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Selection of excipients for polymer coated capsule of Capecitabine through drug-excipient compatability testing

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Abstract: Capecitabine is an orally administered chemotherapeutic agent used in the treatment of metastatic breast cancer and colorectal cancer. 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 compatability stage of development of solid dosage form has increased enormously. The intention of the present work was to study the compatibility of Capecitabine 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 Capecitabine 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, Capecitabine, Excipients

Introduction

Capecitabine is a fluoropyrimidine carbonates with antineoplastic activity and it is an class drugs known as anti-metabolites. Capecitabine is an orally administered chemotherapeutic agent which is converted in liver and tumour to the active agent 5-fluorouracil (5-FU). It is used in the chemotherapeutic treatment of patients with breast and colon cancer. Capecitabine is a prodrug, that is enzymatically converted to 5-fluorouracil in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue. The activation of Capecitabine follows a pathway with three enzymatic steps and two intermediary metabolites, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR), to form 5-fluorouracil.Chemically it is5'-deoxy-5-fluoro-N-[{pentyloxy}carbonyl]-cytidine with empirical formula $C_{15}H_{22}FN_3O_6$ and the molecular weight of 395.35g/mol. It elicits the pharmacodynamic response by resembling as a normal cell nutrient needed by cancer cells to grow. The cancer cells take up the Capecitabine which then interferes with their growth.

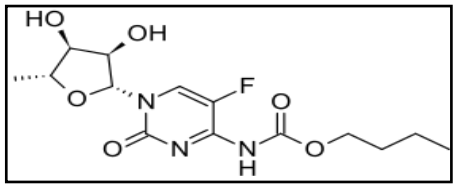

Fig.1.Chemical structure of Capecitabine

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[1-2].

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[3-6]. 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 between the formulation components and therefore selecting excipients with suitable compatibility[7].

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

Materials and methods

Capecitabine as gift sample was Procured from Naprodifescience pvt ltd, Mumbai. The excipients examined were: succinic acid, (Adlab Pharmaceuticals, Pondicherry) ethyl cellulose (Himedia Laboratories Pvt Ltd. Mumbai, india. and Eudragit E 100, (Vikram Thermonik Pvt. Ltd. Hyderabad), Hydroxy propyl methyl cellulose (Chemfield Pharmaceuticals Pvt.Ltd,Mumbai),Carboxy methyl ethyl cellulose (Hetro Lab,Hyderbad). Physical binary mixture Capecitabine: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 75-150µm granulometric fraction was selected. Physical mixture of Capecitabine 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.

Differential scanning calorimetry (DSC)

Samples of individual components as well as each drug-excipient were weighed (Mettler Electranic 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 Capecitabine were recorded on a FTIR multiscope 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 4cm-1.

Results and discussion

DSC Analysis

The differential scanning calorimetry analysis was used for the quantitative evaluation of thermal properties of drugs and polymers such as melting point of the drug and excipients[8-9]. The thermograms of capecitabine showed a sharp endothermic peak at 116.5°C (Fig.1). In majority of the cases, melting endothermic peak of drug[10] was well preserved with slight changes in terms of broadening or shifting towards the lower temperature[11]. The results reported, the petite variation in the melting endotherm of the drug could be due to the addition of excipients, which lower the purity of each component in the mixture and may not necessarily indicate potential incompatability[12-13]. Similarly, the quantity of material used, especially in drug-excipient mixture, affects the intensity of thermogram of the drug. However, in the physical mixture of the Capecitabine with succinic acid or ethyl cellulose or Eudragit E100 or Hydroxy propyl methyl cellulose or Carboxy methyl ethyl cellulose the endothermic peak of both Capecitabine and individual polymer were found (Fig.2 to Fig.7).

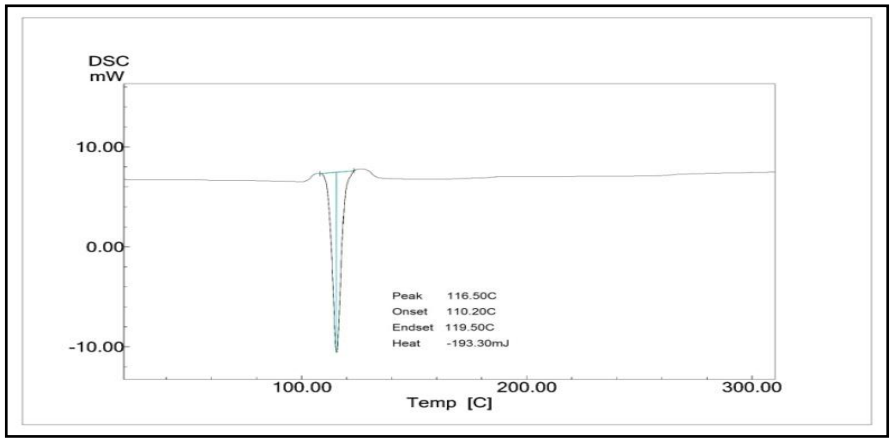

Fig.2. DSC Thermogram of Capecitabine

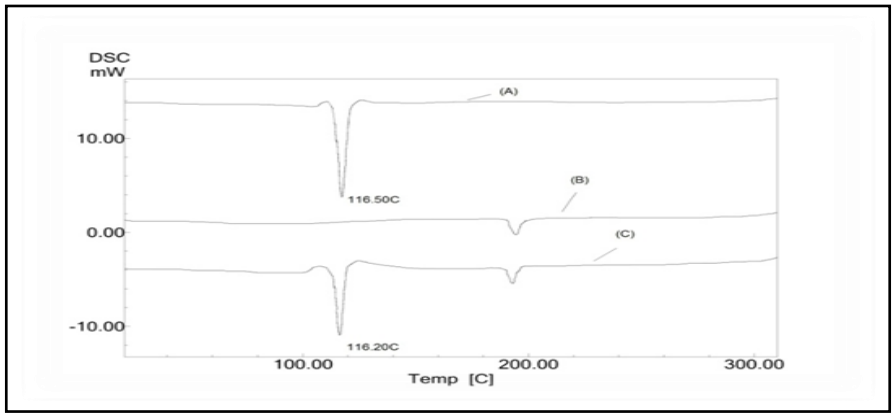

Fig.3. DSC Thermogram of Capecitabine with Succinic acid

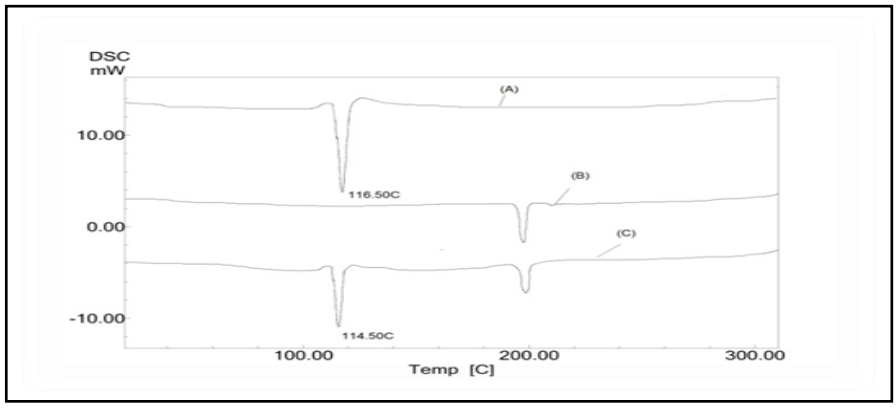

Fig.4. DSC Thermogram of Capecitabine with Ethyl Cellulose

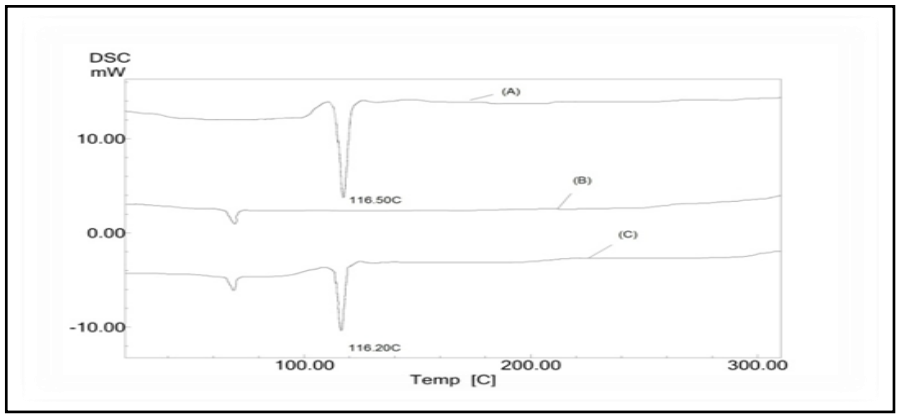

Fig.5. DSC Thermogram of Capecitabine with Eudragit E10

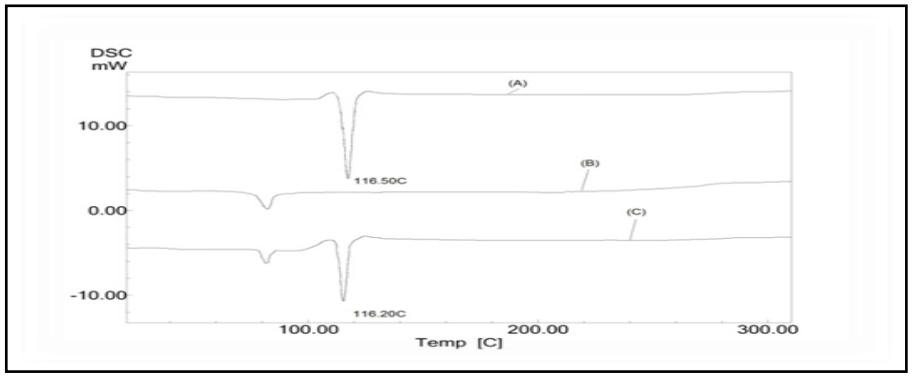

Fig.6. DSC Thermogram of Capecitabine with Hydroxy propyl methyl cellulose

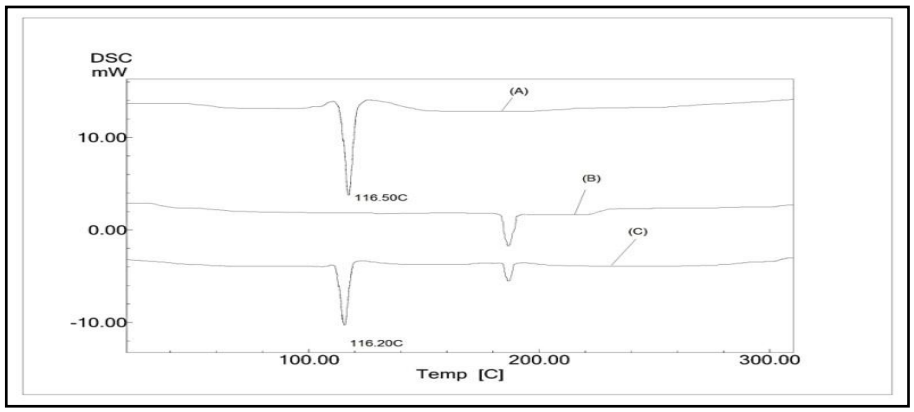

Fig.7. DSC Thermogram of Capecitabine with Carboxy methyl ethyl cellulose

FTIR study

FTIR spectroscopy has been successfully used for exploring the compatibility of molecular conformations, crystal packing and hydrogen bonding arrangements for different solid-state forms of organic compounds. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption peaks. Different characteristic peaks were observed in Capecitabine (Fig.8) at 3273, 3112, 2959, 2932, 1760, 1719, 1678, 1580 and 1501cm-1, were thought to be O-H stretch, CH-Stretch (alkane), CH stretch (aromatic), CH Stretch (alkene) C O stretching from amide I, N-H bending and C-N stretching from amide II,-CH bending, -CH symmetrical deformation, and skeletal vibration of C-O stretching, respectively. The FTIR spectrum of physical mixture of Capecitabine and succinic acid shows a strong absorption peak at 1304 and 1194 cm^{-1} due to symmetric stretching vibration frequency of carbonyl group. The peak due to bending vibrations of COO- is shifted to 1041 cm^{-1}. The CH_2 wagging (1503 cm^{-1}) and C-CH_3 stretching (1416 cm^{-1}) vibrations are also observed. The frequency of absorption of O-H stretching at 1682 cm^{-1} confirms the presence of succinic acid with Capecitabine (Fig. 9). The mixture of Capecitabine and ethyl cellulose shows the characteristic peak at 1504, 1389 and 1417.00 cm^{-1} due to alkaline O-H stretching vibration and C-O vibrations (Fig. 10). The FTIR analysis of the physical mixture of Capecitabine and Eudragit E100 shows characteristics peak at 1204, 1118 and 1050 cm-1due to presence of ester groups as well as the C=O ester vibration bond at 1716 cm-1. In addition –CH2 vibrations can discern at 1389, 1504 and 1579 cm-1. The absorptions at 2740 and 2653 cm-1 can be assigned to the dimethylamino groups of Eudragit E100. The presence of characteristic peaks were confirmed the compatibility of capecetabine and Eudragit E100 (Fig. 11). The FTIR analysis of the Capecitabine and hydroxy propyl methyl cellulose shows characteristic peaks at 1615 cm^{-1} and 1497 $cm^{-1}$are for the polymer and shows compatible with the drug (Fig. 12). Similarly, the characteristic absorption peaks at 1503 cm^{-1}, 1579 cm^{-1} and 1759 cm^{-1} present in the mixture of capecitabine with carboxy methyl ethyl cellulose, indicating there was no interaction between drug and polymer (Fig.13). The FTIR spectrum of samples (Fig. 8 to Fig. 13) showed characteristic absorption bands which were comparable with absorption bands of individual sample. From the result, these prominent peaks of drug were also present in the FTIR spectra of physical mixtures of drug with various excipients. Thus, revealing compatibility of the selected drug with excipients[14-15].

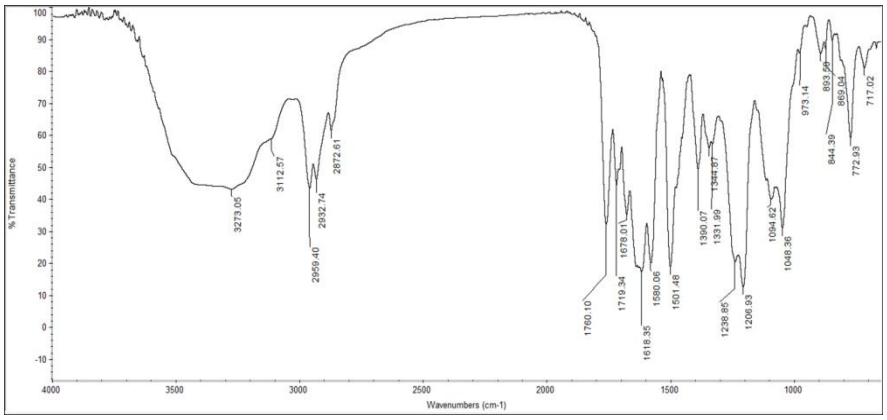

Fig.8.FTIR spectrum of Capecitabine

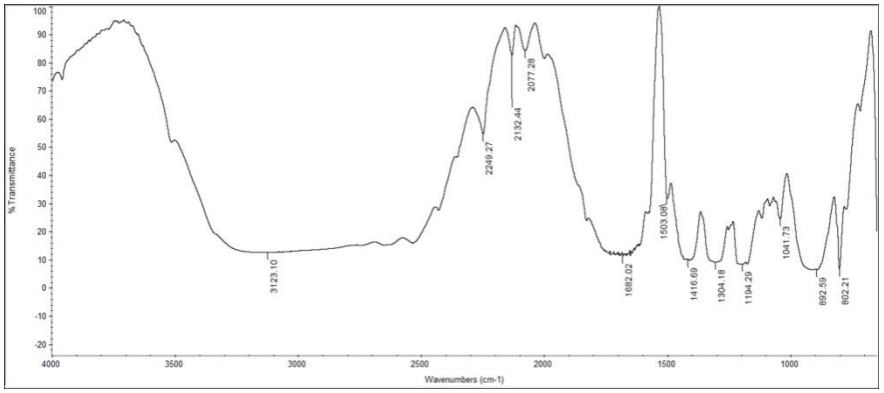

Fig.9.FTIR spectrum of Capecitabine with Succinic acid

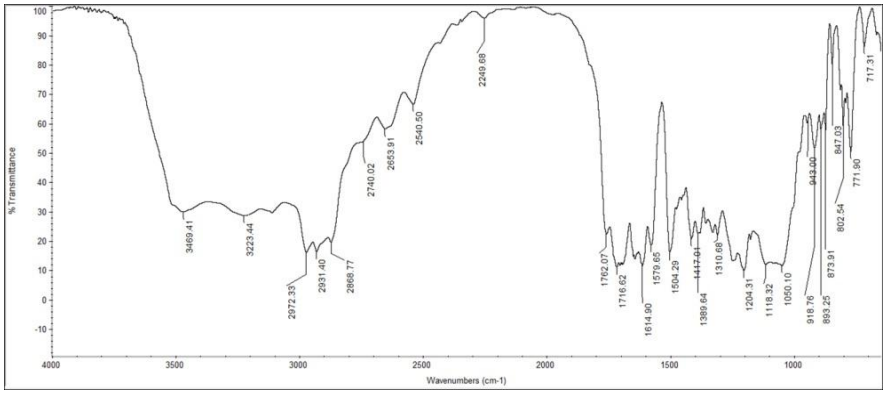

Fig.10.FTIR spectrum of Capecitabine with Ethyl cellulose

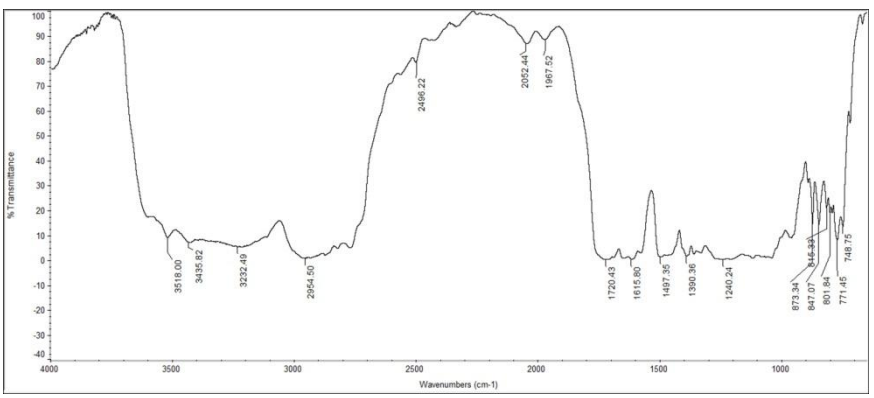

Fig.11.FTIR spectrum of Capecitabine with Eudragit E100

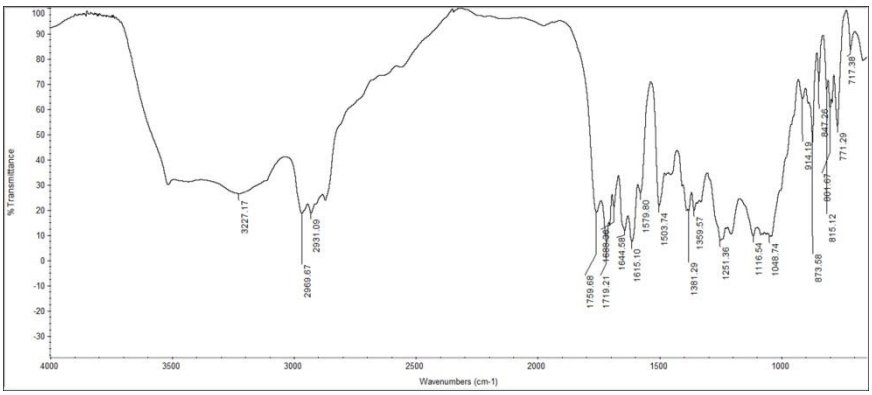

Fig.12.FTIR spectrum of Capecitabine with Hydroxy propyl methyl cellulose

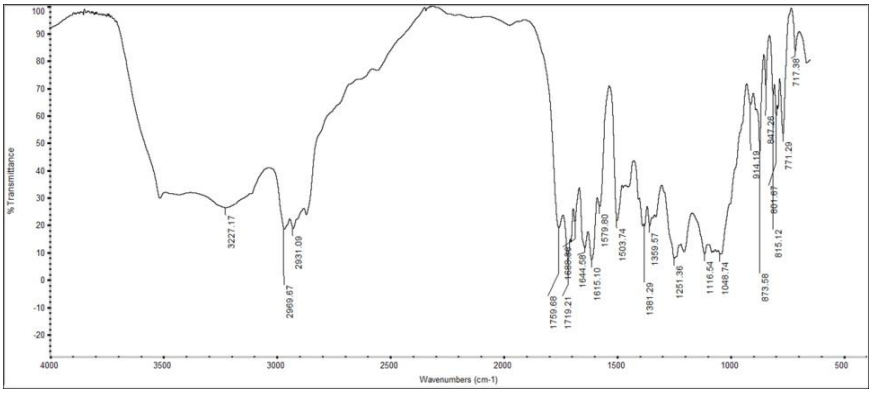

Fig.13.FTIR spectrum of Capecitabine with Carboxy methyl ethyl cellulose

Conclusions

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 Capecitabine. We can conclude that the selected excipients can be further used for formulating Capecitabine polymeric coated capsules

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