Rapidly Disintegrating Tablets Containing Taste Masked Metoclopramide Hydrochloride Prepared by Extrusion–Precipitation Method

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The purpose of this study was to mask the intensely bitter taste of metoclopramide HCl and to formulate a rapid disintegrating tablet (RDT) of the taste-masked drug. Taste masking was done by complexing metoclopramide HCl with aminoalkyl methacrylate copolymer (Eudragit® EPO) in different ratio by the extrusion–precipitation method. Drug–polymer complexes (DPCs) were tested for drug content, *in vitro* taste in simulated salivary fluid (SSF) of pH 6.8, taste evaluation in oral cavity and molecular property. The complex having drug–polymer ratio of 1 : 2 shows significant taste masking, confirmed by drug release in SSF and *in-vivo* taste evaluation; therefore, it was selected for further study. Taste evaluation of DPCs in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value (0.5) within 10 s, whereas, metoclopramide HCl was rated intensely bitter with a score of +3 for 10 s. Tablets were evaluated for various parameters like tensile strength, wetting time, water absorption ratio, *in-vitro* disintegration time, and disintegration in oral cavity. The effect of diluents, lubricants and sweetening agent (Xylisorb) on the disintegration time was also evaluated. Tablets of batch F3 containing mannitol and microcrystalline cellulose in the ratio 1 : 1 and 8% w/w crosspovidone showed faster disintegration (within 20 s) than the marketed formulation (180 s). Good correlation between *in vitro* disintegration behavior and in the oral cavity was recognized. Tablets of batch F3 also revealed rapid drug release (t_{90}, 90 s) in SGF compared with marketed formulation (t_{90}, 600 s).

Key words taste masking; rapidly disintegrating tablet; metoclopramide hydrochloride; Eudragit

Recent advances in novel drug delivery system (NDDS) aims to enhance safety and by the formulating a convenient dosage form for administration to achieve the better patient compliance. One such approach is formulation of rapid disintegrating tablet.[1] Among the dosage forms developed to facilitate ease of medication, the rapidly disintegrating tablet (RDT) is one of the most widely employed commercial products.[2] A rapidly disintegrating tablet is a dosage form placed in patient's mouth. Saliva rapidly dissolves the tablet, thus releasing the active ingredients (either as coated granules or as solubilized drug), which is swallowed with saliva as liquid.[3,4]

The pediatric and geriatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. The characteristic advantage of RDTs such as administration without water, anywhere, anytime leads to their suitability to pediatric and geriatric patients. They are also suitable for mentally ill, bedridden and traveling patients who do not have the ready access to water. The rapid onset of action, increased bioavailability of these tablets makes it popular dosage form in current market.[5,6] RDTs are also used to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules.[7]

Taste masking for some pharmaceutical actives with bitter or unpleasant taste can be challenging for RDTs to achieve patient's acceptability. The mechanisms of the taste masking methods may be summarized as follows. The first is to mask the distasteful sensation by the addition of flavors, sweeteners and effervescent agents. The second is to avoid the bitter drugs coming into direct contact with patients taste buds by coating or granulation.[8—11] The flavor is often overpowered by the taste of the medicine and the use of effervescent agents is not always convenient. In this investigation, polymethacrylates (Eudragit® EPO) was used. Eudragit® EPO is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters. The cationic copolymer dissolved in solution of pH <5. So the copolymer dissolved fast in stomach (pH 1—3) without influencing the bioavailability, but keep intact in buccal cavity (pH 5.8—7.4) with good taste masking. Earlier, Ishikawa *et al.* reported the taste masked granules with Eudragit E100 polymer by mass extrusion method.[2] Zhao *et al.* developed taste masked microspheres using Eudragit EPO, which were incorporated into the rapidly disintegrating tablet.[12] Incorporation of microspheres into RDTs may rupture the coating during tablet compression.

In present investigation it was hypothesized that the anionic metoclopramide may form complex with the cationic Eudragit polymer. Taste masked granules were prepared by simple extrusion precipitation method which offers advantages like ease of preparation, low cost as compared to other methods. The prepared granules were incorporated into RDTs by an economical direct compression method. Taste masked granules Metoclopramide HCl, chemically known as 4-amino-5-chloro-2-methoxy-*N*-[(2-diethyl-amino)ethyl]benzamide, is used to treat diabetic gastroparesis and gastroesophageal reflux disorder (GERD), by stimulating stomach activity to empty the stomach. Commercially, metoclopramide hydrochloride is available in tablet form. Complicating the matter of oral administration of metoclopramide is the fact that patients with gastroparesis often have symptoms such as vomiting and nausea as well as fullness and bloating, each of which can lead to patient discomfort with or unwillingness to swallow the available oral tablet and associated water.[13] If vomiting takes place, the amount of metoclopramide that remains in the stomach is unknown, and the result of treatment is even less predictable. Metoclopramide HCl is an intensely bitter drug; thus in the present study an attempt has been made to mask the taste of metoclopramide

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HCl and to formulate RDTs with good mouth feel so as to enhance the patient compliance. Core tablet, prepared by a direct compression method, was designed to disintegrate and dissolve quickly.

Experimental

Materials Metoclopramide HCl was a gift from Ipca Laboratories (Mumbai, India). Aminoalkyl methacrylate copolymer (Eudragit EPO) was obtained as generous gift from Evonik Degussa India Private Ltd. (Mumbai, India). The diluents used were microcrystalline cellulose PH 102 (Avicel PH 102, JRS Pharma, Mumbai, India), mannitol (Perteck M, Merck, Mumbai, India), α-lactose monohydrate (Tablettose, Meggle, Germany), dicalcium phosphate (Loba Chemicals, Mumbai, India), starch (pregelatinised, 30—150 μm, Colorcon Asia Pvt. Ltd., Goa, India). The superdisintegrants used were crosspovidone (Kopran Pharmaceuticals, Mumbai, India), Croscarmellose sodium (VivaSol, JRS Pharma, Mumbai, India) and sodium starch glycolate (Hi-media Pvt. Ltd., Mumbai, India). All other chemicals used in the study were of analytical grade.

Methods. Preparation of Drug–Polymer Complex (DPC) Metoclopramide HCl and Eudragit EPO complex were prepared using the extrusion–precipitation method. Saturated solutions of metoclopramide HCl and Eudragit EPO were prepared in absolute ethanol in various ratios (Table 1). The gel was formed containing the mixture of the drug and Eudragit EPO. The prepared gel was manually extruded (pressed out) using a syringe (23G) into 0.1 N sodium hydroxide solution with constant stirring at 500 rpm in a mechanical stirrer. The foamy matrix precipitated on the top of the solution was decanted and dried at room temperature for 24 h under vacuum. The dried matrix was subsequently crushed into granules using a mortar. These granules were passed through 60 # sieve.

Characterization of DPC Drug Content: Drug content was determined by dissolving 30 mg of DPC in 100 ml of simulated gastric fluid (SGF) of pH 1.2 and analyzing the samples using UV–Vis Spectrophotometer (1700, Shimadzu, Japan) at λ_{max} 273 nm (Table 1).

Table 1. Drug Content and *in-Vitro* Taste Evaluation of DPCs in SSF

Sr. No.	Drug–polymer ratio	% Drug content[a)]	% Drug release in pH 6.8 buffer[a)]
1	2 : 1	98.89±0.56	2.64±0.32
2	1 : 1	99.12±0.34	1.34±0.12
3	2 : 3	98.96±0.18	0.89±0.42
4	1 : 2	98.36±0.12	0.21±0.26
5	2 : 5	97.67±0.45	0.20±0.18

a) Mean±S.D. (n=3).

Table 2. Bitterness Evaluation of DPCs by Taste Panel

Volunteer	1	2	3	4	5	6
Pure drug	3+	3+	3+	3+	3+	3+
DPC (5 s)	0.5	0.0	0.0	0.5	0.0	0.5
DPC (10 s)	0.5	0.0	1.0	0.5	0.0	0.5

0=tasteless, 0.5=very slight, 1.0=slight, 1.5=slight to moderate, 2.0=moderate, 2.5=moderate to strong, 3=strong, and 3+=very strong.

In Vitro Taste Evaluation: *In vitro* taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. DPC, equivalent to 10 mg of metoclopramide HCl was placed in 10 ml of SSF and shaken for 60 s. The above mixture was filtered through Whatman filter paper. The amount of drug released was analyzed spectrophotometrically at λ_{max} 273 nm (Table 1).

In-Vivo Taste Evaluation[14)]: Taste evaluation was carried out in six healthy human volunteers, with DPC equivalent 10 mg of metoclopramide HCl sample held in the mouth for 5 to 10 s, then asked to spat out and the bitterness level was then recorded. A numerical scale was used with the following values: 0=tasteless, 0.5=very slight, 1.0=slight, 1.5=slight to moderate, 2.0=moderate, 2.5=moderate to strong, 3=strong, and 3+=very strong (Table 2).

Physical Properties of DPC Granules: Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of DPCs were determined (Table 3). Bulk density was determined by USP method I; tapped density was determined by USP method II using a tapped density tester (ETD 1020, Electrolab, Mumbai, India). The compressibity index was calculated from Hausner's ratio and Carr's index (Table 3).

Molecular Properties: Molecular properties of complex were studied by X-ray powder diffraction (XRPD) and Fourier transform-infrared spectroscopy (FT-IR). The X-ray powder diffractograms of the DPC (1 : 2), metoclopramide HCl, Eudragit EPO, and physical mixture of metoclopramide HCl and Eudragit EPO (1 : 2) and DPC were recorded using X-ray diffractometer (Bruker, AXS, D8 Advance, Germany) with monocrotized Cu$K\alpha$ radiation (1.5406 Å), at a speed of 2θ min^{-1} from 3 to 80° (2θ) under the voltage and current of 40 kV and 30 Kv respectively (Fig. 1). Infrared (IR) spectra's of these samples were obtained by KBr disc method (8400 S, Shimadzu Asia Pacific Pvt. Ltd., Japan) in the range of 4000 to 500 cm^{-1} (Fig. 2).

Selection of Superdisintegrant Before formulation of tablets, the best superdisintegrant among crosspovidone, Vivasol, and sodium starch glycolate was screened out. Various batches of tablets were prepared containing a blend of microcrystalline cellulose (MCC) PH 102 and mannitol (1 : 1) as a diluent and superdisintegrant in various concentrations (Table 4). The superdisintegrant with least disintegration time was used for the final formulation of tablets.

Formulation of RDTs Initially the accurately weighed quantities of Avicel PH 102 and mannitol were thoroughly mixed in the glass mortar. Then the DPC equivalent 10 mg of metoclopramide HCl was added to the above mixture of diluents. Then sweetening and flavoring agents were added and mixed thoroughly. Finally magnesium stearate was added and tablets were prepared by direct compression using 7 mm flat faced punches (Table 5).

Evaluation of Tablets Tablets were evaluated for weight variation, friability, according to the Indian Pharmacopoeia, 2007.[15)]

Tablet Tensile Strength[16)]: The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using an Ubique tensile tester by placing tablet between upper and lower platen (60001; Ubique Enterprises, Pune, India). The test was performed by applying a diametrical load, measuring the maximum load F at the tablet fracture, then tensile strength for crushing (T) was calculated using the following equation:

$$T=2F/\pi dt \quad (1)$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Wetting Time and Water Absorption Ratio[4)]: Wetting time of tablet using

Table 3. Physical Properties of DPC Granules[a)]

Drug–polymer ratio	Parameters				
	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)
2 : 1	32.41±0.41	0.45±0.01	0.51±0.044	1.13±0.023	17.76±0.89
1 : 1	31.25±0.21	0.33±0.021	0.38±0.028	1.15±0.16	13.15±0.49
2 : 3	29.19±0.18	0.34±0.014	0.41±0.012	1.20±0.023	16.03±0.65
1 : 2	28.31±0.24	0.35±0.091	0.42±0.023	1.2±0.141	14.66±0.55
2 : 5	26.21±0.34	0.33±0.023	0.391±0.04	1.18±0.16	15.64±0.48

a) Mean±S.D. (n=3).

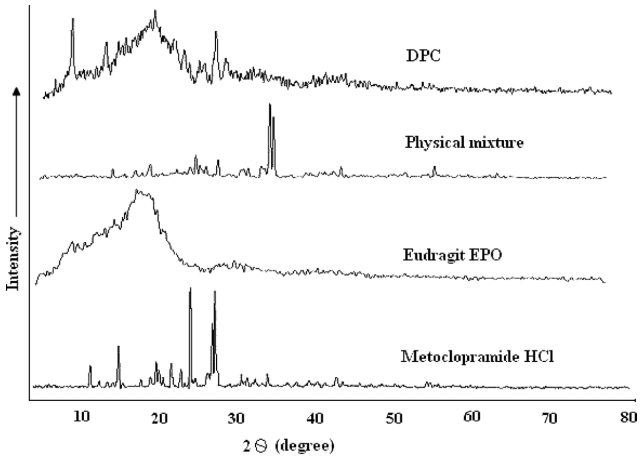

Fig. 1. X-Ray Powder Diffractogram of Metoclopramide HCl, Eudragit EPO, Physical Mixture of Metoclopramide HCl and Eudragit EPO, DPC

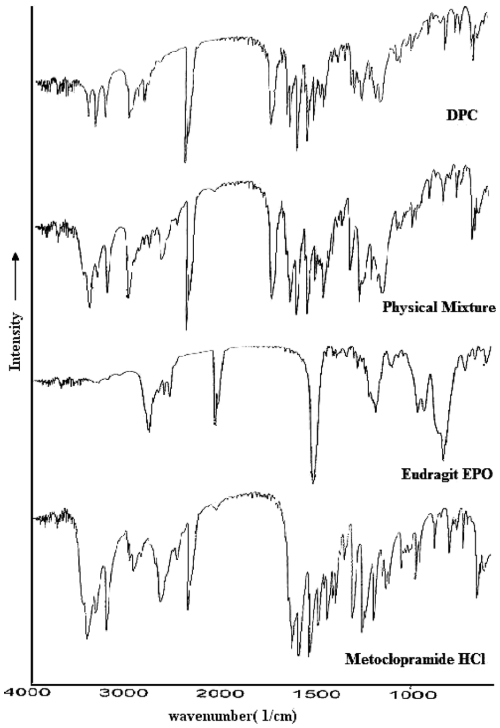

Fig. 2. FT-IR Spectra of Metoclopramide HCl, Eudragit EPO, Physical Mixture of Metoclopramide HCl and Eudragit EPO, DPC

disintegrants was carried out using the method reported by Bi *et al.* (1996) with slight modification.[16] A piece of tissue paper folded twice was kept in a culture dish (internal diameter 9 cm) containing 10 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,

$$R = \left\{ \frac{(Wa - Wb)}{Wb} \right\} \times 100 \quad (2)$$

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

In Vitro Disintegration Study[17]: Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in simulated gastric fluid (37±0.5 °C) using United States Pharmacopeias (USP) disintegration test apparatus. The mean±standard deviation (S.D.) of six tablets were calculated.

Disintegration Time in the Oral Cavity: Measurements of disintegration time in the oral cavity were carried out in 6 healthy volunteers (mean age 23). After the mouth was rinsed with purified water, one tablet was held in the mouth until the tablet disintegrated without chewing. The disintegration time was recorded in seconds. After recording the results the volunteers were asked to spat out the remains of the tablet and mouth was rinsed with purified water.

Drug Content Uniformity[15]: The drug content uniformity of the tablets was measured according to the Indian Pharmacopoeia, 2007. It has been reported that metoclopramide HCl can be detected at 273 and 305 nm. Drug content uniformity was carried out at 305 nm because successive extraction was done using chloroform for which good absorbance was observed at 305 nm as reported in Pharmacopoeia. During dissolution test study, metoclopramide HCl shown good absorbance at 273 nm by using pH 1.2 HCl buffer solution as a dissolution media. Results are shown in Table 6.

Table 4. Disintegration Time for Different Superdisintegrants

Batch	Disintegrant	Disintegrant % w/w	% Diluent w/w[a)]	Disintegration time (s)[b)]
D1	SSG	8	63.47	52±0.16
D2	SSG	10	61.47	58±0.25
D3	SSG	12	59.48	64±0.32
D4	CCS	8	63.47	43±0.17
D5	CCS	10	61.47	33±0.16
D6	CCS	12	59.48	28±0.19
D7	CRP	6	64.67	26±0.23
D8	CRP	8	63.47	20±0.33
D9	CRP	10	61.47	22±0.31
D10	CRP	12	59.48	24±0.28

SSG indicates (sodium starch glycolate); CCS, Vivasol (croscarmellose sodium); CRP (crosspovidone). *a*) 1 : 1 mixture of microcrystalline cellulose and mannitol. *b*) *n*=3.

Table 5. Formulation Compositions of RDTs

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
DPC	30.42	30.42	30.42	30.42	30.42	30.42	30.42
Vivasol	10.00	—	—	—	—	—	—
Sodium starch glycolate	—	10.00	—	—	—	—	—
Crosspovidone	—	—	10.00	10.00	10.00	10.00	10.00
Mannitol	39.67	39.67	39.67	41.17	39.67	39.67	39.67
Avicel PH 102	39.67	39.67	39.67	41.17	—	—	—
Dicalcium phosphate	—	—	—	—	39.67	—	—
Tablettose	—	—	—	—	—	39.67	—
Starch 1500	—	—	—	—	—	—	39.67
Xylisorb	3.00	3.00	3.00	—	3.00	3.00	3.00
Mg stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Strawberry flavour	1.25	1.25	1.25	1.25	1.25	1.25	1.25

Table 6. Evaluation of Rapidly Disintegrating Tablets of Drug–Polymer Complex[a)]

Parameters	F1	F2	F3	F4	F5	F6	F7	Marketed tablet[b)]
Tensile strength, MPa	3.18±0.17	2.54±0.21	3.04±0.12	2.68±0.22	2.54±0.28	2.18±0.21	1.72±0.14	3.14±0.14
% Friability	0.17±0.25	0.32±0.13	0.24±0.08	0.28±0.17	0.36±0.11	0.28±0.21	0.37±0.16	0.18±0.11
Content uniformity, %	99.27±0.20	99.98±0.32	101.34±0.16	100.67±0.11	102.52±0.25	100.13±0.23	98.78±0.45	99.67±0.17
Wetting time, s	49.34±0.52	38.45±0.32	14.12±0.18**	22.33±0.20	30.14±0.24	28.43±0.33	39.00±0.14	155±0.18
Water absorption ratio	52.36±0.34	43.63±0.27	72.81±0.46*	71.27±0.13	62.09±0.33	69.56±0.26	78.37±0.24	44.14±0.24
In-vitro disintegration time, s	54.33±0.24	43.23±0.27	20.00±20**	26.33±0.12	38.66±0.57	30.33±0.23	42.23±0.17	180±0.21
In-vivo disintegration time, s	68.56±0.21	46.25±0.24	22.45±0.16	27.65±0.18	41.68±0.25	35.21±0.41	44.25±0.12	—
Weight variation, mg	124.31±0.21	123.78±0.23	124.67±0.17	125.11±0.15	123.98±0.18	124.45±0.23	125.0±0.16	—

a) Mean±S.D. (n=3). *b*) Perinorm tablet, IPCA Laboratories Ltd., Mumbai, India. Perinorm tablet, IPCA Laboratories Ltd., Mumbai, India. * $p<0.001$, ** $p<0.0001$.

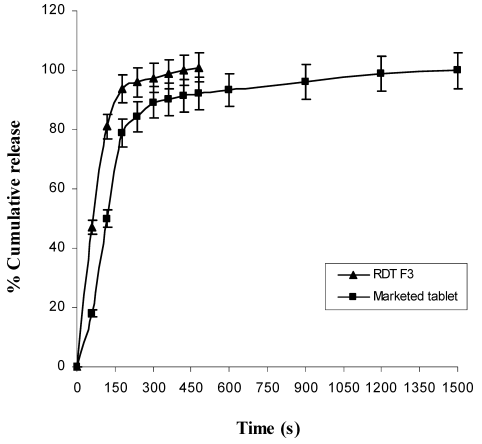

Fig. 3. Dissolution Profiles of Optimized Rapidly Disintegrating Tablet (F3) and Marketed Immediate Release Tablet

Dissolution Study of Tablets: *In vitro* dissolution study on prepared tablets (batch F3) was performed in 500 ml SGF without enzymes using USP type II (paddle) apparatus at 50 rpm, while the dissolution of marketed immediate release tablet was carried out in 900 ml SGF without enzymes using USP type II (paddle) apparatus at 100 rpm and maintain the temperature for both at 37±0.5 °C (Fig. 3). Test sample (5 ml) was withdrawn at particular time interval and replaced with fresh dissolution medium maintained at 37±0.5 °C. The samples then filtered (membrane filter, 0.45 μm) and analyzed using a UV spectrophotometer at λ_{max} 273 nm.

Stability Study of Tablets The stability studies of the optimized tablets were carried out at 40 °C and 75% relative humidity in stability chamber (Remi Instruments, Mumbai, India) for three months. Tablets were withdrawn at 1, 2 and 3 months intervals and evaluated for disintegration time, tensile strength, drug content and *in vitro* release.

Results and Discussion

Characterization of DPCs Percentage drug content in DPCs was found from 97.67 to 99.12. Drug release was observed in SSF from complexes with the drug–polymer ratios of 1 : 2 and 2 : 5 were found to be 0.21%, 0.20%. Paired t test was applied to determine any significant difference in terms of drug release when DPC ratios 1 : 2 and 2 : 5 were used and there observed no significant difference in the drug release ($p>0.05$). Moreover, no significant differences were observed in the values of angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index in case of DPC ratios 1 : 2 and 2 : 5. Thus, there is no advantage in selecting the DPC with ratio 2 : 5, containing the higher polymer concentration which will add cost to the formulation. Therefore, 1 : 2 ratios which contain the lesser amount of polymer than 2 : 5 ratio, was considered the optimal concentration of DPC with significant masking of bitter taste for further studies. Taste evaluation of RDT in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value (0.5) within 10 s, whereas, metoclopramide HCl was rated intensely bitter with a score of +3 for 10 s. The flow properties and compressibility index (Table 3) indicates that DPC granules have good flow with good compressibility that was needed in directly compressible tablet formulations.

Molecular Properties The X-ray diffractogram of metoclopramide HCl confirms its crystalline nature, as evident from the number of sharp and intense peaks (Fig. 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 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 observed between 20 and 30 (2θ); whereas, the intensity of characteristic peaks of pure drug at 20 and 30 (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. The FT-IR spectrum of the physical mixture of drug and polymer showed no significant shift or reduction in intensity of peaks of metoclopramide HCl. However, the FT-IR spectrum of DPC was found to exhibit some significant difference in the characteristic peaks of metoclopramide HCl, revealing modification of the drug environment. As shown in Fig. 2, two peaks of –NH stretch (primary amine) of metoclopramide HCl was observed at 3446 and 3396 cm^{-1}. The dimuniation of these peaks in DPC indicates that there may be interaction of acrylate group with the primary amine.

Effect of Type and Concentration of Disintegrants Initially tablets containing superdisintegrants in the concentrations 8, 10, and 12% wt/wt were tested for disintegration time. From Table 4, it was concluded that the disintegration time increases with increase in concentration of sodium starch glycolate in the tablets. It indicates that increase in the concentration of sodium starch glycolate (SSG) has a negative effect on the disintegration of tablets. One way ANOVA was applied for the disintegration time obtained at different concentrations which showed significant difference in the disintegration time at different concentration of the SSG ($p<0.05$). It was observed that the disintegration time of tablets decreased with increase in the concentration of the

crosscarmellose sodium (CCS). Significant difference in the disintegration time was observed at different concentration of the CCS ($p<0.05$). It was also observed that at higher concentration, formation of viscous gel layer by sodium starch glycolate and crosscarmellose sodium might have formed the thick barrier to the further penetration of the disintegration medium and hindered the disintegration of tablets.[18] In case of tablets containing crosspovidone, increasing concentration of crosspovidone from 8 to 12%, the disintegration times of tablets was not affected significantly ($p>0.05$), which may be due to the higher capillary action and little tendency of the crosspovidone to form viscous gel. Based on the disintegration results (Table 4), the investigated superdisintegrants can be ranked according to their ability to swell in water as crosspovidone>croscarmellose sodium>sodium starch glycolate. On the basis of the results obtained in the preliminary screening studies, the batch containing crosspovidone showed the fastest disintegration. Hence, crosspovidone was selected for the formulation of RDTs.

Evaluation of Tablets Tensile Strength, Friability, Weight Variation and Content Uniformity: The tensile strength of the tablets was found to be 1.72 to 3.04 MPa. Properties like friability, weight variation, and content uniformity of tablets of all the batches were found to be within acceptable limits (Table 6).

Wetting Time and Disintegration Time: The tablets containing the crosspovidone showed the least time of wetting than the Vivasol and SSG. Tablets of batch F3 containing mannitol and microcrystalline cellulose in the ratio 1 : 1 and 8% wt/wt crosspovidone showed faster disintegration, within 20 s, than the marketed tablet (180 s) (Table 6).

Drug Release from RDT[17,19]: From the results of the tests, tablets of batch F3 were considered to posses the best physical properties accompanied with quick disintegration and, therefore, tested and compared with the marketed immediate release tablet for dissolution. The dissolution study of the optimized tablet revealed rapid release of drug (t_{90} of 90 s) in SGF compared with marketed formulation, which had a t_{90} of 600 s (Fig. 3). Thus, a significant difference in the dissolution patterns of the prepared and marketed formulations was observed. From *in vitro* dissolution data it was concluded that there may be rapid release of the drug from F3 formulation as compared with the marketed immediate release tablet. The dissolution process may involve both solubilization and ion exchange of Eudragit EPO in SGF. As Eudragit EPO polymer is soluble below pH 5 the drug gets released from complex in SGF. Moreover, anions from physiological fluid may compete for binding with cationic polymer releasing anionic metoclopramide. Thus, the fast release of drug from the complex may be attributed to combination of above mentioned effects.

One way ANOVA was applied to compare the dissolution profile of optimized RDT and marketed immediate release tablet (Graph pad prism version 4). From the one way ANOVA results p value ($p<0.0001$) was found be significant. That means there is a significant difference observed in the release profile of the marketed immediate release tablet and rapidly disintegrating tablet.

Stability Study of the Tablets A formulation showing minimum disintegration time was selected for stability studies. According to ICH guidelines, selected formulations (F3) were stored at 40 °C temperature and 75% relative humidity (RH) for a period of 3 months. Evaluation parameters studied do not show any major difference and all the values for disintegration time, tensile strength, drug content and *in vitro* release were found to be within acceptable limits.

Effect of Amount and Type of Lubricant on Disintegration Time It is known that magnesium stearate is hydrophobic while talc has hydrophobic and hydrophilic properties.[8] Thus, we selected these materials as lubricants for this study. The effect of the amount and type of lubricant on oral disintegration time of tablets is shown in Fig. 4. As the concentration of magnesium stearate and talc was increased up to 5% there is not much effect on the disintegration time. At the 10% lubricant concentration, the disintegration time of tablet containing magnesium stearate was found to be more than 45 s, whereas, tablets containing talc as a lubricant disintegrates in less than 30 s. The differences in the disintegration time of the tablets could be attributable to differences in the hydrophobic and hydrophilic properties of the two lubricants. Magnesium stearate is well known as a high hydrophobic lubricant, so that the oral disintegration time of tablets containing magnesium stearate is longer than tablets containing talc. The hydrophobic magnesium stearate film forms during blending will have a negative effect on the wettability of the tablet ingredient particles and hence retard water penetration into the tablets. However, if complete coating of lubricant is not formed during blending the lubricant film will not be perfect and water will enter the disintegrant particles and may decrease the disintegration time.[20]

Effect of Diluents on Disintegration Time In this study the different diluents were used to determine the effect of diluents on disintegration time. Diluents used in study were taken as 1 : 1 ratio with mannitol. Microcrystalline cellulose PH 102 shows the shorter disintegration time followed by Tablettose, dicalcium phosphate and finally starch 1500 (Table 6). Microcrystalline cellulose used in 31.73%, due to its high swelling property, it shows quicker disintegration time. Microcrystalline cellulose and dicalcium phosphate (DCP) are hydrophobic while Tablettose (TT) and starch are hydrophilic in nature, but Starch, which is having somewhat binding property; shows the maximum disintegration time.

When microcrystalline cellulose is combined with water soluble mannitol, it shows the shorter disintegration time than other diluents. This may be attributed to the high water

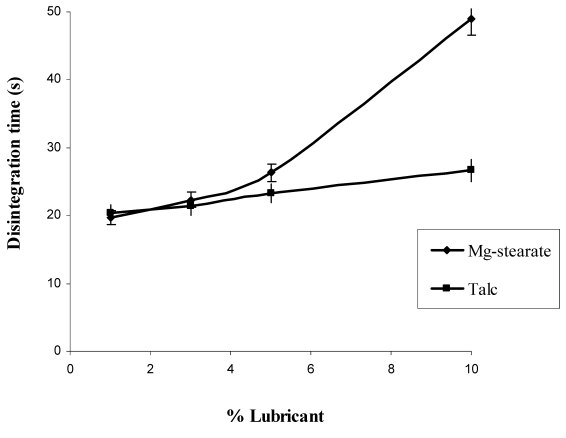

Fig. 4. Effect of Type and Amount of Lubricant on Disintegration Time

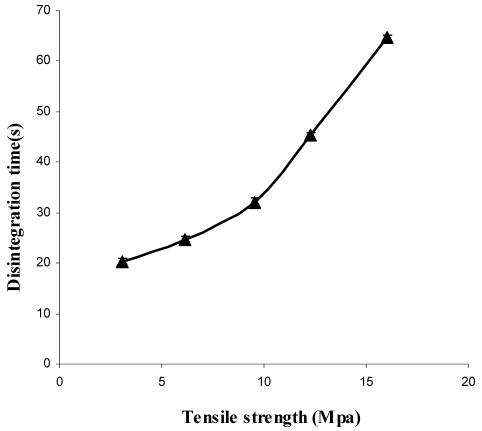

Fig. 5. Effect of Tensile Strength on Disintegration Time

solubility of mannitol which may leave pores in the tablet matrix; afterwards capillary action may be responsible for penetration of the surrounding fluid in the tablet matrix and thereafter rapid disintegration.

Effect of Xylisorb on Disintegration Time The Xylisorb is a polysaccharide containing Xylitol. The Xylitol was used here as a sweetener. Xylitol is a non sugar having negative heat of solution and high water solubility. These properties had some contribution to the rapid disintegration of the tablet and pleasant mouth feel. When the Xylisorb was removed from the optimized formulation there observed increase in the disintegration time. This indicates that Xylisorb has additive effect on disintegration of the tablet in the present formulation.

Effect of Tensile Strength on Disintegration Time The tablets of different hardness were prepared by direct compression. The tensile strength of prepared tablets was determined by using Ubique tensile tester. Tensile strength is an indication of compression force. It was observed that there is linear increment in the disintegration time with increased tensile strength (Fig. 5). Higher the tensile strength, more the bonding of the ingredients occur, that may prevent the ready access of water, ultimately increasing the disintegration time.

Conclusion

The study conclusively demonstrated taste masking of metoclopramide HCl and rapid disintegration as well as dissolution of RDT. Taste masked RDTs of metoclopramide are more palatable form without need of water during administration, helpful to the patients with gastroparesis, having symptoms of vomiting and fullness of gastrointestinal tract (GIT). Thus, the patient-friendly dosage form of intensely bitter drug, metoclopramide HCl is useful one, especially for pediatric, geriatric, bedridden, noncooperative and diabetic gastroparesis patients and can be successfully formulated using this technology.

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