Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 3, 2013

Research Article

DESIGN AND EVALUATION OF INTRAGASTRIC BUOYANT TABLETS OF METFORMIN HYDROCHLORIDE

R. ANANTHAKUMAR[a*], N. RAJA[b], P. MOHAN[b], K. RUCKMANI[c]

[a]Balaji Institute of Pharmacy, Narsampet 506331, [b]Balaji institute of pharmaceutical sciences, Narsampet 506331.Warangal, [c]Anna university of Technology, Tiruchirappalli, Tamilnadu, India. Email: ananth101mmc@gmail.com

Received: 03 Apr 2013, Revised and Accepted: 13 May 2013

ABSTRACT

Objective: The main objective of this study is to investigate the effect of formulation variables on drug release and floating properties of the delivery system. Hydroxy Propyl Methyl Cellulose (HPMC) of different viscosity grades and Carbopol 934P (CP934P) were used in formulating the Gastric Floating Drug Delivery System (GFDDS) employing 2X3 full factorial design. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated fed state gastric fluid (pH 1.2). Effect of various release modifiers was studied to ensure the Floating tablet as Hydro dynamically Balanced System over a prolonged period.

Methods: The tablets were prepared by the wet granulation method, using hydrophilic matrix polymers HPMC K4M, HPMC K100LV, CP934P, sodium bicarbonate. Tablets were physically characterized and evaluated for in vitro release characteristics for 12 h in 0.1mol/l HCl at 37^{0}C. The in vitro drug release, buoyancy lag-time, swelling index were evaluated. It was found that in tablets prepared with HPMC, the presence of CP934P had significant impact on the release and floating properties of the delivery system. In tablets prepared with low viscosity polymer (HPMC K4M), incorporation of CP934P was found to compromise the floating capacity of GFDDS and release rate of metformin hydrochloride.

Results and conclusion: Tablets are prepared with HPMC K4M and CP934P which gives the best in vitro percentage drug release and used as the optimized formulation. The viscosities of HPMC significantly affect the drug release rate, buoyancy lag-time, swelling characteristics of the tablets. By fitting the data in to zero order, first order, Higuchi and Korsemeyer-Peppa's model it concludes that the release followed zero order release, where as the correlation co-efficient (R^2 value) was higher for zero order release. The release mechanism follows Higuchi model, Korsemeyer-Peppa's model and non-fickian diffusion.

Keywords: Metformin hydrochloride; Floating drug delivery; Gastro retention; HPMC; Carbopol 934p; Factorial design; Non-fickian diffusion; Prolonged release.

INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficiency of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine [1]. To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as: floating systems [2, 3], mucoadhesive systems [4, 5], swelling and expanding systems [6], high density systems [7, 8], ion exchange resins [9], osmotic regulated systems [10] which delay gastric emptying. Both single unit systems (tablets or capsules) [11, 12] and multiple unit systems (multi particulate systems) have been reported in the literature. A gastric drug delivery system (GFDDS) is particularly useful for drugs have narrow absorption window in the upper part of gastrointestinal that are primarily absorbed in the duodenum and upper jejunum segments [13]. It retains the dosage form at the site of absorption and thus enhances the bio-availability [14].

Metformin is a biguanide hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus not responding to dietary modification. The drug is stable, does not bind to plasma protein and is excreted unchanged in urine. It has been reported that the absolute bioavailability of Metformin hydrochloride when given orally is 50-60% only because of its narrow absorption window. The biological half-life of Metformin hydrochloride is 1.7 hrs and the main site of its absorption is proximal small intestines [3, 4]. Recently, research has been carried out using Metformin hydrochloride in effervescent-type drug delivery system by using different grades of low density polymer [15]. The GFDDS was planned for Metformin hydrochloride as such a system when administered would remain buoyant on the gastric fluid for a prolonged period of time and release the drug in sustained manner, thus providing the drug continuously to its absorption sites and increasing the magnitude of drug effect. In this way it stands an advantage over conventional dosage form, which needs to be administered twice or thrice a day.

MATERIALS AND METHODS

Materials

Metformin hydrochloride was obtained as a gift sample (Grandix pharma Ltd, Chennai, India). HPMC K4M, HPMC K100LV and Carbopol-934P were procured as a gift sample from Ranbaxy India Pvt. Ltd., Gurgaon, India. Talc, Magnesium Stearate, Hydrochloric acid and PVP K30 were purchased from S.D fine chemicals, Mumbai, India. All the materials received have been used as such in the formulations without any further modification.

Tablet preparation

Floating matrix tablets containing Metformin hydrochloride were prepared by wet granulation method using variable concentrations of HPMC K4M and HPMC K100LV, CP934P with sodium bicarbonate (**Table 1**) [16]. All the ingredients except magnesium stearate and talc were passed through sieve no#60 and blended in glass mortar uniformly. Required quantity of ethanolic PVP K30 was added as a granulating agent to make a coherent mass. The coherent mass was passed through sieve no#16 and the granules were then dried in a hot air oven at a temperature of 60^{o}C for 30 minutes. The dried granules were passed through sieve no#22, mixed with sodium bicarbonate as a gas-generating agent and lubricated with magnesium stearate and talc which previously screened through sieve no#100. The lubricated granules were compressed into tablets using 13mm Beveled edge punch in a Remach 10 station Rotary punching machine.

Compatibility Studies

Compatibility studies of drug with the excipients were determined by I.R. Spectroscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

Table 1: Formulation of floating tablets of Metformin hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6
Metformin.Hcl	500	500	500	500	500	500
HPMC K4M	-	-	62.5	62.5	125	125
HPMC K100LV	125	125	62.5	62.5	-	-
Carbopol-934P	-	75	-	75	-	75
Sodium bicarbonate	50	50	50	50	50	50
Talc	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10

HPMC-Hydroxy propyl methyl cellulose.

(All quantities are given in mg)

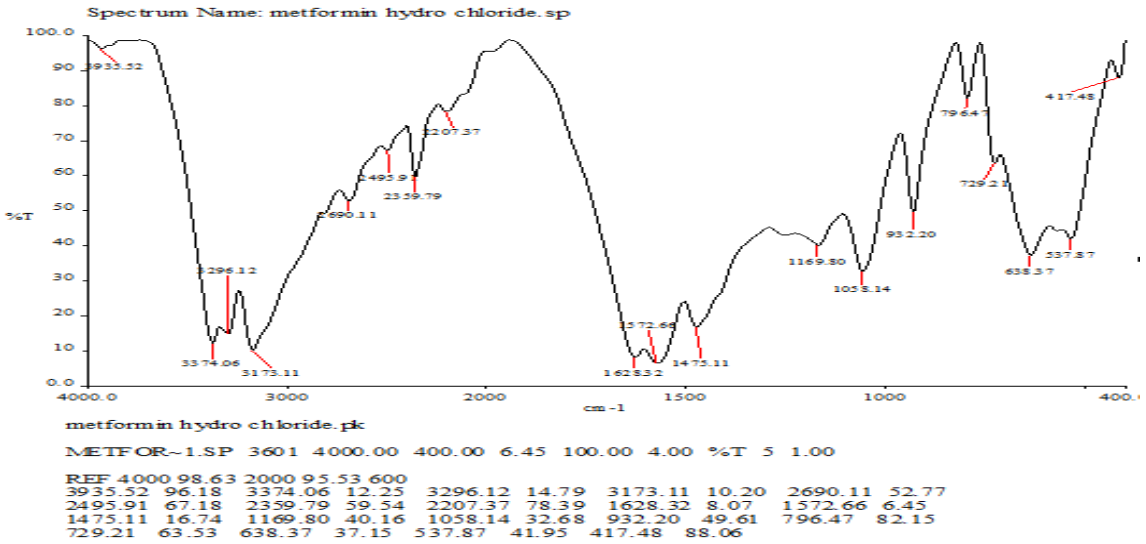

Fig. 1: FTIR Spectrum of Metformin Hydrochloride

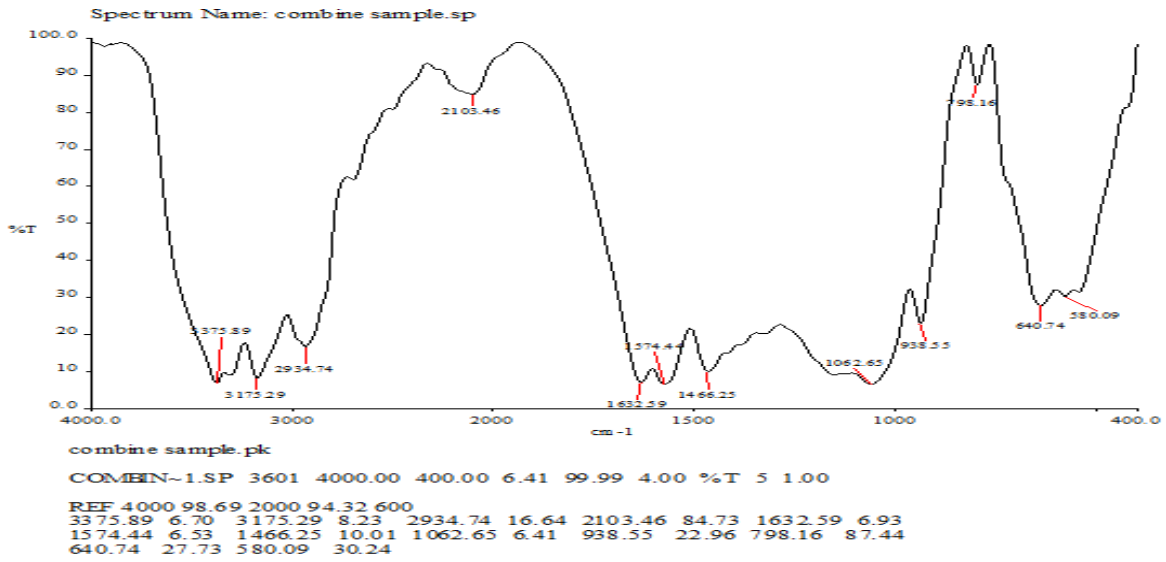

Fig. 2: FTIR Spectrum of Mixture of Metformin Hydrochloride with all excipients

Characterization of granules

The characteristic parameters of the granules were evaluated. The angle of repose and flow rate were determined by the Fixed funnel method. The bulk density and tapped density were determined by the cylinder method. Compressibility Index and Hausner's ratio was calculated to evaluate the micromeritics of the powder.

Characterization of tablets

Drug content and physical evaluation

The drug content of the tablets was determined by weighing powdered tablet equivalent to 100 mg Metformin and dissolved in 0.1 mol/l HCL as solvent and the samples were analyzed spectrophotometrically at 233 nm. Tablets were also examined with

regard to their weight variation (n=10), friability (n=10) and hardness (n=6) [17].

Buoyancy lag-time & Total Floating Time studies

The buoyancy lag-time of the tablets was studied in 100 ml 0.1 mol/l HCL (pH 1.2) at 37± 0.5^{0}C. The time required for the tablet to rise to the surface for float was taken as the buoyancy lag-time and the time extend of floating was recorded as Total Floating Time [18, 22].

Dissolution studies

The release rate of Metformin hydrochloride from floating tablets was determined using USP dissolution testing apparatus- II (Labindia, Paddle type). The test was performed using 900 ml 0.1 mol/l HCL, at 37^o±0.5^{0}C and 100 rpm. A sample(1ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium.The samples were passed through Whatman filter paper and the absorbance of these alequotes was measured at 233 nm.

Swelling characteristics

The swellimg properties of HPMC, CP934P matrix containing drug were determined by placing the tablet in the dissolution test apparatus, in 900 ml 0.1 mol/l HCL at 37^o±0.5^{0}C. The tablets were removed periodically, removed the excess free water and the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU%) according to the equation [19].

$$WU\,\% = \frac{w_t - w_0}{w_0} \times 100$$

Wt = weight of dosage form at time t.

w_0 = initial weight of dosage form

Stability studies

Short-term stability studies were performed at a temperature of 45±1^{0}C/75±5%RH over a period of three months (Sameeksha Pvt.Ltd,) on the promising HBS tablet formulation (F6). The samples were analyzed at weekly intervals for any qualitative and quantitative changes. At the end of three months, in vitro release and in vitro floating studies were performed [20, 21].

RESULTS AND DISCUSSION

In the present work efforts have been made to develop floating drug delivery system for Metformin hydrochloride containing HPMC of different viscosity grades (HPMC K4M and HPMC K100LV) and CP934P. Drug-Excipients compatibility study was done initially and results directed the further course of formulation. The characteristic drug peak at 3375 cm^{-1}, 3296 cm^{-1}, 1628 cm^{-1}, 1572 cm^{-1} and 1058 cm^{-1} responsible for Aliphatic Primary amine, Aliphatic Secondary amine NH Stretch, Aliphatic Secondary amine NH bend, Primary amine NH bend and Primary amine CN Stretch respectively confirms the availability of Metformin Hydrochloride as unchanged with the excipients. The formation of new peaks at 2934 cm^{-1} and 2103 cm^{-1} are responsible for Functional groups of HPMC. Hence the Drug is compatible with the polymers used in the formulations.

The results of micromeritics evaluation were shown in **Table 2**. The angle of repose value ranged between 28^{o}61''±0.15 to 29^{o}58''±0.19. The Bulk Density and Tapped Density ranged between 0.32±0.044 to 0.37±0.045 and 0.32±0.07 to 0.43±0.08 respectively. The Carr's index (%) ranged between 05.90±0.6 to 12.40±0.2. The Hausner's ratio ranged between 1.13±0.04 to 1.19±0.06. The result of Angle of repose indicated the powder blend has acceptable flow properties and the result of Carr's Index, Hausner's ratios indicates the free flowing and compressible properties of the granules.

The weight variation, friability, hardness and content uniformity were found to be within acceptable limits **(Table 2)**. Thus, all the physical properties of these tablets were satisfactory as specified in the Indian Pharmacopoeia.

Invitro buoyancy studies

The results of in vitro buoyancy studies was shown in table-3, supports that the Floating tablet containing HPMC K100LV/HPMC K4M, CP934P polymer shows acceptable buoyancy lag time (BLT) and good total floating time (TFT). Among the formulations, F4 containing HPMC K100LV / HPMC K4M, CP934P showed good BLT of 70 sec, while the other formulations have little higher BLT. This may be due to the difference in concentration of polymers and gas generating agent.

Swelling characteristics

The results of swelling study were illustrated in Fig-3. The swelling of tablets increased as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, the higher swelling index was found for tablets of batch F1 containing CP934P having nominal viscosity of 39,400 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability.

Table 2: Characterization of granules and tablets of Metformin hydrochloride

Parameters	Fl	F2	F3	F4	F5	F6
Angle of repose (θ)*	29±0.31	28±0.15	28±0.11	28±0.13	29±0.41	29±0.34
Bulk density (g/cc)*	0.35±0.04	032±0.04	0.32±0.04	0.37±0.05	0.33±0.04	0.38±0.04
Tap density (g/cc)*	0.39±0.09	0.34±0.07	0.32±0.09	0.37±0.04	0.37±0.04	0.43±0.08
Caar's index*	10.01±0.2	05.90±0.6	09.21±0.8	10.53±0.1	10.95±0.4	12.40±0.2
Hausner's ratio*	1.18±0.02	1.13±0.04	1.14±0.08	1.19±0.06	1.13±0.04	1.13±0.04
Weight variation (%) ***	694.65±2.29	769.50±1.73	693.55±1.18	768.65±1.49	694.55±1.18	768.62±1.29
Friability (%) ***	0.96±0.14	0.72±0.26	0.91±0.11	0.86±0.19	0.79±0.21	0.79±0.21
Hardness (kg/cm^2)**	5.5±0.47	6.0±0.32	6.0±0.54	5.5±0.42	7.0±0.35	7.0±0.35
Content uniformity*** (%)	99±0.56	98.01±0.41	98.05±0.72	97.19±0.35	98.08±0.19	99.05±0.56

Results are presented as mean±standard deviation *(n=3), ** (n=6), *** (n=10)

Table 3: Invitro buoyancy studies of Metformin hydrochloride floating tablet

Batch	Tablet Density (gm/cc)	Buoyancy Lag Time (Sec.)	Total Floating Time (Hrs)
F1	0.84	76	>8
F2	0.73	74	>8
F3	0.87	83	>12
F4	0.94	70	> 12
F5	0.96	86	>12
F6	0.92	89	>12

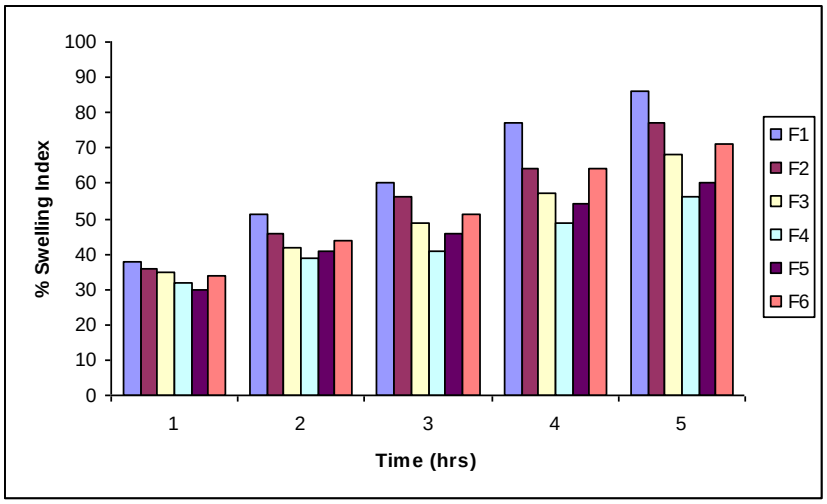

Fig. 3: Comparative Swelling index results of Floating tablets

In vitro dissolution studies

The tablets are subjected to in vitro dissolution study and in vitro release kinetic study. All formulations showed that considerable interest in using different grades of HPMC in controlled release drug delivery system due to their hydrophilic nature and fast hydration. It has been reported that polymers of different viscosity grades can yield different drug release. The release profiles of formulation F1-F6 were shown in Fig-4. The release profiles appear to be biphasic, with initial burst effect followed by a polymer controlled slower release in the second phase. Polymeric system with low viscosity polymer (HPMC K100LV) yielded a faster initial burst effect and incorporation of CP934P decreased the release of Metformin hydrochloride from the GFDDS. Likely due to the fact that CP934P is a cross-linked polymer with high molecular weight and viscosity, and, when contacted with water, it would swell and hold water inside its micro gel network. This particular property may partially be responsible for the retarded release of Metformin hydrochloride from the GFDDS.

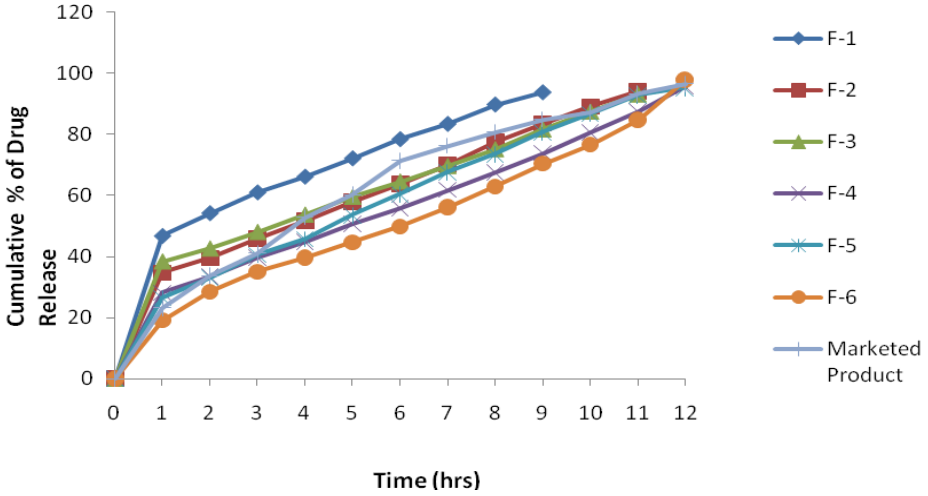

Fig. 4: Comparative in-vitro release data for Metformin hydrochloride Floating tablets formulation (F1-F6) and marketed product

From results of *in vitro* drug release studies using USP dissolution apparatus, it concludes that F6 had better sustained release than the other formulation (**Fig. 4**). To analyze the Metformin release mechanism, the in vitro release data were fitted into various release equations and kinetic models (first order, zero order, Higuchi, Korsemeyer-peppa's plot) **(Table 4)**, as indicated by the value of R^2, the Higuchi model was found to be efficient in describing the diffusion mechanism. To explore the release pattern, results of the in vitro release data of all formulations were fitted to the Korsemeyer-peppa's equation that suggested that the release governed by non-fickian diffusion.

Table 4: Drug release kinetics of Metformin hydrochloride

Formulations	Zero order		First order			Higuchi	Korsemeyer- peppa's plot		Drug release mechanism
	R	K	R	n	K	R	R	n	
F1	0.8207	8.124	0.9553	-0.113	-0.2586	0.9703	0.9553	0.4672	First order non fickian diffusion
F2	0.9312	7.175	0.9555	-0.0946	-0.2178	0.9729	0.9859	0.5245	First order non fickian diffusion
F3	0.9002	6.735	0.9555	-0.0946	-0.2178	0.9694	0.9808	0.4632	First order non fickian diffusion
F4	0.9609	6.703	0.8424	-0.0872	-0.2008	0.9603	0.9791	0.5855	Zero order non fickian diffusion
F5	0.9656	7.183	0.8424	-0.0872	-0.2008	0.9826	0.9929	0.6172	Zero order non fickian diffusion
F6	0.9784	6.984	0.8424	-0.0872	-0.2008	0.9484	0.9685	0.6689	Zero order non fickian diffusion

Comparison with marketed product

From the result the optimized formulation F6 had better control over release rate when compared with the marketed product (Gluformin XL-500mg) **(Figure.5)**. The results indicate that gas generated intra gastric buoyant tablets of Metformin hydrochloride containing HPMC K4M (125mg) and CP934P (75mg) provides a better option for sustained release, results drug available in the dissolved form at its absorption window (i.e., proximal small intestine) thus leads to improve its bioavailability. The drug release rate was sustained for formulation F6 when compared with the marketed product.

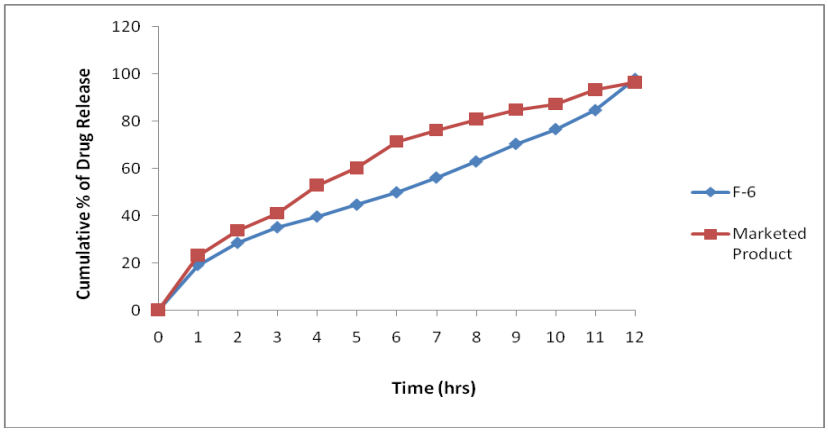

Fig. 5: Comparative in-vitro drug release profile of optimized formulation F6 and marketed product

Stability study

Short-term stability study was performed on the promising formulation F6 by storing the sample at 45±1^{0}C/75±5%RH for three months. Analysis was performed on the drug content, buoyancy lag-time, buoyancy time and drug release parameters. The results indicated that there were no significant changes in drug content, buoyancy lag-time, buoyancy time (Table 5) and dissolution profile of formulation F6 during storage at 45±1^{0}C/75±5%RH for three months (Figure.6).

Table 5: Drug Content and Floating behavior of optimized F6 formulation during Short term stability study

Time (months)	Drug Content (%)	Buoyancy lag-time (sec)	Buoyancy Time (H)
0	99.05±0.56	89	>12
01	98.76±1.06	90	>12
02	99.00±0.25	89	>12
03	98.84±1.2	88	>12

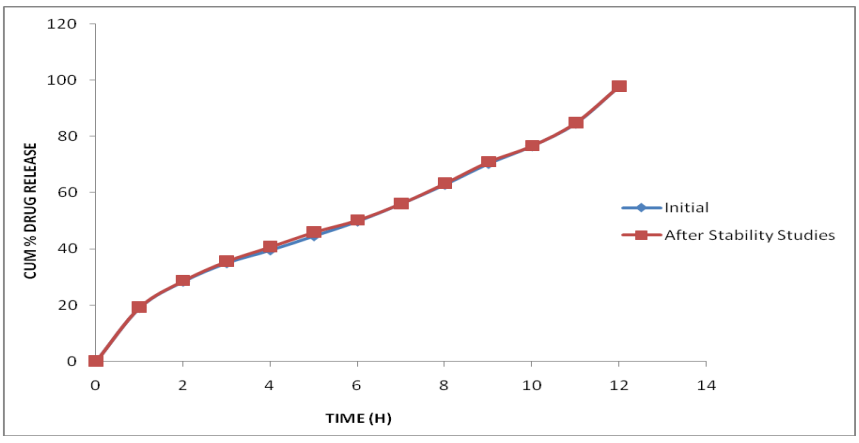

Fig. 6: Comparison of dissolution profile of batch F6 before and after stability studies.

CONCLUSION

Overall this study concludes that viscosity is a major factor affecting the release and floating properties of the GFDDS. The higher viscosity seems to inhibit the initial burst effect of Metformin hydrochloride release from the GFDDS. It was concluded on the basis of buoyancy and drug release kinetics that optimized formulation containing 500mg of Metformin hydrochloride granulated with 125mg of HPMC K4M and 75mg of CP934P gave the best in vitro release of 97.83% in 12 hrs in 0.1 mol/l HCl at 1.2 pH. The release of Metformin hydrochloride from the formulation followed zero order release kinetics. Thus, the result of the current study clearly indicate, a promising potential of the Metformin hydrochloride floating system as an alternative to the conventional dosage form. However, further clinical studies needed to assess the utility of this system for patient suffering from non insulin dependent diabetes mellitus.

ACKNOWLEDGEMENT

The authors are very thankful to Grandix Pharma Ltd., Chennai, India; Ranbaxy India Pvt. Ltd., Gurgaon, India; for providing gift samples and all other supporters who helped to carryout this research work successfully.

REFERENCES

1. Anne Waugh, Allizon Gran. Anatomy and Physiology in Health and Illness, Ross and Wilson, 10th edition, 2006: 293-295.
2. Hoichman D, Gromova LI and Sela J. Gastroretensive controlled release drugs, Pharm Chemistry, 2004; 38(11):621-623.
3. Shweta Arora, Javed Ali, Alka Ahuja, Roop K.Khar, Sanjula Baboota. Floating drug delivery systems: A review. AAPS Pharm Sci Tech, 2005; 6(3): 372-387.
4. Sayantan Chattoraj, Sayui Nath, Arun Jana, Bandyopadhyay AK. Gastroretensive drug delivery systems, Pharma Buzz, 2008, Vol.3:21-27.
5. Robinson Jr., Lee VHL. Fundamentals of controlled drug delivery: Influence of drug properties and routes of drug administration on the design of sustained and controlled release systems In: Robinson Jr. Editors. Controlled drug delivery: fundamentals and applications. 2nd ed. Marcel Dekker Inc; New York. 2005: 3 – 94.
6. Sivakumar HG, Pramod Kumar TM, Gangadharappa H.V. Gastric floating drug delivery systems: A review. Ind J Pharm Edu 2007; 41(4): 295-301.
7. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm., 2000; 5: 125-135.
8. Sanjay Garg and Shringi Sharma. Gastroretensive drug delivery systems, Pharma Tech; 2003:160-166.
9. Brahmankar DM, Jaiswal SB. Controlled Release Medication. Biopharmaceutics and pharmacokinetics a Treatise. 1st Ed. Vallabh prakashan Publisher, New Delhi. 1995: 64-70.
10. Vyas SP, Roop K Khar. Essentials of controlled drug delivery In: Vyas SP Editors. Controlled Drug Delivery – Concepts and Advances. Vallabh Prakashan Publisher, Delhi. 2006: 1 – 53.
11. Xiaoqiang XU, Sun Minjie, Zhi Feng, Hu Yiqiao. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. Int J pharm 2006; (310):139-145.
12. Ziyaur Rahman, Musir Ali, Khar RK. Design and evaluation of bilayer floating tablets of captopril, Acta Pharm 2006; (56):49-57.
13. Sowjanya K, Shobha Deepthi K, Bharathi A. Formulation and evaluation of gastro-retentive floating matrix tablets of Nevirapine. Int J Pharm Pharm Sci 2012; 4 Suppl 5: 368-375.
14. Leon Lachman, Herbert A. Liberman, Joseph L. Kanic. Editors. The theory and practice of industrial pharmacy. 3rd edition (Indian), Varghese publishing house; Mumbai. 430 – 456.
15. Javed Ali, Shweta Arora, Alka Ahuja, Anil K. Babbar, Rakesh K. Sharma, Roop K. Khar. Eur J Pharm Biopharm, 2007; 67:196-201.
16. Tejas Patel, Patel LD, Tamer Patel, Kirit Patel, Tushar patel, Sunil Makwana. Design and Development of Gastric Floating Drug Delivery System Using Factorial Design. Pharma Buzz., 2008. 3: 21-27.
17. Government of India ministry of health and family welfare. The pharmacopoeia of India. Controller of publication.1996.
18. Monoj N.Gambhire, Kshitij W.Ambade, Sushma D.Kurmi. Development and In-vitro evaluation of an oral floating matrix tablet formulation of Diltiazem hydrochloride. AAPS Pharm Sci Tech 2007; 8(3) Article 73: E1-E9.
19. Shoufeng Li, Senshang Lin, Bruce P.Daggy, Haresh L. Mirchandani, Yie W. Chien. Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design. Int J pharm., 2003. 253: 13-22.
20. Raval JV, Patel JK, Naihong Li, Patel MM. Ranitidine hydrochloride floating matrix tablets based on low density polymer: effets of formulation and processing parameters on drug release. Asian J of pharm sci 2007; 2(4):130-142.
21. Swamy PV, Bhosale UV, Hiremath SN, Shirsand SB, Raju SA. Indian Drugs 2008; 45(4):293-300.
22. Bhushan SG, Sadhana S, Viviek BR. Formulation and Optimization of biphasic floating drug delivery system of Verapamil Hydrochloride. Int J Pharm Pharm Sci 2012; 4 Suppl 5: 195-200.