AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

# Formulation Optimization of A Floating Extended Release Matrix Tablet of Metformin Hydrochloride

**Bijan Kumar Gupta*[1], Suman Sudha Sethy[2], Gouranga Nandi[3], Debjani Sarkar[4], Lakshmi Kanta Ghosh[4],**

*1. Zandu Foundation for Health Care, 13, B.T Road, Kolkata- 700 056, India*

*2. University Department of Pharmaceutical Sciences, Utkal University, Vani Vihar, Bhubaneswar – 751004, India*

*3. BCDA College of Pharmacy & Technology, 78, Jessore Road (s), Hridaypur, Barasat, Kolkata – 700 127, India*

*4. Department of Pharmaceutical Technology, Jadavpur University, Kolkata – 700 032, India*

## ABSTRACT

The purpose of the present study was to develop an optimized gastric floating extended release matrix tablet of Metformin hydrochloride (FERMTs) using a hydrophilic polymer, HPMC K4M, a hydrophobic polymer ethyl cellulose and sodium bicarbonate as buoyancy contributor. The formulation of FERMTs were designed by D-optimal mixture design taking % of HPMC K4M, ethyl cellulose and sodium bicarbonate as formulation variables and prepared by wet granulation method. The FERMTs were then evaluated for hardness, friability, weight variation, content uniformity, *in vitro* drug release and floating capacity. Finally, the floating lag time (FLT) and cumulative % drug release at 1h, 2h, 6h and 10h were taken as response variables and the FERMT formulation was numerically optimized by D-optimal mixture design using Design-Expert software (version 8.1). The optimized formula showed excellent floating efficiency over 10 h period with FLT of 9.61 mins. The release profile of optimized formula showed much closed similarity with that of USP reference dissolution profile ($f_2$ value= 87.95). Analysis of dissolution data showed that the kinetic of drug release followed Korsemeyer-Peppas and Higuchi model.

**Keywords**: Floating tablet; Extended-release; Mixture-Design; Metformin hydrochloride.

*Corresponding Author Email: bijangupta@gmail.com

Received 19 June 2012, Accepted 4 July 2012

Please cite this article in press as: Gupta BK *et al.*, Formulation Optimization of A Floating Extended Release Matrix Tablet of Metformin Hydrochloride. American Journal of PharmTech Research 2012.

# INTRODUCTION

Metformin Hydrochloride (MFH) is frequently and widely used in the management of non-insulin dependent (type II) diabetes mellitus, usually in the form of extended release oral preparations (EROPs) or conventional uncontrolled release formulations[1, 2]. The conventional EROPs release the drug in small fraction in stomach and maximum in the intestine due to short and varying gastric residential time. But MFH is mainly absorbed from the stomach and very poorly absorbed from intestine, which results in poor oral bioavailability (52% ± 5%)[3].

Gastric retention of the delivery device for entire period of drug release may be a potential approach for uniform drug release, plasma conc. Vs time profile and improvement of oral-bioavailability. Various techniques and approaches for gastroretentive device of MFH including floating beads, floating tablets, floating microspheres, hydrodynamically balanced systems have been reported[4-11]. But no substantial work has been reported to achieve good floatability along with a highly similar release profile with any official extended release profile of MFH.

Our objective of the present work was to formulate a floating extended release tablet formulation of MFH with a high similarity in release profile with the USP, 2009, test 2[12]. The intradevice gas generation and its entrapment were used in this work to make the tablet buoyant in gastric fluid[13]. Hydroxypropylmethyl cellulose K4M (HPMC K4M) was used as matrix polymer and Sodium bicarbonate ($NaHCO_3$) as gas generating agent. HPMC K4M, ethyl cellulose (EC) and $NaHCO_3$ were considered as formulation variables, where floating lag time (FLT) and Cumulative % drug release (CPR) at 1h, 2h, 6h and 10h were taken as response parameters. D-optimal mixture design was applied to design the formulations and optimize using Design-Expert software (version 8.1). The optimized formula remained floated in 0.1N HCl over 10 hours and showed a highly similar release profile with USP, 2009 (Test 2; $f_2$ value= 87.95).

# MATERIALS AND METHODS

## Materials

Metformin hydrochloride was donated by EMCEE Pharmaceuticals, India, as gift sample; Hydroxypropylmethyl cellulose K4M was donated by Colorcon Asia Pvt Ltd; Ethyl cellulose, Talc and Magnesium stearate were purchased from Loba Chemie Pvt Ltd, Mumbai, India; Ethanol, conc. Hydrochloric acid, sodium bicarbonate anhydrous were purchased from Merck Specialties Pvt Ltd, Mumbai, India. The drug and excipients were used as received without further treatment and the reagents were of analytical grade.

## Preparation of Standard curve

100 mg MFH was accurately weighed and dissolved in phosphate buffer pH 6.8 (PB) and volume made up to 100 ml (solution 1). 10 ml of solution 1 was diluted with PB to make 100ml (solution 2). Different volumes of solution 2 were taken in five different 25 ml volumetric flasks and volumes were made up with 1ml 0.1N HCl acid and sufficient quantity of PB to produce five different standard solutions with concentrations of 4, 8, 12, 16 and 20µg/ml. One of the standard solutions was then scanned from 190 nm to 1100 nm using UV/ Visible Spectrophotometer (SHIMAZDU, PHARMASPEC 1700, Japan) to obtain $\lambda_{max}$. Then absorbance of all standard solutions were measured at observed $\lambda_{max}$. This was repeated for three times. Then the average absorbance vs. conc. was plotted and the equation and $R^2$ value of the curve were obtained. The observed $\lambda_{max}$ was 232 nm and the equation obtained was **y = 0.0798x + 0.0138** and $R^2$ value was **0.9999.**

**Formulation Design of FERMTs**

For formulation of FERMTs, Hydroxy propyl methyl cellulose K4M (HPMC K4M), Ethyl cellulose (EC), $NaHCO_3$ were taken as formulation variables. Talc and magnesium stearate were used as lubricant. The % of MFH, talc and magnesium stearate were kept constant in all batches. The D-optimal Mixture design was adopted to design the experiment using Design-Expert software (version 8.1, Stat-Ease Inc., Minneapolis, USA)[14]. Total amount of three variables in the tablets were fixed at 35.5%. The low and high level of HPMC K4M, EC and $NaHCO_3$ were set at (16.5%-22.5%), (6%-12%) and (7%-10%)respectively. The total weight of tablet was fixed 800mg that included 500 mg of MFH. The Design-Expert software designed the experiment giving 11 different formulas of **FERMTs** with 3 replicates (total 14) shown in **Table 1.**

**Table 1: Formula of FERMTs from code $D_1$ to $D_{14}$ generated by Design-Expert version 8.1**

| Formulation code | Drug(%) | HPMC K4M (%) | Ethyl cellulose (%) | $NaHCO_3$(%) | Magnesium stearate (%) | Talc (%) |
|---|---|---|---|---|---|---|
| D1 | 62.5 | 16.5 | 9 | 10 | 1 | 1 |
| D2 | 62.5 | 22.5 | 6 | 7 | 1 | 1 |
| D3 | 62.5 | 21 | 6 | 8.5 | 1 | 1 |
| D4 | 62.5 | 19.5 | 6 | 10 | 1 | 1 |
| D5 | 62.5 | 19.5 | 9 | 7 | 1 | 1 |
| D6 | 62.5 | 16.5 | 12 | 7 | 1 | 1 |
| D7 | 62.5 | 16.5 | 12 | 7 | 1 | 1 |
| D8 | 62.5 | 17.625 | 10.125 | 7.75 | 1 | 1 |
| D9 | 62.5 | 16.5 | 10.5 | 8.5 | 1 | 1 |
| D10 | 62.5 | 18 | 7.5 | 10 | 1 | 1 |
| D11 | 62.5 | 22.5 | 6 | 7 | 1 | 1 |
| D12 | 62.5 | 19.875 | 7.125 | 8.5 | 1 | 1 |
| D13 | 62.5 | 19.5 | 9 | 7 | 1 | 1 |
| D14 | 62.5 | 17.625 | 8.625 | 9.25 | 1 | 1 |

**Preparation of FERMTs**

The **FERMTs** were prepared by wet granulation method[15]. At first, the drug, HPMC K4M and $NaHCO_3$ were mixed together well by geometric mixing using pestle mortar. EC was dissolved in ethanol. The powder mixture was wet-massed with the EC solution. Then the mass was passed through a sieve (mesh no # 16) to obtain granules. Then the granules were dried in a hot air oven at 60°C for half an hour. The granules were passed through sieve #16 and then sieve #20. The granules those passed sieve #16 but retained on sieve #20, were taken for compression. Prior compression magnesium stearate and talc were mixed with the granules. Then the granules were compressed by tablet compression machine (LABPRESS, 10 Station, REMI, Mumbai, India) using flat shaped punches and 12 mm diameter.

EVALUATION OF FERMTS

**Weight variation and content uniformity test**

Weight variation and content uniformity test were carried out as per USP 2009 to check the uniformity of prepared FERMTs. In both cases relative standard deviation (RSD) and acceptance value (AV) were calculated for each formulation[16].

**Hardness test**

Crushing force was measured using Monsanto Hardness Tester for each formulation to check the mechanical strength of FERMTs. The measurement was repeated in triplicate. The average crushing force for each formulation was then calculated.

**Friability test**

This was carried out to test the friability of the floating tablets using Roche type friabilator. A tablet was weighed accurately and placed in the friabilator. Then it was rotated at 25 rpm for 4 minutes. After that, the tablet was taken out and reweighed. The % friability (f) was calculated using the formula[17]:

$$f = (w_1 - w_2) \times 100\% / w_1$$

Where $w_1$ is the previous weight and $w_2$ is the weight after operation. The study was repeated in triplicate for each formulation and average was calculated.

**In vitro floating test**

In vitro floating test was carried out to evaluate floating property of the FERMTs. The floating lag time (FLT) is the time taken by the tablet to reach the surface of the floating medium after placing of the tablet in the floating medium. The floating time (FT) is time period throughout which the tablet remains buoyant in the floating medium. A tablet was placed in 0.1N HCl acid

in a 100 ml beaker. Then the floating lag time and floating time were observed and noted[18]. The study was repeated three times for each formulation and average FLT and FT were calculated.

**In vitro drug release test**

In-vitro dissolution test was carried out using 6-station USP dissolution test apparatus type-I [Electrolab, 6 stations, Mumbai, India]. 900 ml 0.1N HCl acid (pH 1.2) was taken as dissolution medium and the basket was rotated at 50 rpm. The temperature of water bath was maintained at 37 ± 0.5°C. The tablet was placed in the basket. 5 ml sample from the dissolution medium was taken at predetermined intervals over a period of 10 hours. 5 ml 0.1N HCl acid was added to the dissolution medium each time. The samples were then analyzed after suitable dilution by double beam UV-Visible Spectrophotometer (Pharmaspec-1700, Shimazdu, Japan). The test was repeated with 6 units from each batch. Cumulative % drug release (CPR) at different time points were calculated using the equation of standard curve. The release data were then analyzed to obtain the release kinetic and mechanism[19]. Finally dissolution similarity factor $f_2$ values were calculated to assess the similarity of release profile of FERMTs with the USP 2009 reference for extended release tablet of MFH (Test 2). The formula of $f_2$ value is as follow:

$$f_2 = 50 \times \log \left[ \{1 + (1/n) \sum_{j=1}^{n} (R_j - T_j)^2 \}^{-0.5} \times 100 \right]$$

Where n is the number of time point, Rj is the reference % dissolved and Tj is the test % dissolved. In order to consider the similar dissolution profiles, $f_2$ value should be close to 100. FDA and EMEA suggest that two dissolution profiles are declared similar if $f_2$ is between 50 and 100. The reference dissolution profile for extended release tablet of MFH in USP 2009 is given in **Table 2.**

**Table 2: Dependent & independent variables, reference and target value of response parameters.**

| Sr.No | Independent variables | Dependent variables | USP Reference value of response (test 2) | Target value of response |
|---|---|---|---|---|
| 1 | HPMCK4M (%) | CPR1h | 20 - 40 | 30 |
| 2 | EC (%) | CPR2h | 35 - 55 | 45 |
| 3 | $NaHCO_3$ (%) | CPR6h | 65 - 85 | 75 |
| 4 | - | CPR10h | not less than 85 | 95 |
| 5 | - | FLT (min) | - | 10 |

HPMCK4M = Hydroxypropylmethyl cellulose; EC = Ethylcellulose

**Analysis of the responses and formulation optimization**

Finally the response variables: FLT, cumulative % drug release at 1h, 2h, 6h and at 10h (CPR1h, CPR2h, CPR6h and CPR10h respectively) were analyzed and formulation was optimized

numerically to obtain target FLT (10 mins) and release profile (USP reference release profile for extended release tablet of MFH; **Table 2**) by Design-Expert software following the D-optimal mixture design. After optimization, the floating tablets were prepared as per the optimized formula and evaluated. Then the observed responses were compared to the predicted and target values.

## RESULTS AND DISCUSSION

The content uniformity and weight variation test showed that the acceptance values of all formulations in each case were within the limit prescribed in USP. The prepared FERMTs showed having sufficient mechanical strength. The tablets showed having hardness within the range of 4.75 kg to 5.5 kg. The tablets were compressed with a constant compaction force. The % friability of all formulations was below 1%.

The in vitro floating test showed that the floating lag time (FLT) observed was within the range from 4 mins to 28.5 mins. The total floating time (TFT) for all formulations was observed greater than 10 hours. The generation and subsequent entrapment of $CO_2$ as a result of reaction between $NaHCO_3$ and HCl acid inside the tablet, contributes the buoyancy. The FLT was taken as response variable in this study as all designed formulations showed having TFT more than 10 hours. The ANOVA study yielded the regression model for FLT, which was as follow:

FLT= -202.99A+724.16B+ 4969.9C- 47.56AB – 247.36AC-290.19BC+10.47ABC+ 1.14AB (A-B) +4.4AC(A-C) + 4.5BC (B-C). [A= HPMC K4M, B= EC, C= $NaHCO_3$] ---------- (1)

The values of the coefficients in the model equation 1 indicate that floating lag time is mainly influenced by ethyl cellulose and $NaHCO_3$. The formula with higher amount of EC but same amount of $NaHCO_3$ exhibited higher FLT. It may be due to more entrapment of $NaHCO_3$ by EC that reduce the access of HCl to it (**Figure 3**).

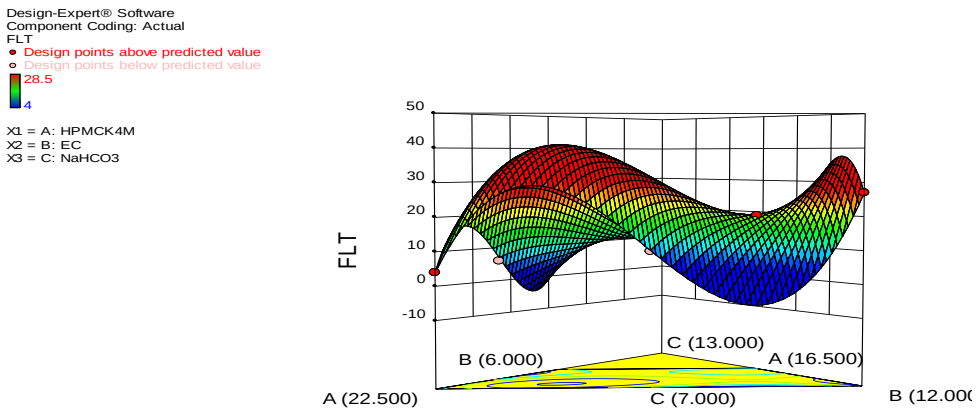


**Figure 3: 3-D curve for response FLT**

*In vitro* dissolution study showed drug-release over 10 hour period from different designed formula (**Figure 1 & 2**). Fitting of the dissolution data into different release kinetic models revealed that the kinetic of drug-release followed Higuchi and Korsmeyer-Peppas (KP) models. The exponent values of KP model obtained were around 0.5, which indicates drug-release by fickian diffusion mechanism[19]. A barrier gel layer was found to form around the outer surface of the tablets. The tablets were also found to swell up because of uptake of water by hydrophilic HPMC K4M. The outer barrier gel layer was found to propagate gradually towards the interior of the tablets. The surface erosion was also found in later stage of dissolution. The small deviation of 'n' value of KP model from 0.5 (value indicating fickian diffusion) might be due to the surface erosion (**Table 3**). Dissolution similarity factor $f_2$ of all designed formula and optimized formula were within the range from 50 to 100 (**Table 3**) which might be considered as 'similar' as per USFDA guideline. The higher $f_2$ value indicates higher degree of similarity. $D_1$ formula showed highest similarity ($f_2$=89.21).

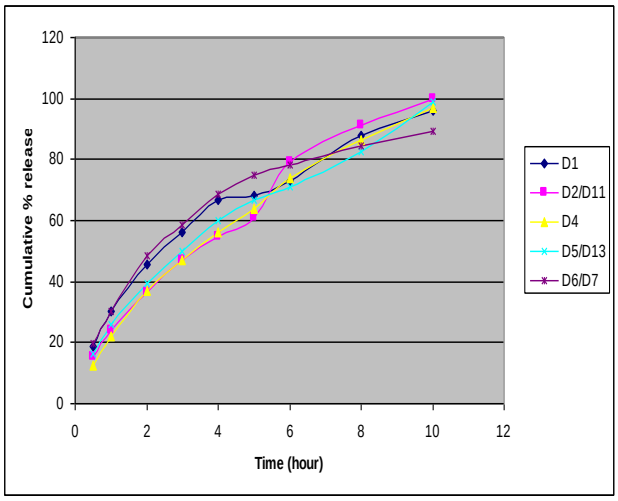


**Figure 1: cumulative % release vs. time profile**

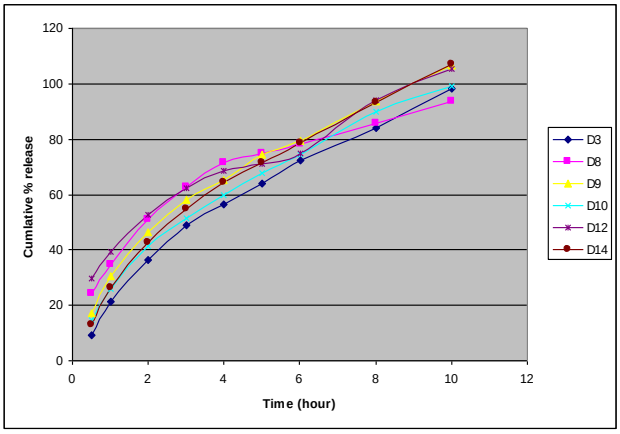


**Figure 2: cumulative % release vs. time profile**

**Table 3: $R^2$ values of different kinetic models & $f_2$ values**

| Formulation code | $R^2$ values | | | | | | Model of best fit | $f_2$ value |
|---|---|---|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Hixson-Crowell | Korsemeyer - Peppas | | | |
| | | | | | $R^2$ | n | | |
| D1 | 0.9308 | 0.7785 | 0.9891 | 0.9813 | 0.9877 | 0.5327 | H/KP | 89.21 |
| D2 | 0.974 | 0.8543 | 0.9867 | 0.9433 | 0.9959 | 0.6323 | KP | 60.45 |
| D3 | 0.9579 | 0.7474 | 0.9985 | 0.9595 | 0.9786 | 0.7485 | H | 59.36 |
| D4 | 0.9664 | 0.8005 | 0.9994 | 0.9836 | 0.9952 | 0.6801 | H | 61.43 |
| D5 | 0.9631 | 0.8191 | 0.9956 | 0.9286 | 0.9967 | 0.5879 | H/KP | 66.63 |
| D6 | 0.8569 | 0.7209 | 0.9602 | 0.9553 | 0.9752 | 0.5116 | KP | 70.97 |
| D7 | 0.8628 | 0.7203 | 0.9634 | 0.9625 | 0.9745 | 0.5231 | KP | 70.56 |
| D8 | 0.8778 | 0.7501 | 0.9702 | 0.9763 | 0.9833 | 0.4537 | KP | 68.51 |
| D9 | 0.9526 | 0.7854 | 0.9969 | 0.8136 | 0.9891 | 0.5869 | H | 59.64 |
| D10 | 0.9604 | 0.7965 | 0.9702 | 0.9629 | 0.993 | 0.6227 | H | 72.46 |
| D11 | 0.9729 | 0.856 | 0.9969 | 0.9496 | 0.9952 | 0.6351 | KP | 60.45 |
| D12 | 0.9641 | 0.8709 | 0.9987 | 0.7801 | 0.9894 | 0.407 | H/KP | 54.95 |
| D13 | 0.9686 | 0.8276 | 0.9844 | 0.9966 | 0.998 | 0.5966 | H/KP | 66.63 |
| D14 | 0.9562 | 0.7672 | 0.9985 | 0.8148 | 0.9852 | 0.6737 | H | 58.74 |
| OF | 0.9749 | 0.9003 | 0.9961 | 0.9799 | 0.9922 | 0.5117 | H/KP | 87.95 |

H- Higuchi; KP- Korsmeyer-Peppas; OF- optimized formula.

The ANOVA study yielded best fitting polynomial regression equations for each response variable.

The regression model of CPR1h was:

CPR1h = 0.384A + 1.622B + 0.846C ---------- (2)

The model equation 2 and the **figure 4** showed that the drug release at 1 hour is greatly influenced by HPMC K4M.

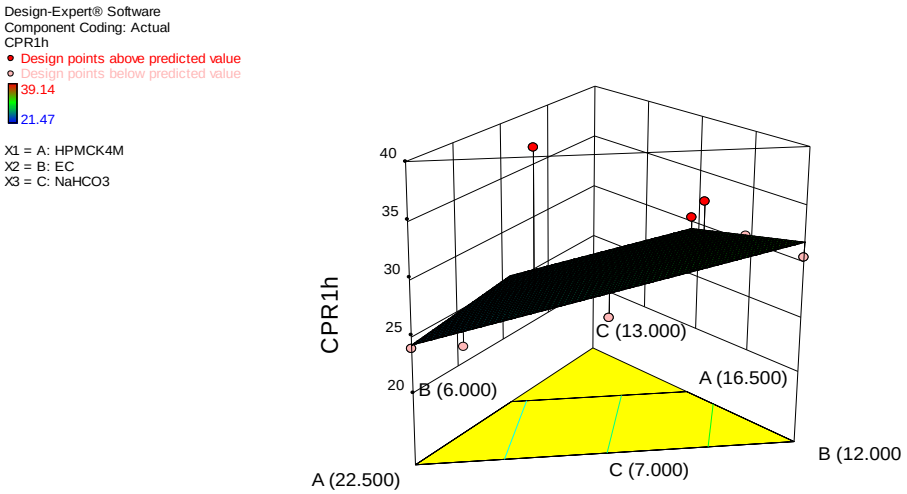


**Figure 4: 3-D curve for response CPR1h**

CPR1h decreases with increase in HPMC K4M and decreases with decrease in EC. It might be due to formation of barrier gel layer around the tablet by hydrophilic HPMC K4M. Hydrophobic EC interferes with the formation of gel layer by decreasing water uptake and results large interstitial channel in the matrix. This promotes faster drug release. Same effect of HPMC K4M and EC on CPR2h was observed (**Figure 5).** The regression equation of CPR2h was:

CPR2h = 0.501A+ 2.48B + 1.51C ---------- (3)

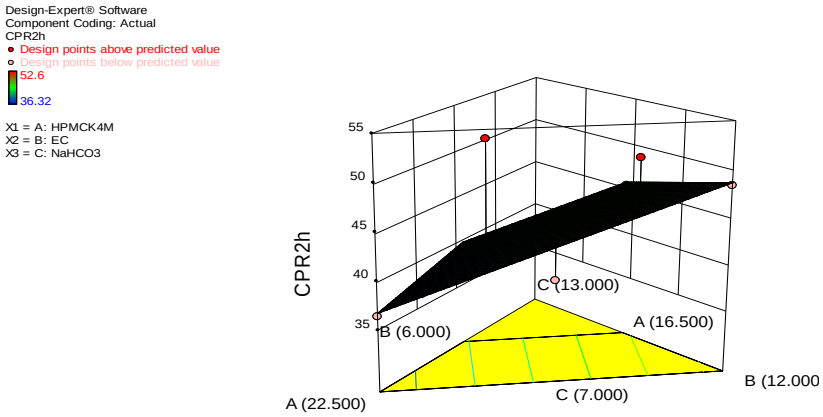


**Figure 5: 3-D curve for response CPR2h**

CPR6h decreases initially but increases later with decrease in HPMC K4M **(Figure 6).** In the higher portion of the range of HPMC K4M, high water uptake and gel formation and low interference of EC causes slower drug release but in the lower portion the range of HPMC K4M, high negative interference of EC in the gel formation increases the drug release. The regression equation of CPR6h was:

CPR6h = 53.92A – 0.253B – 367.56C – 2.78AB + 16.94AC + 11.45BC + 0.034ABC – 0.077AB (A-B) – 0.49AC (A-C) – 0.103BC (B-C) ---------- (4)

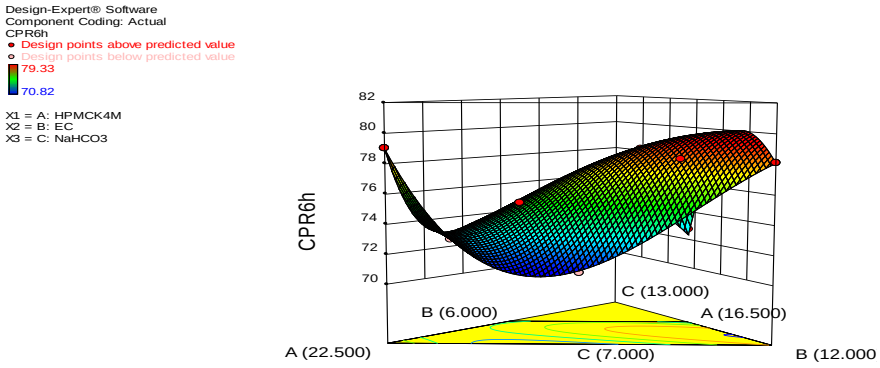


**Figure 6: 3-D curve for response CPR6h**

The regression equation of CPR10h was(figure 7)

CPR10h = 1.62A – 9.97B – 14.64C + 0.401AB + 0.687AC + 1.49BC ---------- (5)

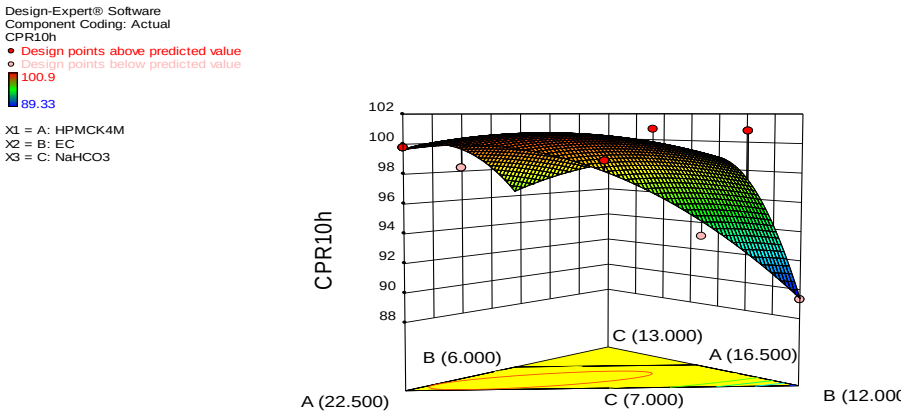


**Figure 7: 3-D curve for responseCPR10h**

The ANOVA study of each of the response variables yielded the best fitting polynomial model for that variable. Only those models were considered which had a high F-value corresponding to $p< 0.05$. Only the model for CPR1h was not significant ($p> 0.05$) (**Table 4**). The 5 polynomial models were then solved simultaneously by numerical methods keeping the target values as given in the **Table 2** to obtain optimized formula. The target for CPR1h, CPR2h, CPR6h, CPR10h and FLT were set at 30%, 45%, 75%, 95% and 10 mins respectively. The optimized levels of formulation-variables were HPMC K4M 18.16%, ethyl cellulose 10.04% and sodium bicarbonate 7.30%. After optimization, the floating tablets were prepared as per the optimized formula and evaluated. The study showed 28.92%, 46.07%, 74.41% and 97.34% drug release at 1h, 2h, 6h and 10h respectively resulted from the optimized floating tablet. The FLT observed was 9.61 mins. The comparison of the observed values with the predicted and target values revealed closeness to the target and predicted values of the responses (**Table 5**). The $f_2$ value of the optimized tablet was 87.95 that indicate a high degree of similarity.

**Table 4: Different statistical parameters for the response variables**

| Response | F-value | p>F | LOF | $R^2$ | Predicted $R^2$ | PRESS |
|---|---|---|---|---|---|---|
| CPR1h | 1.97 | 0.1853 | 235.25 | 0.2640 | 0.0246 | 311.77 |
| CPR2h | 5.50 | 0.02 | 214.37 | 0.5002 | 0.3493 | 279.15 |
| CPR6h | 25.79 | 0.003 | 2.28 | 0.9830 | 0.8904 | 255.20 |
| CPR10h | 7.03 | 0.0084 | 36.87 | 0.8146 | 0.4249 | 114.37 |
| FLT (min) | 60.43 | 0.0006 | 7.50 | 0.9926 | 0.1851 | 837.94 |

**Table 5: Target, predicted and observed responses for optimized floating tablet**

| Response | Target | Predicted | Obtained |
|---|---|---|---|
| CPR1h | 30 | 29.44 | 28.92 |
| CPR2h | 45 | 45.09 | 46.07 |
| CPR6h | 75 | 75.08 | 74.41 |
| CPR10h | 95 | 96.66 | 97.34 |
| FLT (min) | 10 | 10 | 9.61 |

## CONCLUSION

The aim of the present study was to develop an efficient gastro retentive tablet for extended release of metformin hydrochloride. On the basis of in vitro evaluations, an optimized tablet formulation was obtained, that showed an optimum floatability and a highly similar release profile with that in USP, 2009. But, in addition, it needs to be mentioned that future research work should include the evaluations of the in vivo gastric retention capacity as well as in vivo drug release profile both in animal and human models as well as elaborate clinical trials in order to place it as a marketable product.

## ACKNOWLEDGEMENTS

The authors are thankful to BCDA College of Pharmacy & Technology and Dept. of Pharmaceutical Technology, Jadavpur University, Kolkata, India for providing laboratory facilities, to EMCEE Pharmaceuticals, Kalyani, India for donating metformin hydrochloride as gift sample.

## REFERENCES

1. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians; 2008. ISBN 9781860163333. p. 86.
2. Sherwyn Schwartz, Vivian Fonseca, Bret Berner, Marilou Cramer, Yu-Kun Chiang and Andrew Lewin.m Efficacy, Tolerability, and Safety of a Novel Once-Daily Extended-Release Metformin in Patients With Type 2 Diabetes. Diabetes Care2006;29(4): 759-764.
3. Laurence L. Brunton, John S. Lazo, Keith L. Parker (ed), Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed., The McGraw-Hill Companies, Inc., New York, 2006: 1847.
4. Xu GF, Zhang WY. Preparation and in vitro evaluation of gastric floating and sustained-release tablets using carbopol 971PNF. J China Pharma University 34 (4):317-321.
5. Basak SC, Rahman J, Ramalingam M. Design and in vitro testing of a floatable gastroretentive tablet of metformin hydrochloride. Pharmazie 62 (2):145-148.
6. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, Baboota S. Formulation and development of hydrodynamically balanced system for metformin: in vitro and in vivo evaluation. Eur J Pharma Biopharma 67(1):196-201
7. Choudhury PK, Kar M, Chauhan CS.Cellulose acetate microspheres as floating depot systems to increase gastric retention of antidiabetic drug: Formulation, characterization

and *in vitro-in vivo* evaluation. Drug Dev Ind Pharm 34(4):349-354

8. Nath B, Nath LK, Mazumder B, Sharma NK, Sarkar MK. Preparation and in vitro evaluation of gastric floating microcapsules of metformin HCl. Indian J Pharma Edu Res 43(2):177-186.
9. Boldhane SP, Kuchekar BS. Gastro retentive drug delivery of metformin hydrochloride: Formulation and in vitro evaluation using $3^2$ full factorial design. Current Drug Delivery 6(5):477-485.
10. Rajab M, Jouma M, Neubert RH, Dittgen M. Optimization of a metformin effervescent floating tablet containing hydroxyl propyl methyl cellulose and stearic acid. Pharmazie 65(2):97-101.
11. Ameeduzzafar, Bajpai M, Bhattacharya A. Preparation and evaluation of alginate and alginate with pectine gel beads containing metformin hydrochloride using emulsion-gelation method. Indian Drugs 47 (7):56-59.
12. USP-NF 2009, volume 3, The United States Pharmacopeial Convention, Rock Ville, MD, p. 2907.
13. M Chavanpatil, P Jain, S Chaudhari, R Shear, P Vavia. Development of sustained release gastro retentive drug delivery system for ofloxacin: In vitro and in vivo evaluation. Int J Pharma 2005;304:178-18
14. Douglas C. Montgomery. Design and Analysis of Experiments. $5^{th}$ ed. Wiley-India, New Delhi; 2002: 466 & 472.
15. G Nandi, L K Ghosh, B K Gupta, "Development and formulation optimization of a low density floating extended release tablet of clarithromycin. Int J Drug Formul Res 2011; 2(3).
16. USP-NF 2009, volume 1, The United States Pharmacopeial Convention, Rock Ville, MD, p.382 – 385.
17. Gilbert S. Banker and Neil R. Anderson, In: L. Lachman, H. A. Lieberman, and J. L. Kanig eds. The theory and practice of industrial pharmacy.$3^{rd}$ ed. (Indian ed) 1987.Varghese Publishing House, Mumbai, India p.88.
18. Rosa M, Zia H, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994; 105: 65 – 70.
19. Costa P, Lobo JSMS. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 2001; 13:123 – 133.