Formulation Development and Evaluation of Floating Tablet Of Ondansetron Hydrochloride In Combination With Ranitidine Hydrochloride

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Abstract:
Gastroretention 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. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches. Ranitidine is given in combination with ondansetron.In women with heartburn/acid reflux and nausea/vomiting of pregnancy, an observational study found that acid-reducing pharmacotherapy (e.g. antacids, H2 blockers, proton pump inhibitors) combined with anti-emetic therapy resulted in significant improvement in symptoms and well-being three to four days after beginning therapy. The aim of the present study is to prepare fine floating tablets of the combination of the two and investigate the possibility of those tablets as a delivery system for controlled release of ondansetron and immediate release of ranitidine.

Key words: HPMC K 30, PVP K30, Floating drug delivery system, Gastro retentive drug delivery system, Combination, Floating lag time.

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high level of patient compliances. More than50% of the drug delivery systems available in the market are oral drug delivery systems. Controlled-Release drug delivery system (CRDDS) provides drug release at a predetermined, predictable and controlled rate. Controlled-Release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time 3.1 Research Envisaged Oral route was one of the most convenient and preferable ways for drug administration , when the bioavailability of peroral drug delivery systems was determined by various factors, including the retention time of those dosage forms within the gastrointestinal tract (GIT).

It has been reported that the extent of drug absorption from the GIT was related to their contact time with the small intestinal mucosa, while most of the conventional oral delivery systems have shown some limited bioavailability due to fast gastric- 16 emptying time .

Thus, the real challenge of developing a controlled drug delivery system was not just to sustain the drug release but also to prolong the residence time of the dosage form in the stomach or the upper small intestine until all drug released at the desired rate. Hence, an optimum gastro retentive dosage forms system could be defined as a system which would retain in the stomach for a sufficient time interval against physiological barriers with drug releasing in a controlled manner, and finally be easily metabolized in the body.

Floating drug delivery system (FDDS) could basically float in the gastric fluid and prolong GRT to obtain sufficient drug bioavailability, because of their lower bulk density compared to that of the aqueous medium.Ondansetronis a drug of choice in antiemetic category and gives significant result in case of

pregnant women to control severe vomiting. In addition to this acid-suppressive therapy using H2 receptors antagonist e.g. Ranitidine is given in combination with ondansetron.

In women with heartburn/acid reflux and nausea/vomiting of pregnancy, an observational study found that acid-reducing pharmacotherapy combined with anti-emetic therapy resulted in significant improvement in symptoms and well-being three to four days after beginning therapy. The aim of the present study is to prepare fine floating tablets of the combination of the two and investigate the possibility of those tablets as a delivery system for controlled release of Ondansetron and Ranitidine.

EXPERIMENTAL AND RESULTS

Selection of Method for Compression:

The major challenge for tablet manufacture comes from the powder characteristics of material compressed. There are number of compression technology available in pharmaceutical industry.Tablets have been made by granulation, a process that imparts to be primary requiste to formulation for fluidity and compatibility on these bases granulation process can be divided as:

Direct compression:

The term “direct compression” is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

Formulation Development:

Prepration of Instant Layer of Ranitidine hydrochloride (Phase-1)

Fast dissolving tablets of Ranitidine hydrochloridewere prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac- Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included An gle of repose, Bulk density, Tap density, Carr’s index and Hausner’s ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a ‘Rimek mini press 16 station rotary compression machine. Nine formulations of Ranitidine hydrochloride granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 200 mg, were obtained. Composition of tablets is mentioned in Table .

Table 1: Composition of Ranitidine hydrochloride Fast Dissolving Tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Ranitidine hydrochloride	150	150	150	150	150	150	150	150	150
Sodium Starch glycolate	5	7.5	10	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	5	7.5	10	_	_	_
Crospovidone	_	_	_	_	_	_	5	7.5	10
Microcrystalline cellulose	34	31.5	29	34	31.5	29	34	31.5	29
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	200	200	200	200	200	200	200	200	200

Evaluation of Precompression Parameter (Mahalingan *et al.*, 2009)

1. **Angle of repose (θ)**: The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

Table No. 2: Relationship between Angle of Repose (θ) and flow properties

S. No.	Angle of Repose (θ) (degrees)	Flow
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable*
4.	>40	Very poor

***Adding glidant E.g. Talc may improve flow properties**

2. **Bulk density:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

3. **Carr's Compressibility index**: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

Table No. 3: Grading of the powders for their flow properties according to Carr's Index

S. No.	Carr's Compressibility index	Flow
1.	5 – 15	Excellent
2.	12 – 16	Good
3.	*18 – 21	Fair to passable
4.	*23 – 35	Poor
5.	33 – 38	Very poor
6.	>40	Very very poor

***Adding glidant E.g. Talc should improve the flow properties**

4. **Hausners ratio:** It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Table 4:results of pre-compressional parameters of Ranitidine Hcl

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
IF1	0.34	0.43	20.93	1.26	$42^0 25$
IF2	0.33	0.42	21.43	1.27	$42^0 25$
IF3	0.34	0.43	20.93	1.26	$41^0 36$
IF4	0.35	0.4	12.50	1.14	$42^0 26$
IF5	0.34	0.43	20.93	1.26	$43^0 15$
IF6	0.33	0.41	19.51	1.24	$43^0 36$
IF7	0.34	0.42	19.05	1.24	$40^0 56$
IF8	0.35	0.43	18.60	1.23	$41^0 26$
IF9	0.34	0.41	17.07	1.21	$40^0 23$

Evaluation of post compression Parameter

5. **Shape and colour of tablets:**

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

6. **Thickness test**

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

7. **Weight variation test**

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed (Table No.6.15).

Table No. 5: Percentage deviation in weight variation

S. no.	Average weight of a tablet	Percentage deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324 mg	7.5
3.	324 mg or more	5

In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

8. Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

9. **Friability test**

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out,

dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-
The test complies if tablets not loose more than 1% of their weight

Uniformity of drug content:
The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (simulated gastric uid of pH
1.2 without enzymes) and sonicated for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 296.0nm for Ranitidine Hydrochloride.

Table 6: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drugcontent (%)
IF1	3.13 ± 0.21	0.8217± 0.01	Passes	1.42 ±0.03	99.41±0.42
IF2	3.10 ± 0.30	0.7262 ±0.05	Passes	1.45 ±0.05	99.77±0.51
IF3	3.11 ± 0.50	0.5314 ±0.03	Passes	1.41 ±0.03	98.53±0.71
IF4	3.13 ± 0.29	0.6425 ±0.11	Passes	1.40±0.06	99.41±0.49
IF5	3.11 ± 0.51	0.6346 ±0.05	Passes	1.44 ±0.03	99.33±0.66
IF6	3.21 ± 0.40	0.7114 ±0.16	Passes	1.46 ±0.05	98.51±0.75
IF7	3.26 ± 0.29	0.5612 ±0.07	Passes	1.40 ±0.04	99.57±0.42
IF8	3.27 ± 0.71	0.8554 ±0.11	Passes	1.43 ±0.05	98.33±0.62
IF9	3.12± 0.42	0.7377 ±0.15	Passes	1.42 ±0.04	99.65±0.48

Table 7: Results of post-compressional parameters of all formulations

Formulation code	In vitro Disintegration Time (sec.) (n=3) Mean ± SD
IF1	12±1
IF2	10±2
IF3	8±1
IF4	10±2
IF5	7±2
IF6	5±2
IF7	11±1
IF8	8±2
IF9	7±2

Method for Preparation of Ondansetron Hydrochloride Floating tablet:
Direct compression was followed to manufacture the gas generating floating tablets of Ondansetron Hydrochloride. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers, selected drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table No. 6.12 and all the formulation were used for further evaluations parameters.

Optimization of Gastro retentive floating tablets of Ondansetron Hydrochloride

Table No. 8: various formulations of Ondansetron Hydrochloride Gastro retentive Floating tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ondansetron Hydrochloride	8	8	8	8	8	8	8	8	8
HPMC K 15	_	_	_	160	170	180	80	85	90
HPMC K 4	160	170	180	_	_	_	80	85	90
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	82	72	62	82	72	62	82	72	62
Total Weight	300	300	300	300	300	300	300	300	300

Excipients like Sodium bicarbonate, citric acid anhydrous, Magnesium Stearate were selected 1 for the study. Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. Steps involved in the manufacture of tablets, first the drug, polymer and other excipients selected were passed through 40- mesh 'sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5min.

Table No.9:Result of Pre-Compression Properties of Ondansetron Hydrochloride FGR Tablets

Material	Angle of repose(Degree)	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
Ondansetron Hydrochloride					
F1	30.31	0.582±0.002	0.732±0.007	27.33±0.73	0.721±0.01
F2	29.35	0.581±0.008	0.730±0.006	28.33±0.72	0.723±0.01
F3	27.82	0.576±0.002	0.728±0.005	27.30±0.68	0.720±0.01
F4	30.69	0.570±0.007	0.729±0.003	29.30±0.65	0.726±0.03
F5	28.30	0.580±0.003	0.735±0.004	30.30±0.61	0.730±0.04
F6	30.28	0.585±0.003	0.732±0.006	32.80±0.64	0.728±0.06
F7	28.46	0.582±0.004	0.742±0.003	36.24±0.70	0.720±0.03
F8	29.49	0.579±0.002	0.792±0.005	29.72±0.68	0.720±0.04
F9	30.13	0.584±0.004	0.768±0.004	28.52±0.71	0.739±0.03

Evaluation of tablets:
All the tablets were evaluated for following different parameters which includes;

General Appearance
Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter
Thickness and diameter of tablets were determined using Vernier caliper. Five tablets fromeach batch were used, and an average value was calculated.

Drug content
Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N Hcl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and react with dye and analyzed for drug content by UV spectrophotometer at a λmax of 414.0 nm using of 0.1 N Hcl as blank.

Table No. 10:Results of Post Compression Properties of Ondansetron Hydrochloride FGR Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)
F1	3.53±0.05	4.8	300.19± 2.94	0.58 ± 0.10	98.33± 0.92	8
F2	3.94± 0.10	4.4	300.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	10
F3	3.96± 0.05	4.5	300.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	>12
F4	3.95± 0.05	4.7	300.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	>12
F5	3.93± 0.10	5.2	300.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	>12
F6	4.03± 0.06	5.3	300.16 ± 2.33	0.27 ± 0.05	97.50± 1.81	>12
F7	4.05± 0.05	4.8	300.18 ± 3.11	0.29 ± 0.08	98.34 ± 0.37	>12
F8	3.98± 0.05	4.5	300.04 ± 2.56	0.34 ± 0.12	98.31± 0.91	>12
F9	3.69±0.06	4.9	300.02±2.11	0.32±0.09	97.83±0.59	>12

Hardness
For each formulation, the hardness of five tablets was determined using the Monsantohardness tester (Cadmach).

Friability
The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab).Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed afterremoval of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight
Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al* .The tablets were placed separately in a100 ml glass beaker containing 2 simulated gastric fluid (SGF),pH1.2as per USP.Thetime required for the tablet to rise to the surface and float was determined as floating lag time.

Table No. 11: Results of *in-vitro* buoyancy study of Ondansetron Hydrochloride FGR Floating time

Formulation Code	Floating lag times (sec)	Total Floating Time (hrs)
F1	55s	>8
F2	35s	>10
F3	30s	>12
F4	75s	>12
F5	60s	>12
F6	80s	>12
F7	110s	>10
F8	95s	>10
F9	106s	>8

Figure 12: Photographs taken during *in-vitro* floating study of formula F8 in 200 ml 0.1 N HCl at different time intervals.

Dissolution rate studies(IP, 2007)

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75.One Ondansetron Hydrochloride tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to

10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL and take the absorbance at 252.0 nm using spectroscopy.

***In vitro* drug release study of Gastro retentive floating tablet**(IP, 2007)

Table No. 13: *In-vitro* Drug Release Study of GRF Tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26	07.28
1	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87	12.56
1.5	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28	18.58

2	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21	40.28
3	76.34	66.11	67.21	65.71	50.56	67.02	71.13	68.24	56.98
4	82.23	77.33	75.11	82.34	55.00	88.13	91.23	89.12	73.98
6	82.55	97.13	87.13	83.00	56.00	99.13	92.00	99.25	84.16
8	83.00	97.10	94.23	83.21	57.25	99.99	93.00	99.56	89.26
12	84.21	97.23	99.26	83.50	57.85	97.67	94.56	99.76	94.56

Release Kinetics of Ondansetron Hydrochloride Floating Tablets

Table No.14: Zero order release kinetics data Ondansetron Hydrochloride Floating tablet with HPMC K-4 as Binder

S. No.	Time in hrs	% Cumulative drug release		
		F1	F2	F3
1.	0	0	0	0
2.	0.5	08.23	07.14	07.24
3.	1.0	12.32	10.23	11.45
4.	1.5	26.23	22.42	24.23
5.	2.0	42.45	40.32	45.23
6.	3.0	76.23	66.11	67.21
7.	4.0	82.23	77.33	75.11
8.	6.0	82.55	97.13	87.13
9.	8.0	83.00	97.10	94.23
10.	12.0	84.21	97.23	99.26

Table No.15: Zero order release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K-15 as Binder

S. No.	Time inhrs	% Cumulative drug release		
		F4	F5	F6
1.	0	0	0	0
2.	0.5	08.23	07.23	07.45
3.	1.0	10.45	10.45	11.23
4.	1.5	23.76	31.23	38.23
5.	2.0	44.23	48.23	46.32
6.	3.0	65.71	50.565	61.02
7.	4.0	82.34	55.00	88.13
8.	6.0	83.00	56.00	99.13
9.	8.0	83.21	57.25	99.99
10.	12.0	83.50	57.85	99.87

Table No. 15: Zero order release kinetics data OndansetronHydrochloride floating tablet with HPMC K-4+ HPMC K-15 as Binder

S. No.	Time in hrs	% Cumulative drug release		
		F7	F8	F9
1.	0	0	0	0
2.	0.5	08.32	07.26	07.28
3.	1.0	12.23	11.87	12.56
4.	1.5	32.13	26.28	18.58
5.	2.0	47.14	38.21	40.28
6.	3.0	71.13	68.24	56.98
7.	4.0	91.23	89.12	73.98
8.	6.0	92.00	99.25	84.16
9.	8.0	93.00	99.56	89.26
10.	12.0	94.56	99.76	94.56

Table No. 16: First order release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K-4 as Binder

S. No.	Time in hrs	% Cumulative drug release		
		F1	F2	F3
1.	0	0	0	0
2.	0.5	1.967	1.967	1.967
3.	1.0	1.941	1.953	1.947
4.	1.5	1.91	1.889	1.879
5.	2.0	1.776	1.775	1.738
6.	3.0	1.633	1.53	1.515
7.	4.0	1.415	1.355	1.395
8.	6.0	1.199	0.457	1.109
9.	8.0	1.031	0.462	0.761
10.	12.0	0.735	0.442	-0.13

Table No. 17: First order release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K-15 as Binder

S.No.	Time in hrs	Log % Cumulative drug remain to be release		
		F4	F5	F6
1.	0	0	0	0
2.	0.5	1.9627	1.96741	1.9663764
3.	1	1.95207	1.95207	1.9482662
4.	1.5	1.88218	1.8374	1.7907776
5.	2	1.7464	1.71408	1.7298125
6.	3	1.53517	1.69408	1.5182507
7.	4	1.24699	1.65321	1.0744507
8.	6	1.23045	1.64345	1.02564
9.	8	1.22505	1.63094	1.0265478
10.	12	1.21748	1.6248	1.0365

Table No 18: First order release kinetics data OndansetronHydrochloride floating tablet with HPMC K-4 + HPMC K-15 as Binder

S.No.	Time inhrs	Log % Cumulative drug remain to be release		
		F7	F8	F9
1.	0	0	0	0
2.	0.5	0.2938044	1.967	1.9671734
3.	1	0.2889196	1.945	1.9417101
4.	1.5	0.2711443	1.867	1.9107311
5.	2	0.252853	1.79	1.7761198
6.	3	0.1763807	1.501	1.6336704
7.	4	0.0153598	1.036	1.4153073
8.	6	-0.9065783	0.124	1.1997552
9.	8	-0.44855	0.356	1.0310043
10.	12	-0.2083094	0.619	0.7355989

Table No.19: Higuchi release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K-4 as Binder

S.No.	Root Time	% Cumulative drug remain to be release		
		F1	F2	F3
1.	0	0	0	0
2.	0.70711	8.23	7.14	7.24
3.	1	12.32	10.23	11.45
4.	1.27674	26.23	22.42	24.23
5.	1.41421	42.45	40.32	45.23
6.	1.73205	76.34	66.11	67.21
7.	2	82.23	77.33	75.11
8.	2.44949	82.55	97.13	87.13
9.	2.82843	83	97.1	94.23
10.	3.4641	84.21	97.23	99.26

Table No. 20: Higuchi release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K-15 as Binder

S.No.	Root Time	% Cumulative drug remain to be release		
		F4	F5	F6
1.	0	0	0	0
2.	0.70711	8.23	7.23	7.45
3.	1	10.45	10.45	11.23
4.	1.27674	23.76	31.23	38.23
5.	1.41421	44.23	48.23	46.32
6.	1.73205	65.71	50.56	67.02
7.	2	82.34	55	88.13
8.	2.44949	83	56	99.13
9.	2.82843	83.21	57.25	99.99
10.	3.4641	83.5	57.85	99.87

Table No. 21: Higuchi release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K4 + K-15 as Binder

S.No.	Root Time	% Cumulative drug remain to be release		
		F7	F8	F9
1.	0	0	0	0
2.	0.70711	8.32	7.26	7.28
3.	1	12.23	11.87	12.56
4.	1.27674	32.13	26.28	18.58
5.	1.41421	47.14	38.21	40.28
6.	1.73205	71.13	68.24	56.98
7.	2	91.23	89.12	73.98
8.	2.44949	92	99.25	84.16
9.	2.82843	93	99.56	89.26
10.	3.4641	94.56	99.76	94.56

Table No.22: Korsmayer Papas release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K4as Binder

S.No.	log Time	Log cumulative % drug release		
		F1	F2	F3
1.	0	0	0	0
2.	-0.30103	0.9154	0.8537	0.85974
3.	0	1.09061	1.00988	1.05881
4.	0.176091	1.4188	1.35064	1.38435
5.	0.30103	1.62788	1.60552	1.65543
6.	0.477121	1.88276	1.82027	1.82743
7.	0.60206	1.91503	1.88835	1.8757
8.	0.778151	1.91672	1.98735	1.94017
9.	0.90309	1.91908	1.98722	1.97419
10.	1.079181	1.92536	1.9878	1.99677

Table No. 23: Korsmayer Papas release kinetics data Ondansetron Hydrochloride floating tablet with HPMC K-15 as Binder

S.No.	log Time	Log cumulative % drug release		
		F4	F5	F6
1.	0	0	0	0
2.	-0.30103	0.9154	0.85914	0.87216
3.	0	1.01912	1.01912	1.05038
4.	0.176091	1.37585	1.49457	1.5824
5.	0.30103	1.64572	1.68332	1.66577
6.	0.477121	1.81763	1.70381	1.8262
7.	0.60206	1.91561	1.74036	1.94512
8.	0.778151	1.91908	1.74819	1.99621
9.	0.90309	1.92018	1.75778	1.99996
10.	1.079181	1.92169	1.7623	1.99944

Table No.24: Korsmayer Papas release kinetics data OndansetronHydrochloride floating tablet with HPMC K-4 + K-15 as Binder

S.No.	log Time	Log cumulative % drug release		
		F7	F8	F9
1.	0	0	0	0
2.	-0.30103	0.92012	0.86094	0.86213

3.	0	1.08743	1.07445	1.09899
4.	0.176091	1.50691	1.41963	1.26905
5.	0.30103	1.67339	1.58218	1.60509
6.	0.477121	1.85205	1.83404	1.75572
7.	0.60206	1.96014	1.94998	1.86911
8.	0.778151	1.96379	1.99673	1.92511
9.	0.90309	1.96848	1.99808	1.95066
10.	1.079181	1.97571	1.99896	1.97571

Table No. 25: Kinetic data of Ondansetron Hydrochloride floating Tablet in comparison with all Formulation

Formulation		**Zero Order**	**First order**	**Higuchi**	**Korsmayer papas**	**Best fitted Model**
F1	r2	0.441	0.631	0.810	0.849	Korsmayer Papas
F2	r2	0.668	0.858	0.868	0.898	Korsmayer Papas
F3	r2	0.675	0.981	0.896	0.896	First Order
F4	r2	0.496	0.678	0.828	0.852	Korsmayer Papas
F5	r2	0.154	0.333	0.762	0.755	Higuchi
F6	r2	0.581	0.797	0.873	0.860	Higuchi
F7	r2	0.512	0.793	0.847	0.859	Korsmayer Papas
F8	r2	0.632	0.909	0.857	0.899	First Order
F9	r2	0.708	0.969	0.894	0.916	First Order

When the regression coefficient values of were compared, it was observed that 'r' values of higuchi was maximum i.e. **0.909** hence indicating drug release from formulations was found to follow higuchi kinetics.

Formulation development of bilayer tablet

Optimized formulation IF-6 of Instant release layer and optimized formulation of F-8 for control release used for formulation of Bi-layer tablet.

Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

1. General Appearance

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

2. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

3. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

4. Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

5. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

6. Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 150 mg of Ondansetron Hydrochloride was transferred to 100ml standard flask. The powder was dissolved in 150 ml of 0.1 N HCL and made up to volume with 0.1 N HCL. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.1 ml to 10 ml suitably (10 ppm of ranitidine hydrochloride)and prepare individually 10 ppm solution of Ranitidine hydrochlorideanddetermine the Conc. of both drugs using 252 nm for ondansetron Hydrochloride and 298 nm for ranitidine Hydrochloride respectively.

7. Dissolution rate studies

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for OndansetronHydrochloride SR and 1 hr for Ranitidine hydrochlorideIR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5 C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Ultraviolet Labindia 3000+) spectrophotometer at λmax252 nm for ondansetron Hydrochloride and 298 nm for ranitidine Hydrochloride respectively.

Evaluation of bilayer floating tablets

Table No.26:Post-Compressional Parameters of Optimized Formulation

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	5.13 ± 0.21	0.8217± 0.01	Passes	5.42 ±0.03

6. Drug content

Table No. 27:Results of Drug content analysis

Formulation	Ondansetron Hydrochloride (% Label Claim)	Ranitidine Hydrochloride (% Label Claim)
In-house Bilayer floatingtablet	99.56	99.56

7. Dissolution rate studies of Instant layer

Table No. 28:Results of Dissolution rate studies of Instant layer

Time (min)	% Drug Release of Instant layer
15	99.45 %

8. Dissolution rate studies of Floating layer

Table No. 29:Results of Dissolution rate studies of Floating layer

Time (Hour)	% Drug Release of Floating layer
0.5	7.98
1	10.65
1.5	18.51
2	25.25
4	36.23
6	52.25
8	76.26
10	85.25
12	98.23

A dissolution study shows the release of Ondansetron Hydrochloride and ranitidine hydrochloride. The Instant layer of ranitidine hydrochloride release Approx 99.45 percent drug within 15 minutes and control floating layer Ondansetron Hydrochloride shows release up to 12 Hours Approx 98.23 percent of Drug release in 12 hours.

CONCLUSION

The Experiment relates to formulation and development of oral pharmaceutical bilayer tablet of ondansetron and ranitidine for administration of therapeutically and prophylactically effective amount as antiemetic drug substance to obtain both a relatively fast or quick onset of therapeutic effect and mainatainence of a therapeutically active plasma concentration for relatively long period of time. Experiment conclude that Bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

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