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Research Article

Selection of excipients for polymer coated capsule of Celecoxib through drug-excipient compatibility testing

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ABSTRACT

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis. Formulation is considered appropriate when no interactions drug-excipient or excipient-excipient occur. In this sagacity, devising a quick and accurate method to evaluate and choose the best excipients for stable dosage forms constitute, a real achievement in the pre-formulation stage. Recently by the application of thermal analytical techniques at the drug-excipient compatibility stage of development of solid dosage form has increased enormously. The intention of the present work was to study the compatibility of Celecoxib drug substance with the excipients employed in colon target release capsule preformulation by adopting Differential scanning calorimetric (DSC) study and Fourier transform Infra red spectrophotometric study (FTIR). Based on the DSC results Celecoxib was found to be compatible with excipients succinic acid, ethyl cellulose, eudragit-E100, hydroxyl propyl methyl cellulose, carboxy methyl ethyl cellulose. FTIR was used as supportive techniques for the analyses.

Keywords: FTIR; DSC; Celecoxib; Excipients

INTRODUCTION

Celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazolyl]benzenesulphonamide, belong to a novel class of agents that selectively inhibit cyclo-oxygenase-2 (cox-2) enzymes. The introduction of this first selective cox-2 inhibitor in the pharmaceutical market revolutionized the treatment of osteoarthritis, rheumatoid arthritis, inflammatory bowel disease and management of pain. It is one of the top selling molecules, with a worldwide sales of 2614 million dollar in year 2000. US FDA has approved its use in OA, RA and dysmenorrheal with dose strength of 100-200mg once/twice daily.

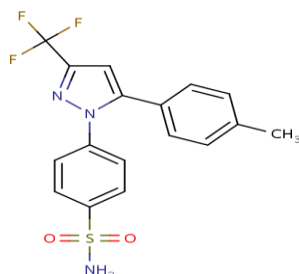


Figure 1: Chemical structure of Celecoxib

Study of drug-excipient compatibility is an important process in the early development stage of stable solid dosage forms. The successful formulation of a stable and effective dosage form depends on a careful selection of the excipients. However, no universally accepted protocol is available for evaluating the drug compatibility with different excipients (Garima chawla et al., 20, 2003.)

A formulation is considered appropriate when no interactions drug excipient or excipient-excipient occur. In this sense, devising a quick and accurate method to test and select the best excipients for stable dosage forms constitute, a real achievement in the preformulation stage. (Thimmasetty.J et al., 4, 2009.) Thermal analysis is one of the most frequently used instrumental techniques on pharmaceutical researches to solve technological problems in the pre-formulation stages of solid dosage forms. In particular, differential scanning calorimetry (DSC) has been proposed as a rapid method for evaluating physico-chemical interactions (Bozdog-pehlivan.S et al., 68, 2011) between the formulation components and therefore selecting excipients with suitable compatibility. (Moorthy.C et al., 4, 2014)

The aim of this work was to evaluate the compatibility between Celecoxib and some pharmaceutical excipients, using thermo analytical techniques (DSC) and Fourier transform infrared spectroscopy (FTIR).

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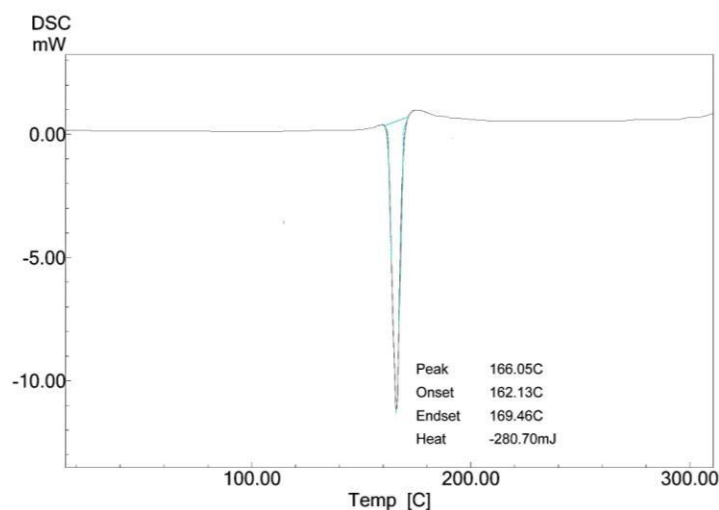


Figure 2: DSC Thermogram of Celecoxib

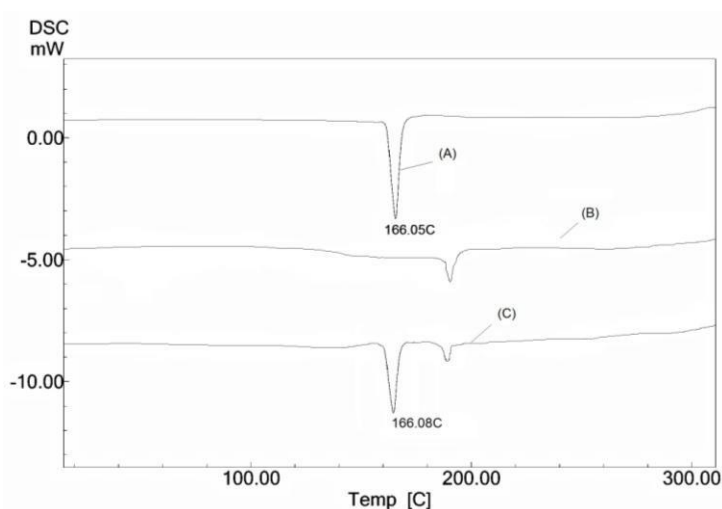


Figure 3: DSC Thermogram of Celecoxib with Succinic acid

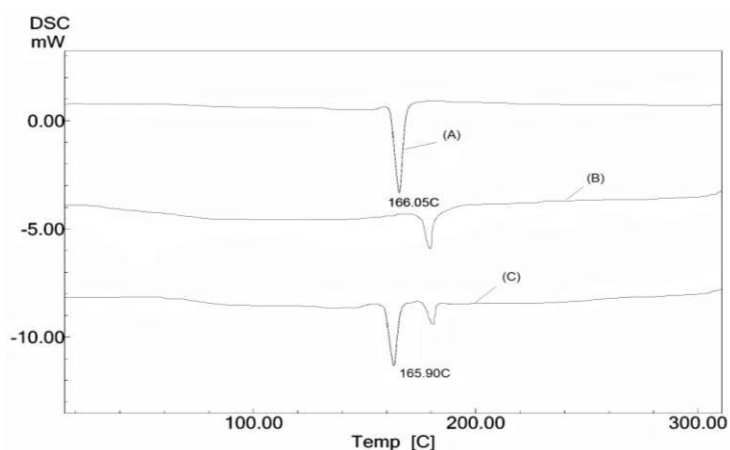


Figure 4: DSC Thermogram of Celecoxib with Ethyl Cellulose

MATERIALS AND METHODS

Celecoxib as gift sample was Procured from ideal lab pvt ltd. The excipients examined were: succinic acid (Adlab Pharmaceuticals, Pondicherry), ethyl cellulose (Himedia Laboratories Pvt Ltd. Mumbai and Eudragit E 100 (Vikram Thermonik Pvt. Ltd. Hyderabad), Hydroxy propyl methyl cellulose (Chemfield Pharmaceuticals Pvt. Ltd, Mumbai), Carboxy methyl ethyl cellulose (He-

tro Lab, Hyderabad). Physical binary mixture Celecoxib:each excipient alone = 1:1 mass/mass ratio obtained by grinding in the agate mortar were also studied.

Sample Preparation

Each material was sieved and the respective 75-150 μ m granulometric fraction was selected.

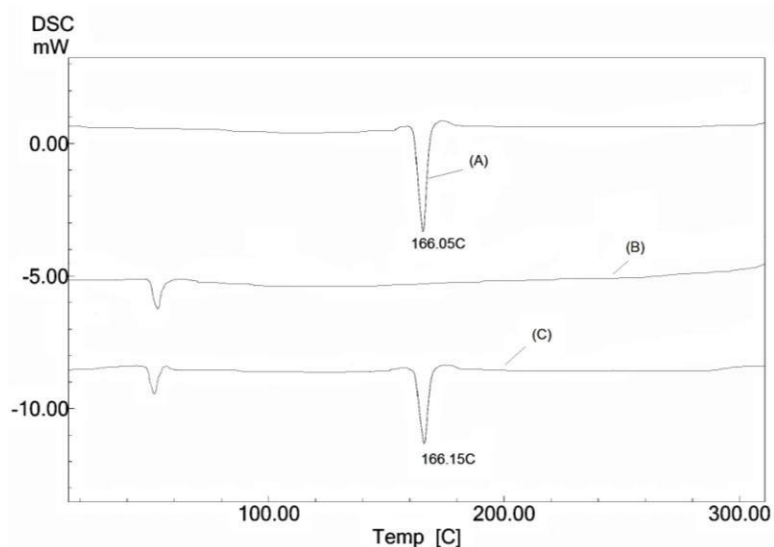


Figure 5: DSC Thermogram of Celecoxib with Eudragit E100

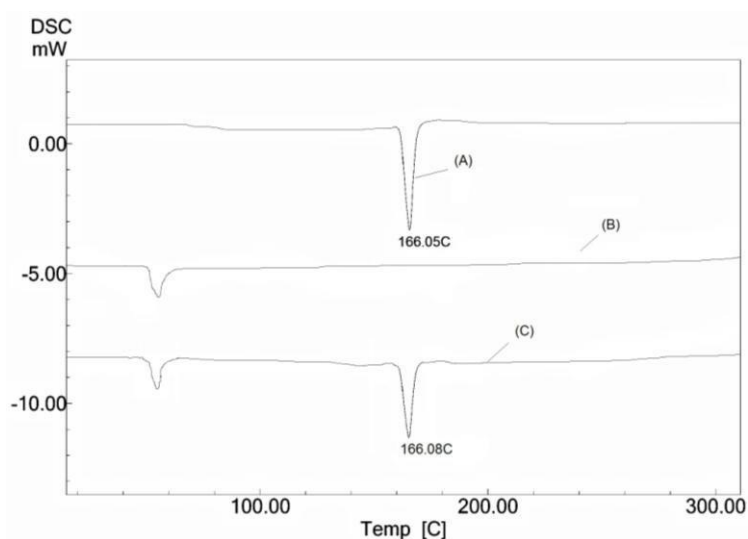


Figure 6: DSC Thermogram of Celecoxib with Hydroxy propyl methyl cellulose

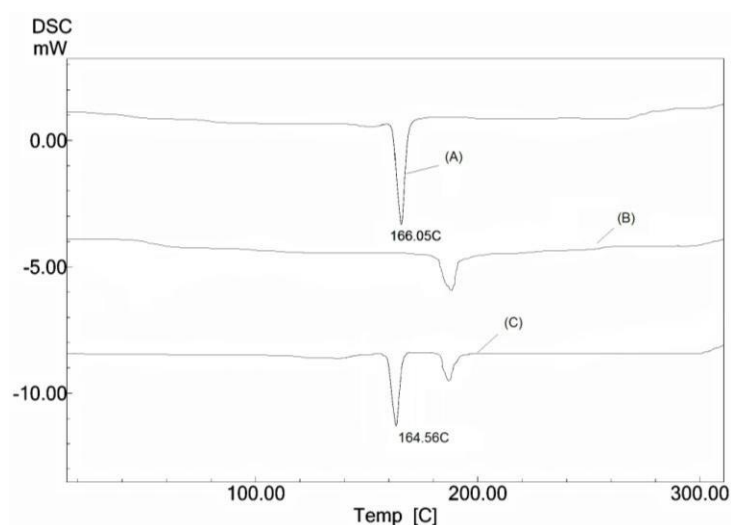


Figure 7: DSC Thermogram of Celecoxib with Carboxy methyl ethyl cellulose

Physical mixture of Celecoxib and each selected excipients were prepared in the 1:1w/w ratio gently blending with spatula at room temperature. The blends were

considered homogeneous mixture when the mixture is used for the further analysis.

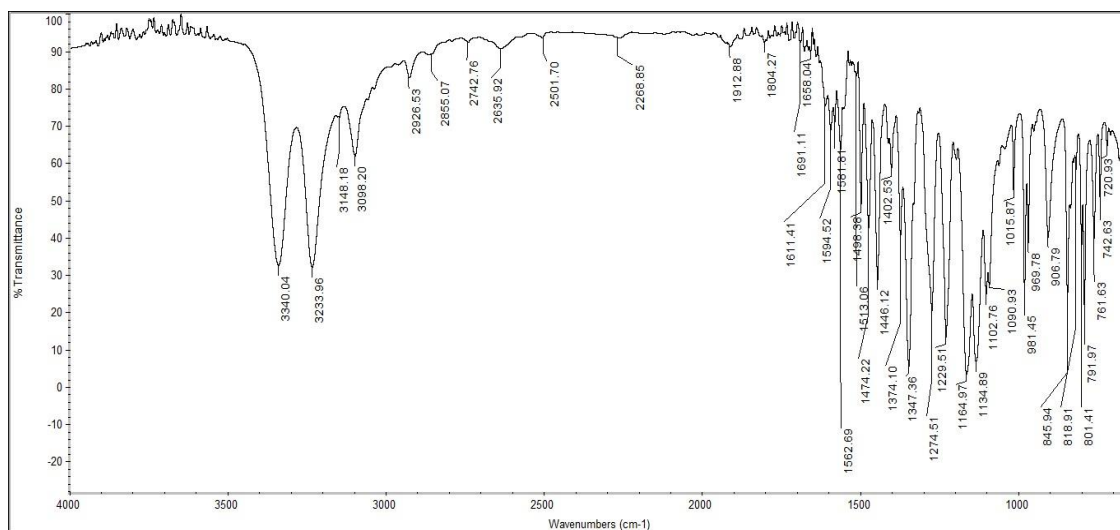


Figure 8: FTIR spectrum of Celecoxib

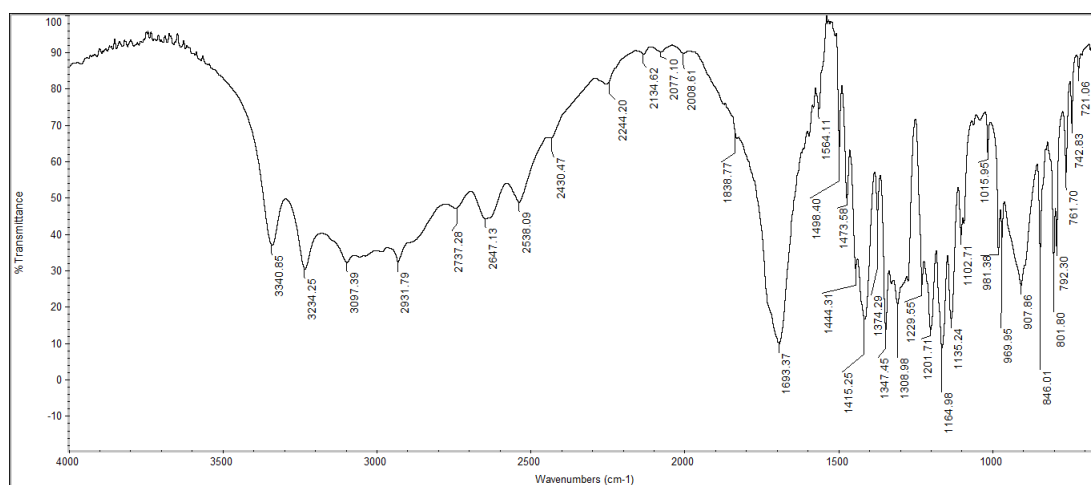


Figure 9: FTIR spectrum of Celecoxib with Succinic acid

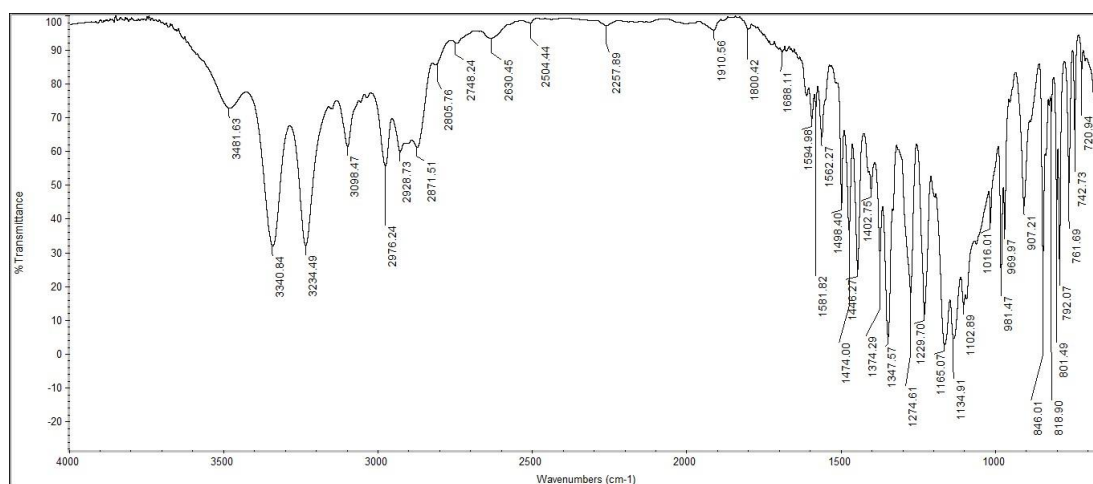


Figure 10: FTIR spectrum of Celecoxib with Ethyl cellulose

Differential scanning calorimetry (DSC)

Samples of individual components as well as each drug-excipient were weighed (Mettler Electronic balance) directly in pierced aluminum crucible pans (5-10 mg) and scanned in the 50-300°C temperature range under static air, with heating rate of 10Kmin⁻¹, using shimadzu DSC-60 equipment.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra Celecoxib were recorded on a FTIR multiscopes spectrophotometer (Perkin Elmer, UK) equipped with spectrum v3.02 software using KBr pellet method. The Spectrum for each sample (an average of 16 co-added scans) was recorded over the 450–4000 cm⁻¹ spectral region with a resolution of 4 cm⁻¹.

RESULTS AND DISCUSSION

DSC Analysis

The DSC analysis allowed the quantitative evaluation of thermal properties of drugs and polymers such as melting point thermogram (Ford.J.L et al., 1989) of celecoxib showed a sharp endothermic peak at 166°C (Figure

2). In majority of the cases, melting endotherm (Ford.J.L et al., 1993) of drug was well preserved with slight changes in terms of broadening or shifting towards the lower temperature (Ahmad, Md. Zaki et al., 3, 2010).

It has been reported that the quantity of material used, especially in drug-excipient mixture (Sonali. S. Bharate

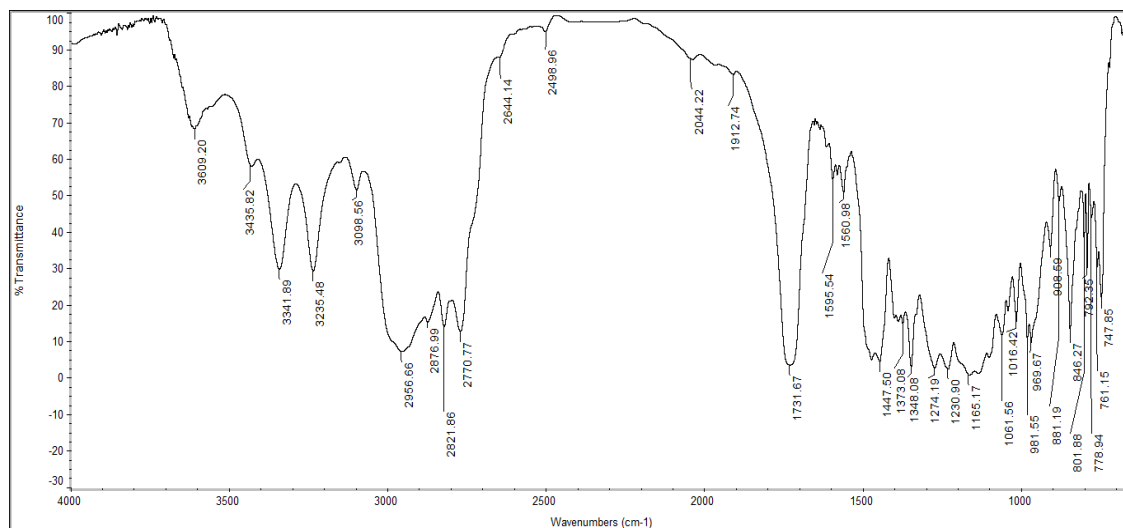


Figure 11: FTIR spectrum of Celecoxib with Eudragit E100

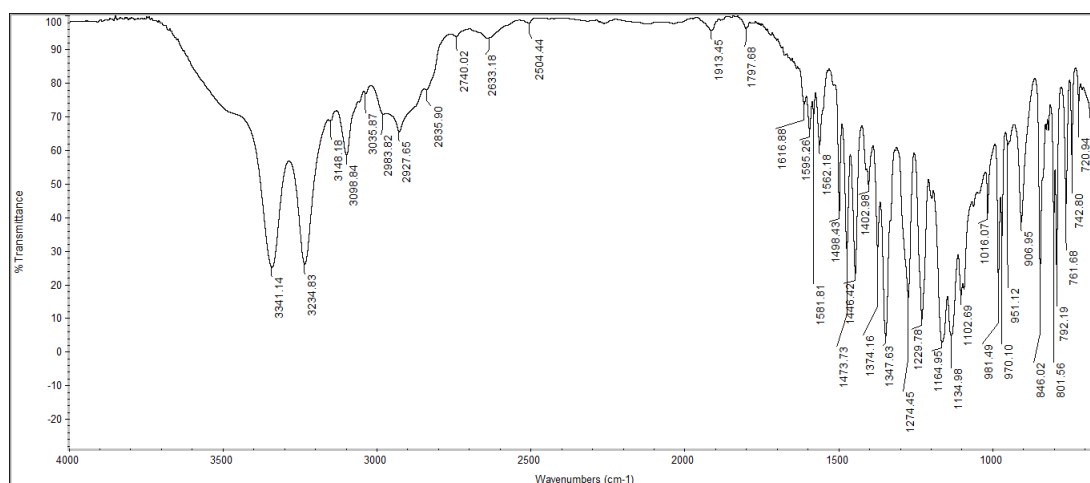


Figure 12: FTIR spectrum of Celecoxib with Hydroxy propyl methyl cellulose

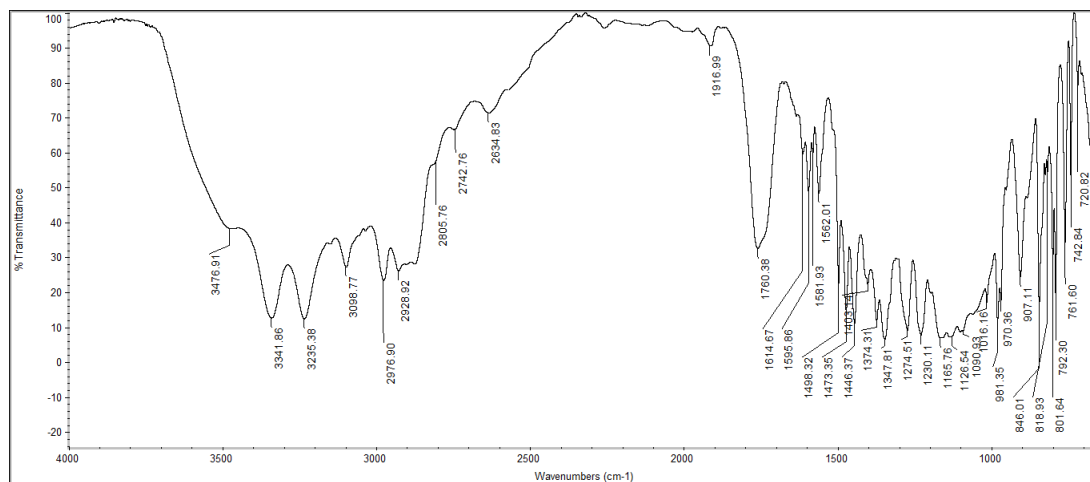


Figure 13: FTIR spectrum of Celecoxib with Carboxy methyl ethyl cellulose

et al., 1, 2010) affects the thermogram of the drug. Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipients (Giron.D et al., 4, 1986) which lowers the purity of each component in the mixture and may not necessarily indicates potential incompatibility (Swamivelmanickam.M et al., 4, 2011). However, in the physical mixture of the celecoxib with succinic acid or ethyl cellulose or Eudragit E100 or Hydroxy propyl methyl cellulose or Carboxy methyl ethyl cellulose the endothermic peak of both celecoxib and individual polymer were found (Figure 3 to Figure 7).

FTIR study

The infrared (FT-IR) spectra were obtained in a KBr pellets using a perkinelmer FT-IR spectrometer spectrum one at resolution 4 cm⁻¹ from 2000 to 400 cm⁻¹. A Typical FT-IR spectra of novel Celecoxib showed absorption at the following wave number in cm⁻¹ 1586.93, 1420.71, 1285.90, 1220.38, 1141.68, 1004.68 & 757.07.

FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different solid-state forms of an organic compound. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption peaks. The FTIR spectra of celecoxib (Figure 8) showed a characteristic S=O symmetric and asymmetric stretching at 1164.97, 1347.36 cm⁻¹, respectively. Medium intensity bands at 3340.04 and 3233.96 cm⁻¹ were seen as doublet, which are attributed to the N-H stretching vibration of -SO₂NH₂ group. The FTIR spectrum of physical mixture of celecoxib and succinic acid shows a strong absorption peak at 1415.25 cm⁻¹ due to symmetric stretching vibration frequency of carbonyl group. The peak due to bending vibrations of COO⁻ is shifted to 907.86 cm⁻¹. The CH₂ wagging (1308.98 cm⁻¹) and C-CH₃ stretching (1201.71 cm⁻¹) vibrations are also observed. The frequency of absorption of O-H stretching at 1693.37 cm⁻¹ confirms the presence of succinic acid with celecoxib (Figure 9). The mixture of celecoxib and ethyl cellulose shows the characteristic peak at 1347.57 cm⁻¹ and 1474.00 cm⁻¹ due to O-H stretching vibration and C-O vibration respectively (Figure 10). The FTIR analysis of the physical mixture of celecoxib and Eudragit E100 shows characteristics shift in peaks at 1230.90 cm⁻¹, 1274.19 cm⁻¹ and 1348.08 cm⁻¹ due to ester groups Eudragit E100, as well as C=O ester vibration at 1731.61 cm⁻¹. The absorption peak of dimethyl amino groups at 2770.77 cm⁻¹ and 2821.16 cm⁻¹ were confirmed the compatibility of celecoxib and Eudragit E100 (Figure 11). The FTIR analysis of the celecoxib and hydroxy propyl methyl cellulose shows characteristic peaks at 1616.88 cm⁻¹ and 1595.26 cm⁻¹ are for the polymer and shows compatible with the drug (Figure 12). Similarly, the characteristic absorption peaks at 1595.86 cm⁻¹, 1614.67 cm⁻¹ and 1760.38 cm⁻¹ present in

the mixture of celecoxib with carboxy methyl ethyl cellulose, indicating there was no modification or interaction between drug and polymer (Figure 13). The FTIR spectrum of samples (Figure 8 to Figure 13) showed characteristic absorption bands (Mura.P et al., 18, 1998) which were comparable with absorption bands of individual sample. The results illustrated that, there were no chemical instabilities in drug-excipient combinations (Tonder.E.C.V et al., 16, 1990)

CONCLUSION

The results demonstrated the applicability of FTIR and DSC methods as fast screening tools to check compatibility in early stages of a preformulation process. Based on our results, all mentioned excipients were found to be fully compatible with Celecoxib. We can conclude that the selected excipients can be further used for formulating Celecoxib polymeric coated capsules.

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