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Formulation and Optimization of Fast Dissolving Tablet of Levocetrizine Hydrochloride

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ABSTRACT

Rhinitis may be of allergic and non allergic origin and the reaction was typically associated to the nasal and ocular symptoms of the disease, allergic rhinitis was associated with a higher burden of asthma and sinusitis. It also affects multiple areas related to quality of life. Due to these reasons, there is a need to develop rapid action producing formulation to treat these allergic conditions. Levocetrizine is the active enantiomer of cetirizine. It is second generation, non-sedative antihistaminic drug with half-life of 8-10 hrs.The usual dose range from 5 to 10 mg. It undergoes extensive metabolism. The objective of the current study was to develop and optimize fast dissolving tablet of levocetrizine hydrochloride to improve bioavailability and increase drug release with rapid onset action.

Key word: Fast dissolving tablet, Superdisintegrant, Rapid action, Patient compliance

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INTRODUCTION

Many patients express difficult to swallow tablets and hard gelatin capsules and thus does not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Many pharmaceutical dosages are administered in the form of pills, granules, powders and liquids. Generally, a pill is designed for swallowing intact or chewing to deliver a precise dosage of medication to patients[1]. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure[2]. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several mouth dissolving drug delivery systems have been developed[3]. Mouth dissolving tablets can be prepared by various conventional methods like direct compression, wet granulation, moulding, spray drying; freeze drying and sublimation. MDTs disintegrate and/or dissolve rapidly in the saliva without the need of water, releasing the drug. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is fast dissolving tablets (FDT)[4,5,6,7]

Levocetrizine

(levocetrizinehydrochloride) 2-[4-[(R)-(4-Chlorophenyl) phenyl methyl]-1-piperazinyl]ethoxy]-acetic acid hydrochloride, is a third-generation non-sedative antihistamine, developed from the second-generation antihistaminecetirizine15. Chemically, levocetrizine is the active enantiomer of cetirizine[8]. The drug having half-life of 6-10 h. Is completely absorbed and extensively metabolized to it pharmacologically active enantiomer of, It is the L-enantiomerof the cetirizine racemate. Levocetrizine works by blocking histamine receptors; it does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever. Since allergic patients have sudden emergency of dosage regimen, MDTs will avoid missing out of dose even during traveling or other situations where there is no access to water.[9]

MATERIALS AND METHODS:

Levocetrizine HCl was obtained as a gift sample from Astron pharmaceutical Pvt Ltd, Gujarat. Sodium starch glycollate from sannofiavenrtis, crosscarmellose sodium, crospovodone and microcrystalline cellulose, and other chemicals were used from college (Laser Chemicals) Ltd. All the other raw materials were of pharmacopoeial grade.

Preparation of Fast Dissolving Tablet

The usual dose range from 5 to 10 mg of Levocetrizine hydrochloride, so 5mg was considered as dose. Drug and superdisintegrant in different ration (table 3.4, 3.5) with other excipients were mixed and prepared for direct compression. The drug and the superdisintegrant were sieved through mesh #60 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 aspartame as sweetening agent .the powder compressed by using rotary tablet machine using 8mm punch. The hardness was adjusted to 2-4kg/cm^2

EVALUATION OF POWDER

a) Bulk Density: Weigh accurately 25g of granules, which was previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Carefully level the granules without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula

Bulk density [BD] = Weight of powder / Bulk volume

b) Tapped bulk density: Weigh accurately 25 g of granules, which was previously passed through 20# sieve and transfer in 100ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/ml by the following formula:

Tapped Density [TD] = Weight of powder / Tapped volume

c) Carr's Index: The Compressibility Index of the granules blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a granules and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TD-BD)*100]/TD$$

d) Hausner's Ratio: The Hausner's ratio is a number that is correlated to the flow ability of a granular material.

$$\text{Hausner's Ratio} = TD/BD$$

Table 1: Effect of Carr's Index and Hausner's Ratio on Flow Property

Carr's Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59

e) Angle of repose: The angle of repose of granules powder was determined by the funnel method. The accurately weight granules were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h/r$$

Where, h and r are the height and radius of the granules cone respectively.

Table 2: Effect of Angle of repose (ϕ) on Flow property

Angle of Repose (Φ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

EVALUATION OF TABLETS

- **Weight Variation Test**

  Twenty tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10 %.

- **Friability**

  For each formulation, pre weighed tablet sample (20 tablets) were placed in the Roche friabilator (Electrolab, Mumbai, India) which is then operated for 100 revolutions. The tablets were deducted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of their weight are considered acceptable. For sintered tablets the friability was almost negligible.

- **Hardness**

  Hardness of tablet was determined using Pfizer hardness tester (Campbell Electronics, Mumbai, India).

- **Content Uniformity**

  Twenty tablets were weighed and powdered in a glass mortar. Quantity of powder equivalent to 150 mg of Levocetrizine hydrochloride was accurately weighed and transferred in a 100 ml volumetric flask add final volume in volumetric flask up to 100ml using6.8 P_H Phosphate buffer. And measure the absorbance of the resulting solution using UV Visible spectrophotometer at of λ_{max} 230 nm. And found the amount of the levocetrizine hydrochloride using the calibration curve method.

- ***In Vitro* Dissolution Study**

  The *in vitro* dissolution study of levocetrizine hydrochloride (n=3) was performed as described in Indian Pharmacopoeia 2010 using USP apparatus II (model TDT-08T, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37^0C ± 0.5^0C using phosphate buffer (pH 6.8; 500 ml) as a dissolution medium for first 21 minuts and followed by phosphate buffer (pH 6.8; 500ml) for remaining hours. At the predetermined time intervals, 10-ml samples were withdrawn, and analyzed at 230 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu).

- **Disintegration Time**

  The test was carried out on 6 tablets using the disintegration apparatus. Phosphate buffer (pH 6.8) maintained at 37ºC ± 2ºC was used as a disintegration media and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Table 4 selection of superdisintegrant combination

Ingredients	P1	P2	P3
Levocetrizine hydrochloride	5	5	5
Crosscarmellose	-	3%	3%
SSG	3%	3%	-
Crospovidone	3%	-	3%
Mannitol	20	20	20
Aspartame	10	10	10
Magnesium stearate	1	1	1
Talc	2	2	2
Avicel PH 101 (MCC)	150	150	150

- **Wetting time**

  A piece of tissue paper folded twice was placed in a small Petridis containing 6ml. of distilled water. A tablet was carefully placed on the surface of the paper and the time required for water to reach the upper surface of the tablet was noted as the wetting time. Less wetting time is the indicates more porous the tablet.[10]

OPTIMIZATION OF VARIABLES USING FULL FACTORIAL DESIGN

A 3^2 randomized full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The concentration ratio of polymer crosspovidon (X_1) and crosscarmellose (X_2) were chosen as independent variables in 3^2 full factorial design, while Q_1, Q_4, Q_{21} (% drug release after 1, 4, 21 minute respectively), disintegration time(DT), wetting time(WT) were taken as dependent variables. The composition of factorial design batches (F1-F9) is shown in Table 3.8 and Table 3.9. The prepared formulations were evaluated for friability and hardness and *in vitro* release study. Statistical treatment was carried out to the factorial design batches using design expert DX8 statease software.

Table 5: Coding of variable

Coded Values	Actual Values	
	X_1 = concentration of crosspovidon	X_2 = concentration of crosscarmellose
-1	2%	2%
0	3%	3%
1	4%	4%

Full Factorial Design Batches

Table 6: full factorial batches

Ingredients	Formulation batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levocetrizine hydrochloride	5	5	5	5	5	5	5	5	5
crosspovidon	3	3	3	4.5	4.5	4.5	6	6	6
Crosscarmellose sodium	3	4.5	6	3	4.5	6	3	4.5	6
Mannitol	20	20	20	20	20	20	20	20	20
Aspartame	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Avicel PH 101 (MCC)…to…	150	150	150	150	150	150	150	150	150

RESULT AND DISCUSSION

Method of analysis of drug

Preparation of standard calibration curve for levocetrizine hydrochloride in 6.8 pH buffer.

One hundred mg of levocetrizine hydrochloride was transferred in 100 ml volumetric flask. The drug was dissolved in 10 ml 6.8 pH phosphate buffer and the volume was adjusted to 100 ml by addition of 6.8 pH phosphate buffer. The 10 ml of above solution was further diluted up to 100 ml with 6.8 pH phosphate buffer to get stock solution of concentration 100 µg/ml. The stock solution was serially diluted with 6.8 pH phosphate buffer to get drug concentration in range of 4-30 µg/ml. The absorbance of the solutions was measured against 6.8 pH phosphate buffer as a blank at 230 nm using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft Excel®. The results of standard curve preparation are shown in Figure1

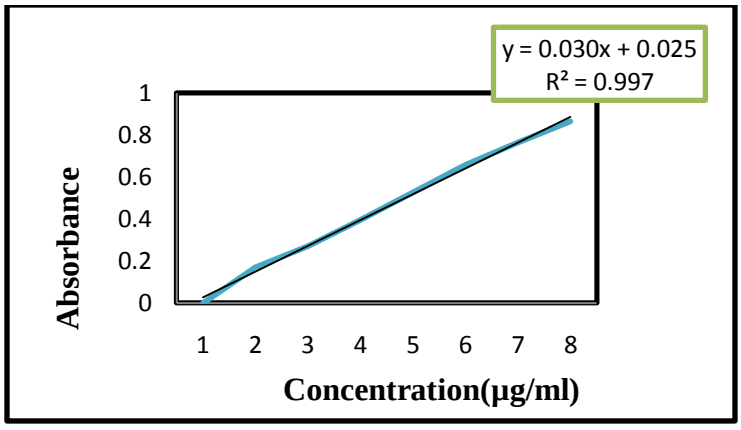

Figure 1 standard graphs with regression coefficient

FT IR STUDY

Table 7: Comparison of Vibration frequency of FTIR-Spectra of Levocetrizine HCl (Pure drug) and Formulation

Functional group	Frequency (cm^{-1})	
	Pure Levocetrizine HCl	**Formulation**
CO stretch	1092.71	1080.17
NH stretch	3282.95	3284.88
CH stretch	2921.29	2917.43
Carbonyl stretch	1658.84	1655.94
CN stretch	1320.32	1317.43
Ether	1472.7	1448.59

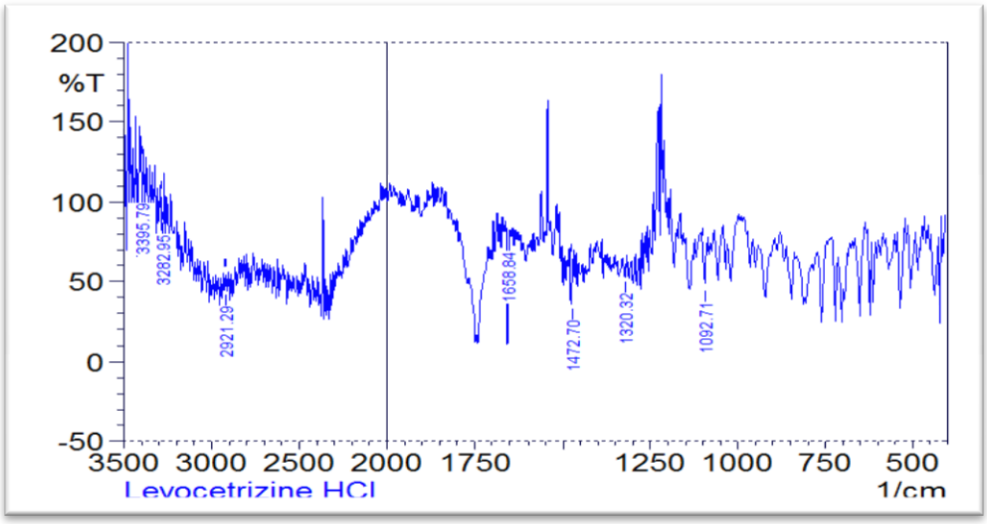

Figure 2: FTIR spectrum of Levocetrizine HCL in KBR disc

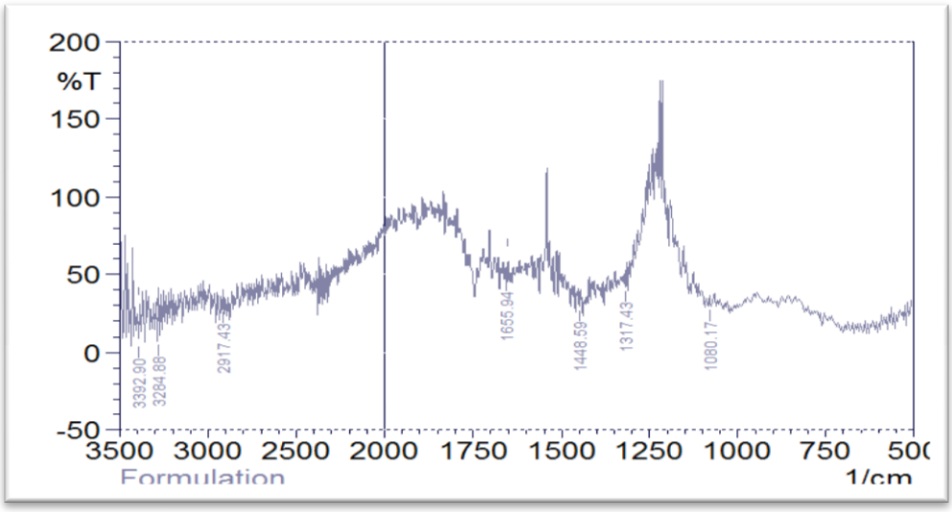

Figure 3: FTIR spectrum of levocetrizine hydrochloride formulation

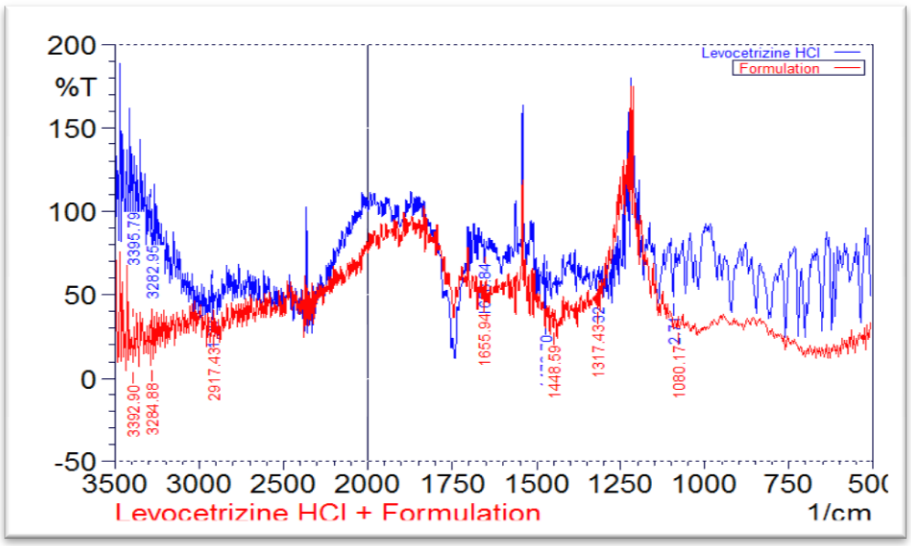

Figure 4: FTIR spectrum of levocetrizine hydrochloride + optimized formulation

Table 8: Preformulation studies of formulated tablet batches

Parameter	Angle of repose(^{0})	bulk density (g/ml)	Tap density (g/ml)	Hausner's ratio	Carr's Index (%)
F1	29.22±0.5	0.55	0.74	1.34	23.60
F2	30.15±0.4	0.58	0.78	1.35	25.14
F3	32.45±0.6	0.59	0.77	1.34	23.64
F4	30.57±0.5	0.54	0.75	1.32	20.14
F5	27.15±0.3	0.58	0.72	1.28	21.25
F6	29.03±0.6	0.53	0.68	1.25	20.38
F7	28.55±0.5	0.55	0.69	1.31	21.22
F8	31.44±0.3	0.58	0.68	2.19	20.45
F9	28.32±0.6	0.54	0.65	1.22	18.93

Table 9: Physical Evaluation Parameters of formulated batches

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
%Drug content	93.45	97.4	92.5	91.4	94.62	96.08	95.2	92.74	97.6
Friability (%)	0.26	0.72	1.16	0.57	0.42	1.03	0.14	0.37	0.09
Hardness (Kg/cm^2)	4.2	4.3	4.1	4.5	4.2	4.1	4.0	4.3	4.0

Table 10: comparative study of %drug release from formulated tablet batchF1-F9

Time (Mins)	CPR F1	F2	F3	F4	F5	F6	F7	F8	F9
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	89.57	87.97	87.97	64.51	85.84	89.57	88.50	87.97	94.90
2	93.77	94.81	94.61	89.75	96.39	92.17	93.22	96.41	99.68
4	93.73	93.72	93.72	98.21	93.72	89.98	89.45	92.14	95.99
6	91.02	90.48	90.48	97.15	93.14	84.56	84.02	87.28	93.30
8	85.60	88.25	88.25	92.33	88.81	83.33	83.32	81.28	92.17
10	82.77	83.32	83.32	89.05	84.42	78.88	80.47	80.54	89.94
12	80.97	81.53	81.53	89.45	79.43	77.57	79.18	79.78	88.22
14	79.67	80.23	80.23	86.12	77.59	74.64	77.33	77.94	86.47
16	76.22	77.32	77.32	81.67	75.71	73.80	74.39	76.07	85.75
21	72.72	74.36	74.36	78.76	74.87	72.94	73.53	74.70	82.35

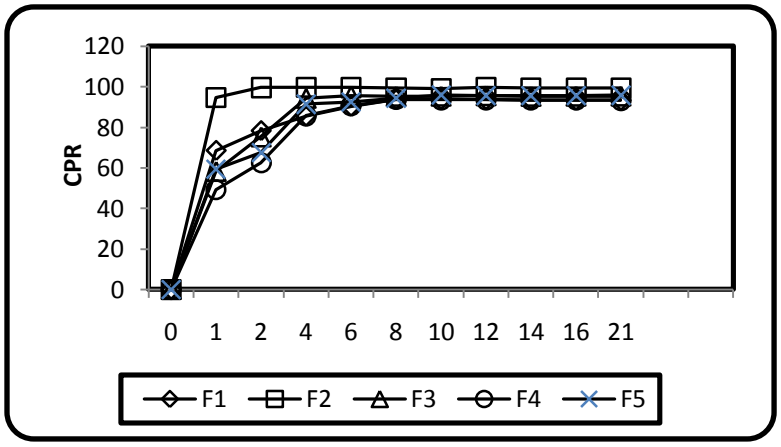

Figure 5: Time Vs %cumulative released of F1-F4

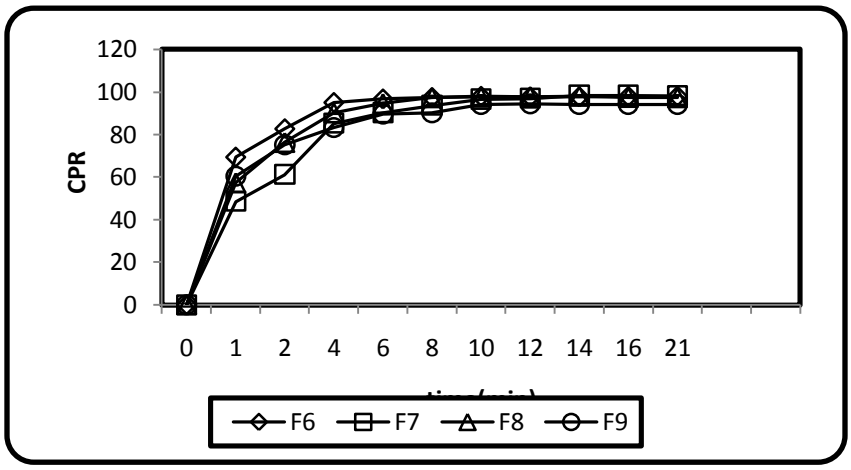

Figure 6: Time Vs %cumulative released of F5-F9

***Invitro* Dissolution Study**

Invitro dissolution of various formulations at different time interval is reported. Optimized formulation of Levocetrizine hydrochloride showed maximum drug release as compared to marketed preparation (Levociz MD). (Table 10)

Table 11: *in-vitro* dissolution profile comparison of prepared tablet with marketed tablet

Time (min)	CPR	
	Formulation	Marketed tablet
1	99.23	54.80
2	99.73	63.30
4	98.72	70.47
6	97.66	76.57
8	98.31	84.54
10	99.83	88.20
12	99.56	93.09
14	98.95	95.97
16	98.90	92.95
21	98.80	93.39

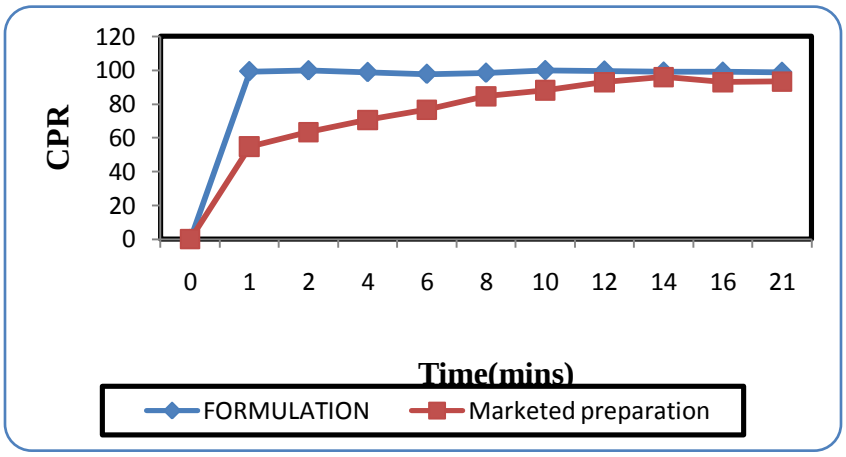

Figure 7 : *in-vitro* dissolution profile comparison of prepared tablet with marketed tablet

CONCLUSION:

In present study levocetrizine hydrochloride fast dissolving tablet prepared by using different types superdisintegrant by direct compression method which was confirmed by various characterization and evaluation studies, Combination of Crospovidone and crosscarmellose sodium gives better result as compared to other formulations. Tablet disintegrates within 4to 5 seconds in mouth having better mouth feel. Tablet show maximum in vitro drug release in 1-3 min as compared to marketed preparation of levocetrizine hydrochloride.

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