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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.