RESEARCH ARTICLE

Comparative study of ion-exchange resin Indion 204 and Indion 214 for the taste masking of metoclopramide hydrochloride and formulation of rapid-disintegrating tablets

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The purpose of this research was to mask the intensely bitter taste of metoclopramide hydrochloride and to formulate a rapid-disintegrating tablet of the taste-masked drug. Taste masking was done by complexing the drug with ion exchange resin, Indion 204 and Indion 214, in different ratios. The complex loading process was optimized for the concentration of resin, swelling time, stirring time, pH, and temperature for maximum drug loading. Drug–resin complexes (DRC) were tested for flow properties, drug content, *in-vitro* release in simulated salivary fluid, and in simulated gastric fluid (SGF), taste evaluation by the panel method. Taste evaluation of DRC revealed considerable taste masking with the degree of bitterness below threshold value (40 µg/ml) in 0 to 5 min. Complex of both Indion 204 and Indion 214 masked the taste, but on the basis of the comparative study, resin 214 was selected for taste masking property. Disintegrant croscarmellose (5% wt/wt) gave the minimum disintegration time in comparison to crosspovidone and sodium starch glycolate. The batch of tablet containing Pearlitol SD and Avicel (PH102) in the ratio 60:40 and 5% (wt/wt) Croscarmellose showed faster disintegration i.e. 32 s, as compare to marketed tablet. It also revealed rapid drug release (t_{80}, 6 min) in SGF compared with marketed formulation (t_{80}, 9 min).

Key words: *Ion exchange resin, metoclopramide hydrochloride, rapid-disintegrating tablets, taste masking*

INTRODUCTION

Metoclopramide hydrochloride is a commonly prescribed drug used for the management of gastrointestinal disorder such as gastric stasis, gastroesophageal reflux, and for the prevention of cancer chemotherapy-induced emesis. A renewed interest is given to this drug since it demonstrated in addition to its antiemetic properties, *in vitro* and *in vivo* radio- and chemosensitizing properties.[1]

However, the oral bioavailability of metoclopramide hydrochloride is highly variable showing values between 32% and 98% due to extensive pre-systemic metabolism.[2] Oral form of metoclopramide hydrochloride often get vomited out before systemic absorption compelling parenteral or rectal administration where both method result in low patient compliance. In this regard, the rapid-disintegrating tablet seems to be an attractive alternative.

Rapid-disintegrating tablets (RDT) are in solid single-unit dosage forms that are placed in the mouth, allowed to disperse/dissolve in the saliva and then swallowed without the need for water. RDT are appreciated by a significant segment of the population, particularly children and elderly who have difficulty in swallowing conventional tablet and capsules, leading to ineffective therapy with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life-style.[3,4]

Ion exchange resins are water-insoluble, cross-linked polymer containing salt forming groups in repeating position on the polymer chain. The unique advantage of ion exchange resins for complexation is their fixed positively or negatively charged functional groups attached to water insoluble polymer backbones. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most of drugs possess ionic sites in their molecule, the resins charge provides means to loosely

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bind such drugs. The binding is generally an equilibrium process, resulting in continuous desorption or elution of drug from the resin as drug is absorbed into the body.[5,6]

Indion 204 and Indion 214 are high purity pharmaceutical grade weak acid cation exchange resins, supplied in hydrogen form as a free flowing powder. They are suitable for pharmaceutical application such as taste masking of bitter drugs. They are based on a cross-linked polyacrylic matrix.

MATERIALS AND METHODS

Materials

Metoclopramide hydrochloride was a gift sample from IPCA Lab. Ltd, Mumbai (India). The resins (Indion) were obtained as a gift sample from ion exchange (India) Ltd, Pune (India). Pearlitol and avicel were obtained as a gift sample from Signet, Mumbai (India). Aspartame was a gift sample from Zydus Cadila, Ahmedabad (India). Croscarmellose sodium, crosspovidone, sodium starch glycolate, aerosil, magnesium stearate, and talc powder were obtained from School of pharmacy, D.A.V.V., Indore (India). All ingredients used were of pharmaceutical grade.

Method

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: 1 ml of each standard solution was placed on the center of the tongue, it was retained in the mouth for 30 s, and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected from the different metoclopramide hydrochloride concentrations as the lowest concentration that had a bitter taste.[7]

Preparation of resinate

In the batch process, different quantities of resin were placed in different beakers containing 25 ml of deionized water and allowed to swell for 30 min. Metoclopramide hydrochloride (according to drug: resin ratio) was added to each beaker and stirred for 30 min. The mixtures were filtered and residues were washed with 75 ml of deionized water. The unbound drug in filtrate was estimated at 308 nm and drug-loading efficiency was calculated.

Optimization of concentration of resin for drug loading

The resin with the highest amount of drug loading was then optimized for various ratios of drugs: resin varying from 1:1 to 1:5 of Indion (204 and 214). The ratio with maximum loading of drug was the optimized ratio. Separate batches of drug resin complex were soaked in 25 ml of deionized water [Table 1].

Optimization of swelling time on drug loading

Separate batches of drug resin complex were soaked in 25 ml of deionized water for 10, 20, 30, 40, 50, 60, and 120 min. The completion in batches process was performed and the loading efficiency of swollen resin at different time was determined [Table 2].

Optimization of stirring time on maximum drug loading

Six batches of drug resin complex, slurred in 25 ml of deionized water were processed at different stirring time i.e., 30, 60, 120, 180, 240, 300, 360, 420 min. The time required for maximum drug loading was optimized [Table 3].

Table 1: Effect of drug resin concentration

Drug: resin ratio	% of drug bound to resin	
	Indion 204	Indion 214
1:1	87.94±0.1	86.36±0.13
1:2	90.80±0.09	88.11±0.07
1:3	91.74±0.07	90.30±0.03
1:4	93.9±0.12	94.95±0.07
1:5	95.11±0.19	96.36±0.11
1:6	95.14±0.13	96.38±0.14

Table 2: Effect of swelling time on maximum drug loading

Swelling time (min)	% of drug bound to resin	
	Indion 204	Indion 214
10	89.47±0.01	87.97±0.07
20	93.52±0.21	93.90±0.13
30	96.40±0.16	95.10±0.09
40	96.40±0.11	97.86±0.14
50	96.41±0.09	97.872±0.02
60	96.42±0.12	97.87±0.09
120	96.42±0.14	97.88±0.11

Table 3: Effect of stirring time on maximum drug loading

Stirring time(min)	% of drug bound to resin	
	Indion 204	Indion 214
5	81.76±0.09	80.79±0.06
10	84.32±0.11	83.90±0.09
20	87.78±0.14	88.32±0.12
30	90.50±0.04	97.23±0.05
40	93.34±0.11	97.23±0.06
60	96.22±0.14	97.24±0.09
120	96.21±0.17	97.25±0.14
180	96.22±0.09	97.26±0.19
240	96.23±0.08	97.32±0.11

Optimization of pH on maximum drug loading

Six batches of drug resin complex, slurred in 25 ml each of solution having pH 1.2, 2, 3, 4, 5, 6, 7, and 8 were maintained at 25°C. The drug-loading efficiency was estimated [Table 4].

Optimization of temperature on maximum drug loading

Six batches of drug resin complex, slurred in 25 ml of deionized water were kept at different temperature conditions i.e. 25°C, 30°C, 40°C, 50°C, 60°C, 70°C, and 80°C using temperature-controlled magnetic stirring for 60 min. The volume of filtrate was made up to 50 ml with DRC washed water. The amount of bound drug was estimated from the unbound drug in filtrate [Table 5].

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 s by each volunteer. Bitterness levels were recorded instantly and then after 30 s and 60 s. The bitterness level was recorded against pure drug using a numerical scale [Table 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.[8,9]

Determination of drug content

Resinate equivalent to 10 mg of drug was stirred with 100 ml of 0.1N HCl for 60 min, 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.[10]

***In vitro** drug release in simulated gastric fluid and simulated salivary fluid*

Drug release from DRC (1:5) in simulated gastric fluid (pH 1.2) [Table 7] using 0.1 N HCl and in simulated salivary fluid (SSF) (pH 6.7) [Table 8] using 0.1 N KOH were determined using a United States Pharmacopoeia (USP) 24 type II dissolution apparatus. The studies were performed at 50 rpm for 10 min and 5 min, respectively. 5 ml of each sample was removed and the absorbance was taken at 308 nm. The cumulative % drug release was estimated accordingly.

IR and DSC study of resinate

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

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 at approximately 30 cm^3/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

Table 4: Effect of pH on maximum drug loading

pH	% of drug bound to resin	
	Indion 204	Indion 214
1.2	92.74±0.06	93.79±0.09
2	93.11±0.19	94.06±0.11
3	93.39±0.09	94.81±0.19
4	94.87±0.12	95.14±0.06
5	95.56±0.11	95.91±0.14
6	96.49±0.08	96.4±0.06
7	96.88±0.15	97.13±0.12
8	95.06±0.09	96.43±0.16

Table 5: Effect of temperature on maximum drug loading

Temperature (°c)	% of drug bound to resin	
	Indion 204	Indion 214
25	97.13±0.16	97.81±0.09
30	97.29±0.12	97.88±0.15
40	97.22±0.09	97.75±0.12
50	97.49±0.19	97.82±0.06
60	97.54±0.12	97.87±0.16
70	97.63±0.15	97.71±0.14
80	97.65±0.06	97.88±0.19

Table 6: Bitterness evaluation by taste panel

Volunteer		1	2	3	4	5	6
Pure drug		4	4	4	4	4	4
Drug resin complex (5sec)	Indion 204	0	0	0	1	1	0
	Indion 214	0	0	0	0	0	0
Drug resin complex (10sec)	Indion 204	0	1	1	0	1	0
	Indion 214	0	1	0	0	0	0
Optimized batch	Indion 204	0	0	0	0	0	0
	Indion 214	0	0	0	0	0	0

Table 7: *In vitro* cumulative % drug release profile in SGF (pH 1.2)

Time (min.)	Cumulative % drug release	
	Indion 204	Indion 214
0	00	00
1	53.05±0.61	60.55±1.1
2	65.66±0.12	71.98±1.2.
3	73.91±0.16	79.22±1.1
4	76.98±0.11	84.67±0.11
5	82.13±0.7	89.76±0.9
6	87.34±0.12	95.25±0.6
7	92.18±0.11	98.30±01.1
8	91.47±0.62	97.19±0.91
9	86.79±0.13	91.94±1.3
10	81.60±0.14	89.86±0.8

were then heated to 400°C while monitoring heat flow.

Selection of disintegrating agent

Various disintegrating agents such as croscarmellose, crospovidone, and sodium starch glycolate were evaluated in different concentration for their disintegrating property. According to minimum disintegration time, they were finally optimized as disintegrants [Table 9].

Blending and tabletting

Metoclopramide hydrochloride tablets were prepared by direct compression as per the formula given in Table 10. The various disintegrants used were crospovidone, croscarmellose sodium, and sodium starch glycolate. The tablets were formulated employing the direct compression method using 8 mm flat-faced punches. The drug resin complex, diluents, superdisintegrant, flavor, and sweetener were passed through sieve number 40. All the above ingredients were properly mixed together. 1% of magnesium stearate and 1% talc were then passed through mesh number 80, mixed and blended with the initial mixture followed by compression of the blend by using Rimek mini press II, 12 station punching machine.

Dissolution study of tablets

In vitro dissolution study on prepared tablets was done in 900 ml SGF without enzymes using USP type II (Paddle) apparatus at 50 rpm and 37±0.5°C.

RESULTS AND DISCUSSIONS

The bitter threshold of metoclopramide hydrochloride

The bitter threshold of metoclopramide hydrochloride recognized by the volunteers was between 35 and 45 μg/ml. From the majority of volunteers it was found that the threshold value of metoclopramide hydrochloride was 40 μg/ml.

Optimization

The drug and resin ratio was optimized for maximum amount of drug loading. The maximum amount of drug loaded was found to be 95.11±0.19 and 96.36±0.11 in the ratio 1:5 for both Indion 204 and Indion 214, respectively.

The swelling and hydrating properties of Indion 204 and Indion 214 affect the rate of ion exchange, which in turn affects the percentage drug loading. The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by the stirring time too. The optimized percentage drug loading (wt/wt) was found to be 96.40±0.16 at a swelling time of 30 min for Indion 204 and 97.86±0.14 at swelling time of 40 min for Indion 214, respectively [Table 2]. Similarly the optimized percentage drug loading was found to be 96.22±0.14 at a stirring time of 60 min for Indion 204 and 97.23±0.05 at a stirring time of 30 min for Indion 214, respectively [Table 3].

Table 8: *In vitro* cumulative % drug release profile in SSF (pH 6.7)

Time (min.)	Cumulative % drug release	
	Indion 204	Indion 214
0	00	00
1	6.25±1.36	0.14±0.124
2	9.05±1.35	0.88±0.128
3	11.13±1.47	6.15±0.172
4	14.36±0.77	14.53±0.59
5	23.01±1.32	16.15±1.50

Table 9: Selection of super disintegrating agent

Formula	C1	C2	C3	C4	C5	C6
Crosspovidone	5	–	–	–	–	–
Croscarmellose	–	5	–	2	3	4
Sodium starch glycholate	–	–	5	–	–	–
Avicel (PH102)	36	36	36	37.5	37	36.5
Pearlitol SD200	54	54	54	55.5	55	54.5
Aspartame	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Evaluation						
Crushing strength (kg/cm^2)	3.5	3.5	3.5	3.5	3.5	3.5
% Friability	0.22	0.28	0.23	0.30	0.34	0.27
Wetting time (sec)	41	30	46	43	35	36
Disintegration time (sec)	48	39	53	49	43	42
Disintegration time in mouth (sec)	53	47	61	54	50	48
Qty = mg/tab (100mg)						

Table 10: Formula of optimized formulation

Name of ingredients	Quantity (for 180 mg tablet)
Drug-resin complex (1:5 ratio)	60 mg (equivalent to 10 mg of drug)
Croscarmellose	9 mg (5)
Avicel	40.4 mg (40)
Pearlitol	60.6 mg (60)
Aspartame	3.6 mg (2)
Magnesium stearate	1.8 mg (1)
Aerosil	1.8 mg (1)
Talc	1.8 mg (1)
Flavor	1 mg

Figures in parenthesis are in percentage

The drug complexation involved exchange of ionizable drug and metal ion in the resin. Such a mode of complexation between drug and resin is affected by the pH of media. Hence, complexation was enhanced and was found to be 96.88±0.15 and 97.13±0.12% maximum at pH 7 for both Indion 204 and Indion 214 [Table 4].

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 and ionizable drug, the temperature does not show any significant effect on the drug absorption, and also cation exchange resins are significantly affected by temperature changes. Uniform drug loading occurred in the experimental range 25-80°C for both resins. At 40°C, the drug loading were 97.22±0.09 and 97.75±0.12 for both Indion 204 and Indion 214, respectively [Table 5].

Drug release from DRC was found to be 98.30±01.1 (7 min) in simulated gastric fluid (pH 1.2) and 92.18±0.11(7 min) in SSF (pH 6.7), respectively [Tables 7 and 8]

In the DSC study, no change was observed in the characteristics peak of the drugs in the physical mixture of drug and polymer. This shows that there is no incompatibility between drug and polymer used.

Physical properties and characterization of metoclopramide hydrochloride-resin complex

Prepared complexes were evaluated for shape, angle of repose, bulk density, tapped density, and Hausner ratio. The bulk and tapped density were found to be 0.646 g/ml and 0.9 g/ml, respectively. The compressibility index was 28.22% and the Hausner ratio was 1.39. The angle of repose was found to be 31.35°. These all parameters were satisfactory and showed that the DRC was of good flow. The drug content was found to be 94.34±0.054 for Indion 204 and 98.86±1.018 for Indion 214, respectively. In IR data [Figures 1 and 2], pure drug shows C-O-C stretching, C-O-C asymmetric stretching, CH_3 stretching 1190.35, 1201.36, 2939.31, respectively, and resin show peak absorption of 1739.67 for $–COO^-$ group. In both IR and DSC [Figures 3 and 4] of the drug-resin complex, the peak for drug and resin were clearly seen and no change was observed in the characteristics of the drugs.

Selection of super disintegrating agent

Among croscarmellose, crospovidone, and sodium starch glycolate (on the basis of disintegration time, wetting time, % friability, crushing strength), the croscarmellose shows short disintegration time of 39 s with good friability and crushing strength. For further studies, croscarmellose sodium was selected as super disintegrating agent [Table 9]. When the blend without DRC was used, no difference was seen in the disintegration time of tablet.

Characterization and evaluation of the tablet blend

Physical properties such as bulk density, tapped density,

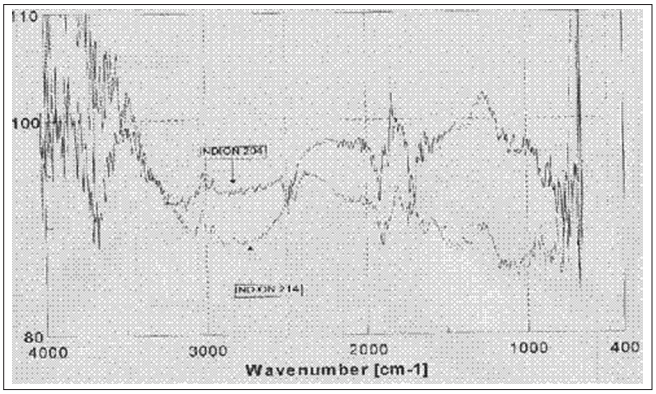

Figure 1: Comparison of IR spectra of both resinates

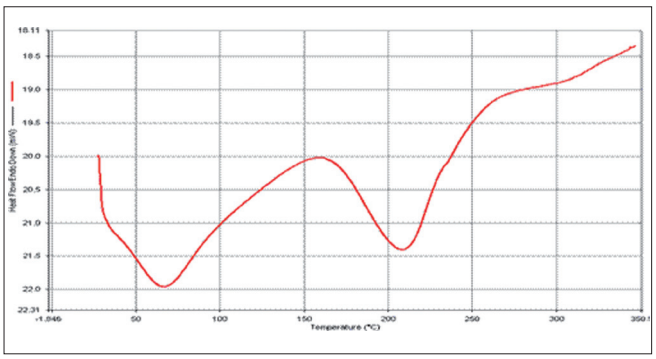

Figure 3: Differential scanning calorimetry of resinate

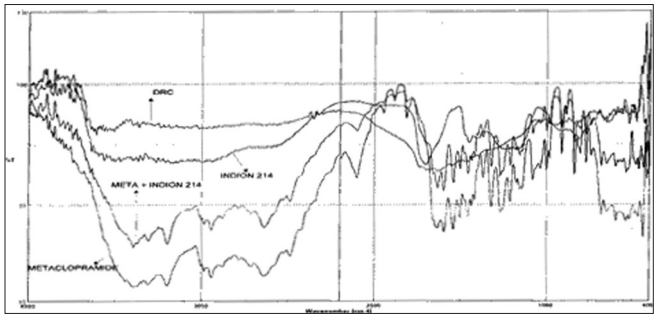

Figure 2: IR spectra showing Resinate, physical mixture of Indion 214 and drug (1:1), Indion 214 and drug alone

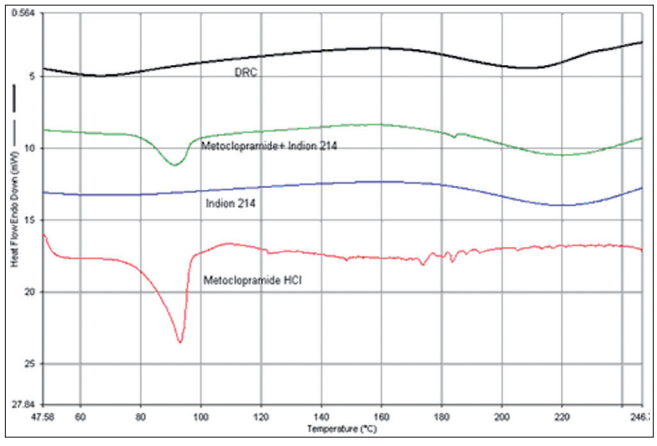

Figure 4: DSC showing resinate, physical mixture of Indion 214 and drug, Indion 214 and drug alone

Table 11: Powder and tablet evaluation of optimized batch

Parameter	Optimized batch	Parameter	Optimized batch
Bulk density	0.551	Max. Wt. variation (%)	6.1
Tapped density	0.80	Tensile strength (kg/cm^2)	3
Compressibility index	31.12%	Friability	0.17
Hausner ratio	1.45	Disintegration time (sec)	32
Angle of repose	25.22°	$t_{80\% \text{ release}}$ (min)	6

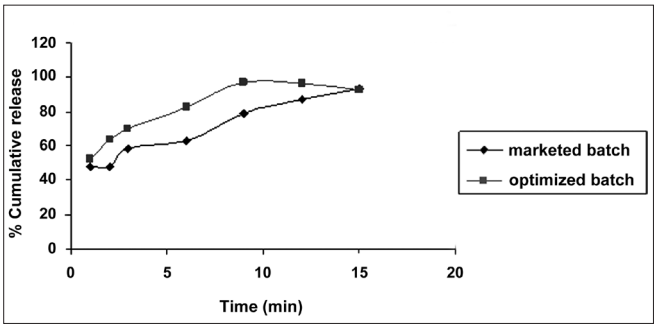

Figure 5: Comparison of marketed and optimized batch

compressibility index, and the angle of repose of blend were determined. The values of parameters such tensile strength, weight variation, % friability, disintegration time were also determined shown in Table 11.

Dissolution study of tablets

Figure 5 revealed the dissolution parameter of marketed formulation studied viz. Perinorm (IPCA Lab. Ltd, Ratlam, India), containing 10 mg of metoclopramide hydrochloride. The results of above table shows that immediate effects are produced as compared to market one.

CONCLUSION

Use of cation exchange resin offers a good method for preparing taste-masking substrates of metoclopramide hydrochloride. The study conclusively demonstrated complete taste masking of metoclopramide hydrochloride and rapid disintegration and dissolution of RDT. Thus, complexation of metoclopramide hydrochloride with Indion 214 increases acceptability and palatability of formulated rapid disintegrating tablets.

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