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RESEARCH ON FORMULATION DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING BILASTINE TABLETS

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ABSTRACT

AIM: To formulation development and evaluation of Mouth Dissolving Tablets of Bilastine H1 Second generation anti Histamine drug by using superdisintegrating agents. Thus mouth dissolving tablets are beneficial to patients who find it difficult to swallow tablets and moreover some of the drugs which are soluble in saliva are absorbed from the mouth, pharynx and oesophagus there thereby avoiding first pass metabolism which enhances bioavailability of the drug.

OBJECTIVE: The objective of the work is to prevent inherent drawbacks associated with conventional tablets such as risk of choking, bitter taste and difficult in swallowing by formulating mouth dissolving tablets of Bilastine there by providing faster disintegration and rapid release, bypassing first pass effect, improved patient compliance and therapeutic effectiveness.

RESULT AND SUMMERY: From the overall results, the study concluded that orally disintegrating tablets of Bilastine could be successfully formulated by direct compression method using crospovidone as superdisintegrant, which could be a promising formulation to effectively treat the symptoms of allergic disorders (e.g. rhinoconjunctivitis and urticaria) in adults and adolescents and, more recently, in children, thereby preventing inherent drawbacks associated with conventional tablets such as risk of choking, bitter taste and difficult in swallowing, also providing faster disintegration, rapid release, bypassing first pass effect, improve patient compliance and therapeutic effectiveness. From all the above observation it was concluded that the formulation F-VII containing crospovidone as superdisintegrant along with mannitol and microcrystalline cellulose as diluent was found to be better one compared to the other formulations and satisfied the criteria for orally disintegrating tablets.

KEYWORDS: Mouth dissolving tablet, improved patient compliance Bilastine, rhinoconjunctivitis and urticaria

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the Mouth Dissolving systems have been the favorite of product development scientists. In similar fashion the oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of langerhans cells makes oral mucosa tolerant to potential allergens.[1]

DIRECT COMPRESSION[36]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can be applied to preparation of ODT[S] because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

Bilastine is a new second generation H1-antihistamine approved for the symptomatic treatment of allergic

rhinitis (AR) and chronic urticaria (CU). Bilastine, with its efficacy and safety profile epitomizes the evolution of research on antihistamines Bilastine works by blocking histamine receptors.

RESULTS AND DISCUSSION

The current study aimed to develop Bilastine mouth dissolving tablets via direct compression employing three superdisintegrants: croscarmellose sodium, crospovidone, and sodium starch glycolate. The study attempted to avoid the inherent problems associated with traditional Bilastine pills, such as choking risk, bitter taste, and difficulty swallowing, by developing Bilastine mouth dissolving. Prior to formulation, preformulation tests were conducted in which specific parameters were assessed. To accomplish quick oral disintegration of Bilastine, seven formulations were developed (three trials with mannitol anhydrous, three trials with sorbitol granular grade, and one experiment with both mannitol anhydrous and microcrystalline cellulose (MCC-112).

PREFORMULATION STUDIES

DRUG - EXCIPIENTS COMPATIBILITY STUDIES

Compatibility studies were carried out by making a blend of several excipients with the medicine and storing it at 40°C/2°C/755%RH for one month. Every 15 days, the mixes were examined for changes such as caking, liquefaction, discolouration, and odour development.

According to the results of the aforesaid drug excipients compatibility study, there was no significant difference between the drug and the excipients. As a result, it was determined that the excipients chosen for the formulation were compatible with Bilastine and appropriate for formulation development.

FT-IR SPECTRAL STUDIES

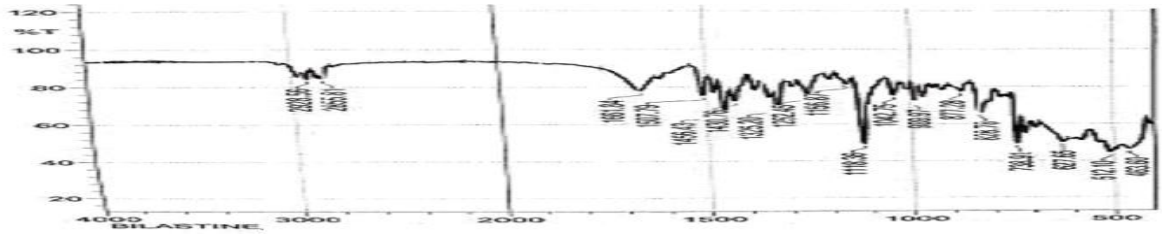


Fig: 1 FT-IR Spectrum of Pure Bilastine

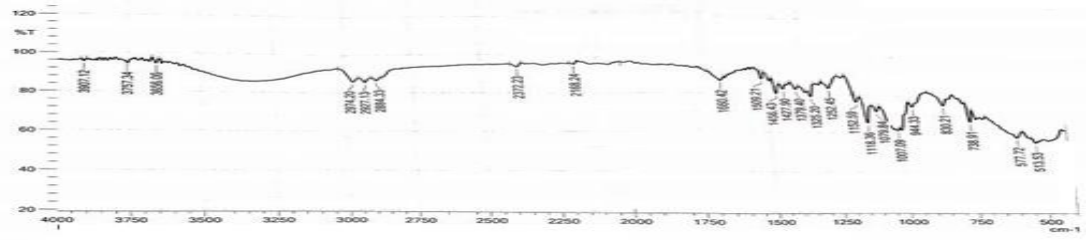


Fig: 2 FT-IR Spectrum of Bilastine+ Croscarmellose sodium

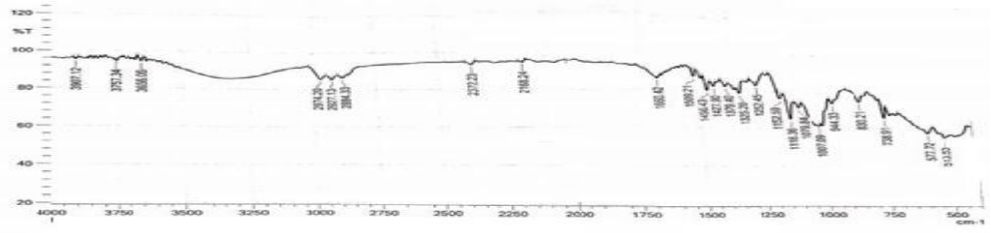


Fig:3 FT-IR Spectrum of Bilastine+ Crospovidone

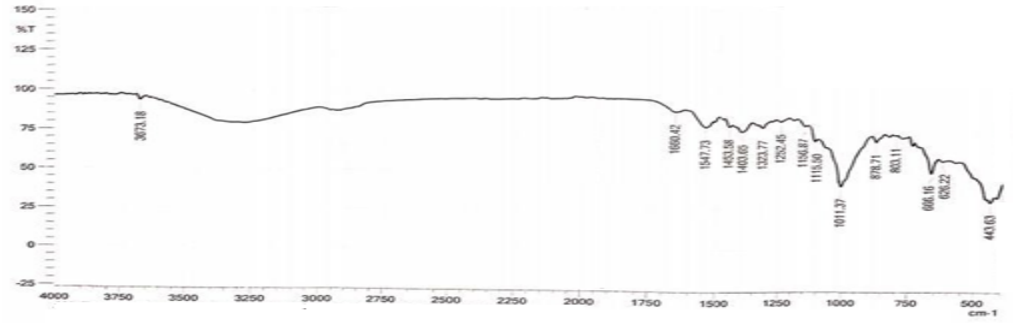


Fig: 4 FT-IR Spectrum of Bilastine+ Sodium starch glycolate

The drug is compatible with all of the excipients, according to FT-IR spectrum investigations. The physical mixture's FT-IR spectrum showed all of Bilastine's distinct peaks, indicating that no pharmacological interaction occurred with the formulation's components.

EVALUATION OF PRECOMPRESSION PARAMETERS

MICROMERITIC PROPERTIES

Angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were all computed for the powder blends. Table 2 highlights the findings.

Table: 1 Precompression Parameters

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm^3)	Tapped Densit (g/cm^3)	Compressibility Index (%)	Hausner'sratio
F-I	32º.11'	0.56	0.690	18.55	1.22
F-II	29º.09'	0.64	0.745	14.09	1.16
F-III	27º.06'	0.30	0.351	13.11	1.15
F-IV	29º.98'	0.31	0.367	13.63	1.15
F-V	26º.23'	0.31	0.360	13.89	1.16
F-VI	25º.09'	0.31	0.378	15.87	1.18
F-VII	22º.98'	0.31	0.368	15.21	1.18

The angle of repose of formulation f-i was determined to be 32o.11', indicating satisfactory flow characteristics. The angle of repose of all the other formulations was found to be between 22o.98' and 29o.98', indicating excellent flow property.

The bulk density was found to be between 0.305 and 0.640 g/cm3, the tapped density was found to be between 0.351 and 0.745 g/cm3, the compressibility index was found to be between 13.11 and 18.55%, and the hausner's ratio was found to be between 1.15 and 1.22.

The foregoing results in terms of micromeritic properties revealed that the flow property of formulation f-i was fair and the other formulations were good.Bilastine mouth dissolvings assessment

POST COMPRESSION PARAMETERS

Table: 2 Post Compression Parameters

Formulation Code	Thickness(mm	Hardness(kg /cm^2)	Weight Variatio (mg)	Friability(%)
F-I	3.20± 0.055	4.50± 0.32	142±1.2	0.24

F-II	3.30± 0.010	4.50± 0.22	140±0.6	0.42
F-III	3.20± 0.017	3.00± 0.27	140±0.4	0.50
F-IV	3.40 ± 0.016	4.50± 0.21	143±0.8	0.46
F-V	3.40 ± 0.020	4.50± 0.49	140±0.4	0.32
F-VI	3.20± 0.062	3.50± 0.29	142±0.9	0.20
F-VII	3.30± 0.018	3.00± 0.24	141±1.4	0.15
Marketed sample	2.90± 0.055	3.50± 0.32	140±0.8	0.26

All the values are expressed as mean± SD, n=3

The thickness of the pills was measured and determined to be between 3.20 0.017 mm and 3.40 0.020 mm. The thickness of all formulations was uniform.

The hardness of the tablets was measured, and the results ranged from 3.00 0.27 to 4.50 0.49 kg/cm2. The produced tablets have adequate mechanical strength and hardness.

The weight variation test was passed by all formulations of Bilastinemouth dissolvingtablets because the values were within the tablet's permissible variation limit.

Similarly, the manufactured Bilastinemouth dissolvingtablets revealed less than 1% weight loss, which is well within the permitted range. As a result, all of the tablets passed the friability test.

Table: 3 Evaluation of Bilastine mouth dissolving Tablets

Formulation Code	**Disintegration Test (Sec)**	**WettingTime (Sec)**	**Water AbsorptionRati**	***In vitro* Dispersion Time (Sec)**	**Fineness of Dispersion**
F-I	28±0.23	102±1.35	80.22±0.52	49±0.14	Passed
F-II	24±0.12	90±1.19	85.36±0.58	38±0.12	Passed
F-III	15±0.10	48±2.28	92.17±0.41	27±0.21	Passed
F-IV	24±0.45	88±0.71	79.25±0.17	39±0.14	Passed
F-V	23±0.58	81±0.10	87.12± 0.14	35±0.43	Passed
F-VI	20±0.35	56±0.21	86.98±0.12	28±0.66	Passed
F-VII	12±0.56	45±0.28	91.24±0.43	24±0.35	Passed
Marketed Sample	17±0.32	54±0.45	94.31±0.21	27±0.26	Passed

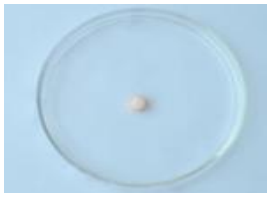
All the values are expressed as mean± SD, n=3

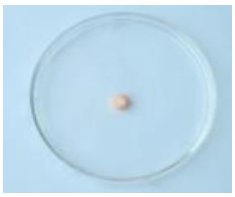
Bilastinemouth dissolvingtablets dissolve in 12 to 28 seconds. The allowable disintegration time limit according to I.P is NMT 30seconds. Formulation F-VII had the shortest disintegration time (12 seconds) when compared to the other formulations. The wetting time of Bilastinemouth dissolvingtablets was determined to be between 45 and 102 seconds. Formulation F-VII with crospovidone as a superdisintegrant had the shortest wetting time (45 seconds). The water absorption ratio of Bilastinemouth dissolvingtablets was between 79.25 and 92.31. The in vitro dispersion time of Bilastine oral dissolvingtablets was reported to be between 24 and 49 seconds. When compared to the other formulations, Formulation F-VII demonstrated the fastest dispersion (24 sec). The dispersions of all seven formulations passed through sieve #22 and passed the fineness of dispersion test. Based on the findings, it was determined that the formulation F-VII had superior tableting properties when compared to the other formulations and commercialised formulations and was chosen as the best formulation.

Figure 5 depicts the in vitro dispersion time of the optimum formulation (F-VII) at different time intervals (0, 10, 15, 20 seconds).

Formulation F-VII In Vitro Dispersion Time at Various Time Intervals

At 0 seconds **At 10 seconds**





At 15 seconds At 20 seconds

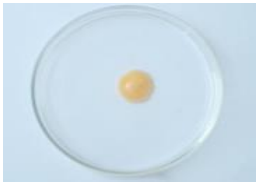


Fig: 5 *In Vitro* Dispersion of Bilastine Mouth dissolving Tablets

ASSAY OF Bilastine BY HPLC METHOD

The assay was carried out using the HPLC method, as described in the methodology section. Figures 6 to 13 show the HPLC chromatograms of Bilastine standard and sample formulations.

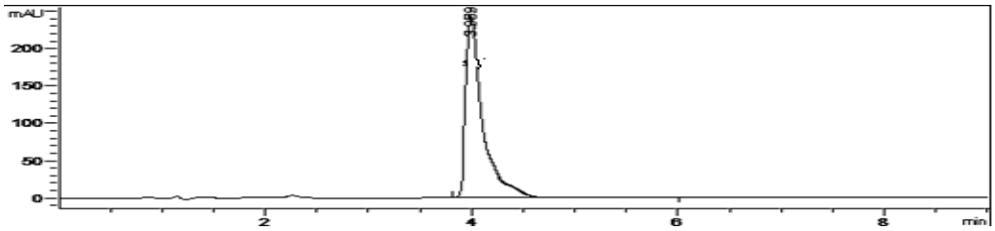


Fig: 6 HPLC Chromatogram of Bilastine (Standard)

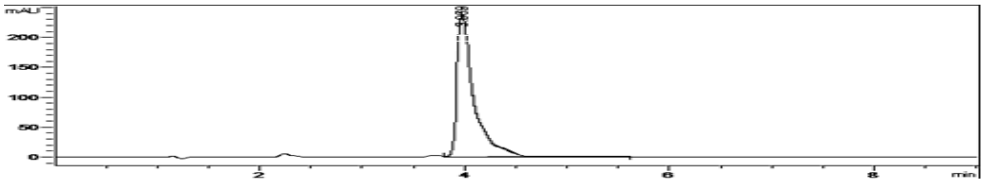


Fig: 7 HPLC Chromatogram of Formulation F-I

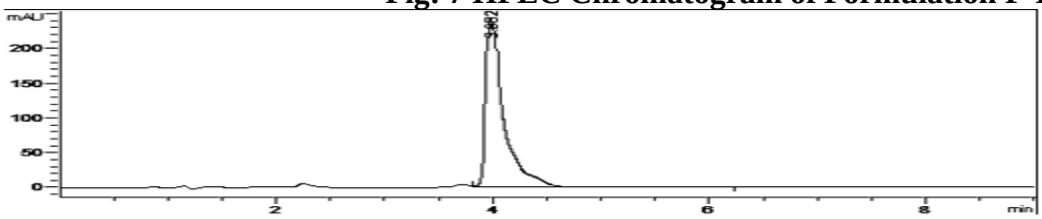


Fig: 8 HPLC Chromatogram of Formulation F-II

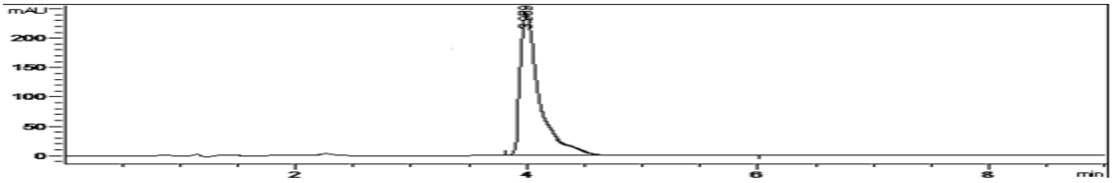


Fig: 9 HPLC Chromatogram of Formulation F-III

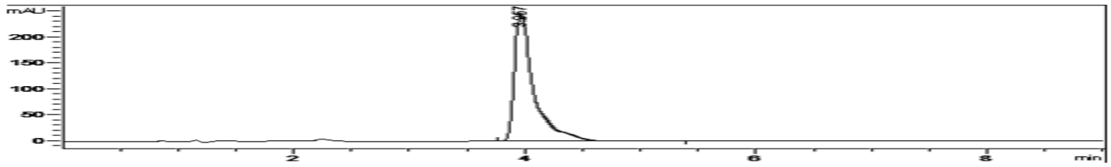


Fig: 10 HPLC Chromatogram of Formulation F-IV

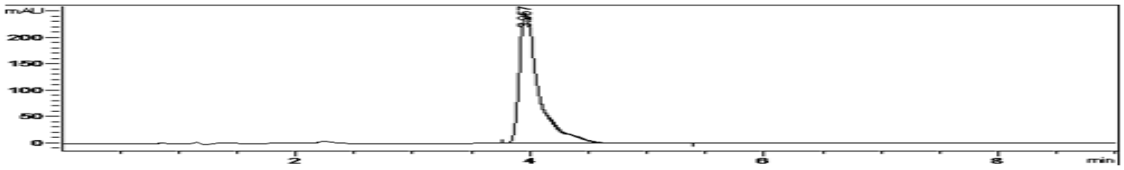


Fig: 11 HPLC Chromatogram of Formulation F-V

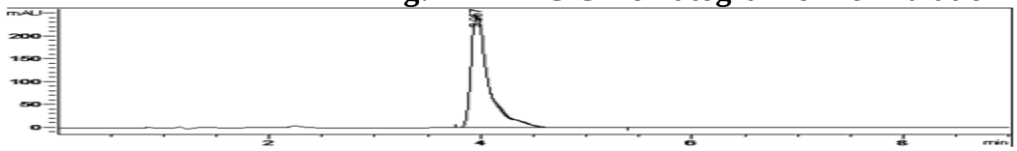


Fig: 12 HPLC Chromatogram of Formulation F-VI

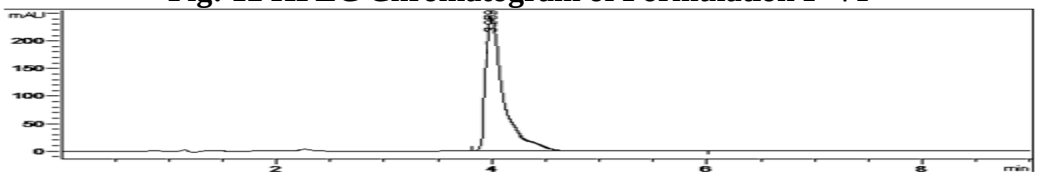


Fig: 13 HPLC Chromatogram of Formulation F-VII

Table: 6 Assay of Bilastine Mouth dissolving Tablets

Formulation Code	Limit (%)	Assay (%)
F-I	90 to 110%	99.50
F-II		98.85
F-III		99.75
F-IV		99.52
F-V		99.55
F-VI		98.82
F-VII		99.87
Marketed sample		98.69

The assay of Bilastine mouth dissolving tablets was found to be in the 98.82 to 99.87% range. According to I.P, the allowable limit for Bilastine content is 90 to 110%. The results showed that the Bilastine assay was within

permissible limits.

IN VITRO DISSOLUTION STUDIES

The *in vitro* drug release of Bilastine mouth dissolving tablets were given intable: 7 and fig: 14

Table: 14 Comparative *In Vitro* Drug Release Studies of Bilastine mouth dissolving

Time(min)	Percentage Drug Release (%)						
	Formulation Code						
	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII
2	20.58±0.48	25.85±0.37	31.48±0.55	18.53±0.33	22.43±0.31	30.10±0.58	35.30±1.18
4	32.23±0.70	34.71±0.60	42.62±0.55	31.17±0.28	31.54±0.52	48.52±0.43	54.15±0.61
6	41.63±0.59	49.88±0.26	61.54±0.20	48.67±0.43	46.64±00.6	59.92±0.98	72.28±0.24
8	65.99±1.23	69.60±0.68	79.56±0.44	58.96±0.70	62.82±0.28	74.18±0.67	85.61±0.52
10	72.30±0.16	76.07±0.50	84.34±0.09	70.73±0.60	73.18±0.07	81.62±0.11	99.85±0.07

All the values are expressed as mean± SD, n=3

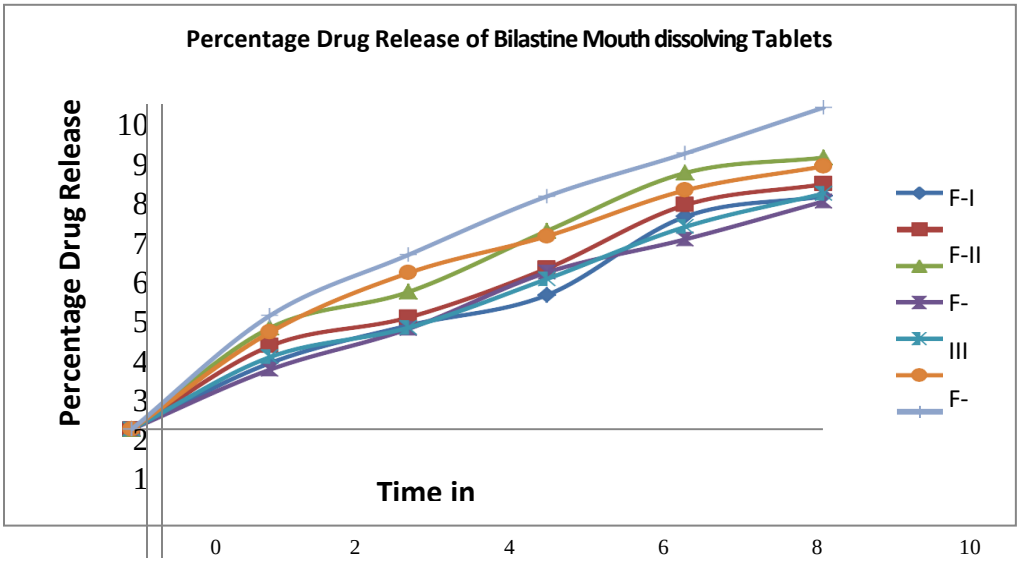


Fig: 14 Comparative *In Vitro* Drug Release Profiles of Bilastine mouth dissolving tablets

Bilastine release was examined for up to 10 minutes in 0.1M hydrochloric acid. F-I (sodium starch glycolate), F-II (croscarmellose sodium), and F-III (crospovidone) were created with mannitol as a diluent, while F-IV (sodium starch glycolate), F-V (croscarmellose sodium), and F-VI (crospovidone) were prepared with sorbitol. Microcrystalline cellulose and mannitol were used to make Formulation F-VII (crospovidone).

At 10 minutes, the drug release of formulations F-I, F-II, and F-III was 72.30 0.16%, 76.07 0.50%, and 84.34 0.09%, respectively. At 10 minutes, the drug release rates of formulations F-IV, F-V, and F-VI were found to be 70.73 0.60%, 73.18 0.07%, and 81.62 0.11%, respectively. The drug release rate of formulation F-VII was reported to be 99.85 0.07% after 10 minutes. The permissible in vitro dissolving limit is NLT 80% of medication release after 10 minutes. Formulations F-III, F-VI, and F- VII passed the in vitro dissolution tests. Higher dissolving rates were reported in formulations F-III, F-VI, and F- VII produced with crospovidone as

superdisintegrant, which could be attributed to rapid disintegration and fine particle dispersion after disintegration. The drug release was greatest in formulation F-VII, which used crospovidone as a superdisintegrant. This could be owing to the superdisintegrant's extremely porous structure with direct compressible carrier (microcrystalline cellulose), which allows for faster water uptake and thus faster disintegration, facile particle breakdown, and rapid dissolution.
The order of dissolving rate augmentation with several superdisintegrants was discovered to be CP>CCS>SSG. Based on quick disintegration time, wetting time, in vitro dispersion time, and dissolving profile, formulation F-VII was identified as an optimised formulation.

COMPARATIVE DISSOLUTION STUDY OF MARKETED FORMULATIONAND OPTIMIZED FORMULATION (F-VII)
The dissolution profile of the optimised formulation (F-VII) was compared to that of the commercially available Bilastine mouth dissolving tablet. Table 29 and Figure 23 demonstrate the comparative medication release profiles.

Table: 8 Comparative *In Vitro* Release Data of Bilastine Marketed Tablet andOptimized Formulation (F-VII)

Time(min)	**Percentage Drug Release (%)**	
	Formulation F-VII	**Marketed Formulation**
2	35.30± 1.18	20.29± 0.28
4	54.15± 0.61	32.16± 1.01
6	72.28± 0.24	54.57± 0.94
8	85.61± 0.52	70.59± 0.51
10	99.85± 0.07	82.52± 0.43

All the values are expressed as mean± SD, n=3

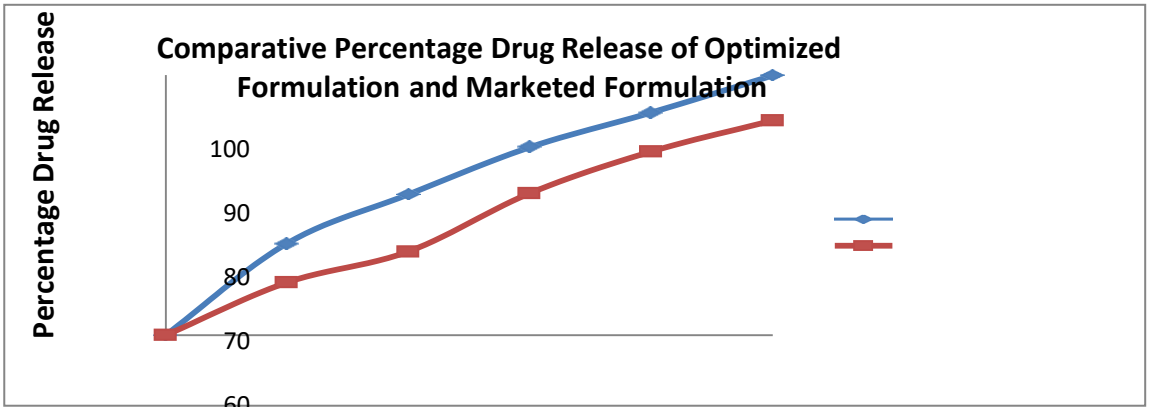


Fig: 15 Comparative *In Vitro* Drug Release Profile of Bilastine MarketedTablet and Optimized Formulation (F-VII)

At 10 minutes, the percentage drug release of the marketed sample and optimised formulation (F-VII) was 82.520.43 and 99.850.07%, respectively.

The drug release of Bilastine mouth dissolvingtablets optimised formulation was found to be greater than that of the commercial product. When compared to the marketed product, the optimised formulation enhanced the percentage drug release by 17.33% at 10-minute intervals.

STABILITY STUDIES: The optimised formulation (F-VII) was chosen for the stability research and stored at 25 2°C/60% 5% RH and 40 2°C/75% 5% RH for three months. At one month intervals, the tablets were examined for several characteristics such as physical appearance, average weight, thickness, hardness, friability, disintegration, in vitro dispersion, fineness of dispersion, dissolution, and assay. Tables 30 and 31 show the outcomes.

Table: 10 Stability Data of Bilastine mouth dissolving tablets Stored at25 ± 2°C/60% ± 5% RH (F-VII)

S. No.	Storage Conditions: 25 ± 2°C/60% ± 5% RH				
	Tests	**Initial Period**	**1st month**	**2nd month**	**3rd month**
1.	Physical appearance*	Complies	Complies	Complies	Complies
2.	Average weight (mg)	141.50	140.37	140.89	140.11
3.	Thickness (mm)	3.30	3.30	3.30	3.30
4.	Hardness (kg/cm^2)	3.00	3.00	3.00	3.00
5.	Friability (%)	0.15	0.17	0.25	0.22
6.	Disintegration test (sec)	12	12	14	11
7.	*In vitro* dispersion time (sec)	24	25	24	23
8.	Fineness of Dispersion	Passed	Passed	Passed	Passed
9.	*In vitro* drug release at the end of 10 min(%)	99.85	99.82	99.76	99.70
10.	Assay (Limit: 90 to110%)	99.87	99.82	99.75	99.72

***Physical appearance:** Pale orange, Uncoated, Round shaped tablets.

Table: 11 Stability Data of Bilastine mouth dissolving tablets Stored at40 ± 2°C/75% ± 5% RH (F-VII)

S. No.	Storage Conditions: 40 ± 2°C/75% ± 5% RH				
	Tests	**Initial Period**	**1st month**	**2nd month**	**3rd month**
1.	Physical appearance*	Complies	Complies	Complies	Complies
2.	Average weight (mg)	141.50	140.97	142.37	141.28
3.	Thickness (mm)	3.30	3.36	3.30	3.32
4.	Hardness (kg/cm^2)	3.00	3.00	3.00	3.00
5.	Friability (%)	0.15	0.20	0.19	0.23
6.	Disintegration test (sec)	12	12	10	08
7.	*In vitro* dispersion time (sec)	24	24	24	23
8.	Fineness of	Passed	Passed	Passed	Passed

	Dispersion				
9.	*In vitro* drug releaseat the end of 10 min (%)	99.85	99.76	99.70	99.60
10.	Assay (Limit: 90 to110%)	99.82	99.78	99.75	99.72

***Physical appearance:** Pale orange, Uncoated, Round shaped tablets

There were no significant changes in physical appearance, average weight, thickness, hardness, friability, disintegration test, in vitro dispersion test, uniformity of dispersion, dissolution, and assay after 3 months of storage at 25 2°C/60% 5% RH and 40 2°C/75% 5% RH. The formulation F-VII was shown to be stable even after 3 months of storage at 25 2°C/60% 5% RH and 40 2°C/75% 5% RH.

SUMMARY AND CONCLUSION

The current study aimed to develop Bilastine mouth dissolving tablets via direct compression employing three superdisintegrants: croscarmellose sodium, crospovidone, and sodium starch glycolate. The study attempted to avoid the inherent problems associated with traditional Bilastine pills, such as choking risk, harsh taste, and difficulty swallowing, by developing Bilastine mouth dissolving tablets tablets.

To accomplish quick oral disintegration of Bilastine, seven formulations were developed (three trials with mannitol anhydrous, three trials with sorbitol granular grade, and one experiment with both mannitol anhydrous and microcrystalline cellulose (MCC-112).

API preformulation studies were conducted, including organoleptic characteristics, solubility, compatibility studies, and FT-IR drug-excipient interaction studies.

Precompression characteristics such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were also determined for the produced mix.

Post compression parameters such as thickness, hardness, weight variation, friability, disintegration, wetting time and water absorption ratio, in vitro dispersion time, fineness of dispersion, assay, and in vitro drug release were examined in the produced tablets.

The following points can be summarised based on the experimental results:

- Bilastine exhibited equivalent colour, taste, and odour to the I.P specification in the preformulation research. According to the findings of the drug excipients compatibility study, the excipients chosen for the formulation were compatible with the API and suitable for formulation development.
- FT-IR spectrum analyses of pure drug and drug with excipients revealed no interaction between the drug and the excipients utilised in the formulation.
- The micromeritic property results show that the flow property of formulation F-I was fair, whereas the flow properties of the other formulations were excellent.
- The thickness of all formulations was uniform. The produced tablets also had adequate mechanical strength and hardness.
- The weight variation and friability tests were passed by all formulations of Bilastine mouth dissolving pills tablets.
- Bilastine mouth dissolving pill disintegration time was determined to be between 12 and 28 seconds. When compared to the other formulations, Formulation F-VII had the shortest disintegration time (12 seconds).
- Bilastine mouth dissolving tablets tablets had a wetting time of 45 to 102 seconds and a water absorption ratio of 79.25 to 92.17, respectively. Formulation F-VII, which used crospovidone as a superdisintegrant, had the shortest wetting time (45 seconds) and the highest water absorption ratio of all

formulations.

- In the in vitro dispersion time evaluation, formulation F-VII demonstrated a faster dispersion time (24 sec) than all other formulations.
- The fineness of dispersion test was passed by all formulations of Bilastine mouth dissolving pills.
- Bilastine tablet assay readings were determined to be within permissible ranges (98.82 to 99.87%).
- In an in vitro drug release research, formulation F-VII produced with crospovidone as a superdisintegrant demonstrated the highest drug release (99.85%) after 10 minutes.
- The order of dissolving rate augmentation with several superdisintegrants was discovered to be CP>CCS>SSG.
- According to the results, the formulation including crospovidone as a superdisintegrant demonstrated improved disintegration time, in vitro dispersion, wetting time, and in vitro drug release.
- As a result, formulation F-VII was chosen as the best formulation in terms of quick disintegration time, wetting time, in vitro dispersion, and drug release.
- A comparison study of the optimised formulation (F-VII) and the marketed product was conducted. At 10 minutes, the in vitro drug release of the optimised formulation (F-VII) was faster (99.85%) than the commercial version (82.52%). According to the findings, the formulation F-VII demonstrated faster drug release than the marketed version.
- The physical appearance, thickness, hardness, average weight, friability, disintegration, in vitro dispersion, fineness of dispersion, assay, and in vitro drug release of the optimised formulation (F-VII) showed no significant changes. The optimised formulation (F-VII) was shown to be stable even after 3 months of storage at 25 2°C/60% 5% RH and 40 2°C/75% 5% RH.

CONCLUSION

Based on the findings, the study concluded that mouth dissolving tablets of Bilastine could be successfully formulated using crospovidone as a superdisintegrant, which could be a promising formulation to effectively treat the symptoms of allergic disorders (e.g. rhinoconjunctivitis and urticaria) in adults, adolescents, and, more recently, children, thereby avoiding inherent drawbacks associated with conventional tablets such as risk of side effects.

Based on the findings, it was determined that the formulation F-VII, which contained crospovidone as a superdisintegrant as well as mannitol and microcrystalline cellulose as diluent, was superior to the other formulations and met the criteria for mouth dissolving tablets.

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