Original Article

Thai Journal of Pharmaceutical Sciences

Statistical optimization and evaluation of flavoxate HCl gastro retentive floating tablets

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Received: Nov 24, 2020
Accepted: Dec 13, 2020
Published: Mar 18, 2021

ABSTRACT

Purpose: The objective of the current study is to develop gastroretentive formulation for flavoxate HCl using polymers of natural and semisynthetic origin in appropriate composition. Flavoxate HCl, a smooth muscle relaxant, mainly used for treating urinary incontinence, urgency of urination. **Materials and Methods:** Floating tablets of flavoxate HCl were prepared using variable amounts of hydroxypropyl methylcellulose (HPMC) K100M and *Lannea coromandelica* gum (LCG) with effervescent mixtures as per 3^2 factorial design by direct compression technique. Amount of release modifiers need to get sustained drug release was labeled as factors. On the other hand, time taken for drug dissolution were labeled as responses (time required for obtaining 10% dissolution, time required for obtaining 50% dissolution, time required for obtaining 75% dissolution, and time required for obtaining 90% dissolution). **Results and Discussion:** Nine formulations were obtained as per design, formulated, and evaluated for quality control parameters. Results reveals that all formulations passed the pharmacopoeial tests. Data obtained from the dissolution study fitted well to kinetic modeling, kinetic parameters were determined. Polynomial equations were derived for responses and checked for validity. **Conclusion:** FX_5 composed of 40 mg of HPMC K100M and 40 mg of LCG, is the best formulation showing similarity $f_2 = 84.65$, $f_1 = 4.3$ with the marketed product (URISPAS). Formulation FX_5 follows first order, whereas release mechanism found to be non-Fickian type ($n = 0.76$).

Keywords: 3^2 Factorial design, flavoxate HCl, gastroretentive, hydroxypropyl methylcellulose K100M, *Lannea coromandelica* gum, non-Fickian diffusion

INTRODUCTION

The design of oral controlled drug delivery systems (DDSs) is targeted to obtain predictable and improved *in vivo* availability. Gastric emptying is a dynamic process and gastroretentivity of dosage form results improved clinical response.[1]

Effectiveness of oral delivery practice was influenced by certain factors such as gastric emptying process, gastrointestinal transit time, drug release pattern from the formulation, and absorption site for drug. Gastric transit time in humans, influences absorption of drugs, can result inappropriate drug release from formulation leading to diminished clinical response. Gastroretention of dosage form has ability to sustain the release of drug at predictive rate, which retain in the acidic environment for a longer period of time than prompt release formulations.

Several difficulties were present in front of researchers for designing controlled release systems for better absorption, improved bioavailability.[2] The controlled gastric retention of solid dosage forms was obtained by numerous mechanisms such as flotation, bioadhesion, high density (sedimentation), modified shape systems, expansion, or by simultaneous administration of pharmacological agents that delay gastric emptying.[3-6]

Floating DDS (FDDS) is also known as hydrodynamically balanced system. FDDSs have a bulk density which is lower than gastric fluids and thus remain buoyant in gastric

environment for prolonged period of time, without affecting the gastric emptying rate. Dosage form is stayed in stomach due to flotation mechanism, which results controlled rate of drug release. After the release of drug, the residual system is run out from the gastroenvironment; this will increases GRT and a better control of fluctuations in plasma drug concentrations.[7-10]

Flavoxate HCl is an antispasmodic. It is a competitive muscarinic blocker, mainly used in the effective management of over active bladder urinary urgency, incontinence. It acts by relaxing the bladder muscles and helps in decreases the feeling of nocturnal polyuria or nocturia. It also helps to decrease the feeling of urination needing to micturate right away more times to bath room as well as pain in bladder.[11,12]

An attempt is made in the current study to develop gastroretentive drug delivery system (preferably by flotation) with the help of polymers (natural – *Lannea coromandelica* gum (LCG) and semisynthetic – hydroxypropyl methylcellulose [HPMC] K100M) along with effervescent mixtures.[13] From the literature, very less work reported for LCG, though it is natural more benefits observed from economy point of view as well as risk incidence also low. Hence, LCG selected as polymer for the formulation development of flavoxate HCl gastroretentive delivery.[9]

Application of polynomial-based response surface morphology (RSM) occupies major volume in case of pharmaceutical product development. Most widely used methods in the above mentioned category as follows: Factorial design (2^3, 3^2, and 3^3), central composite design, and Box–Behnken design.[13,14]

Manufacture of tablets processed by direct compression technique is frequent method, observed in many of pharmaceutical industries.[15]

A two factor, 3-level study (3^2 factorial design) was utilized to observe the combination effect of both natural (LCG) and semisynthetic (HPMC K100M) moieties on the dissolution of formulation (to see the effect of factors on the responses)[5,9] which increases the gastric transit time, improves penetrability of drug through mucosa, thereby improving the clinical efficacy of the active ingredient.

MATERIALS AND METHODS

Materials

A gift sample of flavoxate HCl was procured from Mankind Laboratories, Baddi, India. HPMC K100M was obtained from Loba Chemie Pvt. Ltd., Mumbai, India. LCG was gifted from Sarada Pharmaceuticals, Guntur. All other excipients such as sodium bicarbonate, dibasic calcium phosphate, and magnesium stearate were obtained from S.D. Fine Chem. Ltd., Mumbai, India.

Design and Development of Gastroretentive Floating tablets for Flavoxate HCl

Quantities required for the HPMC K100M, LCG for the development of flavoxate HCl floating formulations was chosen as factors (X_1 and X_2, respectively). Time to obtain dissolution was chosen as responses (time required for obtaining 10% dissolution [$t_{10\%}$], time required for obtaining 50% dissolution [$t_{50\%}$], time required for obtaining 75% dissolution [$t_{75\%}$], and time required for obtaining 90% dissolution [$t_{90\%}$]). RSM prediction equations (polynomial) were derived for responses according to linear stepwise backward regression technique.[16]

The three levels of X_1 (HPMC K100M) were 7.5%, 10%, and 12.5%. Three levels of X_2 (LCG) were 7.5%, 10%, and 12.5% (% with respect to total weight of tablet). Nine flavoxate HCl floating tablet formulations were designed using selected combinations of X_1, X_2, checked for the selection of optimum composition required to meet the primary objective of the study.

Preparation of flavoxate HCl floating tablets

A 3-level, 2-factor design was utilized for the present research work. Amount of HPMC K100M chosen as X_1 and amount of LCG chosen as X_2 shown in Table 1. Three levels of both factors chosen indicated as −1 = 7.5%; 0 = 10%; +1 = 12.5% (% as per average weight of tablet).

Direct compression technique was utilized for the preparation of floating tablets, each containing 200 mg flavoxate HCl. Formulae for the preparation of tablets are presented in Table 2. Accurately weighed ingredients (except flavoxate HCl) were screened for obtaining uniform size to ensure proper mixing, to obtain polymer mixture. The drug was then mixed with the polymer mixture for 10 min for uniform mixing of powder blend. Blend was lubricated with magnesium stearate. Powder blend was subjected to compression with the help of rotary tablet compression machine (tablet Minipress). Compressed tablets were processed for quality control measures as per pharmacopoeia. Final formulations were transferred to airtight and light resistance packaging bottles.

Evaluation of Flavoxate HCl Gastroretentive Floating Tablets[10,17]

Hardness

The breaking/crushing strength for the dosage forms was obtained by the diametric break of tablets with the help of Pfizer tablet hardness tester.

Table 1: Experimental design layout

Formulation code	X_1	X_2
FX_1	1	1
FX_2	1	0
FX_3	1	–1
FX_4	0	1
FX_5	0	0
FX_6	0	–1
FX_7	–1	1
FX_8	–1	0
FX_9	–1	–1
CX_1	–0.5	–0.5
CX_2	+0.5	+0.5

Friability

This test is performed using friability test apparatus (Roche). Selected number of tablets (20) were weighed accurately weight was noted (W_0), tablets were subjected to rotations (25 rpm for 4 min) again weight was noted (W). % weight loss was determined using the following formula:

$$\text{Weight loss (\%)} = (W_0 - W/W_0) \times 100$$

Assay

Assay was performed by triturating stated number of tablets in Indian pharmacopoeia (20) converted to powder, powder equivalent to 100 mg of drug was added in 100 mL of 0.1 N HCl followed by sonication. The solution was filtered through a 0.45 µ membrane filter, suitable aliquots were prepared, and the absorbance of the resultant solution was measured spectrophotometrically at 291 nm using 0.1 N HCl as blank.

Thickness

Thickness formulations were determined using Vernier calipers, by placing tablet between two arms of it.

In vitro buoyancy studies

This test is performed by placing the tablets in a beaker containing 100 mL of 0.1 N HCl (SGF). The time required for the upward movement of tablet to float on the 0.1 N HCl (SGF) was noted to be floating lag time.

In vitro drug release study

The *in vitro* dissolution rate study for formulation trails was performed using USP XXIII Type-II dissolution test apparatus containing 900 mL of 0.1 N HCl operated under conditions like temperature 37 ± 0.5°C and rotated at a speed of 50 rpm. At predetermined time intervals, 5 mL of the samples were withdrawn as per the pharmacopoeial procedure. The resultant samples were analyzed for estimation of drug release by measuring the absorbance at 291 nm using UV–visible spectrophotometer after suitable aliquots. The samplings were performed in triplicate manner ($n = 3$).[11]

The dissolution profile of all the formulations was subjected to kinetic modeling such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to know the drug release mechanisms.[18-20]

Swelling index study

To evaluate swelling index, tablet was placed in USP dissolution apparatus II with 900 mL 0.1 N HCl after measuring the weight of tablet (W_1). Then, weight of tablet (W_2) was determined by virtue of time, that is, at different time intervals, namely, multiples of 2 h (0-2-12) after using blotting paper to remove surplus fluid. Swelling index was calculated using the following formula:[21]

$$\text{Swelling index (\%)} = ([W_{2\_}W_1]/[W_1]) \times 100.$$

RESULTS AND DISCUSSION

Gastroretentive floating tablets of flavoxate HCl were developed as per 3-level, 2-factor design for optimizing the combination of drug release modifiers (HPMC K100M and LCG) along with effervescent mixtures. Formulation design is presented in Table 1. Quantity of HPMC K100M (X_1) and LCG (X_2) chosen as factors and time for obtaining dissolution chosen as responses ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$). Nine trials were developed as per the formulae given in Table 2.

All trials have flavoxate HCl (200 mg) as a gastroretentive formulation, obtained as tablet by direct compression technique. Developed formulations were evaluated for pharmaceutical product performance tests. Data are presented in Table 3. All formulations have sufficient mechanical strength. All formulations found to be less friable, as within the limits. All batches pass the drug content uniformity test. All formulation batches passed the weight variation test. From the swelling study, it is found that all formulation trails were shown swelling phenomenon exposed to simulated gastric

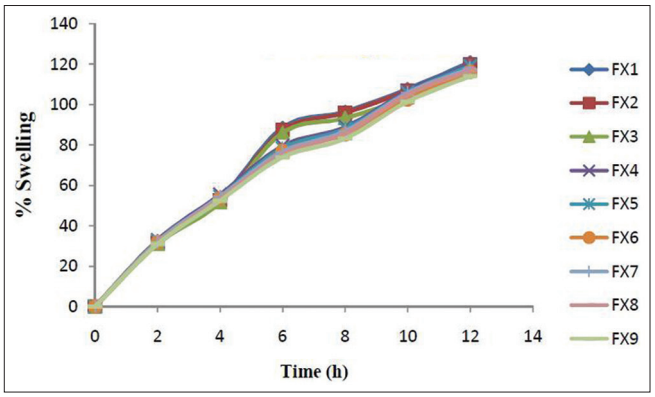

Figure 1: Swelling Profile

Table 2: Formulae for flavoxate gastroretentive floating tablets

Name of ingredients	Quantity of ingredients per each tablet (mg)								
	FX_1	FX_2	FX_3	FX_4	FX_5	FX_6	FX_7	FX_8	FX_9
Flavoxate HCl	200	200	200	200	200	200	200	200	200
Dibasic calcium phosphate	44	54	64	54	64	74	64	74	84
Hydroxypropyl methylcellulose K100M	50	50	50	40	40	40	30	30	30
Lannea coromandelica gum	50	40	30	50	40	30	50	40	30
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	400	400	400	400	400	400	400	400	400

Table 3: Post-compression parameters for the formulations (n=3)

Batch code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Average weight (mg)	Drug content (%)	Floating lag time (s)	Total floating time (h)
FX_1	5.39±0.2	4.32±0.04	0.20±0.13	401.6±2.06	97.37±0.31	47.3±1.2	>18
FX_2	5.20±0.17	4.27±0.02	0.34±0.1	403.61±4.07	97.715±0.36	49.7±1.3	>18
FX_3	5.24±0.2	4.25±0.01	0.24±0.12	400.6±3.06	97.26±0.38	51.75±1.5	>18
FX_4	5.46±0.2	4.24±0.04	0.18±0.13	402.55±2.2	98.96±0.33	48.43±1.4	>18
FX_5	5.26±0.17	4.17±0.03	0.33±0.1	404.54±4.2	99.3±0.39	49.95±1.5	>18
FX_6	5.32±0.18	4.19±0.01	0.22±0.13	401.57±3.2	99.95±0.41	52.84±1.6	>18
FX_7	5.71±0.22	4.28±0.04	0.18±0.12	401.6±2.06	99.91±0.43	50.9±1.5	>18
FX_8	5.48±0.22	4.25±0.02	0.33±0.1	403.65±4.1	99.26±0.49	53.51±1.6	>18
FX_9	5.54±0.26	4.23±0.01	0.22±0.1	400.62±3.1	99.96±0.51	55.5±1.7	>18

Table 4: Regression analysis for factorial trials

Formulation code	Kinetic parameters											
	Zero order			First order			Higuchi			Korsmeyer–Peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
FX_1	21.37	3.77	0.938	1.99	0.052	0.998	0.03	20.83	0.994	1.01	0.80	0.94
FX_2	30.18	3.65	0.895	1.95	0.065	0.995	7.52	20.92	0.981	1.11	0.75	0.91
FX_3	36.29	3.42	0.854	1.87	0.064	0.984	13.45	20.17	0.965	1.18	0.71	0.88
FX_4	19.67	4.02	0.949	2.07	0.068	0.986	2.33	21.95	0.993	0.99	0.82	0.95
FX_5	28.57	3.89	0.910	2.11	0.101	0.978	5.30	21.96	0.984	1.01	0.76	0.92
FX_6	34.71	3.65	0.876	2.04	0.104	0.982	11.23	21.21	0.973	1.17	0.72	0.89
FX_7	25.56	3.84	0.929	2.06	0.076	0.988	3.32	21.43	0.992	1.1	0.77	0.92
FX_8	31.13	3.72	0.896	1.99	0.079	0.977	8.20	21.23	0.980	1.14	0.74	0.90
FX_9	37.07	3.51	0.861	1.97	0.091	0.990	13.93	20.60	0.967	1.19	0.70	0.88
URISPAS	16.01	7.03	0.966	2.02	0.090	0.970	1.28	26.98	0.999	0.998	0.99	0.92

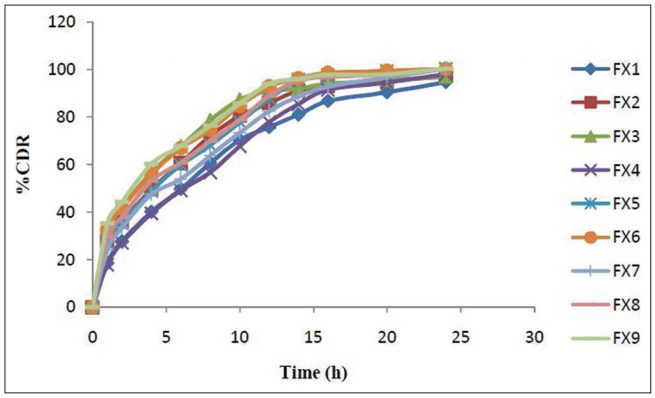

Figure 2: Comparative zero-order plots

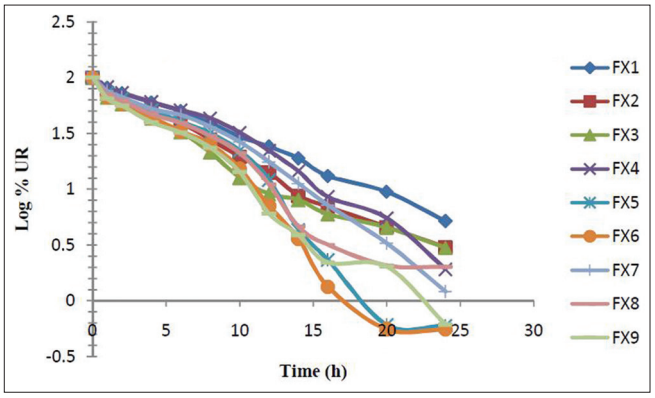

Figure 3: Comparative first-order plots

fluid but stayed without breaking during the study period. Formulation FX_1 was found to have highest swelling property and the same is presented in Figure 1.

Dissolution rate test was carried as per standard procedures, the dissolution specifications such as 900 mL of simulated gastric fluid; paddle was rotated at a speed of 50 rpm, temperature maintained as 37 ± 0.5°C throughout the test period. Dissolution profile was well fit to kinetic modeling, results are presented in Table 4, and the same was presented as plots from Figures 2-5. From the results, observed that there was a clear relation existed between quantities of polymers in combination to the drug release rate (both were inversely proportional to each other).[22] Predicted sustained release of drug was obtained by appropriate composition of factors (X_1, X_2). AQ3

Based on the desirability factor, FX_5 is considered as best formulation among all batches. FX_5 composed of both HPMC K100M and LCG in equal quantity, that is, 40 mg each,

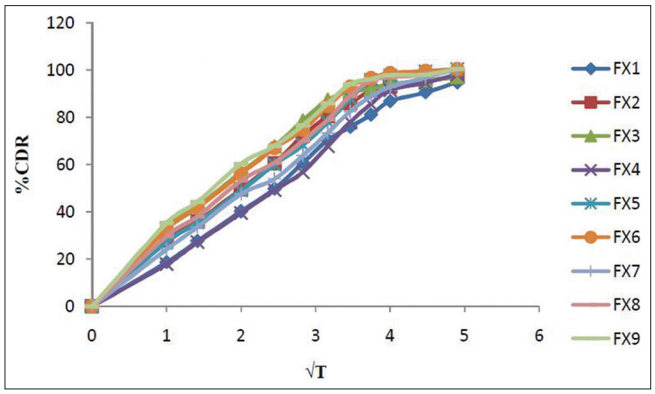

Figure 4: Comparative Higuchi plots

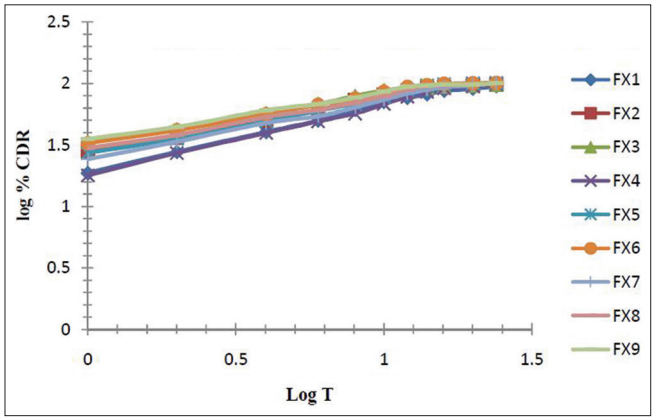

Figure 5: Comparative Korsmeyer–Peppas

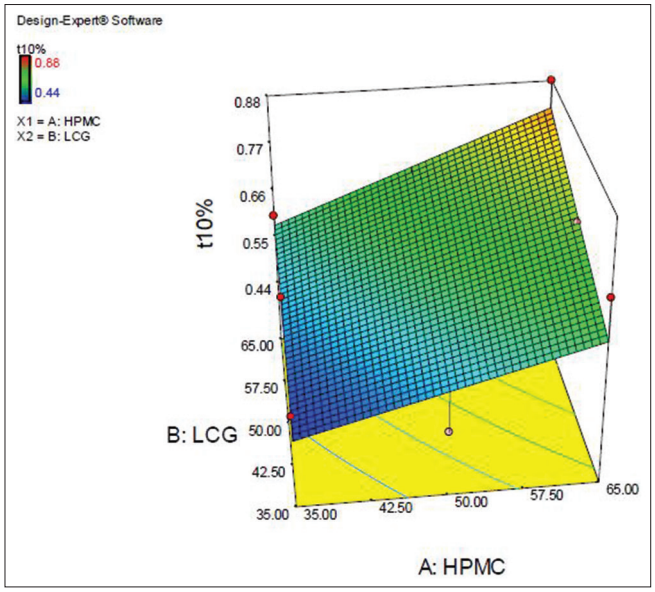

Figure 6: Response morphological plot for $t_{10\%}$

produced promising dissolution characteristics, which helps in meeting the purpose of research by gastroretentivity and optimum delivery of drug from dosage form.

RSM equations (polynomial) were derived for all responses using PCP Disso and RSM plots were obtained with the help of DESIGN-EXPERT 7.0. The response morphological plots are presented as Figures 6-10. Dissolution parameters for FX_1-FX_9 are summarized as Table 5.

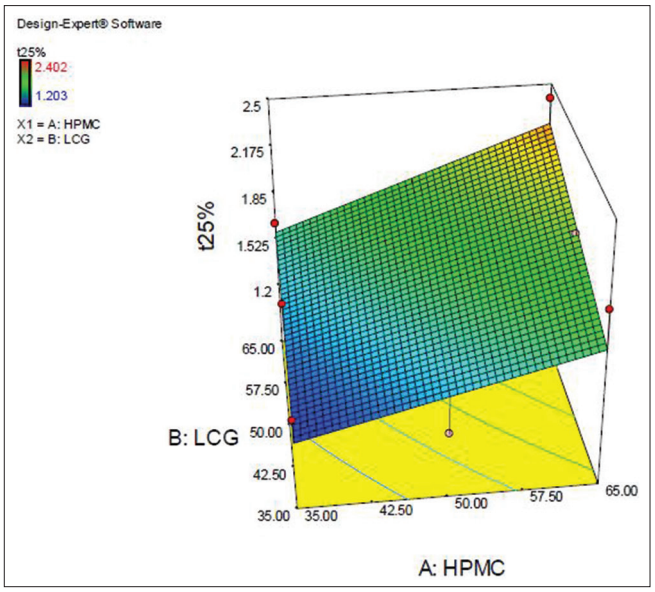

Figure 7: Response morphological plot for $t_{25\%}$

Table 5: Dissolution parameters of moxifloxacin gastroretentive floating tablets

Formulation code	Dissolution parameters				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{1/2}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
FX_1	0.88	2.41	5.79	11.58	19.24
FX_2	0.71	1.93	4.65	9.30	15.44
FX_3	0.72	1.95	4.69	9.37	15.57
FX_4	0.68	1.84	4.42	8.84	14.69
FX_5	0.46	1.24	2.98	5.96	9.91
FX_6	0.45	1.21	2.90	5.80	9.63
FX_7	0.61	1.65	3.97	7.93	13.18
FX_8	0.58	1.59	3.82	7.63	12.68
FX_9	0.51	1.38	3.31	6.62	10.99
URISPAS	0.52	1.40	3.36	6.72	11.16

$t_{10\%}$: Time required for obtaining 10% dissolution, $t_{50\%}$: Time required for obtaining 50% dissolution, $t_{75\%}$: Time required for obtaining 75% dissolution, $t_{90\%}$: Time required for obtaining 90% dissolution

RSM equations for the determination of predicted kinetic parameters are as follows:

$$Y_1 = 0.62+0.11X_1+0.09X_2+0.02X_1X_2+0.142\ X_1^2+0.055X_2^2 \quad (t_{10\%})$$

$$Y_2 = 1.69+0.28X_1+0.28X_2+0.05\ X_1X_2+0.4\ X_1^2+0.16\ X_2^2 \quad (t_{25\%})$$

$$Y_3 = 4.06+0.68X_1+0.55X_2+0.12\ X_1X_2+0.94\ X_1^2+0.37\ X_2^2 \quad (t_{50\%})$$

$$Y_4 = 8.12+1.35X_1+1.1X_2+0.23\ X_1X_2+1.88\ X_1^2+0.73\ X_2^2 \quad (t_{75\%})$$

Table 6: Dissolution parameters for check point formulations

Formulation code	Predicted value					Actual observed value				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
CX_1	0.58	1.61	3.82	7.63	12.61	0.59	1.59	3.80	7.68	12.64
CX_2	0.77	2.11	5.02	10.04	16.68	0.78	2.15	5.05	10.08	16.75

$t_{10\%}$: Time required for obtaining 10% dissolution, $t_{50\%}$: Time required for obtaining 50% dissolution, $t_{75\%}$: Time required for obtaining 75% dissolution, $t_{90\%}$: Time required for obtaining 90% dissolution

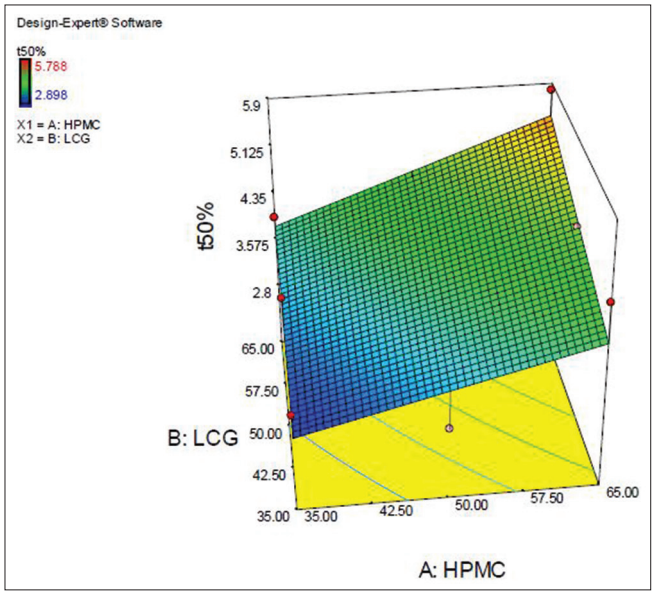

Figure 8: Response morphological plot for $t_{50\%}$

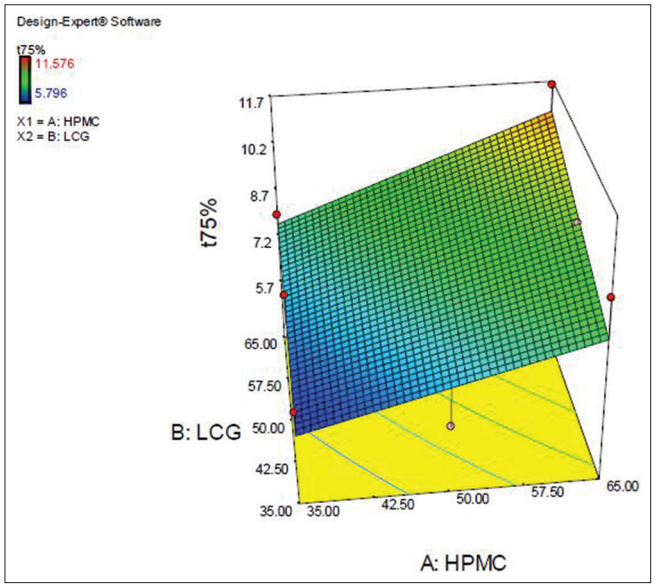

Figure 9: Response morphological plot for $t_{75\%}$

$$Y_5 = 13.48+2.24X_1+1.83\ X_2+0.37\ X_1X_2+3.12\ X_1^2+1.3\ X_2^2\ (t_{90\%}).$$

Results for the predicted responses versus actual responses presented in Table 6. No much deviation was observed in the predicted versus actual responses. It indicates validity of developed equation. FX_5 was considered to be ideal. It shows

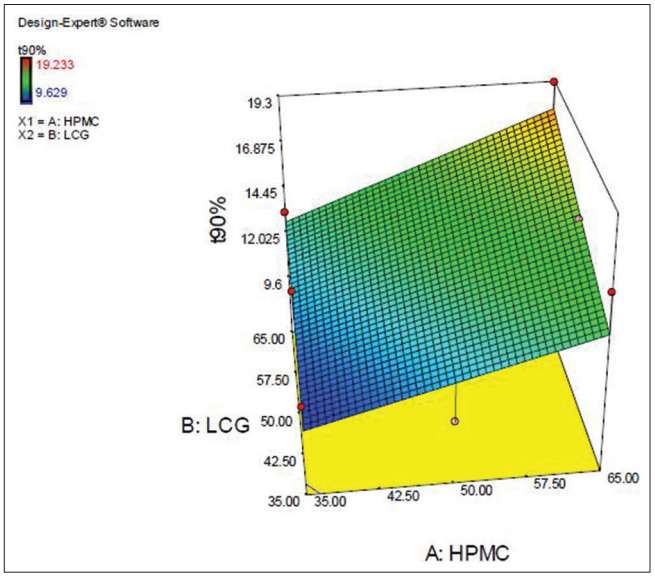

Figure 10: Response morphological plot for $t_{90\%}$

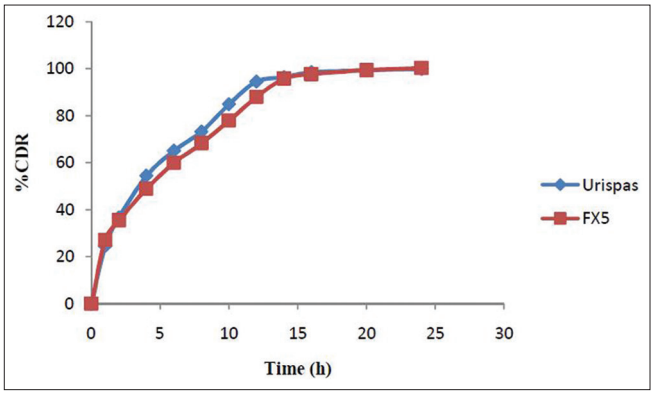

Figure 11: Comparative *in vitro* dissolution profiles for FX_5-URISPAS

similarity factor (f2) 84.65, difference factor (f1) 4.3, and $t_{cal} < 0.05$ when compared with marketed product (URISPAS). Comparative dissolution plots for best formulation (FX_5) and marketed product shown in Figure 11.

CONCLUSION

On the basis of the current research study, the use of macromolecules (natural and semisynthetic polymers) in combination had its own advantages of maintaining integrity and buoyancy of tablets. The effervescent-based FDDS is a promising formulation to obtain gastroretentivity using gel-forming polymers such as HPMC K100M and LCG employing sodium bicarbonate as gas generating agent using 3^2 factorial

design. Among the various FDDS formulations studied, the formulation (FX_5) showed the best result in terms of the required percentage cumulative drug release, floating lag time, and total floating time was considered as the ideal formulation. Best formulation FX_5 follows first-order release and non-Fickian diffusion, it may improve patient compliance by reducing the dosing frequency, which will ultimately improve the clinical response.

ACKNOWLEDGMENT

Authors acknowledge sincere thanks to the management and staff of M.A.M College of Pharmacy, India, for the facilities granted and constant encouragement for the completion of current research investigation.

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Author Queries???
AQ3: Kindly review the sentence as it seems to be incomplete.