The formulation and evaluation of mouth dissolving tablet Levocetirizine by using synthetic Superdisintegrants

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RESEARCH ARTICLE

Rupali Rana*, Nisha Devi, Vishal Kumar, Reena Thakur, Shivali Singla, Sachin Goyal

Himalayan Institute of Pharmacy, Kala-Amb, Distt. Sirmour, Himachal Pradesh (India) 173030

**Corresponding Author's E-mail: ranarupali22@gmail.com*

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ABSTRACT

Aim of this research work was to develop mouth dissolving tablet that disintegrates rapidly in mouth by using tasteless complex of Levocetirizine and β-CD. Mouth dissolving Tablets also called as Orodispersible tablets. Formulated Levocetirizine β-CD complex was characterized by infrared spectroscopy, thermal analysis and X-ray diffraction pattern. Tablets were developed by direct compression method. Superdisintegrants like Sodium starch glycolate (SSG), Crosscarmellose sodium (CCS) and Crosspovidone (CP) were used for the formulation. Every formulation was subjected to in-vitro tests like wetting time, disintegration test and dissolution test. The in-vitro study showed that increasing the concentration of superdisintegrants lowers the wetting time (WT) and disintegration time (DT) and enhances the drug release percentage of the formulations.

The formulation CPX5 was the most effective formulation as it showed wetting time of 12 seconds, disintegration time of 20 seconds and cumulative % drug release of 41 and 99% at 1 and 10 minutes respectively. The study showed that the formulations containing SSG and CP as the superdisintegrants showed better drug release pattern than the formulations with other superdisintegrants. The study also showed that SSG as the superdisintegrant was more effective for the formulation of orodispersible tablets of levocetirizine dihydrochloride.

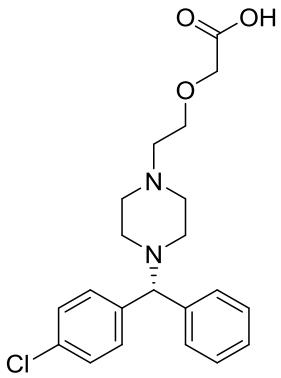
Keywords: β-CD: Cyclodextrin; Disintegration time; Drug release; Levocetirizine, Superdisintegrants; Orodispersible tablets.

1. Introduction

Many patients, particularly old find it difficult in swallowing tablets, capsules, fluids and subsequently do not comply with prescription, which results high frequency of resistance situated research has resulted in bringing out many secure, safe new drug delivery system.Among the several dosage forms developed to improve the difficulty of administration, the mouth dissolving tablet (MDT) is the most generally favored commercial products. (1) The oral cavity is an appealing site for the administration of drugs because of simplicity of administration. Several dosage forms like Tablets, Capsules, and Liquid preparations are administered by oral route. During the most recent decade, mouth dissolving tablet (MDT) advances that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a lot of consideration. The MDT's are also known as fast liquefying, rapid dispersing, rapid dissolve, rapid melt, as well as speedy disintegrating tablet. (2-4) MDTs can be prepared by various conventional methods like direct compression, wet granulation, molding, spray drying, freeze drying and sublimation. Firstly, MDTs disintegrate then dissolve quickly in the saliva without any need for solvents, releasing the drug. A few drugs are absorbed from the mouth, pharynx and esophagus as the saliva goes down into the stomach. In many cases, bioavailability of these drugs is significantly more than those observed from conventional tablet dosage form. (5,6) Levocetirizine is a 3rd-generation of non-sedative antihistamine drug, it is developed from the second-generation antihistamine drug (citirizine).

Chemically, levocetirizine is the active enantiomer of cetirizine. Levocetirizine has shown own efficacy by blocking histamine receptors. It prevents only binding of histamine to its receptors site, but don't prevent its

release from the mast cells. This prevents the release of other allergy synthetic substances and enhanced blood supply to the region, and provides relief from the typical symptoms of roughage fever. Levocetirizine has low oral bio-availability because of high first pass metabolism rate. (7) Hence, formulation in orodispersible form of levocetirizine upgrades the bioavailability, decreases side effects, low dosing, patient compliance, rapid onset of action with great steadiness. In the present work, orodispersible tablets of levocetirizine were prepared by direct compression method using Croscarmellose sodium, sodium starch glycollate and crosspovidone as the superdisintegrants. The aim of the study was to evaluate the effect of the superdisintegrants on wetting time, disintegration time and drug release profile of the orodispersible tablets. The present investigation deals with the improvement of an effective and stable MDT of Levocitrizine having sufficient hardness, low disintegration time and pleasant taste.



(2-[2-[4-[(*R*)-(4-chlorophenyl)-phenyl methyl]piperazin-1-yl]ethoxy] acetic acid)

2. Materials and Methods

2.1 Materials

Levocetirizine dihydrochloride obtained from Vardhman Pharmaceuticals (Paonta Sahib), Crospovidone recieved from Macleod Pharmaceuticals (Baddi). Other excipients used like Camphor, Sodium Saccharin, Microcrystalline Cellulose, Mannitol, Magnesium stearate, Talc were of analyticalgrade.

2.2 Pre-formulation study

Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer. Solubility analysis of drug in various solvents including water, organic solvent methanol and phosphate buffer pH 6.8, was carried out.

2.3 Methods

Levocetirizine -*β*-CD complex (1:1 molar ratio) was prepared by kneading method. Accurately weighed amount of pure drug and *β*-CD was triturated in a clean and dry mortar with a small volume of water-methanol solvent system. The thick slurry was kneaded for 45 min and then dried at 40°C. Dried mass was pulverized and sieved through a (#100) mesh. Mouth dissolving tablet of levocetirizine *β*–CD prepared by direct compression method using sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crosspovidone (CP) as super-disintegrants. *β*–CD was used as complexing agent to improve the dissolution of drug. Microcrystalline cellulose (MCC) and crospovidone were use as binder and super disintegrating agent, respectively. Drug-*β*–CD complex equivalent to 10 mg of drug and all the excipients except magnesium stearate were taken in mortar. Then powder blend was mixed well for 15 to 30 min. The blends were passed through #80 sieves. Lubrication was done using magnesium stearate. Final blend was compressed into tablet by direct compression. **Table 1** shows the composition of different formulation which were undertaken for formulating MDTs.

Table 1 Formula of different trials for the selection of excipients (mg).

Name of ingredients	CPX 1 (mg)	CPX 2 (mg)	CPX 3 (mg)	CPX 4 (mg)	CPX 5 (mg)	CPX 6 (mg)	CPX 7 (mg)	CPX 8 (mg)	CPX 9 (mg)
Levocetirizine - *β*-CD complex*	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
SSG	-	-	10	11	12	-	-	10	-

CCS	11	-	-	-	-		11	-	-
CP	-	10	-	-	-	-	-	-	10
Mg stearate	3	2	3	2	2	3	1	2	1
Aerosil	2	2	2	1	2	2	1	1	2
Mannitol	18	20	17	20	15	15	22	15	10
MCC	68	73	72	70	77	80	74	75	80
*** Complex equivalent to 5 mg of levocetirizine**									

The excipients selected in the above trials were sieved through sieve no.40 and then mixed properly in mentioned proportions (Table 1).

3. Evaluation parameters

3.1 Evaluation and Ccharacterization of Levocetrizine β-CD complex

The preformulation study including Bulk density, tapped density hausner's ratio Porosity, angle of repose and Carr's compressibility index were performed. Organoleptic properties like colour, odour and taste of drug were observed. FTIR study was carried out to determine the functional groups in the drug molecule levocetirizine and *β*-CD and also act as a fingerprint of the molecule.

Prepared tablets were evaluated for various parameters such as uniformity of weight, thickness, hardness, friability, weight variation, wetting time, water absorption ratio, disintegration time and *in vitro* drug release. Uniformity of tablets weigh was done by using digital weighing balance. Hardness was measured by monsanto hardness tester. The thickness of tablets was determined using vernier callipers. Friability was determined in Roche friabilator, by taking ten tablets. Drug release was carried out using USP Type II apparatus in phosphate buffer pH 6.8. (8)

3.2 In-vitro disintegration test

One tablet was placed in each tube of USP tablet disintegration test apparatus (ED-2 SAPO, Electrolab, Mumbai, India) and the basket rack is poisoned in 1 litter beaker containing distilled water at 37ºC ± 0.5ºC. The conditions were maintained in such way that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured.

3.3 Determination of wetting time

For the determination of wetting time of the tablet, a circular piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petri-dish (internal diameter 6.5 cm) containing 10 ml of phosphate buffer (pH 6.8). A tablet was placed on the paper, and the time for complete wetting was measured. Three tablets from each formulation were randomly selected and the average wetting time was recorded. (8,9)

3.4 In- vitro dissolution studies

The study was carried out using USP dissolution test apparatus II (DS 8000, Lab India, Mumbai, India) at 50 rpm in 900 ml of phosphate buffer (pH 6.8) as a dissolution media. The temperature was maintained at 37±0.5ºC. The samples were withdrawn at predetermined time intervals of 0, 2, 4, 6, 10 min. Aliquots (5 ml) were withdrawn, filtered and analysed spectrophotometrically using UV spectrophotometer (3000^{+}, Labindia, Mumbai) at 233 nm. An equal amount of fresh dissolution medium, pre-warmed at 37±0.5ºC, was added after each Ssampling to maintain the sink condition throughout the study. Dissolution study was performed in triplicate for each batch. (10-12)

4. Result and Discussion

The appearance of levocitrizine is white odourless and slightly bitter in taste. The melting point and partition coefficient of drug is 206.66 ± 0.5 and 0.132. X-ray diffraction shown that complex form of drug with *β*-CD was crystalline in nature. The other micrometrics evaluation for all the formulations were also done such as Angle of repose, Bulk density, Tapped density, Void volume, Hausner's ratio, Porosity, Carr's

compressibility index, Drug content their valuable results are shown in **Table 2.**

Table 2. Micrometric properties of powder blend.

Formulation code								
CPX_1	**CPX_2**	**CPX_3**	**CPX_4**	**CPX_5**	**CPX6**	**CPX7**	**CPX8**	**CPX9**
23.93±0.22	30.04±0.23	26.68±0.16	24.93±0.2	25.63±0.56	28.93±0.12	25.4±0.17	27.0±0.16	**29.83±0.18**
0.56±0.38	0.526±0.34	0.470±0.65	0.49±0.12	0.54±0.21	0.520±0.3	0.531±0.2	0.452±0.27	**0.467±0.22**
0.58±0.23	0.595±0.37	0.657±0.30	0.632±0.18	0.617±0.18	0.694±0.28	0.609±0.50	0.588±0.41	**0.544±0.32**
0.3±0.18	1.1±0.28	2.9±0.39	2.2±0.43	1.1±0.19	2.4±0.31	1.2±0.22	2.4±0.31	**1.5±0.25**
1.03±0.02	1.13±0.17	1.30±0.78	1.22±0.18	1.12±0.18	1.32±0.22	1.13±0.29	1.21±0.50	**1.18±0.28**
3.370±0.05	11.5±0.28	27.6±0.42	21.7±0.29	11.9±0.42	25.0±0.12	12.7±0.08	22.0±0.12	**14.0±0.16**
3.44±0.29	12.60±0.39	21.69±0.27	22.22±0.19	12.47±0.19	24.63±0.17	12.8±0.52	22.24±0.25	**14.8±0.21**
92.63±0.17	90.01±0.34	97.07±0.75	99.76±0.87	102.09±0.67	94.06±0.16	90.78±0.32	97.57±0.43	**93.76±0.35**

	Micrometric property	Angle of repose (θ)±SD	Bulk density (gm/ml)±SD	Tapped density (gm/ml)±SD	Void volume (±SD)	Hausner's ratio	Porosity (%)±SD	Carr's compressibility	Drug content (%)±SD

4.1 Fourier Transformer Infrared Spectroscopy (FTIR)

FTIR spectroscopy has been used to assess the interaction between levocetirizine and *β*-CD.

The IR spectrum of levocetirizine, *β*-CD, and physical mixture of sodium starch glycolate, crosspovidone, croscarmellose and mannitol are shown in **Figure 4.1-4.4**

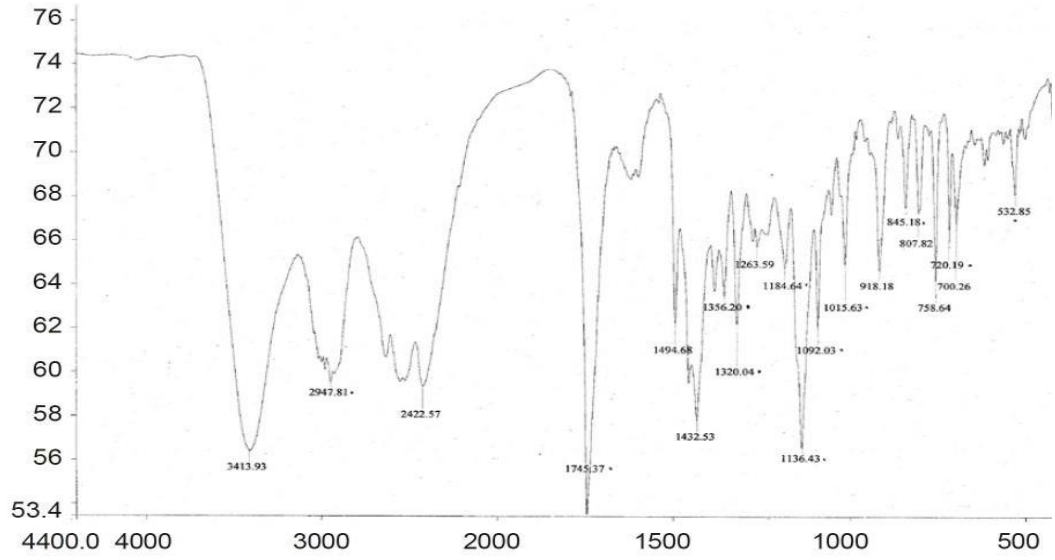


Figure 4.1 FTIR spectrum of Levocitrizine**.**

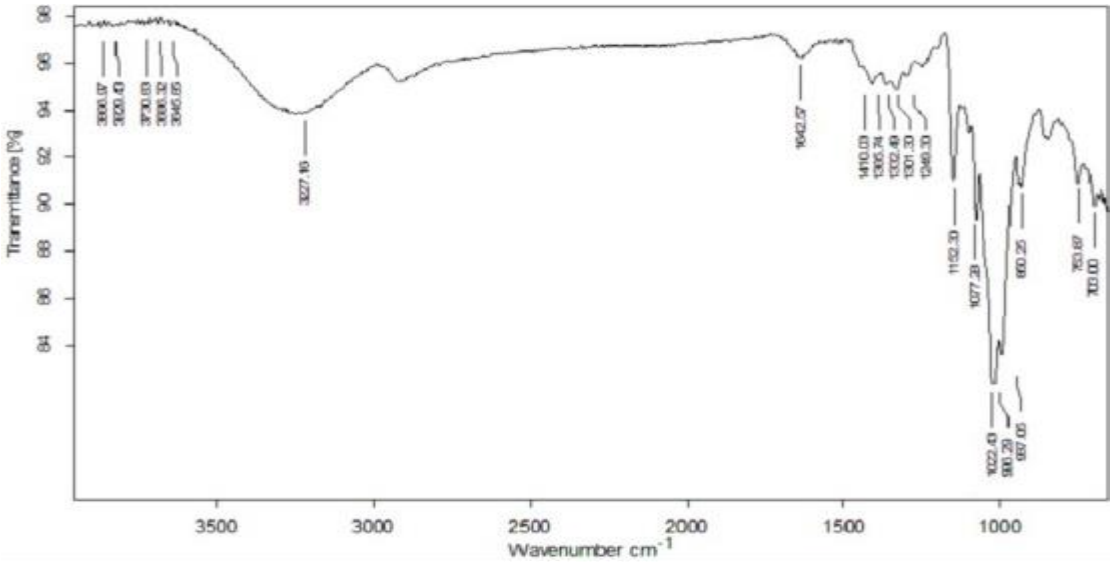


Figure 4.2 FTIR spectrum of *β*-CD

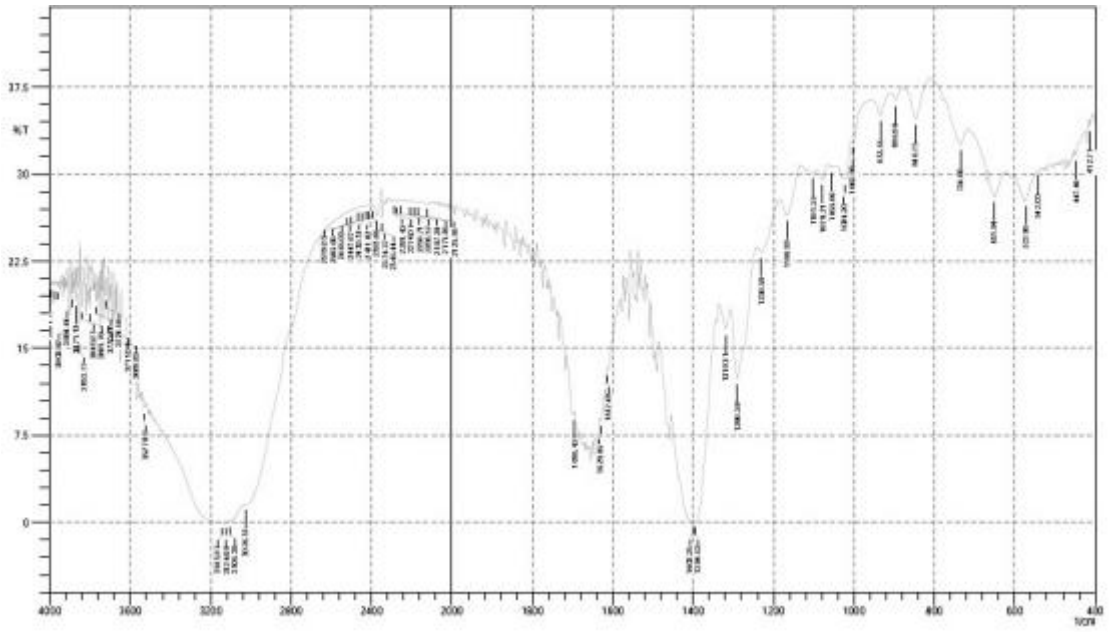


Figure 4.3 FTIR spectrum of physical mixture of drug-*β*-CD complex, sodium starch glycolate and mannitol.

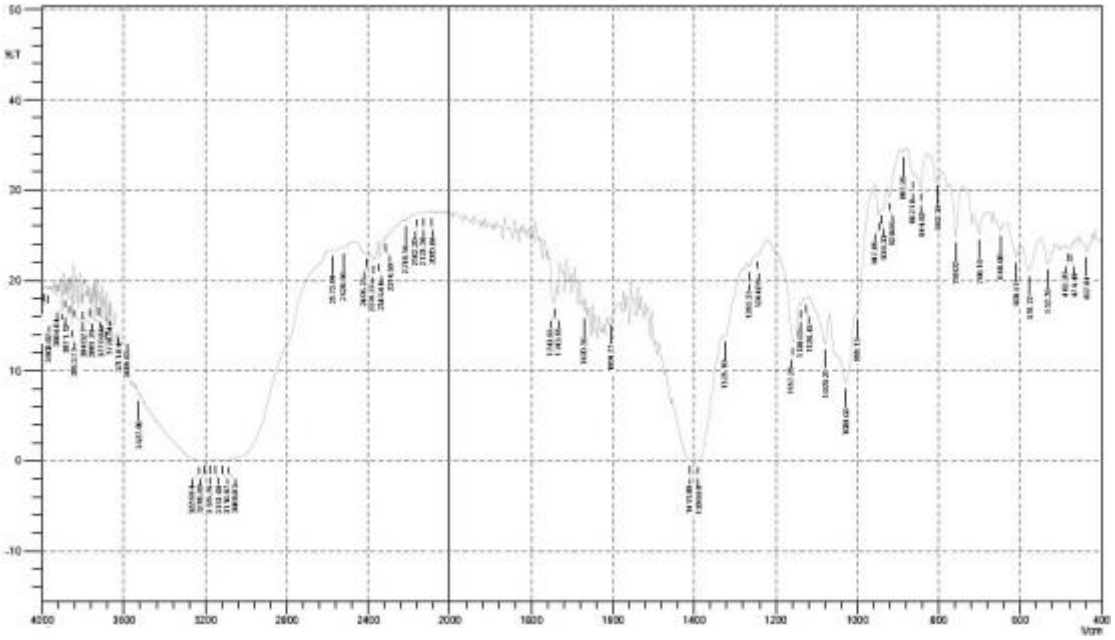


Figure 4.4 FTIR spectrum of levocetirizine-*β*-CD complex.

The IR spectrum of drug, polymer, physical mixture and other excipient did not show any significant change in the characteristic peaks of drug, which proved that the superdisintegrants and the other excipient were compatible with each other. The physical mixtures did not show any sign of discoloration and caking. Thus, the drug and excipient are physically compatible with each other.

4.2 Post- compression parameters

All the formulations were also evaluated for post compression parameters such as Uniformity of weight, Hardness, Thickness, Water absorption, Friability and their valuable results are shown in Table 3.

Table 3 Post Compression Parameters

Formulation Code	Uniformity of weight (mg/tablet) ± SD	Hardness (kg/cm^2) ± SD	Thickness (mm) ± SD	Water absorption ratio (%) ± SD	Friability (%) ± SD
CPX1	98.51±0.04	3.40±0.32	2.69±0.23	73.00±0.17	0.862±0.40
CPX2	100.41±0.12	3.90±0.06	2.00±0.56	65.33±0.45	0.255±0.21
CPX3	95.01±0.22	2.90±0.03	2.34±0.04	81.16±0.62	0.50±0.33
CPX4	92.03±0.3	3.80±0.02	2.43±0.08	91.66±0.98	0.34±0.26
CPX5	100.01±0.16	3.16±0.08	2.83±0.04	70.08±0.72	0.851±0.11
CPX6	98.0±0.01	2.90±0.0 4	2.16±0.07	85.00±0.09	0.255±0.18
CPX7	90.03±0.21	3.12±0.02	2.29±0.02	83.06±0.05	0.593±0.38
CPX8	91.04±0.12	3.20±0.12	2.99±0.05	108.33±0.68	0.341±0.26
CPX9	89.23±0.62	2.30±0.40	2.63±0.61	95.83±0.91	0.672±0.33

4.2.1 Invitro wetting time and disintegration time

Wetting time is closely related to the inner structure of the tablet. The tablet prepared by direct compression method had the wetting time between 12- 38 sec. The result of the wetting time and disintegration test has been shown in table 4

Formulation CPX5 and CPX4 had 12 and 19 sec wetting time, respectively. It had been found that the formulations containing SSG had less wetting time and a rapid decrease in wetting time was observed with an increase in super-disintegrate concentration. Figure 4.5 presents the relationship between wetting time and disintegration time of different fast disintegrating tablets. *In-vitro* dispersion behavior of formulation CPX 5 is presented in Figure 4.6

Table 4 Comparison between wetting time and disintegration time

Formulation code	Wetting time (sec) ± SD (n=3)	Disintegration time (sec) ± SD (n=3)
CPX1	24±0.19	35±0.24
CPX2	22±0.15	49±0.34
CPX3	29±0.20	40±0.29
CPX4	19±0.16	22±0.15
CPX5	12±0.03	20±0.07
CPX6	36±0.22	42±0.32
CPX7	21±0.18	37±0.42
CPX8	22±0.16	39±0.26
CPX9	38±0.24	45±0.39

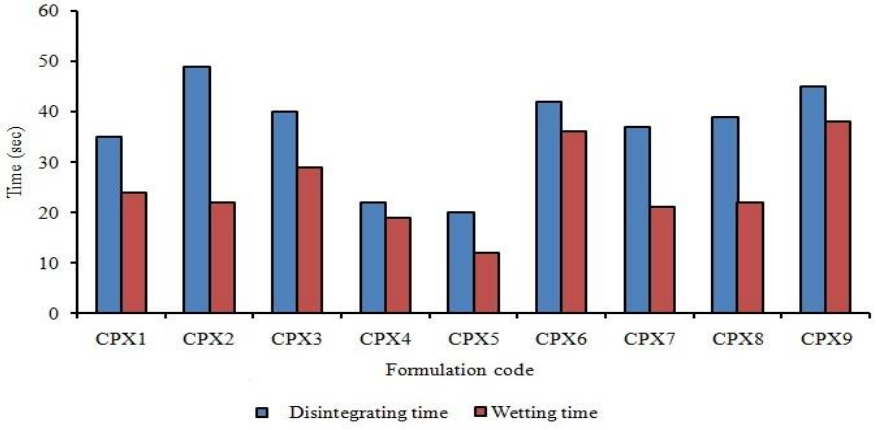


Figure 4.5 Relationship between wetting time and disintegration time of different fast disintegrating tablets (formulation CPX1 – CPX9).

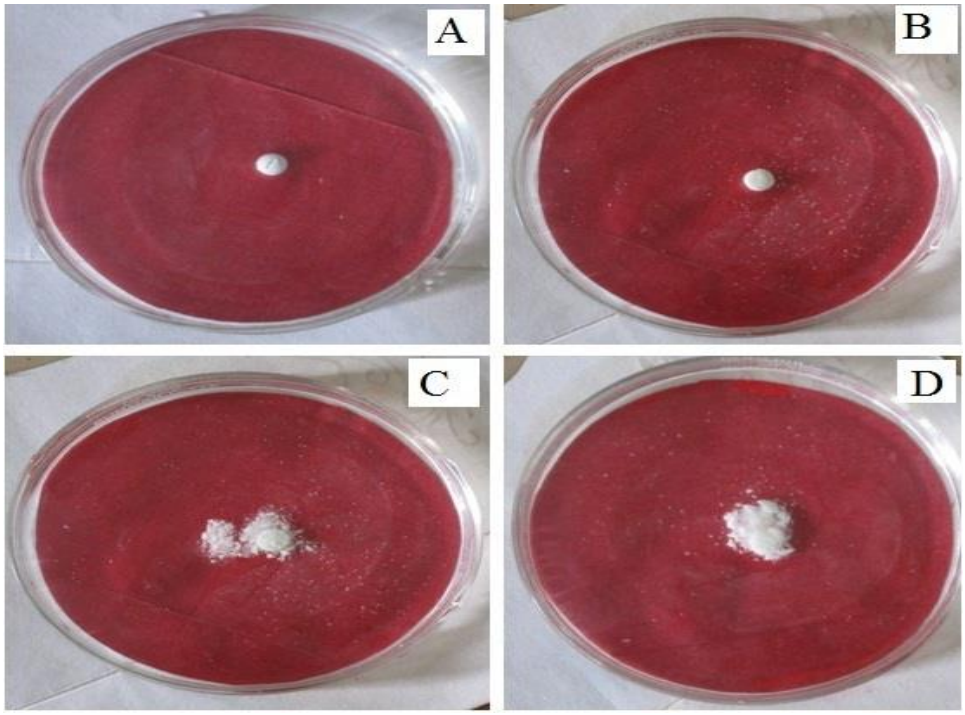


Figure 4.6 *In-vitro* dispersion behaviour of formulation CPX5,after 1 sec (A), after 4 sec (B), after 8 sec (C), after 10 sec (D).

4.2.2 In-vitro release

In Dissolution studies results were shown the drug release profile. In which we observed that drug releasing profile are more than 90% &drug was released within 10 min, their valuable data shown in (Table 5 and 6).

Table 5 *In-vitro* released rate profile of levocetrizine tablets (CPX1- CPX5)

Time (min)	Cumulative percentage drug release (mean ±SD) (n=3)				
	CPX1	CPX2	CPX3	CPX4	CPX5
0	0	0	0	0	0
2	36±0.23	42±0.44	47±0.43	34±0.87	41±0.98
4	52±0.46	55±0.75	58±0.54	54±0.46	61±0.34
6	60±1.03	73±0.05	62±0.26	65±0.66	69±0.12
8	73±0.65	81±0.83	73±0.34	76±0.76	81±0.14
10	89±0.45	92±0.43	90± 0.46	98±0.66	99±0.53

Table 6 *In-vitro* released rate profile of levocetrizine tablets (CPX6 –CPX9)

Time (min)	Cumulative percentage drug release (mean ± SD) (n=3)			
	CPX6	CPX7	CPX8	CPX9
0	0	0	0	0
2	26±0.44	34±0.21	28±0.73	30±0.50
4	48±0.56	59±0.14	45±0.71	48±0.45
6	61±0.29	68±0.27	64±0.64	63±0.22
8	70±0.52	77±0.36	78±0.23	71±0.34
10	85±0.22	93±0.61	95±0.45	83±0.75

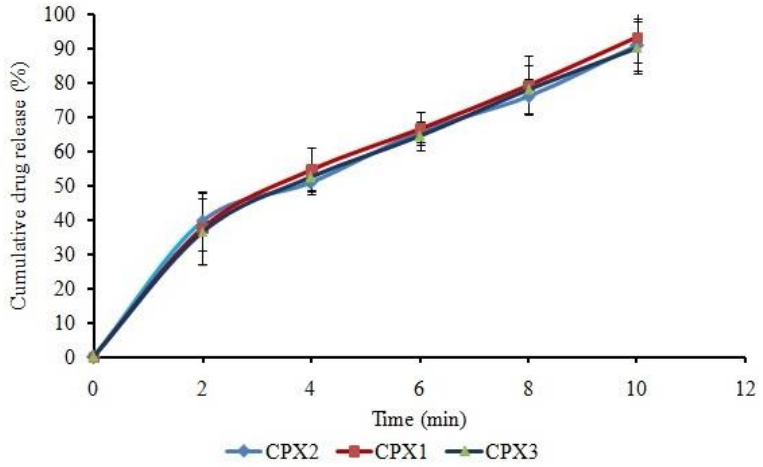


Figure 4.7 *In-vitro* release rate profile of levocetirizine formulation CPX1, CPX2, CPX3

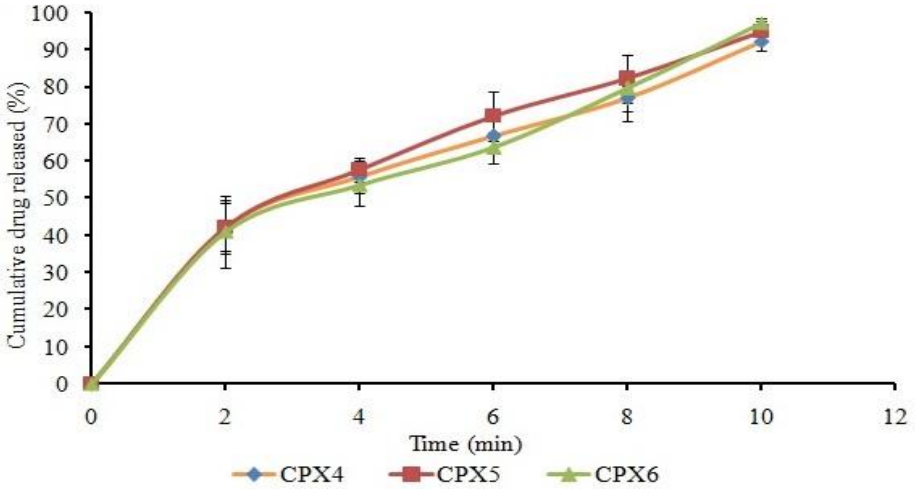


Figure 4.8 *In-vitro* release rate profile of levocetirizine formulation CPX4, CPX5, CPX6)

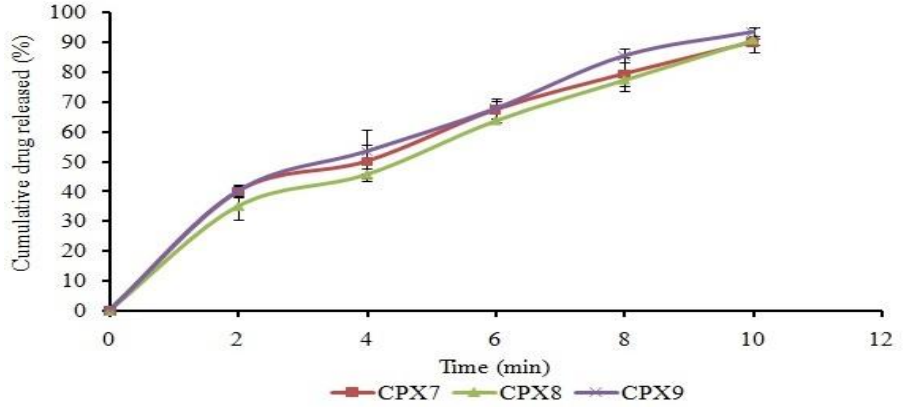


Figure 4.9 *In-vitro* release rate profile of levocetirizine formulation CPX7,CPX8,CPX9

As the concentration of super disintegratents increase, the release of drug also increases. The result suggested that when concentration of sodium starch glycolate use as superdisintegratents increases drug release profile was obtained 99% (Figure 4.7 – 4.8, 4.9).

From the table7 it is evident that the drug release from the developed fast release tablets followed first order release kinetics.

Table 7 Release kinetic data of formulation CPX1 – CPX9

Formulation code	Zero order	First order
	r^2	r^2

CPX1	0.923	0.926
CPX2	0.934	0.939
CPX3	0.944	0.960
CPX4	0.913	0.927
CPX5	0.919	0.935
CPX6	0.839	0.912
CPX7	0.933	0.971
CPX8	0.940	0.951
CPX9	0.939	0.958

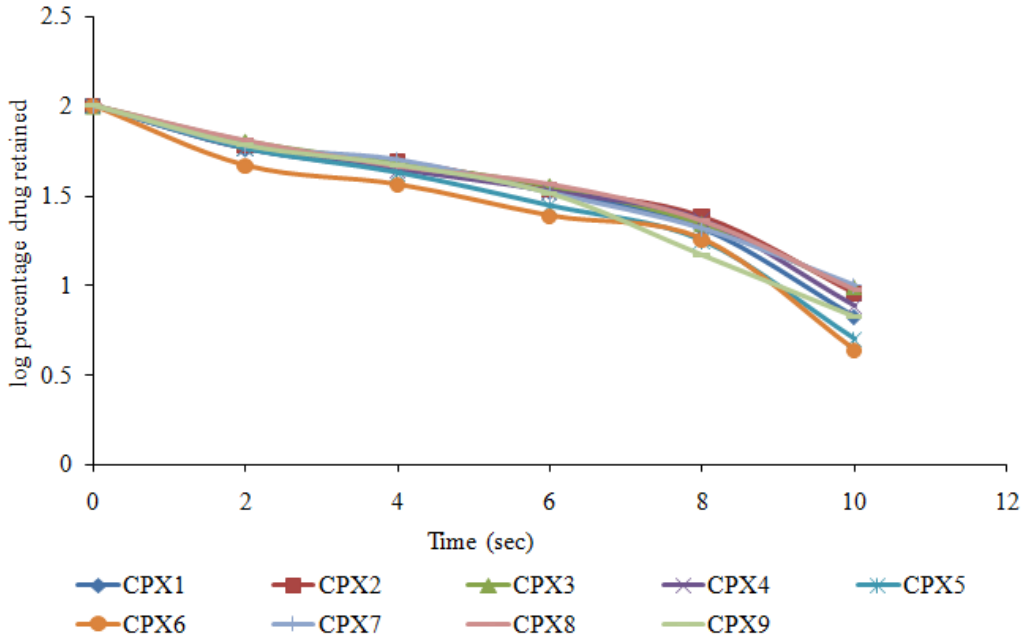


Figure 4.10 First order release profiles of levocetirizine formulation CPX1– CPX9

5. Conclusion

The orodispersible tablets of levocetirizine dihydrochloride were prepared by direct compression method. Various combinations of Sodium Starch Glycolate, Croscarmellose sodium and Crospovidone were used as the superdisintegrants for formulating the orodispersible. It was seen that increasing the concentration of the superdisintegrants decreased the wetting time and disintegration time of the formulations. The combination of SSG & CP was more effective in decreasing the disintegration time as compared to the combination of SSG & CCS and CP & CCS. The in-vitro dissolution study showed that the formulation containing SSG (6%) and CP (4.5%) was more effective in enhancing the rate of drug release from the orodispersible tablets. The comparison of the effect of individual superdisintegrant on the wetting time, disintegration time and dissolution showed that SSG was more suitable for the formulation of orodispersible tablets of levocetirizine dihydrochloride as compared to other superdisintegrants used in the current study. Hence from the present study, it can be concluded the superdisintegrant SSG and CP in appropriate concentration can be used to develop orodispersible tablets of levocetirizine dihydrochloride by direct compression method.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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