

# FORMULATION AND *IN VITRO* EVALUATION OF TASTE MASKED ORODISPERSIBLE TABLET OF METOCLOPRAMIDE HYDROCHLORIDE USING INDION 204

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**Abstract :** The purpose of this research was to mask the intensely bitter taste of metoclopramide hydrochloride and to formulate orodispersible tablet of taste mask drug. Drug- resin complex were optimized by considering parameters such as optimization of resin concentration, optimization of swelling time, optimization of stirring time, optimization of pH and optimization of temperature on maximum drug loading. The effects of variables were observed on maximum amount of the drug loading. During preparation of drug resin complex (resinate), the other variables were kept constant. The resinate was evaluated for taste masking, characterized by differential scanning calorimeter and infra red spectrometer. *In vitro* drug release study of taste masked tablet showed that more than 85 % of the drug release within 10 minutes. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

**Keywords** Metoclopramide hydrochloride, Indion 204, Resinate.

## Introduction

Metoclopramide hydrochloride is a benzamide derivative, structurally related to procainamide and sulpiride, antidopaminergic activity and anti emetic agent. It can be used in the treatment of emesis, as gastrokinetic, in dyspepsia, gastroesophageal reflux disease (GERD). But this drug has bitter taste which may leads to patient's non compliance. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care provider, especially for pediatric patients. Conventional taste masking techniques such as use of sweeteners, amino acids, flavoring agent are often unsuccessful in masking the taste of highly bitter drugs.

Ion exchange resins are water-insoluble, cross-linked polymers containing salt forming groups in repeating positions on the polymer chain.<sup>[1]</sup> It can be used in the drug formulations to stabilize the sensitive

components, sustain release of drug, disintegrate tablets and mask taste.<sup>[2]</sup> The resin form insoluble adsorbates or resonates through weak ionic bonding with oppositely charged drugs so that dissociation of drug resin complex does not occur under the salivary pH conditions. Bitter cationic drugs can get adsorbed onto the weak cation exchange resin of carboxylic acid functionality to form the complex which is non bitter. Indion 204 is a weak acid cation exchange resin based on a cross-linked acrylic-copolymer, divinyl benzene matrix containing carboxylic acid functional groups. It combines with high capacity; it is insoluble in all common solvent, having excellent physical and chemical stability and operating characteristics.

## Materials and Methods

Metoclopramide Hydrochloride was obtained as a gift sample from Modi mundi, Meerut (UP). Resin Indion

204 was gifted by Ion Exchange (India) Ltd. Other chemicals used were of analytical grade.

#### **Assessment of the bitter taste of the metoclopramide hydrochloride (Bitterness threshold)**

The bitter taste threshold value of metoclopramide hydrochloride was determined based on the bitter taste recognized by six volunteers (three females and three males). A series of metoclopramide hydrochloride aqueous solutions were prepared at different concentrations as standard solutions, i.e. 5, 10, 15, 20, 25, 30, 35, 40 and 45 µg/ml respectively.

The test was performed as follows: 1ml of each standard solution was placed on the center of the tongue, it was retained in the mouth for 30 seconds, and then the mouth was thoroughly rinsed with distilled water.<sup>[3]</sup> The threshold value was correspondingly selected from the different metoclopramide hydrochloride concentrations as the lowest concentration that had a bitter taste.

#### **Preparation of resinate**

Resinate were prepared by batch process in which given quantity (mg) of resin was placed in a beaker containing deionized water and allowed to swell for 30 minutes. Accurately weighed metoclopramide hydrochloride (drug: resin ratio) was added and stirred for 30 minutes. The resinate obtained were washed with copious amount of deionized water. The complexes were dried overnight in a hot air oven at 40 °C.

#### **Optimization of concentration of resin on drug loading**

An accurately weighed amount of metoclopramide hydrochloride was added to the different concentration of indion 204 for the determination of optimized ratio with maximum drug loading (Table no 1). Amount of maximum bound drug was determined at 308 nm by UV spectroscopy.

#### **Optimization of swelling time on drug loading**

Indion 204 was soaked in 25ml of deionized water for 10, 20, 30, 40, 50, 60, and 120 minutes. The completion in batch process was performed and the maximum drug loading efficiency with resin swollen at different time was determined. (Table no 2)

#### **Optimization of stirring time on maximum drug loading**

For optimization of stirring time on drug loading, accurately weighed, 100 mg of metoclopramide hydrochloride was added to 500 mg of Indion 204 solution and slurred in deionized water. Six batches with stirring time of 30, 60, 120, 180, 240, 300, 360 and 420 minutes were processed. Amount of maximum bound drug at the end was estimated. (Table no 3)

#### **Optimization of pH on maximum drug loading**

Accurately weighed metoclopramide hydrochloride was added to 500 mg of indion 204 solution and slurred in 25 ml each of pH 1.2, 2, 3, 4, 5, 6, 7, and 8 solutions (prepared from standard solutions of hydrochloric acid and potassium hydroxide), maintained at 25°C. The maximum drug-loading at particular pH was estimated. (Table no 4)

#### **Optimization of temperature on maximum drug loading**

Accurately weighed metoclopramide hydrochloride was added to 500 mg of Indion 204 solution and slurred in 25 ml of deionized water, maintained at different temperature such as 25°C, 30°C, 40°C, 50°C, 60°C, 70°C and 80°C using temperature-controlled magnetic stirring for 60 minutes. Amount of maximum bound drug at the particular temperature was estimated. (Table no 5)

#### **Characterization of metoclopramide hydrochloride-indion 204 complexes**

The drug, resin and resinate were subjected to Fourier Transform Infra Red (FTIR) studies to check drug resin interaction using FT/IR (Jasco – 470 plus).

#### **Taste evaluation:**

Taste evaluation of DRC was performed by volunteers in the age group of 19 to 22 years. The study protocol was explained and written consent was obtained from volunteers. DRC equivalent to 10 mg metoclopramide hydrochloride was held in the mouth for 30 seconds by each volunteer. Bitterness levels were recorded instantly and then after 30 sec, 60 sec. The bitterness level was recorded against pure drug using a numerical scale (Table no 6). A numerical scale was used with the following values: 0 = tasteless, 1= acceptable bitterness, 2= slight bitterness, 3= moderately bitterness and 4= strong bitterness.<sup>[4][5][6]</sup>

#### **Differential Scanning Calorimeter (DSC)**

A differential scanning calorimeter (DSC, Perkin-Elmer) was used. The equipment was calibrated using indium and zinc. Samples were heated at 10 °C/min in aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin-Elmer). The cell had a nitrogen purge flowing approximately at 30 cm<sup>3</sup>/min. The cell and sample were held isothermally at -79°C for 30 min to purge the headspace and sample with nitrogen before heating. The cell and sample were then heated to 400 °C while monitoring heat flow.

#### **Determination of drug content:**

Resinate prepared by above process was evaluated for the drug content. Resinate equivalent to 10 mg of drug

was stirred with 100ml of 0.1N HCl for 60 minutes, till the entire drug leached out, then the solution was filtered. Dilutions were made with 0.1N HCl and the drug content was noted spectrophotometrically at 308 nm using 0.1 N HCl as blank. [7][8]

#### ***In Vitro* drug release study from resinate:**

Resinate equivalent to 10 mg of drug was subjected to dissolution studies using USP type II dissolution apparatus at 50 rpm with temperature of  $37 \pm 0.5^\circ\text{C}$  and 900 ml of SSF (Simulated salivary fluid), similarly SGF (Simulated gastric fluid) was also used as the dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time interval and it was filtered through whatman filter, the solution was checked by UV spectroscopy at 308 nm and quantity of drug release was determined periodically. The testing was carried out in triplicate.

#### **Characterization and evaluation of the tablet blend**

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined.

#### **Formulation and optimization**

The tablet consist of resinate equivalent to 60 mg drug. Avicel (PH 102) and Pearlitel SD200 were selected as diluents. All the six batches were prepared by direct compression method using single punch machine. The hardness of the tablet of each batch were tried to keep constant ( $3 \text{ kg/cm}^2$ ). The weight of the tablet of each batch was adjusted to 180 mg. The tablet was evaluated for its tensile strength, weight variation, % friability, disintegration time. (Table no 7). Dissolution study of tablets was carried out in simulated gastric fluids.

### **Results and Discussion**

#### **The bitterness threshold of metoclopramide hydrochloride:**

The bitterness threshold of metoclopramide hydrochloride recognized by the volunteers was between 35-45  $\mu\text{g/ml}$ . From the majority of volunteers it was found that the threshold value of metoclopramide hydrochloride was found to be 40  $\mu\text{g/ml}$ .

#### **Optimization:**

While studying the effect of concentration of resin on drug loading, maximum drug loading was found in ratio 1:5 (drug: indion 204). [9] Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction is an equilibrium phenomenon, maximum efficiency is best achieved in batch process. Equilibrium time was shorter due to thinner barrier for diffusion of ions, as it is a

continuous motion. Also, higher swelling efficiency in the batch process result in more surface area for ion exchange. Hence the batch process is suitable for smaller particles.

The swelling and hydrating properties of Indion 204 affect the rate of ion exchange, which in turn affects the percentage drug loading. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug-loading efficiency. [5][8] The optimized percentage drug loading (wt/wt) was found to be  $96.40 \pm 0.16$  for Indion 204 with swelling time 30 minute.

The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. The optimized percentage drug loading (wt/wt) was found to be  $96.22 \pm 0.14$  for indion 204 with stirring time 60 minutes. Drug complexation involved exchange of ionisable drug and metal ion in resin. Such a mode of complexation between drug and resin affected by pH of media. Complexation was enhanced and was found maximum at pH 7.

Efficient drug loading on indion 204 in the experimental range  $25-80^\circ\text{C}$ . Increased temperature during complexation increases the ionization of drug and resin. The effect is more pronounced for poorly water soluble and unionized drugs. Higher temperature tends to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone.

As metoclopramide hydrochloride is water soluble ionizable drug, temperature does not show any significant effect on drug absorption and also cation exchange resins are significantly affected by temperature changes.

#### **Taste evaluation by panel method:**

Taste evaluation revealed that indion 204 masks the bitter taste of the drug completely.

#### **Characterization:**

The interaction between the drug and the resin often leads to identifiable change in the IR profile of drug dispersion. So metoclopramide hydrochloride: indion 204 were subjected to IR analysis in order to evaluate possible interaction between drug and Indion 204. From IR data, pure drug shows  $\text{CH}_3$  stretching, NH stretching, C-O stretching and C-Cl stretching at 2879.2, 3449.06, 1648.84 and 95.35 respectively and resin show peak absorption of 1746.23 for  $-\text{COO}^-$  group (Figure 1). So no interaction was observed.

In DSC of drug resin complex, the peak of drug and resin were clearly seen and no change was observed in the characteristics of the drugs. (Figure 2)

The drug content of resin was found to be  $94.34 \pm 0.054\%$ . *In vitro* drug release study was performed in simulated salivary fluid (SSF) pH 6.7 (Figure 3). Samples were withdrawn, analyzed at 308nm and percentage cumulative drug release was determined. The presence of exchangeable ions of ionizable

electrolytes in the salivary fluid may be responsible for this release. So the drug resin complex is stable in salivary pH for a period of administration. The amount released is insufficient to impart bitter taste while the formulation passes through the mouth to further parts of the gastrointestinal (GI) tract. *In vitro* drug release study was also performed in simulated gastric fluids (SGF) pH 1.2 (Figure 4). The drug release from indion 204 was found to be more than 85 % within 10 minutes in simulated gastric fluids (SGF).

#### Dissolution study

Dissolution study of tablets revealed that more than 85 % of the drug was released within ten minutes.(Figure 4)

#### Conclusion

Use of cation exchange resin offers good method for preparing taste-masked substrate of metoclopramide hydrochloride. Results obtained in this work show that drug-resin complex effectively masked bitter taste of metoclopramide hydrochloride. Thus, complexation of metoclopramide hydrochloride with Indion 204 increases acceptability and palatability of formulated rapid disintegrating tablets. The results of this study can also be extrapolated to other intensely bitter drug by suitable selection of resin.

Table no 1 Effect of drug resin concentration

S. No.	Drug :resin ratio	% of drug bound to resin
1	1:1	87.94±0.1
2	1:2	90.80±.09
3	1:3	91.74±0.07
4	1:4	93.9±.12
5	1:5	95.11±.19
6	1:6	95.14±0.13

Table no 3 Effect of stirring time on drug loading.

S. No.	String time	% of drug bound to resin
1	5	81.76±.09
2	10	84.32±.11
3	20	87.78±.14
4	30	90.50±.04
5	40	93.34±.11
6	60	96.22±.14
7	120	96.21±.17
8	180	96.22±.09
9	240	96.23±.08

Table no 2 Effect of swelling time on drug loading

S. No.	Swelling time	% of drug bound to resin
1	10	89.47±.01
2	20	93.52±.21
3	30	96.40±.16
4	40	96.40±.11
5	50	96.41±.09
6	60	96.42±.12
7	120	96.42±.14

Table no 4 Effect of pH on drug loading

S No.	pH	% of drug bound to resin
1	1.2	92.74±.06
2	2	93.11±.19
3	3	93.39±.09
4	4	94.87±.12
5	5	95.56±.11
6	6	96.49±.08
7	7	96.88±.15
8	8	95.06±.09

Table no 5 Effect of temperature on drug loading.

S no.	Temperature(°C)	% of drug bound to resin
1	25	97.13±.16
2	30	97.29±.12
3	40	97.22±.09
4	50	97.49±.19
5	60	97.54±.12
6	70	97.63±.15
7	80	97.65±.06

Table no 7 Powder and tablet evaluation of optimized batch

Parameters	Optimized batch	Parameter	Optimized batch
Bulk density	0.530	Max. Wt. variation (%)	5.9
Tapped density	0.79	Tensile strength (kg/cm <sup>2</sup> )	3
Compressibility index	30.14%	Friability	0.17
Hausner ratio	1.49	Disintegration time(sec)	34
Angle of repose	26.2 <sup>0</sup>	t <sub>80% release</sub> (min)	6

Table no 8 Dissolution study of optimized tablet formulation

S.No	Time (min)	% cumulative release
1	1	51.33±0.62
2	2	62.82±0.19
3	3	67.19±0.32
4	6	80.51±0.14
5	9	96.98±0.43
6	12	92.07±0.7
7	15	90.24±0.27

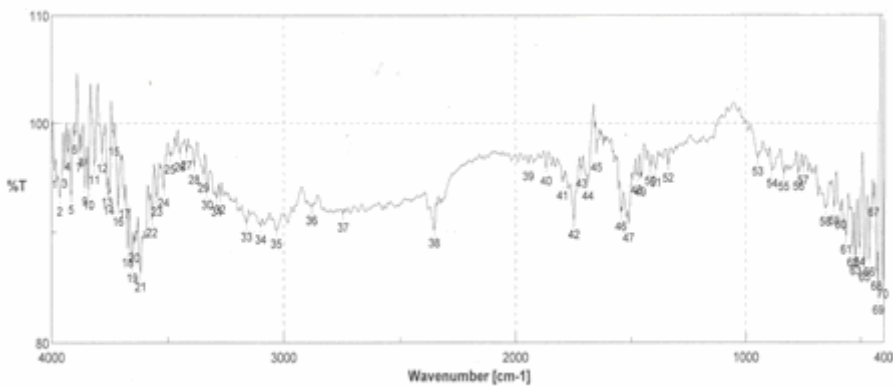


Figure 1 IR spectrum of Indion 204

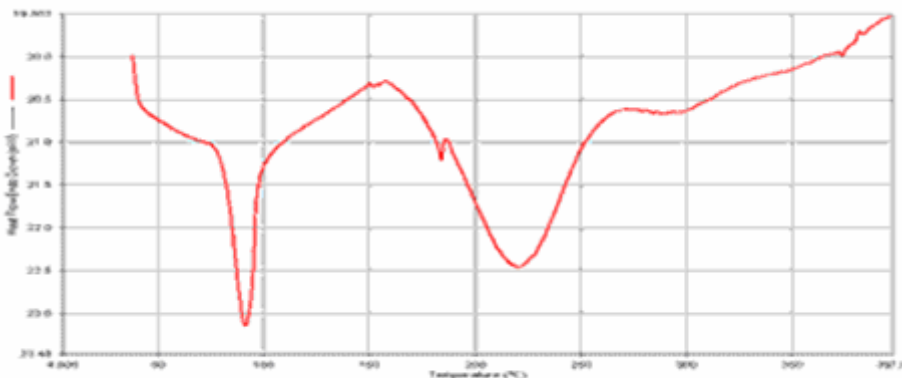


Figure 2 Differential scanning calorimeter of drug resin complex.

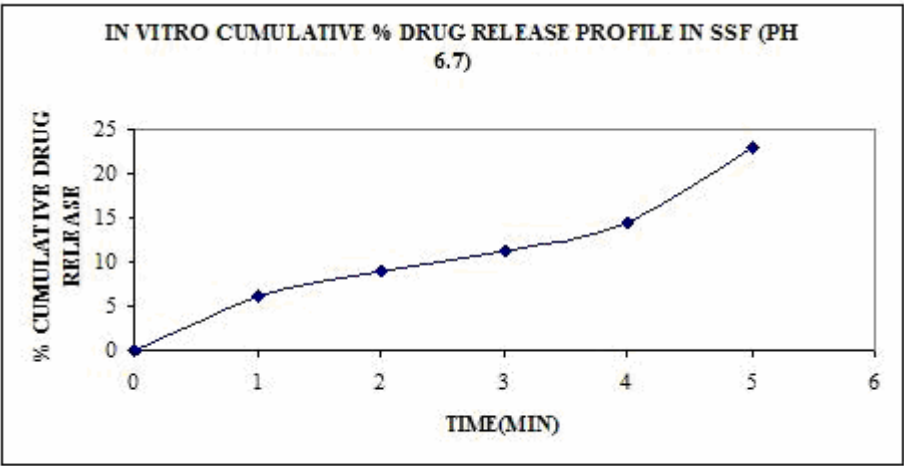


Figure 3 In vitro cumulative % drug release from DRC

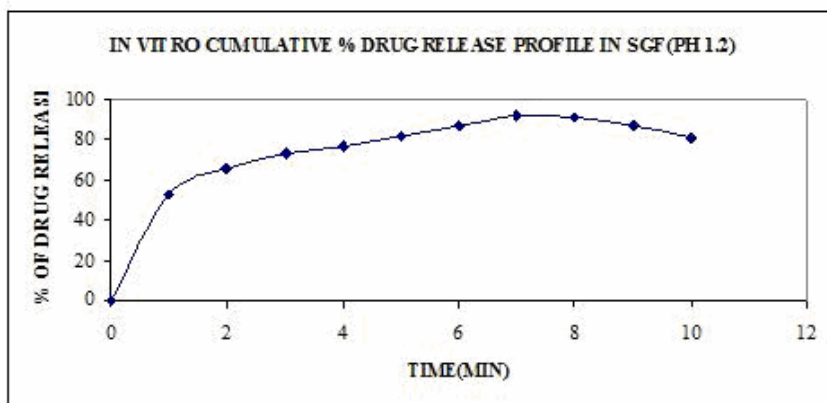


Figure 4 In vitro cumulative % drug release from DRC

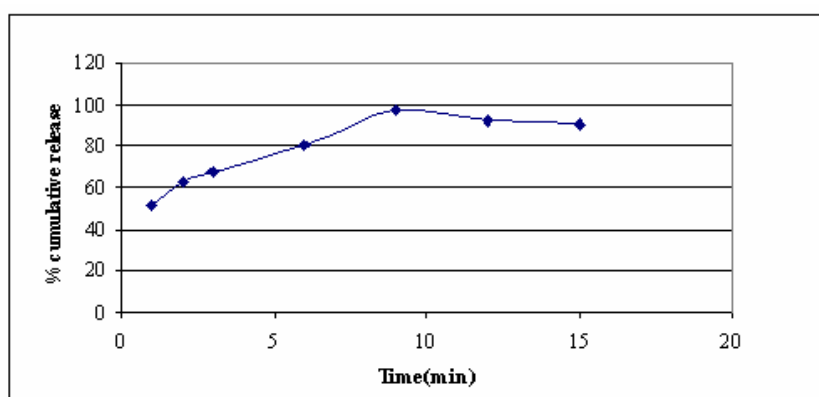


Figure 5 Dissolution study of taste masked tablet.

## References

1. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. *Drug Dev Ind Pharm* 2004; 30:429-48.
2. Agarwal R, Mittal R, Singh A. Studies of Ion-Exchange Resin Complex of Chloroquine Phosphate. *Drug Dev Ind Pharm* 2000; 26:773-76.
3. Gao Y, Cui FD, Guan Y, Yang L, Wang YS, Zhang LN. Preparation of roxithromycin-polymeric microspheres by the emulsion solvent diffusion method for taste masking. *Int J Pharm* 2006; 318:62-69.
4. Pisal S, Zainnuddin R, Nalawade P, Mahadik K, Kadam S. Molecular properties of ciprofloxacin – indion 234 complexes. *AAPS PharmSciTech* 2004; 62:1-8.
5. Pisal S, Zainnuddin R, Nalawade P, Mahadik K, Kadam S. Drug Release Properties of Polyethylene-Glycol-treated ciprofloxacin-Indion 234 Complexes. *AAPS PharmSciTech* 2004; 64:1-6.
6. Malode SS, Belgamwar VS, Sunrana SJ. Studies on taste masking of gatifloxacin using ion exchange resin. *Int J Pharm Exp* 2006; 5:99-102.
7. Chaudhari PD, Chaudhari SP, Lanke SD, Patel N. Formulation and *in vitro* evaluation of taste masked orodispersible dosage form of levocetirizine dihydrochloride. *Indian J Pharm Educ Res* 2007; 41:319-27.
8. Khan S, Guha A, Yeole PG, Katariya P. Strong cation exchange resin for improving physicochemical properties and sustaining release of ranitidine hydrochloride. *Indian J Pharm Sci* 2007; 69:626-32.
9. Raghunathan Y, Amsel L, Hinsvark O, Bryant W. Sustained-release drug delivery system I: Coated ion-exchange resin system for phenylpropanolamine and other drugs. *J Pharm Sci* 1981; 70:379-84.

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