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Original Article

Formulation and evaluation of Taste Masked Mouth Dissolving Tablet of Levocetrizine dihydrochloride by using Ion-Exchange Resin

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ABSTRACT: Levocetirizine dihydrochloride is a third-generation non-sedating anti-histamine drug derived from the second generation anti-histamine cetrizine. It is H1receptorantagonist.Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulinE (IgE) in the membrane lining the nose after allergen exposure. Thus, formulating Levocetirizine into an orodispersible dosage form would provide fast relief. The Levocetirizine is bitter in taste so the Kyron T-134 (ion exchange resin synthetic which is inert organic polymers consist of hydrocarbon network to which ionizable groups are attached and they have the ability to exchange their labile ions for ions present in the solution with which they are in contact) was used to mask the taste and to formulate Mouth dissolving tablets using drug resin complex. The tablets were evaluated for the drug content, weight variation, water absorption ratio, wetting time, invitro disintegration, hardness, friability, thickness. All the parameters were found to be acceptable in range. The optimized formulation was disintegrated in 25 seconds and complete drug was released from tablet in10 minutes. It has been compared with marketed formulation and the drug release rate was found to be enhanced. Thus, results showed that Levocetirizine dihydrochloride was successfully formulated into Mouth Dissolving Tablets.

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INTRODUCTION

Oral route is always the favored route for administration of drugs due to accurate dosage, self-medication, low cost and ease of administration which leads to elevated patient compliance [1]. Solid dosage forms also present considerable administration challenges in children, mentally challenged and uncooperative patients. So, to accomplish the requirements of patients' recent advancements in technology have resulted in development of viable dosage form namely orally disintegrating tablets (ODTs) which disintegrates tablet in mouth without water in few seconds. The MDT formulation is defined by the food and drug administration (FDA) as "A solid dosage form which disintegrates rapidly when sited on the tongue thus realizing and dissolving the active ingredient and allowing absorption through all possible membranes [2].

A wide no. of taste buds is there in our mouth (roof of the tongue, mouth, cheeks and throat). Each bud has 60-100 receptor cells. These cells interact with molecules in saliva and produce a positive/negative sensation. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions to reach the receptor cells inside [3]. Ion exchange resins have been increasingly used for the taste masking of bitter taste drugs. Ion exchange resins are synthetic inert organic polymers consist of hydrocarbon network to which ionizable groups are attached and they have the ability to exchange their labile ions for ions present in the solution with which they are in contact. Levocetrizine dihydrochloride is an orally active and R-enantiomer of cetrizine and is a third generation, nonsedating selective peripheral H1-receptor antagonist used in seasonal allergic rhinitis, perennial allergic rhinitis, and chronic urticaria [4].

Levocetrizine dihydrochloride is absorbed rapidly after oral administration and half-life is 8.3 hr which is appropriate for once a day formulation and provides rapid onset of action for fast relief. But it has a very unpleasant bitter taste requires taste masking [5].

MATERIALS AND METHODS

Materials

Levocitrazine Dihydrochloride, Kyron T 134, Micro Crystalline Cellulose, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Crospovidone, Magnesium Stearate, Talc Mannitol, Menthol Distilled water, Sorenson's buffer pH 6.8, Acetone, HCl, Chloroform, Ethanol, Ether, Methanol.

Methods:

Preparation of Drug Resin Complex by Batch Method

In this method the drug solution is agitated with a quantity of resin particles until equilibrium is established [6]. The resins were first washed with distilled Water till neutralization. 300 mg of resin was placed in a beaker containing 25 ml of deionised water and allowed to swell for 90 min. The pH of the resin solution was adjusted to 6.5 to 7.0 by using 1 M KOH solution than accurately weighed 100 mg of Levocetirizine dihydrochloride was added to the resin solution and stirred for 2-3 hours. During stirring, pH of the sample was checked frequently and adjusted to 6.5 to 7.0 by using 1 M KOH solution. Than the mixture was filtered through Whatman filter paper no. 41 and residue was washed with 75 ml of deionised water and put it for drying at 60 ^{0}C for 3-4 hours in oven.

Formulation of Mouth Dissolving Tablets by Direct Compression

Crosspovidone and SSG were selected as super disintegrates. Flavours, talc (glidant), magnesium Stearate (lubricant), Mannitol & microcrystalline cellulose were selected [6]. Superdisintegrants have excellent disintegrating ability to swell to a large extent when it come in contact with water to disintegrate and has a fibrous nature that allow intraparticulate as well as extra particulate wicking of water even at low concentration. Firstly, the DRC consist of drug-resin complex 20 mg was prepared. The DRC and other Excipients were transferred in RMG (rapid mix granulator) mixer and was mixed for 10 minutes (dry mix) purified water was added if required and for approx. 30 minutes was mixed (wet mix) granules were formed [7]. The wet granules were passed through multimill which was fitted with sieve no.10 and then the wet granules were collected in FBD (fluidized bed dryer) and dried for 5 minutes at temperature of 60^{o}C. The dried granules passed through sieve no. 40 and sizing was done through cad mill using screen of 1.0 mm at slow speed. All the ingredients were passed through sieve no. 40 and blending was performed through rotacube mixer. All the five batches were prepared by direct compression method using single punch machine [8]. The hardness of the tablet of each batch were tried to keep constant (2.4kg/cm^2). The weight of the tablet of each batch was adjusted to 135 mg.

The tablet was evaluated for its weight variation, friability, disintegration time**.** Dissolution study of tablets was carried out in simulated gastric fluid [9].

The trials taken in preparing formulation are shown in Table 1.

Table 1: Formulation of MDTs

Name of ingredients	Formulation code Quantity (in mg)				
	F1	F2	F3	F4	F5
Levocetrizine dihydrochloride	5	5	5	5	5
Kyrone T-134	15	15	15	15	15
Mannitol	72.85	72.85	72.35	72.85	73.35
Magnesium Stearate	2	2	2	2	2
Talcum	2.5	2.5	2.5	2.5	2.5
Colloidal Silicon Dioxide	1.2	1.2	1.2	1.2	1.2
Aspartame	2.5	2.5	2.5	2.5	2.5
Crosspovidone	3.5	4	4.5	5	5.5
Mcc Ph (102)	27	26	25	24	23
Sodium Starch Glycollate	2	2.5	3	3.5	4
Flv Orange Dry	0.8	0.8	0.8	0.8	0.8
Flv Vanilla Dry	0.1	0.1	0.1	0.1	0.1
Menthol	0.05	0.05	0.05	0.05	0.05
Sodium Chloride	0.5	0.5	0.5	0.5	0.5
Total	135	135	135	135	135

Formulation & optimization of drug resin complex

Drug resin concentration 1:3 ratio showed maximum drug loading **(Table 2).**

Table 2: Effect of resin concentration on % drug loading method (n=3)

Resin	Drug + Resin Ratio	% of Drug Loading (±S.D.)
Kyron T-134	1:1	79.15 ± 0.74
	1:2	86.37 ± 0.41
	1:3	**92.12 ± 0.70**
	1:4	91.09 ± 0.69

If further increase the resin concentration (1:4) leads to the saturation of complex formation therefore resin ratio (1:3) was selected as optimized batch.

Drug resin ratio 1:3 showed maximum drug loading at 60 minutes. If further increase the time, did not increase the loading efficiency therefore it was selected as optimized formulation **as** given in Table 3, Fig. 1.

Table 3: Effect of soaking time on % drug loading (n=3)

Resin	Ratio	Soaking Time (min)	% Drug loading(±S.D.)
Kyrone T-134	1:3	10	68.50 ± 0.151
		20	71.80 ± 0.553
		30	79.23 ± 0.118
		60	89.01 ± 0.07
		90	80.35 ± 0.915
		120	75.22 ± 0.534

Drug resin ratio 1:3 showed maximum drug loading at pH 4. It was observed that the drug resin ratio 1:3 have maximum ionization and solubility at pH 4 that's why pH 4 was selected as optimized pH as shown in Table 4.

Table 4: Effect of pH on % drug loading

Resin	Ratio	PH	% Drug loading
Kyrone T-134	01:03	5	61
		5.5	75
		6	82
		6.5	**98**
		7	80

Evaluation of various parameters

Among all the formulations batch F4 showed least disintegration time and wetting time and maximum water absorption ratio therefore batch F4 was selected as optimized batch Table 5.

Table 5: Evaluation parameters

Formulation (±S.D.)	F1	F2	F3	F4	F5
Thickness (mm)	2.9 ±0.00	2.9±0.01	2.9± 0.04	2.9± 0.03	2.9 ± 0.02
Hardness (kg/cm^2)	2.9 ± 0.119	2.6 ± 0.937	2.5 ± 0.856	2.4 ± 0.178	2.6 ± 0.763
Friability (%)	0.21 ± 0.511	0.27 ± 0.632	0.24 ± 0.705	0.18 ± 0.732	0.16 ±0.176
Weight Variation	passes	passes	passes	passes	passes
Disintegration time (sec)	37 ± 0.773	35 ± 0.752	30 ± 0.731	25 ± 0.765	42 ± 0.653
Wetting time (sec)	24 ± 0.579	23 ± 0.374	21 ± 0.552	20 ± 0.413	28 ± 0.118
Water absorption ratio (%)	75.15 ± 0.41	75.93 ± 0.70	78.47 ± 0.54	87.12 ± 0.76	75.10 ± 0.31
Uniformity of Drug content (%)	89.94 ± 0.85	95.11 ± 0.55	97.14 ± 0.70	98.97 ± 0.76	95.71 ± 0.39

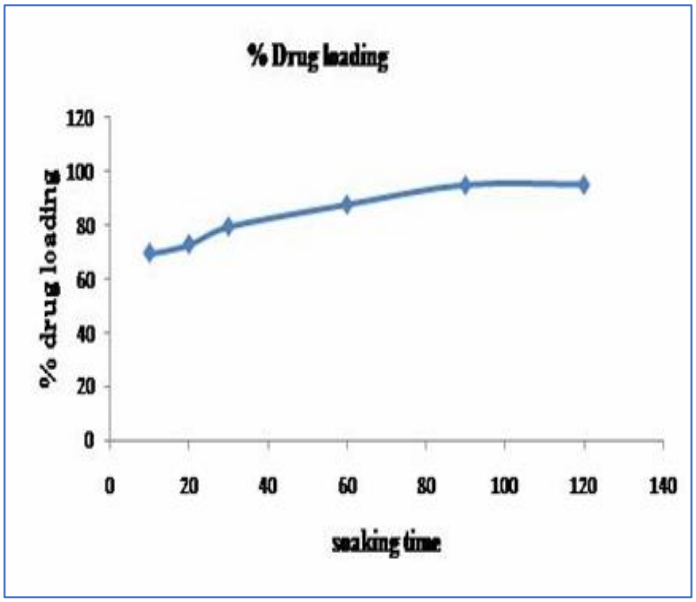

Fig. 1: Effect of soaking Time on % Drug loading

General Appearance

Tablets showed flat, circular shape after direct compression and white in color.

Thickness Test

The thickness of the tablet was measured by using vernier calliper by picking the tablets randomly. Thickness was found in the range from 2.9±0.00mmto 2.9± 0.04 mm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.

Hardness Test

Hardness test was performed by Monsanto Hardness tester. Hardness was found within2.4kg/cm2 to2.9kg/cm2, as the tablets are orodispersible. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The result of hardness for all the formulations are given in and the hardness of the optimized formulation (F4) was found to be 2.4 ± 0.178.

Friability Test

Percentage friability was found well within the approved range (<1%) in all the formulation. Results revealed that the tablets possess good mechanical strength. The result of friability for all the formulations aregiveninTable7and the friability of the optimized formulation (F4) was found to be 0.18 ± 0.732.

Weight Variation Test

All the tablets passed weight variation test as the % weight variation was within the pharmacopeia limits of ±7.5%.

Drug Content Uniformity

Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations was calculated. The % drug content for all the formulations were found between 89.94 ± 0.85 to 98.97 ± 0.76. The % drug content of the optimized formulation (F4) was found to be 98.97 ± 0.76.

Wetting Time

The wetting time in all the formulations was very fast. This may be due to ability of swelling and also capacity of absorption of water. SSG absorbs water rapidly in the formulations and shows fast wetting time. This parameter also duplicates disintegration time in oral cavity as tablet is kept motion less on tongue; hencecorrelationbetweenwettingtimeanddisintegrationtimeinoral cavitycanalso be made. The wetting time of the optimized formulation (F4) was found to be 20 ± 0.413.

Water Absorption Ratio

The ratio values of formulations found in the range of 75.10 ± 0.31 to 87.12 ± 0.76. In case of tablet containing SSG, caused great deal of swelling. In this as the quantity of SSG increased the water absorption so increased due to high swelling property. The water absorption ratio results for all the formulations are given in Table7and the water absorption ratio of the optimized formulation (F4) was found to be 87.12 ± 0.76.

In vitro Disintegration Time

All formulations showed disintegration time within 42 seconds. The DT decreases with increase in the level of SSG 2, 2.5, 3, 3.5, 4 % and Crosspovidone 3.5, 4, 4.5, 5, 5.5 % in the tablets but at concentration 4 and 5.5 DT of batch F5 decreases. Because at a higher level, formation of a viscous gel layer by SSG might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents.

It indicates that increase in the level of SSG had negative effect on the DT of tablets. Thus, tablets containing more than 4% SSG may be retarded the DT time. The results of disintegration time for all the formulations and the disintegration time of the optimized formulation (F4) was found to be 25 ± 0.765 Table 6, Fig. 2.

Table 6: *In vitro* dissolution data of five formulations

S. No.	Time (mins)	% CDR				
		F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	1	55.567 ± 0.323	56.322 ± 0.473	59.631 ± 0.704	60.115 ± 0.793	61.763 ± 0.993
3	2	65.965 ± 0.931	67.208 ± 0.734	70.131 ± 0.770	70.966 ± 0.543	69.611 ± 0.096
4	3	78.516 ± 0.605	80.365 ± 0.119	80.216 ± 0.742	82.742 ± 0.563	80.745 ± 0.631
5	4	81.330 ± 0.664	82.773 ± 0.867	85.117 ± 0.749	85.007± 1.587	86.752 ± 0.119
6	5	84.085 ±0.194	84.324 ± 0.650	88.472 ± 0.943	89.801 ± 0.332	88.733 ± 0.864
7	6	90.137 ± 0.421	92.333 ± 0.712	94.876 ± 0.417	95.519 ± 0.543	92.886± 0.385
8	7	92.395 ± 0.528	93.121 ± 0.488	95.186 ± 0.435	96.831 ± 0.507	93.408 ± 0.
9	8	93.581 ± 0.256	95.067 ± 0.579	97.993 ± 0.701	98.430 ± 0.365	94.865 ± 0.710
10	10	94.414 ± 0.791	96.743 ± 0.406	98.116 ± 0.862	99.732 ± 0.110	97.122 ± 0.830

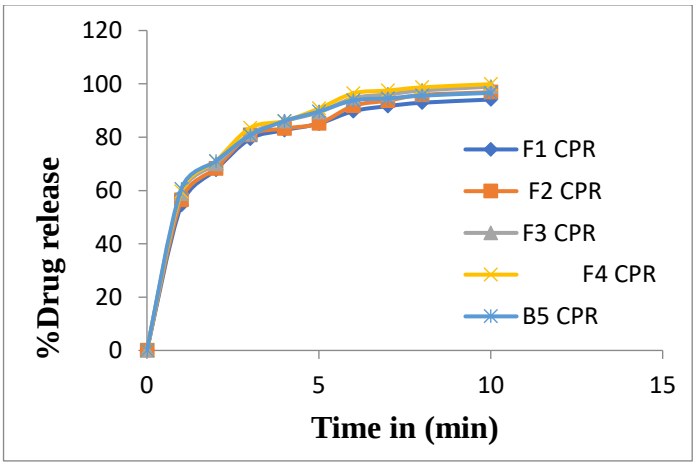

Fig. 2: *In vitro* drug release profile

Formulation F4 have the maximum *in-vitro* drug release in 10 minutes

The time intensity study for taste in human volunteers of the drug, DRC showed that the degree of bitterness ultimately reaching to +0 within 3 minutes which showed the palatability of the formulation concluding that the bitter taste of formulation has been successfully masked Table 7**.**

As the concentration of superdisintegrants increases the disintegration time decreases but at concentration 5.5 (crosspovidone) and 4(SSG) DT of batch F5 decreases Because at a higher level, formation of a viscous gel layer by SSG might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. It indicates that increase in the level of SSG had negative effect on the DT of tablets Table 8.

Table 7: Taste Evaluation

Formulation of Levocetirizine Dihydrochloride	Degree of Bitterness After Time			
	10 Sec	1 min	2 min	3 min
Pure drug	0.5	3	3	3
DRC	0	0	0.5	0.5
MDT	0+	0+	0+	0+

Table 8: Effect of Superdisintegrant on Disintegration Time

S. No.	Superdisintegrants		Disintegration time
	Crosspovidone	SSG	
1	3.5	2	37 ± 0.773
2	4	2.5	35 ± 0.752
3	4.5	3	30 ± 0.731
4	5	3.5	25 ± 0.765
5	5.5	4	42 ± 0.653

Stability studies

The stability studies of optimized formulation were carried out and it was concluded from the results that the formulation F4 was stable for 60 days Table 9.

Table 9: Stability study at Temperature (40°C ±2°C/75% RH ±5%)

S. No.	PARAMETERS	BATCH F_4		
		0 DAY	30 DAYS	60 DAYS
1	Physical appearance	No change	No change	No change
2	Weight gain (mg)	135	135.5	135.8
3	Hardness (Kg/cm^2)	2.4	2.5	2.5
4	% Drug content	98.97	98.15	97.12
5	DT (sec)	25	27	28
6	% Drug released (5 min)	90.801	89.27	88.771

Comparison with marketed product

Brand name: Livot-MD

Company name: Trumac Healthcare

Labelled claim: Each tablet contains 5 mg of Levocetrizine di HCl Table 10, Fig. 4.

SUMMARY

A recent advance in Novel Drug Delivery System aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is Orodispersible Tablet.

Table 10: *In-vitro* release data of the FDT batch F4 and marketed product

Time (min.)	% Drug release	
	F4	Marketed product (Livot-MD)
0	0	0
1	60.115±0.793	56.132 ± 0.341
2	70.966±0.543	65.741 ± 0.633
3	82.742±0.563	74.451 ± 0.847
4	85.007±1.587	81.043 ± 0.912
5	89.801±0.332	87.754 ± 0.482
6	95.519±0.543	92.110 ± 0.632
7	96.831±0.507	94.386 ± 0.002
8	98.430±0.365	96.913 ± 0.030
10	99.732±0.110	97.997 ± 0.022

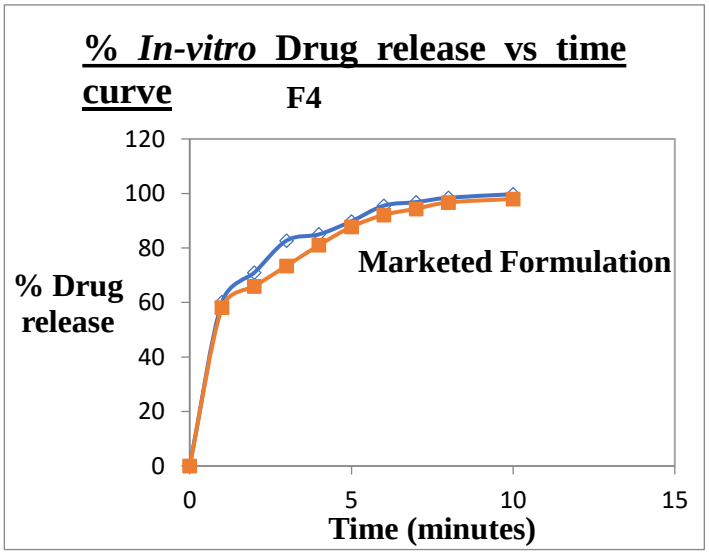

Fig. 3: Comparison of *In-vitro* drug release profile of Levocetrizine dil. HCl tablet formulation F4 with marketed product

Drug loading percentage of Levocetrizine dihydrochloride was established by using deionised water and was found to be 92.12%.

Effect of swelling time was determined in sample containing drug: resin ratio of 1:3, it was found that the drug loading percentage was highest at 120min i.e. 95.22%. Maximum drug loading 0f 98% was obtained at pH 6.5.

The Orodispersible tablets were formulated by direct compression method using different superdisintegrants namely Sodium starch Glycolate, Crosspovidone.

Prepared tablets were evaluated for shape, harness, thickness, friability, uniformity of weight, uniformity of content, wetting time, water absorption ration, disintegration time and in-vitro drug release.

Levocetrizine dihydrochloride orodispersible tablets formulated by using sodium starch glycolate as superdisintegrants, having hardness (2.4 ± 0.178 Kg/cm^2), Friability (0.18 ± 0.732%), Drug Content (4.798 ± 0.622 mg). and it is fulfilling all the parameters. It has shown good *in vitro* disintegration time (25 ± 0.765 sec) compared to other superdisintegrants.

All the five formulations, the disintegration time for all the formulations was less than 42 sec, wetting time was found less than 28 seconds. This indicates rapid disintegration. Water absorption ratio showed good absorptivity in all formulations. Hardness and friability of all the formulations indicated tablets were mechanically stable and percentage weight variation and drug content uniformity found within limits. *In vitro* release for all the formulations was within 10 min.

Stability studies were conducted for formulations F4 at 40ºC ±2ºC/75% RH ±5% for 60 days. Various parameters like hardness, friability, drug content uniformity, in *vitro* disintegration, wetting time were analyzed at a time interval of 30 days till a period of 60 days. Not much variation or change was observed in any parameters throughout the study period. Best-selected formulations F4 found to be stable. The prepared orodispersible tablets disintegrate in seconds without need of water and enhance the absorption; this leads to increase in the bioavailability of Levocetrizine dihydrochloride.

CONCLUSION

In the present study, Levocetrizine dihydrochloride mouth dissolving tablets has been successfully prepared. They were taste masked by using kyron T-134. The MDT formulations of Levocetrizine illustrated all parameters within limit as well as good physicochemical properties. Drug release rate of formulated MDTs was also found to be enhanced as compared to conventional tablet. Kyron T- 134 (15mg) Batch F4 having hardness (2.4 kg/cm^2), friability (0.18%), wetting time (20 sec), thickness (2.9%) and disintegration time (25 sec).

Hence, tablets formulated with Kyron T- 134 not only increases rate of dispersion but also increases rate of drug release.

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