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Systematic identification of thermal degradation products of HPMCP during hot melt extrusion process

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ABSTRACT

A systematic identification of the degradation products of hydroxypropyl methylcellulose phthalate (HPMCP) during hot melt extrusion (HME) has been performed. A reverse phase HPLC method was developed for the extrudates of both hydroxypropyl methylcellulose acetate succinate (HPMCAS) and HPMCP polymers to quantify their thermal hydrolytic products: acetic acid (AA), succinic acid (SA) for HPMCAS and phthalic acid (PA) for HPMCP, without hydrolysing the polymers in strong alkaline solutions. The polymers were extruded in the temperature range of 160–190 °C at different screw rotation speeds and hydrolytic impurities were analysed. Investigation of extruded HPMCP showed an additional thermal degradation product, who is structural elucidation revealed to be phthalic anhydride (PAH). Moreover, two environmental analytical impurities, dimethyl phthalate and methyl benzoate formed *in situ* were recorded on GC–MS and their origin was found to be associated with PAH derivatization. Using the experimental data gathered during this study, a degradation mechanism for HPMCP is proposed.

1. Introduction

Hot melt extrusion (HME) technology, a well established for processing of plastics and polymers, has recently been explored for pharmaceutical applications. HME, being solvent free and continuous processing technique, addresses issues associated with solvent based technologies. During pharmaceutical extrusion, the active pharmaceutical ingredient (API) and polymer (/s) are subjected to high temperature and shear to achieve uniform dispersion of an API into the polymeric matrix. However, the high processing temperatures can present a major challenge for HME especially for thermolabile materials where degradation of an API and potential incompatibilities with polymers during processing has been reported (Crowley et al., 2007,Repka et al., 2007).

Recently, HPMCAS and HPMCP were explored as a polymer matrix for dispersion of an API by HME process due to their ability to enhance stability of amorphous dispersion through hydrogen bonding (Al-Obaidi and Buckton, 2009; Bhardwaj et al., 2014; Ghosh et al., 2011; Tian et al., 2013). However, since these polymers are ester derivatives of HPMC (Shin-Etsu, 2009) and prone to hydrolysis at high-processing temperatures, chemical stability of these polymers is one of the major challenges for their use in HME process. Moreover, recently Sarode et al. (2014) showed process induced generation of acetic acid and succinic acid; whereas authors Dong and Choi (2008) showed formation of succinic acid epimer of an API when HPMCAS based system was processed through HME (Sarode et al., 2014; Dong and Choi, 2008).

European Medicine Agency (EMA) recently issued guidelines on the use phthalate derivatives, including HPMCP, in formulations since these materials have raised concerns about potential human risks. However, currently HPMCP is considered to be safe since there are no reports on potential human toxicity caused by HPMCP (European-Medicines-Agency, 2014). Hydrolysis of HPMCP to phthalic acid (PA) is known as principle degradation product and during extrusion; generation of PA can be expected. However, HPMCP has been sparsely studied for in-process impurities and process induced potential incompatibilities. Moreover, there are no reports on quantitation of PA and related impurities of HPMCP in the melt form without hydrolysing the entire polymer in strong alkaline solutions. Therefore, considering the facts about the HME process, chemistry of HPMCP and EMA guidelines, a rational approach was used where efforts have been made to characterise and quantify the degradation products of HPMCP in its melt form

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by means of analytical tools and degradation mechanism of the polymer was studied.

2. Material and methods

Polymers HPMCAS-LF (average Mw 18000 g/mol, particle size ~5 μm, density 1.27 g/cm^3) and HPMCP (average Mw 45000 g/mol, density 1.29 g/cm^3) were obtained as gift samples from Shin-Etsu Chemical Co., Ltd., Japan. All solvents used were of HPLC grade and. The working standards AA, SA and PA were purchased from Sigma–Aldrich with a purity of 99.7%, 99.0% and 99.5% w/w, respectively.

2.1. Thermogravimetric analysis (TGA)

TGA thermograms of the polymers were obtained using a thermogravimetric analyser (TA Instruments Q500 TGA). Samples weighing approximately 7–8 mg were heated from 20 to 600 °C at a heating rate of 10 °C/min under a nitrogen gas atmosphere. Isothermal TGA tests were also carried out at 160, 170, 180 and 190 °C and the isothermal conditions were maintained over 30 min.

2.2. Hot melt extrusion (HME)

Extrusion of HPMCAS and HPMCP was carried out separately using a co-rotating twin-screw extruder (Pharmalab, Thermo Scientific, UK) with a screw diameter of 16 mm and a screw length to diameter ratio of 40:1. Eight batches were processed with maximum barrel temperatures set at 160, 170, 180 and 190 °C and at two screw speeds, 80 rpm and 100 rpm for each temperature. The polymer was fed into the extruder at the rate of 0.10 kg/h (batch size: 1 kg) using a gravimetric twin-screw feeder (Brabender, Germany).

2.3. Preparation of degradation product by sublimation

Approximately 4 g of HPMCP was placed in a round bottom flask (rbf) attached to a condensation assembly equipped with water circulation and experiment was performed in an atmosphere. The rbf was heated at 160 °C for 1 h and allowed to cool under ambient conditions. In the condensation assembly, the deposited colourless crystalline material on the walls of the condensation unit were collected and stored in a glass vial under a nitrogen environment. Similarly, polymer was subjected to 170, 180 and 190 °C independently and the resulting materials obtained.

2.4. HPLC method

All experiments were performed using a Waters e-2695 separation module integrated with degasser and photodiode array detector (PDA-2998). Peaks were analysed with Empower 3 software. The analysis was carried out at 215 nm by using a Waters Spherisorb, ODS2 Column, 3 μm, and 4.6 × 60 mm column at the flow rate of 1 mL/min. The mobile phase composed of 0.05 M potassium dihydrogen phosphate (pH 3, solvent A) and methanol (solvent B) used in a gradient mode over 25 min. Standard solutions of AA, SA and PA (each concentration 50 μg/mL) were prepared in phosphate buffer and extruded samples (concentration 200 μg/mL) were prepared in the same way and injected into the system.

2.5. Nuclear magnetic resonance (NMR)

Degradation product of HPMCP and pure PA were analysed independently by dissolving in d6-DMSO (NMR grade) and screened for ^{1}H NMR (128 scans), ^{13}C NMR (1024 scans) spins using a Bruker 400 MHz NMR spectrometer.

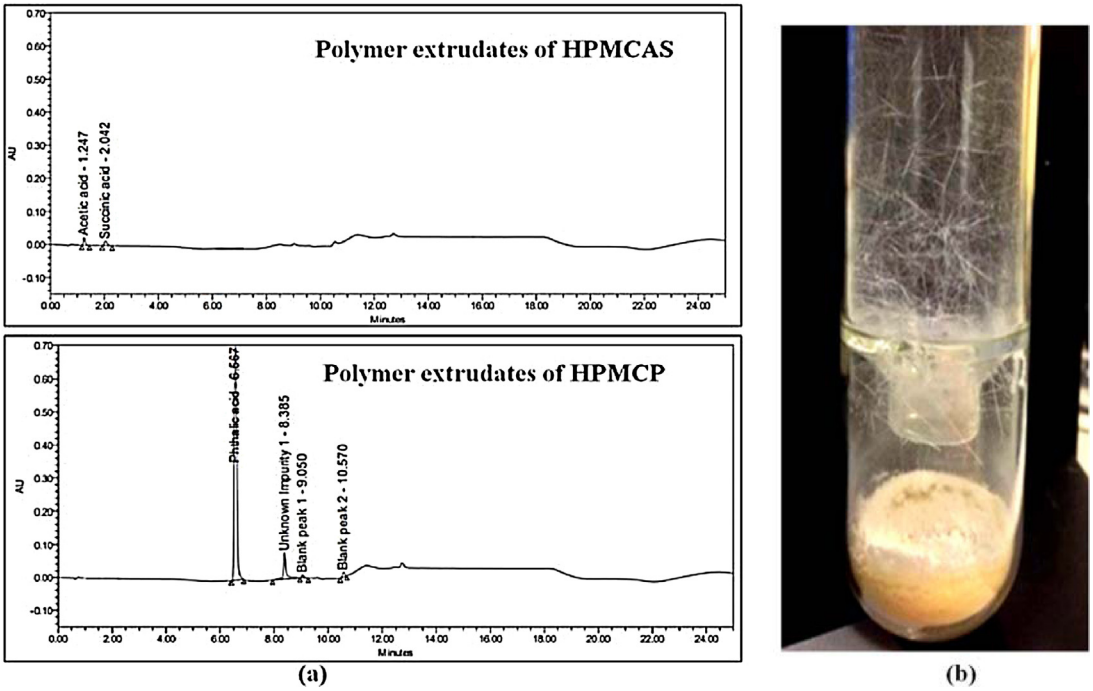

Fig. 1. HPLC chromatograms of extrudates containing both (a) HPMCAS and HPMCP degradants. (b) Sublimation of HPMCP showing vapour condensed degradant crystals (IMP-A).