DESIGN, DEVELOPMENT AND EVALUATION OF FLOATING TABLETS OF TAPENTADOL HYDROCHLORIDE USING CHITOSAN

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ABSTRACT

The aim of the present study was to study effect of Xanthan gum and Chitosan in combination on effervescent floating matrix tablet of water soluble analgesic drug. Tapentadol hydrochloride. Tapentadol 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 4 hours and oral dose is 50 to 250 mg twice a day. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Tapentadol is desirable. The 3^2 full factorial design was employed to study effect of Xanthan gum and Chitosan in combination on Tapentadol hydrochloride floating tablets. Sodium bicarbonate was incorporated as a gas-generating agent. Combination of polymers Xanthan gum and Chitosan was used to retard drug release. The concentration of polymers was varied and their effect on floating time, drug content, % drug release after 8 hours, swelling index and hardness of the tablets was studied. The formulation was evaluated using Infrared-red spectroscopy and Differential Scanning Calorimetry to study drug-excipient compatibility. From the factorial batches, it was observed that formulation containing combination of 20% sodium bicarbonate and 10% citric acid shows optimum floating ability whereas the formulation containing 20% Xanthan gum and 28% Chitosan shows optimum sustained drug release pattern. X ray study of the optimized formulations showed gastro retention for 6 hrs indicating successful floating GRDDS of Tapentadol HCl.

Keywords: Chitosan, Floating tablets, Optimization, Sodium bicarbonate, Tapentadol hydrochloride, Xanthan gum.

INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is filled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.[1] Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.[2]

These considerations have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. [3] Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines [4]. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of

these drugs. [5] Tapentadol is a centrally acting analgesic with a low affinity for opioid receptors. Tapentadol is a synthetic codeine analogue that is a weak mu-opioid receptor agonist. Part of its analgesic effect is produced by inhibition of uptake of nor epinephrine and 5-hydroxytryptamine. In the treatment of mild-to-moderate pain, Tapentadol is as effective as morphine or meperidine. The half life of the drug is about 4 hours and the

approximate equi-analgesic dose is 50-250 mg twice a day. Tapentadol is available in market as immediate release tablet for the treatment of acute pain. Hence for the treatment of chronic and moderate pain a floating controlled release formulation was prepared. Tapentadol hydrochloride is freely soluble in water; hence release retarding polymers such as Xanthan gum and Chitosan plays an important role in controlling the release of Tapentadol from the formulation [6, 7, 8].

MATERIALS AND METHODS

Materials

Tapentadol hydrochloride was procured from JCPL, Jalgaon. Xanthan gum and Chitosan were provided as a gift sample by Vapi Care Pharma Pvt Ltd. Vapi. Other excipients and chemicals were purchased from Pure Chem. Laboratories, Pune and of analytical grade.

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, experiment was conducted considering concentration of Xanthan gum and Chitosan as independent variables. The dependent variables were Y1, percent drug release after 8 hours, Y2; hardness, Y3; swelling index, Y4; floating lag time.

Preparation of Tapentadol HCl tablets

The trial batches were prepared using various concentrations of the sodium bicarbonate and polymers. The concentration of polymers for the factorial design was finalized based on the evaluation of trial batches. In preliminary study, sodium bicarbonate was used in range of 15-20% concentration as floating agent. Citric acid (10%) was used in combination with sodium bicarbonate in all batches. During trial, tablets containing 30-40% of Xanthan gum alone as well as 50-60% of Chitosan alone were prepared and evaluated for floating lag time and drug release pattern. The tablets of trial batches were prepared by direct compression method using 8 station rotary press tablet compression machine using the formulae as shown in table 1.

Table 1: Tablet Formulations for Preliminary Trials

Sr.no.	Ingredients	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12
1	Drug	50	50	50	50	50	50	50	50	50	50	50	50
2	Sod. Bicarbonate	60	60	60	70	60	40	50	50	50	50	50	50
3	Citric Acid	30	30	30	40	30	20	25	25	25	25	25	25
4	Xanthan Gum	-	40	40	40	70	-	-	-	30	40	50	50
5	Chitosan	150	110	100	90	80	180	180	100	70	60	50	70
6	Mannitol	5	5	15	5	5	5	-	20	20	20	20	-
7	Mg. Stearate	5	5	5	5	5	5	5	5	5	5	5	5
	Total Wt.(mg)	300	300	300	300	300	300	310	250	250	250	250	250

*All the weights are in mg.

From the trial batches, the 3^2 full factorial design (table 2) was employed to optimize the concentration of Xanthan gum and Chitosan.

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

Formulation No.	Coded levels	
	Variable 1	Variable 2
I	-1	-1
II	-1	0
III	-1	+1
IV	0	-1
V	0	0
VI	0	+1
VII	+1	-1
VIII	+1	0
IX	+1	+1

Table 3: Levels of investigated variables

	Coded levels		
Variables used	-1	0	+1
Xanthan Gum (mg)	40	50	60
Chitosan (mg)	60	70	80

Depending on the results of the trial batches, tablets were prepared using the factorial design as shown in table 2. All the batches were evaluated for various parameters and the formulations showing optimized results were found out. The concentration of sodium bicarbonate (20%) and citric acid (10%) was finalised and the factorial design was applied to find out the optimized formulation containing Xanthan gum and Chitosan. Magnesium stearate 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 [9].

Angle of repose

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 [10].

Carr's compressibility index

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

Carr's compressibility index = (TBDLBD)/ 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. [11]

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 optimized formulation were evaluated for in-vivo study.

Hardness

Hardness of tablets was determined using Monsanto hardness tester.

Friability

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 [10, 11].

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% I.P. [11].

Drug content

Ten milligrams of the tablet powder was added to 10 ml of 0.1N HCL and drug solution was filtered through Whatman paper no.1. The sample was analyzed for drug content by UV spectrophotometer (Varian Cary 100) at 272 nm after suitable dilutions.

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. [10]

In Vitro Dissolution Studies

The release rate of Tapentadol HCl from floating tablets was determined using United States Pharmacopeia (USP) dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 75 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus hourly for 8 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 272 nm using double beam UV spectroscopy.

Kinetic Modeling 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 modeling of drug release. The kinetic modeling was found out by employing the PCP disso v3 software. [13]

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 tablet of the formulation B5 was selected for in vivo gastro intestinal residence time studies. The tablet was prepared by replacing Drug (50mg) with Barium sulphate. For in vivo testing healthy volunteer was selected. Volunteer was asked to swallow the tablet with sufficient water 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 volunteer 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.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 \quad .... (5)$$

Where, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β_1 to β_5 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 [13, 14].

RESULTS

The various trial batches were conducted to optimize 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 containing 15% and 20% of sodium bicarbonate alone failed to float whereas formulation containing 20% sodium bicarbonate along with 10% citric acid showed good floating. It was observed that formulations containing 150 mg and 180 mg of Chitosan alone showed immediate floating but formulations dissolved within 1 hour. While formulations containing 90mg and 120mg of Xanthan gum alone showed floating within 5min and retardation of drug release for more than 8 hours. Hence combinations of these two polymers were used to get optimum floating ability and drug release. Formulation B5 showed optimum floating and release pattern.

Evaluation of powder blend (B1-B9):-

Angle of repose

Angle of repose of all the powder blends was obtained within the range of 20-30⁰. This indicates that all the powder blends shows good flow property. [11]

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 [10.]

Evaluation of tablets
Table 4: Evaluation results of formulations B1-B9

Formulation no.	% Drug release within 8 hrs.	% Drug Content	Swelling index	Buoyancy Lag Time (sec.)	Hardness (kg/cm²)
B1	98.39	98.60	275.7	49	7.3
B2	99.57	99.24	269.2	64	7.6
B3	99.10	97.89	283.5	52	8.0
B4	100.66	101.09	274.6	67	8.1
B5	102.59	101.80	298.0	60	7.4
B6	100.18	99.93	299.6	61	7.9
B7	98.34	99.56	288.7	73	7.3
B8	101.66	102.37	295.3	56	7.8
B9	100.17	101.46	303.6	76	7.6

Hardness

Hardness of the formulations B1-B9 was observed within the range of 7.3-8.1 kg/cm² as shown in table 4.

Friability

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

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 250 mg ± 5mg. Hence the weight of all formulations was found within the limit [11].

Drug content

The range of % drug content of the formulations B1-B9 was found between 97.89 and 102.37. The tablets showed hardness, friability, thickness, weight variation and % drug content within the limit.

In Vitro Buoyancy Studies

The in-vitro buoyancy study showed the good floating ability of the tablets as shown in the table 4. Buoyancy lag time indicates the time required for the formulation to float in the medium. From table 4, it was observed that formulations B7 and B9 shows comparatively more floating time as compared to other formulations. It was further observed that formulation B1 shows least floating time than others. This indicates that higher concentration of $NaHCO_3$ affects the release pattern of drug from formulation whereas lower concentration (less than 20%) alone fails to float within a minute.

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. Further the formulation containing optimized swelling index was obtained. From the formulation batches, it was observed that the formulations B9 showed maximum swelling index. Formulation B2 showed lowest swelling index.

In Vitro Dissolution Studies

The drug release patterns from all the formulations are shown in tables 4. The percent drug release after 8 hours is as shown in figure 1.
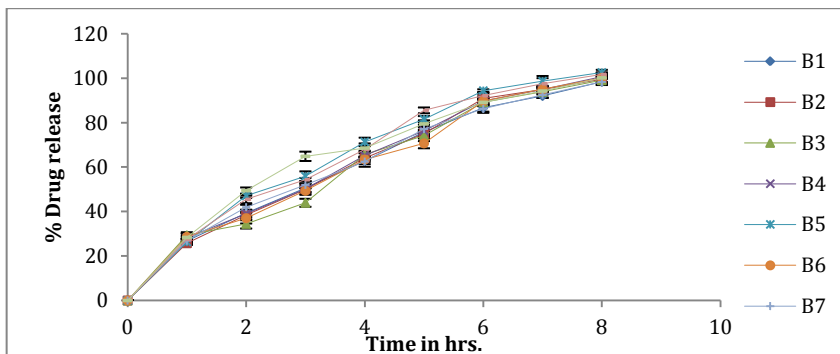

Fig. 1: % Drug release profile of drug from formulation containing Xanthan gum and Chitosan

The drug release profile of formulations B1-B9 indicates that as the concentration of polymers increases, the drug release decreases. From the comparison of release profile of all the batches, it was observed that the formulations containing combination of polymers shows retardation of drug release to greater extent than formulations containing single polymer. The batches B1, B2, B6 and B7 fail to comply with standards for drug release as mentioned for Modified release tablet in USP29.

Kinetic Modeling of Drug Release

From the kinetic modeling study, it was observed that all of the formulations showed Peppas as best fitting model. The equation of the best fitting model is as follows:-

Korsmeyer and Peppas model : F=ktn ……………….. (6)

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 polymers. When kinetic modeling was fitted to batch B5 Peppas type of release pattern shows fair linearity with regression value of 0.6739 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.

Table 5: Kinetic modeling of formulation (B1-B9)

Batch	n	k	Best fitting model
B1	0.6648	25.5012	Peppas
B2	0.7005	24.3969	Peppas
B3	0.6721	24.9256	Peppas
B4	0.6627	26.1460	Peppas
B5	0.6739	27.4041	Peppas
B6	0.6611	25.6446	Peppas
B7	0.6510	26.3374	Peppas
B8	0.6598	27.6942	Peppas
B9	0.6008	30.5068	Peppas

RSM Optimization

Equations of the formulations containing Xanthan gum and Chitosan (B1-B9):

Mathematical modeling mathematical relationships generated using MLRA for the studied response variables are expressed as Equation 07.

Swelling index = +288.62 +9.87*A +7.95*B……….. (07)

Where, A and B represents the effect of variables i.e. concentration of Xanthan gum and Chitosan 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 9.14 in equation (07) implies the

model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A and B, are significant model terms. 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.

Study of swelling index by Response Surface Methodology

Figure 2 shows the profound effect of concentration of the Chitosan and Xanthan gum on the swelling index of the formulation. The counter plot clearly indicates that the swelling index is increased with increase in concentration of Chitosan and Xanthan gum. (Equation 07)
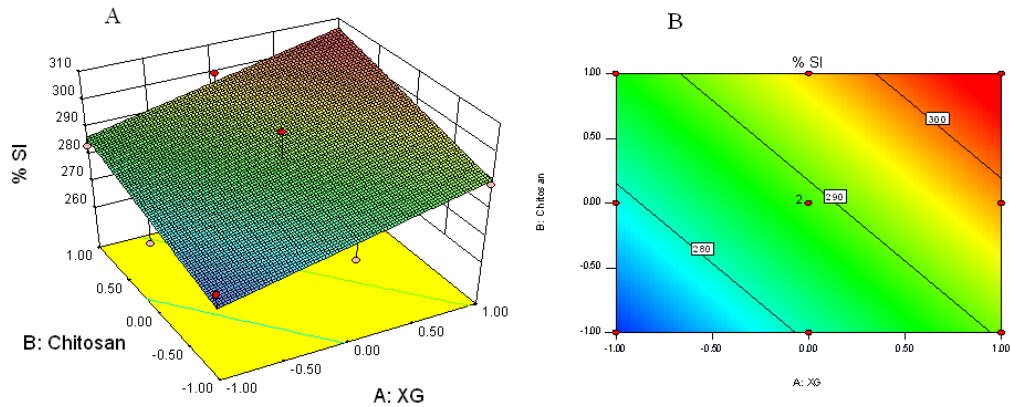
Fig. 2: (A) Response Surface plot showing the influence of Chitosan and Xanthan gum on swelling index and (B) Corresponding contour plot showing the relationship between Chitosan and Xanthan gum

From the formulations containing Chitosan and Xanthan gum, it was observed that the optimized floating and Swelling index was obtained with the formulations B5. From the swelling index study of B1-B9, it was observed that formulations containing high concentration of Chitosan and Xanthan gum shows more swelling index. Maximum swelling index was observed with B9 containing maximum concentration of both the polymers.

Infrared (IR) spectroscopic study of the formulation

Figure 3 shows the Infrared spectroscopic scan of Tapentadol hydrochloride mixed with KBr. The IR scan shows prominent peaks for the various active groups such as 3554 cm-1 corresponding to the N-H stretch in the tertiary amino group, 1457 cm-1 corresponding the C-O stretch between phenolic C and O group.
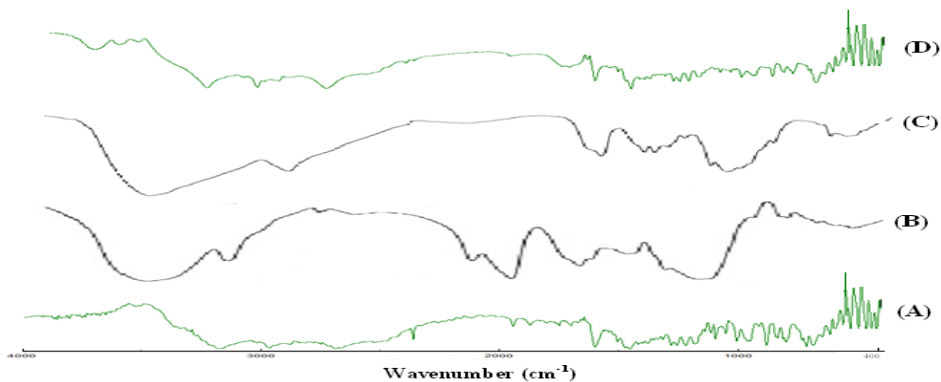
A-Tapentadol, B- Xanthan gum, C- Chitosan, D- Formulation (B5)
Fig. 3: IR Spectroscopic study of drug, polymer and formulations.

The formulations containing the polymers showed all the prominent peaks of Tapentadol 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 Tapentadol hydrochloride released from B5 after storing for 6 months at normal conditions and for 3 month at 40º C temperature 75 % relative humidity.

In-vivo study

In vivo evaluation was carried before meal. The behavior of tablet was studied in one volunteer in real time using radiographic imaging technique. Figure 4 (a) shows x ray of tablet B5 taken 1 hour after administration of tablets. Tablet can be seen in stomach. Next image Figure 8 (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(c) and 8 (d) shows the positions of tablet in stomach after 4 and 6 hours respectively. This indicates that the tablet remained afloat in stomach till 6 hours. From the x-ray study, it was observed that the tablet remained afloat in stomach till the time period of 6 hrs. The tablet remained intact within the stomach, this shows that sustained release pattern of drug from the formulation. This indicates the successful floating gastro retentive drug delivery of Tapentadol HCl.
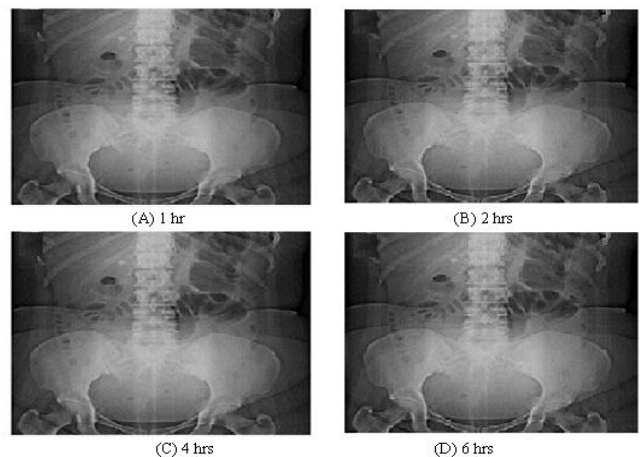

Fig. 4: X-Ray of formulation B5 after time interval (A) 1 hr; (B) 2 hrs; (C) 4 hrs; (D) 6 hrs

DISCUSSION

From the in vitro buoyancy studies, it was observed that lower concentration (less than 20%) of sodium bicarbonate fails to give floating ability to the formulation, while 20% of $NaHCO_3$ with 10% of citric acid is optimum to give good floating property to the formulations. Chitosan (50-60%) alone fails to retard drug release.

Xanthan gum (30-40%) alone gives good retardation of drug release for longer period of time. Chitosan has low gelling and matrix forming property than Xanthan gum. Hence Chitosan alone can't be used as matrix polymer in the formulation of Matrix tablet. Xanthan gum alone as well as in combination with other gums is good matrix polymer to formulate controlled release tablets. From the evaluation of powder blends, it was observed that all the powder blends shows good flow property. From evaluation of formulations B1-B9, it was observed that there is linear relationship between swelling index and concentration of polymers. Maximum swelling index was observed with B9 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 polymers. Batches B4, B5, B8 and B9 show optimum drug release profile but batch B9 fails to float within 1 min. As compared with batch B4 and B8, batch B5 has higher swelling idex as well as optimum FLT and drug release. 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. The tablet remained intact within the stomach, this shows that sustained release pattern of drug from the formulation. This indicates the successful floating gastro retentive drug delivery of Tapentadol HCl.

CONCLUSION

Modified drug release attained in the current study indicates that the matrix tablets of Tapentadol 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 polymers and floating agent is imperative to acquire proper controlled release and flotation of the formulation. High degree of prognosis obtained using RSM corroborates that a 3^2-factorial design is quite efficient in optimizing drug delivery systems that exhibit nonlinearity in response(s).After study of all batches it is concluded that Formulation B5 shows good in vitro as well as in vivo gastro retentive floating drug delivery of Tapentadol HCl.

ACKNOWLEDGEMENT

REFERENCES

1. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site specific delivery. Int J Pharm. 1996; 136: 117-139.
2. Singh BN, and Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release. 2000; 63: 235-239.
3. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006; 3 (2): 217-233.
4. Ali J, Arora S, Khar RK. Floating drug delivery System: A Review. AAPS Pharm Sci Tech. 2005; 06(03): E372-E390.
5. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997,14: 815-819.
6. Dan Anderson, Sarah deQuintana, Karen Hart Valencia, Los Angeles County Dept of Coroner, 1104 N. Mission Road, Los Angeles, CA 90033
7. Richards-Waugh, L. and Kraner, J. New Drugs: Tapentadol. ToxTalk, 2009 33(1): 20-25.
8. Raritan, N.J., NUCYNTA® ER (tapentadol extended-release tablets) Receives FDA Approval for the Management of Moderate to Severe Chronic Pain Janssen Pharmaceuticals, Inc. 2011. (http://nucynta.com/sites/default/files/pdf/nucyntaer-pi.pdf).
9. Brunton L. Parker K. Blumenthal D. I. Buxton, Goodman and Gilman`s: Manual of pharmacology and therapeutics, Mc Graw Hill, New York. p. 358-367.
10. Dave BS, Amin AF, Patel MM. Gastro retentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation AAPS PharmSciTech 2004 34: 1-6.
11. Aulton ME. Alton's Pharmaceutics-The design and manufacture of medicine, second ed., Churchill Livingstone Elsevier: 2008 133, p. 441-450.
12. Lachman L, Lieberman HA, The theory and practice of industrial pharmacy, CBS publishers and distributors, special Indian edition, New Delhi. 2009 p. 300,301,317.
13. Allen LV, Popovich NG, Ansel HC. Ansel's pharmaceutical dosage form & drug delivery system, Lippincott William & Wilkins: 2008 p. 186-203.
14. Jain NK. Response surface optimization of drug delivery system, CBS Publishers and Distributors, New Delhi.
15. Singh B. Comprehensive computer program for the study of drug release kinetics from compressed matrices. Ind. J. Pharm. Sci. 1998 60: 358- 362.
16. Inez Jimenez-Martinezb, Tomas Quirino-Barredab, Leopoldo Villafuerte-Roblesa, Sustained delivery of captopril from floating matrix tablets. International Journal of Pharmaceutics, 2008; 362: 37–43.
17. Sasa Baumgartner a, Julijana Kristl a, Franc Vrecer b, Polona Vodopivec b, Bojan Zorko, Optimisation of floating matrix tablets and evaluation of their gastric residence time, International Journal of Pharmaceutics 2000; 195: 125–135.
18. Abolfazl Mostafavia, Jaber Emamia,, Jaleh Varshosaza, Neal M. Daviesb, Mahboubeh Rezazadeh, Development of a prolonged-release gastroretentive tablet formulation of ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers, International Journal of Pharmaceutics 2011; 409: 128–136.