RESEARCH ARTICLE

Design, Development and Physicochemical Evaluation of Effervescent Tablets of Antihistamine Drug

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ABSTRACT

Purpose: Effervescent bilastine tablets were the focus of this investigation because of their ease of administration and the fact that some patients, especially younger ones or those with impaired swallowing abilities, have trouble ingesting oral dosage forms.

Methods: Using the wet granulation process, 20 mg of effervescent bilastine tablets were produced. Pre-compression properties assessed for powder blend and granule combination. Here are some post-compression properties of the tablets that were examined: friability, hardness, drug content, pH, dissolution time, content uniformity, water content, X-ray, and Differential scanning calorimetry (DSC). We also measured carbon dioxide content and effervescence duration. To get the greatest results, we looked for effervescent systems that dissolved quickly in water and had the right properties before and after compression.

Results: Based on their physicochemical properties, F2 formulations were determined to be best formulations, and the results demonstrated that the wet granulation process had greater flowability.

Conclusion: Sweeteners such as mannitol, sodium saccharine, methylparaben, and citric acid were chosen for this investigation, along with sodium bicarbonate. If you want to hide the bitter flavor of bilastine, sodium saccharine is your best bet. From a physicochemical and physical property standpoint, the wet granulation process outshines the alternatives.

Keywords: Wet granulation, Effervescent tablet, Bilastine, Flowability.

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INTRODUCTION

Despite many drawbacks, such as sluggish absorption and delayed beginning of action, oral administration forms of medications continue to be the most preferred methods. The stability of medications in liquid form is inadequate, and the transit times of slow-release dose forms through the digestive system are prolonged. Because of this, the forms' usefulness is restricted. Therefore, it appears that effervescent tablets are a suitable substitute for oral dosage formulae.[1]

To administer effervescent tablets, simply dissolve or scatter them in water.[2] Tartaric acid and citric acid initiate the CO_2 reaction when they come into contact with carbonates or bicarbonates of alkali metals in the presence of water. As a result, the capsule undergoes rapid internal disintegration when submerged in water. Carbonates, acids, or bicarbonates comprise the majority of effervescent tablets, which are uncoated.[3,4] Medications that are sensitive to stomach acidity or that cause stomach damage can benefit from certain items. Also, effervescent pills are an option for the regularly recommended high-dose medications.[5]

Effervescent tablets are preferable over tablets or capsules for people who have difficulty swallowing them because of their liquid state. However, it is common practice to dissolve one effervescent tablet in three to four ounces of water. Since effervescent goods are already dissolved in a buffer solution, they avoid coming into direct touch with the gastrointestinal (GI) tract.

One more perk of effervescent tablets is that the exact amount that the patient takes really makes it into their stomach. Effervescence reactions actually boost the absorption of active compounds by increasing their penetration into the paracellular route through the CO_2 that is generated.[6,7]

These items include carbon dioxide (CO_2)-releasing active components, acid/salt mixtures, and bicarbonate/carbonate salts. Additional ingredients in effervescent tablets include binders, sweeteners, flavors, fillers, and lubricants.[3] Lubricants that dissolve in water are used to keep the tablet from sticking to the device and to keep insoluble scum from forming on water's surface. In addition, these formulations cannot be made without sweeteners.[8]

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To make tablet, a number of techniques are used, such as the fusion method, direct compression, fluid-bed granulation, and wet granulation. The production of effervescent pills relies heavily on controlled environmental factors. To avoid granulation or tablet adherence to machinery due to absorbed moisture, it is crucial to maintain a moderate temperature (25°C) and relative humidity (RH) of 25% or below in manufacturing locations for these products.[2,5] At the moment, aspirin tablets are the most popular kind of effervescent pill.[9] With its poor solubility and high permeability, bilastine is a medication of the Biopharmaceutical classification system (BCS) class II. Recent FDA approval has been granted to a second-generation H1-antihistamine for the treatment of symptoms related to allergic rhinitis (AR) and chronic urticaria (CU).[9] It is insoluble in water so solubility of bilastine is improved by the effervescent reaction which generate CO_2 gas and forms a clear solution in water. Three superdisintegrant i.e. povidone, PVP K90, and sodium starch glycolate are used to rapid breakdown of tablet and facilitate the faster dissolution of active ingredients. Effervescent tablets produce quicker action for the treatment of allergic patients. Effervescent tablets are more convenient for unconscious patients and also helpful in emergency conditions.[10]

The intention of this investigation was to design and evaluate bilastine effervescent tablets from a physicochemical standpoint. Bilastine effervescent tablets are a more efficacious and rapidly acting option for managing the symptoms associated with allergic rhinoconjunctivitis and other forms of allergic rhinitis. Rashes on the skin, such as wheals or urticaria, can also be soothed with its application. We do not currently have 20 mg effervescent tablets of bilastine in stock. The formulations developed for this study have the same desirable qualities as other effervescent tablets, including an appropriate weight and flavor. This study's effervescent pills are cost-effective for pharmaceutical companies because their weight is approximately half that of other effervescent tablets.[11]

The improved flavor and palatability of effervescent tablets make them a better choice for children. Because of the product's effervescent appearance, ease of use, and attractive colors and flavors, patients are more likely to take the medicine as prescribed.[12,13]

MATERIALS AND METHODS

Chemicals

Saraca (India) supplied the medications, which included bilastine. Loba Chemie Pvt. Ltd. (India) provided the following: sodium saccharin, mannitol, povidone k-90 (PVP), sodium starch glycolate, povidone k-30 (PVP), sodium bicarbonate, methylparaben, and citric acid.

Spectrophotometric Analysis

A standard 100 µg/mL drug solution was divided into several 10 mL volumetric flasks using aliquots ranging from 1.0 to 7.0 mL. Once the flasks were filled, enough 0.1N HCl (pH 1.2) was added. Using a Shimadzu UV-1800 model, the drug absorbance at 281.5 nm was measured to calculate the quantity of bilastine.

Determination of Effervescent Components

Based on the acid-alkali neutralization and the permitted amounts of each component, the effervescent components and their ratios were established. After that, bilastine was added to all the ingredients. Subsequently, we looked into how citric acid and sodium bicarbonate affected solubility, effervescence duration, and pH. Because sweets are required due to the bitter taste of bilastine. As an ingredient in the recipe, sodium saccharine serves as a sweetener (Table 1).

Assessment of powders and granules

The compressibility index, angle of repose, and Hausner's ratio determined the main flowability properties of powders and granules before compression.

Angle of repose (θ)

Loose powder or granules' frictional forces can be calculated using the repose angle. The powder angle is the highest possible angle formed between the surface of the grains or powder and the horizontal plane. A precisely positioned funnel was permitted to convey the grains through a height-controlled system. The produced granule heap's height (h) and radius (r) were then measured, and the method was used to find the angle of repose (θ).

$$\text{Tan } \theta = (h/r).^{12,15}$$

Compressibility index

One way to assess the powder's flowability is to compare its bulk (ρb), tapped density (ρt), and packing down rate. The compressibility index % was determined via

Tapped Density-Bulk Density/ Tapped Density X 100

Hausner's ratio

An essential parameter for determining the flow behavior of granules and powders is Hausner's ratio. This can be determined using this formula: ρt/ρb.

Direct compression method for preparation of effervescent tablets

In 500 mg effervescent tablet of bilastine are prepared by wet granulation method by using a Jaguar JMD 4-8 tablet press with shallow convex shape (12 mm diameter). There are three steps to the wet granulation process: dry mixing and granulation, lubrication of granules, and pressing of granules that have been lubricated. They were finally put in boxes.[14-18]

Step 1. All ingredients pass through mesh no.60.

Step 2. Preparation of blend A

Mix citric acid and sodium bicarbonate

Add PVP K30 and water solution dropwise

Make a blend and pass through sieve no.20 and dry

Step 3. Preparation of blend B

Mix bilastine, (Superdisintegrant) PVP K30/PVP K90/ sodium starch glycolate, mannitol, methylparaben, sodium sachharin

Make a blend

Table 1: Composition of effervescent materials ratio-based determination of effervescent components

Code	*Citric Acid (mg)*	*Sodium Bicarbonate (mg)*	*Effervescent Time (S)*	*Solubility**	*pH*
P1	50	250	55 ± 2.08	2	5.35 ± 0.01
P2	60	240	50 ± 3.21	3	6.30 ± 0.1
P3	70	230	67 ± 1.53	2	6.11 ± 0.07
P4	80	220	73 ± 3.51	4	6.74 ± 0.04
P5	90	210	75 ± 1.83	3	6.47 ± 0.03
P6	100	200	67 ± 1	4	6.13 ± 0.02
P7	110	190	80 ± 2.08	3	5.59 ± 0.07
P8	120	180	77 ± 2	2	6.23 ± 0.09
P9	130	170	65 ± 2.31	3	6.73 ± 0.04
P10	140	160	60 ± 2.50	3	6.75 ± 0.06

*Solubility of formulations using a standard table (5=freely soluble,4=soluble; 3=sparingly soluble;2=slightly soluble; 1 = insoluble;)

Step 4. Mix blend A and B.

Step 5. Compressed the tablet into tablet compression machine.

Physicochemical Evaluation of Tablets

To assess the tablets, the following physicochemical tests were carried out.

Weight variation

A sample of twenty tablets was chosen at random, each of which was weighed separately, and the results were compared with the computed mean weight. Using this procedure, the variance of up to two pills should not be more than the ± 5% of weight allowed by the pharmacopeia.[19]

Friability test

The Roche friability (Electrolab EF-2W) was used to determine the tablet's friability. This apparatus rotates at a speed of 25 rpm, plunging a tablet six inches below the surface with each rotation, thereby subjecting it to the combined effects of shock and abrasion. A pre-weighed sample of tablets was fed through 100 revolutions in the friability. The formula provides the friability.

Friability (%) = W initial – W final / W initial × 100

Required friability was estimated was below 1%.

Thickness

Using a vernier caliper (For-Bro Engineers, India), the thickness of ten randomly chosen tablets was measured.

Hardness test

The hardness or crushing strength of a tablet is amount of force needed to break it down in a compression. Ten randomly chosen tablets were used in this investigation, and each tablet's hardness was measured in kilograms per square centimeter using a hardness tester (Monsanto, Germany).[20]

CO_2 content

In three different beakers, 100 mL of solution 1N sulfuric acid was added to three tablets. The difference between the weight of the tablets before and after dissolving them was computed to establish the amount of emitted CO_2 (mg).[20]

pH

A pH meter (Metrohm, 632, Switzerland) was used to determine the solution's pH by dissolving three tablets in three beakers with 200 mL of water each.[21]

Effervescence time

A clock was used to time how long the tablets bubbled after they were put in three beakers of water. The point at which a clear answer was reached was called "effervescence time."[22]

Assay

After weighing twenty tablets, they were finely pulverized into a powder. With a scale, the right amount of powder (200 mg) was weighed out and mixed with 70 mL of pure water in a 100 mL volumetric flask. It was mixed and shaken for twenty minutes. The flask was then filled with clean water. A Whatman no. 42 filter paper was used to filter the solution after it had been mixed well. The first 10 mL of the liquid was thrown away. After that, titrimetry was used to look at an appropriate aliquot. The filtrate, which was equal to 2 mg/mL, was diluted enough to make a 100 εg/mL solution that can be studied using spectrophotometry.[23]

Content uniformity

After randomly picking 10 tablets, contents of each one were found individually.

Water content

A desiccator with silica gel was used to dry ten tablets for four hours. The amount of water in the sample was found by

Tablet weight before drying – Tablet weight after drying / Tablet weight before drying X 100

Disintegration time

Tablets were placed in each of 6 tubes of disintegration apparatus (Electrolab ED-2ASAPO). Use water as immersion fluid, temperature 25 ± 2 was taken. Complete disintegration was noted, if tablet take more than 5 minutes to disintegration if fails the test.

In-vitro %drug release

We did *in-vitro* dissolution tests in an Electrolab EDT-08LX type 2 (paddle) USP dissolving test apparatus. The temperature was kept at 37 ± 0.5ºC and 900 mL of the dissolution medium (0.1N HCl) was put in a tube with a lid. The paddle was set to 50 rpm. Once every minute, samples were taken. One mL of the breakdown medium was taken out of each sample and added back to it at a temperature of 37 ± 0.5°C. Spectrometry was used to look at the sample that was taken. The absorption was written down, and the drug release percentage was found.[24]

Differential scanning calorimetry

In thermal analysis, differential scanning calorimetry (DSC) is a useful instrument for tracking the temperature-dependent changes in a sample's physical properties. DSC instruments were used to analyze the optimized batch. We put samples

(1–3 mg) in crucible aluminum pans and used a DSC to heat them from 30 to 270°C at a rate of 10°C/min. N2 was used as a purge gas, and 50 mL per minute of flow was used.[25]

X - X - ray biffraction

XRD are generally used for investigating the internal structures and crystal structures of samples. Optimized batch were analyzed by using XRD instrument. Powder X-ray diffractograms were acquired through the utilization of a Shimadzu XRD 6000 diffractometer, which was outfitted with a graphite monochromator and an iron tube. The scans were done at a speed of 2Ø/min and between 5 and 70°C.

RESULTS

When we looked at standard curves of bilastine in 0.1N hydrochloric acid, we found that y=0.0217x–0.0284 and that relationship R^2 = 0.9988. Lastly, some of the formulations were made by measuring effervescent parts, and Table 1 shows ten formulas. Formulas with the best pH, solubility, and effervescence time were chosen. Formulations that bubbled for more than three minutes or formed sludge were thrown out. The P1–P10 versions had different amounts of citric acid and $NaHCO_3$. By changing ratio of effervescent parts, the materials changed how well they mixed and how acidic they were. The P6 formulation was chosen as the best base procedure for the tableting process.

Table 2: Compositions of tablets

Ingredients (mg)	*Formulations*					
	F1	*F2*	*F3*	*F4*	*F5*	*F6*
Bilastine	20	20	20	20	20	20
Citric acid	100	100	100	100	100	100
Sodium bicarbonate	200	200	200	200	200	200
PVP K30	25	-	-	12.5	-	-
PVP K90	-	25	-	-	12.5	-
Sodium starch glycolate	-	-	40	-	-	-
Mannitol	147.5	147.5	132.5	160	160	152.5
Methyl paraben	2.5	2.5	2.5	2.5	2.5	2.5
SodiumSaccharine	5	5	5	5	5	5

Table 3: Assessment of the physical properties of the powder/granule mixture in 500 mg tablets

Physical characteristics	*Formulations*					
	F1	*F2*	*F3*	*F4*	*F5*	*F6*
Bul density ($gmcm^3$)	0.55	0.52	0.55	0.58	0.54	0.50
Tapped density (gm/cm^3)	0.63	0.60	0.71	0.65	0.62	0.59
Hausner's ratio	1.14	1.15	1.27	1.12	1.14	1.18
Carr's index (%)	14.5	13.3	8.5	12	14.8	18
Angle of repose (^{0})	29.67	30.45	35.36	33.51	32.71	37.12

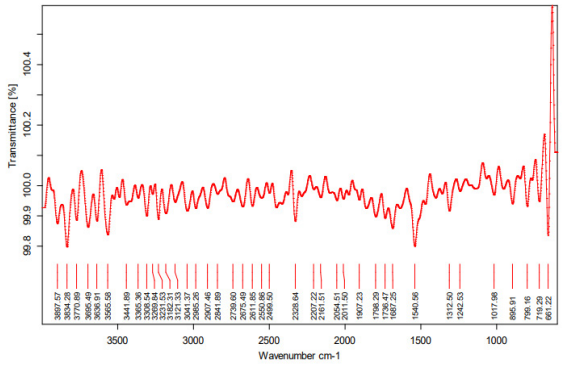

Figure 1: Infrared spectra of bilastine

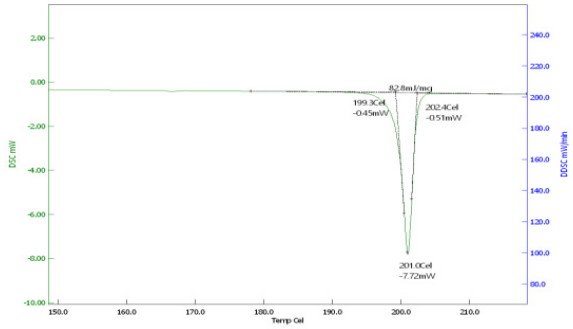

Figure 2: DSC of bilastine

Table 4: Physicochemical evaluation of 500 mg bilastine tablets (Mean ± SD).

Physicochemical evaluation	*Formulations*					
	F1	*F2*	*F3*	*F4*	*F5*	*F6*
Weight variation (%)	491 ± 5.0	495 ± 7.0	492 ± 6.0	492.5 ± 6.5	493.5 ± 5.5	496 ± 7.0
Friability test (%)	0.91	0.95	0.92	0.91	0.93	0.90
Thickness (mm)	4.15 ± 0.005	4.12 ± 0.005	4.16 ± 0.005	4.14 ± 0.005	4.17 ± 0.01	4.12 ± 0.005
Hardness (kg/cm^2)	4.3 ± 0.05	4.5 ± 0.05	4.4 ± 0.05	4 ± 0.11	4.5 ± 0.05	4.6 ± 0.05
pH	6.8 ± 0.04	6.7 ± 0.04	6.7 ± 0.04	6.8 ± 0.04	6.8 ± 0.04	6.7 ± 0.04
Effervescence time (min)	3.35 ± 0.02	3.29+ ± 0.04	1.25 ± 0.08	3.40 ± 0.01	3.42 ± 0.01	1.36 ± 0.01
CO_2 content (mg)	439 ± 1	460 ± 0.58	444 ± 1.53	445 ± 1.16	443 ± 0.58	450 ± 1.15
Assay (mg)	21 ± 0.02	20.3 ± 0.05	21.4 ± 0.04	24.7 ± 0.02	22 ± 0.01	25 ± 0.04
Content uniformity (%)	95.3 ± 3.45	97.1 ± 3.13	89 ± 3.91	91.3 ± 3.95	94.1 ± 2.94	87.3 ± 4.02
Water content (%w/w)	0.21 ± 0.006	0.20 ± 0.012	0.27 ± 0.006	0.24 ± 0.007	0.22 ± 0.008	0.24 ± 0.010
Disintegration time (min)	4.30 ± 0.36	4.10 ± 0.37	2.96 ± 0.12	4.15 ± 0.37	4.00 ± 0.15	2.96 ± 0.50

Table 5: Interpretation of FTIR spectrum of bilastine

Functional groups	*Wavelength (cm^{-1})*
N-H	3441.8
=C-H	3041.3
C-H	2907.4
O-H	2675.4
C=N	2207.2
C=C	1540.5
C=O	1736.4
C-H	799.1

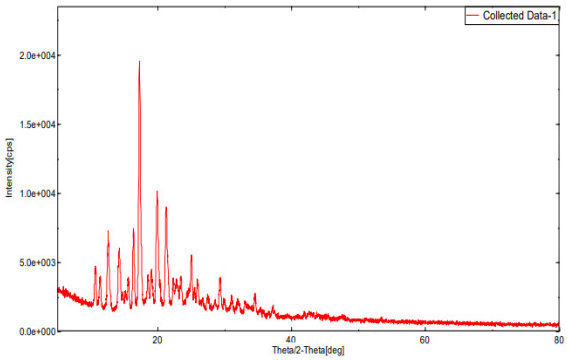

Figure 3: XRD of bilastine

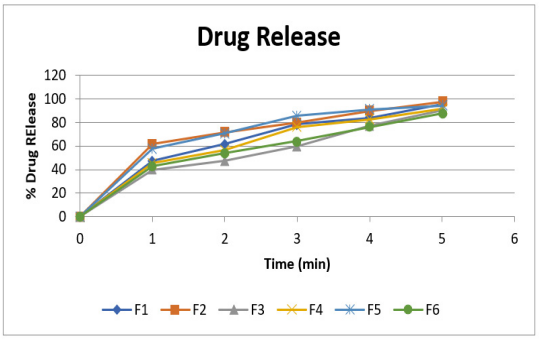

Figure 4: *In-vitro* drug release profile

Six 500 mg tablet formulations were determined to be the best based on the earlier stages. (Table 2).

Assessment of Powders Blend and Granules

Table 3 presents evaluation results for granular and powder blend formulations. Results were compared to those found in standard tables.

Physicochemical Evaluation

By using the wet granulation process, tablets were made. Every one of the physicochemical tests was administered to them. The designed effervescent pills fulfilled the pharmacopeia weight requirements. On entire tablets, physicochemical tests were carried out (Table 4). The weight fluctuation test results for all tablets were within the ± 5% pharmacopeia limitations. The entire formulations' drug content was estimated to be between 85 and 115%.

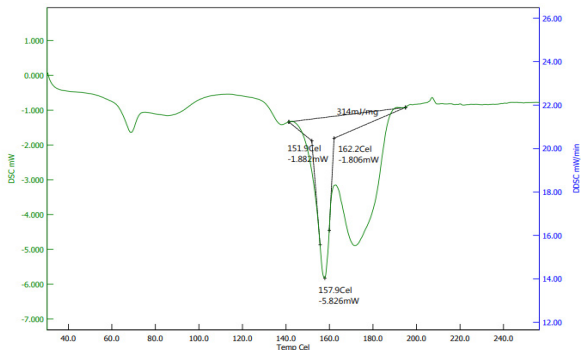

Figure 5: DSC of optimized formulation batch F2

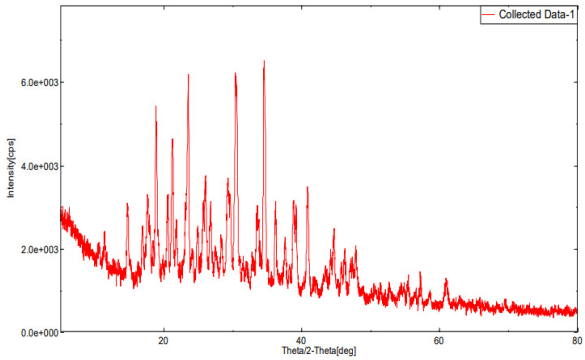

Figure 6: XRD of optimized formulation batch F2

Every formulation was found to have less than 1% friability. A hardness tester was used to measure tablets' hardness. Results fell between 4 and 5 kg/cm^2. The tablets ranged in thickness from 3 to 6 mm. In 200 mL of water were used for the effervescence test. Every formulation had an effervescence period of less than five minutes. In essence, effervescent substances absorb a large amount of moisture. Every formulation had less than 0.5% water content. Formulations should have a pH between 5.5 and 6.9; otherwise, sediment formation and lack of stability may make them unsuitable.

DISCUSSION

Standard tablets and capsules are two examples of oral drug dosage types. They are made to be swallowed or chewed. A lot of the time, kids and older people have trouble taking these dosage forms. These kinds of problems are worse for people who are stuck in bed. It would be nice to have effervescent types of medicines, but 500 mg bilastine is not available in this form. Previous studies have shown that it helps patients tolerate the medicine better and speeds up their recovery, so we chose to make and study the 500 mg effervescent bilastine tablets. A UV spectrophotometer with a maximum wavelength of 281.5 nm was used to draw the standard curve of bilastine in clean water. The outcomes of this were similar to those of the other studies. Acids and bases were used in all formulations because the effervescent reaction in effervescent goods needs them. The pH of the fluid, how well it dissolved, and how long it bubbled was then checked. We used an FTIR spectrometer

to record the IR spectrum of a pure sample of bilastine (Table 5, Figure 1). This spectrum was then compared to the normal functional group frequencies of bilastine. The DSC study of bilastine showed endothermic peaks at 201.0°C, which is close to the melting point listed in the standards (Figure 2). This meant that the drug was in its pure form. The XRD pattern of the pure drug showed strong peaks, which showed that bilastine is a crystal (Figure 3). The diffractograms were made to look at how crystallized the bilastine was. Its diffractograms showed sharp peaks at 12.56, 14.21, 15.56, 16.35, 17.22, 19.84, 21.19, 25.00, and 29.27 degrees.

The extremely bitter flavor of bilastine is a big issue for patients, as previously stated. Consequently, sweeteners were added to enhance the finished product's taste and boost patient acceptance. As a result, at this point, a combination of sweeteners was employed as none of the single sweeteners could hide the off flavor. There was a comparison between the USP tables and each of the physical attributes that are stated in Table 3. Most of the formulations worked well with this method's flowability. The increased compressibility of the granules was a result of their inherent porosity. Because smaller particles adhere and larger ones develop, mean diameter of particles is bigger than an average diameter of particles in dry granulation process. Particle size was greater in the effervescent granules mixture than in the effervescent powders alone. Weight variation, hardness, and friability were all within the limitations set by the pharmacopeia for most formulations.

All formulas have a reduced CO_2 content. These variations can be observed in the way the granules are made. Similar to these findings, another study found that the CO_2 level of citric acid and $NaHCO_3$ formulations was 492 mg per gram. A reduced concentration of CO_2 was achieved with formulation F1. It is recommended that formulas maintain a pH between 6.6 and 6.8. Every single formulation fell inside the range specified in BP for effervescence durations, which were all shorter than 5 minutes. Within 1–4 minutes, all of the formulations demonstrated effervescence. Last but not least, a typical range of 87 to 97% for 500 mg tablets' drug content was determined. All of the formulations' drug content fell within the USP-specified range. All six formulations were tested for dissolving. The release of drug was largely depends on the disintegration time. This is, the faster the disintegration of tablets, better the release. Formulation containing PVP K90 as superdisintegrant shows the release 97.5% of drug in 5 minutes (Figure 4).

Results from the DSC of optimized batch F2 formulation indicated endothermic peaks at 157.9ºC, which is close to the melting point of specified standards (Figure 5). This led to the conclusion that the improved batch formulation was in its pure form. The diffractograms of the optimized batch F2 showed peak at angle of 14.75, 18.82, 21.22, 23.51, 26.03, 30.45, 34.49, 34.66, 38.77, 40.81. Drug peaks in the improved formulation's diffractograms were less intense, suggesting that the drug's crystallinity had decreased (Figure 6). Bilastine's amorphous characteristics, as suggested by the broadened peaks in the optimized formulation, could potentially account for its improved solubility and dissolution.

CONCLUSION

Effervescent bilastine tablets were prepared by wet granulation method and treatment of allergic rhinitis (AR) and chronic urticaria. Bilastine effervescent tablet showcased its potential as a promising dosage form that could enhance the therapeutic experience for patients suffering from allergic conditions. The improved drug release profile, coupled with the convenience of administration, could lead to increased patient adherence to treatment regimens and, consequently, better clinical outcomes. The best formulations were chosen based on the results received at each stage of formulation. Selected sweeteners included citric acid, sodium bicarbonate, mannitol, and sodium saccharine following the necessary investigations. The ready-made pills were put through tests before and after compression. sodium saccharine works better than other sweeteners to cover up bilastine's bitter flavor. Because of their physicochemical properties, the F2 formulation of 500 mg pills was finally chosen as the best formulation. Formulation batch was selected as optimized batch as it shows better flowability of granules, hardness, thickness and friability, pH, 97.5% drug release in 3 minute which contains PVP K90 as superdisintegrant and formed clear solution.

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