An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM (GFDDS) OF ONDANSETRON HCL

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ARTICLE INFO

Key Words

Floating ability;
Ondansetron HCl
Alginate gel beads

Access this article online Website: https://www.jgtps.com/ Quick Response Code:

ABSTRACT

Background: The novel design of an oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drug. **Objective**: The present work attempted to formulate and evaluate Gastro retentive floating drug delivery system of Ondansetron HCL. **Materials and methods:** Pre-formulation studies were performed on the drug. The diameter of beads was determined by screw gauge. The formulations were subjected to moisture content study by using an IR moisture balance by placing the beads at 40°C for 10 min. Beads were studied for swelling characteristics. Morphological examination of the surface and the internal strength of the dried ondansetron HCL beads were carried out using a scanning electronic microscope. In vitro dissolution studies of Ondansetron HCl floating beads were carried out. **Results**: Floating alginate gel beads of Ondansetron HCl showed excellent floating ability, good buoyancy and prolonged drug release. These beads were capable of reducing the frequency of administration and dose dependent side effects associated with the repeated administration of conventional Ondansetron HCl Beads. Ondansetron HCl was compatible and thus suitable for the formulation of Ondansetron HCl floating beads and floating gel. In vitro buoyancy studies were performed for all the formulations, F1 to F6 by using 0.1N HCl solutions .All the formulations were floated. The formulations showed the sustained release for 16 hrs. **Conclusion**: The developed floating beads of Ondansetron HCl may be used in clinic for prolonged drug release for at least 16 h, thereby improving the bioavailability and patient compliance.

INTRODUCTION

The novel design of an oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drug. [1] These considerations have led to the development of controlled-release dosage forms possessing gastric retention capabilities various types of drugs, which can benefit from using gastro retentive devices are (a) drugs acting locally and primarily absorbed in the stomach, (b) drugs that are poorly soluble at an alkaline PH, (c) Those with a narrow window of absorption, (d) drugs absorbed rapidly from the GI tract, and (e) drugs that degrades in the colon. [2-4] Ondansetron is in a class of medication called serotonin 5-HT_3 receptor antagonists. It works by inhibiting the action of serotonin, that may cause nausea and vomiting. After oral administration, approximately 50% of Ondansetron HCl is absorbed from intestinal tract with slower onset of action. [5, 6] Floating drug delivery system is suitable for

ondansetron as the absorption and solubility of Ondansetron HCl is high at stomach pH. Ondansetron HCl dosed was absorbed completely and received first-pass-metabolism in the liver which caused the low bioavailability. [7, 8] Consequently, it is selected as an appropriate drug for the design of gastro retentive floating drug delivery system (GFDDS) with a view to improve its oral bioavailability. In the present work, an attempt has been made to formulate GFDDS of Ondansetron HCl using HPMC K-100, sodium alginate as rate controlling polymer sodium bicarbonate as floating agent, castor oil also added to study the effect of oil concentration in the formulation, Cacl2 as cross-linking agent in order to prolong the drug release, and to impart floating properties to the Ondansetron HCl floating alginate beads. [9-11] Floating alginate beads to are subjected to evaluation, it includes floating lag time, duration of floating, percentage of beads floated, drug entrapment efficiency and drug loading, percentage in, moisture content, swelling index, density were determined. The present work was also attempted to formulate Ondansetron HCl floating beads by using sodium alginate and HPMC K-100 as polymers sodium bicarbonate as floating agent, Gel also evaluated for the following parameters like floating lag time, floating duration, PH measurement, water uptake study.

MATERIALS AND METHODS

Pre-formulation Studies It is extensive information to bring out good quality at high standard at which optimal dosage desired. Pre-formulation studies were performed on the drug, which included solubility and compatibility studies.

Organoleptic Properties It includes study of colour and shape floating beads by visual appearance.

Compatability study by FTIR The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, and easy to administer and safe by FTIR spectroscopy, Compatibility with excipient was confirmed by carried out IR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Formulation of Ondansetron HCl Floating Beads (Table-1 & 2) Ondansetron HCl beads were prepared using emulsion-gelation method and it was effervescent system. Sodium Alginate was dissolved in hot water by heating mantle by maintaining 40°C then Sodium Alginate is kept for cooling later Hydroxy Propyl Methyl Cellulose (K100M) and Ondansetron HCl were dissolved in sodium alginate solution with stirring. Castor oil and Sodium Bicarbonate was added to polymer solution followed by Ondansetron HCl is dissolved water. The homogenized mixture was extruded into calcium chloride solution at room temperature by using 2CC syringe by maintaining constant distance 5cm and speed 2ml per minute. The formed beads were allowed to stand for varying times in the solution for curing then separated by filtration and dried at room temperature used for further studies.

Evaluation of Ondansetron HCl Floating Beads

Study of size and morphology of Ondansetron HCl Beads: The diameter of beads was determined by screw gauge. For this purpose, 20 dried, 20 wet beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Colour and shape of dried beads of each batch was observed.

Determination of the Beads Buoyancy:

The Ondansetron HCl beads (n = 20) were kept in a beaker filled with 50 ml of 0.1 N HCl. The floating ability of beads was measured by visual observation for the overall time period of 24h and floating lag time. The beads that floated on the surface of the medium and those that settledown at the bottom were recovered separately and the floating percentage (%buoyancy) was estimated. The integrity of

the beads was also observed visually during the buoyancy test.

Percentage Yield: The total amount of beads was weighed, and the percentage yield calculated by equation, taken into consideration the weight of drug and polymer.

Percentage Yield = (Practical yield beads/Theoretical yield (Polymer + Drug) X 100.

Determination of Moisture Content: The formulations were subjected to moisture content study by using an IR moisture balance by placing the beads at 40°C for 10 min.

Swelling studies: Beads were studied for swelling characteristics. Sample from drug-loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 900 ml of 0.1 N HCl maintained at 37ºC The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

Swelling ratio = (weight of wet beads/weight of dried beads) ×100

Density measurements: The mean weight and diameter of Ondansetron HCl beads were measured and used mathematically to calculate the densities of the spherical sodium alginate beads using the following equation

D = M/V

Where V = 4/3πr3 (for a typical sphere),

Dis the Ondansetron HCl beads,

M is the Weight of beads.

V is the volume of beads and r is the radius of beads.

Determination of Drug Loading and Entrapment Efficiency: An accurately weighed amount of 10 mg of Ondansetron HCl loaded beads was dissolved in 20ml of0.1 M HCl solution. It was stirred for 2h using magnetic stirrer. The resulting solution was then filtered Ondansetron HCl content was determined spectrophotometrically at 281 nm. Actual drug content (AC) and entrapment efficiency (EE) were calculated according to the following equations. Total entrapment efficiency=surface associated drug+entraped drug.

Bulk Density: A quantity of 2gm of granules from each formula, previously lightly shaken (to break any agglomerates formed) was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at intervals. The tapping was continued until no further change in volume was noted. Loose bulk density (LBD) and tapped bulk density (TBD) were calculated using the equations

LBD=Weight of the granules/Volume of the packing

TBD=Weight of the granules/Tapped volume of the packing

Compressibility index: The loose bulk density and tapped bulk density values were considered for calculating compressibility index this can be calculated by the equation

IC=TBD-LBD/TBD

Where, TBD=Tapped bulk density of granule, LBD=Loose bulk density of granules.

Hausner ratio: The ratio of Tapped density and Bulk density gives the Hausner ratio and it was calculated using the equation

HR =TBD/LBD

Where, TBD=Tapped bulk density of the granules, LBD=Loose bilk density of the granules.

Particle Size Analysis: Particle size distribution was analyzed by placing 5gm of the formulated microspheres in a set of standard test sieves and shaken for a particular time interval using Indian Standard Sieves #16, #20, #30, #40, #60, #80 respectively. The particles collected in each sieve were weighed and the percentage particles retained was calculated.

Percentage Yield: The percent yield of each batch of formulation was calculated using the equation

%yield= (weight of microspheres)/(weight of solid starting material)×100

Scanning Electron Microscopy (SEM):

Morphological examination of the surface and the internal strength of the dried ondansetron HCL beads were carried out using a scanning electronic microscope (SEM- JEOL MODEL 8404; Japan at magnification of 5000 equipped with secondary electron at an accelerating voltage of 10 kV. The sample beads were

mounted on metal grids using double sided tape coated with gold to a thickness of about 30 mm in vacuum evaporator.

Evaluation of In-vitro Drug Release Studies and Drug Release kinetics for Floating Beads: *In vitro* dissolution studies of Ondansetron HCl floating beads were carried out in USP1 beads dissolution test apparatus-II employing a basket at 50 rpm using 900ml of 0.1N HCl at 37±0.5ºC as dissolution medium. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre-filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 281nm using UV-Visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicate. The results of in vitro release profiles obtained for all the Ondansetron HCl formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model)
2. Log cumulative percent drug remaining versus time. (First-order kinetic model)
3. Cumulative percent drug released versus square root of time (Higuchi's model)
4. Log cumulative percent drug released versus log time (korsmeyer-peppas equation)

RESULTS

Solubility Studies From the Solubility of studies Ondansetron HCl found that soluble in pH solutions of 0.1N HCL pH 4.6, pH 6.8, and 7.2.

Organoleptic Properties Ondansetron Hcl floating beads are while yellowish in colour and spherical in shape.

DISCUSSION

In the present study 6 formulations with variable concentrations of sodium alginate, calcium chloride and Castor oil. Concentration of HPMC K-100, drug and Sodium bicarbonate kept constant throughout preparation of formulations. FTIR spectrum peaks were observed with individual compounds have remain unaffected in Floating alginate bead formulations and floating gel formulations indicates Alginate beads formed were not a chemical reaction product, hence, the drug exists in original form and available for the biological action. The mean diameter of wet beads varies from 2.04 to 2.81 and for dried beads 1.02 to 1.56 Sizes of beads increases with increasing polymer concentration. Shape of beads is observed as spherical and whitish in colour. Oil concentration is another important parameter effect on size of beads. Increasing the oil concentration, the size of the beads also increased. Floating lag time of Alginate beads ranges from 2min 30sec to 7min 6 seconds. All the formulations shown less lag time to float. All the formulations exhibited excellent floating ability, percentage ranges from 75.18±0.15 to 94.36±0.67. The oil entrapped alginate beads containing sodium bicarbonate shown floating immediately and remained floating for 24 hours, but they have different floating lag time. The different lag time observed due to different polymer concentration and drug content of the beads. Increase in polymer concentration, floating lag time also increased. [12-15] Percentage yield of floating alginate beads ranges from 84.61±0.57 to 93.71±0.91. Estimation of Moisture content is performed by using IR Moisture balance; Low moisture content in all the floating alginate beads indicated the effectiveness of the adopted drying conditions. Low moisture level ensures better stability of the ondansetron HCL beads. The moisture content of floating beads ranges from 0.41 to 2.27 F4 Formulation shown lowest moisture content Swelling index of beads ranges from 33% to 51% As the amount of polymer was increased, the swelling ratio of beads increased. This result may be because of polymers maximizes the time of rehydration. The polymer mixture is also responsible for different swelling behaviour. [16-19] Density of floating beads was found in the range of 0.48 to 0.57 Density of floating beads is increased with increase in polymer concentration and decreased with increase in oil concentration cacl2 doesn't shown any effect on density of beads. Drug content and Drug entrapment was found in the range of 3.19 to 4.15 and 84.61 to 94.72 respectively On increasing % concentration of sodium alginate and oil, the percentage of drug loading and entrapment efficiency increased, but not at all oil concentration. [20-23]

Table-1: Preliminary Trial Formulations

Trail	Drug	HPMC K-100	$NaHCO_3$	Castor Oil (ml)	Sodium Alginate	$CaCl_2$
T1	50mg	50mg	1%	3ml	1%	8%
T2	50mg	50mg	1%	3ml	2%	8%
T3	50mg	50mg	1%	4ml	1%	8%
T4	50mg	50mg	1%	3ml	1%	9%
T5	50mg	50mg	1%	3ml	2%	9%
T6	50mg	50mg	1%	4ml	1%	9%

Table-2: Ondansetron HCl Floating Beads

FC	Drug	HPMC	$NaHCO_3$	Castor Oil(ml)	Sodium Alginate	$CaCl_2$
F1	50mg	50mg	1%	4ml	1%	8%
F2	50mg	75mg	1%	4ml	2%	8%
F3	50mg	100mg	1%	4ml	3%	8%
F4	50mg	50mg	1%	4ml	1%	9%
F5	50mg	75mg	1%	4ml	2%	9%
F6	50mg	100mg	1%	4ml	3%	9%

Evaluation of Ondansetron HCl Floating Beads

Compatibility Studies

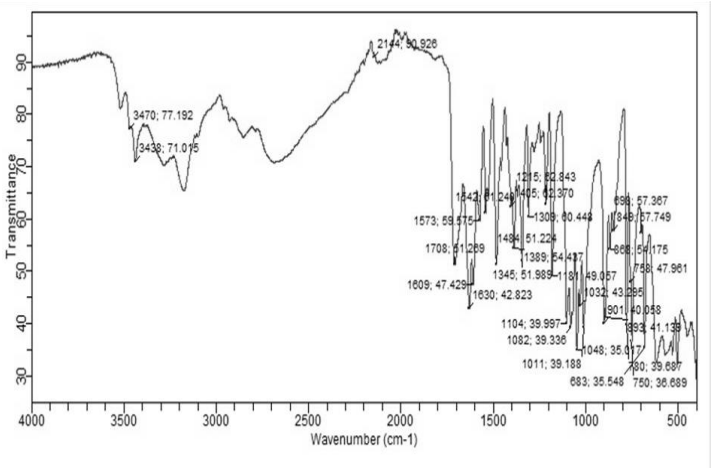

Figure-1: FTIR of Ondansetron HC

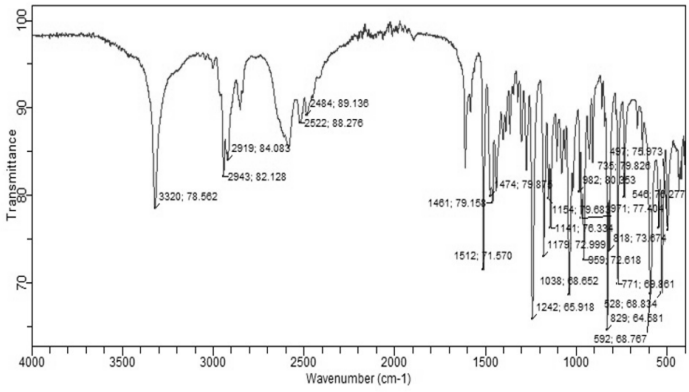

Figure-2: FTIR of Sodium Alginate

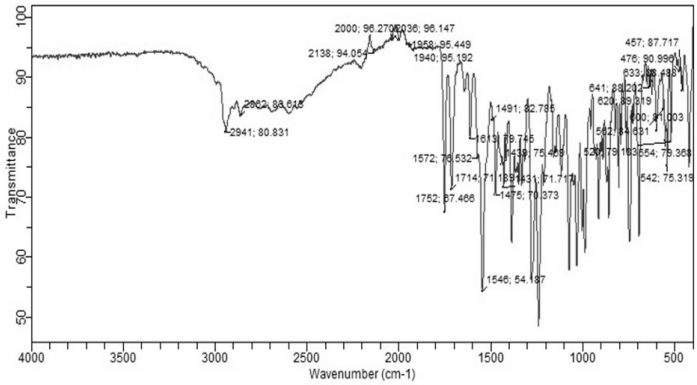

Figure-3: FTIR of HPMC

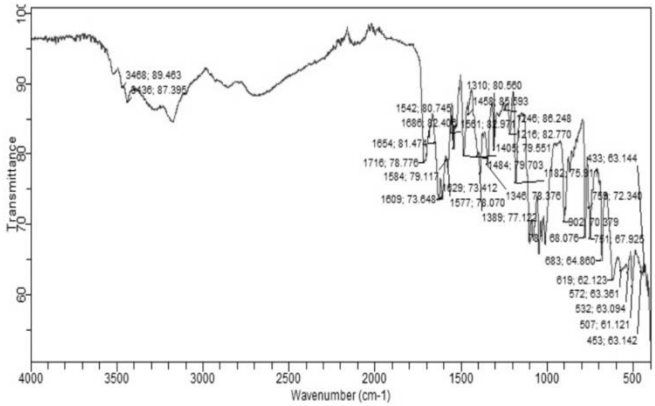

Figure-4: FTIR of BEADS

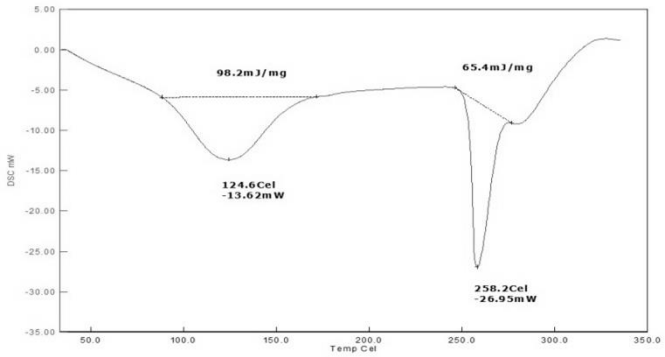

Figure-5: DSC of Ondansetron HCl

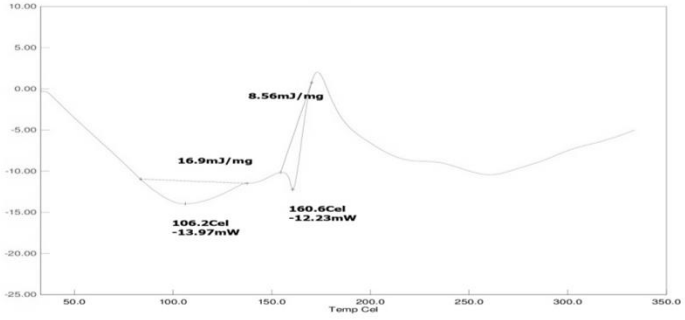

Figure-6: DSC of Beads

Evaluation of Ondansetron HCl Floating Beads:

Table-3: Evaluation Parameters of Preliminary Trail Formulations

S.no	Floating Lag time	Floating Duration	Oil Leakage	Density	%Drug Loading	Percentage Entrapment
T1	10min	21hr	No	0.81	2.01	51.12
T2	15 min	20hr	Yes	0.67	2.16	65.71
T3	3 min	22hr	No	0.62	2.32	90.8
T4	11 min	24hr	Yes	0.51	2.03	75.31
T5	7 min	24hr	Yes	0.53	3.02	86.32
T6	2 min	26hr	No	0.45	3.36	92.69

Table-4: Evaluation Parameters of Ondansetron HCl Floating Beads

FC	Floating Duration (hrs)	Curing time (min)	Floating Lag Time (min)	% Bead Buoyancy
F1	24	20	3min 5sec	92.41±0.082
F2	24	20	4min 30sec	90.08±0.78
F3	24	15	3min 10sec	96.77±0.097
F4	24	15	2min 30sec	95.76±0.17
F5	24	10	1min 2sec	84.57±0.56
F6	24	10	2min 50sec	93.78±0.091

Table-5: Evaluation Parameters of Ondansetron HCl Floating Beads

FC	Mean Diameter (mm) Wet	Dry	Density (gm/cm^3)	Swelling Index (%)
F1	2.04±0.056	1.02±0.021	0.485±0.17	33±0.76
F2	2.07±0.028	1.06±0.045	0.503±0.18	36±0.45
F3	2.08±0.032	1.09±0.043	0.503±0.87	41±0.76
F4	2.05±0.076	1.04±0.051	0.522±0.45	52±0.68
F5	2.06±0.013	1.07±0.023	0.577±0.76	51±0.19
F6	2.09±0.045	1.12±0.043	0.558±0.47	46±0.69

Table-6: Evaluation Parameters of Ondansetron HCl Floating Beads

FC	%Moisture Content	Percentage Yield	%Drug load	%Drug Entarpment
F1	0.91	70.10±0.39	4.14±0.42	90.10±0.86
F2	0.62	83.72±0.89	3.62±0.56	86.72±0.73
F3	0.96	96.61±0.34	3.36±0.78	93.71±0.91
F4	0.41	99.14±0.91	4.15±0.95	90.72±0.24
F5	0.71	90.07±0.57	3.24±0.37	84.61±0.57
F6	0.93	91.04±0.87	3.19±0.56	92.91±0.81

Table-7: *In-vitro* Drug Release Studies

Amount of Drug Release (mg)

FC	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr
F1	8.113	17.57	19.45	23.09	28.46	35.75	39.27	43.66
F2	5.27	10.26	13.75	20.53	24.84	27.66	34.08	40.02
F3	7.875	17.47	18.65	22.82	30.049	34.280	38.074	46.20
F4	3.196	8.539	12.585	16.323	20.609	23.690	30.994	33.42
F5	5.37	12.534	16.562	19.908	24.701	33.68	34.482	37.90
F6	8.65	14.824	17.03	20.12	21.50	26.85	32.24	47.38

Table-8: Zero Oder Drug Release

Time vs Cumulative Percentage of Drug Release

FC	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr
F1	16.81±0.56	37.31±0.12	39.81±0.81	48.72±0.34	64.14±0.12	73.17±0.21	81.27±0.16	84.67±0.25
F2	12.17±0.23	23.68±0.08	31.72±0.13	47.36±0.27	57.31±0.05	63.81±0.25	78.61±0.09	88.78±0.11
F3	18.01±0.17	39.02±0.11	43.19±0.67	51.26±0.05	63.19±0.03	79.36±0.07	87.17±0.57	93.18±0.01
F4	7.19±0.09	19.21±0.41	28.31±0.35	36.72±0.78	46.36±0.37	53.29±0.19	69.72±0.63	75.18±0.77
F5	12.71±0.15	29.63±0.47	39.15±0.24	47.06±0.56	58.39±0.72	79.63±0.67	81.51±0.89	89.61±0.68
F6	21.17±0.78	36.28±0.34	41.69±0.61	49.26±0.45	52.63±0.96	65.72±0.34	78.91±0.17	94.36±0.42

Table-9: First Order Drug Release

Time vs Log percentage of unreleased Drug

FC	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr
F1	1.92	1.79	1.77	1.70	1.55	1.42	1.27	0.93
F2	1.94	1.88	1.83	1.72	1.63	1.55	1.33	1.04
F3	1.91	1.78	1.75	1.68	1.56	1.31	1.10	0.76
F4	1.96	1.90	1.85	1.80	1.72	1.66	1.48	1.39
F5	1.94	1.84	1.78	1.72	1.61	1.30	1.26	1.01
F6	1.89	1.80	1.76	1.70	1.67	1.53	1.32	1.63

Table-10: Higuchi Pharmacokinetic Model

Square root of time vs Percentage of Drug Release

FC	1.41	2	2.44	2.82	3.16	3.46	3.74	4
F1	18.01	39.02	43.19	51.26	63.10	79.36	87.17	84.18
F2	12.17	23.68	31.72	47.36	57.31	63.81	78.61	88.78
F3	16.81	37.31	39.81	48.72	64.14	73.17	81.27	84.67
F4	21.17	36.28	41.69	49.26	52.63	65.72	78.91	95.36
F5	12.71	29.63	39.15	47.06	58.39	79.63	81.51	89.61
F6	7.19	19.21	28.31	36.72	46.36	53.29	69.72	75.18

Table-11: Peppas Pharmacokinetic Model

Log Time vs Log Percentage of Drug Release

FC	0.30	0.602	0.77	0.90	1	1.07	1.14	1.20
F1	1.22	1.57	1.59	1.68	1.80	1.86	1.90	1.92
F2	1.08	1.37	1.50	1.67	1.75	1.80	1.89	1.94
F3	1.255	1.59	1.63	1.70	1.80	1.89	1.94	1.97
F4	0.85	1.28	1.44	1.56	1.66	1.72	1.84	1.87
F5	1.10	1.47	1.59	1.67	1.766	1.90	1.91	1.95
F6	1.32	1.55	1.62	1.69	1.72	1.81	1.89	1.99

Table-12: Drug Release Kinetics

FC	Zero order		First Order		Higuchi		Peppas	
	R^2	K_0%hr	R^2	K_0%hr	R^2	K_0%hr	R^2	N
F1	0.9906	24.193	-0.9537	0.14	0.986	35.67	0.988	0.51
F2	0.9971	13.253	-0.9548	0.070	0988	44.92	0.988	0.85
F3	0.9856	23.604	-0.9746	0.141	0.9891	80.01	0.986	0.80
F4	0.9868	17.399	0.9738	0.105	0.9692	58.98	0.9847	0.43
F5	0.9891	19.483	0.9789	0.107	0.9878	66.045	0.9936	0.67
F6	0.9967	13.841	-0.9744	0.061	0.9874	46.918	0.9959	0.46

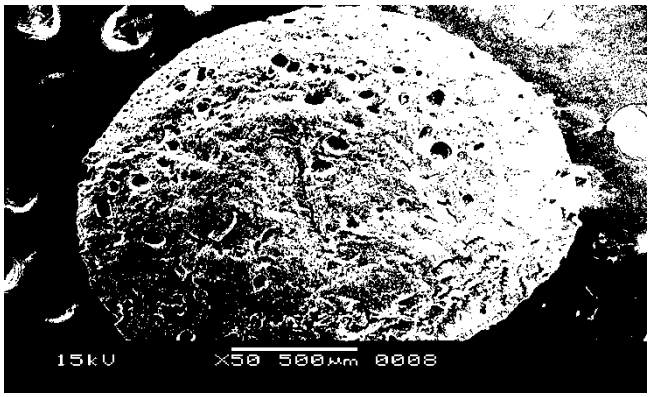

Figure-7: SEM photograph of Ondansetron HCl floating Bead

Encapsulation efficiency and Drug loading was significantly increased by varying sodium alginate. This indicates that at higher amounts of use of sodium alginate higher encapsulation efficiency was obtained due to retardation of drug migration and loss to the external aqueous phases. Similar results were observed with floating Ondansetron HCl microspheres prepared by using hydroxypropyl methyl cellulose and Sodium alginate as polymers. It is observed that increasing $CaCl_2$ concentration increased the drug percentage yield and encapsulation efficiency This may be due to better cross-linking reaction of sodium alginate present in the bead structure with the more abundant presence of calcium ions, thus a better barrier entrapping the drug inside the polymeric matrix structure of the beads is provided. Similar results were observed with calcium. [24-27] *In vitro* drug release studies of Ondansetron HCl were studied by USP 1 dissolution apparatus. Drug release was found to be highest F3, F4. Cumulative release of Ondansetron HCl was decreased with increase in sodium alginate concentration and also calcium chloride concentration. The most retardant drug release effect observed indicates that the release rate is controlled by wall thickness: an increase in polymer ratio will increase the coat thickness surrounding the drug particles, thereby increasing the distance travelled by the drug through the coat causing a greater impedance to drug release. The release was found to be steady and extended upto16 hrs. The in vitro drug release showed the highest regression coefficient value for zero order models indicates diffusion to be the predominant mechanism of drug release. All the formulations follow zero order. In floating alginate bead formulation, most of the formulations shown n value > 0.5 it indicates drug release is by non-Fickian mechanism. [28-30]

CONCLUSION

It was concluded that Floating alginate beads shown extended drug release by 24hours. The developed floating beads of Ondansetron HCl may be used in clinic for prolonged drug release for at least 16 h, thereby improving the bioavailability and patient compliance. The work can be extended to the in vivo studies to conclude in vitro and in vivo correlation. The formulation of floating drug delivery system can be tried with different grades of HPMC and other swellable polymers.

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