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Enhancement of solubility and dissolution of Coenzyme Q_{10} using solid dispersion formulation

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ABSTRACT

This study aimed to develop a stable solid dispersion of Coenzyme Q_{10} (CoQ_{10}) with high aqueous solubility and dissolution rate. Among various carriers screened, poloxamer 407 was most effective to form a superior solid dispersion of CoQ_{10} having significantly enhanced solubility. Particularly, solid dispersion of CoQ_{10} with poloxamer 407 in the weight ratio of 1:5 prepared by melting method enhanced the solubility of CoQ_{10} to the greatest extent. However, it exhibited poor stability and hence Aerosil® 200 (colloidal silicon dioxide) was incorporated into the solid dispersion as an adsorbent to inhibit the recrystallization process. The solid dispersion of CoQ_{10}, poloxamer 407 and Aerosil® 200 in the weight ratio of 1:5:6 exhibited improved stability with no significant change in solubility during the 1-month stability test. Moreover, the solid dispersion formulation containing Aerosil® 200 significantly enhanced the extent of drug release (approx. 75% release) as well as the dissolution rate of CoQ_{10}. In conclusion, the present study has developed the stable solid dispersion formulation of CoQ_{10} with poloxamer 407 and Aerosil® 200 for the enhanced solubility and dissolution of CoQ_{10}, which could also offer some additional advantages including ease of preparation, good flowability and cost-effectiveness.

1. Introduction

CoQ_{10} is found inside the inner mitochondrial membrane and act as an electron shuttle in the mitochondrial respiratory chain and also as a stabilizing agent in cellular membranes (Grossi et al., 1992). It is a physiologically important compound with applications as an antioxidant and in the treatment of cardiovascular disorders such as angina pectoris, hypertension, and congestive heart failure (Greenberg and Fishman, 1990). Recent studies have shown that it has positive effect on migraine headache (Rozen et al., 2002) and neurodegenerative disease such as Parkinsonism. It is also being investigated as treatment for cancer and as relief from cancer treatment side effects (Sakano et al., 2006).

CoQ_{10} is a yellow-orange colored crystalline powder with a melting point of about 50 °C. It is readily soluble in organic solvents and lipids but practically insoluble in water. CoQ_{10} was poorly absorbed from gastrointestinal tract (Kommuru et al., 2001) and its slow absorption (T_{max}, 5–10 h) may be explained by its high molecular weight and poor solubility (Greenberg and Fishman, 1990). To overcome the low solubility and bioavailability of CoQ_{10}, various formulation approaches have been reported in the literature including use of surfactants, cyclodextrins, nanoparticles, micronization, lipids and permeation enhancers (Aungst, 1993; Robinson, 1996). Use of surfactants and cyclodextrins showed lesser improvement in the bioavailability of CoQ_{10}. The U.S. patent number 4869900 disclosed the mixture of CoQ_{10} and Gelucire 50/13 that brought about 1.3 times improvent in area under curve when compared with CoQ_{10} alone in male beagle dogs (Pozzi et al., 1989). Similarly, a research study reported 1.1 times improvent in area under curve from CoQ_{10}-γ-cyclodextrin complex over a physical mixture of CoQ_{10} and microcrystalline cellulose in human (Terao et al., 2006). An another study demonstrated about 1.2 times improvement in area under curve from CoQ_{10}-cyclodextrin complex over crystalline CoQ_{10} in rats (Hatanaka et al., 2008). Lipid formulations of CoQ_{10} have been extensively studied by many investigators (Kommuru et al., 2001; Nazzal et al., 2002b; Carli et al., 2005), however, there is relatively very less work done in the field of solid dispersion (SD) of CoQ_{10}. SD has been demonstrated as a promising technique for improving the bioavailability of poorly water soluble drugs via the enhancement of their solubility and dissolution rate (Chiou and Riegelman, 1971; Leuner and Dressman, 2000). In SD system, drug undergoes particle size reduction and the consequent increase in the surface area results in the improved dissolution (Craig, 2002). Moreover, no energy is required to break up the crystal lattice of a drug in the amorphous state during dissolution process (Taylor and Zografi, 1997) and drug solubility and wettability may be increased by surrounding hydrophilic carriers (Craig, 2002). U.S. patent publication no. U.S.2004/0014817 A1 disclosed the SD composition of CoQ_{10} using

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Kollidon® VA 64 (Copovidone K28) as polymeric carrier prepared at high melting temperature of 120 °C (Rosenberg and Breitenbach, 2004). The formulation was claimed to be stable, however, it was found that the solubility of CoQ_{10} was not much enhanced. A SD of CoQ_{10} prepared with Eudragit® L100-55 was reported in literature which exhibited 100% release of CoQ_{10} in dissolution test (Nazzal et al., 2002a). However, the work employed an aqueous dissolution medium comprising 4% Labrasol and 2% Cremophor® EL which altered the dissolution value significantly. Moreover, use of high volume of organic solvents during preparation of SD and absence of stability data rendered the work less useful. Similarly, a published work on SD of CoQ_{10} used poloxamer 188 as carrier (Bhandari et al., 2007). The work utilized higher proportion of the carrier with little increase in solubility and dissolution. An abstract described the use of poloxamer 407 for the preparation of binary SD of CoQ_{10} (Im et al., 2007). However, no stability test of the SD was performed and no detail description of experiments and results were available. Therefore, the present study aimed to develop the stable SD of CoQ_{10} using poloxamer 407 and Aerosil® 200 with significantly enhanced solubility and dissolution rate. Poloxamers are triblock copolymers of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene). They are extensively used as solubilizers, wetting agents and surface adsorption excipients (Collett and Popli, 2000). Poloxamer 407 (Lutrol® F127) was successfully employed as a SD carrier in previous studies using poorly water soluble drugs such as felodipine (Kim et al., 2006). Poloxamer in SD formulations has double roles, i.e., one as polymeric carrier and other as surface active agent. It has been reported in the literature that the polymeric carrier with surface active properties has additional effect on enhancement of dissolution of poorly water soluble drugs (Serajuddin, 1999; Passerini et al., 2002; Seo et al., 2003). Aerosil® 200 was incorporated into current formulations as it imparted free flowing properties to SD powder and more importantly it can act as recrystallization inhibitor (Chauhan et al., 2005). In the present study, various solid dispersions (SDs) of CoQ_{10} were prepared with poloxamer 407 and Aerosil® 200 and their physicochemical properties as well as dissolution characteristics were evaluated.

2. Materials and methods

2.1. Materials

Coenzyme Q_{10} was a generous gift from Yungjin Pharm. Co. Ltd. (Seoul, Korea). Poloxamer 407 (Lutrol® micro 127 MP), poloxamer 188 (Lutrol® F 68), polyoxyl 40 hydrogenated castor oil (Cremophor® RH40), macrogol 15 hydroxystearate (Solutol® HS15) and povidone K-30 (Kollidon® 30) were obtained from BASF (Ludwigshafen, Germany). Spray-dried lactose (Flowlac® 100) was obtained from Meggle Wasserburg GmbH (Wasserburg, Germany). Colloidal Silicon Dioxide (Aerosil® 200) was obtained from Degussa (Rheinfelden, Germany). Polyethylene glycol 3400 (PEG 3400) was purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). Hydroxypropylmethyl cellulose (HPMC 2910) was obtained from Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan). All other materials and reagents were of analytical grade and used as received without further purification.

2.2. Methods

2.2.1. Screening of carriers

Various carriers were screened for SD preparation with CoQ_{10}. For this purpose, SDs of CoQ_{10} with the carriers in the weight ratio of 1:5 were prepared by both melting method and solvent method whichever applicable. In case of melting method, physical mixtures of CoQ_{10} and various carriers in the weight ratio of 1:5 were melted in the oven set at 70 °C. They were cooled at room temperature for 15 min and then solubility test was carried out with the obtained SDs.

Table 1
Solid dispersions prepared by solvent method.

S. no.	Formulations (w/w)	Solvent system (v/v)
1.	CoQ_{10}:poloxamer 407 = 1:5	Water:ethanol = 5:95
2.	CoQ_{10}:polyethylene glycol 3400 = 1:5	Dichloromethane
3.	CoQ_{10}:povidone K-30 = 1:5	Ethanol
4.	CoQ_{10}:HPMC 2910 = 1:5	Dichlormethane:ethanol = 1:1

In case of solvent method, CoQ_{10} and each carrier in the weight ratio of 1:5 were completely dissolved in the solvent system as given in Table 1. After stirring for 15 min, solvents were evaporated in vacuum dryer at room temperature and then solubility test was carried out with the obtained SDs.

For optimization of drug and carrier ratio, physical mixtures and SDs of CoQ_{10} and poloxamer 407 by melting method were prepared in the weight ratios of 1:1, 1:2, 1:3, 1:5, 1:7 and 1:10. They were then subjected for solubility test.

2.2.2. Solubility test

Solubility of CoQ_{10} was determined by taking amount equivalent to 1 mg of CoQ_{10} in 1 mL of distilled water and stirring at 500 rpm in the oven set at 37 °C. Stirring was kept on for 24 h and 48 h with SDs and physical mixtures, respectively. The samples were then filtered through 0.45 μm pore-sized regenerated cellulose syringe filter (Target®, National scientific, USA), suitably diluted with methanol and analyzed by HPLC. The experiment was performed in triplicates.

2.2.3. HPLC analysis of CoQ_{10}

The amount of CoQ_{10} was determined by using a high-performance liquid chromatography (HPLC) system (Shimadzu Scientific Instrument, MD, USA), consisting of a UV detector (SPD-10A), a pump (LC-10AD) and an automatic injector (SIL-10A). Samples in distilled water were analyzed with the mobile phase consisting of acetonitrile and tetrahydrofuran in the ratio of 65:35 (v/v%) at the flow rate of 1.5 mL/min. Samples in pH 6.8 buffer were analyzed with the mobile phase consisting of tetrahydrofuran and water in the ratio of 78:22 (v/v%) at the flow rate of 1 mL/min. The wavelength of the UV detector was 275 nm and a reversed-phase column (Gemini 5μ C18 110A, Phenomenex, USA) was used. The samples were analyzed at a column temperature of 30 °C.

2.2.4. Stability test

The prepared SDs were stored in air tight container protected from light at room temperature. They were then analyzed for solubility periodically.

2.2.5. Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a DSC unit (Pyris 6 DSC, Perkin Elmer, Netherlands). Indium was used to calibrate the temperature scale and enthalpic response. Samples were placed in aluminum pans and heated at a scanning rate of 10 °C/min from 20 °C to 65 °C.

2.2.6. X-ray diffraction (XRD)

X-ray powder diffraction was performed at room temperature with an X-ray diffractometer (X'Pert PRO MPD, PANalytical Co., Holland). The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 2θ range of 3–40° using a step size of 0.02° at a scan speed of 1 s/step.

2.2.7. Scanning electron microscopy (SEM)

The morphology of the samples was examined by Scanning electron microscope (S4800, Hitachi, Japan). The samples were mounted onto an aluminum stub and sputter coated with platinum particles for 60 s in an argon atmosphere.

2.2.8. Dissolution studies

Dissolution studies of pure CoQ_{10}, physical mixture and SD samples (melting method) were performed in a dissolution tester (DST-810 and DS-600A, Labfine Inc., Suwon, Korea) at the paddle rotation speed of 100 rpm in 300 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C. Each formulation equivalent to 9 mg of CoQ_{10} was filled into size '0' hydroxypropylmethylcellulose (HPMC) capsule. Capsules were then placed inside the sinker and put into the dissolution vessel. At the predetermined time intervals, 3.5 mL of the samples were withdrawn and the equal volume of fresh medium was added into the dissolution vessel. The collected samples were filtered through regenerated cellulose syringe filters. Initial sample volume of 2 mL was discarded and final 1.5 mL was collected and then analyzed by HPLC.

3. Results and discussions

3.1. Screening of carriers

Both polymeric and non-polymeric excipients were screened as carriers. The SDs were prepared by either melting or solvent or both methods depending upon the melting points of carriers. In the case of Aerosil® 200, melting method was used as it functioned as an adsorbent rather than dispersion matrix. The solubility of CoQ_{10} was measured with the obtained SDs and summarized in Table 2.

As shown in Table 2, the highest solubility was achieved when SD was prepared with poloxamer 407 as a carrier by melting method. Interestingly, the solubility was much lower when solvent method was used for the preparation of SD with poloxamer 407. Partial segregation of CoQ_{10} from the bulk was observed during the evaporation of ethanol when SD was prepared by solvent method and subsequently the resultant dried SD showed the endotherm of CoQ_{10} when analyzed by DSC (data not shown). This observation indicated the recrystallization of CoQ_{10} during the process of solvent evaporation, which might have caused the lower solubility of CoQ_{10} from the SDs prepared by solvent method than those from melting method. Compared to poloxamer 407, poloxamer 188 was approximately 4-fold less effective as a carrier in solubilizing CoQ_{10} and this may be attributed to its low molecular weight and lower proportion of hydrophobic segment, polyoxypropylene, in its molecule than poloxamer 407 (Dai et al., 2008). Collectively, among tested carriers, poloxamer 407 appeared to be most effective in solubilizing CoQ_{10} followed by poloxamer 188, HPMC 2910, Aerosil® 200, PEG 3400 and povidone K-30. Therefore, poloxamer 407 was chosen as a carrier for the SD preparation of CoQ_{10} by melting method in subsequent studies.

Table 2
Solubility of CoQ_{10} from various solid dispersion formulations (mean ± S.D., $n = 3$).

Formulations (w/w)	Solubility (μg/mL)	
	Melt method	Solvent method
CoQ_{10}:poloxamer 407 = 1:5	868.8 ± 16.4	145.3 ± 28.3
CoQ_{10}:poloxamer 188 = 1:5	214.8 ± 30.5	–
CoQ_{10}:polyethylene glycol 3400 = 1:5	24.3 ± 0.7	24.3 ± 9.0
CoQ_{10}:povidone K30 = 1:5	–	12.3 ± 5.7
CoQ_{10}:HPMC 2910 = 1:5	–	175.9 ± 66.5
CoQ_{10}:Aerosil® 200 = 1:5	48.6 ± 1.0	–

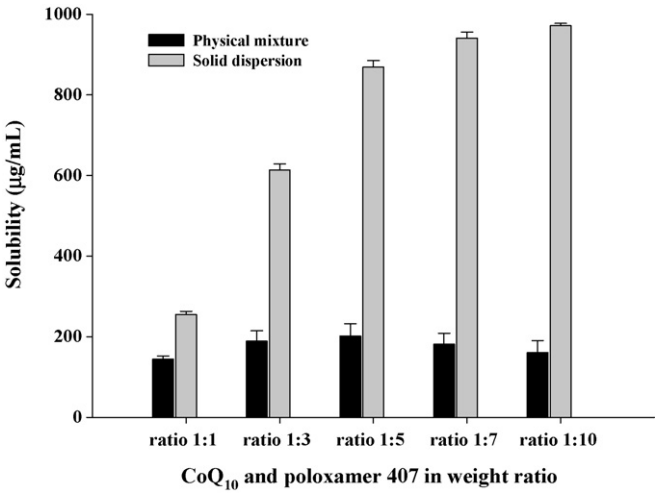

Fig. 1. Comparison of solubility of physical mixtures and SDs of CoQ_{10} with poloxamer 407 at various weight ratios (mean ± S.D., $n = 3$). Concentration of CoQ_{10} equivalent to 1 mg/mL was taken.

3.2. Optimization of drug and carrier ratio

Solubility test was used as a major tool for the optimization of the carrier ratio. As shown in Fig. 1, increasing the proportion of poloxamer 407 in the physical mixtures did not increase the solubility of CoQ_{10} significantly. The critical micelle concentration of poloxamer 407 was found to be 0.0076% (w/v) at 37 °C and 0.18% (w/v) at room temperature (Lee et al., 2008). Hence, the amount of poloxamer 407 in all physical mixtures, subjected for solubility test in the present study, was above critical micelle concentration. Therefore, there must be simultaneous increase in micelles concentration with the increase in concentration of poloxamer 407 in physical mixtures. However, the solubility of CoQ_{10} did not seem to be much affected by micellar concentration, proving inefficiency of micellar solubilization of CoQ_{10}. On the other hand, in the case of SDs, solubility increased greatly with the increase in proportion of poloxamer 407 up to the weight ratio of 1:5. As the drug-carrier ratios increased higher than 1:5, only slight increase in solubility was observed. Overall, the solubility of SDs was significantly higher than that of the physical mixtures. At the weight ratio of 1:5, solubility of CoQ_{10} from SD was more than 4 times higher as compared to that of physical mixture. Those results suggest that the increase in solubility should be mainly due to the amorphous form of CoQ_{10} in polymeric carrier rather than the surface active properties of poloxamer 407. Reduction in crystals size and intimate mixing of the CoQ_{10} with poloxamer 407 in the solid dispersion might have additive effect on the enhancement of the solubility.

Fig. 1 illustrates the solubility when amount of solid dispersion equivalent to 1 mg/mL of CoQ_{10} was taken. However, when the equivalent amount of CoQ_{10} per mL was increased by increasing the amount of solid dispersion added per unit volume (mL) of the medium, the solubility also increased. The linear relationship ($R^2 = 0.9994$) was observed between the amount of solid dispersion (CoQ_{10} and poloxamer 407 at ratio of 1:5) taken and solubility (Fig. 2). The slope of the linear line was 0.87. The results indicated that the solubility of CoQ_{10} was a function of amount of amorphous drug in the SD. Hence, the total percentage of dissolved CoQ_{10} remained nearly constant irrespective of the amount of SD taken.

DSC study supported the result obtained from solubility test. As illustrated in Fig. 3, the DSC thermograms showed the characteristic peak of pure poloxamer 407 and pure CoQ_{10} at 55.3 °C and 49.6 °C, respectively. As the proportion of the poloxamer 407 was increased in the SDs, the peak area of CoQ_{10} decreased and eventually at the

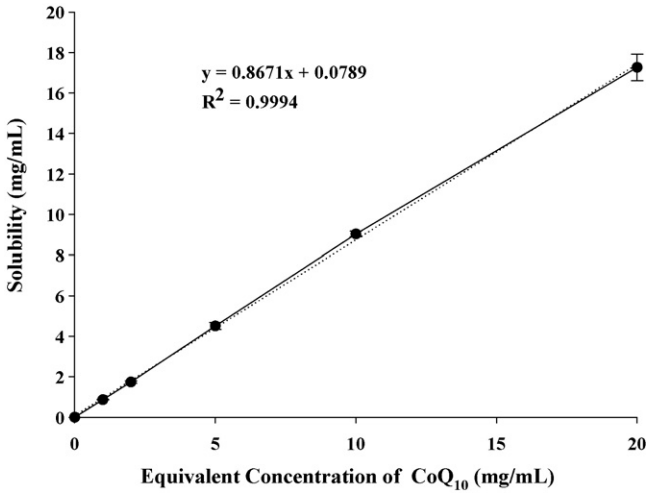

Fig. 2. Solubility of CoQ_{10} as a function of the amount of solid dispersion (CoQ_{10} and poloxamer 407 at weight ratio of 1:5) added per unit volume (mL) of medium (mean ± S.D., $n = 3$).

weight ratio of 1:5, the endothermic peak of CoQ_{10} at 49.6 °C was disappeared. This result indicated that at this ratio most of the drug existed in amorphous form and the amount of poloxamer 407 used was sufficient to solubilize most of the drugs. Hence, the weight ratio of 1:5 was considered to be ideal for the formulation of SD.

3.3. Stability test

The SD of CoQ_{10} prepared with poloxamer 407 at the weight ratio of 1:5 by melting method exhibited poor physical stability. The transparent waxy film obtained by melting method slowly became opaque with time, probably, partly due to the recrystallization of CoQ_{10}. The recrystallization of CoQ_{10} was confirmed by the thermograms obtained by DSC of the SDs when analyzed after 24 h of preparation. Fig. 4 shows the different extent of recrystallization of CoQ_{10} with time from the SD of formula CoQ_{10}:poloxamer 407 = 1:5. XRD analysis was also performed to further confirm the result obtained from DSC. X-ray diffraction patterns for solid dispersions and raw materials are shown in Fig. 5. The characteristic

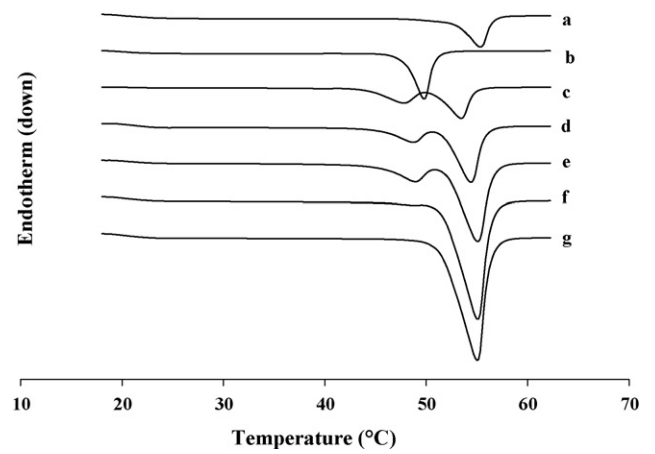

Fig. 3. DSC thermograms of SDs of CoQ_{10} with poloxamer 407 at various weight ratios. (a) Pure poloxamer 407, (b) pure CoQ_{10}, (c) SD (CoQ_{10}:poloxamer 407 = 1:1), (d) SD (CoQ_{10}:poloxamer 407 = 1:2), (e) SD (CoQ_{10}:poloxamer 407 = 1:3), (f) SD (CoQ_{10}:poloxamer 407 = 1:4), and (g) SD (CoQ_{10}:poloxamer 407 = 1:5).

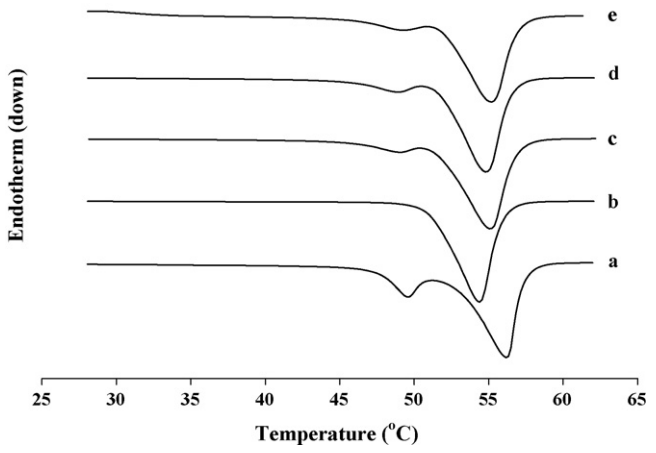

Fig. 4. DSC thermograms of CoQ_{10} and poloxamer 407 in the weight ratio of 1:5 at different time intervals to show the extent of recrystallization. (a) Physical mixture, (b) SD after 12 h, (c) SD after 24 h, (d) SD after 3 days, and (e) SD after 15 days.

peaks of poloxamer 407 and CoQ_{10} appeared at similar position thus making it difficult to interpret the patterns. The characteristic peaks of poloxamer 407 appeared at positions 19.12°, 23.20° and 23.32° and that for CoQ_{10} appeared at 18.73°, 19.12° and 22.93°. Therefore, the patterns were interpreted based on the peak of CoQ_{10} at 18.73° position. SD of formula CoQ_{10}:poloxamer 407 = 1:5 prepared by melting method showed the presence of crystalline CoQ_{10} as evident by the presence of a small peak at 18.73° position. However, compared to the physical mixture, the characteristic peaks of CoQ_{10} and poloxamer 407 were reduced in the solid dispersion indicating that some of the drug was in amorphous state.

To investigate the rate of recrystallization and its effect on the solubility of CoQ_{10}, physical stability study of the SD samples were carried out. Formulations with additional surfactants like Solutol® HS15 and Cremophor® RH40 were prepared as an attempt to prevent recrystallization of CoQ_{10}. It was considered that the use of additional surfactants would be helpful in solubilizing CoQ_{10} and thus in prevention of recrystallization. However, the result was contrary to the early expectations. As shown in Fig. 6, adding

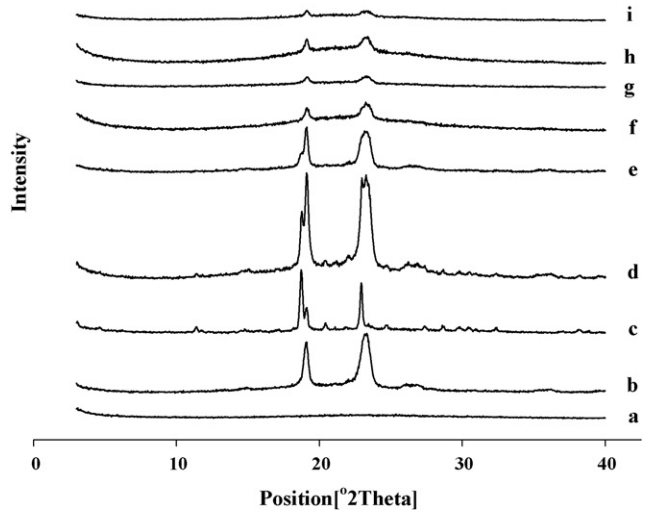

Fig. 5. X-ray diffraction patterns of (a) pure Aerosil® 200, (b) pure poloxamer 407, (c) pure CoQ_{10}, (d) physical mixture (CoQ_{10}:poloxamer 407 = 1:5), (e) SD (CoQ_{10}:poloxamer 407 = 1:5, melting method), (f) SD (CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6, after 1 day), (g) SD (CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6, after 60 days), (h) SD (CoQ_{10}:poloxamer 407:Cremophor® RH40:Aerosil® 200 = 1:5:5:11, after 1 day), and (i) SD (CoQ_{10}:poloxamer 407:Cremophor® RH40:Aerosil® 200 = 1:5:5:11, after 60 days).

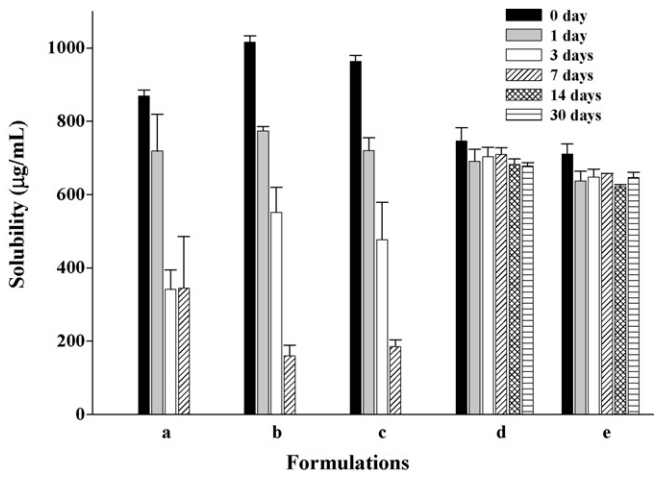

Fig. 6. Stability of SD formulations (mean ± S.D., $n = 3$). (a) CoQ_{10}:poloxamer 407 = 1:5, (b) CoQ_{10}:poloxamer 407:Solutol® HS15 = 1:5:5, (c) CoQ_{10}:poloxamer 407:Cremophor® RH40 = 1:5:5, (d) CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6, and (e) CoQ_{10}:poloxamer 407:Cremophor® RH40:Aerosil® 200 = 1:5:5:11.

surfactants did not improve physical stability of poloxamer 407 formulations and provided even lower solubility at 7 days. The use of Solutol® HS15 or Cremophor® RH40 might have decreased the viscosity of polymeric matrix thereby facilitating the faster recrystallization of CoQ_{10} (Raudonus et al., 2000).

Since the SD formulation only with poloxamer 407 was unstable, the effect of solid adsorbents on the prevention of recrystallization of CoQ_{10} was investigated. Aerosil® 200 was chosen as it is extensively used in pharmaceutical formulations as an adsorbent (Morefield, 2000). Moreover, the use of Aerosil® 200 significantly improved flow property of SD powder. When determined by previously reported method (Dixit and Nagarsenker, 2008), the SD with Aerosil® 200 passed through the funnel within 1 s whereas the powdered SD without Aerosil® 200 showed incomplete powder flow and clogging. SDs with Aerosil® 200 showed better stability (formulations 'd' and 'e' in Fig. 6). Particularly, the SD of CoQ_{10} with poloxamer 407 and Aerosil® 200 in the weight ratio of 1:5:6 exhibited higher solubility and better stability compared to the other SD formulations without Aerosil® 200. Although initial solubility was somewhat lower and there was slight reduction in solubility after 1 day, no significant reduction in solubility was observed for 30 days

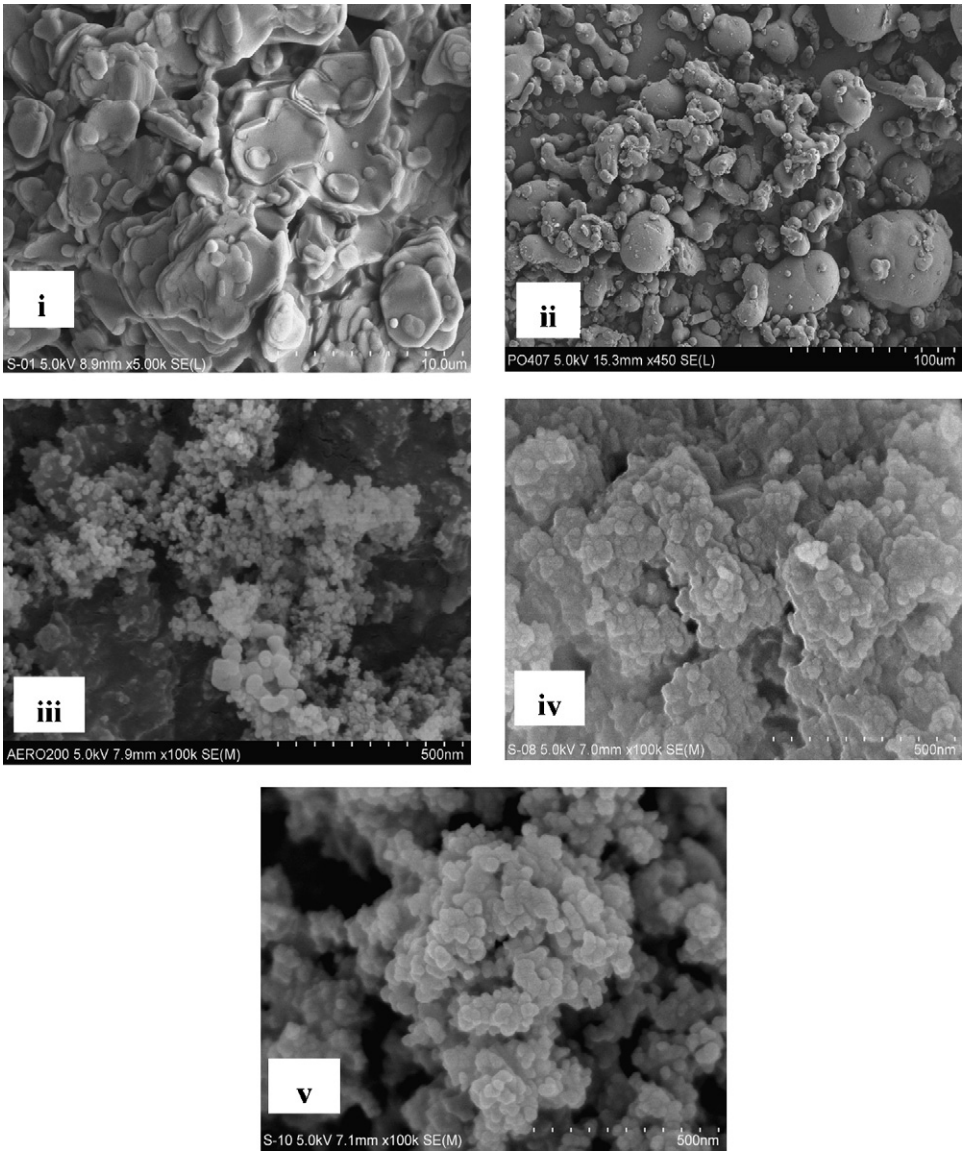

Fig. 7. SEM microphotographs of (i) pure CoQ_{10}, (ii) pure poloxamer 407, (iii) pure Aerosil® 200, (iv) and (v) SD of CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6 (1 day and 60 days samples).

with the SD sample containing Aerosil® 200. Similar observations were made with SD of CoQ_{10} with poloxamer 407, Cremophor® RH40 and Aerosil® 200 in the weight ratio of 1:5:5:11.

As shown in XRD patterns (Fig. 5), no distinct peak of CoQ_{10} at position 18.73° was apparent in case of 1 day and 60 days old SD formulations containing Aerosil® 200. CoQ_{10} might have either existed in amorphous state or presence of small amount of crystalline CoQ_{10} could not have detected owing to very small peaks. Therefore, XRD patterns also confirmed the improved stability of the solid dispersion samples containing Aerosil® 200. The successful use of Aerosil® 200 as solid dispersion stabilizer in the formulations can be related to its intrinsic properties. Aerosil® 200 being very fine in particle size (7–16 nm) (Morefield, 2000) provided large surface area for adsorption, limiting recrystallization process of CoQ_{10}. And due to the presence of surface silanol groups, Aerosil® 200 might have been able to form hydrogen bonds with drug molecules during formulation of solid dispersion (Chauhan et al., 2005), resulting in decrease in initial solubility.

3.4. Scanning electron microscopy (SEM)

SEM pictures of pure CoQ_{10}, pure poloxamer 407, Aerosil® 200 and SD samples were taken to study their morphology (Fig. 7). As shown in Fig. 7 (iv), SD of CoQ_{10} with poloxamer 407 and Aerosil® 200 at the weight ratio of 1:5:6 (1 day after preparation) showed fine granular structures of Aerosil® 200 (7–16 nm) clustered together by the polymeric matrix to form bigger particles. CoQ_{10} was not visibly detected in the photographs and hence may be distributed between surface of Aerosil® 200 particles and polymeric matrix. No significant morphological change was detected in the photograph of the same SD sample after 60 days (v). The addition of Cremophor® RH40 did not change the results of SEM study significantly. From the SEM picture, it can be speculated that CoQ_{10} either existed in amorphous form or very fine crystalline form and its recrystallization or growth was inhibited by the addition of Aerosil® 200.

3.5. Dissolution studies

Fig. 8 shows the dissolution profiles of pure CoQ_{10}, physical mixture and various SD formulations. For dissolution test of SD formulations, fresh samples were used. Pure CoQ_{10} practically remained undissolved in dissolution medium for 24 h. Physical mixture of CoQ_{10} and poloxamer 407 in the weight ratio of 1:5 showed approximately 5% dissolution. As shown in Fig. 7, all SD formulations achieved almost maximum dissolution within 15 min. The initial lag was mainly due to the time needed for HPMC capsule shell to be dissolved before liberating the drug content into the dissolution medium. The SD of CoQ_{10} with poloxamer 407 in the weight ratio of 1:5 showed approximately 85% dissolution. This data is in conformity with solubility data. The fast dissolution kinetics of the solid dispersion may be due to the presence of CoQ_{10} in amorphous state in solid dispersion. In the case of the SD, CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6, the maximum dissolution was around 75% after 24 h. Initially, the extent of dissolution at 15 min was approximately 70% and increased slowly up to 75% at 24 h, which coincided with the results of solubility study. It was noticed that Aerosil® 200 had tendency to retain some portion of CoQ_{10} as adsorbed on it. The SD, CoQ_{10}:poloxamer 407:Cremophor® RH40:Aerosil® 200 = 1:5:5:11 (in weight ratio), showed minimum dissolution among solid dispersion formulations tested, i.e., around 60%. Also, the solubility data for the formulation had lower value than that of other SD formulation used in the dissolution study. Taken all together, the SDs of CoQ_{10} with poloxamer 407 and Aerosil® 200 appeared to be most effective to enhance the extent of drug release as well as dissolution rate.

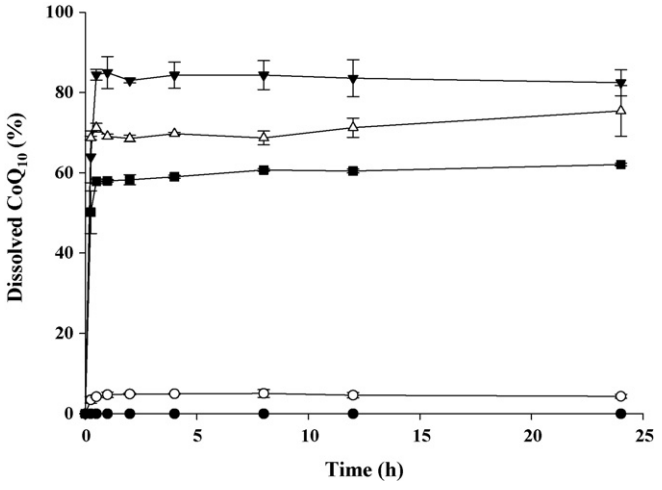

Fig. 8. Dissolution profiles in pH 6.8 phosphate buffer (mean ± S.D., $n = 3$). (●) Pure CoQ_{10}, (○) physical mixture of CoQ_{10}:poloxamer 407 = 1:5, (▼) SD of CoQ_{10}:poloxamer 407 = 1:5, (△) SD of CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6, (■) SD of CoQ_{10}:poloxamer 407:Cremophor® RH40:Aerosil® 200 = 1:5:5:11.

4. Conclusion

The present study has demonstrated that poloxamer 407 could increase the solubility of CoQ_{10} significantly via the preparation of solid dispersion by melting method. Furthermore, the addition of Aerosil® 200 as a recrystallization inhibitor reinforced the stability of the solid dispersions. Therefore, the solid dispersion formulation, CoQ_{10}:poloxamer 407:Aerosil® 200 = 1:5:6 (in weight ratio), appeared to be most effective to enhance the solubility, stability and dissolution among the tested formulations. Moreover, it offers some additional advantages including ease of preparation, good flowability and cost-effectiveness.

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