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RESEARCH ARTICLE

DESIGN AND CHARACTERIZATION OF TASTE MASKED FAST DISSOLVING TABLETS CONTAINING LEVOCETRIZIN DIHYDROCHLORIDE

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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 ion exchange resins i.e Kyron- T-114. The drug: ion exchange resin complex was prepared by batch technique. The fast disintegrating tablets were prepared using microcrystalline cellulose (MCC) PH 102 as diluent along with different proportions of crospovidone (CP) and croscarmellose sodium (CCM) 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. Total six formulations were prepared, out of that, formulation FTLC3 was selected as promising formulation. The In-vitro Dispersion time, Wetting Time, Water Absorption Ratio and In-Vitro drug release of formulation FDLC3 was found to be 14±0.69 sec, 17±0.82 sec, 88±1.29 % and 88.53±1.23 % respectively.

Keywords: Levocetirizine dihydrochloride, Fast disintegrating tablet, Ion exchange resin, Taste masking, Superdisintegrants

INTRODUCTION

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.[1] However, traditional tablets and capsules administered with a glass of water may be inconvenient or impractical for some geriatric patients because of changes in various physiological and neurological conditions associated with aging including difficulty in swallowing/dysphagia, hand tremors, deterioration in their eyesight, hearing, memory, risk of choking in addition to change in taste and smell. Solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally challenged, bed ridden and uncooperative patients. Paediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients travelling with little or no access to water, limit utility of orally administered conventional tablets or capsules.

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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 in the 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.[3] Administration of FDTs is different from conventional tablets, and the FDTs should have several unique properties to accommodate the rapid disintegration time. They should dissolve or disintegrate in the mouth without water or with a very small amount of water as the disintegration fluid is the patient's saliva. The disintegrated tablet should become a soft paste or liquid suspension, which provides good mouth feel and enables smooth swallowing. Fast dissolution or fast disintegration typically requires dissolution or disintegration of a tablet within one minute.[1,2]

Levocetirizine, an isomer of cetirizine, is a highly bitter drug with an antihistaminic action, a high affinity towards histamine receptors compared to cetirizine and its dextro form 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.[4,5] 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 ion exchange resin method. Superdisintegrants was used in the formulation of mouth dissolving tablet of Levocetirizine dihydrochloride. The purpose was to enhance patient compliance and provide fast onset of action.

Therefore, in the present study an attempt is made to design fast dissolving tablets of Levocetirizine dihydrochloride.

MATERIALS AND METHODS:

Levocetirizine dihydrochloride was a gift sample from Ajanta Pharma Ltd., Mumbai. Crospovidone and Croscramellose sodium were procured from SD Fine Chem, Mumbai and all other chemicals used were of analytical grade. Spectrophotometer UV-1800 (Shimadzu, Japan), disintegrationtest apparatus ED, Dissolution test apparatus TDT-08L, Friabilator USP EF-2 (Electrolab, Mumbai).

PREPARATION OF FAST DISINTEGRATING TABLETS LEVOCETIRIZINE DIHYDROCHLORIDE: [6,7]

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. Six 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 (Crospovidone and Croscarmellose Sodium), Microcrystalline cellulose is used as diluent, Mannitol is used as mouthfeel enhancer and

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Aspartame as sweetener. All ingredients were passed through mesh # 60. Before compression hardness was adjusted. Drug-resin equivalent to 5 mg of Levocetirizine dihydrochloride were compressed into tablets (150 mg) using 8mm flat face punch set using a 10 station tablet press. The scheme for oral fast disintegrating tablet formulations using different ingredients is shown in Table-1.

Table-1: Formulations of Levocetirizine dihydrochloride Fast Dissolving Tablets Prepared by Direct Compression Method

Ingredients (mg/tablet)	Formulation code						
	FTL	**$FTLC_1$**	**$FTLC_2$**	**$FTLC_3$**	**$FTLS_1$**	**$FTLS_2$**	**$FTLS_3$**
Levocetirizine dihydrochloride	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Crospovidone	---	1.5	3.0	4.5	---	---	---
Croscarmallose sodium	---	---	---	---	1.5	3.0	4.5
MCC (Avicel PH102)	30	30	30	30	30	30	30
Aspartame	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Sodium stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Flavour (Pineapple)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC (Avicel PH102)	106.0	104.5	103.0	101.5	104.5	103.0	101.5
Total weight	150	150	150	150	150	150	150

FTL- formulation without superdisintegrant**;**
FTLC- formulations containing Crospovidone as superdisintegrant;
FTLS-formulations containing Croscarmallose sodium as superdisintegrant.

EVALUATION OF TABLETS:[8,9]

All the prepared formulations of fast dissolving tablets of Levocetirizine dihydrochloride were evaluated for various pre and post compression parameters. The blends were evaluated for varies pre-compression parameters viz Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose. According to work plan the formulations were evaluated for their drug content uniformity, weight variation, tablet hardness, friability, thickness, disintegration time and *in-vitro* drug release with different media.

1. **Weight Variation:** The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

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2. **Tablet Hardness:** The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using digital hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded (given in table no.5).
3. **Friability:** Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

   Method: 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

   Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

4. **Tablet Thickness:** Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of three tablets of each formulation.
5. **Content Uniformity Test:**[10] The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 50 mg was weighed accurately and dissolved in 50 ml of methanol. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the dilute the solution to obtain 10µg solution. The absorbance of the diluted solutions was measured at 239 nm. The concentration of the drug was computed from the standard curve of the Levocetirizine dihydrochloride in methanol (given in table no.5).
6. **Wetting Time and Water Absorption Ratio:**[11] A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed (given in table no.5).

   Water absorption ratio 'R' was determined using following equation:

$$R = 100 \times \frac{Wa - Wb}{Wb}$$

   Where,

   W_a = weight of tablet before water absorption,

   W_b = weight of tablet after water absorption.
7. ***In-vitro* Dispersion Time:**[12] Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C. Time required for complete dispersion of a tablet was measured. The results were shown in table no.5.

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8. **Dissolution Study:**[12] *In-vitro* dissolution of a Levocetirizine dihydrochloride fast dissolving tablets were studied in USP TDT-08L dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer pH 6.8 was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37±0.5°C and was maintained throughout the experiment. One tablet was used in each test, 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 231 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Levocetirizine dihydrochloride released was calculated and plotted against time. For comparison the dissolution of Levocetirizine dihydrochloride from conventional commercial formulation was also studied. The results are given in table-6 & 7 and figure-2, 3 & 4.

The results of *in-vitro* release data obtained for all formulations were fitted in two popular models of data treatments as follows:

1. Zero-order kinetic model (cumulative percent drug released versus time).
2. First-order kinetic model (log cumulative percent drug remaining versus time).

RESULT AND DISCUSSION:

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. Two 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 was used as ion exchange resins and it was mixed with the drug in 1:1 ratios and evaluated for the extent of complexation, release rate study, sensory evaluation. The prepared drug-resin complex exhibited satisfactory values for release rate study and sensory evaluation which conclude that the prepared complex is taste masked (given in table no. 2 & 3).

In the present study, an attempt was made to design and evaluate fast dissolving tablets of Levocetirizine dihydrochloride by direct compression using blend of crospovidone, and croscarmellose sodium as a superdisintegrants. The prepared formulations were for pre-compression such as angle of repose, bulk density, Hauser ration and Carr's index and post compression parameters such as hardness, friability, weight variation, drug content uniformity, *in-vitro* dispersion time, wetting time, water absorption ratio, *in vitro* drug release pattern (for promising formulations). The pre compression parameters were found to be within the IP limit (given in table no. 4). Estimation of Levocetirizine dihydrochloride in the prepared fast

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dissolving tablets was carried out by extracting drug with methanol and measuring the absorbance at 231 nm. *In-vitro* drug release studies were performed in USP TDT-08L tablet dissolution test apparatus employing paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5ºC as the dissolution medium. Hardness, Avg. weight, thickness and drug content of prepared formulations were found to be in the range of 2.51-2.76 kg/cm^2, 148-156 mg, 2.62-2.80 mm and 99.77-100.43 % respectively. *In-vitro* Dispersion time, Wetting Time, Water Absorption Ratio and *In-Vitro* drug release (promising formulations and control formulation) of all the formulations were found to be in the range of 14 ± 0.69 to 38 ± 1.53 sec, 17 ± 0.82 to 44 ± 1.59 sec, 71± 0.04 to 88± 1.29 % and 7.51± 0.392 to 88.53 ±1.230 % respectively (given in table no. 5 & 6). Out of six formulations, formulation $FDLC_3$ was selected as promising formulation on the basis of *In-vitro* Dispersion time, Wetting Time, Water Absorption Ratio and *In-Vitro* drug release. *The In-vitro* Dispersion time, Wetting Time, Water Absorption Ratio and *In-Vitro* drug release of formulation $FDLC_3$ was found to be 14±0.69 sec, 17±0.82 sec, 88±1.29 % and 88.53±1.23 % respectively.

DRUG RESIN COMPLEX (DRC):

Drug release study:

Table-2: Cumulative percent drug release of Plain Levocetirizine dihydrochloride and DCR (Levocetirizine dihydrochloride: Kyron T-114)

Time in min	Plain Levocetirizine dihydrochloride	Levocetirizine dihydrochloride: Kyron T-114
5	41.12	45.72
10	58.35	65.25
15	69.25	77.20
20	78.36	84.87
25	82.87	88.76
30	86.22	92.09

Cumulative percent drug release values are in percentage

Taste Evaluation of Solid Drug: Resin

Table-3: Sensory evaluation data of drug-Kyron T-114 complexes

Ratio of drug: resin complex	Scores of drug –resin complex					Average bitterness value
	1	2	3	4	5	
Pure Drug	4	4	4	4	4	4
1:1 Drug :resin	1	0	0	0	0	0.2

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Fourier Transform Infra Red (FTIR) Study:

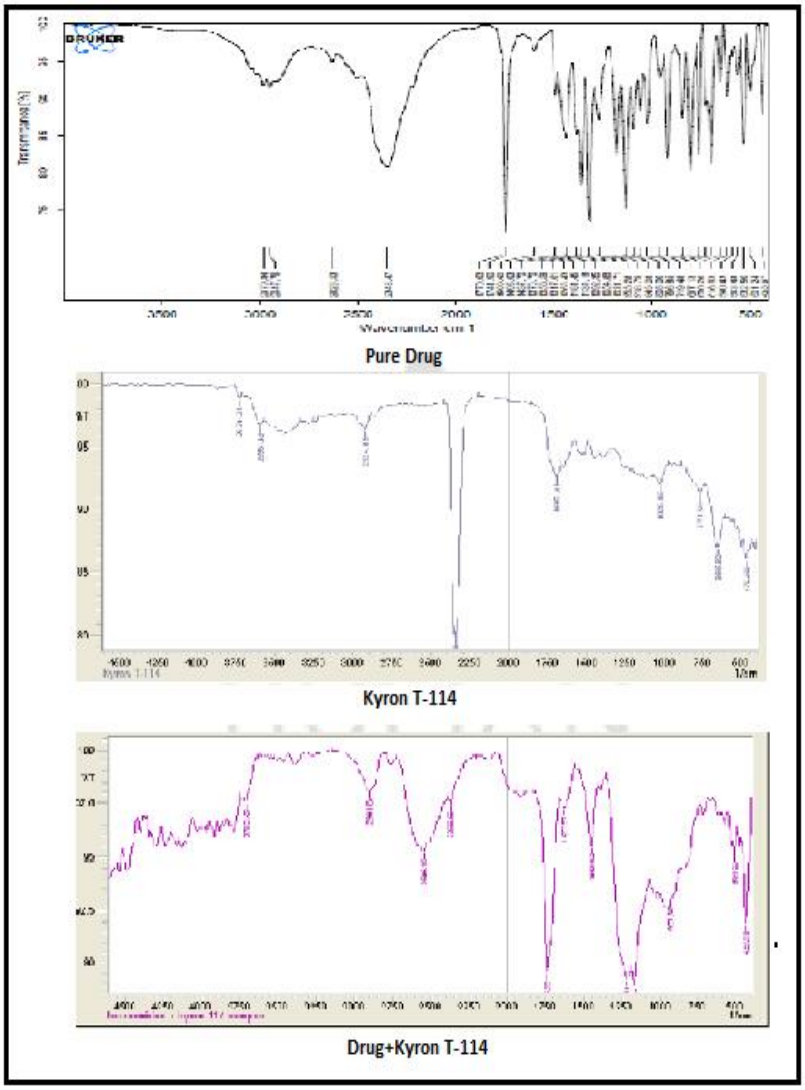

Figure-1: IR spectra

Table-4: Pre-compression Parameters of Formulations Prepared by Direct Compression Method

Parameters	Formulation Code					
	$FTLC_1$	**$FTLC_2$**	**$FTLC_3$**	**$FTLS_1$**	**$FTLS_2$**	**$FTLS_3$**
Angle of Repose (θ)	28.41	26.00	27.02	26.56	26.56	28.59
Bulk Density (gm/cc)	0.56	0.56	0.53	0.56	0.45	0.50
Tapped Density (gm/cc)	0.64	0.64	0.60	0.64	0.53	0.56
Carr's Index (%)	12.46	12.59	11.83	12.46	15.01	11.12
Hausner's Ratio	1.14	1.14	1.13	1.14	1.18	1.12

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Table-5: Post-compression Parameters of Formulations Prepared by Direct Compression Method

Parameters	Formulation Code					
	$FTLC_1$	$FTLC_2$	$FTLC_3$	$FTLS_1$	$FTLS_2$	$FTLS_3$
Hardness*±SD (kg/cm²)	2.53 ± 0.152	2.68 ± 0.05	2.71± 0.20	2.69 ± 0.05	2.51± 0.14	2.76 ± 0.25
Thickness*±SD (mm)	2.62	2.82	2.78	2.78	2.76	2.80
Friability (%)	0.48	0.52	0.50	0.60	0.42	0.65
In-vitro Dispersion time*± SD (Sec)	33 ± 0.69	22 ± 1.10	14 ± 0.69	38 ± 1.53	26 ± 0.69	20 ± 0.82
Wetting Time* ± SD (Sec)	38 ± 1.53	26 ± 1.59	17 ± 0.82	44 ± 1.59	32 ± 1.06	25 ± 0.98
Water Absorption ratio*± SD (%)	76± 0.04	84 ± 0.63	88± 1.29	71± 0.04	78± 1.86	83± 0.51
Percent Drug Content*± SD	99.77±1.28	99.46±0.64	100.16±0.485	100.43±0.61	99.89±1.19	99.89±0.63
Weight Variation (%)	(148-156mg) Within the IP limits of ± 7.5%					

*Average of three determinations

Table-6: Comparative *in-vitro* Dissolution Data of Promising Fast Dissolving Tablet Formulations and control formulation in pH 6.8 Phosphate Buffer

Sl. No.	Time in min	Cumulative Percent Drug Released (%)		
		FTL	$FTLC_3$	$FTLS_3$
1	2	7.51± 0.392	45.17 ±0.941	39.0 ± 0.946
2	4	9.11 ± 0.613	48.95 ±3.200	43.50 ± 1.557
3	6	10.85± 0.612	58.94 ±0.620	47.40 ± 0.947
4	8	11.97± 0.633	65.92 ± 0.715	49.90 ± 1.288
5	10	13.92± 1.332	70.83 ±0.942	58.29± 1.884
6	15	15.56± 1.002	75.55 ± 0.937	64.07 ± 1.885
7	20	18.85± 2.223	77.28 ± 1.235	72.27 ± 1.854
8	25	20.12± 1.213	84.21 ±1.235	76.0 ± 1.587
9	30	23.10± 2.091	88.53 ±1.230	80.92 ±1.565

*Average of three determinations

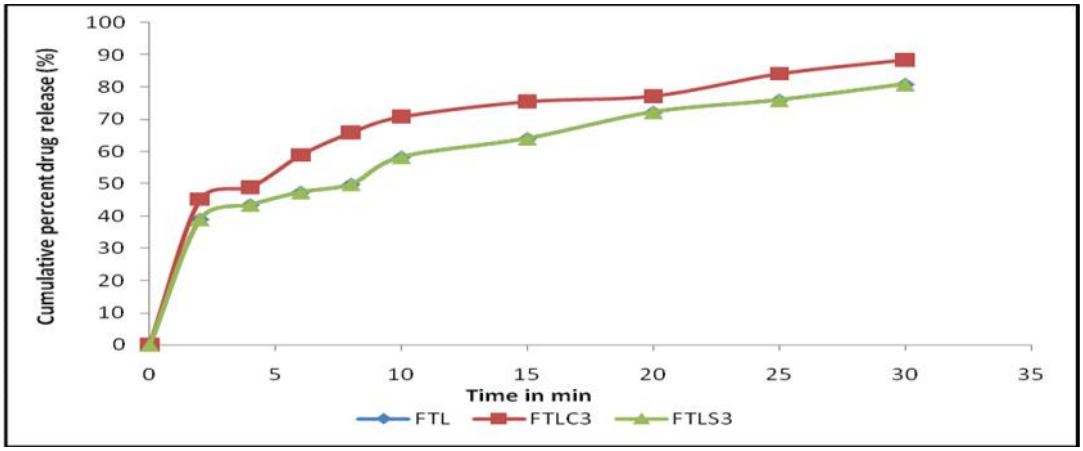

Figure-2: Comparative *in-vitro* Dissolution Data of Promising Fast Dissolving Tablet Formulation and control formulation in pH 6.8 Phosphate Buffer

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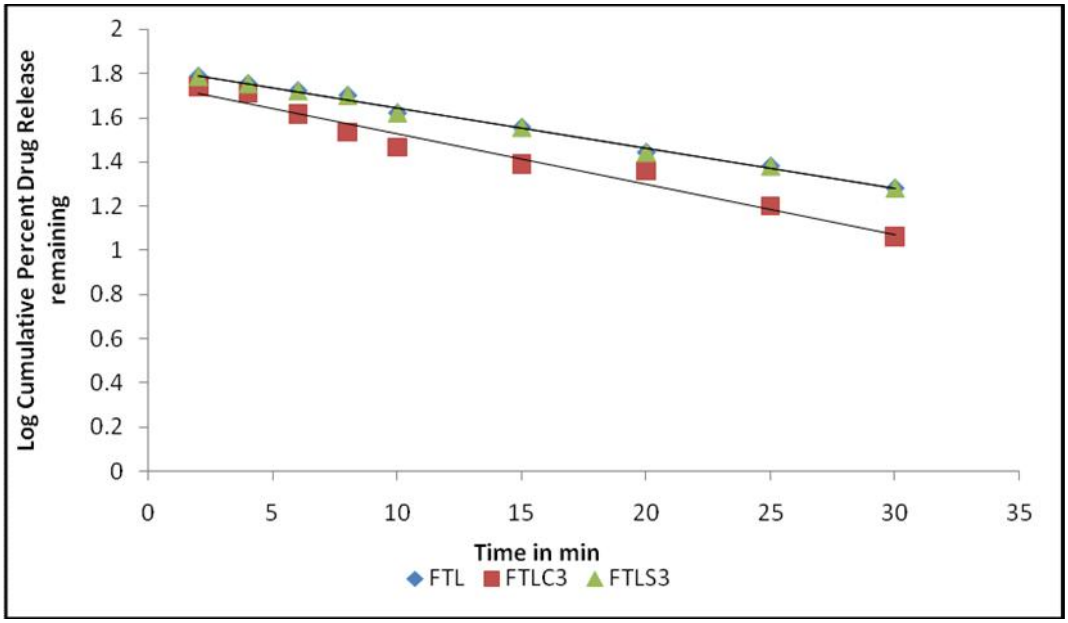

Figure-3: Comparative Log Cumulative Percent Drug Remaining versus Time Plots (First-Order) of Promising Fast Dissolving Tablet Formulations and control formulation in pH 6.8 Phosphate Buffer

Table-7: Comparative *In-vitro* Dissolution Parameters of Promising Fast Dissolving Tablet Formulations and Control Formulation in pH 6.8 Phosphate Buffer

Formulation Code	D_5 (%)	D_{10} (%)	D_{15} (%)	$t_{50\%}$ (min)	$t_{70\%}$ (min)	$t_{90\%}$ (min)
FDL	10.00	13.92	15.56	>30	>30	>30
$FDLC_3$	52.00	70.83	75.55	1.10	4.20	>30
$FDLS_3$	45.00	58.29	64.07	8.0	18.30	>30

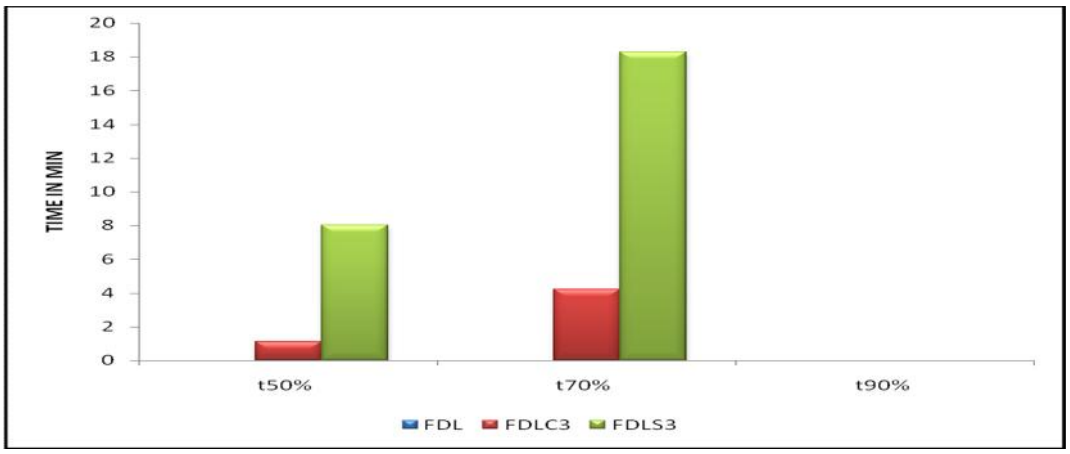

Figure-4: Comparative *In-vitro* Dissolution Parameters of Promising Fast Dissolving Tablet Formulations and Control Formulation in pH 6.8 Phosphate Buffer

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CONCLUSION:

Levocetirizine, an isomer of cetirizine, is a highly bitter drug with an antihistaminic action, a high affinity towards histamine receptors compared to cetirizine and its dextro form 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 ion exchange resin method. Superdisintegrants was used in the formulation of mouth dissolving tablet of Levocetirizine dihydrochloride. The purpose was to enhance patient compliance and provide fast onset of action.

Therefore, in the present study an attempt is made to design fast dissolving tablets of Levocetirizine dihydrochloride.

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