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Formulation of Drug-Resin complex and evaluation of its molecular property & release kinetics

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ABSTRACT

The purpose of this research was to formulate tasteless complexes of Fexofenadin Hydrochloride with Doshion P547 and to evaluate different factor affecting Drug-Resin Complexation wise, effect of batch and column process, complexation time, temperature, and pH on Fexofenadin Hydrochloride loading on Doshion P547 is reported. Drug resin complexes (DRC) were characterized by infrared spectroscopy, thermal analysis. Fexofenadin Hydrochloride release from DRC is obtained at salivary and gastric pH. The efficient drug loading was evident in batch process using activated Doshion P547 with a drug-resin ratio of 1:3. Drug complexation enhanced with pH from 1.2 to 5, while temperature did not affect the complexation process. Infrared spectroscopy revealed complexation of –NH (drug) with Doshion P547. Drug release from DRC in salivary pH was insufficient to impart bitter taste. Complete drug release was observed at gastric pH in 2 hours. Doshion P547 is inexpensive, and the simple technique is effective for bitterness masking of Fexofenadin Hydrochloride.

Keywords: Fexofenadin Hydrochloride, Doshion P547, tasteless complex, Characterization, Release kinetics.

INTRODUCTION

"Worst the taste of the medication, the better the cure" was once the prevailing attitude. Today this trend has been changed and great importance is given to the organoleptic characteristics of pharmaceutical products which include mainly appearance, odor and taste. [1]

In case of tablets, the problem of bitter taste of the drug is often encountered due to release of the active ingredients in the mouth. However it is necessary to investigate taste-masking method before preparation of rapidly disintegrating or mouth dispersible tablets of drugs with bitter taste.

Various techniques could be used to mask the bitter taste of drug. But one of the most economical methods for taste masking is the use of ion exchange resin. Weak ion exchange resins are interesting hydrophobic polymers for the taste masking of bitter drugs because of its complex forming ability, non toxicity and economy as compared to other methods. Other methods are quite tedious and require a long time for processing. It has been evident that ion exchange resin complex doesn't release drug in the saliva and releases the drug immediately in the stomach without affecting its intrinsic bioavailability. [2]

In the present work Fexofenadine Hydrochloride was preferred as a model drug for complexation because of its intense bitter taste. It is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older and for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older. These conditions are commonly found in pediatric patients, where palatability is of main concern. Fexofenadine is available in tablet as oral dosage form. [3],[4]

Fexofenadine Hydrochloride contain tertiary amino group and terminal carboxyl group which has potential for forming complex with cationic exchange resin. In the present work, taste masking of Fexofenadine hydrochloride was performed by using weak cation exchange resin DOSHION P547.

MATERIALS AND METHODS

Materials

Fexofenadin Hydrochloride was a gift sample from Khandelwal laboratory, Thane. The resin, Doshion P547 was procured from Doshion, Ahmadabad & other chemicals & excipient were procured from vendors.

Methods

Preliminary Evaluation of Resin

Doshion P547 particle diameter was measured microscopically. For loading capacity of resin, Ion exchange capacity was calculated by using column method. These involved separating funnel containing 250 ml 0.25 M solution of sodium sulphate to be placed above the column and allowed to drip into column at rate of 2 ml/min. Effluent was collected in conical flask and titrated with 0.1 M NaOH using phenolphthalein as an indicator. [5]
Ion exchange capacity calculated using equation No: I

Equation I

$$IER = \frac{av}{W}$$

Where,
a= Molarity of NaOH
v= Volume of NaOH required.
W= Weight of resin.

Effect of Resin Activation [6]

Doshion P547 placed on a Whatman filter paper (Whatman Asia Pacific Pvt Ltd, Mumbai, India) in a funnel, was washed with deionized water and subsequently with 1N HCl (100 mL). The resin was rewashed with water until neutral pH was reached. DRC was prepared by using100 to 300 mg of acid-activated resin & Fexofenadin Hydrochloride was added to resin slurry under magnetic stirring. Similarly, alkali activation of Doshion P547 was performed, replacing 1 N

HCl with 1 N NaOH. The drug-loading efficiency of activated resin was evaluated spectrophotometrically.

Selection of Resin:
Resins can be selected on the basis of the nature of drug and requirement of formulation. Depending on the basis of acidic and basic nature of the drug, cation and anion exchange resins can be used. In the present work weak cation exchange resin DOSION P547 was selected based on its Ion Exchange Capacity and used for the taste masking of Fexofenadine Hydrochloride.

Formation of Fexofenadin Hydrochloride-Doshion P547Complexes [7]
A glass column (1.4-cm inner diameter, 20-cm length) plugged with cotton was packed with activated Doshion P547 (as per 1:1, 1:2, and 1:3, drug: resin ratio) by gently tapping. The 50 mL of deionized water maintained in the column was drained after 30 minutes. Aqueous drug solution (25 mL as per ratio), added in small portions on top of column, was left to equilibrate for 60 minutes. The solution was drained, and DRC was washed with 500 mL deionized water. Unbound drug from filtrate was estimated at 259 nm.

In a batch process, activated resin was placed in a beaker containing 25 mL of deionized water and allowed to swell for 30 minutes. Accurately weighed Fexofenadin Hydrochloride (as per 1:1, 1:2, and 1:3, drug: resin ratio) was added and stirred for 30 minutes. The mixture was filtered and residue was washed with 75 mL of deionized water. Unbound drug in filtrate was estimated at 259 nm and drug-loading efficiency was calculated.

Optimizing Drug Loading:
Effect of Stirring Time on Complex Formation.
Accurately weighed Fexofenadin Hydrochloride was added to activated resin and slurred in 25 mL of deionized water. Different batches with a stirring time starting from 5 minutes to 190 minutes were processed. Amount of bound drug at the end was estimated at 259 nm. The results are as shown in figure I

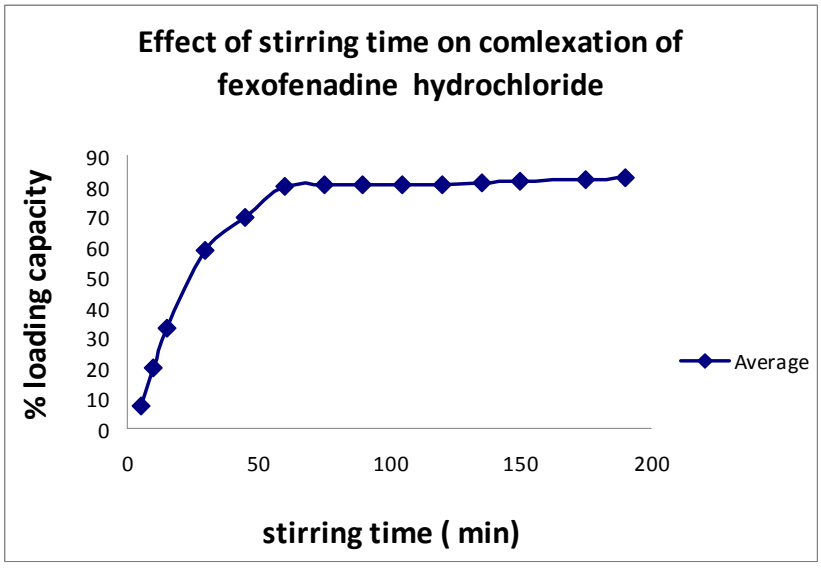

Figure I: Effect of Stirring Time on complexation.

Effect of Temperature and pH on Complex Formation
The complexation of drug with of activated resin,(as per ratio 1:3) slurred in 25 mL of deionized water in a 100 mL beaker, was performed at 27°C, 40°C, 60°C, and 80°C using temperature-controlled magnetic stirring for 60 minutes. The volume of filtrate was made up to 50 mL with

water washings of DRC. The amount of bound drug was estimated spectrophotometrically (259 nm) from the unbound drug in filtrate.

Accurately weighed, drug powder was added to activated resin(as per ratio 1:3) slurred in 25 mL each of pH 1.2, 2, 3, 4, 5, 6 and 7 solutions prepared from standard solutions of hydrochloric acid and sodium hydroxide in a 100-mL beaker, and maintained at 25°C. The drug-loading efficiency was estimated. The results are as shown in figure II

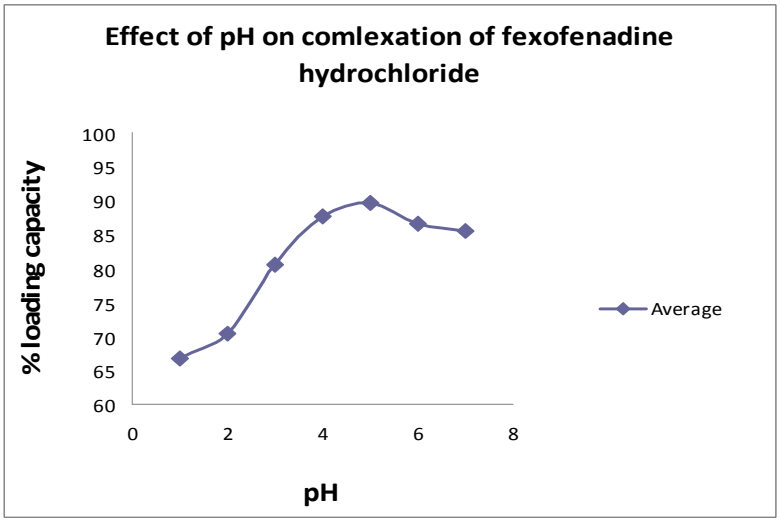

Figure II: Effect Of pH on complexation.

Molecular Properties of Drug Resin Complex

The drug, resin and resinate were subjected to Infra Red spectroscopy (IR200 Thermo electron corporation), the potassium bromide (KBr) palate technique was used for preparation of sample. The IR spectrum was recorded from 4000-400 $cm.^{-1}$. The 3 spectra were comparatively analyzed (Figure III, IV & V). The thermal behavior of Fexofenadine Hydrochloride, DOSHION P547 and Fexofenadine Hydrochloride: DOSHION P547 complex were examined by DSC (Shimadzu TA-60WS) Sample was loaded into an aluminium pan, hermetically sealed and run at scanning rate of 15°C/min over a temperature range of 50°C to 250°C. An empty sealed aluminium pan was used as a reference. DSC thermogram are shown in figure VI, VII & VIII.

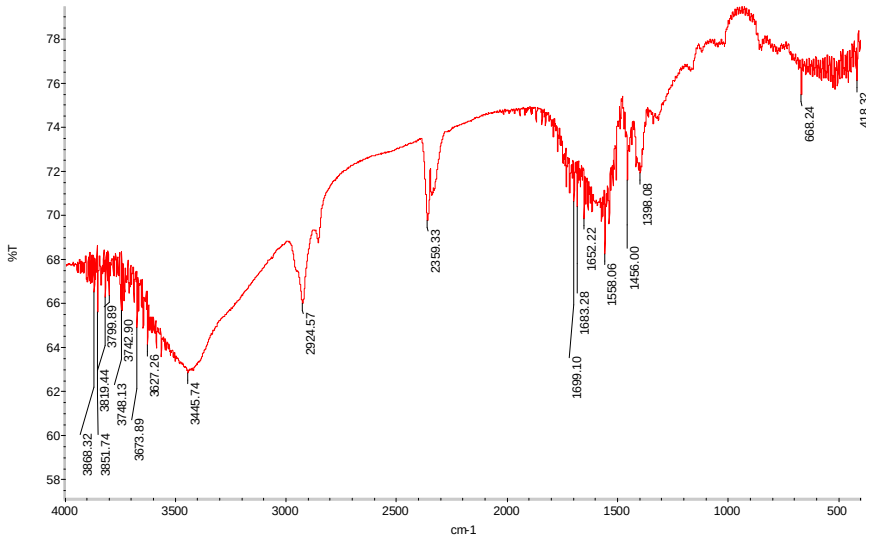

Figure III: Infra Red Spectrum of DOSHION P547 Resin

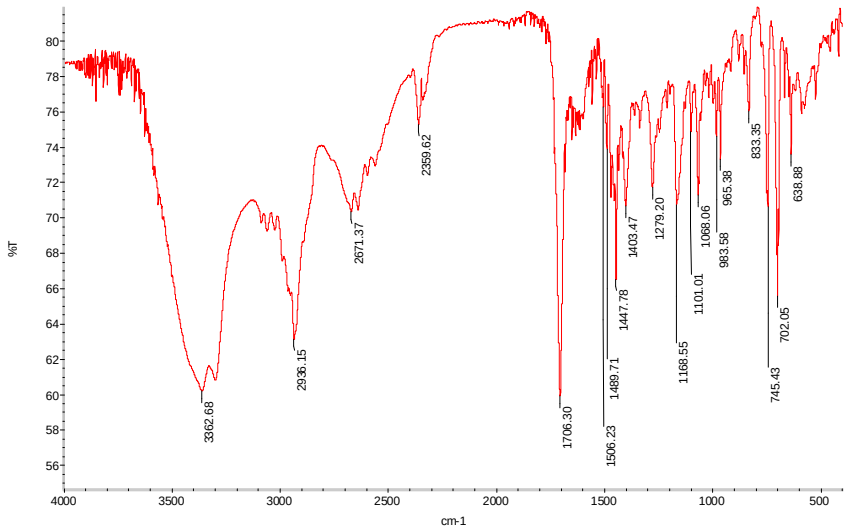

Figure IV: Infra Red Spectrum of Fexofenadine Hydrochloride.

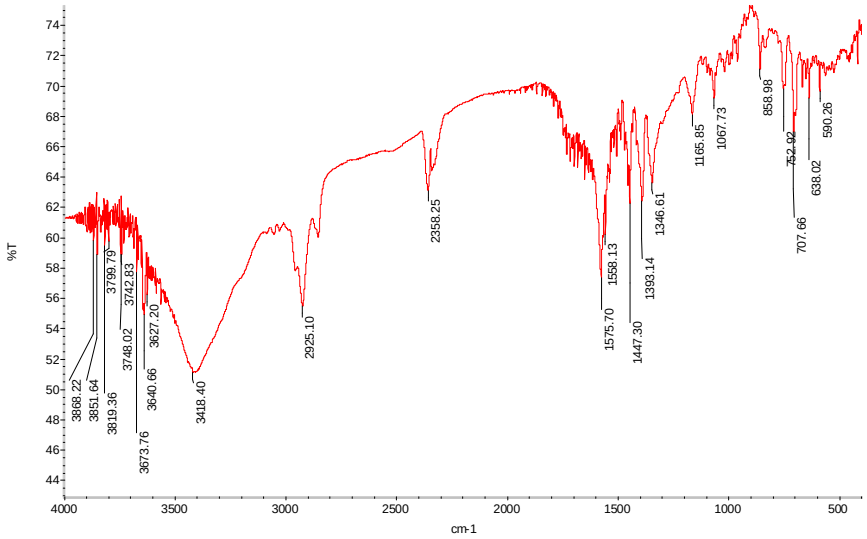

Figure V: Infra Red Spectrum of Fexofenadine: P547 Complex.

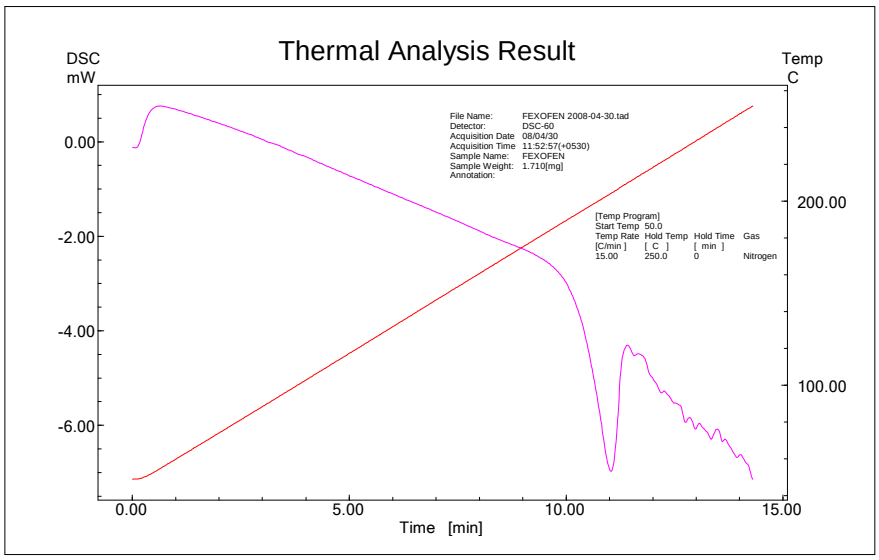

Figure VI: DSC Thermogram of Drug Fexofenadine Hydrochloride.

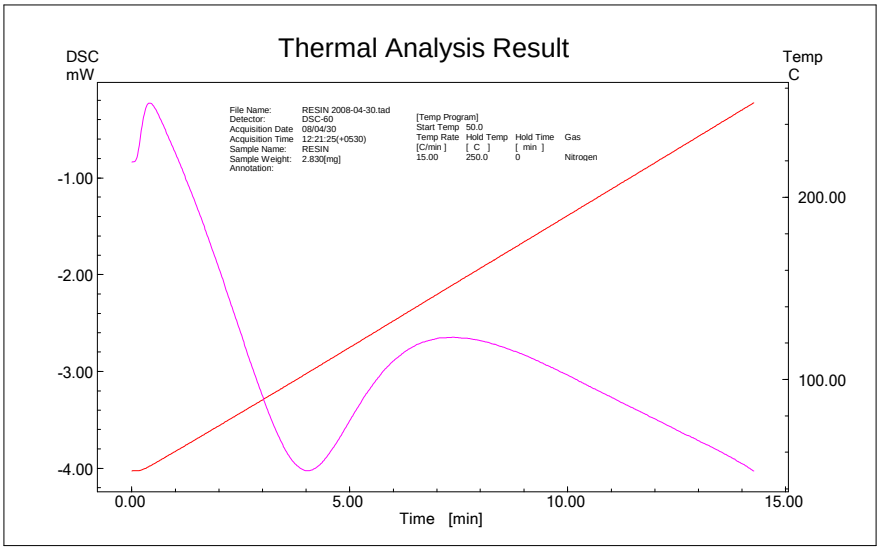

Figure VII: Thermogram of Resin (Doshion P547).

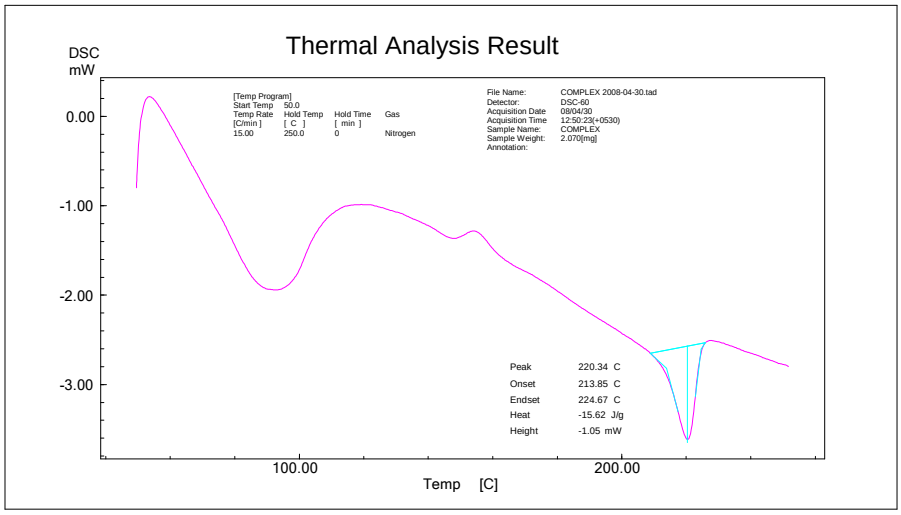

Figure VIII: Thermogram of Drug (Fexofenadine Hydrochloride): Resin (P547) Complex.

Decomplexation of drug-resin complexes:[8]

Decomplexation procedure:

An accurately weighed amount of complex was transferred to a 50-ml volumetric flask; the volume was made with 1 N HCl to break the complex. The volumetric flask was kept in sonicator for 30 min. The samples were filtered through whatman filter paper No 41 and diluted suitably and absorbance was measured at 258.50 nm

Physical properties of resinates:

Table I: Physical properties of Resinate

Parameter	Resinate
Angle of repose	34.5°± 0.19
Bulk density	0.51 ± 0.24
Tapped density	0.60 ± 0.39
Carr's index	18.21 %
Hausner ratio	1.34

Release Kinetics:

Drug release at salivary pH (6.8)

The release of the drug from Drug: Resin complex was studied at the salivary pH (6.8) to determine the amount of the drug that would be released in mouth during the administration of formulation. The bitterness of the taste was related with the amount of drug released in the mouth.

Drug resin complex equivalent to 60 mg of drug was weighed and added to 10 ml of pH 6.8 phosphate buffer solution placed in test tube. The mixture was filtered after shaking for 60 seconds. The filtrate was assayed for drug. [9]

Drug release at gastric pH (0.001 N HCl)

In the present study the (0.001 N HCl) was used as a dissolution media as per the Dissolution guideline For Fexofenadine hydrochloride given By US FDA.

Dissolution Medium: 0.001 N HCl (pH 3), 900 ml**.**
Speed **:** 50 rpm.
Temperature **:** 37.5° C ± 0.5° C.
Apparatus **:** Paddle (USP type II)

Drug: Resin complex equivalent to 60 mg of drug was weighed accurately and subjected to release rate study using USP dissolution apparatus II. Five ml of the aliquot were withdrawn at different time interval of 5, 10, 15, 30, 45, 60, 75, 90 & 120 minutes and replaced with 5ml with fresh dissolution medium. Each 5ml of sample was filtered through Whatman filter paper No 41. The drug concentration in the sample was determined from the standard curve of the drug in 0.001N HCl by spectrophotometrically at (λ_{max}) 258.50 nm.Cumulative percent drug released from complex was also found at each time point (figure IX)

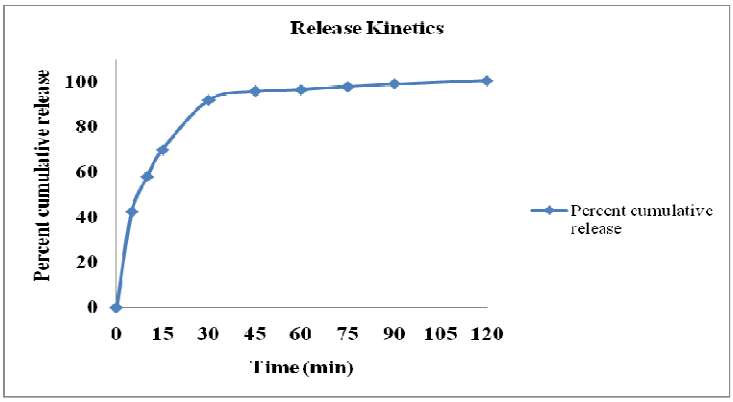

Figure IX: Release Kinetics from DRC

RESULTS AND DISCUSSION

Fexofenadin Hydrochloride, prescribed extensively in both solid and liquid dosage forms, is extremely bitter resulting in poor patient compliance.

Complexation with ion exchange resin is a simple and efficient technique of masking the bitterness [10]. The drug being soluble in water has desired ionization power. The size of Doshion P547 particles obtained, 54 ± 4 µ was in conformation with the reported size (<150 µ), which is useful for taste masking [11]. Substantially small size particles are difficult to process

and particles greater than 200 µ have a tendency to fracture. Doshion P547 is highly porous, and even though insoluble in water, it is capable of hydration. Loading capacity of Doshion P547is a function of exchange of K^+ ions in the resin with ions in solution. The loading capacity of Doshion P547 was found to be 4.89 ± 1.56 mEq/g The percentage drug loading with inactivated resin, treated with acid and alkali, was found to be 66.27 ± 1.98%, 86.22 ± 1.59%, and 32.58 ±1.63% wt/wt, respectively. Highest drug binding on resin was achieved when activated with acid treatments. Fexofenadine Hydrochloride may be loaded on Doshion P547 by batch or column process. The drug-loading efficiency for a drug-resin ratio 1:1, 1:2, and 1:3 of column process was 31.32% ± 1.59%, 35.26% ± 1.16%, and 45.78% ± 0.88% wt/wt and that of batch process was 65.55% ± 0.98%, 71.55% ± 0.88%, and 87.23% ± 1.10% wt/wt. An increase of loading efficiency was observed in batch process, when drug-resin ratio was changed from 1:1 to 1:3. As result from batch process are more promising as compare to column process batch process was selected & batch process was simpler and quicker than the column process difficulty was experienced in handling small particles in the column process. The drug-resin ratio of 1:3 has optimum drug loading. In the case of Fexofenadin Hydrochloride and Doshion P547a drug-loading efficiency of more than 85% wt/wt was achieved with a drug-resin ratio of 1:3. 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 efficacy is best achieved in batch process. Equilibration time was shorter due to thinner barrier for diffusion of ions, as it is in continuous motion. Also, higher swelling efficiency in the batch process results in more surface area for ion exchange. Hence, the batch process is suitable for smaller particles. The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. There was significant difference in percent complexation when we considered time as a factor. From this we concluded that there was significant difference of time on percent complexation of drug. Time required to reach equilibrium was shorter due to thin barrier for diffusion of ions. But, before reaching equilibrium there was significant effect of time on percent complexation. Increasing the stirring time above 60 minutes did not further increase the percent drug loading values. Hence, 60-minute contact time between drug and resin could be optimized to equilibrate the ion exchange process to achieve maximum drug loading. This study indicated that the optimum ion exchange could be completed in a short period of 60 minutes.

Efficient drug loading on Doshion P547occurred uniformly in the experimental temperature range of 27ºC to 80ºC. Drug adsorbate formation may be significantly affected by processing temperature. Increased temperature during Complexation increases ionization of drug and resin. The effect is more pronounced for poorly water soluble and un-ionizable drugs. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Cation exchangers are not affected as significantly by temperature changes as anion exchange resins. In the case of drug-resin adsorbate formation, Fexofenadin Hydrochloride is a slightly water-soluble drug with a pKa of 4.25, & 9.53 that has potential at operational pH to be completely ionized. The continuous stirring in batch process does not allow development of thick exchange zones. This finding explains why temperature does not show any effect on Fexofenadin Hydrochloride-Doshion P547complexation.

Fexofenadin Hydrochloride-Doshion P547complexation involves the exchange of ionizable drug and metal ions in resin, which in turn depends on the pKa of drug and resin. Such a mode of complexation between amino group of Fexofenadin Hydrochloride and $–COO\text{-}K^+$ functionality of Doshion P547 can be affected by the pH of the reacting media. The complexation was enhanced with increasing pH from 1.2 to 5. A maximum of drug loading was obtained at pH range of pH4 to 5 (i.e., at pKa of Fexofenadin Hydrochloride 4.25). As shown in Figure II, as pH

increased above 5, the percentage drug loading decreased. The pH of the solution affects both solubility and the degree of ionization of drug and resin. The results can be attributed to the fact that Fexofenadin Hydrochloride has a pKa 4.25 and hence will have maximum solubility and complete ionization in this range. The decreased complexation at lower pH is due to excess H+ ions in the solution, which have more binding affinity to the – COO-K^+ groups of resin and compete with the drug for binding. The study revealed negligible effect of higher temperature on drug loading, while the pH of media significantly altered the ion exchange complexation process.

Molecular Properties of Drug-Resin Complexes

The infrared spectra of Doshion P547, Fexofenadin Hydrochloride-Doshion P547 complex and Fexofenadin Hydrochloride are depicted in Figure III, IV, and V, respectively. Drug spectrum shows a prominent peak 1706 cm-1 representing -C-O stretching, A Peak at 1279 cm-1 Represents C-N stretching of ter. Amine. A peak at 3362 cm−1 is due to –OH stretching, which lies in standard range of 3200 to 3600 cm−1. The absence of peak at 1706 cm1 & 1279 in DRC (1:3) confirms the complexation drug with resin. The peak at 3362 cm−1 in DRC corresponding to –OH stretching s also absent, which signifies that during DRC formation here was interaction of the amino group of drug with the carboxylic group of Doshion P547

The molecular state of the drug prepared as DRC shows a hollow diffused pattern and the absence of drug peaks. This finding confirms that the entrapped drug is dispersed monomolecularly in the resin bead. In the case of physical dispersions of drug and Doshion P547, drug molecules are outside the resin bead. Thus, DRC is amorphous in nature and shows faster dissolution due to improved solubility. Figure VI, VII and VIII shows DSC curves for DRC, Doshion P547 and pure Fexofenadin Hydrochloride The thermal behavior of the pure drug shows endotherm at 205°C corresponding to melting of pure drug. The thermal behavior of DRC shows absence of endotherm at 205°C corresponding to melting of pure drug. The study confirms the complexation of Fexofenadin Hydrochloride with Doshion P547.

Release Kinetics from DRC Complex

Fexofenadin Hydrochloride release from drug-resin adsorbate was observed, in average salivary pH of 6.8, and in 0.001 N HCl, separately. In vitro drug release in average salivary pH of 6.8 was less than 2% within 60 seconds. The presence of exchangeable ions of ionizable electrolytes in the salivary fluid may be responsible for this release. The DRC 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.

At gastric pH (1.2), more than 95 % of Fexofenadin Hydrochloride was released within 60 minutes, and the release was complete in 120 minutes. The hypothesis that the drug-release equilibrium, similar to drug loading, is highly dependent on the physiological pH can be applied for taste masking without affecting the dosage form characteristics. The exchange process of drug release follows Equation 2. Where, X^+ represents the ions in the GI tract. Particle diffusion and film diffusion are sequential steps in drug release by ion exchange process. Doshion P547-Fexofenadin Hydrochloride complex hydrates by water absorption and then swells in diffusion media, and the subsequent exchange process releases the drug.

Equation I: Drug Release from DRC

$$Resin^- – Drug^+ + X^+ \rightarrow Resin^- – X^+ + Drug^+ \quad (2)$$

The Fexofenadin Hydrochloride release from DRC is controlled by an ion exchange mechanism. The exchange rate is dominated by the rate at which the competing ions diffuse from the media to resin. Solute diffusion is driven by concentration gradient.

CONCLUSION

Complexation between the drug and resin was essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction was an equilibrium phenomenon, maximum efficiency was achieved in batch process. Complete taste masking of model drugs was achieved with selected ion exchange resin (P547). pH of medium, activation of resin and stirring time significantly affected batch complexation process. Studies of molecular property revels formation of complex where as, study of release kinetics through a light on the drug release pattern from DRC.

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