Formulation And Evaluation Of Mouth Dissolving Tablet Of Loratadine

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ABSTRACT
Loratadine (Lor) is classic H1-receptor antihistamines for the relief of allergic diseases such as allergic rhinitis and urticaria. They are competitive inverse agonists of the H1 receptor that have relatively high specificity and can stabilize the receptor in inactive state. They are classified as second generation H1-receptor antihistamines due to non-sedating advantages over the first-generation products. Compared to the first-generation drugs, which rapidly get into central nervous system, Lor have higher peripheral selectivity and do not cross the blood-brain barrier. Thus, they seldom cause side effect like drowsiness or somnolence and can be taken by patients of special occupation including pilots or drivers. To provide the patient with the most convenient mode of administration, there is need to develop a fast-disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without water, anywhere, any time. Such tablets are also called as "melt in mouth tablet." Direct compression, freeze drying, sublimation, spray drying, tablet molding, disintegrant addition, and use of sugar-based excipients are technologies available for mouth-dissolving tablet. The objective of the present study is to design a tablet of Loratadine for delivery through oral cavity. Fast dissolving tablet are prepared when immediate onset of action is desired. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastrointestinal tract and liver. Mouth-dissolving tablets of Loratadine were prepared by direct compression, in which different formulations were prepared with varying concentration of excipients. These tablets were evaluated for their friability, hardness, wetting time, and disintegration time; the drug release profile was studied. Direct compression batch LF3 gave far better dissolution which released 99.10±2.92% in 10 minutes.

KEYWORDS- Loratadine, Mouth dissolving tablet, direct compression, Anti-histamine, Doshion, SuperD33.

1. INTRODUCTION

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with the prescription which results in noncompliance and ineffective therapy. Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration to achieve better patient compliance. Rapidly disintegrating tablet are appreciated by significant segment of the population, particularly pediatric, geriatric, unconscious, and bed-ridden patients who have difficulty swallowing conventional tablet and capsule.[1,2] To overcome this, dispersible tablets and fast-disintegrating tablets have been developed. Most commonly used methods to prepare these tablets are freeze drying/lyophilization, tablet moulding, and direct compression methods. Lyophilized tablets show a porous structure, which causes very quick penetration of saliva into the pores when placed in oral cavity, but it has disadvantage of high cost production process.[3-6]

Conventional loratadine tablet available in the market are not suitable for allergenic conditions where quick onset of action of drug is required. This is because of poor patient compliance, particularly by the geriatric and pediatric patient who experience difficulty in swallowing, and by those who are bed ridden or who are traveling and do not have an easy access to water. Loratadine (Lor) is classic H1-receptor antihistamines for the relief of allergic diseases such as allergic rhinitis and urticaria. They are competitive inverse agonists of the H1 receptor that have relatively high specificity and can stabilize the receptor in inactive state. They are classified as second generation H1-receptor antihistamines due to non-sedating advantages over the first generation products. Lor reaches peak blood concentration 1.5 h after oral dosing and rapidly metabolized by liver through first pass effect. The major active metabolite of Lor is descarboethoxyloratadine, which was four times more potent than Lor the elimination half-life is 8–14 hours for Lor and 17–24 hours for Des, which leads to the 24-hour duration of action when Lor is administered. [7-8]

The rapidly disintegrating tablets in oral cavity can be swallowed with a small amount of water or saliva. The tablet manufactured by any of the above mention methods are composed of drug and other excipients which disintegrate in small amount of water or saliva in the oral cavity within 30 seconds. Hence, an attempt was made to improve the dissolution of loratadine through the formulation of mouth-dissolving tablets with appropriate mechanical strength, which would disintegrate in oral cavity, in less than 30 seconds, and would provide an immediate relief from pain due to its faster dissolution in gastrointestinal tract.

2. MATERIALS AND METHODS

PVP K-30, magnesium stearate, talcum, sodium lauryl sulphate, and aspartame were purchased from CDH (P) Ltd., New Delhi. Loratadine were obtained as a gift sample from Alembic Pharmaceutical Pvt. Ltd, Vadodara. All other materials used were of pharmaceutical grade.

2.1 UV Spectral Analysis: "The ultraviolet absorbance of Loratadine was scanned from 400 to 800 nm then the wavelength of maximum absorbance was compared with reported λ max; 100 mg of Loratadine was accurately weighed and transferred to 100 ml volumetric flask and the drug was dissolved in 100 ml 6.8 phosphate buffer to get a solution of 1000 µg/ml (stock solution I); 10 ml of stock solution I was diluted to 100 ml with 6.8 pH phosphate buffer to get a solution of l00 ug/ml (Stock solution II)".

2.2 Infra Red Spectral Analysis: To determine the identify of medications, infrared spectroscopy was performed. By compressing 3-5 mg of each medication with 100-150 mg of potassium bromide in a KBr press, a pellet with a diameter of around 1 mm was created. Using a Shimadzu FTIR, the pellet was placed within an IR chamber and scanned between wave numbers 4000-600 cm^{-1}.

2.3 Compatibility Studies: The drug-polymer compatibility was first visually assessed. The drug-polymer compatibility was then further verified by taking an IR spectrum thermogram of the drug and polymer, as well as a physical mixing of the two, which demonstrated that the excipients were compatible with the loratadine. [9]

2.4 Formulation And Development

2.4.1. Preparation of mouth dissolving tablets: Loratadine mouth dissolving tablets were made using the direct compression method and the formula found in Table 1. Separately, each ingredient was run through 60 mesh sieves. Each time, a small amount of the medication and microcrystalline cellulose were combined, blended, and set aside to create a homogenous combination. Subsequently, the components were measured and combined in a geometric configuration, and the tablets were formed using a Rimek Compression Machine with an 8mm flat round punch. [7, 10]

Table 1: Formulation Chart

Ingredients (mg)	Formulation								
	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9
Loratadine	10	10	10	10	10	10	10	10	10
Doshion	5	7.5	10	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	5	7.5	10	-	-	-
Super D33	-	-	-	-	-	-	5	7.5	10
Aspartame	3	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1	1
MCC	30	30	30	30	30	30	30	30	30
Mg stearate	1	1	1	1	1	1	1	1	1
D- Mannitol	50	47.5	42.5	50	47.5	42.5	50	47.5	42.5
Total	100	100	100	100	100	100	100	100	100

* Average of three determinations

2.5 Post-Compression Parameters: [11, 12]

2.5.1 Hardness Test: Tablets must have a specific level of checking a hardness or resistance to a cracking, in order to survive handling shocks during production, packaging, and shipment. Using a Monsanto Hardness Tester, the tablets' hardness was assessed. Kg/cm^2 is used to express it. The value of mean and standard deviation was calculated. After three tablets at random were selected from each formulation.

2.5.2 Friability Test: It is a phenomena whereby tablet surfaces that are subjected to mechanical shock or attrition sustain damage and/or exhibit signs of lamination or fracture. The Veego Friabilator was used to assess the friability of tablets. It has a percentage (%) as its expression. After being initially weighted (Winitial), twenty pills were put into the friabilator. The friabilator was run for four minutes at 25 rpm or up to 100 rotations. Once more, the tablets were weighed (Wfinal). Next, the percentage of friability was determined by

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

% friability of tablets less than 1% is considered acceptable.

2.5.3 Weight Variation Test: To look for weight variance, pills were randomly chosen from each formulation and weighed separately. A slight variance in a tablet's weight is permitted by the US Pharmacopoeia. The permitted weight fluctuation is up to the following percentage deviation.

Table 2.5: Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

7.5% maximum variation allowed because the tablet weight in all formulations was greater than 130 mg and less than 324 mg.

2.5.4 Uniformity Of Thickness: A micrometre can be used to measure the crown thickness of a single tablet, allowing for precise measurements and the provision of data regarding tablet variance. A sliding calliper scale is used to measure the overall crown thickness of five or ten tablets that are placed in a holding tray as part of another production control approach. A screw gauge was used to measure the tablet's thickness.

2.5.5 Drug Content Uniformity: 100 mg of medication were put into 100 millilitres of distilled water using four tablets that were weighed, crushed in a mortar, and then weighed powder. the 1000 mcg/ml concentration of it. "1 millilitre of this stock solution is taken and diluted to make a millilitre of distilled water, or l00 µg/ml and next, a 20µg/ml solution was made by diluting 2 millilitres of the stock solution to get 10 millilitres". At 275 nm, absorbance is measured.

2.6.6 Wetting Time: Tablet wetting time was measured using this method. "A tablet was placed on a piece of tissue paper that had been folded twice and placed in a tiny petri dish (i.d. = 6.5 cm) with 10 ml of water". The duration of the tablet's complete wetting was then recorded. Every batch underwent three trials, and the standard deviation was also ascertained.

2.5.7 Water Absorption Ratio: In a tiny petri dish with a piece of tissue paper folded twice, there was six millilitres of water. After being put on the paper, the length of time required for a tablet to get completely wet was measured. Next, the moist tablet was weighed. We used the following calculation to calculate the water absorption ratio, or R.

$$R = 100\ (Wa - Wb)/Wb$$

Where,

Wb - weight of tablet before absorption.

Wa - weight of tablet after absorption

Each formulation was tested with three tablets, and the standard deviation was also found.

2.5.8 In Vitro Disintegration Time: Disintegration is the breakdown process of a tablet into smaller pieces. Using disintegration test equipment in accordance with LP requirements, the in vitro disintegration time of a tablet was ascertained. LP. Details: Put one tablet into each of the basket's six tubes. "Place a disc in each tube and operate the device with an immersion liquid that is 37°±2°C and has a pH of 6.8 (simulated saliva fluid) and the assembly needs to be raised and lowered thirty times per minute at a pH of 6.8 and a temperature of 37°±2°C; the duration in seconds required for the tablet to completely dissolve and leave no discernible mass inside the device was calculated and noted".

2.5.9 In Vitro Dissolution Studies: Using a paddle stirrer running at 50 rpm, the in vitro dissolution of Loratadine mouth dissolving tablets was investigated in a USP XXIII type-II dissolution equipment (Electrolab TDT-06N). As a dissolving media, 900 millilitres of pH 6.8 phosphate buffer were utilised. "Throughout the experiment, the dissolving medium's temperature was kept at 37±0.5 °C; every test used a single pill; five millilitre samples of the dissolving liquid were taken out using a syringe equipped with a pre-filter at predetermined intervals, and the absorbance at 275 nm was used to measure the release of the medication and a new volume of dissolving liquid was added to the volume removed at each time interval". Plotting the cumulative % of released loratadine against time was done.

2.5.10 Stability Testing: 15 tablets were stored at an elevated temperature of 40 ± 2 °C/75±5% RH (Stability chamber, Osworld) for a duration of 60 days (2 months) in order to conduct accelerated stability studies on potential Loratadine formulations LF9. The tablets were visually inspected for physical changes, variations in the drug content, and variations in the in vitro dispersion time at one-month intervals.

3. RESULTS AND DISCUSSION

3.1 Development of Analytical Method by U.V. Spectroscopy: Loratadine's λ max was found to be 275 nm after the diluted samples with concentrations ranging from 2 to 20 µg/ml were scanned using a double beam UV spectrophotometer. The ultraviolet spectrum was shown in figure 1. A double beam UV spectrometer was used to detect the absorbance at 275 nm and plot the calibration curve for loratadine, which has a concentration range of 2–20 µg/ml. These concentrations showed linearity, as did the curve in Figure 2, contained data from the calibration curve.

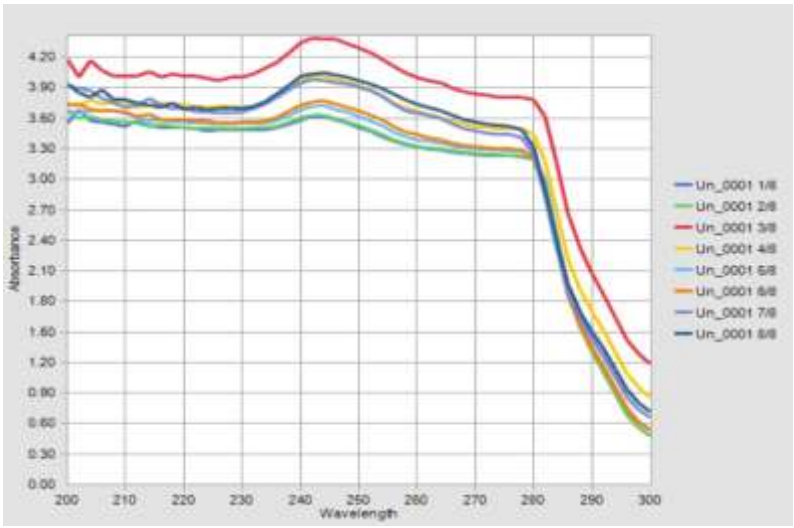


Figure 1: Spectroscopic curve of Loratadine

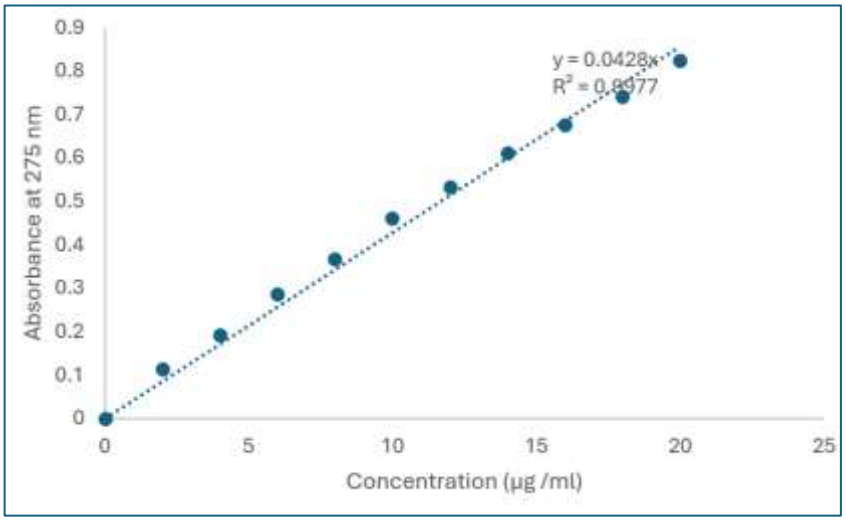


Figure 2: Calibration curve of Loratadine in Phosphate buffer pH 6.8

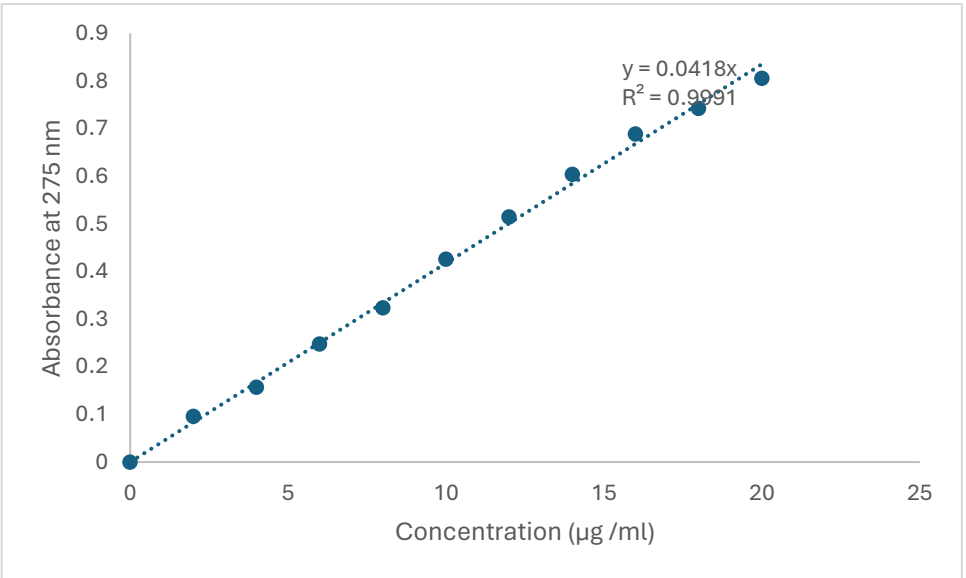


Figure 3: Calibration curve of Loratadine

3.2 IR Spectroscopy: It was discovered that the infrared spectra of the pure drug loratadine resembled that of the normal IP form of the medicine. The following functional groups were visible at the respective frequencies in the loratadine spectrum. The following tables displayed the standard spectra of medications.

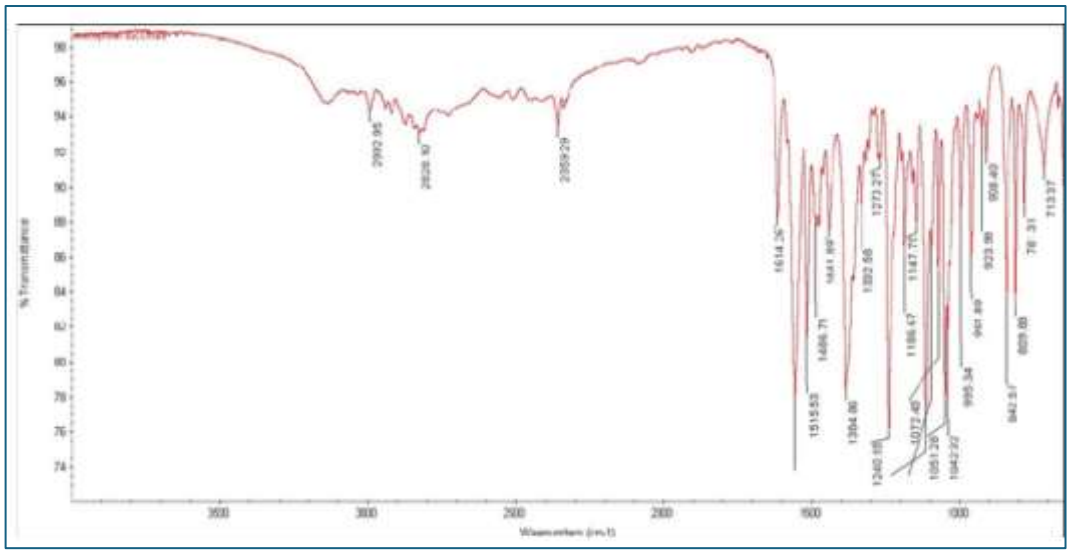


Figure 4: FTIR Spectra of Loratadine (Standard)

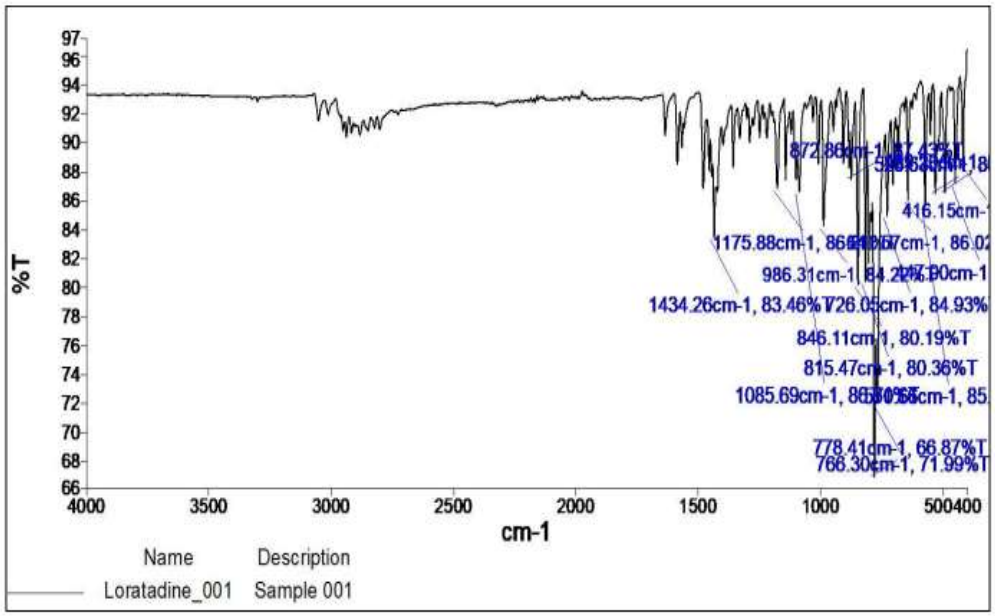
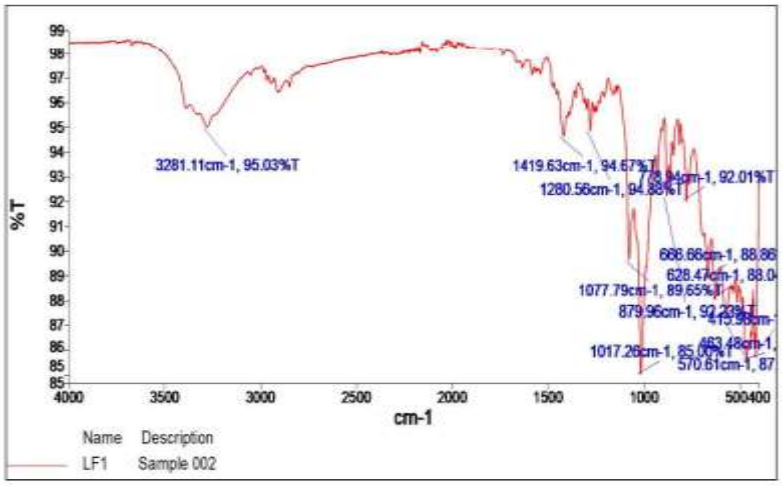


Figure 5: FTIR Spectra of Loratadine (Pure drug)

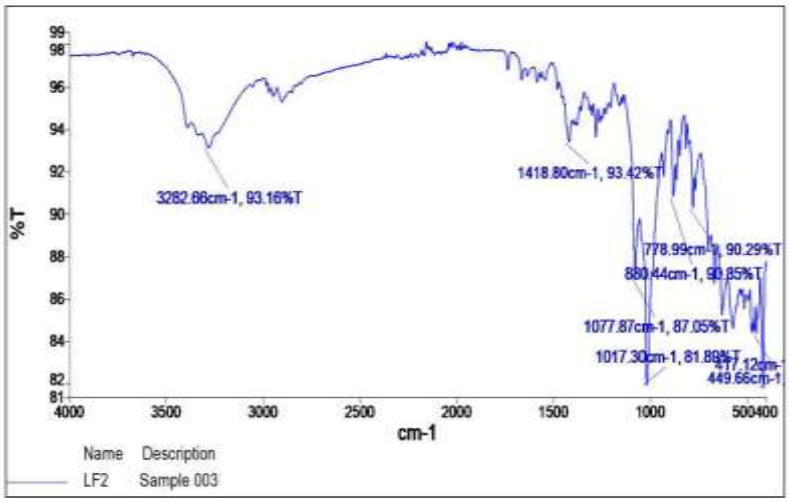
It is clear from the IR studies that there won't be any potential chemical interaction between the medications and the excipients. Thus, the formulation made use of these excipients. There's no characteristic peak emergence or disappearance. This demonstrates that the medication and the polymer employed do not interact.

3.3 Compatibility For a product to be stable, effective, safe, and simple to administer, the medicine and excipients must get along well. An assessment of physical compatibility was conducted using visual aids. Since there was no alteration in the physical description, the study suggests that the medication, polymer, and other excipients were physically compatible with one another. IR spectroscopy was used to examine the samples that had been charged in stability chambers at 45 °C and 75% relative humidity after 30 days. It is clear from the IR studies that there won't be any potential chemical interaction between the medications and the excipients. Thus, the formulation called for the use of these excipients. There's no characteristic peak emergence or disappearance. This demonstrates that the medication and the polymer employed do not interact.

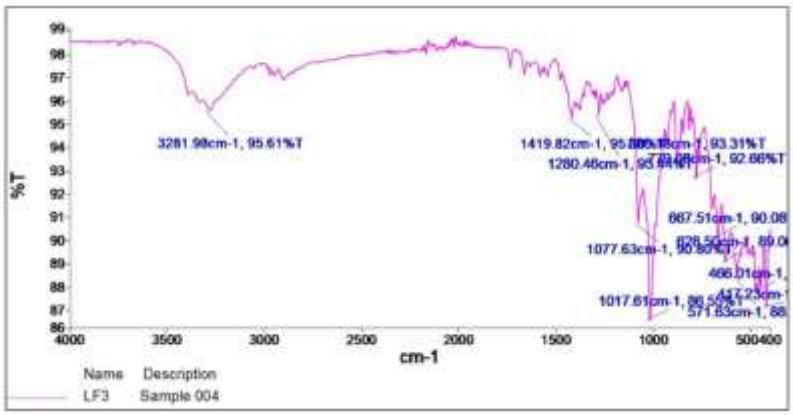
3.3.1 By FTIR Spectra: To evaluate the compatibility of the medications and excipients, FTIR spectra were obtained. The study was carried out in accordance with the protocol described in the material and methods section. Figure 6 shows the representation of the FTIR Spectra.



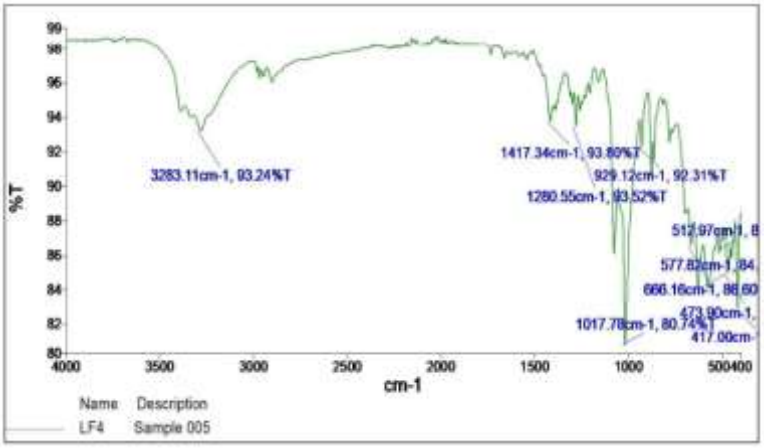
FORMULATION LF1



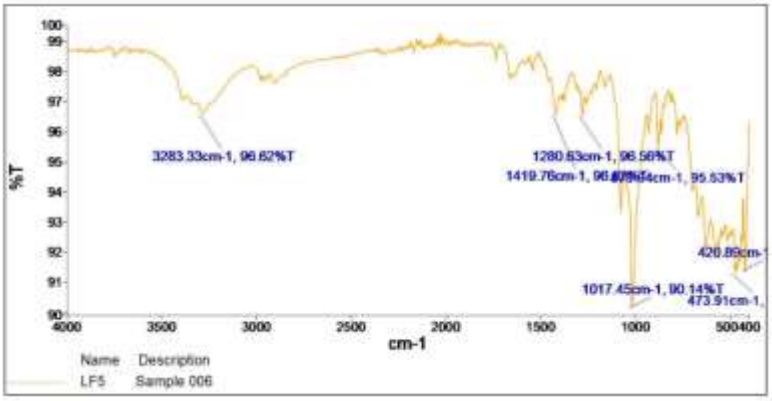
FORMULATION LF2



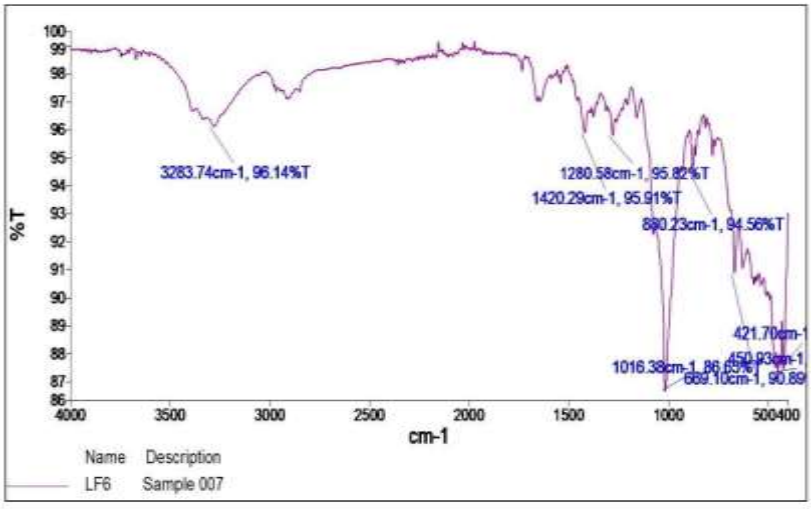
FORMULATION LF3



FORMULATION LF4



FORMULATION LF5



FORMULATION LF6

Figure 6: FTIR Spectra formulation LF1-LF6

Drug compatibility with the physical combination of the drug(s) and polymer. Loratadine FTIR spectra showed a distinctive C=O stretching band at 1052.20 cm^{-1}, which is consistent with the values that have been published. The findings demonstrated that there was no chemical interaction and that the medicine was compatible with all excipients based on changes in the FTIR spectra of the drug and different excipients, either separately or in combination.

3.4 POST-COMPRESSION PARAMETERS:

3.4.1 Hardness: All of the tablets made using both techniques had hardness levels between 2.1±0.02 and 2.5±0.01 kg/cm^2. Table 2 lists the results of the mean hardness test.

3.4.2 Weight Variation Test: In every proposed formulation, there was a weight fluctuation within the range of 99 ± 5 to 104 ± 5 mg. Table 2 displays the results of the mean weight variation test. “Since the average percentage of weight variation was within the pharmacopoeia's limitations, or 7.5%, all of the pills passed the weight variation test”.

3.4.3 Thickness: The average thickness, which varied from 2.31 ±0. 13 mm to 2.45 ±0. 12 mm, was nearly constant throughout all three formulations (n = 3). According to the standard deviation values, every formulation fell inside the given range. Table No. 2 displays the tablet thickness data.

Table 2: Post Compression Parameters (Diameter, Hardness, Thickness, Weight Variation

Formulation Code	Diameter (mm)	Thickness (mm)	Hardnes (kg/cm^2)	Weight Variation (mg)
LF1	3.02 ± 0.011	2.45 ±0.12	2.1±0.02	101 ± 5
LF2	4.03 ± 0.010	2.37 ±0.14	2.3±0.02	102 ± 5
LF3	3.02 ± 0.011	2.41 ±0.12	2.5±0.01	103 ± 5
LF4	3.04 ± 0.012	2.32 ±0.14	2.3±0.02	104± 5
LF5	4.03 ± 0.010	2.39 ±0.15	2.4±0.01	99.6 ± 5
LF6	3.04 ± 0.012	2.42 ±0.16	2.3±0.02	103 ± 5
LF7	4.04 ± 0.010	2.38 ±0.13	2.5±0.05	99 ± 5
LF8	3.03 ± 0.012	2.31 ±0.13	2.4±0.02	102 ± 5
LF9	3.02 ± 0.010	2.352±0.12	2.3±0.02	101 ± 5

3.4.4 Friability Test: All proposed formulations with friability between 0.34 and 0.76% were determined to be well within the permitted range (< 1 %). The findings of the friability investigation were tallied in table 3.

3.4.5 Wetting Time: The internal composition of the tablet has a direct bearing on the wetting time. Table No. 3 presents the wetting time results. The direct compression and sublimation methods of loratadine preparation yielded wetting times ranging from 42.6 ±1.42 to 48.6 ±1.43 seconds.

3.4.6 Water Absorption Ratio: Formulations with a mere 3%of super disintegrant exhibit a lower water absorption ratio than formulations with 12% of super disintegrant; this decrease is also attributed to less swelling property. The formulations prepared using both techniques show wetting times in the range of 60±1.45 to 82±1.15%. It has been noted that as CCS concentrations rise, the water absorption ratio also rises because CCS is produced by the cross-linking process of sodium CMC. The cross-linking process significantly decreased the solubility of sodium CMC in water, allowing the material to expand and absorb water up to 32 times its own weight. Table No. 3displays the water absorption ratio data.

3.4.7 In Vitro Disintegration Time: The amount of time needed for uniform dispersion is used to calculate the in vitro disintegration time. All of the formulations showed rapid disintegration within a few minutes. The data pertaining to in-vitro disintegration can be found in Table No. 3. The regulatory standards were satisfied by the in vitro disintegration time of loratadine synthesised via direct compression, which ranged from 14.12±1.23 to 22.75±2.05 seconds.

3.4.8 Drug Content: For each of the nine formulations, the drug content homogeneity was tested; the findings are listed in table No. 3. For every batch, three trials were subjected to spectrophotometric analysis. The pills' percentage drug content was determined to be 96.5 ± 6.78 to 99.7 ± 6.33% loratadine. The results showed homogeneous mixing because they fell within the range.

Table 3: Post Compression Parameters

Formulation Code	Friability (%)	Wetting Time* (sec)	Water Absorption Ratio	Disintegration time (sec)	Drug Content* (%)
LF1	0.65	44.5 ±1.32	80±1.42	18.12±1.76	97.9 ± 4.98
LF2	0.76	48.5 ±1.34	78±1.34	14.12±1.23	99.5 ± 2.54
LF3	0.58	42.6 ±1.42	75±1.62	13.12±1.56	99.7 ± 6.33
LF4	0.63	45.6 ±1.42	78±1.43	21.23±2.03	98.8 ± 5.85
LF5	0.73	44.2 ±1.05	82±1.15	22.75±2.05	96.5 ± 6.78
LF6	0.65	45.6 ±1.24	73±1.22	19.34±1.78	98.5 ± 5.53
LF7	0.34	48.6 ±1.43	76±1.23	20.54±2.11	99.6 ± 6.32

LF8	0.53	45.3 ±1.25	60±1.45	22.11±2.21	98.6 ± 5.66
LF9	0.72	44.2±1.24	68±1.34	17.46±1.62	97.5 ± 6.33

3.4.9 In Vitro Dissolution Studies: 900 millilitres of phosphate buffer pH 6.8 was used as the dissolving medium in a USP type-II apparatus (USP XXIII dissolving Test Apparatus at 50 rpm) to study the dissolution rate. The dissolution medium was kept at 37±0.5°C in temperature. An aliquot of the medium was taken out and filtered every minute. The UV spectrophotometric method was used to measure the absorbance of the filtered solution at 275 nm, and a standard calibration curve was used to quantify the drug's concentration.

Figures 3.7–3.9 depict the disintegration of loratadine from the tablets. The release profiles are displayed in Table 4. These values shifted when the tablet preparation technique was altered.

The medicine dissolved more quickly in tablets made using the camphor sublimation approach than in tablets made using other methods once the mode of tablet manufacture was switched to sublimation. This could be because of their lowest hardness and their porous nature, which allows for faster water absorption and, in turn, allows sodium starch glycolate to wick through more easily, resulting in speedier breakdown. Due to the tablets disintegrating quickly, all of the formulations had rapid drug release percentages (85.65±1.65% - 99.10±2.92 %).

Following a 10-minute duration, the in vitro dissolving investigation of all formulations (LF1-LF9) yields a maximum drug release of 99.10±2.92 % WN for formulation LF3. For every post-compression characteristic, including hardness, friability, weight variation, and drug content, all of the fractionations fell below the bounds. Here, after 10 minutes, LF3 had better drug release and a shorter disintegration time. Therefore, the optimal formulation was determined to be LF3, which contains Croscarmellose sodium as the disintegrant.

Table 4: Release profile of Loratadine mouth dissolving tablets

S. No.	Time in Min	% Cumulative Drug Release		
		LF1	LF2	LF3
1	0	0.00	0.00	0.00
2	2	87.97±1.65	87.65±2.34	88.18±1.48
3	4	90.12±1.45	91.59±2.58	90.11±2.28
4	6	93.45±1.32	93.11±4.12	92.39±2.12
5	8	96.78±3.06	96.44±3.62	94.21±2.69
6	10	97.67±3.45	97.62±4.59	99.62±2.92

Table 5: Release profile of Loratadine mouth dissolving tablets

S. No.	Time in Min	% Cumulative Drug Release		
		LF4	LF5	LF6
1	0	0.00	0.00	0.00
2	2	85.65±1.65	87.11±1.54	88.45±6.28
3	4	89.14±2.45	88.56±2.63	90.45±4.28
4	6	92.42±1.87	90.23±3.37	90.45±2.28
5	8	95.45±3.06	92.56±2.56	91.18±1.99
6	10	96.67±3.45	95.56±3.62	94.11±4.26

Table 6: Release profile of Loratadine mouth dissolving tablets

S. No.	Time in Min	% Cumulative Drug Release		
		LF7	LF8	LF9
1	0	0.00	0.00	0.00
2	2	88.11±2.32	86.65±2.34	87.18±1.48
3	4	90.23±1.36	88.59±2.58	89.11±2.28
4	6	91.11±2.26	91.56±4.12	91.45±2.12
5	8	94.43±2.11	94.47±3.62	95.75±2.69
6	10	96.62±2.23	96.25±4.52	98.62±2.92

3.4.10 Stability Study

Enhanced composition for 60 days, LF4 was put through stability tests at 40 ± 2°C/75 ±5% RH. The product's description, medication content, and in vitro disintegration time were assessed. Studies on drug release were carried out in accordance with protocol.

Table 7: Description

Storage Condition	Taste	Observation	Inference
RT	Descriptions	No changes of colour in all formulations	Complies with stability condition
40 ± 2°C/75±5% RH	Descriptions	No changes of colour in all formulations	Complies with stability condition

Table 8: Stability data of LF9 formulation

S. No.	Time in Days	Physical Change	% Drug Content	In-vitro disintegration time
1.	1st day	--	99.7±6.33	13.12±1.56
2	30	--	98.2±5.23	12.78±0.99
3	60	--	97.6±5.12	12.07±0.45

4. CONCLUSION

In the current study, superdisintegrants such sodium starch glycolate, microcrystalline cellulose, Doshion, and SuperD33 were used to directly compress mouth-dissolving loratadine tablets. The study and results revealed that the method of preparation of formulation significantly affect the disintegration time, percentage friability, and release of drug. Present study underlines the importance of process variables. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts and direct compression technique would be an effective alternative approach.

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