CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Online at: www.iajps.com *Research Article*

FORMULATION DEVELOPMENT AND EVALUATION OF SUBLINGUAL DRUG DELIVERY SYSTEM OF BILASTINE FOR ALLERGIC RHINOCONJUNCTIVITIS

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Article Received: March 2021**Accepted:** March 2021 **Published:** April 2021

Abstract:

Allergic rhinitis (AR) is very common clinical condition and affects 10–40% of individuals worldwide. It has a substantial negative effect on patient's quality of life (QoL), sleep and daily activities. Various therapeutic classes are used for the management of allergic rhinitis. Among all the classes, H_1 receptor antagonist is used as first line treatment. Many molecules belong to antihistamine class and on the basis of selectivity and its adverse effect it can be classified as first generation, second generation and novel second-generation antihistamine. Among all the molecules, Bilastine is a novel new second generation with selective peripheral, non – sedating, H_1 antihistamine. Its affinity is also higher than the other antihistamine. It belongs to BCS class II drug which has less solubility and high permeability. So, for enhancement of solubility complexation technique is used and inclusion complex of Drug: HP-β-CD (1:2) was prepared by microwave irradiation method. Here great need arises to alter the route of administration of Bilastine for improving absorption and drug release pattern. As per the literature study, it can be concluded that Sublingual route offer immediate drug release directly into systemic circulation, results in rapid on-set of action. In present study sublingual tablet of Bilastine is prepared by direct compression method. The effect of different superdisintegrants (SSG, CCS, Kyron T-314, Indion 414) in two different concentrations are examined for selection of best superdisintegrant. Result of check point batch F 10 suggested that tablet disintegrated within 50 sec. Similarly, in-vitro dissolution study showed 97.68 % drug release in 10 min.

Keywords: *Allergic rhinoconjunctivitis, Quality of life, H_1 receptor antagonist, Bilastine, Sublingual tablet.*

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Please cite this article in press Sadrani Dolly A. et al., ***Formulation Development And Evaluation Of Sublingual Drug Delivery System Of Bilastine For Allergic Rhinoconjunctivitis.,*** *Indo Am. J. P. Sci, 2021; 08(04).*

INTRODUCTION:

Sublingual route (SR) is faster than another oral route. It provides direct drug release into systemic circulation. It is beneficial to achieve faster drug release, rapid absorption; drug is also protected from GI and enzymatic degradation.[1]Bilastine2 – [4-(2-{4[1-(2- ethoxyethyl) – 1 H- 1, 3 benzodiazol – 2yl] piperidine – 1 –yl} ethyl) phenyl] 2 – methyl propenoic acid is novel second generation antihistamine, used in management of allergic rhinoconjunctivitis (ARC) which is caused by pollens, mold, dust mites, animal dander, etc.[2, 3, 4]It is safer and doesn't produce sedative effect and cardio toxic effect. It has less bioavailability (61%) due to incomplete absorption and high /low fatty meal interaction. Sublingual route is considered to be alternative to the oral route. SR is used when it is desired to achieve rapid onset of action, improve the absorption and improve the bioavailability of drug. Various methods are used for the formulation of sublingual tablet (Direct compression, Fast melting technology, Sublimation, Lyophilisation). [5] Among all these method, direct compression is widely utilized. This work is based on the Formulation Development and Evaluation of Sublingual Drug Delivery System of Bilastine for Allergic Rhinoconjunctivitis.

MATERIALS AND METHODS:

MATERIALS

Bilastine was obtained from the Exemed Pharmaceuticals, Vapi, Gujarat, Hydroxypropyl β – Cyclodextrin were obtained from the P C Chem, Mumbai, Indion 414 were obtained from the Ion Exchange Resin of India, Mumbai, MCC 414 were obtained from the Akshar Pharmaceutical, Vapi, Mannitol was obtained from the Loba Chemie, and Stevia Reb A 97 were purchased from the Nutrizo Advancis.

Methods:

Preparation of Inclusion Complex [6]

Bilastine and complexing agent (Hydroxypropyl Beta Cyclodextrin – HPβCD) were taken in different ration (1:1, 1:2 and 1:3). For the preparation of Inclusion complex in appropriate amount of Bilastine and complexing agents are accurately weighed different ratios and dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60ºC in the microwave oven. After the reaction completes, specific amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed molecules. The resulting precipitate was separated using a whatman filter and then dried in an open oven at 40ºC for 48 hours.

Preparation of Sublingual Tablet [7]

The sublingual tablets of Bilastine were prepared by direct compression method. All the Excipients were passed through #60 mesh separately. The Inclusion complex of drug and MCC were mixed by taking a small portion of both each time and blending it to get a uniform mixture and kept aside. The above powder was mixed with the Superdisintegrants (Sodium starch glycolate, Croscarmellose Sodium, Kyron T-314, Indion 414) Sweeteners, mannitol, menthol, lubricant and glidant. The blend was compressed using 6 mm round flat punches to get tablets of 120 mg weight on a single punch tablet machine.

Experimental Section

Strategy I - Preparation of Preliminary Batches for Selection of Superdisintegrants

Strategy II - Preparation of Preliminary Batches for Selection of Concentration of Mannitol

Strategy III – Preparation of Factorial Batches

- On the basis of saturated solubility analysis 1:2 ratio is selected (Drug: HPβCD – 20:40 mg) for inclusion complex.
- Based on drug content, equivalent to 62.3 mg of Bilastine Inclusion complex is taken.

Table No. 1: Strategy I - Preparation of Preliminary Batches for Selection of Superdisintegrants

INGREDIENTS	FORMULATION CODE WITH QUANTITY IN mg							
	T 1	T 2	T 3	T 4	T 5	T 6	T 7	T 8
Inclusion Complex of Bilastine	62.3	62.3	62.3	62.3	62.3	62.3	62.3	62.3
Microcrystalline Cellulose	38.2	35.7	38.2	35.7	38.2	35.7	38.2	35.7
Sodium Starch Glycolate	**2.5**	**5**	-	-	-	-	-	
Croscarmellose Sodium	-	-	**2.5**	**5**	-	-	-	-
Indion 414	-	-	-	-	**2.5**	**5**	-	-
Kyron T 314	-	-	-	-	-	-	**2.5**	**5**
Mannitol	12	12	12	12	12	12	12	12
Stevia Reb A 97	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil 200	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2
Total Weight	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

Table No. 2: Strategy II - Preparation of Preliminary Batches for Selection of Concentration of Mannitol

INGREDIENTS	FORMULATION CODE WITH QUANTITY IN mg					
	M 1	M 2	M 3	M 4	M 5	M 6
Inclusion Complex of Bilastine	62.3	62.3	62.3	62.3	62.3	62.3
Microcrystalline Cellulose	38.2	35.2	32.2	35.7	32.7	29.7
Indion 414	**2.5**	**2.5**	**2.5**	**5**	**5**	**5**
Mannitol	**12**	**15**	**18**	**12**	**15**	**18**
Stevia Reb A 97	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil 200	1	1	1	1	1	1
Talc	2	2	2	2	2	2
Total Weight	**120**	**120**	**120**	**120**	**120**	**120**

In the present work, a 3^2 full factorial design was adopted to find out the optimum combination of independent variables obtain desired values of

1. Wetting Time
2. Disintegration Time
3. % Cumulative Drug Release

Table No. 3: Selection of Independent Variables and Dependent Variables

Independent Variable		Dependent Variable		
X_1	X_2	Y_1	Y_2	Y_3
Concentration of Superdisintegrant	Concentration of Mannitol	Wetting Time	Disintegration Time	% Cumulative Drug Release

Table No.4: Strategy III – Preparation of Factorial Batches

INGREDIENTS	FORMULATION CODE WITH QUANTITY IN mg								
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Inclusion Complex of Bilastine	62.3	62.3	62.3	62.3	62.3	62.3	62.3	62.3	62.3
Microcrystalline Cellulose	38.2	36.2	34.2	35.7	33.7	31.7	33.2	31.2	29.2
Indion 414	**2**	**4**	**6**	**2**	**4**	**6**	**2**	**4**	**6**
Mannitol	**12.5**	**12.5**	**12.5**	**15**	**15**	**15**	**17.5**	**17.5**	**17.5**
Stevia Reb A 97	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil 200	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total Weight	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

Drug Excipient Compatibility Studies:

A physical mixture of Bilastine was prepared by mixing the drug with excipients in 1:1 ratio. These samples were subjected to compatibility studies and stirred for 2 weeks at elevated temperature and humidity conditions of 40 ± 2 ˚C / 75 ± 5 % RH. FTIR spectra of these stored samples were then obtained after 2 weeks.

Evaluation Parameters of Sublingual Tablets [8]

Pre-compression Parameters

1. Angle of Repose

The angle of repose has been defined as the maximum angle possible between the surface of a pile of powder and horizontal plane. The angle of repose was then calculated by the using the following formula:

$$\tan \theta = h / r$$

Where, θ= angle of repose

h= height of the pile

r = average radius of the powder cone

Table No. 5: Angle of Repose (θ) and Flowability

Angle of Repose	Flowability
25 – 30	Excellent
31 – 35	Good
36 – 40	Fair
41 – 45	Passable
46 – 55	Poor
56 – 65	Very poor
> 66	Very very poor

2. Bulk Density

$$\text{B.D (g/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

3. Tapped Density

$$\text{T.D (g/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample after tapping}}$$

4. Carr's Index

$$I = \frac{\text{Tapped Density} - \text{Bulk Density} \times 100}{\text{Tapped Density}}$$

Table No. 6: % Compressibility values and its significance

% Compressibility	Flowability
5 – 15	Excellent
12 – 16	Good
18 – 21	Fairly poor
23 – 35	Poor
33 – 38	Very poor
>40	Not acceptable

5. Hausner's ratio

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Table No. 7: Hausner's ratio Specification

Hausner's ratio	Flowability
1.00 – 1.11	Excellent
1.12 – 1.18	Good
1.19 – 1.25	Fair
1.26 – 1.34	Passable
1.35 – 1.45	Poor
1.46 – 1.59	Very poor
>1.60	Very very poor

Post-compression Parameters of Sublingual Tablet:

1. Weight Uniformity:

The weight of the tablet is routinely measured to ensure that the tablet contains the proper amount of drug. 20 tablets were taken at random for the test and were weighed, individually and the average weight was calculated. The % deviation of each tablet from the average weight was calculated.

Table No. 8: Weight Variation

Sr. No.	Avg. weight of tablet	% Deviation allowed
1	80 mg or <80	10
2	>80 but < 250 mg	7.5
3	250 mg or more	5

2. Hardness:
Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet is placed between the plungers and was tightened from one end, and pressure required to break the tablet diametrically was measured.

3. Friability:
In this test 10 tablets were weighed and placed in a Roche Friabilator test apparatus, and then the tablets were subjected to rolling and repeated shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets will be removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

%Friability = (Initial weight of the tablets − Final weight of tablets) / Initial weight × 100

4. Thickness:
Thickness is the only dimensional variable related to the process. The dimension of tablets was measured using the Vernier calliper scale. Tablet thickness should be controlled within a ±5% variation of the mean value.

5. Water Absorption Ratio:
A piece of tissue paper folded twice was kept in a Petri dish (ID 6.5cm) containing 6 ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and weighed. Water absorption ratio, R was determined according to the following equation:

$$R = \frac{(W_a - W_b)}{W_b} \times 100$$

Where W_a is the weight after water absorption
W_b is the weight before water absorption

6. Wetting Time:
A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured.

7. Disintegration time:
The disintegration time is performed to find out that within how much time the tablet is disintegrated. Availability of drug depends upon solubility. The important step towards a solution is a breakdown of the tablet into small particles (disintegration).

8. Drug Content:
Twenty tablets were taken, powdered and the powder equivalent to 10 mg Bilastine was transferred to a 100 ml volumetric flask and methanol was added. The volume was then made up to the mark with phosphate buffer 6.8 pH. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV spectrophotometer at 282 nm.

9. Dispersion Time:
Dispersion time was measured by dropping a tablet in a beaker containing 50 ml of buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

10. In vitro Drug Release Study:
The release rate of Bilastine from prepared tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 300 ml of simulated saliva fluid (pH6.8). The dissolution test was carried out at 37 ± 0.5 ˚C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2 min time interval (2, 4, 6, 8, 10, 12 min) and the samples were replaced with fresh dissolution medium. The samples were filtered through whattman filter paper. The absorbance of these solutions was measured at 282 nm using UV spectrophotometer; Cumulative percent drug release was calculated using an equation obtained from a standard curve.

Statistical Analysis [9, 10]
The statistical optimization procedure was performed with the help of optimization software Design expert 12.0.0 the software performs the multiple regression analysis (MRA), analysis of variance (ANOVA) and statistical optimization. The polynomial equation was generated to study the effect of independent variables on dependent variables.

Construction of Contour Plot and Surface Plot:
To demonstrate graphically the influence of each factor on the response, Contour plots and surface plots were drawn by using Design Expert 12.0.0. The

quadratic equation from regression analysis was allowed to build the plots by statistical software in which the dependent variable Y_1 and Y_2 was represented by a curvature as a function of independent variables X_1 and X_2.

Stability Study [11]

In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies of the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. In the present study, stability studies were carried out on the optimized formulation. The tablets were stored at 40 ± 2 ˚C/75 ± 5 % RH for the duration of 1 month. After an interval of 1 month, each sample was withdrawn and tested for various physical tests and drug release study.

RESULT AND DISCUSSION

Drug Excipient Interaction Studies:

FTIR peaks of the pure drug, mixture of drug and complexing agent and mixture of drug and all excipients were studied. FTIR study showed that there was no interaction between drug and complexing agent and excipients. So, the drug and complexing agent and excipients are compatible.

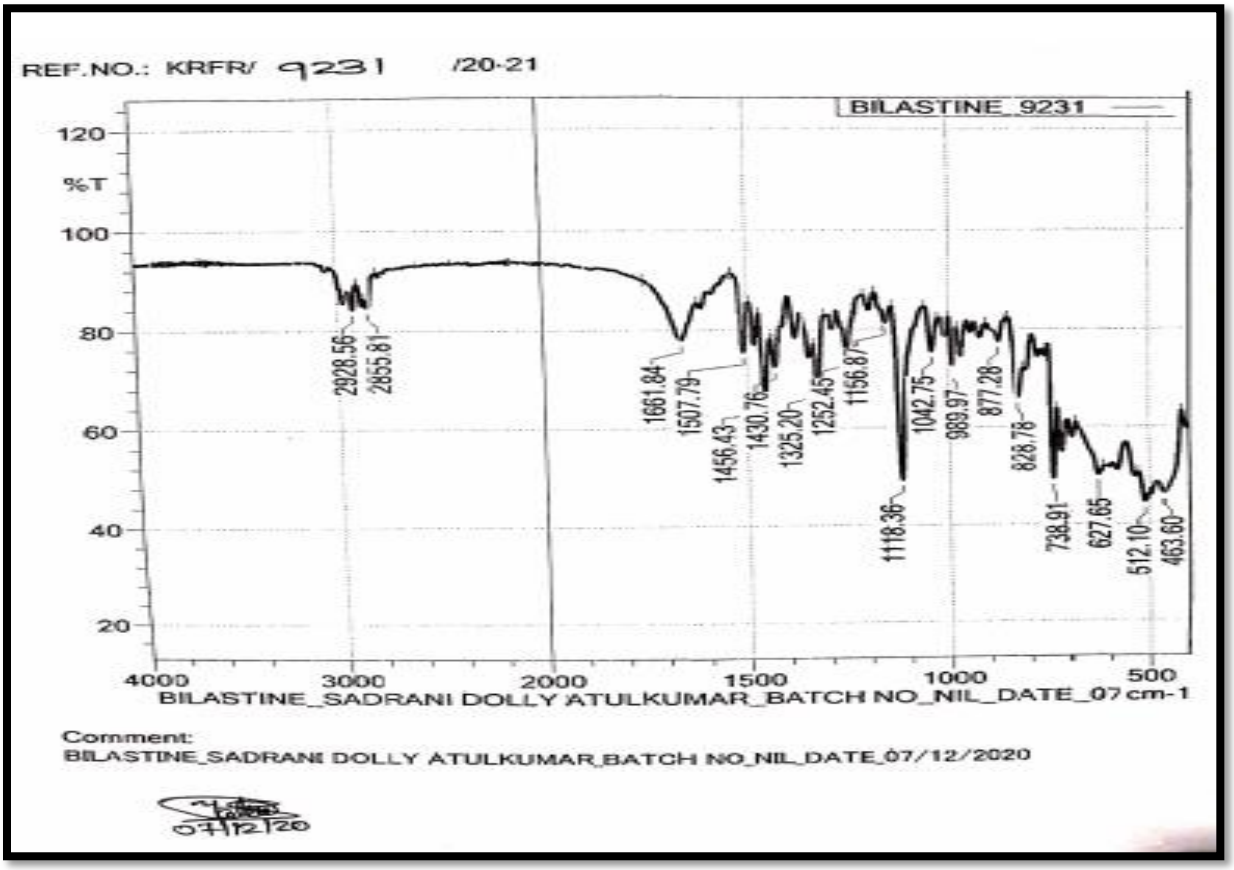

Figure No. 1: FTIR Spectrum of Bilastine

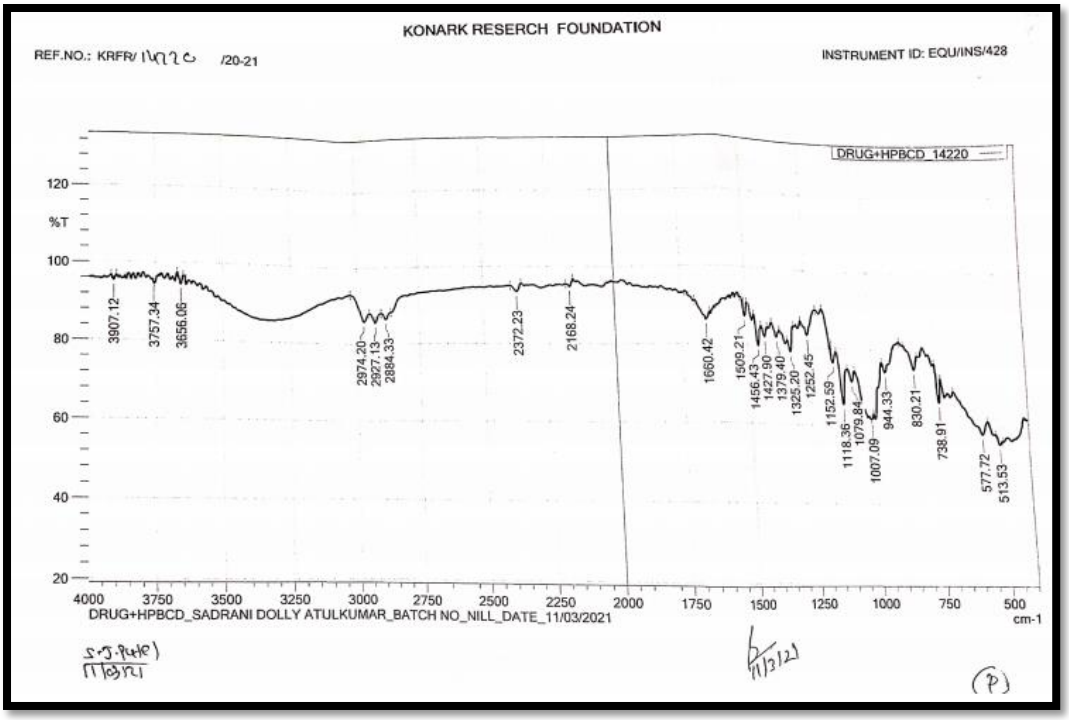

Figure No. 2: FTIR Spectrum of Bilastine + HPβCD

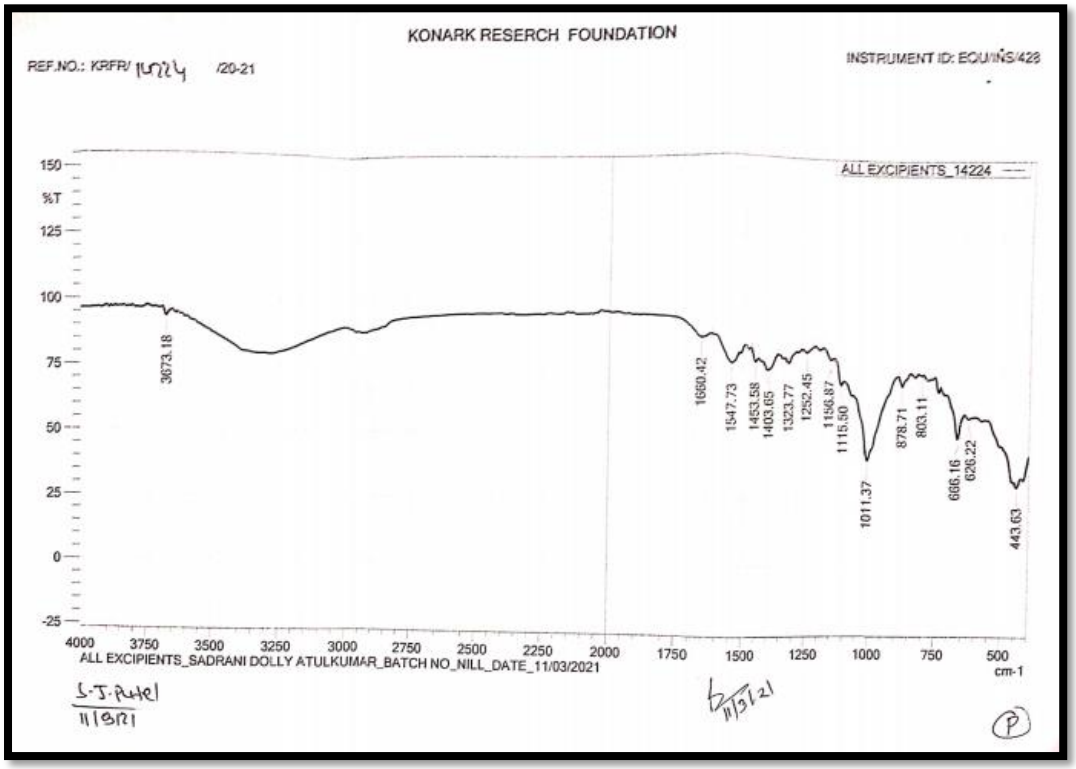

Figure No. 3: FTIR Spectrum of Bilastine + All Excipients

Table No. 9: Evaluation Parameters of Strategy I - Preparation of Preliminary Batches for Selection of Superdisintegrants

Parameters	FORMULATION CODE							
	T 1	T 2	T 3	T 4	T 5	T 6	T 7	T 8
% Friability	0.72	0.84	0.60	0.84	0.72	0.96	0.84	0.72
Hardness (Kg/cm^2) Mean ± SD (n=3)	3.56 ± 0.057735	3.46 ± 0.057735	3.63 ± 0.057735	3.56 ± 0.057735	3.13 ± 0.057735	3.03 ± 0.057735	3.23 ± 0.057735	3.36 ± 0.057735
Wetting Time (sec) Mean ± SD (n=3)	34 ± 1	29 ± 1	34 ± 2	30 ± 2	19 ± 1	17 ± 1	28 ± 2	27 ± 2
Disintegration Time (sec) Mean ± SD (n=3)	83 ± 1	79 ± 2	85 ± 1	80 ± 1	65 ± 1	61 ± 1	73 ± 2	72 ± 1

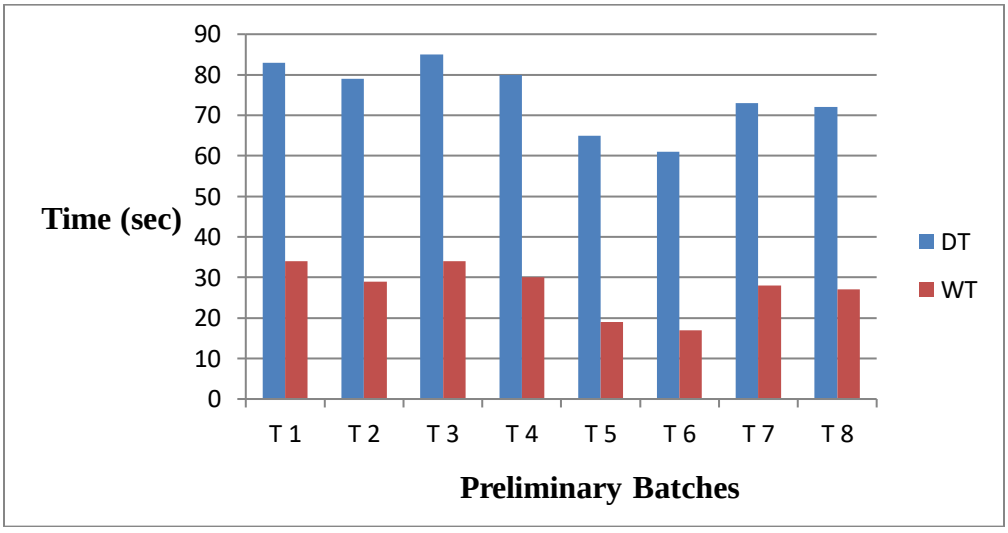

Figure No. 4: Comparison of Disintegration and Wetting Time (sec)

Table No. 10: Evaluation Parameters of Strategy II - Preparation of Preliminary Batches for Selection of Concentration of Mannitol

Parameters	FORMULATION CODE					
	M 1	M 2	M 3	M 4	M 5	M 6
Wetting Time (sec) Mean ± SD (n=3)	45 ± 1	42 ± 0	41 ± 1	37 ± 1	35 ± 0	33 ± 1
Disintegration Time (sec) Mean ± SD (n=3)	65 ± 1	62 ± 1	59 ± 0	54 ± 1	52 ± 0	49 ±1

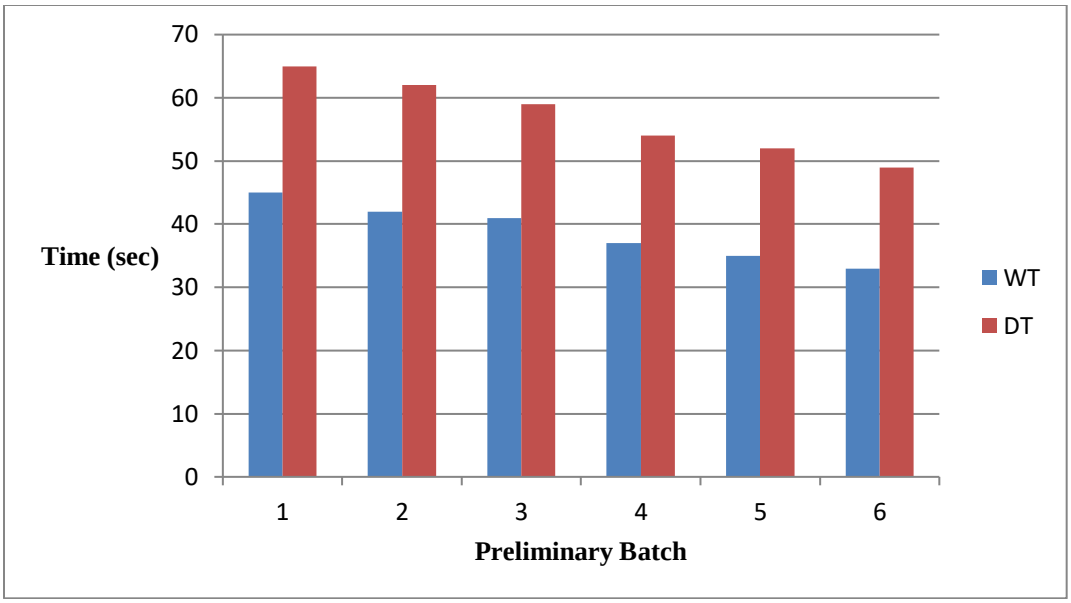

Figure No. 5: Comparison of Disintegration and Wetting Time (sec)

Table No. 11: Pre-compression Parameters for Strategy III – Preparation of Factorial Batches

Formulation	Angle of repose (Ɵ) Mean ± SD (n=3)	Bulk Density (gm/ml) Mean ± SD (n=3)	Tapped Density (gm/ml) Mean ± SD (n=3)	Carr's Index Mean ± SD (n=3)	Hausner's Ratio Mean ± SD (n=3)
F 1	28.33 ± 0.187	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008
F 2	29.19 ± 0.560	0.698 ± 0.027	0.811 ± 0.037	13.968 ± 0.549	1.162 ± 0.007
F 3	29.53 ± 0.467	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008
F 4	28.33 ± 0.187	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008
F 5	29.19 ± 0.137	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008
F 6	28.12 ± 0.005	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008
F 7	29.03 ± 0.410	0.750 ± 0.031	0.883 ± 0.043	15.018 ± 0.634	1.176 ± 0.008
F 8	28.49 ± 0.219	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008
F 9	27.83 ± 0.180	0.732 ± 0.031	0.858 ± 0.043	14.652 ± 0.634	1.171 ± 0.008

Table No. 12:Post-compression Parameters for Strategy III – Preparation of Factorial Batches

Formulation	Weight Uniformity	Hardness (kg/cm^2) Mean ± SD (n=3)	Friability (%)	Thickness Mean ± SD (n=3)	Water Absorption Ratio Mean ± SD (n=3)
F 1	Pass	3.56 ± 0.057	0.715	1.83 ± 0.057	17.257 ± 0.325
F 2	Pass	3.5 ± 0.1	0.834	1.76 ± 0.057	18.909 ± 0.2 67
F 3	Pass	3.63 ± 0.057	0.598	1.83 ± 0.057	19.170 ± 0.253
F 4	Pass	3.53 ± 0.057	0.719	1.83 ± 0.057	18.196 ± 0.127
F 5	Pass	3.5 ± 0.1	0.718	1.73 ± 0.057	19.624 ± 0.172
F 6	Pass	3.56 ± 0.057	0.952	1.83 ± 0.057	17.954 ± 0.319
F 7	Pass	3.6 ± 0.1	0.837	1.73 ± 0.057	17.386 ± 0.198
F 8	Pass	3.56 ± 0.057	0.838	1.86 ± 0.057	18.856 ± 0.339
F 9	Pass	3.63 ± 0.057	0.719	1.83 ± 0.057	19.110 ± 0.213

Table No. 13: Post-compression Parameters for Strategy III – Preparation of Factorial Batches

Formulation	Wetting Time (sec) Mean ± SD (n=3)	Disintegration Time (sec) Mean ± SD (n=3)	Dispersion Time (%) Mean ± SD (n=3)	Drug Content (%) Mean ± SD (n=3)	% Cumulative Drug Release After 10 min Mean ± SD (n=3)
F 1	48 ± 1	85 ± 1	95 ± 1	98.08 ± 0.203	70.39 ± 0.181
F 2	44 ± 0	80 ± 1	93 ± 1	98.80 ± 0.133	74.41 ± 0.640
F 3	39 ± 1	74 ± 0	89 ± 1	97.33 ± 0.266	77.67 ± 0.185
F 4	35 ±1	67 ± 1	85 ± 1	99.82 ± 0.153	82.75 ± 0.650
F 5	29 ± 1	64 ±0	81 ± 1	96.84 ± 0.076	87.86 ± 0.185
F 6	26 ± 1	58 ± 1	77 ± 1	97.688 ± 0.076	91.31 ± 0.325
F 7	26 ±1	57 ±0	77 ± 0	99.82 ± 0.203	92.48 ± 0.355
F 8	21 ±0	52 ± 1	73 ± 1	98.17 ± 0.076	96.15 ± 0.456
F 9	18 ±1	48 ±1	69 ± 1	98.84 ± 0.277	98.17 ± 0.330

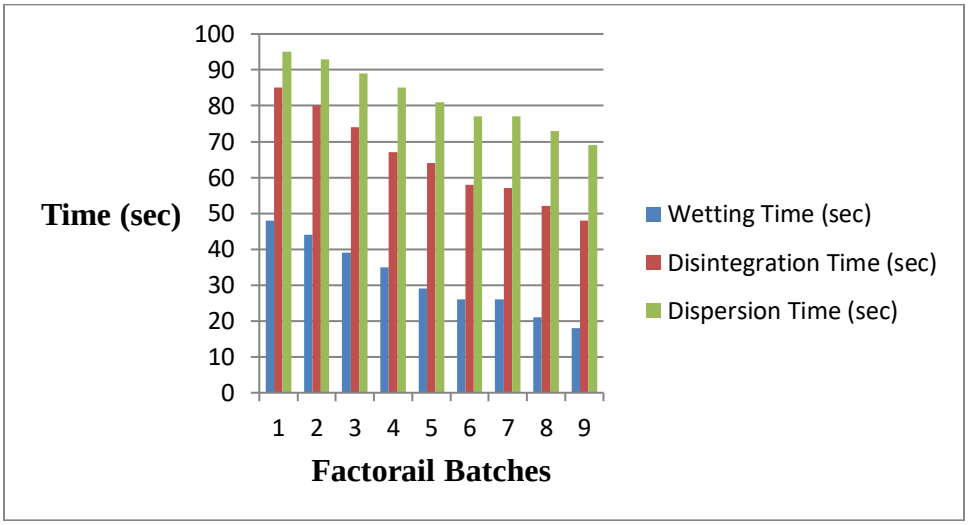

Figure No. 6: Comparison of Wetting, Disintegration and Dispersion Time (sec)

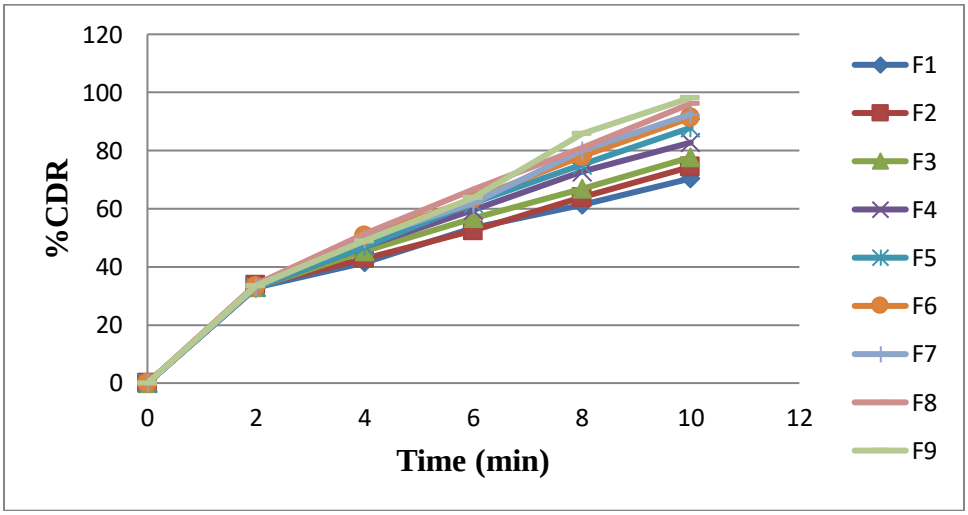

Figure No. 7: % Cumulative Drug Release of Factorial Batches After 10 min

Statistical Analysis

Table No.14: Data Transformation of 3^2 Factorial Designs

Batch Code	Real Values		Transformed Values		Dependent Variable		
	X_1	X_2	X_1	X_2	Y_1	Y_2	Y_3
F 1	2	12.5	-1	-1	48	85	70.39
F 2	4	12.5	0	-1	44	80	74.41
F 3	6	12.5	+1	-1	39	74	77.67
F 4	2	15	-1	0	35	67	82.75
F 5	4	15	0	0	29	64	87.86
F 6	6	15	+1	0	26	58	91.31
F 7	2	17.5	-1	+1	26	57	92.48
F 8	4	17.5	0	+1	21	52	96.15
F 9	6	17.5	+1	+1	18	48	98.17

Effect on Wetting Time (Y_1) – Surface Response Study

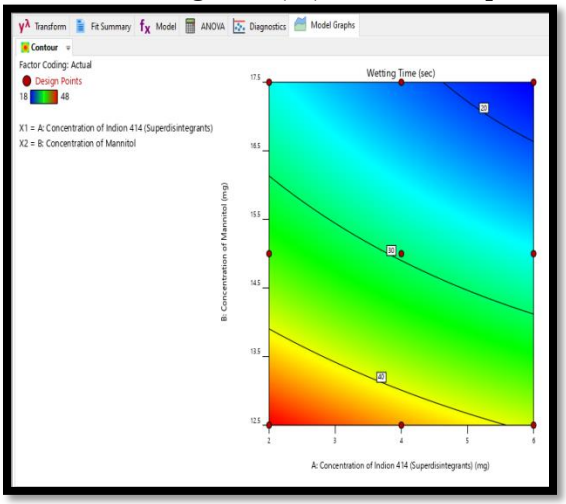

Figure No. 8: Contour Plot of Wetting Time

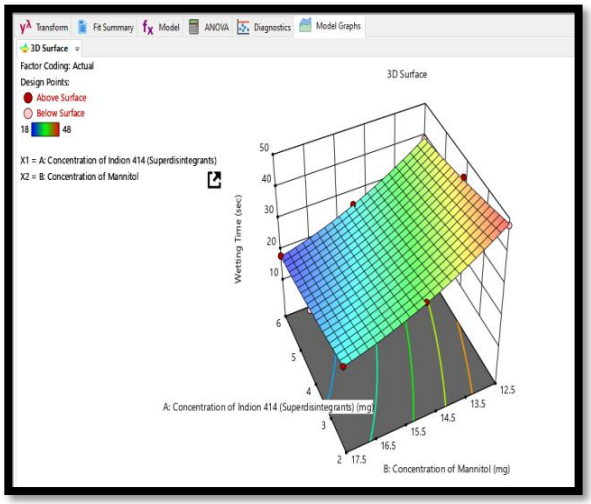

Figure No. 9: 3 – D Response of Wetting Time

Fit Summary

Response 1: Wetting Time

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001		0.9737	0.9614	
2FI	0.7950		0.9689	0.9269	
Quadratic	**0.0278**		**0.9952**	**0.9821**	**Suggested**
Cubic	0.6742		0.9935	0.8521	Aliased

Figure No. 10: Fit summary for Surface Response (Y_1) Wetting Time

ANOVA for Quadratic model

Response 1: Wetting Time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	854.03	5	170.81	335.40	0.0003	significant
A-Concentration of Indion 414 (Superdisintegrants)	112.67	1	112.67	221.24	0.0007	
B-Concentration of Mannitol	726.00	1	726.00	1425.60	< 0.0001	
AB	0.2500	1	0.2500	0.4909	0.5340	
A^2	0.8889	1	0.8889	1.75	0.2782	
B^2	14.22	1	14.22	27.93	0.0132	
Residual	1.53	3	0.5093			
Cor Total	855.56	8				

Figure No. 11: ANOVA for Quadratic model (Y_1) Wetting Time

Fit Statistics

Std. Dev.	0.7136		**R^2**	0.9982
Mean	31.78		**Adjusted R^2**	0.9952
C.V. %	2.25		**Predicted R^2**	0.9821
			Adeq Precision	52.6311

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	29.56	1	0.5319	27.86	31.25	
A-Concentration of Indion 414 (Superdisintegrants)	-4.33	1	0.2913	-5.26	-3.41	1.0000
B-Concentration of Mannitol	-11.00	1	0.2913	-11.93	-10.07	1.0000
AB	0.2500	1	0.3568	-0.8855	1.39	1.0000
A^2	0.6667	1	0.5046	-0.9392	2.27	1.0000
B^2	2.67	1	0.5046	1.06	4.27	1.0000

Figure No. 12: Fit Statistics Table for Surface Response (Y_1) Wetting Time

Effect on Disintegration Time (Y_2) – Surface Response Study

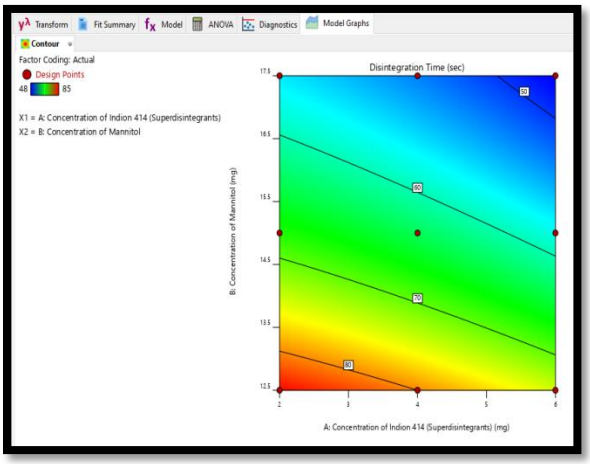

Figure No. 13: Contour Plot of Disintegration Time

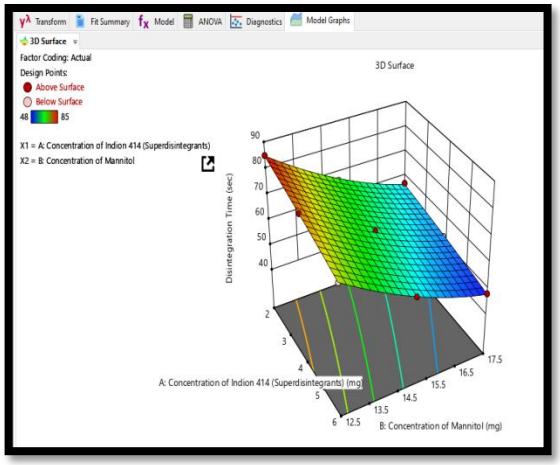

Figure No. 14: 3 – D Response of Disintegration Time

Fit Summary

Response 2: Disintegration Time

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001		0.9780	0.9635	
2FI	0.6397		0.9748	0.9414	
Quadratic	**0.0238**		**0.9965**	**0.9879**	**Suggested**
Cubic	0.7746		0.9938	0.8578	Aliased

Figure No. 15: Fit summary for Surface Response (Y_2) Disintegration Time

ANOVA for Quadratic model

Response 2: Disintegration Time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1280.33	5	256.07	460.92	0.0002	significant
A-Concentration of Indion 414 (Superdisintegrants)	140.17	1	140.17	252.30	0.0005	
B-Concentration of Mannitol	1120.67	1	1120.67	2017.20	< 0.0001	
AB	1.0000	1	1.0000	1.80	0.2722	
A^2	0.5000	1	0.5000	0.9000	0.4128	
B^2	18.00	1	18.00	32.40	0.0107	
Residual	1.67	3	0.5556			
Cor Total	1282.00	8				

Figure No. 16: ANOVA for Quadratic model (Y_2) Disintegration Time

Fit Statistics

Std. Dev.	0.7454		**R^2**	0.9987
Mean	65.00		**Adjusted R^2**	0.9965
C.V. %	1.15		**Predicted R^2**	0.9879
			Adeq Precision	60.7972

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	63.33	1	0.5556	61.57	65.10	
A-Concentration of Indion 414 (Superdisintegrants)	-4.83	1	0.3043	-5.80	-3.86	1.0000
B-Concentration of Mannitol	-13.67	1	0.3043	-14.64	-12.70	1.0000
AB	0.5000	1	0.3727	-0.6860	1.69	1.0000
A^2	-0.5000	1	0.5270	-2.18	1.18	1.0000
B^2	3.00	1	0.5270	1.32	4.68	1.0000

Figure No. 17: Fit Statistics Table for Surface Response (Y_2) Disintegration Time

Effect on % CDR After 10 min (Y_3) – Surface Response Study

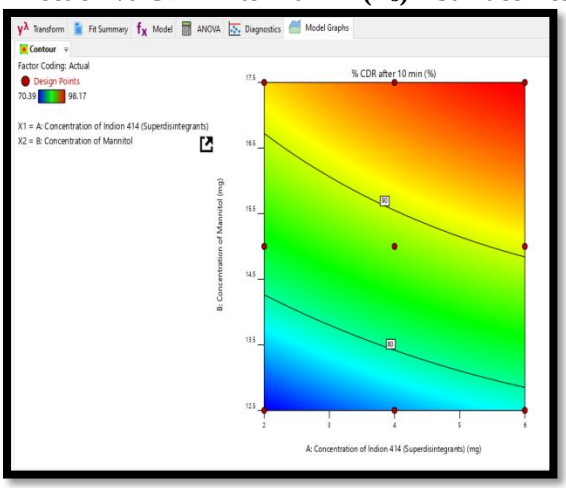

Figure No. 18: Contour Plot of % CDR After 10 min

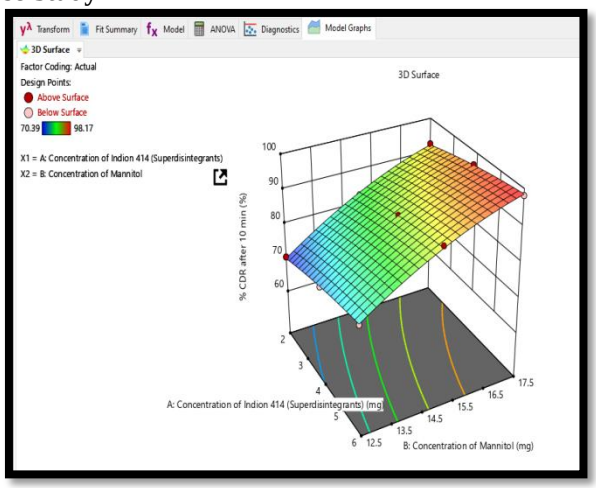

Figure No. 19: 3 – D Response of % CDR After 10 min

Fit Summary

Response 3: % CDR after 10 min

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001		0.9746	0.9586	
2FI	0.6574		0.9709	0.9175	
Quadratic	**0.0350**		**0.9948**	**0.9764**	**Suggested**
Cubic	0.1228		0.9998	0.9946	Aliased

Figure No. 20: Fit summary for Surface Response (Y3) CDR After 10 min

ANOVA for Quadratic model

Response 3: % CDR after 10 min

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	780.33	5	156.07	307.17	0.0003	significant
A-Concentration of Indion 414 (Superdisintegrants)	77.26	1	77.26	152.06	0.0011	
B-Concentration of Mannitol	689.72	1	689.72	1357.53	< 0.0001	
AB	0.6320	1	0.6320	1.24	0.3460	
A^2	0.9203	1	0.9203	1.81	0.2710	
B^2	11.79	1	11.79	23.21	0.0170	
Residual	1.52	3	0.5081			
Cor Total	781.85	8				

Figure No. 21: ANOVA Table for Surface Response % (Y_3) % CDR After 10 min

Fit Statistics

Std. Dev.	0.7128		**R^2**	0.9981
Mean	85.69		**Adjusted R^2**	0.9948
C.V. %	0.8318		**Predicted R^2**	0.9764
			Adeq Precision	49.1759

Coefficients | Coded Equation | Actual Equation

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	87.76	1	0.5313	86.07	89.45	
A-Concentration of Indion 414 (Superdisintegrants)	3.59	1	0.2910	2.66	4.51	1.0000
B-Concentration of Mannitol	10.72	1	0.2910	9.80	11.65	1.0000
AB	-0.3975	1	0.3564	-1.53	0.7367	1.0000
A^2	-0.6783	1	0.5040	-2.28	0.9257	1.0000
B^2	-2.43	1	0.5040	-4.03	-0.8243	1.0000

Figure No. 22: Fit Statistics Table for Surface Response (Y_3) % CDR After 10 min

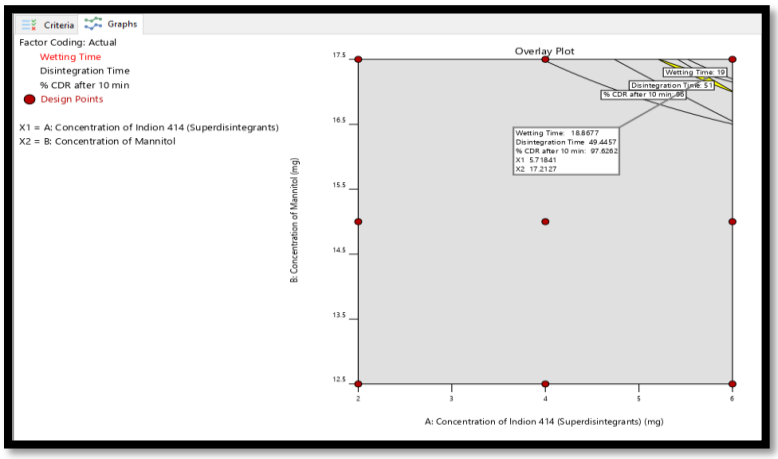

Figure No. 23: Overlay Plot

Table No. 15: Formulation of Checkpoint F 10 Batch

Ingredients	**Quantity (mg)**
Inclusion complex of Bilastine	62.3
Microcrystalline cellulose	29.8
Indion 414	5.7
Mannitol	17.2
Stevia (Reb – A 97)	1.5
Menthol	0.5
Aerosil 200	1
Talc	2
Total Weight	**120**

Table No.16: Evaluation of Checkpoint F 10 Batch

Parameters	Observation
Pre-compression Parameters	
Angle of Repose (Θ)	29.28
Bulk Density (gm/ml)	0.714
Tapped Density (gm/ml)	0.833
Carr's Index	14.285
Hausner's Ratio	1.166
Post-compression Parameters	
Weight Uniformity	Pass
Hardness (kg/cm^2)	3.4
Friability (%)	0.846
Thickness	1.76
Water Absorption Ratio	18.531
Wetting Time (sec)	17
Disintegration Time (sec)	50
Dispersion Time (sec)	74
Drug Content (%)	98.17
% CDR after 10 min	97.68

Table No. 17: Experimental Value of F10 with Predicted Value for Response Variable

Response Variable	F 10	
	Theoretical Value	Experiment Value
Wetting Time (sec)	18.86	17
Disintegration Time (sec)	49.44	50
% CDR after 10 min	97.62	97.68

Stability Study

Stability Study was carried out according to ICH and WHO guidelines. The Check point batch is subjected for stability studies. There was no change appear in organolaptic properties. Formulation was analyzed at the end of 1 month for the Drug – Excipient compatibility study, disintegration, drug content and % CDR. Results showed that there were no significant changes in the evaluated parameters at the end of 1 month.

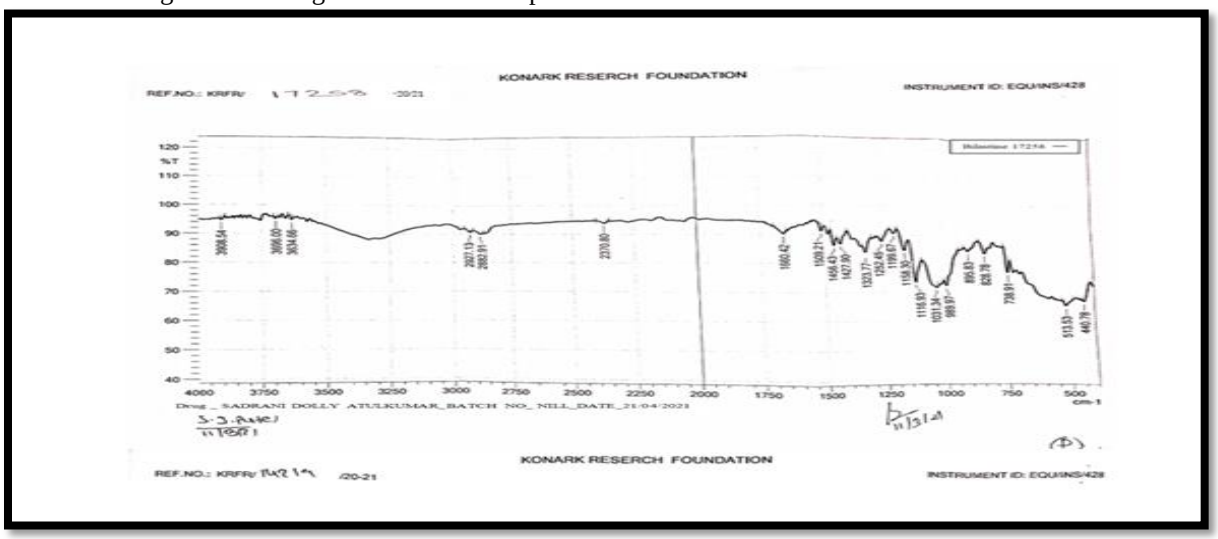

Figure No. 24: FTIR Spectrum of Bilastine Tablet after 1 month

Table No. 18: Stability Study of Check Point F 10Batch After 1 Month

Parameters	Observation					
	Disintegration Time (sec)		Drug Content (%)		% CDR after 10 min (%)	
	Before	After	Before	After	Before	After
Check point F 10 batch after 1 month	50	49	98.17	98.15	97.68	97.61

CONCLUSION:

Formulation of sublingual tablet of Bilastine was prepared by direct compression method. It was concluded that all the evaluation parameters of Check point batchF 10were suitable for sublingual drug delivery. The inclusion complex of Bilastine with HP-β-CD (1:2) prepared using novel Microwave irradiation method showed increase in solubility and higher yield (98.17%) of the product. FTIR studies suggested that there is no interaction between drug and excipients. The optimized check point batch F 10 showed disintegration within 50 sec. Similarly in-vitro dissolution study showed 97.68 % drug release in 10 min.

LIST OF SYMBOLS AND ABBREVIATIONS

% - Percentage
Cm - Centimetre
mg - milligram
sec - Second
g- Gram
ml - Milliliter
nm - Nanometer
SD - Standard Deviation
RH - Relative Humidity
ID - Internal Diameter
AR - Allergic Rhinitis
QoL - Quality of Life
ARC - Allergic Rhinoconjuctivitis
SR - Sublingual Route
HP-β-CD - Hydroxypropyl Beta Cyclodextrin
SSG - Sodium Starch Glycolate
CCS - Croscarmellose Sodium
MCC - Microcrystallone Cellulose
B.D. - Bulk Density
T.D. - Tapped Density
FTIR - Fourier Transform Infrared Spectroscopy
ANOVA - Analysis of Variance
MRA - Multiple Regression Analysis

ACKNOWLEDGEMENT

The author wishes to give thanks to Exemed Pharmaceuticals, Vapi, Gujarat for providing gift sample of Bilastine and also thankful to Co-authors and Principal of BNBSPC Vapi for providing suitable research work laboratory to carried out this project work.

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