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Optimization, Formulation and *In-Vitro* Evaluation of Mouth Dissolving Tablets of Levocetrizine Hydrochloride for the Treatment of Allergic Rhinitis

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Abstract:
New era is an era of novel drug delivery systems. Pediatric, Geriatric and bed ridden patients have difficulties in swallowing tablets. The purpose of the present study was to develop and characterize mouth dissolving tablets of Levocetrizine Hydrochloride by using direct compression technique. Formulations were designed by factorial design technique. Sodium starch glycolate, Crospovidone and Croscarmellose sodium were used as a superdisintegrants while microcrystalline cellulose was used as diluents. The powder blends were prepared and evaluated for the properties such as angle of repose, loose bulk density, tapped bulk density, carr's compressibility index and hausner's ratio. Tablets were evaluated for hardness, friability, drug content, disintegration time, water absorption ratio, *in vitro* drug release in 0.1N HCl. Formulation containing Crospovidone and Croscarmellose sodium in higher concentration showed a rapid disintegration, wetting and *in vitro* drug release as compared to other formulations. Differential scanning calorimetric studies indicated no possibility of interaction between Levocetrizine Hydrochloride and superdisintegrants used in formulation. The optimized formulation showed no change in physical appearance, drug content, disintegration time and dissolution pattern after storage at 40^{o}C/75% RH for three months.
Keywords: *Direct compression; Factorial design; Levocetrizine Hydrochloride; Mouth dissolving tablets.*

Introduction:

Mouth dissolving tablets are synonymous with fast dissolving tablets, Melt in mouth tablets, Rapi-melts, Quick dissolving tablets, Rapidly disintegrating tablets, Porous tablets, Oro-dispersible tablets and Fast disintegrating tablets. Their characteristics benefits in terms of patient compliance, rapid onset of action, increased bioavailability (sometimes bi-pass first pass effect) and good stability make these tablets popular as a dosage form of choice. [1]

Patient often experience inconvenience in swallowing conventional tablets when water is not available. Furthermore, patients who have swallowing problems encounter difficulties in taking tablets, particularly pediatric and geriatric patients. Such problems can be resolved by means of mouth dissolving tablets. This tablet disintegrates instantaneously when put on tongue, releasing the drug, which dissolves or disperses in saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down in the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional dosage form. [2]

Levocetrizine Hydrochloride is levo active form of Cetrizine Hydrochloride which is a racemic mixture. Levocetrizine Hydrochloride is second generation piperazine derivative, potent H_1 selective antihistaminic or antiallergic agent with fewer side effects. [3]

In case of allergic or histaminic reaction a rapid action of the drug is required. Here an attempt had been made to prepare a mouth dissolving tablets of Levocetrizine Hydrochloride which will disintegrate rapidly when kept on tongue, releasing the drug, which dissolves in saliva and absorbed instantly giving an immediate action which is desired in allergic conditions.

The main criteria for mouth disintegrating tablets is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 seconds to 60 seconds without need of water and should have pleasant mouth feel. The disintegrants used should fulfill the criteria by disintegrating he tablets in specified limit time. [4]

Materials and Methods:

Materials

Levocetrizine Hydrochloride was received as a gift sample from Tristar Pharmaceuticals Private Limited (Puducherry, India). Sodium starch

glycolate, Crospovidone, Croscarmellose sodium and Microcrystalline cellulose pH 102 were received as a gift samples from Cipla Laboratories (Mumbai, India). All other ingredients were procured from Loba chemie (Mumbai, India).

Preparation of tablets

Various formulation batches were prepared according to formula shown in table 1. Levocetrizine Hydrochloride was used with SSG, CP and CCS to formulate the Mouth Dissolving Tablet. All the ingredients with drug except Magnesium stearate were taken in the mortar. The powder blend was then mixed well by using mortar and pestle for 15 to 30 minutes, and then each mixture was passed through # 80 sieve. Finally Magnesium stearate was added as a lubricant and mixed thoroughly. The powder blend was compressed using 16 stations tablet compression machine (Cadmach JMD-4-8, Ahemdabad, India) to produce flat faced tablets weighing 200 mg having diameter of 8 mm.

Evaluation of granules

The prepared granules were evaluated for angle of repose, bulk density (BD), tapped bulk density (TBD), compressibility index and hausner's ratio. [5, 6]

Evaluation of tablets

Thickness

The thickness of the tablets was determined using a Vernier caliper. [7]

Hardness

Monsanto hardness tester was used to measure hardness of tablets. The tablet was held along its oblong axis in between the two jaws of the tester and the constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted as the hardness of the tablets. [7]

Friability

This test is carried out by using Roche friabilator. A sample of pre-weighed tablets was placed in plastic chamber of friabilator which revolves at a speed of 25 rpm for four minutes (100 revolutions), dropping the tablets to a distance of 6 inches in each revolution. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as follows,

% Friability = (Initial weight - Final weight / Initial weight) x 100. [8]

Content Uniformity

The amount of the active content can be determined by taking 10 tablets, they are weighed and powdered. Quantity of powder equivalent to 2.5 mg of Levocetrizine Hydrochloride was weighed accurately into a 100 ml volumetric flask and dissolved in 0.1N HCl. The solution was diluted to volume with 0.1N HCl, mixed and filtered. 2 ml of filtrate was diluted up to 10 ml 0.1N HCl, mixed and absorbance was measured at 229.5nm using double beam UV-Visible spectrophotometer (Shimadzu 1700). [8]

In vitro disintegration test

One tablet is introduced in to one tube of USP disintegration test apparatus and a disc is added into the tube. The assembly is suspended in the beaker containing distilled water and the apparatus is operated until the tablet disintegrated and the time required to disintegrate tablet was measured. [8]

Wetting time

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet of known weight was put on the paper and the time required for complete wetting of tablet was measured. [9]

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet of known weight was put on the paper and the time required for complete wetting of tablet was measured. The wetted tablet was then weighed, water absorption ratio R was determined using the following equation. [9]

$$R = \frac{W_a - W_b}{W_a} \times 100$$

Table 1: Composition of Various Mouth Dissolving Tablet Formulations

Sl. No.	Ingredients (mg/tablet)	Formulations											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Levocetrizine Hydrochloride	5	5	5	5	5	5	5	5	5	5	5	5
2	Sodium Starch Glycolate	16	16	4	4	16	16	4	4	---	---	---	---
3	Crospovidone.	10	4	10	4	---	---	---	---	10	10	4	4
4	Cross carramellose sodium	---	---	---	---	6	2	6	2	6	2	6	2
5	Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
6	Aerosil	2	2	2	2	2	2	2	2	2	2	2	2
7	Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
8	Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
9	Flavour(orange)	4	4	4	4	4	4	4	4	4	4	4	4
10	Microcrystalline cellulose	132	138	144	150	136	140	152	152	142	146	148	152

Where W_b is weight of tablet before water absorption and W_a is weight of tablet after water absorption. [9]

Test for Dispersion

Place 2 tablets in 100ml of water and stir gently until completely dispersed. A smooth dispersion is obtained which passes through a sieve screen with a nominal mesh appearance of 710mm (sieve No.22). [9]

In-vitro dissolution studies

The dissolution rate of Levocetrizine Hydrochloride from the tablets was studied in 0.1 N hydrochloric acid using USP XXIII dissolution test apparatus employing paddle stirrer. In this one tablet containing 5 mg of Levocetrizine Hydrochloride, a speed of 100 rpm and a temperature 37° ± 1°C was employed. A 10ml of aliquot of dissolution medium was withdrawn at different time intervals, filtered and assayed for Levocetrizine Hydrochloride content spectrophotometrically at 229.5 nm. [9, 10]

Compatability studies (Differential Scanning Calorimetry)

In drug formulation it is essential to evaluate the possible interactions between the active principle and the superdisintegrants. Levocetrizine Hydrochloride powder was mixed with various superdisintegrants in the ratio of 1:1 and the resulting physical mixture was examined on differential scanning calorimeter. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 10^0C/minute). Thermogram of pure drug was used as a reference. [11]

Stability studies

Stability studies were carried out at 40°C / 75% RH as per ICH guidelines for the optimized formulation for 3 months.

Table 2: Micromeritic Properties of Powder Blend

Formulations Code	Angle of Repose (^{O})	LBD (gm/ml)	TBD (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	21.17±0.222	0.62±0.0005	0.716±0.001	12.418±0.010	1.14 ± 0.001
F2	20.54±0.496	0.63±0.001	0.730±0.001	12.693±0.064	1.14 ± 0.001
F3	21.19±0.581	0.62±0.001	0.717±0.001	12.446±0.058	1.14±0.001
F4	22.11±0.207	0.62± 0.001	0.730±0.0007	14.057±0.074	1.16±0.002
F5	21.17±0.109	0.63±0.0005	0.729±0.0005	12.653±0.074	1.14±0.0001
F6	20.82±0.117	0.62±0.0005	0.717±0.0007	12.546±0.010	1.14±0.001
F7	20.29±0.222	0.62±0.0005	0.730±0.0007	14.102±0.010	1.16±0.0005
F8	21.39±0.473	0.63±0.001	0.730±0.001	12.602±0.225	1.14±0.0005
F9	20.59±0.502	0.63±0.001	0.729±0.0005	12.653±0.074	1.14±0.0005
F10	20.76±0.782	0.63±0.001	0.730 ±0.001	12.699±0.020	1.14±0.0005
F11	21.11±0.543	0.62±0.0005	0.717± 0.005	12.546±0.010	1.14±0.0005
F12	21.00±0.473	0.62±0.001	0.730±0.0005	14.057±0.085	1.16±0.001

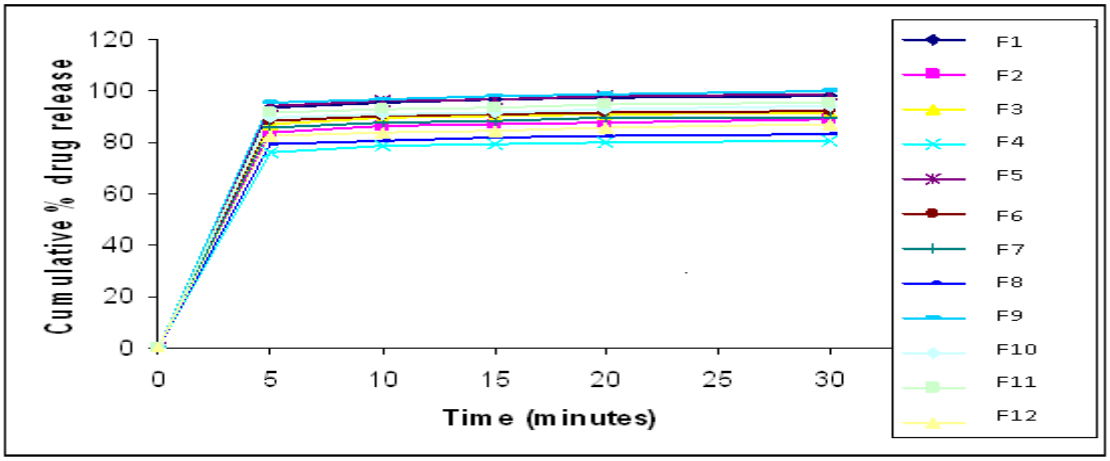


Figure 1: Cumulative % drug release from formulation F1 – F12

Table 3: Physico-chemical properties of Mouth dissolving tablets

Code	Thickness** (mm)	Hardness** (kg/cm^2)	Friability* (%)	Drug Content* (%)	Disintegration time* (minutes)	Wetting time* (minutes)	Water absorption ratio*
F1	2.493±0.02	3.25±0.27	0.249±0.07	100.38 ±0.39	20±1.5275	25±1.52	114.0±0.60
F2	2.480± 0.02	3.83±0.25	0.309±0.07	99.93 ±0.42	22±1.5275	27±1.73	105.90±0.91
F3	2.483±0.01	3.25±0.27	0.361±0.04	98.66 ±0.41	24±1.5275	32±2.00	101.48±0.49
F4	2.476±0.01	3.33±0.25	0.391±0.04	99.19±0.45	34±1.3416	39±2.00	92.74±0.91
F5	2.456±0.01	3.75±0.27	0.384±0.13	100.76±0.42	27±1.000	33±1.52	102.50±0.03
F6	2.446±0.01	3.66±0.25	0.391±0.04	99.48 ±0.37	35±1.5275	42±1.73	97.40±0.26
F7	2.446±0.01	3.25±0.27	0.348±0.14	100.15±0.81	40±1.5275	48±1.52	96.07±0.86
F8	2.443±0.01	3.33±0.25	0.233±0.03	98.68±0.87	52±1.5275	65±1.52	90.93±0.13
F9	2.453±0.01	3.75±0.27	0.323±0.05	100.24±0.38	12±1.1547	16±1.52	124.83±0.31
F10	2.446±0.01	3.66±0.25	0.354±0.07	99.47±0.55	16±1.5275	24±1.52	116.10±1.23
F11	2.450±0.01	3.83±0.25	0.346±0.01	100.61±0.43	24±1.5275	29±1.52	112.05±1.54
F12	2.453±0.01	3.33±0.25	0.35±0.07	99.29 ±0.44	31±1.5275	38±1.52	104.56±1.03

*All the values are expressed as a mean ± SD., n = 3; **All the values are expressed as a mean ± SD., n = 6
All the values are expressed as a mean ± SD., n = 3

The tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 months and 3 months. The samples were analyzed for its hardness, disintegration time, drug content and *in-vitro* drug release. [12]

Results and Discussion:

Twelve formulations were designed, using higher and lower level of superdisintegrants and employing combination of two superdisintegrants at a time (Table 1)

For each designed formulation, blend of drug and excipients was prepared and evaluated; the results were shown in Table 2. Angle of repose was found in the range of 20.298±0.222^{o} to 22.11±0.207^{o} which indicates good flow of the powder for all formulations, bulk density was found between 0.627±0.0005gm/ml to 0.637±0.0005gm/ml and tapped density between 0.717±0.001gm/ml to 0.730±0.0005gm/ml for all the formulations. The Carr's index was found to be in the range of 12.418±0.010 to 14.102±0.0.010 and Hausners ratio was found in the range of 1.14±0.0005% to 1.16±0.002% indicating good flow properties of powder blend.

Tablets were evaluated for different parameters. The results were shown in Table 3. The thickness of tablet was found between 2.443±0.015mm to 2.493±0.024mm.

Table 4: Cumulative % drug release from formulation F1 – F12

Code	Cumulative % drug release
F1	98.222±0.41
F2	88.717±0.44
F3	91.858±0.33
F4	80.472±0.27
F5	98.828±0.21
F6	92.356±0.44
F7	89.991±0.48
F8	83.500±0.42
F9	99.716±0.19
F10	94.152±0.38
F11	95.276±0.29
F12	86.958±0.42

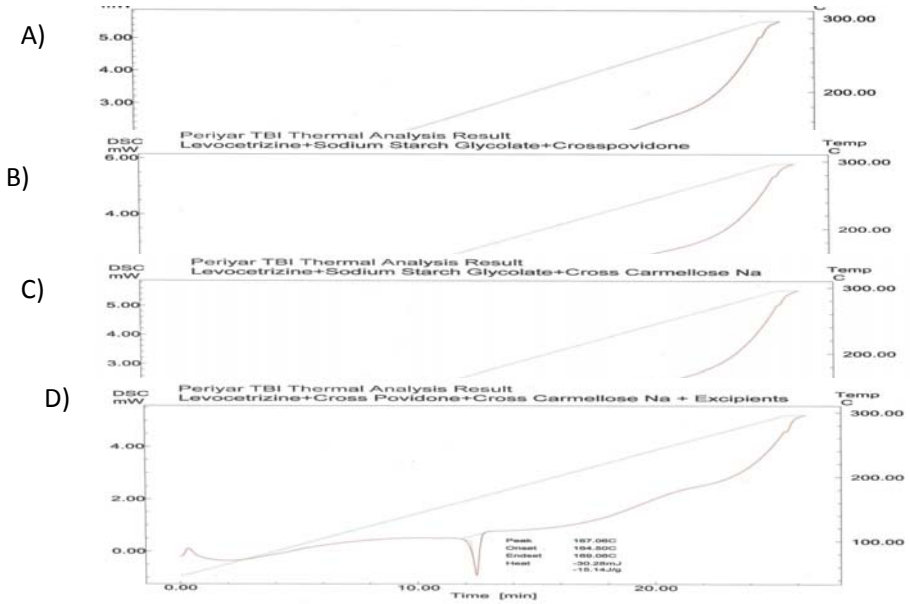
*All the values are expressed as a mean ± SD., n = 3

Table 5: Stability studies of optimized formulation

Formulation F9	Parameters			
	Hardness (kg/cm^2)	Disintegration time (minutes)	% drug content	% Drug release
Before stability	3.75±0.273	12±1.1547	100.2±0.385	99.716±0.19
After stability	3.25±0.2738	20.33±1.056	100.22±0.072	98.250±0.17

*All the values are expressed as a mean ± SD., n = 3

Figure 2: Thermogram of A. Levocetrizine Hydrochloride, B. Levocetrizine Hydrochloride + SSG+ CP, C. Levocetrizine Hydrochloride + SSG+ CCS, D. Levocetrizine Hydrochloride + CP + CCS



Hardness of the tablet for each formulation was 3.25±0.273kg/cm^2 to 3.83±0.258 kg/cm^2. The percent friability of all formulations was ranged from 0.233±0.032% to 0.391±0.042%. Drug content was found to be uniform for all formulations and ranged from 98.66±0.410% to 100.76±0.428%.

The most important parameter that needs to be optimized in the development of mouth dissolving tablets is the disintegration time of the tablets. In the present study all the tablets were disintegrated in <53 seconds. From the results it can be observed that the disintegration time of tablets increases as the concentration of the superdisintegrant decreases. The disintegration times of Crospovidone + Croscarmellose sodium containing tablets are comparatively higher than the other batches of formulation with corresponding concentrations of superdisintgrants.

Since the dissolution process of tablets depends upon the wetting followed by disintegration of the tablets, the measurement of wetting time may be used as another confirmative test for the evaluation of mouth dissolving tablets. There exists a direct correlation between the concentrations of superdisintegrants used in formulation with the wetting time of the tablets. The water absorption ratio was found to be in between 92.74±0.915 to 124.83±0.311.

A smooth dispersion for all the formulations was obtained, which when passed through sieve No. 22, no particles were remained on sieve indicates all the formulation passes the test for dispersion.

In vitro dissolution studies of all the formulations of Levocetrizine Hydrochloride were carried out in 0.1 N HCl. Percentage drug release was calculated at 5, 10, 15, 20 and 30 minutes.The results of *in vitro* dissolution studies of all formulations were shown in Figure 1. The variation in drug release was due to different types of superdisintegrants in different concentrations in all the formulations.

Dissolution study revealed that the almost all the drug released within the 5 minutes from all the formulations.

From the dissolution data it can be observed that Formulation F9 containing CP and CCS

showed the highest percentage of drug release (99.71%). This may be due to the higher concentration of superdisintegrants used in the formulation.

The formulation batches containing Crospovidone + Croscarmellose sodium showed comparatively higher drug release than the other batches of formulation with corresponding concentrations of superdisintgrants.

The results of DSC studies are given in figure 2. Pure Levocetrizine Hydrochloride showed sharp endotherm at 163.07°C. There was no appreciable change in the melting endotherms of Levocetrizine Hydrochloride with Sodium starch glycolate, Levocetrizine Hydrochloride with Crospovidone and Levocetrizine Hydrochloride with Crosscarmellose sodium as compared to the thermogram of Levocetrizine Hydrochloride. It was observed that there were no interaction between drug and superdisintegrants used in the formulations.

There is no significant change in the percentage drug release, disintegration time, hardness and percentage drug content were observed at the end of three months of stability studies. So, it can be said that the formulation F9 is stable for short term storage conditions.

Conclusion:

In the present study Mouth Dissolving Tablets of Levocetrizine Hydrochloride were prepared by using different superdisintegrants as Sodium starch glycolate, Crospovidone and croscarmellose sodium in different concentrations. Twelve formulations were designed, using higher and lower level of superdisintegrants and employing combination of two superdisintegrants at a time. Sodium starch glycolate, Crospovidone and Crosscarmellose sodium were used as a superdisintegrants. From DSC studies it was concluded that there was no interaction between drug and superdisintegrants used in formulations. The total drug from all the batches was found to be released completely with in the first 5 minutes of the dissolution studies.

Formulation F9 shows the highest % drug release and also the wetting time and disintegration time were found to be least with formulation F9. So the formulation F9 was selected as the optimized formulation. The stability studies revealed that the formulation F9 was stable for short term stability studies.

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