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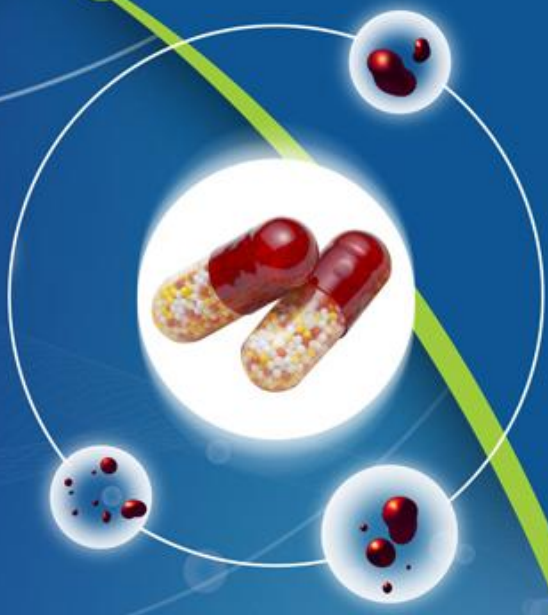

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Research Article

FORMULATION OF GASTRO RETENTIVE FLOATING MICROBALLOONS OF CIPROFLOXACIN HYDROCHLORIDE

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ABSTRACT

The present study involves formulation of microbaloons of Ciprofloxacin HCL as a model drug for prolongation of Gastric resident time. Ciprofloxacin is a second generation Fluroquinolone having bactericidal activity and is used in the treatment of respiratory, urinary tract, gastrointestinal and abdominal infections including Gram-negative (Escherichia coli) and Gram-positive (Streptococcus pneumonia, Streptococcus pyogenes) bacterial pathogens. Ciprofloxacin HCl with pKa value of 4.9 is a weak acid which will remain unionized at acidic pH thus increases absorption in the stomach region. It is primarily absorbed from the stomach and upper part of intestine. The objective of the study was to formulate the microbaloons which are capable of floating on the gastric fluid and release the drug over a period of 24 hours thus increasing bioavailability and decreasing the frequency of dosage. The compatability of Ciproflocxacin HCl and polymers is studied by IR spectroscopy and DSC methods. Microbaloons were formulated by Emulsion solvent diffusion methods using polymers like Eudragit RS100 and Eudragit RL100 in various ratios.

Keywords *: Ciprofloxacin HCL, Fluroquinolone, microballoons*

INTRODUCTION

Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced bioavailability. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels.

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Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microballoons Three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time[1,2]

Stomach is made up of fundus and body regions. They are capable of displaying a large expansion to accommodate food without much

increase in intra gastric pressure. Stomach lining is devoid of villi and it consists of considerable number of gastric pits that contribute to storage capacity of the stomach. There are two main secretions: mucus and acid, produced by specialized cell in stomach lining. Mucus is secreted by goblet cells and gastric acid by parietal cells. The mucus spread and covers the rest of GI tract.[3,4]

Microencapsulation is a process whereby relatively thin coating of polymers are applied to small particles of solid or droplets of liquid and dispersions. Microencapsulation leads to microcapsules or microspheres, which are reservoir type and matrix type respectively. In either case, one or more active ingredient (core) is entrapped within matrix, shell or coat which is usually composed of one or more polymers. The uniqueness of microencapsulation is size of the coated particle (1 –1000µm) and their subsequent use and adaptation to a wide variety of dosage form and product applications, which might not have been technically feasible.[5,6]

Microcapsule developed for use in medicine consists of solid or liquid core material containing one or more drug enclosed in coating. The core may also be referred to as the nucleus or fill and the coating as the wall or shell. Depending upon the manufacturing process, various type of microcapsule structure can be obtained. The most common type is the mononuclear spherical. Microcapsules usually have a particle size range between 1to 2000 µm. Microspheres are solid, approximately spherical particles ranging 1-1000µm in size. They are made up of polymeric substances in which the drug is coated inside it, comprises the core. The substances used in the formulation are biodegradable synthetic polymers and natural products such as starch, gums, proteins, fats and waxes. The natural polymers of choice are albumin and gelatin, the synthetic ones being poly lactic acid and poly glycolic acid. The polymers used to manufacture microspheres are chosen according to their solubility, stability profile, and process safety. The micro particulates delivery system are considered and accepted as a reliable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interest without untoward effects. The term microcapsule is defined as a spherical particle with size varying from 50 nm to 2 mm containing a core substance. Microspheres are, in strict sense, spherical empty particles. However the terms microcapsules and microspheres are often used synonymously. In addition some related terms are used as well for example essentially “micro beads and “beads” are used alternatively. Sphere and spherical particles are used for rigid morphology. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200µm. Solid bio-degradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. These carriers received much attention not only for prolonged release but also for the targeting of anti-cancer drugs to the tumour.[7,8]

METHODOLGY

PREFORMULATION STUDIES

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It is an investigation of physical and chemical properties of a drug substance alone and in combination with excipients. It gives extensive information to bring out good quality at high standard at which optimal dosage desired. Preformulation studies were performed on the drug (Active Pharmaceutical Ingredient), which included melting point determination, solubility and compatibility studies[9][10].

Physicochemical parameters[11],[12]

Organoleptic properties

The physical appearance of drug was observed and compared with the pharmacopoeial specifications.

Solubility study

Solubility of Ciprofloxacin HCl was observed in different solvents such as water, ethanol, and acetone

Identification of drug

Identification by FTIR spectroscopy[13],[14].

FTIR spectral analysis of pure drug and polymers was carried out individually. The absorption maxima in the spectrum were compared with the reference spectrum.

Identification by melting point

Melting point of the drug was determined by capillary tube method using melting point apparatus.

Analytical methods

Determination of λmax

The absorption maximum of the standard solution (Ciprofloxacin HCl in 0.1 N HCl) was scanned between 200- 400 nm regions UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

Development of standard curve of Ciprofloxacin HCl[15],[16].

Preparation of 0.1N HCl**:** 0.1N HCl was prepared according to I.P. 1996. 8.5 ml of HCl was diluted with fresh distilled water to produced 1000 ml.

Preparation of stock solution of Ciprofloxacin HCl in 0.1 N HCl

Accurately weighed 100 mg of Ciprofloxacin HCl was dissolved 0.1N HCl and volume was adjusted to 100 ml with 0.1N HCl to produce a concentration of 1000µg/ml.

Procedure: From the stock solution 10ml was taken and made upto 100ml with 0.1N HCl having a concentration of 100 µg/ml. From this aliquots of 0.2,0.4,0.6,0.8,1.0 ml was taken and made up to 10 ml with 0.1N HCl to make 2, 4, 6, 8, 10 µg/ml solutions respectively. Absorbance values of these solutions were measured against blank (0.1N HCl) at 257 nm using UV-Visible spectrophotometer.

Determination of drug-polymer compatibility[17]

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in fabricating the product. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug polymer molecular contacts to accelerate the reactions if possible.

Fourier Transform Infra-Red (FTIR) spectroscopy

FTIR spectral analysis of pure drug and polymers was carried out individually and also in different ratios, observation was made whether changes in the chemical constitution of drug after combining it with the polymers was occurred or not. The absorption maximums in spectrum were compared with the reference spectrum.

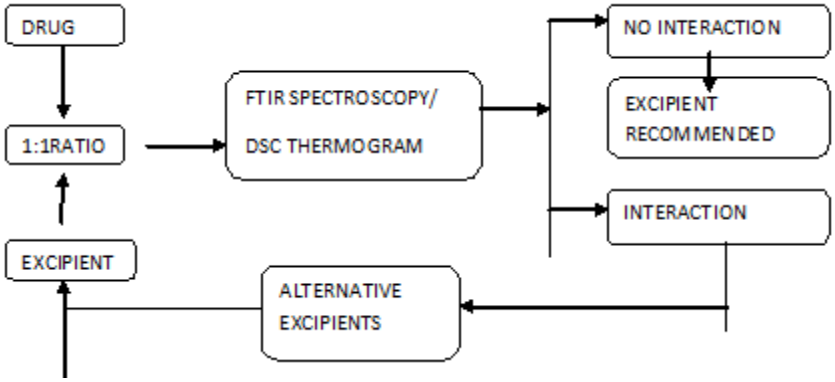


Fig.1: Schematic representation of compatibility studies

Differential Scanning Calorimetry (DSC)

Any possible drug interaction can be studied by thermal analysis. The DSC study was performed on pure drug, Ciprofloxacin HCl + Eudragit RS 100 + Eudragit RL 100.Samples were accurately weighed and put into aluminum pans and then sealed with aluminum lids. The thermograms of the samples were obtained at a scanning rate of 10^0C/min. and at a temperature range of 25-300^0C.The obtained thermograms were used to decide any interaction between drug and polymers.

PREPARATION OF FLOATING MICROBALLOONS[18]

Floating microballoons were prepared by emulsion solvent diffusion method using Eudragit RS 100 and Eudragit RL 100. Seven formulations were prepared using different drug to polymer ratios of 1:1, 1:2, and 1:3. Weighed amount of polymer was dissolved in a mixture of ethanol: dichloromethane (1:1) at room temperature. Ciprofloxacin HCl was mixed with the above solution. The resulting drug polymer solution was poured slowly using glass tube into 200 ml of water containing 0.75 % w/v polyvinyl alcohol, maintained at constant temperature of 40^0 C and preparation was stirred at 300 rpm for 4 hr. The finely developed floating microballoons were then filtered, washed with water and dried overnight at 40^0 C.

RESULT AND DISCUSSION

PREFORMULATION STUDIES

Physicochemical parameters

Organoleptic properties.

Ciprofloxacin HCl was found to be faint to yellow crystalline powder. The physical appearance complied with the reference specifications.

Table 1: Solubility of samples in various solvents

Sl.No	Samples	Solubility		
		Water	Ethanol	Acetone
1	Ciprofloxacin HCl	Sparingly Soluble	Soluble	Soluble
2	Eudragit RS100	Insoluble	Soluble	Soluble
3	Eudragit RL 100	Insoluble	Soluble	Soluble

Identification of drug

Identification of drug by FTIR spectroscopy

The FTIR spectrum of Ciprofloacin HCl was showed in Figure 1.

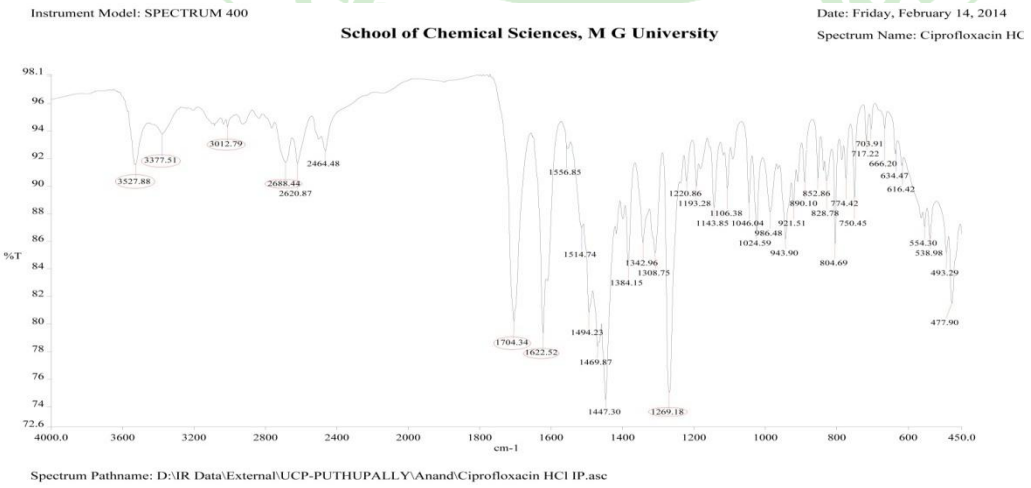


Fig.2: FTIR spectrum of Ciprofloxacin HCl

Interpretation of FTIR Spectrum

Major functional groups present in Ciprofloxacin HCl were showed characteristic peaks in FTIR spectrum. The characteristic peaks of Ciprofloxacin HCl were obtained at 3527.88cm^{-1}, 3377.51 cm^{-1}, 2688.44cm^{-1}, 1704.34 cm-1, 1622.52cm^{-1}, 1269.18 cm^{-1}. The major peaks were identical to functional group of Ciprofloxacin HCl. Hence, the sample was confirmed as Ciprofloxacin HCl.

Table 2: Characteristic frequencies in FTIR spectrum of Ciprofloxacin HCl

Functional Group	Actual wave number(cm^{-1})	Observed wave number(cm^{-}
OH Stretching	3500-3450	3377.51
N-H Stretching	3700-2500	3527.88
C-H Stretching	3300-2800	3012.79
Aromatic CH Stretching	3000-2650	2688.44
C=O Stretching	1750-1700	1704.34
OH bending	1300-1250	1269.18
Quinolones	1650-1600	1622.52

Identification of polymers by FTIR spectroscopy

Major functional groups present in polymethacrylates were showed characteristic peaks in FTIR spectrum. The major peaks were identical to functional group of Eudragit RS 100and RL 100.Hence the sample was confirmed as Eudragit RS100 and RL 100.

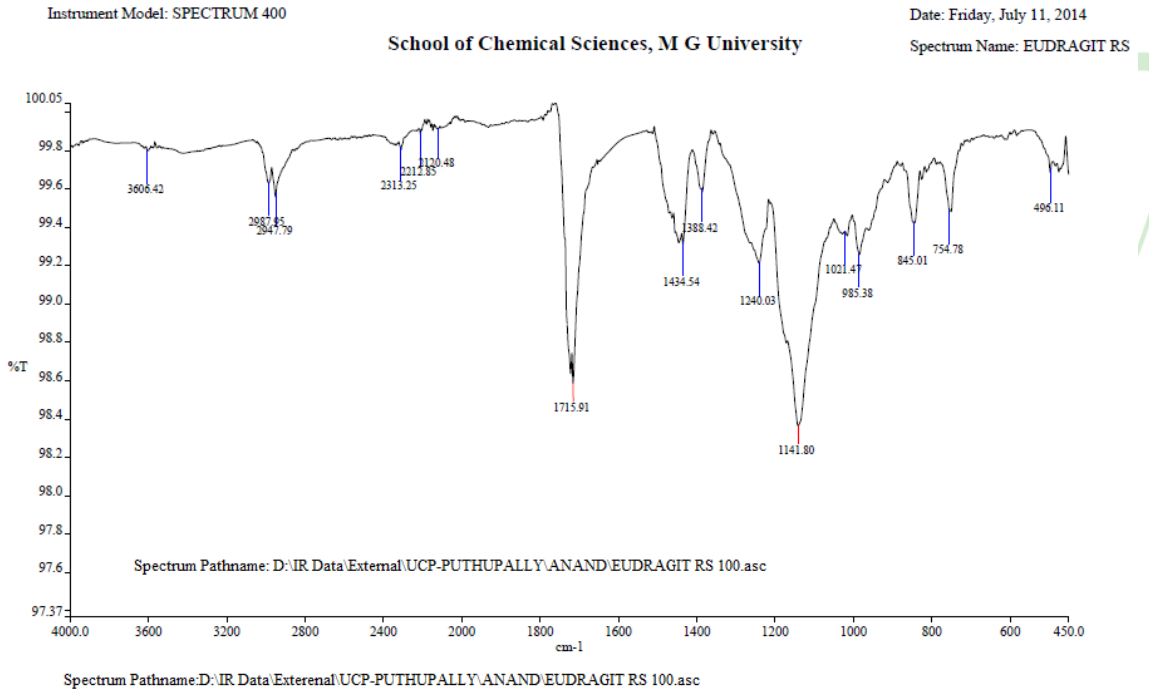


Fig.3: FTIR spectrum of Eudragit RS 100

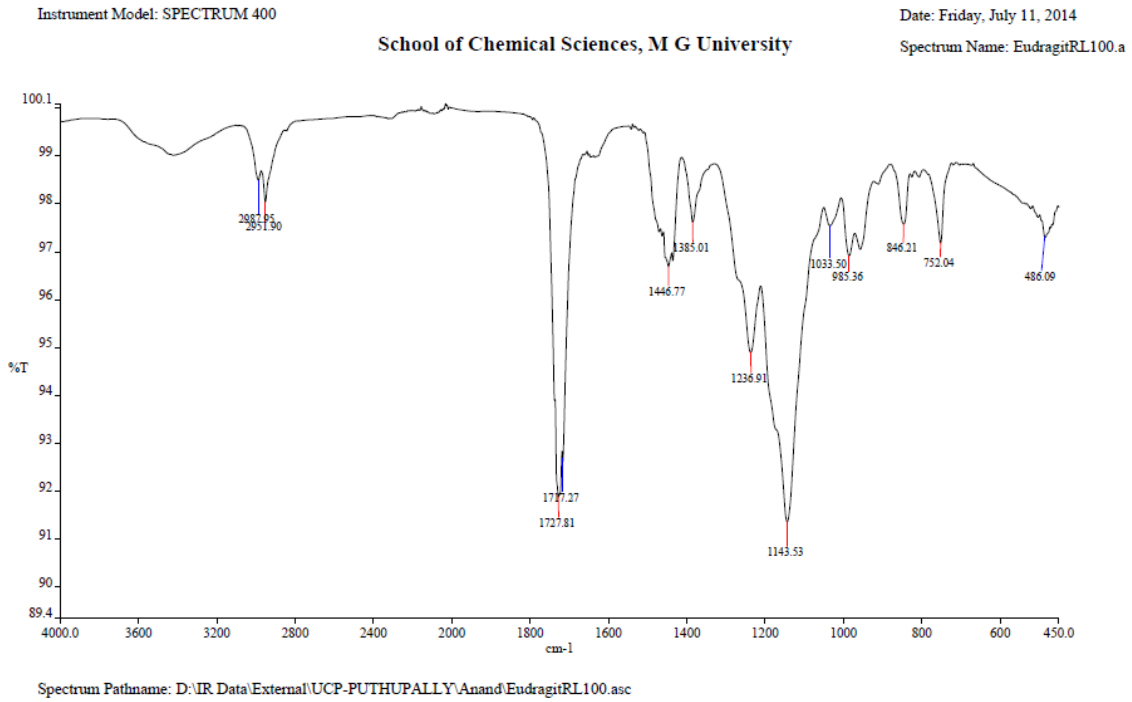


Fig.4: FTIR spectrum of Eudragit RL 100

Identification of drug by melting point.

Melting point of the drug was found to be 255^{0}C, which was in conformity with the reported range.

Analytical Methods

Determination of λmax

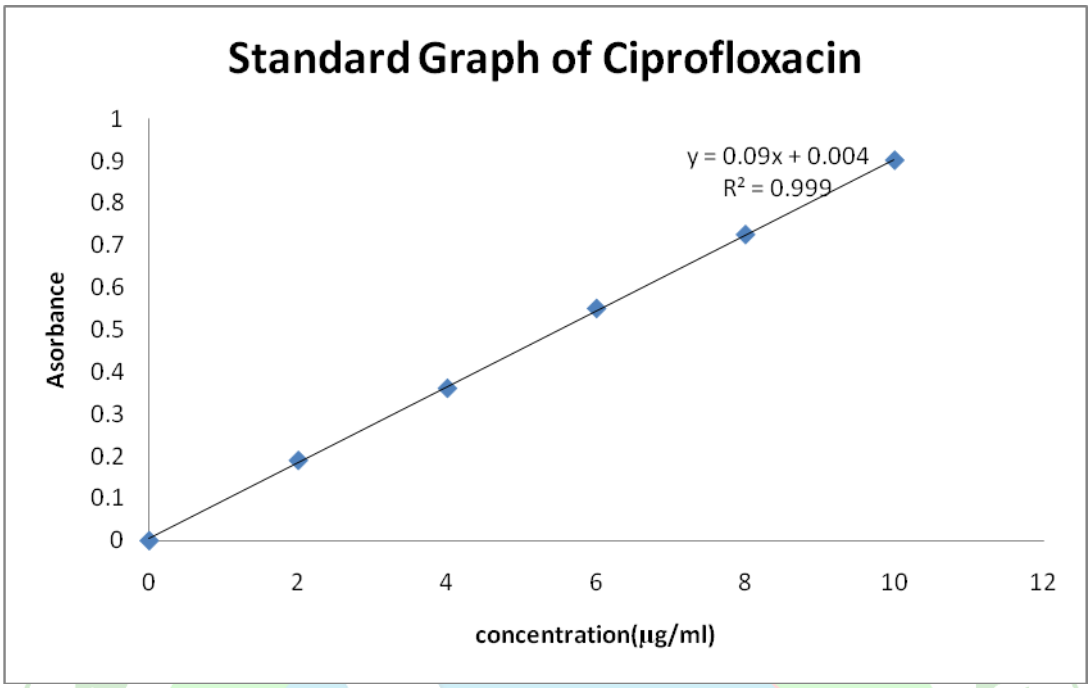
The absorption maximum of the standard solution (Ciprofloxacin HCl in 0.1N HCl) was scanned between 200-400 nm regions in UV-Visible spectrophotometer. The wavelength at which maximum absorbance (λmax) was found to be 256 nm.

Development of standard calibration curve of Ciprofloxacin HCl.

UV absorption spectrum of Ciprofloxacin HCl in 0.1N HCL showed λmax at 256nm. Absorbance obtained for various concentrations of Ciprofloxacin HCl in 0.1N HCl were given in table.3.The graph of absorbance Vs. concenteration for Ciprofloxacin HCl with slope, regression coefficient and intercept was found to be linear in the concentration range of 2-10µg/ml.The drug obeys Beer-Lambert's law in the range of 2-10µg/ml.

Table 3: Standard calibration table for Ciprofloxacin HCl in 0.1N HCl at 256nm.

Concentration (µg/ml)	Absorbance
0	0
2	0.190
4	0.361
6	0.550
8	0.725
10	0.901



Graph.1: Standard Graph of Ciprofloxacin HCl in 0.1N HCl

Table 4: Data for calibration curve parameters

Sl.No.	Parameters	Value
1	Correlation coefficient(r)	0.9998
2	Slope	0.09
3	Intercept	0.0046

Determination of drug-polymer compatibility By FTIR spectroscopy

Table 5: Major peaks observed in FTIR spectrum of Ciprofloxacin HCl and Ciprofloxacin HCl with different polymers used in the formulations

Wave Number (cm-1)	Functional Group	Peak Observed (Yes/No)			
		Ciprofloxacin HCl	Ciprofloxacin HCl+ E RS 100	Ciprofloxacin HCl+ E RL 100	Ciprofloxacin HCl+ E RS 100+ E RL 100
3377.51	OH Stretching	Yes	Yes	Yes	Yes
3527.88	N-H Stretching	Yes	Yes	Yes	Yes
3012.79	CH Stretching	Yes	Yes	Yes	Yes
2688.44	Aromatic CH Stretching	Yes	Yes	Yes	Yes
1704.34	C=O Stretching	Yes	Yes	Yes	Yes
1269.18	OH bending	Yes	Yes	Yes	Yes
1622.52	Quinolones	Yes	Yes	Yes	Yes

FTIR spectrums of Ciprofloxacin HCl with different polymers used in the formulation were taken. The major peaks observed in drug spectrum were also observed in spectrums of drug with polymer; therefore it could indicate that there was no incompatibility between drug and different polymer.

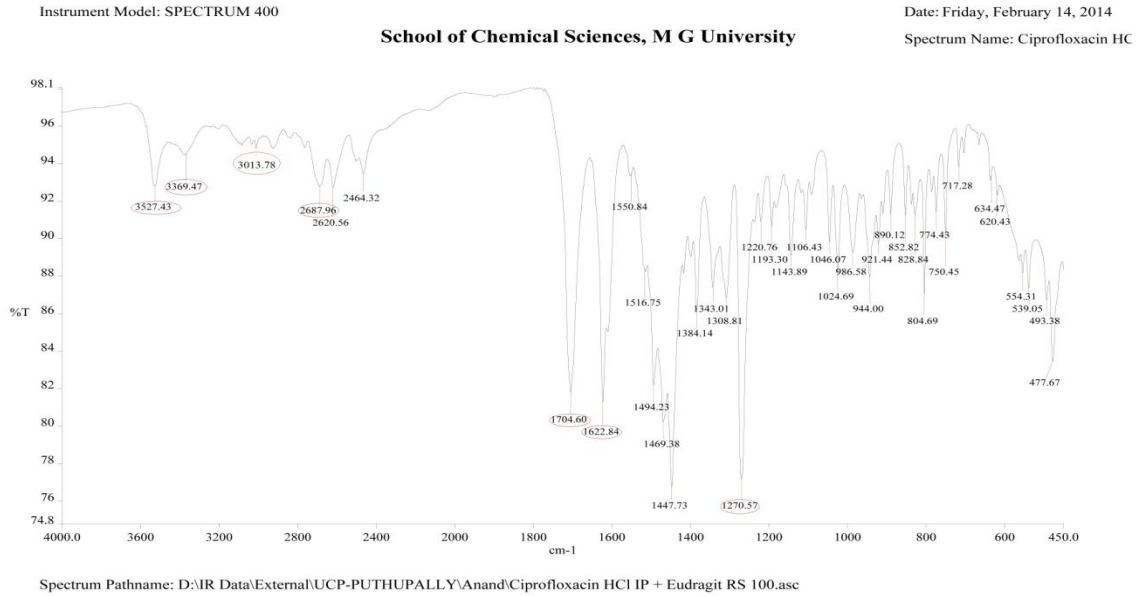


Fig.5: FTIR spectrum of Ciprofloxacin HCl + Eudragit RS 100

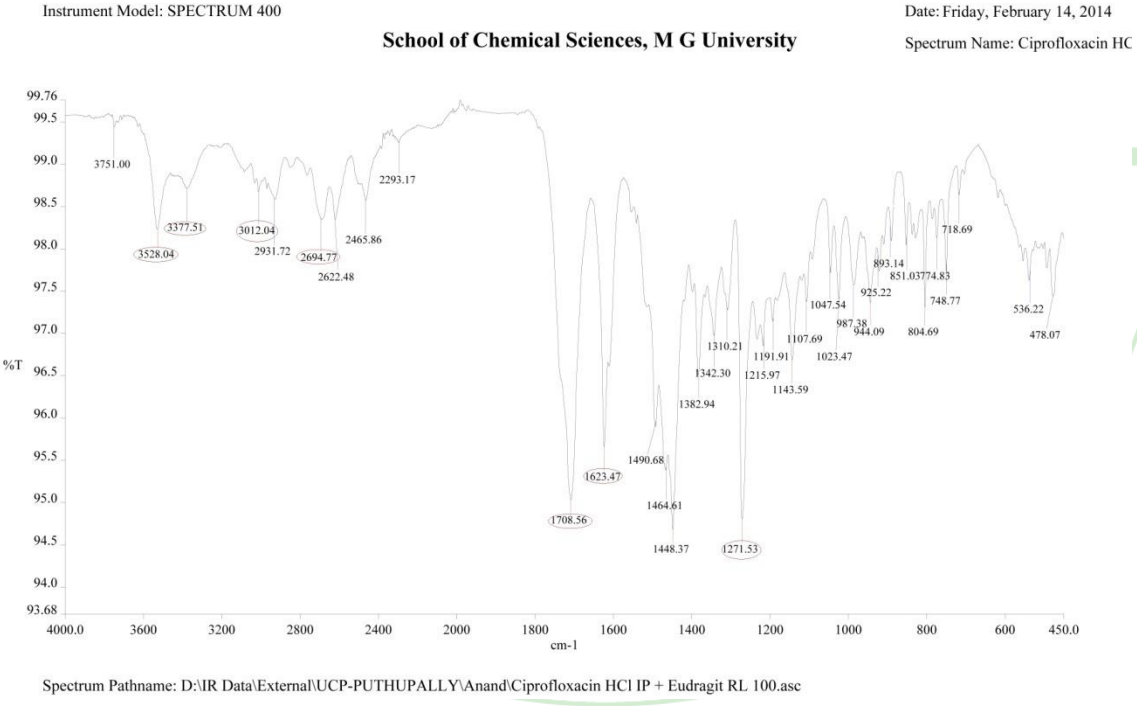


Fig.6: FTIR Spectrum of Ciprofloxacin HCl + Eudragit RL 100

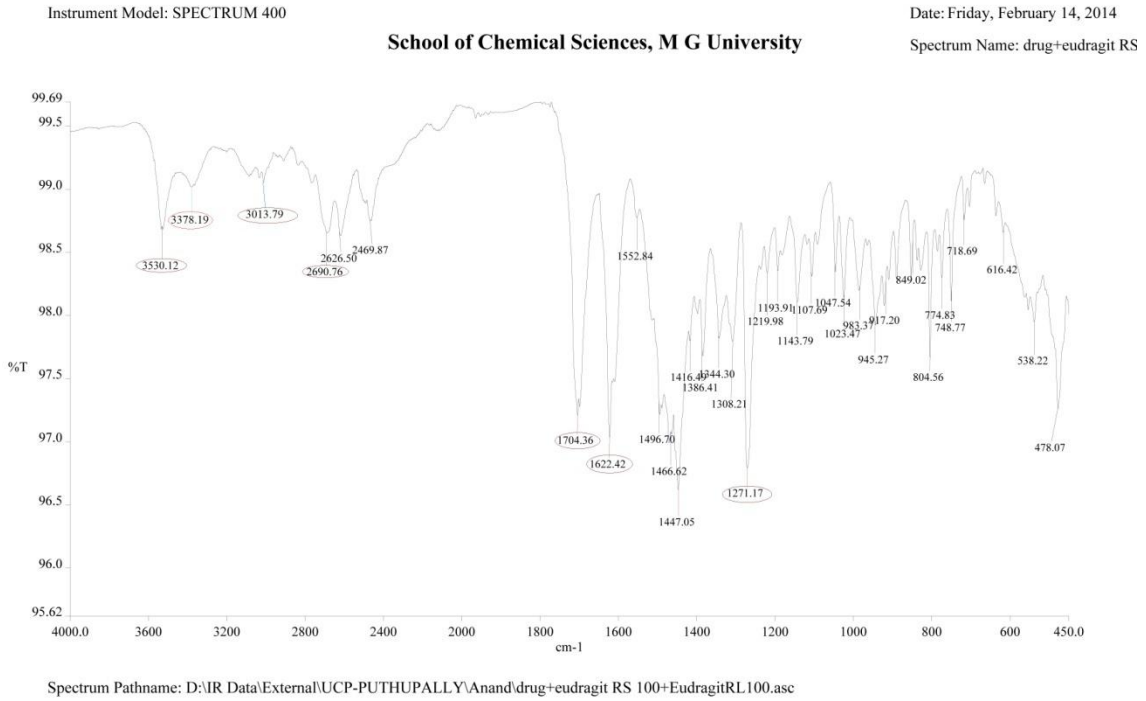


Fig.7: FTIR Spectrum of Ciprofloxacin + Eudragit RS 100 + Eudragit RL 100

By DSC thermal analysis

The comparative DSC thermograms of pure Ciprofloxacin HCl and physical mixture was represented in fig.8 & in fig.9 The DSC thermogram of Ciprofloxacin HCl displayed a characteristic peak at 157.09^{0}C corresponding to its melting point. The physical mixture's peak appeared in the thermogram at 158.55^{0}C. DSC thermogram showed that there was no major difference in peak temperature. Therefore, it could indicate that there was no incompatibility between drug and polymers.

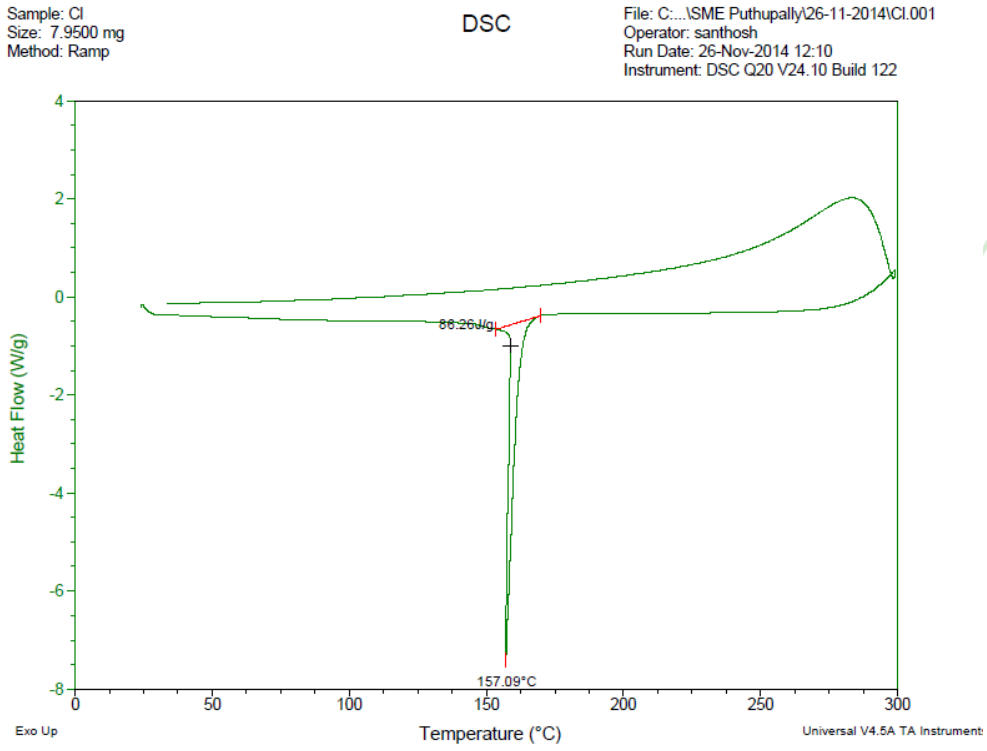


Fig.8: DSC thermogram of Ciprofloxacin HCl

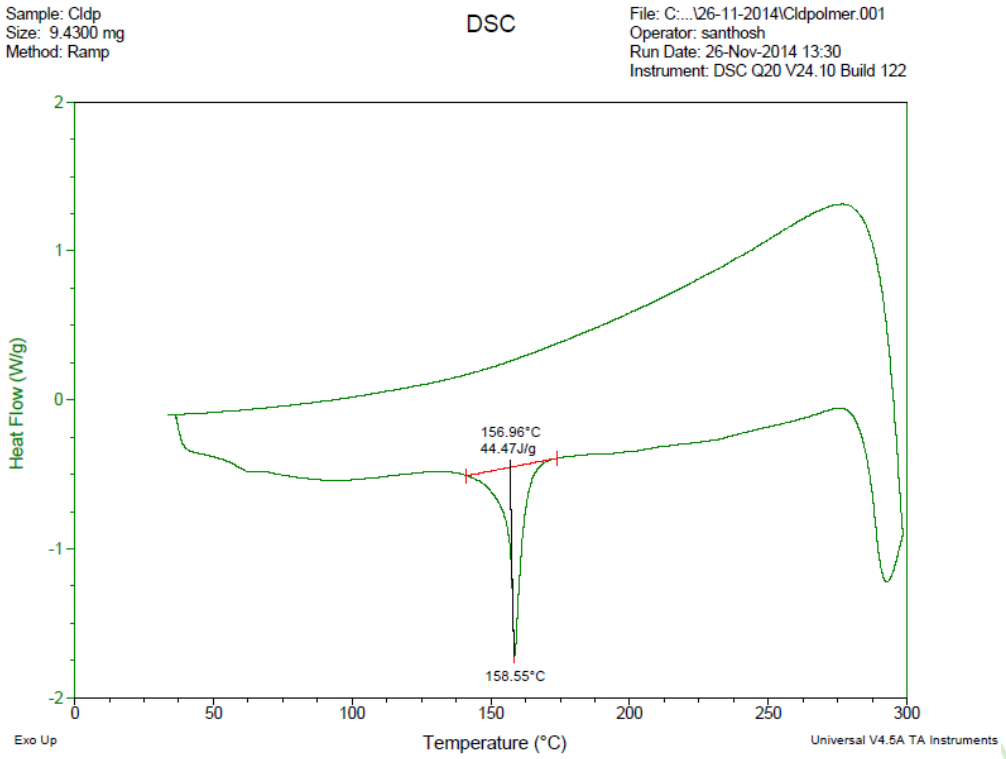


Fig.9: DSC thermogram of Ciprofloxacin + Eudragit RS 100 + Eudragit RL 100

PREPARATION OF FLOATINGMICROBALLOONS

Seven formulations of floating microballoons of Ciprofloxacin HCl were prepared by emulsion solvent diffusion method. Formulations F1, F2 and F3 were formulated with Eudragit RS 100 with a drug polymer ratio of 1:1, 1:2, and 1:3. Similarly, formulations F4, F5 and F6 were formulated with Eudragit RL100 with a drug polymer ratio of 1:1, 1:2, and 1:3. F7, were formulated by using combinations of the two polymers i.e Eudragit RS 100 and Eudragit RL 100 with a drug polymer ratio of 1:1. All the formulations (F1 to F7) of prepared microballoons were taken for further evaluation studies

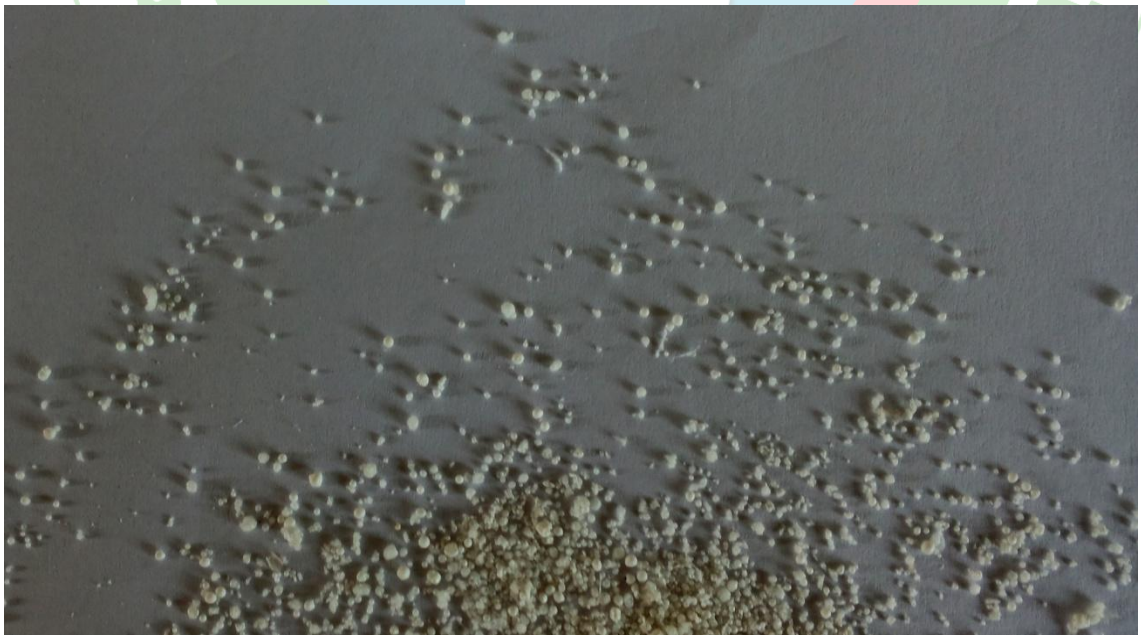


Fig.10: Prepared microballoons of Ciprofloxacin HCl

Conclusion

The present study has been a satisfactory attempt to formulate Floating microballoons of Ciprofloxacin HCl, with a view of improving its oral bioavailability and thus by giving a prolonged release of drug. The identification of drug was carried out by FTIR spectroscopy and melting point. The analytical profile of drug was evaluated for determination of absorption maximum, development of standard curve. FT-IR spectra and DSC thermogram of the physical mixture showed no significant shifting of peaks; therefore it reveals that the drug is compatible with the polymer used.

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