficacy of short-acting sulfonylurea depends on the drug's absorption rate. Hence, to overcome the above-mentioned drawbacks the present study aims to develop Glimepiride as a Floating Drug Delivery System (FDDS) and its evaluation.

The floating tablets of glimepiride were successfully prepared using sodium bicarbonate as a gas-generating agent, hydroxymethyl cellulose (HPMC K15M), along with Carbopol 940 as polymeric matrix. The granules of different formulations were evaluated for various pre-compression parameters like angle of repose, bulk density, and compressibility index. The result of the angle of repose indicates a reasonably good flow property of granules. The compressibility index values further support the flow property of the granules. The compressed tablets of all the formulations were evaluated for physical appearance, thickness, diameter, hardness, friability, weight variation, content uniformity, assay, and dissolution.

The tablets were circular in shape with no visible cracks and a smooth appearance. All the formulations showed reasonably good hardness values. The friability of compressed tablets was also below 1% of their weight, generally considered acceptable, indicating that all the formulations comply with that standard. The weight variation test revealed that the tablets were within the range of the pharmacopeial limit. Content uniformity test compliance that of tablets within the range of pharmacopeial limit.

The floating lag time glimepiride floating tablets, F5 exhibited a short buoyancy lag time of 50 sec compared to other formulations F1, F2, F3, and F4, but the total buoyancy time was over 12 hrs for all the formulations. Floating tablets prepared with the increasing concentration of polymers were found to provide sustainity throughout 12 hrs. Moreover, formulation F5 containing a high percentage of polymer, shows the maximum swelling compared to other formulations. *In-vitro* release studies confirmed that the F5 formulation showed a drug release of 42.14% in 12 hrs. The formulations were found to follow zero-order kinetics. The mechanism of drug release was anomalous diffusion for formulations F1 to F4, which was of non-fickian type, whereas F5 showed a Super case II transport mechanism. Based on the results obtained, F5 was most suitable as a gastro retentive floating drug delivery system compared to the other formulations. The slow release of glimepiride in the gastrointestinal tract could enhance drug absorption, thereby increasing its therapeutic action duration for a longer period.

ACKNOWLEDGEMENT: The authors wish to thank Assam downtown University for providing laboratory facilities.

CONFLICTS OF INTEREST: None

REFERENCES:

1. Bhosale Aishwarya R, Shinde Jitendra V and Chavan Rajashree S: A comprehensive review on floating drug delivery system (FDDS). J Drug Deliv and Ther 2020; 10(6): 174-82.
2. Rajora A and Kalpana N: A critical review on floating tablets as a tool for achieving better gastric retention. critical reviews™. Ther Drug Carr Syst 2022; 39(1): 63-105.
3. Kumar S, Keerthy HS and Prasad Yadav R: Role of floating tablet in oral drug delivery system. Asian J Pharm and Dev 2021; 9(3): 104-11.
4. Pund Suraj B., Vishwas Bhagat C, Deshmukh Madhuri T, Kardile Deepak P and Shete Rajkumar V: A review on floating multi-particulate drug delivery system. Res J Pharm and Tech 2021; 14(7): 3987-92.
5. Megha S and Seema K: Floating drug delivery of antidiabetic drugs: an overview. Int J Pharm Bio Sci 2012; 3(4): 456 – 71.
6. Cruz-Angeles J, Videa M and Maria Martinez L: Highly Soluble Glimepiride and Irbesartan Co-amorphous Formulation with Potential Application in Combination Therapy. AAPS Pharm Sci Tech 2019; 20(144): 1-12.
7. Tucci M, Roca E, Ferrari L, Pia A, Dalla Volta A, Bedussi F, Buttigliero C, Vittorio Scagliotti G, Sigala S and Berruti A: Abiraterone and prednisone therapy may cause severe hypoglycemia when administered to prostate cancer patients with type 2 diabetes receiving glucose-lowering agents. Endocrine 2019; 64: 724–26.
8. Tripathi J, Thapa P, Maharjan R and Hoon Jeong S: Current state and future perspectives on gastroretentive drug delivery systems. Pharm 2019; 11(193): 1-22.
9. Banker GS and Anderson NR: Tablets. In: Lachman L, Liberman HA, Kang JL (Eds) the theory and practice of industrial pharmacy. Varghese Publication House 1991; 296- 302.
10. Raziq A, Umer Jan S, Gul R, Khan Y, Aman T and Akhtar Shah P: Relative comparison of stability and degradation of methylcobalamin tablets of different brands at different storage settings. Int J Appl Pharm 2021; 13(3): 171-75.
11. Qin C, Wu M, Xu S, Wang X, Shi W, Dong Y, Yang L, He W, Han X and Yin L: Design and optimization of gastro-floating sustained-release tablet of pregabalin: in vitro and *in-vivo* evaluation. Int J pharm 2018; 545(1-2); 37-44.
12. Razavi FS, Kouchak M, Feizoleslam F and Veysi M: An overview on floating drug delivery systems (FDDS); conventional and new approaches for preparation and *in-vitro in-vivo* evaluation. FABAD J Pharm Sci 2021; 46(3); 345-62.
13. Reichel RC and Bagyalakshmi J: Formulation and evaluation of Glimepiride as Gastro Retentive Dosage Form 2009; 68-9.

14. Paarakh MP, Jose PA, Setty CM and Christoper GP: Release kinetics–concepts and applications. Int J Pharm Res Technol 2018; 8(1): 12-20.
15. Devi CM, Nath L, Goswami A and Barakoti H: Formulation and Evaluation of Gastro Retentive Floating Tablets of Diclofenac Sodium Based on Effervescent Technology. Int J Pharm Biol Sci 2019; 9(3): 249-55.
16. Rahamathulla M, Alshahrani SM, Al Saqr A, Alshetaili A and Shakeel F: Effervescent floating matrix tablets of a novel anti-cancer drug neratinib for breast cancer treatment. J Drug Deliv Sci Techn 2021; 66(102788): 1-9.
17. Qi X, Haiyan C, Yao R, Fengjiao Y, Ning M and Zhenghong W: Floating tablets for controlled release of ofloxacin *via* compression 2 coating of hydroxypropyl cellulose combined with effervescent agent. Int J Pharm 2015; 489(2): 210-17.
18. Raza A, Shen N, Li J, Chen Y and Wang JY: Formulation of zein based compression coated floating tablets for enhanced gastric retention and tunable drug release. Eur J Pharm Sci 2019; 132: 163-73.
19. Rawat S, Sangali S and Gupta A: Formulation and Evaluation of Floating Matrix Tablets of Acyclovir using 3 2 Factorial Design. Res J Pharm Dos Forms Technol 2018; 10(1): 1-9.
20. Nusrath A, Deepika B, Nagaraju K, Regupathi T, Rao KNV and Dutt KR: Formulation and in vitro evaluation of Cefpodoxime proxetil gastro retentive floating tablets. Innovat Int J Med Pharm Sci 2017; 2(1): 1-7.
21. Radhakant G, Himankar B and Zhao Q: Application of Mathematical Models in Drug Release Kinetics of Carbidopa and Levodopa ER Tablets. J Develop Drugs 2017; 6: 1-8.

How to cite this article:
Sahariah BJ, Gatphoh IL, Talukdar A, Deka MK, Bordoloi R and Melody Devi C: Assessing the floating drug delivery system using the model anti diabetic drug glimepiride. Int J Pharm Sci & Res 2022; 13(8): 3343-49. doi: 10.13040/IJPSR.0975-8232.13(8).3343-49.