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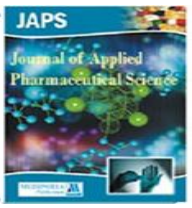

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Levocetirizine orodispersible tablet by direct compression method

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ABSTRACT

Orodispersible tablets are those that dissolve or disintegrate quickly in the oral cavity, resulting in solution or suspension. Allergic rhinitis is a high-prevalence chronic respiratory disease with a negative impact on the subject's quality of life, work activities, productivity or school performance as well as on healthcare costs. Because of its benign nature, the importance of this condition is often underestimated. In the present study orodispersible tablet of antihistaminic agent was prepared by direct compression method using crosspovidone, Crosscarmellose and Indion 414, as superdisintegrants. FT-IR study shows that there is no significant interactions occur between drug and excipient. The tablets prepared were evaluated for various parameters like various density parameters, thickness, hardness, friability, disintegration time, wetting time and In-vitro dissolution time. All the parameters were found to be within limits. The developed formulation of levocetirizine batch F8 (10% Indion 414) showed good palatability and dispersed within 30 seconds as compare to crosscarmellose sodium and crosspovidone. When the results were compared with that of convectional tablets was found to be better with respect to simple manufacturing and allergic rhinitis.

Key words: Orodispersible tablet, antihistaminic agents, superdisintegrants, allergic rhinitis.

INTRODUCTION

While the term "rhinitis" suggests that inflammation of the upper airway would be a cardinal feature, some forms of rhinitis do not involve inflammation. Rather, the term refers to the presence of one or more of the following: Nasal congestion. Pruritus. Sneezing. Anterior or posterior rhinorrhea. Causes of rhinitis are divided most broadly into allergic and non allergic (**Table 1**). This allergic reaction is typically divided into a 2-phase response: an early phase and a late phase. The early phase of Allergic rhinitis occurs within minutes of allergen exposure and is characterized by sneezing, pruritus, rhinorrhea, and nasal congestion. It is produced by activation of tissue mast cells sensitized by IgE antibodies(Nettis et.al, 2009)

These are the traditional drugs of choice for AR and are still considered first-line therapy for mild disease. Antihistamines may be given alone or in combination with intranasal corticosteroids, and they control symptoms of sneezing, nasal itching, rhinorrhea, and conjunctival itching and redness (Valet et.al, 2009). However, antihistamines are generally not fully adequate for treatment of nasal congestion, although some of the newer agents do have decongestant effects. A number of first-generation and second-generation agents are available, in oral and topical form (**Table 2**) (Tinana et.al, 2009). Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of

Table No. 1: Classification of rhinitis

Type	Subtype	Characteristics
Allergic rhinitis	Seasonal, perennial or episodic	IgE to specific allergens produced; when allergen detected by Mast cells, cytokine mediators of allergic symptoms released
Non allergic rhinitis	Vasomotor	Triggered by irritants (perfumes, chlorine, cold air, excercise)
	infections	Consider chronic sinusitis as the cause or as a complicating factor in refractory rhinitis (obtain sinus CT scan)
	Hormonally induced	Non allergies rhinitis in association with pregnancy or the menstrual cycle
	Gustatory	Profuse rhinorrhoe associated with eating
	Granulomotous	Seen in granulomatous disorders such as Wegener granulomatosis, sarcoidosis, medline granuloma and granulomatous infections
	Drug induced	Causative agents include phosphadiesterase inhibitors, oral contraceptives, antihypertensives, aspirin, NSAIDs and intranasal decongestants (rhinitis medicamentosa)
Occupational rhinitis		Can be allergic (exposure to a protein causing allergy in the workplace) or non allergic (e.g irritant)
Mixed rhinitis		Has both IgE mediated and non allergic triggers

Table No. 2: Selective antihistamines regimens

Antihistamines	Usual Adult Dosage
First-generation antihistamine	
Brompheniramine	8 – 12 mg q12h
Chlorpheniramine	4 mg q6 h
Clemastine	1.34 – 2.68 mg q8 - 12h
Diphenhydramine	25 – 50 mg q6 - 8h
Hydroxyzine	25 mg q6 – 8h
Second generation antihistamines	
Cetirizine	10 mg qd
Loratadine	10 mg qd
Fexofenadine	60 mg bid or 180 mg qd
Desloratadine	5 mg qd
Levocetirizine	5 mg qd
Intranasal second generation antihistamines	
Azelastine	2 sprays in each nostril bid
Olopatadine	2 sprays in each nostril bid

this dosage forms for some patients, is the difficulty to swallow. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets (ODTs) are not only indicated for people who have swallowing difficulties, but also are ideal for active people(Chandira et.al, 2009). Orodispersible tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach (Bhandari et.al, 2008). The basic approach in development of ODT is the use of superdisintegrants like cross linked carboxymethyl cellulose (crosscarmellose), Indion 414, crosspovidone etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva (Bhaskaran et.al, 2002).

Levocetirizine, the active isomer of its parent compound, cetirizine, is one of the newest second-generation antihistamines. After only 1 dose, it has been found to suppress the cutaneous allergic response to a significantly greater extent than similar drugs in its class. In addition, levocetirizine is effective in the treatment of nasal congestion.

Mechanism of action

Levocetirizine, the active enantiomer of cetirizine, is anti-histamine; its principal effects are mediated via selective inhibition of H1 receptors.

Uses

Allergic Rhinitis: Levocetirizine is used for the relief from symptoms associated with allergic rhinitis (seasonal and perennial) in adults and children 6 years of age and older.

Chronic Idiopathic Urticaria: Levocetirizine is used for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older (I.P, 2007).

MATERIALS AND METHODS

Materials

Levocetirizine diHcl was procured from Plethico Pharmaceuticals Ltd., Indore as gift sample. Cross carmellose sodium collected from Plethico Pharmaceuticals Ltd., Indore as gift sample. Crospovidone collected from Glenmark, Pune as gift sample. Indion 414 collected from Ion Exchange Pvt. Ltd., Pune as gift sample. Hydrophilic fumed silica, MCC collected as gift sample. Mint flavor was procured from Givaudan (India) Pvt. Ltd. Bangalore as gift sample. Talc and Magnesium stearate brought from SD fine, Mumbai. Materials and Excipients used in preparing tablet were of IP grades.

Selection of Excipients

Excipients are critical to the design of any drug delivery system and play a major role in determining its quality and performance. The following excipients were selected for the formulation of Orodispersible tablets.

Diluents

Tablet prepared using insoluble nature of crystalline cellulose were found to have a gritty mouth feel. To overcome this problem we attempted the use of water-soluble diluents mannitol but the tablet prepared with mannitol often tends to dissolve rather than disintegrate. Thus, novel diluents, a combination of mannitol and microcrystalline cellulose (102) in the ratio of 70:30 were employed in the study (Serasiya et.al, 2009).

Disintegrants

Short disintegration time with good dispersibility is the most important characteristics of an orodispersible tablets. The necessity of an orodispersible tablet is to disintegrate within

seconds, in limited amount of the water available in the form of saliva. This demands the use of special type of disintegrants called as "Superdisintegrants" (Mohanchandran et.al, 2010). In the present study, crosscarmellose sodium, crosspovidone, Indion 414 was used as superdisintegrants (Ashok Kumar et.al, 2009).

Flavoring agent

Mint flavor are intended as flavoring agent and to accelerate the mouth feel of tablet imparting their cooling sensation.

Lubricants/Glidants

Lubricants are intended to reduce the friction during compression and ejection of tablets. In the present study, magnesium stearate and talc were used as lubricants/glidants.

Selection of Tabletting Methodology

While selecting the tablet methodology, compressible characteristics of the drug are to be considered. Direct compression technique offers various advantages to the pharmaceutical formulation in terms of:

- Economy, because less number of processing step, persons and time is required.
- Stability, because product is not required to expose to moisture and heat.
- Performance, since tablets will directly disintegrate gives higher dissolution.

In the present study, the direct compression technique was employed to prepare Orodispersible tablets.

Preparation Of Orodispersible Tablet

Levocetirizine dihydrochloride (5 mg), superdisintegrants in different ratios (Table 3) and excipients were blended using mortar and pestle (Bhavanam et.al, 2010). The drug and the superdisintegrants were sieved through mesh # 120 before blending. The mixture was evaluated for angle of repose, bulk density and compressibility. The mixture was mixed with 1% magnesium stearate as lubricant and saccharine sodium as sweetening agent. The granules were then compressed by using Fluidpack multistation rotary tablet machine using 8 mm punch. The hardness was adjusted to 2-5 kg/cm^2.

Table No. 3 Formulation of orodispersible tablets

Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levocetrizine diHCl	5	5	5	5	5	5	5	5	5
MCC (PH-102)	30	30	30	30	30	30	30	30	30
Crosscarmellose sod.	7	14	21	-	-	-	-	-	-
Crosspovidone	-	-	-	7	14	21	-	-	-
Indion 414	-	-	-	-	-	-	7	14	21
Hydrophilic fumed silica	1	1	1	1	1	1	-	-	-
Pearlitol SD200	97	90	83	97	90	83	97	90	83
Mint flavor (DC 114)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talcum powder	1%	1%	1%	1%	1%	1%	1%	1%	1%
Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%

Procedure for evaluation of tablet

The tablets were compressed using 8 mm diameter, round, biconcave punches on a Fluidpack multistation rotary tablet machine. The tablet weight was kept 140 mg and hardness between 2 – 5 kg / cm^2. Other parameters like size, thickness, shape, hardness, friability, weight variation, wetting time were carried out (Sunada et.al, 2002).

Taste and Colour

The tablets of prepared formulations were observed for taste and colour. Taste was observed by placing the tablets over the tongue until disintegration occurs. Colour was observed by keeping the tablets in the light.

Thickness and Shape

Size (diameter) and thickness was measured using Dial Vernier Caliper.

Hardness

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacturing, packing and shipping.

Friability

Tablets were tested for friability using Electrolab (E2) Friabilator. This is important to know the mechanical strength of the tablet while handling.

$$\frac{(\text{Initial weight} - \text{Final Weight})}{\text{Initial Weight}} \times 100$$

Weight Variation

Weight variation was determined to know whether different batches of tablets have uniformity.

Wetting time

This is carried out to measure the time, which is required for the complete wetting of tablet formulations. A piece of tissue paper folded twice was placed in small Petri dish containing 6 ml of water. A tablet was placed on the paper. When water completely wets the tablet, the time was noted.

In-vitro Disintegration test

I) Wire Basket Type Disintegration Apparatus

In-vitro disintegration time for FDT was determined using USP and modified disintegration apparatus with simulated saliva fluid (pH 6.2-6.8) as the disintegrating medium. Briefly, the apparatus (**Fig 1**).

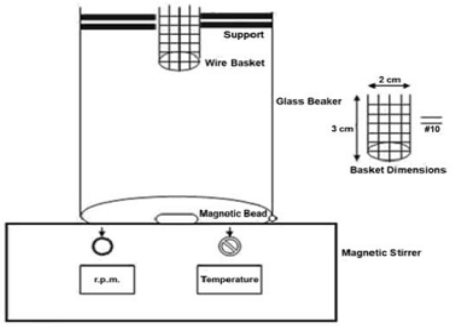

Fig. 1 Wire basket type disintegration apparatus.

Consisted of a glass beaker of 1000 ml capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 ml of disintegrating medium, the basket had only 6 ml of it. A magnetic bead was placed at the bottom of the beaker maintained at 37 ± 2^0C (Sharma et.al, 2009).

II) Petri-Dish Method for Disintegration Test

The disintegration time was measured using a petridish disintegration method. For this purpose, a petridish having a diameter of 10 cm was filled with 10 ml of water or simulated saliva fluid. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine particles was noted (Sharma et.al, 2009).

Drug content

Ten tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 5 mg of Levocetirizine dihydrochloride taken into 50 ml volumetric flask. The amount of drug present in a 5 mg equivalent amount of powder was determined by, dissolving the powder mixture in 10 ml of methanol and suitably diluted with methanol and UV absorbance was measured at 231.5 nm. Drug concentration was determined from standard graph (Shende et.al, 2010).

In vitro dissolution studies

The *In- vitro* dissolution study of the prepared formulations was carried out in USP dissolution test apparatus type 2 (paddle). Release was compared with that of marketed conventional tablet.

Dissolution medium: 900 ml of (pH 6.8 buffer)
Temperature : 37 ± 0.5° C
RPM : 50
Volume withdrawn was 5 ml after 1 minute (Subramanian et.al, 2010).

RESULT AND DISCUSSION

FT-IR studies

The prominent peaks of levocetirizine was observed (Fig 3) at a peak of 3289.12 cm^{-1} due to the N-H stretching, a peak at 2916.7 cm^{-1} due to C-H stretching, a peak at 1650 cm^{-1} observed due to the carbonyl group and a peak at 1458.4 due to ether group. At the lower frequencies 1315.6 (C-N stretching), 1082.2 cm^{-1} (C-O stretching) observed.

When correlated with physical mixture of drug and excipients (Fig 4) the region of 3395.1 cm^{-1} due to the N-H (aromatic) stretching. However other peaks related to C-H, C-O, C-N and ether group stretching remain unchanged (Table No. 5). This indicates that overall symmetry of the molecule might not be significantly changed therefore the FT-IR study revealed that there is no interactions taking place between levocetirizine and excipients.

Standard calibration curve of levocetirizine

Levocetirizine was found to be soluble in organic solvents such as methanol. A simple reproducible method of estimation was carried out in methanol ranging from 4-40 mcg/ml solutions at 231.5 nm against the blank. The standard graph obtained was linear, with regression coefficient 0.994. (Fig 2).

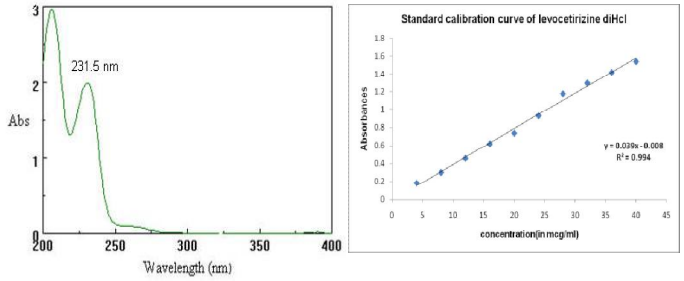

Fig 2 UV spectrum of Levocetirizine.

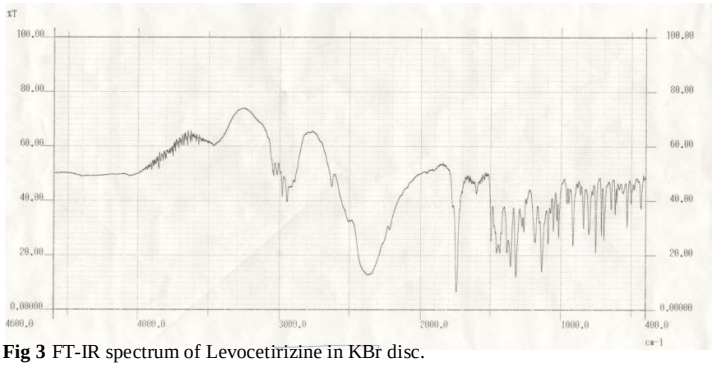

Fig 3 FT-IR spectrum of Levocetirizine in KBr disc.

Fig 4 FT-IR spectrum of Levocetirizine Orodispersible tablets in KBr dics.

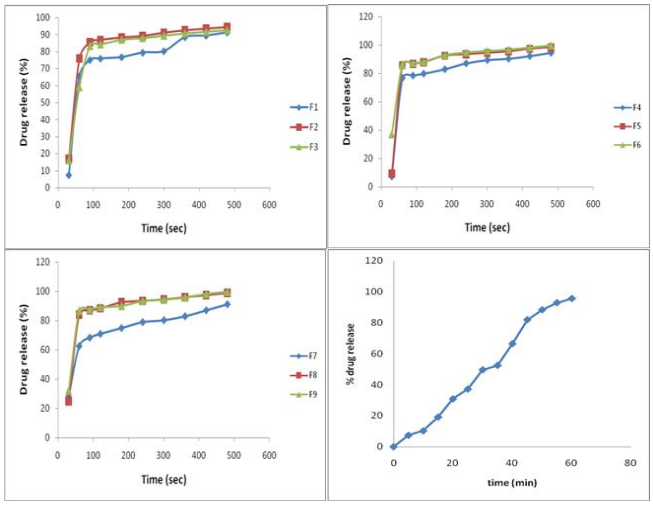

Fig 5 Comparative study of % Drug release (Batch F1- F9 and Marketed tablet).

Formulation of tablets and physical evaluation of tablets

Spray dried Levocetirizine was taken to formulate the Orodispersible tablet so as to disintegrate with in the mouth of the patient especially patient with allergy. Tablet was formulated by using different super disintegrants such as Ac-Di-Sol, Crosspovidone and Indion 414 in the ratio of 5%, 10% and 15% as shown in the (Table 3) represented by F1 to F9 respectively. These formulations were evaluated for the pre compression (Table 4) and post compression parameters (Table 6). Tapped density of the formulations was in between 0.66-0.78 gm/ml, where as the bulk density was in the range of 0.52-0.59 gm/ml. The compressibility values varied from 18.93% - 25.22%. The angle of repose values of the formulations varied from 28˚to 35˚. From these values, it was evident that these blends had good flow properties.

Table 4 Preformulation studies of formulated tablet batches.

Batch	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility %	Hausner's Ratio
F1	$29^0 12'$	0.55	0.73	23.60	1.32
F2	$30^0 56'$	0.59	0.79	25.22	1.34
F3	$32^0 70'$	0.58	0.78	23.61	1.34
F4	$30^0 33'$	0.53	0.7	20.00	1.32
F5	$29^0 81'$	0.57	0.71	19.42	1.25
F6	$32^0 76'$	0.52	0.67	21.57	1.29
F7	$35^0 64'$	0.54	0.69	20.38	1.28
F8	$28^0 91'$	0.58	0.69	18.93	1.19
F9	$31^0 03'$	0.54	0.66	21.32	1.22

Table 5 FT-IR study of Levocetirizine and Physical mixture of drug and excipients.

Material(s)	Functional group(s)	FT-IR signaling(cm^{-1})
Levocetirizine	N-H	3289.0
	C-H	2916.7
	C=H	3044.0
	C-O-C	1458.4
Tablet powder	N-H(aromatic)	3395.1
	N-H	3289.0
	C-H	2916.7
	C-O-C	1458.4

Physical parameters confirmed to the requirements such as taste, and color. Weight variation was found within the specification of I.P 2007. Average weight of all the 9 formulation was found in the range of 142-150 mg. Thickness of the all the formulations was found to be in the range of 2.56- 2.64 mm.

Hardness of the F3, F6 and F9 formulation was found to be 4.0 Kg/cm^2, 3.0 Kg/cm^2 and 4.0 Kg/cm^2 respectively and was comparatively less than other formulation such as F2, F5, F8 having 4.2 Kg/cm^2, 4.5 Kg/cm^2 and 4.0 Kg/cm^2 respectively where as F1, F4 and F7 formulation had hardness of 4.6 Kg/cm^2, 4.8 Kg/cm^2 and 4.5 Kg/cm^2 respectively.

Friability of the F2, F5 and F8 was found to be 0.72, 0.42 and 0.34 % respectively where as F1, F4 and F7 had friability of 0.26, 0.57 and 0.14 % respectively and F3, F6 and F9 had 1.16, 1.03 and 0.37 % respectively.

Wetting time of the formulation F1, F4 and F7 was found to be 52 sec, 49sec, 48 sec respectively where as F2, F5 and F8 was 46sec, 40 sec and 34 sec respectively and F3, F6 and F9 had 43sec, 37sec and 29sec respectively.

Drug content of the F1, F4 and F7 was found to be 98.8, 98.1 and 97.3% w/v respectively where as F2, F5 and F8 was 98.3, 97.9 and 96.7% w/v respectively and F3, F6 and F9 had 98.7, 98.4 and 98.2% w/v respectively. The drug content of marketed tablet was found to be 98.43% w/v.

Disintegration Time Study

Disintegration time of different formulations are shown in (Table 6) and found to be less than 30 seconds. Among the 9 formulations F2, F5 and F8 showed 30 sec, 17 sec and 22 sec respectively by Petri-dish method and 12 sec, 10 sec and 10 sec respectively by basket method. Thus the formulation F2, F5 and F8 containing 10 % super disintegrant such as crosscarmellose sodium, crosspovidone and Indion 414 showed the faster disintegration compared to 5 % and 15% superdisintegrants. The disintegration time of marketed convectional tablet of levocetirizine was found to be 141 sec which is much higher than orodispersible tablets.

Table 6 Physical evaluation of formulated tablet batches.

Parameter(s)	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed Tablet
Thickness (mm)	2.64	2.61	2.63	2.62	2.64	2.61	2.56	2.56	2.58	3.23
Hardness (kg/cm^2)	4.6	4.2	4.0	4.8	4.5	3.0	4.5	4.0	4.0	5.0
Friability (% w/w)	0.26	0.72	1.16	0.57	0.42	1.03	0.14	0.34	0.37	0.098
Wetting time (sec)	52	46	43	49	40	37	48	34	29	130
Disintegration time (sec)										141
Petridish method	35	30	26	38	17	15	37	22	20	
Basket method	22	12	10	17	10	09	20	10	09	
Drug content (% w/v)	98.8	98.3	98.7	98.1	97.9	98.4	97.3	96.7	98.2	98.43

***In vitro* dissolution study**

In vitro dissolution of various formulations at different time interval is reported (Table No. 7). All the formulations released drug at comparatively faster rate than that of the marketed conventional tablet of Levocetirizine (Table No. 8). Formulation with 10% crosscarmellose sodium, crosspovidone and Indion 414 showed maximum dissolution rates with 94.47 %, 98.41 % and 99.04 % respectively of the drug released in 8 minutes (Fig No. 5). Formulation with 10 % Indion 414 released 99.04 % of the drug in 8 minutes as compared to formulation containing 10 % crosscarmellose sodium and crosspovidone. Formulation with 10% Indion 414 was superior compared to other superdisintegrants. The in-vitro dissolution of marketed tablet was found to be 95.56 % w/v in 1 hour (Fig No. 5).

Table 7 Comparative study of % Drug release from Orodispersible tablet of Batch F1-F9

Time Min	% Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
30 sec	7.38	17.08	16.15	7.38	9.23	36.92	28.15	24.92	32.31
60 sec	65.6	75.88	59.26	76.69	85.95	86.26	62.62	84.28	86.67
90 sec	75.2	85.49	83.45	78.47	86.90	87.21	68.39	87.06	87.63
2	76.0	86.89	84.37	79.79	87.86	88.16	70.98	88.47	89.05
3	76.8	88.29	87.13	82.97	92.50	92.81	74.98	92.66	90.01
4	79.4	89.25	88.08	87.09	93.49	94.73	79.02	93.66	93.28
5	80.4	91.11	89.48	89.41	94.49	95.73	80.32	94.65	94.27
6	88.6	92.54	90.88	90.35	95.49	96.74	83.02	96.11	95.72
7	89.4	93.50	91.83	92.21	97.41	98.21	87.11	97.57	98.10
8	91.4	94.47	92.77	94.55	98.41	99.68	91.25	99.04	99.57

Table 8 % Drug release of marketed levocetirizine tablet.

Time (Min)	Drug release (%)
5	7.38
10	10.24
15	19.12
20	30.87
25	37.20
30	49.62
35	52.45
40	66.41
45	81.88
50	88.30
55	92.85
60	95.56

CONCLUSION

In present study Levocetirizine orodispersible tablet prepared using different types and concentrations of superdisintegrant by direct compression method which was confirmed by various characterization and evaluation studies. Indion 414 as superdisintegrant gives better result as compared to crosscarmellose sodium and crosspovidone. Tablets disintegrate within 30 sec in mouth having better mouth feel. Tablet show maximum in-vitro drug release in 1-3 min as compared to marketed levocetirizine tablet.

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