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Formulation and Evaluation of Taste Masked Fast Disintegrating Tablet of Levocetirizine Dihydrochloride

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Bankar A.A.[1*], Bhosale A.V.[2], Patil R.Y.[1], Kakade S.S.[1]

1. P.D.E.A.'s S. U. College of Pharmaceutical Sciences and Research Center, Kharadi, Pune.

2. P.D.E.A.'s S.G.R.S. College of Pharmacy, Saswad, Tal-Purander, Dist-Pune, India.

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ABSTRACT

Levocetirizine dihydrochloride is the active R (-) enantiomer of Cetirizine. It is an orally active and selective H1 receptor antagonist used medically as an Anti-allergic. Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulin E (IgE) in the membrane lining of nose after allergen exposure. Thus formulating Levocetirizine dihydrochloride into fast disintegrating tablets would provide fast relief. The aim of this study was to prepare fast disintegrating tablet of taste masked Levocetirizine dihydrochloride by using direct compression method. To prevent bitter taste and unacceptable odour of the Levocetirizine dihydrochloride, the drug was taste masked with both weak and strong cationic ion exchange resins like Kyron-T-114, Tulsion-335, Kyron T-154, Kyron T-159. The drug: ion exchange resin complex was prepared by batch technique. Among these resins, Kyron-T-114 was selected for further studies because of high drug loading capacity, low cost, and better drug release profile. The fast disintegrating tablets were prepared using microcrystalline cellulose (MCC) PH 102 as diluent along with different proportions of crospovidone (CP), croscarmellose sodium (CCM), and sodium starch glycolate (SSG) as a superdisintegrants. These fast disintegrating tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time (DT), and dissolution study. Study concluded that the fast disintegrating tablet formulation prepared with 4 mg crospovidone showed less disintegration time in comparison with other formulation. The stability studies were carried out for the optimized batch for three months and optimized batch was found to be stable.

INTRODUCTION

Oral route is the most preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, non-invasive method and ease of administration leading to high level of patient compliance. Pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Therefore, to fulfill the needs of such patients, recent advancements in technology have resulted in development of viable dosage alternatives popularly known as fast disintegrating tablets (FDTs) [1,2].

The FDTs also known as orodispersible tablets doesn't require water to swallow[3,4], disintegrate in the mouth, has the ease of administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric and psychiatric patients, allows the manufacture of tablet using conventional processing and packaging equipment at low cost[5].

Levocetirizine, an isomer of cetirizine, is a highly bitter drug [6] with an antihistaminic action, a high affinity towards histamine receptors compared to cetirizine and its dextro form [7] and competitive binding to H1 receptors. In the case of eczema, urticaria, and allergic conditions developed due to insect bites or exposure to pollen grains, patients need immediate relief. Whenever parenteral medication is not possible, orally disintegrating Levocetirizine tablets may be the best alternative to conventional Levocetirizine tablets.

Levocetirizine dihydrochloride is bitter in taste. Taste masking is an essential requirement for fast disintegrating tablets for commercial success. Taste masking is achieved by using ion exchange resin by making drug: resin complex in different ratio. In the present work attempt was made to use ion exchange resins as taste masking agents. Combinations of two superdisintegrants were used in the formulation of mouth dissolving tablet of Levocetirizine dihydrochloride. The purpose was to enhance patient compliance and provide fast onset of action.

MATERIALS AND METHODS

Levocetirizine dihydrochloride was received as a gift sample from Alkem Laboratories Pvt. Ltd. (Mumbai), Kyron T-114, Kyron T-154, Kyron T-159 were received as a gift sample

from Corel Pharmaceuticals Ltd. (Gujarat), Tulsion 335 received as a gift sample from Thermax India Pvt. Ltd. Sodium starch glycolate (SSG), Crospovidone, Croscarmellose Sodium was purchased from Research Lab (Mumbai). Microcrystalline cellulose, Mannitol, Magnesium stearate, Aerosil, Sodium saccharin were of analytical grade.

1. Preparation of Drug -Resin Complex (DRC)

Formulation of drug resin complex was done by the batch process. Kyron T-114, Kyron T-154, Kyron T-159, Tulsion 335 were selected as ion exchange resins. Both strong cationic (Kyron T-154, Kyron T-159) and weak cationic (Kyron T-114, Tulsion 335) exchange resins were weighed accurately and swelled by stirring in 25 ml of water for 30 min using a magnetic stirrer. After 30 min, the accurately weighed quantity of drug was added in slurry of resin with stirring. The resultant mixture of drug and ion exchange resin was stirred for 5 hours. The slurry was filtered off and the filtrate was analyzed for drug complexed with each of the ion exchange resin. The residue was washed with 10 ml water and air-dried. Solid complexes of each of the ion exchange resin with drug were prepared in various ratios, keeping the quantity of drug constant.[8] The percentage of drug loading was calculated for each which is given in Table 2 and 3.

2. Drug Release from Drug Resin complex

2.1. Simulated Salivary Fluid [9]

Solid drug: resin complex equivalent to 5 mg of drug was accurately weighed and added to 5 ml Simulated Salivary fluid pH 6.8 I.P. Aliquot was withdrawn after intervals of 1 min. The sample was filtered through Whatman filter paper. The absorbance was measured at 231 nm. Results for drug release from drug resin complex are given in Table 4.

2.2. Simulated Gastric Fluid [10]

Drug release from drug resin complex in Simulated Gastric fluid was determined using USP dissolution test apparatus II (Model: Disso TDT-08L Apparatus: Electrolab). Accurately weighed drug resin complex equivalent to 5 mg of Levocetirizine dihydrochloride was added to 900 ml simulated gastric fluid for 30 minutes (50 rpm, 37^0 C ± 5^0 C). A 10-ml sample was withdrawn at the 5 min time interval and replacement was made each time with 10 ml of fresh dissolution medium. Each of the 10 ml sample was filtered and analyzed from the

standard curve of the drug in simulated gastric fluid at 231 nm. The reported values of percent drug release are shown in Figure 1, 2 and 3.

3. Evaluation of Taste of Solid Drug: Resin Complex [8]

The healthy human volunteers were used for evaluation of taste and informed consent was obtained from all of them. Bitterness was measured by consensus of a trained taste panel, with sample held in the mouth for 5 to 10 seconds. Then spat out; the bitterness level was then recorded. A numerical scale was used with the following values: 0= tasteless, 1= acceptable bitterness, 2= slight bitterness, 3= moderately bitterness and 4= strong bitterness. The data is given in Table 5 and 6.

4. Assay of drug: resin complexes [10]

Drug resin complex equivalent to 5 mg Levocetirizine dihydrochloride was stirred with 100 ml of 0.1 N HCl for 60 min., so as to release the entire Levocetirizine dihydrochloride from drug resin complex. The mixture was filtered and 1 ml of the filtrate was diluted to 10 ml using 0.1 N HCl. The absorbance of this solution was measured at λmax 231.6 nm using 0.1 N HCl as blank and the content of Levocetirizine dihydrochloride was estimated at λmax 231nm. The data obtained is shown in Table 7.

5. Characterization of drug resin complex [11]

1. Fourier Transform Infra Red (FTIR) Study:

FTIR spectra were obtained by FTIR 8400S Shimadzu spectrometer. Sample was prepared in KBr disks, and spectra were recorded over the wave number 4000- 600 cm^{-1}. All three spectra were completely analyzed shown in Figure 4.

2. X-Ray Powder Diffraction (XRPD) Study:

XRPD pattern of Levocetirizine dihydrochloride, Kyron T-114 and drug resin complex were taken by Bruker D8 Advance. Radiation generated from Copper source with wavelength of 20mA at 40 kV and the scanning rate employed was 1°/min over the 5°to 50° diffraction angle (2θ) range. The XRPD patterns of drug powder is recorded which is shown in Figure 5.

3. Differential Scanning Calorimeter (DSC) Study:

A mettler Toledo (*SW920) Differential Scanning Calorimeter equipped with an in cooler and refrigerated cooling system was used to analyze the thermal behavior of Levocetirizine dihydrochloride, Kyron T-114 and drug resin complex. Sample (5- 10 mg) was heated in hermetically sealed aluminum pans at temperature 10 ˚ C/min nitrogen were purged at 50 mL/min and 100 mL/min through cooling unit. The data obtained is shown in Table 8. The DSC of Levocetirizine dihydrochloride, Kyron T-114 and drug resin complex is shown in Figure 6.

6. Formulation of Fast Disintegrating Tablets [1, 12]

Oral fast disintegrating tablets were prepared by using solid drug: resin complex (1:1 ratio) of Levocetirizine dihydrochloride with Kyron T-114. The complex was taken equivalent to dose of drug. Nine different types of oral fast disintegrating tablets were formed using different types of super disintegrating agents in different proportions.

Complex of drug-resin earlier obtained were mixed/ blended with superdisintegrants (Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium), Microcrystalline cellulose is used as diluent, Mannitol is used as mouthfeel enhancer, Sodium saccharin as sweetener, Vanilla dry as flavouring agent and Magnesium stearate as lubricant. All ingredients were passed through mesh # 60. Before compression hardness was adjusted. Drug-resin equivalent to 5mg of Levocetirizine dihydrochloride were compressed into tablets (150 mg) using 8mm flat face punch set using a 23 station tablet press (RIMEK INDIA). The scheme for oral fast disintegrating tablet formulations using different ingredients is shown in Table 1.

Table 1: Scheme for oral fast disintegrating tablet formulations using different ingredients

Ingredients	Quantity of Ingredients								
	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levocetirizine dihydrochloride : Kyron T-114 complex (1:1 Ratio) equivalent to 5 mg	10.30 mg	10.30 mg	10.30 mg	10.30 mg	10.30 mg	10.30 mg	10.30 mg	10.30 mg	10.30 mg
Croscarmellose Sodium	3	3.5	4	---	---	---	---	---	---
Crospovidone	---	---	---	3	3.5	4	---	---	---
Sodium starch Glycolate	---	---	---	---	---	---	3	3.5	4
Mannitol	40	40	40	40	40	40	40	40	40
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	4	4	4	4	4	4	4	4	4
Sodium sacharin	6	6	6	6	6	6	6	6	6
Vanilla Flavour	1	1	1	1	1	1	1	1	1
Microcrystalline cellulose	84.2	83.7	83.2	84.2	83.7	83.2	84.2	83.7	83.2
Total	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg

7. Evaluation of Powder Blend [1, 12, 13]

The prepared blend is evaluated by following tests.

- Angle of repose
- Bulk density
- Tapped density
- Hauser's ratio
- Carr's index

1. Angle of Repose

Angle of repose was determined by using fixed funnel method. The fixed funnel method employs a funnel that was secured with its tip at a given height (2cm), above the graph paper that was placed on a flat horizontal surface. Tablet blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile. Angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Here, h = Height of pile

r = Radius of pile

θ = Angle of repose

2. Bulk Density

A powder (about 4.5 gm) is passed through a standard sieve No.20. A weighed amount (approximately 4.5 gm) is introduced into a 100ml graduated cylinder. The bulk volume is measured by dropping the cylinder (containing powder) onto a hard wooden surface 3 times from the height of 1 inch at 2 sec. intervals.

Bulk density (ρ) = (Weight of the powder /bulk volume)

3. Tapped Density

Tapped density is ratio of mass of tablet blend to tapped volume of tablet blend. Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured. Then cylinder was allowed to 100 taps under its own weight onto a hard surface. The tapping was continued until no further change in height was noted.

Tapped density = (Weight of the powder / tapped volume)

4. Hausner's Ratio

Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula,

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

5. Compressibility Index (Carr's Index)

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as Carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula,

Compressibility Index (%) = [(Tapped density –Bulk Density) / Tapped density] X 100

8. Evaluation of Tablets [1,12]

The prepared tablets were evaluated for various parameters like hardness, disintegration time, wetting time, thickness, friability, drug content and weight variation and results are shown in Table 10.

1. Weight Variation

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. In practice, 10 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet passes the test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Average weight = Weight of 10 tablet/10

2. Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier caliper. It was determined by checking three tablets from each formulation.

3. Hardness

Hardness is defined as the "force required to break a tablet in diametric compression test." Hardness is hence, also termed as the tablet crushing strength. The resistance of tablets to breakage, under conditions of storage, transportation or handling before usage depends on its

hardness. Tablet hardness was measured with Monsanto hardness tester. A tablet was placed in the hardness tester and load required to crush the tablet was measured. The hardness has influence on disintegration and dissolution time and is as such a factor that may affect bioavailability. The hardness was kept lower as increased hardness delays the disintegration of the tablet.

4. Friability Test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Friability generally reflects poor cohesion of tablet ingredients. Initial weight of 10 tablets is taken and these are placed in the Friabilator, which consists of a circular plastic chamber, divided into 2-3 compartments. The chamber rotating at 25 rpm for 4min and drops the tablets by a distance of 15 cm and gives 100 revolutions. After that, the tablets are weighed once again. The difference in the weight is noted and expressed as percentage. It should be preferably below 1%.

$$\% \text{ Friability} = [(W1-W2)/W1] \times 100$$

Where,

W1= Weight of tablets before test,

W2 = Weight of tablets after test

5. Content Uniformity

10 tablets were powdered and 100 mg drug equivalent powder dissolved in suitable media of 0.1N HCl. Volume of the solution made up to 100 ml by that media. Solution was filtered and diluted 100 times and analyzed using UV- spectrophotometer and further calculation carried out to determine drug content in one tablet.

6. *In-vitro* Disintegration Time

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using Disintegration test apparatus as per I.P. specifications. The test was carried out on 6 tablets using the apparatus specified in Indian Pharmacopoeia 2007. 900 ml of 0.1 N HCl at 37 ± 0.5ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining on the screen was measured.

7. Wetting Time and Water Absorption Ratio

In this method, a piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was kept on the paper and time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio, R, was determined using the following equations:

$$R= \{(W_a-W_b) \div W_a\} \times 100$$

Where,

W_b = Weight of tablet before water absorption, and

W_a = Weight of tablets after water absorption

8. *In-vitro* Release Rate Study of Formulations [12]

In-vitro dissolution of all fast disintegrating tablet i.e. formulation F1 to F9 of drug resin complex was carried out using USP dissolution test apparatus II (Model: Disso TDT-08L, Electro Lab) in simulated gastric fluid. 10 ml of the aliquot were withdrawn at different time interval of 5, 10, 15, 20, 25 and 30 min. and replacement was made each time with 10 ml of fresh dissolution medium. Each of the 10 ml sample was filtered through Whatman filter paper. The absorbance was measured at 231 nm. The drug concentration in the sample was determined from the standard curve of the drug in simulated gastric fluid. The data is given in Table 11 and Figure 7.

9. Accelerated Stability Study of Optimized Batch [12]

The optimized formulation F6 was stored in aluminum capped clear glass vials and were subjected to a storage condition of 40°C±2˚C/ 75%±5% RH for 3 months in humidity chamber. The samples were withdrawn at time intervals of 0, 1, 2, 3 months and evaluated for hardness, friability, disintegration time, drug content and *in-vitro* dissolution study which is shown in Table 12. The data of dissolution of optimized batch F6 is shown in Table 13.

RESULTS AND DISCUSSION

1. Complexation of Levocetirizine dihydrochloride with Ion Exchange Resins

There is very high significant difference in percent drug complexed with different ratios of drug: resin as well as very high significant difference in percent drug complexed with

different types of resin used for complexation. We can conclude that the percent drug complexed is dependent on both drug: resin ratio as well as the type of resin.

Ratio of drug: resin has very high significant effect on percent complexation of drug with resin. As the amount of resin increases, percent complexation also increases. The complexation of drug with different resins showed in Table 2 and 3.

Table 2: Percent drug complexed in various ratios of strong cation exchange resins

Ratio Drug: Resin (% w/w)	Percent drug complexed	
	Kyron T-159 (H^+)	Kyron T-154(Na^+)
1:1	78.564±0.569	21.276±0.825
1:2	95.799±0.461	47.527±0.871
1:3	99.357±0.422	58.302±0.721

Table 3: Percent drug complexed in various ratios of weak cation exchange resins

Ratio Drug: Resin (% w/w)	Percent drug complexed	
	Kyron T-114 (H^+)	Tulsion-335 (H^+)
1:1	88.564±0.569	81.276±0.825
1:2	95.799±0.461	87.527±0.871
1:3	99.357±0.422	78.302±0.721

Percent complexation of drug with Kyron T-159 had good complexation with Levocetirizine dihydrochloride but Kyron T-154 had poor complexation with Levocetirizine dihydrochloride. We can say that as the strong resins compared are in both the forms (native and salt) hence difference was observed in percent complexation. So it was found that resins of H^+ form have high loading capacity, as it possesses lower pH value than Na^+.

Percent complexation of drug with both weak cationic ion exchange resins showed that both the resins had good complexation with Levocetirizine dihydrochloride. Both the weak resins are in native form so they showed good complexation with drug.

2. Release rate study

2.1 Salivary pH

Any substance, which is soluble in saliva will interact with taste buds, and can impart its taste. The reported values of percent drug release in simulated salivary fluid are shown in Table 4.

The electrolyte concentration of the surrounding medium affects release of the drug from resin. It was observed from the data of release that, type of resin showed very high significant difference on the release of drug from the complex. Strong resin showed negligible release in salivary pH after 60 sec. while weak resins showed considerable release at the end of 60 sec. Out of two weak resins Tulsion 335 showed remarkably more release of drug in simulated salivary fluid than Kyron T-114.

Table 4: Percent drug release at salivary pH 6.8 after 60 sec.

Ratio of Drug: Resin	Percent drug release in simulated salivary fluid		
	1:1	1:2	1:3
Drug: Tulsion- 335	26.600±1.069	23.628±1.015	21.711±1.215
Drug: Kyron T-114	8.379±0.449	6.424±0.509	5.620±0.460
Drug: Kyron T-159	7.024±0.581	5.277±0.959	4.385±1.213
Pure Drug	59.410±0.271		

2.2 Gastric pH

The release rate of the drug from each of the ratio of the drug: resin (with Tulsion-335, Kyron T-114, Kyron T-159) complex was studied at the gastric pH in simulated gastric fluid (SGF) to determine the amount of drug that would be released in the stomach after administration of formulation.

Type of resin and its ratio plays very important role in release of drug from complex. Strong resin Kyron T-159 showed release of drug more than 90 mins. While weak resin Kyron T-114 released the drug in 30 mins. This is because drug binds tightly with the strong resin and loosely with weak resins. The cumulative percent release of plain drug and Drug: Kyron T-114 complex and Drug : Kyron T-159 complex in different ratio is shown in Figure 1, 2 and 3.

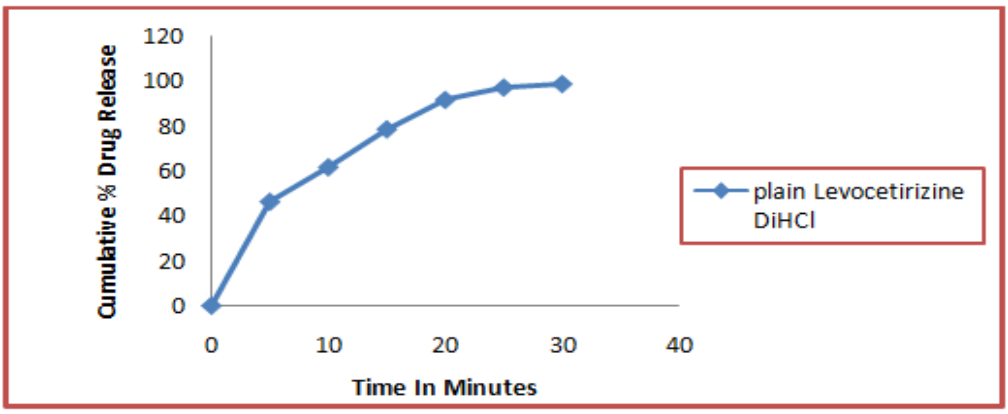


Figure 1: Cumulative percent drug release from plain Levocetirizine dihydrochloride in SGF

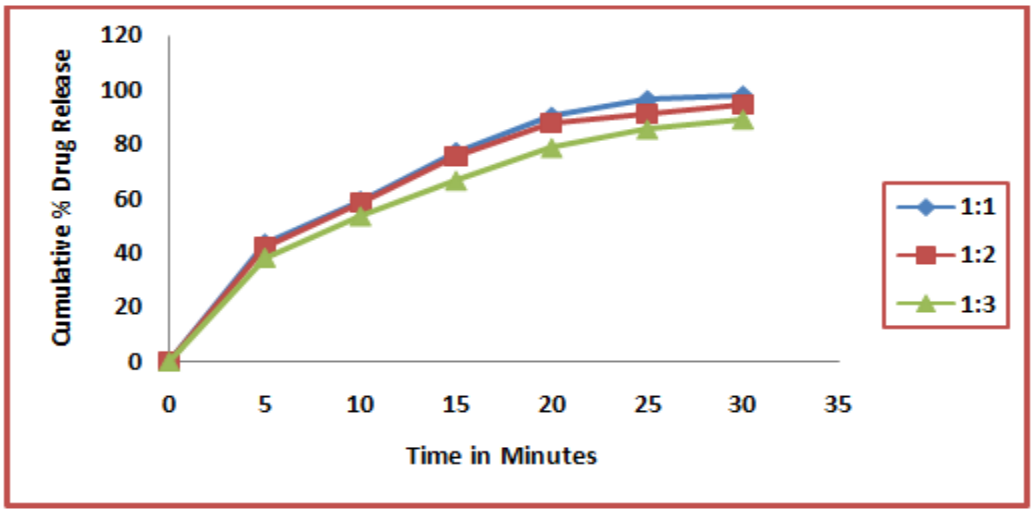


Figure 2 : Cumulative percent drug release from Levocetirizine dihydrochloride: Kyron T-114 in SGF

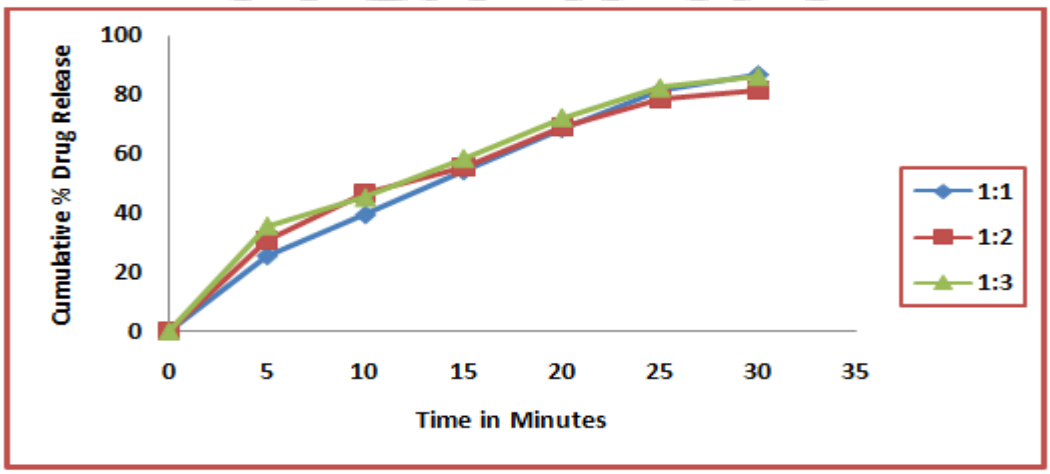


Figure 3: Cumulative percent drug release from Levocetirizine dihydrochloride: Kyron T- 159 in SGF

3. Taste Evaluation of Solid Drug: Resin Complex

The sample of each drug resin complex was subjected to sensory evaluation by a panel of six members with respect to bitter taste. The average bitterness value of each of the ion exchange resin complex with the drug is shown in Table 5 and 6.

Table 5: Sensory evaluation data of drug-Kyron T-114 complexes

Ratio of Drug: Resin Complex	Scores of drug – Kyron T-114 complex						Average bitterness value
	1	2	3	4	5	6	
Pure drug	4	4	4	4	4	4	4
1:1	1	0	0	0	1	1	0.5
1:2	0	1	1	0	1	0	0.5
1:3	0	0	1	1	0	1	0.5

Table 6: Sensory evaluation data of drug-Kyron T-159 complexes

Ratio of Drug: Resin Complex	Scores of drug – Kyron T-159 complex						Average bitterness value
	1	2	3	4	5	6	
Pure drug	4	4	4	4	4	4	4
1:1	1	1	0	1	1	1	0.83
1:2	0	1	1	0	1	1	0.66
1:3	1	0	1	1	0	1	0.66

All the three ratios (1:1, 1:2, 1:3) of Drug –Kyron T-114 complex and Drug-Kyron T-159 was evaluated for taste which showed that drug-Kyron T-114 complex has less bitter taste as compared to drug-Kyron T-159 complex. The bitter taste of Levocetirizine dihydrochloride was equally masked in all the three ratios of drug-Kyron T-114 complex so ratio of drug-Kyron T-114 complex containing less proportion of resin (1:1) was selected for formulation.

4. Assay of drug: resin complexes

Both the samples of drug –resin complex (Drug-KyronT-114, Drug-Kyron T-159) were assayed by UV- spectrophotometer at 231 nm for the determination of percent drug content. The data obtained is shown in Table 7.

Table 7: Percent drug content of drug: resin complexes

Ratio of Drug: Resin (% w/w)	Percent drug content	
	Kyron T-114	Kyron T-159
1:1	99.42±0.35	98.35±0.48
1:2	98.72±0.52	97.43±0.18
1:3	98.63±0.32	96.20±0.65

Both the complexes showed more than 95 % drug content but the ratio 1:1 of Drug-Kyron T-114 complex showed 99.42 % drug content so Drug-Kyron T-114 complex (1:1) was selected for further formulation.

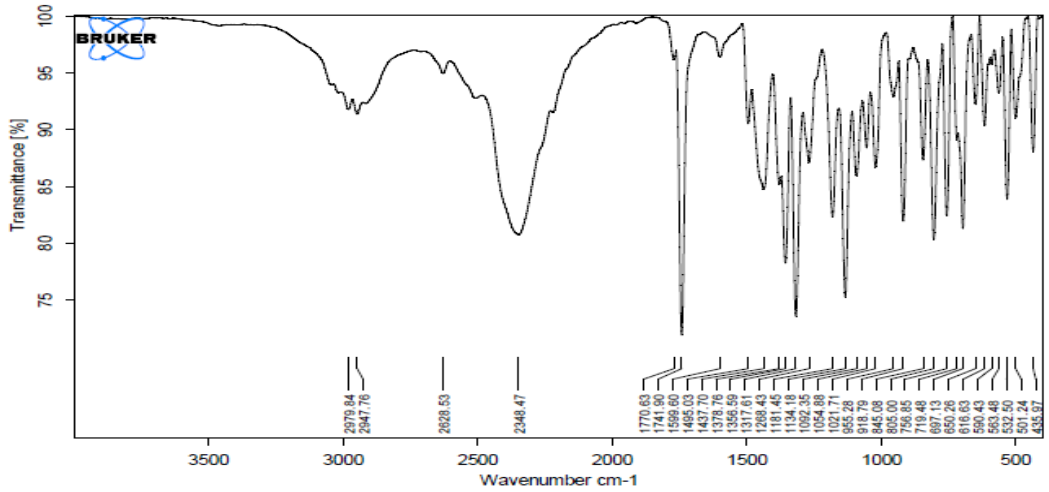
5. Characterization of Drug Resin Complex

1. Fourier Transform Infra Red (FTIR) Study:

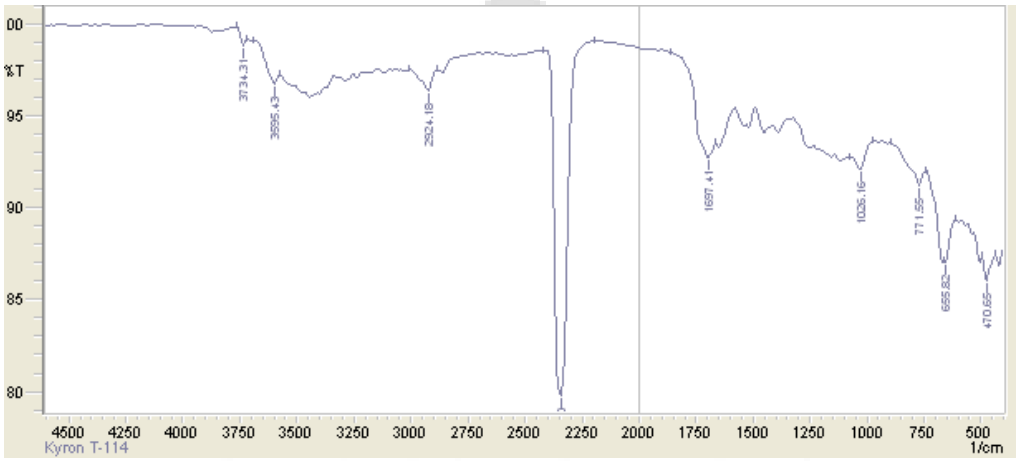
The FTIR spectrum of complex exhibit significant difference in the characteristic spectrum of the Levocetirizine dihydrochloride, revealing modification of the drug environment. The spectrum of pure Levocetirizine dihydrochloride showed characteristic peak at 1741.90, 1317.61, 2348.47, 1134.18, 2979.84 and 756.85 that are assigned to C=O stretching of COOH, C-N, O-H, C-O, C-H and C-Cl stretching respectively.

The absence of Levocetirizine dihydrochloride peak i.e. –O-H stretch at 2348.47 cm^{-1} in drug resin complex confirms the complexation of drug with resin. The spectrum of Kyron T-114 showed distinct C=O stretch at 1697.41 $^{cm-1}$ of the –COOH functional group of the resin, which was not seen in the spectrum of drug resin complex. The functional groups involved in the complexation process were –COOH of Kyron T-114 along with the –O-H of Levocetirizine dihydrochloride. The absence of other peaks of Levocetirizine dihydrochloride in the spectrum of drug resin complex indicated that the drug was completely embedded in the resin polymer matrix and thus the complexation was confirmed assigned to C=O stretching of COOH, C-N, O-H, C-O, C-H and C-Cl stretching respectively.

A. Levocetirizine dihydrochloride



B. Kyron T-114



C. Drug-resin complex

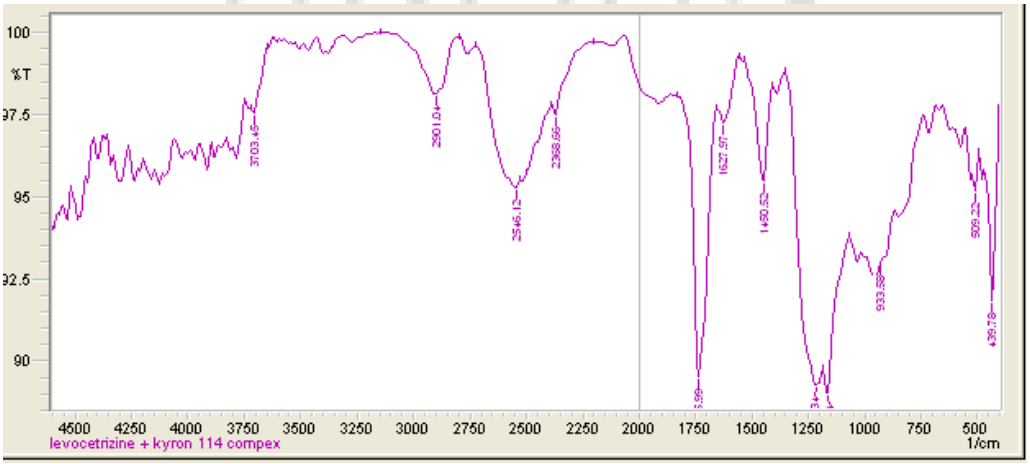
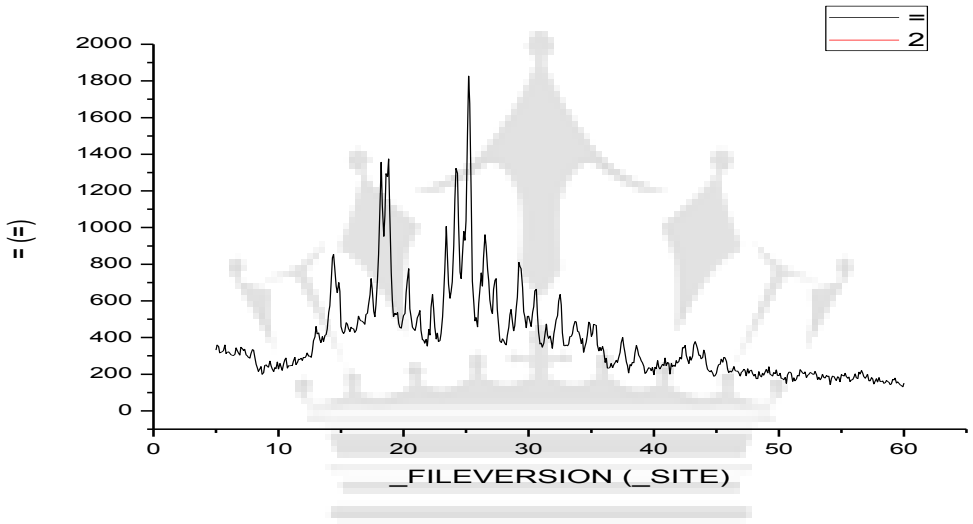


Figure 4: A: FTIR spectrum of Levocetirizine dihydrochloride. B: FTIR spectrum of Kyron T-114. C: FTIR spectrum of Drug Resin Complex

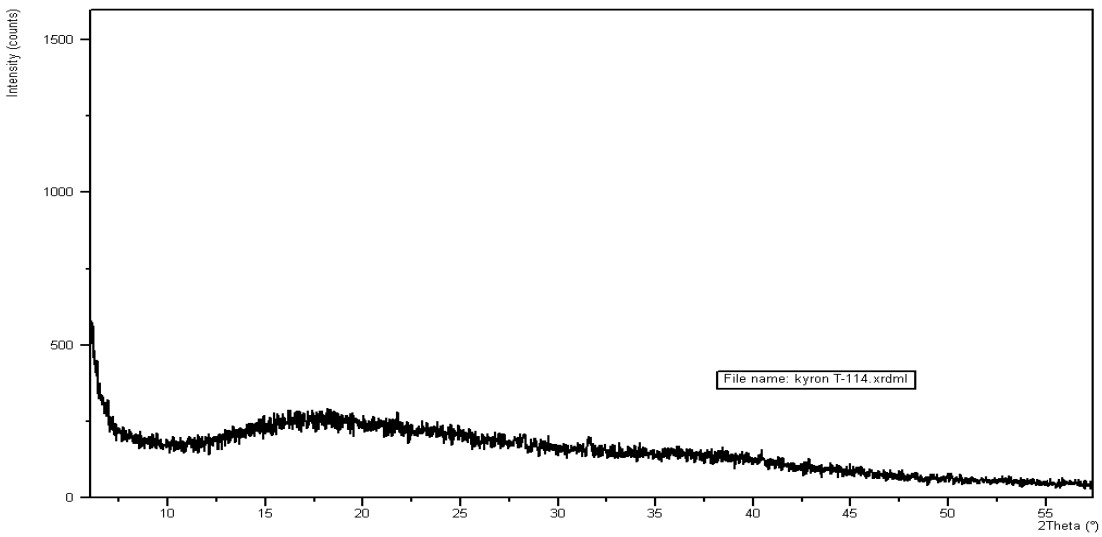
2. X-Ray Powder Diffraction (XRPD) Study:

The XRPD pattern confirms the crystalline nature of Levocetirizine dihydrochloride that is evident from the number of sharp and intense diffraction peaks obtained for drug. The XRPD of resin showed diffused peaks. Only diffused peaks were observed in the diffraction pattern for the complex regardless of presence of drug. According to the data from XRPD, the molecular state of pure drug was crystalline and that of the resin was amorphous. The molecular state of the drug prepared as drug-resin complex was changed from the crystalline to the amorphous.

A. Levocetirizine dihydrochloride



B. Kyron T-114



C. Drug-resin complex

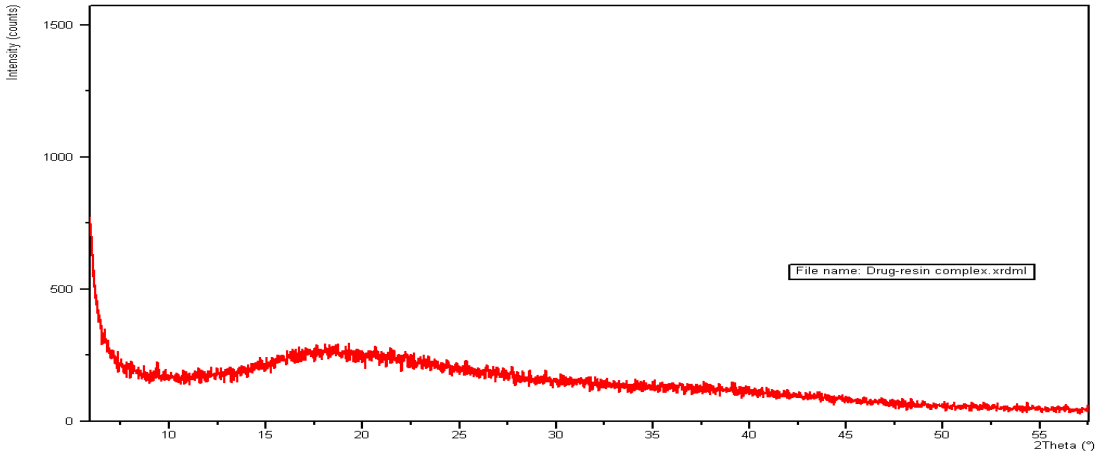


Figure 5 A: XRD Curve of Drug (Levocetirizine dihydrochloride). B: XRD Curve of Resin (Kyron T-114). C: XRD Curve of Drug resin complex

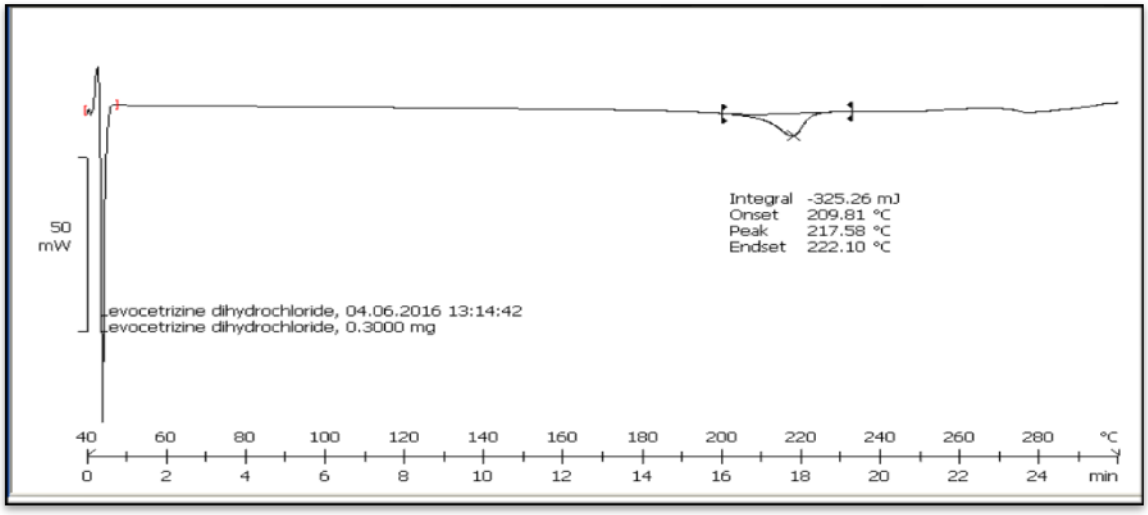
3. Differential Scanning Calorimeter (DSC) Study:

In DSC curve of drug resin complex, the total disappearance of drug melting temperature was occurred, which indicated that drug was completely embedded in resin. The DSC of Levocetirizine dihydrochloride, Kyron T-114 and drug resin complex is shown in Figure 6.

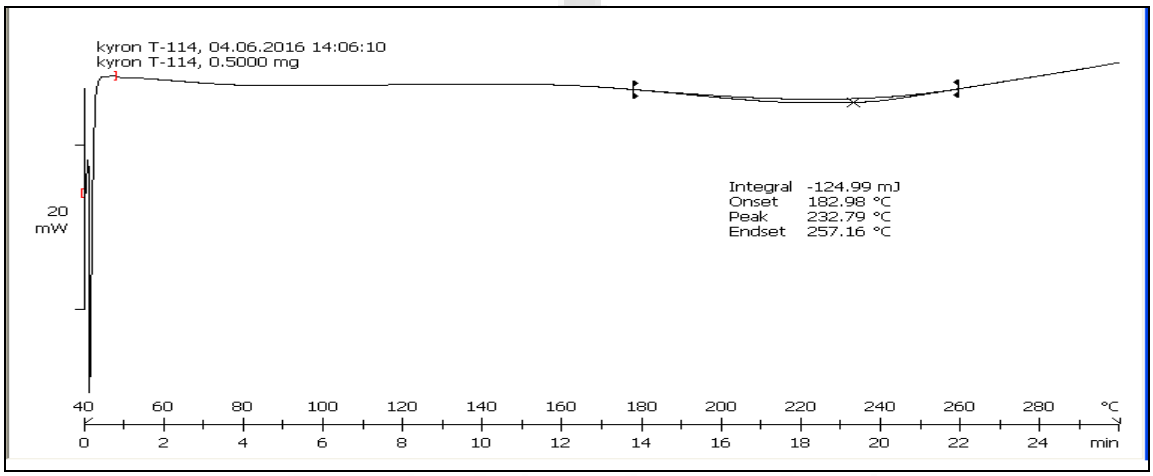
Table No. 8: DSC of resin and solid drug: resin complexes

Sample	Endothermic Peak (°C)
Levocetirizine Dihydrochloride (plain drug)	217.58
Kyron T-114	232.79
Drug –resin complex	200.32

A. Levocetirizine dihydrochloride



B. Kyron T-114



C. Drug-resin complex

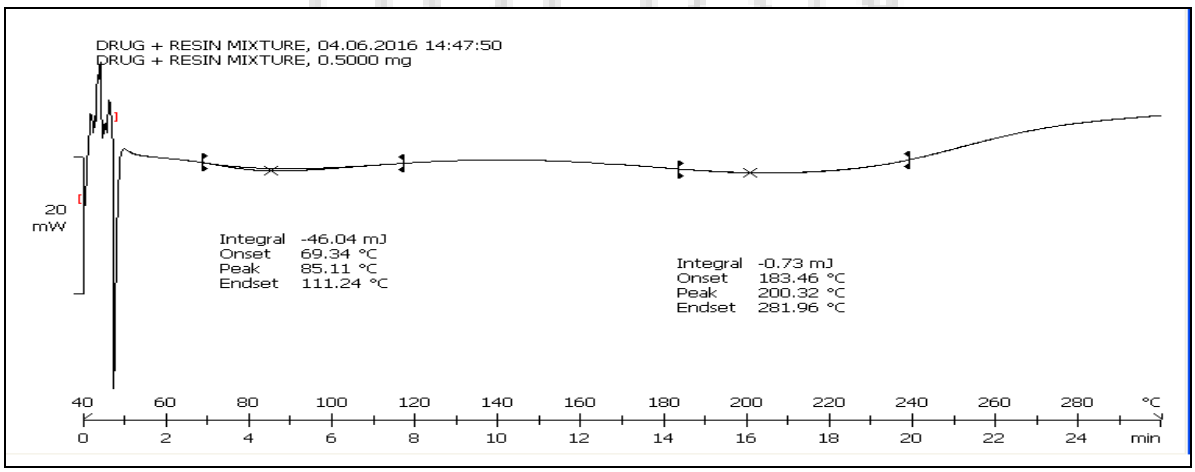


Figure 6 A: DSC curve of drug (Levocetirizine dihydrochloride). B: DSC curve of resin (Kyron T-114) C: DSC curve of drug resin complex

6. Evaluation of Powder blend

The characterization of mixed blend was done for determination of mass-volume relationship parameters. The evaluation parameters like angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index were shown in Table 9.

Table 9: Evaluation of powder blends of Levocetirizine dihydrochloride: Kyron T-114

Formulations	Evaluation Parameter				
	Bulk Density ($gm/cm^{3)}$	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Compressibility Index (%)	Hausner's Ratio (H_R)
F1	0.161±0.28	0.186±0.25	26.85±0.85	13.44±0.6	1.15±0.68
F2	0.159±0.39	0.199±0.36	27.90±0.74	20.10±0.58	1.25±0.58
F3	0.163±0.57	0.193±0.48	28.80±0.96	15.54±0.2	1.18±0.20
F4	0.149±0.69	0.187±0.85	27.55±0.52	20.32±0.8	1.25±0.41
F5	0.151±0.41	0.188±0.63	26.85±0.41	19.68±0.96	1.24±0.56
F6	0.164±0.82	0.187±0.41	26.85±0.63	12.30±0.45	1.14±0.74
F7	0.154±0.36	0.192±0.52	27.88±0.24	19.79±0.68	1.24±0.59
F8	0.148±0.24	0.189±0.63	26.93±0.26	21.69±0.24	1.27±0.58
F9	0.159±0.12	0.195±0.85	27.65±0.48	18.46±0.15	1.22±0.23

Results are mean of three determinations.

From the results of pre-compression studies of the batch F1- F9, it is concluded that powder mixtures have good flow property and compressibility. The Bulk density of powder mixtures were found to be in the range of 0.148-0.168 g/cm^3. Bulk density of F1-F9 formulations were reduced to 0.168-0.148 gm/cm^3, which indicates the higher bulk volume and thereby higher porosity of powder mixture which is desirable to support the rapid disintegration. The values of Carr's index were in the range of 12.30 % - 21.69 % and Hausner's ratio was in the range of 1.14-1.33 were suggesting fairly good flow properties.

The powder blend was compressed using direct compression technique. Tablets prepared by direct compression method have found to be good without any chipping, capping and sticking.

7. Evaluation of Formulation

Prepared tablets were evaluated for physicochemical parameters like hardness, disintegration time, wetting time, thickness, friability, drug content and weight variation and results are shown in Table 10.

Table 10: Evaluation of formulations of Levocetirizine dihydrochloride: Kyron T-114

Formulations	Evaluation Parameter							
	Hardness (Kg/cm^2)	Thickness (mm)	Disintegration time (Sec)	Wetting time (Sec)	Friability (%W/W)	Drug content (%W/W)	% Weight variation	Water absorption ratio
F1	2.51±0.1	3.01±0.31	33±1.92	38±1.31	0.73±0.23	96.55±0.89	149±0.53	83.56±0.92
F2	2.52±0.2	3.02±0.42	28±3.73	41±2.66	0.59±0.58	98.65±0.26	149±0.48	80.85±0.56
F3	2.5±0.12	3.01±0.25	26±2.45	40±2.04	0.68±0.56	98.75±0.36	148.5±0.64	86.56±0.35
F4	2.54±0.1	3.12±0.32	28±3.73	30±2.04	0.52±0.89	99.14±0.58	150±0.73	75.54±0.23
F5	2.51±0.2	3.02±0.4	22±1.92	36±2.04	0.91±0.75	98.88±0.68	150±0.84	78.89±0.58
F6	2.51±0.2	3.01±0.24	20±2.48	26±1.21	0.49±0.59	99.35±0.56	149±0.77	90.51±0.58
F7	2.51±0.3	3.04±0.21	36±4.24	40±2.04	0.58±0.21	98.47±0.64	148.5±0.53	89.31±0.87
F8	2.53±0.2	3.01±0.24	30±1.24	34±0.96	0.62±0.47	98.22±0.63	149±0.42	88.35±0.69
F9	2.52±0.1	3.24±0.32	32±2.69	49±1.61	0.59±0.56	97.15±0.58	148.5±0.56	87.20±0.45

Results are mean of three determinations

Various physical parameters like thickness, hardness, weight variation, friability, hardness, disintegration time were measured to evaluate tablets. It was found that the average thickness of the tablets also ranged between 3.01-3.24 mm; however, the variations have not alarming and remained within the acceptable range. Hardness of tablets of the different formulations varied widely ranging from 2.51 – 2.54 kg/cm^2, all the formulations have therefore thought to show the acceptable hardness.

As per the Pharmacopoeial requirement, formulation of fast disintegrating tablet exhibited disintegration time in ≤60 seconds; F1 to F9 batches passes the disintegration time requirement. From above results, it is observed that all the prepared formulations exhibited disintegration time less than 60 seconds from F1 to F9 batches. F6 batch exhibited the least disintegration time i.e. 20 seconds. So from above observation, it is concluded that the optimized formulations (Batch F6) contain Crospovidone (4 mg) as a superdisintegrants. The results obtained in the *In-vitro* drug release for all formulations F1 to F9 are tabulated in

Table 11. The cumulative percent release of formulations F1 to F9 in 0.1 N HCl is shown in Figure 7.

Table 11: Percent Cumulative drug release of Formulations F1 to F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	35.24 ± 087	33.22 ±0.59	35.62 ±0.68	37.28 ±0.87	40.46 ±0.68	40.75 ±1.4	39.17 ±0.22	30.59 ±0.62	38.28 ±0.87
10	48.23 ±0.65	38.87 ±0.22	41.67 ±0.96	49.32 ±1.15	48.86 ±0.45	57.41 ±0.8	56.87 ±1.12	37.16 ±0.87	47.22 ±0.37
15	65.45 ±1.12	56.87 ±1.12	61.12 ±0.54	60.22 ±0.37	64.45 ±1.12	72.39 ±0.9	68.40 ±1.23	49.32 ±1.15	60.22 ±0.37
20	76.32 ±1.23	68.40 ±1.23	70.54 ±0.43	71.73 ±0.62	74.32 ±1.23	88.29 ±0.6	76.65 ±0.76	62.22 ±0.37	73.73 ±0.62
25	85.42 ±0.76	76.65 ±0.76	80.78 ±0.54	80.27 ±0.21	86.42 ±0.76	92.73 ±0.8	89.51 ±0.33	75.73 ±0.62	83.30 ±0.42
30	90.02 ±0.41	88.51 ±0.33	91.75 ±0.33	88.67 ±0.28	95.62 ±0.21	99.68 ±0.5	92.62 ±1.22	86.75 ±0.42	90.57 ±0.34

The reported values of percent drug release are average values of three readings.

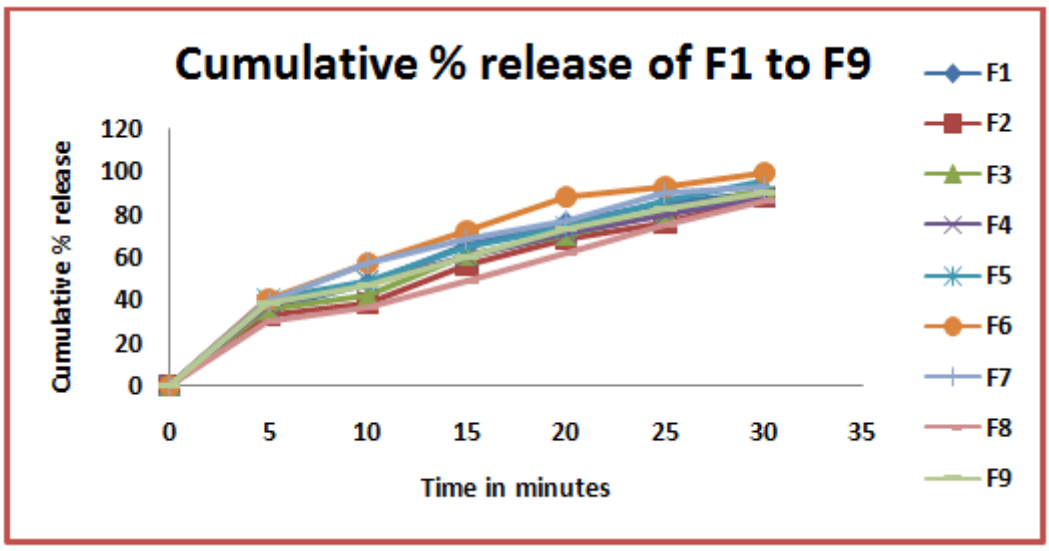


Figure 7: *In-vitro* drug release profile of Levocetirizine dihydrochloride tablets of F1 to F9 formulations

8. Accelerated Stability Study of Optimized Batch

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications. Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form.

The stability study indicates that the formulation is quite stable at different conditions of storage. Accelerated stability studies carried out at 40°C ± 2°C/75% RH ± 5% RH for 3 months.

From the evaluation of dosage form batch F6 was optimized so that this formulation was now processed from beginning to ensure reproducibility of this formulation and then stability study was carried out for three months on new batch formed of F6. Stability studies were carried out as per ICH stability testing guidelines.

Figure 8 shows cumulative percent release of F6 Formulation. Formulation F6 was found to be stable after three months stability study.

Table 12: Stability data for optimized formulation F6

Formulation	Parameters evaluated	Initial	After one month	After two months	After three months
F6	Disintegration time (sec)	20±2.48	20±1.58	19±1.22	19±1.58
	Hardness (kg/cm²)	2.51±0.2	2.44±0.4	2.38±0.6	2.48±0.4
	Friability (%)	0.49±0.9	0.42±0.6	0.48±0.2	0.46±0.4
	% drug content	99.35±0.68	98.5±0.62	98.30±0.80	99.16±0.70

Table 13: Dissolution profile of optimized Batch F6

Time (min)	Initial	After one Month	After two Months	After three months
0	0	0	0	0
5	40.75±1.4	38.56±0.5	39.25±0.37	39.17 ±0.22
10	57.41±0.8	55.36±0.26	56.34±0.59	56.87 ±1.12
15	72.39±0.9	70.58±0.89	73.89±0.85	68.40 ±1.23
20	88.29±0.6	88.39±0.47	86.25±0.49	76.65 ±0.76
25	92.73±0.8	92.04±0.96	91.58±0.57	89.51 ±0.33
30	99.68±0.5	98.20±0.69	97.89±0.65	98.62±1.22

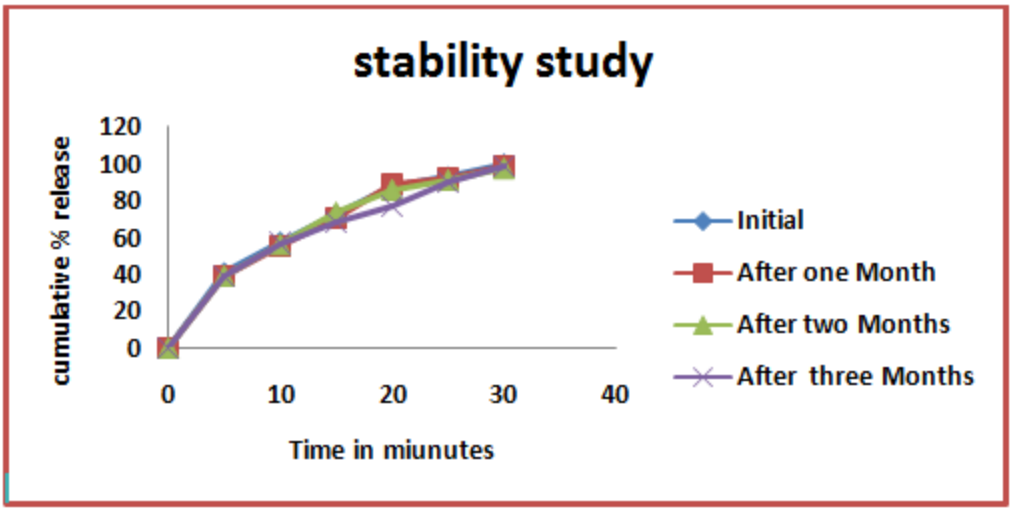


Figure 8: Cumulative Percent release from Levocetirizine dihydrochloride: Kyron T-114 after three months

The stability study showed that the formulation F6 was physically stable when stored at 40±2°C and 75±5 % RH for three months and there was no significant difference in dissolution for optimized formulation.

CONCLUSION

- Levocetirizine dihydrochloride is the active R (-) enantiomer of Cetirizine. It is an orally active and selective H1 receptor antagonist used medically as an antiallergic. Our aim was to prepare fast disintegrating tablets with quality consistent by using production friendly direct compression which avoids costly technology, equipment and lengthy manufacturing process. The process is simple and easy to demonstrate as observed from results of batch manufactured.

- In present work, attempt was made to use ion exchange resins as taste masking agents. Three superdisintegrants were used in the formulation of fast disintegrating tablet of Levocetirizine dihydrochloride. The purpose was to enhance patient compliance and provide fast onset of action.

- Kyron T-114, Tulsion 335, Kyron T-154, Kyron T-159 were used as ion exchange resins and it was mixed with the drug in different ratios and evaluated for the extent of complexation, release rate study, sensory evaluation. Results showed that with Kyron T-114 in drug to resin ratio of 1:1 gave maximum amount of complexation.

- These drug-resin complex exhibited satisfactory values for angle of repose and bulk density. The disintegration tests conducted on these products showed that there is faster disintegration of the tablets, taking 20 to 30 seconds, which is much less than the official limit for fast disintegrating tablets (3 minutes). The diameter and thickness of tablet is uniform and weight variation is very well within ±7.5% of the standard value in all batches.

- The measured average hardness of all the formulations met the in house limits. The % drug content of tablets in all formulations is found to be between 85-100% which complied with limits established in Indian Pharmacopoeia. The % friability is less than 1% in all the batches, ensuring that the tablets were mechanically stable.

- All the tablets passed the weight variation test as % weight variation is within the Pharmacopoeial limit i.e.7.5% to be compliance with the Indian Pharmacopeia standards. Optimized batch F6 showed very less disintegration time (20 sec) and wetting time (26 sec).

- Results of taste evaluation by panel method revealed that Kyron T-114 mask the bitter taste of drug at 1:1 ratios. The data indicated that, there was a difference between the ratings of taste attributed to effective masking the bitter taste of Levocetirizine dihydrochloride.

- Stability study was conducted. There is no significant change in taste, color at significant temperature. There is no significant variation in the disintegration time, hardness, friability and *in-vitro* dissolution profiles after three months of stability studies for the optimized formulation F6 at 40°C/75% RH.

- Finally, it was concluded that the objective of taste masking and formulation development and evaluation of fast disintegrating tablets of Levocetirizine dihydrochloride was achieved. The effective taste masking is achieved for Levocetirizine dihydrochloride by preparation of complex using Kyron T-114 (1:1).

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