

Available online on 15.07.2018 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Research Article

FORMULATION OPTIMIZATION AND EVALUATION OF GASTRORETENTIVE TABLETS OF ONDANSETRON HCL

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ABSTRACT

The aim of the work is to design Gastroretentive tablets of Ondansetron HCl for gastric retention by using 3^2 factorial designs. Floating tablets of Ondansetron HCl were prepared by direct compression method using polymers, sodium alginate and excipient. Gastroretentive tablets of Ondansetron HCl were successfully prepared by effervescent technique using different gel forming polymers- HPMC K200M, and sodium alginate. Formulation was optimized by design expert software. Floating tablets were evaluated for floating time, floating lag time, drug content, raft measurement and in vitro dissolution profile. The lag time is between 17-22 sec and floating time of the formulations for 12 hrs. The best fit model is Korsmeyer Peppas Model. From the study it is proof that the sustain release by floating tablets of Ondansetron HCl can be develop. Optimized batch selected was A3, The prepared gastroretentive test formulation was found to exhibit satisfactory physico-chemical characteristics at the end of 3 months, during the stability studies. The optimized formulation A3 was found to be stable at 40^{0C}/ 75% RH.

Keywords: Gastric retention time, Ondansetron HCl, HPMC, sodium alginate, measurement of raft, Factorial design, stability studies.

Article Info: Received 07 April, 2018; Review Completed 03 June 2018; Accepted 03 June 2018; Available online 15 July 2018



Cite this article as:

Shaikh SN, Razzak BAA, Khan GJ, Formulation optimization and evaluation of gastroretentive tablets of ondansetron HCl, Journal of Drug Delivery and Therapeutics. 2018; 8(4):185-195

DOI: <http://dx.doi.org/10.22270/jddt.v8i4.1763>

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INTRODUCTION

Oral delivery of drug is the most preferred route of drug delivery due to ease of administration, patient compliance & flexibility in formulation. Conventional oral dosage forms achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. It is having low bulk density that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the Gastric juice of stomach without affecting the gastric emptying rate for a prolonged period of time^{1,2}. Bioavailability^{1,2}.

Raft forming system:

This system focus more for delivery of antacid and delivery of drugs used to treat gastrointestinal infection and disorders. The basic mechanism involves formation

of viscous cohesive gel when the system comes in contact with gastric fluid. In this each portion of liquid swells and forms a continuous layer of gel known as raft. The raft floats because of buoyancy created by formation of CO₂. This raft acts as a physical barrier to prevent the reflex of gastric content into the esophagus. This raft forming system contains a gel forming agent and alkaline bicarbonates or carbonates which is responsible for making the system less dense than the gastric fluid and to float on the gastric fluid^{3,4}.

Effect of sodium bicarbonate on the drug release from raft forming system:

Sodium bicarbonate is used as a gas generating agent. Gas generating agent sodium bicarbonate interacts with the gastric acid and generates carbon dioxide which gets entrapped within the swellable matrix. Carbonate or bicarbonate may be present in the amount ranges from

5% to 50% and preferably from about 10% to 30% by weight of composition. Increasing the concentration of bicarbonate decreases the floating lag time because of faster and higher carbon dioxide generation. At higher concentration of effervescent agent, coating of the tablet becomes less stable. This is because of increase in the internal pressure and there by rupturing the polymer coating which ultimately results in sudden increase in drug release^{5,6,7}.

Therefore the present study is planned to formulate & evaluate floating tablet of Ondansetron hydrochloride using HPMC K200M & HPMC K4M polymers, sodium alginate & excipients. Floating drug delivery systems have an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Dosage forms with a prolonged GRT will bring about new and important therapeutic options. The data obtained thus

suggests that floating delivery system of Ondansetron hydrochloride can be successfully designed to give controlled drug delivery and improved oral bioavailability.

MATERIALS AND METHODS

Ondansetron HCl, HPMC K-200 M, HPMC K-4 M, Sodium Bicarbonate, Citric Acid, Magnesium Stearate, Talc, Lactose, Sodium Alginate And Avicel-101.

For study purpose, 9 formulations with different excipient were prepared as shown in table 1. Mixture passed through the sieve for purpose of uniformity of particle and remaining particle again triturated and mixed. Floating tablet was prepared by dry compression method. The tablet was compressed using (9mm punch) set in a compression machine.

Table 1: Optimization batches design

Ingredients	Formulation batch code								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Ondansetron Hcl	20	20	20	20	20	20	20	20	20
HPMC K-200 M	30	30	30	40	40	40	50	50	50
HPMC K-4 M	20	30	40	20	30	40	20	30	40
Sodium alginate	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	45	45	45	45	45	45	45	45	45
Citric acid	15	15	15	15	15	15	15	15	15
Talc	05	05	05	05	05	05	05	05	05
Magnesium stearate	05	05	05	05	05	05	05	05	05
Lactose Q.S.	80	70	60	70	60	50	60	50	30
Total	250	250	250	250	250	250	250	250	250

Evaluation Parameters:

Pre-compression evaluation parameters:

Angle of repose, bulk density, tapped density, carr's index and hausner's ratio were evaluated to determine the flow property of the prepared powder mixture.

Post- compression evaluation parameters:

Thickness:

Thickness was measured using a vernier caliper. Five tablets of the formulation were picked randomly and thickness was measured individually.

Hardness:

Hardness was measured using Monsanto hardness tester. The hardness expressed in kg/cm². For each batch three tablets were tested.

Friability:

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were deducted and weighed again. The percentage friability was measured using formula,

$$\% F = \{1 - (W_t / W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablets

Wt. = Weight of tablets after revolution

Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

Drug Content Uniformity:

Ten tablets for each batch was taken and triturated. Powder equivalent to 20 mg of drug was weighed and was transferred to breaker and 0.1N HCl was added and it was then shaken for 5 min and finally 0.1N HCl was added to make the volume up to 100 ml and solution was then sonicated for 15 min and filtered through Whatman filter paper. Finally, a solution was diluted suitably and the absorbance of the resultant solution was measured to determine the drug content spectrophotometrically at 310 nm using UV/Visible spectrophotometer Shimadzu 1800 against 0.1N HCl blank.

In-vitro Buoyancy Studies:

The in-vitro buoyancy was determined by floating lag time. The time required for the tablet to rise to the surface and float was determined as floating lag time. In

this the tablets were placed in 100 ml beaker containing 0.1 N HCL.

Swelling index study:

For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet was removed from beaker and weighed again up to 12 h. The swelling index was calculated using following formula.

$$\text{Swelling index (S.I.)} = \{(\text{wt}-\text{wo}) / \text{WO}\} \times 100$$

Where, S.I. = Swelling index

Wt. = Weight of tablet at time t

WO = Weight of tablet before placing in the Beaker.

Raft strength measurement

1. A tablet powder equivalent to unit dose was transferred to 150 ml of 0.1 N HCl and maintained at 37°C in a 250 ml glass beaker.
2. Each raft was allowed to form around an L-shaped wire probe (Height 9 cm and wide at bottom surface 2 cm) held upright in the beaker throughout the whole period (30 min) of raft development.
3. Raft strength was estimated using the modified balance method.
4. Water was added drop wise to the left sided beaker and the weight of water required to break the raft was recorded.

Raft weight and raft volume measurement

1. Raft volume and raft weight Rafts were calculated by taking unit dose for 30 min in glass beakers of 150 ml 0.1 N HCl but without the inclusion of a wire probe.
2. Each beaker used for raft formation was reweighed (W1).
3. Note the volume of beaker before formation of raft. (M1).
4. The position to which the top of each raft reached was marked on the outside of the beaker.
5. The total weight of the beaker and contents was obtained after raft development (W2).
6. The weight of each raft was then calculated from the formula:

Raft weight = Total weight of the beaker and contents was obtained after raft development (W2) – Pre-weighed beaker used for raft formation (W1).

1. The raft was then removed from the beaker by carefully decanting off the liquid and tipping the raft into a pre-tarred plastic weighing petri plate.
2. This was left to stand for 30 s, excess subnatant liquid was drained off and the raft was weighed (W3).

3. Remaining liquid was removed from the inside of the beaker with a paper towel and it was then refilled with water to the marked position (M2).
4. Finally beaker was weighed (W4).
5. The volume of each raft was then calculated from the formula:

Raft volume = Final volume of 0.1 N HCl after formation of raft (M2) – Initial volume of 0.1 N HCl before formation of raft (M1) Where raft volume is measured in ml. and all weights are measured in gm.

The formula assumes that the density of the subnatant liquid is the same as that of water.

Acid neutralization capacity

- 1) A tablet powder equivalent to unit dose was transferred to a 250 ml beaker; 50 ml of water was added to it and was mixed on a magnetic stirrer for 1 min.
- 2) A 30-ml volume of 1.0 N HCl was added with continued stirring on the magnetic stirrer for 10 min after addition of the acid.
- 3) Stirring was discontinued briefly and the gum base was removed using a long needle without delay.
- 4) The needle was promptly rinsed with 20 ml of water, and the washing was collected in the beaker; stirring was resumed for 5 min.
- 5) Titration was begun immediately. Excess HCl was titrated against 0.5 N sodium hydroxide to attain a stable pH of 3.5.
- 6) The number of mEq of acid consumed by the tablet tested was calculated by the following formula:

$$\text{Total mEq} = (30 \times \text{N HCL}) - (\text{V NaOH} \times \text{N NaOH})$$

Where, N HCl = Normality of HCl; V NaOH = Volume of NaOH required; and N NaOH = Normality of NaOH.

In Vitro Dissolution Studies:

In-vitro drug release studies of the prepared floating tablets were conducted for a period of 12 hrs. Using USP type II apparatus (paddle) at 37± 0.5°C and at 50 rpm speed at pH 1.2. After withdrawing, the samples were analyzed by a UV spectrophotometer at 310 nm.

Stability studies of optimized formulation:

Procedure:

In the present study, stability studies were carried out at room temperature 40 ± 20°C and 75 ± 5% RH for a specific time period up to 3 Months for selected formulations. For stability study, the tablets were sealed in aluminium packaging coated inside with polyethylene.

RESULTS AND DISCUSSION

FT-IR Study of Drug

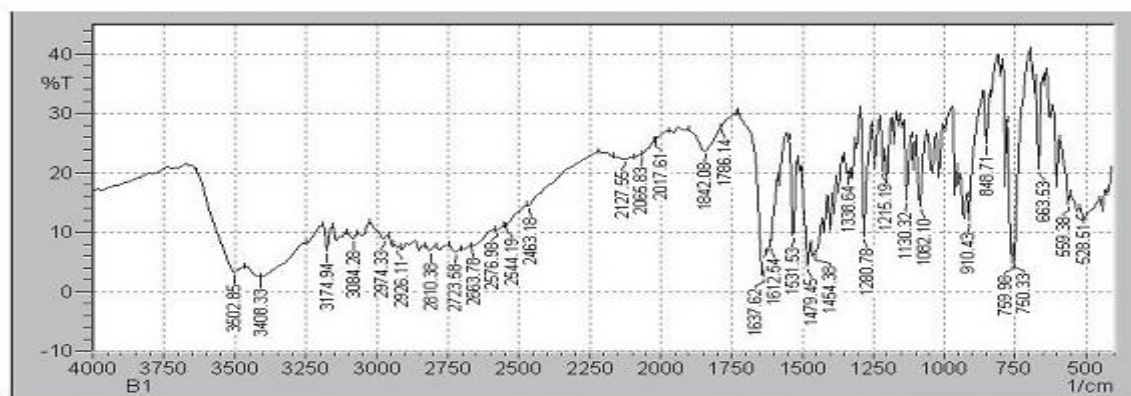


Figure 1: FT-IR spectra of Ondansetron HCl.

Table 2: Interpretation of FT-IR spectra of Ondansetron HCl (pure drug)

Sr. No	Functional group	Characteristic peaks cm ⁻¹	Observed peaks cm ⁻¹
1	N-H	3000-3700	3502.85
2	C-H	2700-3300	2810.38
3	C=O	1600-1900	1637.62
4	C=N	1600-1900	1612.54
5	C-H	1300-1500	1338.64
6	C-C	800-1200	910.43

FTIR Spectra of Ondansetron HCl (Pure Drug).

The IR spectrum of pure drug was found to be similar to the reference standard IR Spectrum of Ondansetron HCl given in Indian pharmacopoeia. The IR Spectrum value of Odansetron HCl shown in table 2.

Drug - Excipient Compatibility Studies

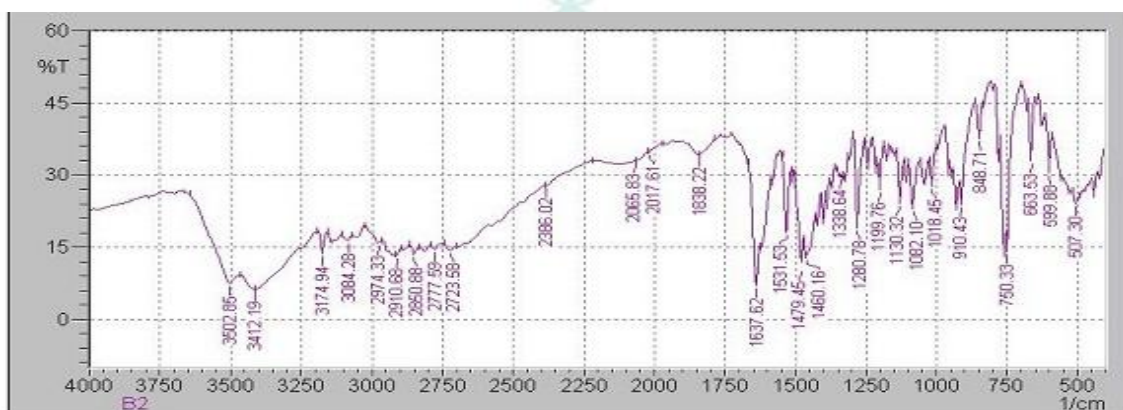


Figure 2: FT-IR spectra of Drug + HPMC K200 M

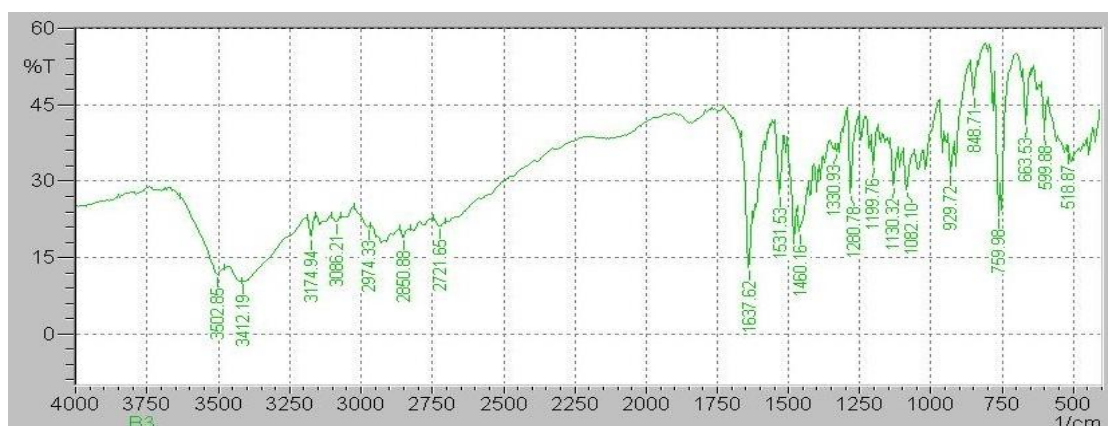


Figure 3: FT-IR spectra of Drug + HPMC K4 M

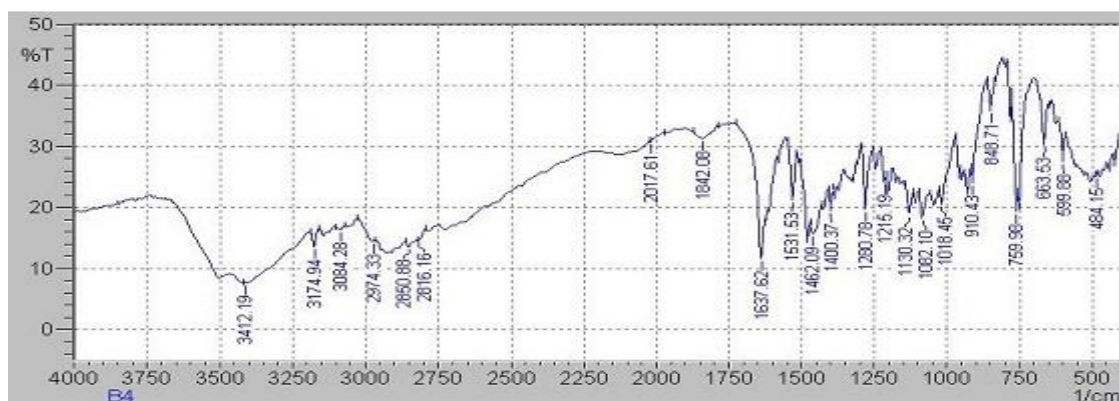


Figure 4: FT-IR spectra of Drug + HPMC K200 M+HPMC K4M

Drug - Excipient Compatibility Studies

Compatibility studies of pure drug Ondansetron HCl with polymers were carried out prior to the preparation of tablets. IR spectra of pure drug Ondansetron HCl and that of with polymers were obtained, which are shown in figure No.1 to Figure No.4 All the characteristic peaks

of Ondansetron HCl were present in spectra thus indicating compatibility between drugs. It shows that there was no significant change in the chemical integrity of the drug.

DSC OF Ondansetron HCl: differential scanning calorimetric (DSC)

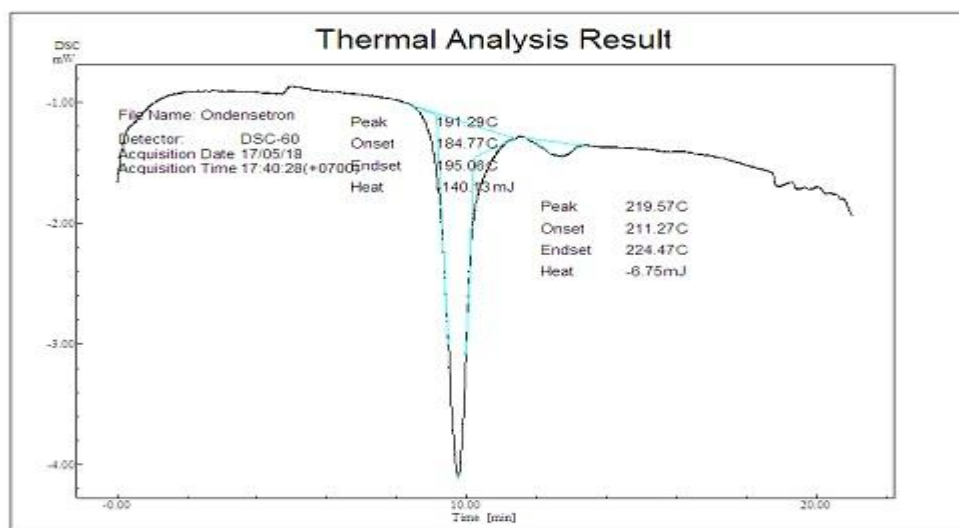


Figure 5: Differential Scanning Calorimetry Ondansetron HCL

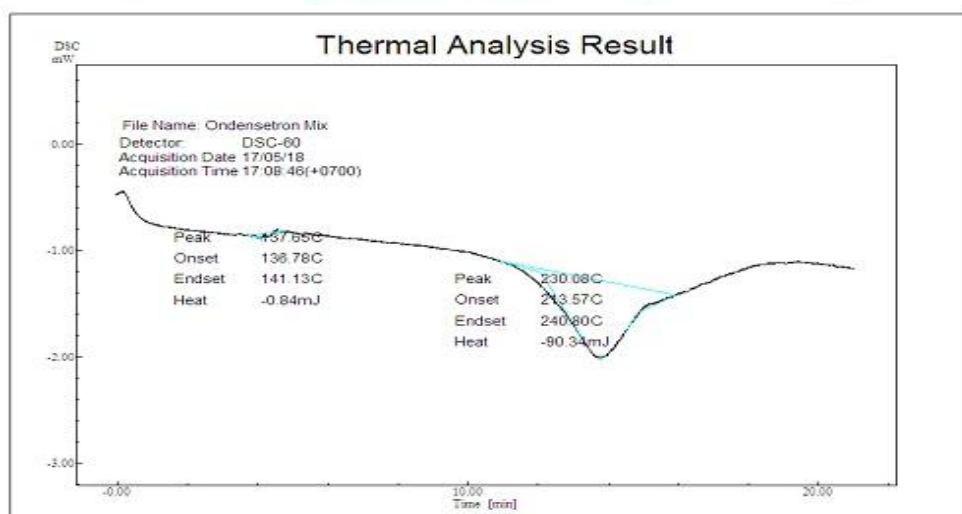


Figure 6: DSC of Ondansetron HCl with Excipients

Studies were carried out using DSC 60, having TA60 software, shimadzu, and Japan. Accurately weight sample were placed on aluminum plate, sealed with

aluminum lid and heated at a constant rate 5 °C/min over a temperature rang 0 to 250 °C. Ondansetron HCl showed in figure 5 & 6.

Table 3: Pre Compression Parameter optimized batches:

Batch No.	Angle Of Repose (°)	Bulk Density (gm./ml)	Tapped Density (gm./ml)	Hausner's Ratio	Carr's Index (%)
A1	29.68±0.46	0.728±0.02	0.823±0.005	1.12±0.02	11.21±0.02
A2	30.96±0.01	0.684±0.01	0.782±0.001	1.14±0.02	12.53±0.02
A3	27.92±0.02	0.632±0.002	0.715±0.001	1.13±0.02	11.60±0.02
A4	27.47±0.07	0.589±0.001	0.647±0.001	1.09±0.04	8.96±0.02
A5	26.56±0.02	0.561±0.002	0.624±0.002	1.11±0.01	10.09±0.02
A6	23.74±0.02	0.543±0.001	0.602±0.001	1.10±0.02	9.80±0.01
A7	25.64±0.01	0.518±0.001	0.582±0.001	1.12±0.02	10.99±0.00
A8	26.10±0.02	0.482±0.001	0.562±0.001	1.17±0.02	14.53±0.02
A9	26.11±0.01	0.561±0.01	0.637±0.001	1.11±0.01	10.09±0.01

The prepared gastroretentive drug delivery system for raft forming tablets were characterized for angle of repose, bulk density, tapped density, carr's index and hausner's ratio which are shown in table. Angle of

repose of all batches was within 23.74° – 30.96°, carr's index of all batches was within 8.96 – 14.53 and hausner's ratio of all batches was found within 1.09– 1.17 which indicate good flow property of powder.

Table 4: Post-Compression Parameters of optimized batches:

Formulations	Weight Variation (mg)	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	(%)Drug Content
A1	250±0.2	5.9 kg/cm ²	4.5	0.49±0.11	99.31
A2	251±0.1	5.8 kg/cm ²	3.5	0.42±0.01	98.86
A3	249±0.0	5.9 kg/cm ²	4.5	0.41±0.00	98.64
A4	251±0.3	6.0 kg/cm ²	3.3	0.50±0.09	98.02
A5	249±0.4	6.2 kg/cm ²	4.2	0.48±0.07	97.53
A6	249±0.0	6.5 kg/cm ²	4.5	0.43±0.02	97.75
A7	250±0.4	6.3 kg/cm ²	4.5	0.41±0.00	98.02
A8	250±0.2	6.4 kg/cm ²	4.4	0.45±0.04	98.41
A9	249±0.07	5.2 kg/cm ²	3.5	0.51±0.02	99.08

Hardness test

The measured hardness of tablets of each batch ranged between 5.2 to 6.5kg / cm² This ensures good handling characteristics of all batches.

Thickness

The measured thickness of tablets of each batch ranged between 3.3 to 4.5 this ensures good handling characteristics of all batches.

Friability test

The values of friability test of tablets of each batch ranged between 0.41-0.51% The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight variation test

The percentage weight variations for tablets of each batch ranged between 249-251mg all the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug content uniformity

The percentage of drug content was found to be between 97.53% and 99.31% of It Ondansetron hydrochloride, which was within acceptable limits. The results of drug content uniformity in each batch.

Table 5: In-vitro buoyancy study of optimized batches

Formulation Codes	Floating Lag Time (Sec)	Total FLT Hours
A1	17 ± 0.1	>12
A2	17 ± 0.1	>12
A3	30 ± 0.2	>12
A4	32 ± 0.3	>12
A5	20 ± 0.1	>12
A6	18 ± 0.1	>12
A7	20 ± 0.2	>12
A8	19 ± 0.1	>12
A9	22 ± 0.4	>12

Buoyancy study

On immersion in 0.1N HCl solution pH (1.2) at 37°C, the tablets floated, and remained buoyant without disintegration. The results of buoyancy study and showed buoyancy character of prepared tablet of formulation. Formulation shows floating lag time as 17sec. which was less compared to other formulations.

Table 6: Data for Raft Strength and Acid Neutralizing Capacity:

Batch no	Raft Strength (gm)	Acid Neutralizing Capacity (mEq)*
A1	0.58±0.1	6±0.2
A2	0.65±0.2	7±0.1
A3	0.59±0.1	6±0.1
A4	0.57±0.1	6±0.0
A5	0.59±0.0	6.5±0.0
A6	0.66±0.2	7.2±0.1
A7	0.66±0.3	6.6±0.1
A8	0.68±0.1	7±0.1
A9	0.73±0.2	7.1±0.1

Raft strength, Acid Neutralizing Capacity

All the parameters are evaluated using 0.1 N HCl in specific procedure taking 10 tablets for evaluation of both the evaluation parameter

According to data of both specific evaluation parameter of the raft forming formulation, A9 batch was having

maximum raft strength, & Acid Neutralizing Capacity range between (6-7.2). So it was selected as an ideal formulation as raft formation tablet.

% Swelling Index of Optimized batches in graphical presentation:

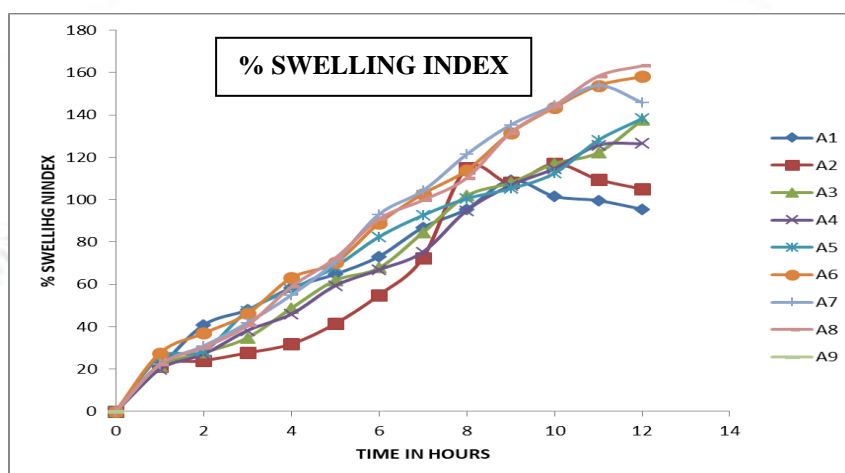


Figure 7: % swelling index of optimized batches

Swelling Index:

Swelling index of all batches i.e. A1 to A9 is maximum % of wt. 95.5%, 105.01%, 137.65%, 126.53%, 138.30%, 158.13%, 145.90%, 163.26% and 108.41 respectively. Show in figure No.7

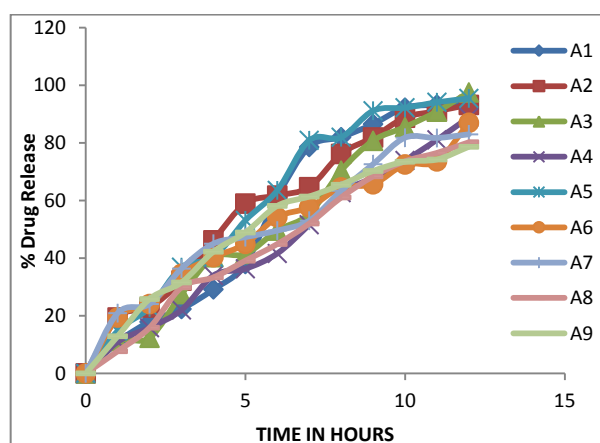


Figure 8: % Drug Release in Graphical Presentation: (A1 to A9)

In Vitro dissolution studies:

The release rate of Ondansetron hydrochloride from floating tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (1 ml) of the solution was withdrawn from the dissolution apparatus, and volume equivalent to the amount of sample withdrawn was replaced with fresh dissolution medium. The samples were visualized on UV at 310nm after appropriate dilutions. Absorbance data obtained was substituted in the equation of standard curve and values were calculated for total cumulative amount of drug released. All the nine formulation of prepared floating tablets of Ondansetron hydrochloride were subjected to in-vitro release studies these studies were carried out using dissolution apparatus, 0.1N HCL (pH 1.2)

The drug release batch A1, A2, A3, A4, A5, A6, A7, A8 and A9 were found 94.30%, 93.15%, 97.48%, 88.87%, 95.44%, 86.96%, 82.94%, and 80.22%, and 78.63% respectively.

Data analysis:

Table 7: In-vitro Drug release data Analysis

Batch	Zero order		First order		Higuchi		Korsmeyer-peppas		Hixson-Crowell	
	R	Slope	R	Slope	R	Slope	R	Slope	R	Slope
A1	0.9512	8.4131	0.8466	0.0860	0.9612	39.002	0.9873	1.0206	0.7144	0.5168
							N			
							0.9307			

Data Analysis:

The in-vitro release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, higuchi equation, korsmeyer-peppas and Hixson-Crowell models to ascertain the mechanism of drug release. The results of linear regression analysis of data including regression coefficient are summarized in Table 7.

When the regression coefficient 'r' value of Zero order and korsmeyer-peppas plots were compared, it was

observed that the 'r' values of Zero order was found to be 0.9512 whereas the 'r' values of korsmeyer-peppas plot was found to be 0.9873 indicating drug release from optimized formulation was found to follow Korsmeyer-peppas kinetics.

The in-vitro dissolution data was fitted to Korsmeyer-equation, values of exponent 'n' was found to be 0.9307 indicating that the drug release is by Anomalous transport mechanism.

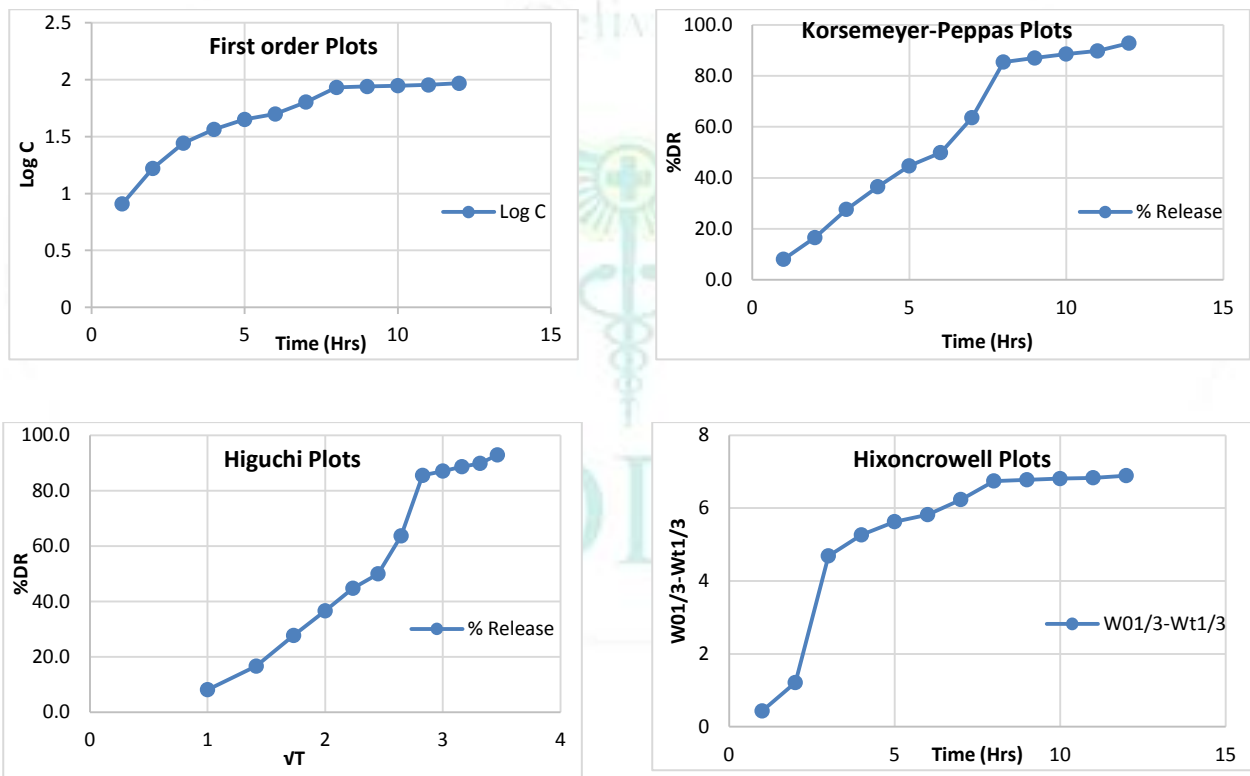


Figure 9: Release Profile of Ondansetron HCl

Table 8: Result of ANOVA

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model significant/ Not-Significant
%drug release	280.57	12	55.76	63.28	<0.0001	0.9784	Significant
Raft strength	0.0293	12	0.0049	7.34	0.0105	0.8399	Significant

Design-Expert® Software
 Trial Version
 Factor Coding: Actual

Raft strength (gm)

● Design points above predicted value

○ Design points below predicted value

0.57 0.73

X1 = A: HPMC K4M
 X2 = B: HPMC K 200M

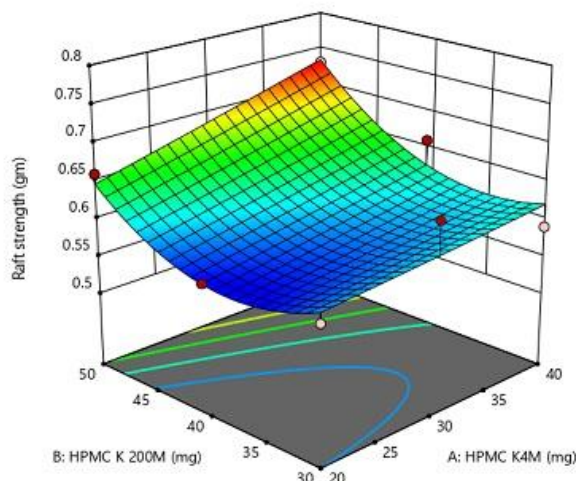


Figure 10: A response surface plot showing effect of concentration of independent variables on the Raft strength.

Design-Expert® Software
 Trial Version
 Factor Coding: Actual

Raft strength (gm)

● Design Points

0.57 0.73

X1 = A: HPMC K4M
 X2 = B: HPMC K 200M

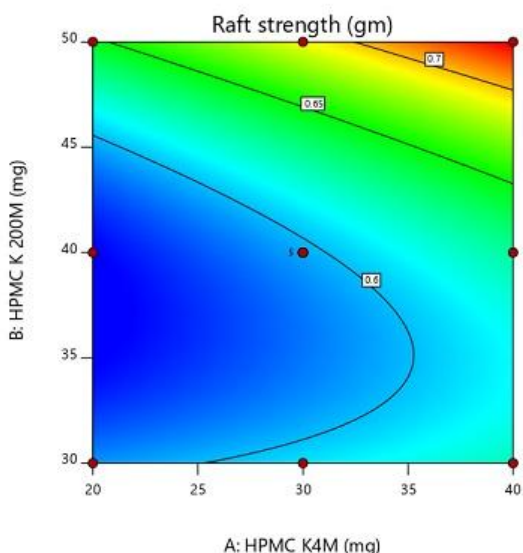


Figure 11: A counter plot showing relationship between various levels of independent variables to gain fixed value of Raft strength.

Design-Expert® Software
 Trial Version
 Factor Coding: Actual

CDR (%)

● Design points above predicted value

○ Design points below predicted value

78.63 94.3

X1 = A: HPMC K4M
 X2 = B: HPMC K 200M

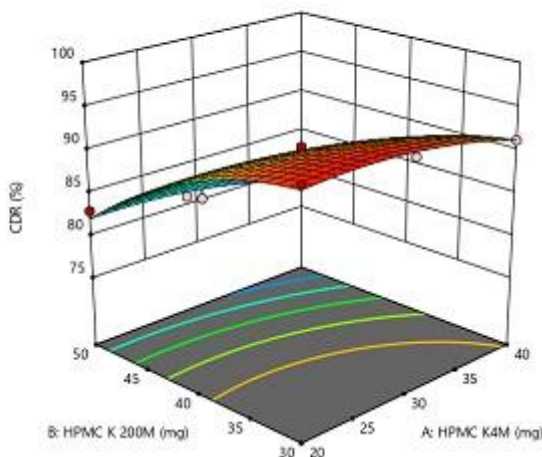


Figure 12: A response surface plot showing effect of concentration of independent variables on the % drug release

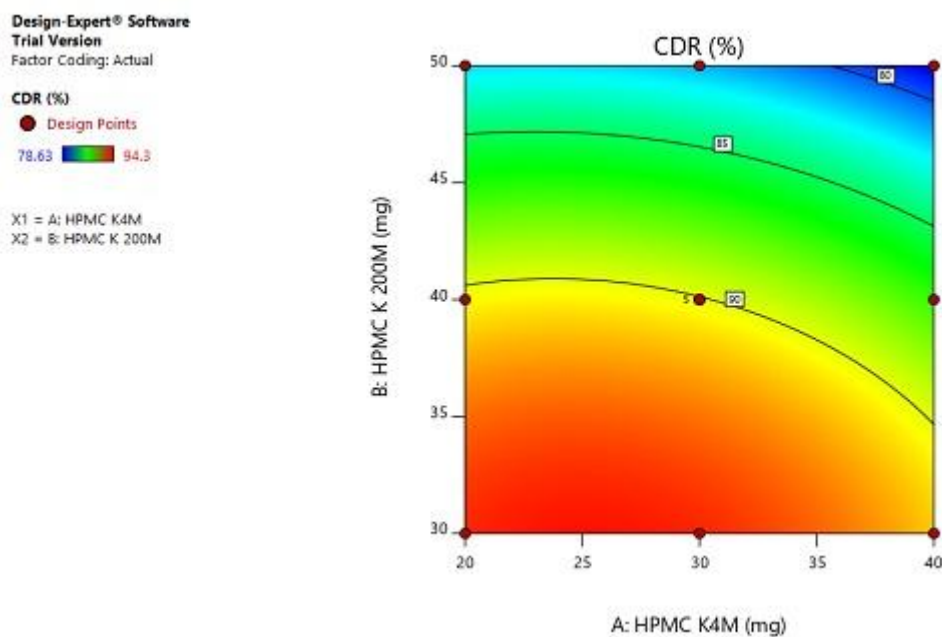


Figure 13: A counter plot of showing relationship between various levels of independent variables to gain fixed value of % drug release.

Stability Study

Table 9: Stability study of optimized formulation batch

Condition	Time (month)	Hardness (Kg/cm ²)	Friability (%)	Drug content (%)	Floating lag time (Sec)	% Drug release
Accelerated temperature 40°C and 75% RH	3	4.2	0.46	97.48	23	92.39

No significance changes are observed after stability study.

%Drug Release in Graphical Presentation

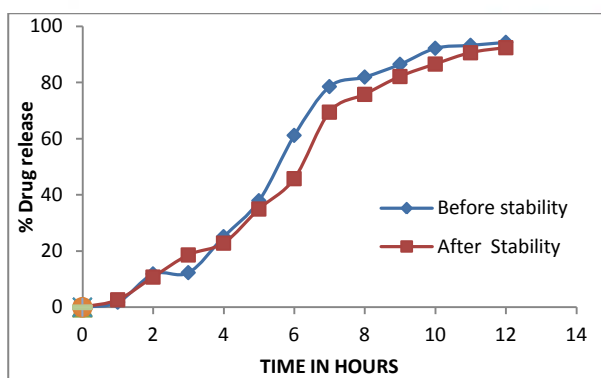


Figure 14: Stability Studies batch In Vitro %Drug Release

CONCLUSION

Many patients are suffering from the gastro-esophageal reflux disease and this can be overcome by using raft forming floating tablet of Ondansetron hydrochloride. It was concluded that raft forming floating tablet containing HPMC K 200M, HPMC K 4M, sodium alginate and sodium bicarbonate form raft on 0.1N HCL which form suffering raft strength to prevent reflux of the gastric content.

The data obtained thus suggests that gastroretentive drug delivery system can be successfully designed to give controlled drug delivery, improve bioavailability and other desirable characteristics.

The present study shows that Ondansetron HCl can be made into floating Dosage form and raft forming by direct compression technique. Floating tablet of Ondansetron HCl is shorter lag time.

Ondansetron HCl floating tablet were prepared by direct compression technique and found to be good with chipping, capping, and sticking.

FIR and DSC study indicates no drug-excipient interaction in the formulation.

The in-vitro dissolution profile of optimized floating tablet formulated of Ondansetron HCl were found sustained drug release up to 12 hours and release can be extended for longer period over 12 hours by increasing the concentration of polymers.

3² full factorial design and optimization technique successfully used in the development of floating tablet.

Comparing the all formulations, formulation A3 was considered as optimized formulation which exhibited 97.48% of drug release in 12 hours, and floating lag time of 30 sec, total floating over 12 hours.

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