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Research Article

Hydroxypropyl Methylcellulose Acetate Succinate: Potential Drug–Excipient Incompatibility

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Abstract. The stability of hydroxypropyl methylcellulose acetate succinate (HPMC-AS) and its potential incompatibility with active pharmaceutical ingredients (API) carrying hydroxyl group(s) were investigated in this research. HPMC-AS may undergo hydrolysis under harsh processing conditions with the generation of succinic acid and acetic acid, which can form ester bond(s) with the hydroxyl group(s) in API. In this case, the hot-melt extrusion (HME) product prepared from HPMC-AS and our model compound (compound A) was tested after heating at 140°C up to 5 h. The succinate esters of compound A and its epimer were found in the product, suggesting potential drug–excipient incompatibility during formulation development. In addition, dyphylline was also tested with HPMC-AS and the potential incompatibility was further confirmed.

KEY WORDS: drug–excipient incompatibility; hot-melt extrusion; hydroxypropyl methylcellulose acetate succinate (HPMC-AS); solid dispersion; succinic acid.

INTRODUCTION

Hydroxypropyl methylcellulose acetate succinate (hypromellose acetate succinate, HPMC-AS, Fig. 1a) is an enteric coating material developed for both regular enteric coating and sustained release formulations. Recently, HPMC-AS was also used in new technologies such as solid dispersion (1). With various contents of acetyl and succinoyl groups in the polymer, there are several types of HPMC-AS, which dissolve at different pH levels. Type L HPMC-AS represents polymer with high ratio of succinoyl substitution to acetyl substitution (S/A ratio), while type H with a low S/A ratio and type M with a medium S/A ratio. With a high S/A ratio, type L HPMC-AS dissolves at a lower pH ($\geq$5.5), compared with pH$\geq$6.0 for type M and pH$\geq$6.8 for type H (2).

With the implementation of high-throughput screening in the pharmaceutical industry, more poorly soluble compounds are produced. Consequently, innovative pharmaceutical technologies are developed to enhance absorption and bioavailability of these compounds. Among these, solid dispersion (3) has been widely used in both preclinical and clinical formulation development as a successful approach to deliver insoluble compounds for increasing exposure in animals and man. There are a variety of approaches for preparing solid dispersion, such as hot-melt extrusion (HME), spraying drying and solvent co-precipitation, using polymers as carriers. With test compounds being highly dispersed in the polymer matrix, usually at the molecular level or in microcrystalline phase, solid dispersion system provides a large surface area of the compounds that greatly improves the dissolution, and therefore, the absorption, particularly for BCS Class 2 compounds (4). In addition, due to the interaction between the polymer and active pharmaceutical ingredient (API) molecules in solid dispersion, the amorphous API in solid dispersion is physically more stable than its pure form in amorphous phase (5).

HPMC-AS is a widely used excipient in the solid dispersion technologies (1,6,7). Its capability of forming a solid dispersion and inhibiting the crystallization of the API from the dispersion matrix has been investigated, together with other related polymers including hypromellose (HPMC), hypromellose phthalate (HPMCP), methacrylic acid ethyl acrylate copolymer (MAEA), and povidone (PVP). Among these polymers, in addition to its comparable ability to form an amorphous solid dispersion, HPMC-AS has the best crystallization inhibition effect (1). However, HPMC-AS may undergo relatively extensive hydrolysis under harsh processing conditions, such as HME process at elevated temperature. Upon hydrolysis, free acetic acid and succinic acid are produced (2), which may react with the API, due to the local acidic environment. Among the possibilities, one potential reaction is the esterification of the hydroxyl group in an API.

To evaluate the drug–excipient compatibility during formulation development, many techniques can be used, such HPLC (8), thermal analysis (DSC (9) and simultaneous TG-DSC (10)), FT-IR spectroscopy (10), powder X-ray diffraction (10), scanning electron microscopy (10), etc. To accelerate the drug–excipient compatibility screening and formulation development, approaches using high throughput technology (8,11) and statistical experimental design (8,12,13) were reported.

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In this work, we are reporting the drug–excipient interaction between HPMC-AS and API, using compound A and dyphylline as model compounds, due to the esterification of the hydroxyl group(s) with succinic acid, which is generated from the hydrolysis of HPMC-AS. In order to improve the exposure of compound A, which is a BCS Class 2 compound, the HME process was used to prepare a solid dispersion at 140°C using HPMC-AS. Due to the processing temperature at 140°C and the lower boiling point of acetic acid (118°C), neither acetic acid nor its reaction with compound A was monitored in this work. To further confirm the reaction, dyphylline was selected as the other model compound. The generation of the dyphylline succinate esters provides stronger evidence for generalizing this class of reaction to other compounds carrying hydroxyl group(s).

MATERIALS AND METHODS

Materials

HPMC-AS (Grade AS-LF, Lot# 409069) was obtained from Shin-Etsu Chemical Co. Ltd. Succinic acid (SA, Lot# 755512) was bought from Fisher Scientific Company. The crystalline monohydrate of compound A was prepared in house. Dyphylline (Lot# A0227668) was purchased from Acros Organics.

Instruments

A HAAKE Minilab micro compounder (Thermo Electron Corporation, Waltham, MA, USA) was used to prepare the hot-melt extrusion at a temperature of 140°C.

An ion chromatography (Dionex Corporation, Sunnyvale, CA, USA) was employed to measure the level of succinate ion using an IonPac AS-17 column (4×250 mm, temperature set at 30°C) and an electrochemical detector at a flow rate of 0.8 mL/min of pure water as the mobile phase. The injection volume was 25 μL.

HPLC (Agilent 1100, Agilent Technologies, Inc., Palo Alto, CA, USA) was used to analyze the samples of the solid dispersion to detect any degradants of compound A and Dyphylline. A Phenomenex Luna C18(2) column (4.6× 150 mm, 5 μm) was used for both compounds. Compound A and Dyphylline were detected at 230 and 275 nm, respectively. Water and acetonitrile with 0.05% trifluoroacetic acid (TFA) were used as mobile phases, with a 20-min linear gradient (compound A: 30% to 70% acetonitrile; dyphylline: 5% to 20% acetonitrile) followed by an isocratic condition for 5 min for both compounds (70% and 20% acetonitrile for compound A and Dyphylline, respectively).

Mass Spectrometers (Finnigan LCQ, Thermo Electric Corporation, Waltham, MA and 3200 Q-TRAP® LC/MS/MS System, Applied Biosystems, Foster City, CA) were used to perform analysis on compound A (Finnigan LCQ) and Dyphylline (3200 Q-TRAP®), as well as their degradation products using an APCI source. Both instruments were calibrated prior to use.

Experimental

A physical mixture of compound A and SA (50:50 by weight) was prepared by grinding in a mortar with a pestle. The mixture was then placed in a 140°C oven for an hour. The resulting powder was dissolved in acetonitrile/water (50:50 by volume) at 0.2 mg/mL for HPLC-MS analysis.

The HME powder of compound A was obtained from our formulation scientist and the powder was placed in the 140°C oven and samples were withdrawn after 0, 1, 3, and 5 h of heating. The samples were dissolved in acetone/water (50:50) at 1 mg/mL level and were analyzed by both HPLC and ion chromatography. For comparison, compound A was also stored in the 140°C oven for 5 h and samples were withdrawn for analysis in a 0.2 mg/mL solution.

In order to confirm there is no interference from HPMC-AS on the detection of SA, both 1 mg/mL HPMC-AS and HME solutions spiked with 10 ng/mL SA were tested.

Dyphylline, as the other model compound, was tested under 140°C for 5 h in the following three formats: (a) pure powder; (b) physical mixture with SA (50:50); (c) physical mixture with HPMC-AS with a drug–excipient ratio of 40:60 to mimic a 40% loading HME composition. The samples were dissolved in diluent (95% pH 8.25 50 mM phosphate buffer+5% acetonitrile) to form a 0.1 mg/mL solution of dyphylline for HPLC analysis.

RESULTS AND DISCUSSION

With one hydroxyl group in the structure, compound A (Fig. 1b) was obtained as a monohydrate. It melts and loses water at 138°C. The molecular weight of compound A is 536.8. Dyphylline (Fig. 1c) has a molecular weight of 254.2 with a melting point around 160–164°C. Dyphylline has two hydroxyl groups in its structure.

By injecting 0.1, 0.4, 1, 2, 4, 8, and 20 ng/mL solutions of SA, the detection limit of SA on ion chromatography is determined as 2 ng/mL (Fig. 2a). Consequently, for compound A HME samples whose working solution is 1 mg/mL (equivalent to 0.2 mg/mL of compound A), the detection level for SA in the sample powder is 0.002% (*w*/*w*).

After the physical mixture of compound A and SA was heated to 140°C for an hour, the melt was analyzed on HPLC (Fig. 3). The results indicated that compound A partially converted to its epimer, and both compound A and its epimer formed esters with SA, which was confirmed by the MS spectra (Fig. 4). Compound A and its epimer have a molecular weight of 536.8, and the two compounds have the same MS spectra (Fig. 4a). Similarly, their esters have a molecular weight of 636.9 and they have the same MS spectra as well (Fig. 4b). Upon MS/MS, compound A and its epimer were fragmented to 352.8 and 282.0, and their esters to 452.8, 434, 334.8, and 265.4.

Upon ion chromatographic analysis of the compound A HME samples after being heated at 140°C in the oven for 5 h, no free SA was detected (Fig. 2b) and no interference from HPMC-AS was observed. Upon HPLC analysis, the peaks of the esters of compound A and its epimer were observed (Fig. 3), which were not detected in the initial HME sample prior to heat treatment. In addition, as the control, pure compound A, after being under the same condition for 5 h, partially converted to its epimer, as shown in Fig. 5. The results suggest that, in the HME samples, compound A and its epimer did form esters after hydrolysis of HPMC-AS in the matrix, and with time, more esters were produced.

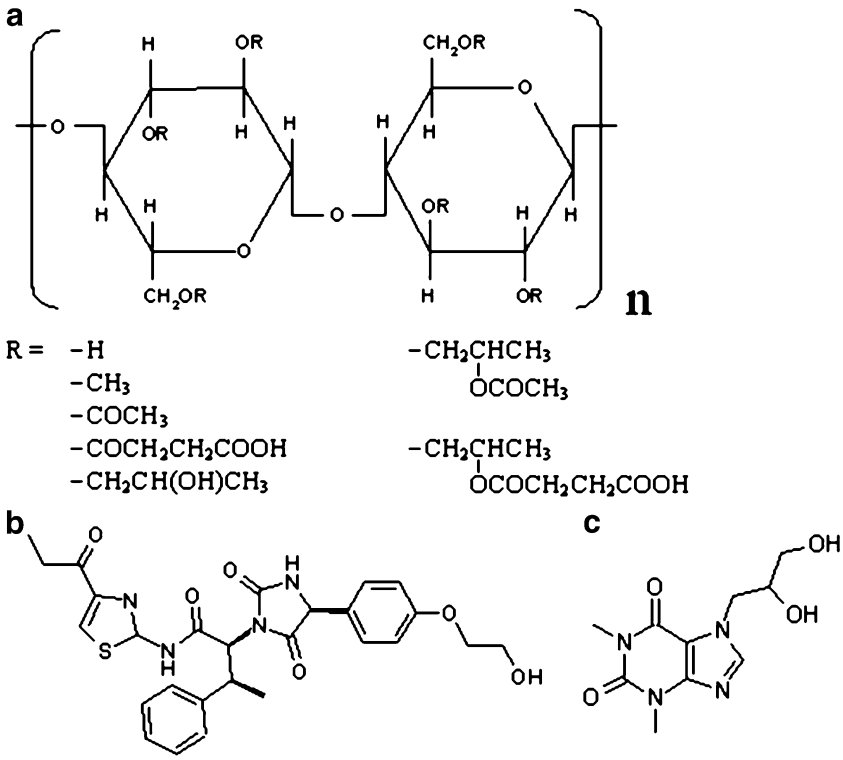

Fig. 1. Structures of: **a** HPMC-AS (adopted from reference (2)); **b** compound A; and **c** dyphylline

As the other model compound, dyphylline showed no sign of degradation after heat treatment. However, five degradants were observed in the physical mixture of dyphylline and SA, as labeled in Fig. 6. The molecular weights were determined in mass spectrometer. Interestingly, all the degradants were detected as proton and sodium adducts in their MS spectra (Fig. 7), with stronger intensity of the former. According to the MS spectra, the

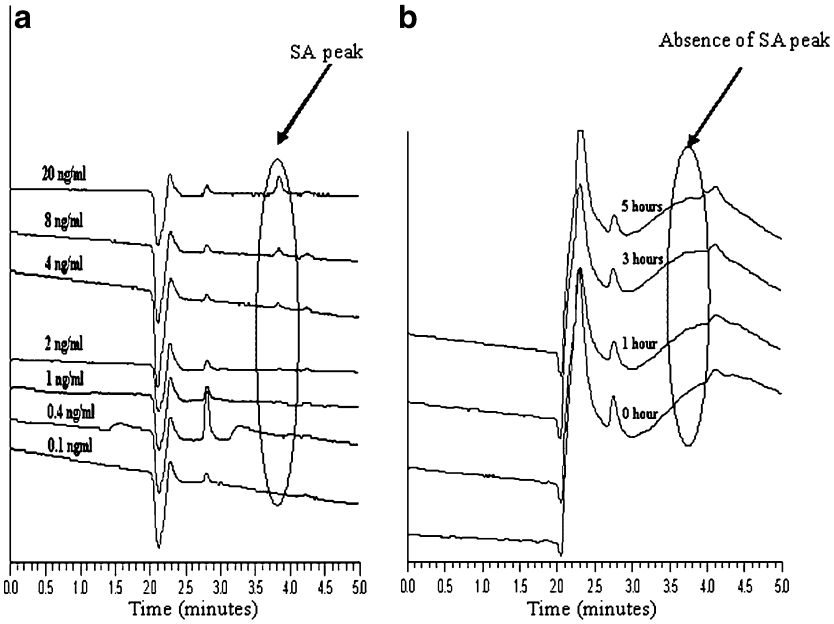

Fig. 2. Ion chromatography results. **a** SA standard solutions with concentrations of 0.1, 0.4, 1, 2, 4, 8, and 20 ng/mL, respectively; **b** HME under 140°C for 0, 1, 3, and 5 h, respectively

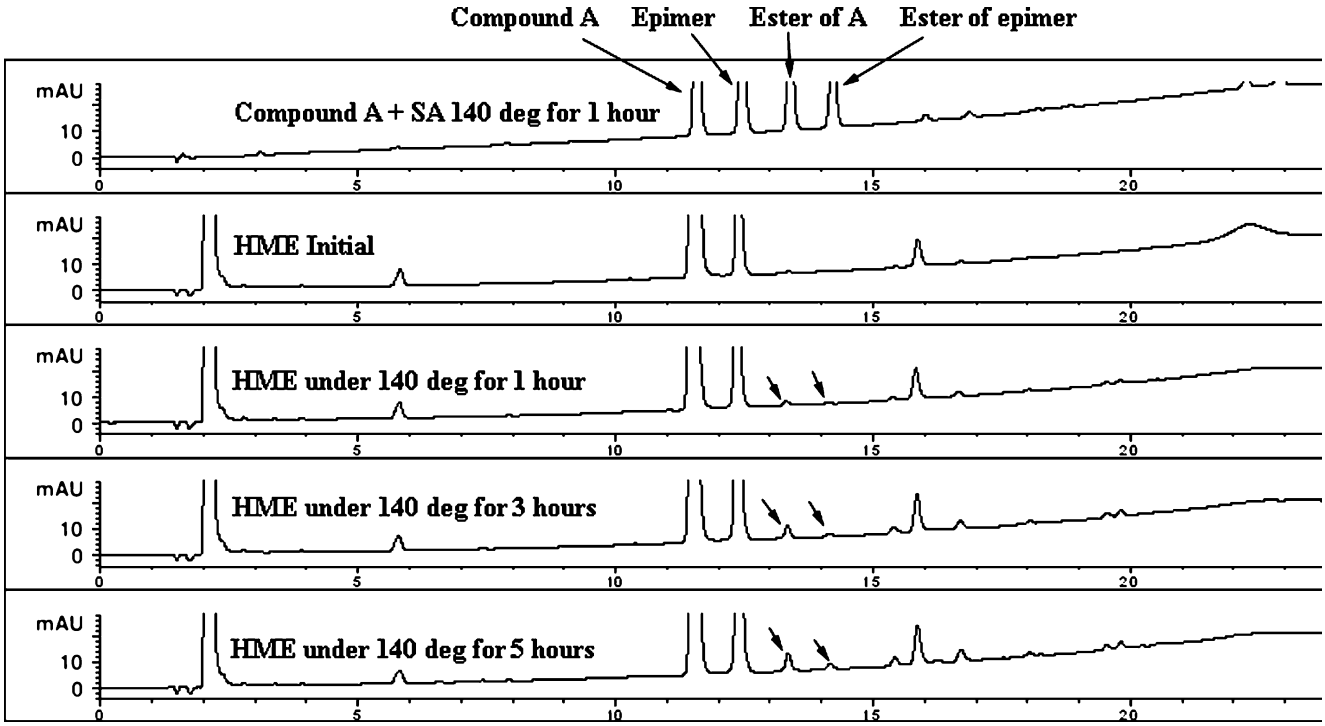

Fig. 3. HPLC results indicating ester formation of SA with compound A in its pure form and in the HME

degradants are assigned as mono-esters (peaks #1 and #2), di-ester of one dyphylline molecule with two succinic acid molecules, and di-esters of two dyphylline molecules with one succinic acid molecule (peaks #4 and #5). The following two pairs, peaks #1 and #2 as well as peaks #4 and #5, were not distinguished further due to the purpose of this work was to investigate on the potential of ester formation, which is obvious based on the above results.

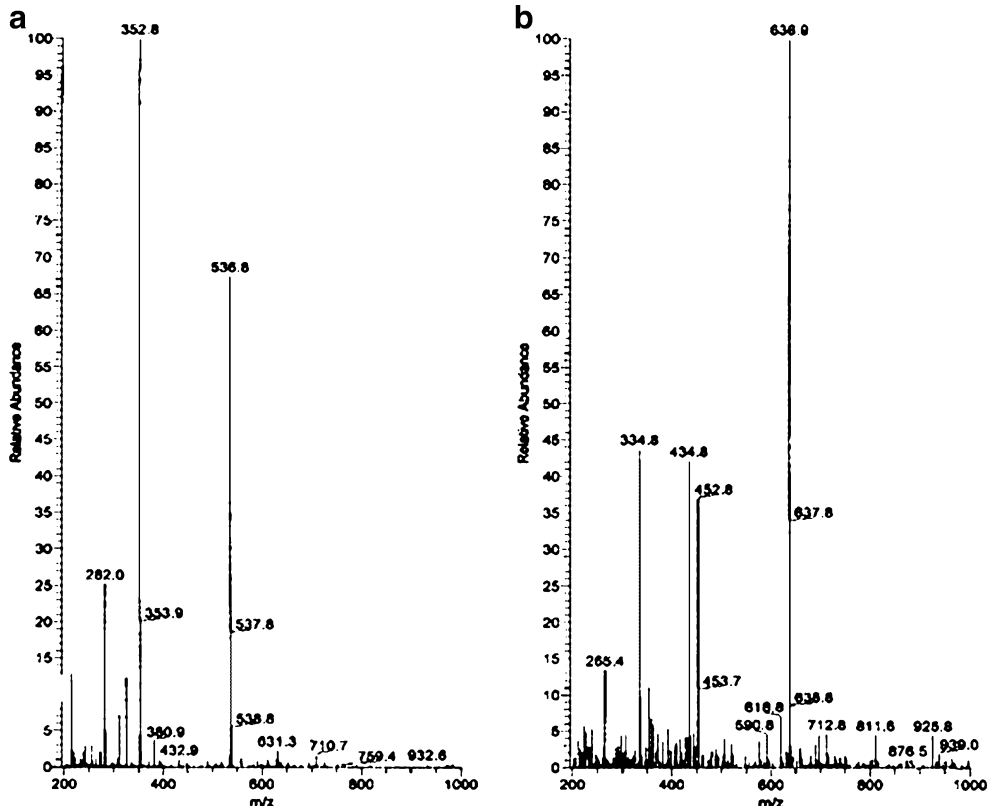

Fig. 4. MS results. **a** Compound A and its epimer; **b** esters of compound A and its epimer with SA

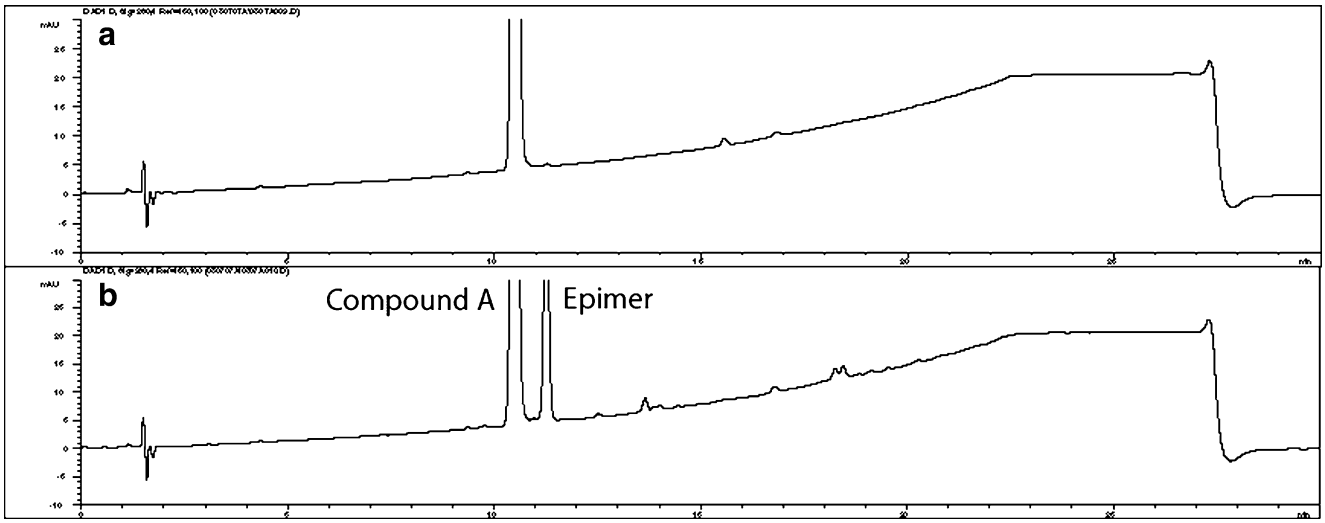

Fig. 5. HPLC chromatograms of compound A: **a** before and **b** after heat treatment

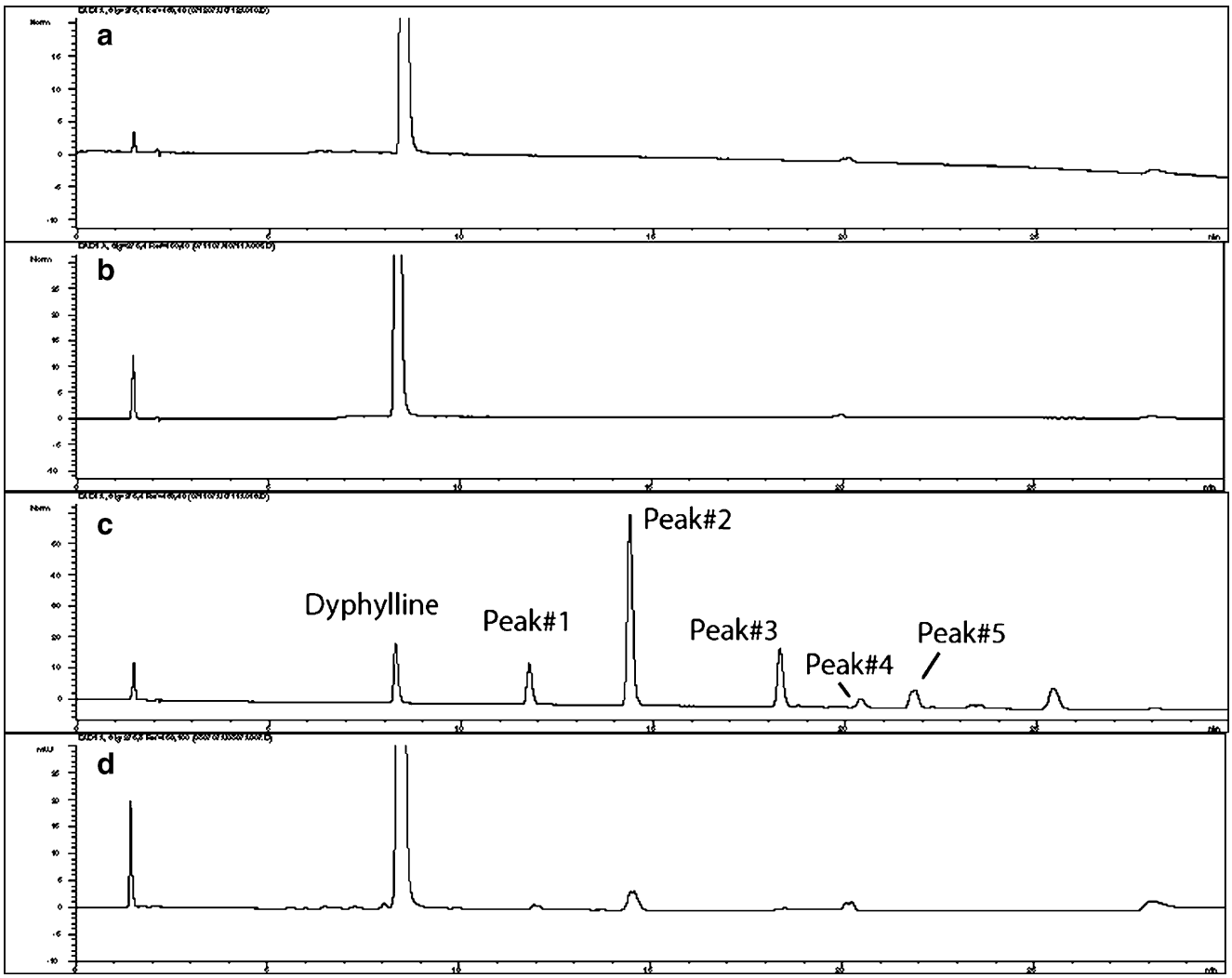

Fig. 6. HPLC chromatograms of: **a** dyphylline samples prior to heat treatment, represented by pure drug substance; **b** dyphylline under 140°C for 5 h; **c** dyphylline+SA physical mixture under 140°C for 5 h; **d** dyphylline+HPMC-AS under 140°C for 5 h

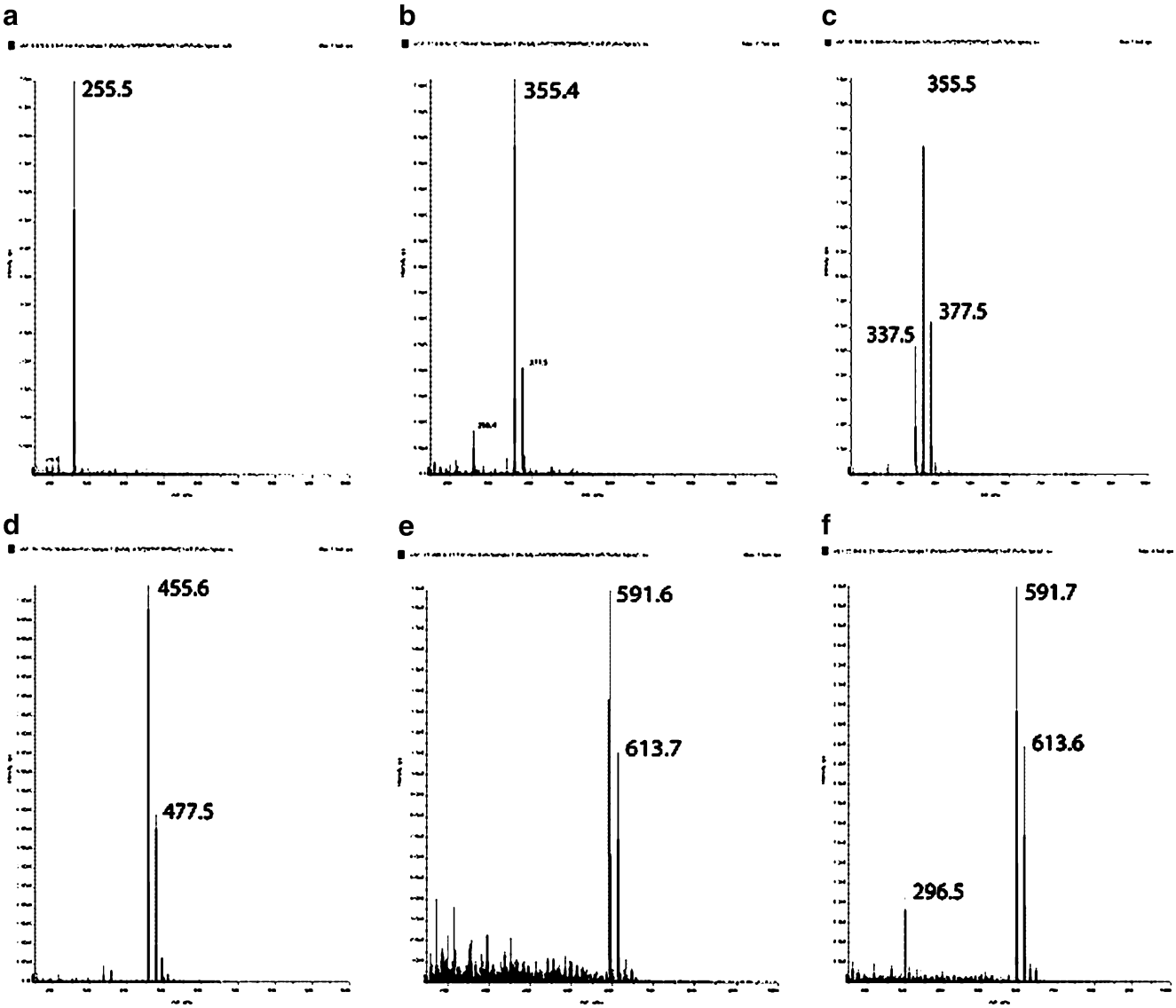

Fig. 7. MS spectra of: **a** dyphylline; **b** peak#1; **c** peak#2; **d** peak#3; **e** peak#4; **f** peak#5

Upon heat treatment, three degradants were observed in the physical mixture of dyphylline and HPMC-AS, identified as two mono-esters (peaks #1 and #2) and one di-ester of two dyphylline molecules with one succinic acid molecule (peak #4).

The ester formation of both compound A and dyphylline with succinic acid at elevated temperature suggests potential risk for the long-term stability as well as complication of the toxicology profile of the product. During formulation development, extra attention should be paid to the use of HPMC-AS when there is hydroxyl group in the API, particularly for the manufacture of HME product, where higher processing temperature should be avoided as much as possible. In addition to temperature, as indicated by the product brochure (2), higher relative humidity may also induce the hydrolysis of HPMC-AS. Consequently, during the storage of such products, it is necessary to control the environmental relative humidity to lower level, so that the hydrolysis of HPMC-AS is minimized.

Since HPMC-AS is a popular polymer for enteric coating and solid dispersion, in addition to the API, some other excipients with hydroxyl groups (such as lactose and mannitol) may potentially have "excipient–excipient" interactions with HPMC-AS, which may be of interest to the formulation scientists, and its impact on the formulation development needs further evaluation.

CONCLUSIONS

HPMC-AS potentially undergoes hydrolysis to produce succinic acid and acetic acid. When hydroxyl group (s) exists in the structure of an API, due to the potential of ester formation with succinic acid and/or acetic acid, use of HPMC-AS in the formulation should be cautioned. Under such circumstances, the drug–excipient interaction between the API and HPMC-AS needs to be fully characterized.

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