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EVALUATION OF COMPATIBILITY OF PHARMACEUTICAL FORMULATION EXCIPIENTS WITH ETODOLAC

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ABSTRACT

Selection of Pharmaceutical excipients based on drug excipient compatibility is a part of preformulation study. The compatibility between etodolac and commonly used pharmaceutical excipients in the formulation of nanoparticles was assessed by using Fourier-transform infrared spectroscopy (FTIR) and Differential scanning colorimeter (DSC). The study was carried out by using drug and its pharmaceutical excipients individually and their physical mixture with ratio of 1:1. Results showed that no interactions between etodolac and pharmaceutical formulation excipients were observed by both Fourier-transform infrared spectroscopy and Differential scanning colorimeter. Drug excipient compatibility study of etodolac loaded nanoparticles confirmed the absence of drug excipient interaction in the Nano formulation. Hence, results of the study concluded that modified release nanoparticles of etodolac can be successfully prepared by using Eutragit RS 100 as coating material.

Keywords: Nanoparticles, Etodolac, Fourier-transform infrared spectroscopy and Differential scanning colorimeter

INRODUCTION

Preformulation study is an essential prerequisite before development of dosage forms. Among various parameters of Preformulation study like determination of solubility, melting point, analytical method development, solid state stability, bulk

density, true density, compressibility, carrr's index, drug excipients compatibility study also assume significant role **[1, 2]**. Drug excipients compatibility studies are usually carried out to suspect any possible interaction between drugs in same formulation or interaction between drug and excipients **[3, 4]**.

In general, Drug interaction studies are based on the accelerated stability studies. It requires exposing the sample to moisture and maintaining it at different temperature like 4˚C, 37˚C (room temperature) and 60˚C maintained for a period of 45 days or more, followed by assay of the sample at periodic intervals. Instrumental methods of analysis like UV spectroscopy, HPLC methods etc. are used to estimate amount of drug remaining at the specified days. Drug interaction can be confirmed by performing elaborate studies, which involves more quantities of sample, solvent and time [**5-11]**. Now-a-days the drug interaction studies are more effectively done by the thermal methods which comprises differential scanning calorimeter, Thermal gravimetric analysis etc. Among this, differential scanning calorimetric (DSC) is considered to be more reliable and better method. DSC requires only few hours to study the sample by using the temperature programming method **[12-14]**.

"Differential Scanning Colorimetry" is one among various techniques of Thermal analysis. In this technique specific physical properties of a material are measured as a function of temperature. Thermal analysis is generally defined as "A Group of technique in which a physical property of a substance or its reaction products are measured as a function of temperature, whilst the substance is subjected to a controlled temperature program'. These methods find widespread application in both quality control and research field. Current area of application includes environmental measurement, composition analysis, product reliability, Stability, Chemical reactions and dynamic properties **[15-20]**.

Thermal analysis has been used to determine the physical and chemical properties of polymers, (like HPMC K4, HPMC K4 100M, Prinogeletc), as well as active pharmaceutical ingredients used in development of formulation. Combined modern thermal analysis instrument can be used to the measure transition temperature, weight losses and energies of transition, dimensional changes, modules changes and viscoelastic properties. Purity of materials can be determined by using the temperature of phase

changes and reaction as well as heats of reaction.

Etodolac is a non-steroidal anti-inflammatory agent prescribed for the treatment of acute pain, osteoarthritis, and rheumatoid arthritis at an oral dose of 200 mg twice daily; up to 1,200 mg daily may be given if necessary. It has also been reported to be effective in the treatment of gout by lowering uric acid blood levels in humans. The drug shows high therapeutic index between gastric irritation and anti-inflammatory effects. Recent studies have proved that etodolac has antitumor effect on different human cancer cells. Etodolac is one of the selective COX-2 inhibitors; it possesses 10-fold COX-2 selectivity over COX-1 responsible for the production of prostaglandins involved in cytoprotection of gastric mucosa and regulation of the renal blood flow. ET thus safely treats inflammatory disorders without causing gastric irritation, ulceration, or bleeding.

Rheumatoid arthritis is a chronic autoimmune disease that causes continuous articular devastation and bone deterioration. It is associated with chronic inflammation and tissue damage. The activation of the immune inflammatory reactions during night cycle forces the symptoms to worsen in the early morning resulting in sleep disturbances related to quality of sleep and discontinuity. Symptoms continue over the morning time and include joint stiffness and functional disability.

Etodolac (ETD), a non-steroidal anti-inflammatory drug, used to manage rheumatoid arthritis associated symptoms via inhibition of cyclooxygenase pathways and other inflammatory mediators. ETD is a selective COX-2 inhibitor, which inhibits only cyclooxygenase- 2 mediators. It causes less gastrointestinal complication compared to the majority of other NSAIDs. Etodolac tablets (conventional dosage form) are widely used as treatment option. Conventional delivery systems of etodolac were found to engender stomach complications such as nausea, epigastric pain, heartburn, and indigestion. Delayed drug release formulation would be a suitable solution especially for chronic patients.

Thus, a specialized drug delivery device is thought to be helpful in delivering a loading dose in the early morning and a maintenance dose over the day time. Therefore, researches were directed towards designing a bilayer tablet to include a fast release layer for rapid onset of action, beside a sustained release layer for drug level maintenance. Nevertheless, the rapid drug release in the stomach prevents the success of the system,

due to manifested side effects on gastric mucosa. Recently, another sigmoid release profile has attracted many workers interested in the field of pharmaceutical formulation, the so-called pulsatile drug delivery system. Multiple benefits could be acquired through the new design as the delivery device was capable of releasing the drug in a controlled programmable strategy after a precisely calculated lag phase. Different formulation approaches could be applied with the new design, either single or multiunit systems supplied with controlled release coating materials. Multicoating of tablets with time dependent polymers providing a lag-time prior to drug release initiation could attain the goal for pulsatile release.

MATERIALS AND METHODS

Etodolac (99.79%) donated by M/S Shasun pharmaceuticals, Puducherry and Eutragit RS 100 was procured from Sigma Aldrich. All chemicals used in the study were of analytical grade and used without further purification.

Experimental Studies:

Physico-chemical characterization of the formulation

Differential scanning calorimetry (DSC)

ETD thermograms were performed using a differential calorimeter (Shimadzu DSC 60) to determine the DSC thermal traces. Samples of ETD, Eudragit RS 100 and physical mixture of the ingredients were weighed and placed in a standard aluminum pan. The instrument was calibrated with indium, dry nitrogen was used as a carrier gas with a flow rate of 20 mL/min and a scan speed of 10°C /min up to 300°C was employed. The weight of each sample was 5–10 mg. The main transition temperature (Tc) was determined as the onset temperature of the highest peak. Enthalpy values (DHm) were automatically calculated from the area under the main transition peak. The heat flow was measured for all samples **[21-25]**.

Fourier transform infrared (FT-IR) spectroscopy

FT-IR spectra were obtained for the pure ETD, Eutragit RS 100 and physical mixture of the ingredients of the optimized formula in the range of 4000–500 cm_1. Each sample was placed in the light path of sample cell of FT-IR spectrophotometer (Cary 630, Agilent Technologies, Danbury, USA) and the spectrum was recorded.

RESULTS AND DISCUSSION

DSC is used in pharmaceutical industry to determine possible incompatibilities between different components blended in the formulation according to the appearance, shift and disappearance of peaks in the corresponding enthalpies. DSC curves

(shown in **Figure 1-3**) were used to determine the compatibility of ETD with various added excipients.DSC measures the heat loss or gain resulting from physical or chemical changes within the sample as a function of temperature. A sharp symmetric melting endoderm can indicate relative purity, where broad, asymmetric curve suggests impurities or more than one thermal process. The loss of water present in the compound is usually indicated by the endothermic peaks produced in DSC below 120^{o}C. DSC analysis were performed to find out the physical nature of the Etodolac and also to confirm absence of drug-polymer interaction. Individual thermograms of pure drug, polymer and physical mixture were obtained and the thermograms of DSC are shown below, (**Figure 1-Figure 3)**. .The thermograms of DSC thermogram of Physical mixture Etodolac with Eutragit RS 100showed the characteristic peaks of the drug corresponding to the melting point at 144^{o}C. This confirms that there was no interaction between the drug and polymer. The FT-IR spectra were shown from **Figure 4** to **Figure 6**. On comparison of the individual spectra of the pure sample with that of physical mixtures, no prominent difference in the spectrums was seen.

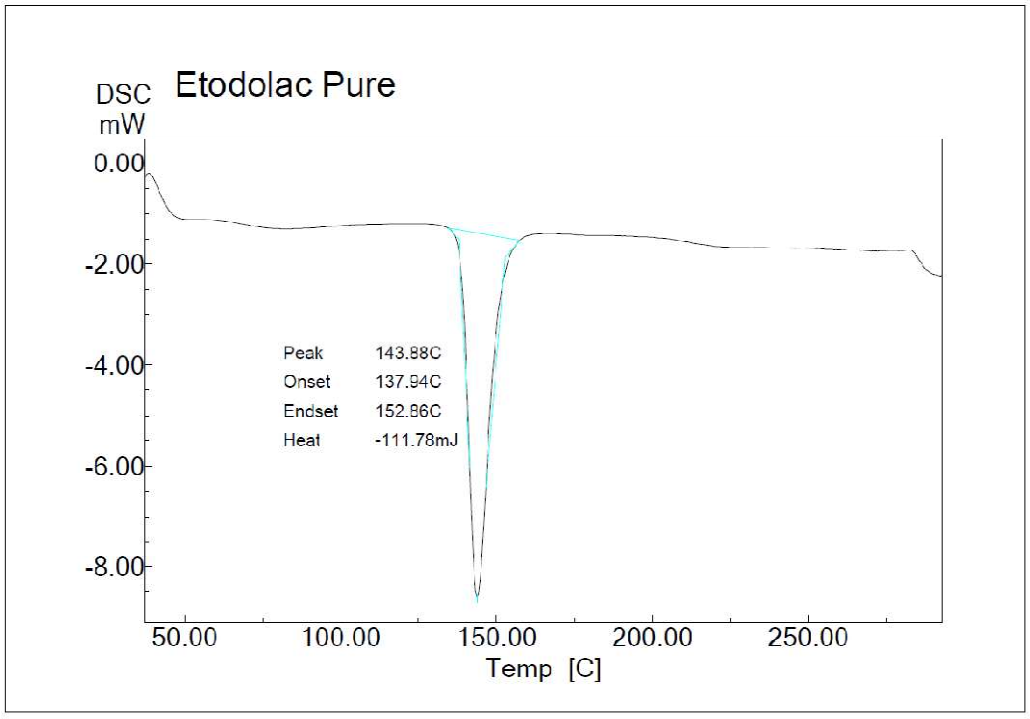

Figure 1: DSC thermogram of Pure Etodolac

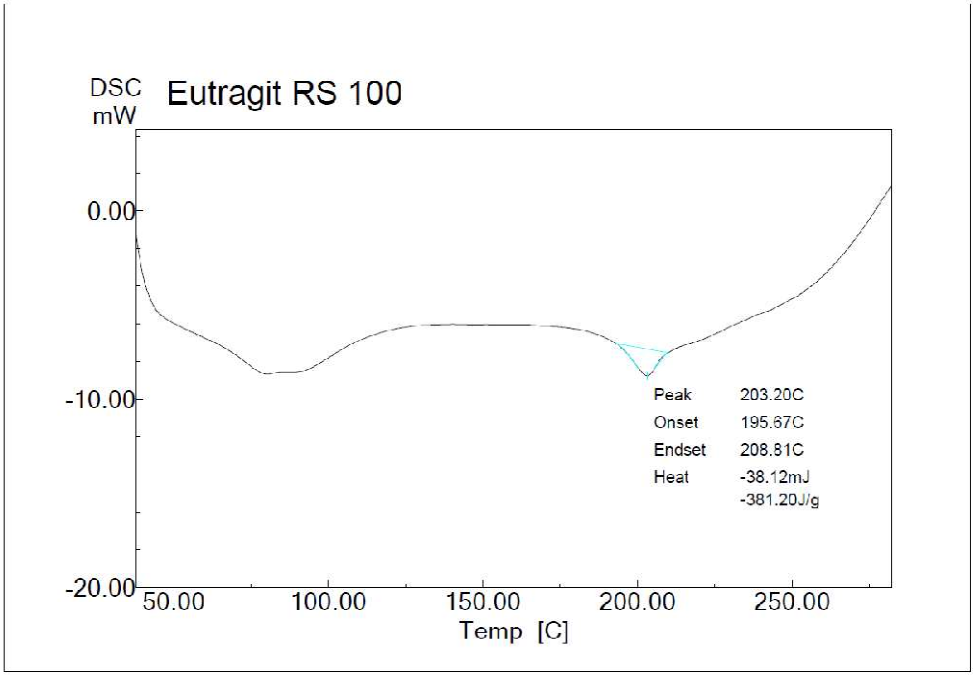

Figure 2: DSC thermogram of Eutragit RS 100

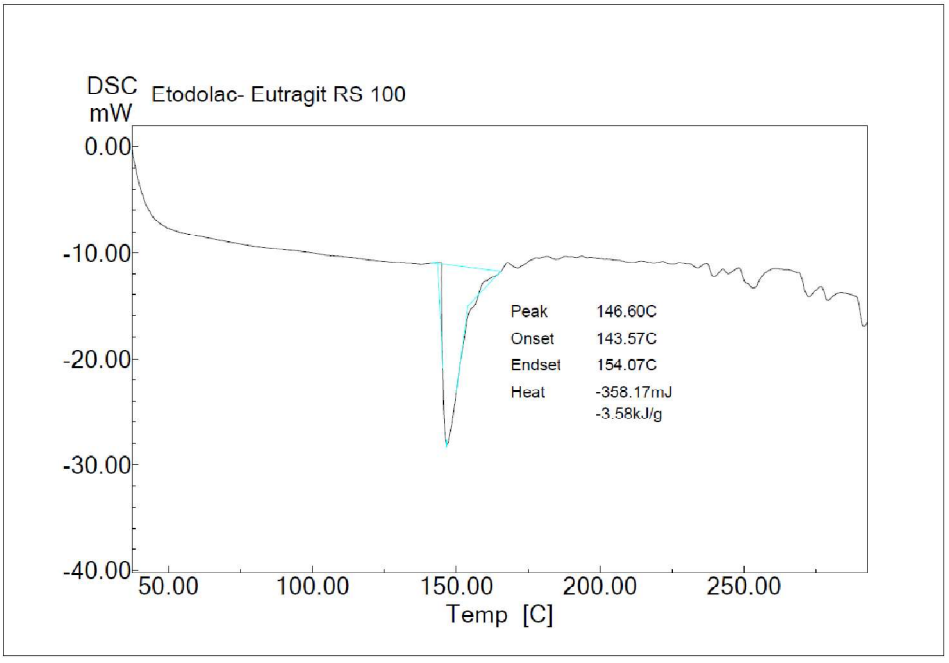

Figure 3: DSC thermogram of Physical mixture Etodolac with Eutragit RS 100

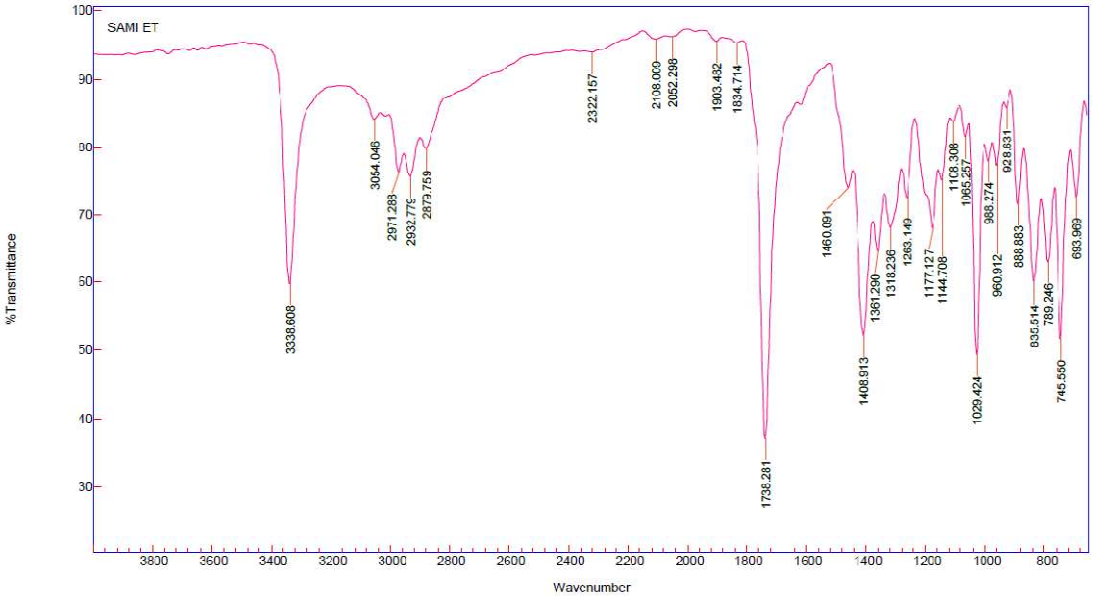

Figure 4: FTIR Spectra of Pure Etodolac

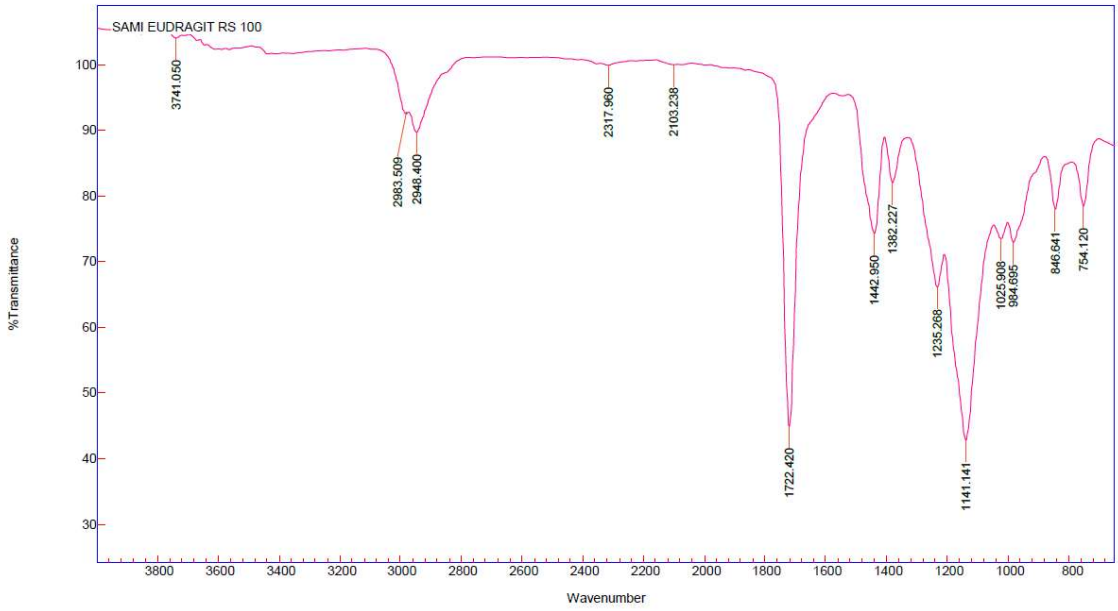

Figure 5: FTIR Spectra of Eutragit RS 100

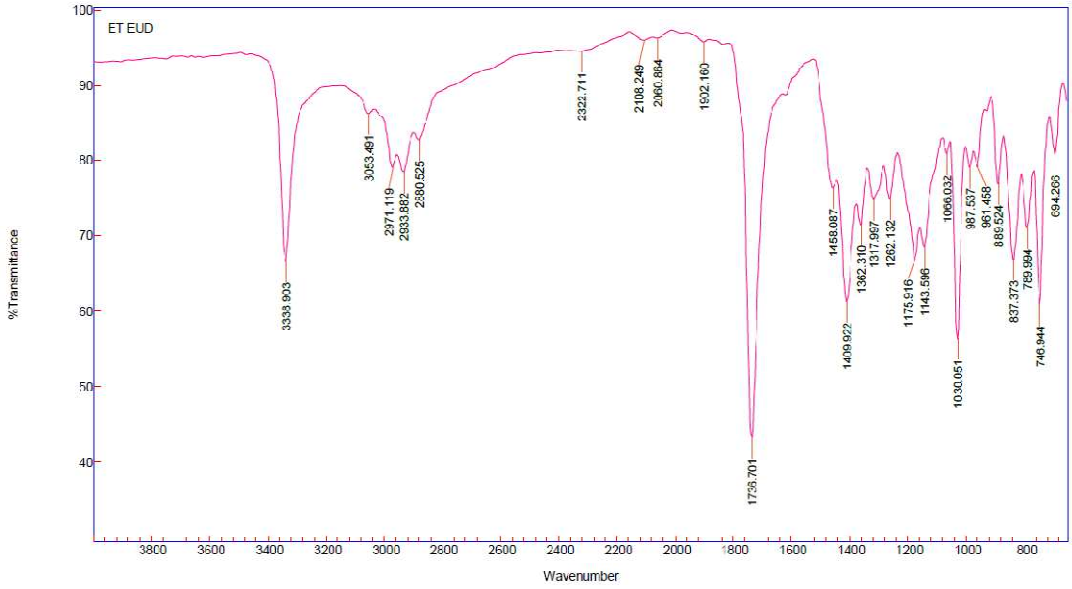

Figure 6: FTIR Spectra of Physical Mixture of Etodolac with Eutragit RS 100

CONCLUSION

Drug excipient compatibility is a part of Preformualtion study and the compatibility has to be ascertained before developing the formulation. In this study the drug-excipient compatibility studies employing DSC and FTIR have been carried out to confirm the inertness of Pharmaceutical excipients towards drug entity. In this study we have selected Eudragit RS 100 as polymer for the preparation of polymeric nanoparticles.FT-IR spectra indicate that there are no major degenerative changes. DSC thermograms also support the FT-IR data. Hence, the studies confirm the chemical inertness of the Eutragit RS 100 polymer with the drug Etodolac. From the results obtained we can conclude that Eutragit RS 100 polymer is compatible with the drug Etodolac to formulate Etodolac RS100 nanoparticles.

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