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A Path for Horizing Your Innovative Work

FORMULATION AND EVALUTION OF FAST DISPERSIBLE TABLET OF FEXOFENADINE HCl.

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Abstract: The purpose of this research was to formulate tasteless complexes of Fexofenadine Hydrochloride with Kyron-134 and to formulate tasteless complex into fast-Dispersible tablets (FDT) for the treatment of allergic rhinitis & chronic idiopathic urticaria. Tasteless Drug resin complexes (DRC) were prepared using combination of Kyron-134 & drug in different ratio(1:3) and evaluated for different factor affecting Drug-Resin Complexation, Complexation time, stirring time, soaking time, temperature, and effect of pH on Fexofenadine Hydrochloride loading on Kyron-134. Fexofenadine Hydrochloride release from FDT is obtained at salivary and gastric pH. Infrared spectroscopy & DSC revealed Complexation of –NH (drug) with Kyron-134. Drug release from FDT in salivary pH was insufficient to impart bitter taste. Complete drug release was observed at gastric pH. The values of pre-compression parameters evaluated, were within prescribed limits and indicated good free flowing properties. The tablets were evaluated for post-compression parameters such as weight variation, hardness, and friability, wetting time, content uniformity, disintegration time and dissolution. The study conclusively demonstrated significant taste masking of API and rapidly dispersible and dissolution. Maximum loading was obtained at drug–resin ratio 1:3, pH 6-7, temperature 60 ºC, soaking time 60 min and stirring time 5-6 hr. Formulation D-5 containing Kyron-314 (66.66%) & CSS (33.33%) show optimum result among all formulation. The studies indicate that the formulation was taste masked drug can be formulated in to FDT with view to enhance patient compliance & to obtain faster onset action of the drug which would be advantageous in comparison to the currently available conventional forms. Formulations D-5 was found to be palatable with in vitro disintegration time of 20 s Dissolution studies showed complete release of D-5 within 30 min.

Keywords: Fexofenadine Hydrochloride, Fast-Dispersible tablets (FDT), Kyron-134, *In-vitro* drug release

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance.

It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Fast Dispersible Tablet (FDT) is one among such approaches.[1] Improved patient compliance has achieved enormous demand. When an orodispersible tablet is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.

Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is Dysphagia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a no. of pathological conditions including stroke, parkinson's disease, neurological disorders, AIDS etc. Parkinsonism, Motion sickness, Unconsciousness, Elderly patients, Children, Mentally disabled persons, Unavailability of water.[2] To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec. without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 sec to 3 min. Most of the FDTs include certain super disintegrants and taste masking agents. [3]

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 & may be acceptable to the industry. 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. In this method the degree of taste masking depends upon the degree of cross-linking and drugs should have an ionic charge. 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. [4]

In the present work Fexofenadine Hydrochloride (2^{nd} generation antihistamine) 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. API competes with histamine for H_1 – receptor sites on effector cells in the gastrointestinal tract, blood vessels and respiratory tract; it appears that API does not cross the blood brain barrier to any appreciable degree, resulting in a reduced potential for sedation & drowsiness.[5]

Taste masking was done by molecular complexing of Fexofenadine HCl with Kyron-134(Polacrilin potassium USP-NF) by simple Ion exchange method. Fexofenadine Hydrochloride contain tertiary amino group and terminal carboxyl group which has potential for forming complex with cationic exchange resin. The taste masked complex was further formulated into orally dispersible tablet by direct compression method using different Superdisintegrants.

The aim of this present work is to formulate and evaluate fast dispersible tablet of fexofenadine HCl by direct compression method using different superdisintegrant. Commercially, In Conventional fexofenadine tablet available in the market are not suitable for acute allergic conditions where quick onset of action of drug is required. This is because poor patient compliance particularly by the geriatric and

pediatric patients who experience difficulty in swallowing or who are traveling and don't have an easy access to water. In the present study an attempt has been made to mask the taste of Fexofenadine HCl and to formulate Fast Dispersible tablet with good mouth feel so as to enhance the patient compliance. The best formulation is to be selected on the basis of evaluation characteristics. In the present work, taste masking was done by molecular complexing of Fexofenadine HCl with Kyron-134(Polacrilin potassium USP-NF) by simple Ion exchange method & then prepared fast dispersible tablet.

MATERIALS AND METHODS

Fexofenadine HCl was supplied as gift sample from Orbicular Pharmaceutical Technology Pvt Ltd, Hyderabad. MCC, Lactose, Aspartame, Cross-poidone, CCS, SSG and other polymers were obtained from Orbicular P'cal Tech. Pvt Ltd. Kyron-134 & 314 were obtained from Corel Pharma Chem , Ahmedabad**.**

Drug excipients compatibility study

FT-IR spectra of drug and mixture of optimized formulation were recorded with a FT-IR spectrophotometer (Shimadzu Corporation, Japan, 8400s) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100. The disc was placed in the sample holder and scanned from 4000 to 400 cm^{-1}.

METHODOLOGY

Construction of standard curve for Fexofenadine HCl

A. Preparation of Standard Calibration Curve of Fexofenadine HCl in pH 6.8 buffer

One hundred mg of Fexofenadine HCl was transferred in 100 ml volumetric flask. The drug was dissolved in 5 ml ethanol and the volume was adjusted to 100 ml by addition of 6.8 pH buffer to get stock solution of concentration 1000 µg/ml. The stock solution was serially diluted with 6.8 pH buffer to get drug concentration in range of 100-500 µg/ml. The absorbance of the solutions was measured against 6.8 pH buffer as a blank at 258 nm using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft Excel®.

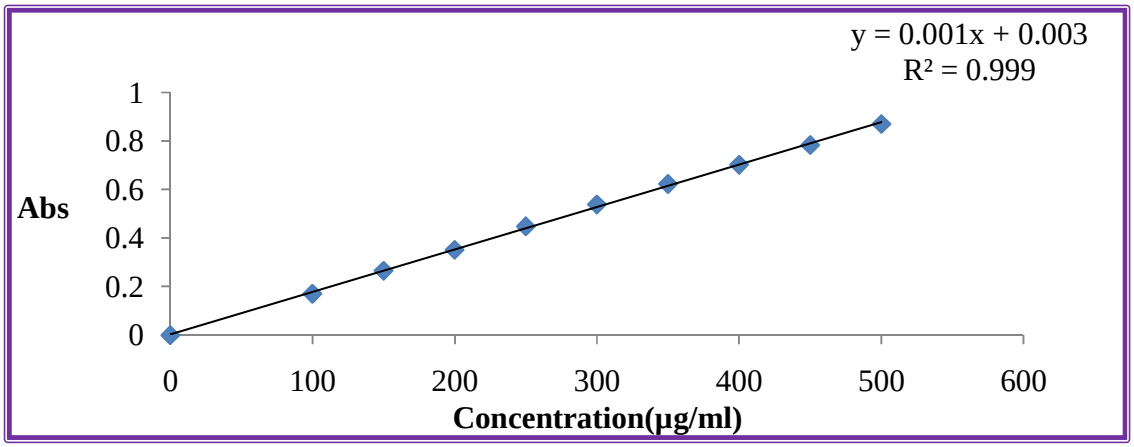

Figure 1 standard calibration curve Fexofenadine HCl in 6.8 pH buffer

B. Preparation of Standard Calibration Curve of Fexofenadine HCl in 0.1 N HCl

One hundred mg of Fexofenadine HCl was transferred in 100 ml volumetric flask. The drug was dissolved in 5 ml ethanol and the volume was adjusted to 100 ml by addition of 0.1 N HCl to get stock solution of concentration 1000 µg/ml. The stock solution was serially diluted with 0.1 N HCl to get drug concentration in range of 50 -400 µg/ml. The absorbance of the solutions was measured against 0.1 N HCl as a blank at 258 nm using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft Excel®.

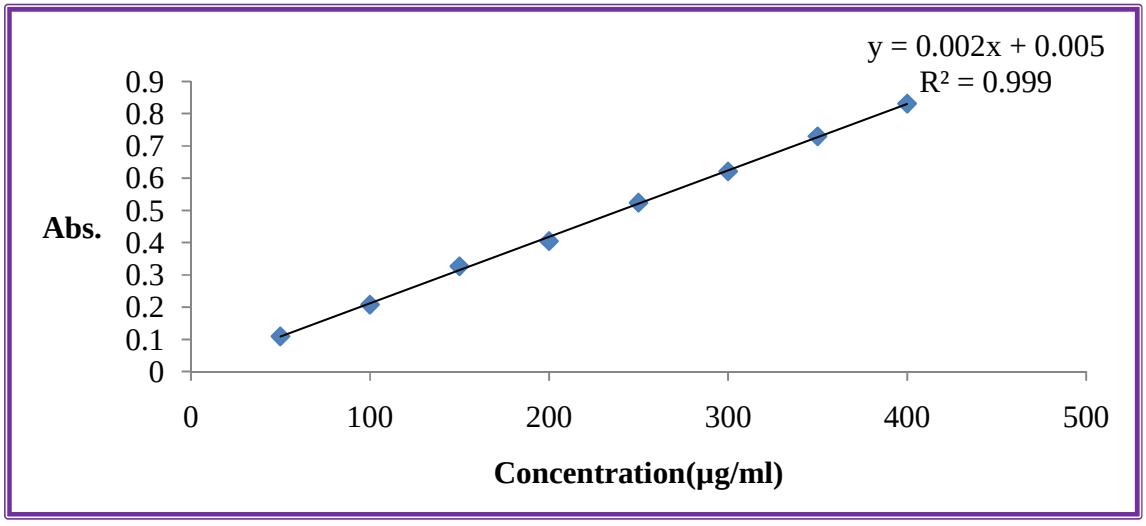

Figure 2 standard calibration curve Fexofenadine HCl in 0.1 N HCl

C. Formulation of drug resin complex (DRC) [6,7]

1) Preparation of drug –resin complex (DRC)

The drug: resin was taken in the ratio 1:1, 1:2, 1:3. The resin (Kyron-134) was dissolved in water (q.s) taken in container-1 and stirred for an hour. The pH of resin solution was adjusted to 6.5-7.0 by using 1 M KOH. Now accurately weighed drug (As per ratio) were added slowly and stirred for 5-6 hr. During stirring, pH of solution was checked frequently and adjusted to 6.5-7.0 by using 1 M KOH. After 3-4 hr, the drug resin complex (DRC) was separated from dispersion by filtration and washed with three portions of 50 ml of demineralised water. Complex was dried and then evaluated for taste and drug-loading efficiency.

2) Characterization of DRC [8]

The DRC solution was filtered through filter paper and filtrate was dried to obtain complex in powder form for characterization.

a. Drug content

Drug content was determined by dissolving 30 mg of DPC in 100 mL of simulated gastric fluid (SGF) of pH 1.2 buffer and analyzing appropriately diluted sample by UV-Vis Spectrophotometer at λ_{max} 254 nm using pH 1.2 buffer (SGF) as a blank.

b. *In vitro* taste evaluation

Taste of DRC was studied in vitro by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. DRC, equivalent to 60 mg of API was placed in 10 mL of SSF and shaken for 60 seconds. The amount of drug released was analyzed using UV spectrophotometer at λ_{max} 258 nm. The ratio in which minimum amount of drug release takes place was taken as optimized ratio for further study.

c. Molecular properties

Molecular properties on complexation were studied by Infrared spectroscopy (IR). Infrared (IR) spectra of these samples were obtained by KBr disc method (Perkin Elmer) in the range of 4000 to 400 cm^{-1} with resolution 1 cm^{-1}.

d. Drug release from DRC

Drug release from DRC (1:3) in 0.1 N HCl was determined using a USP type II dissolution apparatus. Accurately weighed DRC equivalent to 60 mg of Fexofenadine HCl was added to 500 ml 0.1 N HCl for 30 minutes (50 rpm, 37°C). A 10-ml sample was withdrawn, filtered and analyzed. Drug release from the DRC was also performed in

10 ml of pH 6.8 buffer solution (simulated saliva fluid) by adding 60 mg of the DRC to a test tube, shaken for 60 seconds, filtered and filtrate was assayed for drug.

3) Optimization of Drug Resin Complex [9, 10]

a. Effect of pH on complex formation

The Complexation of drug with of activated resin (1:3) slurred in 30 mL of deionized water in a 50 mL beaker, was performed at different pH using pH strip paper for 4-5 hr. The volume of filtrate was made up to 50 mL with water washings of DRC. The amount of bound drug was estimated spectrophotometrically (258 nm) from the unbound drug in filtrate.

b. Effect of temperature on drug loading

The Complexation of drug with of activated resin, (1:3) slurred in 25 mL of deionized water in a 100 mL beaker, was performed at 30°C, 40°C, 50, 60°C, and 80°C using temperature controlled magnetic stirring for 4-5 hr. The volume of filtrate was made up to 50 mL with water washings of DRC. The amount of bound drug was estimated spectrophotometrically (258 nm) from the unbound drug in filtrate.

c. Effect of soaking time of resin on drug loading

The complexation of drug with of activated resin, (1:3) slurred in 25 mL of deionized water in a 100 mL beaker. Different batches with a soaking time starting from 0 minutes to 120 minutes were processed. Amount of bound drug at the end was estimated at 258 nm.

d. Effect of stirring time on drug loading

The Complexation of drug with of activated resin, (1:3) slurred in 25 mL of deionized water in a 100 mL beaker. Different batches with a stirring time starting from 30 minutes to 6 hr were processed. Amount of bound drug at the end was estimated at 258 nm.

D. Formulation of taste masked fast dispersible tablet of fexofenadine HCl

Fast dispersible tablets of Fexofenadine Hydrochloride: Kyron-134 complex was prepared using direct compression method after incorporating superdisintegrant such as croscarmellose sodium, Kyron-314, Sodium Starch Glycolate in different concentrations. A {3, 3} Simplex Lattice design was employed in the present study. In these design we check the effect of different superdisintegrants in combination. In this design the amount of intragranular concentration of Superdisintegrants(10%) were selected as independent variable & dependent variable were disintegration time

& wetting time , and experimental trials were performed for all 10 possible combinations. The amount of intragranular concentration of Superdisintegrants, Kyron-314 (X1), croscarmellose sodium (X2) and sodium starch glycolate (X3) were selected as independent variable. The Disintegration time (R1), Wetting time (R2) were selected as dependent variables. The composition of factorial design batches (D1-D10) is shown in Table1. Resinate, and Avicel PH 102 & lactose were mixed thoroughly in a glass mortar using a pestle. Superdisintegrant was incorporated in the powder mixture; Aspartame (Sweetening agent), Flavor (orange flavor), Aerosil, were added to enhance the palatability and flow property of tablets & finally Magnesium Stearate was added as lubricant.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_{12} + b_{13}X_{13} + b_{23}X_{23} + b_{123}X_{123} \quad \text{.....5.1}$$

Blend containing Fexofenadine Hydrochloride: Kyron-134 complex along with excipients was compressed by using 10 mm diameter flat-faced punches. Compression force was kept constant for all formulations.

In the given formulations Avicel PH102 was used as directly compressible diluent. It has high swelling index which facilitates the rapid disintegration. Aspartame was selected as sweetening agent due to its intense sweetness. So, it has been used in very small proportion. Orange flavor was selected due to its popularity in pediatrics formulation. Croscarmellose sodium, kyron-314, sodium starch glycolate used, as a superdisintegrants. The different formulations prepared were shown in Table No.1

EVALUATION PARAMETER[11, 12, 13]

Pre and post Compression Parameters: Parameters like bulk density (BD), tapped density (TD), Carr's index (CI), housner's ratio, angle of repose were evaluated before compression. And the parameters like weight variation, hardness (Monsanto Hardness Tester), disintegration time, wetting time, friability (using Friabilator USP EF-2), were evaluated after compression of the tablet.

Uniformity of drug content: Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1 N HCl, the drug content was determined measuring the absorbance at 258 nm using a UV/Visible Spectrophotometer (UV-1800).

In-vitro release study: **Apparatus: USP XXIV dissolution testing apparatus II (paddle method)**	
Dissolution medium	0.1 N HCl
Temperature	37± 0.5 ^{0}C
RPM	50
Vol. withdrawn and replaced	10ml every 5 min.
λ max	258nm
Blank solution	0.1 N HCl
Duration of study	30 min.
Volume of dissolution media	500ml

Procedure: Dissolution study was conducted to determine the drug release from the tablets using USP apparatus type - II (paddle type). A 10 ml sample was withdrawn at 5 minutes time intervals and replaced by an equal volume of prewarmed 0.1 N HCl. Samples withdrawn were filtered through Whatmann filter paper (0.45 micron).The amount of Fexofenadine HCl released was analyzed at 258 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan).

***In-vitro* disintegration time:**

The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus with lid on upper side and the time (second) taken for complete disintegration of the tablet in distilled water at 37±0.5 °C with no palatable mass remaining in the apparatus was measured.

Wetting time[14]

A conventional method was used to measure wetting time and capillarity of the orodispersible tablets. The tablet was placed in a petridish of 5.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

Statistical Analysis

The statistical analysis of the factorial design batches were performed by multiple regression analysis and analysis of variance (ANOVA) using Microsoft Excel® 2007. To demonstrate graphically the influence of each factor on response, the response surface plots was generated using Design expert ® software.

RESULTS AND DISCUSSION

Compatibility studies: Study is carried out using FTIR spectrophotometer (FTIR 8400S Spectrophotometer Shimadzu, Japan) & DSC (Differential Scanning Calorimetry).

FTIR spectrophotometer

The Fexofenadine HCl exhibits peak due to C-O stretching (1709) and C-N stretching of tertiary amine (1279) group. The infrared spectra of Fexofenadine Hydrochloride, Kyron-134, and Fexofenadine Hydrochloride-Kyron-134 complex are depicted. Drug spectrum shows a prominent peak 1709 cm-1 representing -C-O stretching, A Peak at 1279 cm-1 Represents C-N stretching of tertiary Amine. The absence of peak at 1709 & 1279 cm-1 in DRC confirms the complexation drug with resin. The peak at 3362 cm−1 in DRC was corresponding to –OH stretching also absent, which signifies that during DRC formation here, was interaction of the amino group of drug with the carboxylic group of Kyron-134. It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and polymers. Hence, it was concluded that no physical or chemical interactions of Fexofenadine HCl with Kyron-134, CCS, SSG, Kyron-314, Lactose, MCC pH 102 and Flavor.

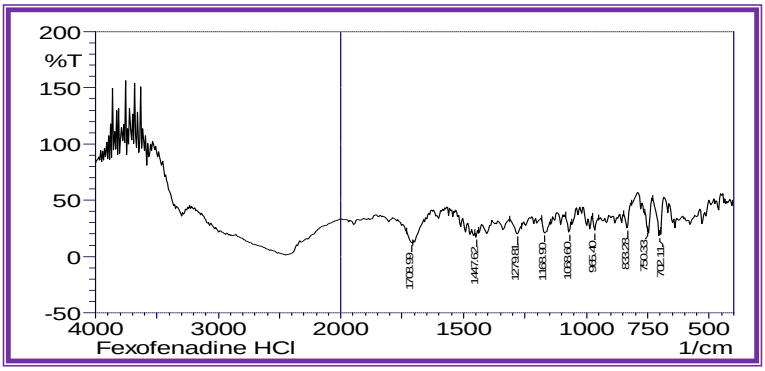

Figure 3 FTIR spectrum of pure Fexofenadine HCl

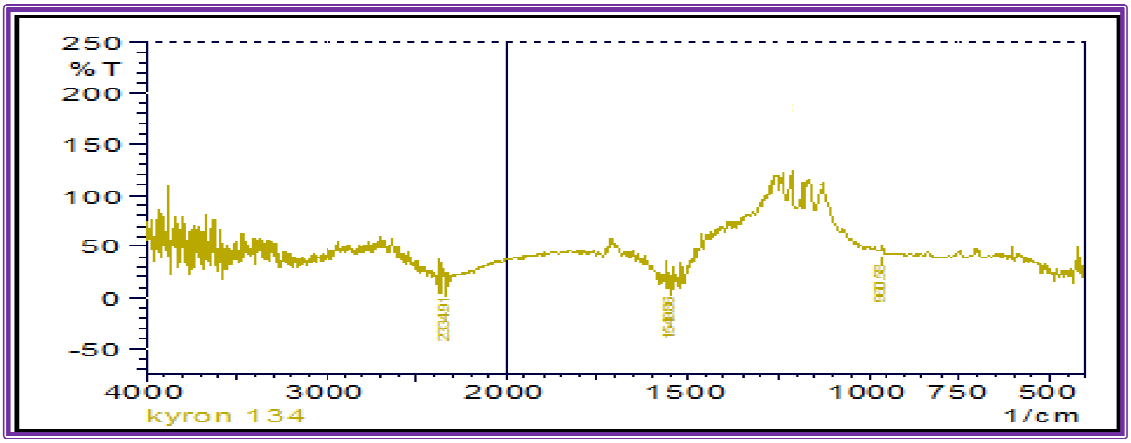

Figure 4 Spectrum of Kyron-134

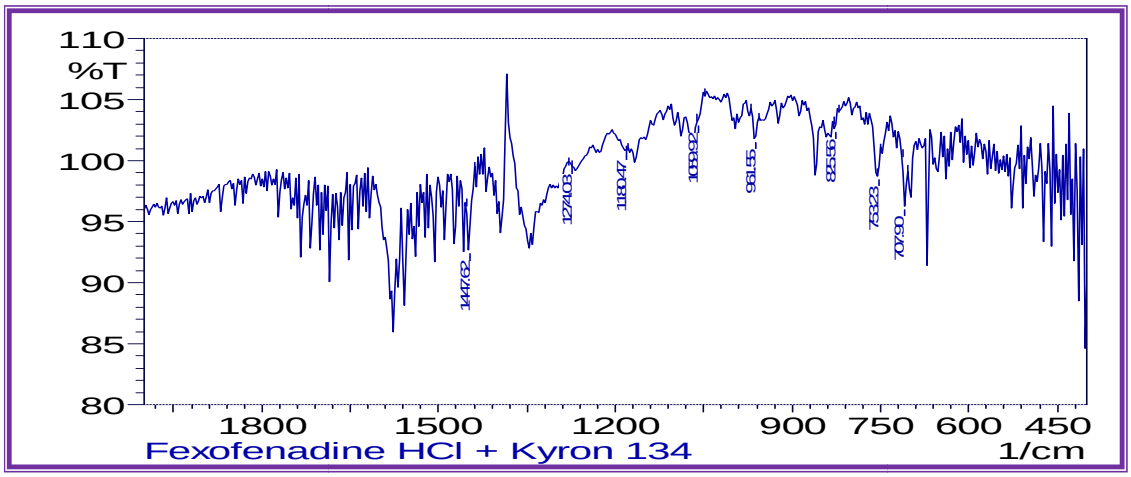

Figure 5 FTIR spectrum of DRC (Fexofenadine HCl+Kyron-134)

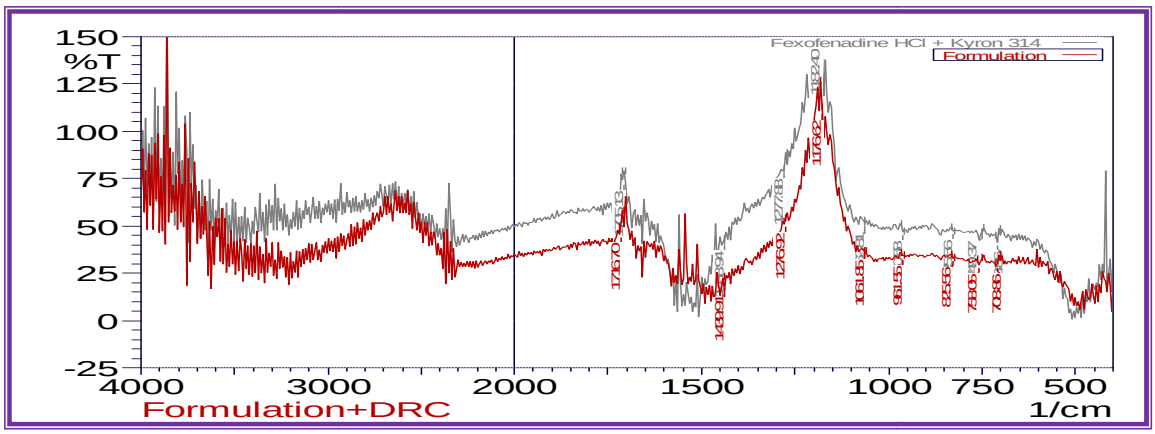

Figure 6 FTIR spectrum of DRC & Formulation

DSC (Differential Scanning Calorimetry)

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 Kyron-134, drug molecules are outside the resin bead. Thus, DRC is amorphous in nature and shows faster dissolution due to improved solubility. 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 Fexofenadine Hydrochloride with Kyron-134.

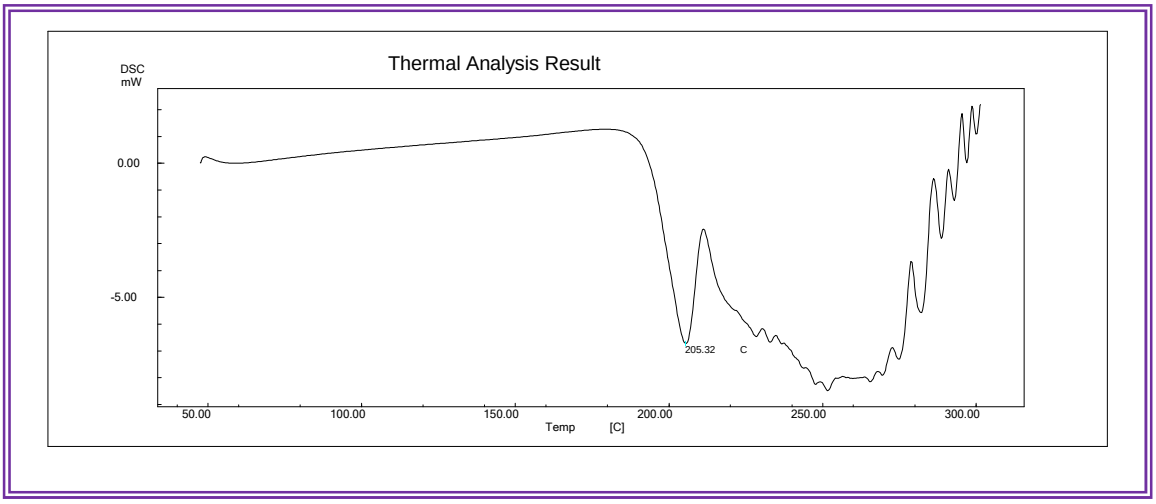

Figure 7 DSC of Fexofenadine HCl

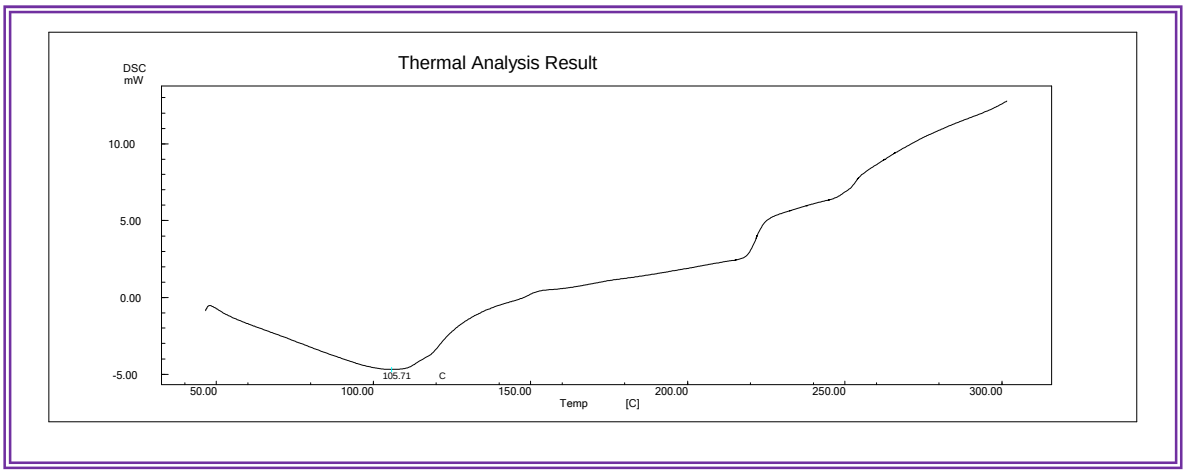

Figure 8 DSC of DRC

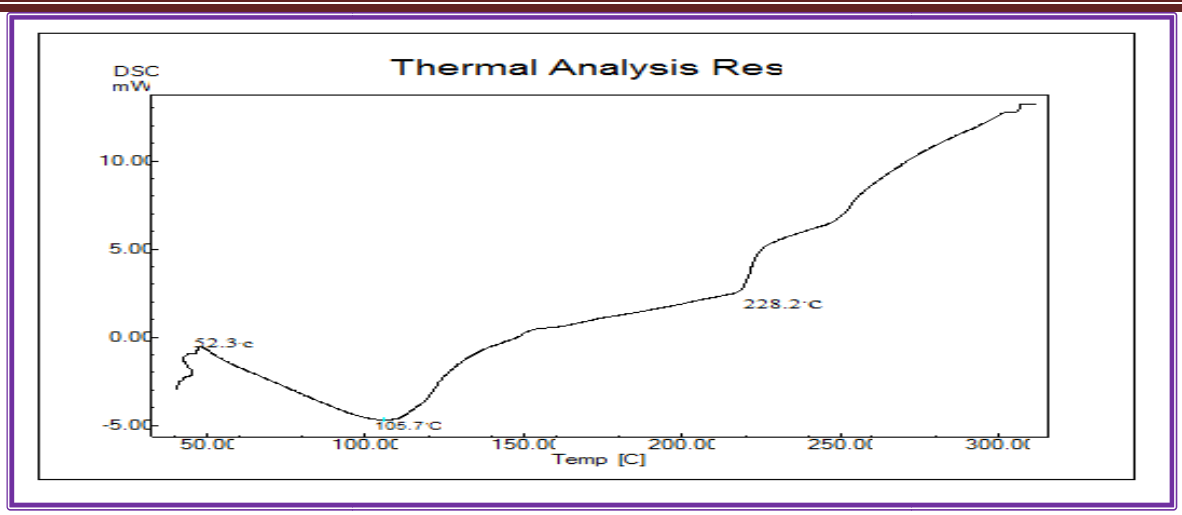

Figure 9 DSC of Formulation

Characterization of DRC

Drug content

Percentage drug loading in DRCs was found from 98.0 to 99.40.

***In vitro* taste evaluation**

Drug release was observed in SSF from complexes with the drug-polymer ratios of 1:1, 1:2 and 1:3 were found to be 1.8±0.32, 1.2±0.12 and 0.65±0.42 respectively. Thus 1:3 ratios, which showed lesser amount of % drug release, were considered the optimal concentration of DRC with significant masking of bitter taste.

Molecular properties

The infrared spectra of Fexofenadine Hydrochloride-Kyron-134 complex are depicted. Drug spectrum shows a prominent peak 1709 cm-1 representing -C-O stretching, A Peak at 1279 cm-1 Represents C-N stretching of ter. Amine. The absence of peak at 1709 & 1279 cm-1 in DRC (1:3) confirms the complexation drug with resin. The peak at 3362 cm−1 in DRC was corresponding to –OH stretching also absent, which signifies that during DRC formation here, was interaction of the amino group of drug with the carboxylic group of Kyron-134.

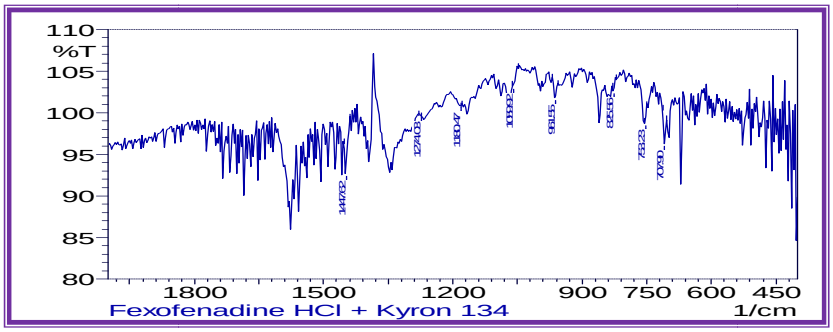

Figure 10 FTIR spectrum of DRC (Fexofenadine HCl+Kyron-134)

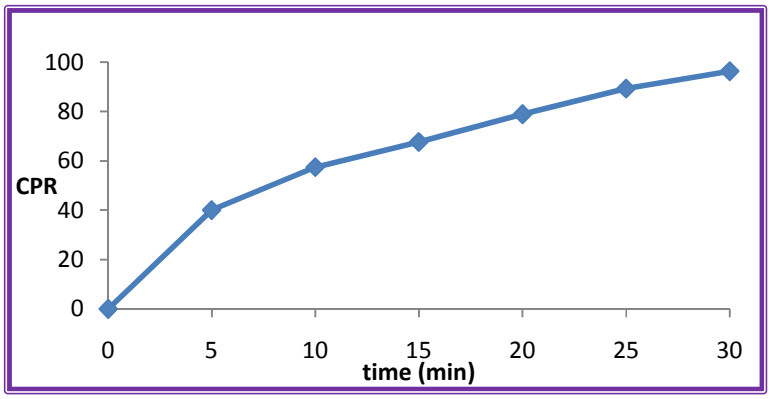

Figure 11 Drug release form DRC

Fexofenadine HCl release from drug-resin complex was observed in average salivary pH of 6.8, and at gastric pH of 1.2, separately. 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), 95-98% of Fexofenadine HCl was released within 30 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

$$Resin^- - Drug^+ + X^+ \rightarrow Resin^- - X^+ + Drug^+$$

Where, X^+ represents the ions in the GI tract.

Particle diffusion and film diffusion are sequential steps in drug release by ion

exchange process. Kyron T-134-Fexofenadine HCl complex hydrates by water absorption and then swells in diffusion media, and the subsequent exchange process releases the drug. Taste evaluation in volunteers confirmed that the taste of Fexofenadine HCl was masked by complexing with Kyron T-134. The majority of the volunteers found the DRC to be tasteless and agreeable. When DRC is exposed to a low pH, it causes dissociation of the complex. The presence of H^+ ion in the medium causes displacement of Fexofenadine HCl, thus facilitating drug release. This finding has been well supported by in vitro drug release in 0.1 N HCl.

Fexofenadine HCl -Kyron T-134 complexation involves the exchange of ionizable drug and hydrogen ions in resin, which in turn depends on the pKa of drug and resin. Such a mode of complexation between basic group of Fexofenadine HCl and –COO-H^+ functionality of Kyron T-134 can be affected by the pH of the reacting media. 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 Fexofenadine HCl have a pKa between 9.5-13 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^- groups of resin and compete with the drug for binding.

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 achieved in batch process. Equilibration time was shorter due to thinner barrier for diffusion of ions, as it is in continuous motion.

Optimization of Drug Resin Complex

Effect of pH on complex formation

The effect of pH of resin dispersion on the % drug loading. The complexation was enhanced with increasing pH from 4 to 8. A maximum of 92.02% drug loading was obtained at pH 6-7 (near to pKa of fexofenadine HCl). 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 Fexofenadine HCl has a pKa between 9.5 and 13.2 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^- groups

of resin and compete with the drug for binding.

Effect of temperature on drug loading

Efficient drug loading on Kyron T-134 occurred uniformly in the experimental temperature range of 30ºC to 80ºC as shown in table. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Fexofenadine HCl is a slightly water-soluble drug with a pKa of 9.5 to 13.2 that has potential at operational pH to be completely ionized. The continuous stirring in process does not allow the development of thick exchange zones so temperature may not show any effect on Fexofenadine HCl- Kyron T-134 complexation.

Effect of soaking time of resin on drug loading

The results reveal that a 60 minute swelling time of Kyron T-134 in deionized water gave the maximum Fexofenadine HCl loading of 93.02% wt/wt. This may result of maximum swelling and hydrating properties of Kyron T-134 that affect the rate of ion exchange. Less drug-loading efficiency may be observed in unswollen resin matrix because the exchangeable groups of resin are latent and coiled toward the backbone.

Effect of stirring time on drug loading

The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. The percentage drug loading (wt/wt) with a stirring time of 0.5 to 6 hr. Increasing the stirring time above 5 hr did not further increase the complexation values. Hence, 5 hr 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 period of 5 hr.

Pre-compression parameters:

The evaluation was carried out using the parameters like bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose as per the procedure described in Preformulation study. The tablet blend of all the batches were evaluated for different derived properties viz.-angle of repose (between 20-30), Bulk density (between 0.57-0.78 gm/cm3), Tapped Density (0.63–0.86 gm/cm3), Compressibility index (between 11-15, and flowability (good). The results of Angle of repose and compressibility indicated that the flowability of blend is significantly good. So the flow of the prepared mass from the hopper was able to fill the die completely for compression.

After the lubrication the blend ready for compression had good flow property and excellent compressibility.

Post-compression parameters

All the prepared tablets showed acceptable pharmaceutical properties. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness were shown in the range of 4.0–5.0 kg/ cm2 in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was less than 1% and meets the official limit. Here the to check the combination effect of different superdisintegrants 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 15± 0.66–48±0.87. Wetting time of fast dispersible tablet, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in range of 20-50 sec. The percentage drug content of all the tablets was found to be between 97-100 % of fexofenadine HCl which was within acceptable limit

***In vitro* release studies**

From the dissolution profile of all the batches it was found that there was fast drug release at initial state of dissolution. The initial rise in the drug release was dependent upon the effectively and concentration of superdisintegrants. Here to check the combination effect of different superdisintegrants on drug release profile. Formulations D1, D2, D4, D5, D7, D9, and D10 showed more than 90% of drug release within 30 min, whereas in formulation D3, D6, D8 showed 85-90% of drug release within 30 min. Among ten batches, batch D5 is selected as optimized batch because of its lowest disintegration time and highest drug release. Stability study was performed on formulation D5.

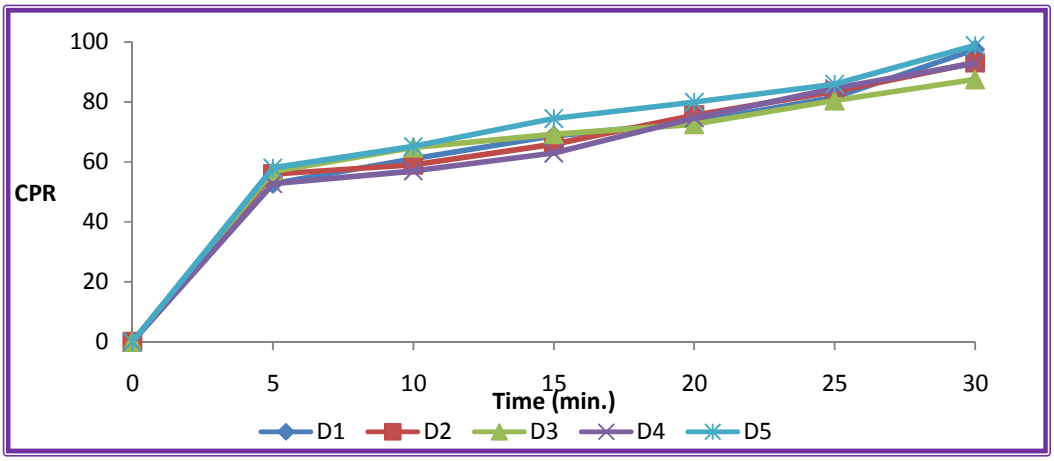

Figure 12 *In vitro* release studies of D1-D5 Batches

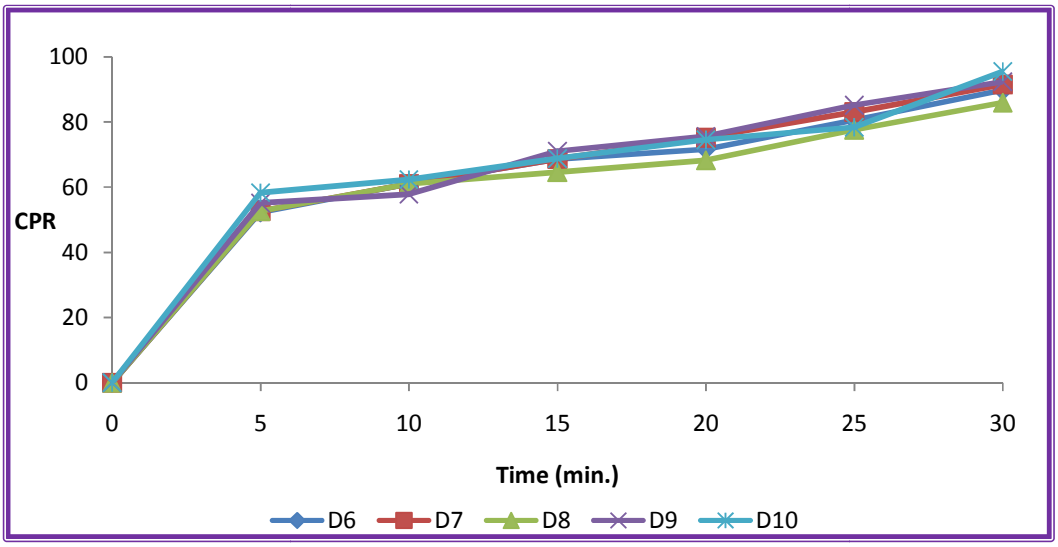

Figure 13 *In vitro* release studies of D6-D10 Batches

Statistical Analysis

A) Full and reduced model for disintegration time:

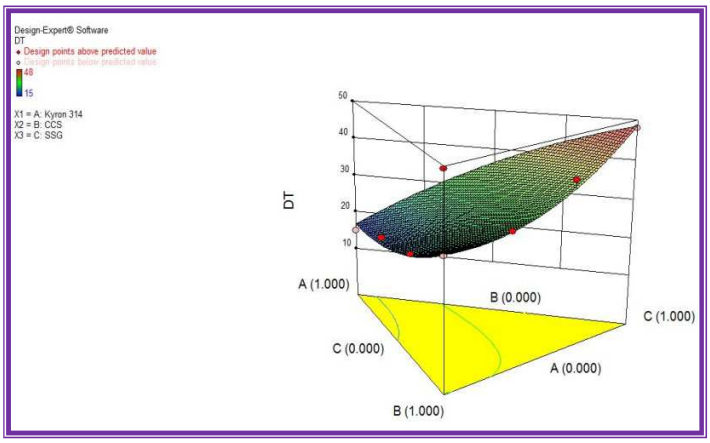

Figure 14 3-D graph showing effect of Kyron-314, CCS & SSG on disintegration time

Full model:

$Y = 1581 - 1565.31X_1 - 1551.57X_2 - 1533.57X_3 - 76.41X_{12} - 87.60X_{23} - 42.59X_{13}$…. 5.2

Reduced model:

$Y = 678.68 - 663.25X_1 - 648.74X_2 - 631.06X_3 - 39.71X_{12} - 50.90X_{23}$ …… 5.3

Using simplex lattice design form the regression analysis and 3-D surface plot it is obtained that Kyron-314 with combination of CCS is very effective to decrease the disintegration time which is desirable. From the reduced model generated for disintegration time, it can be concluded that high level of factor X_3 should not be selected for lower disintegration time. The high value of X_{12} and X_{23} coefficient also suggest that the interaction between X_1, X_2 and X_3 has significant effect on disintegration time. Combination of X_1 and X_2 is very effective to decrease the DT which is desirable, while combination of X_1 and X_3 should be avoided.

B) Full and reduced model for wetting time:

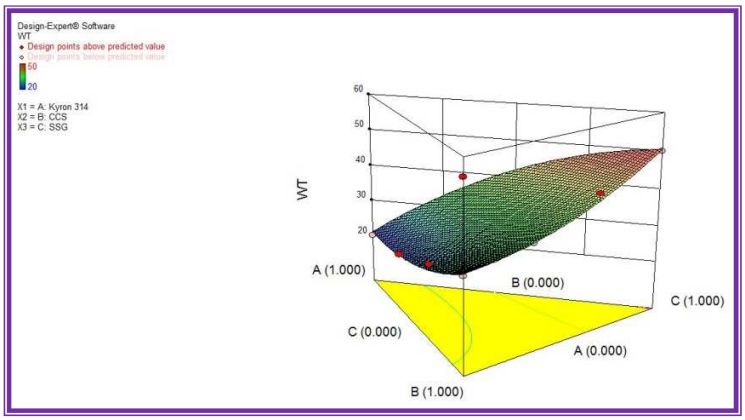

Figure 15 3-D graph showing effect of Kyron-314, CCS & SSG on wetting time

Full model:

$Y = 1084 - 1063.88X_1 - 1052.14X_2 - 1033.98X_3 - 55.41X_{12} - 56.79X_{23} - 20.94X_{13}$….. 5.4

Reduced model:

$Y = 640.29 - 620.30X_1 - 608.19X_2 - 590.40X_3 - 37.36X_{12} - 38.74X_{23}$ ……. 5.5

Using simplex lattice design form the regression analysis and 3-D surface plot it is obtained that Kyron-314 with combination of CCS is very effective to decrease the wetting time which is desirable. From the reduced model generated for wetting time, it can be concluded that high level of factor X_3 should not be selected for lower wetting time. The high value of X_{12} and X_{23} coefficient also suggest that the interaction between X_1, X_2 and X_3 has significant effect on wetting time. Combination of X_1 and X_2 is very effective to decrease the WT which is desirable, while combination of X_1 and X_3 should be avoided.

CONCLUSION

During the last decade, fast dispersible tablets that make tablets disintegrate in the mouth without chewing and additional water intake has drawn a great deal of attention. Thus taste masking of oral pharmaceuticals has become a potential tool to improve patient compliance and commercial success of the product. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolyte that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion-exchange is reversible and stoichiometric with the displacement of one ionic species by another.

Molecular properties of resinate were studied using DSC and FTIR, both suggested complexation between drug and resin. The change in crystalline form of drug to amorphous form due to monomolecular dispersion was suggested by these studies.

The complexes were successfully formulated into fast dispersible tablets. Three superdisintegrants were screened in order to determine most suitable superdisintegrant, among these, 10% w/w superdisintegrants was selected and tried for further studies. A total number of ten formulations were prepared by direct compression technique.

The study conclusively demonstrated significant taste masking of fexofenadine HCl and fast dispersion and dissolution of FDT Complete taste masking of fexofenadine HCL was achieved with selected ion exchange resin (Kyron-134). Formulation D-5 containing Kyron-314 (66.66%) & CSS (33.33%) show optimum result among all formulation. The various formulations were compared with respect to in vitro disintegration time and in vitro release profile. Formulations D-5 was found to be palatable with in vitro disintegration time of 20 sec Dissolution studies showed complete release of D-5 within 30 min.

Table 1

Tablet composition of different formulations

Batch (mg)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Drug (mg Equiv.)	60	60	60.	60	60	60	60	60	60	60
Kyron-314	35	-	-	11.66	23.33	11.66	23.33	-	-	11.33
CCS	-	35	-	23.33	11.66	-	-	11.66	23.33	11.33
SSG	-	-	35	-	-	23.33	11.66	23.33	11.66	11.33
Tablettose	15.5	15.5	15.5	15.5	15.5	15.5	15.5	15.5	15.5	15.5
MCC pH-102	14	14	14	14	14	14	14	14	14	14
aspartame	5	5	5	5	5	5	5	5	5	5
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Mag. Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
AVO-SIL	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total wt.	350	350	350	350	350	350	350	350	350	350

Table 2

Standard Calibration Curve of Fexofenadine HCl in pH 6.8

Concentration (µg/ml)	Absorbance
0	0.000
100	0.171 (0.003)
150	0.266 (0.004)
200	0.352 (0.002)
250	0.449 (0.010)
300	0.539 (0.004)
350	0.624 (0.005)
400	0.703 (0.003)
450	0.784 (0.007)
500	0.871 (0.006)

Correlation coefficient = 0.999

Absorbance = 0.001 × concentration + 0.003

Values in parenthesis indicates standard deviation (n = 3)

Table 3

Standard Calibration Curve of Fexofenadine HCl in 0.1 N HCl

Concentration (µg/ml)	Absorbance
0	0.000
50	0.110 (0.004)
100	0.208 (0.009)
150	0.327 (0.007)
200	0.405 (0.004)
250	0.524 (0.003)
300	0.621 (0.008)
350	0.730 (0.010)
400	0.831 (0.007)

Correlation coefficient = 0.999

Absorbance = 0.002 × concentration + 0.005

Values in parenthesis indicates standard deviation (n = 3)

Table 4

Percentage drug content in DRC

Sr.No	Drug-polymer ratio	% Drug content*
1	1: 1	91.89±0.56
2	1: 2	89.96±0.18
3	1: 3	94.12±0.34

*** Results are the mean of three observations ± SD**

Table 5

Drug release of DRC in pH 6.8 buffer (SSF)

Sr. no.	Drug-polymer ratio	% drug release in pH 6.8 buffer
1	1: 1	1.8±0.32
2	1: 2	1.2±0.12
3	1: 3	0.65±0.42

*** Results are the mean of three observations ± SD**

Table 6

Drug release from DRC

Time (min)	% Cumulative drug release
0	0
5	40.12
10	57.55
15	67.77
20	78.99
25	89.83
30	96.32

Table 7

Effect of pH on DRC

pH	% Drug Loading
4-5	69.73 ± 0.99
5-6	77.45 ± 1.05
6-7	92.02 ± 0.97
7-8	82.02 ± 0.97
Results are the mean of three observations ± SD	

Table 8

Effect of temperature on DRC

Temperature	% Drug Loading
30	89.73 ± 0.99
40	87.45 ± 1.05
50	84.02 ± 0.97
60	91.02 ± 0.97
80	85.45 ± 1.05
Results are the mean of three observations ± SD	

Table 9

Effect of soaking time

Time (min.)	% Drug Loading
0	65.38 ± 1.08
15	72.07 ± 0.96
30	86.16 ± 1.63
60	93.02 ± 1.88
90	92.23 ± 1.43
120	93.23 ± 1.39
Results are the mean of three observations ± SD	

Table 10

Effect of stirring time

Time (hour)	% Drug Loading
0.5	51.38 ± 1.00
1.0	63.07 ± 0.96
2.0	76.16 ± 1.63
3.0	83.02 ± 1.50
4.0	90.23 ± 1.5
5.0	93.23 ± 1.00
6.0	94.02 ± 1.50

Results are the mean of three observations ± SD

Table 11

Pre-compression parameters of Factorial batches

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	Carr's index	Hausner's ratio
D1	0.44±0.01	0.54±0.044	25.41±0.41	18.51±0.77	1.22±0.52
D2	0.44±0.021	0.55±0.028	27.05±0.21	20.0±0.25	1.25±0.16
D3	0.46±0.014	0.57±0.012	28.19±0.18	19.29±0.16	1.23±0.23
D4	0.45±0.019	0.55±0.023	25.21±0.24	18.18±0.17	1.22±0.14
D5	0.45±0.023	0.54±0.042	30.18±0.34	16.66±0.45	1.20±0.16
D6	0.46±0.015	0.57±0.061	27.20±0.24	19.29±0.57	1.23±0.18
D7	0.45±0.021	0.56±0.034	27.22±0.34	19.64±0.43	1.24±0.21
D8	0.46±0.017	0.56±0.044	28.34±0.32	17.85±0.61	1.21±0.31
D9	0.43±0.023	0.55±0.041	26.65±0.55	21.81±0.45	1.27±0.17
D10	0.45±0.012	0.54±0.032	24.34±0.43	16.66±0.62	1.20±0.22

Results are the mean of three observations ± SD

Table 12

Post-compression parameters of Factorial batches

Parameter / Batches	Disintegr-ation time (sec)	Wetting time (sec)	Hardness Kg/cm^2	Content uniformity	Weight variation	Friability %
D1	15±0.66	20±0.93	4.5±0.43	98.23±0.13	352.2±1.6	0.16±0.12
D2	30±0.57	32±1.17	4.34±0.64	97.56±0.25	353.2±1.8	0.19±0.89
D3	48±0.87	50±1.55	4.7±0.98	100.9±0.37	349.2±1.5	0.26±0.43
D4	23±0.52	27±0.93	4.8±0.61	100.7±0.41	348.2±1.1	0.31±0.67
D5	20±0.69	22±1.67	4.4±0.91	99.82±0.59	353.2±1.4	0.42±0.45
D6	42±0.77	45±1.81	4.9±0.51	98.88±0.61	354.2±1.9	0.29±0.82
D7	34±0.81	37±1.98	4.7±0.13	100.9±0.79	347.2±1.4	0.17±0.12
D8	39±0.84	43±0.77	4.8±0.29	99.89±0.81	350.2±1.9	0.21±0.52
D9	31±0.45	35±1.23	4.9±0.38	98.29±0.12	351.2±1.6	0.25±0.91
D10	24±1.18	30±2.05	4.25±0.52	100.1±0.40	352.2±1.7	0.34±0.72
Results are the mean of three observations ± SD						

Table 13

***In vitro* dissolution data of Factorial batches**

Time (min.)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	52.73	55.95	56.76	52.73	57.97	52.33	52.73	52.73	55.15	58.37
10	61.03	59.09	64.74	57.01	65.16	61.03	61.03	61.03	57.86	62.35
15	68.67	65.88	69.23	62.96	74.50	68.67	68.67	64.65	71.07	68.81
20	73.22	75.61	72.58	74.64	79.96	71.61	75.24	68.31	75.67	74.57
25	81.46	83.49	80.40	84.52	85.91	80.61	83.11	77.66	85.16	78.40
30	97.48	93.11	87.54	92.96	98.80	89.78	91.52	85.96	92.40	95.57

REFERNCES

1. Chein YW: Oral Drug Delivery and Delivery Systems. 2nd Ed. New York: Marcel Dekker; **1992**.

2. Kaur T, Bhawandeep G, Sandeep K and Gupta GD: Mouth dissolving tablets: a novel approach to drug delivery. Int J Curr Pharm Res. 2011; 3: 1-7.

3. Augsburger LL and Stephen WH: Orally disintegrating tablets pharmaceutical dosage forms: tablets. Infroma Healthcare Publication, 3rd Ed. 2; 293-312.

4. Nanda A, Kandarapu R and GARG S: An update on taste masking technologies for oral pharmaceuticals. Ind. J. Pharm. Sci. 2002; 64: 10–17.

5. Fexofenadine HCl, November 2011, www.wikipedia.org/Fexofenadine

6. Patel TN, Patel RP and Patel BV, Taste Masking of Topiramate by Newer Range of Ion-Exchange Resin. International Journal of Pharmaceutical Sciences and Nanotechnology. 2010; 3: 1105-10.

7. Devi NK, Rani AP, Madhavi BR: Studies on taste masking of levocetrizine di hydrochloride using ion – exchange resins. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2010; 1: 245-253.

8. Mundad A, Meshram D, Banbale H, Bhalekar M and Avari J: Formulation and evaluation of dispersible taste masked tablet of Roxithromycin. Asian Journal of Pharmaceutics, 2008, 116-119.

9. Puttewar TY, Kshirsagar MD, Chandewar AV and Chikhale RV: Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. Journal of King Saud University (Science). 2010; 22: 229–240.

10. Wani SU, Shamkuwar P and Nagnath A: Formulation of Drug-Resin complex and evaluation of its molecular property & release kinetics. Scholars Research Library. Der Pharmacia Lettre. 2010; 2(5): 155-164.

11. Lachman L, Lieberman HA and Kanig JL: The Theory and Practice of Industrial Pharmacy, 4th Ed, Varghese publishing house, Mumbai **1987**: 171-293.

12. Wells JI and Aulton ME, Pharmaceutics the science of dosage form design; 2nd Ed, Churchill Livingstone. **2002**: 223-253.

13. Indian Pharmacopoeia, the Indian pharmacopoeia commission, Ghaziabad, volume-I, **2010**: 187-193.

14. Simone S and Peter CS: Fast dispersible ibuprofen tablets. European Journal of Pharmaceutical Sciences. 2002; 15: 295–305.