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# Formulation and *in vitro* Evaluation of Taste Masked Orodispersible Tablet of Metoclopramide Hydrochloride

**Jayashri G. Mahore* [1], Kamlesh J. Wadher [1], Milind J. Umekar [1]**

**[1]Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur-441, Maharashtra, India.**

***Corresponding author : jayashri_mahore@rediffmail.com***

**Abstract:** In the present work, orodispersible tablets of Metoclopramide HCl were designed by preparing tasteless complexes of Metoclopramide HCl with weak cation ion exchange resins (Indion 234). The ion exchange complex were prepared by the batch process using activated Indion-234 with a drug: resin ratios 1:1,1:2 and 1:3 (% w/w) and IR analysis, assay content and decomplexation studies give evidence of complex formation. Drug shows maximum complexation with resin in pH range 4-6, while activation of ion exchange resin affects the percent drug loading. Drug release from drug: resin complex in salivary pH was insufficient to impart bitter taste. A study on super-disintegrants i.e., Croscarmellose sodium, Sodium starch glycolate, Crospovidone along with directly compressible mannitol to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and *in vitro* dispersion time. Based on *in vitro* disintegration time (approximately 10 s), formulations were tested for *in vitro* drug release pattern (in pH 1.2 buffer), the formulation prepared by direct compression method using microcrystalline cellulose and 4.6% w/w crospovidone was found to be a better formulation ($t_{50\%}$ = 4 min) based on the *in vitro* drug release characteristics compared to conventional commercial tablet formulation ($t_{50\%}$ = 15 min). Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

**Keywords:**Oral dispersible Tablet● Metoclopramide HCl● Ion exchange Resin●Indion234.

## Introduction

Many conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtained rapid and complete systemic drug absorption. Such immediate release products results in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects [1]. Tablets are the most widely used dosage form because of its convenience in terms of self- administration, compactness and ease in manufacturing. Dysphasia is a common problem encountered in all age groups in concern to solid dosage forms, which results in high incidence of non-compliance and ineffective therapy. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth. [2, 3] ODTs are useful in patients [4], such as pediatric, geriatric, bedridden or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup [5] leading to ineffective therapy [6], with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [7-8].

Metoclopramide hydrochloride a derivative of para-aminobenzoic acid, is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux [9] and for the prevention of cancer chemotherapy- induced emesis [10]. 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 ODTs. Metoclopramide HCl is an intensely bitter drug; hence, if it is incorporated directly into an ODT the main objective behind formulation of such a dosage form will definitely get futile.

Ion exchange resins have been used as drug carriers in pharmaceutical dosage forms for taste masking [11]. Ion exchange resins are cross linked water-insoluble polymers carrying ionizable functional groups. Drugs can be loaded into an ion exchange resin by an exchanging reaction, and hence a drug–resin complex is formed [12].

Drug is released from the resinate by exchanging with ions in the gastro-intestinal fluid, followed by drug diffusion [13]. There are literature reports on the interaction of amine drugs with polycarboxylic acid ion- exchanged resin [11, 14] that indicated these resins might be very useful in the taste masking. One study indicated that saliva, with an average pH of 6.7 and a cation concentration of 40 meq/L, [15] would only elute a few percent of drug from polycarboxylic acid resin adsorbate. Thus in the present study an attempt has been made to mask the taste of Metoclopramide HCl and to formulate ODTs with good mouth feel so as to prepare a "patient-friendly dosage form."

## Materials and Methods

### Materials

Metoclopramide Hydrochloride was a gift from IPCA Laboratories Ltd. (Mumbai, India). Indion 234 was a gift from Ion Exchange, India Ltd., (Mumbai, India). Sodium starch glycolate, Croscarmellose sodium and Crospovidone were provided as gift samples by Maple Biotech Pvt. Ltd, (Pune, India). All other chemicals used in the study were of analytical grade.

### Method

***Purification of ion exchange resin [16]***

Indion 234 was washed with distilled water. The wet resin was activated by 0.1M HCl 300ml followed by washing with distilled water and was dried overnight in hot air oven at $50^0$C and was stored in an air tight glass vial.

***Preparation of Metoclopramide resinate [16]***

Metoclopramide Hydrochloride resinate was prepared using a batch process. For preliminary study, we optimized the ratio of resin to drug at 1:3. Resin (3 g) was placed in an Erlenmeyer flask and then 250 ml of distilled water was added. The mixture was shaken in the water bath at $37^0$C. The supernatant was collected and assayed spectrophotometrically at a wavelength of 273 nm (Techcomp, UV 2300, Shanghai, Japan) to determine the drug-loading equilibrium time. Then, the Metoclopramide Hydrochloride resinates were separated from the filtrates by filtration, washed several times with distilled water, dried overnight at $50^0$C and kept in a desiccator.

**Characteristics of Metoclopramide resinates**

***Metoclopramide content***

Metoclopramide resinate (50 mg) was placed in a beaker to which 0.4 M HCl (50 ml) was added for eluting Metoclopramide from the resinate. The eluate was decanted and replaced with the same volume of fresh eluent. The volume of eluate was measured and assayed for the content of Metoclopramide by spectrophotometry at wavelength of 273 nm. The elution process was stopped when the absorbance of the last eluate was lower than 0.01. The sum of the content of Metoclopramide in each eluate was equal to the total content of Metoclopramide in resinate. (Table 1)

***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. Solid drug: resin complex equivalent to 10 mg of drug was subjected to release rate study. Weighed quantity added to 10 ml phosphate buffer pH 6.8 I.P. Aliquot was withdrawn after 2 min. The sample was filtered through whatman filter paper. The absorbance was measured at 273.20 nm (Table 1).

***MolecularProperties:*** 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 Drug: Indion 234 (1:3), metoclopramide HCl, and Indion 234 were recorded. using a Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Saint Jurie, Clubac, Canada) with monocrotized Cu Kα radiation (1.314 A0), 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)

***Selection of Superdisintegrant and Formulation of ODTs***

Before formulation of tablets, the best superdisintegrant among Sodium starch glycolate, Croscarmellose sodium and Crospovidone was screened out (Table 2). The best superdisintegrant screened was used for the final formulation of tablets (Table 3). Tablets were prepared in various batches containing a blend of microcrystalline cellulose and mannitol (1:1) as a diluent and superdisintegrant in various concentrations (Table 4). Tablets were prepared by direct compression using 8-mm flat-faced punches.

**Physical Properties of the Tablet Blend [17]**

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined (Table 5). Bulk density was determined by the USP method I; tapped density was determined by USP method II. Percent compressibility was calculated using Equations 1.

Percent compressibility =
$\{( D t - D b ) / D t \} \times 100$ ……(1)
Where, Dt and Db are tapped and bulk densities.

**Evaluation of Tablet:**

The prepared orodispersible tablets were evaluated for hardness, weight variation, thickness, friability and drug content (Table 6) [18, 19]. Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier calliper. Weight variation test was performed according to the official method.

**Wetting Time and Water absorption ratio [20]**

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorbtion ratio 'R' was determined using the equation,

$R= 100 (W_a-W_b) / W_b$ .....(2)

Where, $W_b$ is weight of tablet before water absorption

$W_a$ is weight of tablet after water absorption.

**In Vitro Disintegration Time:**

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 because many reports [21-23]indicated the unsuitability of the conventional disintegration test apparatus for RDT. Briefly, the apparatus consisted of a glass beaker 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.

**In-vitro Dissolution studies:**

The In-vitro dissolution studies were carried out using USP apparatus type II (paddle) at 50 rpm. The dissolution medium used was pH 1.2 buffer (900 ml) maintained at 37 ± 0.5°C. Aliquots of dissolution media were withdrawn at different intervals and content of Metoclopramide Hydrochloride was measured by determining absorbance at 273.20 nm. The dissolution experiments were conducted in triplicate. Results were shown in figure 3 and figure 4.

**Comparison of Optimized Formulation with Conventional Marketed Tablet**

In vitro Dissolution studies for optimized formulation and uncoated conventional tablet were also carried out (Figure 5).

**TAB.1.DRUG CONTENT AND IN VITRO TASTE EVALUATION OF DPCS IN SSF**

| Ratio of drug: resin | 1:1 | 1:2 | 1:3 |
|---|---|---|---|
| Amount of Metoclopramide HCl per 100mg of drug resin complex*. | 98.292 ± 0136 | 98.793 ± 0.129 | 99.242 ± 0.128 |
| % Drug dissolved in SSF after Time 2min* | 5.204 ± 0.268 | 4.440 ± 0.338 | 1.196 ± 0.198 |
| Pure drug | 94.97 ± 0.941 | | |

*Results are t mean of 3 observations ± SD

**TAB. 2. SELECTION OF SUPERDISINTEGRANT**

| Sr. No. | Batch | Disintegrant | Disintegrant (%w/w) | Disintegration Time (Sec)* |
|---|---|---|---|---|
| **1** | **$S_1$** | **-** | - | 120.34±1.78 |
| **2** | **$S_2$** | **CCS** | 4 | 70.36±1.04 |
| **3** | **$S_3$** | **CCS** | 6 | 55.95±2.62 |
| **4** | **$S_4$** | **CCS** | 8 | 42.26±2.53 |
| **5** | **$S_5$** | **SSG** | 4 | 160.45±1.72 |
| **6** | **$S_6$** | **SSG** | 6 | 149.1±2.17 |
| **7** | **$S_7$** | **SSG** | 8 | 101.33±1.03 |
| **8** | **$S_8$** | **CP** | 4 | 50.05±1.22 |
| **9** | **$S_9$** | **CP** | 6 | 35.30±1.48 |
| **10** | **$S_{10}$** | **CP** | 8 | 20.73±2.45 |

**Mean ± S.D. (n= 3)*

**TAB. 3. OPTIMISATION OF SUPERDISINTEGRANT**

| Sr. No. | Batch | Disintegrant | Disintegrant (%w/w) | Disintegration Time (Sec)* |
|---|---|---|---|---|
| 1 | $S_8$ | CP | 4 | 50.05± 1.22 |
| 2 | $S_9$ | CP | 6 | 35.30±1.48 |
| 3 | $S_{10}$ | CP | 8 | 20.73±2.45 |
| 4 | $S_{11}$ | CP | 5 | 45.12±1.34 |
| 5 | $S_{12}$ | CP | 7 | 24.31±2.01 |

**Mean ± S.D. (n= 3)*

**TAB. 4. FORMULATION COMPOSITION ODT**

| Sr. No. | Tablet Ingredient per Tablet (mg) | Formulation | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** |
| **1** | **DRC*** | 43.3 | 43.3 | 43.3 | 43.3 | 43.3 | 43.3 | 43.3 |
| **2** | **Mannitol** | 96 | - | 48 | 64 | 72 | 32 | 24 |
| **3** | **MCC** | - | 96 | 48 | 32 | 24 | 64 | 72 |
| **4** | **Crospovidone** | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **5** | **Aspatame** | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **6** | **Magnesium Stearate** | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **7** | **Flavor** | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 |

*- Drug resin complex (DRC) equivalent to 10 mg of Metoclopramide HCl.

**TAB. 5. PHYSICAL PROPERTIES OF TABLET BLEND**

| Batch No. | Bulk density (g/mL) | Tapped density (g/mL) | Angle of Repose* (°) | % Compressibility |
|---|---|---|---|---|
| **F1** | 0.56 | 0.65 | 26.56±0.70 | 13.84 |
| **F2** | 0.55 | 0.66 | 27.13±0.78 | 26.16 |
| **F3** | 0.54 | 0.64 | 25.25±0.67 | 15.15 |
| **F4** | 0.57 | 0.67 | 26.88±0.44 | 14.92 |
| **F5** | 0.54 | 0.65 | 27.61±0.63 | 16.92 |
| **F6** | 0.55 | 0.65 | 25.70±0.63 | 15.38 |
| **F7** | 0.56 | 0.66 | 26.45±0.85 | 15.15 |

**Mean ± S.D. (n=3)*

**TAB. 6. PHYSICAL PROPERTIES OF TABLET.**

| Batch No. | Friability * | Hardness †(Kg/cm$^2$) | Thickness† | % Weight variation# | Disintegration time (Sec)* | Wetting time (Sec)@ | % Water absorption ratio@ |
|---|---|---|---|---|---|---|---|
| F1 | 0.78± 0.12 | 4.13±0.24 | 2.40 ± 0.05 | 148.44± 1.50 | 57.52±0.41 | 10.04± 1.44 | 84.64 ± 0.34 |
| F2 | 0.75± 0.34 | 4.23±0.30 | 2.49 ± 0.02 | 150.71± 1.85 | 37.50 ± 1.04 | 10.91± 0.90 | 82.64 ± 0.21 |
| F3 | 0.73± 0.36 | 4.19±0.29 | 2.50 ± 0.08 | 150.64± 1.66 | 25.55 ± 1.32 | 10.95± 1.31 | 88.80 ± 0.15 |
| F4 | 0.76± 0.22 | 4.14±0.21 | 2.42 ± 0.09 | 151.70± 1.33 | 30.37 ± 0.66 | 11.09± 0.61 | 83.75 ± 0.20 |
| F5 | 0.75± 0.44 | 4.25±0.26 | 2.45 ± 0.04 | 149.12± 2.23 | 45.24 ± 0.75 | 11.60± 1.23 | 72.8 ± 0.35 |
| F6 | 0.71± 0.24 | 4.10±0.27 | 2.47 ± 0.03 | 150.57± 1.79 | 49.94 ± 1.34 | 11.68± 0.40 | 79.50 ± 0.32 |
| F7 | 0.72± 0.59 | 4.45±0.12 | 2.52 ± 0.07 | 150.94± 1.45 | 57.09 ± 0.76 | 13.34± 1.10 | 75.43 ± 0.60 |

** n=3, † n=6, # n=20 @ n=3*

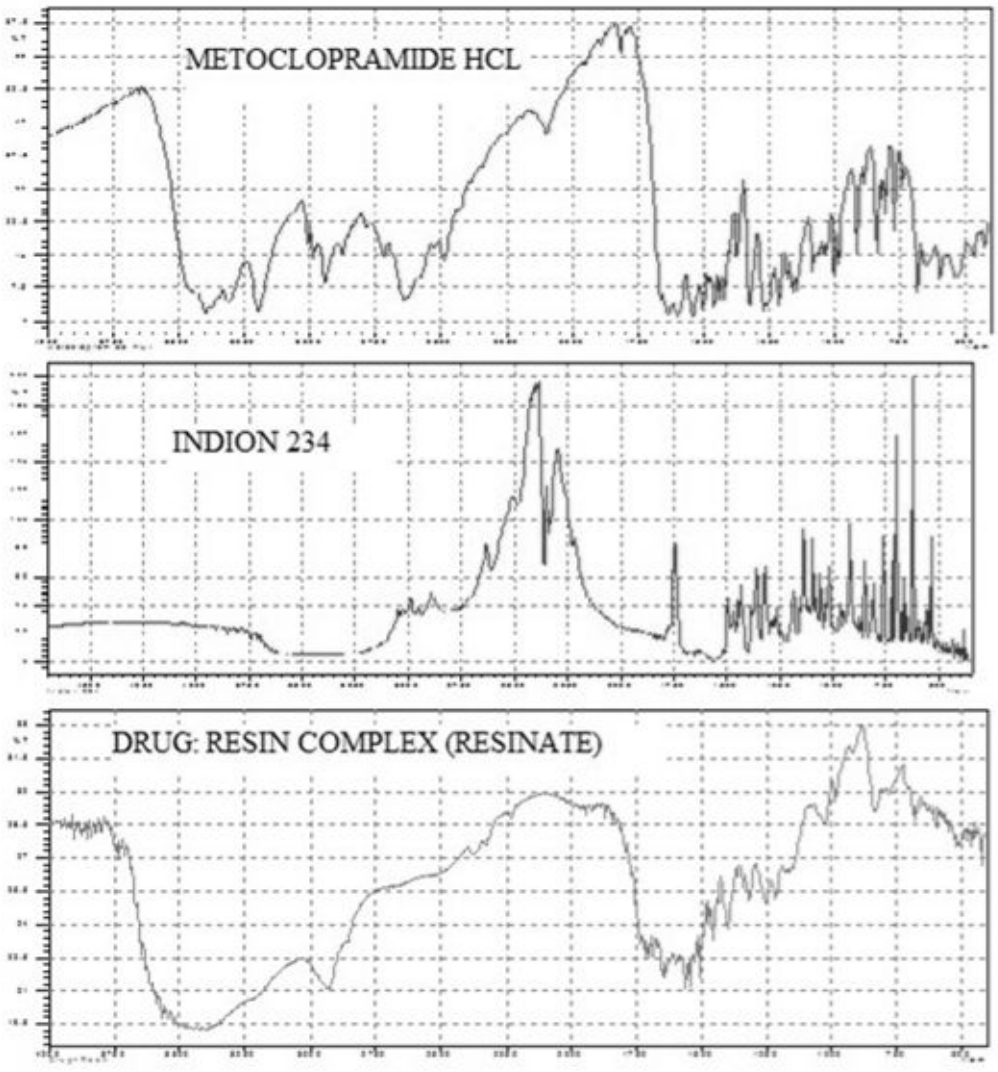


**FIGURE1: FOURIER TRANSFORM INFRARED SPECTRA OF METOCLOPRAMIDE HCL, INDION 234, AND DRUG-RESIN COMPLEXES (DRC).**

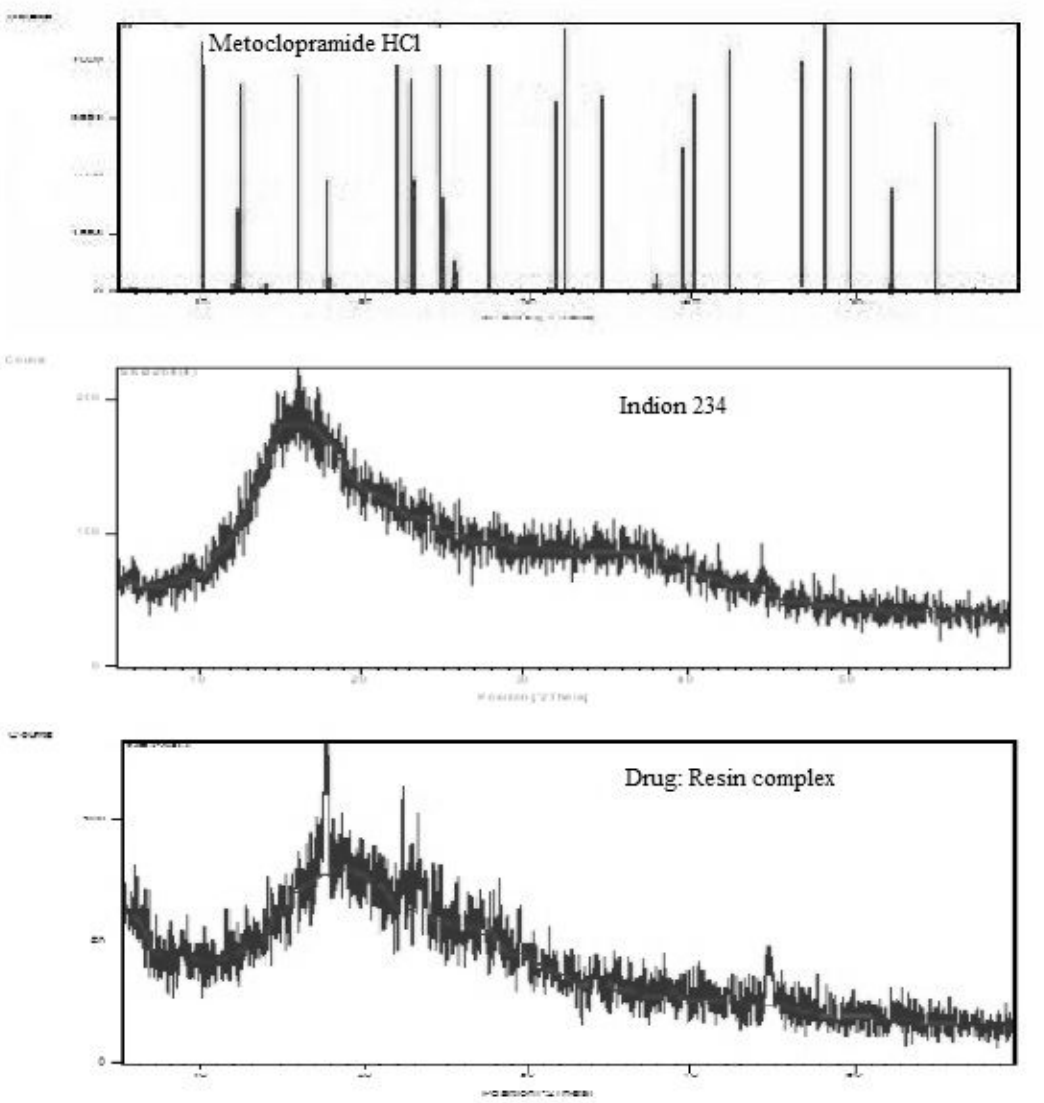


**FIG.2. X-RAY DIFFRACTION PATTERN OF METOCLOPRAMIDE HCL, INDION234 AND DRUG: RESIN COMPLEX**

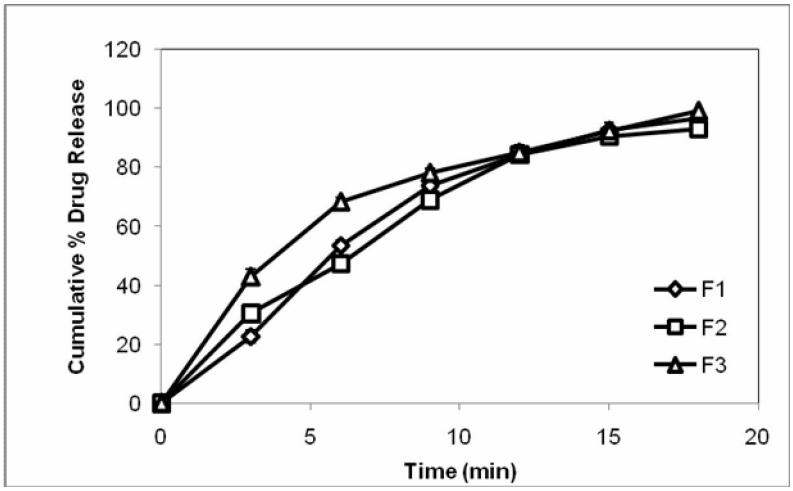


**FIG. 3. IN-VITRO RELEASE PROFILE OF TABLETS OF BATCHES F1 TO F3 CONTAINING DIFFERENT RATIOS OF BINDERS**

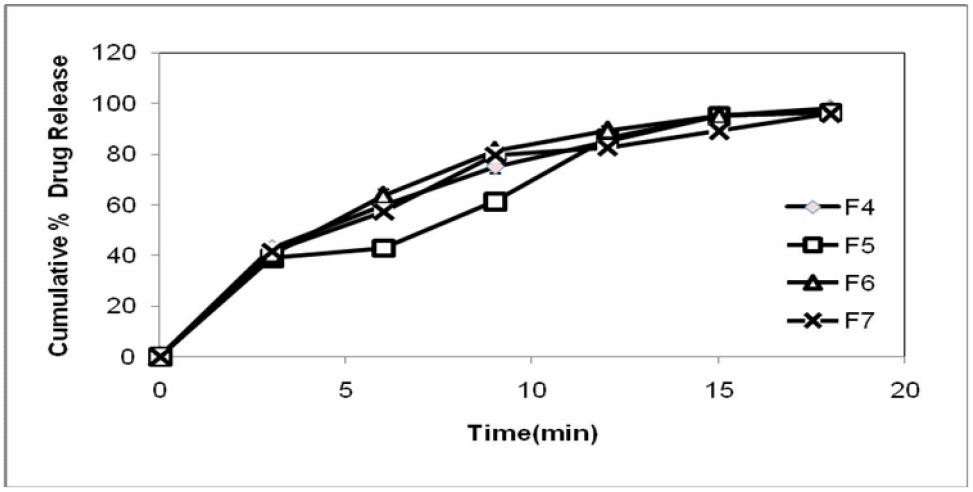


**FIG. 4. IN-VITRO RELEASE PROFILE OF TABLETS OF BATCHES F4 TO F7 CONTAINING DIFFERENT RATIOS OF BINDERS**

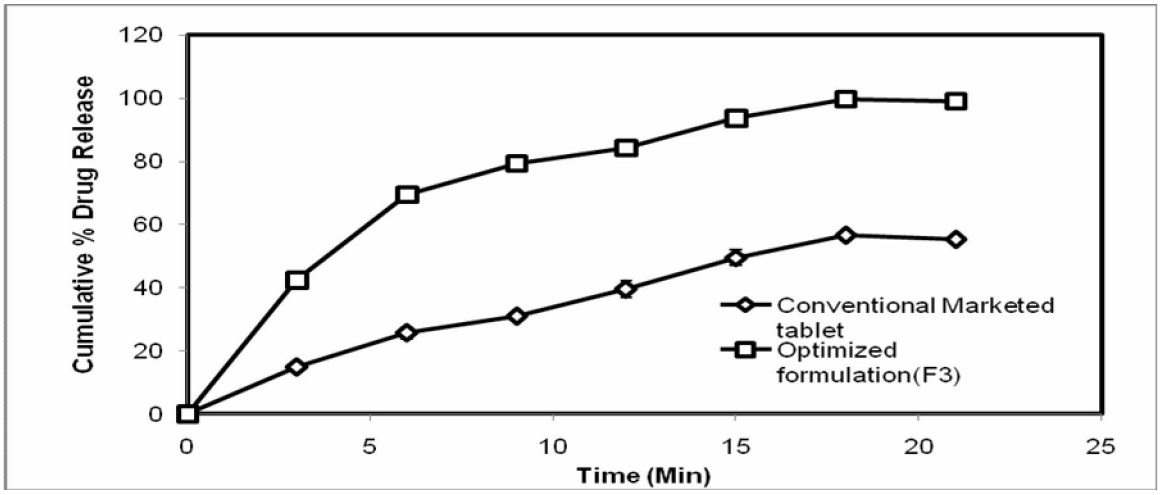


**FIG. 5. IN-VITRO RELEASE PROFILE OF CONVENTIONAL MARKETED TABLET AND OPTIMIZED FORMULATION (F3)**

## Results and Discussion

### Characterization of DRCs

Percentage drug loading in DRCs was found from 98.29 to 99.24. No drug release was observed in SSF from complexes with the drug-polymer ratio of 1:3 and ratios with lesser drug, therefore, the ratio 1:3 was considered the optimal DRC with complete masking of bitter taste for further studies.

The x-ray diffractogram of metoclopramide HCl confirms its crystalline nature, as evidenced from the number of sharp and intense peaks (Figure 2). The diffractogram of resin (Indion 234) showed diffused peaks, indicating its amorphous nature. However, the diffraction pattern of DRC (1:3) represents complete disappearance of crystalline peaks of drug. These finding suggest the formation of new solid phase with a lower degree of crystallinity due to complexation .

The infrared spectra of Metoclopramide HCl, Indion 234 and drug: resin complex shown in Figure 1. Drug spectrum shows prominent peaks at 3305.76 cm -1, 3396.41 cm-1, 1596.95 cm-1, 693 cm-1 corresponding to the -NH stretching, -OH stretching, C=O and C-Cl stretching respectively (Figure 1.1). Indion 234 shows a characteristic peak at 1674 cm-1, at 1764 cm-1 corresponding to –C=O stretching of aryl acids, and at 1602 cm-1 due to aromatic C=C stretching (Figure 1.2). Drug: resin complex spectrum (Figure 1.3) shows absence of characteristic drug peaks at 3305.76 cm-1. Subtraction spectrum did not show the characteristic peak of drug at 3305.76 cm-1 corresponding to –NH stretching. This indicates interaction of amine group of drug with Indion 234.

**Selection of the Superdisintegrant**

The formulation of orordispersible tablet was made by using metoclopramide- resin complex. Batches $S_1$ to $S_{10}$ were prepared by direct compression to select the disintegrant, from the results shown in Table 3, it can be concluded that the tablets containing crospovidone ($S_7$ to $S_9$) exhibit quick disintegration time and followed by croscarmellose sodium and sodium starch glycolate. The probable reason for delayed disintegration time of the tablets might be slow water uptake or more felling tendency of croscarmellose sodium and sodium starch glycolate than crospovidone. Hence crospovidone was selected as a disintegrant for the further studies.

From the results shown in Table 3 is obvious that the maximum concentration of crospovidone might be less than 8%. Batches $S_8$ to $S_{12}$ were prepared to optimize the optimum concentration of crospovidone in order to obtained rapid disintegration at minimum concentration. The composition and results of batches are shown in Table 4. Batch $S_{12}$ had shown more decrease in disintegration time for this reason batch $S_{12}$ was selected. Sometimes increase in disintegrant concentration decreases disintegration time, such behaviour of superdisintegrant may be due to the blockade of capillary pores which prevents the entry of fluid into the tablet.

**Physical Properties of the Tablet Blend**

The tablet blend of all the batches was evaluated for different derived properties viz- angle of repose (between 25 to 27), bulk density (between 0.54 to 0.57 $gm/cm^3$), Compressibility index (between 13 to 16). The results angle of repose and compressibility indicated that the flowability of blend is significantly good.

All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 4.10 ± 0.27 to 4.45 ± 0.12 $Kg/cm^2$ in all the formulations. The hardness of all tablets was kept within the above mentioned range to compare the disintegration time between the formulations prepared using different disintegrants and their varying concentrations. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was between 2.40±0.05 – 2.52±0.07 mm showing fairly uniform tabletting.

The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of Orodispersible tablet. The values were found to be in the range of 25.55 ± 1.32 to 57.52 ± .041 sec. The wetting time and water absorption time was also in acceptable limit i.e. between 13.34 ± 1.10 to 10.04 ±1.44 sec and 72.8 ± 0.35 to 88.75 ± 0.20.

The time intensity study for taste in human volunteers of both the DRC and ODT revealed considerable masking of the bitter taste of metoclopramide 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 ODT**

All the tablets prepared were subjected for release profile. The tablets prepared from crospovidone i.e. F1 to F7 showed a drug release between 93.82 to 99.23 % (Figure 3 and 4).

Among seven batches, batch F3 which contain MCC and Mannitol in 1:1 ratio along with 7 mg of crospovidone was selected as optimized batch because of its lowest disintegration time and highest drug release.

The drug release of the marketed product and F3 formulation was found to be 56.48 ± 2.23 and 99.12 ± 1.98 at the end of 15 minutes.

From the above observations, it may be concluded that optimized formulation is better than marketed conventional tablet in release rate of drug.

## Conclusion

The study conclusively demonstrated complete taste masking of metoclopramide HCl and rapid disintegration and dissolution of ODT. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of metoclopramide 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 non co-operative patients, can be successfully formulated using this technology.

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