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BISOPROLOL-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

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ABSTRACT

Fast dissolving drug delivery systems offers a solution for pediatric, geriatric, mentally ill people and those patients having difficulty in swallowing tablets or capsules. In the present study, an attempt had been made to prepare fast dissolving tablets of Bisoprolol Fumarate, an antihypertensive agent. The main objective of the present study was to the preformulation studies were performed to know the physio-chemical and mechanical properties of Bisoprolol Fumarate for formulation development of Bisoprolol Fumarate FDTs. The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. The drug-excipient compatibility studies were conducted to characterize the drug Bisoprolol Fumarate present in FDTs. Preformulation, formulation and evaluation of Bisoprolol Fumarate to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and bioavailability and also to improve bioavailability and antihypertensive agent. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, precompression parameters and powder flow properties. Results showed that physical mixtures of Bisoprolol Fumarate and various excipients as mannitol, and avicel PH 101as diluents, and croscarmellose sodium, crospovidone as superdisintegrants were evaluated for preformulation studies parameters. It was concluded that the drug Bisoprolol Fumarate was found to be compatible with various excipients which were selected for the formulation development of the Bisoprolol Fumarate FDTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

KEYWORDS: Bisoprolol Fumarate, Compatibility, Excipients, Development, Preformulation, Formulation.

INTRODUCTION

Preformulation Studies[1-140]

Preformulation is essentials of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form new drug, it is essential that certain fundamental physical and chemical properties of drug powder are determined. This information may dictate many of subsequent event and approaches in formulation development. The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

One of the objectives of this study is to development of drug delivery systems by building scientific pharmaceutical research information depend on formulation scientists to join the knowledge and experience as well as experimental and practical results of this study with regard to information in previous studies, and approved references. It was found to be that the most important concepts and basics of preformulation studies such as definitions, methods, conclusion, idea, and types of pharmaceutical analysis techniques using in evaluation of preformulation studies parameters, in this study that we focused on developing drug delivery systems and linking the formulation development to establish the basics of pharmaceutical research in

studying the drug-excipient compatibility, dug with various excipients, which is important for the safety, effectiveness, quality, formulation, stability, bioavailability, and pharmacokinetics of the drug etc.

Determination of physical chemical properties of API substance with the goal of developing a new drug which is safe stable and efficacious, each API, has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation, the purpose of preformulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form, inappropriate preformulation study results in poor stability of active ingredients increase the overall cost of development and increased development time, preformulation studies help to fortify the pharmaceutical scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, enhance public safety standards, improve product quality, promote the implementation of new technologies, aids policy development and regulatory decision making and after compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

Preformulation Study Objectives: To establish the Physico-chemical parameters of a new API entity, determine its kinetics and stability, establish its compatibility with common excipients, it provides insights into how drug products should be processed and stored to ensure their quality, estimate problem may arise during formulation that is stability problem poor *in-vivo* dissolution, poor bioavailability, to interpret BCS classification of drugs and its significance and develop optimal drug delivery system.

Drug-Excipient Compatibility Study: The primary objective of this investigation was to identify a stable storage condition for API in solid state and identification of compatible excipients for its formulation. Incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance.

Dosage Forms: DF contain API and pharmaceutical excipients, which are intended to generate an ideal formulation and manufacturability of pharmaceutical products, thereby enabling a much safer and more effective administration. Pharmaceutical excipients are ideally inactive and have no impact on the stability or therapeutic effect of the active ingredient. On the other hand, there are studies that have presented that some pharmaceutical excipients are just allegedly described as inactive ingredient. Some pharmaceutical excipients have the capacity to affect API, efficacy by affecting its pharmacokinetics. Excipients can affect the physical and chemical form of pharmaceuticals by several factors such as hydrogen bond interaction, polymorphic conversion, and others. Accordingly, drug-excipient compatibility should be conducted so as to determine any drug-excipient interactions that may obstruct the stability, bioavailability, and manufacturability of pharmaceutical dosage forms.

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical Excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal

Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation Parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability is not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

In the present study, it was proposed to Bisoprolol Fumarate -excipient compatibility studies of the safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage., with commonly different excipients using for formulation development of FDTs.

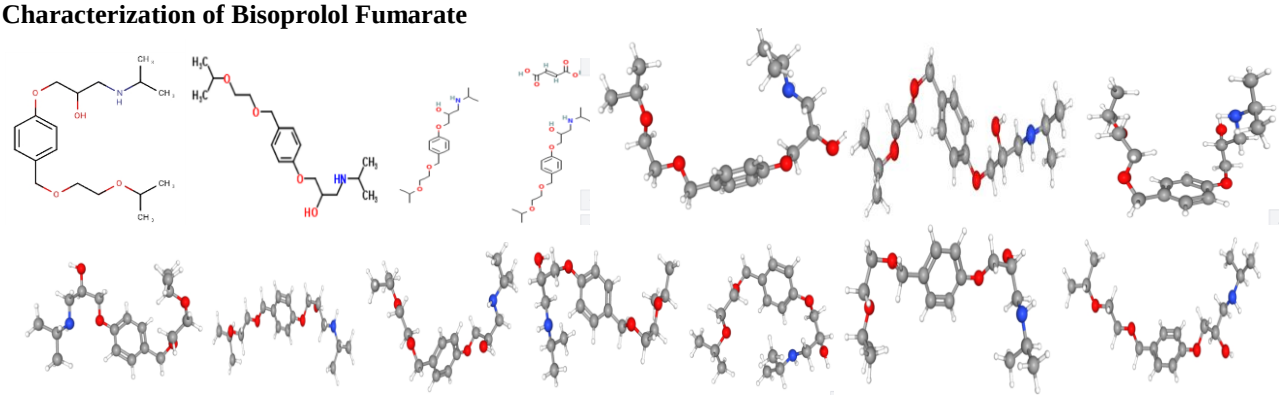
MATERIALS AND METHODS

Bisoprolol Fumarate as a gift from (Modern Pharmaceutical Industry Company-Yemen). While Talc, Crospovidone, Croscarmellose Sodium, Aspartame, Aerosil, Magnesium Stearate, Avicel PH 101, Mannitol and other materials were obtained as a gift from (Shaphaco Pharmaceutical Industry Company-Yemen).

Evaluation of Drug-Excipient Compatibility Studies Methods[40-258]

Table 1: Bisoprolol Fumarate Data.

Characterization of Bisoprolol Fumarate



Bisoprolol Fumarate Structure and 3D Conformer

Chemical Structure	(±)-1-[[a-(2-isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)2-propanol fumarate.	**Appearance**	It is a white crystalline and amorphous powder
Chemical Formula	**C**40 **H**66**N**2 **O**12	**Drug Solubility**	Readily soluble in water 0.0707mg/ml, methanol, ethanol, and chloroform.
Molecular Weight	767.0 g/mol.	**BCS**	Class-I Drug
Drug Action and Use	Bisoprolol is cardioprotective because it selectively and competitively blocks catecholamine (adrenalin) stimulation of beta-1 adrenergic receptors (β1 adrenoreceptor) mainly found in the heart muscle cells and heart conduction tissue (cardio specific) but also found in juxtaglomerular cells in the kidney. Bisoprolol is indicated for the treatment of mild to moderate hypertension . it may be used off-lable		

	to treat heart failure, atrial fibrillation, and angina pectoris.		
Bisoprolol Pharmacokinetics			
Drug Absorption	The bioavailability is about 90% due to the minimal first pass effect. Absorption is unaffected by food intake. Peak plasma concentrations of Bisoprolol are attained within 24 hrs and steady state concentrations are achieved within 5 days of adminstration. Cmax 64 ± 21 ng/ml.	**Drug Distribution**	Volume of distrbution Is 3.5 L/kg. The mean Vd was found to be 230L/kg in heart falure patients. Protein Binding: Plasma protein binding is about ~30%.
Drug Metabolism	Bisoprolol is maily metaabolzed by CYP3A4 (95%) WhearasCYP2D6play a minor role . The CYP3A4 mediated metabolism of Bisoprolol appears to be non -stereoselective.	**Drug Excretion**	Route of elimination Is eliminated equally by both renal and hepatic pathways. Total body clearance in healthy patients was determined to be 14.2L/h.
The Elimination Half-Life (T1/2)	The elimination half-life is about 10 –12 hours.	**Availability**	Tablets: 2.5mg, 5mg, 10mg.

Table 2: Pharmaceutical Excipients Data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration%	Solubility	Incompatibilities	Notes
Croscarmellose Sodium (Ac-Di-Sol)	Cellulose, carboxymethyl ether, sodium salt, crosslinked	Tablet and capsule disintegrant.	0.5-5% 10-25%	Insoluble in water	Incompatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.	White or grayish-white powder
Microcrystalline Cellulose (Avicel)	Cellulose	Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant.	5–20% 20–90%	Practically insoluble in water	Incompatible with strong oxidizing agents.	Crystalline powder
Crospovidone (PVPP)	1-Ethenyl-2-pyrrolidinone homopolymer	Tablet disintegrant.	2–5%	Practically insoluble in water	Compatible with most organic and inorganic pharmaceutical ingredients.	Hygroscopic powder
Mannitol (Emprove)	Mannitol	Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent.	10–90%	Freely soluble in water	Incompatible with may be salted out by potassium chloride or sodium chloride. Sodium cephapirin. xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.	Crystalline powder
Magnesium Stearate (magnesium salt)	Octadecanoic acid magnesium salt	Tablet and capsule lubricant.	0.25 - 5.0%	Practically insoluble in water	Incompatible with strong acids, alkalis, and iron salts.	Greasy
Talc	Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate. Mg6(Si2O5)4(OH)4.	Anticaking agent, glidant, diluent, lubricant.	1.0–10.0% 5.0–30.0%	Practically insoluble in dilute acids and alkalis, organic solvents, and water.	Incompatible with quaternary ammonium compounds.	is a very fine, white to grayish-white, crystalline powder.
Aerosil	Aerosil; Cab-O-Sil, Cab-OSil M-5P, colloidal silica, fumed silica, fumed silicon dioxide, SAS, silica colloidalis anhydrica	Adsorbent; anticaking agent glidant; viscosity-increasing agent	0.1–1.0% 2.0–10.0% widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient.	Practically insoluble in organic solvents, water. -hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system.	Incompatible with diethylstilbestrol preparations.	A submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

According to Bisoprolol Fumarate and excipients data as shown in Tables 1 and 2, it was selected that the different excipients to preformulation study with Bisoprolol Fumarate in the present study, the equipments used as shown in Table 3.

Table 3: The Equipment's Used.

No	Equipment's
1	Fourier Transform Infrared Spectrophotometer
2	UV/VIS Spectrophotometer
3	Melting Point Tester
4	Moisture Tester
5	Density Tester
6	pH Meter
7	Ultra-sonic
8	Accelerate Stability Study Chamber
9	Electronic Balance

Determination of The Organoleptic Properties

The organoleptic properties like color, odor and taste of the API was evaluated. Color a small quantity of Bisoprolol Fumarate was taken in a butter paper and viewed in well illuminated place. Taste and odor very less quantity of Famotidine was used to assess the taste with the help of tongue as well as smelled to get odor. The organoleptic properties of the API substance were assessed.

Solubility Analysis

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in distilled water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. The bioavailability of drug is affected by various excipients in formulation. The approximate solubility of a compendial substance is indicated by one of the following descriptive terms. Solubility of Bisoprolol Fumarate in distilled water, methanol and ethanol was determined by using Sonicator at room temperature. Approximate solubility of drugs as per B.P was indicated in Table 4.

Table 4: Solubility Specification of Drugs.

Solubility	Approximate Volume of Solvent in ml per gm of Solute
Excellent	Less than 1
Very soluble	1 to 10
Freely soluble	10 to 30
Soluble	30 to 100
Sparingly soluble	30 to 100
Slightly soluble	1000 to 10000
Very slightly soluble	1000 to 10000
Practically insoluble/ Insoluble	More than 10000

UV-Visible Spectrophotometric Method

Determination of λ Max for Bisoprolol Fumarate

The absorption spectra of Bisoprolol in phosphate buffer at pH 6.8 were studied. A Preliminary scanning of Bisoprolol in phosphate buffer to determine the ʎ max by screening a 10 ug /ml solution of Bisoprolol in phosphate buffer screening 5ug/ml these between 200 -400 nm.

0.896 g of NaOH and 6.804 g of KH2PO4 dissolved in sufficient quantity of distilled water, complete volume to 1000 ml distilled water and mixed well by sonication**.**

Preparation of Calibration curve Solutions

Preparation of phosphate buffer (pH 6.8): 100 mg of Bisoprolol was weighed accurately and dissolved in 100 ml of phosphate buffer (6.8 pH) in 100 ml volumetric flask to obtain a stock solution. Divide of 4 ml, 5 ml, 8 ml, 10 ml, 12 ml, 15 ml were taken and transferred to 100 ml volumetric flask and volume was complete to 100 ml by phosphate buffer (pH 6.8).

The absorbance of these solutions was measured at 227 nm against a blank of phosphate buffer. The calibration curve was plotted between concentration and absorbance.

Preformulation Studies

Preformulation studies are initiated to define the physical and chemical properties of the agent. The key goals of preformulation studies are to ensure the delivery of drug product with acceptable stability, bioavailability, and manufacturability.

Melting Point Determination of Bisoprolol Fumarate

Melting point of the Bisoprolol Fumarate was determined by capillary method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid.

Drug-Excipient Compatibility Studies

A physical mixture including Bisoprolol Fumarate and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure drug and physical mixes were obtained, and the spectra of the both drug and mixture of excipient with drug were compared to look for any incompatibilities.

FTIR Spectroscopy Study

FTIR study KBr-disc method was used to record the FTIR spectra and KBr pellets were made in 1:100 ratio of sample and KBr. FTIR spectra was recorded using FTIR spectrum in a range of 4000-400cm^{-1}. Different functional groups of test compound for distinctive vibrational frequencies are identified using FTIR spectroscopy. FTIR spectra were used for the investigation of interaction in the physical mixture of API and excipient through shifting of peaks to lower or higher wavenumbers and appearance or disappearance of characteristic peaks of functional groups for pure API in

physical mixture. FTIR spectroscopic study was performed to check the compatibility between API, and different excipients in amount (5mg:5mg) as ratio (1:1) as shown in Table 5. The FTIR spectra of a API alone and API with excipients were obtained by KBr method and compared with the standard FTIR spectrum of the pure API. Infrared spectrophotometer is not only used for determining the compatibility of excipients with the APIs, but also for API identification.

Preparation of IR Samples

The sample was determined by the disc method. Triturate 5mg of the substance to be examined with 300-400 mg of finely powdered and dried potassium bromide R or potassium chloride R. Each excipient was mix with Bisoprolol Fumarate equally then of potassium bromide is added to the mixture. Carefully grind the mixture, spread it uniformly in a suitable die, and submit it to a pressure of about 800 MPa (8 $t \cdot cm^{-2}$). Then the tablets were inserted to the device and the Infrared spectra was recorded at mild-infrared light in wavenumber range of 4000 cm^{-1} to 400 cm^{-1}. After that the spectra were compared with the reference.

Infrared Spectral Study of Samples in Room Condition

Compatibility studies were performed by preparing blend of different excipients with Bisoprolol Fumarate in room condition as shown in Table 5.

Table 5: Samples of Bisoprolol Fumarate and Different Excipients for Compatibility Studies.

No	Component(s)	Amount (5mg:5mg)
1	Bisoprolol Fumarate	1
2	Bisoprolol and Avicel PH 101	(1:1)
3	Bisoprolol and Crospovidone	(1:1)
4	Bisoprolol and Talc	(1:1)
5	Bisoprolol and Aspartame	(1:1)
6	Bisoprolol and CCS	(1:1)
7	Bisoprolol and Mannitol	(1:1)
8	Bisoprolol and Mg. Stearate	(1:1)
9	Bisoprolol and Aerosil	(1:1)

Preparation of Bisoprolol Fumarate Formulations

Mixing was done by using geometric mixing, in which all excipients were accurately weighed then all of them except silicon dioxide, magnesium stearate, were blended with specified quantity of Bisoprolol for 15minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve # 18 for particle size uniformity. This method of ordering mixing of excipients with Bisoprolol in first sex formulae. Then each mixture has compressed directly into tablets using rotary tablet compression machine of punch size 6.25mm (7mm) to prepare tablets each weighing 100 mg as shown in Table 6.

Table 6: Composition of Bisoprolol Fumarate Formulations FDTs.

Ingredients	Quantity per Tablet (mg)					
	Formulation Code					
	F1	F2	F3	F4	F5	F6
Bisoprolol Fumarate	5	5	5	5	5	5
Avicel PH 101	30	33	31	34.5	32.5	30
Mannitol	59	54	54	54	54	54
Crospovidone	2	4	6	---	---	---
Croscarmellose Sodium	---	---	---	2	4	6
Aspartame	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1
Mg Stearate	1	0.5	---	1	0.5	1
Talc	---	0.5	1	0.5	1	1

Evaluation of Pre-Compression Parameters of Formulations

Bulk Density

Bulk density (ρb) was determined by placing pre sieved drug excipients mixture into a graduated cylinder and measuring the volume (Vb) and weight (M).

ρb = M/Vb.

Tapped Density

The measuring cylinder containing a known quantity of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the drug excipients mixture was measured. The tapped density (ρt) was calculated using the following formula. ρt = M/Vt.

Angle of Repose

Angle of repose (**θ**) was determined using funnel method. The drug excipients mixture was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the pile (r) was measured and the angle of repose was calculated. **θ** = tan -1 (h/r). As shown in Table 6.

Carr's Index

Carr's Index or % compressibility is helpful to determine flow properties of powder mixtures, which is calculated as follows:

C = (ρt–ρb)/ρt X 100 Where, ρt - Tapped density, ρb - Untapped bulk density.

Hausner's Ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula.

Hausner's ratio = ρt\ ρb Where, ρt - Tapped density ρb - Bulk density. As shown in Tables 7 and 8.

Table 7: Powder Flow Properties.

Description of Flow	Angle of Repose (θ)
Excellent	≤25
Very Good	25 – 30
Good	31 – 35
Fair	36 – 40
Passable (but flow aid might be needed)	41 – 45
Poor (agitation or vibration needed)	46 – 55
Very Poor	>56

Table 8: Powder Flow Properties.

Description of Flow	Carr's Index (%)	Hausner Ratio
Excellent	≤10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very Poor	32 – 39	1.46 – 1.59
Very, Very Poor	>40	>1.60

RESULTS AND DISCUSSION

Preformulation Studies

Characterization of Bisoprolol Fumarate

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Bisoprolol was found to be White to off white, amorphous powder, odorless was observed in the study and the taste was found to be bitter. Bisoprolol showed similar color, taste and odor as per IP specification as shown in Table 9.

Physical Identification of Bisoprolol

Bisoprolol is white to off-white, amorphous powder.

Table 9: Organoleptic Properties of Bisoprolol Fumarate (AP)I.

Tests	Specification	Observation
Color	White or almost White	White to off-White
Odor	Odorless	Odorless
Taste	Bitter	Bitter less
Appearance	Amorphous	Amorphous

Solubility Analysis

Solubility profile of Bisoprolol indicated that the drug is the solubility studies of drug (API) revealed that Bisoprolol was very soluble in water, freely soluble in methanol. which confirm with the USP.

Characterization of Bisoprolol Fumarate by UV Spectroscopy

Wave length of Famotidine in Phosphate buffer (PH 6.8) by UV Scanning, at 227 nm as shown in Figure 1.

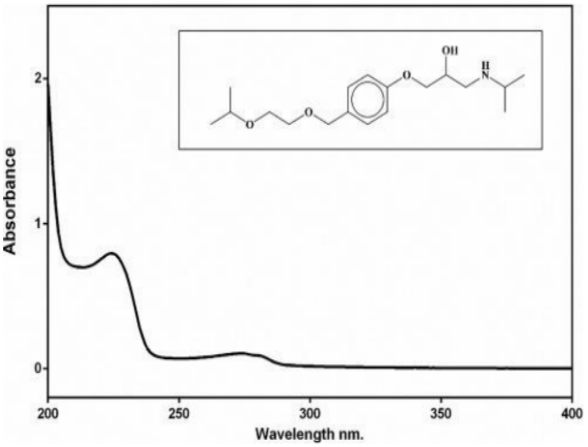


Fig. 1: UV Scanning of Bisoprolol Fumarate in Phosphate Buffer (pH 6.8).

Calibration Curve of Bisoprolol Fumarate

The calibration curve of Bisoprolol was prepared in phosphate buffer (pH 6.8). The plot of different concentrations of Bisoprolol versus absorbance was found linear at 227 nm in calibrations. The absorbance at different concentrations is shown in Table 10. The data of standard curve was linearly regressed. The slope and correlation coefficient values of phosphate buffer calibration was found 0.0364 and 0.9975 respectively. The intercept on Y-axis was found 0.00346. The calibration curve is shown in Figure 2.

Table 10: Calibration Curve of Bisoprolol Fumarate in Phosphate Buffer (pH 6.8).

No	Concentration µg/ml	Absorbance
1	0	0
2	4	0.1488
3	5	0.1787
4	8	0.2867
5	10	0.3607
6	12	0.4155
7	15	0.5579

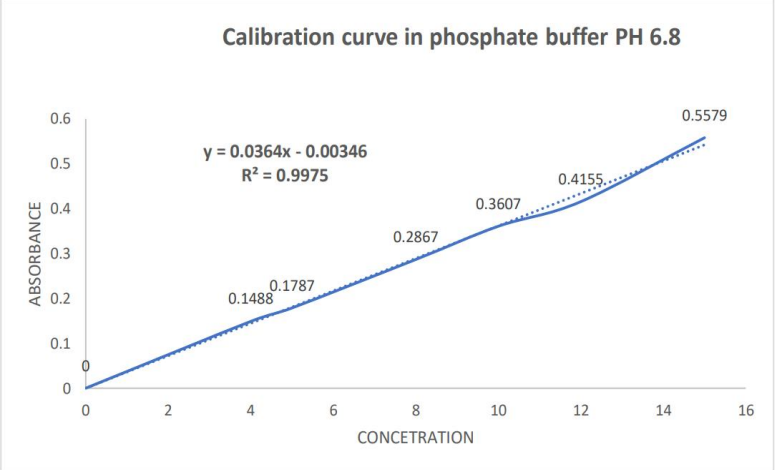


Fig. 2: Standard Calibration Curve of Bisoprolol Fumarate in Phosphate Buffer (pH 6.8).

Melting Point Determination of Bisoprolol Fumarate

Melting point of pure Bisoprolol was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Bisoprolol by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath. The rise in temperature was viewed through screen. The temperature at which the drug started melting was recorded. The melting point range of Bisoprolol was identical to reference melting point stated in BP (95-105°C). The sample started to melt at 95°C, and turned into liquid at 102°C, indicating that the sample used is pure. That reading has stated in Melting point tester. (automatic melting point) SMP30 (Stuart) as shown in Table 11.

Table 11: Results of Melting Point of Bisoprolol Fumarate.

Test	Temp Rang Analyzed (Melting)	Results
Test I Bisoprolol	(95-105 °C)	102 °C
Test II Bisoprolol	(95-105 °C)	102 °C

Characterization of Bisoprolol Fumarate by FTIR

FTIR spectrum studies indicated that major functional groups present in Bisoprolol show characteristic peaks in IR spectrum. Figures (3) to (7) show peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different excipients. The major peaks are identical to functional group of Bisoprolol. Hence, it was confirmed that there was compatibility between drug and various excipients, thus conforming that no interaction of drug occurred with the components of the formulation excipients.

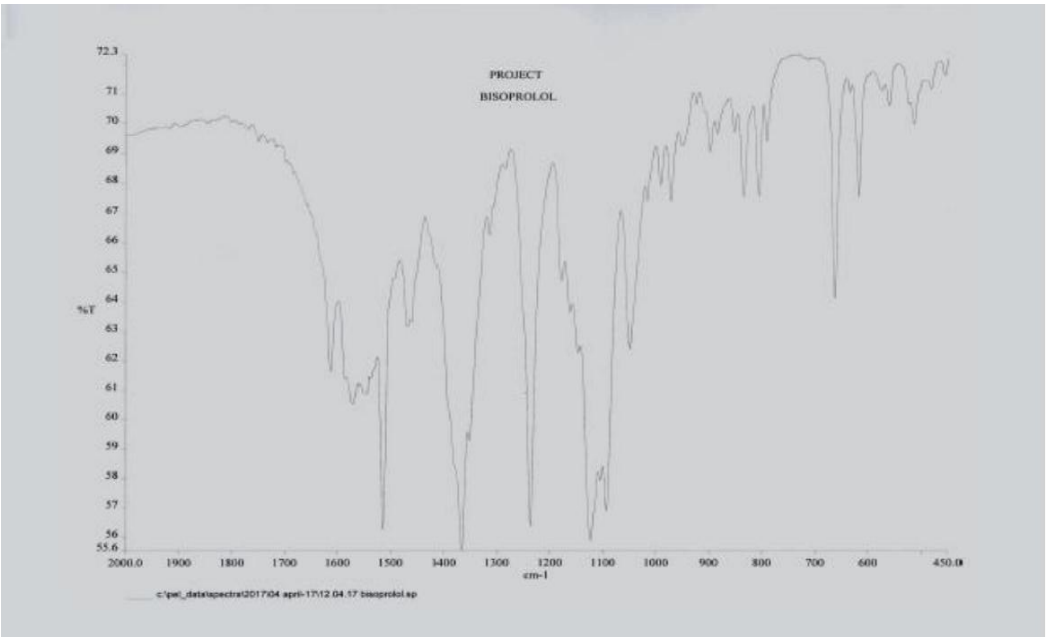


Fig. 3: FTIR Spectrum of Pure Bisoprolol Fumarate.

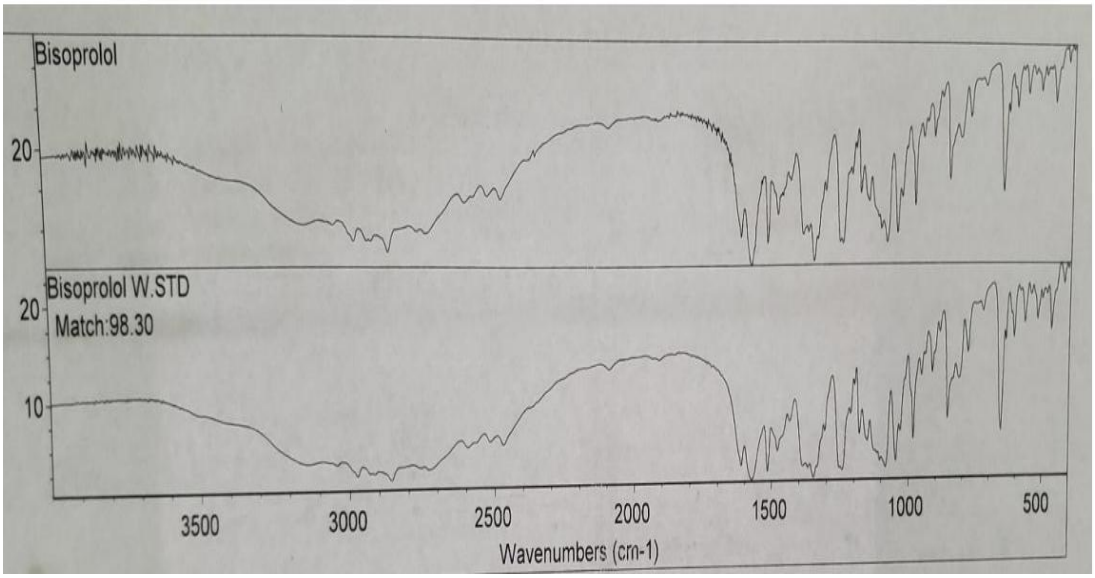


Fig. 4: FTIR Spectrum of Pure Bisoprolol Fumarate with STD.

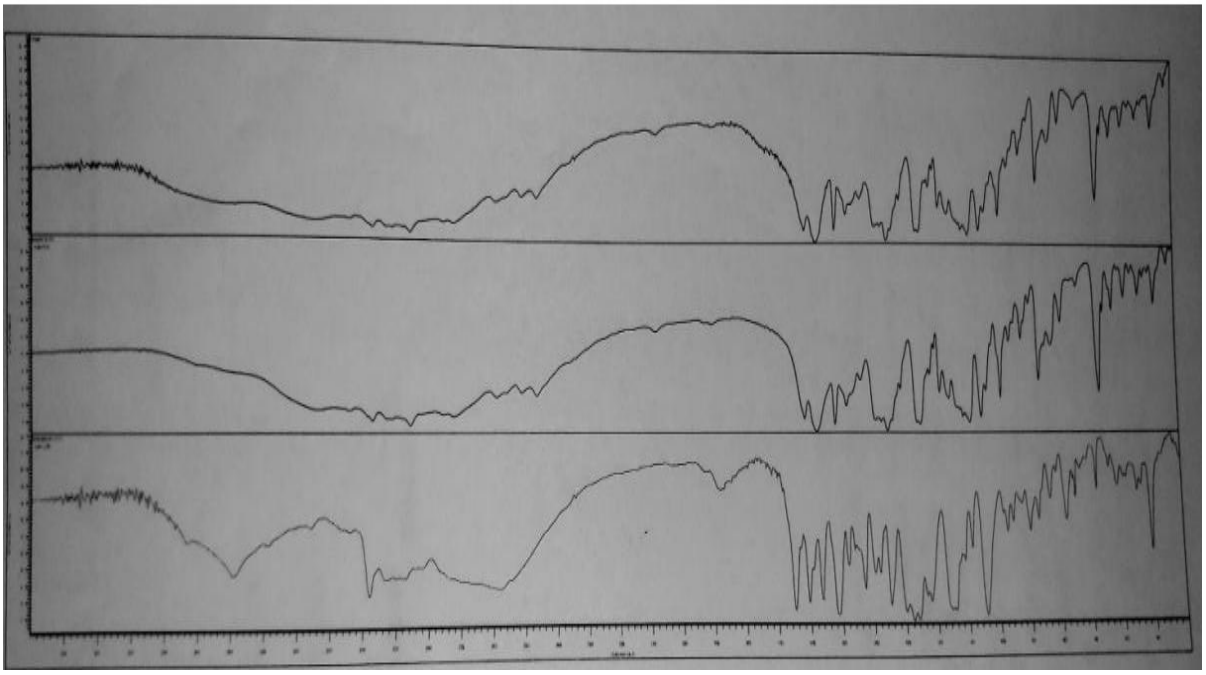


Fig. 5: FTIR Spectrum of Physical Mixture of Bisoprolol Fumarate and CCS.

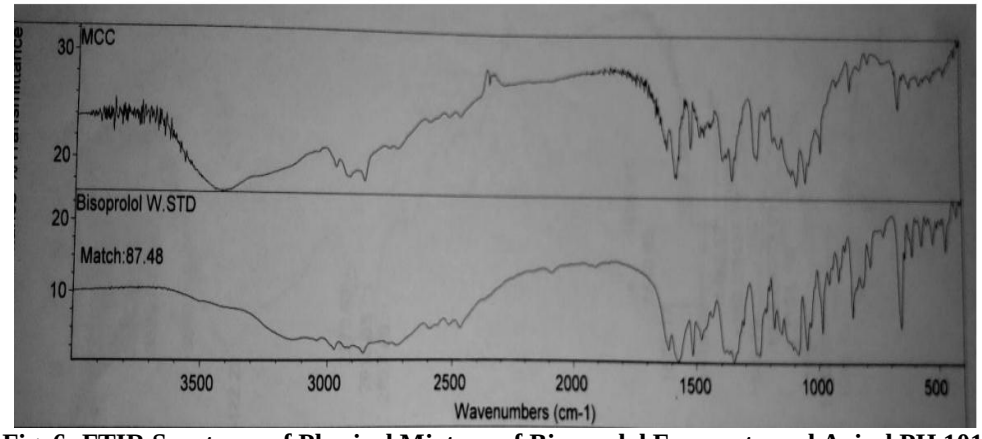


Fig. 6: FTIR Spectrum of Physical Mixture of Bisoprolol Fumarate and Avicel PH 101.

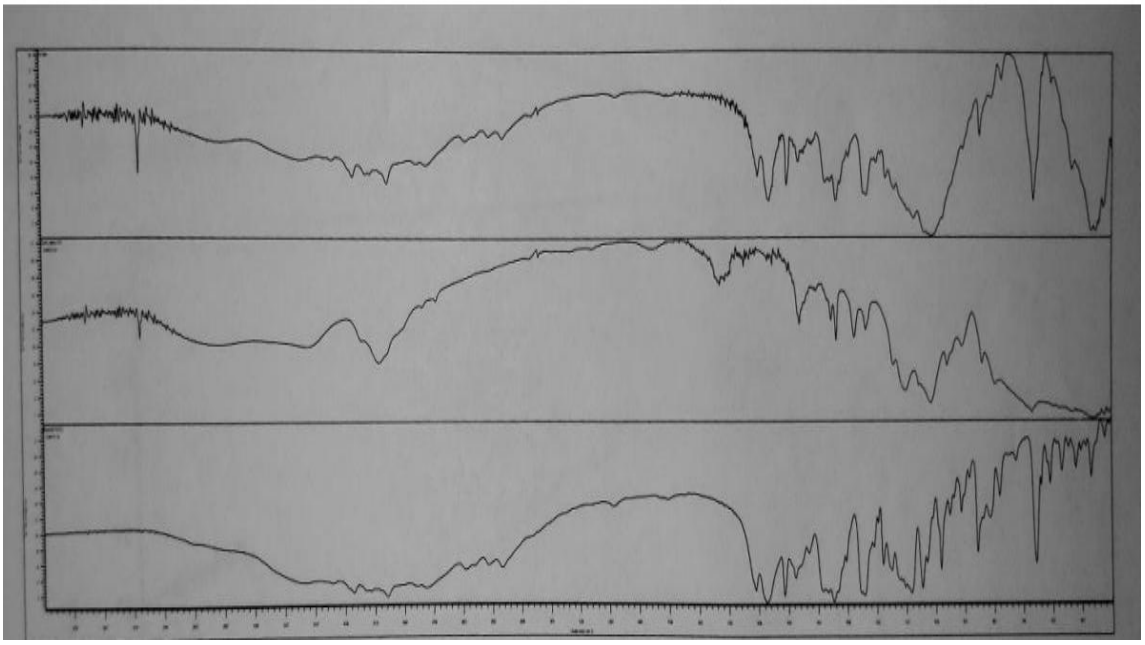


Fig. 7: FTIR Spectrum of Physical Mixture of Bisoprolol Fumarate and Talc.

Micromeritic Properties of Bisoprolol Fumarate

Evaluation of Precompression Parameters

Table 12: Preformulation Parameters of Bisoprolol Fumarate Powder Flow Properties.

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Compressibility Index (%)	Hausner's Ratio	Evaluation of Angle of Repose
F1	23	0.4	0.5	20	1.23	Fair
E2	28	0.26	0.32	18	1.25	Fair
F3	28	0.27	0.34	21	1.26	Passable
F4	19	0.52	0.52	21	1.26	Passable
F5	20.4	0.47	0.47	12.5	1.4	Excellent
F6	20.46	0.55	0.56	15	1.17	Good

Angle of repose of all the formulations were found to be between 19 to 28 which indicates no all have excellent property. The bulk density was found to be between 0.26 to 0.55 g/cm3, the tapped density was found to be between 0.32 to 0.56 g/cm3, the compressibility index was found in the range of 12 to 20 % and the Hausner's ratio lies between 1.17 to 1.4. The above results in terms of micromeritics properties revealed that the flow property of F1, F2 are Fair and F3, F4, are Passable, F5 is Excellent, F6 is good as shown in Table 12.

CONCLUSION

The compatibility studies of physical mixtures of Bisoprolol Fumarate with different used excipients such as mannitol, and avicel PH 101 as diluents, and croscarmellose sodium, crospovidone as superdisintegrants were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Bisoprolol Fumarate formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Bisoprolol Fumarate was found to be compatible with various excipients which were selected for the formulation development of the Bisoprolol Fumarate FDTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

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