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Formulation Development Optimization And Characterization Of Oro-Dispersible Tablet Of Bilastine

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Abstract: This study aimed to develop and optimize Oro-Dispersible Tablets (ODTs) of Bilastine, a second-generation antihistamine, using Cotton Candy (CC) and Direct Compression (DC) methods. Bilastine ODTs were formulated with varying concentrations of superdisintegrants, sweeteners and lubricants. The CC method utilized a novel approach of incorporating Bilastine into partially recrystallised granules prepared from cotton candy fibers, while the DC method employed a conventional tableting process. Formulations were evaluated for disintegration time, wetting time, hardness, friability, and in vitro drug release. Optimization was achieved through a Design of Experiments (DoE) by using Central Composite Design (CCD) approach, resulting in ODTs with disintegration times of < 30 seconds and drug release > 90% in 10 minutes. The generated batches were prepared and evaluated. The BLS6 was given as the best batch by the design expert software using central composite design (CCD). In-vitro drug release of the optimized formulation (BLS6) was obtained 98.83 % in 10 min and disintegration time within 13.00 seconds. Characterization studies revealed that CC-ODTs exhibited faster disintegration and superior drug release profiles. These findings demonstrate the potential of Cotton Candy technology in developing rapid-disintegrating, high-performance ODTs of Bilastine, offering improved patient compliance and therapeutic outcomes.

Keywords: Oro-Dispersible Tablets, Bilastine, Cotton Candy, Direct Compression, Superdisintegrants, Design of Experiments.

INTRODUCTION[1,2,3,4]

Oro-Dispersible Tablets when placed in the oral cavity swiftly melts in saliva without the need of water and disperses rapidly before swallowing. In cases like this, bio- availability is significantly more than that seen from typical tablet type of dosage. Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self-medication, pain avoidance, and the most importantly the patient compliance. ODTs should have an in vitro disintegration time of approximately 30 sec or less. Bilastine is a new highly selective H1-receptor antagonist developed for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria. It is an antiallergic agent whose main mechanism of action is the inhibition of immune system mediated by the interaction of histamine on its H1-receptor. The Cotton Candy method offers a promising alternative to traditional tablet formulation techniques, particularly for APIs with poor water solubility or requiring rapid absorption. This study explores the application of Cotton Candy technology in the development of Oro-Dispersible Tablets (ODTs) of Bilastine, a second-generation antihistamine, with the goal of creating a patient-friendly and effective dosage form. Bilastine is a potent, effective antihistamine without sedation, without cardiac toxicity. Bilastine has a moderate high affinity for histamine H1 receptors. The absence of sedation with Bilastine is an important advantage in terms of patient safety, including for example read safety.

MATERIALS AND METHODS:

2.1 Materials :

Bilastine was obtained from gift sample Medley Pharma Ltd, Andheri. MCC PH102, sucralose, orange flavour, aerosil were received as gift sample from Medley Pharma Ltd, Andheri, and Magnesium Stearate were received as gift sample from Loba Chemie, Mumbai. & Partial recrystallized candy floss granules were made in the laboratory from cotton candy.

Fig. 1 : Preparation of Cotton Candy Floss In the Lab

Partial recrystallization of candy floss :-

1. Start with a batch of candy floss, which is essentially spun sugar.
2. Dissolve the candy floss in a small amount of water or a suitable solvent.
3. Heat the solution gently to ensure complete dissolution of the sugar.
4. Allow the solution to cool slowly, which will initiate the recrystallization process.

5. As the solution cools, some of the sugar will start to crystallize, while the rest remains in a dissolved state.
6. Control the cooling rate to promote the formation of desired crystal sizes and shapes.
7. Once the desired level of partial recrystallization is achieved, separate the crystals from the remaining solution through filtration or other separation methods.
8. The resulting crystals can be collected and used as desired.

Fig. 2 : Partial recrystallized granules of candy floss

2.2 Experimental Methods :

Central composite design (CCD) was used for experimental design containing two independent variables crospovidone (X1) and MCC PH 102 (X2) were investigated at three levels as low, medium and high given in table 1. While putting the values nine batches were generated using DoE software (version 13). In that independent variables were investigated in the response i.e. percentage drug release (Y1), disintegration time (Y2). The statistical experimental design was evaluated through the analysis of variance (ANOVA) test using the Design Expert software.

Table No. 1: Independent Variables and their Levels of Central Composite Design

Independent Variable	Unit	Levels				
		-ᾱ	**Low**	**Medium**	**High**	**+ᾱ**
Crospovidone	%	1.378	2	3.5	5	5.621
MCC PH 102	%	32.928	35	40	45	47.071

2.3 Preformulation Study of Bilastine :

Organoleptic Properties : Organoleptic properties of Bilastine such as colour, odour, taste, were evaluated for tablets from each batch were randomly selected and taste tested, colour visually compared and odour checked.

1. **Bulk Density (BD)** [18,19]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned

$$BD = \frac{Mass\ of\ the\ powder\ (M)}{Bulk\ \ volume\ of\ the\ powder\ (Vb)}$$

2. **Tapped Density (TD)**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density appara

$$TD = \frac{Mass\ of\ the\ powder\ (M)}{Tapped\ volume\ of\ the\ powder\ (Vd)}$$

3. **Carr's Index (Or) % Compressibility**

Compressibility index (CI) was determined by measuring the initial volume (V0) and final volume (V) after hundred tapings of a sample in a measuring cylinder. CI was calculated using equation

$$\text{Carr's Index (CI)} = \frac{Vo-V}{V} \times 100$$

4. **Angle of Repose**

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipients blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\tan\theta = \frac{h}{r}$$

Where, h= height of the pile of the blend

r= radius of the pile of the blend

5. **Hausner's Ratio**

A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using following formula

$$\text{Hausner's Ratio} = \frac{Tapped\ Density}{Bulk\ Density}$$

Table No. 2 % Drug Released of Batches generated by CCD

Ingredient (mg/tablet)	Batches								
	BLS1	**BLS2**	**BLS3**	**BLS4**	**BLS5**	**BLS6**	**BLS7**	**BLS8**	**BLS9**
Bilastine	20	20	20	20	20	20	20	20	20
MCC PH 102	94.14	80	70	90	65.84	80	80	70	90
Partially Crystallized Sugar	70	84	86	66	90.16	77	70	95.5	69
Sucralose	2	4	4	4	3	4	4.76	3	3
Crospovidone	7	2.7	10	10	7	7	11.24	4	4
Orange flavor	3	6	6	6	6	6	6	6	6
Magnesium Stearate	2	2	2	2	4	3	4	2	4
Aerosil	2	2	2	2	4	3	4	2	4
Avg.Wt.(mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Preparation of Bilastine Oro-Dispersible Tablet by Direct Compression Method :-

1. Weighed all the ingredients properly.
2. Bilastine, sucralose, orange flavor, magnesium stearate, aerosil and were passed through sieve # 60 mixed it in a polybag.
3. MCC PH102, crospovidone, partially crystallized sugar were passed through sieve # 22. mixed in a poly bag.
4. The lubricated blend were compressed on 200 mg weight to produce tablet by using 8 mm FFBE punch on 12 station multi tooling CIP Lab Press.

Post Compression Parameter of Oro-Dispersible Tablet of Bilastine

1. Weight Variation

To determine weight variation, 20 tablets of each formulation were individually weighed using an electronic balance, the average weight was calculated, and the individual tablet weight was then compared to the average value.

2. Thickness

Tablet thickness is a crucial element in both duplicating appearance and counting with filling machinery. The uniform thickness of the tablets is used as a counting mechanism by some filling equipment. Micrometer was used to measure thickness.

3. Hardness

The tablets' crushing strength was determined using a Monsanto hardness tester. Three tablets were randomly sampled from each formulation batch, and the average reading was recorded.

4. Friability

For assessing the friability, Roche friabilator was utilized. Twenty tablets was be precisely weighed before being inserted in the 25 rpm-revolving tumblers. After four minutes, the tablets were reweighed and calculated.

the % weight loss.

$$\% \text{ Friability} = \frac{\text{Initial wt.of Tablets} - \text{Final wt. of Tablets}}{\text{Initial wt.of Tablets}} \times 100$$

5. Wetting Time

12 cm × 10.75 cm of double-folded tissue paper was placed in a 9 cm-diameter petri dish containing 9 ml of buffer solution pH 6.8. On the tissue paper, a tablet was placed and the time required for complete wetness was recorded. Three tablets were chosen at random from each formulation, and the average wetting time was recorded.

6. Water Absorption Ratio

The weight of the tablet before keeping in Petri dish was noted (Wb). Fully wetted tablet from the petri dish was taken and reweighed (Wa). The water absorption ratio R can be determined according to the following formula.

$$\text{Water Absorption Ratio} = \frac{Wa - Wb}{Wa} \times 100$$

Where,

Wa is the weight of the tablets before the test and

Wb is the weight of the tablet after water absorption.

RESULT:

Solubility of Bilastine

Table No. 3 : Solubility of Bilastine in Different buffer solutions

Sr. No.	Buffer (pH)	Solubility (mg/ml)
1	0.1N HCl Buffer	0.139±0.02
2	Phosphate Buffer pH 6.8	0.221±0.01

Determination of UV Spectrum and Calibration Curve of Bilastine

UV spectrum of bilastine was presented in fig. 4 and the calibration curve shows the straight-line equation given in fig. 5.

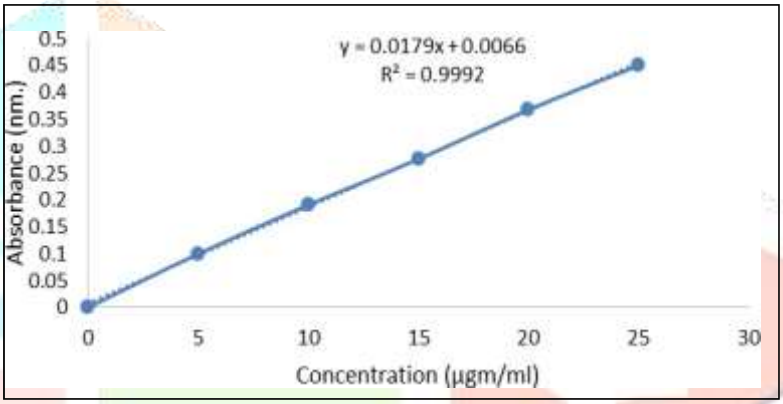

Fig. 4 : Wavelength Maxima of Bilastine in phosphate buffer pH. 6.8

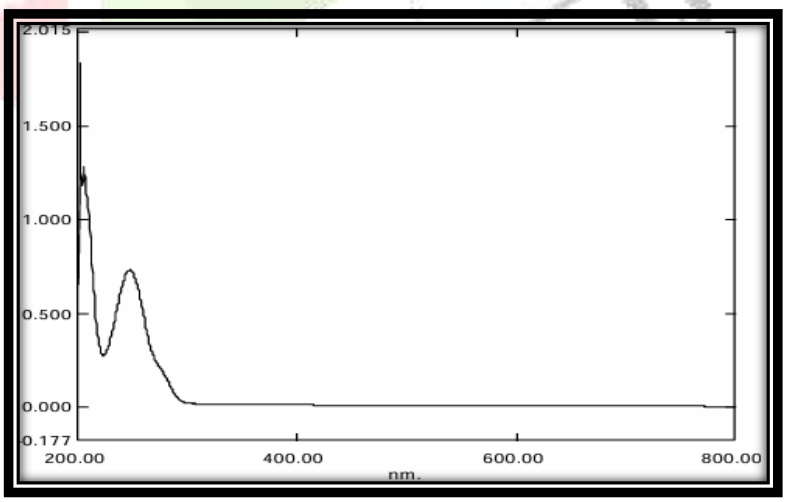

Fig. 5: Calibration curve of Bilastine in Phosphate Buffer pH 6.8

1. **Fourier Transform Infrared Spectroscopy (FTIR) :**

FTIR results indicated when the IR spectrum of the drug and crospovidone were compared with that of the mixture of drug and excipients to analyze drug excipient interaction given in fig 6,7,8

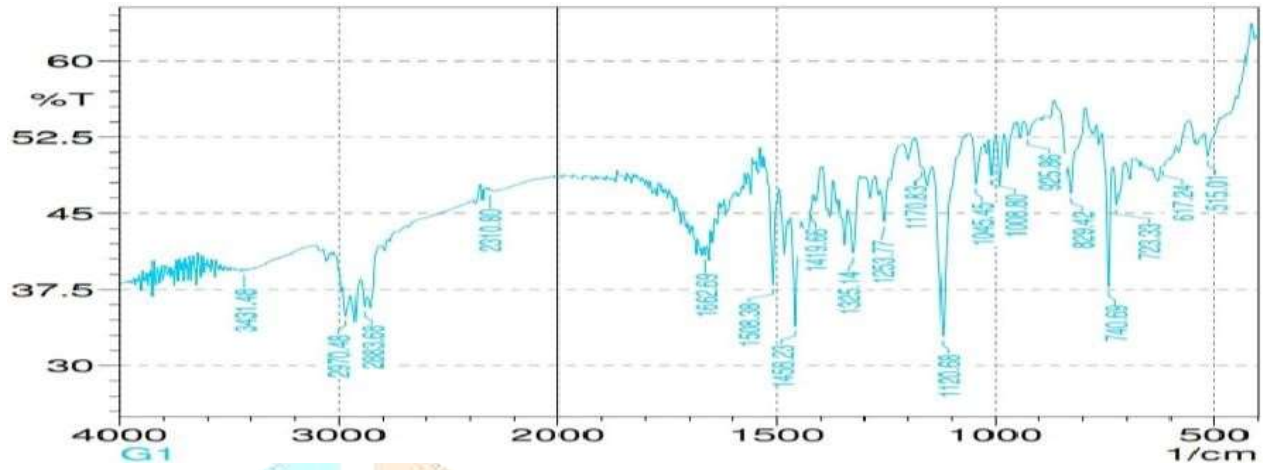

Fig. 6 : FTIR Spectra of Bilastine

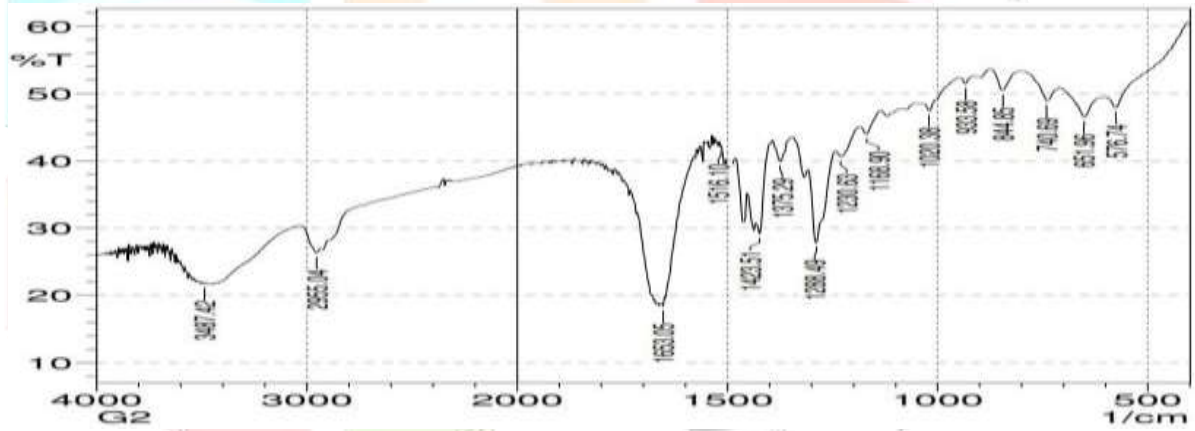

Fig. 7 : FTIR Spectra of Crospovidone

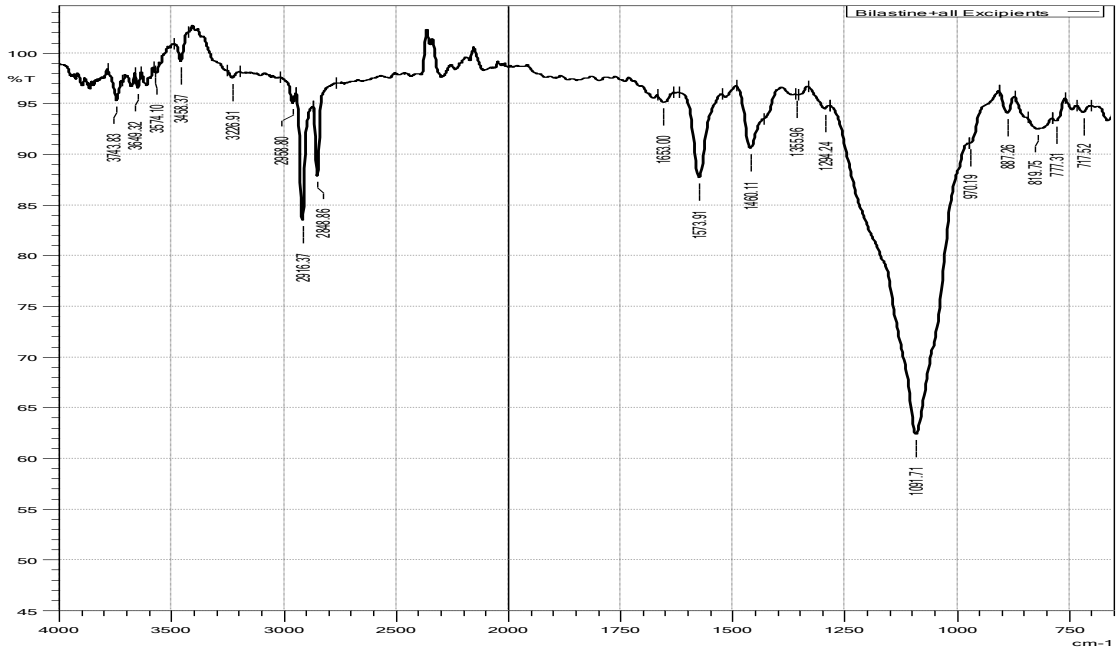

Fig. 8 : Overlay Spectra of Bilastine + All Excipients

1. **Differential Scanning Calorimetry (DSC)**

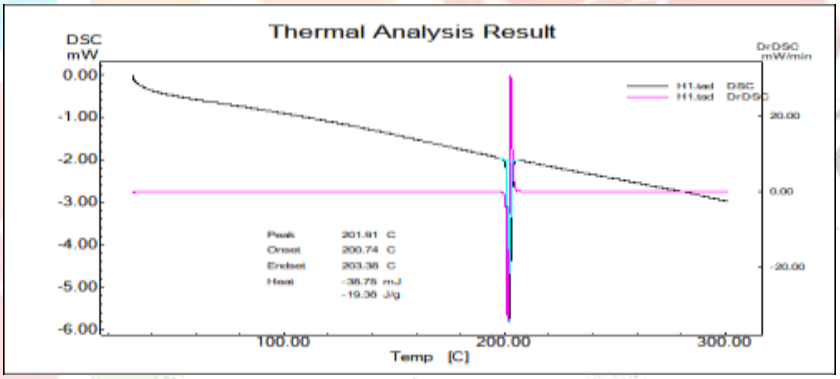

Fig. 9 : DSC Thermogram of Bilastine

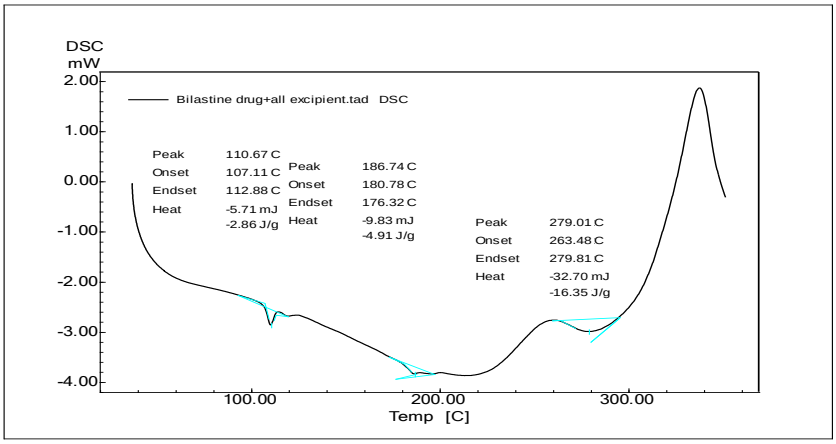

Fig. 10 : The DSC Thermogram of Bilastine and Bilastine with all excipients

Table No. 4 : The DSC Thermogram of Bilastine and Bilastine with all excipients

Sr. No.	Chemical	DSc Thermal Transition (℃)	Enthalpy (J/g)
1	Bilastine	201.91	- 19.38
2	Bilastine + All Excipients	186.74	-4.94

3. Optimization and Data Analysis of Optimized Oro-Dispersible Tablet of Bilastine :

Using the CCD method 9 batches of Oro-Dispersible tablets were prepared by taking a different concentration of independent factors produced by DoE software and evaluated using various parameters like % drug release, Disintegration time and wetting time

Table No. 5: Central Composite Design with Dependent Variables

Batches	Variable Level in Coded Form		Dependent variables (Y)	
	X1	X2	% Drug Release (%)	Disintegration Time (Sec)
BLS1	0	+α	102.70	14.5
BLS2	-α	0	98.53	12.31
BLS3	+1	-1	98.53	15.22
BLS4	+1	+1	102.37	16.2
BLS5	0	- α	98.53	13.6
BLS6	0	0	98.83	13.5
BLS7	+α	0	102.07	13.85
BLS8	-1	-1	99.71	12.1
BLS9	-1	+1	104.14	11.4

Effect of Independent Variables on

% Drug Release :-

Final equation in terms of coded form

% DR= + 9.31771 + 0.008997 X1 + 0.017182 X2

Concerning dissolution, the results of multiple linear regression analysis showed that the coefficients X1 and X2 bear positive sign. It revealed that % drug release increases with increases in both crospovidone

and MCC PH102. Less amount of crospovidone was expected to increase the % drug release due to faster disintegration of tablet. ANOVA was used to identify the significant effect. The result was found to be significant at that level of probability ($p<0.0481$).

Table No. 6 : % Drug Released for Preliminary Trial Batches of Bilastine ODTs :

Time (Min)	Batches				
	B1	**B2**	**B3**	**B4**	**B5**
0	0	0	0	0	**0**
2	15.34	23.89	30.09	32.15	**33.62**
4	29.20	40.12	44.84	47.79	**49.26**
6	39.23	56.34	61.65	64.01	**82.01**
8	61.65	76.99	81.12	83.78	**88.20**
10	80.76	86.73	89.68	90.27	**99.42**

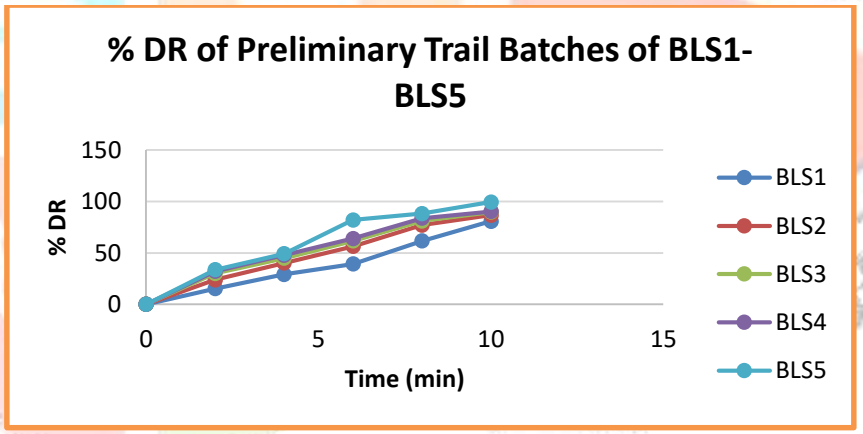

Fig. 11 : In-Vitro Drug Released Study of Preliminary Trial Batches of Bilastine Oro-Dispersible Tablet (B1-B5)

Table No. 7 : Post Compression Parameters of Batches Generated by CCD

Time (min)	% Drug Release Batches								
	BLS1	**BLS2**	**BLS3**	**BLS4**	**BLS5**	**BLS6**	**BLS7**	**BLS8**	**BLS9**
0	0	0	0	0	0	**0**	0	0	0
2	41.00	38.94	42.77	42.77	36.58	**38.94**	46.61	41.30	47.49
4	63.72	58.70	56.05	69.03	63.13	**45.43**	61.65	46.61	69.91
6	82.01	78.17	70.50	83.78	77.88	**69.91**	87.02	71.98	86.73

8	94.70	92.34	91.16	96.76	92.63	**89.09**	95.88	90.27	96.17
10	102.70	98.53	98.53	102.37	98.53	**98.83**	102.07	99.71	104.14

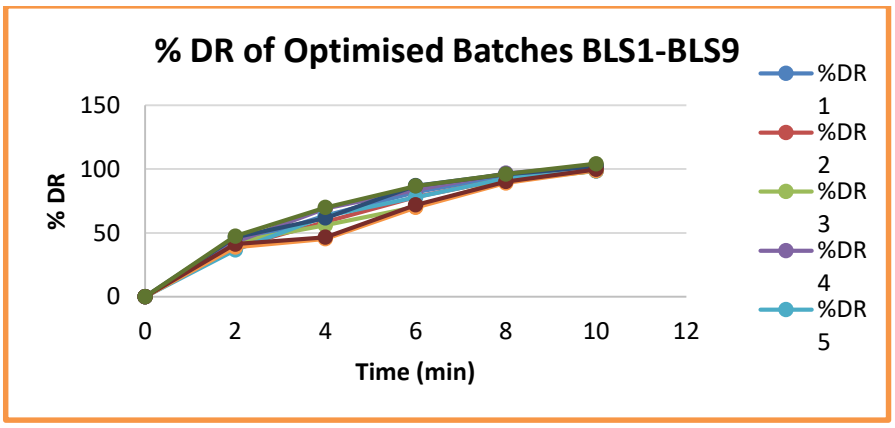

Fig. 12 : In-Vitro Drug Released Study of Optimized Batches of Bilastine ODTs Generated by CCD (BLS1-BLS9)

Disintegration Time :-

Final equation in terms of coded form

DT= + 3.09515 + 0.114378 X1 + 0.004783 X2

Concerning disintegration time, the results of multiple linear regression analysis showed that the coefficients X1 and X2 bear positive sign. It revealed that disintegration time increase with increase in crospovidone and MCC PH102. Crospovidone 3.5% w/w and MCC PH102 40% w/w were selected as optimum concentration that showed the minimum disintegration time of 11 seconds. It was observed that further increase in concentration of superdisintegrant led to the increases in disintegration time. ANOVA was used to identify the significant effect. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.0298$)

Graphical Representation :-

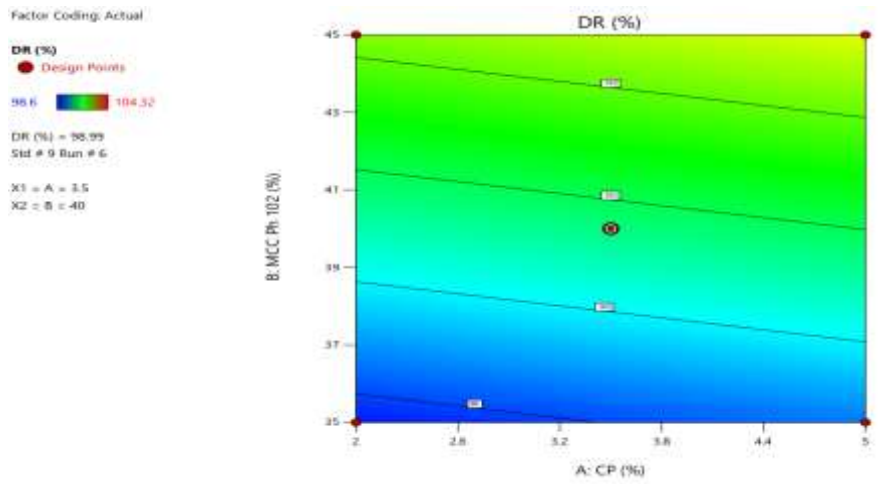

Fig. 13 : Response Surface Contour Graph Showing the Influence of Crospovidone (X1) and MCC PH 102 on

% Drug Release (Y1)

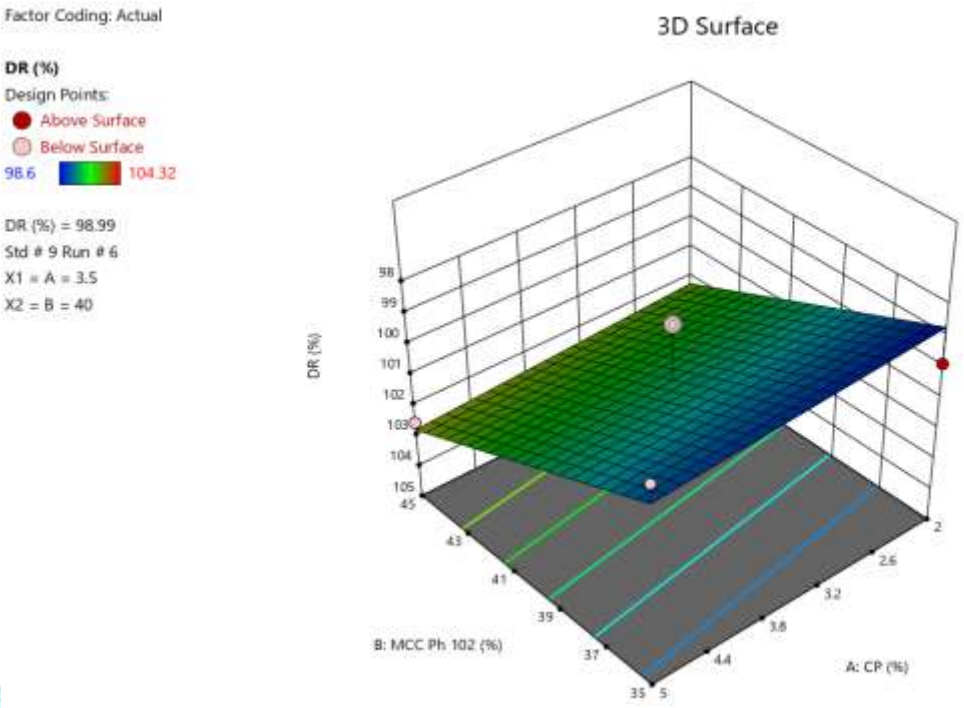

Fig. 14 : 3D Response Surface Graph Showing the Influence of Crospovidone and MCC PH 102 on % Drug Release (Y1)

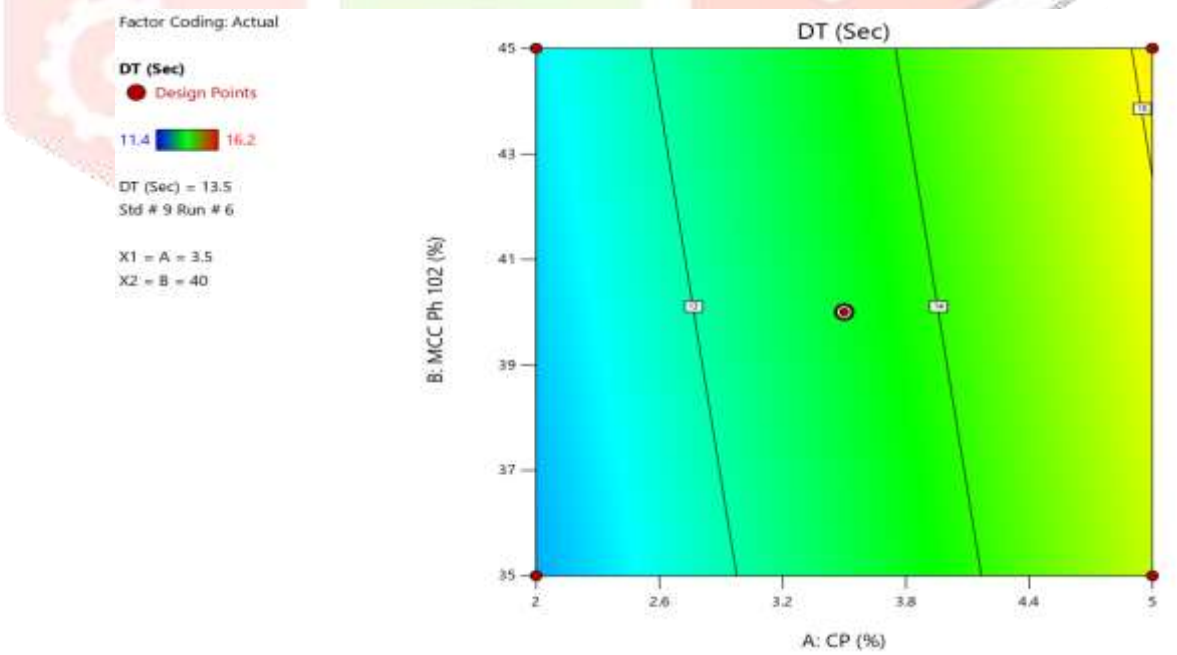

Fig. 15: Response Surface Contour Graph Showing the Influence of Crospovidone (X1) and MCC PH 102 on the

Disintegration Time (Y2)

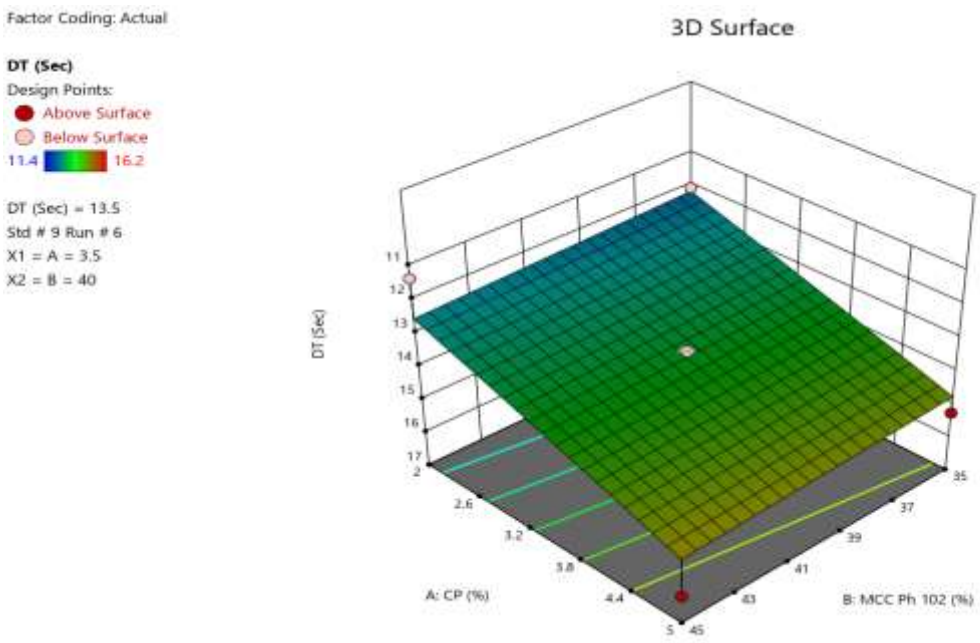

Fig. 16 : 3D Response Surface Graph Showing the Influence of Crospovidone (X1) and MCC PH 102 on the Disintegration Time (Y2)

Table No. 8: Evaluation of Post-Compression Parameters of optimized Batches of Bilastine Oro-Dispersible tablet

Batch	Weight Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness(Kg/Cm^2)	Friability (%)	Wetting Time (Sec)	D.T (Sec)	Water Absorption Ratio	Drug Content (%)
BLS1	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS2	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS3	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS4	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS5	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS6	**1.86.8±0.75**	**3.97**	**8.0±0.1**	**1.5±0.15**	**0.6±0.06**	**3.46**	**14.4**	**74.47**	**99.36**

BLS7	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS8	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36
BLS9	1.86.8±0.75	3.97	8.0±0.1	1.5±0.15	0.6±0.06	3.46	14.4	74.47	99.36

CONCLUSION:

The formulation development and optimization of Oro-Dispersible Tablets (ODTs) of Bilastine using Cotton Candy (CC) and Direct Compression (DC) methods have been successfully achieved. The CC method demonstrated superior performance, producing ODTs with faster disintegration times, improved drug release profiles, and enhanced dissolution rates. The optimization process, guided by a Design of Experiments (DoE) approach, resulted in the identification of critical factors and interactions, enabling the development of high-performance ODTs. The generated batches were prepared and evaluated. The BLS6 was given as the best batch by the design expert software by using central composite design (CCD). In-vitro drug release of the optimized formulation (BLS6) was obtained 98.83 % in 10 min and disintegration time within 13.00 seconds. These findings suggest that the Cotton Candy technology has the potential to revolutionize the formulation of ODTs, offering a rapid, convenient, and patient-friendly dosage form for Bilastine and potentially other active pharmaceutical ingredients. Future studies should focus on scaling up the CC process, exploring other APIs, and conducting clinical trials to further validate the efficacy and safety of CC-ODTs.

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