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Preformulation Characterization towards Formulation development of Metoprolol tartarate Microparticles

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Abstract:
Hypertension is one of the primary risk factors for heart disease and stroke, the leading causes of death due to its high prevalence all around the globe. Approximately 7.5 million deaths worldwide occur due to hypertension and predicted to increase to 1.56 billion adults with high blood pressure in 2030. The main objective of this research work was to conduct Preformulation analysis of Metoprolol tartrate beta-blocker antihypertensive medicine in order to produce a stable, robust system for effective management of hypertension. Preformulation is the study of the chemical and physical properties of the drug components prior to the compounding process of the formulation. The purpose of the study is to understand the nature and characteristics of each component and to optimize conditions of the dosage form manufacture. Metoprolol tartrate is rapidly absorbed from both gastric and intestinal regions, after oral administration. Metoprolol Tartrate microparticles were prepared with varying concentrations of rate retarding polymers such as Ethyl cellulose, Eudragit RL100, HPMC and solvents such as Ethanol and DCM using solvent evaporation technique to enable sustained release delivery system. The Preformulated microspheres were evaluated for physiochemical parameters. Fourier Transform-Infrared (FTIR) spectral analysis of drug and polymers revealed the absence of drug-polymer interactions and further confirmed by DSC thermo grams. The prepared microspheres of Metoprolol Tartrate reduce the need for multiple dosing and provide improved patient compliance.

Key Words: Preformulation, Metoprolol tartrate, excipients, BCS, solubility, FTIR, DSC.

Introduction

The aim of the present work was to study the preformulation characterization for Metoprolol Tartrate, a beta-blocker antihypertensive medicine towards development of novel oral drug delivery system, in order to produce a stable, robust and therapeutically effective system.Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for development of dosage forms in which drug can reside in the stomach for a longer period of time than conventional dosage forms.[1]. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. Hence, design of specific dosage form and formulations is the primary step in preformulation study. Bio pharmaceutical classification system (BCS) is an advanced tool used for classifying medicine bases on dissolution, water solubility and intestinal permeability ,all parameters were observed and it was found that the physical appearance and melting point of drug were concordant.[2,3].

Microspheres are the carrier linked drug delivery system in which particle sizeisrangesfrom1-1000μmrangeindiameterhavingacoreofdrugand entirely outer layers of polymer as coating material and are defined as Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles.[4,5].

Hypertension is one of the primary risk factors for cardiac diseases and stroke, and alarming causes of death due to its high prevalence all around the globe. Hypertension is a serious heart condition in which the blood pressure in the arteries throughout the body is high. Blood pressure involves two measurements, systolic and diastolic. Normal blood pressure is equal to or less than 120/80 mmHg. High blood pressure is above 140/90 mmHg.[6,7].

Development of suitable dosage form to control and manage hypertension for prolonged period of time, prevents sudden episodes of cardiac attacks. Hence we aimed in developing suitable sustained release microparticles using Metoprolol tartrate for effective management of hypertension. Thus microspheres containing antihypertensive drug, metoprolol tartarate were prepared using polymers like Eudragit RL 100, ethyl cellulose, HPMC and PVP and solvents like ethanol, DCM, liquid paraffin and surfactants tween 80, etc by solvent evaporation method.[8,9].

Material and Methods

Materials

Metoprolol tartrate was obtained as gift sample from Zim Laboratories Mumbai, Eudragit RL 100 from Saimira Inno pharm, Chennai; Ethyl Cellulose and HPMC from S.D Fine Chemicals Ltd Mumbai.

Methods

Preformulation studies

Prior to development of formulation of a medicinal product (Active pharmaceutical ingredient) in suitable dosage form, it is essential to identify and authenticate the drug (API) and to investigate physical and chemical properties of a drug substance, to find effective, stable and safe dosage form. It is the first step in rational development of dosage form.[10,11].

Organoleptic Properties of drug

The Organoleptic properties like physical state, color, taste, odor etc., of the drug were reported with help of the descriptive terminology. It helps in identification and authentication of the drug.[12,13].

Melting point

In this method a small amount of drug was filled in capillary tube open at both the ends and it was placed along with thermometer in melting point apparatus.[14].

Determination of Solubility Profile of Metoprolol Tartrate

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some required aqueous solubility to elicit sufficient therapeutic response. The solubility of drug was illustrated using various descriptive terminology specified in Indian pharmacopoeia, 2007.[15,16].

Descriptive term	Parts of solvent required for 1partof solute
Very soluble	Lessthan1
Freely soluble	From 1to10
Soluble	From 10to30

Sparingly soluble	From 30to100
Slightly soluble	From 100to 1,000
Very slightly soluble	From 1,000to 10,000
Practically insoluble	Greaterthanorequalto10,000

Table 01:Description of solubility

UV-Spectroscopy: Determination of λ_{max} of Metoprolol tartrate in Phosphate buffer pH 7.4 by UV Spectroscopy

The absorption maximum of the standard solution was scanned between 200 and 400 nm on Shimadzu-1700 Pharma spec UV-visible spectrophotometer. The absorption maximum obtained with drug being examined corresponds in position and relative intensity to those in the reference spectrum[17,18]

Development of Standard Curve of Metoprolol Tartrate in 0.1NHcl

Preparation of Stock Solution of Metoprolol Tartrate in 0.1 N Hcl:

Calibration curve of Metoprolol Tartrate in 0.1 N Hcl:

About 100mg of Metoprolol Tartrate was accurately weighed and dissolved in little quantity of 0.1N HCl and volume was adjusted to 100ml with the same solvent to prepare standard solution having concentration of 1000µg/ml. From this solution, 10mlwas pipette out and made up to 100mlwith0.1N HCl to produce100µg/ml.[19,20].

From above stock solution, aliquots of 1,2, 3 ,4 and 5 ml were transferred to10ml volumetric flasks and final volume was made to10ml with 0.1N HCl to get concentrations 10 to 50 µg/ml. Absorbance values of these concentrations were measured against blank 0.1 N HCl at 274 nm using UV-visible spectrophotometer.[21,22].

Development of Standard Curve of Metoprolol Tartrate in pH 7.4 Phosphate Buffer

Preparation of Stock Solution of Metoprolol Tartrate in pH 7.4 Phosphate Buffer:

About 100mg of Metoprolol Tartrate was accurately weighed and dissolved in little quantity of pH 7.4phosphate buffer and volume was adjusted to 100 ml with the same to prepare standard solution having concentration of 1000µg/ml. From this solution, pipette out 10ml and

made up to 100ml with pH7.4 phosphate buffer to produce 100 µg/ml.[23,24].

From above stock solution, aliquots of 1,2,3,4 and 5ml were transferred to 10 ml volumetric flasks and final volume was made to10ml with pH7.4 phosphate buffer to get 10 to 50µg/ml. Absorbance values of these solutions were measured against blank (Phosphate Buffer pH 7.4) at 274 nm using UV-visible spectrophotometer.[25,26].

Compatibility studies using Fourier-Transform Infrared Spectroscopy- (FT-IR)

Drug-Polymer interactions were studied by FT-IR Spectroscopy. The spectra were recorded for pure drug, pure polymer. Physical mixture of drug and polymer (10 mg of sample and 40mg of KBr was taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet marker and was compressed at 10 kg/cm^2 using hydraulic press. The pellet was kept in a sample holder and scanned from 4000 cm^{-1} in SHIMADZU IR Prestige 21 FT-IR spectrophotometer).[27,28].

Differential Scanning Calorimetry:

DSC analysis was performed to observe and characterize any changes, if occurs, during thermal exposure of samples. The test was carried out using a thermal analysis system (Pyris 6 DSC) which was heated at a rate of 20 degree per minute.[29,30] The results were shown in Fig: 2.

Loss on Drying

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.[31,32].

$$\text{Loss on drying} = \frac{\boldsymbol{Initialweightofsubstance - Finalweightofsubstance}}{\boldsymbol{Initialweightofsubstance}} \times 100$$

Result and Discussion

Preformulation Studies

Organoleptic Properties: The fine white colored drug was Odourless, with metallic taste
Colour: White ,Odour : Odourless, Taste: Metallic, Appearance : Fine powder

Melting point: Melting point value of metoprolol tartrate sample was found to be in range of 136.2°C.The official range is between 136-138°C.

Determination of solubility profile of Metoprolol Tartrate

Name of solvent	Parts of solvent required per part of solute	Solubility
Distilled water	10	Very soluble
Ethanol(95%)	40	Freely soluble
Chloroform	400	Sparingly soluble
Ether	600	Practically insoluble
0.1 N HCl	10	Very soluble
Phosphate bufferpH7.4	70	Freely soluble

Table 02: The solubility of Metoprolol Tartrate in different solvents

Drug Was BCS Class I High Solubility and High Permeability.

Determination of (λ max)

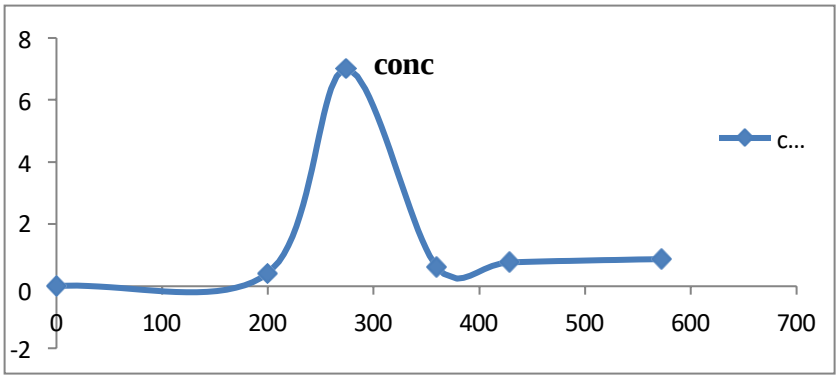


Figure 01: Determination of λ max of Metoprolol Tartrate

Development of Standard Curve of Metoprolol Tartarate in Phosphate Buffer pH 7.4:

Preparation of Standard Curve of Metoprolol Tartrate by using 0.1N Hcl

The UV absorption spectrum of Metoprolol Tartratein 0.1NHclshows λ max at 274.5nm.

Absorbance obtained for various concentrations of Metoprolol Tartrate in 0.1 N Hcl are given in Table 03. The graph of absorbance vs. concentration for Metoprolol Tartrate was found to be linear in the concentration range of 10-50µg /ml. The drug obeys Beer -Lambert's law in the range of 10-50µg /ml.

S.No	Concentration µg /ml	Absorbance at 274nm
1	0	0
2	10	0.134
3	20	0.272
4	30	0.406
5	40	0.546
6	50	0.680

Table 03: Standard curve of Metoprolol Tartrate in 0.1NHcl

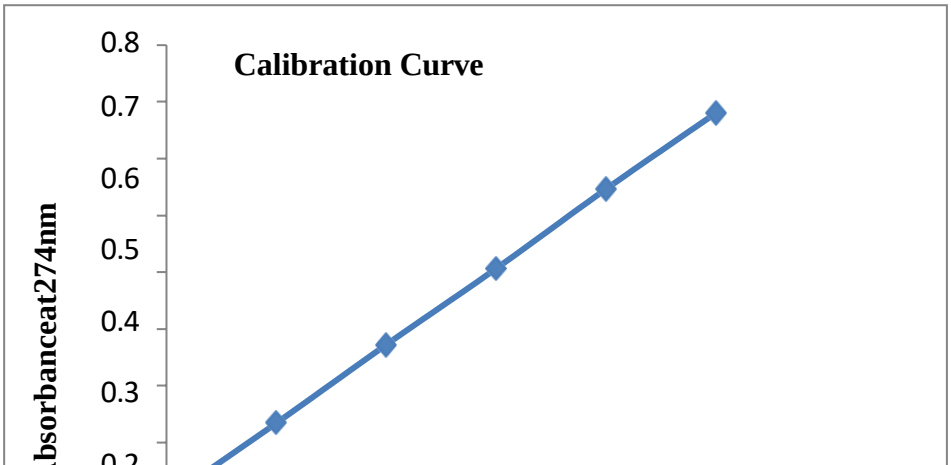


Figure 02: Standard curve of Metoprolol Tartrate in 0.1N HCL

Preparation of standard curve of Metoprolol Tartrate by using pH 7.4 Phosphate Buffer:

UV absorption spectrum of Metoprolol tartrate pH 7.4 phosphate buffer shows λ max at 274.5 nm. Absorbance obtained for various concentrations of Metoprolol Tartrate in pH phosphate Buffer are given in **Table 20** The graph absorbance vs. concentration for Metoprolol Tartrate was found to be linear in the concentration range of 10-50µg /ml. The drug obeys Beer-Lambert's law in the range of10-50µg /ml.[33]

S.No.	Concentration(µg/ml)	Absorbance at 274nm
1	0	0
2	10	0.132
3	20	0.263
4	30	0.401
5	40	0.526
6	50	0.657

Table 03: Standard curve of Metoprolol Tartrate by using pH 7.4 Phosphate Buffer

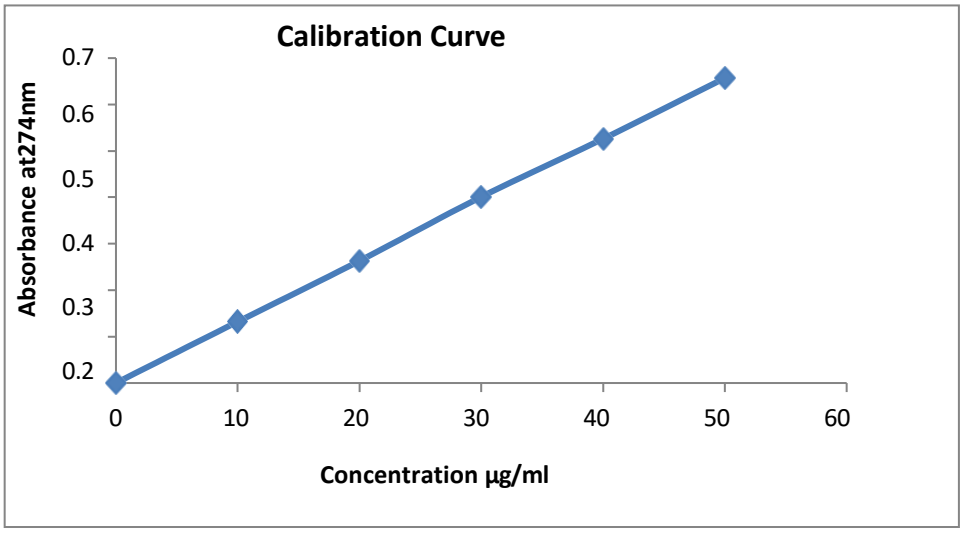


Figure 03: standard curve of Metoprolol Tartrate by using pH 7.4Phosphate Buffer

Compatibility studies (FT-IR) Metoprolol Tartarate

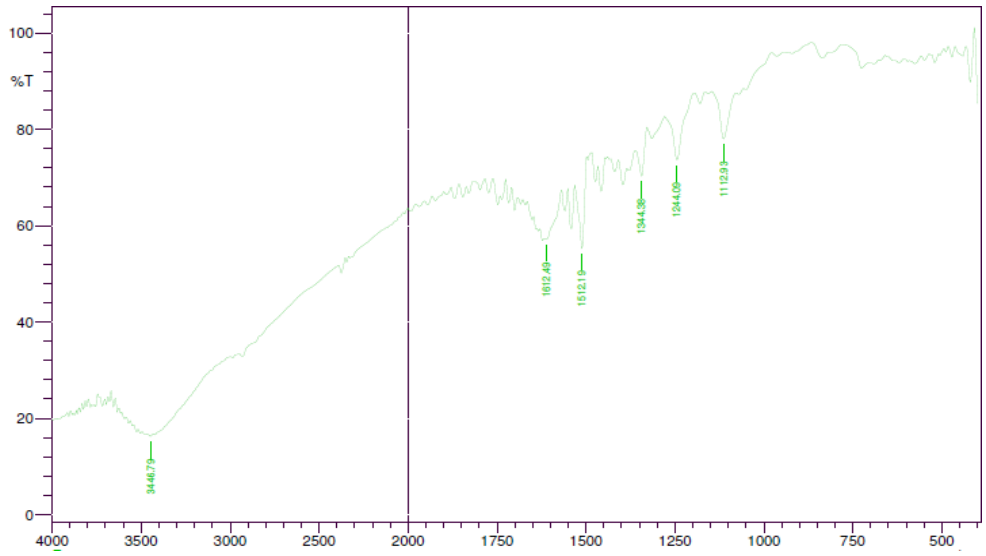


Figure 04: FT- IR spectra of Metoprolol Tartrate

Ethyl Cellulose

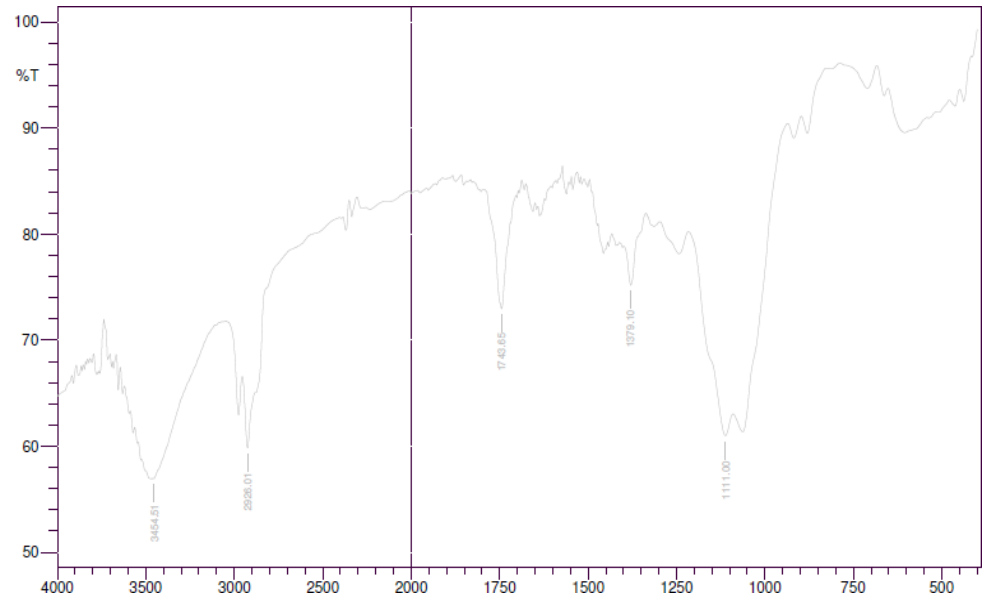


Figure 05 : FT- IR Spectra of Ethyl Cellulose

Hydroxyl Propyl Methyl Cellulose

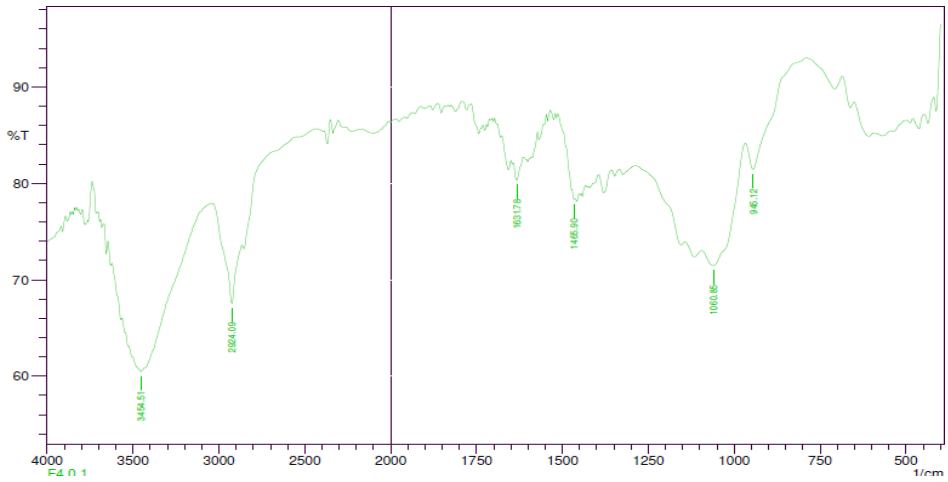


Figure 06: FT-IR spectra of HPMC

EudragitRL100

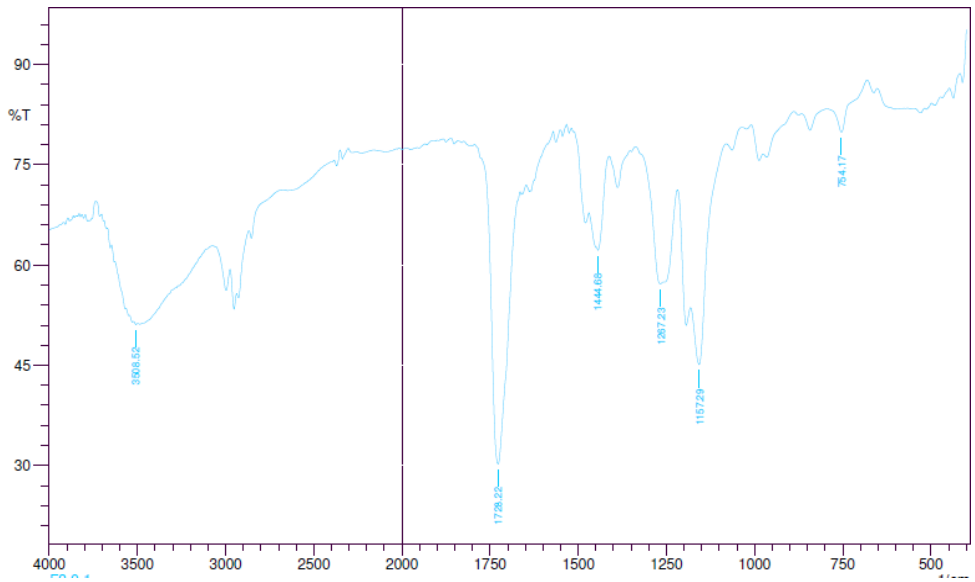


Figure 07: FT-IR Spectra of Eudragit RL100

Drug + Ethyl Cellulose

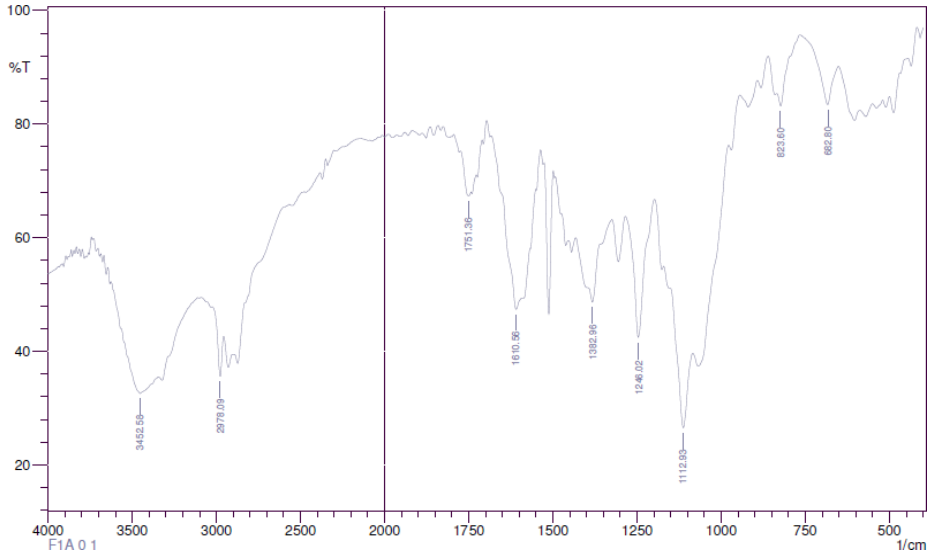


Figure 08 : FT – IR Spectra of Drug + Ethyl Cellulose

Drug + Eudragit RL100

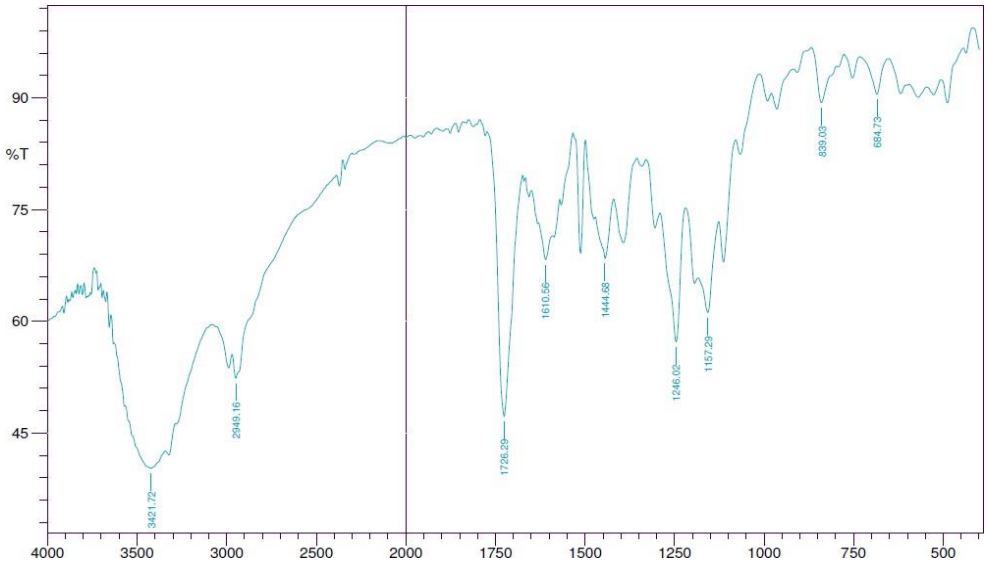


Figure 09 : FT- IR Spectra of Drug+ Eudragit RL100

Drug+ HPMC

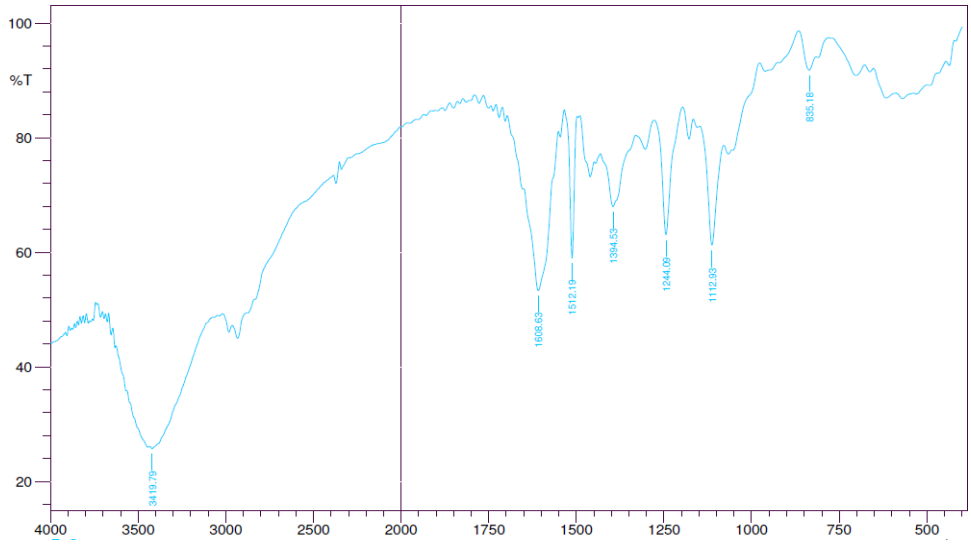


Figure 10 : FT-IR Spectra of Drug+HPMC

Drug + PVP

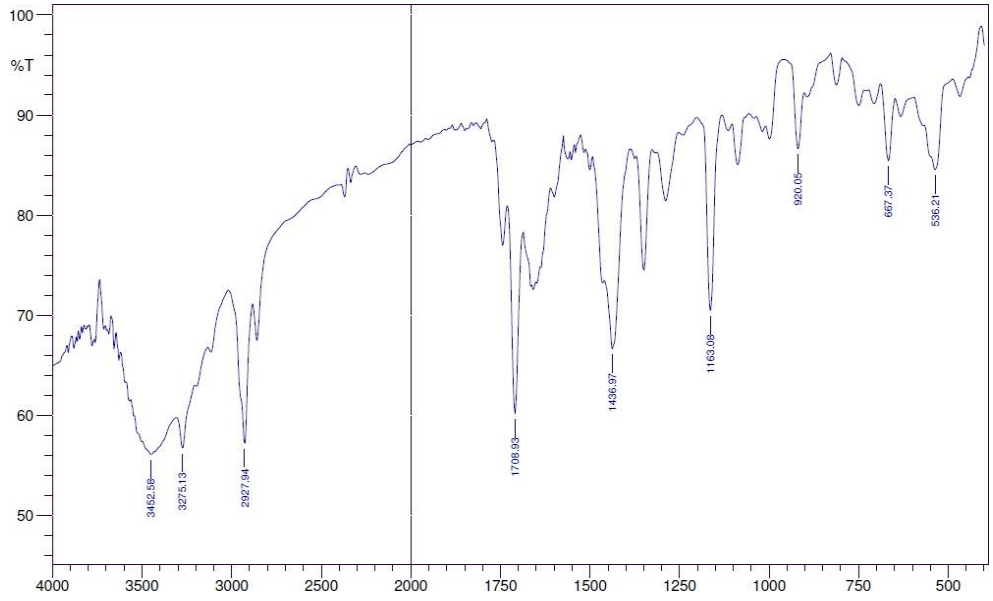


Figure 11 : FT-IR Spectra of Drug+ PVP

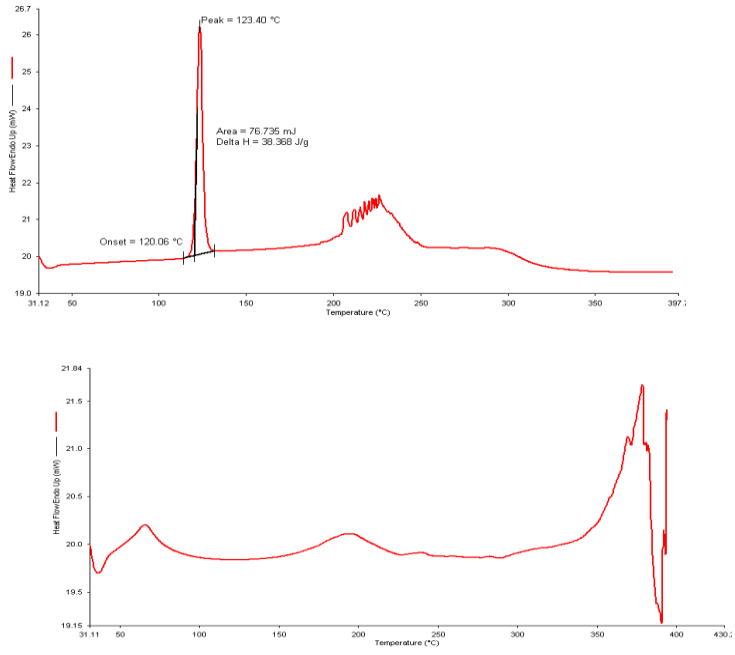
The possible interaction between drug and polymer can be studied by FTIR spectroscopy. According to the Figure, Metoprolol tartrate showed prominent peaks due to the presence of C-H stretching alkyl group at 2900, 2980 cm^{-1} and C-H bending alkyl group at 1380,1480 cm-

^{1} and C=O stretching at 1020-1120 cm-^{1} and C-N stretching at 2200-2300 cm-^{1} and O-H stretching at 3100-3500 cm-^{1}.

The major peaks observed in drug spectrum were also observed in spectrum of drug with polymer, therefore it indicates that there is no interaction between drug and polymer**.** There are no extra peaks other than the normal peak in the spectra of the mixture of the drug and polymers and hence there is no interaction with the drug and polymer and they are compatible with each other.[33]

Differential Scanning Calorimetry:

Metoprolol tartrate exhibits endothermic peak at 123.40 (Fig:12), the same melting endotherm also observed in the DSC graph of physical mixture of drug and polymer, indicates that there was no mutual interaction between drug and polymer.



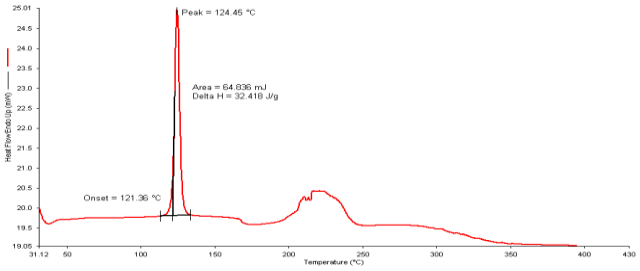


Figure :12 DSC curve of pure Metoprolol tartrate, Eudragit RL 100 and Mixture of drug and polymer

CONCULSION

In the present work, preformulation studies of antihypertensive drug metoprolol tartrate was carried out. preformulation analysis is one among most important phase in developing safe, effective and stable dosage form and outcomes of the studies have great impact on further development of final dosage form. The physical appearance, organoleptic characteristics complies with standards of Indian pharmacopeia.

With good physicochemical properties, the drug belongs to BCS Class I (High Solubility and High Permeability)and metoprolol tatrtarte is soluble in distill water, ethanol, 0.01NHcl and PBS pH 7.4. The calibration curves of drug were prepared in 0.01N Hcl and PBS pH 7.4in the concentration ranges 10 to 50ug/ml and exhibits straight line, indicating that the drug follows Beers law within the specified concentration range . FTIR spectroscopy revealed no interaction between the drug and excipients, hence drug is compatible with polymers like ethyl cellulose, HPMC, EudragitRL100, PVP. DSC studies confirmed absence of chemical interaction between the drug and polymers. This study shows satisfactory result for all preformulation characterization and on the basis of the results, we concluded that the Ethyl cellulose, HPMC, Eudragit RL 100, and PVP can be selected for preparation of antihypertensive micro particle formulation.

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