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Characterization of CoQ 10-lauric acid eutectic system

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ABSTRACT

Solid state characterization of coenzyme Q10 (CoQ 10) was carried out using differential scanning calorimetry (DSC), variable temperature X-ray diffractometry (VT-XRD) and hot/cold stage microscopy (H/CSM). It revealed that CoQ 10 exists in two polymorphic forms. The recrystallized samples of CoQ 10 melted at different temperatures either due to the wide crystal size variation or change in crystallinity. Further, the binary mixture of CoQ 10 and lauric acid (LA) formed eutectic mixture in the ratio 70:30 melting at 37.93 °C, which was close to the predicted eutectic composition of 87.7:12.3 melting at 38.98 °C. The values of actual liquidus temperatures for CoQ 10 are higher than the predicted liquidus temperatures. The experimental heat of fusion at eutectic point was less than the calculated heat of fusion. Activity coefficient of CoQ 10 in the binary mixture was less than unity, which indicates the attraction between the components of eutectic mixture.

1. Introduction

Coenzyme Q10 (CoQ 10) is a poorly water soluble [1] vitamin like substance. It is a lipophilic, naturally occurring substance having a role as an intermediate of electron transport system, an antioxidant, and is involved in cellular metabolism [2]. Apart from poor water solubility, bioavailability of CoQ 10 is limited by its high molecular weight [1] and efflux by *p*-glycoprotein [3]. Various methods for enhancement of bioavailability of CoQ 10 are reported in literature. Self nanoemulsifying drug delivery system (SNEDDS) of CoQ 10 with Witepsol® H35, Solutol® HS15, and Lauroglycol® FCC has been reported. The formulation provided 90% release of CoQ 10 in pH 6.8 phosphate buffer and displayed 4.6 and 5.2 fold increase in AUC and C_{max}, respectively, over powder formulation [4]. Spray drying of CoQ 10 with polymeric excipients such as polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose acetate succinate (HPMCAS) or hydroxypropylmethyl cellulose pthalate (HPMCP) generated amorphous CoQ 10, resulting in enhanced bioavailability by reducing the time for dissolution of 50% CoQ 10 by 100% or more [5].

CoQ 10 has a dose of 100–3000 mg per day [6], a melting point of around 50 °C [7], and a log *P* of about 15 [8]. This makes it a good candidate for oral delivery using lipidic formulations. For oral delivery using lipidic formulation, we carried preliminary investigations for *in-situ* crystallization of binary mixture of CoQ 10 and lauric acid (LA) using DSC. Binary lipidic mixture of CoQ 10-L-menthol investigated by DSC is reported in literature [9]. Few examples of eutectic mixtures having applications in drug delivery are lidocaine–prilocaine [10], aspirin–acetaminophen–urea [11], and curcumin with conformers such as nicotinamide, ferulic acid, hydroquinone, *p*-hydroxybenzoic acid, and L-tartaric acid [12].

Thermal characterization of various compositions of CoQ 10-LA products revealed generation of eutectic mixture of CoQ 10 with LA. This work covers the solid state characterization of CoQ 10 and construction of binary phase diagram for eutectic mixture of CoQ 10 and LA.

2. Materials and methods

2.1. Materials

All the experiments were carried out on commercial reduced CoQ 10 samples procured from Hangzhou Joymore Technology Co., Ltd., China. At the time of experimentation, the samples contained less than 29.4% of reduced CoQ 10 due to its oxidation during storage. Oxidized CoQ 10 from Hangzhou Joymore Technology Co., Ltd., China was used as a reference sample. Sample of LA was obtained from Loba Chemie Pvt., Ltd., India.

2.2. Methods

2.2.1. CoQ 10:LA mixtures for generation of eutectic system

Eutectic mixtures of CoQ 10 with LA were prepared by weighing the different proportions of CoQ 10:LA in the range between 5:95

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and 95:5 in the DSC pans. It was then subjected to heat–cool–heat cycle protocol mentioned in the proceeding section.

2.2.2. Differential scanning calorimetry (DSC)

Heat-flux DSC measurements were performed with the DSC instrument (TA Q2000, New Castle, Delaware, USA equipped with TA Universal Analysis software). It was calibrated for temperature and heat flow by using high purity indium standard. Accurately weighed amount 2.5–5 mg of CoQ 10, LA, and CoQ10:LA binary mixture were weighed in Tzero aluminium pan and heated to 80 °C, at the heating rate of 10 °C/min, and then held isothermally for 5 min. The sample was then cooled to −80 °C, held isothermally for 5 min, followed by heating at the same rate as mentioned previously. Nitrogen was purged during the DSC operation at the rate 50 ml/min.

2.2.3. Hot and cold stage microscopy (H/CSM)

Hot stage microscopy (HSM) and cold stage microscopy (CSM) of CoQ 10 samples were performed on Leica DMLP polarized microscope (Leica Microsystems Wetzalar GmBH, Germany) equipped with Linkam LTS 350 hot/cold stage. Small quantity of sample was placed on a glass slide, mixed with silicon oil, and covered with a glass cover slip. It was heated and cooled using a protocol similar to DSC operation.

2.2.4. Variable temperature X-ray diffractometry (VT-XRD)

Powder X-ray diffraction patterns were recorded on diffractometer using Cu-Kα X- ray radiation at 40 kV power and 40 mA current. The wavelength of radiation was 2.54 Å. X-ray diffraction patterns were collected over 2θ range 3–40 at the scan rate of 0.01 and scan speed of 0.1. The measurements were carried out on the variable temperature stage to confirm the presence of pure components at different temperature. The heating and cooling protocol was similar to DSC.

3. Results and discussion

3.1. Solid state characterization of CoQ 10

3.1.1. DSC and H/CSM

All the experiments were conducted using reduced CoQ 10. However, due to its low atmospheric stability, it converted into the oxidized CoQ 10, and very small quantity of reduced CoQ 10 remained in the sample. This was evident from the orange colour of sample, since oxidized CoQ 10 is orange in colour while reduced CoQ 10 is of white colour [13]. Thus, all the studies were carried out on the CoQ 10 which was predominantly in the oxidized form.

The DSC analysis of CoQ 10 was performed under different experimental protocols and the same is represented in Figs. 1 and 2. Fig. 1 shows the heat–cool–heat cycle of CoQ 10 at a fast cooling rate of 16 °C/min. Sample of the pure oxidized CoQ 10 was also characterized using similar protocol. First heating cycle of CoQ 10 and oxidized CoQ 10 indicated melting endotherm at 50.80 and 51.28 °C, respectively. This is in conformity with reported literature, wherein melting points of 49.5 [14] and 49 °C [15] have been reported for reduced and oxidized forms of CoQ 10, respectively.

Thereafter, molten samples of CoQ 10 were cooled to −80 °C at a fast cooling rate of 16 °C/min. Commercial and pure oxidized samples of CoQ 10 exhibited a recrystallization exotherm at around −14.58 and −8.98 °C, respectively. This event was much sharper in case of oxidized CoQ 10.

Second heating cycle of commercial CoQ 10 indicated a subtle event at −72.60 °C, which can be attributed to amorphous phase. It shows another exothermic event at −33.4 °C, which can be attributed to crystallization of amorphous CoQ 10. A combination of exothermic–endothermic–exothermic–endothermic events was observed at 16.11, 23.79, 26.34, and 45.52 °C. A similar set of events was observed for oxidized CoQ 10 at 16.11, 23.31, 25.06, and 48.72 °C .The oxidized CoQ 10 did not exhibit the thermal event corresponding to amorphous phase at any temperature. Therefore, the exothermic event at around 33 °C was also absent in oxidized CoQ 10.

A heat–cool–heat cycle at a heating and cooling rate (slow) of 10 °C/min was carried out in an attempt to further resolve these events. Fig. 2 captures the heating curve, along with photomicrographs taken using hot stage microscope, at slow cooling rate. In the first cooling cycle, it shows recrystallization exotherm at −14.2 °C. In slow and fast cooling, recrystallization of CoQ 10 occurred nearly at the same temperature. It was reported for CoQ 10 that lower the rate of cooling of molten sample, lower is the temperature of recrystallization [16]. This was not observed in this study because difference in two cooling rates may not be too high.

In the second heating cycle, a glass transition event at approximately −72.6 °C indicated that only partial

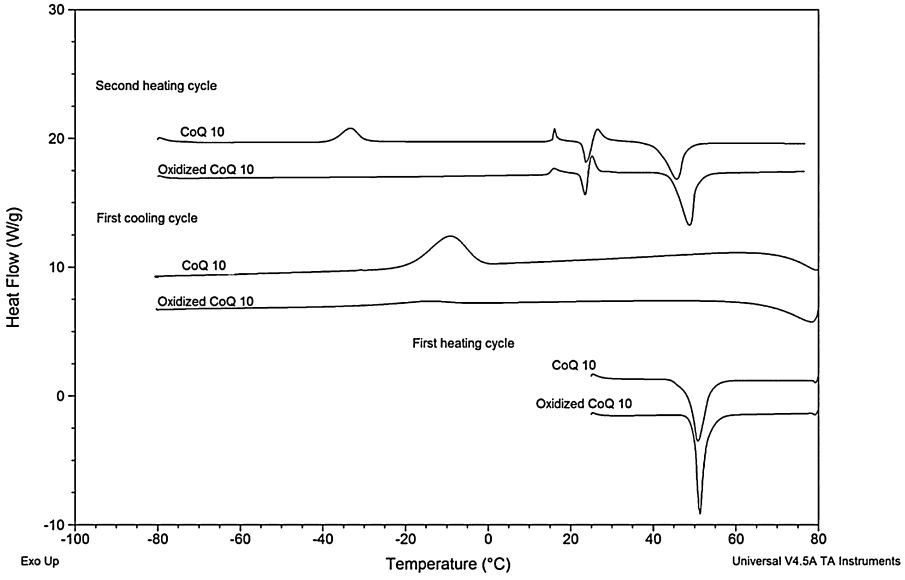

Fig. 1. Heat–cool–heat curves of commercial CoQ 10 and oxidized CoQ 10 sample in which cooling was carried out at a fast rate of 16 °C/min.