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Taste Masking of Ondansetron Hydrochloride by Polymer Carrier System and Formulation of Rapid-Disintegrating 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 rapid-disintegrating tablet (RDT) of the taste-masked drug. Taste masking was done by complexing ondansetron HCl with aminoalkyl methacrylate copolymer (Eudragit EPO) in different ratios by the precipitation method. Drug-polymer complexes (DPCs) were tested for drug content, in vitro taste in simulated salivary fluid (SSF) of pH 6.2, and molecular property. Complex that did not release drug in SSF was considered taste-masked and selected for formulation RDTs. The complex with drug-polymer ratio of 8:2 did not show drug release in SSF; therefore, it was selected. The properties of tablets such as tensile strength, wetting time, water absorption ratio, in vitro disintegration time, and disintegration in the oral cavity were investigated to elucidate the wetting and disintegration characteristics of tablets. Polyplasdone XL-10 7% wt/wt gave the minimum disintegration time. Tablets of batch F4 containing spray-dried mannitol and microcrystalline cellulose in the ratio 1:1 and 7% wt/wt Polyplasdone XL-10 showed faster disintegration, within 12.5 seconds, than the marketed tablet (112 seconds). Good correlation between in vitro disintegration behavior and in the oral cavity was recognized. Taste evaluation of RDT in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value (0.5) ultimately reaching to 0 within 15 minutes, whereas ondansetron HCl was rated intensely bitter with a score of 3 for 10 minutes. Tablets of batch F4 also revealed rapid drug release (t_{90}, 60 seconds) in SGF compared with marketed formulation (t_{90}, 240 seconds; $P < .01$). Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

KEYWORDS: Taste masking, rapid-disintegrating tablets, ondansetron HCl, Eudragit EPO, superdisintegrants.

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INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication.[1] Among the dosage forms developed to facilitate ease of medication, the rapid disintegrating tablet (RDT) is one of the most widely employed commercial products.[2-4] The RDT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an RDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.

RDTs are useful in patients,[4,5] such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup,[6] leading to ineffective therapy,[7] with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style.[8] RDTs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething,[9] and to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules.[10]

Ondansetron HCl is a potent antiemetic drug[11] indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis and also used in the early onset of alcoholism.[12] In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as RDTs. Ondansetron HCl is an intensely bitter drug; hence, if it is incorporated directly into an RDT the main objective behind formulation of such a dosage form will definitely get futile.[2,13,14] Thus in the present study an attempt has been made to mask the taste of ondansetron HCl and to formulate RDTs with good mouth feel so as to prepare a "patient-friendly dosage form."

MATERIALS AND METHODS

Materials

Ondansetron HCl (Batch No. B12005) was a gift from Neon Laboratories (Palgher, India). Aminoalkyl methacrylate copolymer (Eudragit EPO) was a gift from Degussa India Private Ltd (Mumbai, India). The diluents used were

Table 1. Drug Content and In Vitro Taste Evaluation of DPCS in SSF

Serial No.	Drug-Polymer Ratio in DPC	Amount of Ondansetron HCl per 100 mg of DPC*	% Drug Dissolved in SSF*
1	7.0:3.0	69.52 ± 0.05	ND
2	7.5:2.5	73.50 ± 0.32	ND
3	8.0:2.0	78.43 ± 0.56	ND
4	8.5:1.5	83.92 ± 0.51	0.80 ± 0.32
5	9.0:1.0	89.19 ± 0.65	2.00 ± 0.21
6	9.5:0.5	94.21 ± 0.48	4.60 ± 0.42

*Results are the mean of 3 observations ± SD.

ND indicates not detectable

microcrystalline cellulose (Ceolus KG 802, Asahi Kasei Chemicals Corporation, Tokyo, Japan), spray-dried mannitol (Parteck M 200, Merck, Darmstadt, Germany), and spray-dried lactose (Flowlac 100, Meggle, Wasseburg, Germany). The superdisintegrants were crospovidone (Polyplasdone XL-10, ISP Technologies, Inc, Calvert City, KY), croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Wallingstown, Ireland) and sodium starch glycolate (Primojel, DMV International, Belle Mead, NJ). All other chemicals used in the study were of analytical grade.

Preparation of Drug-Polymer Complex (DPC)

Ondansetron HCl and Eudragit EPO complex were prepared using the precipitation method. Saturated solutions of ondansetron HCl and Eudragit EPO were prepared in absolute ethanol in various ratios (Table 1) and injected into 0.1 N sodium hydroxide with constant stirring at 500 rpm in a mechanical stirrer. The foamy matrix obtained on the top of the solution was separated and dried at room temperature for 24 hours under vacuum. The dried matrix was subsequently pulverized and finally stored in a tightly closed container for further studies.

Characterization of DPC Drug Content, In Vitro Taste Evaluation, and Molecular Properties

Drug content was determined by dissolving 100 mg of DPC in 500 mL of simulated gastric fluid (SGF) and analyzing 1mL of appropriately diluted sample at 249 nm (Table 1).

In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.2) to predict release in the human saliva. DPC, equivalent to 10 mg of ondansetron HCl (equivalent to 8 mg ondansetron, ie, its dose), was placed in 10 mL of SSF and shaken for 60 seconds. The amount of drug released was analyzed at 249 nm (Table 1).

Molecular properties on complexation were studied by x-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR). The X-ray powder diffractograms of the DPC (8:2), ondansetron HCl, Eudragit EPO, and physical mixture of ondansetron HCl and Eudragit EPO (8:2) were recorded using a Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Saint Jurie, Clubac, Canada) with monocrotized Cu Kα radiation (1.314 A^0), at a speed of 2θ min^{-1} from 10° to 60° (2θ) under the voltage and current of 40 Kv and 30 Kv respectively (Figure 1). Infrared (IR) spectra of these samples were obtained by KBr disc method (8400 S, Shimadzu Asia Pacific Pvt. Ltd, Singapore) in the range of 4000 to 500 cm^{-1}(Figure 2).

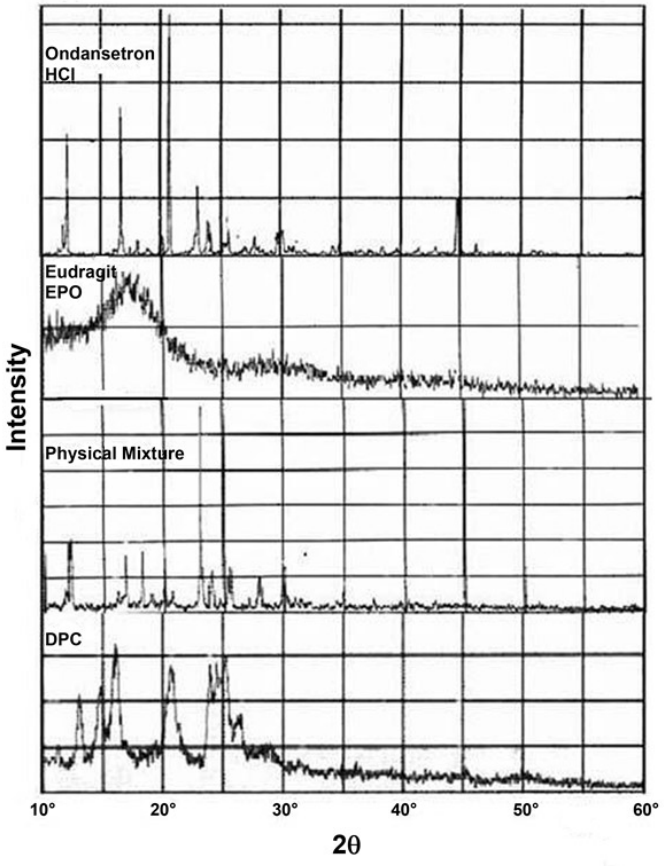

Figure 1. X-ray powder diffractograms of ondansetron HCl, Eudragit EPO, physical mixture of ondansetron HCl and Eudragit EPO, and drug-polymer complexes (DPC).

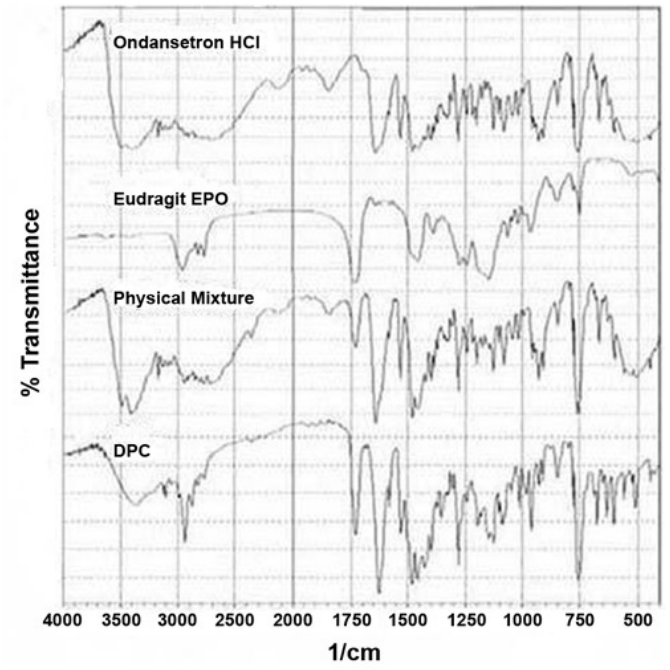

Figure 2. Fourier transform infrared spectra of ondansetron HCl, Eudragit EPO, physical mixture of ondansetron HCl and Eudragit EPO, and drug-polymer complexes (DPC).

Selection of Superdisintegrant and Formulation of RDTs

Before formulation of tablets, the best superdisintegrant among Polyplasdone XL-10, Ac-Di-Sol, and Primojel was screened out. Tablets were prepared in various batches containing a blend of microcrystalline cellulose and spray-dried mannitol (1:1) as a diluent and superdisintegrant in various concentrations (Table 2). The best superdisintegrant screened was used for the final formulation of tablets (Table 3). Tablets were prepared by direct compression using 8-mm flat-faced punches.

Physical Properties of the Tablet Blend[15]

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:

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

$$\text{Hausner ratio} = \frac{Dt}{Db} \quad (2)$$

where, Dt and Db are tapped and bulk densities.

Evaluation of Tablets

Wetting Time and Water Absorption Ratio[16]

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. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$R = \left\{\frac{(W_a - W_b)}{W_b}\right\} \times 100 \quad (3)$$

where, W_b and W_a were the weights of the tablet before and after study.

Tablets were also evaluated for hardness, tensile strength, friability, weight variation, and drug content (Table 5).

In Vitro Disintegration Study

In vitro disintegration time for RDTs was determined using USP and modified disintegration apparatus with SSF (pH 6.2) as the disintegrating medium. During this study we made an attempt to develop a more suitable apparatus for RDT (Figure 3) because many reports[17-20] indicated the unsuitability of the conventional disintegration test apparatus for RDT. Briefly, the apparatus consisted of a glass beaker

Table 2. Disintegration Time of Different Superdisintegrants

Batch	Disintegrant	Disintegrant, % wt/wt	Diluent, % wt/wt*	Disintegration Time, s†
A1	—	—	100	65
A2	CRP	5	95	11
A3	CRP	6	94	8
A4	CRP	7	93	7
A5	CRP	8	92	8
A6	CRP	10	90	10
A7	CRP	12	88	10
A8	CCS	8	92	31
A9	CCS	10	90	24
A10	CCS	12	88	18
A11	SSG	8	92	42
A12	SSG	10	90	39
A13	SSG	12	88	32

CRP indicates Polyplasdone XL-10 (Crospovidone); CCS, Ac-Di-Sol (Croscarmellose sodium); SSG, Primojel (Sodium starch glycolate); —, ingredient not added.
*1:1 mixture of microcrystalline cellulose and spray-dried mannitol.
†n = 3.

Table 3. Composition of Rapid-Disintegrating Tablets

	Batch						
Ingredients, mg	F1	F2	F3	F4	F5	F6	F7
DPC	12.76	12.76	12.76	12.76	12.76	12.76	12.76
Microcrystalline cellulose	99.74	—	—	49.87	49.87	33.25	33.25
Spray-dried mannitol	—	99.74	—	49.87	—	66.50	—
Spray-dried lactose	—	—	99.74	—	49.87	—	66.50
Polyplasdone XL-10	8.75	8.75	8.75	8.75	8.75	8.75	8.75
Aspartame	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Mint flavor	QS	QS	QS	QS	QS	QS	QS
Orange flavor	QS	QS	QS	QS	QS	QS	QS

DPC indicates drug polymer complex. Formula for one tablet is shown in the table. Each tablet contains 10 mg of ondensatron HCl; QS, quantity sufficient.

of 1000-mL capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 mL of disintegrating medium, the basket had only 6 mL of it. A magnetic bead was placed at the bottom of the beaker maintained at 37 ± 2°C. Disintegration time was determined at 25 and 50 rpm and compared with results obtained from the USP disintegration test apparatus and the in vivo disintegration test.

In Vivo Disintegration Time, Sensory Evaluation of Roughness[20] and Taste Evaluation[21,22]

In vivo disintegration was performed on 6 healthy human volunteers, from whom informed consent was first obtained. One tablet was held in the mouth after rinsing and the time required for complete disintegration of the tablet was recorded (Table 6). The disintegrated material was held in the mouth for another 60 seconds, and then spat out. The mouth was rinsed with water without swallowing the disintegrated material and, finally, the roughness levels were recorded on a numerical scale ranging from 0 to 3 where 0, 1, 2, and 3 indicate no, slight, moderate, and high roughness, respectively. Taste evaluation was done using the time intensity method on 11 healthy human volunteers from whom informed consent was first obtained. The DPC equivalent of 10 mg of ondansetron HCl was held in the mouth for 10 seconds and then spat out, and 1 RDT (containing 10 mg ondansetron HCl) was held in the mouth until complete disintegration. Bitterness was recorded immediately and at several intervals for 15 minutes according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness (Table 7).

Dissolution Study of Tablets

In vitro dissolution study on prepared tablets (batch F4) and marketed tablet was done in 500 mL SGF without enzymes using USP type II (paddle) apparatus at 50 rpm and 37 ± 0.5°C (Figure 4).

Results and Discussion

Characterization of DPCs

Percentage drug loading in DPCs was found from 98.0 to 99.31. No drug release was observed in SSF from complexes with the drug-polymer ratio of 8:2 and ratios with lesser drug, therefore, the ratio 8:2 was considered the optimal DPC with complete masking of bitter taste for further studies.

The x-ray diffractogram of ondansetron HCl confirms its crystalline nature, as evidenced from the number of sharp and intense peaks (Figure 1). The diffractogram of polymer (Eudragit EPO) showed diffused peaks, indicating its amorphous nature while the diffraction pattern of the drug polymer physical mixture showed simply the sum of the characteristic peaks of pure drug and the diffused peaks of

Table 4. Physical Properties of Tablet Blend*

	Formulation						
Property	F1	F2	F3	F4	F5	F6	F7
Angle of repose, degrees	42.16 ± 0.55	21.56 ± 0.65	22.11 ± 0.51	28.01 ± 0.44	28.88 ± 0.32	24.02 ± 0.47	24.76 ± 0.32
Bulk density, g/cm^3	0.26 ± 0.29	0.46 ± 0.63	0.49 ± 0.25	0.49 ± 0.36	0.51 ± 0.24	0.47 ± 0.19	0.51 ± 0.20
Tapped density g/cm^3	0.35 ± 0.35	0.50 ± 0.42	0.54 ± 0.28	0.58 ± 0.19	0.60 ± 0.39	0.54 ± 0.23	0.57 ± 0.15
% Compressibility	25.48 ± 0.13	8.37 ± 0.17	9.82 ± 0.23	14.43 ± 0.30	15.04 ± 0.37	11.47 ± 0.18	11.73 ± 0.09
Hausner ratio	1.34 ± 0.16	1.10 ± 0.17	1.16 ± 0.14	1.17 ± 0.14	1.17 ± 0.12	1.12 ± 0.16	1.13 ± 0.10

*Values shown in table are the mean of 3 determinations ± SD.

Table 5. Evaluation of Tablets*

Parameters	Formulation						
	F1	F2	F3	F4	F5	F6	F7
Tensile strength, Mpa	8.70 ± 0.10	11.80 ± 0.11	9.71 ± 0.04	9.59 ± 0.09	9.71 ± 0.06	11.80 ± 0.11	9.16 ± 0.05
% Friability	0.13 ± 0.21	0.24 ± 0.25	0.21 ± 0.13	0.18 ± 0.14	0.18 ± 0.11	0.21 ± 0.05	0.24 ± 0.21
Content uniformity, %	99.45 ± 0.30	102.11 ± 0.39	100.17 ± 0.28	100.17 ± 0.29	99.91 ± 0.41	100.88 ± 0.45	102.37 ± 0.22
Wetting time, s	9.67 ± 0.11	18.0 ± 0.32	19.33 ± 0.29	14.67 ± 0.21	15.67 ± 0.18	15.33 ± 0.19	16.67 ± 0.22
Water absorption ratio	84.62 ± 0.19	82.31 ± 0.16	84.2 ± 0.21	82.87 ± 0.22	83.27 ± 0.11	82.5 ± 0.19	83.78 ± 0.16

*Results are the mean of 5 observations ± SD.

polymer, indicating presence of drug in the crystalline state. However, the diffraction pattern of DPC represents complete disappearance of crystalline peaks of drug, especially those situated between 26° and 60° (2θ); whereas, the intensity of characteristic peaks of pure drug situated at 20.3° and 16.6° (2θ) was reduced and peaks were also found to be broadened. These findings suggest the formation of a new solid phase with a lower degree of crystallinity due to complexation, which coincides with the conclusion of Fernandes and Veiga.[23]

The FTIR spectrum of the physical mixture of drug and polymer showed no significant shift or reduction in intensity of peaks of ondansetron HCl. However, the FTIR spectrum of DPC was found to exhibit some significant difference in the characteristic peaks of ondansetron HCl, revealing modification of the drug environment. As shown in Figure 2, a broad band of bonded -OH of ondansetron HCl was observed from 3481 to 3245.97 cm^{-1}. DPC showed diminution and shifting of this peak from 3481 to 3311 cm^{-1}. Diminution and shifting of DPC peaks suggests the formation of new N-H stretching, which was previously absent in the pure drug. This shows the probability of formation of cation on the indole ring of ondansetron HCl that would have formed a complex with polymer by electrostatic force of attraction due to the negative charge of the carboxylate ions.

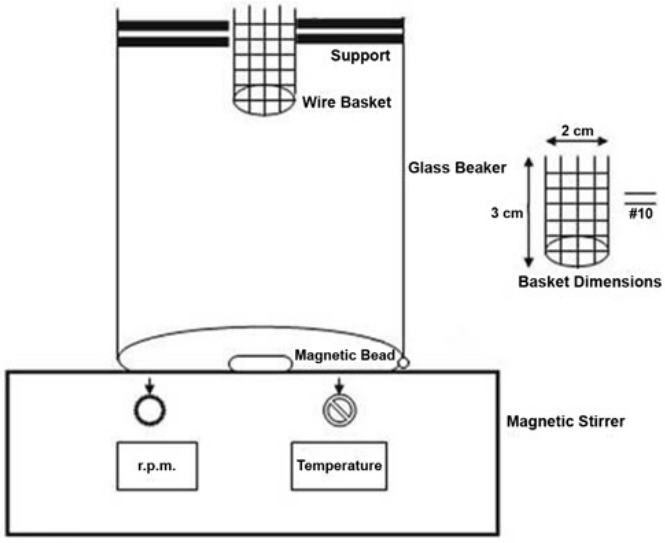

Figure 3. Schematic presentation of modified disintegration test apparatus.

Selection of the Superdisintegrant

Initially tablets containing superdisintegrants in the concentrations 8, 10, and 12% wt/wt were tested for disintegration time. Tablets containing Polyplasdone XL-10 showed quick disintegration followed by Ac-Di-Sol and Primojel. The probable reason for delayed disintegration of the tablets with Ac-Di-Sol and Primojel might be due to their tendency to gel more than Polyplasdone XL-10. This result coincides with the findings of Patel et al.,[14] wherein they formulated orodispersible tablets of rofecoxib. Hence, Polyplasdone XL-10 was selected for the formulation of RDTs. After selection, the concentration of Polyplasdone XL-10 was further reduced to get the minimum optimal concentration. Polyplasdone XL-10 7% wt/wt was selected as the optimum concentration that showed minimal disintegration time of 7.33 seconds. It was observed that further increase in concentration led to the increase in disintegration time. Such delay in disintegration may be because of the higher water requirement by a larger amount of Polyplasdone XL-10, which consequently transformed into swelling force for rapid disintegration of the tablet.

Physical Properties of the Tablet Blend

The tablet blend of all the batches showed good flowability (angle of repose <30°) and compressibility, except batch F1 with an angle of repose of 42.6°. Poor flowability of F1 may be attributed to the presence of only microcrystalline cellulose having filamentous particles as a diluent.

However, flowability of the blend increased with increasing concentrations of spray-dried mannitol or spray-dried lactose, as they have a spherical granular shape.

Table 6. Comparison of Disintegration Time of Rapid-Disintegrating Tablets and Marketed Tablet by Different Methods*

Formulations	Disintegration Time, s			
	USP Apparatus	Modified Apparatus (50 rpm)	Modified Apparatus (25 rpm)	In vivo Disintegration
F1	6	10	11	12
F2	11	12	18	18
F3	12	17	19	19
F4	7	9	13	13
F5	9	11	13	13
F6	10	10	14	14
F7	9	12	15	15
Marketed mouth dissolving tablet	68	100	105	112

*Results are the mean of 3 observations.

Wetting, Disintegration Time, Taste, and Sensory Evaluation of RDTs

Properties like hardness, friability, weight variation, and content uniformity of tablets of all the batches were found to be within acceptable limits.

Tablets of batch F4 containing spray-dried mannitol and microcrystalline cellulose in the ratio 1:1 and 7% wt/wt Polyplasdone XL-10 showed faster disintegration, within 12.5 seconds, than the marketed tablet (112 seconds). The difference was significant with a *P* value less than .01. Batch F6, containing a higher amount of spray-dried mannitol, showed increased wetting and disintegration time. Increase in wetting and disintegration time may be due to the increase in polyol quantity in the tablet formulation. As polyols are readily soluble in water, there exists a competition between spray-dried mannitol and Polyplasdone XL-10 for water penetrating into the tablet, consequently leading to poor swelling of Polyplasdone XL-10 with subsequent delay in disintegration.[24] Disintegration time of tablets of batch F5 containing microcrystalline cellulose and spray-dried lactose in a 1:1 ratio was also slightly more than F4, probably because of the formation of a sticky layer due to the dissolution of lactose and subsequent hindrance in the further ingress of water into the tablet.

Table 7. Comparative Taste Evaluation*

Form of Ondansetron HCl	Degree of Bitterness After Time					
	10 s	1 min	2 min	5 min	10 min	15 min
Pure drug	0.5	3	3	3	2	2
DPC	0	0	0.5	0.5	0	0
Unflavored tablet of DPC	0	0	0	0	0	0
Flavored tablet of DPC	0 +	0 +	0 +	0 +	0 +	0 +

*Results are the mean of 11 observations.
+ indicates palatability; DPC, drug-polymer complex.

Between the 2 stirrer speeds, 25 rpm was found to provide more comparable results with the in vivo test. Disintegration times of tablets from all the batches at 25 rpm were found nearly same as in vivo disintegration time (Table 6). Thus, the test apparatus with a stirring speed of 25 rpm was considered the most suitable.

The time intensity study for taste in human volunteers of both the DPC and RDT revealed considerable masking of the bitter taste of ondansetron HCl with degree of bitterness below the threshold value (0.5) ultimately reaching to 0 within 15 minutes. Sensory evaluation of the optimized tablet proved good palatability.

Drug Release from RDT

From the results of the tests, tablets of batch F4 were considered to posses the best physical properties accompanied with quick disintegration and, therefore, tested and compared with the marketed tablet for dissolution. The dissolution study of the optimized tablet revealed rapid release

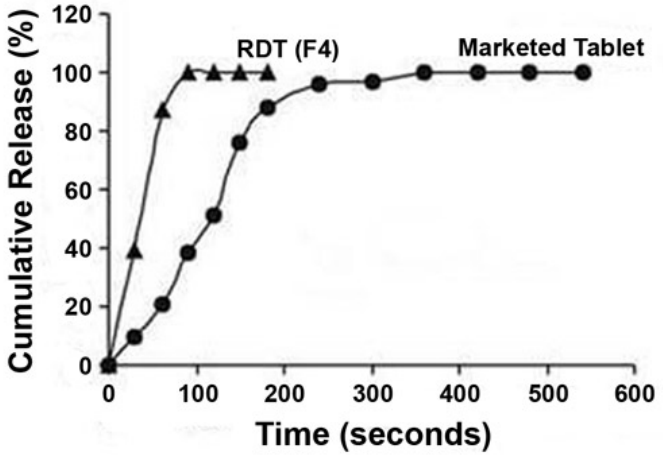

Figure 4. Dissolution profiles of optimized rapid-disintegrating tablet (RDT) (F4) and marketed tablet.

of drug (t_{90} of approximately 60 seconds) in SGF compared with marketed formulation, which had a t_{90} of approximately 240 seconds. Thus, a significant ($P < .01$) difference in the dissolution patterns of the prepared and marketed formulations was observed. The dissolution process might have involved both ion exchange and solubilization of Eudragit EPO.

CONCLUSION

The study conclusively demonstrated complete taste masking of ondansetron HCl and rapid disintegration and dissolution of RDT. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of ondansetron HCl in a more palatable form without water during emesis.

Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and noncooperative patients, can be successfully formulated using this technology.

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