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Original Article

Formulation and Evaluation of Orodispersible Tablets of Ondansetron Hydrochloride

K.S.G. Arulkumaran*, J. Padmapreetha*, K. Selvaraju*, M. Ambiga*, K. Kamalanathan*

Abstract

The purpose of this research work is to formulate and evaluate the Orodispersible drug delivery system of already used therapeutic molecule to enhance bioavailability and effectiveness of the drug. Among ODT drugs, the most promising antiemetic is Ondansetron hydrochloride and it was selected for the present study. Thus the objectives of the drug work were to formulate and evaluate Orodispersible tablets of Ondansetron hydrochloride, having adequate mechanical strength, rapid disintegration and fast action. Pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index & post compression parameters like wetting time, water absorption ratio, in-vitro disintegration and in-vitro dispersion time were studied. The hardness, friability and drug content of all the formulations were found to be with in the limits. The best formulation F10 have shown good disintegration time, dissolution time and dispersion time. The best promising formulation were also being found to be stable at 40°C±75%. Finally the in-vitro drug released characteristics of best formulation was compared to commercial formulation.

Keywords: Orodispersible, Ondansetron HCL, Crospovidone, Croscarmellose sodium, superdisintegrants, dispersion, disintegration, dissolution.

Author Affilation: *Department of Pharmaceutics, KMCH College of Pharmacy, Kovai Estate, Coimbatore, Tamil Nadu - India

Reprint Request: Dr. K.S.G.Arulkumaran, Vice Principal, Kmch College Of Pharmacy, Kalapatti Road, Coimbatore-48

Email: yesmiarul@yahoo.com

Introduction

Tablets are solid preparations intended for oral administration. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy[1]. Orodispersible tablets are gaining prominence as new drug delivery systems. These dosage forms dissolves or disintegrate in oral cavity within a minute without the need of water or chewing[2]. Hence the present work was aimed to formulate the orodispersible tablets of ondansetron hydrochloride, that are designed by using natural polymer (Treated agar) and synthetic polymers namely crospovidone and croscarmellose sodium. Ondansetron hydrochloride is a selective serotonin 5-HT3 receptor antagonist indicated for the prevention of nausea and vomiting. Effervescent substances like sodium bicarbonate and tartaric acid accelerates the superdisintegrant action and masks the bitter taste of ondansetron hydrochloride[3]. Faster the drug in the solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down in to the stomach. In such case, bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both, industry and academia[4].

Materials and Methods

Ondansetron Hydrochloride was obtained as a gift sample from Madras Pharmaceuticals Chem. Limited, Chennai. Sodium bicarbonate, talc and tartaric acid were obtained as a gift sample from SDFCL Fine Chem. Limited, Mumbai. Treated agar and DEC (corn starch: mannitol) was obtained as a gift sample from Rea Chem. Laboratory Chemical, Chennai. Croscarmellose sodium was obtained as a gift sample from Mingatai Chemicals Co. Ltd, Taiwan. Crospovidone was obtained as a gift sample from ISF Technologies, Chennai. Aspartame was obtained as a gift sample from Nutra sweet company, Mumbai. Orange 1208 was obtained as a gift sample from Firminch Ltd., Mumbai. Magnesium stearate was obtained as a gift sample from Vijlak Pharma Ltd., Hyderabad.

2.1. Preparation of Directly Compressible Excipient[5]

The directly compressible excipient (DCE) was prepared using a local variety of food grade corn starch along with mannitol in 1:1 ratio using 10% w/w starch paste for granulation.

Method

All the ingredients were powdered separately in a dry, clean porcelain mortar and passed through # 60 mesh sieve and mixed well in geometrical ratio. Granulating fluid, starch paste (10% w/w) is added to the powder mixture in small quantities, while mixing thoroughly after each addition until a coherent mass was formed. Then it was passed through # 44 mesh sieve and the wet granules were spread on a paper and dried in hot air oven at 55-60°C. The dried granules were then passed through # 36 mesh sieve.

2.2. Preparation of treated agar[5]

Treated agar (TAG) powders were prepared by taking 10 gm agar powder in distilled water (100 ml) and stirring at 50 rpm with a three- bladed mechanical stirrer for one day. This causes water absorption and swelling. Then the liquid was poured in a large petri-dish and allowed for drying up to three days in incubator at 37±1°C and then the mass was pulverized and sifted through # 80 mesh sieve.

2.3. Preparation of Orodispersible tablets[5]*:*

Orodispersible tablets of Ondansetron hydrochloride were prepared by effervescent method according to the formula. All the ingredients were passed through # 60 mesh sieves separately. The drug and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Sodium bicarbonate and tartaric acid were pre-heated at a temperature of 80°C for 2 h to remove absorbed/ residual moisture and thoroughly mixed in a mortar to get a uniform powder and then added to the above blend. Then the other ingredients were mixed in geometrical order but magnesium stearate and purified talc were added at the last and mixed for further two minutes. The blend was compressed using 9 mm flat round punches to get tablets of 200 mg weight on 10-station rotary tablet machine. A batch of 60 tablets was prepared for all the designed formulations.

Table 1: Formulation design for Ondansetron hydrochloride tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	4	4	4	4	4	4	4	4	4	4
NaHCO3	18	18	18	18	18	18	18	18	18	18
Tartaric acid	18	18	18	18	18	18	18	18	18	18
Treated agar	_	10	15	20	_	_	_	_	_	_
Crospovidone	_	_	_	_	10	15	20	_	_	_
Croscarmellose sodium	_	_	_	_	_	_	_	10	15	20
Aspartame	8	8	8	8	8	8	8	8	8	8
Orange 12809	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1
DCE	146	136	131	126	136	131	126	136	131	126
Total weight	200	200	200	200	200	200	200	200	200	200

2.4. Evaluation of tablet

The prepared tablets were evaluated for various official and nonofficial specifications.

Pre-compression evaluation[6]:

The quality of a tablet is generally dictated by the quality of physiochemical properties of then granule blend prepared. There are many process variables which may affect the characteristics of the finished tablet. Hence the prepared granules were evaluated for the mass-volume relationship parameters like bulk density, tapped density, Angle of Repose, Compressibility index and Hausner's ratio. The results obtained are given in Table 2.

Table 2: Pre-compression evaluation of Ondansetron hydrochloride

Formulations	Parameters				
	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
F1	0.463±0.003	0.543±0.002	34.96±0.051	14.81±0.015	1.18±0.010
F2	0.468±0.005	0.545±0.003	31.31±0.032	14.88±0.085	1.17±0.010
F3	0.471±0.013	0.569±0.006	31.08±0.091	14.30±0.135	1.18±0.010
F4	0.481±0.041	0.561±0.001	31.24±0.250	14.31±0.120	1.15±0.030
F5	0.540±0.010	0.613±0.009	30.25±0.230	11.61±0.162	1.23±0.105
F6	0.552±0.002	0.632±0.010	30.92±0.023	12.51±0.023	1.14±0.001
F7	0.568±0.001	0.663±0.001	29.51±0.022	14.53±0.250	1.12±0.038
F8	0.414±0.005	0.479±0.008	28.83±0.031	14.26±0.300	1.16±0.005
F9	0.395±0.040	0.444±0.005	28.25±0.054	13.17±0.100	1.15±0.015
F10	0.372±0.001	0.310±0.031	28.17±0.061	13.30±0.064	1.15±0.065

Post-compression evaluation:

Weight variation[7]:

Twenty tablets were taken and their weights were determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Average weight was compared with the individual weight and the percentage deviation of individual tablet was calculated.

Thickness[8]:

The thickness of the tablets was determined by using vernier caliper of Electro lab model. Five tablets are randomly selected from each batch. It is expressed from mm and the average values were calculated.

Hardness [8]:

Hardness was determined by taking five tablets from each formulation and was measured by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^3.

Friability[9]:

The friability of the tablet was measured using a Roche friabillator (Electro lab, India).Twenty reweighed tablets were rotated at 25 rpm for 4 rpm and dropping the tablets at a height of 6 inches at each revolution and the tablets were subjected to 100 revolutions. The tablets were then dedusted using soft muslin cloth and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured as per the following formula.

Percentage friability = (Initial weight – final weight/ Initial weight) ×100

Table 3: Post-compression evaluation of Ondansetron hydrochloride

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	200.4±0.84	2.35±0.03	2.20±0.10	0.831±0.01
F2	200.2±1.35	2.34±0.01	2.13±0.20	0.781±0.03
F3	200.1±0.06	2.34±0.03	2.13±0.21	0.836±0.07
F4	200.3±0.94	2.32±0.01	2.30±0.17	0.747±0.08
F5	200.1±0.05	2.31±0.01	2.33±0.11	0.814±0.04
F6	200.3±0.94	2.34±0.01	2.40±0.26	0.832±0.01
F7	200.2±0.05	2.32±0.00	2.02±0.15	0.780±0.10
F8	199.9±1.10	2.33±0.01	2.16±0.11	0.907±0.08
F9	200.2±1.30	2.34±0.00	2.20±0.10	0.941±0.04
F10	199.8±1.34	2.32±0.01	2.26±0.05	0.922±0.01

Table 4: Post-compression evaluation of Ondansetron hydrochloride

Formulation code	*In vitro* Dispersion time(sec)	Wetting time(sec)	Disintegration time(sec)	Water absorption ratio	Assay (%)
F1	60.37±0.40	41.03±0.05	50.73±0.64	39.30±0.81	90.44±0.50
F2	49.16±0.15	35.83±0.73	42.26±0.35	33.06±0.51	96.54±0.48
F3	43.36±0.40	32.66±0.57	40.56±0.45	43.66±0.41	97.37±0.57
F4	40.52±0.44	30.23±0.32	36.13±0.20	33.56±0.58	100.85±0.16
F5	38.56±0.77	33.23±0.25	34.40±0.60	33.70±0.34	99.52±0.17
F6	35.26±0.28	31.63±0.30	32.18±0.23	27.96±0.95	100.48±0.22
F7	32.41±0.17	28.46±0.30	29.63±0.40	32.76±0.68	101.29±0.34
F8	30.37±0.22	30.40±0.36	25.26±0.17	31.36±0.32	102.55±0.48
F9	28.44±0.50	28.30±0.40	22.15±0.17	30.50±0.50	100.15±0.27
F10	26.45±0.41	26.26±0.30	20.27±0.40	29.50±0.30	99.96±0.06

***In vitro* dispersion time[10]:**

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 10ml of simulated saliva fluid of pH 6.8. After dropping a tablet in the simulated saliva fluid, the tablet started to swell quickly, broke and followed by dispersed. Five tablets from each formulation were randomly

selected and in vitro dispersion time was performed and it was expressed in seconds.

Wetting time[11]:

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place.

A piece of tissue paper folded double was placed in a petri plate (internal diameter is 6.5cm) containing 6ml of purified water. A tablet having a small amount of Eosin dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time.

Disintegration time[12]:

Disintegration time was measured using disintegration test apparatus. A tablet was placed in each six tube of the basket. The basket with the bottom surface is made up of stainless - steel screen (mesh no. 10) was immersed in water maintained at 37°C as the disintegration fluid and the paddle at 100rpm as stirring element was used. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Water absorption ratio[11]:

A piece of double folded tissue paper was kept in a petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. The weight of tablet before keeping in petri-dish was noted as (Wb) and after completely wetted tablet in petri plate was noted as (Wa). The wetted tablet was removed and reweighed. Water absorption ratio, R was determined according to the following equation.

$$R = 100 (Wa - Wb) / Wb$$

Where, Wb and Wa are before and after water absorption, respectively.

Drug content[13]:

Ten tablets from each batch were weighed and powdered. The required amount of the powder equivalent to 4 mg of ondansetron hydrochloride was dissolved in 100 ml of phosphate buffer pH6.8. From this solution 1 ml was taken and made up to 100 ml by using phosphate buffer pH6.8 and the solution was filtered by using whatman filter paper. The solution was analysed for drug content at 248nm using UV visible spectrophotometer.

2.5. In vitro drug release study[14]:

In vitro dissolution of the orodispersible tablets was studied in USP XXIII type-II dissolution test

Table 5: In vitro drug release data (F1-F10)

Formulation code	% Cumulative release					
	5 min	10 min	15 min	20 min	25 min	30 min
F1	56.15	62.08	62.95	64.37	65.80	66.69
F2	66.14	80.60	82.66	84.19	85.18	85.63
F3	66.98	82.94	83.92	85.46	86.45	87.45
F4	72.19	84.63	86.71	88.80	89.27	90.28
F5	67.80	81.78	84.94	87.57	88.03	90.67
F6	77.15	80.07	89.63	92.28	93.85	94.89
F7	74.47	90.26	92.26	94.50	95.00	96.59
F8	74.98	84.21	87.93	84.48	91.04	92.61
F9	76.65	89.74	91.31	92.88	94.46	95.50
F10	77.78	91.45	95.20	96.79	98.39	99.49

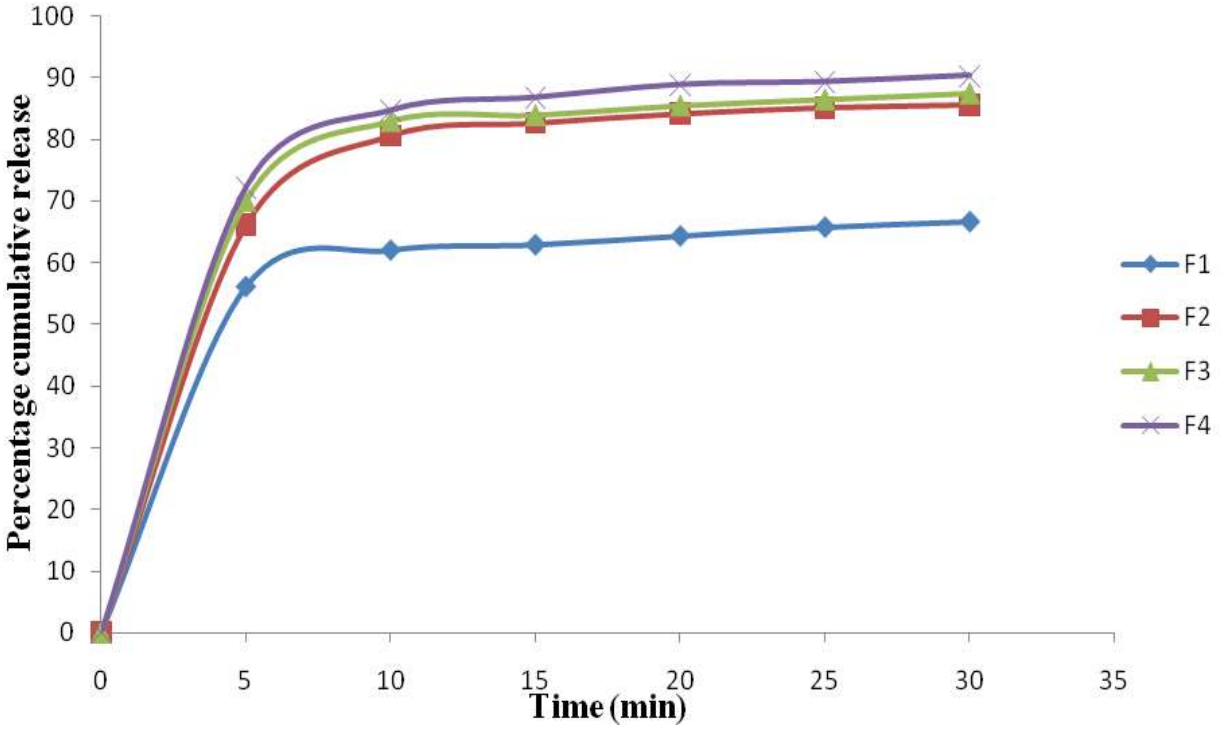

Fig. 1: In vitro drug release for F1, F2, F3 and F4

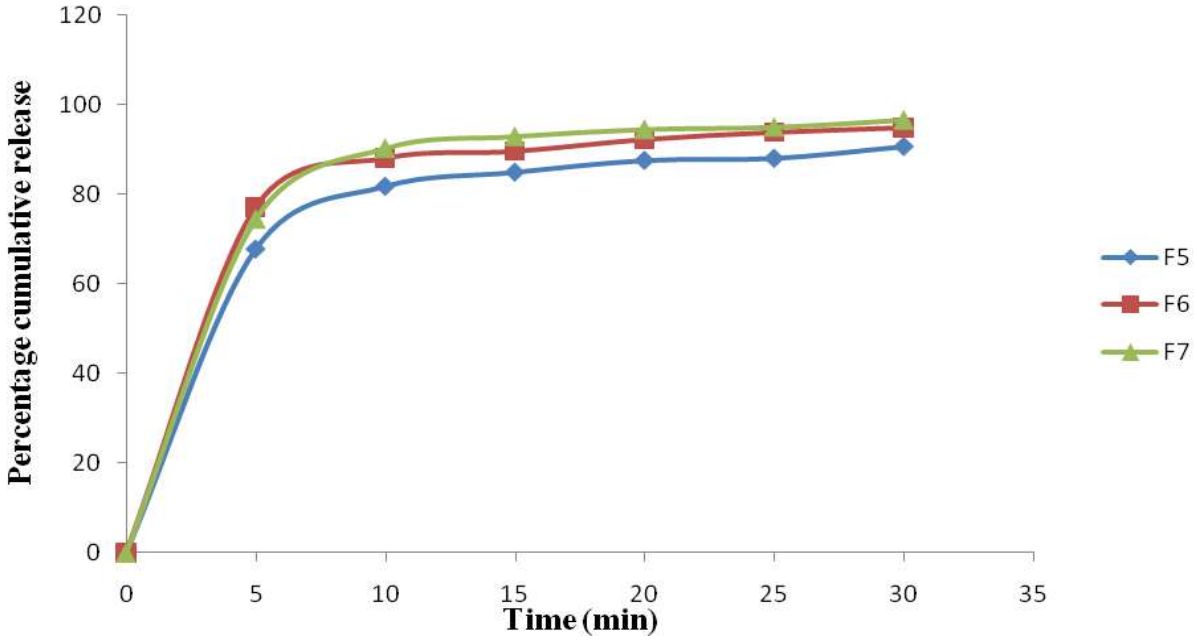

Fig. 2: In vitro drug release for F5, F6 and F7

apparatus (Electro lab, model: TDT-06N) employing a paddle stirrer at 50 rpm using 900ml of pH 6.8 phosphate buffer at 37±0.5o C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 248 nm. The volume withdrawn at each time interval was replaced with

fresh quantity of dissolution medium. Cumulative percent of the drug released was calculated and plotted against time. The results obtained are given in Table 5.

Dissolution Condition:

Apparatus : USP XX111 paddle apparatus 2. RPM : 50
Medium : phosphate buffer (pH 6.8)
Sampling Interval : Every 5 minute.
Sampling Volume : 5 ml.
Study Period : 30 min

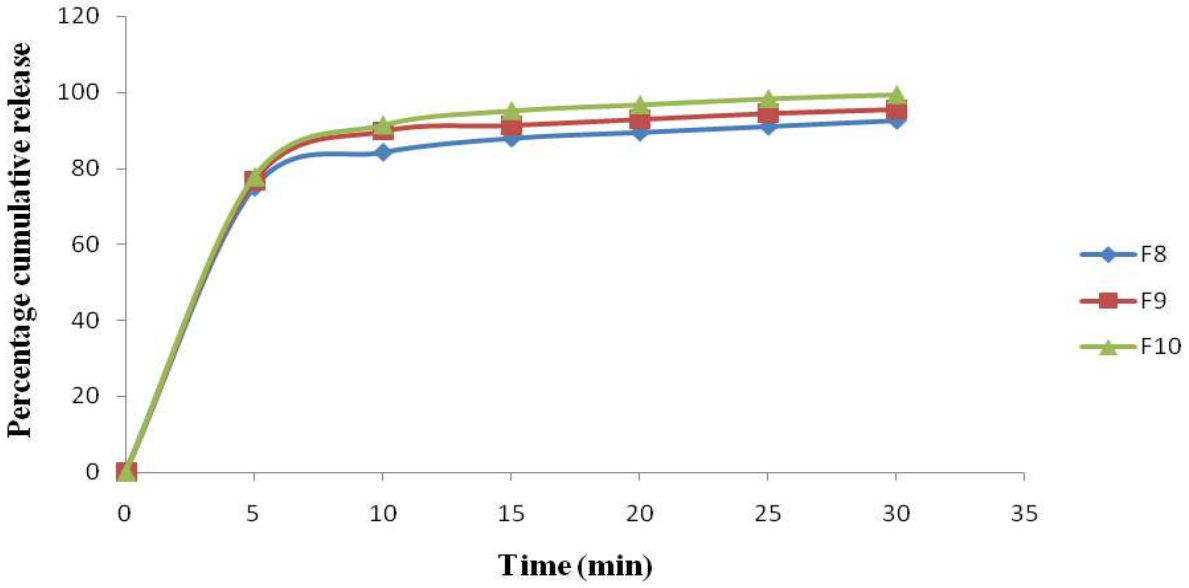

Fig. 3: In vitro drug release for F8, F9 and F10

2.6. Accelerated stability studies[15]:

The goal of a stability program is not uniquely defined, but depends on the stage of development of the product in question. At the very onset of development, it is desired to know what the inherent stability of the drug substance is and what interactions with the excipients can be expected. On the analytical side, it is usually supported by an assay procedure, which helps in developing the stability program.

The stability program varies from one dosage form to another and formulation to formulation.

Accelerated stability studies are of great interest and are attractive as which can document satisfactory results under stressed conditions time saving can be achieved.

Table 6: Stability data for formulation F10

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Hardness (kg/cm^2)	2.93±0.02	2.92±0.01	2.89±0.01	2.86±0.01
Disintegration time (sec)	23.63±1.46	23.45±1.01	23.38±0.05	24.30±0.17
Drug content (%)	100.10±0.13	99.92±0.05	99.88±0.08	99.58±0.36
In vitro drug release (%)	99.41±0.17	99.69±0.16	99.44±0.11	99.89±0.08

Results and Discussion

Weight variation

The weight variation in all the ten formulation was found to be 199.8±1.34 to 200.4±0.84mg. Formulations were within pharmacopoeial limits with free flow of the powder blend and demonstrating the efficiency of compression of particles into tablets.

Hardness

The Hardness was maintained to be within 2.02±0.15 to 2.40±0.26 kg/cm2 as these tablets are rapidly disintegrating. No variation in the hardness was found which clearly indicates that the proper blending of the mixture for the preparation of orodispersible tablets. The prepared tablets in all the formulation possess good mechanical strength with sufficient hardness.

Thickness

Thickness of all tablets prepared in the range of 2.31±0.01 to 2.35±0.03 mm was acceptable without much variation.

Percentage friability

Percentage Friability is below 1% in all the formulation and values obtained lies between 0.747±0.08 to 0.941±0.04%. It indicated that of good mechanical resistance of the tablets.

Wetting time

The Wetting time was rapid in croscarmellose sodium followed by crospovidone, treated agar. The value lies between 26.26±0.30 to 41.03±0.05 sec. Figure 4: depicts the relation between the concentration of superdisintegrants and wetting time. It indicated that as concentration of disintegrant increases the time taken for wetting was reduced. Wetting time is used a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in the presence of little amount of water.

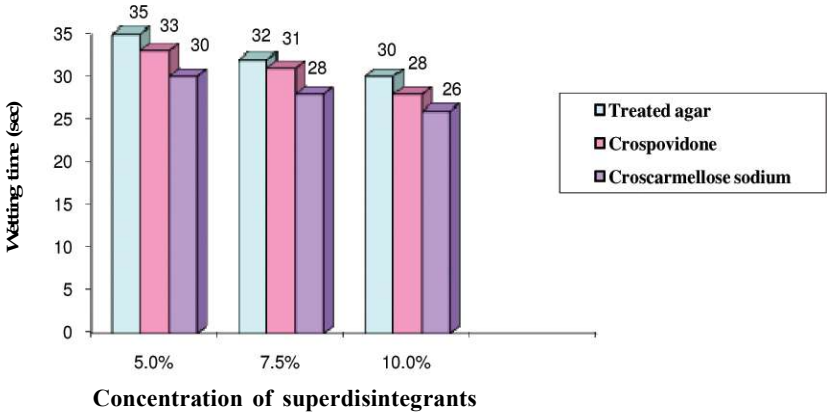

Fig. 4: Wetting time of different superdisintegrants with different concentration

Dispersion time

Further the tablets were subjected in vitro dispersion in which the time taken by the tablet to produce complete dispersion is measured. The values for all the ten formulations lie between 26.45±0.41 to 60.37±0.40 sec. The in vitro dispersion time was rapid in croscarmellose sodium followed by crospovidone and treated agar. The comparative results are shown in the following figure 5.

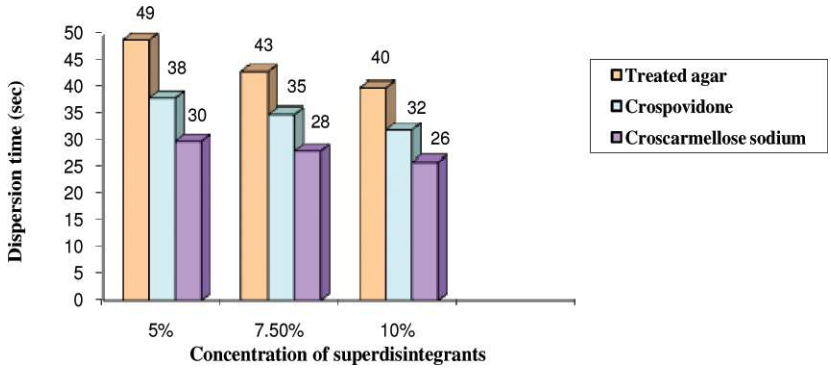

Fig. 5: Dispersion time of different superdisintegrants with different concentration

Disintegration time

The disintegration time for the entire formulations lie between 20.276±0.402 to 50.73±0.646 sec. Figure 6: depicts the disintegration behaviour of the tablets in water. This rapid disintegration of the oral dispersible tablets were due to penetration of saliva into the pores of the tablets, which leads to the swelling of super disintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. Batch F10 was selected as best formulation containing croscarmellose sodium as superdisintegrant in 10% concentration. It was observed that less disintegration time of 20 sec was observed when croscarmellose sodium was used as superdisintegrant, may be due to swelling at faster rate upon contact with water and elimination of lump formation after disintegration when compared with crospovidone and treated agar.

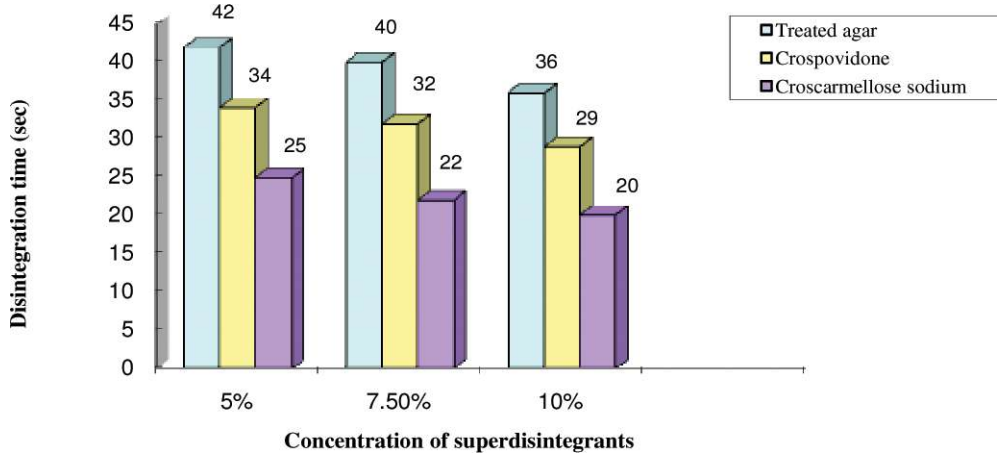

Fig. 6: Disintegration time of different superdisintegrants with different concentration

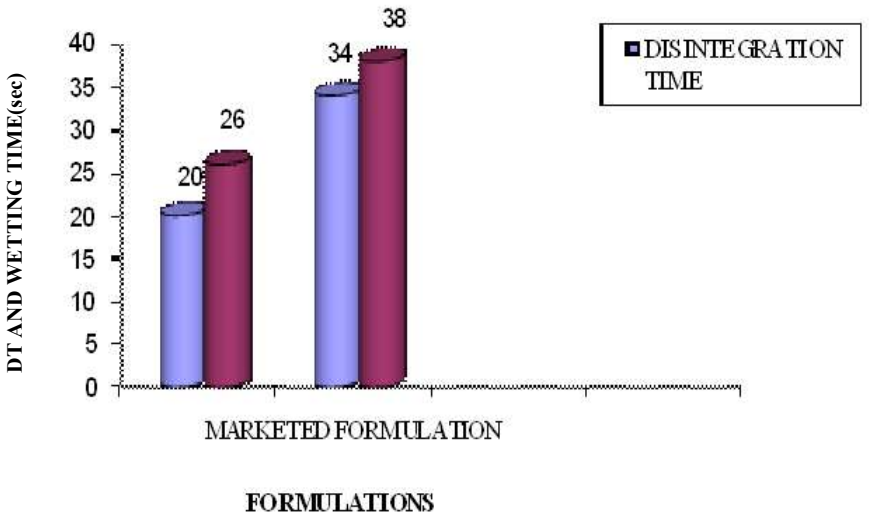

Fig. 7: Comparison of disintegration time and wetting time of best formulated tablet with marketed tablet

Finally the disintegration time of best formulation was compared with marketed formulation the results showed that formulated tablet disintegrated in 20 sec as compared to 34 sec for marketed Ondansetron tablet (ZOFER ODT). The formulation F10 was found to be the best, as this formulation showed less disintegration time and possessing good tableting properties.

The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. This signifies that disintegrant concentration in 10% is suitable for the formulation of orodispersible tablets of Ondansetron hydrochloride.

The various dissolution parameter values viz., percent drug dissolved in 4 min (D4), t50% and t70% for promising formulations of 10% concentration of all the three different polymers (i.e.) F4, F7, F10 were compared with the control shown in Table 7 and the dissolution profile depicted in figure 8. This data reveals that the F10 formulation shows faster drug release compared to the commercial formulation (CF) based on t50% and t70% values in pH 6.8 Phosphate buffer. The best formulation F10 compared with marketed formulation.

Table 7: In vitro dissolution parameters in pH 6.8 phosphate buffer

Formulation code	$t_{50\%}$ (min)	$t_{70\%}$ (min)	d_4 (%)
F1	7.49	10.49	55.30%
F4	5.53	7.75	68.54%
F7	5.17	7.23	75.705
F10	5.02	7.03	74.16%
CF	5.72	8.01	65.77%

The Control formulation of (F1), 10% concentration of superdisintegrants for (F4, F7, F10) and commercial formulation of in vitro cumulative drug release was shown in the figure 8. The best and marketed formulation is depicted as shown in figure 9.

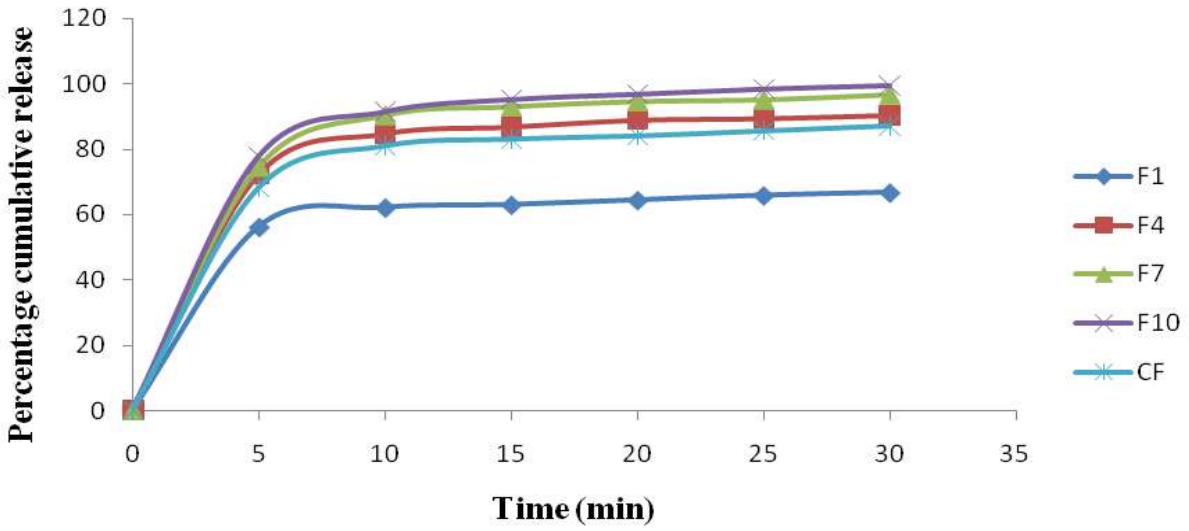

Fig. 8: Percentage cumulative drug release for F1, F4, F7, F10 and commercial formulation

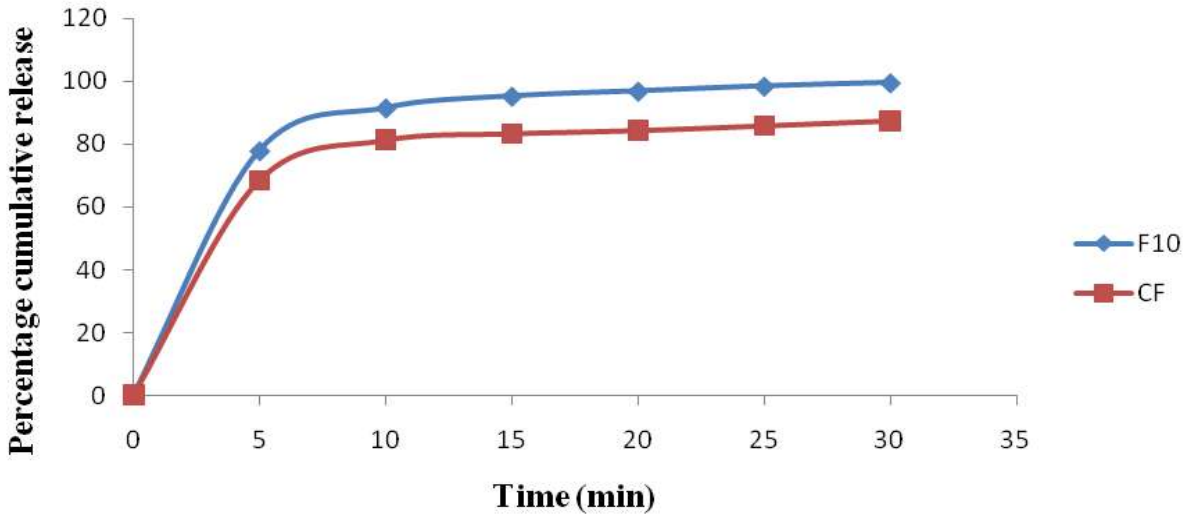

Fig. 9: Percentage cumulative drug release for F10 and marketed formulation

Conclusion

Orodispersible tablets of Ondansetron hydrochloride are prepared by direct compression method. The formulation F10 containing 10% of superdisintegrant (i.e.) Croscarmellose sodium has shown best release with 99.46% at the end of 30 min. The effervescent mixture further assists in taste masking and have pleasant mouth feel of Ondansetron hydrochloride. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. *In vitro* drug release from the tablets shows significantly rapid dissolution. Hence it could be concluded that the orodispersible tablets of ondansetron hydrochloride would be quite effective in emesis, providing quick onset of action without need for water for swallowing or administration.

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