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Research Article

FORMULATION AND OPTIMIZATION OF BIPHASIC FLOATING DRUG DELIVERY SYSTEM OF VERAPAMIL HYDROCHLORIDE

BHUSHAN S. GULECHA[1*], SADHANA SHAHI[2], VIVEK B. RAJENDRA[1]

[1]Sherya Life Sciences, B9/2, MIDCW lauj, Aurangabad-431136, [2]Government College of Pharmacy Aurangabad- 431001

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ABSTRACT

The biphasic floating drug delivery system was developed to achieve maximum release quickly followed by a sustained release phase in the treatment of treatment of angina pectoris, hypertension and supraventricular tachyarrhythmia. Verapamil hydrochloride exhibits of its pH dependent solubility. It is highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH). Biphasic tablets were prepared by direct compression method, using polymers such as hydroxyl propyl methyl cellulose K4M, K15M and microcrystalline cellulose PH 102, and other standard excipients. 3^2 factorial design was applied for optimization

Concentration of HPMC and concentration of sodium bicarbonate were selected as independent variables and studied at 3 levels. Dependent variables were floating lag time and *in vitro* drug release. Tablets were evaluated for physical characteristics hardness, % friability, floating lag time, swelling index, *in vitro* drug release. Responses were subjected to multiple regression analysis. It was concluded that release was more retarded with HPMC K15M than HPMC K4M. Release decreased with increasing concentration of HPMC. Floating lag time decreases with increased concentration of sodium bi carbonate.

Keywords: Gastric floating drug delivery system, HPMC, Floating lag time, Verapamil hydrochloride, Factorial design

INTRODUCTION

An oral controlled release system has been a challenge to formulation scientists because not all drugs or therapeutic agents are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed in a particular portion of GIT. A gastric floating drug delivery system (GFDDS) can overcome these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. [1] Various approaches have been proposed to control the gastric residence of drug delivery systems in the upper part of the GIT including floating drug delivery systems (FDDS) [2,3] high density DDS , mucoadhesive systems [4], swelling and expanding DDS [5,6], modified shape systems and other delayed gastric devices . FDDS is a gastroretentive dosage form (GRDF), which can prolong the gastric residence time (GRT) to produce an acceptable drug bioavailability. [7] FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* non-effervescent and effervescent systems, have been used in the development of FDDS. The effervescent system uses matrices prepared with swellable polymers and effervescent components *e.g.* sodium bicarbonate and citric acid or stearic acid. In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy on these dosage forms. [8] The biphasic system is used mostly when maximum relief needs to be achieved quickly followed by a sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics and antiallergenic agents are mainly used for this system. [9]

Verapamil hydrochloride exhibits of its pH dependent solubility. It is highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH). [10] Verapamil hydrochloride is the first calcium channel blocker and used for the treatment of angina pectoris, hypertension and supraventricular tachyarrhythmia. Verapamil hydrochloride is approximately 90 % absorbed from gastrointestinal tract, but has low bioavailability of 22 ± 8 %. Biological half life of verapamil hydrochloride is 4.0 ± 1.5 h. [11]

The objective of this study was to develop a novel optimized GFDDS containing verapamil hydrochloride having a bulk density lower than that of gastric fluids and remaining buoyant on the stomach contents. Objective was achieved by applying factorial design. HPMC K15M and HPMC K4M were selected for the study. Independent variables were selected as concentration of HPMC and concentration of sodium bicarbonate and studied at 3 levels. Dependent variables were floating lag time and *in vitro* drug release.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride was received as a gift sample from Shreya Lif Science Pvt Ltd.(Aurangabad, India). MCC PH 102 was obtained from RanQ Remedies Pvt Ltd,India.Lake quinoline yellow was supplied from Ideal Cure Pvt Ltd,India.Acdisol was kindly provided by JRS Pvt Ltd,India. HPMC K4M and HPMCK15 M was obtained from Pioma Chemicals,India. Sodium bicarbonate was purchased from Canton Laboratories Pvt Ltd. Talc and magnesium stearate were received from Analyst India and Health Care Pvt Ltd respectively.

Formulation of bi-layer floating tablets

Bi-layer floating tablet contains two layers; one immediate release layer and second sustained release layer of verapamil hydrochloride. Accurately weighted 60 mg of immediate release layer powder blend and 240 mg of floating sustained release layer powder blend individually. Batches of bilayer tablets were prepared by direct compression method according to formula given in Table 1. Initially immediate release powder blend fed manually into the dies of 16 stations CIP tablet compression machine (CIP machinaries Pvt Ltd India) and then compressed at low compression force to formed uniform layer of powder. Sustained release layer was formed by compressing power blend (Table 2,3) over pre-compressed immediate release layer with increased compression force with 16 stations CIP tablet machine by using 9.5 mm flat faced punch.

Table 1: Composition of immediate release layer for factorial batches

S. No.	Ingredients(mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Verapamil	14.00	14.00	14.00	14.00	14.00	14.00	14.00	14.00	14.00
2.	Microcrystalline Cellulose PH 102	43.3	43.3	43.3	43.3	43.3	43.3	43.3	43.3	43.3
3.	Crosscarmellose Sodium	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20
4.	Lake Quinoline Yellow	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
5.	Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Average Weight of Immediate layer		60.00	60.00	60.00	60.00	60.00	60.00	60.00	60.00	60.00

Table 2: Composition of sustained release layer for factorial batches with HPMC K4M

S. No.	Ingredients(mg/tab)	K4F1	K4F2	K4F3	K4F4	K4F5	K4F6	K4F7	K4F8	K4F9
1.	Verapamil	106.00	106.00	106.00	106.00	106.00	106.00	106.00	106.0	106.0
2.	Microcrystalline Cellulose PH 102	43.87	49.70	37.70	28.70	34.70	22.70	13.70	19.70	7.70
3.	Hydroxy Propyl Methyl Cellulose (K4M)	60.00	60.00	60.00	75.00	75.00	75.00	90.00	90.00	90.00
4.	Crosscarmellose Sodium	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
5.	Sdium Bicarbonate	18.00	12.00	24.00	18.00	12.00	24.00	18.00	12.00	24.00
6.	Talc	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
7.	Magnesium Stearate	2.30	2.30	2.30	2.30	2.30	2.30	2.30	2.30	2.30
Average Weight of Sustain layer		240	240	240	240	240	240	240	240	240

Table 3: Composition of sustained release layer for factorial batches with HPMC K15M

S. No.	Ingredients (mg/tab)	K15F1	K15F2	K15F3	K15F4	K15F5	K15F6	K15F7	K15F8	K15F9
1.	Varapamil	106.00	106.00	106.00	106.00	106.00	106.00	106.00	106.00	106.00
2.	Microcrystalline Cellulose PH 102	43.87	49.70	37.70	28.70	34.70	22.70	13.70	19.70	7.70
3.	Hydroxy Propyl Methyl Cellulose (K15M)	60.00	60.00	60.00	75.00	75.00	75.00	90.00	90.00	90.00
4.	Crosscarmellose Sodium	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
5.	Sodium Bicarbonate	18.00	12.00	24.00	18.00	12.00	24.00	18.00	12.00	24.00
6.	Talc	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
7.	Magnesium Stearate	2.30	2.30	2.30	2.30	2.30	2.30	2.30	2.30	2.30
Average Weight of Sustain layer		240	240	240	240	240	240	240	240	240

Factorial Design

A 3^2 randomized full factorial design was used for optimization. The amount of HPMC (X1) and amount of sodium bicarbonate (X2) were selected as independent variables. The time required for 50% drug dissolution (T/50%) and floating lag time and swelling index were selected as dependant variables.

Evaluation of bi-layer floating tablets

Prepared bi-layer floating tablets were evaluated for hardness, friability, disintegration time for immediate release layer, percent drug release, thickness, floating lag time, and total floating time for floating sustained release layer. The results are shown in Table 4,5

***In vitro* buoyancy studies**

The tablets were placed in a 100-mL glass beaker containing simulated 0.1N hydrochloric acid, as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time. [12]

Swelling study

Gastro retentive tablet was weighed individually (designated as W1) and placed separately in glass beaker containing 200 ml of 0.1N HCl and incubated at 37ºC ± 1ºC. At regular 1h time intervals until 24h, the tablet was removed from beaker, and the excess surface liquid was removed carefully using the filter paper. The swollen tablet was then re-weighed (W2) and swelling index (SI) was calculated using the following formula. [13]

$$SI = (W2 - W1)/W1$$

***In vitro* drug release study**

In vitro drug release study was performed using USP XXII paddle apparatus (Lab India 2000) at 100 rpm in simulated gastric fluid without enzyme of pH 1.2. Temperature was maintained at 37 ± 0.5°C. Sample 5ml was withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by using UV spectrophotometer (UV Shimadzu 1700 Pharmaspec) at λmax 278 nm.

RESULTS AND DISCUSSION

Bi layer tablet formulations were prepared as per the table 1, 2, 3. All formulations were evaluated for hardness, friability, disintegration of immediate release layer, floating lag time, percent drug release. The hardness of all formulations was found to be 7-8 kg/cm2. The thickness of formulations was between 3.4 mm to 3.5 mm. The friability was between 0.3% – 0.5 % for all the formulations, which was an indication of good mechanical resistance of the tablet. Floating lag time was found minimum16 s and maximum 108 s. Total floating time of the formulations was observed more than 12 h.

Floating lag time

During the study when tablet dipped in 0.1N hydrochloric acid, the media goes into tablet matrix, the interaction of acidic fluid with sodium bicarbonate resulted in to formation of carbon dioxide gas and that entrapped in swollen gel thus causing floatation. [14] From the results (Table 4, 5) the buoyancy lag-time of tablets depends on the amount of sodium bicarbonate involved in CO_2 formation. For a floating system, the ideal matrix or coating material should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and allow release of CO_2 to promote floating. HPMC concentration and viscosity grade also have impact on floating lag time. As concentration of HPMC increases floating lag time increases. HPMC K4M shows less floating time as compared to HPMC K15M. [15]

Drug release

The *in vitro* dissolution study of verapamil hydrochloride bi-layer floating tablets were performed using 900 ml 0.1 N HCL dissolution media. The study was done 37 ± 0.5°C temperature and 100 rpm.

Immediate release layer get completely dissolved within 15-20 min and 25-30% drug released among the total dose. Concurrently floating sustained release layer releases the drug up to 12 h. From the figure 1, 2 it is observed that release was sustained more with HPMC K15M As compared with HPMC K4M. Release retarded with the increase in HPMC concentration. [16] Sodium bicarbonate have no effect on drug release. The entire release pattern shows matrix order due to fast release from immediate release layer and sustained release from floating matrix layer.

Swelling index

The swelling of the polymers can be measured by their ability to absorb water and swell. Swelling index is the parameter which indicates the swelling capacity of hydrophilic polymers in presence of aqueous medium. The swelling of the polymers used was determined by water uptake of the tablets. The percent swelling of the tablets was determined at different time intervals. The complete swelling was achieved at the end of 6–8 h for all the developed formulations. The integrity of the formulations was also found to be maintained upto 24 h in all the formulations. Swelling is also a vital factor to ensure buoyancy and drug dissolution of the matrix tablet. The tablets containing HPMC K4M and HPMC K15M showed higher swelling index. [17] This may be due to very high viscosity and high molecular weight which uptakes more amount of water and thus shows more swelling.

Table 4: Evaluation of Factorial Batches (HPMC K4 M)*

Formulation Code	Parameters						
	Hardness (Kg/Cm²)*	Friability (%)*	Thickness (mm)*	DT of Immediate Release Layer (sec)‡	$T_{50\%}$ Drug Release (Min)‡	Floating Lag Time (Sec) †	Swelling Index †
K4F1	7±0.79	0.5±1.20	3.4±0.23	50±0.35	32±1.09	40±1.11	1.5±1.23
K4F2	8.09±1.29	0.3±1.45	3.5±0.34	53±0.53	32±1.05	60±1.06	1.64±1.02
K4F3	8.16±1.30	0.4±2.00	3.4±0.30	50±0.46	30±1.11	16±1.07	1.9±0.99
K4F4	7.57±1.24	0.3±1.57	3.5±0.50	54±0.29	385±1.24	53±0.98	2.2±1.42
K4F5	8.14±1.00	0.5±1.43	3.4±0.29	50±0.34	383±1.16	75±0.94	2.34±1.03
K4F6	8.16±0.89	0.3±1.20	3.4±0.57	55±0.73	382±1.32	20±0.83	2.45±1.96
K4F7	7.50±0.92	0.4±1.32	3.4±0.49	50±0.24	468±1.45	78±1.04	2.99±1.43
K4F8	8.10±0.99	0.4±1.00	3.5±0.39	55±0.41	467±1.23	100±1.13	3.13±1.95
K4F9	7.26±1.29	0.3±1.25	3.5±0.22	50±0.33	468±1.49	30±1.14	3.19±1.27

*All values are expressed as means ± SD (n=20); ‡ All values are expressed as means ± SD (n=6); †All values are expressed as means ± SD (n=5)

Table 5: Evaluation of Factorial Batches (HPMC K15 M)*

Formulation Code	Parameters						
	Hardness (Kg/cm²)*	Friability (%)*	Thickness (mm)*	DT of Immediate Release Layer (sec) ‡	$t_{50\%}$ Drug Release (min) ‡	Floating Lag Time (sec) †	Swelling Index †
K15F1	7.20±0.99	0.4±1.22	3.5±0.40	54±0.32	34±1.21	49±1.32	1.2±1.43
K15F2	8.11±0.48	0.3±1.20	3.4±0.36	53±0.57	35±1.04	67±1.23	1.42±1.23
K15F3	8.22±0.81	0.5±1.16	3.5±0.32	50±0.41	34±1.21	22±1.25	1.77±1.77
K15F4	7.15±1.20	0.4±1.32	3.5±0.36	51±0.79	444±1.05	62±1.42	1.99±1.23
K15F5	7.70±1.11	0.3±0.98	3.5±0.31	53±0.99	441±1.07	83±1.06	2.17±1.22
K15F6	7.23±0.99	0.3±1.02	3.4±0.98	56±0.91	442±1.21	27±1.03	2.32±1.65
K15F7	8.14±1.04	0.5±1.04	3.4±0.74	51±0.37	497±1.31	87±1.11	2.58±1.88
K15F8	8.0±1.07	0.4±1.17	3.4±0.46	55±0.20	493±1.20	108±1.16	2.89±1.52
K15F9	8.45±1.08	0.5±1.18	3.4±0.34	50±0.39	498±1.07	36±1.17	3.02±1.45

*All values are expressed as means ± SD (n=20);‡ All values are expressed as means ± SD (n=6); †All values are expressed as means ± SD (n=5)

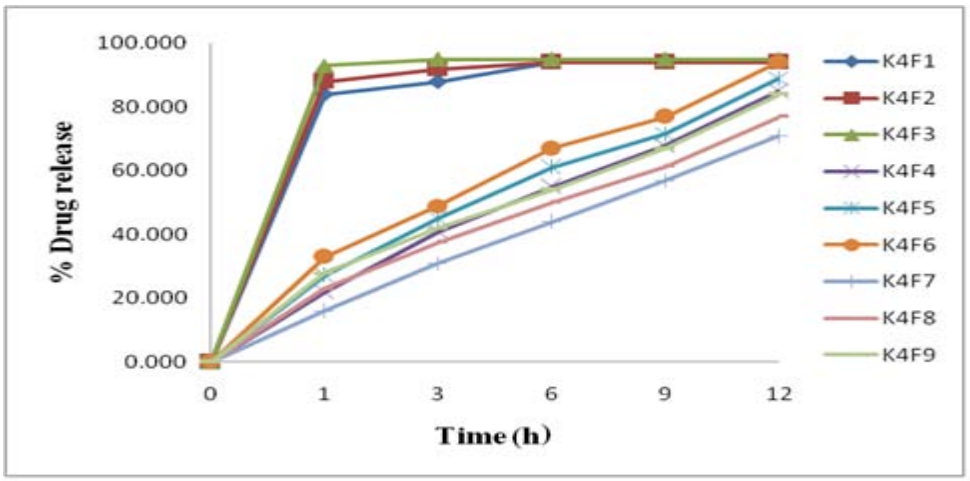

Fig. 1: *In Vitro* Drug Release of Factorial Batches HPMC K4M

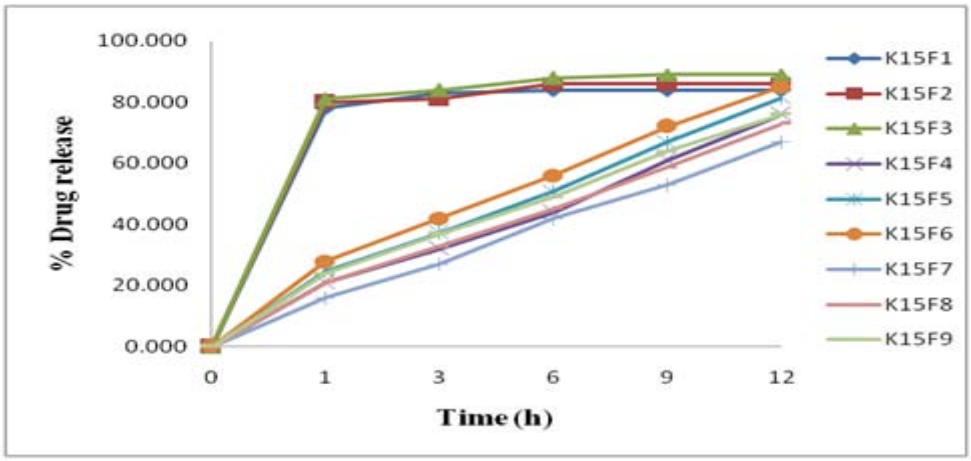

Fig. 2: *In Vitro* Drug Release of Factorial Batches HPMC K15M

Multiple regression analysis of 3^2 factorial design

The responses of factorial design Y_1 (Floating lag time), Y_2 (Drug release) were subjected to multiple regression analysis by PCP DISSO software. Surface response plots and coefficient values indicate both independent variables X_1 (HPMC concentration) and X_2 (Sodium bicarbonate) affect responses.

The factorial equations for the three responses as per the coefficient obtained were as follows:

$Y_{1K4M} = 50.33+15.33X_1-28.17X_2$

$Y_{2K4M} = 383.33+217.66X_1-133.33\ X_1X_2$

$Y_{1K15M} = 60.11+15.5X_1--28.83X_2$

$Y_{2K15M} = 442.33+230.83X_1--177.16X_1X_2$

Where Y_1 = Floating Lag time

Y_2 = Time required for release of 50% of loaded drug dose.

The coefficient b_0 is the arithmetic mean of the 9 responses and b_1 is estimated coefficient for the factor X_1 and similarly b_2, b_{11} & b_{12} for the respective terms X_2, X_1^2 & X_1X_2 (Table 6-9). The main effects (X_1 &X_2) represents average results of changing one factor at a time from low to high value. The term X_1^2 indicates curvilinear relationship. The interaction X_1X_2 shows how dependent variable changes when two or more factors are simultaneously changed. Thus for response Y_1 of K4M and K15M, we get a linear decline as X_2 increases indicating the effect of sodium carbonate with increase in value of which results in decline of lag time. With increase in X_1 we get linear increase indicating effect of HPMC with increase in value resulting in increased lag time. In response plot Y_2 of K4M and K15M, we observed linear decline as X_1 increases indicating the effect of HPMC. Moreover it also has the term X_1 X_2 which explains the contributing effect of both the variables as evident from the curvilinear plot (Figure 3-6).

Table 6: Responses Y1 (Floating lag time) and Y2 (Time required for 50 % drug release) for factorial batches with HPMC K4 M

Response	Factorial batches								
	K4F1	K4F2	K4F3	K4F4	K4F5	K4F6	K4F7	K4F8	K4F9
Floating lag time (sec) (Y1)	40	60	16	53	75	20	78	100	30
Time required for 50%drug release (min)(Y2)	32	32	30	385	383	382	468	467	468

Table 7: Responses Y1 (Floating lag time) and Y2 (Time required for 50 % drug release) for factorial batches with HPMC K15 M

Response	Factorial batches								
	K15F1	K15F2	K15F3	K15F4	K15F5	K15F6	K15F7	K15F8	K15F9
Floating lag time (sec) (Y1)	49	67	22	62	83	27	87	108	36
Time required for 50%drug release (min)(Y2)	34	35	34	444	441	442	497	493	498

Table 8: Coefficients for factorial batches with HPMC K4 M

Responses studied	Coefficients for K4M				
	Bo	b1	b2	b12	R^2
Floating lag time (sec)(Y1)	52.33	15.33	-28.17	--	0.95
Time required for 50%drug release (min)(Y2)	383.33	217.66	--	-133.33	1

Table 9: Coefficients for factorial batches with HPMC K15 M

Responses studied	Coefficients for K15M				
	Bo	b1	b2	b12	R^2
Floating lag time (sec) (Y1)	60.11	15.5	-28.83	--	0.94
Time required for 50%drug release (min)(Y2)	442.33	230.83	--	-177.16	1

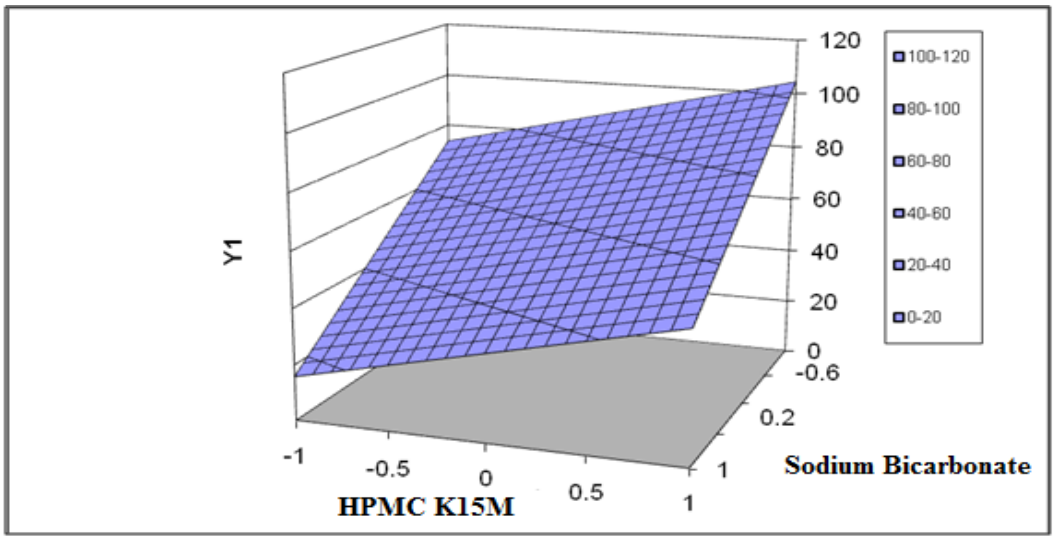

Fig. 3: Surface response plot of floating lag time for factorial batches with HPMC K15M

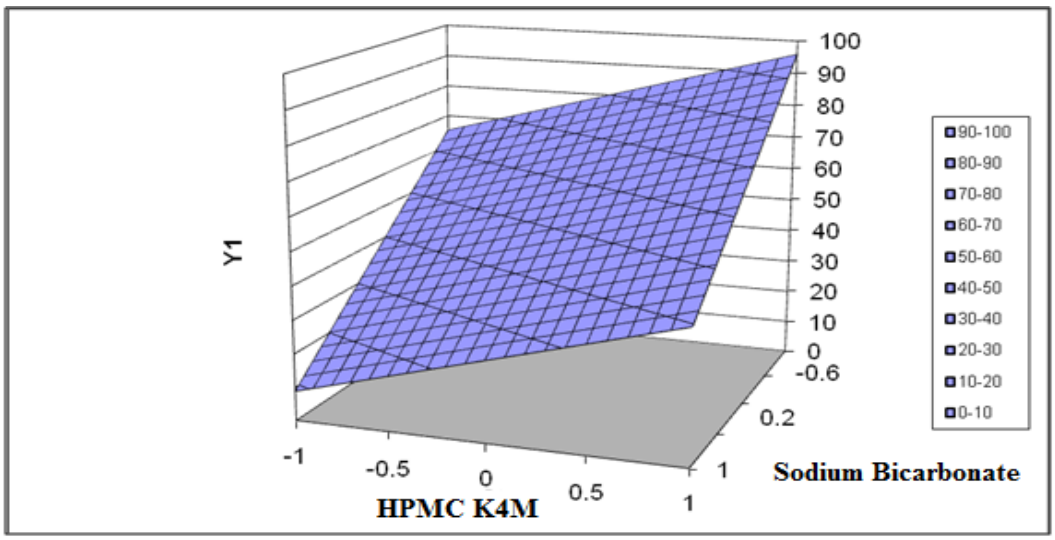

Fig. 4: Surface response plot of floating lag time for factorial batches with HPMC K4M

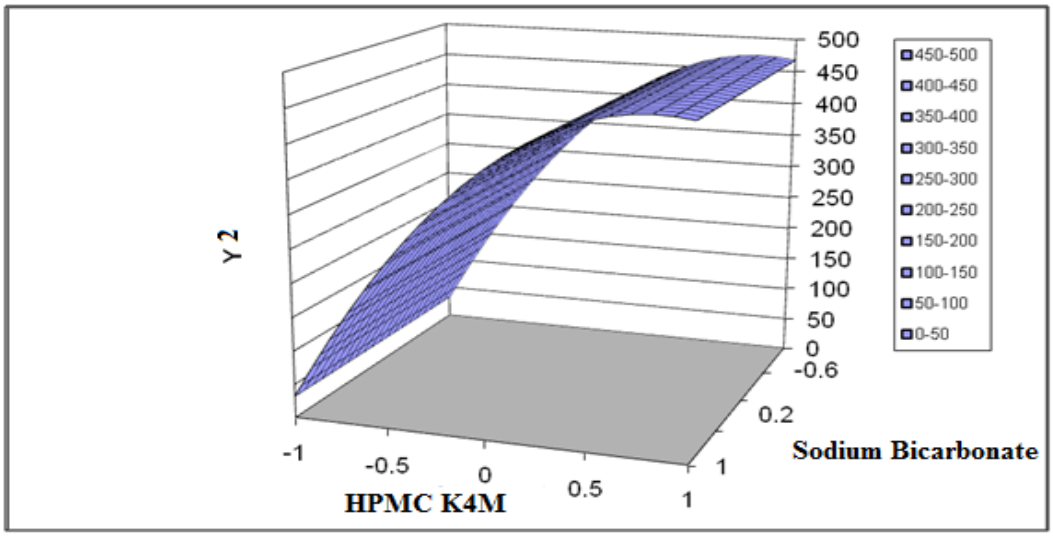

Fig. 5: Surface response plot of drug release for factorial batches with HPMC K4M

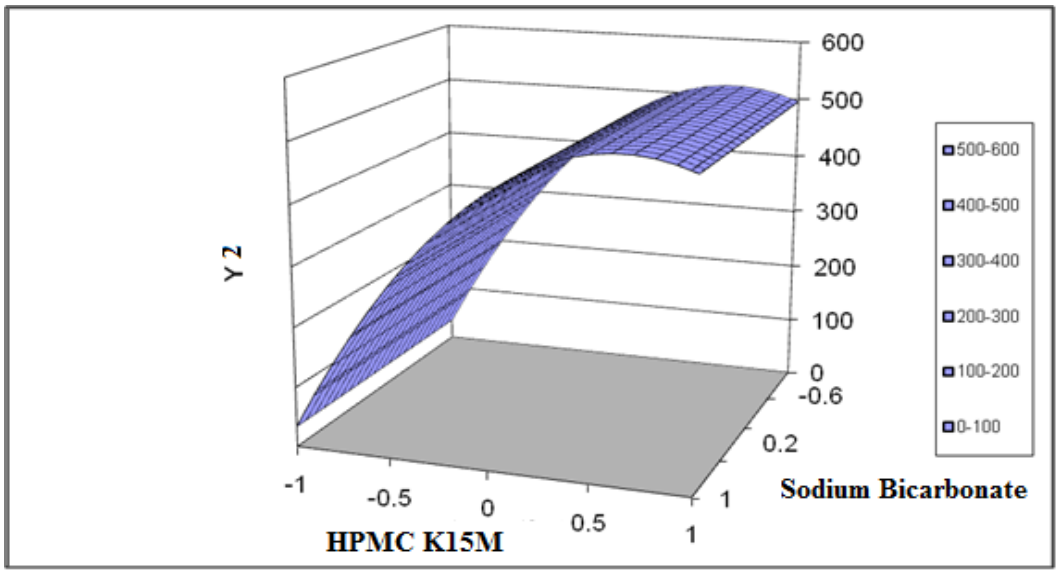

Fig. 6: Surface response plot of drug release for factorial batches with HPMC K15M

CONCLUSION

In conclusion, bi-layered sustained release formulation for verapamil was successfully developed. Release was more sustained with HPMC K15M than HPMC K4M. Release decreased with increasing concentration of HPMC. Floating lag time decreases with increased concentration of sodium bi carbonate. Formulation code K4F6 and K15F6 was best optimized as compared to others as they show acceptable sustained release with lesser floating lag time.

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