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Research Article

DESIGN AND DEVELOPMENT OF QUICK DISSOLVING TABLET CONTAINING LORATADINE BY DIRECT COMPRESSION METHOD

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ABSTRACT

Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine which is widely used for the symptomatic relief of allergic conditions such as runny nose, itchy or watery eyes, sneezing, and nasal or throat itching and chronic urticaria. In such severe allergic cases, quick onset of action is of prime importance. In the present study the direct compression method was adopted to manufacture the quick dissolving tablets, since it is very simple and do not require any sophisticated equipments. This technique has been applied to prepare stable formulation because of the availability of improved patient and eco-friendly excipients Pharmaburst 500® and Flowlac 100® processed in combination by diligently avoiding the usage of deliquescent components reportedly claimed for reference listed drug product Claritin Reditab®. No typical interaction between drug and major (critical and non-critical) excipients were confirmed by DSC, XRD and FTIR during preformulation studies. The blend was examined for pre-compression parameters such as Angle of Repose, Loose Bulk Density, Tapped Density, Bulkiness, Carr's Index and Hauner's Ratio. The prepared tablets, designed as per 3^2 factorial design layout, were evaluated for almost all significant post-compression test parameters. Uniformity of dosage unit by content uniformity, evaluated by HPLC method, confirmed no evidence of drug content variability. Stability study was conducted at accelerated storage condition and prepared quick dissolving tablets were found to be suitable with respect to morphological characteristics and with in-vitro drug release mechanism & similarity factor (F2) comparison unaffected after 90 days. The present research work could therefore provide the opportunity and form the basis as suitable platform technology to further pursue & own the research in section 505 B (2).

Keywords: Loratadine, Pharmaburst 500®, Flowlac 100®, section 505 B (2).

1. INTRODUCTION

The oral route of administration still continue to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. Tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. Patients often experience difficulty in swallowing conventional tablets when water is not available nearby. Furthermore, pediatric and geriatric patients may also feel the inconvenience of swallowing because of under developed and degenerating nervous systems1respectively. Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be

absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes[2].

Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine with no significant antimuscarinic activity. It is used for the symptomatic relief of allergic conditions such as runny nose, itchy or watery eyes, sneezing, and nasal or throat itching and chronic urticaria[3]. It is also licensed to alleviate itching due to hives. It does not readily cross the blood brain barrier. Due to a bypass of first-pass metabolism, approximately 40% of the absorbed loratadine is absorbed via the oral mucosa[4]. Hence, an attempt was made for preparation of oral disintegrating tablets (ODT) of loratadine with an aim of reducing the lag time and providing faster onset of action to relieve the allergic conditions immediately.

Orally disintegrating tablets are synonyms with quick dissolving tablet, mouth dispersible tablet, melt in mouth tablet, rapidmelt, porous tablet or rapidly disintegrating tablet. Orally disintegrating tablets are tailor made for these patients as they immediately release the active drug, when placed on the tongue, by rapid disintegration, followed by dissolution of the drug. European pharmacopoeia[5] defines "Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed". Orodispersible tablets disintegrate within 3 minutes. Orally disintegrating tablets combine the advantage of both liquid and conventional tablet formulations allowing the ease of swallowing the drug in the form of liquid dosage form. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The main purpose of this work is only to improve patient compliance without compromising the therapeutic efficacy.

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is

attributable to a quick intake of water into the tablet matrix, which creates porous structures and result in rapid disintegration. Hence the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate

disintegrating agent and using highly water soluble excipients in the formulation. Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as, mechanical strength of tablet, taste and mouth feel, swallowability, drug dissolution in saliva, bioavailability and stability. Various processes employed in formulating ODTs include Freeze-Drying or Lyophilization, cotton candy process, molding, spray drying, mass extrusion and compaction (wet granulation, dry granulation, direct compression).

In the present study the direct compression method was adopted to manufacture the ODT tablets, since it is very simple and do not

require any sophisticated equipments. The direct compression represents the simplest and most cost effective tablet manufacturing

technique. This technique has been applied to prepare stable ODT formulation because of the availability of improved patient and eco-friendly co-processed excipients Pharmaburst 500® and Flowlac 100® in combination by diligently avoiding the usage of deliquescent components claimed for reference listed drug product Claritin Reditab® (Zydis Lyophillization Technology owned by R.P. Schering Inc.) The present research work could therefore provide the opportunity and form the basis to further pursue & own the research in section 505 B (2).

2. MATERIALS AND METHODS

2.1 Materials

Micronized Loratadine reference standard (Purity: 99.93%) and Micronized Loratadine drug (CEP grade) was kindly supplied by Morepen Laboratories Ltd, Parwanoo, India and was used as received. Pharmaburst 500® (SPI Pharma), Flowlac 100® (Meggle-Pharma), Aspartame (Nutrasweet), Aerosil 200 (Evonik), Strawberry flavor (Covidien, Mallinckdrot), Sodium Stearyl Fumarate (Covidien, Mallinckdrot) were used. All other chemicals and reagents used, generally recognized as safe (GRAS) by global regulatory bodies, were of pharmaceutical grade.

2.2 Equipments/ Instruments

Single rotary compression machine (Cadmach), Electronic Weighing Balanace (Mettler (AE 100)), Friabilator (Electrolab (Model No. EF-2)), Disintegration Tester (Electrolab (Model No. EF-2)), Tapped Density Tester (Electrolab (Model No. EF-2)), Digital pH meter (Toshniwal), Hot air oven (Multispan), Electric oven (Cintex), Thickness tester (Campbell Electronics), Hardness tester (Monsanto), U.V. Visible Spectrophotometer (Shimadzu), HPLC-UV-1000 (Shimadzu), Differential Scanning Calorimeter (Perkin Elmer), FTIR Spectrophotometer (Perkin Elmer), X-Ray Diffractometer (Rigaku D-MAX11), Scanning Electron Microscope (Jeol, JSM-5300) were employed during the course of present research work.

2.3 Method

2.3.1 Standard Calibration Curve of Loratadine

Solutions ranging from 2 to 16 ppm were prepared using 0.1N HCl of pH 1.2 (Simulated gastric fluid (SGF) without enzyme); separately, absorbance was measured for each solution at λmax of 254 nm using Shimadzu UV/ visible 1700 spectrophotometer, graph was plotted for absorbance versus concentration of Loratadine.

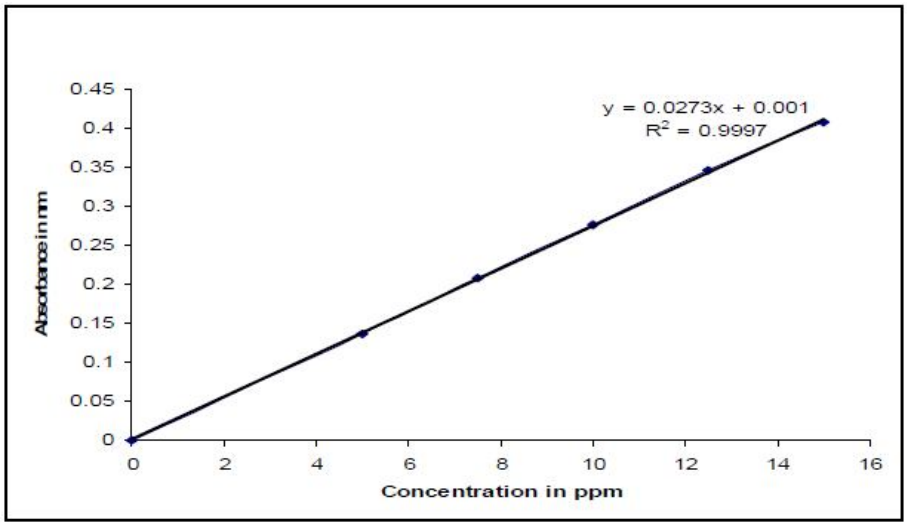

Fig. 1: Absorbance values in nm for standard calibration curve of Loratadine in 0.1 N HCl of pH 1.2 at λmax of 254 nm

2.3.1 Preformulation Studies

2.3.1.1 Determination of Loratadine pH Solubility Profile

Upon building-up experimental facts & figures based on reported case[6], Solubility of loratadine was determined at pH 1.2, 2.5, 4.5, 6.5 and distilled water (DW) using the shake-flask method by placing excess amount of drug separately in 30 ml vials then 20 ml buffer solution of respective pH was added to each vial. The vials were sealed well and covered with opaque aluminum foil then incubated together in a shaking water bath at 25 degree centigrade for 72 hours. Samples were filtered and suitably diluted. The diluted samples, along with an appropriate standard curve, were analyzed by Shimadzu UV/ visible 1700 spectrophotometer at λmax of 254 nm to determine the dissolved quantity of loratadine.

2.3.1.2 Drug excipient compatability study

For performing drug-excipient compatability study, analytical techniques were referred from literatures[7, 8, 9, and 10] and adopted for the analytical suitability of present work.

2.3.1.2.1 Solid state characterization by Differential Scanning Calorimetry (DSC) of physical mixtures (drug and different major excipients)

API Loratadine (drug) along with different excipients (Table 1) were evaluated by using Differential scanning colorimeter (Perkin Elmer, USA). Calorimetric measurements were made with an empty cell (high purity alpha alumina discs) as the reference. The instrument was calibrated using high purity indium metal as a standard. The scans were recorded in a nitrogen atmosphere at a heating rate of

10°C/min. The drug- excipients ratios for filler, disintegrants, sweetener, glidant and lubricant were randomly selected basis actual targeted concentration proposed into the formulation.

Table 1: Physical mixtures for characterization by DSC

S. No.	Ingredients	Ratio	Quantity Taken (g)
1	Loratadine Ph. Eur (API)	1:0	1
2	API + Pharmaburst 500®	1:5	0.5 + 2.5
3	API + Flowlac 100®	1:5	0.5 + 2.5
4	API + Avicel PH 102	1:5	0.5 + 2.5
5	API + Aspartame	1:2.5	1 + 2.5
6	API + Aerosil-200	1:2.5	1 + 2.5
7	API + Sodium stearyl fumarate	1:2.5	1 + 2.5

2.3.1.2.2 Solid state characterization by X-ray diffraction (XRD) of drug, blend ready for compression and crushed tablet.

Drug, final blend for compression and crushed tablet (representing optimized formulation randomly chosen based on outcome of response surface plots) evaluated by using XRD (Rigaku D- MAX11, Japan).

2.3.1.2.3 Solid state characterization by FTIR of drug, blend ready for compression and crushed tablet.

Drug, final blend for compression and crushed tablet (representing optimized formulation randomly chosen based on outcome of response surface plots) were evaluated by using FTIR (Perkin Elmer, USA). The sample was dispersed in KBr powder and analyzed. Spectra were obtained by powder diffuse reflectance on a FT-IR spectrophotometer type FT-IR 1600 Perkin Elmer Co.

2.3.2 Preparation of Loratadine Tablets (Preliminary trials and factorial design)

The tablets were prepared by simple blending of active pharmaceutical ingredient (API) Loratadine (PSD: D90<20micron) with filler, disintegrants, flow promoter and lubricant followed by direct compression. 1000 tablets were prepared for each proposed formulation. Properly weighed Pharmaburst 500®, Flowlac 100®, Avicel PH 102, Aspartame, Strawberry flavour , Aerosil-200, Purified talc and active ingredient were sifted through BSS sieve no. 40 and then taken in a photo film container and blended in a laboratory designed small drum blender machine for 20 minutes to ensure thorough mixing and phase homogenization. The blending was continued for another 10 minutes with sodium stearyl fumarate (previously sifted through BSS sieve no. 60). Blend thus made ready for compression was preserved in double lined polyethylene bag contained in triple layered aluminum pouch until further evaluation, followed by compression using 16 station single rotary compression machine (Figure 2 & Figure 3 reveals the compression details).

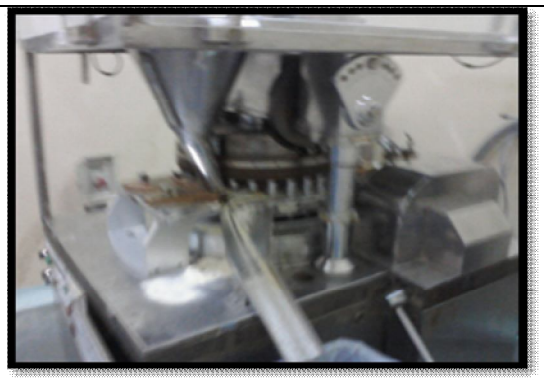

Fig. 2: Ongoing process using single rotary compression machine

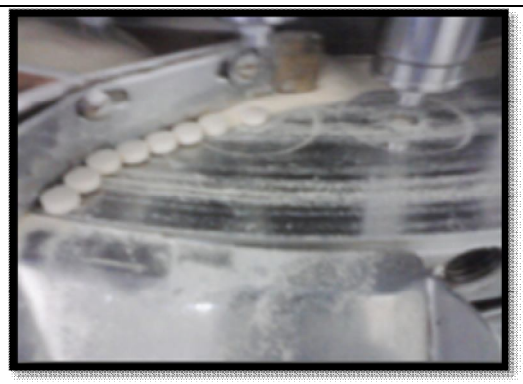

Fig. 3: 6.4 mm round standard concave D tooling punches & corresponding die used for the compression of resultant tablets.

Table 2: Formulation design of oral disintegrating tablets of Loratadine as per 3^2 factorial design layout

Formulation Ingredients	FORMULATION CODES FOR DIFFERENT TRIAL RUNS									
	Pharmaceutical category	F1	F2	F3	F4	F5	F6	F7	F8	F9
		mg/ Tablet	mg/ Tablet	mg/ Tablet	mg/ Tablet	mg/ Tablet	mg/ Tablet	mg/ Tablet	mg/ Tablet	mg/ Tablet
Loratadine Ph. Eur	API	10	10	10	10	10	10	10	10	10
Pharmaburst 500® (A)	Disintegrant	50	60	70	50	60	70	50	60	70
Flowlac 100®(B)	Disintegrant/ Filler	7.5	7.5	7.5	10	10	10	5	5	5
Avicel PH 102	Filler	24.9	14.9	4.9	22.4	12.4	2.4	27.4	17.4	7.4
Aspartame	Sweetner	2	2	2	2	2	2	2	2	2
Strawberry flavour	Flavourant	3	3	3	3	3	3	3	3	3
Aerosil-200	Glidant	1	1	1	1	1	1	1	1	1
Purified talc	Glidant/ Lubricant	1	1	1	1	1	1	1	1	1
Sodium stearyl fumarate	Lubricant	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Theoretical Tablet Weight		100	100	100	100	100	100	100	100	100

Optmization of formulation using 3^2 full Factorial Design

A 3^2 randomized full factorial design was adopted to optimize the variables. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations[11]. The amounts of pharmaburst 500® (A) and the amount of flowlac 100® (B), were selected as independent variables. The disintegration time (DT) and percent friability (%F) were selected as dependent variables. The actual formulation design of oral disintegrating tablets of Loratadine according to factorial design (3^2) layout is shown in Table 2. The data was interpreted using response surface methodology (Design Expert 8.0 Software).

Regression polynomials for the individual dependant variables (disintegration time and percent friability) were calculated with the help of Design Expert 8.0 software and applied to approximate the response surface and contour plots. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b0 + b1A + b2B + b12AB + b11A^2 + b22B^2 \quad \text{.....(1)}$$

Where, Y is the dependent variables, b0 is the arithmetic mean response of the nine runs, b1 is the estimated coefficient for the factor A, b2 is the estimated coefficient for the factor B. The main effects (A and B) represent the average result of changing one factor at a time from its low to high value. The interaction terms (AB) show how the response changes when two factors are simultaneously changed.

The polynomial terms (A2 and B2) are included to investigate non-linearity. Formulation of desired characteristics can be obtained by factorial design application

2.3.2 Physical evaluation of prepared blend for compression[12, 13, 14, 15, 16]

2.3.2.1 Angle of repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granular cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r) \quad \text{.....(2)}$$

Where h and r are the height and radius of the cone.

Angle of Repose (θ)	Type of Flow
< 20	Excellent
20 – 30	Good
30-34	Passable
>35	Very poor

2.3.2.2 Loose Bulk Density (BD)

Accurately weighed blend, 50 g, was transferred in 100 ml graduated cylinder. Blend was carefully leveled without compacting, and read the unsettled apparent volume (V0). Apparent bulk density in gm/ml was calculated by the following formula:

$$\text{Bulk Density} = \frac{\text{Mass of powder (M)}}{\text{Volume of powder (V)}} \quad \text{.....(3)}$$

2.3.2.3 Tapped Bulk Density (TD)

Accurately weighed blend, 50 g, was transferred in 100 ml graduated cylinder. Then the cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Cylinder was tapped for 500 times initially and then measured the tapped volume (V1) to the nearest graduated units, taping was repeated for an additional 750 times and tapped volume (V2) was measured to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2) should be taken. Tapped bulk density in gm/ml was calculated by the following formula:

$$\text{Tapped Density} = \frac{\text{Mass of powder (M)}}{\text{Tapped volume (V)}} \quad \text{.....(4)}$$

2.3.2.4 Bulkiness

Reciprocal of bulk density is known as bulkiness. It is expressed by cc/gm.

$$\text{Bulkiness} = \frac{1}{\text{Bulk Density}} \quad \text{.....(5)}$$

2.3.2.5 Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index} = \frac{\text{TD - BD}}{\text{TD}} \text{ X } 100 \quad \text{.....(6)}$$

2.3.2.6 Hausner Ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material.

$$\text{Hausner Ratio} = \frac{\text{TD}}{\text{BD}} \quad \text{.....(7)}$$

Carr's Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00 – 1.11
11-15	Good	1.12 - 1.18
16-20	Fair	1.19 - 1.25
21-25	Passable	1.26 -1.34
26-31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
>38	Very, very poor	>1.60

2.3.3 Evaluation of tablets

2.3.3.1 Appearance

Twenty tablets of each formulation were taken to check any discoloration or surface roughness in the tablet formulation.

2.3.3.2 Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Mettler Toledo electronic balance and the test was performed according to the established method[17].

2.3.3.3 Hardness

The hardness of five tablets was determined using the monsanto hardness tester and the average values were calculated.

2.3.3.4 Thickness

The thickness of the tablets was determined by using Digital vernier calipers. Five tablets were used, and average values were calculated.

2.3.3.5 Friability

The friability of twenty tablets was measured by Roche friabilator for 4min at 25rpm for 100 revolutions. Accurately weighed twenty tablets were placed into Roche friabilator for 100 revolutions than dedusted and weighed again.

$$\% \text{ Friability} = \frac{WO - W}{WO} \times 100 \quad \text{.....(8)}$$

Where, WO = Initial weight of tablets, W = Final weight of tablets

2.3.3.6 Disintegration time[18]

The test was carried out on six tablets using 0.1 N HCl at $37^0C + 10^0C$ was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

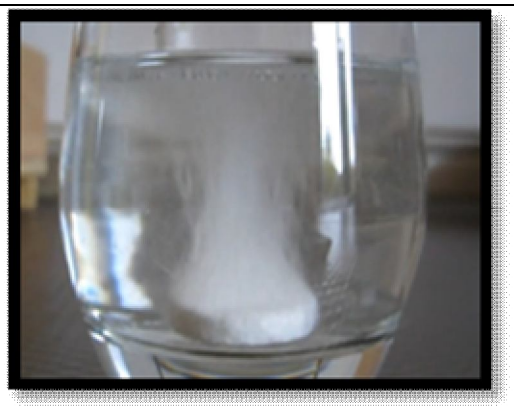

Figure 4. Photograph showing qualitative dispersion behavior of tablet (optimized batch).

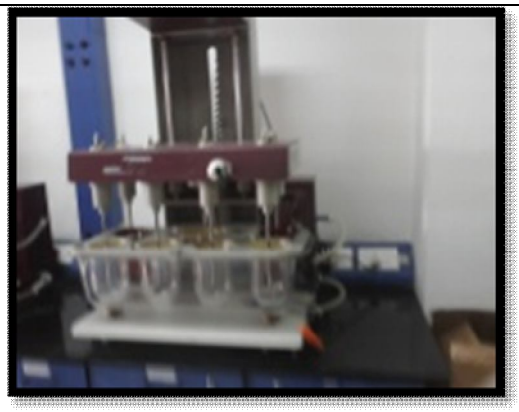

Figure 5. Photograph showing Type II dissolution apparatus (Distek model®)

2.3.3.7 In-vitro drug release profile of formulated tablets[18]

The dissolution of oral disintegrating tablets of loratadine was carried out in USP-II (paddle type) dissolution apparatus. The dissolution medium was 900 ml of 0.1N HCl pH 1.2 maintained at 37°C. One tablet was placed into each of the six dissolution vessels. The paddle was rotated at 50 rpm and 10 mL aliquot (sample solution) from each vessel was withdrawn after every 2 minutes till 10 minutes. Sample solution was filtered through 0.45µm membrane filter and its absorbance was measured at 254 nm.

2.3.3.8 Uniformity of dosage unit by content uniformity

The tablets (n=10) were evaluated for drug content by referring reversed phase (RP) HPLC method of technical data package (TDP) of active pharmaceutical ingredient Loratadine E.P. supplied by M/s Morepen Laboratories Ltd. The method described in TDP is also in line with current European Pharmacopoeia. Chromatographic data was acquired using Winchrome software.
The fine tuned reversed phase (RP) HPLC method was explored for formulation using Shimadzu model HPLC system to suitably proceed as follows;

Chromatographic conditions

The separation of compound was made on an Lichropher RP-18e, (5µm, 250mm×4.0mm), with column oven temperature 30°C. The mobile phase pumped at a flow-rate of 1.0 mL/min. Detection was set at a wavelength of 254nm. The injection volume was 20 µl & run time 15 minutes.

Preparation of buffer (0.2 M)

Dissolved 15.42 g of ammonium acetate in 1 L of water (HPLC grade) and filtered through 0.45µm or finer porosity filter.

Preparation of mobile phase

Prepared a mixture of 20 parts of buffer and 80 parts of methanol and degassed the mixture.

Preparation of standard solution

Weigh and transfer accurately 100 mg of Loratadine working standard into a 100 mL volumetric flask, Add 30 mL of mobile phase. Dissolve make upto volume with mobile phase. Dilute 5 mL of this solution to 100 mL with mobile phase. Filter the solution through 0.45µm or finer porosity membrane filter.

Preparation of sample solution

Transferred one tablet into a 200 mL volumetric flask. Added about 60 mL of mobile phase and sonicated for about 15 minutes with intermittent shaking. Made up the volume with mobile phase and mixed. Filtered through 0.45µm nylon filter and discarded first few ml of the filtrate.

Carried out the same procedure on another nine tablets.
All the volumetric flasks containing Loratadine were wrapped with aluminum foil and stored in the dark until used.

Evaluation of system suitability parameters
Injected the standard solution into the chromatograph and monitored the chromatograms. The system was suitable for analysis if and only if; the tailing factor for Loratadine was not more than 2.0, the column efficiency determined from the Loratadine peak should not be less than 2000 theoretical plates, the relative standard deviation for five replicate injections of standard solution was not more than 2.0%.

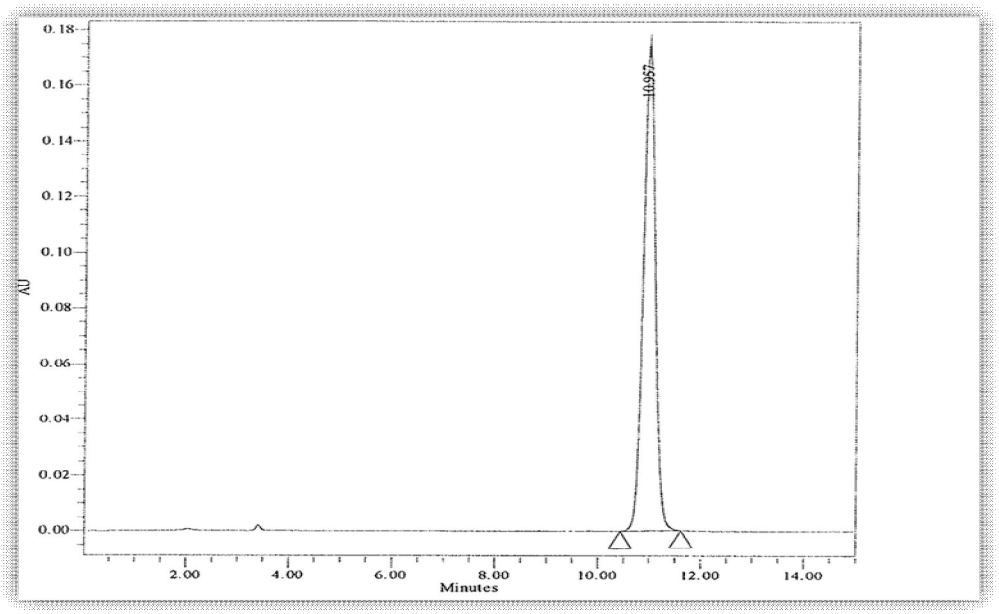

Fig. 6: A typical chromatogram of Loratadine standard (10µg/ ml) showing retention time at 10.957 minutes

Procedure
Injected sample solution (single injection) into the chromatograph and recorded the chromatograms. The retention time of sample, Loratadine peak is about 10.9 minutes.

Calculations
Individual content of Loratadine was calculated by the equation;

$$\frac{AT \times DS \times P \times 1}{AS \quad DT \quad 100} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$$

Where;
AT = Average Area counts of Loratadine peak in the chromatograms of the sample solution.
AS = Average area counts of Loratadine peak in the chromatograms of the standard solution as obtained under system suitability.
DS = Dilution factor of the standard solution in mg/mL
DT = Dilution factor of the sample solution.
P = Percent potency of Loratadine working standard, on "as is" basis.

2.3.3.9 Comparison of drug release of optimized test formulation (Formulation Code F3) with Claritin Reditab ®, Schering-Plough, UK (Batch Number: 99F1441).

The developed optimized formulation was quantitatively assessed for comparative dissolution as functional behavior against marketed product Claritin Reditab ®, Schering-Plough, UK (Batch Number: 99F1441).

2.3.3.10 Stability Study

Ageing (stability) study was determined on optimized batch to check any changes in morphological characteristics and in-vitro drug release behavior. The tablets packed in triple laminated aluminum pouch were stored at condition 40°C±2°C/ 75%RH±5%RH for period of 90 days. Tablet morphology and dissolution were evaluated after the period of 90 days. F2 was calculated to compare drug release characteristics at initial time point and after 90 days.

Fig. 7: Photograph showing accelerated stability condition of Stability Chamber (Thermolab®) used for studying aging behavior of optimized formulation

The similarity factors were determined for comparison of dissolution profiles.

2.3.3.11 Scanning electron microscopy

Tablet inner structure morphology was examined using scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive tape and then sputter coated for 8 min at 1.1 LV under argon atmosphere with gold palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilford PANF 50, film) using a 5 kV accelerating voltage, 26–28mm working distance, and a probe current of 3×10−11 amps.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies

The growing importance of orally dispersible tablets was under lined recently when European Pharmacopoeia adopted the term “Orodispersible tablets” and given the limit as 3 min for dispersion in the mouth, when taken orally.

The absorption maximum (λmax) for Loratadine was found to be 254 nm in simulated gastric fluid. Standard calibration curve (figure 1) of Loratadine was measured in 0.1 N HCl and was found to be linear with correlation coefficient being 0.9997. Wherever possible, mean of the readings were taken to minimize the errors.

During the process of development of novel oral disintegrating tablets of Loratadine, preformulation studies were undertaken and the results generated are discussed hereunder;

3.1.1 Determination of Loratadine pH Solubility Profile

The solubility profile of loratadine measured in various pH media within the range of GIT is present in figure 8. The lowest value for solubility (0.005- 0.008mg/ml) was obtained in the highest pH media (7.5, 6.5) tested and the highest value of about 4.15 mg/ml was obtained in pH 1.2 medium. The solubility

changed significantly within the well-accepted pH range of the stomach (fasting/fed state), with a dramatic fall when the pH was increased from 1.2 to 2.5 (0.60 mg/ml).

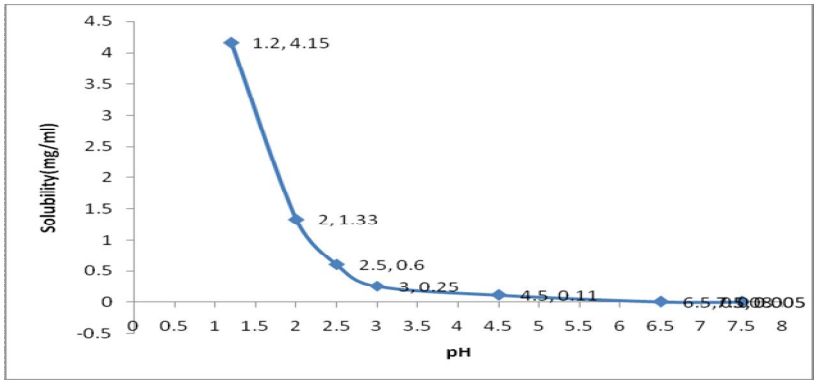

Fig. 8: Photograph showing Loratadine pH Solubility Profile

3.1.2 Drug excipient compatibility study

3.1.2.1 Solid state characterization by Differential Scanning Calorimetry (DSC) of physical mixtures (drug and different major excipients).

Results indicated that there was no incompatibility of excipients with Loratadine (Figure 9a-9f). The DSC thermogram of physical mixture showed sharp distinct endothermic peaks for Loratadine and likely excipients which corresponds to individual drug without exhibiting any distinguished modification, which indicates that Loratadine presented into the physical mixture is compatible with the excipients intended for direct compression (i.e by dry process).

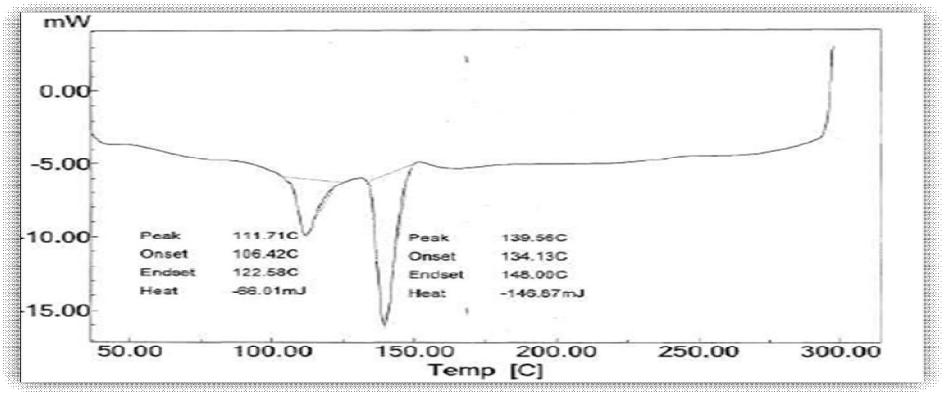

Fig. 9a: DSC Thermal Analysis result – Loratadine (API)

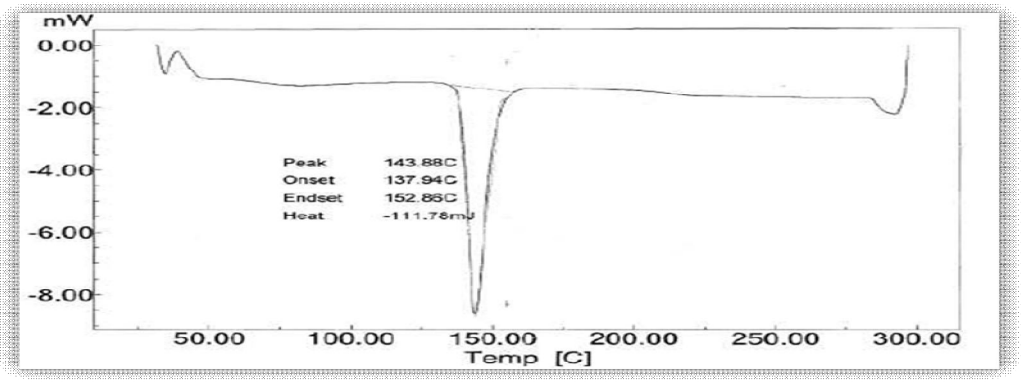

Fig. 9b: DSC Thermal Analysis result – Loratadine (API) + Pharmaburst 500®

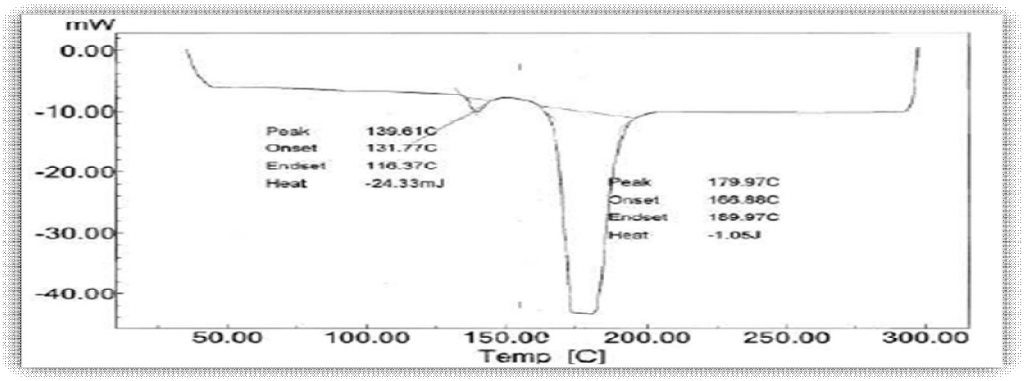

Fig. 9c: DSC Thermal Analysis result – Loratadine (API) + Flowlac 100®

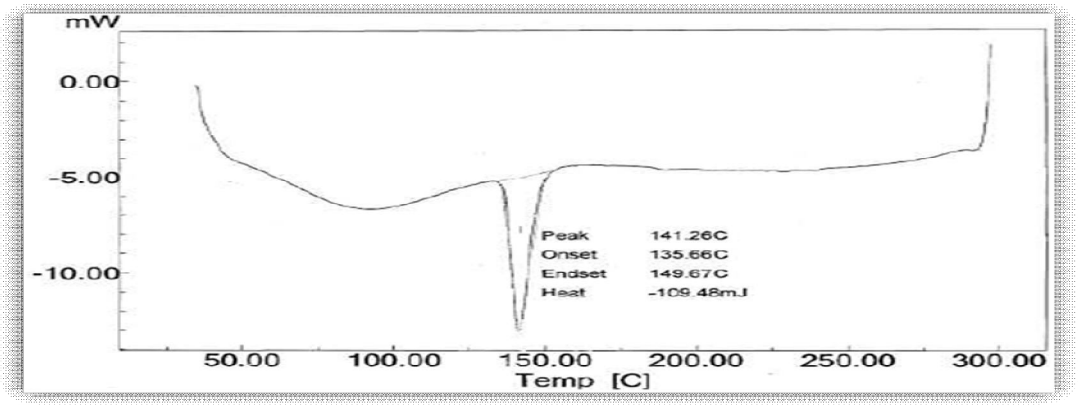

Fig. 9d: DSC Thermal Analysis result – Loratadine (API) + Avicel PH 102

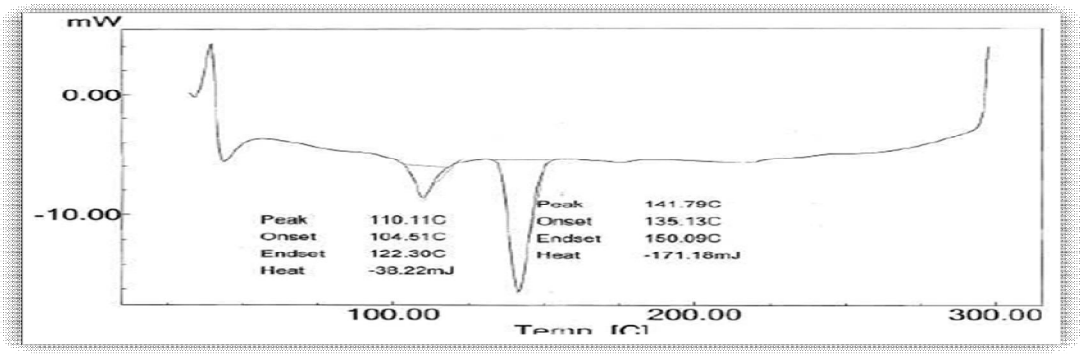

Fig. 9e: DSC Thermal Analysis result – Loratadine (API) + Aspartame

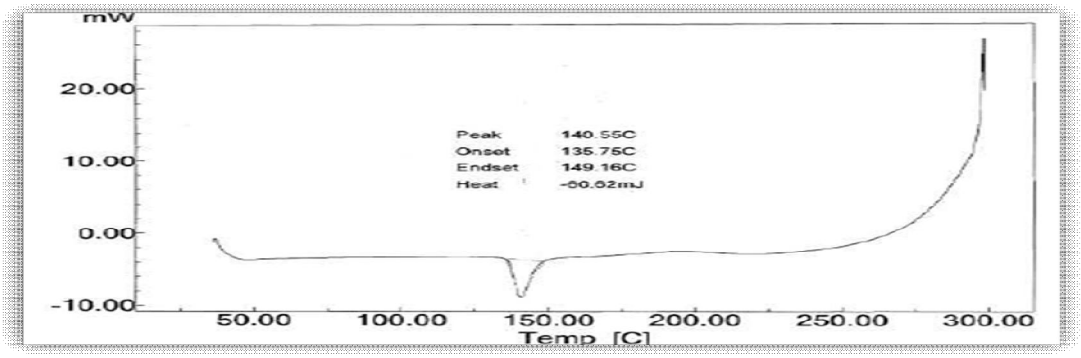

Fig. 9f: DSC Thermal Analysis result – Loratadine (API) + Aerosil 200

3.1.2.2 Solid state characterization by X-ray powder diffraction (XRPD) of drug, blend ready for compression and crushed tablet.

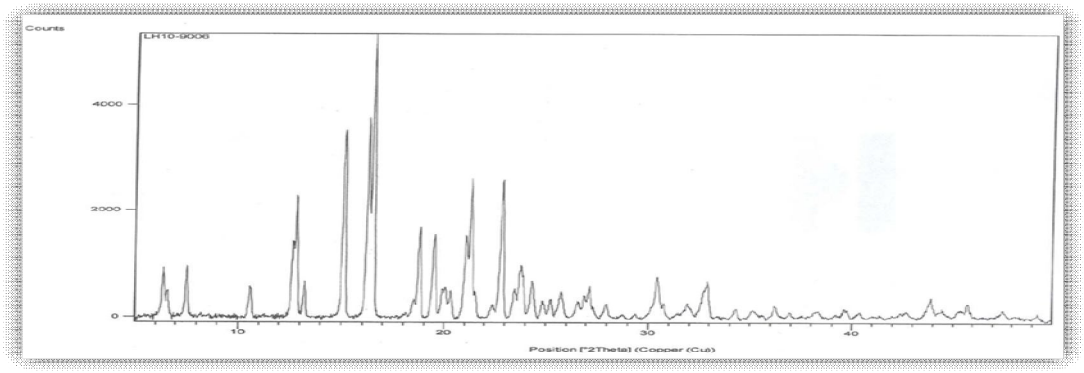

Fig. 10a: XRPD investigation of pure drug-Loratadine (API)

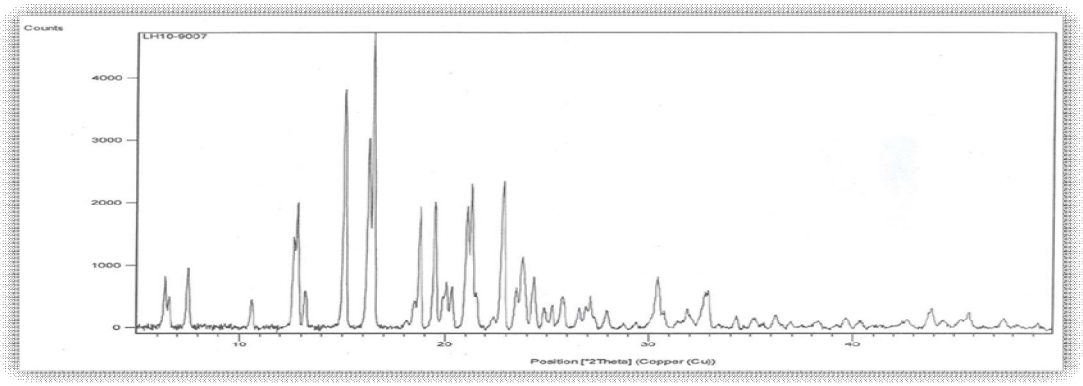

Fig. 10b: XRPD investigation of blend ready for compression (Formulation Code F3 randomized based on factorial design)

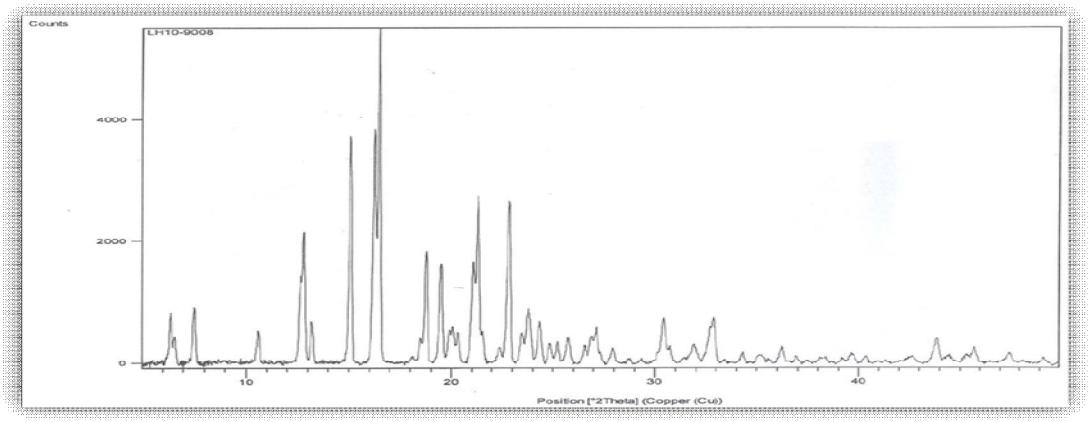

Fig. 10c: XRPD investigation of crushed tablet (Formulation Code F3 randomized based on factorial design)

Structural changes of Loratadine crystals in different samples were investigated by X-ray powder diffraction (Figure 10a-10c). X-ray powder diffraction was used to investigate the starting materials Loratadine, blend ready for compression (untreated) and crushed tablet (treated). Visual inspection did not reveal any significant difference in crystal structure, i.e. the diffractograms of the pure drug, blend ready for compression and crushed tablet seemed to be very similar. The diffractograms of Figure 10b and Figure 10c also displayed the original crystal characteristic values of the starting material Loratadine

API. Consequently, both DSC and XRPD studies demonstrated the stable crystalline form of Loratadine and absence of any well defined interaction with major proposed proprietary excipients.
Results of incompatibility were also substantiated with FTIR inputs (Figure 11a-11c).

3.1.2.3 Solid state characterization by FTIR of drug, blend ready for compression and crushed tablet.

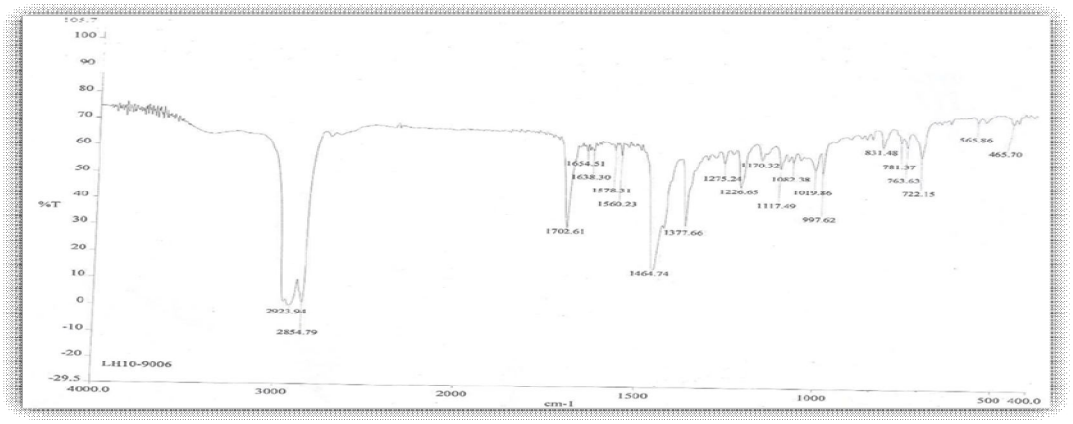

Fig. 11a: IR spectrum of pure drug-Loratadine (API)

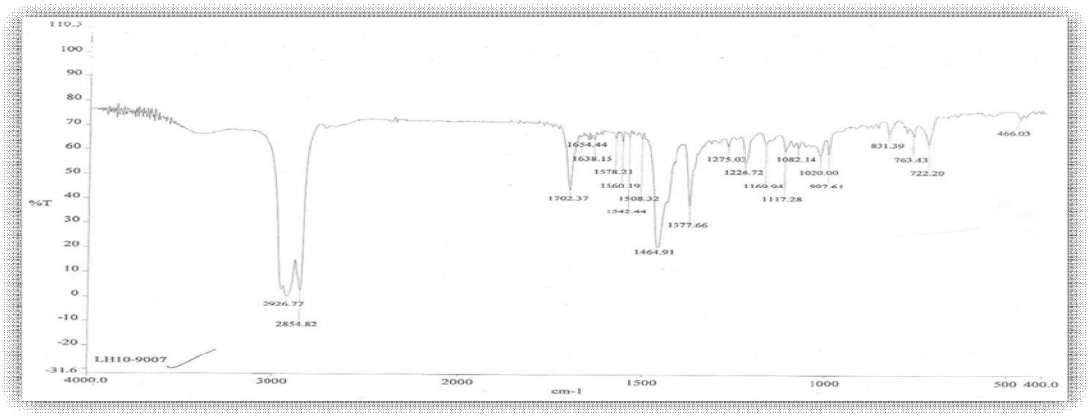

Fig. 11b: IR spectrum of blend ready for compression
(Formulation Code F3 randomized based on factorial design)

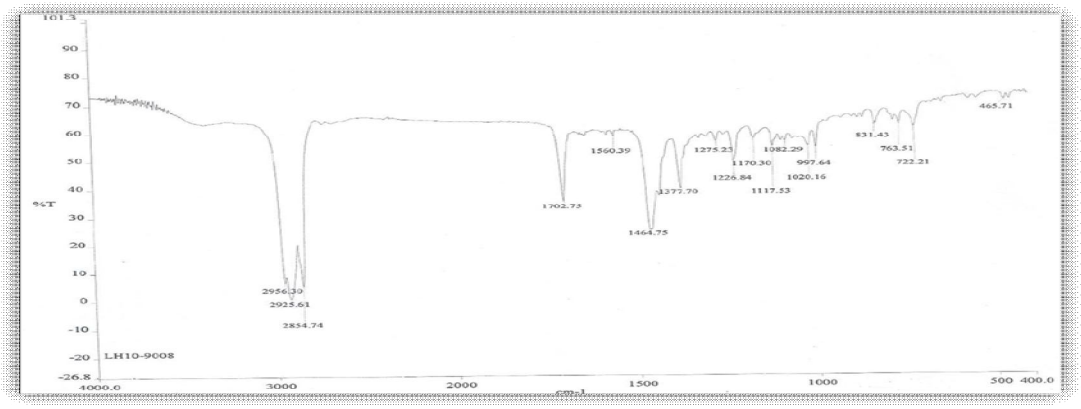

Fig. 11c: IR spectrum of crushed tablet
(Formulation Code F3 randomized based on factorial design)

3.2 Optimization of formulation using response surface quadratic model.

As evident from Table 3 (actual screenshot), the model F-value of 206.59 implied that the model was significant. There was only a 0.05% chance that a "Model F-value" this large could occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms were significant. In this case A, B, A2, B2 were significant model terms. Values if greater than 0.1000 would indicate the model terms were not significant. (R^2=0.9971), as seen from figure 12a, the surface response plot revealed that a corresponding increase in the friability (%w/w) was observed with increase in concentration of Pharmaburst 500®. This may be due to linearity in formation of interstitial pores/ channels with increased concentration of superdisintegrant thereby leading to moderately tender solid state characteristics of tablet. The results also laid down predictive indications that the effect of concentration of Pharmaburst 500® was more pronounced than the effect of concentration of flowlac 100®; that is, as the concentration of Pharmaburst 500® increased the friability also increased.

Moreover it is also apparent from Table 4 (actual screenshot), the Model F-value of 154.42 implied the model was significant. There was only a 0.08% chance that a "Model F-value" this large could occur due to noise. Values of "Prob>F"indicated that A, B, A2, B2 were significant model terms. (R^2=0.9961), as seen from figure 13a, the surface response plot revealed that a corresponding decrease in the disintegration time (seconds) was observed with increase in concentration of Pharmaburst 500®. The results also further substantiated predictive indications that the effect of concentration of Pharmaburst 500® was more pronounced than the effect of concentration of Flowlac 100®; that is, as the concentration of Pharmaburst 500® increased the disintegration time (seconds) decreased.

The response surface plots have therefore laid down predictive understanding that the desired oral disintegrating tablets with friability in the range 0.075 %w/w – 0.112%w/w and disintegration time in the range 18 –83 seconds could be obtained by using ratio, as mg/ tablet, of Pharmaburst 500® and Flowlac 100® in the range of 70:5, 50:7.5, 60: 7.5, 70: 7.5 and 50:10. From these experimental designs, keeping concentration of Flowlac 100® as 7.5%w/w was also fairly established, with also due relevance to the pronounced effect of concentration of Pharmaburst 500®.

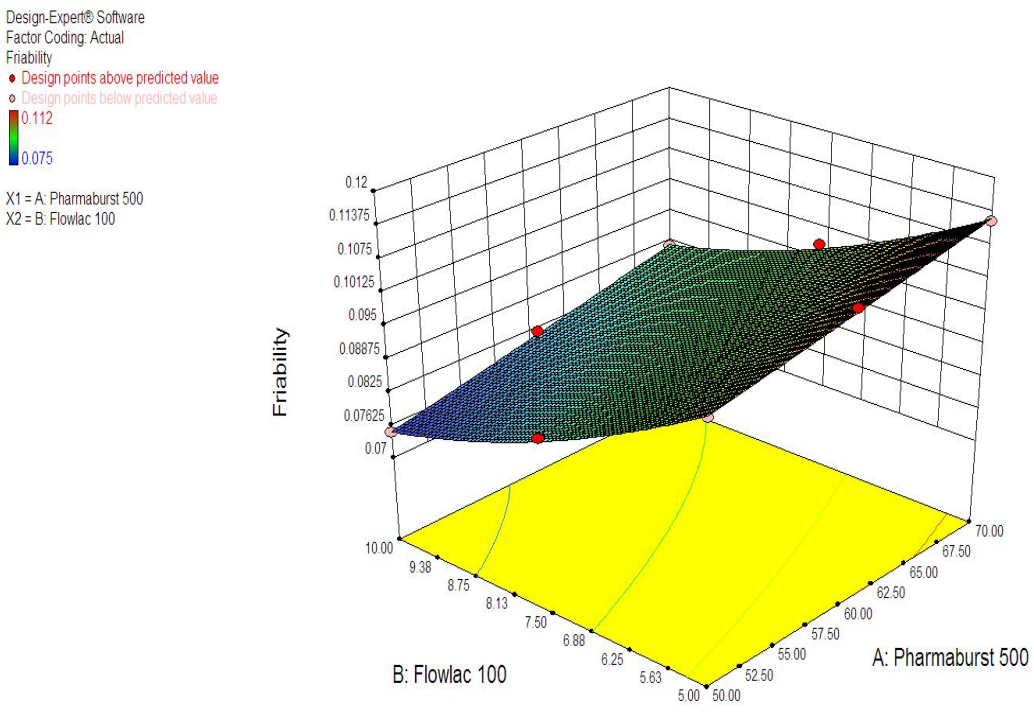

Fig. 12a: Surface response plot for friability (%w/w)

Table 3: Response 1- Friability (%w/w): Analysis of variance (ANOVA) for Response Surface Quadratic Model

Response 1 Friability

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1.215E-003	5	2.429E-004	206.59	0.0005	significant
A-Pharmaburst 500	*2.042E-004*	*1*	*2.042E-004*	*173.62*	*0.0009*	
B-Flowlac 100	*9.882E-004*	*1*	*9.882E-004*	*840.33*	*< 0.0001*	
AB	*2.250E-006*	*1*	*2.250E-006*	*1.91*	*0.2606*	
A^2	*5.556E-008*	*1*	*5.556E-008*	*0.047*	*0.8419*	
B^2	*2.006E-005*	*1*	*2.006E-005*	*17.06*	*0.0258*	
Residual	3.528E-006	3	1.176E-006			
Cor Total	1.218E-003	8				

The Model F-value of 206.59 implies the model is significant. There is only a 0.05% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B, B^2 are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Std. Dev.	1.084E-003	R-Squared	0.9971
Mean	0.093	Adj R-Squared	0.9923
C.V. %	1.16	Pred R-Squared	0.9778
PRESS	2.703E-005	Adeq Precision	42.165

The "Pred R-Squared" of 0.9778 is in reasonable agreement with the "Adj R-Squared" of 0.9923.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	0.091	1	8.083E-004	0.089	0.094	
A-Pharmaburst 500	5.833E-003	1	4.427E-004	4.424E-003	7.242E-003	1.00
B-Flowlac 100	-0.013	1	4.427E-004	-0.014	-0.011	1.00
AB	7.500E-004	1	5.422E-004	-9.755E-004	2.476E-003	1.00
A^2	1.667E-004	1	7.668E-004	-2.274E-003	2.607E-003	1.00
B^2	3.167E-003	1	7.668E-004	7.264E-004	5.607E-003	1.00

Final Equation in Terms of Coded Factors:

$$\begin{aligned} \text{Friability} = {} & \\ & +0.091 \\ & +5.833E\text{-}003 * A \\ & -0.013 * B \\ & +7.500E\text{-}004 * A * B \\ & +1.667E\text{-}004 * A^2 \\ & +3.167E\text{-}003 * B^2 \end{aligned}$$

Final Equation in Terms of Actual Factors:

$$\begin{aligned} \text{Friability} = {} & \\ & +0.14272 \\ & +1.58333E\text{-}004 * \text{Pharmaburst 500} \\ & -0.014533 * \text{Flowlac 100} \\ & +3.00000E\text{-}005 * \text{Pharmaburst 500} * \text{Flowlac 100} \\ & +1.66667E\text{-}006 * \text{Pharmaburst 500}^2 \\ & +5.06667E\text{-}004 * \text{Flowlac 100}^2 \end{aligned}$$

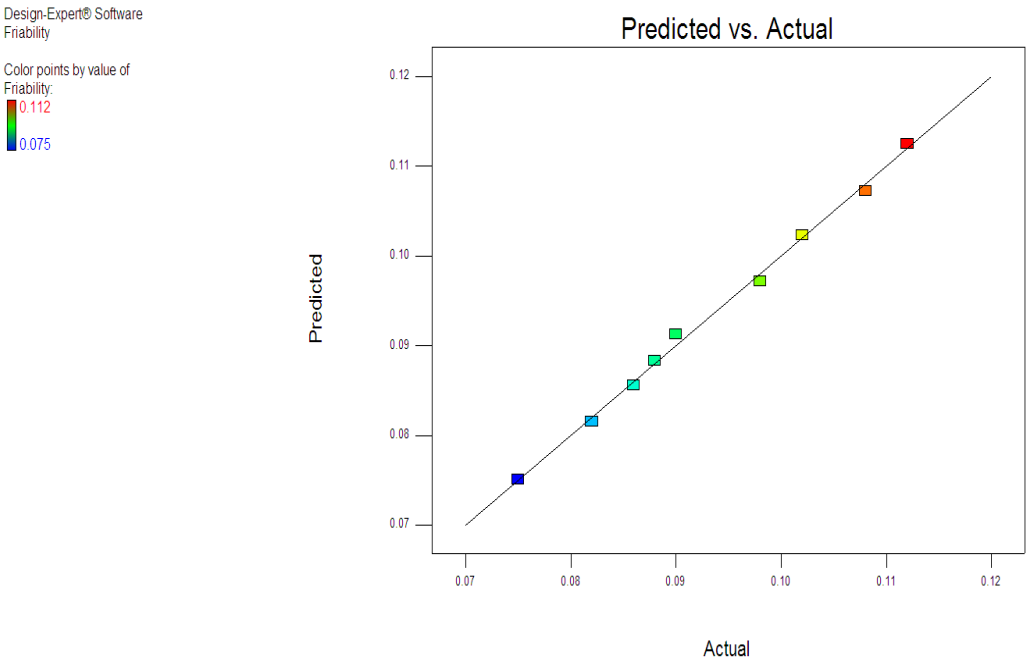

Fig. 12b: Predicted vs. Actual plot for friability (%w/w)

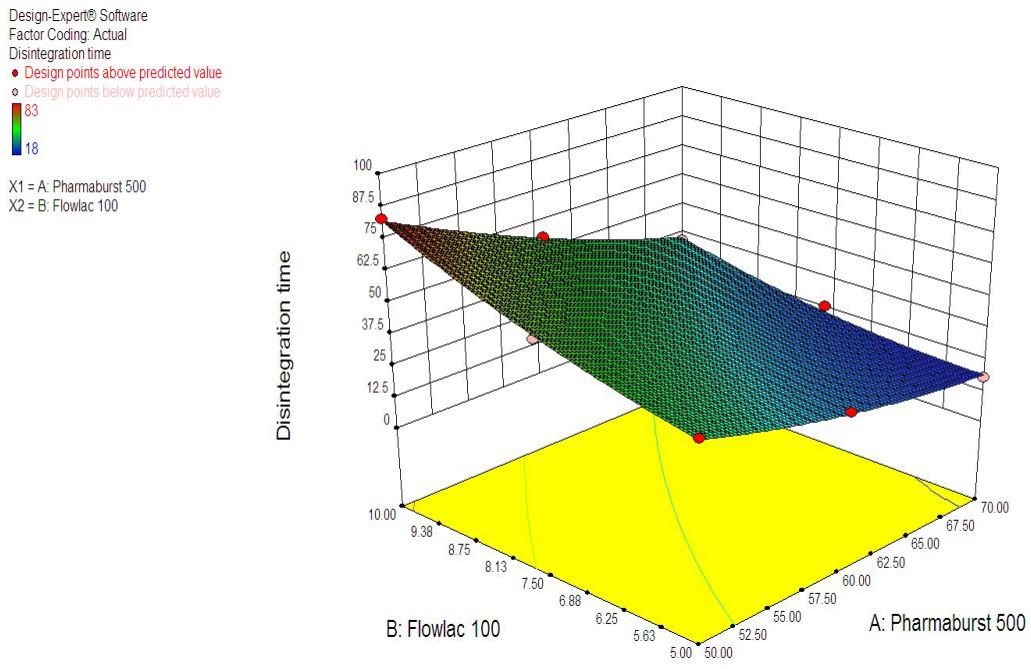

Fig. 13a: Surface response plot for Disintegration time (Seconds)

Table 4: Response 2- Disintegration Time (Seconds): Analysis of variance (ANOVA) for Response Surface Quadratic Model

Response 1 Disintegration time

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	3195.58	5	639.12	154.42	0.0008	significant
A-Pharmaburst 500	*1908.17*	*1*	*1908.17*	*461.03*	*0.0002*	
B-Flowlac 100	*1120.67*	*1*	*1120.67*	*270.77*	*0.0005*	
AB	*110.25*	*1*	*110.25*	*26.64*	*0.0141*	
A^2	*24.50*	*1*	*24.50*	*5.92*	*0.0931*	
B^2	*32.00*	*1*	*32.00*	*7.73*	*0.0690*	
Residual	12.42	3	4.14			
Cor Total	3208.00	8				

The Model F-value of 154.42 implies the model is significant. There is only a 0.08% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B, AB are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Std. Dev.	2.03	R-Squared	0.9961
Mean	43.00	Adj R-Squared	0.9897
C.V. %	4.73	Pred R-Squared	0.9561
PRESS	140.68	Adeq Precision	37.927

The "Pred R-Squared" of 0.9561 is in reasonable agreement with the "Adj R-Squared" of 0.9897.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	38.00	1	1.52	33.17	42.83	
A-Pharmaburst 500	-17.83	1	0.83	-20.48	-15.19	1.00
B-Flowlac 100	13.67	1	0.83	11.02	16.31	1.00
AB	-5.25	1	1.02	-8.49	-2.01	1.00
A^2	3.50	1	1.44	-1.08	8.08	1.00
B^2	4.00	1	1.44	-0.58	8.58	1.00

Final Equation in Terms of Coded Factors:

$$\begin{aligned}\text{Disintegration time} = {} & +38.00 \\ & -17.83 * A \\ & +13.67 * B \\ & -5.25 * A * B \\ & +3.50 * A^2 \\ & +4.00 * B^2\end{aligned}$$

Final Equation in Terms of Actual Factors:

$$\begin{aligned}\text{Disintegration time} = {} & +171.50000 \\ & -4.40833 * \text{Pharmaburst 500} \\ & +8.46667 * \text{Flowlac 100} \\ & -0.21000 * \text{Pharmaburst 500} * \text{Flowlac 100} \\ & +0.035000 * \text{Pharmaburst 500}^2 \\ & +0.64000 * \text{Flowlac 100}^2\end{aligned}$$

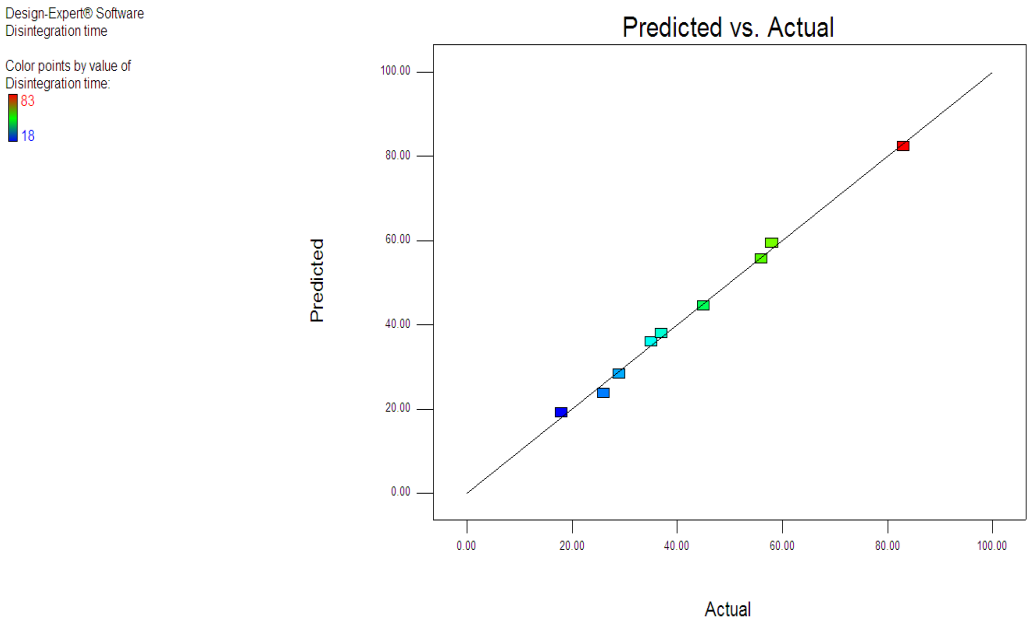

Fig. 13b: Predicted vs. Actual plot for Disintegration time (Seconds)

3.3 Evaluation of physical blend

3.3.1 Angle of Repose

The data obtained for angle of repose for all the batches prepared are tabulated in Table 5. The values were found to be in the range of 16.25 to 28.34. All the formulations showed the angle of repose less than 30° which reveals good to fair inherent flow property of the powder blend.

3.3.2 Bulk Density and Tapped Density

Loose bulk density (LBD) and tapped bulk density (TBD) of the powder blends of all the batches are shown in Table 5. The loose bulk density and tapped bulk density of all the batches were varied from 0.325 to 0.341 g/cc and 0.380 to 0.520 g/cc.

3.3.3 Bulkiness

The bulkiness was in the range of 1.980 to 3.076 cc/g.

3.3.4 Carr's Index (Compressibility Index)

Results of Carr's index are shown in Table 5. The values were found to be in the range of 12.924 to 23.461. Results clearly showed that flowability of all the batches is satisfactory and also the blend has good compressibility as per the Table 5.

3.3.5 Hausner Ratio

The Hausner ratio of all the batches prepared ranged from 1.150 to 1.296. Results are tabulated in Table 5. The results obtained indicated that all the powder blends had appreciable flow property.

Table 5: Results of evaluated physical blends for formulation codes F1 to F9

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Bulkiness (cc/g)	Compressibility Index (%)	Hausner Ratio
F1	27.12±0.095	0.390±0.082	0.483±0.062	2.564±0.051	19.254±1.314	1.238±0.097
F2	17.12±0.049	0.330±0.012	0.387±0.017	3.030±0.046	14.728±0.923	1.172±0.092
F3	16.25±0.057	0.339±0.019	0.390±0.021	2.949±0.065	12.924±0.837	1.150±0.11
F4	19.36±0.061	0.331±0.024	0.398±0.012	3.021±0.028	16.834±1.021	1.202±0.053

F5	17.88±0.072	0.325±0.013	0.380±0.015	3.076±0.035	14.473±0.775	1.169±0.010
F6	16.11±0.062	0.330±0.012	0.387±0.017	3.030±0.042	14.728±1.609	1.172±0.022
F7	34.38±0.098	0.398±0.053	0.520±0.038	2.512±0.068	23.461±0.712	1.296±0.091
F8	28.34±0.063	0.393±0.021	0.505±0.011	1.980±0.066	22.170±0.583	1.284±0.015
F9	21.10±0.052	0.341±0.023	0.423±0.017	2.930±0.038	19.385±0.697	1.240±0.089

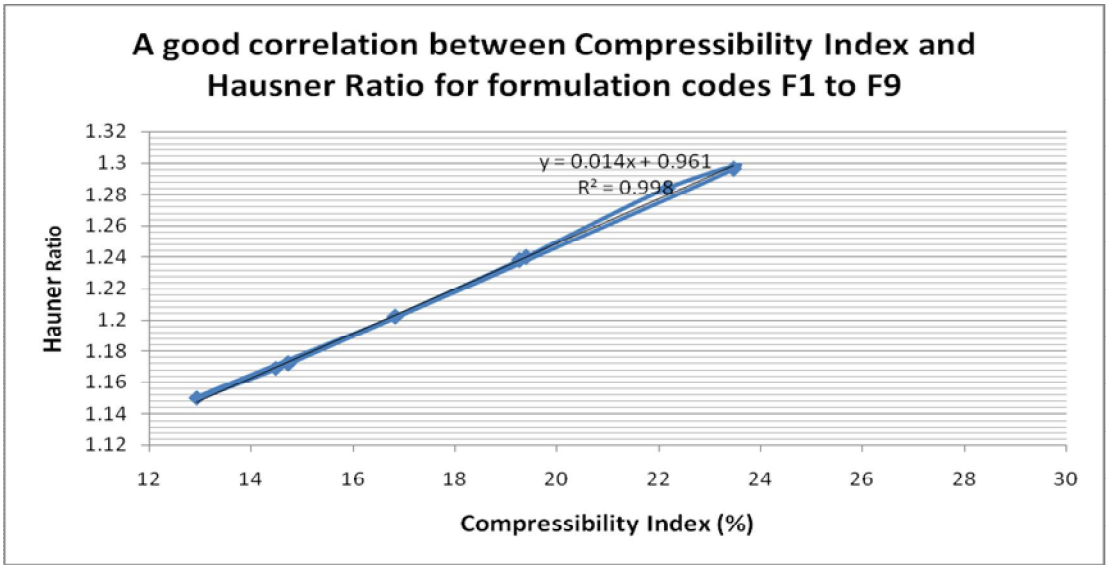

Fig. 14: Compressibility Index vs. Hausner Ratio Plot

3.4 Evaluation of prepared oral disintegrating tablets

3.4.1 Appearance

Tablets prepared were randomly picked from each batch examined under lens for shape and in presence of light for color. Tablets showed standard concave surfaces with circular shape. Tablets were white to off white in colour.

3.4.2 Weight variation

The weight variation for all the formulations is shown in Table 6. All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the pharmacopoeial limits of ±7.5%.

3.4.3 Hardness

Hardness or crushing strength of the tablets of all the batches was found to be ranging from 3.0 to 4.0 kP. The mean hardness test results are tabulated in Table 6. The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness.

3.4.4 Thickness

The results of thickness for tablets are shown in Table 6. The mean thickness of tablets (n=3) prepared using combination of specific grades of key functional excipients pharmaburst 500®, flowlac 100® and Avicel PH 102 was found be ranging from 3.44 to 3.50 mm.

3.4.5 Friability

Friability values of all the batches were in the range of 0.075 % to 0.112%. The obtained results were found to be well within the approved range (<1%) in all the designed formulations. That indicated tablets possess good mechanical strength. Friability results of all the batches are tabulated in Table 6.

3.4.6 Disintegration time

The disintegration time (Table 6) of all the formulated tablets (F1 to F9) between 18 to 83 seconds. This indicated that all the tablets met the basic requirement of oral disintegrating (dispersible) tablet as per the definition of current European Pharmacopoeia. This therefore laid down a basis to understand the in-vitro drug release behavior of all the formulated tablets (F1 to F9) and thereafter arriving to conclusion for selecting optimized formulation batch based on combinatorial impacts of flow property of blend, friability, disintegration time and drug release behavior of tablets.

Table 6: Results of evaluated In-Process Parameters; formulation codes F1 to F9

Formulation Code	Weight Variation (mg)	Hardness (kP)	Thickness (mm)	Friability (%)	Disintegration Time (Seconds)
F1	100.48±0.96	3.56±0.053	3.48±0.012	0.086	58
F2	100.12±0.53	3.78±0.15	3.47±0.013	0.09	37
F3	99.85±0.23	3.58±0.11	3.47±0.014	0.098	26
F4	100.14±0.28	3.58±0.12	3.48±0.012	0.075	83
F5	100.15±0.68	3.73±0.082	3.46±0.028	0.082	56
F6	98.95±0.28	3.47±0.38	3.47±0.017	0.088	35
F7	100.08±0.75	3.44±0.27	3.46±0.037	0.102	45
F8	99.56±0.57	3.81±0.086	3.48±0.031	0.108	29
F9	100.18±0.37	3.95±0.018	3.45±0.041	0.112	18

3.4.7 In-Vitro drug release behavior of formulated tablets

The in-vitro drug release profile for all the formulated tablets (F1 to F9) are shown in figure 15. Over all, the ODT formulations of loratadine showed an average of 89.10 to 99.38 % drug release range at the end of 10 min and it was also observed that only formulation codes F9 and F3 took shortest time to release the more than average of 99% of drug at the end of 10 min. As can be further seen from table 7 & figure 15 that only formulation codes F2, F6, F7 and F8 demonstrated drug release more than average of 95 % at the end of 10 minutes but lesser than 99%. Remaining three formulation codes F1, F4 & F5 showed drug release less than an average of 95%.

This laid down a basis to call for more stringent pharmaceutical comparison among formulation codes F9, F3, F2, F6, F7 and F8, considering parameters flow property of blend, friability and disintegration time also, to select optimized formulation, as no statistical significant difference ($p>0.05$, one way ANOVA) was observed among drug release profiles of formulation codes F9, F3, F2, F6, F7 and F8 (figure 15).

As evident from table 6, F9 showed fastest disintegration time, 18 seconds, but with highest friability loss among all above comparable batches. Also as can be seen in table 5, F9 demonstrated fair flow characteristics by virtue of angle of repose, Carr's index and Hausner ratio. Friability loss bit minimized for batch F8, with appreciable fast disintegration time, but flow characteristics (passable) were not even as fair as with F9. For batch F7 values representing flow characteristics still slightly worsen as compared with F7 with concomitant worsening of disintegration time. Batches F2, F3 and F6 showed good flow characteristics, minimized friability loss and also fast disintegration time. A scientifically based fair decision was materialized to randomly select F3, however, as optimized formulation/ batch among later

three batches based on the observed fact that F3 took shortest time to release the more than average of 99% of drug at the end of 10 min. The qualitative dispersion behavior of F3 is pictorially shown in fig. 4.

Table 7: In-Vitro Drug Release (Cumulative Percent Release) values of formulation codes F1 to F9

Time (Minutes)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	77.3	89.2	91.31	88.43	75.2	89.36	88.14	85.13	94.19
4	78.12	91.28	95.87	75.62	78.16	94.17	93.42	92.34	98.27
6	85.33	93.17	97.82	83.37	86.18	95.88	94.86	94.12	98.35
8	91.26	94.25	98.17	86.39	89.26	97.16	96.13	95.88	98.98
10	92.28	96.72	99.42	89.1	92.34	98.23	97.11	97.25	99.38

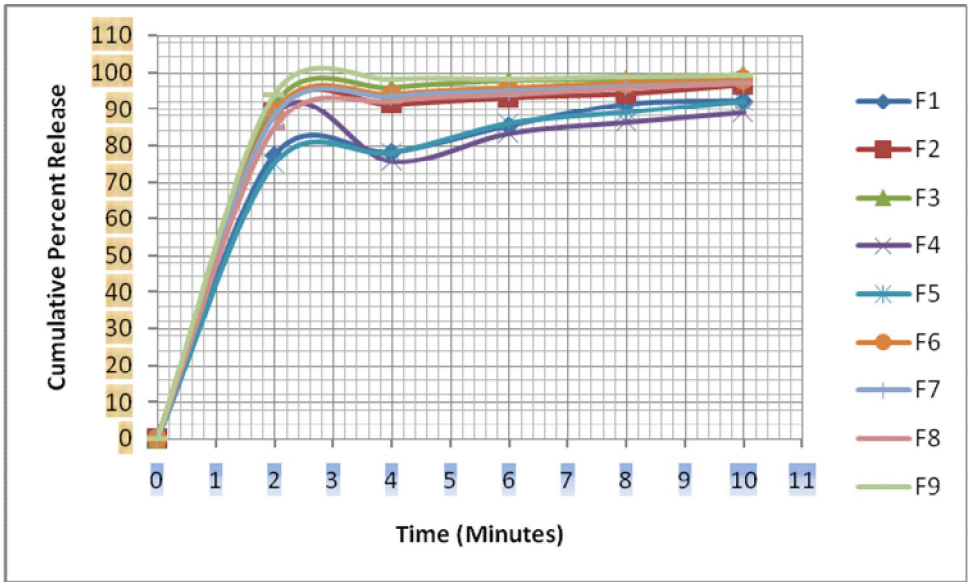

Fig. 15: In-Vitro Drug Release Profile of formulation codes F1 to F9

Based on empirical calculations for Korsmeyer-Peppas equation, the n values were found between 0.5 and 1.0 for the release of Loratadine from all the formulations, indicating non-fickian release kinetics, which is indicative of drug release mechanisms involving diffusion mechanism thereby resulting into rate controlled water uptake behavior of porous network of tablet.

3.4.8 Uniformity of dosage units by content uniformity (Estimation by HPLC)

Thus based on the combinatorial results of flow property of blend for compression, friability, disintegration time and in-vitro drug release behavior, optimized formulation F3 was finalized. In the present research work, test for drug content uniformity (Estimation by HPLC) was only performed for optimized formulation (F3). Drug content uniformity in the formulations was found to be 98.844% to 102.160%. The results are tabulated in Table 8. Ten typical chromatograms representing individual tablets of optimized batch are placed in figure 16a to figure 16j. Typical chromatogram of Loratadine standard (10µg/ ml) showing retention time at 10.957 minutes is placed in figure 16.

Table 8: Area counts of sample, mg per unit, & % of claim (ACTUAL SCREENSHOT PASTED)

Claim (mg)	Area Counts of Sample	Assay	
		(mg per Unit)	% of Claim
10	2776840	9.87	98.72870876
	2785461	9.9	99.03522271
	2807957	9.98	99.83505311
	2821391	10.03	100.3126901
	2780106	9.88	98.84482923
	2794772	9.94	99.36626916
	2873356	10.22	102.1602713
	2786496	9.91	99.07202145
	2788888	9.92	99.15706743
	2796434	9.94	99.42536047

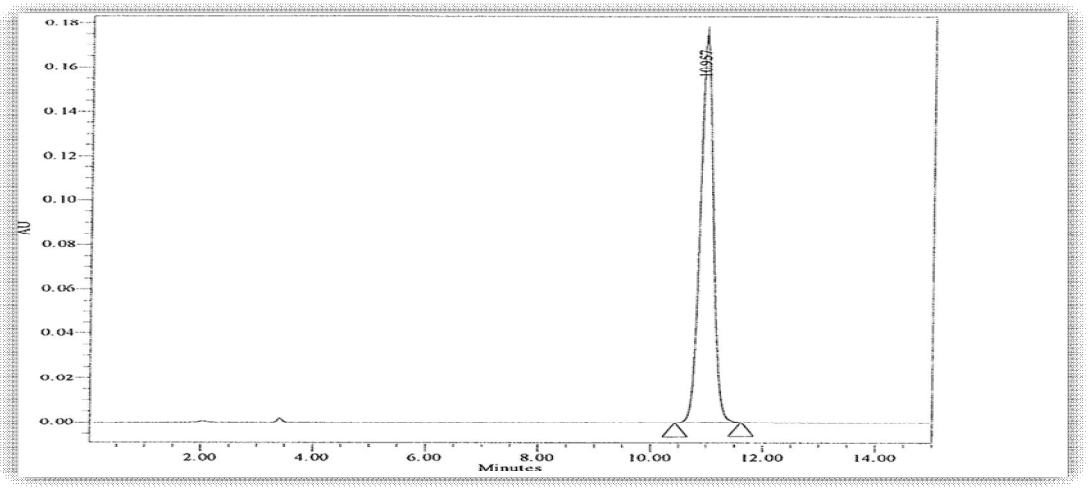

Fig. 16: A typical chromatogram of Loratadine standard (10µg/ ml) showing retention time at 10.957 minutes

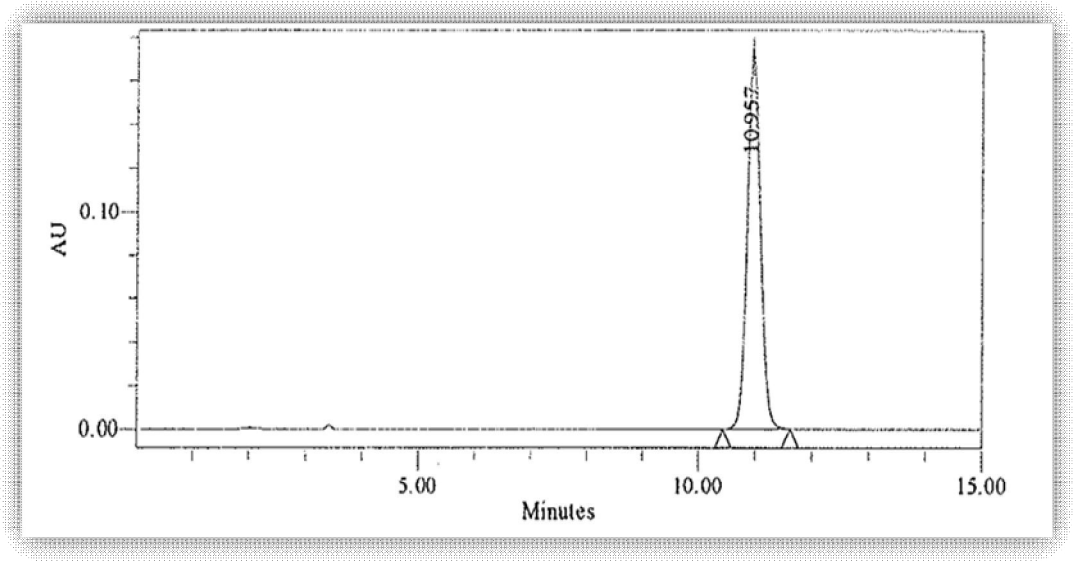

Fig. 16a: A typical chromatogram for test sample showing retention time at 10.957 minutes

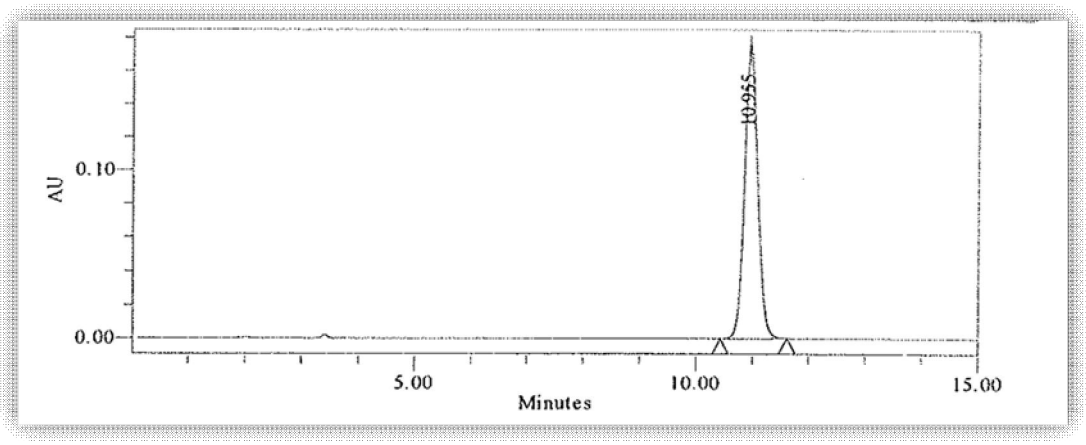

Fig. 16b: A typical chromatogram for test sample showing retention time at 10.955 minutes

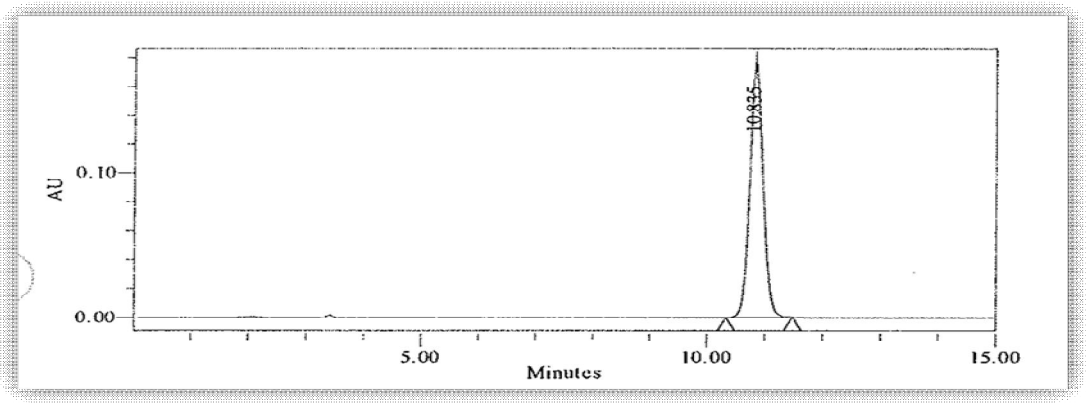

Fig. 16c: A typical chromatogram for test sample showing retention time at 10.835 minutes

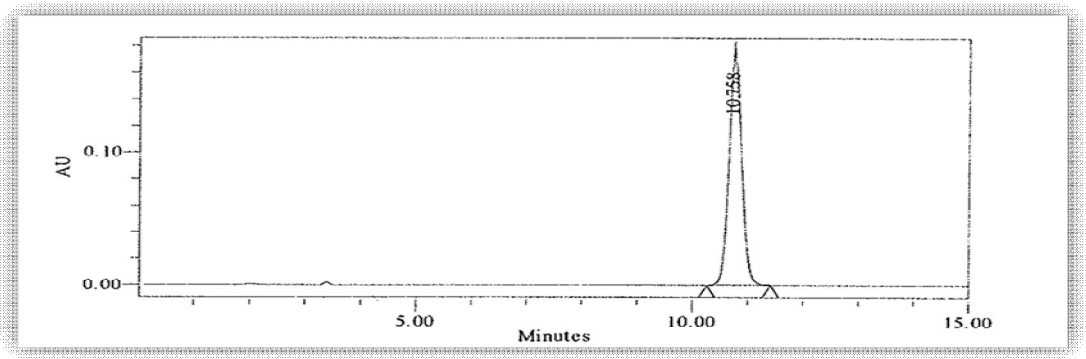

Fig. 16d: A typical chromatogram for test sample showing retention time at 10.758 minutes

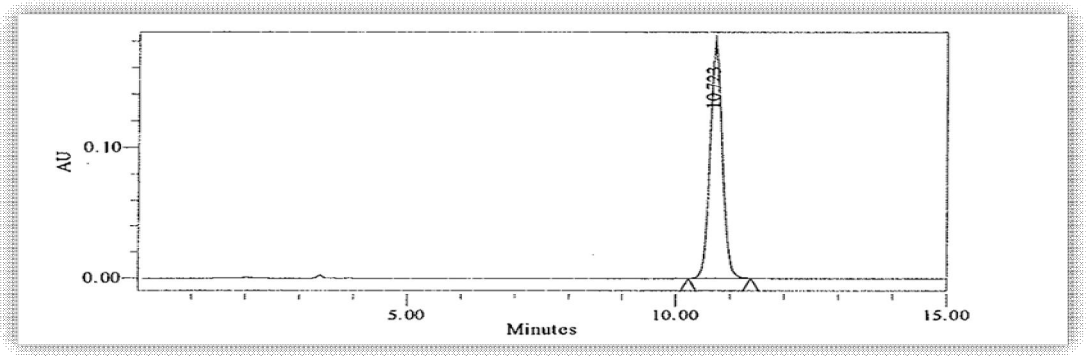

Fig. 16e: A typical chromatogram for test sample showing retention time at 10.723 minutes

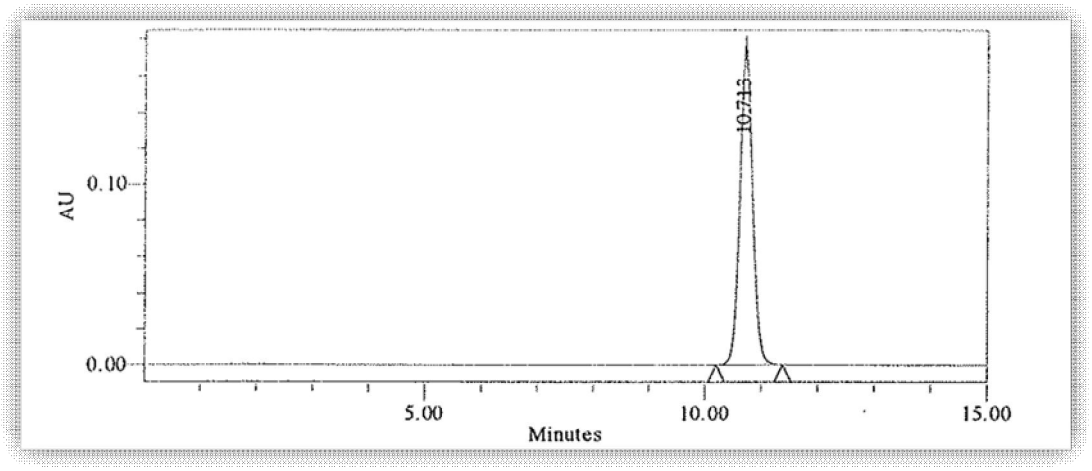

Fig. 16f: A typical chromatogram for test sample showing retention time at 10.713 minutes

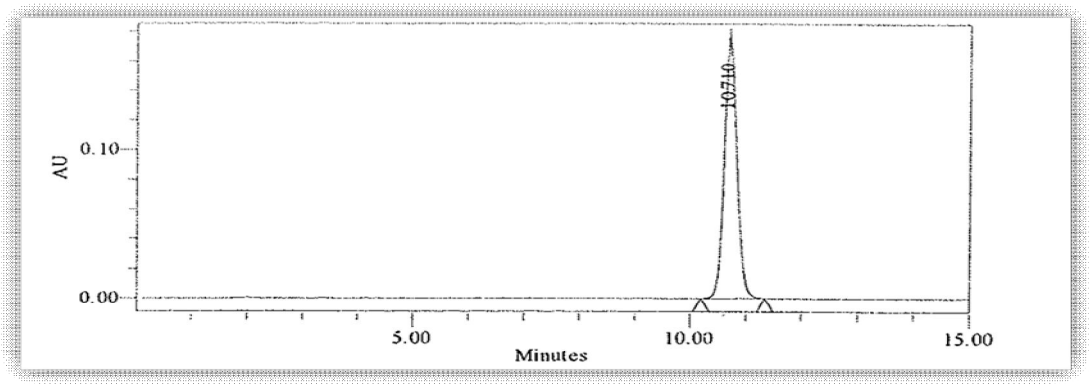

Fig. 16g: A typical chromatogram for test sample showing retention time at 10.710 minutes

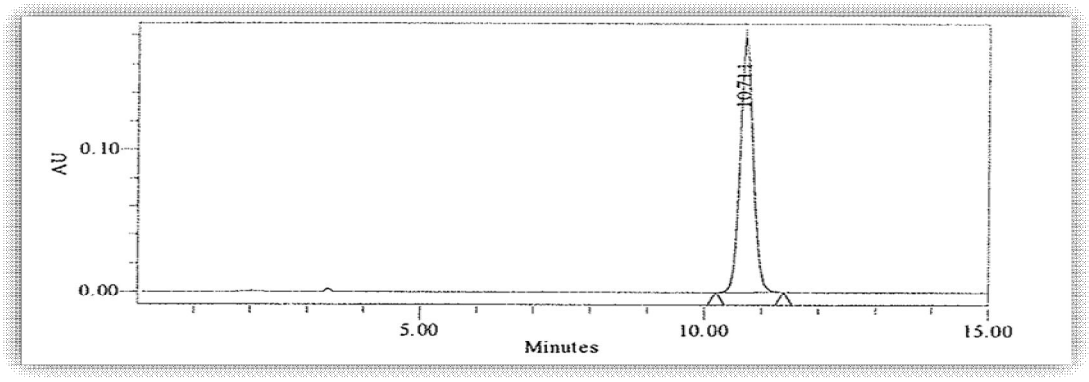

Fig. 16h: A typical chromatogram for test sample showing retention time at 10.711 minutes

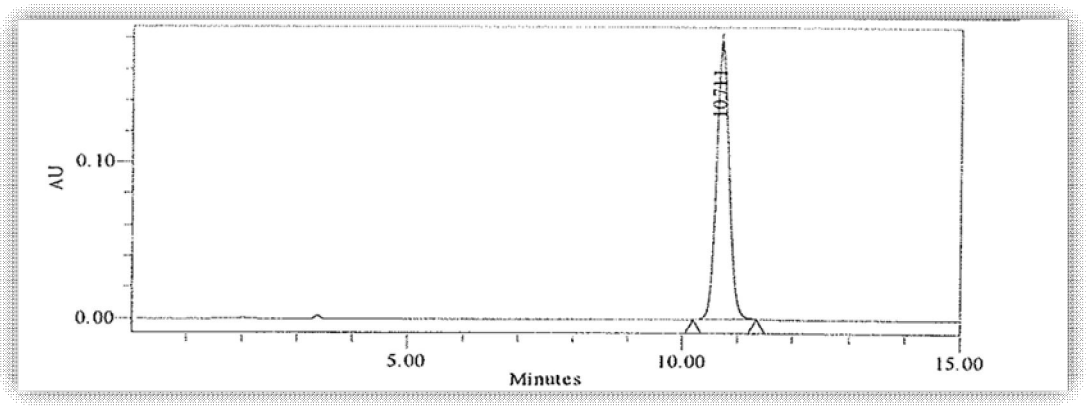

Fig. 16i: A typical chromatogram for test sample showing retention time at 10.711 minutes

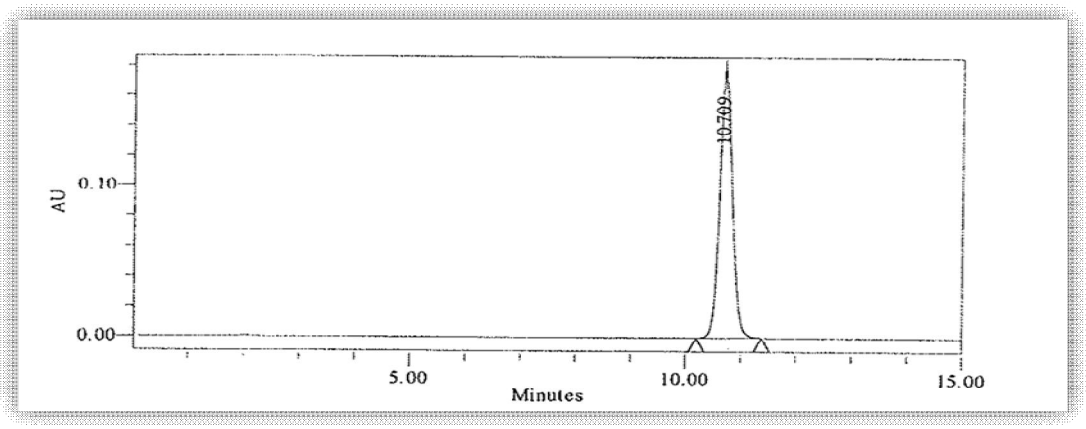

Fig. 16j: A typical chromatogram for test sample showing retention time at 10.709 minutes

3.4.9 Comparison of drug release of optimized test formulation (Formulation Code F3) with Claritin Reditab®, Schering-Plough, UK (Batch Number: 99F1441).

For performing comparative drug release study, UK based reference listed drug Claritin Reditab® , Schering-Plough, UK (Batch Number: 99F1441) was kindly obtained from M/s Ranbaxy Laboratories Limited, Gurgaon, India. Formulation F3 was compared with marketed formulation (Claritin Reditab®; Oral Disintegrating) to establish pharmaceutical equivalence, as no oral disintegrating generic version is found in India after critical literature survey. F3 was found to be comparable with reference listed drug product (F2 = 80.12) (figure 17).

Table 9: Comparative drug release between test formulation and reference formulation

Time (Minutes)	Test formulation (F3)	Reference formulation (Claritin Reditab)
2	91.31	88.85
4	95.87	92.68
6	97.82	95.25
8	98.17	98.09
10	99.42	101.25
F2 (Similarity Factor)= 80.12		

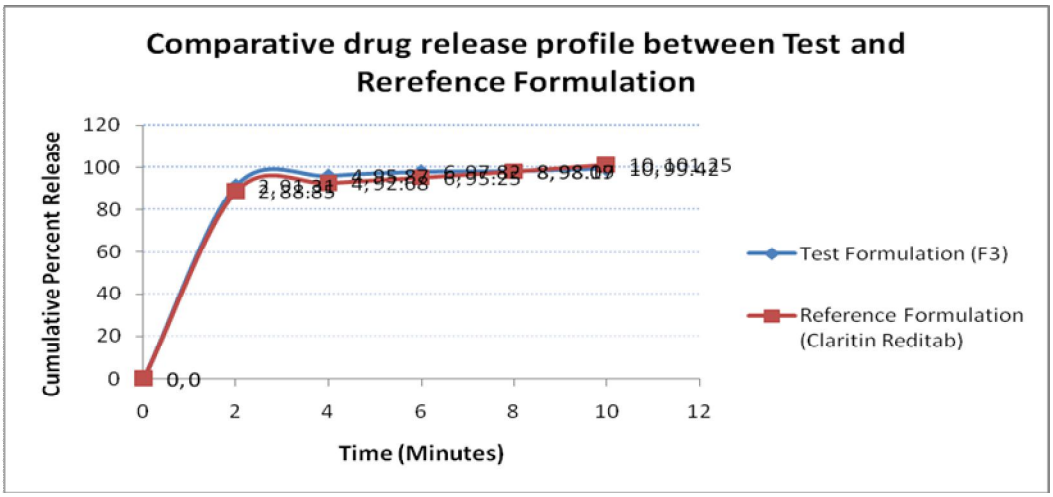

Fig. 17: Comparative drug release profiles between Test and Reference Formulation

3.5 Stability study of tablets

Formulation F3 was selected for accelerated stability studies. F3 was placed at 40°C/ 75% RH for 90 days. After 90 days, tablets were examined for in-vitro drug release characteristics. No statistical significant change ($p>0.05$, one way ANOVA) in drug release values was observed when values compared with 0 day (Initial) formulation (Table 10, figure 18).

Table 10: Comparison of drug release values at Initial and 90 days

Time (Minutes)	Test formulation (Initial)	Test formulation (After 90 days)
	F3	F3
2	91.31	92.07
4	95.87	93.96
6	97.82	97.25
8	98.17	99.12
10	99.42	99.86
F2 (Similarity Factor)= 91.79		

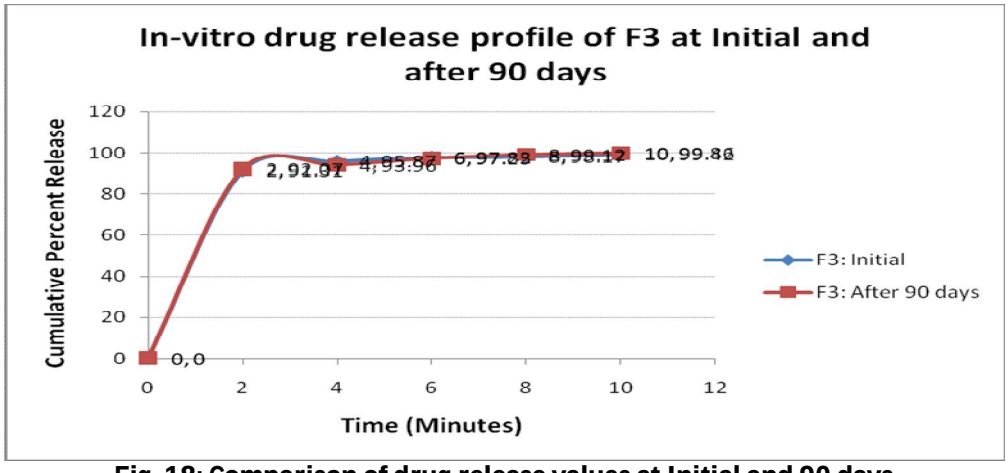

Fig. 18: Comparison of drug release values at Initial and 90 days

The percent released versus time of stored tablets demonstrates a bit modification in the amount of drug release with time. Freshly prepared optimized tablets (F3) released nearly 99.42 % Loratadine after 10 minutes, whereas tablets (F3) after storage at 40°C±2°C/ 75%RH±5%RH for period of three months demonstrated practically indifferent drug release nearly 99.86 % at the same time point (Figure 18). Statistically modification in extent of drug release was also found to be insignificant (One Way ANOVA, $P > 0.05$). In terms of Korsmeyer-Peppas equation, the values of n are between 0.5 and 1.0, indicating no change in release mechanism (rate controlled water uptake behavior of porous network of tablet) after three months storage at the specified condition. It can, therefore, be concluded that the prepared tablets are stable at 40°C±2°C/ 75%RH±5%RH for period of three months.

F2 was also calculated to compare drug release characteristics at initial time point and after 90 days and was found to be indicating similarity in profiles (F2 = 91.79).

Morphological characteristics were also studied through scanning electron microscopy at initial (Fresh) and 90 days (Aged) to substantiate any changes in inner structures of tablet during storage for 90 days at accelerated condition (40°C/ 75% RH) .

Figure 19a shows the inner structures, at low (25X) and high (200X) magnification, of the tablets at zero (0) day (initial time point) prepared using the formulation by direct compression method. In order to investigate the structure in more detail, images of different magnifications were taken and compared. As can be understood from Figure 19a even though the granules on the tablet surface were compressed at reasonable compression force to result into tablets of optimum hardness (3.0 kP – 4.0 kP), however there existed many empty spaces between the granules throughout the tablet where water could be absorbed by capillary forces. It is these pores that increase the absorption of water by capillary forces. At higher magnification, a detailed distribution of pores can be observed. Upon contact with water or saliva, the granules could easily dissociate, and the whole tablet disintegrated to form a paste like, which could be easy to swallow.

After storage at 40°C±2°C/ 75%RH±5%RH for period of 90 days, it was visualized as pores became smaller; however the inner structures of granules remained practically unaffected. It is, therefore, apparent that a very modification in porous structures during storage, as evidenced by the electron micrographs (Figure 19b), may be responsible for the insignificant changes in drug release rate and mechanism after storage.

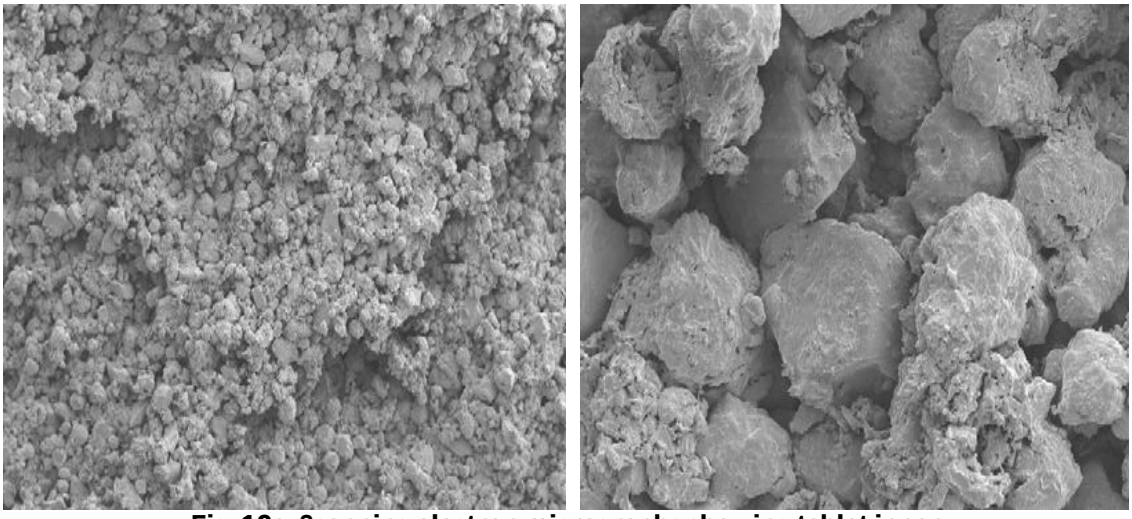

Fig. 19a: Scanning electron micrographs showing tablet inner structures of 0 day at magnification 25X (left image) and 200X (right image)

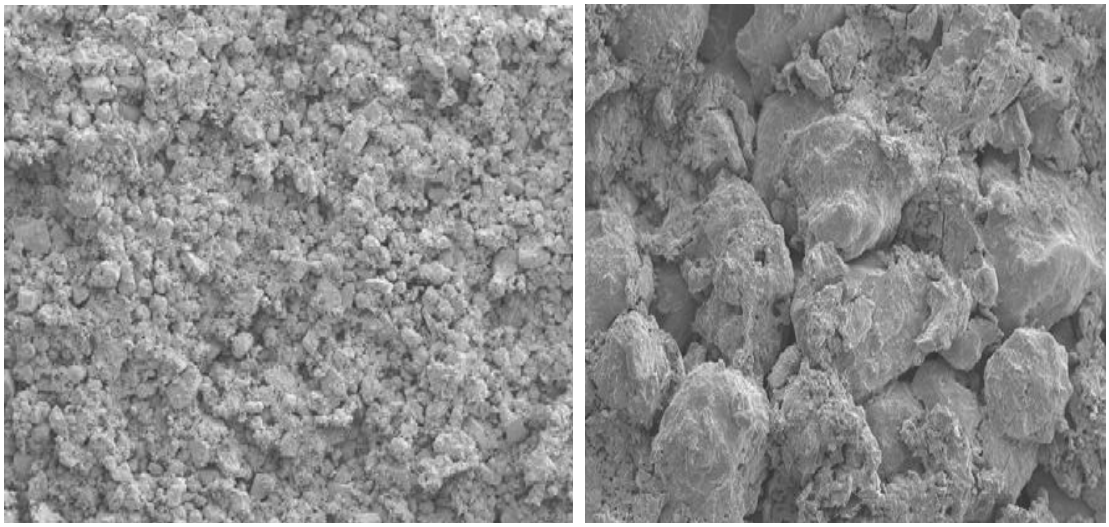

Fig. 19b: Scanning electron micrographs showing inner structures of tablet after 90 days at magnification 25X (left image) and 200X (right image)

4. CONCLUSION

The above results suggest that the formulated quick dissolving tablets of Loratadine exhibited good physical parameters and rapidly disintegrating without affecting the release profile and hence expected to be very effective in case of elderly and pediatric patients. The overall results indicated that formulation code F3 had a higher edge compared to other trials satisfying all the criteria for a orally disintegrating tablet.

This direct compression process is simple, reproducible and robust to prepare orally disintegrating tablets of Loratadine and other antihistamine drugs using availability of improved patient and eco-friendly excipients Pharmaburst 500® and Flowlac 100® processed in combination.

Loratadine showing enhanced dissolution, may lead to improved bioavailability, improved effectiveness and hence better patient compliance. Stability study conducted at accelerated storage condition revealed that prepared quick dissolving tablets were found to be suitable with respect to morphological characteristics and with in-vitro drug release mechanism & similarity factor (F2) comparison unaffected after 90 days.

The present research work could therefore provide the opportunity and form the basis as suitable platform technology to further pursue & own the research using other potent drugs in section 505 B (2).

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