A New Formulation Approach of Oro-Dispersible Tablet of Bilastine by Incorporating Co-Processed Super-Disintegrants

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Abstract

The major goal of this study is to prepare an Oro-dispersible tablet of Bilastine, to treat the symptoms of allergic rhinitis and chronic urticaria. It has a high level of selectivity for the H1 histamine receptor. It is under BCS class II medicines and has a 61% oral bioavailability, which limits its absorption dissolution rate. To provide the greatest therapeutic benefit, the bioavailability must be increased. This study uses superdisintegrants to make Bilastine more soluble and dissolve more easily. Nine formulations were produced employing varying quantities of superdisintegrants and co-processed super-disintegrants, such as Crospovidone, sodium starch glycolate, and croscarmellose sodium. Mannitol, microcrystalline cellulose as diluents, magnesium stearate, and talc were the additional excipients utilized. The pre-compression parameters and post-compression parameters were performed and were found within the limit. The drug and excipient compatibility study was carried out by FTIR and DSC and found there was no interactions.

Keywords: *Orodispersible tablets, Bilastine, Co-processed superdisintegrants, Direct compression, Invitro dispersion time.*

1. Introduction

Due to their ease of use, portability, accurate dosing, and low cost of production, tablets are most widely used solid dose form. As a result, numerous initiatives have been made to develop compounds that work best in solid dosage forms and provide dependable and efficient plasma concentrations after delivery. In particular for young patients and senior patients who are bedridden, experience nausea, or have mental conditions, swallowing issues are the main concern with oral dosage forms. To alleviate this problem and improve the patient's intake and compliance, a solid dose form has been developed that may quickly dissolve even when given orally without water. (1)

As soon as the dosage form meets saliva, it commences to break down; full breakdown typically occurs 30 to 50 seconds after ingestion. After the solution containing the active ingredient enters the body, the gastrointestinal tract's epithelium absorbs it, performing the intended function and producing the desired effect. As the medication dissolves and is absorbed more quickly, the therapeutic effect increases. (2)

A novel second-generation antihistamine called Bilastine is approved to treat the symptoms of chronic urticaria and allergic rhinitis. It exhibits a high level of H1 histamine receptor specificity. It is under BCS class II medicines and has a 61% oral bioavailability, which limits its absorption dissolution rate. It requires increase in the bioavailability to get the maximum therapeutic effect. (3)

2. Materials and Methods

Materials:

The pure drug of Bilastine was gained as free sample from “Shilpa pharmaceuticals” Hyderabad. Croscarmellose sodium, Crospovidone, Microcrystalline cellulose, Mannitol, Magnesium stearate and Talc. All the compounds and chemicals used in the present investigation are of analytical rating. All the studies were carried out using double distilled water.

Drug excipients compatibility studies by FTIR

FTIR spectroscopy determines the functional groups in the drug molecule. The electromagnetic radiation passes through the sample range 400 cm-1 and 4000 cm-1. The molecules present in drug and polymer have their bonds are occupied by electromagnetic radiation, causing them to spin. The wavelength of the radiation absorbed is a property of the bond that absorbs it. (4)

Drug excipients compatibility studies by DSC

Conducting the thermal analysis using DSC investigations, the potential for any interactions between Bilastine and the excipients in floating tablets was evaluated. For DSC studies pure drug (Bilastine) and the tablets of optimised formulation F6 were taken, and the thermal behaviour of samples were determined using DSC at heating rate of 10^0C /min. The measurements were performed at a heating range from 30 to 200 0C under nitrogen atmosphere. (4)

In this study, the direct compression method and superdisintegrants were used to produce Bilastine orodispersible tablets. The concentration of Bilastine employed in this study was 20 mg. The key determining factors in the formulation development for the current experiment were the type and concentration of superdisintegrants as well as the properties of the medication. In different combinations and concentrations, numerous superdisintegrants were used. (4)

Method of Preparation – Direct Compression

•Using Co-processed super-disintegrants, super-disintegrants and the direct compression approach, ODTs of Bilastine were prepared using the formulas in table I. The 20 mg of Bilastine was produced into 200 mg pills. Mannitol and MCC were utilized as diluents in each formulation. (5)

• Prior to mixing, the required amount of Bilastine and other excipients were carefully weighed and passed through a #40 mesh sieve. After being pulverized for 15 minutes, all the components were placed to mortar in a geometric arrangement. The obtained powder blend was further compacted to tablets using a Rotary tablet press with 12 stations by adding magnesium stearate and talc in the appropriate amounts. (5)

Table I: Master formula for Oro dispersible tablets

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
BILASTINE (mg)	20	20	20	20	20	20	20	20	20
CROSCARMELLOSE SODIUM (mg)	-	20	15	-	-	-	-	10	10
SODIUM STARCH GLYCOLATE (mg)	-	-	-	20	-	-	-	10	5
CO-PROCESSED SUPERDISNTEGRANT (mg)	25	-	-	-	15	20	15	-	-
MICROCRYSTALLINE CELLULOSE (mg)	30	25	40	40	30	25	30	25	30
MANNITOL (mg)	115	120	110	110	120	125	125	120	125
MAGNESIUM STEARATE (mg)	10	10	10	5	10	5	5	10	5
TALC (mg)	5	5	5	5	5	5	5	5	5

****Mass of each tablet 200mg****

Co-processed superdisintegrants

The co-processed super-disintegrants were prepared using the solvent evaporation technique. 10 ml of ethanol were combined with croscarmellose sodium and sodium starch glycolate in ratios of 1:1, 1:2, and 1:3. The 250 ml beaker was thoroughly mixed, and the mixture was whirled until the majority of the ethanol evaporated. A 44-mesh filter was used to filter the wet coherent material. The wet granules had been heated to 60° C for 20 minutes in a hot air oven to dry them. A 44-mesh sieve was used to filter the dry grains before they were placed in an airtight container. [6]

PRE-COMPRESSION STUDIES

The initial formulation assessment represents the first step in creation of pharmacological dose form. It is the analysis of a drug's physical and chemical properties, both by itself and in combination with excipients. It offers a wealth of information to produce products of good quality and high standards at the necessary optimal dosage. The medication (API) underwent preformulation tests, including studies of solubility, compatibility, and melting point.

Blend's flow characteristics (before to compression) were described using the angles of repose, Carr's index, and Hausner's ratio. [7]

Angle of Repose

We use the static funnel method to compute the angle of repose. The bottom tip of the funnel was secured into position such that it rested exactly 2.0 cm above the surface of the powdered material after being raised in height until it touched the top of the powder blend pile. Pour the powdered mixture freely up the funnel's top. To determine the angle of repose, the width and height. [7]

Bulk Density (ρb)

The powder mixture was placed into a graduated cylinder in order to calculate the bulk density. Calculate the powder mixture's mass (m) and bulk volume (Vb) values. [8]

Tapped Density (ρ_t)

A required quantity of powder blend was within the measuring cylinder, and it was tapped 100 times throughout a predetermined period of time. Estimate the minimum volume that the cylinder can hold (Vt) and the mass of the powder (m). [8]

Compressibility index [Carr’s Index]

Flow property properties of Carr's powder blend are determined by the compressibility index. The potential powder arch and stability are directly correlated with the percentage compressibility of the powdered blend. [9]

Hausner’s Ratio

It is used to calculate a powder blend's flow characteristics. By dividing the bulk density ratio by the density of the tapping ratio, the ratio may be computed. [9]

POST-COMPRESSION STUDIES

Invitro Disintegration time

Pill disintegration test gear was used to measure the disintegration intervals for all formulations. The basket rack was installed to allow the tablets to move up and down when they were 2.5 cm above the liquid's surface and 2.5 centimetres from the bottom of the beaker, respectively. Every one of the tubes of the device used to test for disintegration received six pills individually. 28 to 32 cycles every minute are used to push the bin retaining the pills upward and downward over 5 to 6 cm. To prevent floating, each tablet might have a perforated disc put to it. The tablet must shatter into fragments, and each of those bits must move through the 10-mesh screen in the allotted amount of time. If one or two of the first batch's tablets don't dissolve, the process is repeated with 12 additional pills. [8]

Invitro Dispersion time

By dropping the developed tablet into 10 ml measuring cylinder that was filled with 6 ml of pH 6.8 buffer and maintained a temperature of 37.5°C, the in vitro dispersion time of the developed tablet was calculated. We timed how long it took for three randomly selected pills from each recipe to disintegrate fully. [10]

Drug content

From every preparation, 10 tablets were randomly selected and finely powdered. Weighed aliquots of a single dose of powder were obtained, combined with 100 ml of pH 6.8 phosphate buffer, filtered, diluted, and drug concentration readings were taken using a uv-vis Spectrophotometer at 278 nm in triplicate. [11]

$$Drug\ content = \frac{Concentration \times Dilution\ factor}{1000} \quad (1)$$

Invitro Dissolution studies

The USP II paddle method was used at 50 rpm in 900 ml of phosphate buffer with a pH of 6.8 as the dissolve medium for the in vitro dissolving tests on all of the produced Bilastine tablets. The dissolving liquid was kept at temperature of 37.5°C. 10ml of the chemical under study was taken several times. For the duration of the experiment, buffer with a pH of 6.8 was substituted to keep the volume constant. After the samples had been properly diluted, the amount of medication released from each formulation at 278 nm was measured using a UV-VIS spectrometer. [12]

3. Results and Discussion

Calibration curve: At a maximum recorded wavelength of 278 nm, Bilastine calibration curves were created. By taking out 10 ml of the standard solution into a phosphate buffer solution with a pH of 6.8, 100 g/ml of the standard solution was produced. In order to establish concentrations of 10, 20, 30, 40, and 50 g/ml, 1, 2, and 3 ml of this standard solution were pipetted into separate volumetric flasks of 10 ml each. These flasks were then diluted with 10 ml with phosphate buffer at pH 6.8. The curve was shown in the figure 1. [13]

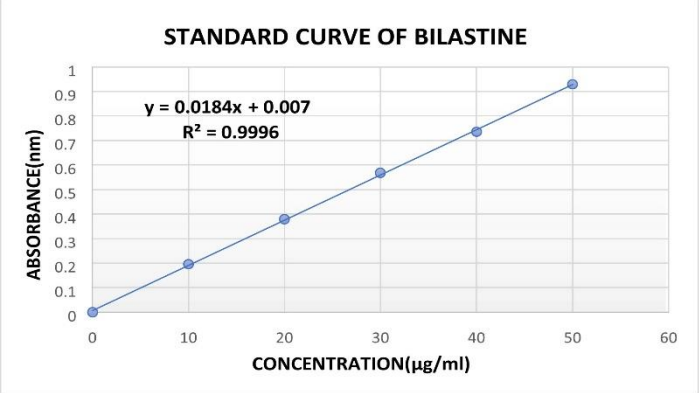

Figure No. 8 Calibration curve of Carvedilol

Pre-compression parameters: All formulation batches and their pre-compression parameters evaluated results are showed in table II. For all powder blend compositions, the bulk and tapped densities range from 0.280 to 0.409 and 0.302 to 0.481, respectively. The tolerable Carr's index and angle of repose value ranges for the created powder mix for direct compression are 4.43 to 14.95 and 19.08 to 27.77, respectively.

Table II: Pre-compression parameters of Formulations

Formulation	Angle of Repose(⁰) ± SD	Bulk Density (gm/ml) ± SD	Tapped Density (gm/ml) ± SD	% Compressibility Index ± SD	Hausner's Ratio ± SD
F1	25.35±0.040	0.352±0.002	0.368±0.0015	4.43±0.171	1.046±0.0018
F2	25.63±0.028	0.280±0.001	0.316±0.0005	11.57±0.462	1.130±0.0059
F3	19.08±0.400	0.409±0.0015	0.481±0.0011	14.95±0.210	1.175±0.0029
F4	27.77±0.315	0.309±0.0005	0.330±0.002	6.15±0.425	1.065±0.0048
F5	19.83±0.155	0.322±0.0005	0.365±0.0023	11.76±0.398	1.133±0.0051
F6	23.24±0.080	0.303±0.0020	0.353±0.001	14.07±0.362	1.163±0.0049
F7	25.19±0.023	0.307±0.0015	0.34±0.001	9.50±0.441	1.105±0.0054
F8	25.87±0.051	0.285±0.0020	0.302±0.0015	5.51±0.216	1.058±0.0024
F9	27.60±0.386	0.303±0.0011	0.323±0.0017	6.08±0.448	1.064±0.0050

Drug excipients compatibility studies:

FTIR spectrum of pure drug Bilastine showed principle peaks at 2926.89 cm-1, 2881.15 cm-1,1455.97cm-1,1251.72 cm-1,1155.66 cm-1, 873.66 cm-1,625.79 cm-1 characteristic to C-H stretching (-CH2, -CH3 group), C-H stretching (-CH2, -CH3 group), O-H bending (Carboxylic Acid), C-N stretching (aromatic amine), C-O stretching (aliphatic ether), C=C bending (Alkene), C-H bending functional groups respectively. The FTIR spectra's are shown in figure 2,3,4 &5 respectively. (4)

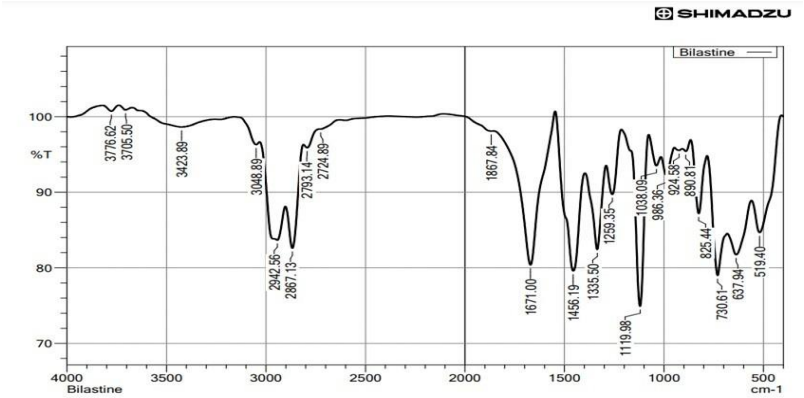

Figure No. 1: FTIR spectrum of carvedilol standard

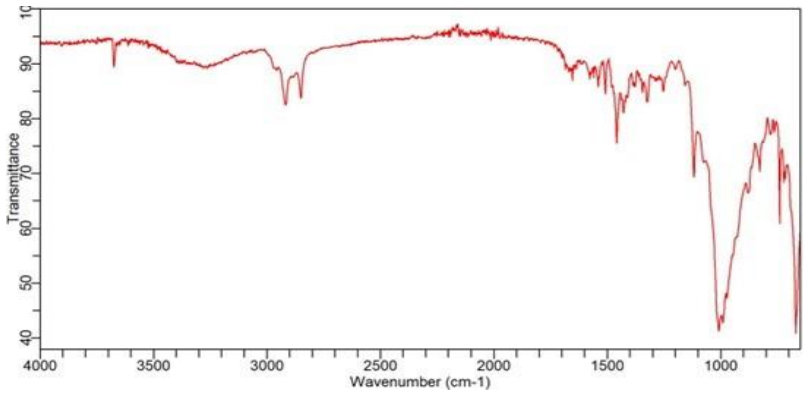

Figure No: 2: FTIR Spectrum of Bilastine, polymers, and excipients (Physical Mixture 1)

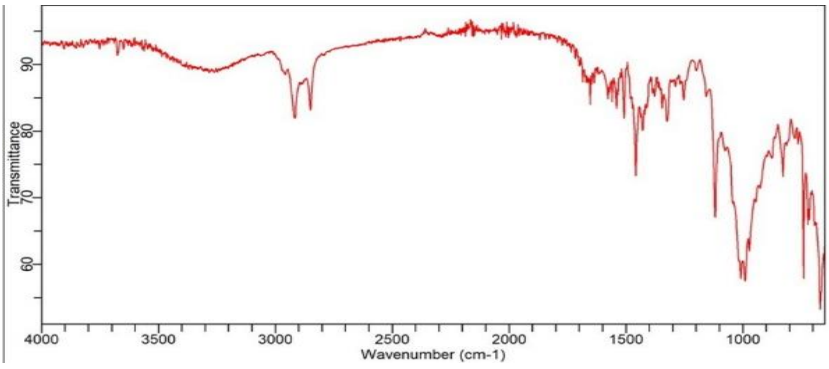

Figure No: 3: FTIR Spectrum of Bilastine, polymers, and excipients (Physical Mixture 2)

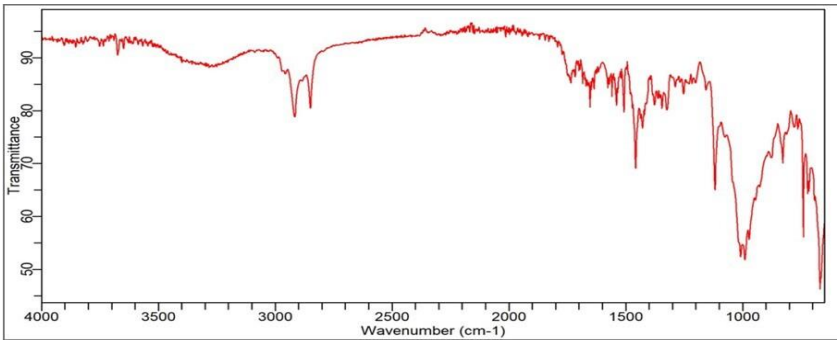

Figure No: 4: FTIR Spectrum of Bilastine, polymers, and excipients (Physical Mixture 3)

Drug polymer compatibility studies using DSC:

After stability testing, the likelihood of any interactions between Bilastine and excipients in floating tablets was evaluated by doing heat analysis by DSC investigations. After conducting stability tests, pure medicine (Bilastine) and tablets of the improved formulation F6 were used for DSC experiments. Thermal behaviour of the samples were assessed using DSC at heating rate of 10°C/min. The experiments were carried out under nitrogen at temperature range of 30 to 200°C. The DSC sharp peaks are shown in the figure 6a & 6b respectively.

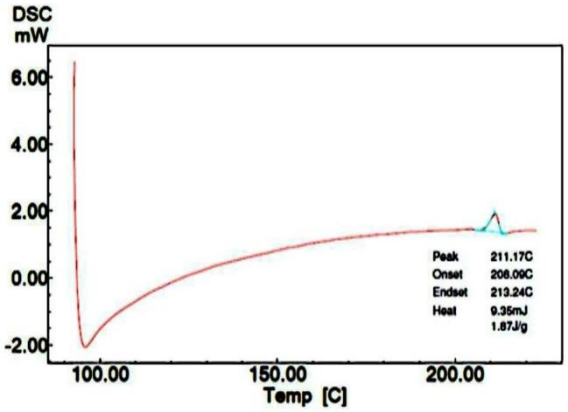

Figure No. 5 a. DSC thermogram of pure Bilastine

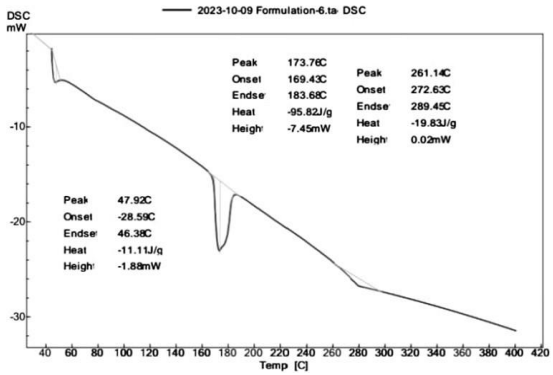

Figure No. 5 b. DSC thermogram of formulation F9

Post compression parameters

The mean values of thickness ranges from 3.1 to 4.63 mm, hardness ranges from 3.1 to 5, Friability 0.111 to 0.191%, weight variation 194.02 to 211.06 and drug content ranges from 86.95 to 96.73% of prepared Oro dispersible tablets is recorded in the table 3 along with S.D shown in table III. The Pharmacopeial limit was found to be fulfilled for weight variation and percentage friability across all formulations of all batches.

Table III: Evaluation of Post-compression parameters

Formulation	Weight Variation(mg) ± SD (n=20)	Thickness (mm)± SD n=5	Friability (%) ± SD n=10	Hardness (kg/cm^2) ± SD (n=3)	Drug Content (%) ± SD
F1	198.97 ± 0.840	3.43 ± 0.152	0.119 ± 0.015	3.9 ± 0.1	90.03 ± 0.313
F2	194.53 ± 0.980	3.16 ± 0.057	0.184 ± 0.023	3.33 ± 0.11	95.28 ± 0.954
F3	211.06 ± 1.74	4.63 ± 0.152	0.034 ± 0.014	5 ± 0.2	86.95 ± 0.543
F4	206.74 ± 1.213	4.2 ± 0.1732	0.074 ± 0.020	4.66 ± 0.25	87.31 ± 0.683
F5	200.05 ± 0.852	3.73 ± 0.152	0.111 ± 0.041	3.96 ± 0.20	89.03 ± 0.415
F6	196.73 ± 0.908	3.36 ± 0.305	0.14 ± 0.029	3.43 ± 0.05	96.73 ± 0.313
F7	197.25 ± 0.848	3.33 ± 0.208	0.121 ± 0.020	3.66 ± 0.15	93.11 ± 0.415
F8	194.02 ± 1.156	3.13 ± 0.057	0.191 ± 0.014	3.1 ± 0	94.20 ± 0.271
F9	198.6 ± 0.797	3.5 ± 0.1	0.119 ± 0.020	3.7 ± 0.36	91.03 ± 0.718

***In- vitro* dissolution study:**

The USP II paddle method at 50 rpm in 900 ml of phosphate buffer with a pH of 6.8 was used as the dissolve medium for the in vitro dissolving experiments on all of the produced Bilastine tablets. The dissolving liquid was maintained at temperature of 37.5°C. 10ml of the chemical under study was taken several times. For the duration of the experiment, phosphate buffer with a pH of 6.8 was substituted to keep the volume constant. After the samples had been properly diluted, the amount of medication released from each formulation at 278 nm was measured by UV-visible spectrometer. [14]

Formulations F8 containing of super-disintegrants Croscarmellose sodium (2%) & sodium starch glycolate (2%), F2 containing super-disintegrants Croscarmellose sodium (2%), F6 containing co-processed superdisintegrants (4%), and F7 containing combination of superdisintegrants Crospovidone (2%) & showed drug release of 95.48 ± 0.804, 93.47 ± 0.280, 92.73 ± 0.977 and 90.74 ± 0.449 % respectively at end of 50 minutes. Formulations F3 and F4 containing superdisintegrants croscarmellose sodium and sodium starch glycolate (5%) and (4%) showed drug release of 88.39 ± 0.784 and 87.08 ± 0.521 % respectively at the end of 50 minutes. Formulations F9 containing Sodium starch glycolate (4%) & croscarmellose sodium (2%), F1 formulation containing co-processed superdisintegrants (6%) and F5 containing co-processed superdisintegrants (8%) showed drug release of 90.65 ± 0.305, 89.23 ± 0.424 and 88.46 ± 0.674 % respectively at the end of 60 minutes, the results are shown in figure 7 &8, table IV & V respectively.

Table IV: Cumulative Drug Release of Formulation (F1-F4)

TIME (MIN)	% DRUG RELEASE ± SD			
	F1	F2	F3	F4
0	0	0	0	0
10	20.41 ± 1.426	28.32± 3.969	19.12± 0.860	32.72 ± 0.561
20	32.12± 0.716	36.15± 4.920	26.19± 0.546	41.69 ± 1.477
30	39.69± 0.971	44.90± 1.542	40.78± 0.940	50.02± 2.770
40	57.28± 1.236	57.99± 0.375	49.15± 1.337	62.19± 0.932
50	71.15± 1.851	75.03± 0.280	56.89± 1.935	79.35± 1.079
60	85.20± 0.424	87.15±0.322	71.01± 1.478	91.48± 1.057

Table V: Cumulative Drug Release Formulation (F5-F9)

TIME (MIN)	% DRUG RELEASE ± SD				
	F5	F6	F7	F8	F9
0	0	0	0	0	0
10	39.12± 0.466	46.79 ± 3.028	22.89 ± 1.272	18.92 ± 2.383	15.98 ± 1.275
20	48.96± 1.154	58.12 ± 3.687	30.52 ± 4.194	25.12 ± 3.527	23.92 ± 0.847
30	56.19± 2.630	65.81 ± 4.092	43.15 ± 3.061	32.29 ± 3.249	31.12 ± 1.059
40	68.91± 1.165	81.23 ± 2.121	55.20 ± 1.773	40.19 ± 0.560	39.21 ± 3.712
50	80.15± 1.982	95.92 ± 0.377	69.92 ± 0.449	52.27 ± 0.804	48.92 ± 0.464
60	92.98± 0.674	-	77.01±0.215	60.78±0.498	57.01 ± 0.305

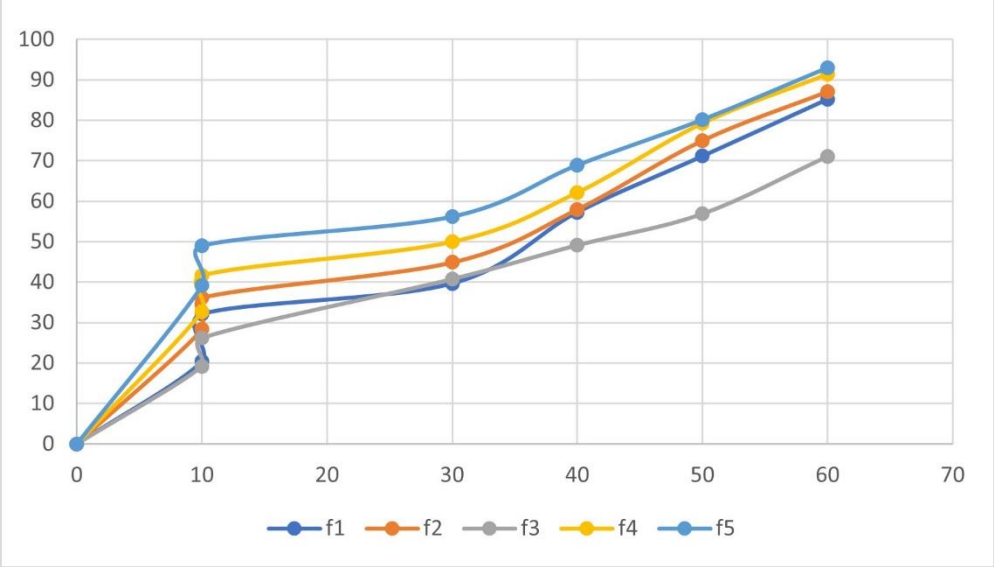

Figure No: 6 In-vitro Dissolution profile for F1-F5 Formulations

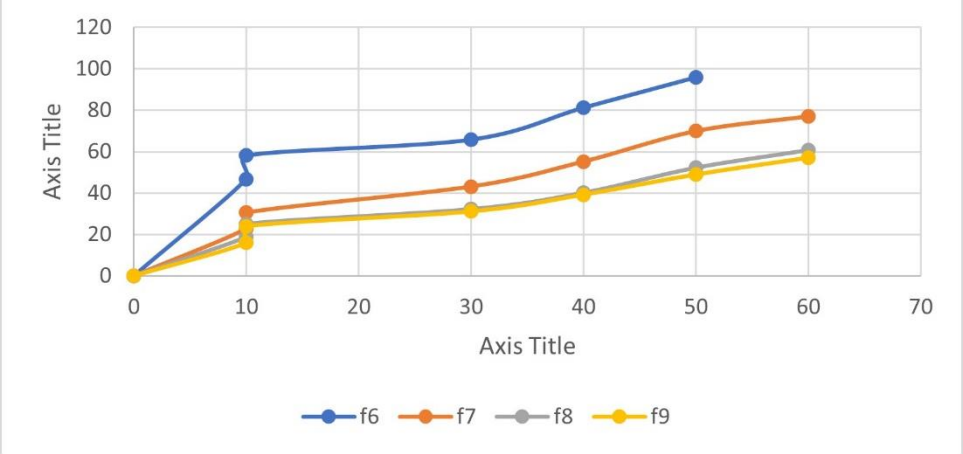

Figure No: 7 In-vitro Dissolution profile for F6-F9 Formulations

4. CONCLUSION

The existing study's aim was to create and evaluate orodispersible tablets for the antihistamine medication Bilastine. In this study, it was discovered that Bilastine orodispersible tablets made with Crospovidone, Sodium starch glycolate, and Co-processed super-disintegrants were the best way to speed up dissolution and boost the drug's bioavailability.

The conclusion of present study is given below:

- The spectral (UV and FTIR) characteristics of the Bilastine were examined. In phosphate buffer at pH 6.8, Bilastine exhibited highest absorption at wavelength 278 nm. It was discovered that the standard curve's regression coefficient was 0.9996, indicating a linear connection between concentration and absorbance. Bilastine, superdisintegrants, and other excipients had no interactions, according to the FTIR data.
- Nine formulations designated F1 to F9 were created by the direct compression method employing different concentrations and combinations superdisintegrants, notably croscarmellose sodium, crospovidone and sodium starch glycolate. F1 contains Co-processed super-disintegrants (6%), F2 contains croscarmellose sodium (2%), F3 contain Croscarmellose sodium (6%), F4 contains Sodium starch glycolate (4%), F5 contains Co-processed superdisintegrants (8%), F6 contains Co-processed super-disintegrants (4%), F7 contains Co-processed superdisintegrants (2%), F8 and F9 contains Croscarmellose sodium (2%). The other excipients used were Mannitol and Microcrystalline cellulose as diluents, Magnesium stearate and talc as glidants and lubricants.

- When the superdisintegrants are used in higher concentration (within the permitted limits) as well as when used in combination, the wetting and disintegration was quick which in turn improves dissolution profile. Disintegration is much affected by hardness. Lower the hardness, the time taken for disintegration will be less & vice versa.
- The post-compression studies were all analysed for the tablets. Based on the findings of the drug content analysis, it was determined that the drug was circulated consistently throughout the tablet and that any variations fell within allowable bounds. (86.95 ± 0.543 to 96.73 ± 0.271%).
- Even though all the formulations showed good results, Formulation F6 was identified as best and ideal formulation based on wetting time, *Invitro* disintegration time, *Invitro* dispersion time and *Invitro* % drug release.
- The optimized formulation F6 containing combination of Co-processed superdisintegrants (4%) showed maximum drug release of 95.92 ± 0.804 % at end of 50 minutes.
- The stability investigation of the improved formulation F6 revealed no appreciable alterations in the tablet's physical attributes, physicochemical characteristics, or in vitro drug release.
- The optimized formulation showed better release at the end of 50 minutes when compared to the marketed conventional product of Bilastine (Bilahist 20mg).
- ODT is superior to traditional tablets since it acts quickly and has a higher bioavailability. For patients who are unable to swallow, such as the elderly, those who have had strokes, those who are bedridden, and those who refuse to swallow, such as paediatric, geriatric, and psychiatric patients, ODT gives more compliance.
- Thus, the results of existing study clearly represent that Bilastine can be formulated as Oro-dispersible tablets using super-disintegrants like Croscarmellose sodium, Crospovidone, sodium starch glycolate and Co-processed super-disintegrants, by direct compression method which have increased the bioavailability of Bilastine and improved the patient compliance in case of paediatric, geriatric and bedridden patients.

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