International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1073-1093 www.ijprajournal.com ISSN: 2249-7781

Formulation and Development of Bilastine 20mg and Montelukast Sodium 10 Mg Coated Tablet

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Date of Submission: 15-10-2021 Date of Acceptance: 27-10-2021

ABSTRACT

BILASTINE AND MONTELUKAST SODIUM TABLETS designed to show if once daily oral combination given to patients with Seasonal Allergic Rhino Conjunctivitis and mild to moderate asthma on total symptom scores (TSS) and if the combination therapy reflects an improvement in quality of life as accessed via the Asthma Quality of Life Questionnaire (AQLQ) over a longer time period when compared to monotherapies with combination of Montelukast 10 mg and Bilastine 20 mg coated tablets. The study population included patients inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting beta-agonists provided inadequate clinical control[1].Bilastine, and Montelukast with its efficacy and safety profile epitomizes the evolution of research on antihistamines , Bilastine works by blocking histamine receptors and micronized size of Montelukast sodium (250micometer)combination showing a cysteinyl Leukotriene receptor antagonist, with effects of anti-inflammatory, suppress oxidative stress and reduce affect cytokine production, may limited progression of the disease on COVID-19 infection[3]. Coated tablets of Bilastine and Micronized Montelukast sodium were prepared using Lactose anhydrous Dc grade, Microcrystalline cellulosepH112,Sodium starch glycolate and Crosspovidone as superdisintegrants tablets prepared by direct compression method. Coated tablets prepared were evaluated for various parameters like weight variations, hardness, friability, in vitro dispersion time, drug content by dissolution, Disintegration time. The tablets compared with innovator tablets method possess a weight variation below ±5%, hardness of 7 to 9.0 Kg/cm², percentage friability of 0.7, in vitro dissolution time of 10 mins, Disintegration time of 12secs, and in vitro drug release showed 90% to 95.00% within 15 min. The formulation contains Crosspovidone and Sodium Starch Glycolate shows better Disintegration time and 99% drug release within 30 min. Bilastine and Montelukast sodium tablets compare with marketed product physical parameters and dissolution parameters are shows similar results to the formulated tablets based on physical and chemical parameters optimised our formula with marketed product of Bilastine 20 mg and Montelukast sodium 10 mg coated tablets.

Key words: Microcrystalline Cellulose pH 112, Lactose anhydrous (DCgrade), Pregelleatinazed starch, Sodium Starch glycolate type A (derived from potato), Colloidal silica anhydrous, Cross povidone, Talc and Magnesium Stearate, Opadry white, purified water

AIM:

Formulation and Development of Bilastine20mg and Montelukast sodium10mg Coated Tablets

OBJECTIVE:

- To enhance patient compliance and adherence to therapy
- To formulate fast dissolving tablet of Bilastine and Micronized form of Montelukast sodium (250micrometer) using superdisintegrants in different concentration by direct compression method.
- Screening of the various natural and synthetic Superdisintegrants.
- To carry out in-vitro evaluation of the optimized formulation.
- To carryout short term stability studies of optimized formulation.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1073-1093 www.ijprajournal.com ISSN: 2249-7781

I. INTRODUCTION

From time immemorial, drugs have been an inseparable part of mankind's history since they fulfil one of our most basic necessities. To administer these drugs in an appealing and palatable form and in the required amount and rate, they have to be developed into an acceptable dosage form. Thus, the concept of formulation development was evolved, resulting in solid, liquid and semi-solid dosage form.

Solid dosage forms

Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. These have been developed into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms for the constant rate of drug release.

Oral route is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems.

ADVANTAGES-

They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects.

The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture and/or for providing a desired drug delivery system. The tablets and capsules can be made directly from powders or from granules and pellets, or from film coated multiple units.

II. INNOVATOR PRODUCT

BITOSEN

List of excipients

Microcrystalline Cellulose
Sodium Starch glycolate type A (derived from potato)
Colloidal silica anhydrous
Cross povidone
Talc
Magnesium Stearate

III. PHARMACEUTICAL FORM

Film coated Tablet. Oval biconvex scored white colour film coated tablets (length 8 mm, width 5 mm).

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

IV. THERAPEUTIC INDICATIONS

Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

Bilastine is indicated in adults and adolescents (12 years of age and over).

4.1Posology and method of administration

Posology

Adults and adolescents (12 years of age and over)

20 mg Bilastine (1 tablet) once daily for the relief of symptoms of allergic rhino conjunctivitis (SAR and PAR) and urticaria.

Paediatric population

There is no relevant use of Bilastine in children aged 0 to 2 years for the indications of allergic rhino-conjunctivitis and urticaria. The safety and efficacy in children below 12 years have not yet been established.

Duration of treatment:

For allergic rhinitis the treatment should be limited to the period of exposure to allergens. For seasonal allergic rhinitis treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance. In perennial allergic rhinitis continued treatment may be proposed to the patients during the allergen exposure periods. For urticaria the duration of treatment depends on the type, duration and course of the complaints.

Interaction with alcohol: The psychomotor performance after concomitant intake of alcohol and 20 mg bilastine was similar to that observed after intake of alcohol and placebo.

Interaction with lorazepam: Concomitant intake of Bilastine 20 mg and lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of lorazepam.

Paediatric population

Interaction studies have only been performed in adults. Extent of interaction with other medicinal products and other forms of interaction is expected to be similar in paediatric population from 12 to 17 years of age.

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no or limited amount of data from the use of Bilastine in pregnant women.

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Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development .As a precautionary measure, it is preferable to avoid the use of BIOSEN during pregnancy.

Breast-feeding: The excretion of Bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of Bilastine in milk . A decision on whether to discontinue/abstain from Ilaxten therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of bilastine therapy for the mother.

Fertility: There are no or limited amount of clinical data. A study in rats did not indicate any negative effect on fertility S

V. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antihistamines for systemic use, other antihistamines for systemic use

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H_1 receptor antagonist affinity and no affinity for muscarinic receptors.

Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses.

In clinical trials performed in adult and adolescent patients with allergic rhino conjunctivitis (seasonal and perennial), Bilastine 20 mg, administered once daily for 14-28 days, was effective in relieving symptoms such as sneezing, nasal discharge, nasal itching, nasal congestion, ocular itching, tearing and ocular redness. Bilastine effectively controlled symptoms for 24 hours.

In two clinical trials performed in patients with chronic idiopathic urticaria, Bilastine 20 mg, administered once daily for 28 days was effective in relieving the itching intensity and the number and size of wheals, as well as the patients discomfort due to urticaria. Patients improved their sleep conditions and their quality of life.

No clinically relevant prolongation of QTc interval or any other cardiovascular effect has been observed in the clinical trials performed with Bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days in 9 subjects, or even when co administered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects). Additionally a thorough QT study including 30 volunteers has been performed.

In controlled clinical trials at the recommended dose of 20 mg once daily, the CNS safety profile of Bilastine was similar to placebo and the incidence of somnolence was not statistically different from placebo. Bilastine at doses of up to 40 mg q.d. did not affect psychomotor performance in clinical trials and did not affect driving performance in a standard driving test.

Paediatric population

Adolescents (12 years to 17 years) were included in the clinical development. 128 adolescents received Bilastine during the clinical studies (81 in double blind studies in allergic rhino-conjunctivitis). A further 116 adolescent subjects were randomised to active comparators or placebo. No differences in efficacy and safety between adults and adolescents were seen.

The European Medicines Agency has deferred the obligation to submit the results of studies with Ilaxten in one subset of the paediatric population in the treatment of allergic rhino-conjunctivitis and the treatment of urticaria (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed. The mean value of Bilastine oral bioavailability is 61%.

Distribution

In vitro and in vivo studies have shown that Bilastine is a substrate of Pgp “Interaction with ketoconazole, erythromycin and diltiazem” and OATP “Interaction with grapefruit juice”. Bilastine does not appear to be a substrate of the transporter BCRP or renal transporters OCT2, OAT1 and OAT3. Based on in vitro studies, Bilastine is not expected to inhibit the following transporters in the systemic circulation: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and NTCP, since only mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated $IC_{50} \geq 300$ μM, much higher than the calculated clinical plasma C_{max} and therefore these interactions will not be clinically relevant. However, based on these results inhibition by Bilastine of transporters present in the intestinal mucosa, e.g. P-gp, cannot be excluded.

At therapeutic doses Bilastine is 84-90% bound to plasma proteins.

Biotransformation

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Bilastine did not induce or inhibit activity of CYP450 isoenzymes in in vitro studies.

Elimination

In a mass balance study performed in healthy volunteers, after administration of a single dose of 20 mg ^{14}C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged Bilastine, confirming that Bilastine is not significantly metabolized in humans. The mean elimination half-life calculated in healthy volunteers was 14.5 h.

Linearity

Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability.

Renal impairment

In a study in subjects with renal impairment the mean (SD) $AUC_{0-\infty}$ increased from 737.4 (±260.8) ngxhr/ml in subjects without impairment (GFR: > 80 ml/min/1.73 m^2) to: 967.4 (±140.2) ngxhr/ml in subjects with mild impairment (GFR: 50-80 ml/min/1.73 m^2), 1384.2 (±263.23) ngxhr/ml in subjects with moderate impairment (GFR: 30 - <50 ml/min/1.73 m^2), and 1708.5 (±699.0) ngxhr/ml in subjects with severe impairment (GFR: < 30 ml/min/1.73 m^2). Mean (SD) half-life of Bilastine was 9.3 h (± 2.8) in subjects without impairment, 15.1 h (± 7.7) in subjects with mild impairment, 10.5 h (± 2.3) in subjects with moderate impairment and 18.4 h (± 11.4) in subjects with severe impairment. Urinary excretion of Bilastine was essentially complete after 48 -72 h in all subjects. These pharmacokinetic changes are not expected to have a clinically relevant influence on the safety of Bilastine, since Bilastine plasma levels in patients with renal impairment are still within the safety range of Bilastine.

Hepatic impairment

There are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolized in human. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination, biliary excretion is expected to be only marginally involved in the elimination of Bilastine. Changes in liver function are not expected to have a clinically relevant influence on Bilastine pharmacokinetics.

Elderly

Only limited pharmacokinetic data are available in subjects older than 65 years. No statistically significant differences have been observed with regard to PK of Bilastine in elderly aged over 65 years compared to adult population aged between 18 and 35 years.

Paediatric population

No pharmacokinetic data are available in adolescents (12 years to 17 years) as the extrapolation from adult data was deemed appropriate for this product.

5.3 Preclinical safety data

Non-clinical data with Bilastine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproduction toxicity studies effects of Bilastine on the foetus (pre-and post-implantation loss in rats and incomplete ossification of cranial bones, stern brae and limbs in rabbits) were only observed at maternal toxic doses. The exposure levels at the NOAELs are sufficiently in excess (>30 fold) to the human exposure at the recommended therapeutic dose.

In a lactation study, Bilastine was identified in the milk of nursing rats administered a single oral dose (20 mg/kg). Concentrations of Bilastine in milk were about half of those in maternal plasma. The relevance of those results for humans is unknown.

In a fertility study in rats, Bilastine administered orally up to 1000 mg/kg/day did not induce any effect on female and male reproductive organs. Mating, fertility and pregnancy indices were not affected.

As seen in a distribution study in rats with determination of drug concentrations by autoradiography, Bilastine does not accumulate in the CNS

MONTELUKAST SODIUM DRUG LITERATURE:

Medicine Overview OF Montelukast

Montelukast sodium is a drug used for long-term prevention of asthma, to relieve allergy symptoms, such as a runny nose, nasal congestion and sneezing.

THERAPEUTIC CLASS OF Montelukast

Antiasthmatic drugs- (Leukotriene receptor antagonists)

WHY Montelukast IS PRESCRIBED

Montelukast is prescribed for the treatment of:

- Allergic asthma
- Allergic rhinitis
- Exercise-induced asthma

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Montelukast is a selective Leukotriene receptor antagonist that inhibits the effects of cysteinyl Leukotriene in the airways. Cysteinyl Leukotriene and Leukotriene receptor occupation have been correlated w/ the path physiology of asthma, including airway oedema, smooth muscle contraction, and altered cellular activity associated w/ the inflammatory process, which contribute to the signs and symptoms of asthma.

Precautions

Report to the physician if the patients are allergic to Montelukast or any other drugs. Not intended for the treatment of acute asthma attacks. Patient with aspirin-sensitive asthma should continue to avoid aspirin and other NSAIDs. Avoid abrupt substitution to oral or inhaled corticosteroids. Pregnancy and lactation.

Contraindications of Montelukast

Hypersensitivity

Side Effects

Report to the physician immediately if the patients are having any of these following symptoms:

• Dizziness, Fatigue, Fever,Rash,Abdominal pain,Dyspepsia, Dental pain, Gastroenteritis, Weakness,Cough,Nasal congestion,Aggression,Agitation,Angioedema, Arthralgia,Bleeding tendency, Bruising,Cholestasis,Diarrhoea,Dream abnormalities,Drowsiness,Oedema,Eosinophilia,Hallucinations,Hepatic eosinophilic infiltration (rare),Hepatitis, Hypersensitivity, Hypoaesthesia,Insomnia,Irritability, Muscle cramps,Myalgia,Nausea, Palpitation, Pancreatitis, Paraesthesia,Pruritus, Restlessness, Seizure,Urticaria, Vasculitis,Vomiting, Anaphylaxis,Churg-strauss syndrome

Food to Avoid

If allergic to any food, please consult with the physician.

During therapy avoid taking- St. John's wort (Reduced serum levels).

Alcohol Interaction

Consumption of alcohol is not advisable.

Pregnancy/Lactation Protocol

Pregnancy Category: B

Please consult with the physician during pregnancy and lactation.

Storage

Store at 25°C. Protect from moisture and light.

VI. EXPERIMENTAL WORK AND RESULTS

Drug profle: Bilastine

TABLE-1

Description	White to almost white solid
Form	Crystalline powder
Chemical name	Bilastine-d6

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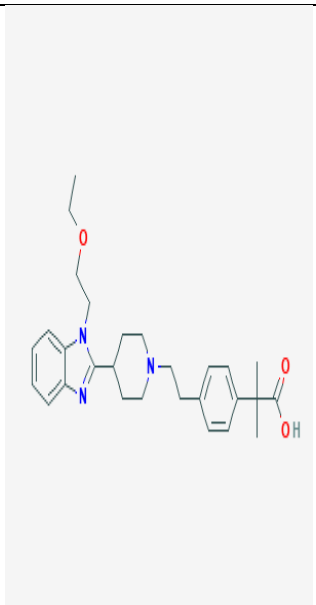
Structure	
Molecular formula	2-[4-[2-[4-[1-(2-ethoxyethyl)benzimidazol-2-yl]piperidin-1-yl]ethyl]phenyl]-2-methylpropanoic acid.
Molecular Weight	463.622 g/mol
Melting Range	>195ºC (dec.)
Solubility	Chloroform (Slightly), Methanol (Slightly)
Therapeutic Category	Pneumology-allergology
Storage Conditions	Store in well closed container away from sun light

Drug Profle: Montelukast Sodium

TABLE-2

Description	**Montelukast sodium is a hygroscopic, optically active, and white to off-white powder.**
Chemical name	**[R-(E)]-1-[[[1-[3-[2-(7-chloro-2 quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid**

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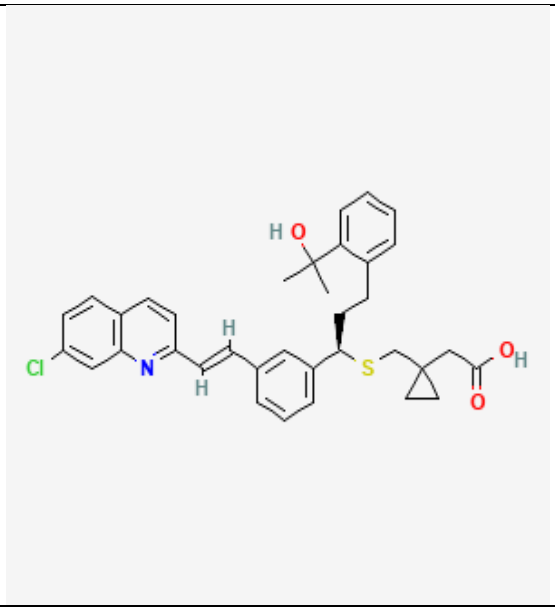
Structure	
Molecular formula	**$C_{35}H_{36}ClNO_3S$**
Molecular Weight	**608.17**
Melting Range	**84-90°C**
Solubility	**Freely soluble in ethanol, methanol, water. Insoluble in acetonitrile /Monosodium salt**
Therapeutic Category	**Antiasthmatic**
Storage Conditions	**stored at 25 °C and protected from light and moisture with exposure for short periods to temperatures of 15-30 °C permitted**

Certificate of analysis of Bilastine

TABLE-3

S.No	TEST	Specifications	Results
1.	**Description**	White to almost white crystalline powder	White crystalline powder
2.	**Solubility**	sparingly soluble in methanol & soluble in methylene chloride	Complies

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3.	**Identification a) By HPLC** **b) By IR**	Principle peak obtained with assay solution has same retention time as that of peak due to standard Bilastine. IR spectrum of sample should be concordant with standard spectrum of Bilastine	Complies
4.	**Loss on Drying**	Not more than 1.0%w/w	0.33%w/w
5.	**Residue on Ignition**	Not more than 0.1%	0.07%
6.	**Heavy metals**	Not more than 20 ppm	Less than 20 ppm
7.	**Assay(on dried basis by HPLC)**	NLT 98.0% and NMT 102.0%w/w	99.6%w/w
8.	**Specific optical rotation**	Between +41° & + 51°	49.5°

Certificate of analysis of Montelukast Sodium

TABLE-4

S.No	TEST	Specifications	Results
9.	**Description**	White to almost white crystalline powder	White crystalline powder
10.	**Solubility**	sparingly soluble in methanol & soluble in methylene chloride	Complies
11.	**Identification b) By HPLC** **b) By IR**	Principle peak obtained with assay solution has same retention time as that of peak due to standard Montelukast sodium IR spectrum of sample should be concordant with standard spectrum of Montelukast sodium	Complies

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12.	**Loss on Drying**	Not more than 1.0%w/w	0.33%w/w
13.	**Residue on Ignition**	Not more than 0.1%	0.07%
14.	**Heavy metals**	Not more than 20 ppm	Less than 20 ppm
15.	**Assay(on dried basis by HPLC)**	NLT 98.0% and NMT 102.0%w/w	99.6%w/w

Materials used

TABLE-5

S.No	**Ingredients**	**Pharmaceutical Status**	**Purpose**	**Supplier**
1	Bilastine	IHS	Active ingredient	Matrix laboratories, Hyd
2	Montelukast sodium micronized form	IHS	Active ingredient	ORNET PHARMA
3	Pregellatinised starch	USP	Diluent,Binder	Signet chemical corporation Pvt ltd
5	Microcrystalline Cellulose (PH 102)	USP	Diluent	Wei Ming pharmaceutical Mfg.Co, Ltd
6	Anhydrous Lactose DC-Grade	USP	Diluent	Signet chemical corporation Pvt ltd
7	Sodium Starch glycolate type A (derived from potato)	USP	Binder	Signet chemical corporation Pvt ltd
8	Cross povidone	USP	Disintegrant	Aditya chemicals
9	Talc	USP	Lubricant	Mittal polymers
10	Colloidal Silica anhydrous	USP	Glidant	Mittal polymers
11	Magnesium Stearate	USP	Lubricant	Mittal polymers

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12	Opadry white	IHS	COLOURING AGENT	Signet chemical corporation Pvt ltd

Instruments used

TABLE-6

S.NO	Equipment	Company
1	Electronic balance	Mettle Toledo,USA
2	Bulk density apparatus	Electrolab ,Mumbai
3	Rapid mixer granulator	Anchor, Mumbai
4	Double cone blender	Erweka
5	Rotary Tablet punching machine	Rimek, Mumbai
6	Friability test apparatus	Electro lab, Mumbai
7	Tablet hardness tester	Schleuniger hardness tester
8	Disintegration test apparatus	Electrolab , Mumbai
9	Tablet dissolution apparatus	Electrolab , Mumbai
10	HPLC	Schimadzu

VII. PREFORMULATION CHARACTERSTICS OF BILASTINE AND MONTELUKAST SODIUM:

PREFORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Objective

The overall objective of Preformulation testing is to generate information useful to the formulation in developing stable and bio available dosage forms.

Scope

The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Physical Properties

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

S.No	Drug	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner Ratio
1.	Bilastine	0.520	0.650	20.0	1.25

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2.	Montelukast sodium(micronized form)	0.560	0.68	19.25	1.20

TABLE-8

VIII. COMPARATIVE FORMULATION OF BILASTINE 20MG AND MONTELUKAST SODIUM 10MG FILM COATED TABLETS

TABLE-9

S.NO	INGREDIENTS	F-1(mg)	F-2(mg)	F-3(mg)	F-4(mg)	Optimised formula
1	**Bilastine**	**20mg**	**20mg**	**20mg**	**20mg**	**20mg**
2	**Montelukast sodium(micronized form)**	**10.5mg**	**10.5mg**	**10.5mg**	**10.5mg**	**10.5mg**
3	Lactose anhydrous (DCgrade)	**45mg**	**39mg**	**35mg**	**35mg**	**35mg**
4	Microcrystalline Cellulose pH 112	**30mg**	**32.5mg**	**32.5mg**	**32.5mg**	**32.5mg**
5	Sodium Starch Glycolate - A	**10mg**	**12mg**	**15mg**	**15mg**	**15mg**
6	Pregelleatinazed starch	**5mg**	**5mg**	**6mg**	**6mg**	**6mg**
7	Cross povidone	**4mg**	**5mg**	**5mg**	**6mg**	**6mg**
8	Talc	**0.5mg**	**1.0mg**	**1.0mg**	**1.0mg**	**1.0mg**
9	Colloidal Silica anhydrous	**3mg**	**3mg**	**3mg**	**3mg**	**3mg**
10	Magnesium stearate	**2mg**	**2mg**	**2mg**	**2mg**	**2mg**
	Total uncoated tablet weight(mg)	**130mg**	**130mg**	**130mg**	**130mg**	**130mg**
11	Opadry white	**2.0mg**	**2.0mg**	**2.0mg**	**2.0mg**	**2.0mg**
12	Purified water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
	Coated tablet weight(mg)	**132mg**	**132mg**	**132mg**	**132mg**	**132mg**

MANUFACTURING FLOW CHART

Bilastine 20mg and Montelukast sodium 10mg film coated tablets g were prepared by Direct compression Method

Dispensing of all Excipients

Sieving & Mixing

Blending

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Compression

Coating

IX. MANUFACTURING PROCESS

Direct compression: (F1 – F5)

Weigh accurately Bilastine, Montelukast sodium (250micrometer), Lactose anhydrous (DCgrade), Microcrystalline Cellulose pH 112, Sodium Starch Glycol late – A, Pregelleatinazed starch, Cross Povidone, Pass through 40 mesh and mix and collect in poly bags. Blend the above ingredients in a double cone blender for 15 minutes. Weigh Talc, Colloidal Silica anhydrous, magnesium stearate, talc accurately, pass through 60 meshes and add to the above blend. Compress the tablets with 8mm punches .After compression subjected to film coating by Opadry white solution till again weight to 132mg.

X. ANALYTICAL DATA

Bilastine 20mg and Montelukast sodium 10mg Film coated tablets Analysis compare with marketed tablets

Physical parameters

a. Weight Variation test

Twenty tablets were collected and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The weight variation limits are given in below table.

Table No. 9: Weight Variation limits

Average weight of tablet (X mg)	Percentage Deviation
80 mg or less	10
80mg to 250mg	7.5
more than 250 mg	5

b.Thickness

Twenty tablets were collected and each table t thickness was measured by using vernier caliper. The allowable limit is ± 0.3%.

c. Hardness

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. If the table t is too hard, it may not disintegrate in the required period of time and if it is too soft, it will not withstand the handling during coating, packaging and shipping operations. Hardness was measured using hardness tester. For each batch three tablets were tested and mean was calculated.

10.2 Disintegration Study:

The hardness of the dry granulated and compressed tablets was adjusted depending on the settings of the device used for compression. The disintegration time of tablets was then determined according to the US Pharmacopeia (USP) test for uncoated tablets in 37°C deionised water. Comparable results are obtained compared to the inventive examples above using the direct compression method.

Table:10

s.no	Parameter	F-1	F-2	F-3	F-4	F-5	**BITOSEN**
1	Average weight (mg)	131.5mg	132mg	132mg	129.5mg	132mg	128mg

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2	Thickness (mm)	3.64	3.73	3.70	3.54	3.57	3.52mm
3	Hardness (kg)	5	6	7	7	7	6.5
4	Disintegration time (min)	18	15	11	13	15	12
5	Friability (%)	1	0.9	0.8	0.8	0.8	0.8

The disintegration time of tablets was determined according to the US Pharmacopeia (USP) test for uncoated tablets in 37°C deionized water. The reported result is an average of 6 measurements. As can be determined from the data below, the disintegration time is short, and comparable between both the inventive and comparative examples.

TABLE-11

S.NO	Formulations	Disintegration time(mins)
1	F-1	14-20
2	F-2	11-15
3	F-3	8-11
4	F-4	8-11
5	F-5	10-12

10.2.Dissolution Study:

For the tablet formulations of inventive examples and comparative examples, the dissolution test was carried out according to the following dissolution test methods and conditions.

Dissolution conditions and methods:

The test was carried out using tablets at a paddle speed of 50 revolutions per minute (RPM) according to method 2 (Paddle) of dissolution test of the USP, using 900 mL of acetate buffer at pH 4.5. The temperature of the medium is maintained at 37°C ± 0.5°C using a water bath. Sample solutions were obtained at 5, 10, 15, 20, 30, 45 and 60 minutes after starting the test, and filtered through a 0.45 µm PVDF Millipore syringe filter.

Multimedia dissolution profiles are generated in the hydrochloric acid medium at pH 1.2 and in phosphate buffer solution at pH 6.8 also according to method 2 (Paddle) of dissolution test of the USP. Analogously, the dissolution is tested under the alternative conditions: 250 mL of acetate buffer at pH 4.5, method 2 (Paddle) with PEAK vessels at a paddle speed of 50RPM.

Dissolution analytical test method details:

Equipment:

- A High Performance Liquid Chromatography system with isocratic elution capability, a Spectrophotometric UV detector and an auto sampler (Waters Alliance 2695 separations module, Waters 2487 dual λ absorbance detector or equivalent).
- Data handling system (Waters Empower work station or equivalent).
- Analytical column: A stainless steel column 150 mm long, 4.6 mm internal diameter filled with octadecylsilyl silica particles as a stationary phase with size 3.5µm. (Use: Xterra RP18, 150 mm length, 4.6 mm internal diameter, 3.5µm particle size or equivalent).
- Dissolution Tester (Make: Electrolab, model TDT-08L or equivalent).

Preparation of analytical solutions:

Buffer: Prepare 10mm Di Potassium Hydrogen Phosphate Anhydrous. For example, transfer 1.76 gm of Di Potassium Hydrogen Phosphate Anhydrous in to beaker containing 1000 mL of Milli-Q- grade water. Adjusted pH to 6.8 with Diluted Orthophosphoric acid. Filter through 0.45µ micron or finer porosity membrane filter **Mobile phase:** Buffer: Acetonitrile (65:35 v/v).

Preparation of diluent: Mix water and Acetonitrile in the ratio of 50:50 (v/v) and degas.

Preparation of dissolution media: Prepare acetate buffer solution pH 4.5 in purified water as mentioned in the Ph. Eur. 5.17.1 For example: Dissolve 29.9 g of Sodium acetate trihydrate and

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16.6 mL of Acetic acid into a 10,000 mL beaker containing 8,000 mL of purified water. Dissolve and dilute to 10000 mL with water and mix. Adjust the pH to 4.5 if necessary, with Acetic acid or diluted Sodium hydroxide solution.

Standard solution: Prepare a solution containing 0.022 mg/mL of Bilastine in diluent. For example, weigh and transfer about 22 mg of Bilastine working standard into 50 mL clean, dry volumetric flask add about 10 mL of diluent and sonicate to dissolve. Further add 30mL of dissolution media and sonicate for 2 minutes. Make up the volume with Dissolution media. Dilute 5 mL to 100 mL with dissolution media. Prepare it in duplicate.

Sample solution: Set the parameters of instrument as mentioned above. Place one tablet each in six vessels containing the dissolution medium, which has been equilibrated at 37°C±0.5°C and start the dissolution tester. At the specified time interval withdraw sample solution from each vessel. Filter through 0.45µm syringe filter, discarding first few mL of filtrate.

HPLC chromatographic conditions:

- Column: Xterra RP18, 150mm length, 4.6mm internal diameter, 3.5µm particle size or equivalent
- Flow rate: 1.0 mL/min
- Detection: UV, 215 nm
- Injection Volume: 10 µL
- Data acquisition time: 5 minutes
- Pump mode: Isocratic
- Column temperature: 30° C

Precautions during dissolution test

Saturate the filter with about 10 mL of sample solution before collection of samples. Use prefilter at the end of dissolution cannula during sample collection in dissolution vessel.

0.45µm PVDF (Make: Millipore or Whatman). During the sample filtration avoid entrapment of air bubbles in to the filter. In case of dissolution profiles, use separate filter at each time point.

Evaluation of system suitability

Equilibrate the column and system at the initial composition for 30 minutes. Inject the dissolution media as blank into the liquid chromatographic system and record the chromatogram. Inject the STD-I solution, five times into the liquid chromatographic system and record the chromatogram. Symmetry factor should be not more than 2.0 for the Bilastine peak from the standard chromatogram. %RSD for Bilastine peak areas of five injections from STD-I should be not more than 2.0. Inject STD-II solution in duplicate into the liquid chromatographic system and record the chromatogram. Calculate the similarity factor between two standard preparations. The similarity factor between two standard preparations should be in between 0.98 to 1.02.

Calculation of Similarity factor

Similarity factor = Average area of STD − I Average area of STD − II × Weight of STD − II Weight of STD − I

$$\text{Similarity factor} = \frac{\text{Average area of STD-I}}{\text{Average area of STD-II}} \times \frac{\text{Weight of STD-II}}{\text{Weight of STD-I}}$$

Procedure

Inject the sample solution into the liquid chromatography and record the chromatogram. Retention time of Bilastine is about 2.8 minutes.

Calculation

% Labelled amount as Bilastine = At As × Ws 50 × 5 100 × 900 Lc × P

$$\%\ \text{Labelled amount as Bilastine} = \frac{At}{As} \times \frac{Ws}{50} \times \frac{5}{100} \times \frac{900}{Lc} \times P$$

Where,

At

: Area of peak corresponding to Bilastine in test solution chromatogram

As

: Average area of peak corresponding to Bilastine obtained from STD-I chromatograms.

Ws

: Weight of Bilastine working standard used for the preparation of STD-I (mg).

Lc

: Label claim of Bilastine (mg).

P

: % Potency of Bilastine working standard on as is basis.

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Table: Comparative dissolution profiles of Bilastine20mg and Montelukast sodium 10mg film coated tablets with BITOSEN tablets

In Acetate buffer pH 4.5, Paddle-50 RPM, USP TYPE-II APPARATUS

TABLE-12

Time in minutes		%Mean cummulative amount of drug dissolved				
	F-1	F-2	F-3	F-4	F5	**BITOSEN**
5	54	45	48	52	54	60
10	78	79	75	77	78	80
15	82	85	88	88	88	92
20	90	95	95	95	95	98
30	95	99	99	98	99	100
45	99	100	100	100	100	100
60	100	100	100	100	100	100

pH 4.5 phosphate buffer, Paddle-50 RPM, USP TYPE-II APPARATUS

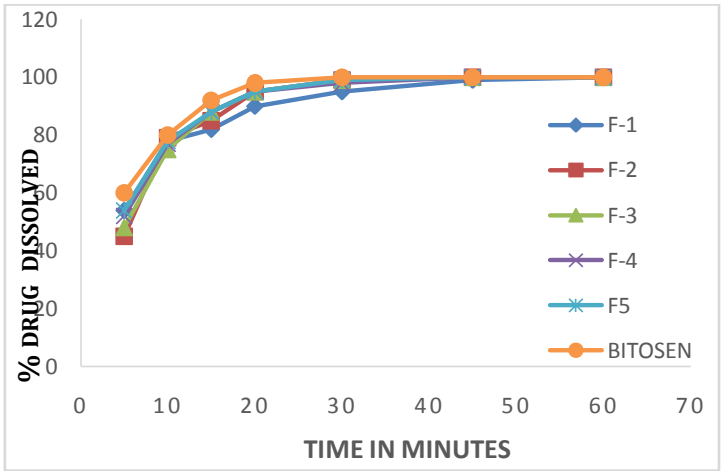

Table: Comparative dissolution profiles of Bilastine tablets 20 mg with BITOSEN

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In Phosphate buffer solution pH 6.8, Paddle-50 RPM,USP TYPE-II APPARATUS 900Ml

TABLE-13

Time in minutes	%Mean cummulative amount of drug dissolved					
	F-1	F-2	F-3	F-4	F-5	**BITOSEN**
5	54	45	48	54	55	56
10	71	59	62	65	67	77
15	77	65	73	75	78	85
20	80	70	79	80	85	88
30	86	76	85	89	90	95
45	90	81	90	92	95	99
60	92	84	95	99	99	100

pH 6.8Phosphate buffer, Paddle-50 RPM, USP TYPE-II APPARATUS

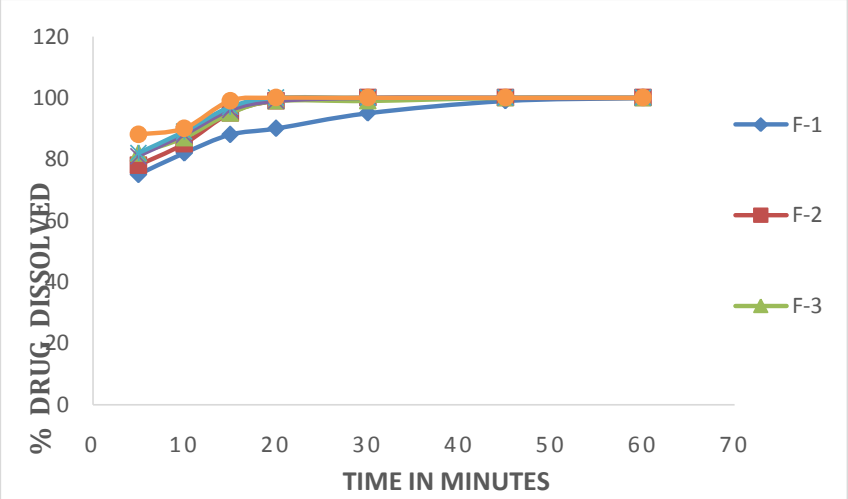

Table: 14 Comparative dissolution profiles of Bilastine tablets 20 mg with BITOSEN
In Hydrochloric acid media pH 1.2, Paddle-50 RPM, 900Ml USP TYPE-II APPARATUS

Time in minutes	%Mean cummulative amount of drug dissolved					
	F-1	F-2	F-3	F-4	F-5	**BITOSEN**
5	75	78	82	81	82	88
10	82	85	87	88	89	90
15	88	95	95	96	97	99
20	90	99	99	99	100	100
30	95	100	99	100	100	100
45	99	100	100	100	100	100
60	100	100	100	100	100	100

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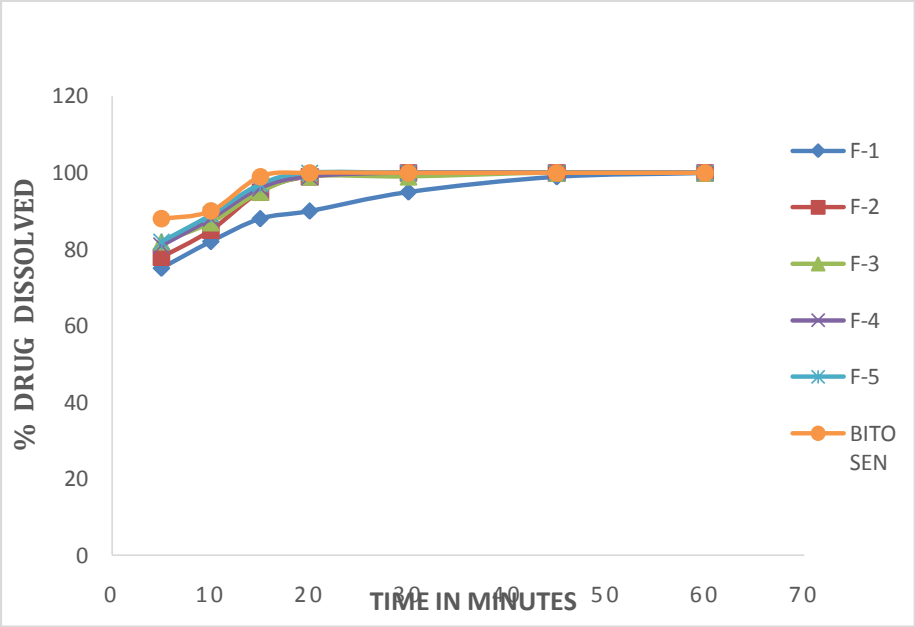
Hydrochloric acid media pH 1.2,, Paddle-50 RPM, USP TYPE-II APPARATUS



As can be seen from the tables above, the comparative dissolution studies of Bilastine drug profile are improved with respect to their dissolution times compared to the comparative examples when assessed using acetate buffer at pH 4.5. The presence of water-soluble filler therefore enables the improvement of dissolution of polymorph 2, such that it is comparable to the composition comprising polymorph 1. The inventive examples show comparable dissolution profiles of the Bilastine tablets 20mg release of drug faster when assessed in phosphate buffer of hydrochloric acid media at pH 6.8 and 1.2, respectively.

Chromatographic Conditions for Montelukast sodium Analysis

The chromatographic method used for quantification of Montelukast was a modification of the method .Drug quantification was performed with HPLC with ultraviolet (UV) detection (Agilent HPLC system 1100/1200 series; Agilent, USA), using a C_{18} column (RP Agilent Eclipse XDB, 250 mm × 4.6 mm, 5 µm particle size), and ammonium acetate buffer pH 5.5 (A) and methanol (B) as mobile phase, delivered on a linear gradient. The selected gradient started with 10% of solvent B, which was increased to 50% within 2 min, and 90% within 4 min; at 11.30 min, the initial conditions of analysis were re-established. Injection volume was 100 µL, flow rate was 1 mL min^{-1}, run time was 12.30 min, detection wavelength was 284 nm and column temperature was 20°C.

The corresponding in vivo drug absorption profiles were obtained after deconvolution of the oral data using the Wagner-Nelson equation (Eq. 1)

$$\%absorbed=A(t)A(\infty)\times100=A(t)+k\int t\tau=0A(\tau)d\tau k\int\infty\tau=0A(\tau)d\tau\times100$$

Where A (t) is the amount of drug in the system at time t and k is the first-order elimination rate constant . The elimination rate constant was obtained from the slope of the terminal logarithmic concentrations of the in vivo montelukast oral data. The linear trapezoidal method was used to calculate the area under the curve of each in vivo % drug absorbed over 4-h profile ($AUC_{0-4\,h}$in vivo).

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In Vitro/In Vivo Relationship

MONTELUKAST SODIUM DISSOLUTION PROFILE

TABLE-15 :0.1% SLS MEDIUM AS A DISSOLUTION MEDIA

S.NO	TIME (mins)	% Montelukast released in Dissolution medium					
		Formula -1	Formula-2	Formula-3	Formula-4	Formula-5	BITOSEN
1	5mins	45	45	45	46	46	54
2	10mins	60	75	75	77	77	82
3	15mins	75	81	85	90	90	98
4	20mins	82	85	90	95	96	99
5	30mins	90	95	96	99	100	100
6	45 mins	98	98	99	100	100	100
7	60mins	100	100	100	100	100	100

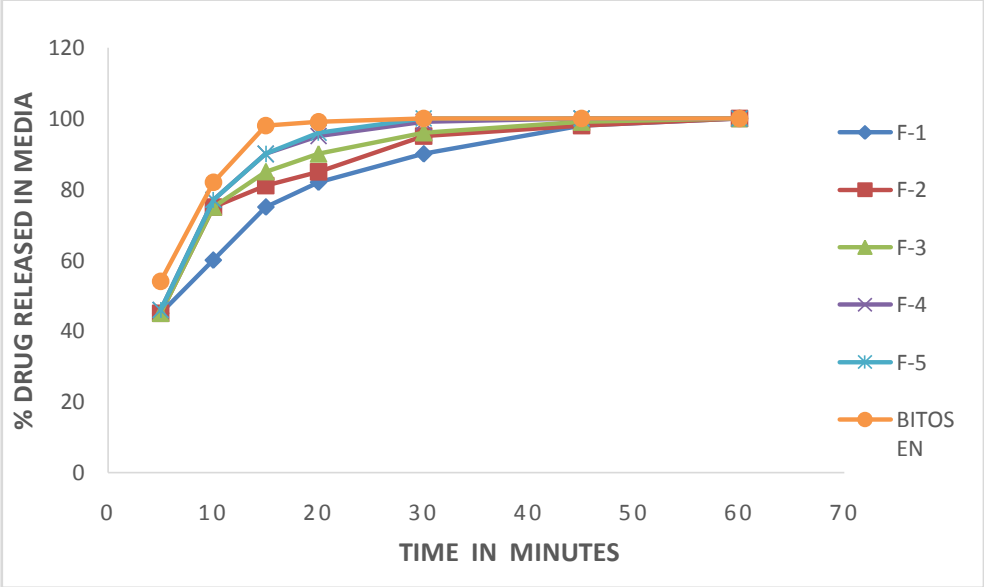

TABLE-16

$P^{H\ 2.0}$ ACIDIC BUFFER AS A DISSOLUTION MEDIA

S.NO	TIME (mins)	% Montelukast released in Dissolution medium					
		FORMULA-1	Formula-2	Formula-3	Formula-4	Formula-5	BITOSEN
1	5mins	10	15	20	25	25	30
2	10mins	15	20	25	32	30	35
3	15mins	25	36	45	47	50	55
4	20mins	35	40	50	55	57	67
5	30mins	50	55	60	70	72	75
6	45 mins	70	75	85	85	88	88
7	60mins	80	85	90	90	99	99

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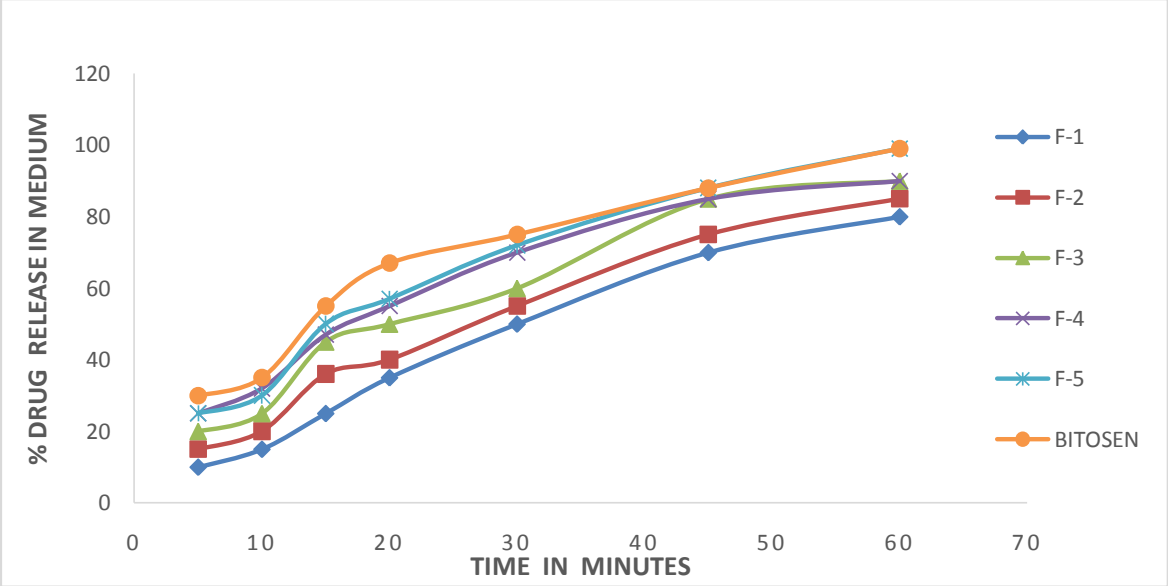
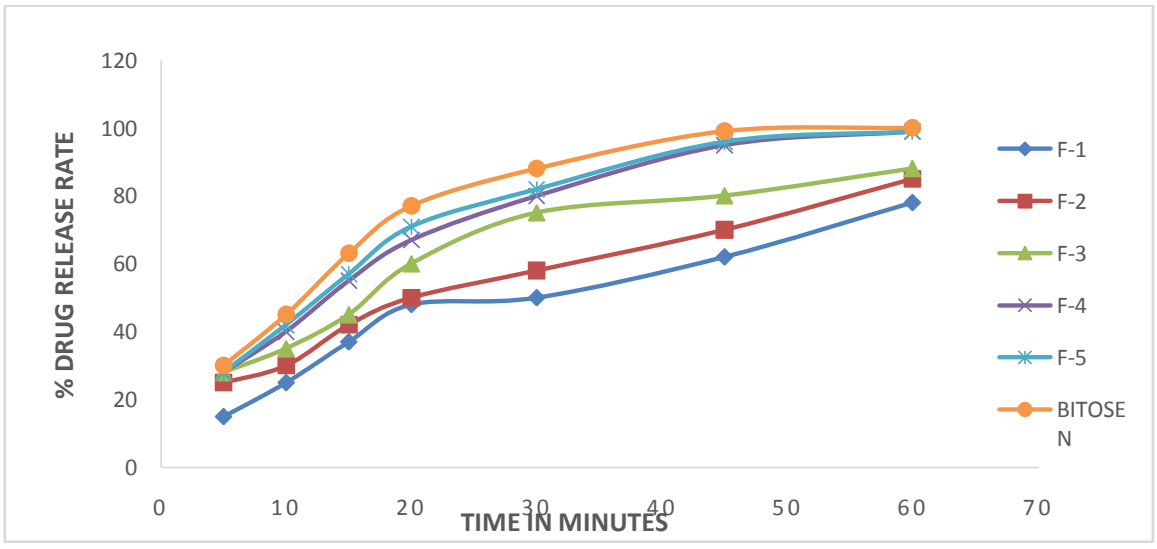


TABLE-17
PH 6.8 PHOSPHATE BUFFER

S.NO	TIME (mins)	% Montelukast released in Dissolution medium					
		Formula-1	Formula-2	Formula-3	Formula-4	Formula-5	BITOSEN
1	5mins	15	25	28	28	28	30
2	10mins	25	30	35	40	42	45
3	15mins	37	42	45	55	57	63
4	20mins	48	50	60	67	71	77
5	30mins	50	58	75	80	82	88
6	45 mins	62	70	80	95	96	99
7	60mins	78	85	88	99	99	100



International Journal of Pharmaceutical Research and Applications
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XI. DISCUSSION

The project work entitled as, formulation development and evaluation of Bilastine20mg and Montelukast 10mg film coated tablets. In this present study the characters of the reference product were evaluated the results were fall within official standards. Bilastine is maximum soluble in phosphate buffer of hydrochloric acid media at pH 6.8 and 1.2, respectively. Montelukast sodium is maximum soluble in 0.1% SLS MEDIA, P^{H} 2.0 ACIDIC BUFFER AS a DISSOLUTION MEDIA, P^{H} 6.8 PHOSPHATE BUFFER. Based on the result of Drug excipients compatibility studies the choice of excipients was decided in the present case excipients such as Microcrystalline cellulose, Lactose anhydrous DC grade, Pregelleatinazed starch,Crosspovidone, sodium starch glycolate, Colloidal silica Talc and Magnesium stearate.The blend has been selected to improve the formulation development. Blend was made by the appropriate combination of API and excipients by using direct compression approach. The blend which has been prepared by direct compression approach (Data not shown). Hence the attempt was taken the results indicate that the blend has excellent flow properties and compressibility Index. After achieving the prototype formulation the tablets were characteristised to appearance, thickness, weight variation, dissolution, and assay were performed.

Formulation-I has been taken by direct compression method by trial and error method. The overall drug release was found to be 80%. Increases the drug releases, another attempt was made to decrease the diluent concentration and increase the disintegration concentration by direct compression. In trail 2 initial release of the drug is less when compared to that of the reference listed drug. So another trail was made to increase the initial drug release as well as reduced the cost of product with further decrease the concentration of diluents and increase concentration of low cost diluent Lactose anhydrous (DC Grade). Here also the initial release was less than the innovator. This trail follows the initial release but later not match with innovator. Trail 3 was developed by. Now by taking all the observations from the above formulations which have been taken to study the effects of different inactive ingredients in various concentrations, the optimized formulation has been developed. The formulation 4 was designed having the similar dissolution profiles with that of the reference listed drug. Reproducible trail performed as formulation 5 physical and chemical parameters were followed as per pharmacopoeias standards and release also matches with reference formulation. Montelukast sodium shown faster release in SLS MEDIA and Bilastine shown faster release in ph 6.8 phosphate buffer similar release behaviour showing with Reference sample. Final FORMULA 5 optimized and developed formulation.

XII. CONCLUSION

The project work entitled, formulation development and evaluation of Bilastine 20mg and Montelukast sodium 10mg film coated was comapare with BIOSEN film coated tablets carried out in the study. It was mainly concentrated on the optimization of the formulation to meet the official requirements mainly dissolution parameters. The optimized formulation F4 and Formulation F5 was closer with the reference product. Tablets were evaluated for Weight variation, thickness, hardness, friability and assay. It was revealed that the result of F4 and F5 formulations had acceptable physical parameters. In the present study Bilastine 20mg and Montelukast sodium 10mg film tablets have been formulated by using direct compression technique, to provide a safe, to maintain constant drug concentration in blood, minimize dose frequent administration and improve patient compliance. Pre and post formulation parameters were studied for the formulated batches.

Drug Excipients compatibility studies were performed using HPLC. The chromatogram of pure drug and physical mixtures of drug results were studied for 1 month stress condition, and 3 months Accelerated condition. As the present efforts are directed towards the formulation development of an immediate release tablet dosage form of an antihistaminic drug Bilastine and montelukast during this stage of investigation, various factors are included in optimizing of the formulation. Primarily the effect of concentrations of various inactive ingredients .The effect of the diluent concentration, disintegrant concentration, lubricant concentration, played a key role in optimizing the formula.

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about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor. Please refer to this study by its ClinicalTrials.gov identifier (NCT number): NCT02761252.

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