Available online on 20.11.2021 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

Development and Evaluation of Gastro Retentive Floating Drug Delivery System of Ondansetron Hydrochloride

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Article Info:



Article History:

Received 09 September 2021
Reviewed 29 October 2021
Accepted 13 November 2021
Published 20 November 2021

Cite this article as:

Niranjan AK, Kumar A, Development and Evaluation of Gastro Retentive Floating Drug Delivery System of Ondansetron Hydrochloride, Journal of Drug Delivery and Therapeutics. 2021; 11(6):150-158

DOI: <http://dx.doi.org/10.22270/jddt.v11i6.5084>

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Abstract

The Aim of the present study was to develop & evaluate Gastro-retentive floating Tablet of Ondansetron hydrochloride. The Objective was to calibrate and validate the UV-spectroscopy analytical method and to prepare and optimize the GR Floating tablets of Ondansetron hydrochloride in terms of dissolution release profile. The FDDS of the drug can minimize the fluctuation of drug plasma levels and result to associated adverse reactions, dosing frequency, and improved patient compliance. Conventionally, Ondansetron hydrochloride is taken up 2-3 times daily in the treatment of nausea and vomiting. Gastro retentive floating tablet of Ondansetron hydrochloride is better suited for treatment of postoperative nausea vomiting. In the present study, nine Gastro retentive Floating tablet formulations (F1, F2.....F9) of Ondansetron hydrochloride were prepared by the method of direct compression and polymers HPMC K15 were used and Guar gum and Chitosan, in different quantity to normalise their effect on the release profile of drug. Target release profile was >80% release of drug in 12 hours. Tablets were evaluated for various parameters namely: thickness, weight variation, friability, hardness, assay, in-vitro buoyancy study & drug release. Formulation F8 containing Chitosan (26.66% w/w), Guar gum (26.66% w/w) and Sod. Carbonate (25.83% w/w) had the desirable release profile.

Keywords: Ondansetron hydrochloride; Gastro retentive floating tablet, Chitosan, Guar gum, Drug release

INTRODUCTION

Drug taken by oral administration is that the foremost easy and favourite suggests that of any other drug delivery to the systematic circulation of the body. Nowadays Oral drug delivery system have been accelerated interest in pharmaceutical industries field to gain enhanced therapeutic benefits of drug, like simple dose drug 'administration, patient conformity and flexibility' in formulation of drug. Medicine which can be simply absorbed by alimentary canal or gastro intestinal tract (GIT) and have short half-life therefore it is eliminated very fast from the body cavity. Regular dosage of medicine is necessary to gain appropriate therapeutic effect ¹.

To stay away from these type of restriction, the appropriate result of Oral Sustained-Controlled release Formulations have a good chance to release the drug gradually into the alimentary canal and in the Gastro- intestinal tract ² (GIT) and It maintain an efficient amount of concentration level of drug in the circulation for lengthy time period. Once a drug taken by oral (administrative drug) route, such type of drug delivery path would be prevented release of drug in the

abdomen and the drug release during a very guarded manner, so that the drug are often equipped instantly on the absorption site among the GIT channel ³.

These path of Drug Delivery Systems (DDS) mainly face two type of adverse condition; firstly it shows very less gastric retention time (GRT) and also shows Unpredictable minimum GET, which may end in partial drug unleash from the measure type between the absorptive zone (Stomach or higher area of small intestine) resulting in diminish effectualness of administered drug dose. To specific site of drug which is taken by the path of 'orally administered controlled release' measure form DDS, It is fascinating to know a prolong retention period by the path of drug delivery. long-lasting gastric retentive drug improves the drug bioavailability, will increase the amount of drug dosage unleash, decreases drug wastage, and enhance solubility of the drug that square measure became less soluble throughout a high level proton concentration setting ⁴. Conjointly prolonged GRT among the abdomen are often helpful in the confined action among the uppermost region of the GIT (Ex. Ulcer treatment), (Amit Kumar Nayak 2010).

Gastro-retentive DDS is associated to prolong approach of stomachal period, by use of targeting site-specific drug which is released among GIT upper channel for local or general effects ⁵. Gastro mindful measure forms will stay among the stomachal part for long time periods and thus considerably increase the stomachal withholding time gastric retention time (GRT) of medication. the previous few years many gastro retentive drug delivery system(DDS) approaches being designed and developed, including high density (sinking) systems which means preserved within rock bottom of the abdomen, rarity (floatation) systems which is reason of buoyancy in stomachal fluid, Muco-adhesive systems which increase bioadhesion of drug in to abdomen, membrane extendible swellable, unfoldable, or systems that have a limits removal of the measure forms by the help of the sphincter of abdomen magnetic systems, super porous gel systems ⁶, etc.

Requirement of Gastro-retention

- The drugs which are absorbed in the variable gastric emptying time.
- Those drugs which are absorbed by the help of GIT's proximal part.
- General or Sustained drug delivery (SDD) intended to the stomach and proximal part of the small intestine to treat many types of diseases ⁷.
- Drugs which are insoluble and not degrade at the basic pH levels.
- Certain type of 'peptic ulcers caused by H. Pylori. (Amit Kumar Nayak et al., 2010').

Aspects of GRDDS Formulation:

- The drug should not contain any effect on gastric motility of GIT ⁸.
- It should be suitable to ingest for patients.
- The formulation must show complete 'degradation and evacuation of the system when the drug completely releases.
- It shows very effective retention in the stomach ⁹.
- The drug must contain proper amount of drug dose loading capacity & also control drug release report.
- It should not give any side effects or other common unwanted action. (Vinod K.R. *et al.*, 2010)

MATERIALS AND METHODS

Ondansetron was obtained as a gift from Aurobindo Pharma Ltd. Gaddapotharam, Andhra Pradesh. HPMC K 15 M, Chitosan & Guar gum were procured from Sigma Aldrich. All other substances were of analytical grade. All chemicals were pure and of analytical grade.

Drug Identification

Organoleptic property of the drug

The drug evaluated for the organoleptic property like color, odor.

Melting point observation

Melting point of ONDCL is found to be 182°C.

Analytical Methodology

Determination of λ_{\max} of ONDCL

0.1mg/ml concentration of ONDCL stock solution was prepared in distilled water and further (0.5ml in 10ml) diluted with water to obtain 5 μ g/ml concentration solution. This prepared solution of compound was scanned in UV-Visible spectrophotometer in the range of 200-400nm using distilled water as blank at the wavelength of 310nm λ_{\max} of ONDCL was recorded.

Standard Calibration Curve

Preparation of standard stock solution

ONDCL 10mg was weighed in 100ml volumetric flask and the solution prepare to the mark in volumetric flask with distilled water to acquire 0.1mg/ml solution.

Preparation of calibration and samples validation

Calibration sample (5, 10, 15, 20, 25 μ g/ml) in the singlet and validation samples (6, 16, 24 μ g/ml) in triplicate were prepared by appropriate dilution of stock solution.

Preparation of calibration curve

The absorbance reading of calibration and validation samples were measured against distilled water as blank in UV-Vis. spectrophotometer at 310nm (λ_{\max}). Then absorbance values of the calibration sample were plotted against their respective concentration to obtain the calibration curve.

Validation of the analytical method

Linearity

The absorbance value of the calibration sample was plotted against their respective concentration to obtain the calibration curve, and linear regression was performed ¹⁰. Linearity was accessed by correlation coefficient determination (r^2).

Accuracy

Mean concentration value for each data of validation samples were calculated and %error (a measure of accuracy) for each concentration calculation with the formula,

$$\% \text{error} = (\text{calculated mean concentration} - \text{actual concentration}) / \text{actual concentration} * 100.$$

Precision

Percentage relative standard deviation value was calculated (as a measure of precision) for each set of concentration by given formula,

$$\% \text{RSD} = \text{standard deviation} / \text{calculated mean concentration} * 100.$$

Drug excipients interaction study by FT-IR

The interaction studies of various excipients with ONDCL ¹¹ recorded by FT-IR Analysis.

Table 1: The ratio of ONDCL and excipients blend. (Yadav Priyanka. 2014)

Sr. No.	Excipients	Ratio w/w	Total blend mg
1	Pure Drug	1:1	100
2	Drug +HPMC K15	1:1	100
3	Drug + Guar gum	1:1	100
4	Drug + Sod. Bicarbonate	1:1	100
5	Drug + Chitosan	1:1	100

Preparation of blend for Formulation

Table 2: Ingredients used in tablets formulations;

Sr.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ondansetron	32	32	32	32	32	32	32	32	32
2	Sod. Carbonate	42.5	47.5	52.5	57.5	62.5	67.5	72.5	77.5	82.5
3	HPMC K 15 M	80	40	40	160	-----	-----	80	-----	80
4	Guar gum	40	80	40	-----	160	-----	80	80	-----
5	Chitosan	40	40	80	-----	-----	160	-----	80	80
6	Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Purified Talc	3	3	3	3	3	3	3	3	3
8	Lactose	60	55	50	45	40	35	30	25	20
	Total Quantity	300	300	300	300	300	300	300	300	300

Evaluations of Powder Blend for Tableting

Pre-compressional evaluation of powder blend:

For pre-compressional study of the powder blend of all the formulations was examine by the as angle of repose, tapped density, Hausner's ratio and bulk density ¹².

Angle of repose (θ)

The formulated powder blend is intended to measurement of θ and this is found in the range of 27^o.08' - 30^o.26', which shows a good flow property of formulated powder blend'. Results were given in Table no. 8.

Bulk density: For the measurement of Bulk density of the material (powder blend) in the range between 0.299 g/ml - 0.307 g/ml, which shows that the formulated powder blends were not too bulky ¹³. That result was shown in Table no. 8.

Tapped density: Tapped density of the powder blend was within the range between 0.422 g/ml - 0.45 g/ml. The results were shown in Table no. 8.

Hausner's Ratio: For the measurement of the Hausner's ratio of the compound material was found to be within 1.36 to 1.43, which shows that flow properties are good for formulated powder blend ¹⁴. The results were shown in Table no. 8.

In the above results -It had been concluded that the angle of repose (< 30^o) indicate good flow properties of the formulated powder blend. It was additionally followed by very good flow properties. Density and hardness of powder were interconnected properties. And also powder density may be tablet porosity, influence compressibility, dissolution, and other properties. Results indicate that the powder blend of all the formulations possessed adequate flow properties (Amit K. Jain et al., 2011).

Formulation of ONDCL Gastroretentive Floating Tablets

Method of Preparation

All the materials were weighed and sieved by 300 μ m (#50) sieve and mix with a mortar and pestle. The powder blend was directly compressed into core tablet using 9mm circular biconcave punch on Rotatory tablet punching machine ¹⁵. Tablets were like 32 mg of ONDCL (tablet weight 300mg).

Evaluation of Floating Tablets of ONDCL

Post-compressional estimation of Ondansetron hydrochloride floating tablet:

Formulated Tablets which were subjected to assessment tests these also shows general appearance, friability, hardness, diameter, thickness, weight variation and drug content ¹⁶.

General appearance:

Prepared tablets were white and some batches show some variation in colour, round, biconvex shaped without any defect on sides. Every tablet was pleasurable to the eye in appearance ¹⁷.

Hardness of tablet:

Hardness is the basic parameter of tablets were measured by the instrument Monsanto hardness tester and was found between of 3.5 - 4 kilogram per square centimeter, which shows that good mechanical strength and provide great ability to withstand chemical and physical stress though handling during transportation and loading-unloading ¹⁸. The results were shown in Table 9.

Diameter and Thickness of tablets:

The diameter and thickness of all the formulations were

measured by instrument Vernier scale micrometer ¹⁹ and were ranged between 3.5 – 4mm, this indicate the uniformity of tablets with having the similar particle size distribution in the formulation and no deformity. The results were mentioned in Table no. 9.

Friability Test of the tablets: Friability of all the formulation was lie between 0.1% -0.80% and the friability was less than 1% altogether the formulations, which shows that a good mechanical resistance of the tablet. The values of Hardness test and friability Percentage indicates good handling property of finally prepared tablets ²⁰. Results were shown in Table no. 9.

Weight variation Test of the all formulation:

For the analysis of weight variation it should performed according to the procedure given in the pharmacopoeia. All the developed tablet formulations (F1 to F9) passes weight variation test because the percentage weight variation range within the pharmacopoeial standard limit ($\pm 5\%$). hence all the formulations of tablet are acceptable. The results are given in Table no. 9.

Evaluation/ Estimation of tablet ingredient:

In the formulation for estimation of percentage of all the ingredient was in the range 99% to 104% and this confirm 'that the drug was uniformly distributed in' the all tablets.

Here the share of drug content in the entire formulations tablets are compressed with official specification: as per U.S.P (Ranges: 90% to 110%) ²¹. The results/data were shown in Table no. 9.

From the above result it had been concluded that each one the tablet formulation shows standard pharmacopoeial specification & formulated with the pharmacopoeial standard for friability, drug content, and weight variation. (Jain A K. or USP 30, NF2007)

In Vitro Buoyancy Studies:

The formulations takes time to emerge on the superior medium known as FLT (Floating Lag Time) sometime BLT (Buoyancy Lag Time) and the complete duration of time taken by individual tablet is named as TFT ^{22, 23} (Total Floating Time) (Margret Chandria et al., 2009; Riteshkumar et al., 2010; Ravikumar et al., 2009). In this regard the buoyancy studies results are often accomplished that the batch have HPMC only polymers and its combined with Sodium carbonate gives more relevant floating lag time in comparison to batch containing Guar gum polymers alone and its combination with HPMC. Floating of the tablet formulation shows variation from polymer to polymer that is governed by both the buoyancy of the hydrocolloid leading matter and the dissolution media. (Nagarwal et al, 2010).

The conditions of dissolution test were as follows (IP. 2018)

Table 3: Dissolution test Conditions;

Apparatus	Type-I Indian pharmacopoeia (Paddle type)
Analytical method	UV-spectroscopy (310nm)
Dissolution media	500ml distilled water
Speed and time	50 rpm for 15 hours
Temperature	37 \pm 0.5°C
Sample amount	5ml with replacement
Sampling time	30min, 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h.

RESULTS AND DISCUSSION

Analytical Method Development

Calibration of pure drug

The pure drug absorbances with their respective concentrations are mentioned in below table.

Table 4: Pure drug absorbance with their respective concentrations

Concentration(μ g/ml)	Absorbance(nm)
5	0.154
10	0.300
15	0.458
20	0.605
25	0.741

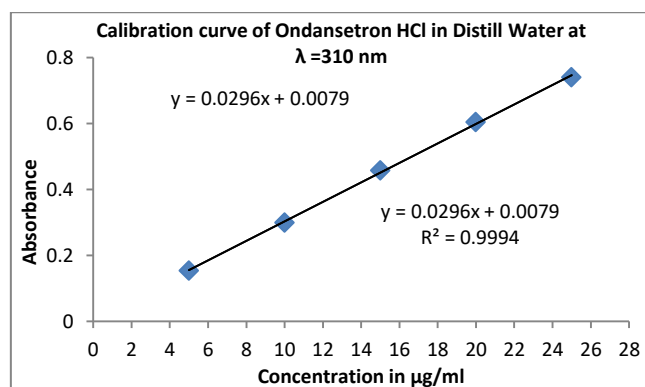


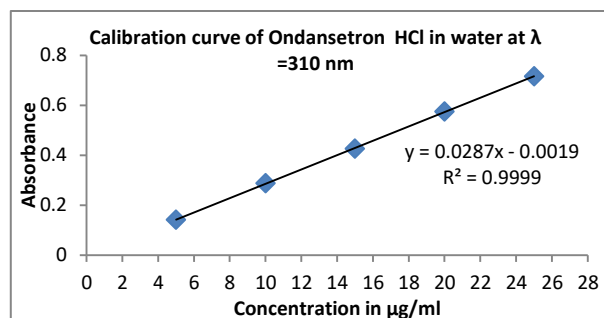
Figure 1: Calibration curve of pure drug and excipients by UV- spectroscopy

Calibration data of drug with excipients

The calibration data of drug with excipients is shown in below table.

Table 5: Concentration and absorbance value of the calibration sample

Concentration (µg/ml)	Absorbance(nm)
5	0.141
10	0.287
15	0.426
20	0.574
25	0.715

**Figure 2:** Calibration curve of pure drug and excipients by UV- spectroscopy**Validation of UV analytical method**

Linearity and range: Worth of correlation coefficient was found to be $r^2 = 0.999$ in Conc. Taken from 5, 10, 15, 20, 25(µg/ml), that indicated a linear graph in between concentration and absorbance. The spectrum for this method was 5-25(µg/ml).

Accuracy and precision: The exactness (measured by % error) and precision (measured by % RSD) for both intraday and interday studies, as mentioned below, were found within the acceptable range of 2%. Thus method was accurate as well as precise. The SD, RSD, accuracy, and precision data of intraday are recorded in table given below.

Table 6: Intraday accuracy and precision by UV spectroscopy method

Actual conc. (µg/ml)	Mean conc. (µg/ml).	SD	% RSD	% Bias	% Drug recovery
6	6.24	0.020117	0.003221	4.08	104
16	15.73	0.053224	0.003383	-1.66	98.33
24	24.03	0.034843	0.001449	0.15	100.15

The RSD, accuracy, and precision data of intraday are recorded in table given below.

Table 7: Intraday accuracy and precision by UV spectroscopy method

Actual Conc. (µg/ml)	Day 1	Day 2	Day 3	Mean conc.	% Error	% RSD
6	5.88	6.24	6.06	6.06	1	2.9
16	15.96	15.73	16.09	15.92	-0.45	1.14
24	23.29	24.03	24.00	23.77	-0.94	1.76

Estimation Parameter of Powder Blend

The estimation parameter like angle of repose, bulk density, tapped density, Hausner's ratio, given the following table given below.

Table 8: Evaluation parameters and values;

Parameters	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉
Bulk density	0.299	0.30	0.30	0.306	0.30	0.30	0.30	0.306	0.307
Tapped density	0.45	0.44	0.43	0.434	0.434	0.428	0.428	0.422	0.424
Hausner's ratio	1.43	1.41	1.43	1.41	1.44	1.426	1.42	1.37	1.36
Angle of repose	27°.08'	27°.36'	28°.16'	27°.76'	28°.34'	28°.55'	29°.21'	30°.11'	30°.26'

FT-IR Analysis

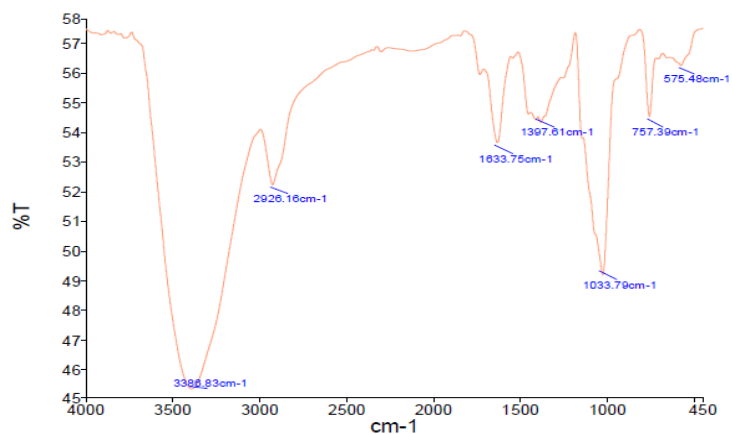


Figure 3: FTIR of ONDCL (Pure Drug)

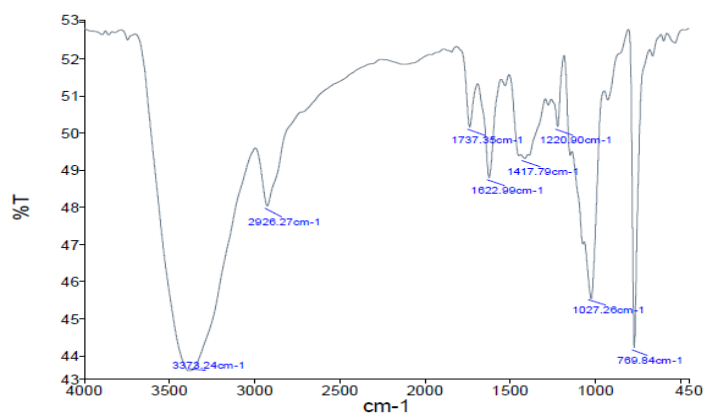


Figure 4: FTIR of ONDCL and HPMC K15M

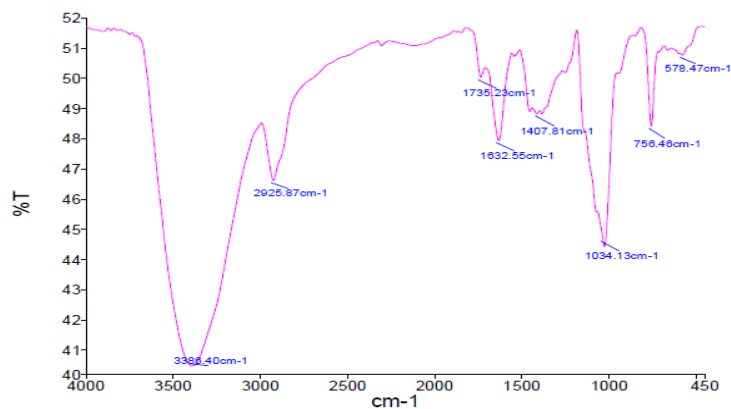


Figure 5: FTIR of ONDCL and Guargum

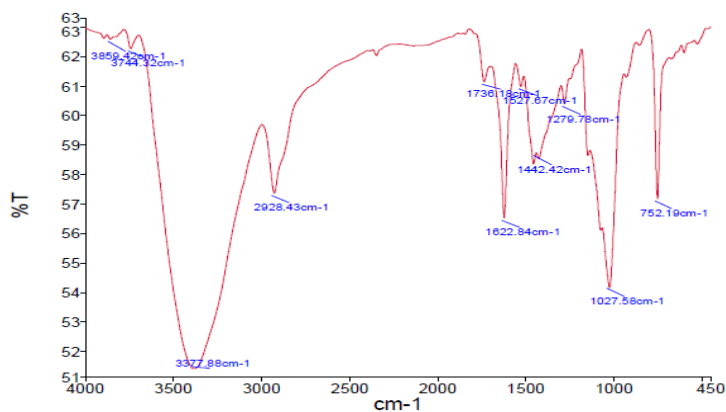


Figure 6: FTIR of ONDCL and Sodium Carbonate

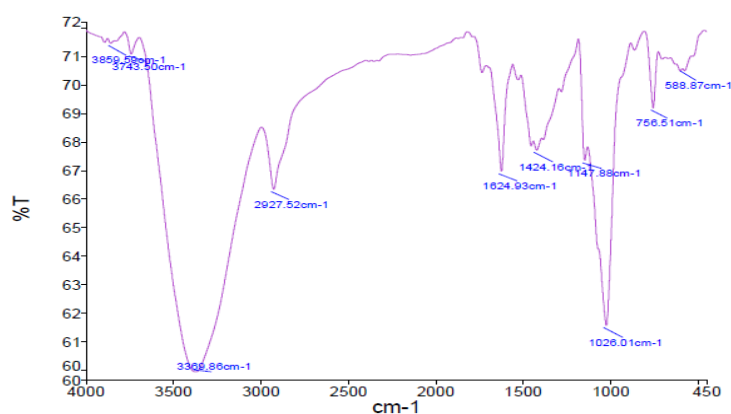


Figure 7: FTIR of ONDCL and Chitosan

Evaluation of Formulated Tablets

In the estimation parameters of the formulations like diameter, hardness, weight variation, thickness, friability, and percentage drug Ingredient were given in below table.

Table 9: Evaluation parameters and their values

PARAMETERS	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Weight variation	99±1	99±1	99±1	99±1	99±1	99±1	99±1	99±1	99±1
Thickness	1.67	1.66	1.68	1.69	1.68	1.67	1.68	1.66	1.67
Diameter	4.00	3.99	3.52	3.73	3.50	3.63	3.52	3.53	3.93
Hardness	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5
Friability	0.8%	0.5%	0.7%	0.6%	0.8%	0.5%	0.4%	0.1%	0.3%
% drug content	102%	104%	100.2%	101.1%	99.2%	99%	99.9%	99.2%	98.5%

Dissolution test

The dissolution study of Gastro Retentive Floating tablets of ONDCL using USP type 2 dissolution apparatus which shown in table no. 10.

Table 10: All formulations percentage drug release with the respect of time

% Drug release									
Time(h)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0.5	62.159	49.165	46.131	42.404	29.120	29.056	26.556	22.47540	22.654
1	78.476	70.493	64.118	70.807	47.275	45.813	41.49	32.55081	31.564
2	91.482	94.601	80.233	96.073	68.121	64.341	46.58	43.14467	42.236
3	94.063	108.64	83.331	105.60	74.004	73.953	63.78	50.31844	49.523
4	95.312	114.09	84.745	108.30	85.377	76.324	66.78	54.95942	57.425
5	97.573	117.68	86.409	110.23	86.817	79.292	72.91	57.71926	59.452
6	98.062	120.00	87.271	112.59	87.872	79.921	73.45	60.57032	62.845
7	105.74	125.76	90.326	118.48	93.074	81.743	66.71	61.72459	63.953
8	109.04	127.71	93.310	128.12	96.268	86.616	78.15	62.925	66.482
9	110.19	130.44	93.016	131.18	97.839	88.394	80.03	65.5647	67.968
10	112.78	132.18	99.190	133.27	98.449	89.792	81.43	66.5781	69.435
11	113.28	132.61	101.07	132.77	99.747	90.729	82.67	73.74959	72.624
12	114.66	127.67	101.12	137.07	99.804	90.743	87.56	82.62827	79.652
13	116.33	130.59	101.30	131.32	100.98	91.405	89.11	87.90040	88.785
14	117.40	134.28	102.85	132.48	101.36	92.333	92.22	94.80778	93.245
15	117.79	128.98	101.25	133.70	102.76	93.867	96.63	98.96598	96.865

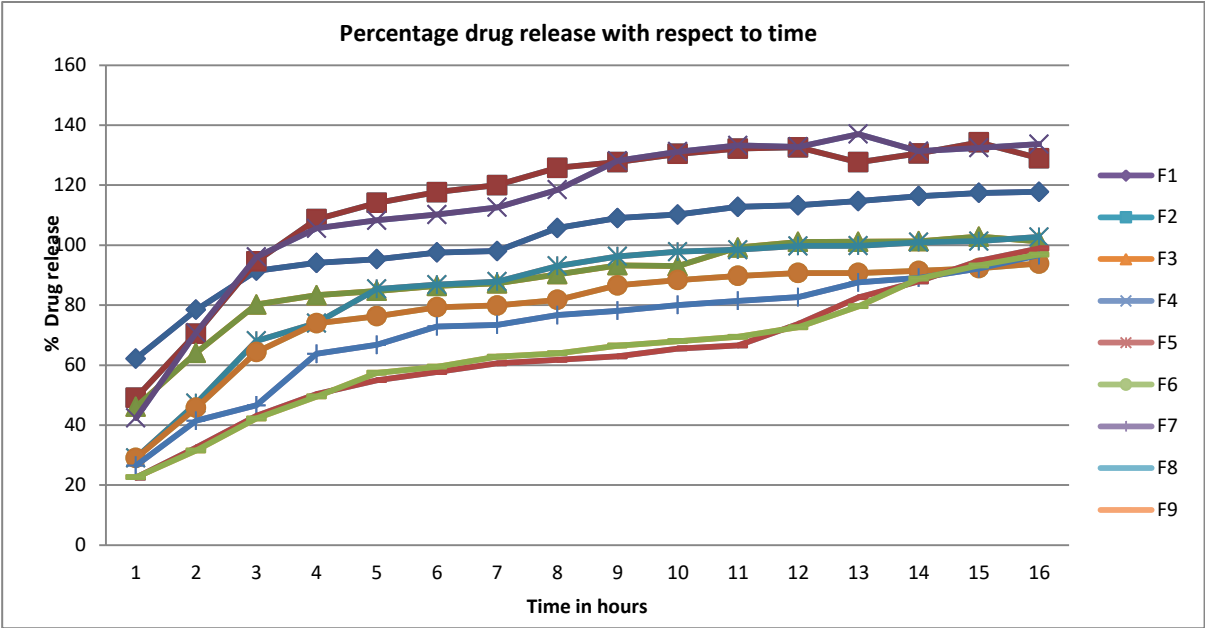


Figure 8: Release profile of ONDCL

The Gastro Retentive formulation (F₈) of ONDCL was given maximum release in the distilled water, so this formulation could be used for further study.

In Vitro Buoyancy Studies:

Among the nine formulations, the formulations F1 – F9 (containing various type of Natural polymer and HPMC K15M) Floated immediately.

All the formulations remained buoyant up to 24hours. The results were represented in Table no. 11 & Figure 9.

Table 11: Floating Study of ONDCL Tablets

Formulation Code	Buoyancy Lag Time	Total Floating Time (Hrs)
F1	Floats Instantly	>24hrs
F2	Floats Instantly	>24hrs
F3	Floats Instantly	>24hrs
F4	Floats Instantly	>24hrs
F5	Floats Instantly	>24hrs
F6	Floats Instantly	>24hrs
F7	Floats Instantly	>24hrs
F8	Floats Instantly	>24hrs
F9	Floats Instantly	>24hrs

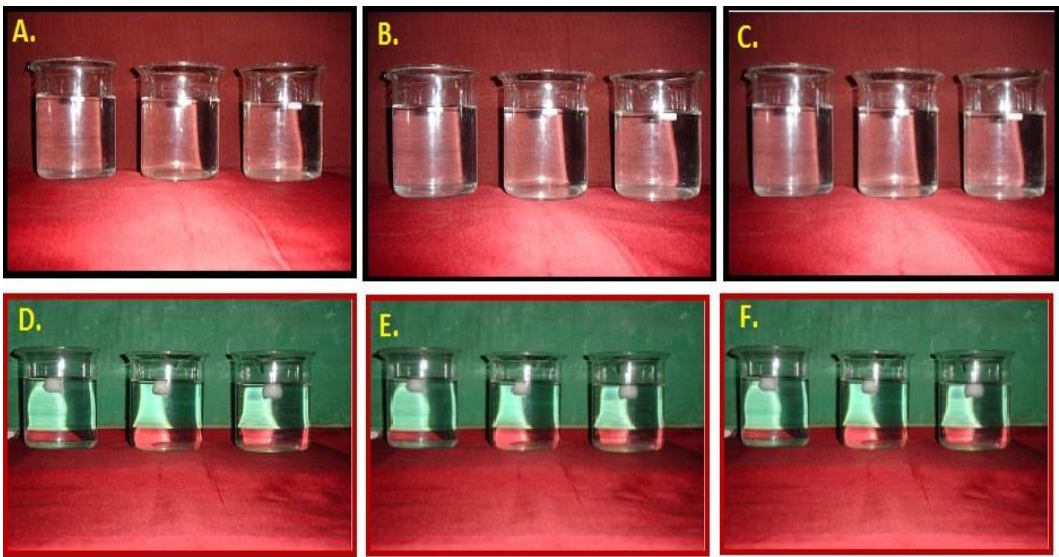


Figure 9: Floating Study (A. F1, F2 & F3 Floats instantly, B. F4, F5 & F6 Floats instantly, C. F7, F8, & F9 Floats instantly, D. F1, F2 & F3 Still Floats after 12 Hours, E. F4, F5 & F6 Still Floats after 12 Hours, F. F7, F8, & F9 Still Floats After 12 Hours)

CONCLUSION

In the present study result is visibly point out the probability to prepare Ondansetron hydrochloride in the form of FDDS with extension of GRT and controlled drug release. The upcoming studies may be extension to disclose the pharmacokinetic parameters which is associated to bioavailability and clinical studies of upcoming compounds, which may prove that this type of the formulation safely administered for the curing from nausea with improved therapeutic efficacy. Gastro retentive Floating tablet (F1, F2, F3, F4, F5, F6, F7 F8 & F9) of the Ondansetron hydrochloride were directly compressed formulation which was prepared by using HPMC K15, Chitosan, Guar gum and Sodium Bicarbonate. 'All the formulations were studied for hardness, weight variation, thickness, friability', assay, drug release and Floating studies. Formulation F₈ had achieved the target release profile of >80% in 12h. F-8 formulation stored for further product development studies.

Acknowledgments

The authors are grateful to Hygia Institute of Pharmaceutical Education & Research, Lucknow, U.P. for providing research facilities.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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