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Rahul Gupta
Rajeev academy for pharmacy, Chhatikara, Mathura, UP, India

Gulshan Chhabra
Rajeev academy for pharmacy, Chhatikara, Mathura, UP, India

Dr. Kamla pathak
Rajeev academy for pharmacy, Chhatikara, Mathura, UP, India

Harish Kr Bishnoi
Guru Jambheshwar University of Science & Technology, Hisar, Haryana, India

Anil Kumar
Guru Jambheshwar University of Science & Technology, Hisar, Haryana, India

Correspondence
Rahul Gupta
Rajeev academy for pharmacy, Chhatikara, Mathura, UP, India

To formulate and evaluate taste masked chewable tablet of Levocetirizine dihydrochloride and Montelukast sodium using ion exchange resin as a drug carrier

Rahul Gupta, Gulshan Chhabra, Dr. Kamla Pathak, Harish Kr Bishnoi and Anil Kumar

Abstract
The aim of this research was to mask the bitter taste of Levocetirizine dihydrochloride & Montelukast sodium using ion exchange resin and to formulate a taste masked chewable tablet formulation with better patient compliance.Tulsion-335 & kyron T-114 containing crosslinked polyacrylic backbone were used as taste masking agents. The drug resin complex was prepared by complexation of drug with resin using batch processes taking different drug: resin ratio 1:1, 1:2, 1:3 respectively. The optimum drug resin ratio & time required for maximum complexation was optimized. The drug resinate was evaluated for assay (% drug content), % drug release, micromeritics properties, SEM, DSC, DRS & taste characterstics of the formulation. SEM photomicrograph of drug resin complex revealed that entrapment of drug has been achieved. DSC thermogram revealed that there is change in melting point of levocetrizine and montelukast and sharp peaks changes into broad peaks in drugs resin complex. DRS shows disappearance of stretching vibration of amine functional group at 3323 and 3407 cm^{-1} in Levocetirizine dihydrochloride and Montelukast sodium respectively and appearance of new stretching vibration of amide group at 3409 cm^{-1} in drug resin complex confirming the formation of amide linkage. The taste perception has been achieved by amide formation.
Further SEM, DSC & DRS study confirmed the monomolecularity of entrapped drug in the ion exchange resin beads. The taste evaluation depicted the successful taste masking of drug: resin complexes. Chewable tablets were developed from drug: Tulsion-335 in optimum ratio of 1:1, 1:2 & 1:3. The formulations were evaluated for the uniformity of dispersion, disintegration time & *in vitro* drug release. The maximum drug release was found to be 98.25% of Levocetirizine dihydrochloride & 98.55% of Montelukast sodium in 60 minutes for F3 formulation. Thus, Complexation with ion exchange resin is a simple and efficient technique of masking the bitter taste.

Keywords: Ion exchange resin (IER), Drug resin complex (DRC), SEM (Scanning Electron microscopy), DSC (Diffusion scanning Calorimetry), DRS (Diffuse Refractro Spectroscopy)

1. Introduction
Administration of drug having bitter taste with oral drug delivery by taste masking of bitter drug with IER for the acceptable level of palatability for pediatrics & geriatric patients. Taste masking is the novel approach for the patient compliance. Taste masking can be done by different techniques by addition of flavouring agent and sweetening agent, microencapsulation, inclusion complexation, solid dispersion, bitterness inhibitor, taste masking by polymer coating taste masking by effervescent granules, by ion exchange resin, prodrug approach and lipophillic vesicles.
Ion exchange resin (crosslinked water insoluble polymer carrying ionisable functional group) was used as a drug carrier in pharmaceutical dosage form for taste masking. The drug resinate complex can also be used as a reservoir that causes a change of drug release in hydrophilic polymer tablet.
An attempt was made to mask the taste of drug (weakly basic anionic) by using Tulsion-335, Kyron T-114 weak acid cation exchange resin with a crosslinked polyacrylic backbone and carboxylic functional group having H+ ionisable species. The complex was used to formulate the chewable tablet having pleasant taste. Drug for taste masking Levocetirizine dihydrochloride (antihistaminic) having low dose (5 mg), bitter taste in combination of Montelukast sodium (antiasthmatic) having low dose (10 mg) and bitter taste.

Drug resin complex formed due to ion exchange reactions. The drug is diffused from such resinates in gastric fluid by exchanging ions.

Material and Methods

Materials

Levocetirizine dihydrochloride, Montelukast sodium, Tulsion-335,
Kyron T-114, Micro crystalline cellulose (MCC) plain, mannitol,
Sorbitol, pineapple flavour, tartrazine yellow colour were obtained
From morepen laboratories, parwanoo (H.P.), India

Preparation of calibration curve

Standard stock solution preparation (1000 ppm)

Take standard weight of Montelukast sodium 50 mg & Levocetirizine dihydrochloride 25 mg in 50 ml volumetric flask. Add 25 ml diluent and mix. Make up volume 50 ml with diluent and inject directly.

For Montelukast sodium

100 ppm (50%) 5 ml of stock solution transfer to 50 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
200 ppm (100%) 5 ml of stock solution transfer to 25 ml volumetric flask
Make up volume with diluent shakes and inject directly.
300 ppm (150%) 7.5 ml of stock solution transfer to 25 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
400 ppm (200%) 10 ml of stock solution transfer to 25 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
500 ppm (250%) 5 ml of stock solution transfer to 10 ml volumetric flask
Make up volume with diluent shakes and inject directly.

For Levocetirizine dihydrochloride

100 ppm (50%) 5 ml of stock solution transfer to 50 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
150 ppm (75%) 15 ml of stock solution transfer to 100 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
200 ppm (100%) 10 ml of stock solution transfer to 50 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
250 ppm (125%) 25 ml of stock solution transfer to 100 ml. volumetric flask
Make up volume with diluent shakes and inject directly.
300 ppm (150%) 15 ml of stock solution transfer to 50 ml. volumetric flask
Make up volume with diluent shakes and inject directly.

Purification of ion exchange resin

Tulsion-335 and kyron T-114 were washed with distilled water. The wet resins were activated with 0.1 M HCL 500 ml followed by washing with distilled water & were dried overnight in hot air oven at 50 °C and were stored in air tight glass vials.

Preparation of drug resin complex

Drugs Levocetirizine dihydrochloride & Montelukast sodium were mixed separately with both the resins in drug: resin ratio of 1:1, 1:2, 1:3.Two hundred ml. Of distilled water was added to the mixture and sttired continuously on magnetic sttirer (whirlmetic –mega, spectrolab, Mumbai, India) for 12 hrs, until equilibrium was attained. Aliquots from the reaction mixtures were withdrawn and filtered through Whatmann filter paper no. 41after every hour were analysed. After appropriate dilution at 230 and 344 nm by HPLC (High performance liquid chromatography). The process was continued till the concentration value of two consecutive aliquots were almost constant. The readings were taken each of six formulations containing varying concentration of drug: resin 1:1, 1:2, 1:3 respectively. Dried the complex at 50 °C for 24 hrs. Then collect the taste masked complex in glass vials till the further use.

SEM (Scanning electron microscopy) of drugs, resin & drug resin Complex

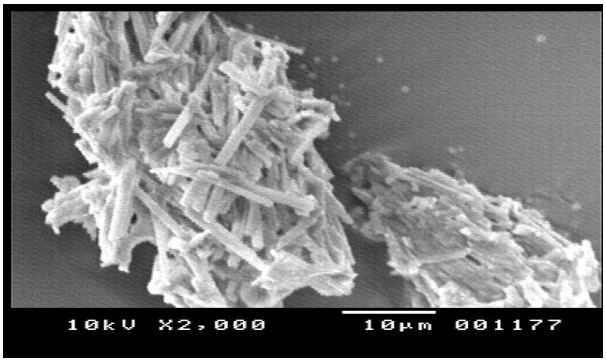


Fig 1.1: Levocetirizine dihydrochloride

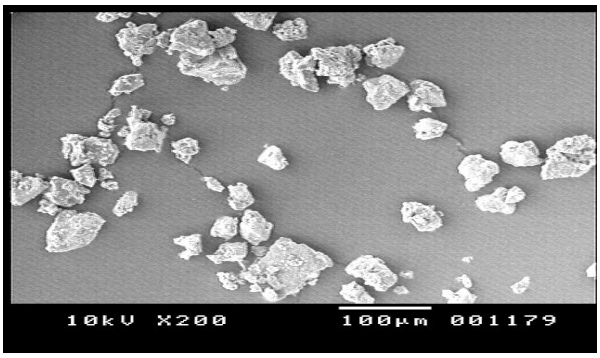


Fig 1.2: Montelukast sodium

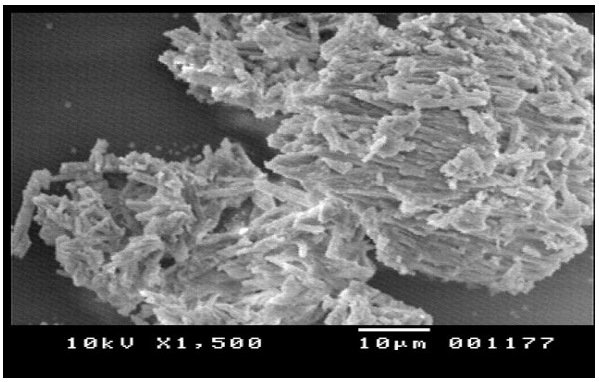


Fig 1.3: Tulsion-335 (Ion exchange resin)

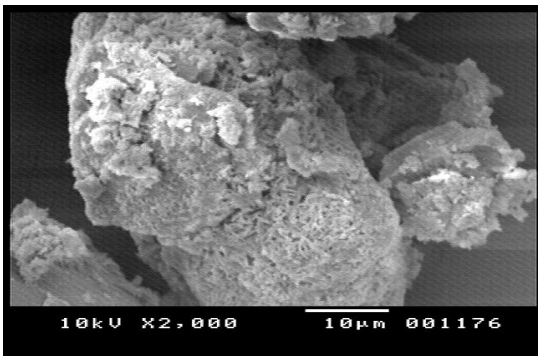
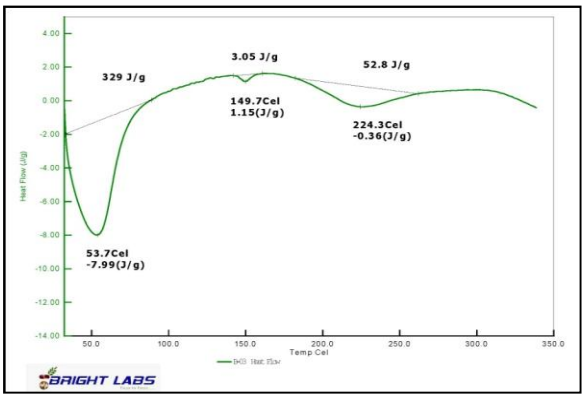
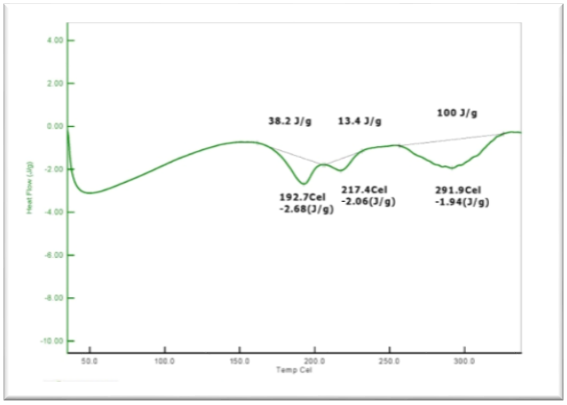


Fig 1.4: Drugs resin complex

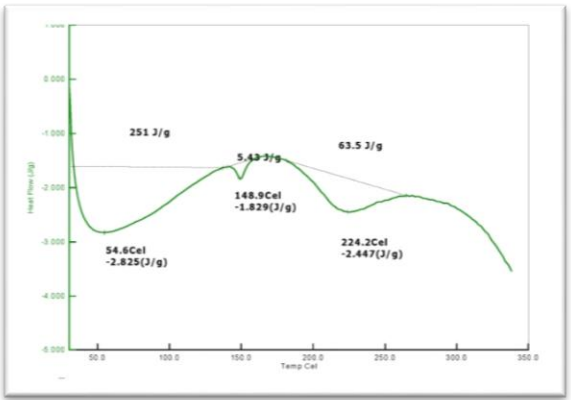


Drugs resin complex

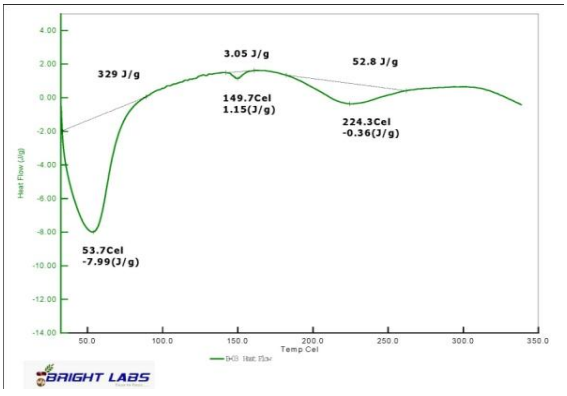
DSC (Differential Scanning Calorimetry) of drugs, resin & drug resin complex



Levocetirizine dihydrochloride

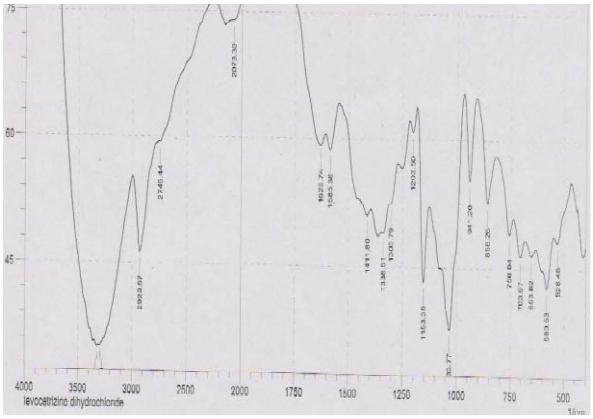


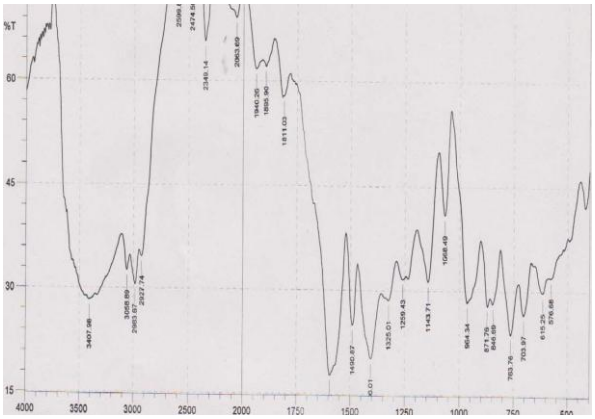
Montelukast sodium

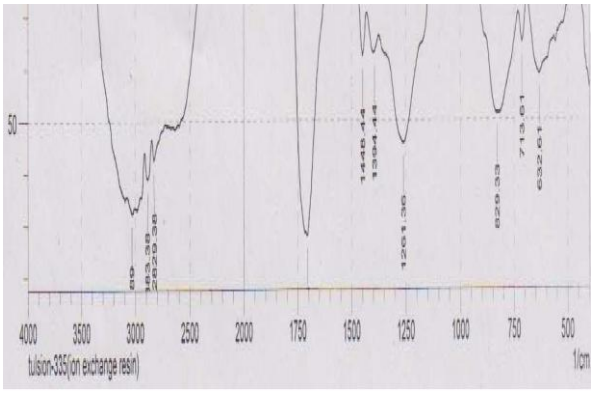


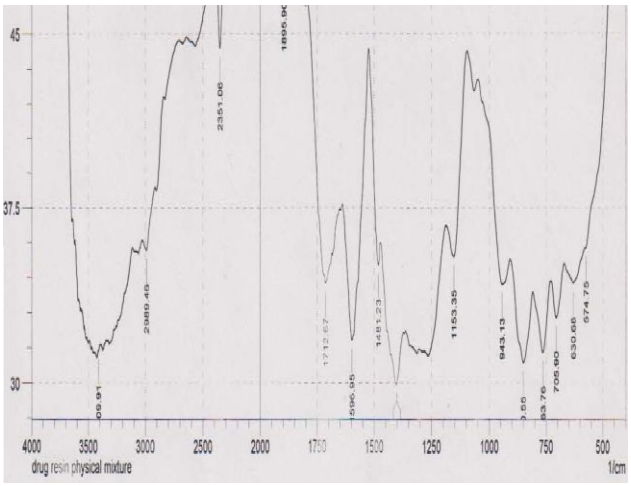
Tulsion-335(ion exchange resin)

DRS (Diffuse refractro spectroscopy) of drugs, resin & drug resin complex









Interpretation of SEM, DSC and DRS

Molecular properties of F3 formulation depicted by SEM, DSC AND DRS shows that complexation has been achieved in drug resin mixture. In SEM entrapment of drug has been achieved in SEM of drug resin complex and there is change in crystalline state of drug to amorphous. In DSC there is change in melting point of drug 192.7° of levocetrizine and 148º of montelukast sharp peaks changes into 217º and 291° with broad peaks showing change in crystalline state of drug to amorphous. DRS shows disappear in peak of amine functional group in Levocetirizine dihydrochloride and Montelukast sodium at 3323 and 3407 frequency appearance of peak in drug resin complex at 3409 frequency showing formation of amide group thus taste perception has been achieved by amide formation and using this complex tablets at 638 mg wt. were compressed.

Preparation of taste masked granules from complex

Take the15 gm of complex (drug: resin) equivalent to 15mg of both drugs taken for 250 tablets. Then we prepare the granules using the drug: resin complex mixture with the other excipients after passing through sieve no. 30 i.e.275 mg MCC, 180mg of pharmatose DCL-15 for each tablet of 630 mg. Then we dried the prepared granules in FBD for 30 minutes at temp 60 °C. The prepared dried granules were passed through sieve no.20 for preparation of tablet from these granules.

Formulation of chewable tablets

We formulate the chewable tablets with varying concentration of DRC, disintegrant and diluents. After weighing the granules 157.5 gm. Having 15gm DRC equivalent to drugs in combination of 15mg drug in each tablet for 250 tablets. List of excipients used in varying concentration for six formulations is in table 1.1

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Levocetirizine dihydrochloride	5	5	5	5	5	5
Montelukast sodium	10	10	10	10	10	10
Tulsion-335	15	30	45	-	-	-
Kyron T-114	-	-	-	15	30	45
MCC plain	280	280	280	280	280	280
Mannitol	75	75	75	75	75	75
Crosspovidone	5	5	5	5	5	5
Pharmatose DCL-15	170	170	170	170	170	170
Talcum	2.5	2.5	2.5	2.5	2.5	2.5
Pineapple	3	3	3	3	3	3
Saccharine	3	3	3	3	3	3
Tartrazine yellow	4	4	4	4	4	4

Tablets were compressed using standard flat 9.5mm punches. The hardness was found between 3-5 kg/cm, friability was less than 1% and weight variation was in ±7.5% of the average weight of tablets.

ng ion exchange resin tulsion-335(cationic) was found to be successful.

Evaluation of prepared taste masked chewable tablet

Drug content

Levocetirizine dihydrochloride & Montelukast sodium present in the DRC were eluted by using HPLC Mobile phase (A) 2.78 gm NaH2Po4 in 1000ml water (pH-4.0) Mobile phase (B) Acetonitrile at λmax 230 nm. Acetonitrile is used as diluents. Method used for elution was gradient elution technique. As theF2 andF3 formulations having drug: resin ratio (1:3) were showing acceptable taste. The drug content of F2 & F3 was calculated & found to be 99.62 & 98.57% Levocetirizine dihydrochloride & 95.73 & 95.96% Montelukast sodium were eluted. Thus results are showing F3 was showing better result as compared to F2 formulation.

Physical parameters of taste masked chewable tablets

Physical parameters	F1	F2	F3
Average wt. of tablets (mg)	639.6 ± 12.0	639.4 ± 12.0	639.7 ± 13.0
Average thickness (mm)	3.78 ± 0.25	3.76 ± 0.20	3.75 ± 0.16
Hardness (Kg)	3.0 ± 0.19	3.0 ± 0.17	3.0 ± 0.21
Disintegration time (min)	15 ± 0.28	13 ± 0.48	13 ± 0.45
% Friability	0.23 ± 0.05	0.21 ± 0.06	0.24 ± 0.04

***In –vitro* drug release study of prepared taste masked chewable tablet**

Drug release study was performed by USP type ɪɪ tablet dissolution apparatus. DRC equivalent to 5 mg Levocetirizine dihydrochloride & 10 mg Montelukast sodium was taken in 900ml in 0.5% sodium dodecyl sulphate in water at pH 6.8 and drug release for 15, 30, 45 & 60 min was to found out 57.55%, 87.55%, 96.88% and 98.25% respectively for F3 formulation having drug: tulsion (1:3) and having acceptable taste masking the bitter taste of Levocetirizine

dihydrochloride & Montelukast sodium in combination for the relief of asthmatic patient.

***In-Vitro* Dissolution profile of taste masked chewable tablet of Levocetirizine dihydrochloride & Montelukast sodium**

Dissolution media – 0.5% sodium dodecyl sulphate in water (pH-6.8)
Apparatus –paddle
Volume – 900 ml
Speed of paddle – 50 rpm
Temperature - 37± 0.5 ºC

Drug	Time(min.)	F1	F2	F3
Levocetirizine dihydrochloride				
1.	15	60.22 ± 0.42	58.64 ± 0.38	57.55 ± 0.36
2.	30	87.55 ± 0.26	91.22 ± 0.34	87.55 ± 0.41
3.	45	94.52 ± 0.18	96.25 ± 0.32	96.88 ± 0.38
4.	60	96.28 ± 0.24	97.25 ± 0.32	98.25 ± 0.26
Montelukast sodium				
1.	15	57.84 ± 0.28	57.55 ± 0.28	58.65 ± 0.34
2.	30	89.55 ± 0.20	90.25 ± 0.22	88.68 ± 0.18
3.	45	93.58 ± 0.25	96.88 ± 0.34	92.58 ± 0.24
4.	60	95.58 ± 0.31	97.58 ± 0.28	98.55 ± 0.25

***In-vivo* taste masking study**

Six tablets were administered to six volunteers and effect of taste masking studied by taste perception. The taste was found to be acceptable.

Result, Discussion and Conclusion

In the present work, chewable tablets were prepared ion exchange resin (taste masking) technique and evaluated for disintegration time, % cumulative drug release (%CDR) drug content, hardness and friability. The chewable tablet of were prepared by addition method using tulsion-335 (taste masking agent), sweetening agent like mannitol Sachharine in different concentration. A total three formulations were prepared in varying concentration of Drug: Tulsion-335 (1:1, 1:2, 1:3) and evaluated for weight variation, thickness, friability, hardness, disintegration time, wetting time, assay. The results of all formulations for Weight variation, Friability, Hardness and Assay were found to be within the IP limit and no significant variation. The Disintegration time for all formulations was found to be 10 to 15 minute.F3 (1:3) showing better drug release as compared to F1 and F2.Thus, F3 was selected best formulation. Drug Levocetirizine dihydrochloride (antihistaminic) and Montelukast sodium (antiasthmatic) having bitter taste extensively so that poor patient compliance. Complexation with ion exchange resin is a simple and efficient technique of masking the bitter taste. Drug being solubilised in water has desired ionization power. Tulsion-335 is highly porous and insoluble in water. It has hydration capacity. Loading capacity of tulsion-335 is a function of exchange COO^- ions in the resins with ions in solution. The equilibrium ions exchange in solution is affected by sttiring time. The pH also affects if increase in pH then higher will be the diffusion of ions between drug and resin. Molecular properties of F3 formulation depicted by SEM, DSC AND DRS shows that complexation has been achieved in drug resin mixture. In SEM entrapment of drug has been achieved in SEM of drug resin complex and there is change in crystalline state of drug to amorphous. In DSC there is change in melting point of drug 192.7° of levocetrizine and 148º of montelukast sharp peaks changes into 217º and 291° with broad peaks showing change in crystalline state of drug to amorphous. DRS shows disappear in peak of amine functional group in Levocetirizine dihydrochloride and Montelukast sodium at 3323 and 3407 frequency appearance of peak in drug resin complex at 3409 frequency showing formation of amide group thus taste perception has been achieved by amide formation.

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