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Taste Masking of Ondansetron Hydrochloride and Formulation of Fast Dissolving Tablets

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ABSTRACT

The purpose of this research was to mask the intensely bitter taste of Ondansetron HCl and to formulate a Fast dissolving tablet (FDT) of the taste-masked drug. Taste masking was done by complexing Ondansetron HCl with aminoalkyl methacrylate copolymer (Eudragit EPO) in different ratios by the extrusion method and Novel wet granulation method. Taste masked complex were analyzed with FTIR, DSC and XRD. Drug-polymer complexes (DPCs) were tested for drug content, in vitro taste in simulated salivary fluid (SSF) of pH 6.8, and molecular property. In vitro release profile obtained at SSF pH 6.8 indicate that perceivable amount of drug will not be released in saliva. The taste masked granules were directly compressed in to tablets using crosscarmellose sodium (Ac-Di-Sol) as a super disintegrantes. Tablets of batch F4 containing microcrystalline cellulose and lactose in the ratio 1:1 and 6% wt/wt Ac-Di-Sol showed faster disintegration, within 34 seconds, than the marketed tablet (102 seconds). . Tablets of batch F4 also revealed rapid drug release (t_{90} , 240 seconds) at acidic pH 1.2 of the stomach compared with marketed formulation (t_{90} , 600 seconds). The observed polymer interaction and reduced crystallinity may be reason for increased dissolution rate. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration and dissolution of the formulated tablets.

Key words: Taste masking, Ondansetron HCl, Fast dissolving tablet, Eudragit EPO.

INTRODUCTION

Although various novel and advanced drug delivery systems have been introduced in for therapeutic use, the popularity of oral dosages form, particularly tablets have not been eclipsed, because tablets still have numerous advantages. However, one important drawback of tablets as a dosages form is the need to swallow. Dysphasia or general difficulties in swallowing of the tablets may be a problem for geriatric, pediatric [1] or traveling patients, if the latter do not have

access to water. Among the dosage forms developed to facilitate ease of medication, the fast dissolving tablet (FDT) is one of the most widely employed commercial products [2-4]. The FDT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an FDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration. More than 50% of the pharmaceutical products are orally administered for several reasons, and undesirable taste is one of the important formulation problems encountered with such oral products. Taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment, especially in pediatrics. Therefore, formulation of taste-masked products is a challenge to the pharmacists [5-6]. Ondansetron HCl is a potent antiemetic drug indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis, and is also used in the early onset of alcoholism [7]. In general, emesis is preceded with nausea and, in such a condition, it is difficult to administer drug with a glass of water. Hence, it is beneficial to administer such drugs as fast dissolving tablets (FDTs). Ondansetron HCl is an intensely bitter drug; hence, if it is incorporated directly into an FDT, the main objective behind formulation of such a dosage form will definitely be futile [8]. Thus, in the present study, an attempt has been made to mask the taste of Ondansetron HCl and to formulate FDTs with a good mouth feel so as to prepare a "patient-friendly dosage form."

EXPERIMENTAL SECTION

Ondansetron HCl was obtained as a gift sample from Cadila Pharmaceutical limited, Ahmedabad. Aminoalkyl methacrylate copolymer (Eudragit EPO) was a gift from Degussa India Private Ltd (Mumbai, India). Cross carmellose sodium (Ac-Di-Sol), Crosspovidone were received as a gift sample from Torrent Research Center Ahmedabad, Micro crystalline cellulose, Lactose, D-Mannitol, magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. Sodium saccharine was purchased from Loba Chemicals Mumbai. All other chemicals used in the study were of analytical grade.

Preparation of drug polymer complex

The drug polymer complex (DPC) was prepared by using different ratio (1:1, 1:3, 1:5) of Ondansetron HCl and Eudragit EPO. A gel containing Ondansetron HCl and Eudragit EPO was prepared by gradual addition of 10 % ethanol using a mechanical stirrer in a glass beaker. The gel was manually extruded through a syringe. The ethanol was evaporated by keeping the extrudates overnight at room temperature. The solidified gel in the shape of string was crushed and sieved through sieve sized 255 μm to make the granules.

Selection of Eudragit EPO for the taste masking of Ondansetron HCl

A simplified dissolution taste was performed to determine the optimum fraction of polymer for taste masking of Ondansetron HCl. This is an in-vitro test to evaluate the degree of masking the bitter taste of the fine granules, under the assumption that the fine granules would be held in mouth together with 10 ml of salivary fluid, with weak mixing by the tongue for 60 seconds [9]. The method was as follows: the drug polymer complex (DPC) containing 10 mg of Ondansetron HCl were mixed with 10 ml of simulated salivary fluid (SSF) in a 10 ml syringe by revolving the syringe end to end for 60 seconds. Thereafter solution Ondansetron HCl was filtered and amount of drug release was determined spectrophotometrically at 249 nm. For W1 formulation in-vitro evaluation taste was done by triturating five tablets and powder equivalent to 10 mg of Ondansetron HCl was placed in 10 ml of SSF and shaken for 60 seconds. The amount of drug release was analyzed at 249 nm (Table-1)

Table-1. Drug content and In-Vitro Taste Evaluation of Drug Polymer Complex in SSF

Drug Polymer Ratio in DPC	% Drug Dissolve in SSF (pH 6.8)†	% Drug Content in Gastric (pH 1.2)†
1:1	2.0±0.21	98.42±0.25
1:3	0.82±0.15	98.72±0.41
1:5	0.41±0.05	99.12±0.08
W1 (1:5)	0.43±0.76	99.16±0.18

† Results are the mean of 3 observations ± SD.

Characterization of Drug Polymer Complex

Thermal analysis

DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The sample were heated in a sealed aluminium pans at a rate of 10⁰ C per min in a 30 to 300⁰ C temperature under nitrogen flow of 40 ml/min.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The Spectra was recorded as a dispersion of the sample in Potassium Bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm⁻¹ and the resolution was 1 cm⁻¹.

X-ray Diffraction (XRD) studies

X-ray Diffraction analysis was carried out to evaluate the degree of crystallinity. The pure Ondansetron HCl, pure Eudragit EPO, and drug polymer complex (1:5) were subjected to powder XRD (P.W. 1729, X-Ray Generator, Philips, Netherland) at 2 Θ angles between 2⁰ and 38⁰ in increments of 0.4⁰.

Drug Content

DPC equivalent to 10 mg of drug was stirred by using magnetic stirrer with 100 ml of 0.1 N HCl for 60 minutes, till the entire drug leached out from complex, than the solution was filter through whatman filter paper. Further solution was diluted with 0.1 N HCl and the drug content was determined spectrophotometrically at 249 nm. (Table 1)

Selection of Superdisintegrants

Before formulation of FDT, the best superdisintegrants among Ac-Di-Sol, and Crosspovidone was screened out. Tablets were prepared in different batches containing a blend of MCC and lactose (1:1) as a diluents and superdisintegrant in various concentrations (Table 2).

Table-2-Disintegration time of Different Super Disintegrants

Batch	Disintegrants	Disintegrants % w/w	Diluents % w/w†	Disintegration time, s ⁺
B1	—	—	100	63
B2	CCS	4	96	38
B3	CCS	6	94	33
B4	CCS	8	92	35
B5	CRP	4	96	45
B6	CRP	6	94	43
B7	CRP	8	92	42

CCS- Cross carmellose sodium (Ac-Di-Sol), CRP- Crosspovidone

†1:1 mixture of MCC and lactose; ⁺ n=3.

Tablet Manufacturing

Preparation of tablet by direct compression method

Fast dissolving tablet of Ondansetron HCl were prepared by direct compression method. All the raw materials were passed through a # 60 sieve prior to mixing. Drug polymer complex (1:5), containing amount equivalent to 10 mg of Ondansetron HCl, was mixed with the other excipients. The powder blend was lubricated with magnesium stearate and compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Preparation of Tablet using wet granulation method

Powdered D-Mannitol and pure drug mixed properly with 30% powdered Eudragit EPO. Now this powdered blend converted in to wet mass using absolute ethanol. Wet mass than passed through # 30 sieves to make granules. Resulting granules were mixed with 80% lactose and remaining amount of powdered Eudragit EPO and converted in to wet mass using absolute ethanol following sieving through # 30 sieves and resulting granules were dried at room temperature under vacuum. Dried granules were mixed with remaining amount of lactose and passed out from # 40 sieve, mixed with croscarmellose sodium, saccharine Na and mint flavor. Finally lubricated with magnesium stearate and compressed at constant force in to tablets using concave punches (9 mm diameter) in a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad,India.)

Table-3 Tablet Formulation

Ingredients mg	Batch						
	F1	F2	F3	F4	F5	F6	W1
Ondansetron HCl	-	-	-	-	-	-	10
Eudragit EPO	-	-	-	-	-	-	50
DPC	60	60	60	60	60	60	-
MCC	169	-	-	84.5	84.5	56.5	-
Lactose	-	169	-	84.5	-	-	84.5
D-Mannitol	-	-	169	-	84.5	113	84.5
Ac-Di-Sol	15	15	15	15	15	15	15
Mag.Stearate	1	1	1	1	1	1	1
Saccharin-Na	3	3	3	3	3	3	3
Mint flavor	2	2	2	2	2	2	2

Table-4 Physical Properties of Tablet Blend

Formulation	Bulk density	Tapped Density	Carr's Index (%)	Hausner's Ratio	Angle of Repose ⁽⁰⁾
F1	0.46±0.61	0.51±0.42	8.37±0.19	1.10±0.16	21.56±0.55
F2	0.26±0.21	0.35±0.35	20.48±0.13	1.34±0.23	23.15±0.54
F3	0.49±0.16	0.55±0.29	9.92±0.28	1.15±0.13	23.12±0.50
F4	0.48±0.12	14.72±0.19	1.17±0.01	28.01±0.76	14.72±0.19
F5	0.52±0.27	0.61±0.05	16.04±0.36	1.16±0.14	29.88±0.56
F6	0.53±0.02	0.60±0.43	11.03±1.16	1.12±0.21	24.75±0.32
W1	0.45±0.11	0.68±0.43	30.03±0.12	1.51±0.21	29.75±0.82

Data are expressed as mean ± S.D. (n = 3)

Characterization of powder flow properties [10]

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined (Table-4). Bulk density was determined by the USP method I; tapped density was determined by USP method II using a tapped density tester (Electrolab, ETD

1020, Mumbai, India). Percent compressibility and Hausner ratio were calculated using Equations 1 and 2:

$$\text{Percent compressibility} = \{(D_t - D_b) / D_t\} \times 100 \quad (1)$$

$$\text{Hausner ratio} = D_t / D_b \quad (2)$$

Where, D_t and D_b are tapped and bulk densities

Characterization of Tablet Properties

Uniformity of Mass

The test was performed as per specification given in I.P.1996 [11] on 20 tablets. The maximum acceptable limit is $\pm 7.5\%$ deviation of an individual mass from average mass.

Measurement of Tablet Friability

Tablet Friability was measured using Roche Friabilator according to specification given in IP 1996. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by the fracture and abrasion was recorded as the % weight loss. Friability below 1% was considered acceptable.

$$F\% = \left(1 - \frac{W}{W_0}\right) \times 100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

Hardness

Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

Uniformity of Drug Content

The test is obligatory for tablets containing less than 10 mg or less than 10 % w/w of active ingredient [12]. This test was performed as per Indian Pharmacopoeia, 1996. A tablet was crushed and dissolved in 1 ml of dilute hydrochloric acid and 30 ml of distilled water. This solution was shaken for 15 min. the volume of this solution was made up to 50 ml with distilled water and centrifuged. Five milliliters of the clear supernatant was mixed with 10 ml of 0.1 M hydrochloric acid, and made up to 100 ml with distilled water. The absorption of the solution was determined spectrophotometrically at 249 nm. The same procedure was followed for another nine tablets.

Wetting time

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time [13].

In-vitro Disintegration Time

Disintegration of fast disintegrating tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* condition. The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the center of the Petri dish, and the time necessary for the complete disintegration of the tablet into fine particles was noted as disintegration time.

In- vitro Dissolution Study

Tablet test condition for the dissolution rate studies were used according USP specification [14] using USP 24, type I 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 100 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to $37 \pm 0.5^\circ \text{C}$. The drug concentration was determined spectrophotometrically at 249 nm using UV spectrophotometer (Shimadzu S 1700, Japan).

Stability Study

Representative samples (F4, and W1) were placed in a controlled cabinet at $40^\circ \text{C} \pm 2^\circ \text{C}$ and $75\% \pm 5\% \text{RH}$ for 3 months. The effect on various tablet properties such as Friability, hardness and disintegration time was measured. The data were analyzed by one way analysis of variance (ANOVA). A value of $P < 0.05$ was considered as significant.

RESULTS AND DISCUSSION

Characterization of Drug Polymer Complex

Percentage drug content of drug polymer complex and batch W1 in gastric (pH 1.2) was found from 98.42 to 99.16. The drug release in SSF was found least with drug polymer complex ratio (1:5). Thus it is selected as optimized ratio for the development of formulation. In case of batch W1 30% and then 70 % of total amount of Eudragit EPO were used to form taste mask granules in (1:5) ratio with drug. The taste masked granules prepared with this Novel wet granulation method showed slightly higher drug release than DPC (1:5) in SSF.

The DSC thermograms of pure Ondansetron HCl, Eudragit EPO, Physical Mixture and drug polymer complex (DPC) are shown in (Figure 1a, 1b, 1c, and 1d). Thermal profile of pure product exhibited a single endothermic effect corresponding to the melting of Ondansetron HCl ($T_{\text{fus}} 186.4770 \text{C}$, $\Delta H_{\text{fus}} 107.379 \text{ J/g}$) while amorphous nature of polymer. The DSC curve of physical mixture shown progressive broadening and lowering of drug melting temp and concomitant reduction of its enthalpy. In DSC curve of DPC total disappearance of drug melting temperature. These finding suggest the formation of new solid phase with lower degree of crystallinity.

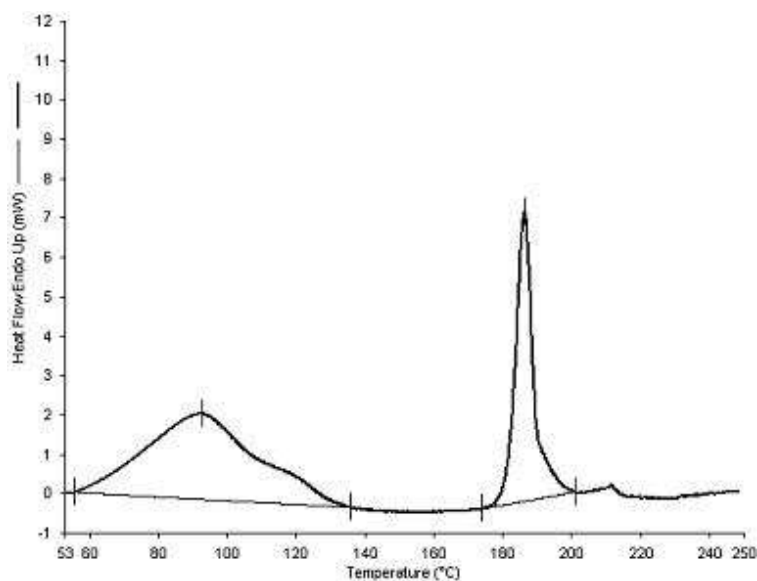
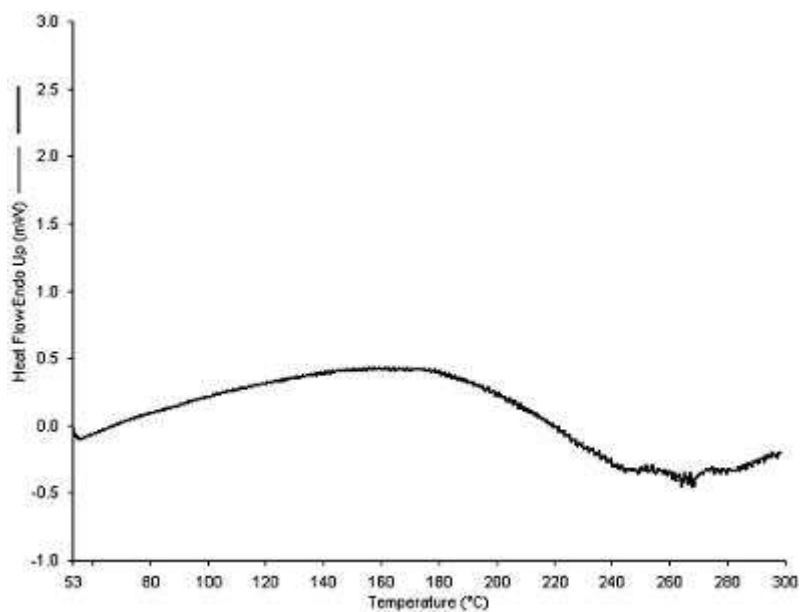
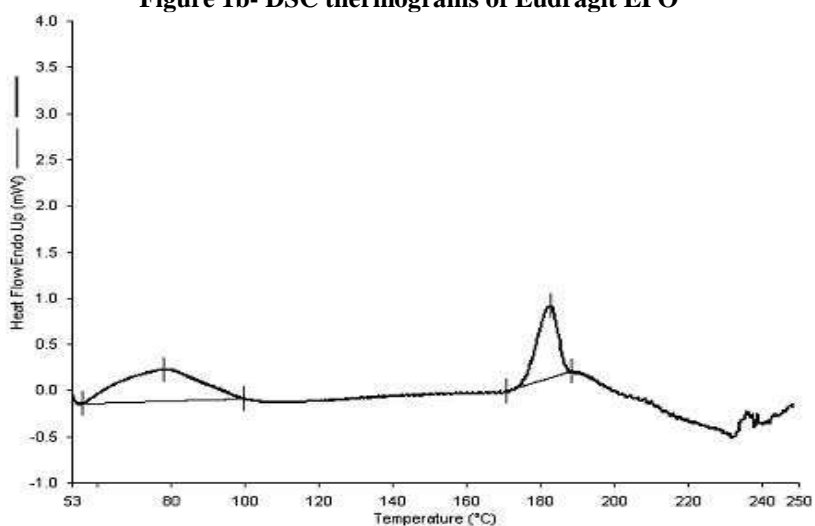
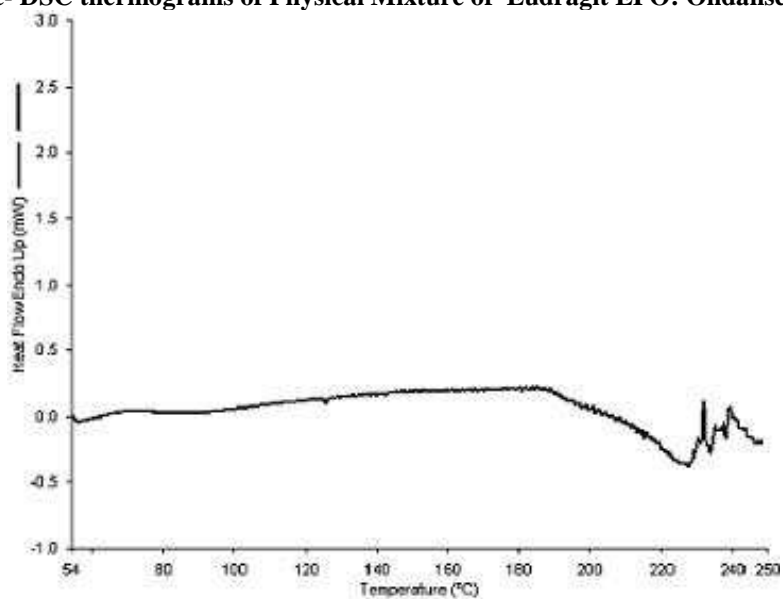


Figure 1a- DSC thermograms of pure Ondansetron HCl

**Figure 1b- DSC thermograms of Eudragit EPO****Figure 1c- DSC thermograms of Physical Mixture of Eudragit EPO: Ondansetron HCl****Figure 1d- DSC thermograms of Drug Polymer Complex (DPC)**

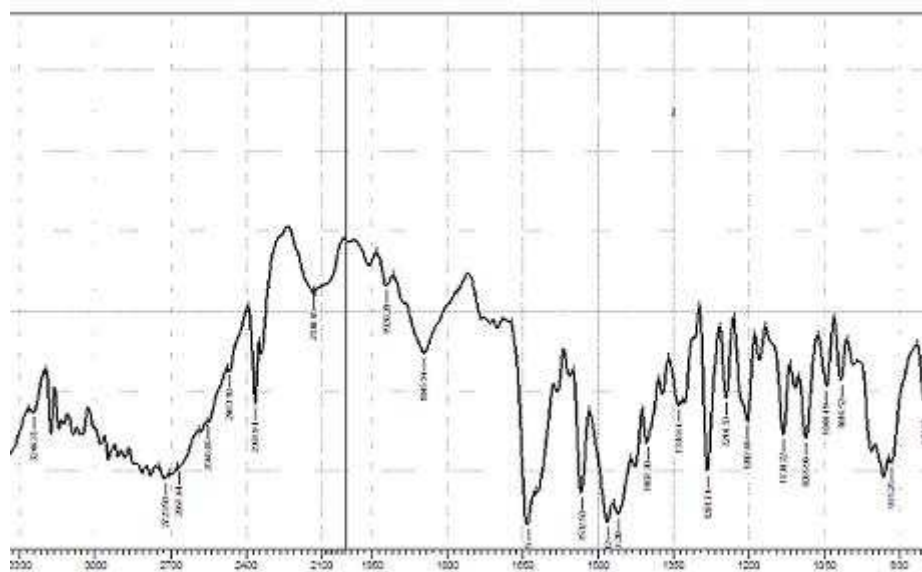


Figure 2a- FTIR spectra of pure Ondansetron HCl

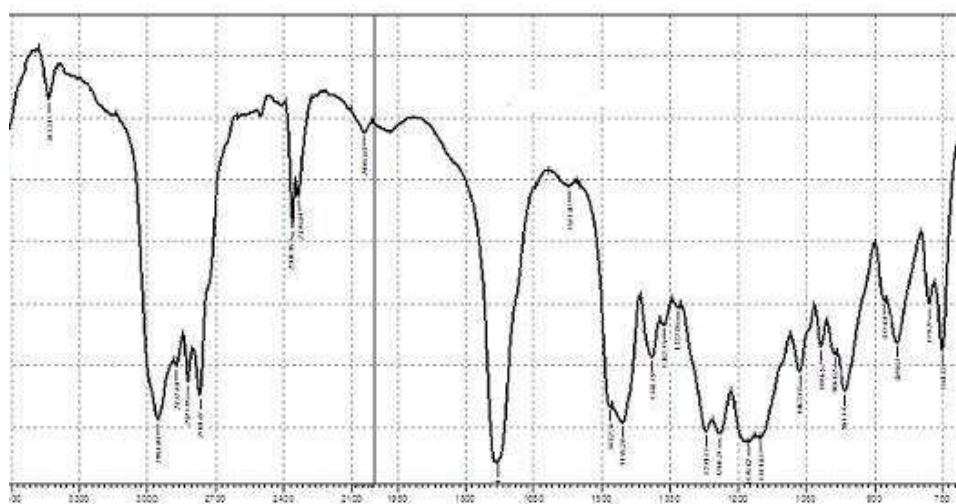


Figure 2b- FTIR spectra of Eudragit EPO

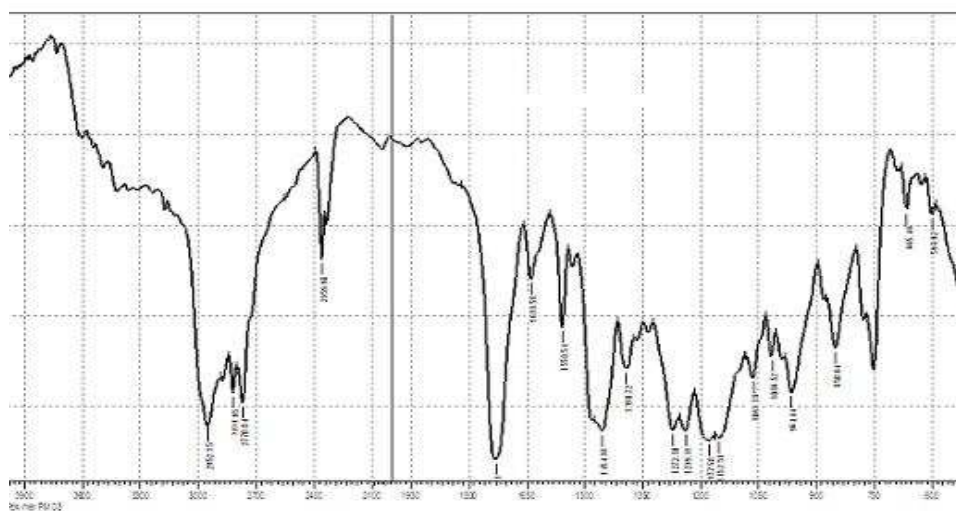


Figure 2c- FTIR spectra of Physical Mixture of Eudragit EPO: Ondansetron HCl

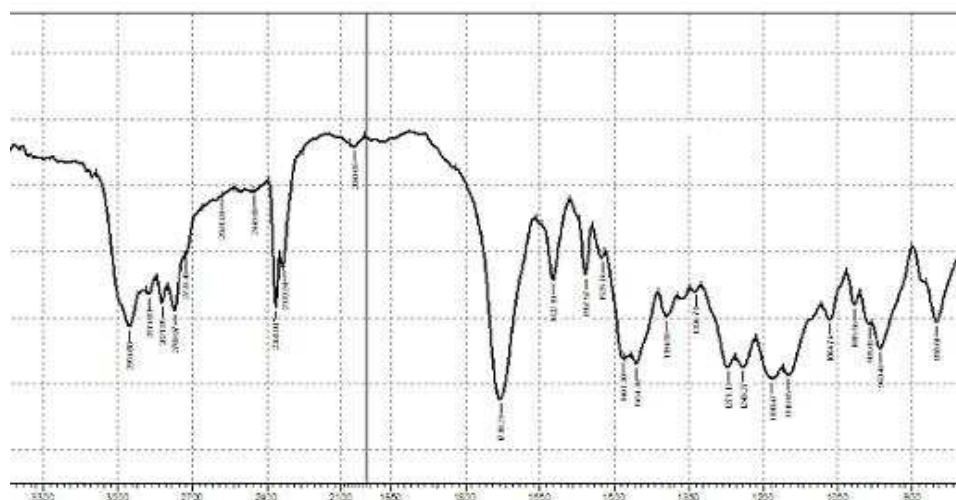


Figure 2d- FTIR spectra of Drug Polymer Complex (DPC)

The FTIR spectrum of pure Ondansetron HCl, Eudragit EPO, Physical Mixture and drug polymer complex (DPC) are shown in (Figure 2a, 2b, 2c, and 2d). The FTIR spectrum of drug and polymer showed no significant shift or reduction in intensity of peaks of Ondansetron HCl. However, the FT-IR spectrum of DPC was found to exhibit some significant difference in the characteristic peaks of Ondansetron HCl, revealing modification of drug environment. As shown in figure a broad band of bonded –OH of Ondansetron HCl was observed from 3491.7 to 3245.31 cm^{-1} . DPC showed the absence of peak at 3491.7 to 3245.31 cm^{-1} suggest the formation of complexation of drug with polymer.

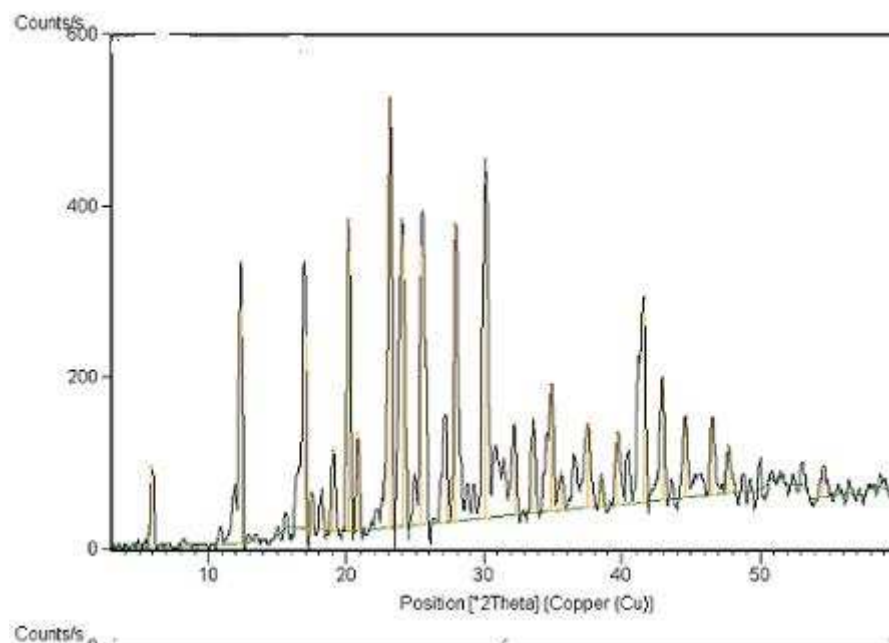


Figure 3a- X-Ray diffraction pattern of pure Ondansetron HCl

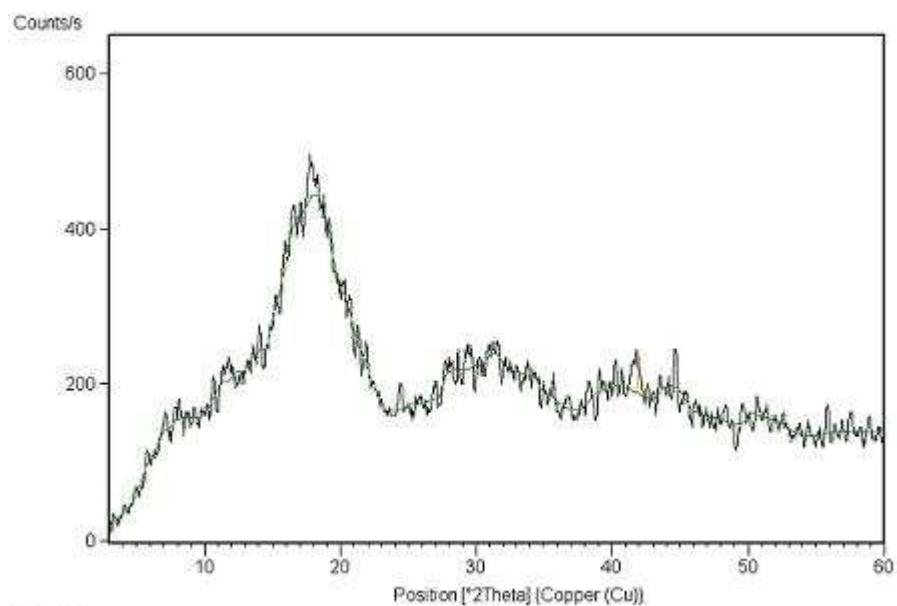


Figure 3b- X-Ray diffraction pattern of Eudragit EPO

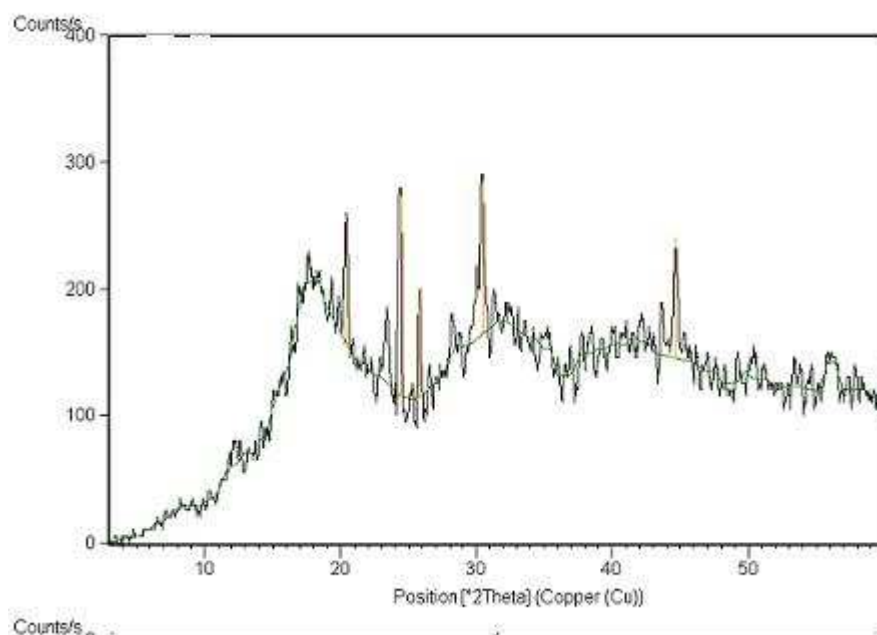


Figure 3c- X-Ray diffraction pattern of Physical Mixture of Eudragit EPO: Ondansetron HCl

The x-ray diffractogram of pure Ondansetron HCl, Eudragit EPO, Physical Mixture and drug polymer complex (DPC) are shown in (Figure 3a, 3b, 3c, and 3d). The x-ray diffractogram of Ondansetron HCl confirms its crystalline nature, as evidenced from the number of sharp and intense peak. The diffractogram of polymer (Eudragit EPO) showed diffused peak, indicating the amorphous nature, while the diffraction pattern of drug polymer physical mixture showed simply the sum of characteristic peaks of pure drug and the diffused peaks of polymer, indicating presence of drug in crystalline state. However the diffraction pattern of DPC represents complete disappearance of crystalline peaks of drug especially those situated between 20° and 60° (2θ). These finding suggest the formation of new solid phase with a lower degree of crystallinity due to complexation.

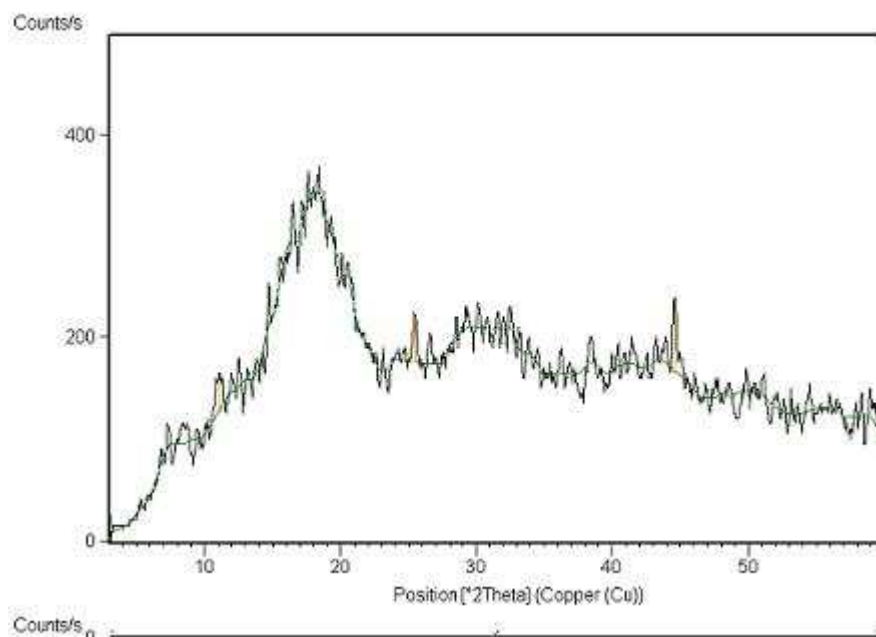


Figure 3d- X-Ray diffraction pattern of Drug Polymer Complex (DPC)

Selection of Super disintegrants

Initially the tablets containing superdisintegrants in the concentration 4, 6, and 8% w/w were tested for disintegration time. Tablet containing Ac-Di-Sol (6%) shows quick disintegration than crosspovidone. Ac-Di-Sol having excellent disintegration ability. The fibrous nature of Ac-Di-Sol allows intraparticulate as well as extraparticulate wicking of water even at lower concentration. However, Ac-Di-Sol is made by cross-linking (etherification) of sodium carboxymethylcellulose, which greatly reduce its water solubility, while permitting the material to swell and absorb water in amount of several times its own mass without losing its fibrous structure. If Ac-Di-Sol is added in the higher concentration, it makes Ac-Di-Sol more viscous and adhesive [15] this can be the possible reason for the increase of disintegration time of the tablet containing more than 6% of Ac-Di-Sol.

Characterization of Powder Flow Properties

To determine the suitability of the powder blend for tablet compression, all formulation were characterized for various flow properties. The tablet blend for all the batches showed good flow ability (angle of repose $< 30^{\circ}$).

Table-5 Characterization of Tablet Properties

Formulations	Thickness (mm)	Weight (mg)	Friability (%)	Hardness (kg/cm ²)	Disintegration time (s)	Wetting time (s)
F1	3.1±0.02	250.3±0.94	0.89±0.28	3.8±0.23	37±1.25	47±1.30
F2	2.9±0.09	249.8±1.13	0.86±0.16	3.7±0.72	39±1.30	48±1.80
F3	3.1±0.04	250.0±1.03	0.73±0.83	3.5±0.43	40±2.23	52±2.30
F4	2.8±0.02	250.6±1.51	0.66±0.35	3.5±0.58	34±1.10	42±1.20
F5	3.2±0.03	249.8±1.94	0.65±0.24	3.7±0.59	36±1.36	45±1.54
F6	3.1±0.01	250.4±0.87	0.52±0.29	3.6±0.76	38±1.38	48±1.32
W1	3.3±0.09	250.2±1.09	0.40±0.12	3.7±0.14	35±1.46	43±1.73

Data are expressed as mean \pm S.D. (n = 3)

Characterization of Tablet Properties

Tablets of all the batches were characterized for various tablet properties such as hardness, friability, weight variation, content uniformity, disintegration time and wetting time (Table-5).

It was found that all the tablets prepared by direct compression and wet granulation method described above, independently of their composition, were found to be in acceptable limits for the properties like hardness, friability, weight variation and content uniformity. The friability was observed to be below 1%, which is regarded to be good mechanical resistance.

Tablets of F4 containing lactose and MCC in the ratio 1:1 and 6% Ac-Di-Sol shows faster disintegration and least wetting time with in 34 seconds and 42 seconds respectively. As lactose dissolves quickly it creates pores rapidly encouraging penetration of water into the tablets and this led to quick disintegration of the tablets Batch F3 and F6 containing higher amount of D-Mannitol showed increased wetting and disintegration time. Increase in wetting and disintegration time may be due to increase in polyol quantity in tablet formulation. As polyol are readily soluble in water there exist a competition between mannitol and Ac-Di-Sol for water penetration in to tablet, consequently leading to poor swelling of disintegrant with subsequently delay in disintegration [16].

Disintegration time of batch F5 Containing MCC and D-mannitol in a 1:1 ratio was also slightly more than F4 may be due to lesser penetration of water than F4. The disintegration time and wetting time for batch W1 was found to be 35 and 43 seconds respectively. Disintegration time for the marketed formulation was found to be 102 seconds.

Dissolution Profile

All the formulations prepared with 6 % Ac-Di-Sol release more than 90% drug in 240 seconds. Erosion of tablets is probably an important mechanism of drug release, science very rapid disintegration was noticed with these tablets by visual inspection during dissolution and disintegration studies. From the result of the test, tablet of batch F4 and W1 were considered to possess quick disintegration therefore tested and compared with marketed formulation for dissolution (Figure 4). The dissolution study of batch F4 and W1 revealed rapid release of drug 99% and 98% respectively in 300 seconds at gastric pH 1.2, compared with marketed formulation which had 90 % of drug release in 600 seconds.

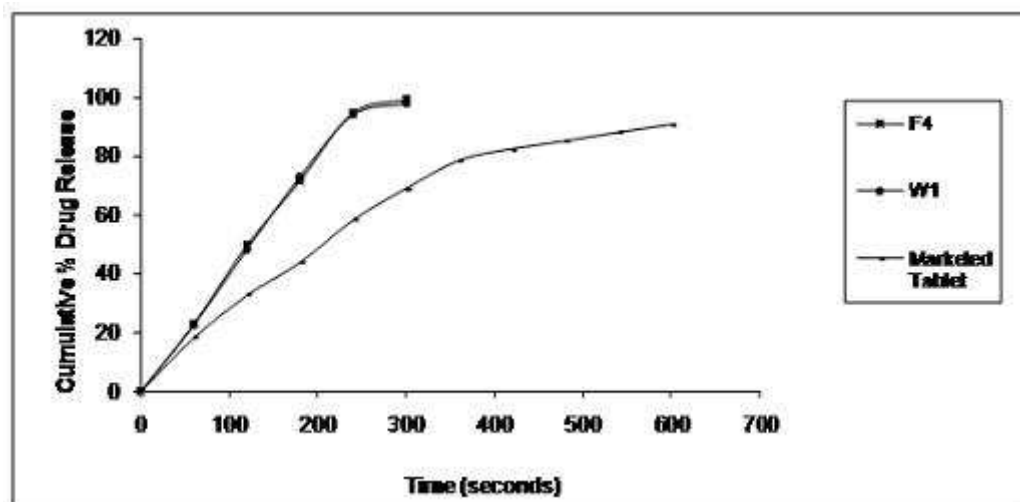


Figure 4- Dissolution profile of batch F4, W1 and Marketed Tablet

Stability Study

Stability study was performed for the formulation F4, and W1 for 3 month as per ICH guidelines, and there was no significant variation observed in physical properties such as hardness, friability and disintegration time of all the formulations ($P > 0.05$).

CONCLUSION

Result of present study indicates the complexation of Ondansetron HCl and Eudragit EPO can not only mask its bitter taste significantly but also improve the dissolution profile. By employing both the direct compression and wet granulation methods fast dissolving tablets of 250 mg weight with a taste acceptable to patients and sufficient structural integrity could be prepared. From all the super disintegrants studied, tablets containing 6% Ac-Di-Sol gave the highest improvement in disintegration and dissolution profile of Ondansetron HCl. In addition, from stability studies it can be concluded that at $40^{\circ} \text{C} \pm 2^{\circ} \text{C}$ and $75\% \pm 5\% \text{ RH}$ no significant change in the quality of the tablets during storage is to be expected.

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