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Research Article

FORMULATION AND EVALUATION OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM CONTAINING COMBINATION OF GLIPIZIDE AND METFORMIN HYDROCHLORIDE

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ABSTRACT

Objective: Is to develop a gastroretentive drug delivery system of glipizide and metformin hydrochloride is to overcome the biggest problem in oral drug delivery is low and erratic drug bioavailability.

Methods: Seven formulations containing retardant material and alkalizing agent were prepared with solubilizing agent in different ratios. The ability of various polymers to retain the drug when used in different concentrations was investigated. It was found that sodium bicarbonate reacts with HCl and produce CO_2 which creates pores in tablet and elevates swelling by wetting polymer. Hence, it helps in maintaining the buoyancy. The release rate could be modified by varying the polymer ratio, concentration of alkalizing, and solubilizing agent. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, buoyancy, and *in vitro* dissolution studies.

Results: The *in vitro* drug release profiles obtained for tablets (F2) made with combinations of hydroxypropyl methylcellulose (HPMC) K4M, HPMC, and K100M showed lesser floating lag time (<60 seconds) and a prolonged floating duration (>14 hrs) with controlled and sustained release of MHCl and GD.

Conclusion: Controlled release floating drug delivery of GD and MHCl showed sufficient release for an extended period of time. As a result, the frequent dosing and possible incomplete absorption of drug can be avoided.

Keywords: Controlled drug release, Gastro-retentive drug delivery system, Metformin hydrochloride, Glipizide.

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INTRODUCTION

Gastroretentive dosage forms are a variable process and it as ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Gastroretensive systems 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 for drugs that are less soluble in a high pH environment [1-5].

Metformin HCl and glipizide is an anti-diabetic drug. Glipizide and metformin HCl combination is used to treat high blood sugar levels that are caused by a type of diabetes mellitus or sugar diabetes called Type 2 diabetes. Normally, after the food intake, pancreas releases insulin to help the body to store excess sugar for later use. This process occurs during normal digestion of food. In Type 2 diabetes, body does not work properly to store the excess sugar and the sugar remains in the bloodstream. Chronic high blood sugar can lead to serious health problems in the future. With two actions, the combination of glipizide and metformin HCl helps body to cope with high blood sugar [2]. Glipizide stimulates the release of insulin from the pancreas, directing the body to store blood sugar. Metformin HCl has three different actions: It slows the absorption of sugar in small intestine; it also stops the liver from converting stored sugar into blood sugar and it helps body to use natural insulin more efficiently [6-11]. In diabetic patient, the absorption of glipizide is erratic because of impaired gastric function and motility. To overcome these drawbacks glipizide will be formulated as gastro-retentive drug delivery system (GRDDS).

The main aim to develop the metformin HCl as GRDDS, which not only releases the drug in the absorption window but also provides controlled release drug profile, that may result patient compliance and therapeutic success. The main objective of this work is to formulate and evaluate floating tablets of metformin HCl and glipizide.

METHODS

Glipizide, metformin HCl, hydroxypropyl methylcellulose (HPMC) (K100M and K4M) was gifted from Yarrow Chemicals Ltd., Mumbai and polyvinylpyrrolidone (PVP) K25 gifted from SDFCL Mumbai.

Methods

Preparation of GD and MHCl gastroretentive tablet by wet granulation method

Accurately weighed out all materials according to the formula (Table 1) and shift the material through 80 number mesh. Mixed the drug, polymer and citric acid by geometrical mixing in a double polybag for 10 minutes. To this mixture added sodium bicarbonate as a gas generating agent. Again mixed for 5 minutes. The mixture was granulated using PVP K25 by dissolved in sufficient isopropyl alcohol and passed through sieve number 12. Granules were air dried and were passed through sieve number 20. To the dried granules magnesium stearate and talc were added and it is further mixed in a blender.

Formulation

Angle of repose

The angle of repose of powder was determined by the funnel method using formula [3] (Table 2):

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

h=Height of the pile, r=Radius of the pile.

Bulk density

The apparent bulk density in g/ml was calculated using the formula [4]:

Bulk density=weight of powder/bulk volume.

Table 1: Formula for gastroretentenive tablet

FC	GD (mg)	MHCl (mg)	HPMC K100M	HPMC K4M	PVP K25 (mg)	Citric acid	$NaHCO_3$ (mg)	Mg stearate (mg)	Talc (mg)
F1	5	500	-	100	30	50	90	5	5
F2	5	500	60	40	30	50	90	5	5
F3	5	500	100	-	30	50	90	5	5
F4	5	500	20	85	30	50	85	5	5
F5	5	500	40	60	30	50	90	5	5
F6	5	500	50	50	30	60	80	5	5
F7	5	500	100	-	30	55	85	5	5

FC: Fenoprofen calcium, HPMC: Hydroxypropyl methylcellulose, PVP: Polyvinylpyrrolidone

Tap density

Tap density was determined by 500 tap method. Tapped density was calculated using the formula [4]:

Tap density=weight of powder/tapped volume.

Carr's index (%)

The powder blend (5 g) was weighed and was transferred to a measuring cylinder, and then it was subjected to 100 tappings. The tapped density and poured density were noted (Table 3).

Carr's index was calculated by the following formula [3]:

Carr's index (%)=(tap density-bulk density)/tap density × 100.

Hausner's ratio

Hauser's ratio was calculated by the following formulae [3]:

Hausner's ratio=tapped density/bulk density.

Compression of tablet

Tablets were compressed on a degree of substitution-16 mm punch using multistation tablet punching machine punch with flat surface and round shape.

Postcompression parameters

Weight variation

The weight variation test was carried out to determine to what extent the weight of an individual tablets deviates with respect to the average tablet tested. To calculate the weight variation, 20 tablets at random were weighed and then the average weight was noted. Then, the weight deviation and percentage deviation were calculated [3] (Table 4).

Hardness

Five tablets were randomly picked from each formulation, and the mean hardness was determined using Monsanto hardness tester [3,12-14].

Thickness

About 10 tablets were selected randomly and thickness was measured using vernier caliper scale, which permits accurate measurement [3,12-14].

Friability

A minimum of 40 tablets were randomly selected and the total weight was noted. The weighed tablets were placed in the Roche friabilator and allowed to make 100 revolutions at the rate of 25 rpm for 4 minutes. The tablets were dusted and weighed again. The % friability was calculated using the formula [3,15,16].

$$\% \text{ Friability} = \frac{\text{Initial weight-final weight}}{\text{Initial weight}} \times 100$$

Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in electro lab United States Pharmacopoeia (USP) disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube, and the basket rack was positioned in a 1 L beaker containing 0.1 N HCl buffer solution at 37°C±1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted [3].

Table 2: Effect of angle of repose on flow property

Angle of repose (θ)	Type of flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Very poor

Table 3: Relation between % compressibility and flowability

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table 4: Weight variation for uncoated tablets

Average weight	Maximum % difference allowed
<80	10
80-324	7.5
>324	5

Drug content uniformity

About 10 tablets were randomly selected and crushed. Then, these tablets were dissolved in a small quantity of methanol and the volume was made up to 100 ml with 0.1 N HCl. The solution was then filtered and the absorbance was measured at 275.80 nm and 259.60 nm, respectively, using 0.1 N HCl as a blank. The test results were interpreted with the limits of British pharmacopoeia [3,17,18].

***In vitro* drug release study**

In vitro drug release study was performed using USP Type II dissolution apparatus. 0.1 N HCl (900 ml) maintained at a temperature of 37°C±0.5°C as dissolution medium. The RPM was maintained at 50. The absorbance was taken at the λ_{max} of GD (275.80 nm) and at the isoabsorptive point of two drugs (259.5 nm) using UV spectrophotometer [5].

Drug release kinetic data analysis

To describe the kinetics of the release process of drug in the different formulations, models were fitted to the dissolution data of optimized formulations using linear regression analysis.

Zero order kinetics

To study the zero order release rate kinetics, the release rate data were fitted to the following equation.

$Q_t=Q_0+K_0t$

Where, Q_t=amount of drug dissolved in time t
Q_0=initial amount of drug in the solution
K_0=zero order release constant.

First order kinetics
To study the first order release rate kinetics the release rate data were fitted to the following equation:

$\text{Log } Q_t=\log Q_0+K_1 t/2.303$

Where, Q_t=amount of drug released in time t
Q_0=initial amount of drug in the solution
K_1=first order release constant.

Higuchi model
Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is:

$Q_t=K_h\ t\ ½$

Where, Q_t=amount of drug released in time t
K_h=Higuchi dissolution constant.

Korsmeyer and Peppas model
This model is generally used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved:

$Mt/M\infty=K_{tn}$

Where Mt/M∞=fraction of drug release
K=release constant
t=release time

n=dissolution exponent for the drug release that is dependent on the slope of the matrix dosage form.

If the exponent n=0.5 or near, then the drug release mechanism is Fickian diffusion and if n have value near 1.0, then it is non-Fickian diffusion (Table 5).

The results obtained from *in vitro* drug release studies were plotted adopting five different mathematical models of data treatment as follows:

- Cumulative percent drug release versus time (zero order rate kinetics)
- Log cumulative percent drug retained versus time (first order rate kinetics)
- Higuchi classical diffusion equation (Higuchi matrix)
- Log of cumulative percent drug release versus log time (Peppas equation).

Stability studies
The stability testing was done by exposing the prepared tablets to temperature and humidity according to the ICH guidelines for a period of 6-month. The conditions were 40°C±2°C/75%±5% relative humidity (RH) and stability studies were carried out for initial 3 months and 6 months. At the end of the 6 months hardness, friability, disintegration, and drug content evaluation were performed [19,20,21].

Table 5: "n" values for Korsmeyer and Peppas model

Release exponent	Drug transport mechanism
n=0.5	Fickian diffusion or square root of time kinetics
0.5<n < 1	Anomalous (non-Fickian diffusion)
n=1	Case II transport
n>1	Super case II transport

RESULTS AND DISCUSSION

Preformulation studies
The identification of the drug done by Fourier transform infrared is similar to that of reference. Compatibility study concludes that there is no interation between the drug and polymer.

Evaluation of floating tablet
Pre-compression parameters
Precompression parameters of the formulation such as Angle of repose, Bulk density, Porosity and Compressibility index are discussed in Table 6.

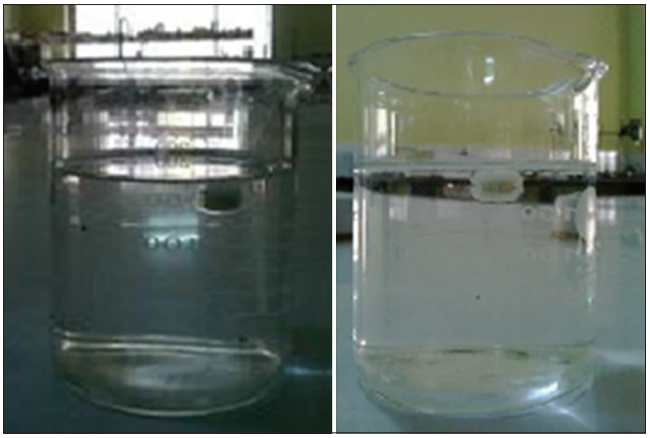

Fig. 1: Floating of formulation

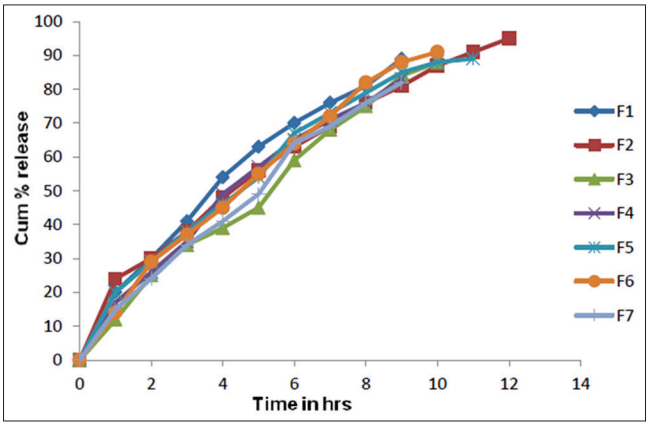

Fig. 2: Swelling index of all formulation

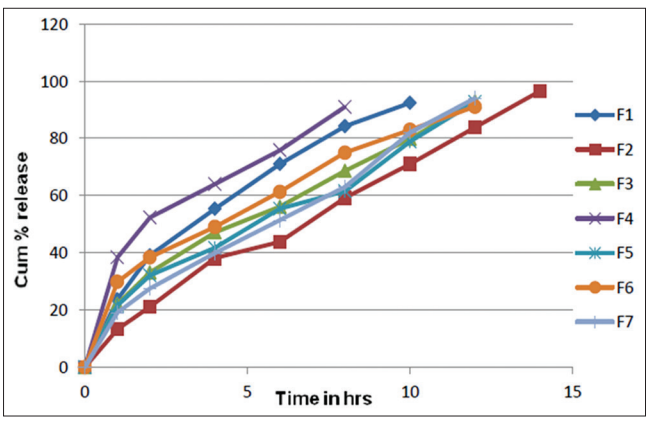

Fig. 3: *In vitro* release of all formulations

Table 6: Angle of repose, bulk density, porosity and compressibility index

FC	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carrs index (%)	Hausners ratio	Compressibility index (%)
F1	32°15’	0.492	0.685	28.18	1.39	13.14
F2	28°48’	0.522	0.711	26.58	1.36	12.30
F3	33°13’	0.445	0.720	38.19	1.62	15.90
F4	25°28’	0.588	0.657	10.50	1.12	15.35
F5	28°73’	0.470	0.685	31.39	1.46	12.57
F6	29°93’	0.481	0.633	24.01	1.32	14.37
F7	32°15’	0.492	0.685	28.18	1.39	13.14

FC: Fenoprofen calcium

Table 7: Physicochemical parameters of core tablet

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)
F1	5.91±0.001	10.2	6.0	0.651	1.40
F2	5.65±0.004	10.2	6.0	0.431	1.02
F3	5.56±0.005	10.4	5.5	0.521	1.15
F4	5.61±0.004	10.1	5.2	0.473	1.15
F5	5.45±0.003	10.4	6.0	0.417	1.40
F6	5.38±0.004	10.4	5.5	0.554	1.15
F7	5.65±0.003	10.1	5.6	0.661	1.40

FC: Fenoprofen calcium

Post-compression parameters

All formulations remained white, smooth, flat faced circular with no visible cracks. The results are shown in Table 7. All the formulations showed values within the prescribed limits for tests like hardness, friability, and weight variation which indicate that the prepared tablets are of good standard quality.

Content uniformity

The % amounts of drug content of the different formulations have been shown in Table 8. The % amounts of drug content of all formulations were found to be in the range of 98.19-103.07%, i.e., within±5% limit.

Buoyancy evaluation

All the formulations were found to be floating in the release medium chosen as long as the study was conducted (Table 9). The buoyancy might have resulted due to the polymers chosen (low density) and the CO_2 liberated by the sodium bicarbonate after the interaction with HCl.

Swelling index

The swelling index of floating tablets of F1-F7 is shown in Fig. 2. HPMC K4M and HPMC K100M (F6, F7) swelled rapidly at the beginning in 0.1 N HCl. Tablets containing combination of HPMC K4M and HPMC (F2) showed constant increasing in swelling index up to 12 hrs. The combination of HPMC K4M and HPMC K100M resulted in a higher swelling index compared with HPMC K100M alone. The HPMC grade also affects the swelling and hydration with considerably higher swelling index for HPMC K100M than HPMC K4M. HPMC K4M exhibited lower swelling index, but there was no decrease in swelling rate.

***In vitro* dissolution study**

The *in-vitro* dissolution of gastric-oral floating tablets was carried out in 0.1 N HCl medium. *In vitro* release profile of GD and MHCl from the floating tablet was examined in 0.1N HCl for 14 hr. All the tablets were prepared by effervescent approach (Figure 3).

Model plot of GRDDS released from formulation

In the kinetic release the zero order, first order, Higuchi model and Krosmeyer-Peppas model and the values the ‘n’ values is within the limit. The Krosmeyer-Peppas equation suggested that, all the formulation showed drug release by non-fickian diffusion mechanism. From the obtained results (Figs. 4-11) the floating tablet of GD and MHCl may increase the bioavailability.

Table 8: Results of content uniformity test

Formulations	% amount of drug content
F1	98.19
F2	99.60
F3	101.06
F4	98.65
F5	102.12
F6	99.01
F7	103.07

Table 9: Results of FLT and total floating time

FC	FLT (seconds)	Total floating time (hrs)
F1	54	>10
F2	45	>12
F3	85	>12
F4	45	>14
F5	62	>12
F6	125	>12
F7	130	>12

FLT: Floating lag time

Table 10: Release kinetic profile of different formulations

FC	Zero order	First order	Higuchi	Korsmeyer–Peppas	
	r2	r2	r2	r2	n
F1	0.8595	0.9813	0.9957	0.5892	0.49
F2	0.9954	0.8358	0.9471	0.7507	0.47
F3	0.9594	0.9174	0.9891	0.6115	0.49
F4	0.8595	0.9534	0.9869	0.4609	0.51
F5	0.9647	0.8861	0.9734	0.6146	0.48
F6	0.9238	0.9725	0.9948	0.5487	0.46
F7	0.9827	0.8804	0.9614	0.6561	0.49

Kinetic values obtained from different plots of formulation

The cumulative percentage of drug release as a function square root of time (Higuchi plot) was linear and it suggested that the release of GD and MHCl, HPMC K100M, and HPMC K4M was diffusion controlled. The n values obtained from the Peppas-Korsmeyer equation suggested that all the formulation showed drug release

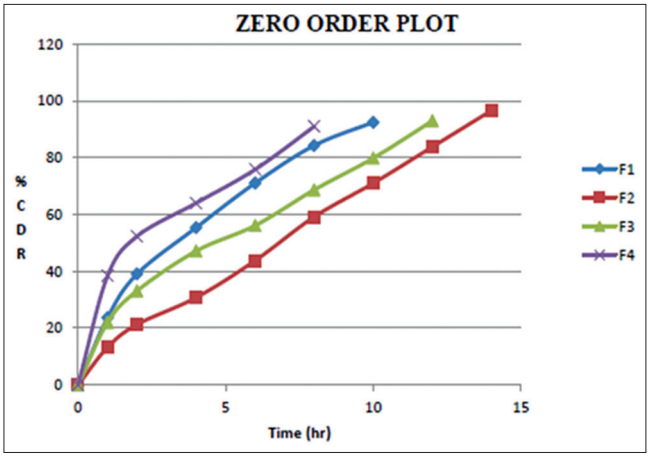

Fig. 4: Zero order plot for F1, F2, F3 and F4

Fig. 5: Zero order plot for F5, F6 and F7

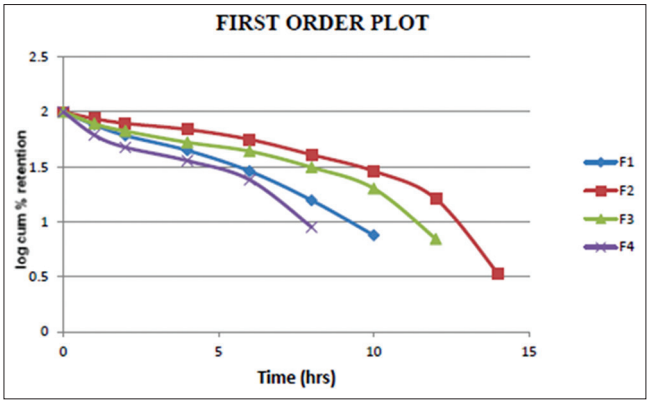

Fig. 6: First order plot for F1, F2, F3 and F4

by non-Fickian diffusion mechanism. From the above results, the floating tablet of GD and MHCl may increase the bioavailability with once daily dosage form.

Stability study parameters of formulation

Stability study of formulation F2

The optimized floating tablets were selected for stability study on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The tablets were investigated at 40°C/75% RH for 6 months. From the data, the formulation is found to be stable under the conditions mentioned above since there was no significant change in the percentage amount of drug content. Thus, it was found that the floating tablets of MHCl and GD were stable under these storage conditions for at least 6 months.

Fig. 7: First order plot for F5, F6 and F7

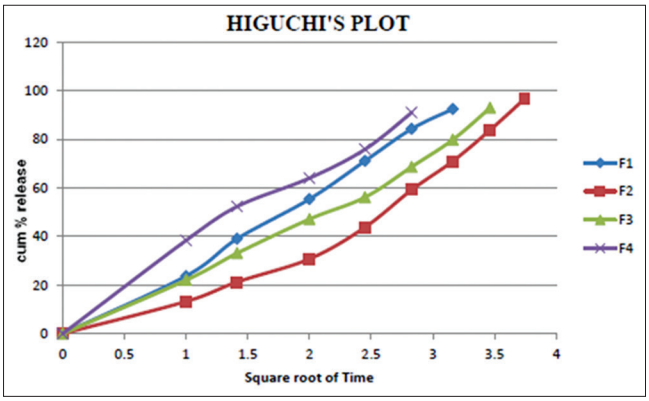

Fig. 8: Higuchi's plot for F1, F2, F3 and F4

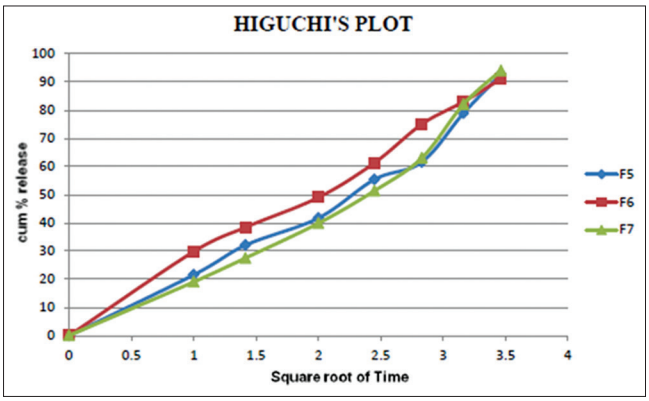

Fig. 9: Higuhi's plot for F5, F6 and F7

CONCLUSION

The present investigation of tablet form of gastric oral floating controlled drug delivery of GD and MHCl is prepared using the retardant,

Table 11: Stability study parameters of formulation F2

Evaluation parameters	Initially	After 3 months	After 6 months
Weight variation (%)	1.02	1.02	1.02
Hardness	6.0	6.0	6.0
Friability (%)	0.431	0.452	0.452
Floating lag time (seconds)	45	45	45
In vitro dissolution study (after 14 hrs) (%)	96.63	96.45	96.39

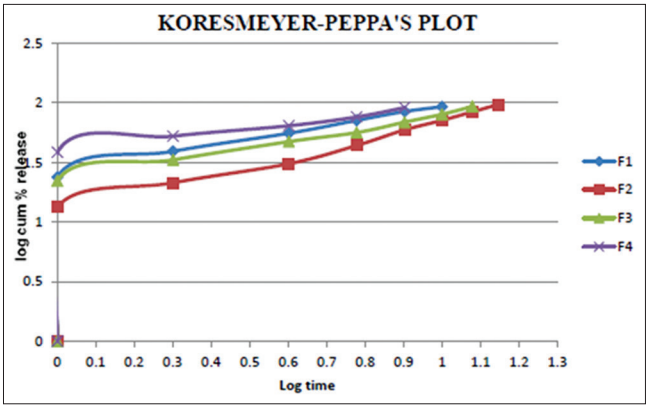

Fig. 10: Korsmeyer-Peppas plot for F1, F2, F3 and F4

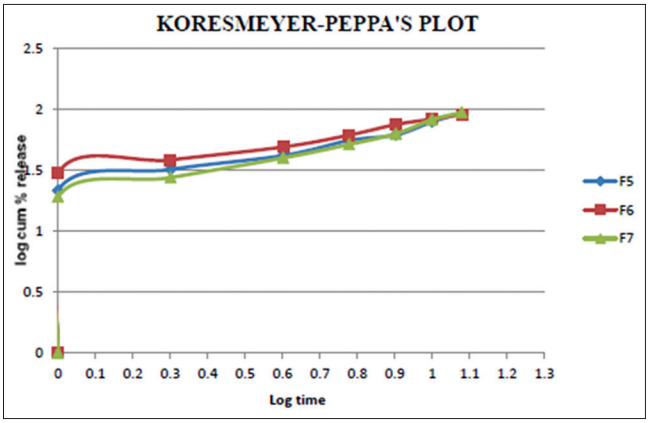

Fig. 11: Korsmeyer–Peppas plot for F5, F6 and F7

alkalizing and solubilizing agent, proved to be an ideal formulation as it released the drug in controlled fashion for extended period of time by maintaining the buoyancy. Controlled release floating drug delivery of GD and MHCl showed sufficient release for extended period of time. As a result, the frequent dosing and possible incomplete absorption of drug can be avoided. The *in vitro* drug release profiles obtained for tablets (F2) made with combinations of HPMC K4M, HPMC, and K100M showed lesser floating lag time (<60 seconds) and a prolonged floating duration (>14 hrs) with controlled and sustained release of MHCl and GD.

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REFERENCES

1. Nayak AK, Maji R, Das B. Gastroretentive drug delivery system. Asian J Pharm Clin Res 2010;3(1):1-2.
2. Raja BD, Thakkar HR, Paramasivam S, Jamsheer AK, Adimoolam S. Formulation and evalution of gastroretentive floating tablets of glipizide. Int J Res Ayur Pharm 2011;2(3):911-7.
3. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and *in vitro* evaluation. AAPS Pharm Sci Tech 2004;5(2):e34.
4. Prajapati ST, Patel LD, Patel DM. Studies on formulation and *in vitro* evaluation of floating matrix tablets of domperidone. Indian J Pharm Sci 2009;71(1):19-23.
5. Gohel MC, Mehta PR, Dave RK, Bariya NH. More relevant dissolution method for evalution of floating drug delivery system. Dissol Technol 2005;22-5.
6. Joseph NJ, Lakshmi S, Jayakrishnan A. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: *In vitro* and *in vivo* evaluation in rabbits. J Control Release 2002;79(1-3):71-9.
7. Gohel MC, Mehta PR, Dave KR. A more relevant method for evaluation of floating drug delivery system. Dissol Technol 2004;22:5.
8. Vedha HB, Brahma RA, Samyuktha RB. Floating drug delivery of nevirapine as a gastroretentive system. J Young Pharm 2010;2(4):350-5.
9. Available from: http//www.slideboom.com/presentation/288556/ Methods to evaluate the compability of drug with exipients. [Last accessed on 2015 Feb 02].
10. Kulkarni AP, Jaiswal M, Jawale BS, Shirolkar SV, Kasture PV. Development and evaluation of press-coated tablets for chronotherapeutical drug delivery using gellable and permeable polymer. Der Pharma Lett 2010;2(4):482-97.
11. Government of India, Ministry of Health and Family Welfare. Indian Pharmacopeia. Vol.2. Ghaziabad: The Indian Pharmacopoeia Commission; 1996. p. 659-61.
12. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm 2001;220(1-2):13-21.
13. Basak SC, Rahman J, Ramalingam M. Design and *in vitro* testing of a floatable gastroretentive tablet of metformin hydrochloride. Pharmazie 2007;62(2):145-8.
14. Hui M, Ozkan Y. Bilayer buoyant tablet consisting one immediate release layer and one sustained release layer. Drug Dev Ind Pharm 2000;26(8):857-66.
15. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained-release tablet capable of floating on gastric fluid with prolonged gastric resident time. Yao Xue Xue Bao 1997;32(10):786-90.
16. Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of nicardipine hydrochloride. Pharmazie 2003;58(1):38-43.
17. Hou SY, Cowles VE, Berner B. Gastric retentive dosage forms: A review. Crit Rev Ther Drug Carrier Syst 2003;20(6):459-97.
18. Steingoetter A, Kunz P, Weishaupt D, Mäder K, Lengsfeld H, Thumshirn M, *et al.* Analysis of the meal-dependent intragastric performance of a gastric - retentive tablet assessed by magnetic resonance imaging. Aliment Pharmacol Ther 2003;18(7):713-20.
19. The European Agency for the Evaluation of Medical Products, ICH Topic Q2B Note for Guidance on Validation of Analytical Procedures: Methodology GPMP/ICH/281/95. Geneva, Switzerland: IFPMA; 1996. p. 1-8.
20. Umamaheswari RB, Jain S, Tripathi PK, Agrawal GP, Jain NK. Floating-bioadhesive microspheres containing acetohydroxamic acid for clearance of *Helicobacter pylori*. Drug Deliv 2002;9(4):223-31.
21. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: Design and release kinetics. Drug Dev Ind Pharm 2000;26(9):965-9.