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Formulation and evaluation of loratadine chewable tablets

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ABSTRACT

Loratadine, histamine H_1 receptor antagonist used in the treatment of allergic rhinitis and urticaria Administration of Loratadine through oral route is a challenge in children, who have not yet learned to swallow tablets. In the present study five batches of Loratadine chewable tablet dosage form at the dose of 5 mg was formulated and evaluated. Results showed that thickness, weight variation, friability, hardness, and content uniformity of all five formulations were within the acceptance limits. But in the in-vitro dissolution study, formulation 1, 2 and 5 demonstrated better cumulative drug release than formulation 3 and 4. However, cumulative drug release of formulation 5 was comparable with innovator than formulation 1 and 2. Three month stability study of formulation 5 revealed that there were no significant change in physical parameters, drug content and dissolution profile. Hence the study concludes that Loratadine chewable tablets formulated using Avicel CE 15 and starch paste (Formulation 5) showed better characteristics of chewable table.

Keywords: Loratadine, Chewable tablets, Avicel CE 15, Microcrystalline cellulose and guar gum

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INTRODUCTION

Loratadine is a piperidine derivative and is a long acting selective peripheral H_1 antagonist which lacks CNS depressant effects used in the treatment of allergic skin disorder, specially atopic dermatitis and urticaria, allergic rhinitis, acute coryza, ocular allergies at the dose of 10 mg once a day in adult and 5 mg (if ? 30 kg) or 10 mg (if ? 30 kg) in 2 – 12 years children [1]. Administration of drugs through oral route is the most common and the easiest way to administer a drug. But it is a challenge in children who have not yet learned to swallow tablets. Hence it was decided to formulate Loratadine chewable tablet to improve the compliance in children. Additionally, chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action. The main objectives of the present study were to formulate and evaluate Loratadine chewable tablet dosage form at the dose of 5 mg and to study the various formulation variables that affect the drug release.

MATERIALS AND METHOD

This study was conducted at Micro Advanced Research Centre of Micro labs, Bangalore and at Annamalai University. All chemicals and reagents used for this study were of analytical grade. Chemicals used along with supplier details are as follows Loratadine (Urolabo, Spain), Microcrystalline cellulose 70% and guar gum 30% (Avicel CE 15 - FMC Biopolymer), Lactose monohydrate (Pharmatose-200M - DMV Fonterra), Mannitol (Pearlitol-25C - Roquette), Ethyl cellulose (Ethocel std 10FP - Colorcon), Maize starch (Universal), Povidone K 30 (PVP K 30 - Signet), D&C Yellow No.6 (Colorcon), Citric acid (Kinsun), Raspberry flavour (Givaudan), Aspartame (Manus aktteva), Sodium starch glycolate (Signet), Colloidal silicon dioxide (Aerosil - Cabot) and Magnesium stearate (Ferro).

EXPERIMENTAL

Identification and flow property of loratadine

Loratadine was identified by organoleptic evaluation, UV Spectroscopy, FT-IR spectroscopy [2] and Differential Scanning Calorimetry [3]. Flow properties of Loratadine were determined by Carr's index, Hausner's ratio and angle of repose [4].

Drug-excipient compatibility study

Compatibility between Loratadine and excipients were studied after exposing the blend at 25^{o}C / 60% RH and 40^{o}C / 75% RH. The bend was observed for any physical change in 15th and 30th day. Further compatibility was confirmed by Differential Scanning Calorimetry [5].

Preparation of loratadine chewable tablets

Chewable tablets containing 5 mg Loratadine were prepared with a total tablet weight of 550 mg by wet granulation method. Quantity of Loratadine and excipients are given in Table 1. Loratadine and other required excipients were sieved and mixed at a slow speed in "Rapid Mixer Granulator" to get a dry mix. Povidone K 30 and D&C Yellow were dissolved in purified water to get a binder. Maize starch and D&C Yellow were dissolved in purified water to get a starch paste. Dry mix was added to either binder or starch paste, granulated and the obtained wet mass was dried in "Fluidized bed dryer" at 60^{o}C. Dried granules were sieved through 20# mesh sieve. Excipients like lubricant and flavoring agents were then added to get a blend which was assessed for its flow properties. Blend with good flow property was compressed using 12 mm standard flat punches with plain surface on both sides to get chewable tablets.

Physical characteristics of loratadine chewable tablets

Prepared tablets were evaluated for thickness and diameter using "Digital Vernier Caliper" (Make by: Mitutoyo Corp.), friability using "Friabilator" (Make by: Electrolab) and hardness using "Tablet Hardness Tester" (Make by: Dr.Schleuniger Pharmatron) and weight variation [6-9].

Drug content uniformity

Drug content uniformity was determined by HPLC. Mobile phase was prepared by filtering and degassing mixture of 0.01 M Dibasic potassium phosphate, methanol and acetonitrile (7:6:6) and adjust the pH to 7.2 with 10% phosphoric acid solution. Similarly diluent was prepared by transferring 400 ml of 0.05 N Hydrochloric acid and 80 ml of 0.6 M Dibasic potassium phosphate to a 1000 ml volumetric flask which was diluted with a mixture of methanol and acetonitrile (1:1) to the volume. Standard sample was prepared by weighing 50 mg of Loratadine equivalent to 99.8% of Loratadine working standard, dissolved and diluted with diluent up to the mark in a 100 ml volumetric flask. From the above solution, 5 ml was pipette out and made up to 50 ml with diluent. Test sample was prepared by powdering 10 tablets and weighed accurately the equivalent weight of one tablet and transferred into a 100 ml volumetric flask, dissolved and diluted with diluent up to the mark. About 15 µL of sample was injected through BDS Hypersil C8, (150mm×4.6mm) 5µm with the flow rate and retention time of 1.0 ml / min and 9.5 min respectively at the column temperature of 25^{0} to 35 ^{0}C and the samples were scanned at 280 nm [10].

***In-vitro* dissolution studies**

The release rate of Loratadine from chewable tablet of all 5 formulations and innovator was carried out using Electrolab TDT-06P (USP Type ll - Paddle). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37±0.5 ^{0}C and at 50 rpm. Sampling (5 ml) was at done

15, 30, 45 and 60 min and it was replaced with equal volume of fresh dissolution medium. Standard stock solution of Loratadine was prepared by adding 40 mg of Loratadine into a 200 ml volumetric flask followed by 20 ml of methanol which was sonicated for about 10 min. 140 ml of diluent was then added, sonicated to dissolve and diluted up to the mark with diluent. About 5.0 ml of standard stock solution was diluted to 100 ml with dissolution medium and filter through 0.45 µ filter to get a standard solution. The absorbance of standard solution and sample preparation were measured at 280 nm using dissolution medium as blank [11, 12].

Stability study

Stability study was carried out by exposing the best formulation at 25^{o}C / 60 % RH and 40^{o}C / 75 % RH for 3 months. Samples were checked for any changes in physical parameters, drug content and dissolution profile after each month [13].

RESULTS AND DISCUSSION

Identification and flow properties of loratadine

Loratadine found to be white to off-white crystalline powder, tasteless, odorless in organoleptic evaluation. UV spectroscopy study showed that the maximum absorbance at 280 nm after baseline correction in the UV spectrophotometer, when 10 µg/ml solution of Loratadine in 0.1 N HCl was scanned between 200 to 400 nm. FT-IR study concludes that characteristic peaks of Loratadine standard and sample were comparable (Figure 1, 2 and 3) in the range of 4000-450 cm^{-1}. DSC study of Loratadine revealed sharp peak (Melting Point) at 139.56^{0}C and the melting range was between 134.13^{0}C to 148.00^{0}C (Figure 4). The study on flow properties of the Loratadine API showed that the flow was moderate / Passable.

Drug-excipient compatibility study

Results of drug-excipient compatibility study showed that there were no significant physical changes on 15th and 30th day and DSC studies confirmed the amorphous nonsolvated form of drug and no interaction between Loratadine and excipients as there were no significant changes in endothermic peak for Loratadine on 30th day (Figure 5).

Physical characteristics of the tablet blend

Prepared blend was analyzed for various flow properties such as Carr's index, Hausner's ratio, angle of repose and results are tabulated in Table 2. Carr's index, Hausner's ratio, angle of repose of formulation F 1, F 3, F 4 and F 5 were in the range of 12.48 to 12.89, 1.14 and 24.67 to 27.78 respectively. Whereas F 2 showed 14.99, 1.17 and 28.08 respectively. However, the outcomes of these parameters indicated good flow properties of all formulations and suitable for compression. The moderate flow property of the Loratadine API was enhanced by addition

of glidant colloidal silicon dioxide, further the major excipients in the blend were filler microcrystalline cellulose which is granular and has good flow.

Physical characteristics of loratadine chewable tablets

Results of physical characteristics of Loratadine chewable tablets of all 5 formulations are listed in Table 3.

Diameter and thickness

Diameter of all five formulations were within 12 ± 0.03 to 12 ± 0.04 which showed uniform diameter of tablets. Thickness of F 3, F 4 and F 5 were in the range of 3.8 to 3.9 whereas F 1 and F 2 had thickness around 4.3. However, tablet thickness was within ± 5% variation of standard value.

Weight variation

Weight variation ranges from 550 to 554 mg. However, tablets represented all formulations passed weight variation test as the % weight variation was within the limits of ± 5%. However, F 5 had less weight variation among 5 formulations.

Hardness

The maximum and minimum hardness among the 5 formulations were found to be 45 N and 97 N respectively. However, F 5 had 85 – 97 N which indicates adequate mechanical strength.

Friability

The maximum and minimum friability among the 5 formulations were found to be 0.315% and 0.168% respectively. However F 5 had the least friability. The percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Drug content uniformity

The maximum drug content among all 5 formulations was found to be 102.00% and minimum drug content among all 5 formulations was found to be 98.20%. Tablets represented all formulations complies with pharmacopeial limits. Results of drug content uniformity test of all formulations are listed in Table 4.

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In-vitro dissolution studies

Percentage cumulative drug release of all 5 formulations of Loratadine chewable tablets were listed in Table 5. However, F 1, F 2 and F 5 demonstrated better drug release (Figure 6) and the percentage cumulative drug release of innovator and F 5 were comparable (Figure 7) than F 1 and F 2.

Stability study

Results of stability study of F 5 demonstrated no significant changes in physical parameters, drug content and dissolution profile after each month. Results of stability studies are listed in Table 6.

Table 1: Formulations of Loratadine chewable tablets 5mg

S.No.	Ingredients	Quantity Per Tablet (mg)				
		F 1	F 2	F 3	F 4	F 5
1.	Loratadine	5.00	5.00	5.00	5.00	5.00
2.	Lactose monohydrate	200.00	206.00	376.48	381.48	356.48
3.	Mannitol	132.75	132.75	120.00	120.00	120.00
4.	Microcrystalline cellulose	180.00	180.00	-	-	-
5.	Ethyl cellulose	-	-	20.00	15.00	-
6.	Avicel CE 15	-	-	-	-	40.00
7.	Povidone K-30	10.00	10.00	-	-	-
8.	Maize starch	-	-	15.00	15.00	15.00
9.	Purified water	q.s	q.s	q.s	q.s	q.s
10.	D&C yellow No.6	1.25	1.25	1.12	1.12	1.12
11.	Citric acid	2.00	2.00	1.40	1.40	1.40
12.	Raspberry flavor	2.50	2.50	2.00	2.00	2.00
13.	Aspartame	6.00	6.00	5.00	5.00	5.00
14.	Sodium starch glycolate	6.00	-	-	-	-
15.	Colloidal silicon dioxide	1.50	1.50	2.00	2.00	2.00
16.	Magnesium stearate	3.00	3.00	2.00	2.00	2.00
Tablet Weight (mg)		**550**	**550**	**550**	**550**	**550**

F = Formulation and q.s = Quantity sufficient

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Table 2: Flow properties of the tablet blend

Formulation	Bulk density (gm/ ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
F 1	0.547	0.625	12.48	1.14	27.78
F 2	0.431	0.507	14.99	1.17	28.08
F 3	0.487	0.559	12.88	1.14	26.06
F 4	0.385	0.442	12.89	1.14	24.67
F 5	0.581	0.665	12.63	1.14	25.55

Table 3: Physical characteristics of Loratadine chewable Tablets

Formulation	F 1	F 2	F 3	F 4	F 5
Diameter (mm)	12 ± 0.03	12 ± 0.04	12 ± 0.03	12 ± 0.03	12 ± 0.04
Thickness (mm)	4.3 ± 0.04	4.3 ± 0.03	3.9 ± 0.02	3.8 ± 0.02	3.9 ± 0.02
Weight variation (mg)	550 ± 8	552 ± 9	551 ± 6	554 ± 7	552 ± 5
Hardness (N)	70 - 80	45 - 55	75 - 87	80 - 88	85 - 97
Friability (%)	0.282	0.265	0.296	0.315	0.168
Drug content (%)	100.84 ±1.08	99.06 ±0.96	99.80 ±1.21	98.20 ±1.05	102.00 ±1.08

Table 4: Drug Content Uniformity of Loratadine chewable Tablets

Formulation	F 1	F 2	F 3	F 4	F 5
Drug content (%)	100.84 ±1.08	99.06 ±0.96	99.80 ±1.21	98.20 ±1.05	102.00 ±1.08

Table 5: Percentage Cumulative Drug release of all formulations

Sampling Time (min.)	Mean % drug release					
	F 1	F 2	F 3	F 4	F 5	Innovator
15	96.90	87.00	24.80	26.40	29.40	33.80
30	105.10	97.50	38.00	49.40	55.40	58.30
45	109.20	103.40	53.80	70.50	80.40	82.10
60	111.50	105.80	63.80	88.80	99.30	97.80

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Table 6: Stability data of formulation 5

Test parameters	Initial Value	Stability Results					
		25^{0}C /60 RH			40^{0}C/75 RH		
		1 Month	2 Month	3 Month	1 Month	2 Month	3 Month
Appearance	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Average weight (mg)	554.20	554.00	553.80	553.70	553.90	553.70	553.70
Dissolution (%)	99.80	99.80	99.60	99.60	99.60	99.60	99.40
Assay (%)	102.00	101.50	100.70	100.70	101.30	101.10	100.70

Figure 1: FT-IR Spectrum of Loratadine Sample

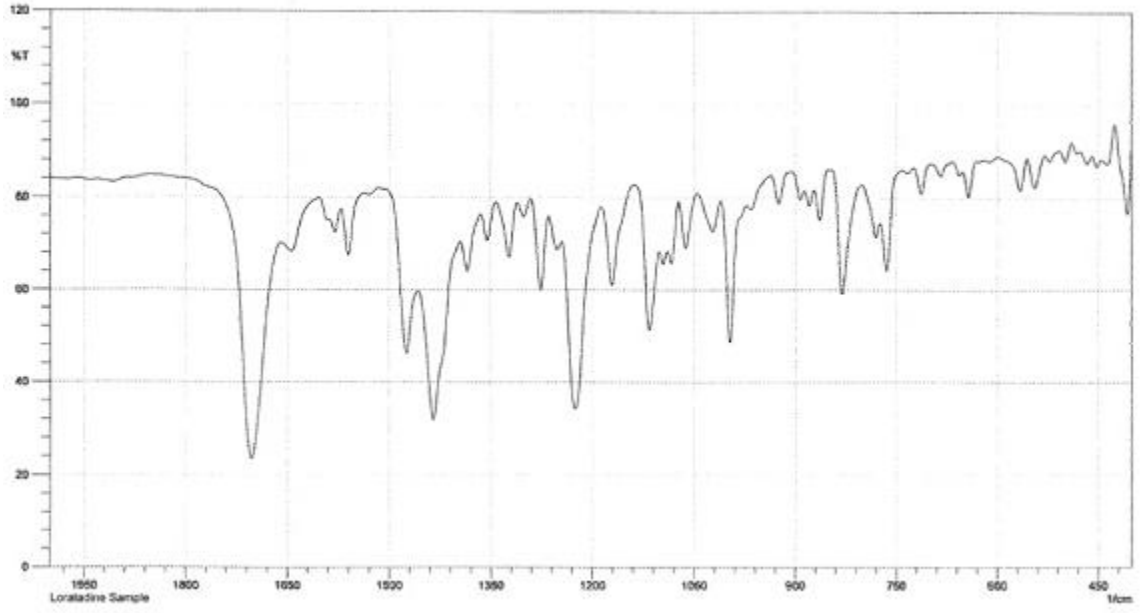

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Figure 2: FT-IR Spectrum of Loratadine Standard

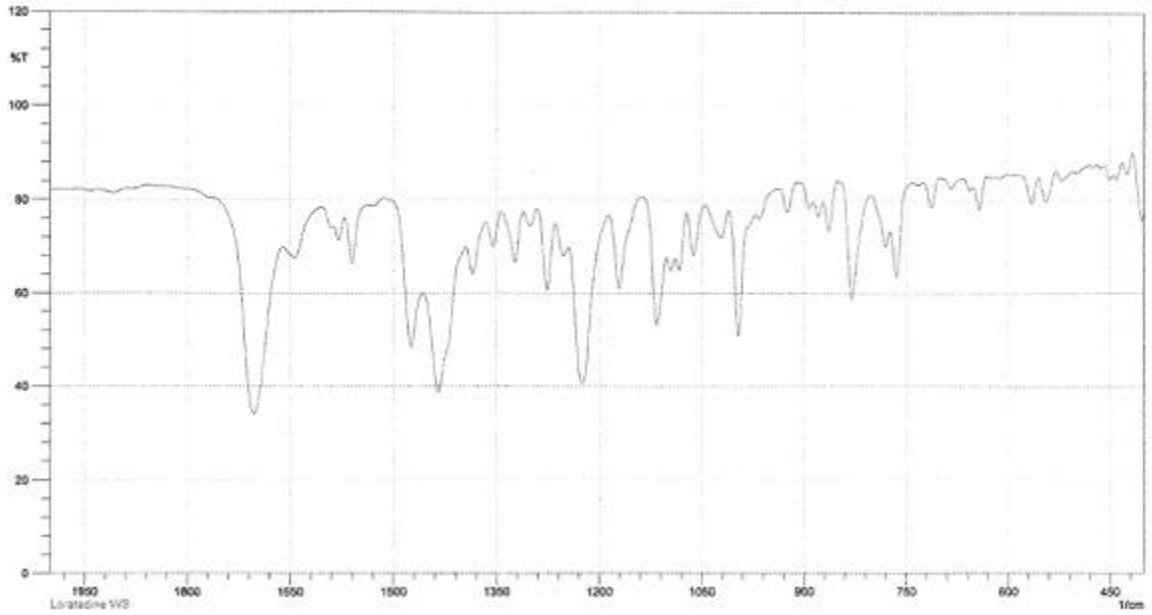

Figure 3: FT-IR Spectrum of Loratadine Standard and Sample

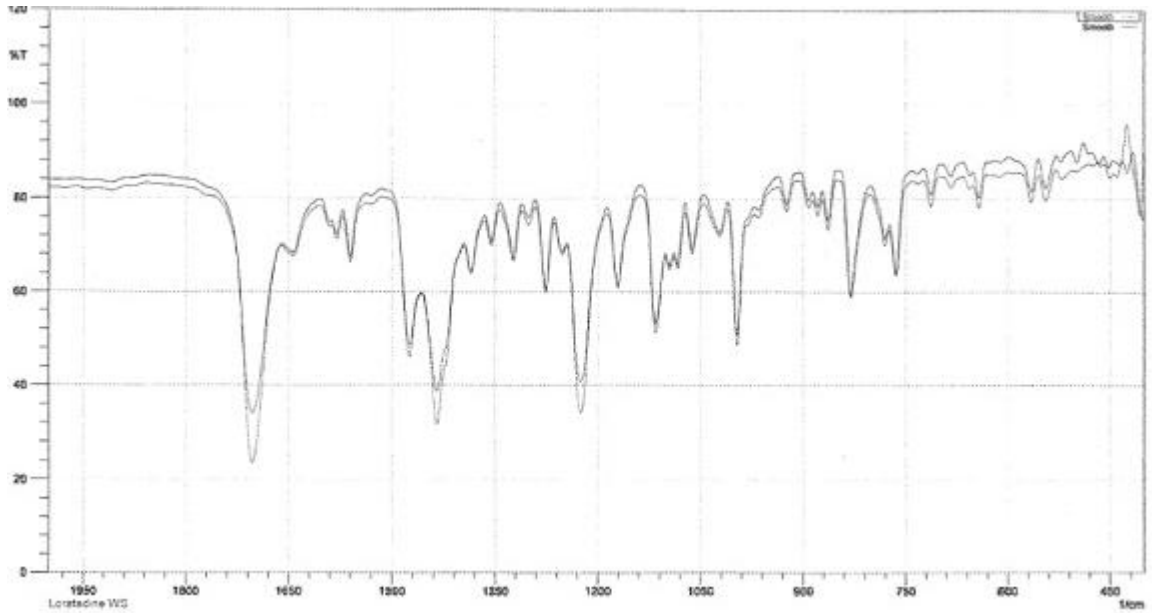

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Figure 4: DSC Thermogram for Loratadine API

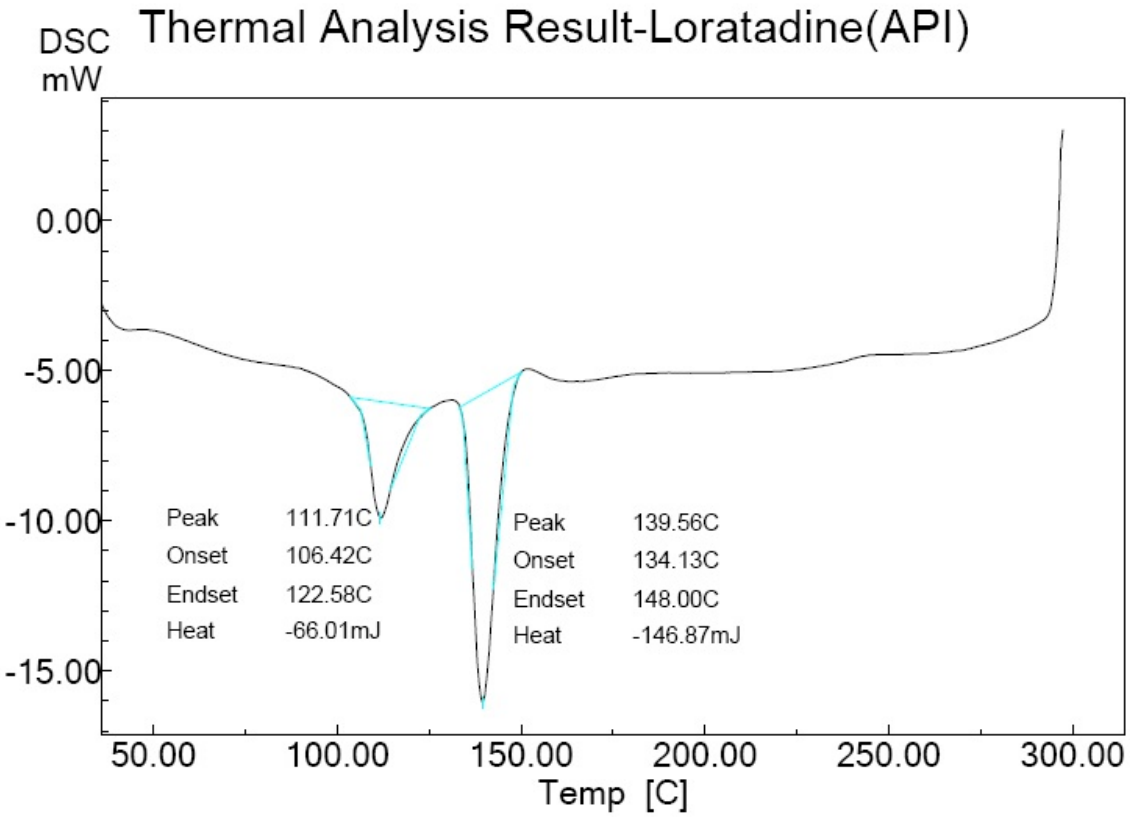

Figure 5: DSC Thermogram of Loratadine Lactose Monohydrate

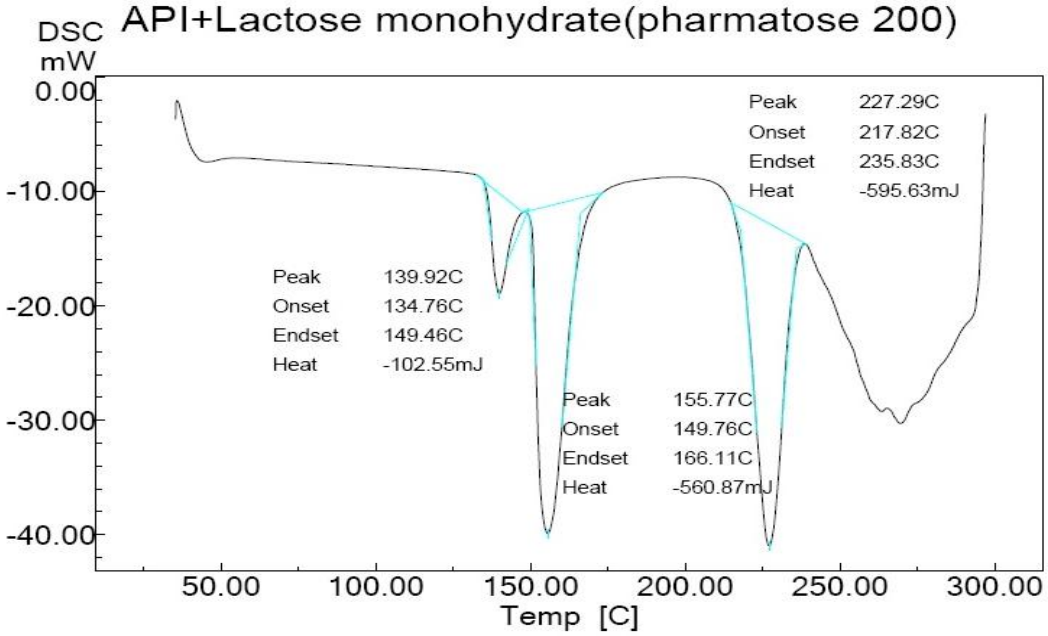

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Figure 6: Percentage Cumulative Drug Release of all formulations

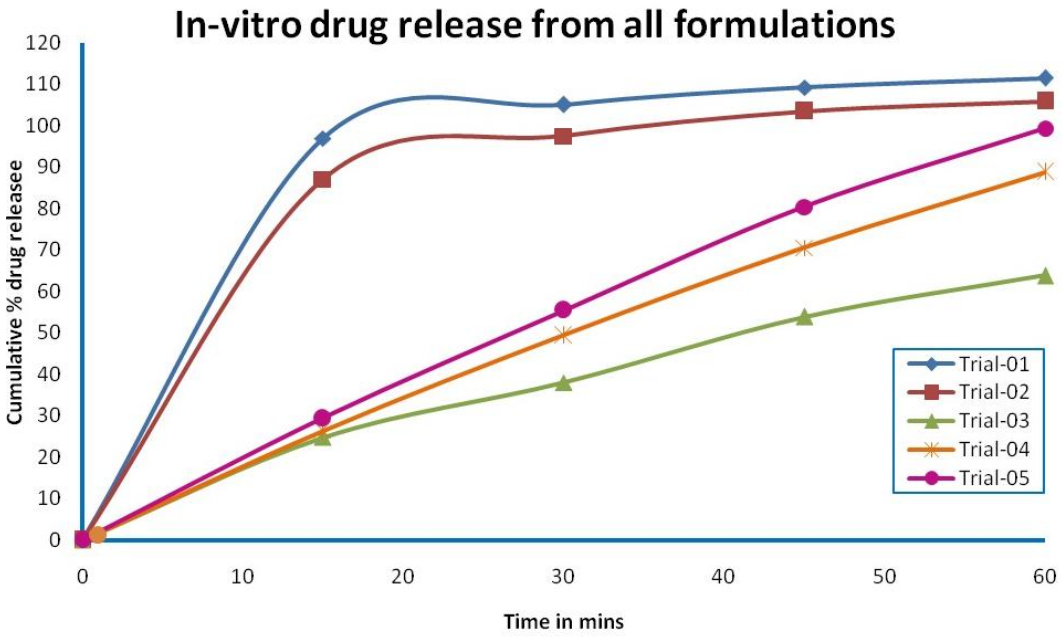
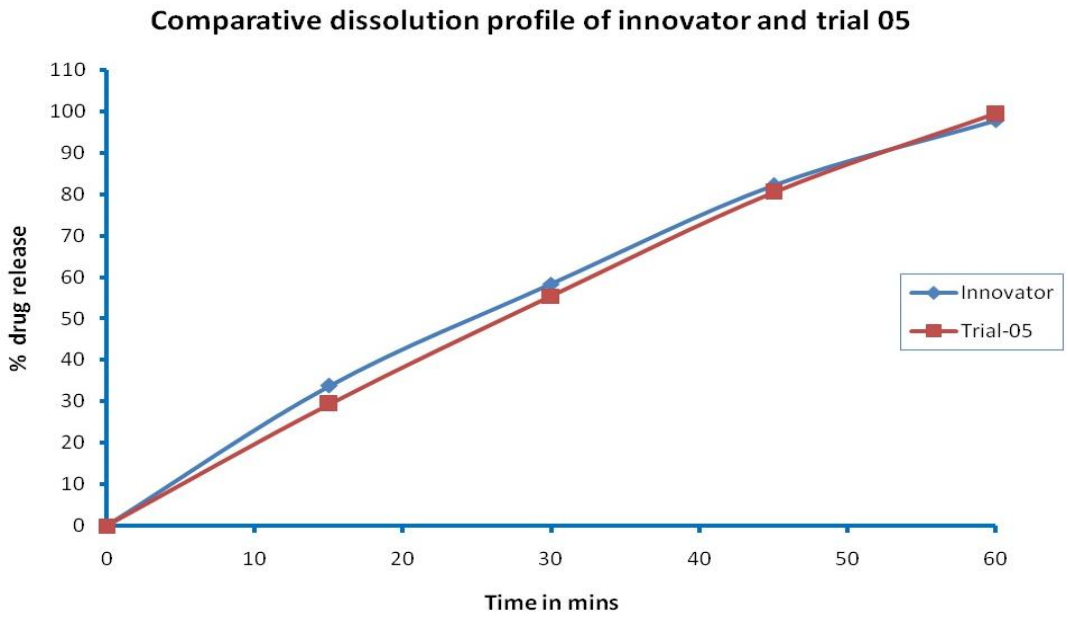


Figure 7: Comparative Dissolution Profile of Innovator and Formulation 5



CONCLUSION

From the study it was concluded that the Loratadine was formulated as chewable tablets by using Avicel CE 15 (Microcrystalline cellulose 70% and guar gum 30%) and starch

paste showed better physical character of chewable tablets and better dissolution profile which was comparable to the innovator. Moreover, 3 month stability study showed no significant changes in physical parameters, drug content and dissolution profile. Hence, the chewable tablet formulations of Loratadine may be an advantageous alternative for other oral conventional Loratadine formulation and improve the compliance of in children, not yet learned to swallow tablet in the treatment of allergic rhinitis and urticaria.

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