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Development & optimization of fast Dissolving tablet of levocetirizine HCL

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Abstract

Levocetirizine (as Levocetrizine hydrochloride) is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine Cetirizine. Levocetirizine Hcl works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. Fast dissolving tablets of Levocetrizine HCl were prepared using sodium starch glycolate, Croscarmellose sodium and Crosspovidone as superdisintegrants by direct compression method. The tablets prepared were evaluated for various parameters like weight variations, hardness, friability, *in vitro* dispersion time, drug content, wetting time, *in vitro* drug release, FTIR and XRD. The tablets prepared by direct compression method possess a weight variation below ±7.5%, hardness of 3 to 4.0 Kg/cm², percentage friability of 0.51 to 0.85, *in vitro* dispersion time of 17 to 58 seconds, Wetting time of 13 to 48 seconds, and *in vitro* drug release showed 94% to 99.00% within 20 min. The formulation (MD6) contains Crosspovidone and Sodium Starch Glycolate shows better Dis-integration time and 99% drug release within 20 min.

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INTRODUCTION

Many conventional oral drug and products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. Such immediate products results in relatively rapid and complete systemic drug absorption and onset of accompanying pharmacodynamic effects. Tablets are the most widely used dosage form because of its convenience in terms of self-administration, compactness and easy in manufacturing[1].

Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional tablets and capsules. When water is not available, in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis[2].

Advantages of this drug delivery system include administration without water. Some drug are absorbed from mouth, pharynx and esophagus as the saliva passes down in to the stomach and in such cases bioavailability of drug is increased, pre-gastric absorption can result in improved bioavailability and as a result to reduce dosage form, improved reduction of unwanted effects.[3]

Antihistamines are effective in reducing pruritis, sneezing and watery rhinorrhea, and are a mainstay therapy for allergic rhinitis. Second generation antihistamines have shown favorable effect on sleep in patients with allergic rhinitis and are in general recommended for mild to moderate disease as first-line therapy, but not effective in nasal congestion.[4]

Primary requirements to manufacture fast dissolving tablets [5, 6]:

• **Selection of the API(Active Pharmaceutical Ingredients):** Ideally the API selection should be dependent upon the potency and therapeutics range of the drug. As the drug load is the major factor to consider for this dosage form as the size of the tablet is dependent upon the dose, potent API may be appropriate to select.

• **Taste masking**: - Most fast dissolvable films must include substance to mask the taste of the active ingredient as with all immediate release products coming in contact with tongue. E.g.: menthol, peppermint, thymol, eucalyptol, fruit punch, bubble gum, fructose, aspartame, sucralose, sucrose.

• **Selection of a carrier:** The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

MATERIAL AND METHODS

Levocetirizine HCl was obtained from Dagon pharmaceuticals pvt. Ltd, Vadodara, (Gujarat), Croscarmellose sodium were obtained from Metro chemical Pvt. Ltd, Solan (H.P.), Crosspovidone and Sodium starch glycolate were obtained from Shreeji chemicals, Mumbai (Maharashtra), microcrystalline cellulose, magnesium stearate, aerosol were obtained from loba chemie pvt. Ltd. Mumbai (Maharashtra).

METHODS:

Fast dissolving tablets of Levocetrizine Hcl were prepared by direct compression method according to the formula given in Table-1. All the ingredients were weighed and kept separately. Then the weighed ingredients were mixed in geometrical order with weigh Levocetrizine Hcl and blend together to get uniform mixture. Then tablets were compressed using 6.5mm sizes biconvex round punch to get tablet using Rimek Compression machine.

EVALUATION:

Analytical method for estimation of Levocetrizine HCl:

Identification of drug was carried out by FTIR (Perkin Elmer Instruments, USA). Standardization of the drug was carried out by using UV visible spectrophotometer (1700-Shimadzu, Japan). XRD (X-ray Diffraction) studies were also carried out to assess drug excipient compatibility.

Standard calibration curve of Levocetrizine HCl in acetate buffer pH 6.8[7]:

Solution ranging from 2 to 10 µg/ml were prepared using buffer (pH 6.8); separately, absorbance was measured for each solution at λ_{max} of 231nm using Shimadzu UV/visible 1700 spectrophotometer, graph was plotted for absorbance versus concentration of Levocetrizine HCl.

FTIR Studies[8]:

IR spectra for pure drug Levocetrizine HCl and Levocetrizine HCl fast dissolving tablet formulations like MD1, MD2, MD3, MD4, MD5 and MD6 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Shimadzu corporation 8600, Japan) with KBr pellets.

XRD Studies[9]:

The spectra were recorded using a Philips, PW-171, x-ray diffractometer with Cu-NF filtered CuKα radiation. Quartz was used as an internal standard for calibration. The powder x-ray diffractometer was attached to a digital graphical assembly and computer with Cu-NF 25 KV/20 mA tube as a CuKα radiation source in the 2θ range 0-50°.

Physical Characterization[10]:

The fabricated tablets were characterized for weight variation (n=10), hardness (n=5, Monsanto hardness tester), and % friability (n=5, Roche friabilator, ElectroLab, Mumbai, India).

Wetting time[11]:

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

Drug content uniformity[12]:

Ten tablets were weighed and powdered. An amount of the powder equivalent to 10mg of Levocetrizine HCl was dissolved in 100ml of pH 6.8 buffer, filtered, diluted suitably and analyzed for drug content at 231nm using UV-Visible spectrophotometer (UV 160 Shimadzu, Japan).

***In-vitro* disintegration time[13]:**

I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37°±2°C. The time in sec. taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In-vitro* dissolution studies[14]:**

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of dissolution medium was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 231 nm and concentration of the drug was determined from standard calibration curve.

Table 1: Formulation of Levocetirizine HCl fast dissolving tablets prepared by direct compression method.

Ingredients	Formulation code								
	MD1 (mg)	MD2 (mg)	MD3 (mg)	MD4 (mg)	MD5 (mg)	MD6 (mg)	MD7 (mg)	MD8 (mg)	MD9 (mg)
Levocetirizine Hcl	10	10	10	10	10	10	10	10	10
Micro Crystalline Cellulose	75	75	75	75	75	75	72	72	72
Croscarmellose sodium	10	--	--	5	5	--	5	5	--
Sodium starch glycolate	--	--	10	--	5	5	--	5	5
Crosspovidone	--	10	--	5	--	5	5	--	5
Sod. Saccharine	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	5	5	5
Mg stearate	1	1	1	1	1	1	1	1	1
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

RESULTS AND DISCUSSION

Fig-1 Standard calibration curve of Levocetrizine HCl in 6.8 pH buffer Solutions at λ_{max} 231nm.

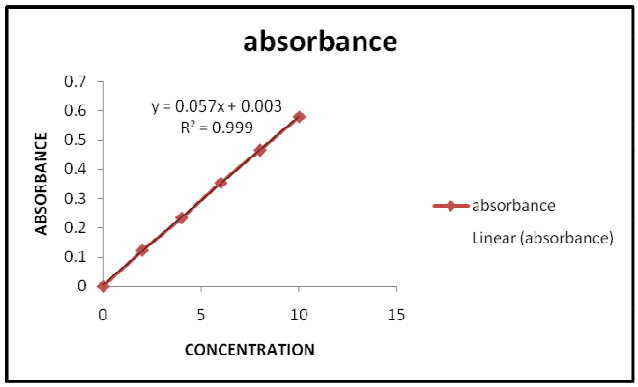


Fig-2 IR Spectra Levocetirizine HCl

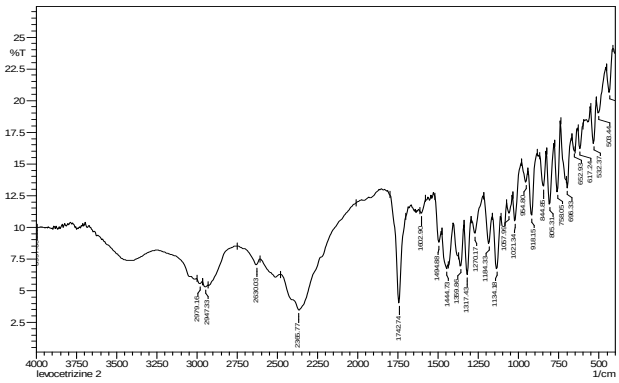


Fig-3: IR Spectra of formulation MD4 (CCS & CP)

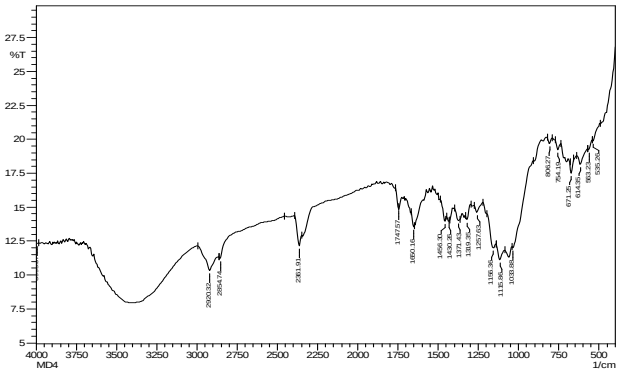
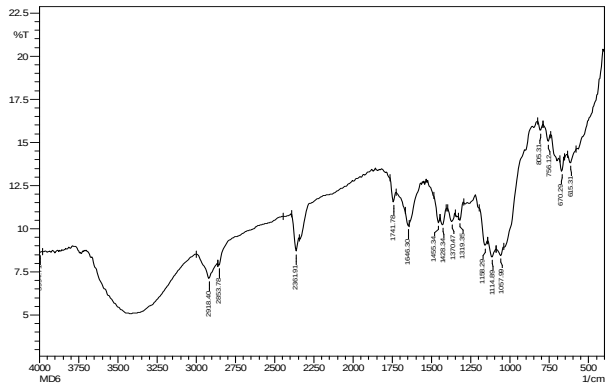


Fig-4 IR Spectra of formulation MD6 (CP&SSG)



FTIR was used to determine the drug-polymer compatibility; *Table 2* shows the FTIR spectra of pure Levocetirizine Hcl and mixture of pure drug and disintegrating agent. The spectra of pure Levocetirizine Hcl shows characteristic peaks at 1742 cm^{-1} due to stretching vibrations of –COOH group, the peak at 2947 cm^{-1} due to CH_2 stretching and the peaks at 758 cm^{-1} due to C-CL stretching. The similar peaks were also observed in the spectra of mixture of Levocetirizine Hcl and polymers with slight deviations. This indicate that the drug is stable and there is no drug-disintegrating interaction.

Table-2 Data obtained from compatibility study of drug polymer and formulations by FTIR spectroscopy

Sample code	Drug / Polymer	Principal absorption peaks of different groups found in IR Absorption spectrum, wavelength in cm^{-1}				
		-NH bend piperazine (cm^{-1})	CH_2 Stretch (cm^{-1})	OCH_3 stretch (cm^{-1})	-C-Cl (cm^{-1})	-COOH stretch (cm^{-1})
1	Levocetirizine Hcl	1602	2947	-	758	1742
MD1	Drug + CCS	1645	-	2852	752	1743
MD2	Drug + CP	1650	2917	2854	755	1743
MD3	Drug + SSG	1650	2918	2853	758	1743
MD4	Drug + (CCS+CP)	1650	2920	2854	754	1747
MD5	Drug + (CCS+SSG)	1645	2919	-	755	1743
MD6	Drug + (CP+SSG)	1646	2918	2853	756	1741

XRD studies:

The X-ray diffractograms of pure Levocetirizine Hcl, formulation MD4 and MD6 are presented in fig no 5-7. Levocetirizine Hcl has shown characteristic intense peaks between 2θ of 15° and 25° due to its crystalline nature. Whereas, in the MD4, MD5 and MD6 formulation shows intense peak between 2θ of 15° and 30°

Fig-5 Pure Drug (Levocetirizine HCl)

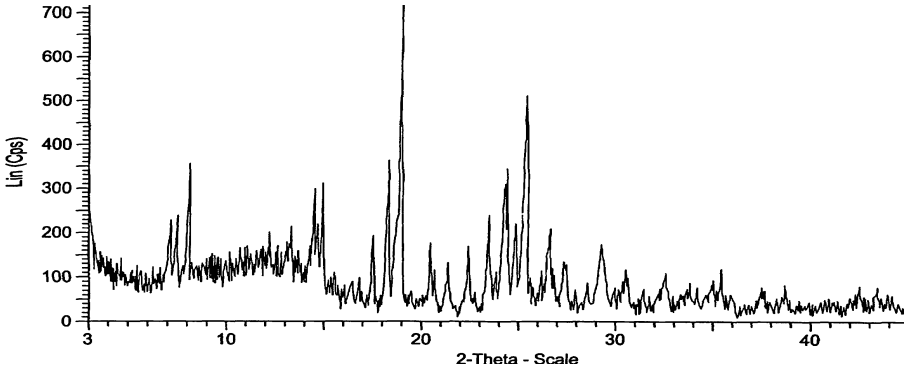


Fig-6 XRD analysis of formulation MD4

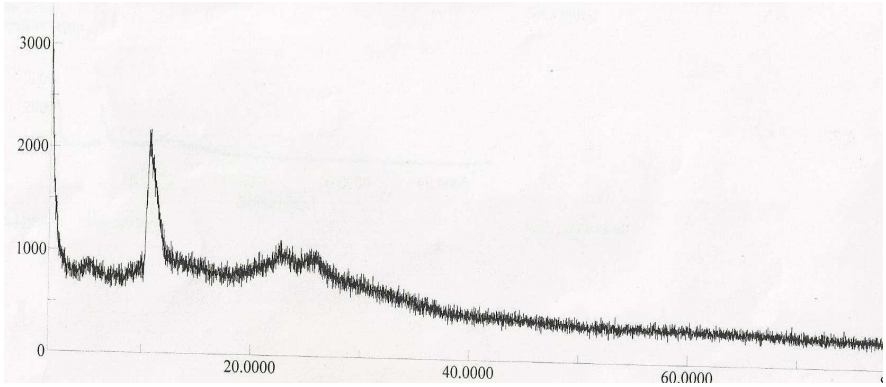
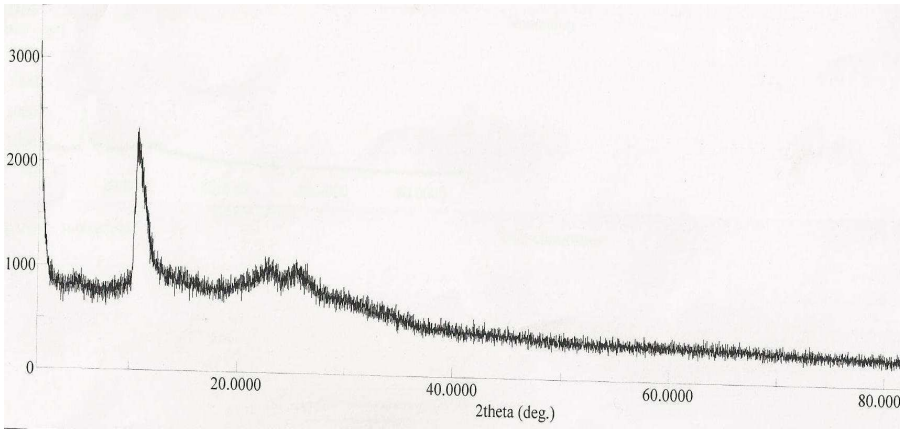


Fig-7 XRD analysis of formulation MD6



Angle of repose (θ):

The data obtained from angle of repose for all the formulations were found to be in the range of 23°.75 and 27°.47. All the formulations prepared by the direct compression technique showed the angle of repose less than 30°, which reveals good flow property.

Bulk density:

Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.44 gm/cm^3 to 0.49 gm/cm^3

Hausner ratio:

Hausner ratio of entire formulation showed between1.20 to 1.30 indicates good flow properties.

Carr's consolidation index:

The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 17.85% to 24.13%. The directly compressible granulations had shown excellent compressibility index values up to 15% result in good to excellent flow properties.

Table-3 Pre-compression parameters of direct compression method.

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's Ratio
MD1	0.47	0.58	27.47	20.00	1.23
MD2	0.48	0.58	23.75	17.85	1.20
MD3	0.46	0.57	26.56	18.60	1.26
MD4	0.47	0.59	25.64	19.27	1.25
MD5	0.49	0.59	26.56	18.29	1.21
MD6	0.47	0.60	22.78	21.42	1.27
MD7	0.45	0.57	27.47	21.60	1.26
MD8	0.44	0.57	24.70	22.47	1.29
MD9	0.46	0.60	25.64	24.13	1.30

Hardness:

The hardness of the tablets prepared by direct compression method was maintained within the range of 3.00 kg/cm^2 to 4.00kg/cm^2 was considered adequate for mechanical stability.

Friability test:

The friability was found in all designed formulations in the range 0.51 to 0.85% to be well within the approved range (<1%).The friability study results were tabulated in Table 4.

Weight variation test:

The weight variation was found in all designed formulations in the range 98 to 102 mg. The mean weight variation test results are tabulated in Table 4. All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e. in the pharmacopoeia limits.

Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 2.73 ± 0.020 mm to 3.21 ± 0.017 mm. The standard deviation values indicated that all the formulations were within the range. The results of thickness for tablets were shown in Table 4. The tablet prepared with aerosil showed highest thickness because of their least density.

Table-4 Post-compression parameters for Direct Compression method

FC	Hardness * (Kg/cm²) ± SD	Friability (%)	Thickness* (mm) ± SD	Weight variation* (mg)± SD
MD1	3.20 ± 0.10	0.68	3.18 ± 0.13	98.35 ± 1.8
MD2	3.20 ± 0.15	0.51	3.21 ± 0.16	100.50 ± 0.5
MD3	4.10 ± 0.15	0.60	2.73 ± 0.10	99.80 ± 1.7
MD4	3.20 ± 0.20	0.65	3.10 ± 1.17	101.20 ± 1.0
MD5	4.10 ± 0.20	0.58	3.16 ± 0.15	100.65 ± 0.7
MD6	3.40 ± 0.25	0.59	3.17 ± 0.09	100.90 ± 1.9
MD7	3.80 ± 0.10	0.78	3.05 ± 1.20	102.05 ± 0.5
MD8	3.90 ± 0.20	0.84	2.88 ± 0.12	100.80 ± 1.5
MD9	4.10 ± 0.20	0.73	3.21 ± 1.14	99.75 ± 1.9

***In- vitro* disintegration time:**

The *in-vitro* disintegration time is measured by the time taken to undergo complete disintegration. Rapid disintegration within several minutes was observed in all the formulations. The *in-vitro* disintegration time of fast dissolving tablets prepared by direct compression method were found to be in the range of 19 to 58 sec fulfilling the official requirements. By the addition of super disintegrants the disintegration time increased significantly ($P<0.05$) tablets prepared. Based on the *in-vitro* disintegration time, formulation MD4 and MD6 were found to be promising and showed a disintegration time of 19 and 25 sec respectively.

Wetting time:

Wetting time is closely related to the inner structure of the tablet. The wetting time of Levocetirizine Hcl tablets prepared by direct compression method were found to be in the range of 13 to 47 sec. Promising formulations MD4 and MD6 showed a wetting time of 16 and 13sec respectively, which facilitate the faster dispersion in the mouth.

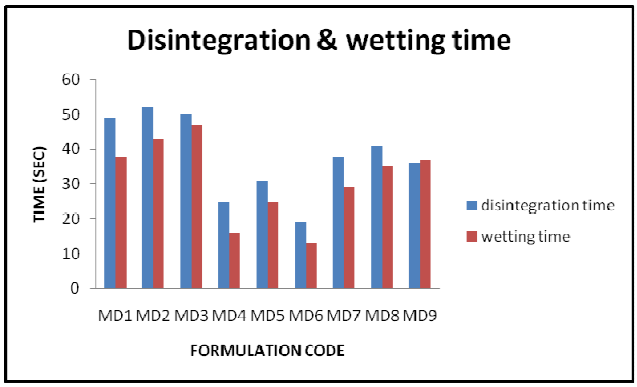
Drug Content:

The drug content uniformity was performed for all the 9 formulations. All samples were analyzed spectrophotometrically. The percentage drugs content of the tablets were found to be between 93.76 ± 0.9 to 100.0 ± 0.5% of Levocetirizine HCL.

Table-5 Post-compression parameters for Direct Compression method:

FC	Disintegration time* (sec)± SD	Wetting time* (sec) ± SD	Drug Content* (%) ± SD
MD1	49 ± 1.0	38 ± 2.5	90.5 ± 2.0
MD2	52 ± 2.5	43 ± 1.5	98.4 ± 0.5
MD3	50 ± 1.5	47 ± 1.5	94.1 ± 1.5
MD4	25 ± 3.0	16 ± 2.0	93.6 ± 1.0
MD5	31 ± 2.0	25 ± 2.0	100.0 ± 1.0
MD6	19 ± 3.5	13 ± 1.5	98.1 ± 2.0
MD7	38 ± 1.5	29 ± 1.5	96.0 ± 2.5
MD8	41 ± 2.5	35 ± 2.5	97.2 ± 1.0
MD9	36 ± 3.0	37 ± 3.5	99.6 ± 0.5

Fig-8 comparison of disintegration time & wetting time



***In-vitro* dissolution studies:**

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution

medium was maintained at 37±0.5°C, aliquot of dissolution medium was withdrawn at every 5 min. interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 231nm and concentration of the drug was determined from standard calibration curve.

The dissolution of Levocetirizine Hcl from the tablets is shown in (Fig. 9-10) and (Table 6) shows the drug release profiles. These values changed with change of method of preparation of tablets.In case of tablets prepared by direct compression technique the values decreased with increase in the concentration of croscarmellose sodium, crospovidone and sodium starch glycolate. The rapid increase in dissolution of Levocetirizine Hcl with the increase in sodium starch glycolate may be due to rapid swelling and disintegrating tablets rapidly into apparently primary particles.

Table-6: *In Vitro* Release rate profile of Levocetirizine Hcl formulations in (pH 6.8)

TIME (min)	% DRUG CUMULATIVE RELEASE								
	MD1	MD2	MD3	MD4	MD5	MD6	MD7	MD8	MD9
0	0	0	0	0	0	0	0	0	0
5	66.56	68.74	77.74	74.79	71.37	75.1	70.91	71.22	72.93
10	73.24	76.18	83.32	80.84	77.43	88.13	77.74	81.77	79.91
15	83.48	84.1	90	90.77	87.2	91.7	88.44	92.01	90.62
20	96.36	97.44	97.91	98.53	99.46	99.15	99.62	99	99.77
25	91.39	91.39	96.67	95.12	99.31	99	99.15	97.6	99.31
30	90.93	90.46	96.36	92.94	98.53	97.75	98.68	97.29	98.53

Fig-9: *In Vitro* Release rate profile of Levocetirizine Hcl formulations in MD1 - MD5

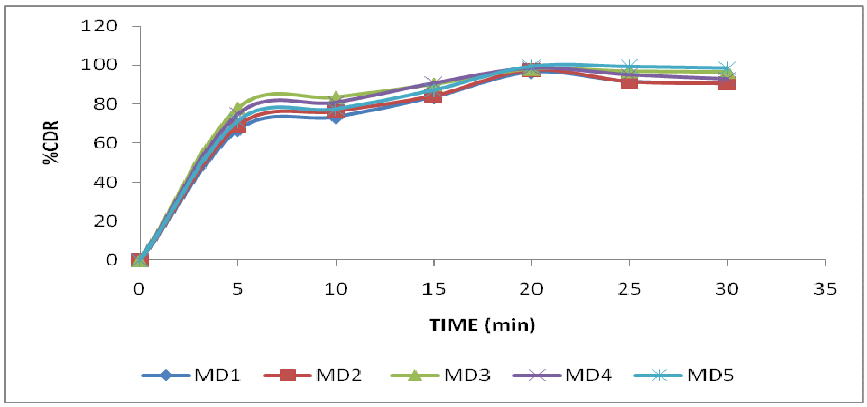
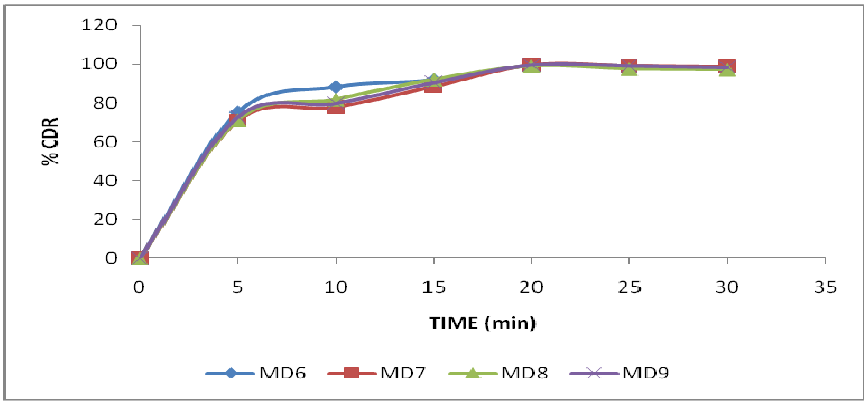


Fig-10: *In Vitro* Release rate profile of Levocetirizine Hcl formulations in MD6 – MD9



STABILITY STUDY:

Stability studies for the developed formulations were carried out as per ICH guideline by storing the selected formulations at 40°C/75% RH up to one month. The formulation MD6 was selected on the basis of their high cumulative percentage drug release, and also results of *in-vitro* disintegration time, wetting time, and *in-vitro* dispersion studies. The tablets were analyzed for the colour, hardness, drug content uniformity and cumulative % drug released *in-vitro* disintegration time up to one month. From the obtained data of tablet evaluation parameters indicated that stable formulations can be developed by direct compression method.

Table-7: Accelerated stability study of optimized formulation MD6 at 40°C / 75 % RH for one month.

Period	Hardness (kg/cm²)	Disintegration time (sec.)	Wetting time (sec.)	Drug content (%)	%Drug release
0 days	3.40 ±0.17	19±1	13±2	98.10±1.9	99.15±2.0
15 days	3.50±0.30	21±3	17±1	97.50±2.0	98.50±2.0
30 days	3.70±0.10	24±1	19±1	96.00±2.0	98.00±2.0

CONCLUSION

Orodispersible tablets of Levocetirizine Hcl were successfully formulated by employing direct compression method. Percentage weight variation and drug content uniformity were found to be within the approved range (Indian Pharmacopoeia Standards) for all the formulations.

The *in-vitro* disintegration, *in-vitro* dispersion, wetting time parameters revealed that sodium starch glycolate, croscarmellose sodium, crospovidone alone and in combinations. This acts as superdisintegrants, reveals good results in all the formulations. Among the formulation, MD6 exhibited 99% of drug release within 20 minutes and also less Dis-integration time i.e 19 secs. Therefore MD6 was found to be optimized formulation.The accelerated stability studies carried out for MD4 and MD6 formulation at 40°C and 75%RH for one month, after 15 days interval the formulation was examined for physical appearance, hardness, friability, thickness, drug content, disintegration time, dispersion time, wetting time.

The formulation exhibited no change in physical appearance, hardness, friability, thickness, drug content, disintegration time, dispersion time, wetting time revealing excellent stability of the formulated formulation.

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