

# Development and Evaluation of Fast Disintegrating Tablets of Ondansetron with Natural and Synthetic SuperDisintegrating Agents

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## Abstract

Ondansetron a widely prescribed anti-ulcer drug belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor solubility and dissolution rate and having high permeation rate. In the present work, oral disintegrating tablets of Ondansetron were developed with a view to enhance the patient compliance and provide quick onset of action. Ondansetron is a serotonin 5-HT<sub>3</sub> receptor antagonist used mainly as an anti-emetic (to treat nausea and vomiting).

It affects both peripheral and central nerves. Ondansetron reduces the action of the vagus nerve, which deactivate the vomiting centre, and also block serotonin receptors in the chemoreceptor trigger zone. It has slight effect on vomiting caused by motion sickness, since drug is highly bitter.

The drug solid dispersed coated granules showed no bitterness in the taste. Oral disintegrating tablets prepared by direct compression method using super disintegrants like cross povidone, cross carmellose sodium, sodium starch glycolate, in different concentrations and evaluated for the pre-compression parameters such as bulk density, compressibility and angle of repose.

The arranged batches of tablets were evaluated for hardness, weight variation, thickness, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory.

**Aim:** The aim of the present study is to formulate and evaluate fast disintegrating tablets of Ondansetron by direct compression method employing super disintegrating agents.

### The objective of present study:

- The purpose of this research was to mask the strongly bitter taste of Ondansetron HCL and to formulate a rapid - disintegrating tablet.
- To formulate an orally disintegrating tablet so that it can be administered to paediatric and geriatric patients.

## Introduction

### Fast Dissolving Tablets

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as “a solid dosage form containing medicinal substance or active ingredient which disintegrate fast usually within a few seconds when placed upon the tongue.”

FDTs differ from traditional tablets as they are designed to be dissolved on the tongue rather than swallowed whole.

Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, porous tablets, quick dissolving tablets, fast dissolving tablets.

According to US Food and Drug Administration 2008 publications of guidance are:

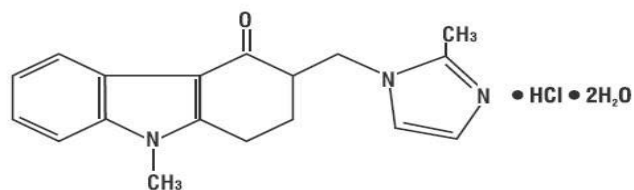
1. FDTs should have an In vitro disintegrating time of approximately 30 sec or less (using United States Pharmacopeia disintegration test or equivalent).

2. Generally, the FDT tablet weight should not exceed 500 mg, although the combined influence of stable weight, size and component solubility all factor into the acceptability of an ODT for both patients and regulators.

3. The guidance serves to define the upper limits of the FDT category, but it does not replace the original regulatory definition mentioned.

## Materials and Methods

### Drug description (Fig no 1)





IUPAC name: 9-methyl-3-[(2-methylimidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4-one

Generic name: Ondansetron

Brand name: Vomikind

Description: White powder, crystalline

Melting point: 231-232° C

Molecular weight: 293.36296 g/mol.

Category: Anti-emetic

## Materials Used (Table 1)

### Equipments used

Equipments used in the formulation are listed below:

- Electronic digital balance
- Sixteen station rotary tablet punching machine
- Pfizer hardness tester
- Friability tester
- Disintegration apparatus
- Dissolution apparatus
- Double beam UV- spectrophotometer

## Methods

S.no	Ingredients	Category
1.	Microcrystalline cellulose	Diluents
2.	Mannitol	Sweetening agent
3.	Crosscarmellose sodium	Super disintegrant
4.	Ispaghula husk	Natural Superdisintegrant
5.	Sodium starch glycolate	Super disintegrant
6.	Sodium saccharine	Artificial sweetener
7.	Magnesium stearate	Lubricant
8.	Talc	Glidant

### Pre formulation studies

**Angle of repose:** The resistance forces in a free powder can be measured by the angle of repose ( $\theta$ ). It is an symptomatic of the flow properties of the powder. It is known as maximum angle possible between the surface of the mound of powder and the horizontal plane (Table 2).

$$\tan (\theta) = h / r$$

$$\theta = \tan^{-1} (h / r)$$

Sr. No.	Angle of Repose (°)	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

Where,  $\theta$  is the angle of repose

h is the height in cms

r is the radius in cms.

**Bulk Density ( $D_b$ ):** It is measured by pouring the powder (passed through standard sieve # 20) into a measuring cylinder, the initial weight was noted. This initial volume is called the bulk volume. The bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$D_b = M / V_b$$

Where, M is the mass of powder

$V_b$  is the bulk volume of the powder.

**Tapped Density ( $D_t$ ):** Volume measured by tapping the powder for 100 times and the tapped volume was noted if the difference between these two volumes is less or more than 2%, tapping is continued for 1250 times and noted. Tapping was continued until the successive volumes are less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$D_t = M / V_t$$

Where, M is the mass of powder

$V_t$  is the tapped volume of the powder.

**Hausner's ratio:** Hausner's ratio is an indirect index of ease of powder flow. It is calculated by following formula (Table 3).

$$\text{Hausner's ratio} = D_t / D_b$$

Where,  $D_t$  is tapped density.

$D_b$  is bulk density.

**Compressibility index:** The compressibility index (Carr's Index) was determined by using following equation (Table 4).

$$\text{Carr's Index (\%)} = [(D_t - D_b) \times 100] / D_t$$

Where,  $D_t$  is the tapped density of powder

$D_b$  is the bulk density of powder.

**Formulation development (Table 5): Method of formulation:** Fast disintegrating tablets of ondansetron Hcl containing different concentrations of super disintegrants were prepared by direct compression method all the ingredients without magnesium stearate and talc were sifted through the sieve #44 and are mixed for about 15min to make a uniform blend. Magnesium stearate and talc were passed through sieve #60 and mixed with above powder for sufficient time, usually 5-7mins.

**Table 3:** Relationship between flow characters and Hausner's ratio.

Flow Character	Hausner's Ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very Poor	1.46-1.59
Very Very Poor	>1.60

**Table 4:** Relationship between % compressibility and flow ability.

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
< 40	Very very poor

The prepared powder were evaluated for various pre formulation parameters like bulk density, tapped density, angle of repose, carr's index and Haunser ratio and compressed using sixteen station rotary tableting machine. Finally all the evaluation tests were conducted.

### Evaluation tests

**Weight variation:** Tablets are considered to contain a definite amount of drug in a specific amount of tablet formula; the weight of the tablet is measured to help in such a way that the tablet contains the accurate amount of drug. Average weight of 20 tablets were selected randomly from the lot and weighed individually to check for weight variation (Table 6)

**Thickness:** The thickness of pre-weighed 10 tablets of each formula was measured using a micrometer. It is measured by placing it between two anvils and rotating the sliding knob until the tablet was tightly fitted and the reading was noted. The

tablet thickness should be controlled within a  $\pm 5\%$  variation of a standard value.

**Hardness:** Hardness or tablet crushing strength, the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is measured in  $\text{kg cm}^2$ . Usual range of hardness for conventional tablets is 4-6  $\text{kg/cm}^2$ . The hardness for FDTs should be preferably 2-3  $\text{kg/cm}^2$ .

**Friability (F):** Friability of the tablet is determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

**Wetting time:** Tissue paper folded and placed in a Petri plate (internal diameter is 6.5 cm) containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C.

**Disintegration time:** According to this method, a Petri dish of 10cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the centre of the Petri dish, and the time necessary for the complete disintegration of the tablet into fine particles was noted as disintegration time.

**Dissolution studies:** Tablet test condition for the dissolution rate studies were used according to USP specification using USP type II apparatus. The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2). The temperature of the dissolution medium and the rate of agitation were maintained at  $37 \pm 0.5^\circ \text{C}$  and 50 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time intervals and the volume was replaced by fresh dissolution medium, pre warmed to  $37 \pm 0.5^\circ \text{C}$ . The drug concentration was determined spectrophotometrically

**Table 5:** Formula used in formulation of ondansetron Hcl fast disintegrating tablets.

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Ondansetron Hcl	4	4	4	4	4	4	4	4	4
Sodium starch glycolate	6	8	10	-	-	-	-	-	-
Crosscarmellose sodium	-	-	-	6	8	10	-	-	-
Ispaghula husk	-	-	-	-	-	-	6	8	10
Mannitol	80	80	80	80	80	80	80	80	80
Microcrystalline cellulose	200	198	196	200	198	196	200	198	196
Sodium saccharin	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	6	6	6	6	6	6	6	6	6
Total	300	300	300	300	300	300	300	300	300

**Table 6:** Weight Variation Limits for Tablets (I.P).

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

at 249 nm using UV spectrophotometer.

## Results and Discussions

### Pre formulation studies (Table 7)

**Organoleptic and flow properties:** Various Organoleptic and flow properties studies have been done and the results are based on standard given. Therefore pre formulation values are within the limits.

### Evaluation tests of ondansetron fast disintegrating tablets (Table 8):

- The hardness was found to be in the range of 2.5 to 3.0

kg/cm<sup>3</sup>.

- Tablet thickness was maintained between 2.14 to 2.86 cm.
- The friability was found to less than 1% was indication of good mechanical resistance of tablets.
- As the powder was free flowing tablets produced were of uniform weight with acceptable weight variation (≤ 1.19%) due to uniform die fill.

**Standard graph of ondansetron Hcl (Table 9):** The absorbance of above solutions was recorded at  $\lambda_{max}$  (249nm) of the drug using double beam UV -visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis) (Fig no 2).

A spectrum of the working standards was obtained by scanning from 200-400 nm by UV double beam spectrophotometer against the reagent blank to fix absorption maxima. The  $\lambda_{max}$  was found to be 249 nm. Hence all further investigation was carried out

**Table 7:** Flow properties.

Code	Angle of repose( $\theta$ )	Bulk density (gm/cm <sup>3</sup> )	Tapped Density (gm/cm <sup>3</sup> )	Carr's index(%)	Hausner Ratio
F <sub>1</sub>	34.6	0.40	0.663	15.610	1.235
F <sub>2</sub>	37.2	0.46	0.701	15.730	1.811
F <sub>3</sub>	29.6	0.35	0.698	15.919	1.177
F <sub>4</sub>	38.6	0.43	0.695	14.155	1.177
F <sub>5</sub>	35.3	0.42	0.696	14.864	1.178
F <sub>6</sub>	35.7	0.43	0.694	11.697	1.787
F <sub>7</sub>	31.3	0.42	0.698	13.242	1.160
F <sub>8</sub>	29.6	0.47	0.700	12.528	1.141
F <sub>9</sub>	39.6	0.43	0.822	14.325	1.162

**Table 8:** Evaluation tests of Ondansetron Hcl fast disintegrating tablets.

Code	Hardness (kg/cm <sup>2</sup> )	Thickness (cm)	Friability%	Weight variation(mg)	Wetting time(sec)	Disintegration time (sec)
F <sub>1</sub>	2.8	2.24	0.27%	100.02	35sec	24sec
F <sub>2</sub>	3.0	2.14	0.13%	100.05	41sec	30sec
F <sub>3</sub>	2.6	2.34	0.87%	100.03	39sec	25sec
F <sub>4</sub>	2.7	2.55	0.21%	100.04	41sec	28sec
F <sub>5</sub>	3.0	2.67	0.28%	100.01	43sec	29sec
F <sub>6</sub>	2.5	2.36	0.27%	100.34	45sec	33sec
F <sub>7</sub>	3.0	2.30	0.54%	100.01	30sec	33sec
F <sub>8</sub>	2.5	2.56	0.20%	100.03	27sec	35sec
F <sub>9</sub>	3.0	2.38	0.42%	100.06	27sec	36sec

**Table 9:** Standard graph of Ondansetron Hcl.

Concentration( $\mu$ g/ml)	Absorbance
0	0
2	0.14
4	0.28
6	0.42
8	0.56
10	0.71

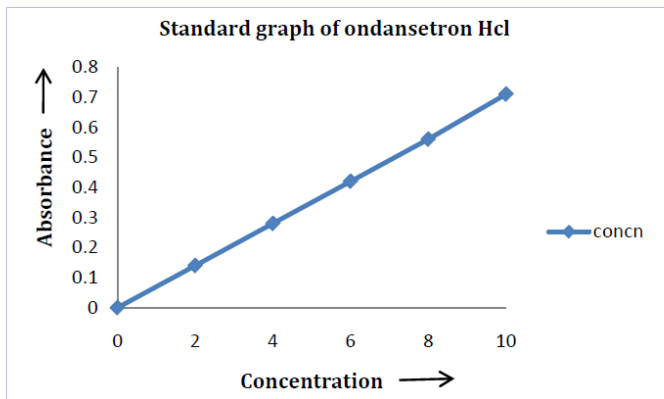


Figure 2: Graph plotted between concentration and absorbance.

at same wavelength. After conducting a number of trials, the concentration range which obeyed Beer's law was found to be between 0-100 µg/ml. A calibration curve was conducted, which had a slope of 0.07.

### In vitro drug release studies

In vitro drug release profiles of Ondansetron from the Formulation ODT Tablets

#### Sodium starch glycolate (Table 10) (Fig no 3):

Table 10: In vitro drug release of ondansetron with Sodium starch glycolate.

Time(in mins)	% drug release		
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>
0	0	0	0
5	63.8	61.5	60.5
10	79.2	68.1	65.1
15	83.4	75.7	70.7
20	87.5	83.2	79.5
25	92.4	88.7	82.2
30	98.1	92.8	90.2

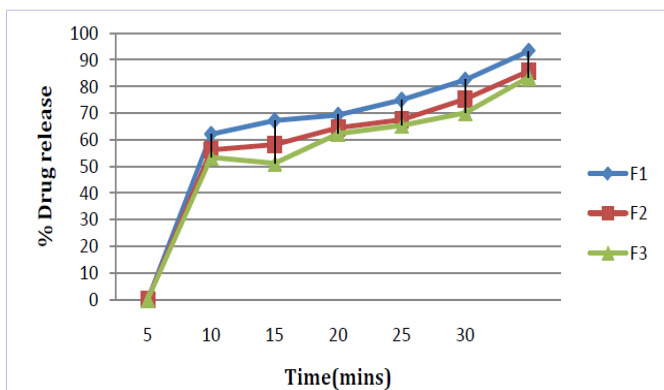


Figure 3: Graph plotted between concentration and absorbance with SSG.

Time(in mins)	% Drug Release		
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>
0	0	0	0
5	62.1	56.2	53.4
10	67.2	58.2	51.2
15	69.3	64.5	62.3
20	75	67.5	65.4
25	82.5	75.3	70.1
30	93.3	85.8	83.5

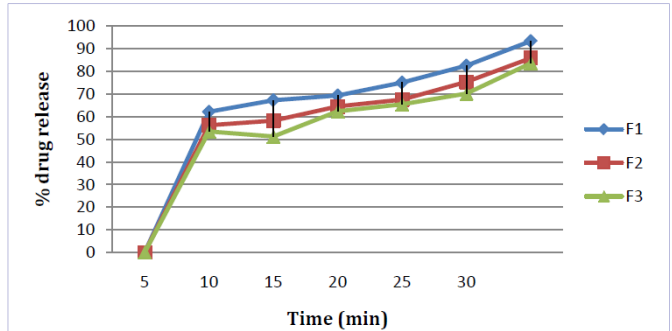


Figure 4: Graph plotted between concentration and absorbance with CCS.

#### Ispaghula husk (Table 12) (Fig no 5):

Table 12: In vitro drug release of Ondansetron with ispaghula husk.

Time( in mins)	% Drug Release		
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>
0	0	0	0
5	72.3	67.3	64.2
10	75.6	70.1	68.8
15	79.9	75.3	72.6
20	82.6	77.1	74.3
25	90.8	81.2	79.5
30	95.3	90.4	86.3

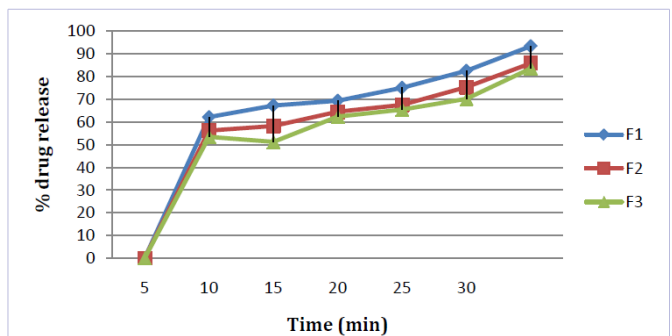


Figure 5: Graph plotted between concentration and absorption with ispaghula husk.

### Conclusion

Fast disintegrating tablets have possible advantages over usual dosage forms, with improved patient observance, convenience, bioavailability and rapid onset of action. They are good substitute for drug delivery to geriatric and paediatric patients. They have major advantages of both solid and liquid dosage forms, as they remain solid during storage, which assist in stability of dosage forms and transform into liquid form within

few seconds after its administration Thus FDT has great scope for being immediate drug delivery.

All the formulation was evaluated for bulk density, tapped density, Hauser's ratio, compressibility index and angle of repose. As the powder was free flowing, tablets produced were of uniform weight with acceptable weight variation ( $\leq 1.19\%$ ) due to uniform die fill. Thus the observation of the study can be summarized as

- Tablet prepared by direct compression method were found to be good, without any chipping, sticking and capping.
- The hardness was found to be in the range of 2.5 to 3.0 kg/cm<sup>3</sup>.
- Tablet thickness was maintained between 2.14 to 2.86 cm.
- The friability was found to less than 1% was indication of good mechanical resistance of tablets.

It is concluded that the formulated fast disintegrating tablets of ondansetron using sodium starch glycolate was capable of exhibiting immediate release properties. Among all the formulations F-1 prepared with sodium starch glycolate in concentration 6% as super disintegrant exhibit least disintegration time(24 sec) and showed maximum drug release of 98.1% within 30 mins. As the concentration of super disintegrant in the formulations increased the disintegration time was found to decrease. From the characterisation of fast disintegrating tablets of ondansetron it can be concluded that formulation containing sodium starch glycolate 6% is most acceptable.

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