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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF CHEWABLE TABLETS CONTAINING NON- SEDATING ANTIHISTAMINE

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ABSTRACT
Various formulations of Loratadine Chewable tablets containing different pharmaceutical compositions with simple manufacturing procedures were developed by using different excipients. The excipients used here are Lactose, Mannitol, Ethyl cellulose, Microcrystalline cellulose, Maize Starch, Citric Acid, Aspartame, Colloidal silicon dioxide, Magnesium Stearate, D & C Yellow No 10 and Raspberry flavour. Oral chewable tablets are the most preferred among the conventional dosage forms due to its aesthetic appeal and ease of administering to children, which has entered the market.
Loratadine is formulated into chewable tablets by wet granulation method using suitable excipients as mentioned earlier, which are evaluated by using simple analytical equipments. The chewable tablet was better presented using artificial sweetener Aspartame and Raspberry flavour as flavouring agent. The chewable tablets are prepared to ensure that they are easily crushed by chewing. The tablets were evaluated for weight variation, hardness, friability; drug content and mouth feel along with *in-vitro* dissolution. As per monograph, the chewable tablets are not required to comply with disintegration test.
Wet granulation process using Mannitol, Lactose, Micro crystalline cellulose (Avicel-CE 15), Ethyl cellulose and Sweeteners and Flavours were found to be simple and robust method to prepare chewable tablets.
KEYWORDS: Antihistamines, Loratadine chewable tablet, Mannitol, Lactose, Ethyl Cellulose, Microcrystalline cellulose, Wet Granulation process

INTRODUCTION

Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing.
Successful tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipient to perform a specific function in a tablet formulation, such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic, are one type of functional excipient commonly used in chewable tablet formulations to mask unpleasant tastes and facilitate pediatric dosing. [1]
Ideally chewable formulations should have smooth texture upon disintegration, pleasant taste and no bitter or unpleasant after taste. Upon chewing, they are broken down in the mouth and release their ingredients in the process and therefore, do not have much lag time as required for the disintegration of tablets before absorption from stomach.[2]
Loratadine is a piperdine derivative and is a long acting selective peripheral H1 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 in 2-12 years children.[3]
Children find it difficult to swallow the normal tablets of Loratadine. So in order to avoid this problem, chewable tablets are most preferable. 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.[4]
Chewable tablets are often employed when active ingredient is intended to act in a localised manner rather than systemically.[5]
Chewable tablet is one that is palatable and may be chewed and ingested with little or no water.[6]
Manufacturing of chewable tablet is generally done using either a wet granulation process or direct compression. Increasingly, micronized and submicron forms of therapeutically and/or physiologically active substances are being incorporated into tablet formulations to take advantage of the enhanced absorption characteristics of these forms[7,8]
They are also used in the administration of antacids and carminatives (to remove excessive amount of gas in the stomach and intestines) [9]
Mannitol is widely used as an excipient in chewable tablets for its non hygroscopic nature for moisture sensitive drugs.[10]
Chewable tablet formulations, particularly those containing pharmaceutically active agents, present issues of organoleptic characteristics of odor, taste, appearance and mouth feel. The formula ingredients and manufacturing process both play a role in obtaining the desired organoleptic properties.[11,12]

Advantages of chewable tablets:[13,14]

- Provide quick and complete disintegration of the tablet and thus obtain a rapid drug effect after swallowing and dissolution.
- Easy administration, especially for children and elderly people.
- Could be administered when water is not available

The main objective of present study is to formulate and evaluate Loratadine chewable tablet dosage form with different excipients and their impact on the formulations and there by develop the robust formula with better patient compliance and drug release. The manufacturing process used was wet granulation process.

MATERIALS AND METHODS

Loratadine (micronised) was procured from Matrix Labs, India, Co-processed Micro crystalline cellulose and Guar gum (Avicel CE 15) from FMC Biopolymers USA, Mannitol (Pearlitol 25C) and Maize Starch from Roquette France, Ethyl Cellulose (Ethocel Std 10FP) from Colorcon, Povidone K-30 from ISP, Citric acid from Kinsun International China , Raspberry flavour from Givaudan UK Ltd, Aspartame from Manus Aktteva, India, Colloidal

silicon dioxide from Cabot Sanmar Ltd India, Magnesium stearate from Ferro Portugal were of pharmaceutical grade.

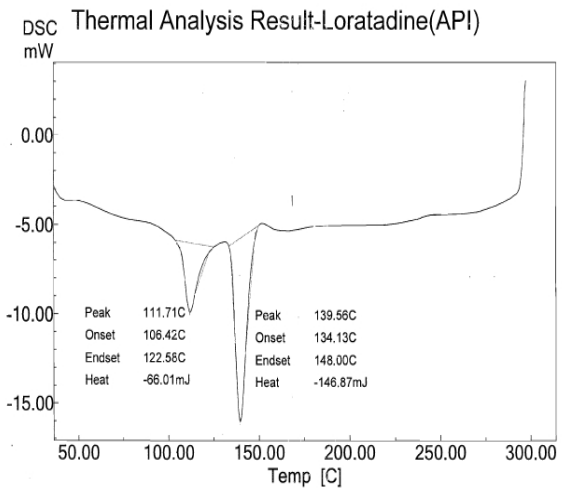
PREPARATION

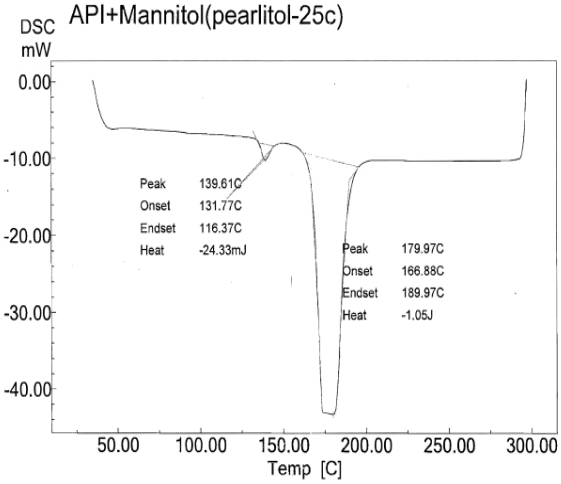
Preformulation Studies: Preformulation studies were carried out for Loratadine and the probable excipients used in the development of this formulation.

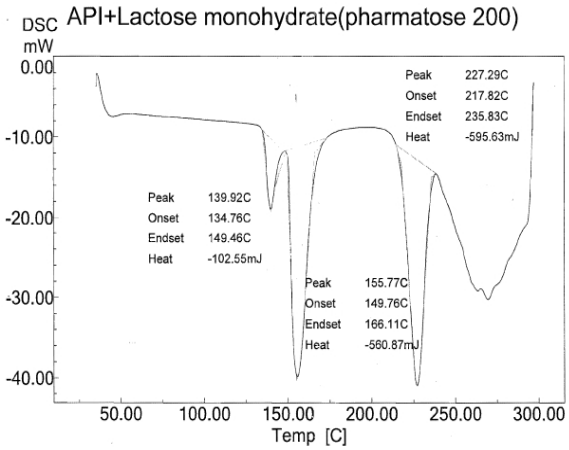
The Loratadine was mixed with the individual excipient as per the predetermined ratio as given below (table 1) and each admixture was filled in glass vial and closed with a rubber stopper and aluminum seal. These vials were charged in stability at Stress condition like 40^0 C / 75 % RH and room temperature of 25^0 C / 60 % RH for a period of one month. Similarly the API was also kept in these two conditions in similar way. The samples were observed for any physical change in 15 days and in 30 days.

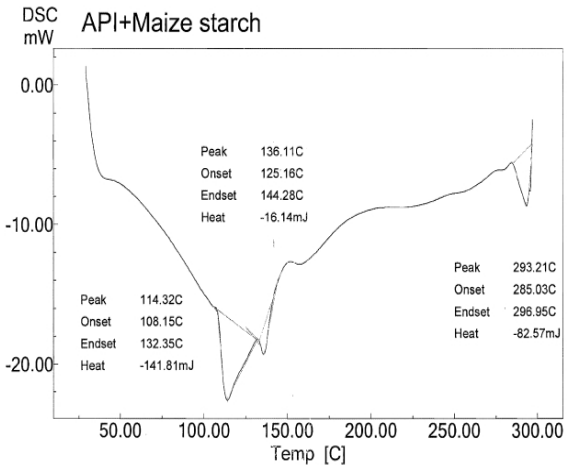
Table 1: Drug Excipient compatibility studies

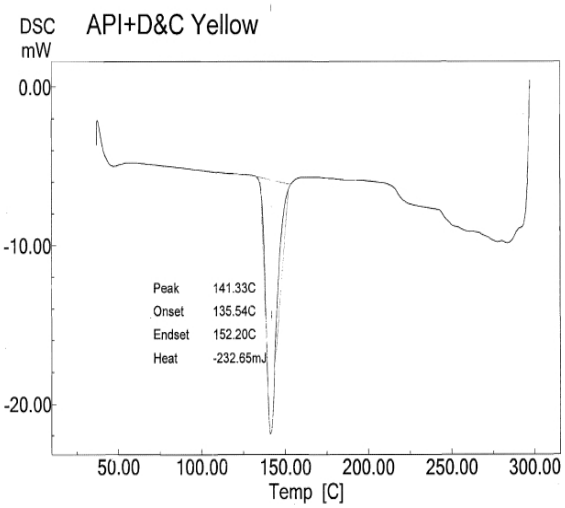
Sl. No	Name of the Ingredient	
1	Loratadine (API)	1:0
2	API + Lactose Monohydrate (Pharmatose 200)	1:10
3	API + Mannitol (Pearlitol 25C)	1:10
4	API + Maize Starch	1:5
5	API + D & C Yellow	1:0.05
6	API + Citric Acid	1:0.5
7	API + Raspberry flavour	1:0.05
8	API + Aspartame	1:0.5
9	API + Colloidal Silicon dioxide	1:0.5
10	API + Magnesium Stearate	1:0.5

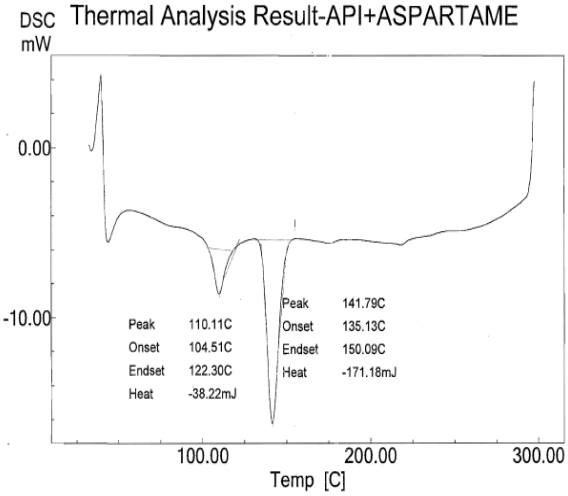


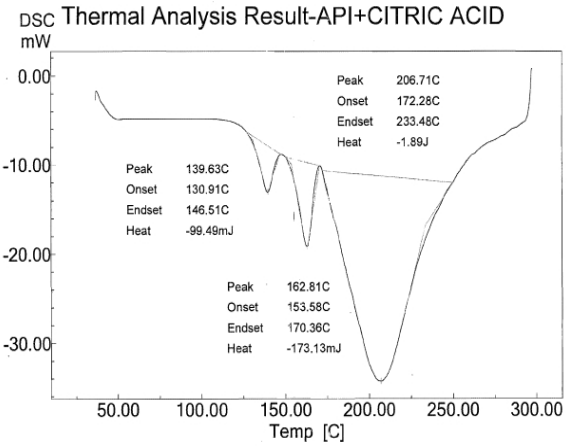


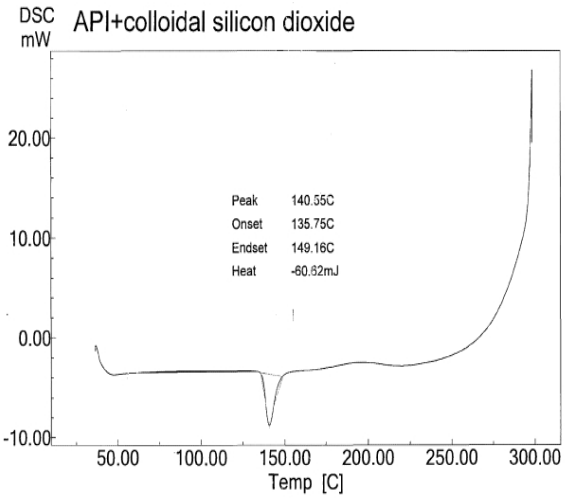


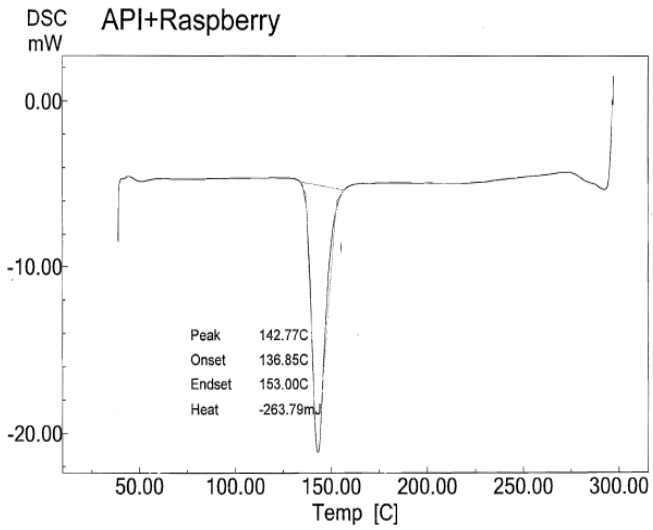


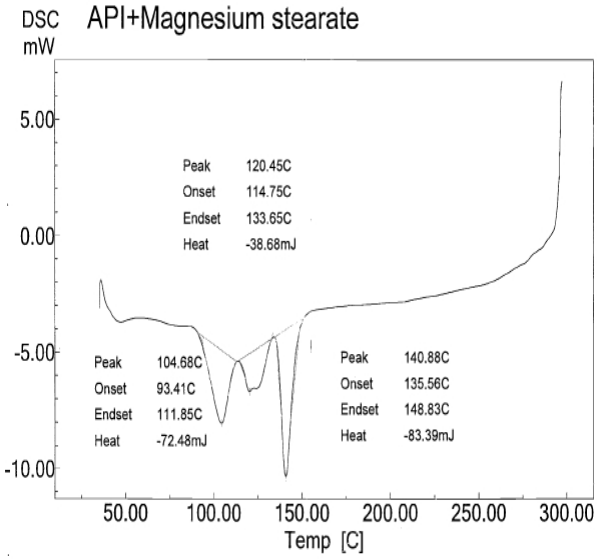

DSC
mW
API+D&C Yellow
0.00
-10.00
-20.00
Peak 141.33C
Onset 135.54C
Endset 152.20C
Heat -232.65mJ
50.00 100.00 150.00 200.00 250.00 300.00
Temp [C]


DSC
mW
Thermal Analysis Result-API+ASPARTAME
0.00
-10.00
Peak 110.11C
Onset 104.51C
Endset 122.30C
Heat -38.22mJ
Peak 141.79C
Onset 135.13C
Endset 150.09C
Heat -171.18mJ
100.00 200.00 300.00
Temp [C]


DSC
mW
Thermal Analysis Result-API+CITRIC ACID
0.00
-10.00
-20.00
-30.00
Peak 206.71C
Onset 172.28C
Endset 233.48C
Heat -1.89J
Peak 139.63C
Onset 130.91C
Endset 146.51C
Heat -99.49mJ
Peak 162.81C
Onset 153.58C
Endset 170.36C
Heat -173.13mJ
50.00 100.00 150.00 200.00 250.00 300.00
Temp [C]


DSC
mW
API+colloidal silicon dioxide
20.00
10.00
0.00
-10.00
Peak 140.55C
Onset 135.75C
Endset 149.16C
Heat -60.62mJ
50.00 100.00 150.00 200.00 250.00 300.00
Temp [C]


DSC
mW
API+Raspberry
0.00
-10.00
-20.00
Peak 142.77C
Onset 136.85C
Endset 153.00C
Heat -263.79mJ
50.00 100.00 150.00 200.00 250.00 300.00
Temp [C]


DSC
mW
API+Magnesium stearate
5.00
0.00
-5.00
-10.00
Peak 120.45C
Onset 114.75C
Endset 133.65C
Heat -38.68mJ
Peak 104.68C
Onset 93.41C
Endset 111.85C
Heat -72.48mJ
Peak 140.88C
Onset 135.56C
Endset 148.83C
Heat -83.39mJ
50.00 100.00 150.00 200.00 250.00 300.00
Temp [C]

There were no physical changes observed in these admixtures for one month at stress condition as well as in room temperature. These data of thermal graphs and no change in physical appearance of these pre-formulation samples indicates that the Loratadine API is compatible with these above mentioned excipients used in the development of chewable formulation.

Chewable tablets containing Loratadine 5 mg were prepared by selecting the excipients used in pre-formulation studies.

The chewable tablet of Loratadine was prepared by using aqueous wet granulation technique with Micro crystalline cellulose, Lactose Monohydrate and Mannitol as diluents. Ethyl Cellulose as polymer for taste masking. Povidone and Maize starch as binder. Apart from this we have used flavours like Raspberry and Aspartame as Sweetener. Citric acid is used as taste enhancer. Pharma grade colors are used like D&C Yellow No 10, FD&C Yellow No.6 and FD &C Red No 40 as colors. Sodium starch glycolate as disintegrant, Colloidal silicon dioxide and Magnesium stearate as glidant and lubricant respectively. (Table2)

Preparation of Granules

Sifting: Sift Loratadine (micronized), Ethyl cellulose, Lactose monohydrate and Mannitol through 40# mesh.

Dry mixing: Load the above materials into Rapid Mixer Granulator (RMG) and mix for 15 minutes at slow speed.

Binder preparation: Dissolve Povidone K 30, and D&C Yellow in purified water. Stir well to dissolve completely.

Preparation of Starch paste: Dissolve Maize starch, and D&C Yellow in small quantity of purified water separately. Stir well to dissolve completely and add both into the required amount of boiled water with continuous stirring.

Granulation: Add the binder solution / starch paste to the dry mix materials slowly and granulate well.

Drying: Dry the wet mass into Fluidized bed dryer at 60ºC.

Sifting and Milling: Sift the dried granules through 20# mesh. Over sized granules pass through multi mill fitted with 2.0 mm screen, further pass the granules through 20# mesh completely.

Lubrication: Load the sifted granules into blender and add citric acid, Raspberry flavour, aspartame and colloidal silicon dioxide. Mix for 20 min at slow speed. Then add magnesium stearate which is sifted through 60# mesh and Mix for 5 min at slow speed.

Compression: Compress the blend by using 12 mm standard flat circular punches with plain surface on both sides. The weight, hardness and thickness were adjusted to get uniform tablets by using 8 station tablet compression machine

Physical characteristics of the Blend:

The tablet blends prepared were analyzed for various micrometric and flow properties shown in table 3.

Evaluation of tablets

Friability test[15]

Friability of tablets was determined using Roche Friabilator (Electrolab, Mumbai).The tablets were subjected to the combined effect of abrasions and shock in a Friabilator at 25 rpm and dropping the tablets at a height of six inches in each revolution. Pre weighed sample of tablets was placed in a Friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability is given by the formula:

$F = (1-W_o/W) \times 100$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

Table 2: Formulation of chewable tablet (composition)

Ingredients						
	Trial 001	Trial 002	Trial 003	Trial 004	Trial 005	Trial 006
Loratadine (Micronised)	5	5	5	5	5	5
Micro crystalline cellulose (Avicel-pH 101)	180	180	----	----	----	-----
Lactose Monohydrate	200	206	335.75	340.75	310.75	161
Mannitol (Pearlitol 25C)	132.75	132.75	150	150	150	350
Ethyl Cellulose (Ethocel Std 10FP)	----	----	25	20	----	---
Micro crystalline cellulose and Guar gum (Avicel-CE 15)	----	----	----	----	50	----
Povidone K-30	10	10	----	----	----	----
Maize Starch	----	----	18	18	18	18
Purified Water	q s	q s	q s	q s	q s	q.s
D&C Yellow No 10	1.25	1.25	1.25	----	1.25	---
D & C Red No 40	----	----	----	----	----	1
FD &C Yellow No 6	----	----	----	1.25	----	--
Citric Acid	2	2	2	2	2	2
Raspberry flavour	2.50	2.50	2.50	2.50	2.50	2.5
Aspartame	6	6	6	6	6	5
Sodium starch glycolate	6	----	----	----	----	----
Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	3	3	3	3	3	4
Tablet weight (mg)	**550**	**550**	**550**	**550**	**550**	**550**

Hardness[15,16]

Hardness or tablet crushing strength (F_c) was measured using Dr.Schleuniger digital hardness tester

Weight variation[15]

All the formulated tablets passed weight variation test as the % weight variation was within the limits of ± 5 % of the weight. The prepared formulation complies with the weight

variation test. The results of weight variation and other physical parameters of all batches are shown in table 5.

Drug content uniformity

The drug content among all formulations was found to be 98.20 % to 102.00% from all formulations. The results of drug content of all batches are shown in table 4.

Table 3: Powder flow properties of the blend

SL No.	Trials	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (^{0}C)	Loss on drying (%)
1	001	0.547	0.625	12.48	1.14	27.78	1.93
2	002	0.431	0.507	14.99	1.17	28.08	1.67
3	003	0.487	0.559	12.88	1.14	26.06	1.86
4	004	0.385	0.442	12.89	1.14	24.67	1.42
5	005	0.581	0.665	12.63	1.14	25.55	1.65
6	006	0.592	0.710	16.61	1.19	26.01	1.60

Table 4: Content uniformity of the tablets

SL.No.	Trials	Drug content (%) (Mean±SD)
1	Trials -01	100.84 ± 1.08
2	Trials-02	99.06 ± 0.96
3	Trials-03	99.80 ± 1.21
4	Trials-04	98.20 ± 1.05
5	Trials-05	102.00 ±1.08
6	Trial-06	101.00 ±1.02

Table 5: Physical Characteristics of Loratadine Chewable Tablets

Trial	Weight variation range (mg)	Friability (%)	Hardness range (Newton)	Diameter(mm)	Thickness (mm)
001	545-555	0.282	70-80	12±0.03	3.9 ±0.04
002	545-560	0.265	45-55	12±0.04	4.3±0.03
003	543-557	0.296	75-87	12±0.03	3.9±0.02
004	548-560	0.315	80-88	12±0.03	3.8±0.02
005	543-557	0.248	85-97	12±0.04	3.9±0.02
006	548-556	0.180	90-105	12±0.04	3.7±0.02

In-vitro dissolution studies

Table 6: Percentage Cumulative Drug release of all formulations

Time in minutes	Mean % drug release (Mean±SD)					
	Trial-01	Trial-02	Trial-03	Trial-04	Trial-05	Trial-06
15	96.9 ± 4.16	87.0 ±5.57	24.8±2.57	26.4±5.17	29.4±2.61	25.4±2.51
30	105.1±3.78	97.5 ±3.41	38.0±3.34	49.4±8.64	55.4±2.77	51.6±2.78
45	109.2±1.96	103.4±4.55	53.8±3.98	70.5±12.26	80.4±2.81	76.5±2.71
60	111.5±1.67	105.8±1.90	63.8±7.52	88.8±9.59	99.3±3.37	95.2±3.46

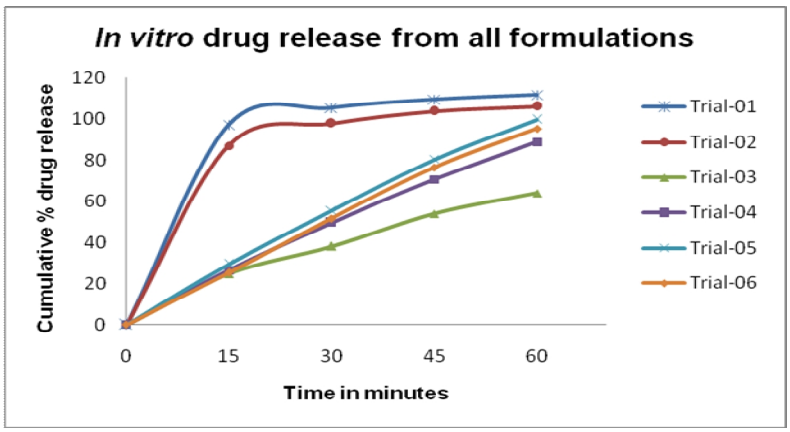


Fig. 1: Percentage cumulative drug release of all formulations

DISCUSSION & CONCLUSION

The objective of this research work was to formulate and evaluate the chewable tablets of Loratadine 5mg.The tablets were prepared by wet granulation method. The different excipients were tested for their compatibility with Loratadine, which revealed that there was no chemical and physical interactions occurred, which was evident by DSC thermal analysis graphs. The pre-formulation parameters such as bulk density, tapped density, compressibility index and hausner ratio were analyzed for prepared blend before compression. The thickness, hardness, friability, weight variation and drug content uniformity was also evaluated for prepared tablets.

From all obtained results, it was found that the Trials 3,4, 5 & 6 shows slow drug release up to 60mins but Trial 5 was the best one with almost 100% drug release at the end of 60 minutes which is formulated without use of Ethyl cellulose and also having 100% drug content.

Hence, finally it was concluded that the Trial 5 is the optimized formulation which complies all ideal characteristics of chewable tablets. The Loratadine chewable tablet with formulation Trial 5 concluded the robust formula with better patient compliance and drug release.

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