International Journal of Pharmaceutical Applications ISSN 0976-2639.
Vol 2, Issue 3, 2011, pp 181-194 http://www.bipublication.com

EFFECT OF POLYMER AND GAS FORMING AGENT ON FLOATING DRUG DELIVERY OF TRAMADOL HYDROCHLORIDE USING RESPONSE SURFACE METHODOLOGY: IN VITRO AND IN VIVO EVALUATION

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ABSTRACT:-

Tramadol hydrochloride is a synthetic opioid used as a centrally acting analgesic and effective in both experimental and clinical pain. The half-life of the drug is about 5.5 hours and oral dose is 50 to 100 mg every 4 to 6 hours. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of tramadol is desirable. The 3^2 full factorial design was employed for formulation of tramadol hydrochloride tablets. Sodium bicarbonate was incorporated as a gas-generating agent. The concentration of sodium bicarbonate required for optimum floating ability was finalised by 3^2 full factorial design along with HPMC K4M independent variable. Combination of polymers hydroxy propyl methyl cellulose (HPMC) grade K4M and hydroxy propyl cellulose (HPC) was used to achieve sustained release effect. The concentration of polymers was considered as the independent variables and dependent variables were floating time, drug content of formulation, and % drug release after 10 hours, swelling index and hardness of the tablets. The drug-excipient compatibility was studied with the help of Infrared-red spectroscopy. In vivo drug release pattern was studied using the X-ray radiographic technique. From the factorial batches, it was observed that formulation containing combination of 10% sodium bicarbonate and 10% citric acid shows optimum floating ability whereas the formulation containing 75 % HPMC K4M and 50% HPC shows optimum sustained drug release pattern with adequate floating. X ray study of the optimised formulations showed gastroretention for 6 hrs indicating successful floating GRDDS of tramadol HCl.

KEYWORDS:-Tramadol hydrochloride, Floating tablets, Optimization, HPMC K4M, Sodium bicarbonate, Hydroxy propyl cellulose.

[I] INTRODUCTION

Gastro retentive drug delivery system is commonly employed for the formulation of controlled release drug delivery in stomach. Among the various approaches for formulating the gastro retentive drug delivery system, floating system is one of the most commonly used. Floating system involves the gas forming agent that helps in keeping the formulation in buoyant state and hence avoids its passage stomach facilitating the controlled release of drug from formulation. [1]

Tramadol is a centrally acting analgesic with a low affinity for opioid receptors [2]. Tramadol is a synthetic codeine analogue that is a weak m-opioid receptor agonist. Part of its analgesic effect is produced by inhibition of uptake of norepinephrine and 5-hydroxytryptamine. In the treatment of mild-to-moderate pain, tramadol is as effective as morphine or meperidine. The half life of the drug is about 4-5 hours and the approximate equianalgesic dose is 50-100 mg for every 4-6 hours. Hence to reduce the

frequency of administration and to improve the patient compliance, the sustained release preparation of tramadol hydrochloride is preferred over the conventional formulation. Tramadol hydrochloride is freely soluble in water; hence release retarding polymers such as HPMC K4M, eudragit L-100 and Guar gum plays an important role in controlling the release of tramadol from the formulation [3, 4].

The floating of the formulation can be achieved by incorporating gas generating agent such as sodium bicarbonate. But the concentration of sodium bicarbonate not only affects the floating ability but also affects the release pattern of drug. The trial batches were conducted to finalise the concentration of sodium bicarbonate but it was observed that addition of 10% citric acid assists in increasing floating ability as well as sustained release effect. Hence to obtain an optimised formulation with good floating and sustained release effect, the factorial design was employed using concentration of sodium bicarbonate and HPMC K4M as independent variables. Second factorial design was employed for optimising the concentration of polymers (HPMC K4M and HPC) in combination to achieve optimum sustained release effect keeping the concentration of sodium bicarbonate and citric acid constant. HPMC K4M was used as a common polymer in both factorial designs because it is commonly used for formulation of floating tablets [5]. Hence to obtain the adequate floating and sustained drug release, mixture of polymers in various concentrations were utilised using 3^2 full factorial design. The objective of the present study was to find out the concentration of sodium bicarbonate as well as individual polymer to obtain floating GRDDS using gas forming agent and to confirm this by using the in vivo (x ray) technique [6].

[II] MATERIALS AND METHODS

2.1. Materials

Tramadol hydrochloride was provided as a gift sample from JCPL, Jalgaon and hydroxy propyl methyl cellulose K4M and hydroxy propyl cellulose were obtained as a gift sample from Vapi Care Pharma Pvt Ltd. Vapi. Other excipients and chemicals were of analytical grade and purchased from Pure Chem. Laboratories, Pune.

2.2. METHODS

Experimental design:

A 3^2 level full-factorial design includes 9 full-factorial design points; according to the model, total 9 experiments were conducted. This design involves dependent variables and independent or controlled variables X1 and X2. In the present study, two different experiments were conducted considering concentration of sodium bicarbonate, HPMC K4M and HPC as independent variables. In first experiment, the independent variables were concentration of sodium bicarbonate (X1) and concentration of HPMC K4M (X2), whereas in the second experiment concentration of HPMC K4M (Y1) and concentration of HPC (Y2) were considered as the independent variables. The dependent variables were Z1, percent drug release after 10 hours, Z2; hardness, Z3; swelling index, Z4; % drug content, Z5; floating time.

Preparation of Tramadol HCl tablets:

The trial batches were prepared using various concentrations of the sodium bicarbonate and the concentration of sodium bicarbonate and polymers for the factorial design were finalised based on the evaluation of trial batches. In preliminary study, sodium bicarbonate was used in range of 8-50% concentration as floating agent. Citric acid (10%) was used in combination with sodium bicarbonate in all batches. In trial batches, HPMC K4M was used as a controlled release polymer and the effect of concentration of polymer and gas forming agent on floating ability and release pattern was found out. The tablets of trial batches weighing 400 mg each were prepared by direct compression method using 8 station rotary press tablet compression machine using the formulae as shown in table 1.

Ingredient	Trial batches								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Tramadol HCl	100	100	100	100	100	100	100	100	100
Sodium Bicarbonate	200 (50%)	120 (30%)	120 (30%)	60 (15%)	80 (20%)	32 (8%)	40 (10%)	40 (10%)	40 (10%)
Citric Acid	-	-	40 (10%)	60 (15%)	40 (10%)	40 (10%)	40 (10%)	40 (10%)	40 (10%)
HPMC K4M	75	90	75	100	150	150	-	100	100
HPC	-	-	-	-	-	-	150	100	75
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Mannitol	20	80	60	75	25	73	65	15	40
Tablet weight	400	400	400	400	400	400	400	400	400

*All the weights are in mg.

Table 1. Tablet Formulations for Preliminary Trials

From the trial batches, the 3^2 full factorial design (table 2) was employed to optimise the concentration of sodium bicarbonate.

Batch code*	Variable Level in Coded Form	
	X1	X2
F1/H1	-1	-1
F2/ H2	-1	0
F3/ H3	-1	+1
F4/ H4	0	-1
F5/ H5	0	0
F6 / H6	0	+1
F7/ H7	+1	-1
F8/ H8	+1	0
F9/ H9	+1	+1

* Where batch code 'F' represents formulation of $NaHCO_3$ and HPMC K4M whereas Batch code 'H' represents formulation of HPMC K4M and HPC.

Table 2: 3^2 Full Factorial Design for the preparation of batches

a) Independent Variables $NaHCO_3$(X1) and HPMC K4M(X2)

Coded levels	Actual Values(mg)	
	X1	X2
-1	32	150
0	40	175
+1	48	200

b) Independent Variables HPMC K4M (Y1) and HPC (Y2)

Coded levels	Actual Values(mg)	
	Y1	Y2
-1	50	50
0	75	75
+1	100	100

Table 3: Levels of investigated variables

Depending on the results of the trial batches, tablets were prepared using the factorial design as shown in table 2 and 3. All the batches were evaluated for various parameters and the formulations showing optimised results were found out. The concentration of sodium bicarbonate (10%) and citric acid (10%) was finalised and the factorial design was applied to find out the optimised formulation containing HPMC K4M and HPC. Magnesium stearate (5 mg) was used in each formulation for the purpose of lubrication. The polymers were added in the formulation as specified in the factorial design. All the ingredients were uniformly mixed in powder form in the polythene bag and the resultant powder mixture was compressed in the 8-station rotary press tablet compression machine. The tablets were round and flat with an average diameter of 9 mm and a thickness of 5 mm.

Evaluation of powder blend:

The powder blend used for preparation of tablets was evaluated for angle of repose, and compressibility index.

Angle of repose:

The angle of repose is a relatively simple technique for estimation of the flow property of a powder. Powders with low angle of repose are

free flowing and those with a high angle of repose are poorly flowing powders [7].

10 gm of powder was passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:-

Angle of repose (θ) = $\tan^{-1}$ (height /radius) (1)

The angle of repose less than 30^0 usually indicate a free- flowing material and more than 40^0 suggests a poorly flowing material [8].

Carr`s compressibility index:

The Carr's compressibility index was calculated by calculating the tapped and bulk density using the 100 ml measuring cylinder. Compressibility is calculated by the formula.

Carr`s compressibility index = (TBD-LBD)/TBD X100 (2)

Where, TBD is tapped bulk density and LBD is loose bulk density. A carr`s index greater than 25 is considered to be an indication of poor flowability, and below 15, of excellent flowability. [9]

Evaluation of tablets:

All the formulations were evaluated for various parameters such as hardness, friability, weight variation, % drug content, buoyancy lag time, swelling index, in-vitro drug release, release experiments, IR spectroscopy and optimised formulation were evaluated for in-vivo study.

Hardness:

Hardness of tablets was determined using monsanto hardness tester.

Friability:

For each formulation, the friability of 20 tablets was determined using the Roche friabilator. In this test tablets were subject to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighted 20 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 mins. The tablets were then dusted and reweighed. Percent friability (%F) was calculated as follows,

% F= (loss in weight / initial weight) x 100 (3)

Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable [8, 9].

Thickness:

Thickness of all tablets was measured using a vernier calliper.

Weight variation:

The weight of 20 tablets was taken on electronic balance and the weight variation was calculated. The weight variation tolerance allowed for tablet weighing 324 mg and more is 5% [8].

Drug content:

To calculate the drug content, the tablets were triturated in the morter. Ten milligrams of the tablet powder was added to 10 ml of distilled water and drug solution was filtered through Whatman paper no.1. The sample was analyzed for drug content by UV spectrophotometry (Varian Cary 100) at 270 nm after suitable dilutions. Drug stability in the 0.1 N HCl and distilled water was checked using UV spectrophotometry for a period of 10 hours.

Buoyancy Studies:

In vitro buoyancy was determined by buoyancy lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Swelling index:

The swelling index of the tablets was calculated in order to find out the swelling ability of the tablets. For calculating the swelling index, the previously weighed tablets were placed in the 100 mL beaker containing 0.1 N HCl. The tablets were removed at the time interval of 1 hr for 8 hours and weighed. The swelling index of the tablets can be measured by studying its dimensional changes, weight gain or water uptake. Hence swelling index was calculated by the formula;

Swelling index= (Wt-Wo) X 100/Wo (4)

Where, Wt= Final weight of tablets at time 't' ;Wo= Initial Weight of tablets. [7]

In Vitro Dissolution Studies:

The release rate of tramadol HCl from floating tablets was determined using *United States Pharmacopeia (USP)* 24 dissolution testing apparatus 2 (paddle method). The dissolution

test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 60 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus hourly for 10 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 270 nm using double beam UV spectroscopy. Cumulative percentage drug release was calculated using PCP disso software.

Kinetic Modelling of Drug Release:

The dissolution profile of all the batches was fitted to zero order, first-order, matrix, Hixon-Crowell, Korsemeyer and Peppas to ascertain the kinetic modelling of drug release. The kinetic modelling was found out by employing the PCP disso v3 software. [10]

Stability Study:

Stability studies were conducted on the optimized tablet batches (E2 and G4) to assess their stability after storage. They were packed in Alu – Alu pouches and stored under the storage conditions of 25°C ± 2°C temperature and 60% ± 5% relative humidity and the accelerated stability study was conducted under storage conditions of 40°C ± 2°C temperature and 75% ± 5% relative humidity for a period as prescribed by ICH guidelines. The tablets were withdrawn after a period of 7, 14 days, 1, 2, 3 and 6 months and analyzed for physical characterization (Visual defects, dissolution and FTIR) and percentage assay.

Infrared (IR) spectroscopy:

The drug excipient compatibility and the drug polymer interaction were detected by the IR spectroscopic studies. The polymer- polymer compatibility is also found out by the IR spectroscopic studies.

In-vivo study:

X- Ray technique was used to determine the gastric residence time of the tablets. Floating tablets of the formulation F6 and H4 were selected for in vivo gastro intestinal residence time studies. The tablets were prepared by replacing barium sulphate (5%) with mannitol. For in vivo testing healthy volunteers were selected. Volunteer was asked to swallow the tablet with sufficient water after meal in the afternoon under the supervision of registered doctor. This was noted as zero time reading. The successive images were then recorded at regular intervals over a period of 6 hours. The X-ray of the tablet in the volunteers was recorded at intervals of 1, 2, 4 and 6 hours.

Optimization Data Analysis and Validation of **Optimization Model:**

Various RSM computations for the current optimization study were performed employing Design Expert software (Version 8.0.2, Stat-Ease Inc, Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as Equation 5.

$$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X1X2 + \beta 4X1^2 + \beta 5X2^2 \quad (5)$$

Where, β0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β1 to β5 are the coefficients computed from the observed experimental values of Y; and X1 and X2 are the coded levels of the independent variable(s). The terms X1X2 and Xi 2 (i = 1 to 2) represent the interaction and quadratic terms, respectively. Statistical validity of the polynomials was established on the basis of ANOVA provision in the design expert software. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations. Also, the 3-D response surface graphs and 2-D contour plots were constructed in MS-excel environment using the output files generated by the design expert software. Eight optimum checkpoints were selected by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The formulations corresponding to these checkpoints were prepared and evaluated for various response properties. Subsequently, the resultant experimental data of response properties were quantitatively compared with that of the predicted values. Also, linear regression plots

between observed and predicted values of the response properties were drawn using MS-excel, forcing the line through origin. [11, 12]

[III] RESULTS

3.1. Preliminary trial batches:

The various trial batches were conducted to optimise the concentration of $NaHCO_3$ (Table 1).

Trial batches were evaluated for parameters such as buoyancy lag time and % drug release after 8 hours. Formulations 50% and 30% of sodium bicarbonate alone did not show any floating whereas formulation containing 30% sodium bicarbonate alongwith 10% citric acid showed floating but failed to give sustained release effect in spite of presence of HPMC K4M. Further it was observed that formulation containing 15% concentration each of sodium bicarbonate and citric acid as well as formulation containing 20% of sodium bicarbonate and 10% citric acid showed immediate floating but failed to give controlled release pattern and dissolved completely within 5 mins. Formulation containing 8% sodium bicarbonate showed good sustained release property but failed to give immediate floating effect. Further trial batches were conducted using HPMC K4M and HPC keeping concentration of NaHCO3 constant (Table 1). It was observed that formulation containing 150 mg HPC without HPMC K4M showed floating within 5 mins but formulation dissolved within 15 mins. Batches containing 100mg and 75mg HPC along with 100 mg HPMC K4M showed satisfactory floating and release pattern. From the trial batches, it was observed that 8-12% sodium bicarbonate was sufficient to give good buoyancy to the formulations. As HPMC is most commonly used sustained release polymer, it was incorporated along with sodium bicarbonate in all formulations to produce a sustained release floating drug delivery system.

3.2. Evaluation of powder blend (F1-F9 and H1-H9):-

Angle of repose: Angle of repose of all the powder blends was obtained within the range of $20\text{-}30^0$. This indicates that all the powder blends shows good flow property. [8]

Carr's compressibility index: The compressibility index of all the powder blends was obtained below 10. The compressibility index indicates the good flowability of the powder blend. (7)

3.3. Evaluation of tablets:

Formulation no.	% drug release within 10 Hours	Time required for 50% drug release (t_{50}) (mins)	%Drug Content	Swelling Index	Buoyancy Lag Time (mins)	Hardness (Kg/cm^2)	Best fitting model
F1	83.48	5.4	99.04	193.24	2.15	8.6	Peppas
F2	81.69	4.45	97.56	203.01	2	9.6	Hix.crow
F3	100	0.25	96.01	-	dont float	8.8	
F4	78.69	4.5	101.90	181.39	2	11.2	Matrix
F5	80.44	6	97.98	206.21	1.30	10.4	Peppas
F6	80.51	4.5	101.44	221.25	1	8.6	Hix.crow
F7	76.15	4.55	98.70	185.67	1.30	9.8	First order
F8	78.08	4.5	102.87	206.17	0.45	10.4	First order
F9	75.73	4.45	101.67	222.05	0.55	9.8	First order

Table 4. Evaluation results of formulations F1-F9

Formulation no.	% drug release within 10 Hours	Time required for 50% drug release (t_{50}) (mins)	%Drug Content	Swelling Index	Buoyancy Lag Time (mins)	Hardness (Kg/cm^2)	Best fitting model
H1	78.02	3.4	98.64	152.59	0.50	9.4	Peppas
H2	72.30	5.35	96.13	175.81	1	9.8	Peppas
H3	75.52	5.5	97.21	184.04	1-1.5	10.2	Peppas
H4	82.25	4.4	102.64	183.87	1	9.6	Peppas
H5	73.92	5.3	101.64	200.25	0.45	8.0	First order
H6	78.36	4	99.01	222.16	1.30	8.4	First order
H7	77.71	4.55	95.93	202.48	5	8.6	First order
H8	72.922	5	99.44	225.75	1.40	7.8	First order
H9	73.26	4.5	100.64	227.82	2	7.6	First order

Table 5. Evaluation results of formulations H1-H9

3.3.1. Hardness

Hardness of the formulations F1-F9 was observed within the range of 8.6-11.2 kg/cm^2 as shown in table 4 and 5. The hardness of H1-H9 was found between 7.6-10.2 kg/cm^2.

3.3.2. Friability

Friability of the tablets was observed below 0.30% for all batches which was in the acceptable limit.

3.3.3. Thickness

The thickness of all the tablets was found within the range of 5 ± 2 mm.

Weight variation: The weight of all the tablets was found within the range of 400 mg ± 5mg. Hence the weight of all formulations was found within the limit [8].

3.3.4. Drug content

The range of % drug content of the formulations F1-F9 was found between 96.01 and 102.87, whereas in the batches H1-H9, the % drug content was found in the range of 95.93-102.64.

The tablets showed hardness, friability, thickness, weight variation and % drug content within the limit. The in-vitro buoyancy study shows that all the formulations shows good floating property.

3.3.5. In Vitro Buoyancy Studies

The in-vitro buoyancy study showed the good floating ability of the tablets as shown in the table 4 and 5. Buoyancy lag time indicates the time required for the formulation to float in the medium. From table 4, it was observed that formulations F1 and F2 shows comparatively more floating time as compared to other formulations. It was further observed that formulation F3 shows no floating as well as immediate dissolution of tablet. This indicates that higher concentration of $NaHCO_3$ affects the release pattern of drug from formulation whereas lower concentration (less than 10%) alone fails to float within a minute.

3.3.6. Swelling index

From the swelling index study of all the batches, it was observed that the increase in the concentration of polymers increases the swelling property of the tablets as shown in table 4 and V. Further the formulation containing optimized swelling index was obtained. From the formulation batches, it was observed that the formulations F9 and H9 showed maximum swelling index.

3.3.7. In Vitro Dissolution Studies

The drug release patterns from all the formulations are shown in tables IV and V. The percent drug release after 10 hours is as shown in figure 1 and 2.

Fig: 1. % Drug release profile of drug from formulation containing NaHCO3 and HPMC K4M.

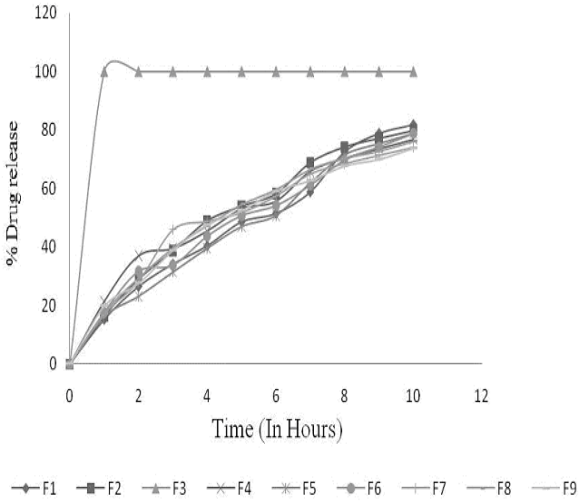
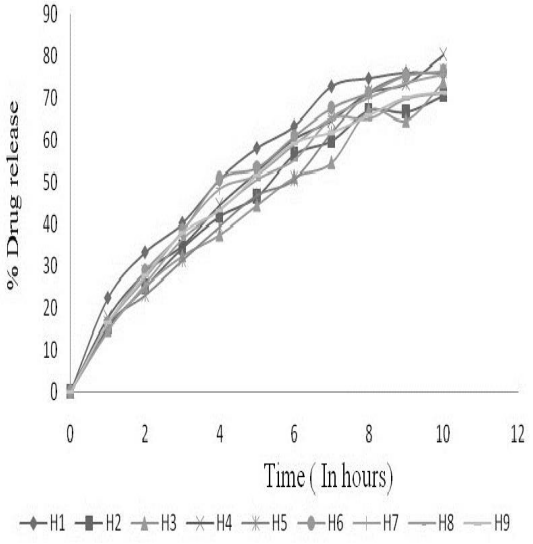


Fig: 2. % Drug release profile of drug from formulation containing HPMC K4M and HPC.



From the drug release profile of F1-F9, it was that formulations containing 8% $NaHCO_3$ shows rapid drug release whereas formulations containing 12% $NaHCO_3$ shows slow drug release. This indicates that $NaHCO_3$ affects the drug release pattern. Formulations F4-F6 shows satisfactory drug release pattern. It was further observed that the drug release was retarded from the formulations containing more concentration of HPMC K4M.

The drug release profile of formulations H1-H9 indicates that as the concentration of polymer increases, the drug release was retarded. From the comparison of release profile of both all the batches, it was observed that the formulations containing combination of polymers shows more retardation in drug release in less concentration as compared to HPMC K4M alone. This indicates that combination of polymers are more efficient in formulating the sustained release dosage form.

3.3.8. Kinetic Modelling of Drug Release

From the kinetic modelling study, it was observed that most of the formulations showed Peppas and first order model as best fitting model. Hixson-Crowell and Matrix models were also observed as the best fitting in some formulations. The equations of the best fitting model are as follows:-

Korsmeyer and Peppas model : $F=kt^n$ (6)

First order: $\ln F = k X t$ (7)

Hixson and Crowell powder dissolution method: $F=100 (1-(1-kt)^3)$ (8)

Higuchi Matrix: $F=k\sqrt{t}$ (9)

where F is the fraction of drug release, k is the release constant, t is the time and n is diffusional coefficient.

From the in-vitro dissolution studies and the response surface curves, it was observed that the drug release pattern was influenced by the variation in the concentration of gas forming agent as well as polymers. When kinetic modelling was fitted to batch F6 Hixon-Crowell type of release pattern shows fair linearity with regression value of 0.9949 indicating that drug release mechanism from this formulation was diffusion controlled.

H4 follows Peppas type of release pattern this indicates that the release mechanism is not well known or more than one type of release phenomena is involved as fickian diffusion (Higuchi Matrix), anomalous transport, zero order release. None of the formulations fit into zero order equation indicating that the dissolution rate of drug is independent of the amount of drug available for dissolution and diffusion from the tablets.

RSM Optimization:

Equations of the formulations containing $NaHCO_3$ and HPMC K4M (F1-F9):

Mathematical modelling mathematical relationships generated using MLRA for the studied response variables are expressed as Equations 10 and 11.

Dissolution Profile = 79.98 -3.08A+0.20B (10)

Swelling index = 188.76 +34.6A-21.17B+59.9AB^2 (11)

Where, X1 and X2 represents the effect of variables i.e. concentration of NaHCO3 and HPMC K4M respectively.

All the polynomial equations were found to be statistically significant ($P < 0.01$), as determined using ANOVA, as per the provision of Design Expert software. The Model F-value of 24.98 in equation VI implies the model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A are

significant model terms. The Model F-value of 4.58 implies the model is significant.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case AB are significant model terms. (equation 11). The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response.

Equations of the formulations containing HPMC K4M and HPC (H1-H9):

Mathematical modelling expressing the effect of concentration of HPMC K4M and HPC are given in Equations 12 and 13.

Dissolution Profile = 74.38 -0.42A -1.71B-0.34AB-2.79A^2+4.90B^2 (12)

Swelling index = 198.30 +24.30A+16.21B (13)

Where A represents the concentration of HPMC K4M and B represents the concentration of HPC.

While considering the dissolution profile, the model F- value of 15.74 implies the model is significant. Values of " Prob> F" less than 0.0500 indicate model terms are significant. In this case B, A2, B2 are significant model terms.

While considering the swelling index, The Model F-value of 101.60 implies the model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.

Study of Dissolution profile by Response **Surface Methodology:**

From the response surface plot and contour plot, it was observed that the concentration of sodium bicarbonate affects the drug release pattern. The optimum drug release profile was obtained with 10% concentration of sodium bicarbonate (figure 3).

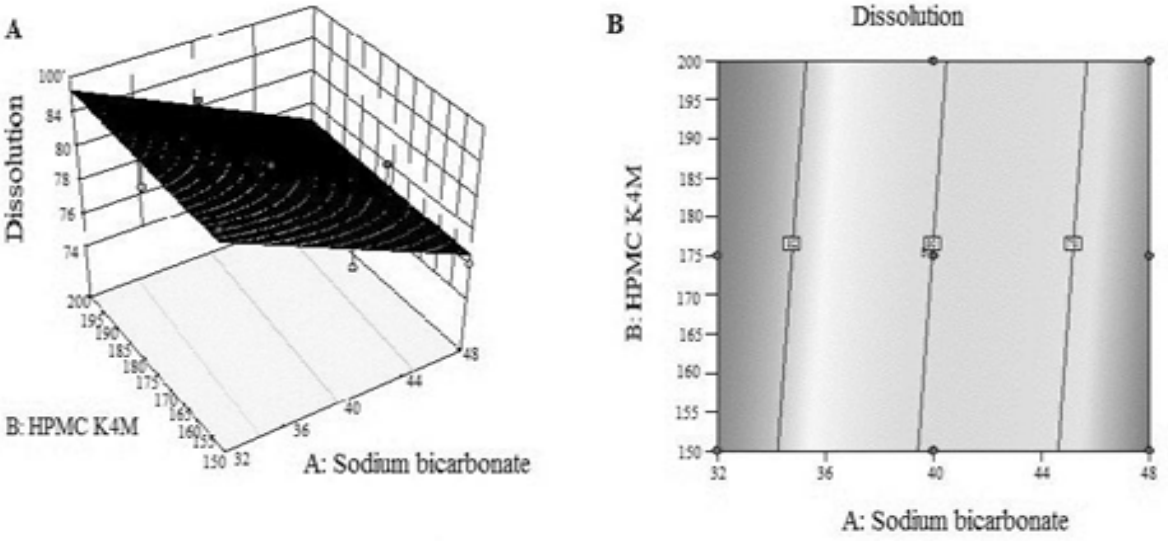


Fig: 3. (A) Response Surface plot showing the influence of NaHCO3 and HPMC K4M on dissolution profile and (B) Corresponding contour plot showing the relationship between various levels of 2 polymers.

Figure 4 shows the combined effect of polymers on drug release pattern. The plots indicates that optimum drug release pattern was obtained with formulation containing 75mg HPMC K4M and minimum concentration (50mg) of HPC.

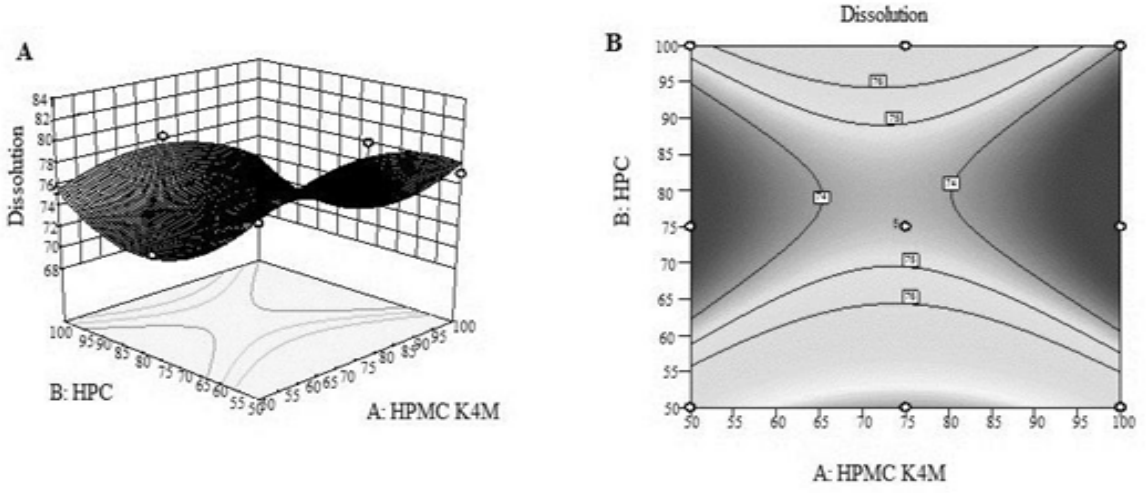


Fig: 4. (A) Response surface plot showing the influence of HPMC K4M and HPC on dissolution profile and (B) corresponding contour plot showing the relationship between various levels of two polymers.

Study of swelling index by Response Surface Methodology:

Figure 5 shows the profound effect of concentration of the sodium bicarbonate and HPMC K4M on the swelling index of the formulation. The counter plot clearly indicates that the swelling index is increased with decrease in concentration of HPMC K4M and increase in concentration of sodium bicarbonate. (Equation 11)

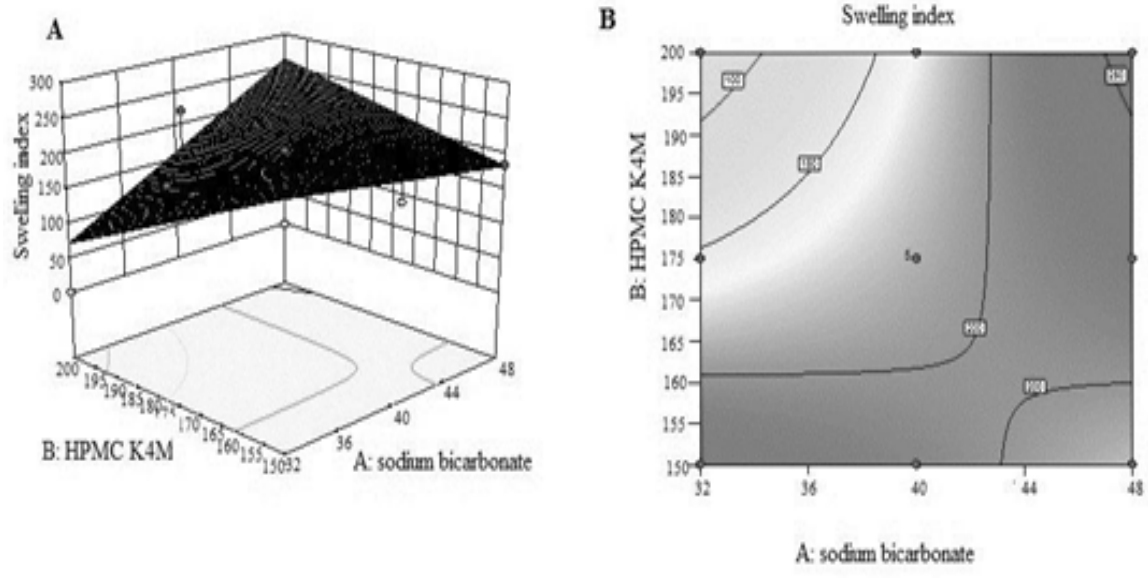


Fig: 5. (A) Response Surface plot showing the influence of NaHCO3 and HPMC K4M on swelling index and (B) Corresponding contour plot showing the relationship between NaHCO3 and HPMC K4M.

Figure 6 indicates the effect of HPMC K4M and HPC on swelling index of the formulation. Figure 6 (B) shows that swelling index of formulation increases with increase in concentration of both the polymers. Hence polymer concentration was found responsible for the swelling index of the formulations. This can be illustrated from equation 13.

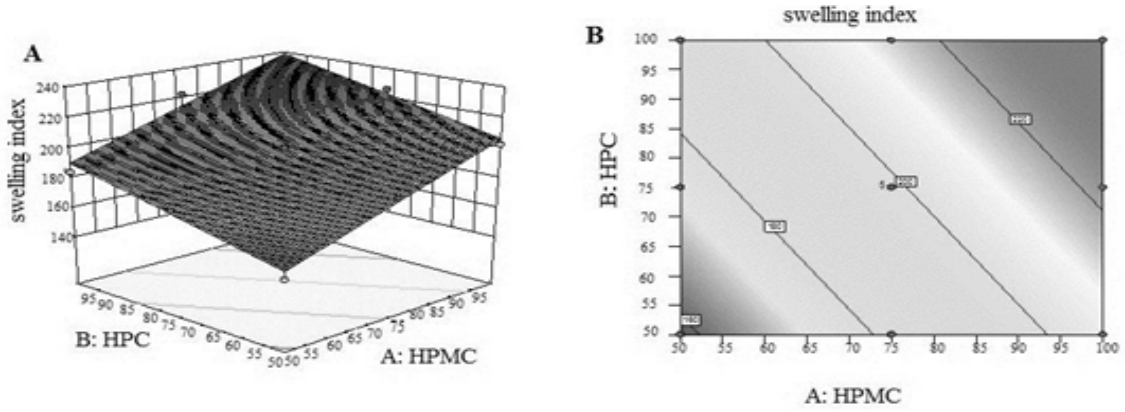


Fig: 6. (A) Response surface plot showing the influence of HPMC K4M and HPC on swelling index and (B) corresponding contour plot showing the relationship between various levels of two polymers.

From the formulations containing sodium bicarbonate and HPMC K4M, it was observed that the optimised floating and drug release profile was obtained with the formulations containing 10% sodium bicarbonate. Formulation F6 was found the optimised batch.

From the swelling index study of F1-F9, it was observed that formulations containing low concentration of HPMC K4M shows more swelling index. It was further observed from the contour graph that sodium bicarbonate also affects the swelling index of the formulation. Increased concentration of sodium bicarbonate resulted in more swelling of formulations. From formulations H1-H9, it was observed that there is linear relationship between swelling index and concentration of polymers. Maximum swelling index was observed with H9 containing maximum concentration of both the polymers.

3.3.9. Infrared (IR) spectroscopic study of the formulation:

Figure 7 shows the Infrared spectroscopic scan of tramadol hydrochloride mixed with KBr. The IR scan shows prominent peaks for the various active groups such as 3551 cm^{-1} corresponding to the N-H stretch in the tertiary amino group, the intense peak 1287 corresponding to the C-O stretch of ether group, 1457 cm^{-1} corresponding the C-O stretch between phenolic C and O group.

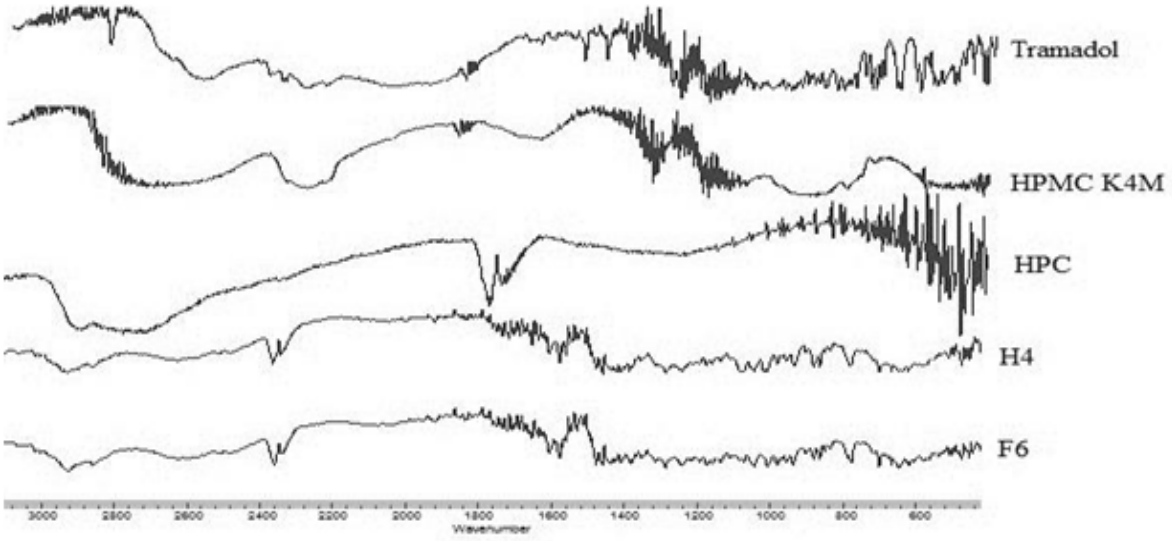


Fig: 7. IR Spectroscopic study of drug, polymer and formulations.

The formulations containing the polymers showed all the prominent peaks of tramadol HCl with no change in the intensity of the peaks. This indicates that there is no interaction

between the excipient and drug that can affect the efficacy of drug.

Stability study:

There was no significant difference in floating time, % drug content and amount of tramadol hydrochloride released from E2, and G4 after storing for 6 months at normal conditions and for 3 month at 40^{o} C temperature 75 % relative humidity.

3.3.10. In-vivo study

In vivo evaluation was carried out in fed state. The behaviour of tablet was studied in 2 volunteers in real time using radiographic imaging technique. Figure 8 (a) and 9 (a) shows x rays of tablets F6 and H4 respectively, taken 1 hour after administration of tablets. Tablet can be seen in stomach. Next image Figure 8 (b) and 9 (b) taken at 2 hours shows change in position of tablet, this shows that tablet did not adhere to gastric mucous. Also swelling of the tablet can be visualized.

Figure 8(d) and 9 (d) shows the position of tablets in stomach after 6 hours. This indicates that the tablets remained afloat in stomach till 6 hours.

The amount of barium sulphate was sufficient to ensure visibility by X- ray and at the same time was low enough to enable tablets to float. It can be seen that these tablets had density greater than tablets from formulations F6 and H4 and they had floating lag time of 230 and 300 seconds respectively. But the tablets containing $BaSO_4$ were identical with tablet formulation E2 and G4 in regards of other ingredients, their quantities and hardness.

From the x-ray study, it was observed that the tablets remained afloat in stomach till the time period of 6 hrs. Both the tablets remained intact within the stomach, this shows that sustained release pattern of drug from the formulation was observed. This indicates the successful floating gastroretentive drug delivery of tramadol HCl.

[IV] DISCUSSION

From the trial batches, it was observed that 8-12% $NaHCO_3$ was sufficient to give good buoyancy to the formulations. From the evaluation of powder blends, it was observed that all the powder blends shows good flow property.

From the in vitro buoyancy studies, it was observed that higher concentration of $NaHCO_3$ affects the release pattern of drug from formulation whereas lower concentration (less than 10%) alone fails to float within a minute. The in-vitro buoyancy study shows that 10% concentration of $NaHCO_3$ and citric acid are optimum to give good floating property to the tablets.

From the swelling index study of F1-F9, it was observed that formulations containing low concentration of HPMC-K4M shows more swelling index. It was further observed from the contour graph that $NaHCO_3$ also affects the swelling index of the formulation. From formulations H1-H9, it was observed that there is linear relationship between swelling index and concentration of polymers. Maximum swelling index was observed with H9 containing maximum concentration of both the polymers.

From the in-vitro dissolution studies and the response surface curves, it was observed that the drug release pattern was influenced by the variation in the concentration of gas forming agent as well as polymers. The Infrared studies show that there is no interaction between the excipient and drug that can affect the efficacy of drug.

From the x-ray study, it was observed that the tablets remained afloat in stomach till the time period of 6 hrs. Both the tablets remained intact within the stomach, this shows that sustained release pattern of drug from the formulation was observed. This indicates the successful floating gastroretentive drug delivery of tramadol HCl.

CONCLUSION:

Regulated drug release attained in the current study indicates that the matrix tablets of tramadol hydrochloride, prepared using various polymers, can successfully be employed as a once-a-day oral controlled release drug delivery system. High floating ability of the formulation is likely to increase its GI residence time, and eventually, improve the extent of bioavailability. However, appropriate balancing between various

levels of the 2 polymers is imperative to acquire proper controlled release and flotation of the formulation. High degree of prognosis obtained using RSM corroborates that a 2-factorial design is quite efficient in optimizing drug delivery systems that exhibit nonlinearity in response(s). Formulation F6 (containing 40 mg NaHCO3 and 200 mg HPMC K4M) and H4 (containing 75 mg HPMC K4M and 50 mg HPC) shows good in vitro as well as in vivo gastroretentive floating drug delivery of tramadol HCl.

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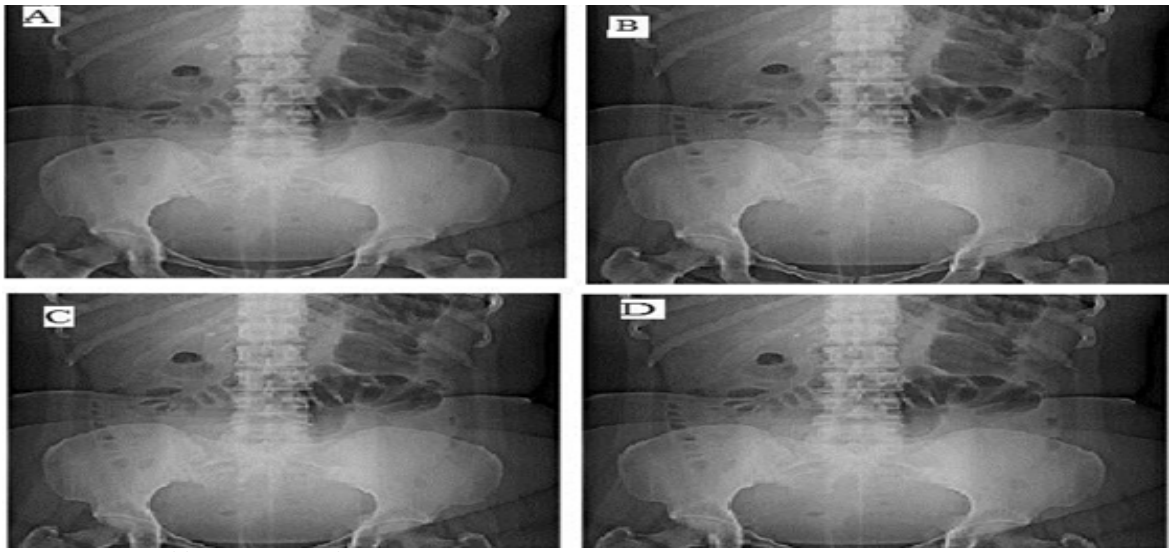

Fig: 8. X-Ray of formulation F6 after time interval (A) 1 hr; (B) 2 hrs; (C) 4 hrs; (D) 6 hrs

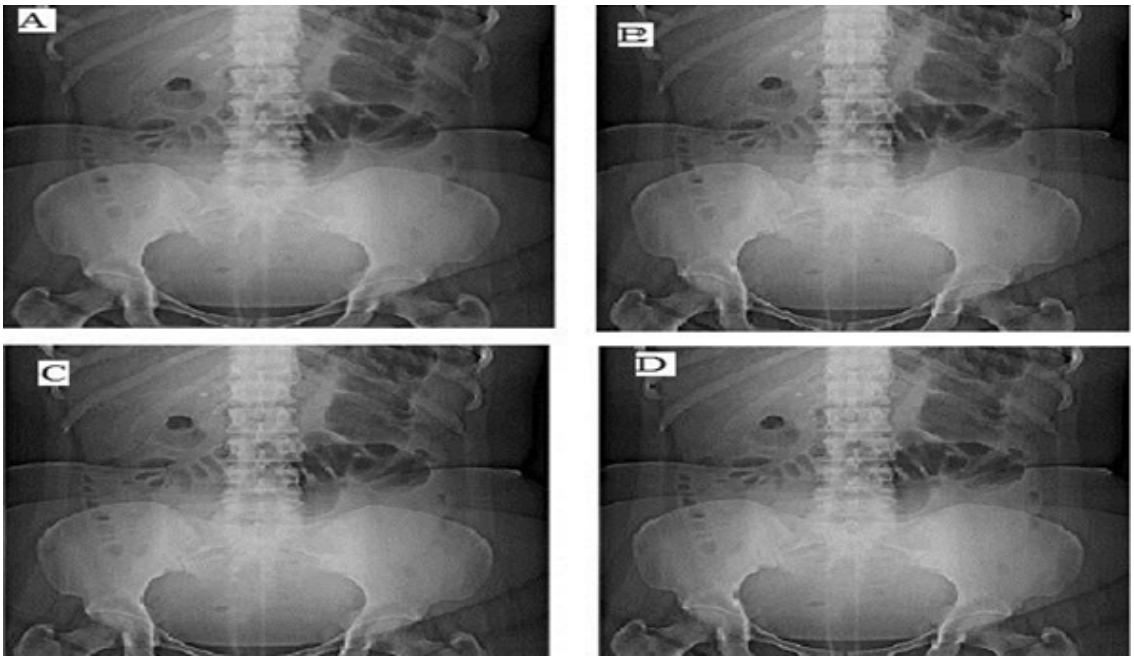

Fig: 9. X-Ray of formulation H4 after time interval (A) 1 hr; (B) 2 hrs; (C) 4 hrs; (D) 6 hrs