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Use of bi-layer tablet technology to formulate dual-release dosage form of extended-release Montelukast and immediate-release Bilastine

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Abstract

Bilayer tablets containing Montelukast sodium, a bronchodilator, and Bilastine, an antihistamine, were formulated and assessed for pharmaceutical parameters. Twelve immediate-release Bilastine formulations, seven controlled-release Montelukast sodium formulations, and fourteen bilayer formulations were prepared. Stability studies employing FTIR, TGA, and SEM validated compatibility with excipients. Bilastine granules demonstrated bulk and tapped densities ranging from 0.33 to 0.38 g/mL and 0.429 to 0.488 g/mL, respectively. Carr's index, Hausner ratio, and angle of repose suggested favorable flowability. All tablets met the weight variation criteria (<7.5%); however, Montelukast (M1, M2) exhibited hardness levels below 5 kg/cm², and the bilayer tablets demonstrated variability in hardness. Bilastine disintegrated in less than 3 minutes, whereas Montelukast required 15 to 60 minutes for disintegration. In dissolution tests, the B1-B3 Bilastine formulations demonstrated the highest release after 60 minutes, while the M6-M7 Montelukast formulations released over 60% within 6 hours. Six bilayer formulations; B2+M6, B2+M7, B3+M3, B3+M6, B3+M6, and B3+M7 exhibited optimal release for both active pharmaceutical ingredients (APIs), indicating that Montelukast sodium and Bilastine can be effectively formulated into bilayer tablets with satisfactory release profiles.

Keywords: Bilayer tablet; Montelukast; Bilastine; Immediate release; Sustained release

Introduction

Medicines are prepared in highly intricate ways to facilitate the delivery of active pharmaceutical ingredients (APIs) at the site of action. The API is distributed in the dosage form in a way that ensures minimal loss and the highest possible absorption of API in the systemic circulation (Adepu and Ramakrishna, 2021). Tablets are the most widely used among the solid oral dosages. Though it has multiple categories and types, the immediate release and the controlled release forms of the tablets are the most abundantly marketed drugs. The therapeutic design of these types of formulations is usually linked to the bioavailability of those drugs. The manipulation of formulations is done by using various excipients with specific functions (Bhalani *et al.* 2022). Administration of more than one drug to achieve a therapeutic goal is a common phenomenon. To treat a disease condition or a number of disease conditions at a single time, there may be

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a need for the administration of more than one drug (Kadam *et al.* 2019). However, the co-administration of individual drugs every time will increase costs and incompatibilities. Monotherapy has some more problems associated with pharmacodynamics, such as risky side effects, complicated treatment regimens, growth of resistance in the patients towards the monotherapy, and so on (Morales, 2013; Nasr Esfahani *et al.* 2019). Besides, a study design also found a better treatment strategy in combination therapy compared to monotherapy. As combination therapy is a matter of choice nowadays, scientists have prepared a single solid dosage form in which a tablet containing two different medicines side by side—one side is comprised of immediate and the other side is comprised of controlled-release tablets—is designated as a bilayer tablet (Deepika Gupta, 2023). Thus, the bilayer form of the tablet enhances patient compliance and convenience.

Allergic rhinitis (AR) is often related with conjunctivitis. It is defined as a symptomatic disorder of the nose. The major characteristics are itching, nasal discharge, sneezing, and nasal airway obstruction prompted by an IgE-mediated immune response due to allergen exposure. AR affects 10% to 40% of the population (Miraglia Del Giudice *et al.* 2020). Usually, AR is parallelly expressed with urticaria while affecting. A second-generation antihistamine of the non-sedative class is the drug of choice for this type of patient. Bilastine, a second-generation antihistamine, is a better drug among these classes due to its absence of sedative effects, unaffecting nature on nerves, as well as longer duration of action in the body (Ridolo *et al.* 2015). It is available in the market as immediate-release tablets and syrup. Adults and teenagers aged 12 and older are prescribed 20 mg per day of oral Bilastine, whereas children aged 6 to 12 are given 10 mg of oral Bilastine once daily. These antihistamines are the H1 receptor antagonists that inhibit the agonistic activity of the histamine, which is released on the allergen attack. Due to its faster onset of action, Bilastine is prescribed to a significant number of the AR and urticaria patients (Leceta *et al.* 2021). Additionally, the allergic reactions associated with AR and urticaria can be a bit more problematic when the allergen is introduced into the airways and is detected by the immunocytes. The immunocytes then release the cysteinyl leukotrienes (CystLTs), which is an arachidonic acid derivative (Peters-Golden *et al.* 2006). The leukotrienes are responsible for airway congestion as well as many other effects, including smooth muscle contractions, proliferation of airway smooth muscles, mucus secretion, apoptosis of eosinophils, edema or leakage in blood vessels, epithelial hypertrophy, etc. There are two types of receptors of cysteinyl leukotrienes (CystLT1 and CystLT2); among them, CystLT1 is associated with most of the pathologic conditions producing LTD4, LTC4, and LTE (Jo-Watanabe *et al.* 2019). Montelukast, a selective CystLT1 antagonist, is a popular drug of choice for chronic allergic rhinitis and urticaria patients. Montelukast, with lesser side effects, is a better drug in the case of episodic or multiple-triggered wheezing, asthma exacerbation, and persistent apnea due to contraction of the airways (Lee and Kim, 2020).

Allergic rhinitis and urticaria are linked to the histamine production as well as the production of 5-hydroperoxyeicosatetraenoic acid (a precursor of leukotriene) (Marques *et al.* 2022). The allergen attack in the histamine receptor and cysteinyl leukotriene receptors happens simultaneously, and thus the co-administration of Bilastine and Montelukast sodium is required for the treatment of both allergic attacks and the consequential effects of bronchospasm as well as mucus secretion. In the study, a bilayer tablet consisting of Bilastine immediate-release and Montelukast sodium sustained-release formula was formulated, and their characteristics were evaluated with the help of appropriate measurements.

Materials and methods

Raw material sourcing

APIs (Bilastine and Montelukast sodium) were purchased from local vendor. Sodium Starch Glycolate (NaSG), Cross Carmellose Sodium and Avicel 101 (MCC), Cross Povidone, Hypermellose, Mannitol, Starch, Ethyl Cellulose, Hydroxy Propyl Cellulose, Methocel K4M, Magnesium Stearate Colloidal Silica was purchased from local vendor. All the chemicals were of analytical grade.

Instruments

ELECTROLAB EF-2 Friabilator (USP) machine (Electrolab, India), Killian tablet compression machine (ROMACO), ELECTROLAB ED-2L disintegration tester apparatus (Electrolab, India), PerkinElmer Spectrum Two Fourier Transform Infrared (FTIR) spectrophotometer (PerkinElmer, USA), the Electrolab Inspire 8 dissolution testing machine (Electrolab, India), and PerkinElmer Thermogravimetric Analyzer TGA 8000 (PerkinElmer, USA) were used throughout the experimentation for respective analysis.

Evaluation of the prepared formulas

Pre-formulation studies of the blended powder portion

The pre-compression parameters of the formulation mixture were assessed before the compression process. Various tests were conducted to evaluate the powder blends, with each test performed on every batch of granules prepared. Bulk density, Carr's compressibility index, angle of repose, tapped density, Hausner's ratio, all of these parameters of the Bilastine and Montelukast sodium powder were calculated using the associated formula (Beakawi Al-Hashemi and Baghabra Al-Amoudi, 2018).

Characterization and compatibility testing of both immediate release (IR) and sustained release (SR) granules

To examine the interactions among the formulation's various components, the formulations were placed in separate vials, ensuring that each was isolated. The study also considered the usual mixtures. Samples were kept at a constant temperature of 25°C with relative humidity levels between 30% and 65% (Waterman, 2011). These samples were incubated under three conditions: room temperature (25 °C± 2 °C and 60% ± 5% RH), accelerated conditions (40 °C± 2 °C and 75% ± 5% RH), and dry heat (50 °C) for one month. For the accelerated condition samples, the LDPE plugs were punctured.

Drug-excipient activity and interaction studies using FTIR

The compatibility between the drugs and their respective excipients was assessed using FTIR spectroscopy. Each drug, Bilastine, and Montelukast sodium underwent 24 scans at a resolution of 4 cm^{-1} across the 4000–650 cm^{-1} range. The resulting spectra were analyzed for the key peaks of the drugs, any shifts or masking of these peaks, and the appearance of new peaks indicated interactions with polymers.

Drug-excipient activity and interaction studies using TGA

The TGA curves were obtained with a PerkinElmer Thermogravimetric Analyzer TGA 8000. Using a platinum pan, approximately 6.966 mg of sample was heated from 30 to 800°C at 20°C min^{-1} and kept on 800°C for 3 minutes. Then the temperature in again decreased from 800°C to 50°C at a rate of 40°C min^{-1} under the nitrogen flow at 20.0 ml/min. The equipment was calibrated beforehand with a standard reference of calcium oxalate.

Drug-excipient activity and interaction studies using SEM

The SEM technique was used in this study to inspect the surface condition of the formulated samples. The morphology of the excipients' treated formulation was screened by Field Emission Scanning Electron Microscope (Model: JSM 7610F, JEOL, Japan) at a 15-kV accelerating potential in BCSIR, Dhaka, Bangladesh. Dried samples were set at the specimen stub with the help of epoxy glue or sticky tape capable of transmitting electrical flow. The specimens were vacuum-coated in an argon atmosphere with gold before the test procedure.

Formulation development of the immediate-release Bilastine tablets

A total of twelve formulations (B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11, and B12) were prepared using five different disintegrants of various amounts (Table I). Those were sodium starch glycolate, croscarmellose sodium, cross-povidone, hypermellose, and starch. In every case, the disintegrants are used in various quantities, and the total amount was adjusted by a microcrystalline cellulose binder (Avicel 101). The other excipients used in this formulation are filler, API (Bilastine), lubricant, and glidant. Wet granulation was used to form the tablets. The materials were first put through a weighing procedure. In a mortar, the material Avicel 101 was placed. By using a pestle and a few drops of water, the Avicel 101 was triturated into mucilage. The components that weren't lubricant and glideant were then blended. A 40-mesh screen was used to filter the resulting slurry. The amalgamation was then dried at 30 and 45°C Celsius until the loss on drying (LOD) level dropped to around 5%. After mixing the lubricant and glidant, the mixture was sieved through a 30-mesh sieve (Shanmugam, 2017).

Formulation preparation of the sustained-release Montelukast sodium tablets

A total of seven formulations (M1, M2, M3, M4, M5, M6, M7) were prepared using different combinations of release retardants such as Croscarmellose Sodium, Hypromellose, Polyvinyl pyrrolidone, Methocel K4M, Hydroxypropyl Cellulose, and ethyl cellulose in various combinations (Table II). The total amount is adjusted by a microcrystalline cellulose binder (Avicel 101). The other excipients used in the formulations are API, lubricant, and glidant. A wet granulation technique was again used to form sustained-release Montelukast sodium tablets.

Table I. Formulations of Bilastine immediate-release tablets

Ingredients	Justification	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12
Bilastine	API	20	20	20	20	20	20	20	20	20	20	20	20
sodium starch glycolate	Disintegrating agent	2	4	6									
croscarmellose sodium	Disintegrating agent				2	5							
cross povidone	Disintegrating agent						2	4	6				
hypermellose	Disintegrating agent									2	4		
starch	Disintegrating agent											6	8
Mannitol	Filler	30	30	30	30	30	30	30	30	30	30	30	30
Avicel 101 (MCC)	Binder	38	36	34	38	35	38	36	32	38	36	34	32
Magnesium stearate	Lubricant	5	5	5	5	5	5	5	5	5	5	5	5
Colloidal silica	Glidant	5	5	5	5	5	5	5	5	5	5	5	5
Total		100	100	100	100	100	100	100	100	100	100	100	100

Compression of tablets

Using a single punch compression machine, the tablets were compressed. The Bilastine and Montelukast sodium tablets were kept at a hardness range of 4–8 kg and 10–20 kg, respectively, with a fill weight of 100 mg and 100 mg, respectively. The tablets were circular and had a smooth surface that showed no signs of cracks or discontinuities.

Table II. Formulations of Montelukast sodium sustained release tablets

Ingredients	Justification	M1	M2	M3	M4	M5	M6	M7
Montelukast sodium	API	10	10	10	10	10	10	10
Hypromellose	Release retardant	20	30	20	25	15		5
Croscarmellose sodium	Release retardant	20	10	5	5	10		
PVP	Polymer			3	3	3		
Ethylcellulose	Release retardant							30
Hydroxypropyl cellulose	Release retardant							18
Methocel K4M	Release retardant						50	
Avicel 101 (MCC)	Filler	46	44	56	51	56	38	35
Magnesium Stearate	Lubricant	2	3	3	3	3	1	1
Colloidal silica	Glidant	2	3	3	3	3	1	1
Total:		100	100	100	100	100	100	100

Bilayer tablets preparation

From all the Bilastine formulations, the pre-compression evaluation and the post-compression evaluation results indicate that the B2 and B3 formulas were the most optimized formulas as immediate release dosage forms. On the other hand, the results from the pre- and post-compression evaluation of Montelukast sodium formulations indicate that all of them exhibited sustained release dosage form. The bilayer formula was designed in a way that both the immediate and sustained release dosage forms were compressed side by side. So, by combining the best formulas of the immediate and sustained release formulas, there are a total fourteen formulations.

Post compression evaluation

Following the granules' compression into tablets for immediate release Bilastine tablets, sustained release Montelukast sodium tablets, and bi-layered tablets, these experiments were carried out. Diameter, weight variation, hardness, and friability of the prepared tablets were recoded following appropriate measures.

In-vitro disintegration time determination

The disintegration test was performed with the Basket-Rack Assembly technique and the Disintegration Tester (Erweka, Germany) as the test instrument. The basket rack assembly consisted of six glass tubes, with a 10-mesh sieve at the bottom. The medium, which was kept at 37°C and contained distilled water, saw the basket hoisted and lowered 30 times per minute. Six tablets were inserted in each tube to measure the average disintegration time, and the time it took for the tablet to dissolve without leaving any attractive mass in the device was recorded (Zheng *et al.* 2022).

Preparation of the standard curves

To make a stock solution of Bilastine pure powder, 20 mg of the drug was dissolved in 100 ml of phosphate buffer (pH 6.8). To create a 100-mL mother solution (100µg/ml), mix 50 mL of the solution with 50 mL of phosphate buffer. A volume of 10 mL was extracted and diluted with 100 mL of phosphate buffer solution to achieve a final concentration of 10 µg/mL. The aforementioned solution was further diluted using phosphate buffer to create a series of dilutions. The solution contains various quantities of Bilastine, including 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, and 10 µg/ml. The absorbance of the aforementioned dilutions was measured at a wavelength of 283 nm using a UV spectrophotometer, with phosphate buffer providing the blank solution, and a standard was constructed accordingly (Fig. 1). Similarly, a standard curve for Montelukast sodium was obtained by measuring absorbance values at 287.3 nm wavelength in a UV spectrophotometer of the diluted preparations of Montelukast sodium mother solution (Fig. 1).

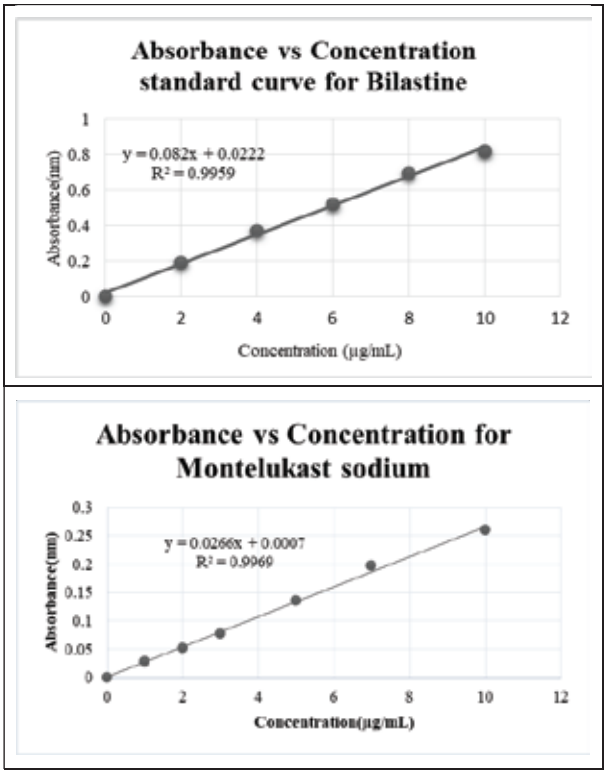

Fig. 1. Calibration curve data of Bilastine in phosphate buffer of pH 6.8 and Calibration curve data of Montelukast Sodium in phosphate buffer of pH 6.8

Dissolution testing

In vitro dissolving studies of the formulated Bilastine immediate-release (IR) tablets were executed using USP class II equipment at 37°C and 50 revolutions per minute (rpm). The dissolving medium was 900 milliliters of 0.1 N hydrochloric acid (HCl). The release rates of matrix tablets were tested in an acidic HCl solution at pH 1.2 for 5, 10, 15, 30, 45, and 60 minutes. The samples were removed from the dissolving media at predefined intervals and replaced with new dissolution media of the appropriate pH. The quantities of medication in the samples were determined using calibration curves. The drug's dissolution at various time intervals was shown as a curve reflecting the proportion of release with time. Likewise, dissolution of the Montelukast sodium SR tablets was done in 0.1 N hydrochloric acid (HCl) and a 6.8 pH phosphate buffer media and the samples were taken from the

dissolving media at predefined intervals (5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, and 360 minutes) (Bose *et al.* 2013).

Results and discussion

Precompression parameters evaluation

Evaluation studies of the Immediate release Bilastine granules and Sustained release Montelukast sodium granules

The bulk density for every formulation ranged from 0.33-0.38, indicating reasonable packability (Table III). The tapped density values were between 0.429 and 0.488 g/mL. The angle of repose data for all batches showed good to acceptable flow characteristics. The formulation with cross-povidone (B5) had the highest flowability, whereas the formulation with hypermellose (B9) had the lowest. Carr's index was in a range of 14 to 20, suggesting good to acceptable flowability. B1, B3, B6, B7, and B8 fell inside this range. The Hausner's ratio for all formulations ranged from satisfactory to fair (1.12-1.25). The formulation granules are blended in a perfect manner, and the powder is up to the USP accepted criteria. Regarding the sustained release Montelukast sodium formulations, the granules have the angle of repose found under 30, which means the formulations had good flowability. Carr's index indicates good flowability within the range of 12–15. Here, M3, M4, M5, M6, and M7 had good flowability. On the other hand, a range of 18–21 indicated fair flowability of the granules. Here, M1 and M2 showed such a type of flowability. And Hausner's ratio < 1.25 indicated a good flow of the granules. All the formulations had a quality of fair flow rate.

Drug stability

Stability evaluation by FTIR analysis

To check the stability of Bilastine with the formulation's excipients, Montelukast with the excipients, and bilayer formulations, FTIR analysis was conducted. FTIR analysis of pure Bilastine revealed that peak of O-H stretching (3300-3500 cm^{-1}), C-H stretching (1450-1600 cm^{-1}), C=N stretching (3300-3500 cm^{-1}), and C=O stretching (1600-1900 cm^{-1}) (Patil *et al.* 2023). All the peaks were seen at the nearly similar positions in the FTIR spectrum of all the Bilastine formulations (Fig. 2a); it indicated the compatibility of Bilastine with the excipients. The FTIR spectrum of pure Montelukast exhibited aliphatic O-H stretching (3200-3600 cm^{-1}), carboxylic O-H stretching (2500-3300 cm^{-1}), C=O stretching (1600-1900 cm^{-1}), C-H stretching (1450-1600 cm^{-1}), and C-Cl stretching (600-800 cm^{-1}) (Fig. 2b), and in the

Table III. Pre-compression Properties of Bilastine and Montelukast sodium Formulations

Type	Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index	Hausner ration	Angle of repose
Bilastine immediate release formulations	B1	0.343	0.438	14.5	1.24	17.78
	B2	0.332	0.435	13.3	1.18	16.61
	B3	0.34	0.429	14.89	1.22	17.42
	B4	0.375	0.468	12.78	1.12	15.65
	B5	0.342	0.431	13.21	1.16	14.86
	B6	0.389	0.488	15.47	1.23	16.26
	B7	0.353	0.476	15.33	1.12	17.02
	B8	0.34	0.45	15.87	1.19	17.77
	B9	0.359	0.463	12.22	1.12	19.89
	B10	0.372	0.482	11.72	1.13	19.41
	B11	0.369	0.478	13.66	1.24	18.79
	B12	0.359	0.488	13.98	1.19	19.09
Montelukast sodium controlled release formulations	M1	-	-	19.5	1.22	21.5
	M2	-	-	20	1.25	19.8
	M3	-	-	14	1.19	26.47
	M4	-	-	10.48	1.11	23.9
	M5	-	-	12.05	1.16	18.57
	M6	-	-	11.86	1.15	20.7
	M7	-	-	10.98	1.13	21.6

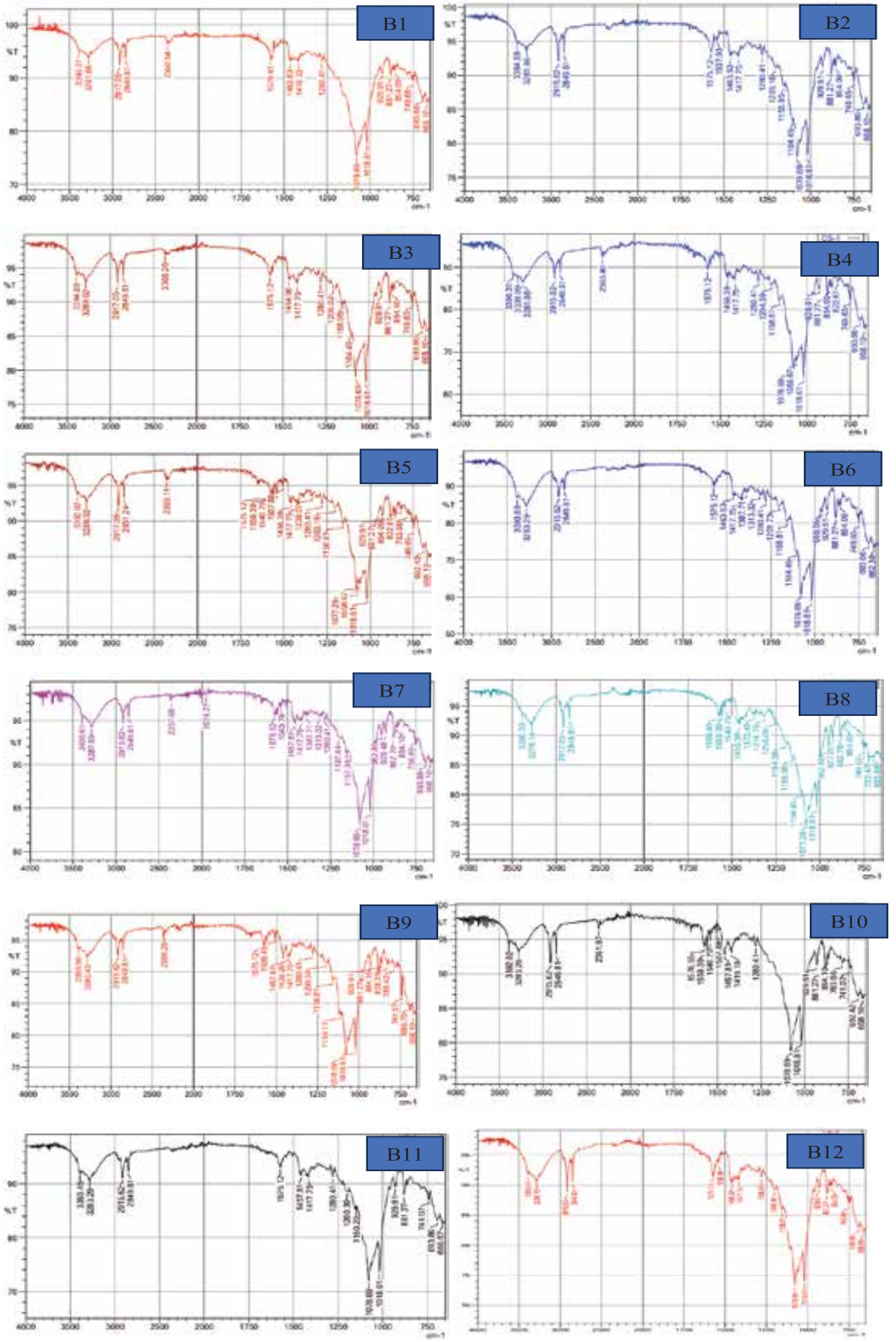

Fig. 2a: FTIR of Bilastine immediate release formulations

spectrum of all Montelukast sodium formulations, the respective spectrum was found (Fig. 2c) (Shruthi *et al.* 2016). In the FTIR spectrum of the bilayer formulations, indicative peaks of Bilastine and Montelukast molecules were present distinctively at their respective positions (Fig. 2d). So, no interactions occurred in the bilayer formulations.

Stability evaluation by TGA analysis

The analysis indicates that Bilastine, Montelukast and their bilayer formulations were stable (Fig. 3). The weight loss pattern in the TGA test revealed that Bilastine, Montelukast sodium with their excipients, were in that form, facilitating the faster dissolution. The thermogravimetric

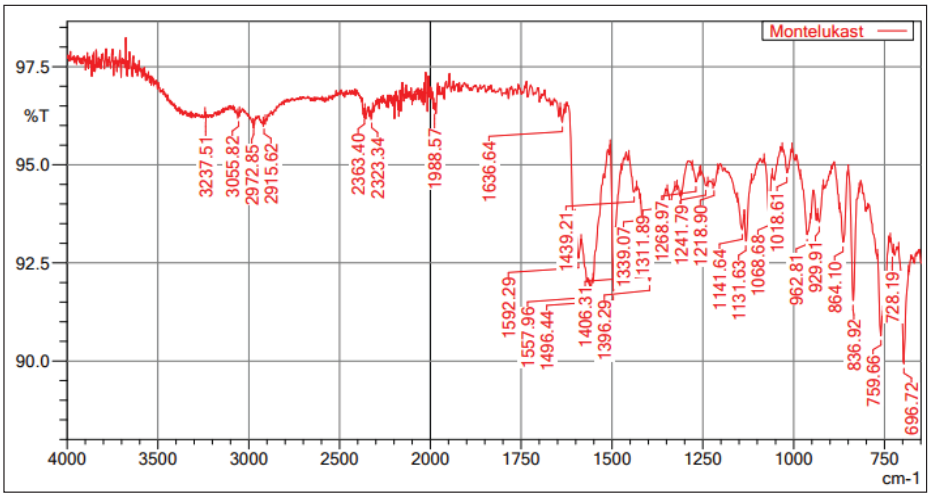

Figure 2b. FTIR of Montelukast sodium Pure Drug

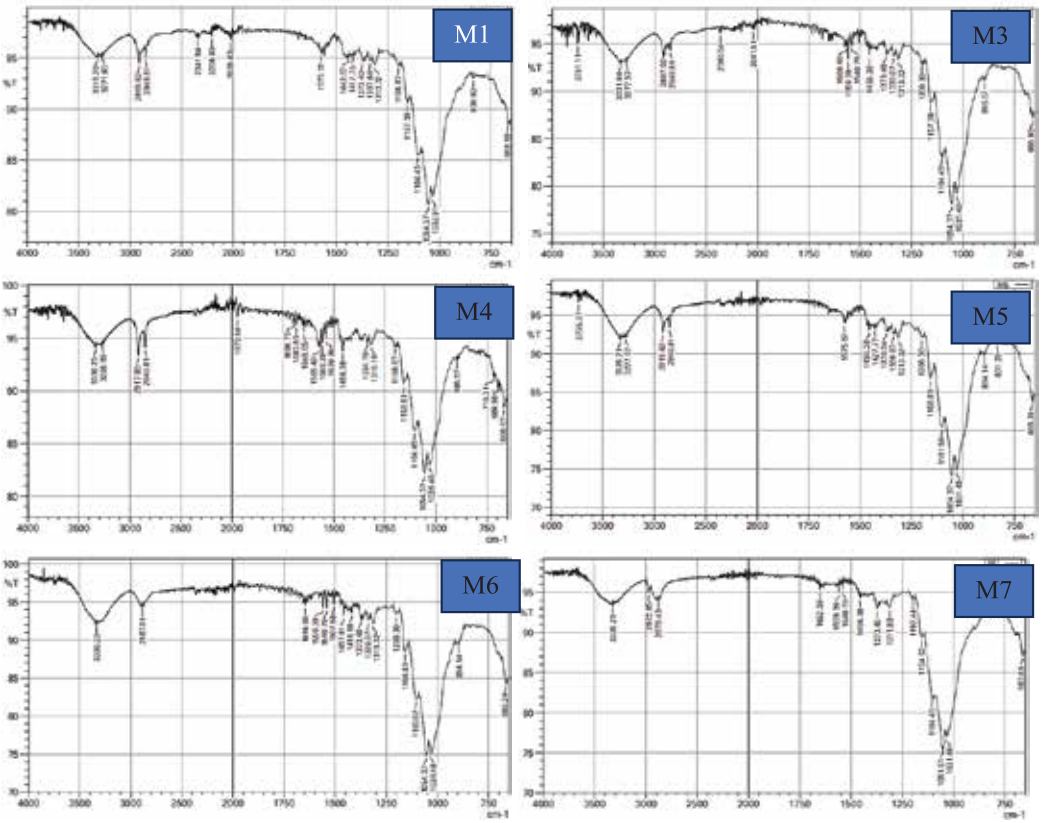

Fig. 2c. FTIR of Montelukast sodium sustained release formulations

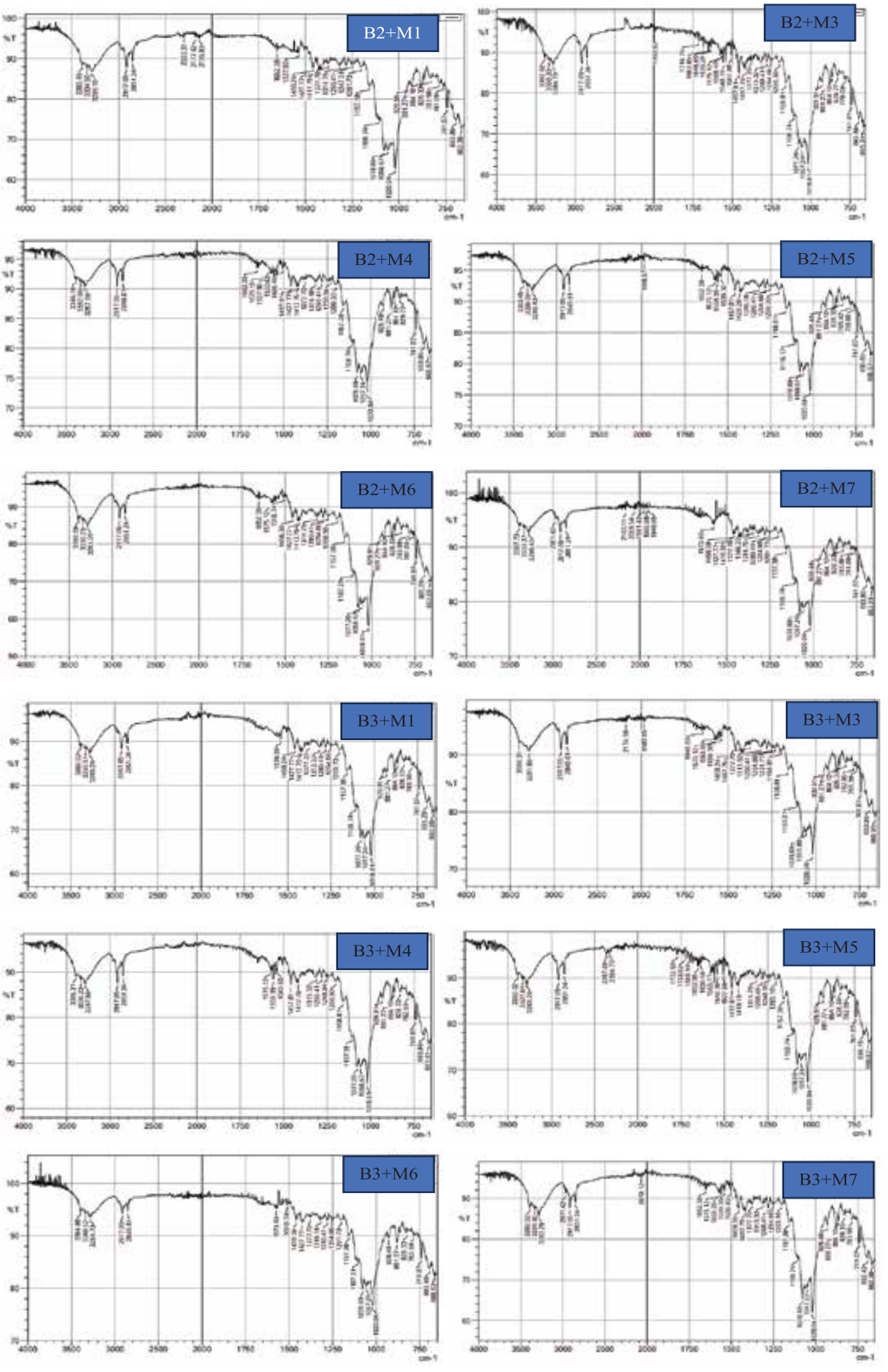

Fig. 2d. FTIR of sustain release and bilayer formulations

analysis (TGA) of pure Bilastine and Montelukast sodium, together with their formulations including different additives, provides substantial insights into their thermal stability and degradation behavior at elevated temperatures. The TGA curves illustrate the weight loss characteristics of these compounds in relation to temperature, aiding in the comprehension of their stability when mixed with different excipients used to regulate release rates. In this instance, weight loss patterns vary for Montelukast sodium formulations that include release retardants such as croscarmellose sodium, hypromellose, and Methocel K4M. Bilastine and Montelukast sodium, in both their pure forms and bilayer formulations, have stable thermal characteristics. The use of excipients such as ethylcellulose and hydroxypropylcellulose further affects the solubility and stability of these formulations. This comprehensive TGA study indicates that the formulations are designed to promote expedited dissolving while ensuring stability, which is essential for their intended medicinal uses.

Stability evaluation by SEM analysis

The SEM analysis revealed a heterogeneous surface morphology in bilayer tablet formulations, with varied particle sizes indicating different components (Fig. 4a to 4h). Montelukast appears as irregular, crystalline particles well-distributed within a polymeric matrix of HPMC,

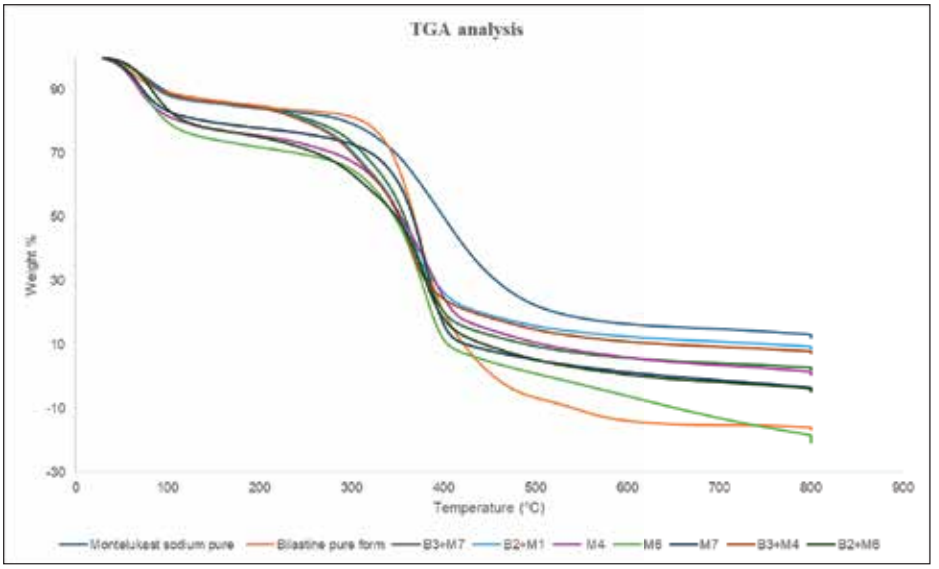

Fig. 3. TGA graph of different Bilastine immediate release formulations, Montelukast sodium-controlled release formulations and bilayer formulations

SEM analysis:

Fig. 4a. SEM images display a heterogeneous surface morphology with varied particle sizes and shapes, characteristic of the different components within the formulation. The Montelukast API appears as irregularly shaped particles, suggesting crystalline nature. (Montelukast Sodium API)

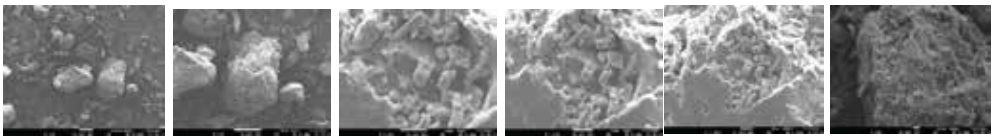

Fig. 4b. SEM images of Montelukast formula containing API, HPMC, HPC, Ethylcellulose. (M7)

Fig. 4c. SEM images of Bilastine formulation containing Sodium starch glycolate as a disintegrating agent. (B1, B2, B3)

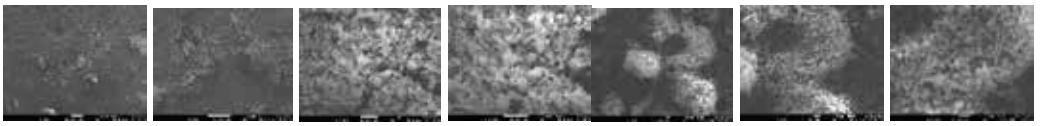

Fig. 4d. SEM images of Bilastine formulation containing Hypermellose as a disintegrating agent. (B9, B10)

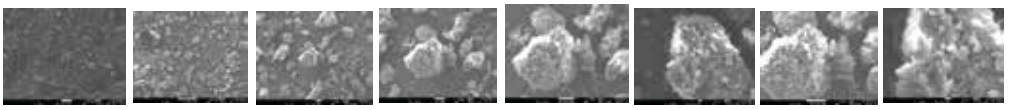

Fig. 4e. SEM images of bilayer formed with Montelukast (hypromellose, croscarmellose sodium and polyvinyl pyrrolidone as release retardant) and Bilastine (sodium starch glycolate as disintegrating agent) (M4 + B3)

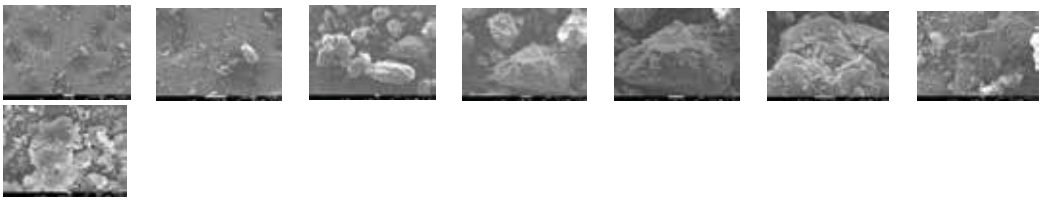

Fig. 4f. SEM images of bilayer formula with Montelukast (hypromellose and crosscarmellose sodium as release retardant) and Bilastine (sodium starch glycolate as disintegrating agent) (M1 +B2)

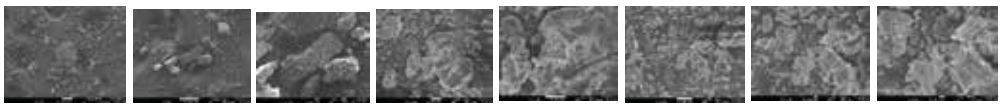

Fig. 4g. SEM images of bilayer formula with Montelukast (Hypromellose, Ethylcellulose, and Hydroxypropyl cellulose as release retardant) and Bilastine (sodium starch glycolate as disintegrating agent) (M7 +B3)

Fig. 4h. SEM images of bilayer formed with Montelukast (methocel K4M as release retardant) and Bilastine (sodium starch glycolate as disintegrating agent) (M6 +B2)

HPC, and Ethyl Cellulose, contributing to a controlled release profile by forming a gel-like barrier. Ethyl Cellulose further slows drug diffusion due to its hydrophobic nature. In contrast, the Bilastine layer, containing Sodium Starch Glycolate (SSG), shows a more porous, rough texture, characteristic of a rapid-disintegrating formulation, enhancing water uptake and swelling for quick action. Methocel K4M in the Montelukast layer enhances sustained release, while the high porosity in the Bilastine layer facilitates rapid disintegration, essential for immediate drug release and managing allergic symptoms. The M7 formula combines hydrophilic and hydrophobic excipients, ensuring a balanced, extended-release of Montelukast and prompt relief from Bilastine.

Post compression results

Weight variation

The granules were compressed using a single-channel tablet compression machine. As per USP guidelines, the tablet's theoretical weight is 100 mg, and so only 7.5% weight variation is acceptable for the tablets. It means the acceptable range of tablets is between 92.5 mg and 107.5 mg. All the prepared tablets were within acceptable range (Table IV).

Table IV. weight variation of all the formulations

Formulation	Weight (gm)	Variation (%)	Formulation	Weight (gm)	Variation (%)	Formulation	Weight (gm)	Variation (%)
B1	96.2	3.8	M1	98.3	1.7	B3 + M1	195	2.5
B2	95.1	4.9	M2	101.4	1.4	B2 + M1	198	1
B3	93.9	6.1	M3	99.2	0.8	B3 + M2	200	1
B4	93.5	6.5	M4	97.7	2.3	B2+ M2	201	0.5
B5	94.4	5.6	M5	102.1	2.1	B3 + M3	197	1.5
B6	97.5	5.5	M6	98.5	1.5	B2 + M3	198	1
B7	98.2	1.8	M7	98.9	1.1	B3 + M4	199	0.5
B8	101.3	1.3				B2 + M4	202	1
B9	93.1	6.9				B3 + M5	203	1.5
B10	92.3	7.3				B2 + M5	201	0.5
B11	95.6	4.4				B3 + M6	199	0.5
B12	96.8	3.2				B2 + M6	201	0.5
						B3 + M7	198	1
						B2 + M7	199	0.5

Table V. Diameter and thickness data of the tablets

Formulation	Diameter (mm)	Thickness (mm)	Formulation	Diameter (mm)	Thickness (mm)	Formulation	Diameter (mm)	Thickness (mm)
B1	7	2.75	M1	6.99	2.71	B3 + M1	10.03	3.33
B2	6.99	2.73	M2	6.99	2.67	B2 + M1	10.01	3.31
B3	7.01	2.76	M3	7.01	2.74	B3 + M2	9.98	3.32
B4	6.98	2.65	M4	6.98	2.71	B2+ M2	9.99	3.3
B5	6.99	2.67	M5	6.99	2.69	B3 + M3	10.04	3.34
B6	6.99	2.78	M6	7	2.73	B2 + M3	10.01	3.32
B7	7.01	2.75	M7	7.01	2.7	B3 + M4	10.02	3.31
B8	6.97	2.76				B2 + M4	10.02	3.33
B9	6.97	2.78				B3 + M5	9.99	3.31
B10	6.98	2.75				B2 + M5	10.00	3.3
B11	6.99	2.72				B3 + M6	9.98	3.32
B12	6.98	2.74				B2 + M6	9.99	3.34
						B3 + M7	10.01	3.33
						B2 + M7	10.03	3.32

Table VI. Hardness values of the tablets

Formulation	Hardness	Formula	Hardness	Formulation	Hardness
B1	3.31	M1	4.65	B3 + M1	5.3
B2	3.45	M2	4.64	B2 + M1	6.14
B3	3.47	M3	5.96	B3 + M2	5.41
B4	3.68	M4	6.64	B2+ M2	5.46
B5	3.56	M5	5.54	B3 + M3	5.63
B6	3.75	M6	5.96	B2 + M3	5.31
B7	3.42	M7	9.01	B3 + M4	5.21
B8	3.59			B2 + M4	3.48
B9	3.78			B3 + M5	3.8
B10	3.72			B2 + M5	4.25
B11	4.07			B3 + M6	5.64
B12	4.52			B2 + M6	7.62
				B3 + M7	6.28
				B2 + M7	6.04

Diameter and thickness

A micrometer screw gauge measures the thickness and diameter of tablets. The variation of the data showed that the dye compression contributed to the very small variation in the thickness of the tablets. The sustained-release formulation tablets showed a very similar diameter and thickness data with a small variation (Table V). The diameter and thickness data indicated all bilayer tablets were almost the same in shape from every dimension.

Hardness

Hardness data was collected after calibrating the movable plunger at zero. Then the tablet was put into both plungers, making just contact with the tablets. Then the machine was manually used to get the hardness data. The hardness data of immediate release tablets indicates the acceptable limit of the immediate release tablets. Here, the hardness of sustained-release tablets has an acceptable limit, which is > 5 kg/cm^2 (Karim *et al.* 2016). Without M1 and M2, all other tablets are within acceptable limits (Table VI). The bilayer formulations had variations in the hardness data, but without B2 + M4, B3 + M5, and B2 + M5, all other formulations showed hardness of sustained release predominantly.

Friability

The friability tester machine is spun at 25 rpm for 4 minutes for 10 tablets, letting 100 spin all together. The maximum range of accepting friability is 0.5-1% (Karim *et al.* 2016). The friability data of the Bilastine tablets were at a lower

Table VII. The friability data of the tablets

Formulation	Friability	Formulation	Friability	Formulation	Friability
B1	0.45	M1	0.35	B3 + M1	0.11
B2	0.43	M2	0.47	B2 + M1	0.13
B3	0.39	M3	0.42	B3 + M2	0.08
B4	0.56	M4	0.39	B2+ M2	0.14
B5	0.53	M5	0.49	B3 + M3	0.07
B6	0.41	M6	0.51	B2 + M3	0.09
B7	0.39	M7	0.43	B3 + M4	0.08
B8	0.38			B2 + M4	0.11
B9	0.59			B3 + M5	0.08
B10	0.57			B2 + M5	0.16
B11	0.49			B3 + M6	0.14
B12	0.51			B2 + M6	0.11
				B3 + M7	0.1
				B2 + M7	0.09

level, indicating better compression (Table VII). The sustained-release tablets also showed better friability values. The bilayer tablets revealed very perfect data about lower dusting properties and the better quality of the tablets.

Disintegration

Disintegration times for five tablets per formulation and compaction pressure were measured using the USP disintegration apparatus. The water bath temperature ranged from 33 to 43 °C to study temperature impact on disintegration. Tablets were considered disintegrated when no firm core remained. Disks were not used to avoid mechanical damage.

Table VIII. Disintegration time of all the tablets

Formulation	Time	Formulation	Time	Formulation	Time
B1	1 min 25s	M1	20 min 12s	B3 + M1	23 min 20s
B2	1 min 56s	M2	25 min 6s	B2 + M1	20 min 12s
B3	1 min 30s	M3	23 min 42s	B3 + M2	25 min 6s
B4	1 min 10s	M4	25 min	B2+ M2	24 min 34s
B5	58s	M5	27 min 40s	B3 + M3	23 min 42s
B6	3 min 14s	M6	28 min 50s	B2 + M3	26 min 37s
B7	2 min 55s	M7	35 min 12s	B3 + M4	25 min 30s
B8	3 min 20s			B2 + M4	23 min 21s
B9	3 min 48s			B3 + M5	26 min 10s
B10	3 min 39s			B2 + M5	27 min 40s
B11	2 min 54s			B3 + M6	28 min 50s
B12	2 min 35s			B2 + M6	27 min 30s
				B3 + M7	35 min 12s
				B2 + M7	37 min 41s

Tablets were preheated to the same temperature as the disintegration medium to ensure equilibrium. Further experiments involved preheating tablets to 25-45°C before testing at 37°C, with variations in preheating temperature and duration to check reversibility. The immediate release disintegration time is optimum within 3 minutes. The data were within the accepted range (Table VIII). The sustained-release tablets have a limit of more than 15 minutes to 60 minutes (Ahmed *et al.* 2020). The disintegration data indicated the acceptable range and more precision of the data. Disintegration of bilayer tablets was performed prior to the breakdown of the sustained release dosage forms. The ultimate disintegration time is of the sustained release portion of the bilayer tablets.

Dissolution

In the dissolution test, 31.7% and 53.4% of drugs were released from the pure Bilastine formulation after 5 and 60 minutes, respectively (Table IX). Among the Bilastine immediate-release formulations, B1 (72.66%), B2 (74.80%), and B3 (75.35%) had the highest release profile within 60 minutes with more than 70% drug release pattern. But, after 5 minutes, drug release from B1 was only 35.76%, whereas the release from B2 (65.55%) and B3 (65.88%) was more than 65%. B4, B5, B6, B7, and B8 formulations had the percent drug release between 60% and 70%. The B9 formulation had the lowest percent (42.90%) of drug release after 60 minutes.

After 6 hours, only 26.27% Montelukast sodium was released from the pure formulation (Table X). The dissolution profile indicates that the M6 (63.28%) and M7 (71.56%) formulations showed more desired drug release after 6 hours. With 43.81% drug release value after 6 hours, the M2 formulation showed the slowest release pattern among the Montelukast formulations.

Among the bilayer tablets, more than 70% Bilastine was released from B3 + M3 (70.65%), B3 + M4 (72.86%), B3 + M5 (71.23%), B3 + M6 (72.65%), B3 + M7 (73.47), B2 + M6 (73.57%), and B2 + M7 (70.56%) formulations after 60 minutes (Table XI). On the contrary, the B3 + M1 (65.17%), B3 + M3 (63.22%), B2 + M3 (60.33%), B3 + M5 (61.44%), B2 + M5 (63.18%), B3 + M6 (68.31%), B2 + M6 (63.56%), B2 + M7 (70.14%), and B3 + M7 (69.32%) formulations released more than 60% of Montelukast sodium after 6 hours. Among them, the B2 + M7 formulation showed the highest percentage (70.14%) of Montelukast release after 6 hours. So, both the drugs optimally released from B2+M6, B2+M7, B3+M3, B3+M6, B3+M6, and B3+M7 formulations.

Table IX. Release percentage of pure Bilastine and the its formulations

Formulations	5 min	15 min	30 min	45 min	60 min
Pure drug	31.7%	36.9%	45.76%	50.12%	53.4%
B1	35.76%	68.43%	69.90%	70.37%	72.66%
B2	65.55%	68.98%	71.80%	73.67%	74.80%
B3	65.88%	69.48%	72.24%	74.40%	75.35%
B4	49.76%	53.67%	57.2%	62.31%	66.46%
B5	50.51%	54.67%	55.44%	60.80%	63.80%
B6	55.34%	59.90%	63.34%	65.51%	67.78%
B7	51.10%	54.78%	58.09%	61.10%	64.98%
B8	50.23%	53.31%	56.70%	60.34%	63.30%
B9	24.93%	27.46%	35.28%	38.71%	42.90%
B10	25.56%	28.89%	34.70%	40.81%	44.77%
B11	27.50%	30.49%	35.57%	42.48%	47.09%
B12	28.76%	32.21%	37.34%	45.83%	50.89%

Table X. Percent drug release of Montelukast sodium and its formulations

Formulations	10 min	30 min	60 min	120 min	180 min	240 min	300 min	360 min
Pure	2.24%	3.81%	7.38%	12.67%	19.51%	23.27%	24.67%	26.27%
M1	3.24%	8.24%	16.27%	27.16%	36.64%	42.61%	47.91%	52.12%
M2	4.94%	6.27%	11.46%	19.37%	27.55%	38.65%	41.65%	43.81%
M3	4.61%	5.66%	9.34%	16.84%	25.67%	38.56%	42.61%	45.91%
M4	3.81%	8.54%	18.64%	26.98%	37.65%	43.65%	53.96%	57.34%
M5	4.32%	6.87%	18.56%	28.97%	39.48%	46.75%	52.68%	56.14%
M6	5.61%	3.56%	22.78%	34.68%	42.87%	49.67%	55.67%	63.28%
M7	5.68%	11.12%	19.52%	35.25%	47.42%	55.23%	67.69%	71.56%

Table XI. Percent drug release of all the bilayer formulations

Formulation	Bilastine release					
	5 mins	10 mins	20 mins	30 mins	45 mins	60 mins
B3 + M1	35.76	42.46	50.64	59.64	65.49	69.78
B2 + M1	40.67	45.67	51.97	58.67	63.73	68.56
B3 + M2	30.37	34.67	39.37	43.28	51.67	57.89
B2+ M2	31.97	36.54	41.17	46.19	53.79	59.66
B3 + M3	31.79	37.71	49.73	57.97	63.79	70.65
B2 + M3	39.84	43.56	49.71	56.37	61.95	67.56
B3 + M4	43.97	51.72	57.29	61.89	67.31	72.86
B2 + M4	38.08	42.57	49.28	58.24	63.27	68.87
B3 + M5	40.19	45.37	53.61	61.07	66.28	71.23
B2 + M5	37.53	41.31	47.31	53.78	60.83	67.94
B3 + M6	45.31	51.27	56.38	62.49	67.05	72.65
B2 + M6	45.37	52.47	58.23	64.24	69.13	73.57
B3 + M7	43.47	49.02	55.31	60.26	67.82	73.47
B2 + M7	39.23	43.76	50.22	59.3	64.87	70.56

Continued

The tablet was submerged into acidic pH 1.2 HCl solution for 1 hour and then the tablet was taken out and again submerged into pH 6.8 phosphate buffer.

	Montelukast sodium release						
	10 mins	30 mins	60 mins	180 mins	240 mins	300 mins	360 mins
B3 + M1	12.27	25.38	33.95	42.92	50.68	58.33	65.17
B2 + M1	9.04	20.01	29.88	36.17	45.26	53.08	58.31
B3 + M2	11.24	16.37	22.33	29.07	36.41	43.62	48.99
B2+ M2	6.34	15.32	21.09	30.28	38.71	45.91	51.2
B3 + M3	8.2	17.82	26.36	34.58	42.88	53.92	63.22
B2 + M3	13.24	20.07	27.34	36.99	45.34	53.94	60.33
B3 + M4	11.98	17.33	27.58	34.05	40.95	49.87	58.24
B2 + M4	12.05	19.92	28.07	37.35	44.91	53.66	59.39
B3 + M5	11.58	20.68	31.82	40.77	48.94	58.31	61.44
B2 + M5	9.87	16.93	25.61	36.98	47.81	57.66	63.18
B3 + M6	12.64	25.94	38.61	45.62	53.64	60.43	68.31
B2 + M6	11.88	21.34	30.22	39.45	49.33	56.91	63.56
B3 + M7	13.66	24.51	32.94	40.92	49.55	59.34	69.32
B2 + M7	11.55	25.37	31.67	40.18	52.74	63.27	70.14

Conclusion

Bilastine, an antihistamine drug, and Montelukast sodium, a leukotriene antagonist, were included in this study to form twelve Bilastine immediate release tablets, seven Montelukast sustained release tablets, and fourteen bilayer tablets from those drugs by making a variation in the disintegrating agents and release retardants. In pre-compression evaluations, Carr's compressibility index, bulk density, tapped density, Hausner's ratio, angle of repose of the Bilastine immediate release granules, and Montelukast sustained release granules belonged to fair ranges. Stability studies indicated good compatibility among the drugs and excipients. After compression, hardness, thickness, friability, and weight variation data showed acceptable ranges. The disintegration times of the Bilastine immediate release tablets were less than 3 minutes, and the Montelukast sodium sustained release tablets were between 15 and 60 minutes. The B1, B2, and B3 Bilastine formulations, as well as M6 and M7 showed the highest release percentage values. Among the bilayer formulations, six formulations (B2+M6, B2+M7, B3+M3, B3+M6, B3+M6, and B3+M7) exhibited higher drug release patterns of both drugs, indicating compatible and desired Bilstine and Montelukast sodium bilayer formulations.

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