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Taste abatement of Metoclopramide Hydrochloride using ion exchange resins

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Abstract

The purpose of present research work was mask the bitter taste of Metoclopramide HCl using weak cation ion exchange resins (Indion 234) that contained crosslinked polyacrylic backbone. The drug resin complexes (DRC) were prepared by batch process by taking drug: resin ratios 1:1, 1:2 and 1:3. The optimum drug: resin ratio and the time required for maximum complexation was determined. The drug resinates were evaluated for the drug content, taste, micromeritic properties, drug release and infrared studies. The effect of batch process, complexation time, activation of ion exchange resin, temperature, complexation mode and pH on Metoclopramide HCl loading with Indion-234 were also carried out. IR analysis, assay content and decomplexation studies give evidence of complex formation. The taste evaluation depicted the successful taste masking of Metoclopramide HCl with drug resin complexes

Key words - Metoclopramide Hydrochloride, Indion 234, Drug resin complex

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Introduction

Metoclopramide HCl is a gastrointestinal stimulant used to treat gastro esophageal reflux, erosions or ulcers of esophagus[1], nausea, vomiting , heartburn, prolonged fullness after meals and loss of appetite in patients with diabetes [2]. The major problem occurs with this is its bitterness [3]. Administration of an orally having bitter and obnoxious tastes with acceptable level of palatability is a challenge to the pharmacist in the present world, especially in pediatric and geriatric formulation. Thus taste masking in the present day pharmaceutical industry has become a potential tool to improve patient compliance and commercial success of the product [4]. Recent years have seen a tremendous progress in the technique of masking the unacceptable taste of an orally administered pharmaceuticals, such as filling in capsules[5], coating with water in soluble polymers or pH dependent water soluble polymer[6,7], adsorption on ion-exchange resin (IER) [5-7], micro encapsulation with various polymers [8], complexing with cyclodextrin [9], chemical modification such as use of insoluble prodrugs [10- 12], effervescent systems, salt formation[13,14] . IER are

water insoluble cross linked polymer containing salt forming group in repeating position on the polymer chain [15]. IER are polymeric particles (or Gels) that contain basic or acidic group, which can form ionic complexes with oppositely charged drugs. The resins are insoluble solids that are not absorbed from GIT; hence, they do not have significant associated side effect [16]. The complex of cationic drug and weak ion exchange resin does not break at the pH of saliva i.e. 6-7 with cation concentration of 40 meq/lit. [17], but at high cationic concentration in stomach and pH 1.2, free drug is immediately released. This implies that while passing through mouth, the group remains in the complex form, thereby imparting no bitter taste in the mouth. This property was exploited to formulate the consumer friendly dosage form.

Materials and Methods

Materials:

Metochlopramide Hydrochloride and Indion 234 were obtained as a gift samples from IPCA Laboratories Ltd. (Mumbai, India) and Ion Exchange Ltd. (Mumbai, India) respectively. All other ingredients used throughout the study were of analytical grades and were used as received.

Methods:

Preparation of Resinate: [18-19],

Resinate were prepared using batch method. The resins were first washed with distilled water till neutralization. 300 mg of resin was placed in a beaker containing 250 ml of deionised water and allowed to swell for 30 min. accurately weight 100 mg of Metoclopramide hydrochloride was added to the resin solution and stirred for 60 min. The mixture was filtered through Whatman filter paper no. 41 and residue was washed with 75 ml of deionised water. Unbound drug in filtrate was estimated at 273 nm and drug loading efficiency was calculated.

Optimization of Metoclopramide HCl- Indion 234 complexation:

The drug loading onto resin was optimized by considering various parameters such as concentration of resin, swelling time and stirring temperature. These parameters were studied and optimized for the maximum amount of drug loading.

Optimization of concentration of resin for drug loading:

The resin which showed the highest amount of drug loading was then optimized for various drug: resin concentrations varying from 1:1 to1:3.Accurately weight Metoclopramide HCl (100 mg) was added to the 100, 200 and 300 mg of Indion 234 respectively. The best ratio showing maximum adsorption of drug was then optimized.

Effect of swelling time on drug loading:

Separate batches of Indion 234 (300 mg) were soaked in 250 ml of deionised water contained in a beaker for 10, 20, 30 40, 50, 60 and 120 minutes. The complexation in batch process was performed and the loading efficiency with resin swollen at different time was determined.

Optimization of stirring time, pH, Temperature on maximum drug loading: [18-19]

For optimization of stirring time on drug loading accurately weight Metoclopramide hydrochloride (100 mg) was added to 300 mg of Indion 234 solution and slurred in 250 ml of deionised water. Six batches with stirring time of 15, 30, 45, 60, 120 and 240 mins were

processed. Amount of bound drug at the end was estimated at 273 nm by UV spectroscopy and the time required for maximum adsorption of drug was optimized.

For optimization of pH on drug loading, accurately weight, 100 mg of drug was added to 300 mg of resin solution in 250 ml deionised water. The pH of the solution was maintained at 1, 2, 3, 4, 5, 6, 7, and 8 using standard solution of hydrochloride acid and sodium hydroxide and maintained at 25^0C. The drug loading efficiency at particular pH was estimated.

For optimization of temperature on drug loading Metoclopramide hydrochloride- Indion 234 complex formulations were carried out at temperature range from 25^0C to 80^0C and the effect of temperature on drug loading was studied.

Characterization of Resinate:

Infra Red (IR study):

The drug, resin and resinate were subjected to Fourier Transform Infra Red (FTIR) studies to check the interaction in the resinate. The KBr disk method was used for preparation of samples and the spectra were recorded over the wave number 4000 to 400 cm^{-1}. Then the spectra were comparatively analyzed for drug interaction.

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 100 ml of 1 N HCl and the drug content was noted spectrophotometrically at 273 nm using 1 N HCl as blank.

Taste Evaluation: [18]

Bitterness evaluation test was performed to compare the bitterness of the drug- resin complex to that of metochlopramide hydrochloride. The healthy human volunteers were used for evaluation of taste masking and the feedback was obtained from all of them. Taste evaluation was done by a panel of 10 members using time intensity method. Sample equivalent to 10 mg i.e. dose of drug was held in mouth for 10 sec. Bitterness levels were recorded instantly and then after 10 sec, 1, 2, 4, 6, and 8 minutes. Volunteer's opinion for bitterness values were rated by giving different score values i.e. 1: no bitterness, 2: acceptable bitterness, 3: slight bitterness, 4: moderately bitterness, 5: strong bitterness.

In vitro dissolution:

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 ± 0.5^0 C and 900 ml 1.2 pH buffer used as the dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time interval and it was filtered through Whatman filter paper no. 41. Absorption of the filtered solution was checked by UV spectroscopy at 273 nm and quantity of drug released was determined periodically. The testing was carried out in triplicate.

Results and Discussion

Metoclopramide hydrochloride was loaded on indion 234 by batch process. Batch process is simpler and quicker than column process. Complexation between drug and resin is essentially a process of diffusion of ions between the resin and the surrounding drug solution. As reaction is an equilibrium phenomenon, maximum efficiency is best achieved in batch process. Also, higher swelling efficiency in the batch process results in more surface area for ion exchange. Hence the batch process was selected.

The drug loading in various drug: resin concentration was found to be 68.74 ± 1.14, 88.01 ± 1.23 and 91.08 ± 1.51 respectively for 1:1, 1:2 and 1:3ratio as shown in Figure 1.

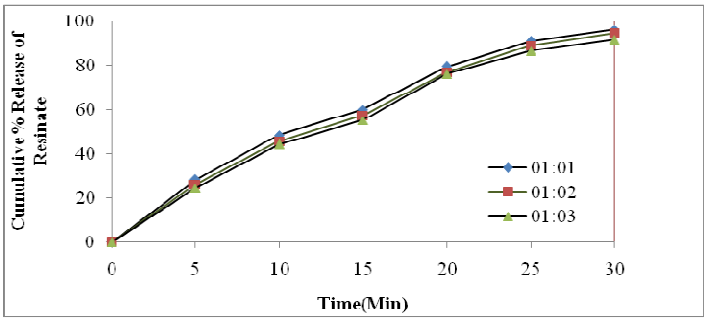

Figure 1: Percent drug complexed in various ratios of strong cation exchange resin

Swelling time showed the significant effect on drug loading showing that the swelling of resin enhances the drug loading capacity of resin. Percent drug loading with swelling time of 10, 20, 30, 40 and 50 minutes was found to be 55.43 ± 1.74, 74.11 ± 1.82, 92.62 ± 1.43, 87.33 ±1.24 and 85.31 ± 1.78 % (w/w) respectively as shown in Figure 2.Thus the 30 minutes swelling time was used as optimized time for drug loading. The swelling and ion exchange, which in turn affects the percentage loading. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug loading efficiency.

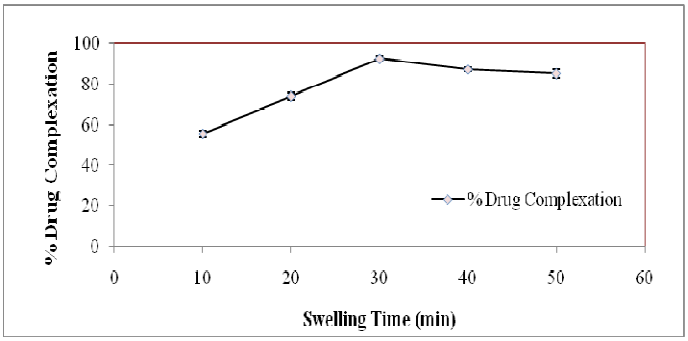

Figure 2: Effect of time of swelling of resin on complexation

The equilibrium ion exchange in solution occurs stoichiometrically and hence it is affected by stirring time. The percent drug loading (w/w) with stirring time of 15, 30, 45, 60, 120 and 240 min was found to be 51.29 ± 1.63, 66.31 ± 1.73, 81.77 ± 1.61, 93.01 ± 1.73, 91.31 ± 1.41 and 92.92 ± 1.80 respectively. These figures reveal that as time increased percent drug loading is increased rapidly. Increase in stirring time above 120 min did not further increase the percent drug loading. Hence 120 min contact time between drug and resin could be optimized to equilibrate ion exchange process to achieve maximum drug loading.

Resin: drug complexation involved exchanged of ionisable drug and metal ion in resin. Such a mode of complexation between drug and resin can be affected by pH of media. Such a mode of complexation between drug and resin can be affected by pH of media. Complexation

was enhanced between pH 3 to 5; a maximum of 92.22 ±0.355 w/w, drug lading was obtained at pH 5. As pH increases above 5 percent drug loading decreases as shown in Figure 3.

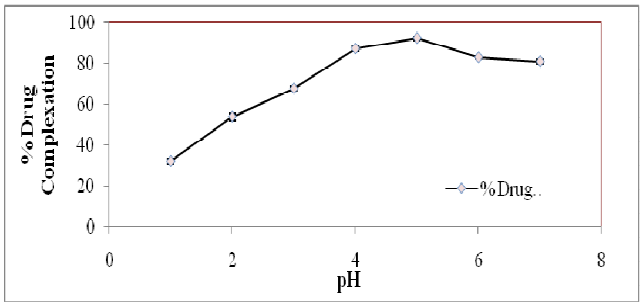

Figure 3: Effect of pH on percent drug – resin complexation

pH of the solution affects both solubility and degree of ionization of drug and resin. Results can be attributed o fact that a cationic drug is ionized at lower pH value and hence demonstrate high binding capacity while at higher pH protonated fraction of cationic drug decreases and hence interaction with resin also decreases. Hence Metoclopramide hydrochloride as a cationic drug will have maximum solubility and complete ionization in this range. Decreased complexation at lower pH i.e. below 3 is due to excess H^+ ions in solution which have more binding affinity to the –coo group of resin and compete with drug for binding.

Efficient drug loading on idion 234 occurred uniformly (92.55 ± 0.59 % w/w) in the experimental temperature range of 25^0C to 80^0Cas shown in Table 1.

Table 1: Effect of Temperature on percent drug complexation

Temperature(^{0}C)	**% Drug complexation***		
	Indion 234		
	1:1	**1:2**	**1:3**
Room temperature	70.23 ± 0.51	82.56 ± 0.50	91.47 ± 0.62
40	72.03 ± 0.59	80.45 ± 0.62	92.55 ± 0.59
50	70.64 ± 1.25	81.11 ± 1.21	91.40 ± 1.10
60	72.21 ± 1.10	81.58 ± 1.16	93.07 ± 1.23

**Mean ± S.D. (n= 3)*

Increased temperature during complexation increases the ionization of drug and resin. The effect is more pronounced for poorly water soluble and unionized drugs. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. As metochlopramide hydrochloride is water soluble drug and ionisable drug temperature does not show any significant effect on drug adsorption and also Cation exchange resins are not significantly affected by temperature changes.

The infrared spectra of Metoclopramide HCl, Indion 234 and drug: resin complex shown in figure 4, 5 and Figure 6 respectively. 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 4). 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 5). Drug: resin complex spectrum (Figure 6) 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.

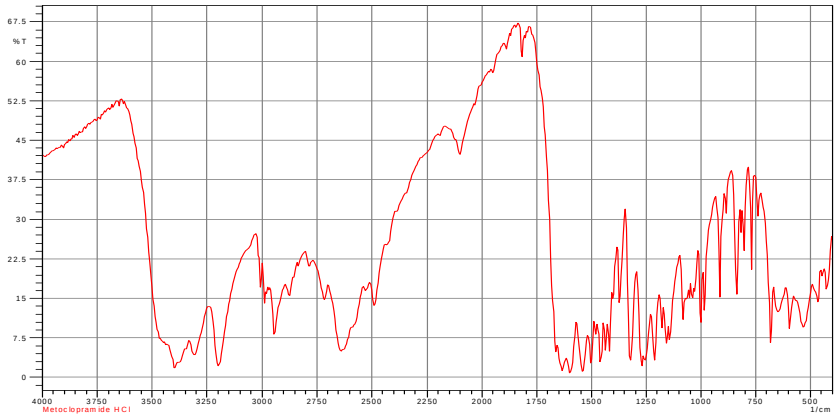

Figure 4: IR spectra of a. Metoclopramide HCl.

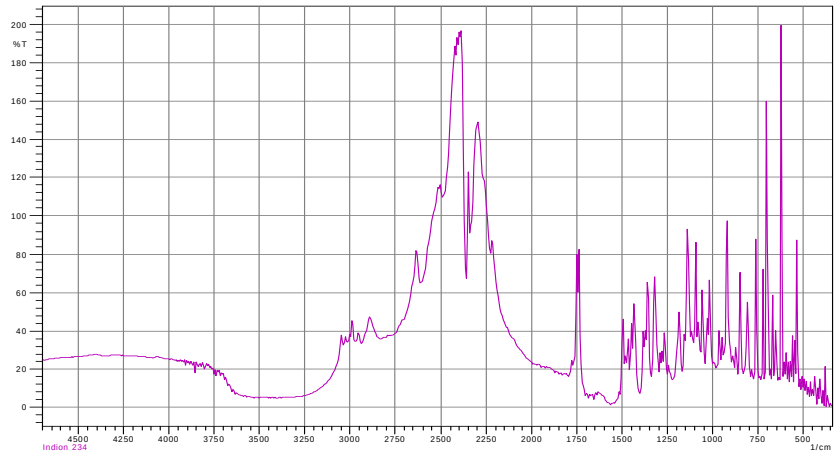

Figure 5: IR spectra of Indion 234

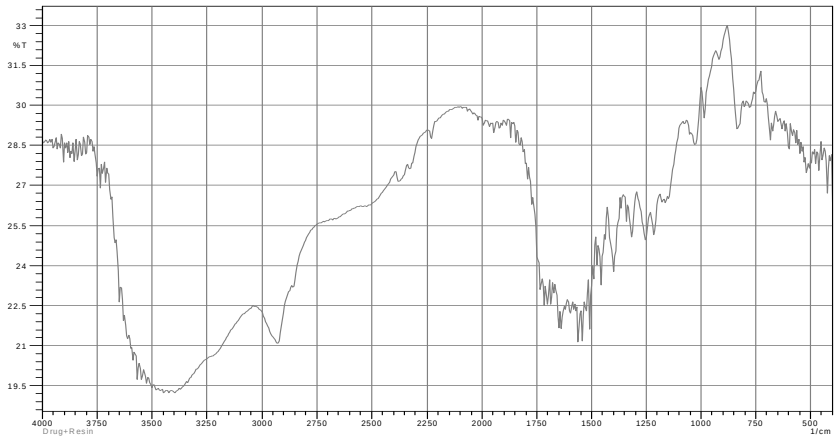

Figure 6: IR spectra of Metoclopramide HCl: Indion 234 complex

This indicates interaction of amine group of drug with Indion 234 as shown in figure 4, 5 and 6. The drug content in resinate was found to 99.1%. The dissolution profile of drug showed drug release within 30 minutes as shown in Figure 5. Results of evaluation of these indicated complete masking of bitter taste as no bitterness was felt in the drug resin complex**.**

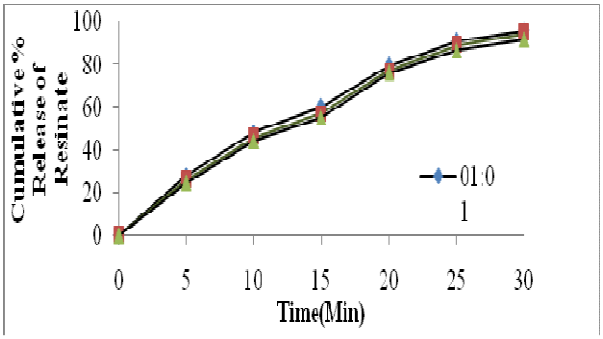

Figure 5: In-vitro release profile of Metoclopramide hydrochloride: Indion 234

Conclusion

Metochlopramide hydrochloride, a bitter drug could be successfully taste masked using suitable ion exchange resin. The process of taste masking was optimized with respect to parameters like time required for complexation, pH effect, swelling time of resin and temperature. The taste masked complex was incorporated into patient compliant and palatable dosage form.

Acknowledgments

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