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Fixed Dose Formulation Development and Evaluation of Bilastine and Montelukast Sodium Tablets

Umesh Chandra[1*], Manish Kumar[1], Arun Garg[1], Shrestha Sharma[1] and Pankaj Gupta[1]

[1]Department of Pharmacy, School of Medical and Allied Sciences, K. R. Mangalam University, Sohna Road, Gurugram, Haryana-122003, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The present research work was carried out to formulate stable fixed dose combination tablets of Bilastine and Montelukast Sodium, used to treat allergic rhinitis associated with asthma and rhino-conjunctivitis on basis of pre and post post-compression parameters evaluation and drug-drug-excipients compatibility studies.
Methods: Direct compression methodology was used for tablet production and final composition of drugs and excipients was optimized by evaluating pre and post compression evaluations of blend and tablets respectively. The chemical instability and stability studies were carried out using HPLC method.
Results: The Evaluation of pre-compression parameters of batch F1 to F5 shows that as we increase the amount of sodium starch glycolate and colloidal silicon dioxide from F1 to F5, bulk density and tapped density increases slightly whereas the compressibility index and hausner's ratio of tablets was shifted from excellent to good. Angle of repose shows excellent flow property from F3-F5. After evaluation of post-compression parameters from F1 to F5, there is no significant

**Corresponding author: E-mail: umeshchandra4185@gmail.com;*

difference in diameter, thickness and average weight of tablets. The hardness of tablets was decreased slightly from F1 to F5 therefore, the % friability was found to be increased from F1 to F5 and disintegration time was found to be decreased from F1 to F5. Dissolution studies shows % release of Bilastine and Montelukast was increased towards F1 to F5 as the percentage of Sodium Starch Glycolate increases. The drug-drug-excipients compatibility shows that there is no physical and chemical incompatibility between the drug-drug-excipients at accelerated conditions. The stability studies show that % assay of long term and accelerated samples are within 100±2%.
Conclusion: The optimized composition found in order to scale up the production of tablets.

Keywords: Bilastine; montelukast sodium; pre and post-compression evaluation; drug-drug-excipients compatibility; Stability study.

ABBREVIATIONS

BLS : Bilastine
MTK : Montelukast Sodium
MCC : Microcrystalline cellulose
SSG : Sodium starch glycolate
CSD : Colloidal silicon dioxide
MS : Magnesium stearate
Nd : Not detected
LT : Long term
Inj : Injection
Mg : Milligram
Ml : Millilitre
Mm : Millimetre
F : Formulation,
RH : Relative humidity
Nm : Nanometre

1. INTRODUCTION

Bilastine is H_1-antihistamine and anti-allergic drug used to treat allergic rhinitis and rhino-conjunctivitis. The drug has a quick rapid action with an extended half-life [1,2]. Montelukast is a leukotriene receptor antagonist used to treat asthma. The cells responsible for inflammation such as mast cells and basophils develop leukotrienes towards the early phase, and eosinophils and macrophages produce them in the next phase. Leukotriene C4, D4, and E4 are cysteinyl leukotrienes that contribute towards the production of mediators of inflammation in the esophageal airways [3,4].

In most of the cases these two diseases are associated with each other and enhance the morbidity and mortality around the world [5]. Therefore, fixed dose combination of Bilastine and Montelukast was approved recently by many drug regulatory authorities in the world [6]. In this study, we have successfully attempted to develop fixed dose uncoated tablets of Bilastine and Montelukast with label claim of 20 mg and 10 mg respectively.

The effective solid dosage formulation is based on the selection of suitable excipients, used to facilitate administration, improve patient compliance, promote drug release and bioavailability and preserve the medicine from degradation [7]. Therefore, pre and post compression evaluations was carried out to finalized the best manufacturing formula for formulation development and to ensure the stability of the product, drug-drug-excipient compatibility investigation was performed to find out the possible interactions between drugs and excipients [8]. Excipients used in the formulation of tablets include microcrystalline cellulose PH-102, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. Direct compression methodology was used for tablet production. Pre compression evaluation involves the optimization of flow properties i.e. tapped density, untapped density, compressibility index, hausner's ratio and angle of repose [9]. The controls of all excipients were available in Indian pharmacopoeias and one of the excipient was human or animal origin. Post compression evaluation involves the investigation of description, diameter, thickness, weight variation, hardness, friability, disintegration time and dissolution studies of the tablets [10]. The chemical instability due to drug-drug-excipient compatibility was determined by HPLC chromatographic system. The principle of this technique is to measure the changes in the peak area count of the drug in the presence of other drug(s) and excipient(s) which may be used as an indication of chemical incompatibility, with the appearance, shift or disappearance of characteristic peaks or change in the retention time indicating a possible interaction [11,12].

The present investigation was an attempt to formulate a tablet dosage form on basis of pre and post compression evaluation and drug-drug-excipient compatibility study which helps in

developing safe, stable and bioavailable dosage form.

2. MATERIALS AND METHODS

2.1 Chemical and Reagent

Bilastine and Montelukast Sodium APIs were generously gifted from M/s. Synokem Pharmaceuticals Limited, Haridwar. Excipients i.e. Microcrystalline Cellulose, Sodium Starch Glycolate, Colloidal Silicon Dioxide and Magnesium Stearate used in formulation were of formulation grade. The components of the mobile phase, i.e., Acetonitrile, Milli-Q water, triethylamine, orthophosphoric acid were of HPLC/analytical grade.

2.2 Instrumentation

Analytical weighing balance (Mettler Toledo), conta/bin blender, tapped density apparatus, tablet compression machine, Pfizer tablet hardness tester, disintegration apparatus (Labmatrix), dissolution apparatus (Lab India DS8000)**,** stability chambers, HPLC with PDA detector (Make: Shimadzu LC-2030 CHT), sonicator, oven, and pH meter were used during experiment.

2.3 Preparation of Blend and Tablets

The required quantity of Bilastine, Montelukast Sodium, Microcrystalline Cellulose, Sodium Starch Glycolate and Colloidal Silicon Dioxide were weighed accurately as per Table 1 and pass through sieve 40# in geometric proportions and collected in conta/bin blender and mixed for 10 minutes. Magnesium Stearate was sieved through 60# sieve and added in blender and mixed properly to formulate blend for F1 to F5. The blend for each formulation batch was divided into two parts, one part was used for pre-compression evaluation and second part was used for preparation of tablets using direct compression method for post-compression evaluation. Fast disintegrating uncoated tablets trials batches from F1 to F5 with composition of excipients as per Table 1 were prepared by direct compression technique using 10 station compression tablet punching machine having punch diameter of 8.60 mm, round shaped, biconvex with both sides plain.

2.4 Pre-compression Characterization of Blend

2.4.1 Bulk density (Untapped density)

The bulk density is a measurement tool used to measuring the untapped volume of a known mass of powder blend.

Procedure: A 100 ml empty graduated measuring cylinder was weighed and filled with the formulation blend up to the mark with the help of a funnel and noted the weight of measuring cylinder having blend. The exact weight of blend required to fill the measuring cylinder was calculated by minus the weight of empty cylinder and bulk density was calculated using below formula:

Bulk density of mixture = M/Vo (g/ml)

Where,
M = Weight of blend required to fill 100 ml measuring cylinder.
Vo = Volume of measuring cylinder (100 ml).

2.4.2 Tapped density

The tapped density is a measurement tool used to measuring the tapped volume of a known mass of powder blend.

Table 1. Formulation of blend with different concentration of excipients

API/Excipient	Quantity (mg)/tab				
	F1	F2	F3	F4	F5
Bilastine	20.19	20.19	20.19	20.19	20.19
Montelukast Sodium	10.48	10.48	10.48	10.48	10.48
Microcrystalline Cellulose PH-102	196.33	193.33	190.33	185.33	182.33
Sodium Starch Glycolate	0	2	4	8	10
Colloidal Silicon Dioxide	1	2	3	4	5
Magnesium Stearate	2	2	2	2	2
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight (mg/tab)	230.00	230.00	230.00	230.00	230.00

Procedure: A 100 ml empty graduated measuring cylinder was weighed and filled with the formulation blend up to the mark with the help of a funnel and noted the weight of measuring cylinder having blend and kept on the tapped density apparatus set for 500 taps and started the apparatus. Volume of measuring cylinder was noted when tapped density apparatus stopped. The tapped density was calculated as the mass of mixture divided by the tapped volume.

Tapped density of mixture = W/Vf (g/ml)

Where,
W = Mass of the blend taken
Vf = Tapped volume of blend after tapping

2.4.3 Compressibility index (%)

It is measured on the basis of bulk density (untapped density) of mixture and tapped density of mixture. The % compressibility of the mixture was determined using the below formula.

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Untapped density}}{\text{Tapped density}} \times 100$$

2.4.4 Hausner's ratio

The Hausner's ratio is a statistic used to determine the flow ability of a pharmacological drug ingredient using results of tapped density of mixture and untapped density of mixture.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.4.5 Angle of repose

The internal angle between the pile's surface of the powder mixture and the horizontal surface is theoretically defined as the angle of repose.

Procedure: The known amount of drugs and excipient mixture prepared for F1 to F5 (in gm) as per Table 1 was poured via a funnel attached to a 4 cm high burette stand. On the table, graph paper was placed beneath the funnel. The pile's height and radius were measured. Angle of repose of the mixture was calculated using the below formula.

Angle of repose (θ) = $\tan^{-1}(h/r)$

Where,
h = Height of the pile,
r = Radius of the pile

2.5 Post-compression Characterization of Tablets

2.5.1 Description

Prepared tablets were inspected in light under a lens to identify the shape and colour of the tablets.

2.5.2 Diameter

The diameter of the tablets was measured using a vernier caliper scale by selecting 10 tablets randomly from the developed batch.

2.5.3 Thickness

The thickness of 10 pre-weighed tablets from the same batch was measured using a vernier caliper scale in millimetres and the average thickness was calculated. The thickness of the tablets is mostly connected to the hardness of the tablets and can be utilized as an initial control parameter.

2.5.4 Weight variation test

Accurately weighed 20 tablets collected randomly and calculate their average weight using analytical balance, also these 20 tablets weighed individually and compared with the obtained average weight. This test is an indication of drug content uniformity in each tablet. Maximum 7.5% difference is allowed as per IP 2018 for tablets having average weight between 130-324 mg. Average weight was calculated as mentioned below:

$$\text{Average weight (mg/Tablet)} = \frac{\text{Weight of 20 Tablets (in mg)}}{20}$$

2.5.5 Hardness test

Tablets must have a particular degree of strength, or hardness and resistance to friability, in order to withstand mechanical shocks during manufacturing, packing, and transportation. Ten tablets were chosen at random from the

formulation batch, and the mean and standard deviation values were computed. The tablet hardness was evaluated using a Pfizer hardness tester. It is measured in kilograms per square centimetre.

2.5.6 Friability test

When tablets are subjected to mechanical force or wear, tablet surfaces are damaged and/or exhibit indications of lamination or breaking. Therefore, friability of tablets was evaluated by Roche Friabilator apparatus and its value is expressed in %. Tablets with a friability of less than 1% are deemed acceptable.

Procedure: Dedusted the tablets and weighed thirty tablets (Weight more than 6.5 gm as per IP 2018, Page no. 309) and noted the values as $W_{initial}$ and placed in the friabilator. The friabilator was run at 25 revolutions per minute for 4 minutes (100 revolutions). The tablets were weighed once again and noted the value as W_{final}. The % friability was then computed as follows:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

2.5.7 Disintegration time

Disintegration Time of developed tablet formulation was carried out by using a Disintegration Test apparatus.

Procedure: Placed one dosage unit in each of the six tubes of the basket and a disc was placed above the tablet. Apparatus was operated using 1000 ml water maintained at 37°C. All tubes having tablets were visually observed and notes the time when all tablets were disintegrated completely.

2.5.8 Dissolution testing

The process by which a drug or substance dissolves and forms a solution is known as dissolution. Dissolution testing evaluates the extent and rate of solution formation from a dosage form such as a pill, capsule, ointment, or other similar substance.

Procedure: Placed one tablet in each of the six vessels of the dissolution apparatus (USP Type-2) containing pre-heated 0.5% Sodium Lauryl Sulphate dissolution medium maintained at temperature 37±2°C. Performed the dissolution test as per optimized dissolution at 75 rpm and collected the aliquot after 45 minutes and samples were analyzed by HPLC method.

2.6 Drug-Drug/Drug-Excipient Compatibility Studies

A drug excipient compatibility study was carried out to assess the compatibility of Bilastine and Montelukast sodium drug substances with each other and with other excipients. Individual excipients were mixed with the APIs and exposed to solid-state stress conditions such as heat, light, and humidity under stability chambers. The compatibility of drug substances / Excipient combinations were investigated and only those found compatible were used in formulation of Bilastine and Montelukast sodium uncoated tablets.

2.6.1 Preparation and storage of drug-drug-excipient compatibility samples

To determine the drug/drug-excipients compatibility study, known amount of drug(s) and excipient(s) (around 400 mg Bilastine, 200 mg Montelukast and 400 mg of each excipient) were weighed individually or in combination as per drug/drug-excipients mentioned in Table 5 and transferred into glass vials, mixed well and further weighed and divided each sample into two parts and placed in properly labelled glass vials. (Each vials containing about 200 mg Bilastine, 100 mg Montelukast). One part was charged in stability chamber at $30^0C \pm 2^0C$/ 75% ± 5% RH and second part at $40^0C \pm 2^0C$/ 75% ± 5% RH for 04 weeks. Before charging noted the visual observation once for all samples.

2.6.2 Observation of compatibility samples

Remove the drug-drug-excipients compatibility sample vials which were charged in stability chambers at $30^0C \pm 2^0C$/ 75% ± 5% RH and $40^0C \pm 2^0C$/ 75% ± 5% RH and allowed them to attain the room temperature and recorded the physical and chemical observations.

Physical observation: Organoleptic characteristics and physical instability of samples, such as colour and texture, were evaluated at the end of the first, second, third, and fourth weeks of sample stored at $30^0C \pm 2^0C$/ 75% ± 5% RH as well as $40^0C \pm 2^0C$/ 75% ± 5% RH and reported in result if there is any change observed in any samples.

Chemical observation: The chemical observation of drug-drug-excipient compatibility sample stored at $40^0C \pm 2^0C$/ 75% ± 5% RH was determined by HPLC chromatographic system. The principle of this technique is to measure the changes in the peak area count of the drug in the presence of other drug(s) and excipient(s) (% Assay) which may be used as an indication of chemical incompatibility, with the appearance, shift or disappearance of characteristic peaks or change in the retention time indicating a possible interaction.

Chromatographic Conditions: A Shimadzu LC-2030 HPLC with Hypersil BDS C-18 Column (100×4.6 mm, 3 µm) as a stationary phase and 0.1% v/v Triethylamine buffer of pH-3.00: Acetonitrile as a mobile phase in gradient mode. The buffer was filtered through 0.45 µm membrane filter and degassed by sonication. The mobile phase solvent was pumped at 1ml/min, column oven temperature kept at 40°C and λ max was set at 220 nm. Injection volume for all samples was fixed at 10 µl and under these conditions; the run time was 13 min.

I. Preparation of Diluent

Acetonitrile: Water, 1:1, and same used as blank solution

II. Preparation of Blank solution

Diluent used as blank solution

III. Preparation of Standard Solution

The stock solution of Bilastine and Montelukast was prepared by transferring the 101.40 mg of Bilastine and 52.65 mg of Montelukast Sodium (equivalent to 50.75 mg of Montelukast) into 100 ml volumetric flask. About 70 ml of acetonitrile was added to the flask and sonicated at temperature below 20°C, with occasional shaking and final volume was made up to 100 ml with acetonitrile. Further 5 ml of this stock solution was transferred into 25 ml of volumetric flask and the final volume was made up with diluent to get final concentration of 200.89 µg/ml of Bilastine and 100.71 µg/ml of Montelukast (after potency correction, 99.06% for Bilastine and 99.23% for Montelukast) and used as standard solution after filtration through 0.45 µm nylon syringe filter.

IV. Preparation of drug-drug-excipient compatibility samples solution

Transferred the one vial content in 100 ml volumetric flask with the help of funnel and washed the vial with acetonitrile to ensure complete transfer of content. Placed the volumetric flask in sonicator for 20 minutes below 20°C, with occasional shaking and final volume was made up with acetonitrile. A 5 ml solution was transferred into a 25 ml volumetric flask and volume made up with diluents and filtered through a 0.45 µm nylon syringe filter and used as a sample solution.

Note: Repeat the above process for all compatibility samples solution preparation.

2.7 Stability Studies

On the basis of pre and post compression parameters, to be finalized formulation from F1 to F5 was charged for long term and accelerated condition as per guidelines provided by Indian drug regulatory agency (Table 2) and after six months charged stability samples were analyzed by a HPLC chromatographic conditions mentioned at 2.6.2.2.

3. RESULTS AND DISCUSSION

3.1 Evaluation of Pre-compression Parameters of F1 to F5

The Evaluation of pre-compression parameters of batch F1 to F5 shows that as we increase the amount of sodium starch glycolate and colloidal silicon dioxide from F1 to F5, bulk density and tapped density increases slightly whereas the compressibility index and hausner's ratio of tablets was shifted from excellent to good. Angle of repose shows excellent flow property from F3 to F5. The results of pre-compression parameters evaluation of batch F1 to F5 are summarized in Table 3.

Table 2. Stability study conditions as per Indian guidelines

Study	Storage condition	Minimum time period
Long-term	30°C ± 2°C/75% RH ± 5% RH	6 months/12 months if fails in 6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

3.2 Evaluation of Post-compression Parameters of F1 to F5

White coloured, round shaped, biconvex, uncoated tablets having both sides plain was prepared using direct compression technology and after evaluation of tablets it is found that there is no significant difference in diameter, thickness and average weight in all formulation trails from F1-F5. The hardness of tablets was decreased slightly from F1 to F5 therefore, the % friability was found to be increased from F1 to F5 and disintegration time was found to be decreased from F1 to F5. Dissolution studies shows that the % release of Bilastine and Montelukast was increased towards F1 to F5 as the percentage of Sodium Starch Glycolate (used as disintegrant) increases. After analyzing all pre and post compression parameters F4 formulation was qualify all general specification, therefore we selected the F4 for scale up production of tablets. The results of post-compression parameters evaluation of batch F1 to F5 are summarized in Table 4.

Table 3. Evaluation of pre-compression parameters of batch F1 to F5

Pre-compression parameters	Formulation trial batches				
	F1	**F2**	**F3**	**F4**	**F5**
Bulk density (g/ml)	0.41±0.12	0.42±0.15	0.42±0.12	0.43±0.11	0.43±0.08
Tapped density (g/ml)	0.45±1.04	0.45±0.83	0.46±0.55	0.48±0.42	0.48±0.53
Compressibility index	08±0.61	08±0.55	09±0.63	10±0.86	11±0.81
%	Excellent	Excellent	Excellent	Excellent	Good
Hausner's ratio	1.09±0.02	1.09±0.03	1.10±0.02	1.11±0.02	1.12±0.01
	Excellent	Excellent	Excellent	Excellent	Good
Angle of repose (θ)	27.15º±1.23	26.26º±1.02	24.78º±1.12	23.04º±0.95	22.16º±0.98
	Good	Good	Excellent	Excellent	Excellent

Table 4. Evaluation of post-compression parameters of batch F1 to F5

Sr. No.	Parameter	F1	F2	F3	F4	F5
1.	Diameter (mm)	8.60±0.2	8.60±0.2	8.60±0.2	8.60±0.2	8.60±0.2
2.	Thickness (mm)	3.70±0.2	3.70±0.2	3.70±0.2	3.70±0.2	3.70±0.2
3.	Weight variation (mg)	230±1.2	230±0.8	230±0.2	230±0.4	230±0.2
4.	Hardness (kg/cm2)	4.6±0.1	4.3±0.1	4.4±0.1	4.0±0.1	3.8±0.1
5.	Friability	0.3%	0.4%	0.4%	0.5%	0.8%
6.	Disintegration Time (min)	18	14	8	4	3
7.	Dissolution-45 min	BLS-32	BLS-55	BLS-86	BLS-98	BLS-99
	(% release)	MTK-48	MTK-72	MTK-96	MTK-101	MTK-101

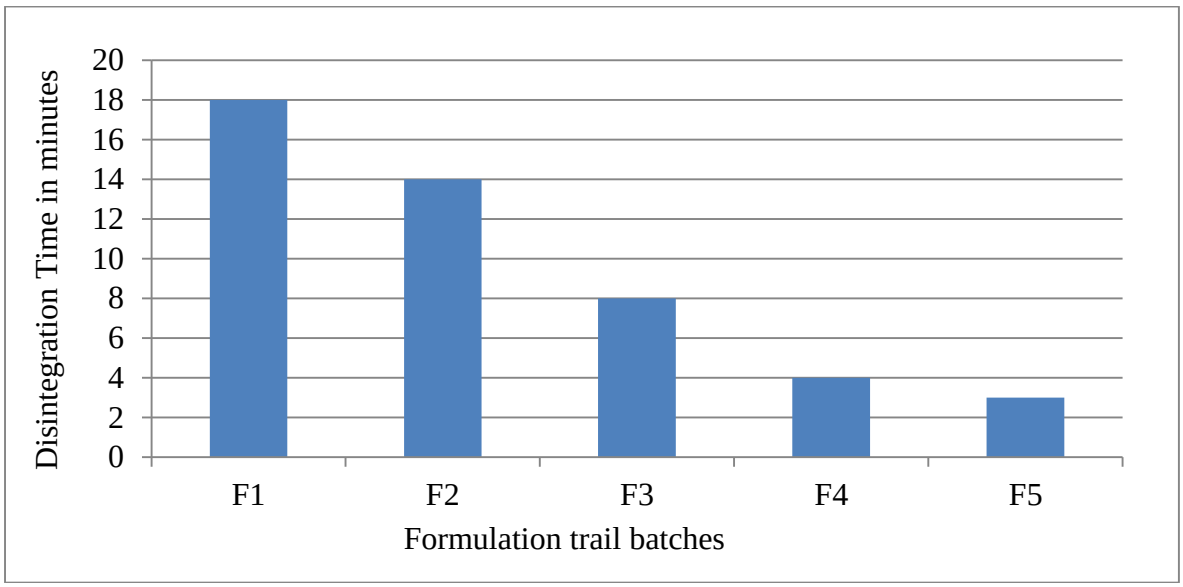

Fig. 1. Disintegration time of F1 to F5 in minutes

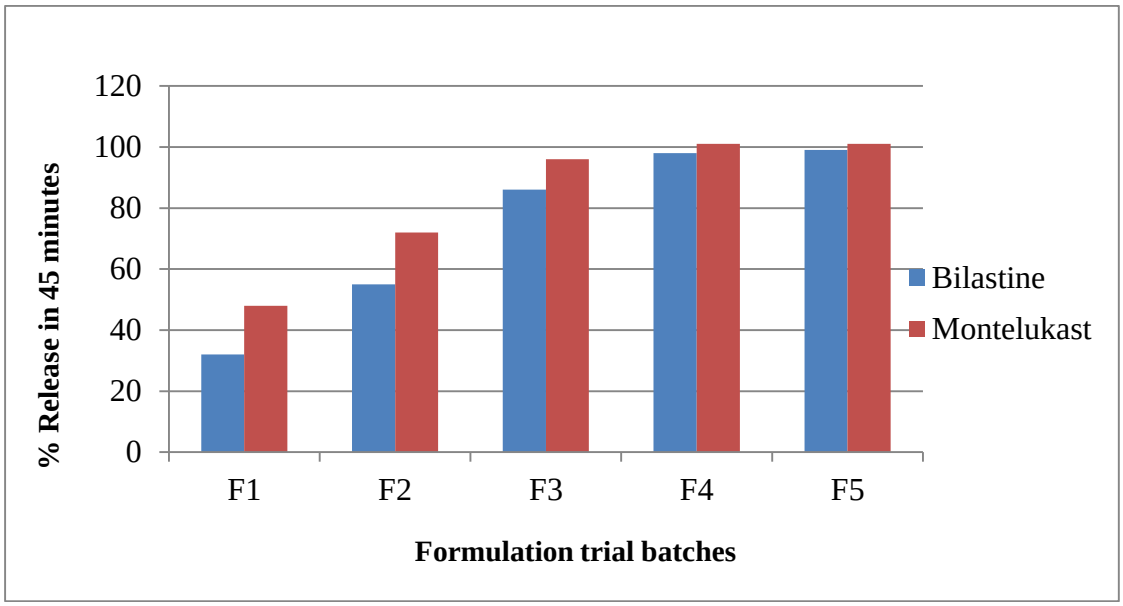

Fig. 2. % Release of Bilastine and Montelukast in F1 to F5

3.3 Evaluation of Drug-drug-excipients Compatibility Samples

3.3.1 Physical observation

Physical instability of drug-drug-excipients compatibility samples was monitored at initial and at temperature 30^0C ± 2^0C/ 75% ± 5% RH and 40^0C ± 2^0C/ 75% ± 5% RH for first four weeks and visual observations was noted such as change in the colour and texture of drug or blend. It is concluded that binary mixture did not undergo any physical instability in terms of colour and texture of samples at tested stability conditions vs sample kept at ambient conditions. The results of physical observations of drug-drug-excipients compatibility samples are summarized in Table 5.

3.3.2 Chemical observation

Chemical instability of drug-drug-excipients compatibility samples was monitored at temperature 40^0C ± 2^0C/ 75% ± 5% RH stored for four weeks. After the completion of stability storage period, drug-drug-excipient compatibility samples were removed from chamber and kept at room temperature. Sample solutions using each vial were prepared separately as per procedure and each sample was analyzed using a HPLC system. The concentration of each sample containing Bilastine and Montelukast were calculated by comparing it with freshly prepared standard solution of Bilastine and Montelukast and also noted the all quantifiable peaks or impurities, if observed. The Area count of standard solution of Bilastine and Montelukast are summarized in Table 6A and mean area of Bilastine and Montelukast was used for calculation of % assay of compatibility samples. After examination of resulting chromatograms, it was found that there is no loss in terms of % assay of both drugs which means that no incompatibility between the drug-drug-excipients at temperature 40^0C ± 2^0C/ 75% ± 5% RH. The results of chemical observations of drug-drug-excipients compatibility samples are summarized in Table 6B and 6C.

3.3 Stability Studies

Stability study was carried out of the finalized drug product of Bilastine and Montelukast tablets (Batch No. UMC_005) with label claim 20 mg and 10 mg respectively prepared as per F4 manufacturing formula and charged for long term and accelerated conditions for 6 months and analyzed using a validated HPLC method. The Area count of standard solution of Bilastine and Montelukast are summarized in Table 7A and mean area of Bilastine and Montelukast was used for calculation of % assay of stability samples. The % assay of stability samples of Bilastine and Montelukast were calculated and found within specification limit (98-102%) and are summarized in Table 7B and 7C.

Table 5. Result of Physical observations of drug-drug-excipients compatibility samples

		Physical observations		
Sr. No.	**Drug: Drug/Excipient**	**Initial**	**$30^0C \pm 2^0C$ & 75 ± 5% RH (1-4 Weeks)**	**$40^0C \pm 2^0C$ & 75 ± 5% RH (1-4 Weeks)**
1	Bilastine (BLS)	Complies	Complies	Complies
2.	Montelukast Sodium (MTK)	Complies	Complies	Complies
3.	BLS + MTK	Complies	Complies	Complies
4.	BLS + MTK + MCC	Complies	Complies	Complies
5.	BLS + MTK + SSG	Complies	Complies	Complies
6.	BLS + MTK + CSD	Complies	Complies	Complies
7.	BLS + MTK + MS	Complies	Complies	Complies
8.	BLS + MTK + MCC + SSG + CSD + MS	Complies	Complies	Complies

Table 6A. Area count of standard solution of Bilastine and Montelukast

Standard solution Injection no.	**Bilastine**	**Montelukast**
	Area Count	**Area Count**
Replicate-1	4015142	1439670
Replicate-2	4019566	1439477
Replicate-3	4013861	1438755
Replicate-4	4012905	1436879
Replicate-5	4017913	1439382
Replicate-6	4009892	1438286
Mean Area Count	4014880	1438742
SD	3494.2	1047.8
%RSD	0.1	0.1

Table 6B. Result of Chemical observations of Bilastine at Accelerated conditions

Chemical observations of Bilastine at $40^0C \pm 2^0C/75 \pm 5\%RH$					
Sr. No.	**Drug-Drug/Excipient**	**Corrected Bilastine weight taken in mg**	**Area Count**	**% Assay**	**Any degradationNMT 2.0%**
1.	Bilastine (BLS)	98.58	3984936	101.1	Nd
2.	Montelukast Sodium (MTK)	--	--	--	--
3.	BLS + MTK	100.10	4030844	100.7	Nd
4.	BLS + MTK + MCC	100.00	4009946	100.3	Nd
5.	BLS + MTK + SSG	99.61	4000874	100.5	Nd
6.	BLS + MTK + CSD	100.30	4026690	100.4	Nd
7.	BLS + MTK + MS	99.50	4013590	100.9	Nd
8.	BLS + MTK + MCC + SSG + CSD + MS	99.69	4012263	100.7	Nd

Table 6C. Result of Chemical observations of Montelukast at Accelerated conditions

Chemical observations of Montelukast at $40^0C \pm 2^0C/75 \pm 5\%RH$					
Sr. No.	**Drug-Drug/Excipient**	**Corrected Montelukast weight taken in mg**	**Area Count**	**% Assay**	**Any degradationNMT 2.0%**
1.	Bilastine (BLS)	--	--	--	--
2.	Montelukast Sodium (MTK)	48.48	1391028	100.4	Nd
3.	BLS + MTK	50.54	1446141	100.2	Nd
4.	BLS + MTK + MCC	49.59	1433081	101.2	Nd
5.	BLS + MTK + SSG	49.87	1427952	100.2	Nd
6.	BLS + MTK + CSD	50.07	1437983	100.5	Nd
7.	BLS + MTK + MS	50.15	1436833	100.3	Nd
8.	BLS + MTK + MCC + SSG + CSD + MS	49.75	1436722	101.1	Nd

Table 7A. Area count of standard solution of Bilastine and Montelukast

Standard solution Injection no.	Bilastine	Montelukast
	Area Count	Area Count
Replicate-1	4002349	1420789
Replicate-2	3997103	1421888
Replicate-3	3992820	1423207
Replicate-4	3993912	1421977
Replicate-5	4008637	1424668
Replicate-6	3990124	1417085
Mean Area Count	**3997491**	**1421602**
SD	**6883.1**	**2579.3**
%RSD	**0.2**	**0.2**

Table 7B. Six Month Long term and Accelerated stability result of Bilastine

Sample id. of Batch No. UMC_005	Claim(mg)	Area counts		%Assay of Bilastine		
		Inj-1	Inj-2	Mean	mg/tab	% of label claim
LT_6_MONTH	20	3980519	3988446	3984483	20.024	**100.1**
ACCELERATED_6_MONTH	20	3989755	3992493	3991124	20.057	**100.3**
				Avg	20.041	100.2
				SD	0.0233	0.14
				%RSD	0.0	0.1

Table 7C. Six Month Long term and Accelerated stability result of Montelukast

Sample id. of Batch No. UMC_005	Claim(mg)	Area counts		%Assay of Montelukast		
		Inj-1	Inj-2	Mean	mg/tab	% of label claim
LT_6_MONTH	10	1425995	1428269	1427132	10.110	**101.1**
ACCELERATED_6_MONTH	10	1423937	1425521	1424729	10.093	**100.9**
				Avg	10.102	101.0
				SD	0.0120	0.14
				%RSD	0.0	0.1

4. CONCLUSION

As per the present investigation, a manufacturing formula (F4) for preparation of fixed dose uncoated tablets of Bilastine and Montelukast Sodium was optimized after evaluating results of pre and post compression evaluation parameters and selected for scale up production. Physical and chemical observations show that binary mixtures of drugs and excipients did not undergo any physical and chemical instability in terms of colour, texture and % assay of drugs. Long term and accelerated stability studies results shows that the developed formulation withstands without any loss of drugs content and % assay of Bilastine with Montelukast are within 98-102%. Developed formulation ensures content uniformity and better stability with low cost to producer as well as to patients. The combination of Bilastine with Montelukast gives additive benefits to patients in comparison to either drug alone and could improve the quality of life to those patients who are very sensitive towards allergens or seasonal discomfort by decreasing the pills load.

DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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