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FORMULATION AND DEVELOPMENT OF BILASTINE TABLETS 20MG

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ABSTRACT

Bilastine is a new second generation H1-antihistamine approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU). Bilastine, with its efficacy and safety profile epitomizes the evolution of research on antihistamines Bilastine works by blocking histamine receptors. Fast dissolving tablets of Bilastine were prepared using Mannitol Dc grade, sodium starch glycolate and Crosspovidone as superdisintegrants and Colloidal silica, Talc, Magnesium stearate by direct compression method. The tablets prepared were evaluated for various parameters like weight variations, hardness, friability, in vitro dispersion time, drug content, wetting time, in vitro drug release. The tablets prepared by direct compression method possess a weight variation below ±7.5%, hardness of 3 to 4.0 Kg/cm², percentage friability of 0.85, in vitro dispersion time of 10 secs, Wetting time of 10 seconds, and in vitro drug release showed 94% to 99.00% within 15 min. The formulation contains Crosspovidone and Sodium Starch Glycolate shows better Disintegration time and 99% drug release within 20 min. Bilastine tablets compare with marketed product physical parameters and dissolutiion

parameters are shows similar results to the formulated tablets based on physical and chemical paramed optimised our formula with marketed product of bilastine tablets 20 mg.

KEYWORDS: Mannitol Dc grade, Microcrystalline Cellulose, Sodium Starch glycolate type A (derived from potato), Colloidal silica anhydrous, Cross povidone, Talc and Magnesium Stearate.

INTRODUCTION

From time immemorial, drugs have been an inseparable part of mankind's history since they fulfill 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.

Conventional medication systems that require multi-dose therapy are not without problems. With a view to overcoming these problems, the current trend in pharmaceutical research is to

design and develop new formulations, thereby enhancing the therapeutic efficacy of existing drugs. Moreover, the impetus for research into drug delivery can be attributed to the exorbitant cost and large development period involved in 'new drug development' with concomitant recognition of the therapeutic advantages of Controlled / Sustained drug delivery.[2]

AIM: Formulation and development of Bilastine tablets 20mg.

OBJECTIVE

- To enhance patient compliance and adherence to therapy.
- To formulate fast dissolving tablet of Bilastine 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.

1.0 Innovator product

Ilaxten 20 mg tablets

Each tablet contains 20 mg of bilastine.

2.0 List of excipients

Microcrystalline Cellulose

Sodium Starch glycolate type A (derived from potato)

Colloidal silica anhydrous

Cross povidone

Talc

Magnesium Stearate

3.0 Pharmaceutical form

Tablet.

Oval biconvex scored white tablets length 8 mm, width 3.6mm.

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

4.0 Therapeutic indications

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

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

4.1 Posology 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 rhinoconjunctivitis (SAR and PAR) and urticaria.

The tablet should be taken one hour before or two hours after intake of food or fruit juice (see section 4.5).

Special populations

Elderly

No dosage adjustments are required in elderly patients (see sections 5.1 and 5.2).

Renal impairment

No dosage adjustment is required in patients with renal impairment. (see section 5.2).

Hepatic impairment

There is no clinical experience in patients with hepatic impairment. Since bilastine is not metabolized and renal clearance is its major elimination route, hepatic impairment is not expected to increase systemic exposure above the safety margin. Therefore, no dosage adjustment is required in patients with hepatic impairment (see section 5.2).

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.

Method of administration

Oral use.

The tablet is to be swallowed with water. It is recommended to take the daily dose in one single intake.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Paediatric population

Efficacy and safety of bilastine in children under 12 years of age have not been established.

In patients with moderate or severe renal impairment coadministration of bilastine with P-glycoprotein inhibitors, such as e.g, ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasmatic levels of bilastine and therefore increase the risk of adverse reactions of bilastine. Therefore, coadministration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with food: Food significantly reduces the oral bioavailability of bilastine by 30%.

Interaction with grapefruit juice: concomitant intake of bilastine 20 mg and grapefruit juice decreased bilastine bioavailability by 30%. This effect may also apply to other fruit juices. The degree of bioavailability decrease may vary between producers and fruits. The mechanism for this interaction is an inhibition of OATP1A2, an uptake transporter for which bilastine is a substrate (see section 5.2). Medicinal products that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of bilastine.

Interaction with ketoconazole or erythromycin: Concomitant intake of bilastine and ketoconazole or erythromycin increased bilastine AUC 2-fold and C_{max} 2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since bilastine is substrate for P-gp and not metabolised (see section 5.2). These changes do not appear to affect the safety profile of bilastine and ketoconazole or erythromycin, respectively. Other medicinal products that are substrates or inhibitors of P-gp, such as cyclosporine, may likewise have the potential to increase plasma concentrations of bilastine.

Interaction with diltiazem: Concomitant intake of bilastine 20 mg and diltiazem 60 mg increased C_{max} of bilastine by 50%. This effect can be explained by interaction with intestinal efflux transporters (see section 5.2), and does not appear to affect the safety profile of bilastine.

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.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Ilaxten 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 (see section 5.3). 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.

5.0 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 rhinoconjunctivitis (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 coadministered 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.

Elderly patients (≥ 65 years) included in phase II and III studies showed no difference in efficacy or safety with respect to younger patients. A post-authorization study in 146 elderly patients showed no differences in the safety profile with respect to the adult population.

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 (see section 4.5 "Interaction with ketoconazole, erythromycin and diltiazem") and OATP (see section 4.5 "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

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.

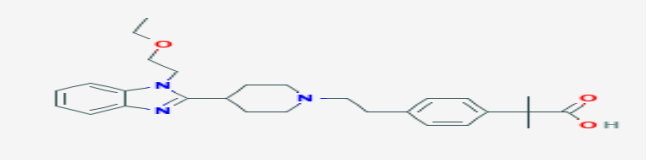
Paediatric population: No pharmacokinetic data are available in adolescents (12 years to 17 years) as the extrapolation from adult data was deemed appropriate for this product.

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, sternebrae 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.

Experimental work and Results

Drug profle: Bilastine

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

Certificate of analysis of Bilastine

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
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°

7.0 Excipents Profile

1. Cellulose, Microcrystalline

Nonproprietary Names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms: Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

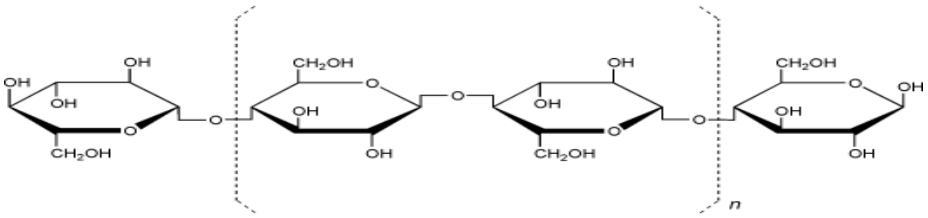
Chemical Name: Cellulose

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000

Where n ≈ 220.

Structural Formula



Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8]and disintegrant properties that make it useful in tableting.

Description: Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is

commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties

Angle of repose

49° for Ceolus KG;

34.4° for Emcocel 90M.[9]

Density (bulk)

0.337 g/cm^3;

0.32 g/cm^3 for Avicel PH-101;

0.29 g/cm^3 for Emcocel 90M;

0.29 g/cm^3 for VivaPur 101.

Density (tapped)

0.478 g/cm^3;

0.45 g/cm^3 for Avicel PH-101;

0.35 g/cm^3 for Emcocel 90M.

Density (true): 1.512–1.668 g/cm^3

Flowability: 1.41 g/s for Emcocel 90M.

Melting point: Chars at 260–270°C.

Moisture content: Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Particle size distribution: Typical mean particle size is 20–200 μm. Different grades may have a different nominal mean particle size.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area

1.06–1.12 m^2/g for Avicel PH-101;

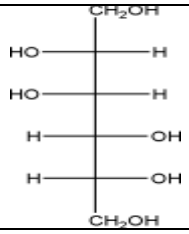
1.21–1.30 m^2/g for Avicel PH-102;

0.78–1.18 m^2/g for Avicel PH-200.

2.0 Mannitol

Grade	Description	Applications
Pearlitol 100 SD Pearlitol 200 SD	Fine particle size Medium particle size	Excellent Diluent-binder for direct compression applications (Fast Dissolving, chewable, oraldispersible, effervescent tablets

Table. 5.

Synonyms	**Mannite, Pearlitol, manna sugar, cordycepic acid.**
Non proprietry Names	BP: Mannitol JP: D-Mannitol PhEur: Mannitolum USP: Mannitol
Chemical Name	D-Mannitol
Empirical formula	$C_6H_{14}O_6$
Structural Formula	
Molecular Weight	182.17
Description	Mannitol occurs as white,odorless crystalline powder or free flowing granules, sweet in taste
Functional categories	Sweetening agent, tablet and capsule diluent, tonicity agent, vehicle
Solubility	Solvent at 20°C Alkalies soluble Ethanol 1in 8 Ether practically insoluble Water 1in 5.5
Loss on Drying	0.3%
Melting point	166-168°C
Bulk Density	0.430 g/cm^3 for powder; 0.7 g/cm^3 for granules
Tap Density	0.734 g/cm^3 for powder; 0.8 g/cm^3 for granules
True Density	1.514 g/cm^3
Stability and storage conditions	Stable in dry state and in aqueous solution. Should be stored in a well closed container in a cool and dry place
Incompatibilities	Precipitation has been reported to occur when a 25%w/v mannitol solution was allowed to contact plastic.
Applications	Diluent, also suggested as plasticizer in soft gelatin capsules, granulation containing mannitol have the advsntage of being dried easily.

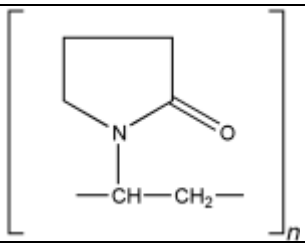
Magnesium Stearate

Table. 9.

Synonyms	**Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.**
Non proprietary names	BP: Magnesium stearate JP: Magnesium stearate PhEur: Magnesii stearas USPNF: Magnesium stearate
Chemical Name	Octadecanoic acid magnesium salt
Empirical formula	$C_{36}H_{70}MgO_4$
Molecular weight	554
Stractural formula	$[CH_3(CH_2)_{16}COO]_2Mg$
Description	Magnesium stearate is a very fine, light white, precipitated or milled; The powder is greasy to the touch and readily adheres to the skin.
Functional categories	Tablet and capsule lubricant
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol
Melting point	117–150°C (commercial samples); 126–130°C (high purity magnesium stearate).
Bulk density	0.159 g/cm^3
Tapped density	0.286 g/cm^3
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
Stabilityand storage conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Applications	Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams

Crosspovidone

Synonyms	Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer
Non Proprietary Names	BP: Crospovidone PhEur: Crospovidonum USPNF: Crospovidone
Description	Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder
Chemical name	1-Ethenyl-2-pyrrolidinone homopolymer
Empirical formula	$(C_6H_9NO)_n$ >1 000 000

Stractural formula	
Functional categories	Tablet disintegrant
Solubility	practically insoluble in water and most common organic solvents
pH	pH = 5.0–8.0 (1% w/v aqueous slurry)
Density (bulk)	0.3–0.4 g/cm^3
Density (tapped)	0.4–0.5 g/cm^3
Moisture content	Maximum moisture sorption is approximately 60%.
Stability and storage conditions	Crospovidone is hygroscopic; it should be stored in an airtight container in a cool, dry place.
Incompatibility	Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials
Applications	Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs

Talc

Synonyms	**Magsil, Magsil Star, purtalc, steatite, soap stone**
Non Proprietary Names	BP: Purified talc JP: Talc PhEur: Talcum USP: Talc
Description	It is a very fine, white to greyish white colored, odourless, impalpable, unctuous crystalline powder. Soft to touch and free from grittiness
Empirical formula	$Mg_6 (Si_2O_5)_4(OH)_4$
Functional categories	Anticaking Agent, Glidant, Tablet & capsule diluent, Lubricant
Solubility	Practically it is insoluble in dilute acids, and alkalis, organic solvents and water.
Loss on drying	It is less than 1.0%
Stability and storage conditions	Talc is stable material, and may be sterilized by heating at 160^{0}C for not less than 1 hour. It should be stored in a well-closed container in a cool place.
Incompatibilities	It is incompatible with quaternary ammonium compounds.
Safety	On oral ingestion it is not going to absorb in the body. Intranasal or intravenous abouse may cause granulomas in the tissue.
Applications	Use Conc. Dusting Powder : (90—99) Glidant and tablet lubricant : (1—10) Tablet and Capsule diluent : (5—30) It is now used as a dissolution retardant in the development of controlled release products.

Materials used

S. No	Ingredients	Pharmaceutical Status	Purpose	Supplier
1	Bilastine	IH	Active ingredient	MSN laboratories, Hyd
2	Microcrystalline Cellulose (PH 102)	USP	Diluent	Wei Ming pharmaceutical Mfg.Co, Ltd
3	Mannitol DC-Grade	USP	Diluent	Signet chemical corporation Pvt ltd
5	Sodium Starch glycolate type A (derived from potato)	USP	Binder	Signet chemical corporation Pvt ltd
6	Cross povidone	USP	Disintegrant	Aditya chemicals
7	Talc	USP	Lubricant	Mittal polymers
8	Colloidal Silica anhydrous	USP	Glidant	Mittal polymers
9	Magnesium stearate	USP	Lubricant	Mittal polymers

Instruments used

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

8.0 Preformulation characterstics of Bilastine

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 bioavailable 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.

Determination of Bulk density and Tapped density: Bulk density is the ratio of the weight of a powder to the volume it occupies. It is expressed as gm/ml. Volume occupied by powder includes volume of the solid portion of the particle and voids between the particles. Bulk density is important in determining the size of the containers needed for handling and processing.

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density, and tapped density were calculated using the following formulas:

Bulk density $= W / V_o$

Tapped density$= W / V_F$

Where,

W = weight of the powder

V_O = initial volume

V_F = final volume

Flow Properties: Irregular flow of powders from the hopper produces tablets with non uniform weights. As respects content uniformity and dose precision can not be achieved in a production of tablets & capsules. Flow properties depend on particle size shape porosity and density of bulk powder. The flow characteristics are measured by angle of repose: Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the height of a pile of the powder and the horizontal plane.

$$\tan Q = \frac{H}{R}$$

Where, H = Height of pile.

R = Radius of the base of pile.

Q = Angle of repose.

Lower, angle of repose better the flow property through and irregular surface of the particles give higher angle of repose. It can be decreased by addition of lubricants, of low concentration decreases the angle of repose at high concentration; enhances angle of repose.

Fines (passed through mesh 100) increases angle of repose. Method: A glass tunnel is held in place with a clamp on ring report over a glass plate, powder (weighed) and poured in tunnel keeping the orifice of tunnel blocked. When powder is emptied from funnel, angle of heap to horizontal plane is measured with protector. Highest of pile (h) and radius of the base (r) is measured with ruler. Thus the angle of repose is measured.

Relationship belongings angle of repose (a) & powder flow

S. No.	Angle of repose (a) degrees	Flow
1	< 25	Excellent
2	25-30	Good
3	30-40 *	Passable
4	40 & above	Very poor

Compressibility Index: Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements.

Compressibility Index Range

S. No.	% Compressibility Index	Flow ability
1	5-12	Excellent
2	13-17	Good
3	18-22	Fair-passable
4	23-32	Poor
5	33-38	Very poor

Compressibility index were calculated using the formula:

Compressibility index=T.D-B.D/T.D*100

Hausner ratio: It indicates the flow property of the powder and

Measured by the ratio of tapped density to bulk density.

Hausner Ratio	Properties
0 -1.2	Free flowing
1.2 -1.6	Cohesive powder

Hausner ratio=T.D\B.D

Where,

T.D= Tapped density, B.D= Bulk density

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

8.0 Comparative Formulation of Bilastine Tablets 20mg.

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	Mannitol Dc grade	55.5mg	48mg	40mg	40mg	40mg
3	Microcrystalline Cellulose	30mg	33mg	38mg	38mg	38mg
4	Sodium Starch glycolate type A (derived from potato)	10mg	12mg	15mg	15mg	15mg
5	Cross povidone	4mg	5mg	5mg	6mg	6mg
6	Talc	0.5mg	1.0mg	1.0mg	1.0mg	1.5mg
7	Colloidal Silica anhydrous	3mg	4mg	4mg	4mg	4mg
8	Magnesium stearate	2mg	2mg	2mg	2mg	2mg
	Total tablet weight(mg)	125mg	125mg	125mg	125mg	125mg

Manufacturing Flow Chart

Bilastine tablets 20mg were prepared by Wet granulation method

Dispensing of all Excipients

↓

Sieving & Mixing

↓

Blending

↓

Compression

9.0 Manufacturing Process

- **Direct compression: (F1 – F4):** Weigh accurately Bilastine, Microcrystalline Cellulose and Mannitol DC grade, Sodium Starch Glycolate, Colloidal Anhydrous Silica, and Magnesium Stearate pass through 40 mesh and mix and collect in poly bags. Blend the above ingredients in a double cone blender for 15 minutes. Weigh magnesium stearate accurately, pass through 60 mesh and add to the above blend. Compress the tablets with 8mm punches.

10.0 Analytical Data: Bilastine Tablets 20mg Method of Analysis comapre with marketd bilastine Ilaxten 20 mg 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. 3: 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 table t 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 deionized water. Comparable results are obtained compared to the inventive examples above using the direct compression method.

Table.

S. No	Parameter	F-1	F-2	F-3	F-4	Ilaxten 20 mg tablets
1	Average weight (mg)	126.4mg	125.2mg	125.3mg	124.5mg	-
2	Thickness (mm)	3.56-3.64	3.38-3.43	3.21-3.24	3.47-3.50	5.00mm
3	Hardness (kg)	5	6	7	7	5
4	Disintegration time (sec)	18	15	11	8	10
5	Friability(%)	1	0.9	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.

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	Ilaxten 20 mg tablets	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 25RPM.

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 and degas.

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 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.

Table: Comparative dissolution profiles of Bilastine tablets 20mg with Ilaxten 20 mg in Acetate buffer pH 4.5, Paddle-50 RPM, 900mL.

Time in minutes		%Mean cummulative amount of drug dissolved			
	F-1	F-2	F-3	F-4	Ilaxten 20 mg
0	0	0	0	0	0
5	54	45	48	52	54
10	78	79	75	77	78
15	82	85	88	88	88
20	90	95	95	95	95
30	95	99	99	98	99
45	99	100	100	100	100
60	100	100	100	100	100

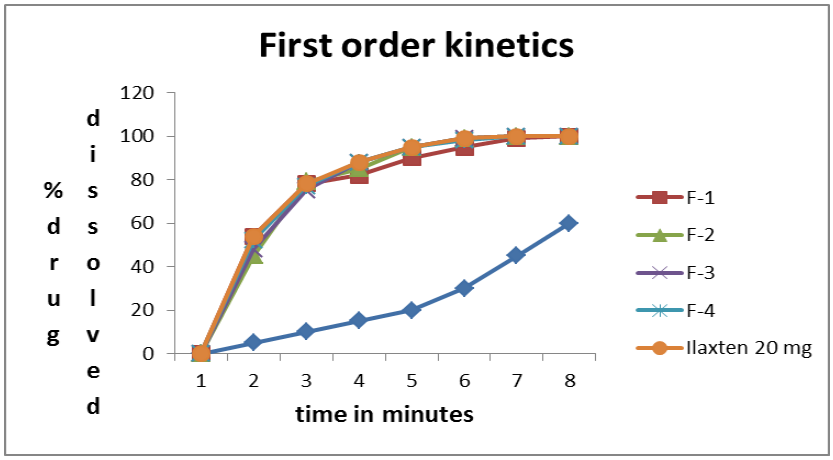


Table: Comparative dissolution profiles of Bilastine tablets 20 mg with Ilaxten 20 mg in Phosphate buffer solution pH 6.8, Paddle-50 RPM, 900mL.

Time in minutes	%Mean cummulative amount of drug dissolved				
	F-1	F-2	F-3	F-4	Ilaxten 20 mg
0	0	0	0	0	0
5	54	45	48	54	55
10	71	59	62	65	67
15	77	65	73	75	78
20	80	70	79	80	85
30	86	76	85	89	90
45	90	81	90	92	95
60	92	84	95	99	99

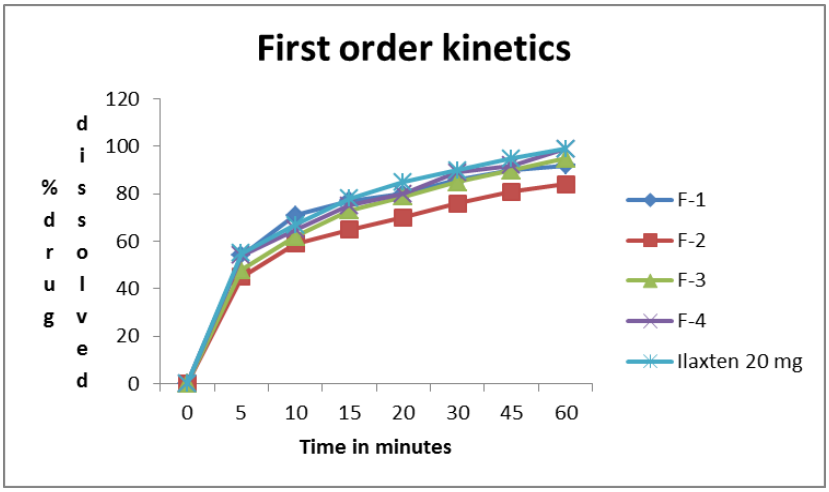
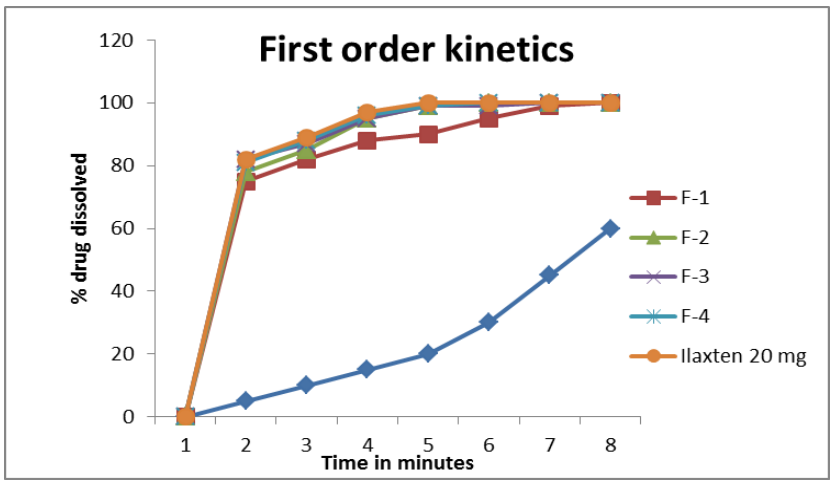


Table: Comparative dissolution profiles of Bilastine tablets 20 mg with Ilaxten 20 mg in Hydrochloric acid media pH 1.2, Paddle-50 RPM, 900mL.

	%Mean cummulative amount of drug dissolved				
Time in minutes	**F-1**	**F-2**	**F-3**	**F-4**	**Ilaxten 20 mg**
0	0	0	0	0	0
5	75	78	82	81	82
10	82	85	87	88	89
15	88	95	95	96	97
20	90	99	99	99	100
30	95	100	99	100	100
45	99	100	100	100	100
60	100	100	100	100	100



As can be seen from the tables above, the inventive compositions 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 a 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.

V. DISCUSSION

The project work entitled as, formulation development and evaluation of bilastine 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. Based on the result of Drug excipients compatibility studies the choice of excipients was decided in the present case excipients such as Microcrystalline cellulose, Mannitol DC grade, Crosspovidone, sodium starch glycolate, 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, assay and stability study were performed.

Formulation-I has been taken by direct compression method by trail and error method. The over all drug release was found to be 75%. Increase the drug release, another attempt was made to decreasse 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 Mannitol. 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.

VI. CONCLUSION

The project work entitled, formulation development and evaluation of Bilastine tablets 20mg was comapare with Ilaxten 20 mg 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 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 formulations had acceptable physical parameters. In the present study Bilastine 20mg 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 a antihistaminic drug Bilastine 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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