RESEARCH ARTICLE

TASTE MASKING AND FORMULATION DEVELOPEMENT &EVALUATION OF MOUTH DISSOLVING TABLETS OF LEVOCETRIZINE DIHYDROCHLORIDE

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ABSTRACT

Levocetrizine dihydrochloride is the active R (-) enantiomer of cetrizine. It is an orally active and selective H_1 receptor antagonist used medically as an Antiallergic. Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulin E (IgE) in the membrane lining the nose after allergen exposure. Thus formulating Levocetirizine dihydrochloride into a mouth dissolving tablets would provide fast relief. Levocetirizine dihydrochloride is bitter in taste so the Kyron T-134 (ion exchange resin) was used to mask the taste and formulated a mouth dissolving tablets using drug resin complex. Results show that effective taste masking is achieved for Levocetrizine dihydrocloride by preparing drug-resin complex using Kyron T-134. The tablets have evaluated for the drug content, weight variation, and water absorption ratio, wetting time, in vitro disintegration, hardness, friability, thickness uniformity and *in-vitro* dissolution. The tablets disintegrated *in- vitro* within 29 to 59 seconds. . The % drug content of tablets in all formulations was found to be between 90-110% which complied with limits established in Indian Pharmacopoeia. In vitro drug release profile of tablets is shown 99% drug release in 10 minutes. The results show that Levocetirizine dihydrochloride is successfully formulated into a mouth dissolving tablet and can be prepared at industry scale for production purposes.

Key words: Levocetirizine dihydrochloride, Allergic rhinitis, Super disintegrants, Ion exchange resin, Mouth dissolving tablets.

INTRODUCTION AND EXPERIMENTAL

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, 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 cater the needs of such patients, recent advancements in technology have resulted in development of viable dosage alternatives popularly known as orally disintegrating tablets (ODTs)[1,2].During the past decade, the FDT (fast dissolving tablet) technology, which makes tablets dissolve or disintegrate in the mouth without additional water intake, has drawn a great deal of attention.The technology is also referred to as fast disintegrating tablet, fast dispersing tablet, rapid dissolve tablet, rapid melt tablet, quick disintegrating tablet, and orally disintegrating tablet. The FDT formulation is defined by the Food and Drug Administration (FDA) as **''a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue''**.The tablets disintegrate into smaller granules or melt inthe mouth from a hard solid structure to a gel like structure, allowing easy swallowing by the patients. The disintegration time for those tablets varies from a few seconds to more than a minute [2,3].

Levocetrizine dihydrochloride is the active R (-) enantiomer of cetrizine.It is an orally active and selective H_1 receptor antagonist used medically as an antiallergic. It is bitter in taste. Taste masking is an essential requirement for mouth dissolving tablets for commercial success.Taste masking is achieved by using ion exchange resin by making drug: resin comlex 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 Levocetrizine dihydrochloride. The purpose was to enhance patient compliance and provide fast onset of action.

Materials and Methods

Levocetrizine dihydrochloride was obtained from Karunesh Remedies Ltd, Anklehwar, Gujrat. Sodium starch glycolate, cross carmellose sodium, crospovidone were obtained from Vijlak Pharma Ltd, Hyderabad.

Preparation of Drug-Resin Complex:

- First of all distilled water was added in beaker and then added slowly Kyron T-134 added under continous stirring into the vortex taking precaution to avoid lump formation and allowed it to swell for 2 hour.
- Levocetrizine Dihydrochloride was added slowly under continous stirring to above resin solution.
- Stirring was continued for 3 hours and allow it for 24 hours.
- The solution was filtered by using whatmann filter paper no 41.Residue/slurry was taken out and put it for drying at 60^{O}C for 3-4 hours in oven.
- The dry powder is the Drug –Resin complex (DRC).

Preparation of Drug Granules:

- Granules of drug-resinate earlier obtained were mixed/ blended with superdisintegrants (both Sodium Starch

Glycolate, Croscarmellose Sodium),microcrytalline cellulose is used as diluent, mannitol is used as mouth feel enhancer, aspartame as sweetner, orange dry as flavouring agent, talc as glidantand magnesium sterate as lubricant. All ingredients were pass through mesh # 60 .Before compression hardness was adjusted. Drug-resinate equivalent to 5mg of Levocetrizine dihydrochloride were compressed into tablets using 8mm Flat Face Punch set using a 23 station tablet press (RIMEK INDIA).

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Table no.1 Formulation composition of batc F1 to F5

Name of Ingrdients	Formulation code Quantity (in mg)				
	F1	F2	F3	F4	F5
Levocetrizine Dihydrochloride	5	5	5	5	5
Kyron T-134	15	15	15	15	15
Crosscarmellose Sodium	2.5	3	3.5	4	4.5
Sodium Starch Glycolate	2	2	2	2	2
Mannitol	73	73	73	73	73
Magnesium Stearate	2	2	2	2	2
Colloidal Silicon Dioxide(Aerosil 200)	1.2	1.2	1.2	1.2	1.2
Talcum	2.5	2.5	2.5	2.5	2.5
Aspartame	3	3	3	3	3
Flv orange dry	0.8	0.8	0.8	0.8	0.8
Menthol	0.05	0.05	0.05	0.05	0.05
MCC PH (102) up to	135	135	135	135	135

EVALUATION OF POWDER BLEND:

The prepared blend is evaluated by following tests.

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

Angle of repose:

Angle of repose was determined by using fixed funnel method. The fixed funnel method employ 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. Granules or tablet blend were 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

Bulk density:

Bulk density was determined by pouring a weighed quantity of tablet blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume.

$$\text{Bulk Density} = \frac{m}{v} = \frac{m}{\pi r^2 h}$$

Here; **m** = weight of powder or granules (gm.)

v = Bulk Volume ($cm.^3$)

π = 22/7 = 3.14

r = Radius of Cylinder (cm.)

h = Height reached by powder in cylinder (cm.)

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 100tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted.

$$\text{Tapped Density} = \frac{m}{v} = \frac{m}{\pi r^2 h}$$

Here; **m** = weight of powder or granules (gm.)

v = Tapped Volume ($cm.^3$)

π = 22/7 = 3.14

r = Radius of Cylinder (cm.)

h = Height reached by powder in cylinder after tapping (cm.)

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

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

Carr's Index (Compressibility 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

$$\text{Carr's Index} = (1 - \frac{\text{Bulk Density}}{\text{Tapped Density}}) \times 100$$

EVALUATION OF TABLETS

These tests are as following:-

- Appearance
- Thickness
- Hardness
- Weight variation
- Friability
- Disintegration
- Uniformity of dispersion
- Wetting Time
- Water absorption ratio
- Drug content
- *In vitro* Dissolution
- Stability studies

Appearance:

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. Tablets have smooth, clean surface, round concave shaped, white color tablet with pleasant taste.

Thickness:

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm.

Hardness:

The hardness of tablet is an indication of its strength against resistance of tablets to **capping,** abrasion or breakage under conditions of storage, transportation and handling before usage. Measuring the force required to break the tablet across tests it. Hardness of 10 tablets (randomly) from whole tablet batch was determined by Monsanto hardness tester. Hardness measured in kg/cm^2.

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula

$$\%f = \frac{W_0 - W_1}{W_0} \text{ x } 100$$

Here, %f = Percentage friability

W_0 = Initial weight (Before test)

W_1 = Final weight (After test)

Disintegration test:

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Wetting Time:

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petridish containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time.

Water Absorption Ratio:

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper. The wetted tablet was then weighed. Water absorption ratio, R was determined by using following formula

$$R = \frac{W_a - W_b}{W_b} \text{ x } 100$$

Here, R = Water absorption ratio

W_b = Weight of tablet before water absorption

W_a = Weight of tablet after water absorption

Drug content:

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

***In-vitro* drug release studies:**

The mouth dissolving tablets are subjected to *in-vitro* drug release studies in 0.1N HCl for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in dissolution test apparatus USP type II using specified volume 900ml of dissolution media maintained at 37±0.5°C. The tablets are directly placed in medium with paddle then rotated at 50 rpm. 5ml of the sample from the dissolution medium are withdrawn at each time interval (1, 2, 3, 4 ,5, 6, 7, 8, 9, 10 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with

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0.1N HCl. These samples were analyzed spectrophotometrically and further calculation was carried out to get drug release. The drug released data were plotted as cumulative % drug release Vs time.

Stability study:

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 F4 optimized so that this formulation was now processed from beginning to ensure reproducibility of this formulation and then stability study were carried out for three months on new batch formed of F4. Stability studies were carried out as per ICH stability testing guidelines (ICH guidelines). The optimized formulation F4 was stored in aluminium 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.

RESULT AND DISCUSSION:

FLOW PROPERTIES OF GRANULES:

Angle of Repose of Granules:
All batches were evaluated for flow property. The results of all the batches were shown in table 18.

Table 2: Angle of repose of granules of batch F1 to F5

Batch No.	Height of Pile (cm)	Radius (r) (cm)	Tan θ	Angle of Repose(θ)
F1	2.0	3.951	0.506	26.85
F2	2.0	3.777	0.529	27.90
F3	2.0	3.638	0.549	28.80
F4	2.0	3.834	0.522	27.55
F5	2.0	3.660	0.506	26.85

From the results of flow properties of the all batches, it is concluded that all batches had good flow property.

Table 3: Physicomechanical properties of batch F1 to F5

Batch No.	Mass of powder blend (gm)	Initial volume (ml)	Bulk Density (gm/cm^3)	After Tap volume (ml)	Tapped Density (gm/cm^3)	Hausner's Ratio (H_R)	Carr's Index (%)
F1	10	14.9	0.161	12.9	0.186	1.15	13.42
F2	10	15.1	0.159	12.1	0.199	1.24	19.86
F3	10	14.7	0.163	12.5	0.193	1.17	14.96
F4	10	16.1	0.149	12.9	0.187	1.25	19.87
F5	10	15.9	0.151	12.8	0.188	1.24	19.49

From the results of precompression studies of the batch F1-F5, it is concluded that powder mixtures has good flow property and compressibility property. 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-F5 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 12.58 - 25.34 and Hausner's ratio was in the range of 1.14-1.33 were suggesting fairly good flow properties.

Post-compression parameters-

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. Various physical parameters like thickness, hardness, weight variation, friability, hardness, disintegration time were measured to evaluate tablets. It is found that the average thickness of the tablets also ranged between2.51 -2.59 mm; however, the variations have not alarming and remained within the acceptable range.Hardness of tablets of the different formulations varied widely ranging from 2.3 – 2.8 kg/cm^2 (Table 3), all the formulations have therefore thought to show the acceptable hardness.

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Table 4: Post Compression Evaluation

Batch No.	Thickness	Hardness	Weight Varation	Friability
F1	2.54 ±0.015	2.6 ± 0.199	134.05±2.25	0.445
F2	2.51± 0.013	2.8 ± 0.263	133.95±2.43	0.443
F3	2.59±.012	2.4 ± 0.648	133.5±2.32	0.296
F4	2.54± 0.015	2.3 ± 0.288	134.1±2.25	0.444
F5	2.52± 0.023	2.4 ± 0.733	133.9±2.29	0.259

Table 5: Post Compression Evaluation

Batch No.	Average Disintegration Time (sec)	Average Wetting Time (sec)	Water absorption ratio(%)	% drug content
F1	59 ± 0.365	18 ± 0.324	76.41 ± 0.96	96.99 ± 0.928
F2	53 ± 0.863	16 ± 0.231	78.46 ± 0.392	97.37 ± 0.586
F3	42 ± 0.863	16± 0.621	78.34 ± 0.503	97.62 ± 1.613
F4	36 ± 0.563	15 ± 0.503	83.17 ± 0.52	98.93 ± 0.914
F5	29 ± 0.261	14 ± 0.365	85.23 ± 0.183	99.62± 0.381

As per the pharmacopoeial requirement, formulation of fast disintegrating tablet exhibited disintegration time in ≤60 seconds; F1 to F5 batches passes the disintegration time requirement. From the above it is observed that all the prepared formulations exhibited disintegration time less than 60 seconds from F1 to F5 batches. F5 batch exhibited the least disintegration time i.e. 29 seconds. So from above observation it is concluded that the optimized formulations (batch F5) contains disintegrants in the ratio of 4.5:2 (Croscarmellose sodium: sodium starch gycolate). Wetting time from F1 and F5 were 14 and 18 respectively and those were significantly lower due to highly porous structure. Due to high levels of croscaremellose sodium and sodium starch glycolate, there was high water uptake. % drug content is in the range of 96.99-99.62, also within the limits.

In-vitro drug release:

Dissolution parameter:

Medium: 0.1 N HCl

Volume: 900 ml

Apparatus: USP Type II (Paddle)

Speed: 50 rpm

Time Point: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 minutes

Temperature: 37^{o}C

Identification: At 230.1 nm in UV-Visible spectrophotometer

Table 6: *In-vitro* drug release profile of batches F1 to F5

Time (min)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	23.806	20.903	22.645	21.484	24.968
2	29.032	29.613	29.613	27.871	30.194
3	38.323	38.903	39.484	39.484	40.065
4	54.581	54.000	52.839	53.419	55.161
5	62.129	63.290	63.871	59.806	63.871
6	66.774	67.355	67.935	70.258	69.097
7	77.806	75.484	76.645	79.387	79.548
8	87.677	84.774	89.419	87.516	90.000
9	90.000	91.742	91.742	93.112	93.484
10	96.387	96.968	97.548	98.125	99.290

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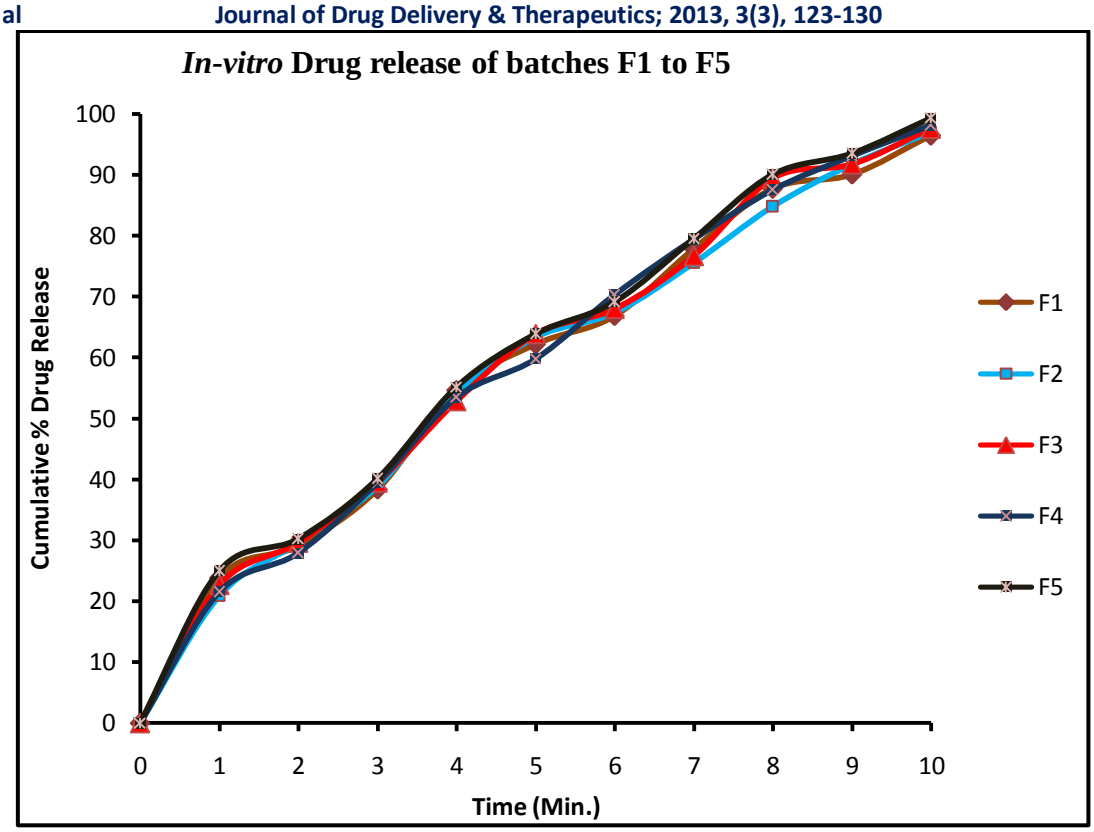

Figure 1: *In-vitro* drug release of batches F1 to F5

The highest release was obtained with the optimum level of super disintegrates in batches F3, F4, F5 and drug release was found to be 97.548, 98.125 and 99.290 % respectively in dissolution period 10 minutes. Amongst all these batches F5 showed highest drug release having ratio of 4.5 : 2 (croscarmellose sodium: sodium starch glycolate) i.e. 99.290% in 10 min. Hence, batch F5 was selected as optimized batch.

STABILITY STUDIES OF OPTIMIZED BATCH:

Table 7: Stability data for optimized formulation F5

Formulation	Parameters Evaluated	Time interval (months)			
		0	1	2	3
F5	Disintegration time (sec)	22	23	21	23
	Hardness (kg/cm^2)	2.4	2.5	2.4	2.6
	Friability (%)	0.314	0.309	0.328	0.322
	% drug content	99.29	99.45	99.23	98.76

Table 8: Dissolution profile of optimized batch F5

Time (min)	Cumulative % drug release			
	Initial	After 1 month	After 2 months	After 3 months
0	0	0	0	0
1	22.645	22.065	20.903	23.226
2	27.290	26.129	26.129	29.613
3	37.161	38.903	38.323	39.484
4	54.000	55.742	51.677	56.323
5	64.452	65.613	62.710	63.871
6	69.097	70.258	68.516	70.839
7	80.710	78.968	79.548	81.290
8	89.419	91.742	88.258	87.677
9	92.323	94.645	94.645	90.581
10	99.290	98.710	99.290	98.129

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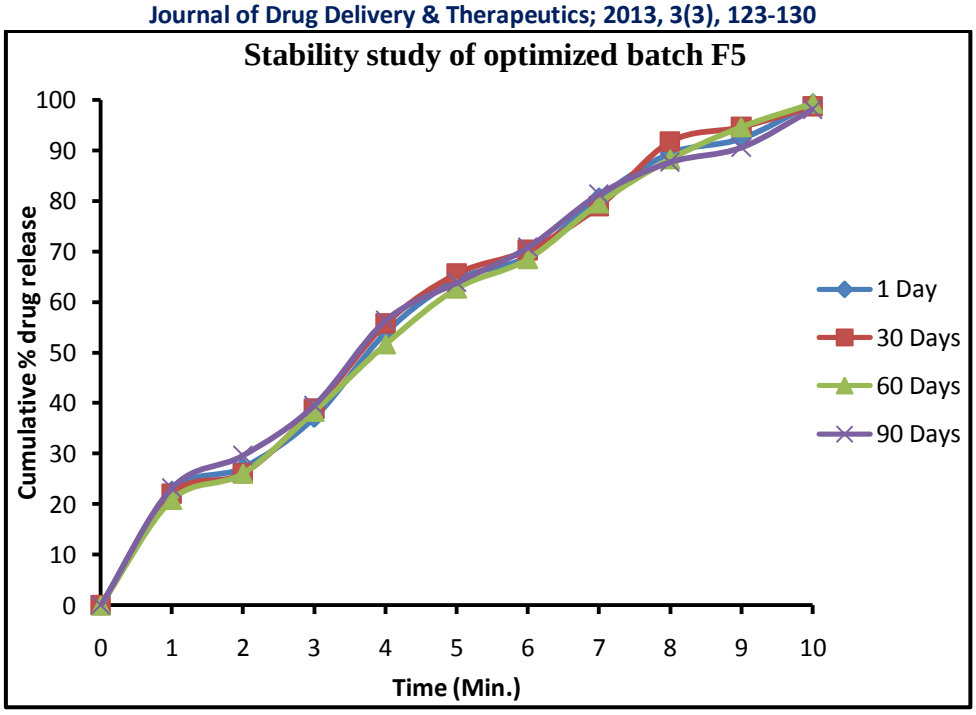

Figure 2: Dissolution profile of optimized formulation F5

The stability study revealed that all the formulations were physically stable when stored at 40 ± 2^0 c and 75±5 % RH till 3 months and there was no significant difference in dissolution for optimized formulation.

CONCLUSION:

Levocetrizine dihydrochloride is the active R (-) enantiomer of cetrizine.It is an orally active and selective H_1 receptor antagonist used medically as an antiallergic. Our aim was to prepare mouth dissolving 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 result batch manufactured.

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 Levocetrizine dihydrochloride. The purpose was to enhance patient compliance and provide fast onset of action.

Kyron T-134 was used as ion exchange resins and it was mixed with the drug in different ratios and evaluated for the extent of complexation. Results show that with Kyron T-134, drug to resin ratio of 1:3 gave maximum amount of complexation.

These drug-resin complex exhibited satisfactory values for angle of repose and bulk density. Drug content estimation showed more than 90% of the drug present. The disintegration tests conducted on these products show that, there is faster disintegration of the tablets, taking 29 to 59 seconds, which is much less than the official limit for fast disintegrating tablets (1minutes). After disintegration, the dispersion produced was smooth with pleasant mouth feel and the bitter taste was totally masked.

The tablet's diameters and thickness 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 90-110% 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 pass the weight variation test as % weight variation is within the pharmacopoeial limit i.e.7.5% to be compliance with the Indian pharmacopeias standards. Optimized batch F5 show very less disintegration time (29 sec) and the wetting times in the batch F5 is also less.

Results of taste evaluation by panel method revealed that Kyron T-134 (R) mask the bitter taste of drug at 1:3 ratios. The data was indicating there is a highly significant difference between the ratings of taste, attributed to effective masking the bitter taste of Levocetrizine dihydrocloride effectively.

In vitro drug release profile of tablets in shown 99% drug release in 10 minutes indicating that the drug will be absorbed faster in the mouth, pharynx and oesophagus and thus enhance the bioavailability by pregastric absorption through mouth, pharynx and oesophagus.

Stability study was conducted. There is no significant taste, color change at significant temperature. There is no significant variation in the disintegration time, hardness, friability and *in-vitro* dissolution profiles at months of stability studies for the optimized formulation F5 at different temperatures.

In conclusion, the objective of taste masking and formulation development & evaluation of mouth dissolving tablets of Levocetrizine dihydrocloride was achieved. The effective taste masking is achieved for Levocetrizine dihydrocloride by preparation of complex using Kyron T-134. The formulated tablets that had a good taste and rapidly disintegrated in the mouth are useful and practical for pediatric and geriatric formulation. Thus, the formulated tablets of Levocetrizine Dihydrochloride can be prepare at industry scale for production purpose.

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