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Saturated fatty acids and fatty acid esters promote the polymorphic transition of clarithromycin metastable form I crystal

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ABSTRACT

The phase transition of active pharmaceutical ingredients should be taken into account during manufacturing, processing- and storage, because different crystal forms lead to different physical properties of formulations. The phase transition of clarithromycin (CAM) metastable form I to stable form II was investigated on heating with additives such as fatty acids or fatty acid esters. Differential scanning calorimetry analyses revealed that when form I was heated with additives, the phase transition temperature of form I decreased close to the melting points of the additives. Powder X-ray diffraction analyses indicated the tentative presence of a non-crystalline component during the transition of form I to form II on heating with additives. These observations implied that CAM form I dissolved in the melted additives on heating and the dissolved CAM crystallized to form II. Reduction of transition temperatures in the presence of additives were also observed for the crystals of nifedipine form B and carbamazepine form III. These results suggested that the phenomena can be widely applicable for simultaneous crystalline phase transition and granulation using binder additives.

1. Introduction

Clarithromycin (CAM) is a 14-membered macrolide antibiotic with broad-spectrum activity against various bacteria. CAM has been widely used for the clinical treatment of various infectious diseases including the eradication of *Helicobacter pylori*. Eight crystal forms of CAM have been reported: form 0 (ethanol solvate; Spanton et al., 1999), form I (Liu et al., 1999), form II (Tozuka et al., 2002), form III (acetonitrile solvate; Liang and Yao, 2008), form IV (hydrate; Avrutov et al., 2003), form V (Gruss et al., 2008), hydrochloride salts (Parvez et al., 2000; Noguchi et al., 2014), and methanol solvate (Iwasaki et al., 1993). Because different crystal forms lead to different physical properties such as solubility, dissolution rate, compression ability, and bioavailability (Yu et al., 1998; Fujiki et al., 2015), the phase transition of active pharmaceutical ingredients must be taken into account during processing and storage. At present, CAM formulation for medical treatment contains the most stable form II (Liu et al., 1998). However, the manufacture of form II requires significant time and cost because it is prepared by the crystalline phase transition from metastable form I by heating over 140 °C (Tozuka et al., 2002).

Recently, the effects of wet granulation on CAM crystal forms were investigated (Nozawa et al., 2015). Phase transition from CAM form I to form II was promoted by wet granulation using water in the presence of polysorbate 80, polyoxyl 40 stearate or macrogol 400, and polymorphic transition from form II to form I during wet granulation using an organic solvent such as ethanol can be prevented by including these additives. This phenomenon makes it possible to manufacture products containing stable form of CAM using organic solvents without contamination of crystalline polymorphs. Phase transition from form I to form II was also reported to be induced by a melt granulation process (Itai et al., 2014). Phase transition from form I to form II was completed during melt granulation at a temperature much lower than 140 °C under the presence of low melting binders such as fatty acids and fatty acid esters. These phenomena can be applied to simultaneous granulation and crystalline phase transition to reduce time and costs for manufacturing granules made from CAM form II. However, their mechanisms are yet to be defined.

Abbreviations: CAM, clarithromycin; GM, glycerin monostearate; LW, lubliwax-101; TR-FB, triglycerin full behenate; DSC, differential scanning calorimetry; PXRD, powder X-ray diffraction.

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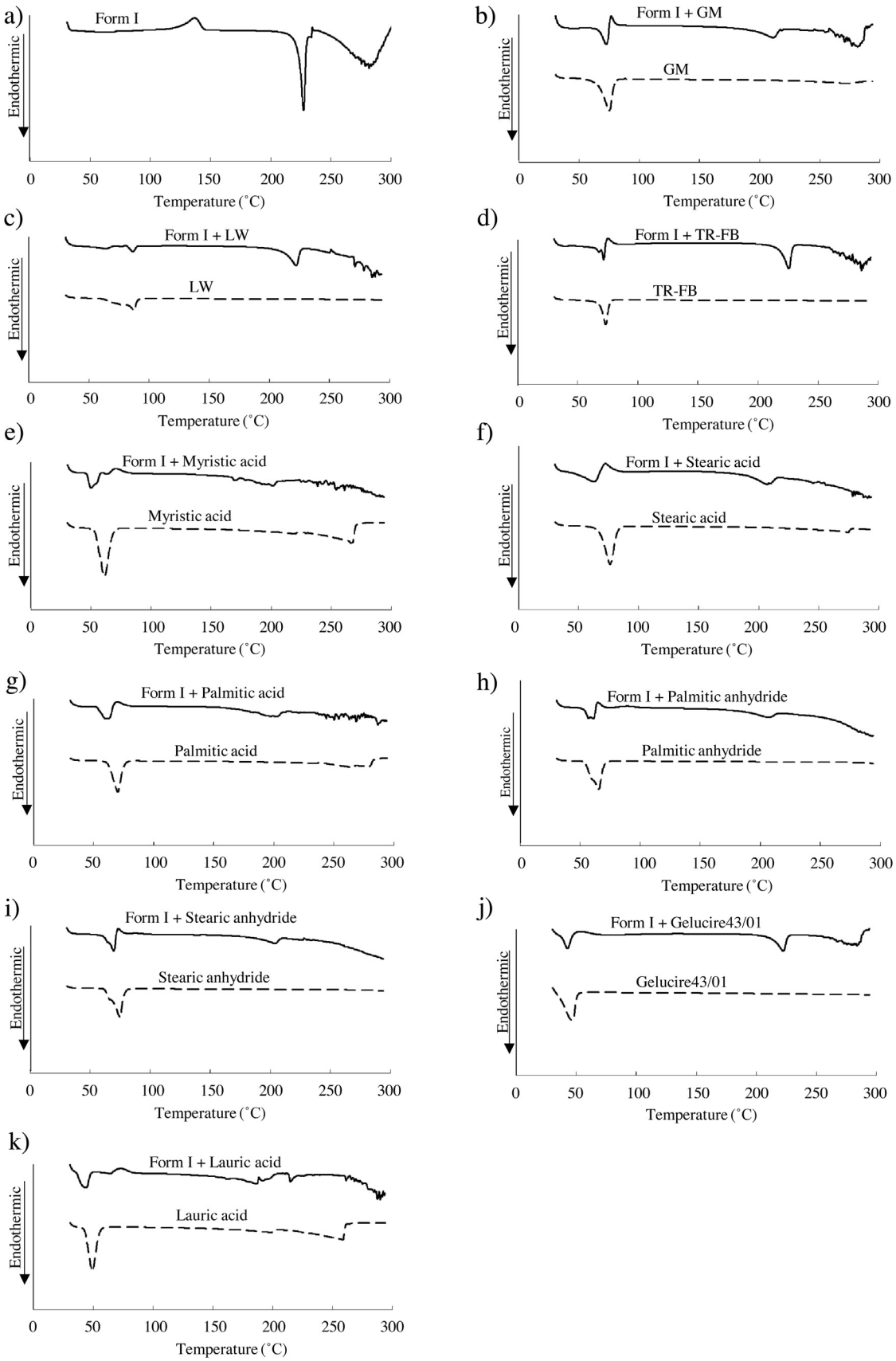

Fig. 1. DSC thermograms of CAM form I/additive mixture Form I, (b) Form I + GM, (c) Form I + LW, (d) Form I + TR-FB, (e) Form I + Myristic acid, Form I + Stearic acid, (g) Form I + Palmitic acid, (h) Form I + Palmitic anhydride, (i) Form I + Stearic anhydride, (j) Form I + Gelucire43/01, (k) Form I + Lauric acid. Solid and dotted lines indicate the DSC profiles of form I + additive and additive only, respectively.