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RESEARCH PAPER

Preparation and Characterization of Coenzyme Q_{10}–Eudragit® Solid Dispersion

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ABSTRACT

A solid dispersion of Coenzyme Q_{10} and Eudragit L 100-55 was prepared using solvent evaporation method. Solid dispersion, physical mixture, and pure compound were then characterized using differential scanning calorimetry and powder x-ray diffraction. Solubility of CoQ_{10} in different surfactant media was measured, and a suitable dissolution medium was developed to compare the dissolution patterns of the solid dispersion, physical mixture, and the pure compound. Combining labrasol with different surfactants in dissolution media demonstrated an additive effect on CoQ_{10} solubility. The solubility of CoQ_{10} in a 4% Labrasol/2% Cremophor EL solution was 562 μg/ml, which was five times higher than the combined solubility in 5% Labrasol (91 μg/ml) and 5% Cremophor EL (7.8 μg/ml). Moderate change in the crystalline pattern of CoQ_{10} was observed, which was attributed to solvent displacement rather than the degree of crystallinity change. The dissolution test indicated that the in-vitro release of Coenzyme Q_{10} from its solid dispersion was much faster than its physical mixture, which in turn was faster than the pure drug. The amount of drug released in 12 hours from solid dispersion, physical mixture, and the pure drug was 100, 26.5 and 12.5% respectively. CoQ_{10} was photostable throughout the dissolution experiments.

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INTRODUCTION

Coenzyme Q_{10}, also known as ubiquinone, is a physiologically important compound that acts as an electron shuttle in mitochondrial respiratory chain and as a stabilizing agent in cellular membranes (1). It is used as a nutritional supplement and is recommended for the treatment of various cardiovascular disorders such as angina pectoris and congestive heart failure (2).

Coenzyme Q_{10} is poorly and slowly absorbed from the gastrointestinal tract due to its high molecular weight and poor aqueous solubility (2), thereby presenting a challenge in the development of a formulation for oral administration. Another unfavorable characteristic of the drug is its photolability. CoQ_{10} is a yellow crystalline powder that gradually decomposes upon exposure to light. Nazzal et al. (3) have reported the conversion of ubiquinone to ubichromenol in an aqueous solution upon exposure to fluorescent light.

Different CoQ_{10} formulations were reported, some of which were introduced into the market as oil-solubilized or powder-filled capsule formulations (2,4). Other ubiquinone formulations reported include a solubilized system with soy lecithin (5), a micellar solution of CoQ_{10} with polyoxyethylene (60) hydrogenated castor oil (6), lipid microspheres prepared as a soybean oil emulsified with yolk phospholipids (7), a solubilized CoQ_{10} in a blend of polysorbate 80 and medium-chain triglycerides (8), and a redispersable dry emulsion prepared by spray drying oily emulsion with a suitable adsorbent (9). No dissolution profiles were reported for most of these formulations, either due to their oily nature and poor aqueous solubility or due to the absence of a suitable dissolution medium.

There has been a great interest over the years in using solid dispersions to improve the dissolution rate and the bioavailability of poorly soluble drugs (10). Various inert materials such as polyethylene glycol (11–13), polyvinylpyrrolidone (11,14,15), and hydroxypropylmethylcellulose (16) have shown to improve the dissolution rate of many drugs. Among the carriers used in the formation of solid dispersions are the acrylic copolymers commercially available as Eudragits® (17–19). A review of the literature did not indicate any information on the improvement of CoQ_{10} dissolution by solid dispersion techniques.

The objectives of this study were

- to prepare a solid dispersion formulation of CoQ_{10},
- to investigate the physical interactions between CoQ_{10} and a carrier polymer (Eudragit L100-55),
- to develop a suitable aqueous dissolution medium that can differentiate between formulation variables, and
- to evaluate the photostability of CoQ_{10} throughout the dissolution experiments.

EXPERIMENTAL

Chemicals

Ubiquinone (CoQ_{10}) was a generous gift from Kyowa Hakko USA (New York, NY). Eudragit® L 100-55, a copolymer of methacrylic acid and ethyl acrylate, was obtained from Rohm GmbH (Germany). Polyoxyl 35 castor oil (Cremophor EL), polyoxyl 40 hydrogenated castor oil (Cremophor RH40), sodium lauryl sulfate and polyoxypropylene–polyoxyethylene block copolymer (Pluronic F68 and Pluronic F88) were obtained from BASF Corp (Mount Olive, NJ). Polyoxyethylene (20) sorbitan monolaurate (Tween 20), polyoxyethylene (20) sorbitan monopalmitate (Tween 40), and polyoxyethylene (20) sorbitan monooleate (Tween 80) were obtained from Amresco (Solon, OH). Lecithin was obtained from the American Lecithin Company (Oxford, CT). Labrasol, a polyglycolyzed glyceride from coconut oil, was obtained from Gattefosse (France). Sodium taurocholate, potassium chloride, sodium hydroxide, acetic acid, potassium phosphate and high-performance liquid chromatography (HPLC) grade methanol and *n*-hexane were purchased from VWR Scientific (Minneapolis, MN). All the chemicals were used as received.

Solubility Studies

Solubility of CoQ_{10} in fed and fasted-state simulated intestinal fluid (FeSSIF and FaSSIF, respectively), and in water as a function of Tween 80 and Tween 80/Labrasol concentration (Table 1) as well as in an aqueous media comprising 4% Labrasol and 2% Cremophor EL, Cremophor RH40, Pluronic F68, Pluronic F88, SLS, Tween 20, Tween

40, Tween 80, and Labrasol (Fig. 1) was determined as follows.

Excess CoQ_{10} was added to 10 ml of the media and the mixtures were shaken for 24 hr at 37°C in a thermostatically controlled shaker (Environ-Shaker 18, Lab-line Instruments, Melrose, IL). After 24 hr, aliquots were filtered using a 0.45 μm Fisherbrand nylon filters and assayed by HPLC. The compositions of the FaSSIF and FeSSIF are given in Table 2. To simulate experimental conditions, dissolution of an excess 750 mg of CoQ_{10} filled in capsule size 00 in 900 ml of the dissolution medium was measured using USP XXIII rotating paddle apparatus (VanKel, mod. VK7000, Cary, NC) at 37°C and a rotating speed of 50 rpm. Composition of the dissolution media used was 4% Labrasol and 2% Tween 80, 4% Labrasol and 2% Cremophor EL, and 4% Labrasol and 2% Cremophor RH40. Samples were withdrawn at fixed time intervals and assayed by HPLC.

Table 1

Solubility of CoQ_{10} in a Solution of Tween 80 and Labrasol/Tween 80 Mixture

	Percent Labrasol				
Percent Tween 80	0%	1%	2%	3%	4%
0.50	6.3	105.9	216.4	264.8	343.5
1	15.4	148.2	281.7	323.3	328.7
2	53.2	177.7	338.1	366.8	470.7
3	82.7	193.4	452.6	450.1	580.7

Table 2

Compositions of Fasted and Fed-State Simulated Intestinal Fluid (FaSSIF and FeSSIF, respectively)

FaSSIF	
Na taurocholate	3 mM
Lecithin	0.75 mM
KH_2PO_4	3.9 g
KCl	7.7 g
NaOH	q.s. pH 6.5
Distilled water	q.s. 1 L
FeSSIF	
Na taurocholate	15 mM
Lecithin	3.7 mM
Acetic acid	8.65 g
KCl	15.2 g
NaOH	q.s. pH 5.0
Distilled water	q.s. 1 L

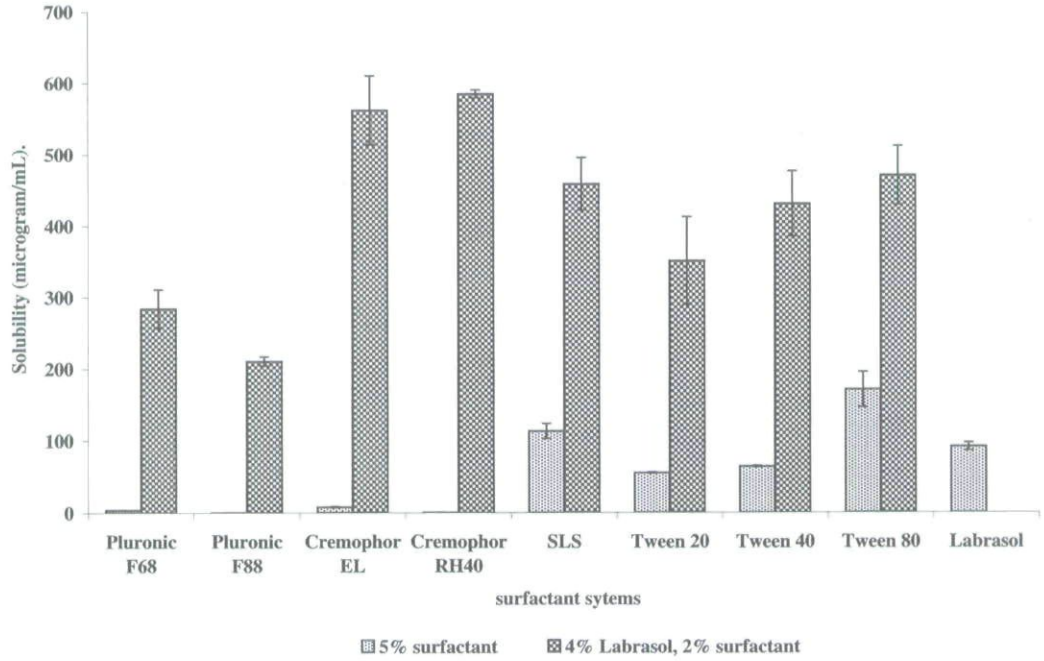

Figure 1. Coenzyme Q_{10} solubility in 5% Labrasol and in a mixture of 4% Labrasol and 2% of the given surfactant ($n = 3$).

Preparation of Solid Dispersion

Solid dispersion was prepared by the solvent evaporation method. Coenzyme Q_{10} (1 g) was dissolved in 70 ml of acetone. Eudragit L 100-55 (0.5 g) was dissolved in 10 ml of ethanol and then added to the acetone–CoQ_{10} solution. CoQ_{10} is insoluble in ethanol; thus, acetone was used as a co-solvent in the preparation of the solid dispersion. The acetone–ethanol solvent mixture was removed under vacuum in a rotary evaporator (BUCHI® model B-480, Brinkmann Inst., Waterbury, NY) at 40°C. After complete evaporation, the solid mass was removed from the evaporating flask with a metal spatula. The solid dispersion was further dried at 40°C for 24 hr. The dried solid mass was pulverized with a mortar and pestle and passed through # 20 mesh and stored in amber bottles.

Preparation of the Physical Mixture

Coenzyme Q_{10} (1 g) and Eudragit L 100-55 (0.5 g) were grounded and mixed using a mortar and pestle, and stored in amber bottles.

Preparation of Tablets

Solid dispersion, physical mixture or reference compound corresponding to 100 mg in weight of CoQ_{10} were mixed with lactose (100 mg), talc (5%) and magnesium stearate (1%). Tablets were prepared by compressing the mixtures in a 8 mm die with a compression pressure of 0.5 tons using a Carver® press model C (Carver Inc., Wabash, IN) attached to a semiautomatic compression assembly model 2826 (Carver). The dwell time used for compression was 2 s.

Differential Scanning Calorimetry (DSC)

The thermal characteristics of the solid dispersion physical mixture, and pure CoQ_{10} were determined using a differential scanning calorimeter (DSC 7, Perkin Elmer, Norwalk, CT). An equivalent weight of 2.5 mg of CoQ_{10} in each preparation was sealed in the aluminum pan. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2 at a heating rate of 10°C/min. The scanning range used was from 25 to 70°C.

Powder X-ray Diffraction

The powder x-ray diffraction (PXRD) patterns of CoQ_{10}, physical mixture, and solid dispersion were obtained using a Philips Norelco diffractometer (Philips Analytical Inc., Natick, MA) fitted with a copper target. Measurements were carried out using 40 kV voltage and 20 mA current. Samples were scanned from 10° 2θ to 40° 2θ at a rate of 2θ/min.

Dissolution Studies

Dissolution profiles of tablets containing pure CoQ_{10}, physical mixture, and solid dispersion were determined using a USP XXIII rotating paddle apparatus (VanKel) at 37°C and a rotating speed of 50 rpm in a 900 ml of dissolution medium. The dissolution medium used was an aqueous solution of 2% Cremophor EL and 4% Labrasol mixture as proposed in this study. Samples (5 ml) withdrawn at fixed time intervals were filtered using a 10 μm VanKel filter and assayed for CoQ_{10} by the HPLC method reported later in this paper. The dissolution experiments were carried out in triplicates.

Dissolution Photostability of Coenzyme Q_{10}

Coenzyme Q_{10} was dissolved in a 4% Labrasol/2% Cremophor EL micellar solution at a concentration equivalent to 70 μg/ml. The solution (900 ml) was then placed in the vessel of the USP XXIII rotating paddle apparatus at ambient light conditions and equilibrated to 37°C with stirring at 50 rpm. In addition, photostability of the solution was examined under fluorescent light equivalent to 440 and 880 foot candle (fc), using 40 W general electric cool white fluorescent lamps, and UV irradiation (350 nm), using 15 W general electric black light UV lamps, at 37°C in a light stability chamber (HOTPACK™, Philadelphia, PA). The distance between the sample and light source was 25 cm. Samples were withdrawn at fixed time intervals and assayed for CoQ_{10} and its major photolytic decomposition products by HPLC.

HPLC Analysis

A detailed HPLC method for the analysis of aqueous CoQ_{10} samples was described by Nazzal et al. (3). Briefly, CoQ_{10} and its degradation products were analyzed at ambient temperature utilizing a

C18, 3.9 mm × 150 mm reverse phase chromatography column (Nova-Pak; Waters, Milford, MA). The mobile phase consisted of methanol : *n*-hexane (9:1) and was pumped at a flow rate of 1.5 ml/min. The HPLC instrument consisted of a 510 pump (Waters), 712 WISP autosampler (Waters), and a 490E UV detector (Waters) set at a wavelength of 275 nm. The chromatographic data was managed using Star 5.3 software (Varian, Walnut Creek, CA).

RESULTS AND DISCUSSION

Solid Dispersion Studies

Solid dispersion of CoQ_{10} was prepared with Eudragit L 100-55, as the latter is known to release the drug in the intestine (pH). Coenzyme Q10 has been reported to be abs rom the intestinal region (20). Several reporte dies involved the use of Eudragit L 100-55 in the preparation of solid dispersions and coprecipitates (17,21,22). The solid dispersion prepared by the present method provided a yield value of 87.3% of the drug. The solid dispersion obtained was compressed as tablets to provide a dosage form containing 100 mg of CoQ_{10}. The tablets obtained with the physical mixture and the drug were found to have a hardness of 7 kg, where as the tablets prepared with solid dispersion had a hardness of 12 kg.

Solubility Studies

Coenzyme Q_{10} is practically insoluble in aqueous medium. Moreover, it does not demonstrate preferential solubility at different pH media because of its unionizable nature. Thus, an alternative dissolution medium should be introduced to provide adequate aqueous solubility and sink conditions. The dissolution medium should have the ability to discriminate the dissolution patterns of different formulations. Micellar solubilization using surfactants and/or glycerides in the dissolution medium provides an attractive approach to obtain the desired medium. Thus, solubility of CoQ_{10} in different surfactant systems was initially investigated. The solubilities reported in this paper are at the end of a 24-hr period. This time period was selected for obtaining relative solubilities because they did not attain equilibrium even after continuous shaking for 2 weeks.

Solubility of CoQ_{10} in Tween 80 and Labrasol mixtures is given in Table 1. It is interesting to observe the synergistic effect of combined surfactant system on the solubility of CoQ_{10}. Solubility in 5% Labrasol was only 91 μg/mL (Fig. 1), and that in 5% Tween 80 was 171 μg/ml; however, the solubility in a combined mixture of 4% Labrasol and 2% Tween 80 exceeded 470 μg/ml. Enhanced solubility in the binary system of Labrasol and Tween 80 might be due to the formation of a microemulsion. It was reported by Malcomson (23) that the solubilization of a drug into the microemulsion system would be increased over that of the corresponding micelle due to the formation of an extra potential locus for drug solubilization. A micelle solution is applied to systems containing just surfactants in solvents.

Similar results were obtained with seven additional surfactants. The solubility of CoQ_{10} was determined in 5% solution of Pluronic F68, Pluronic F88, Cremophor EL, Cremophor RH40, SLS, Tween 20, and Tween 40. These values were compared with that of the solubility of CoQ_{10} in a media composed of 4% Labrasol and 2% of the given surfactant. As shown in Fig. 1, the additive effect was mostly evident with Cremophor EL and Cremophor RH40, where the solubility of the compound in 5% of the surfactant was 7.8 and 0.3 μg/ml, respectively. The solubility of CoQ_{10} in the Labrasol/Cremophor EL or Labrasol/Cremophor/RH40 mixture exceeded 562 and 584 μg/ml, respectively, which is about 5 times higher than the combined solubility in both Labrasol and the surfactant.

For comparison, solubility of the compound in FaSSIF and FeSSIF, which were proposed as physiologically more relevant media for invivo/invitro correlation (24,25), was 2.09 and 10.02 μg/ml, respectively. Compositions of the two media are given in Table 2. Mixtures of 4% Labrasol and 2% of Tween 80, Cremophor EL, or Cremophor RH40 were selected as candidate dissolution media. As reported in the experimental section, the dissolution of pure CoQ_{10} has also been determined in the selected dissolution media. The amount of CoQ_{10} dissolved in all the dissolution media reported here exceeded 260 μg/ml within the first hour, which would provide a sink condition with eight times the solubility of conventional 30 mg CoQ_{10} tablet/capsule. The usual daily dose of the nutritional compound is 30 mg twice daily or 60 mg once

a day. The dissolution medium selected for all subsequent studies was 4% Labrasol and 2% Cremophor EL.

PXRD, DSC, and Dissolution Studies

Dissolution profiles of the solid dispersion, physical mixture, and pure CoQ_{10} tablets prepared under a compression pressure of 0.5 tons are given in Fig. 2. Even though the sink conditions were maintained using the proposed surfactant media, only the solid dispersion tablets containing 100 mg of CoQ_{10} led to a 100% release within 12 hr compared with 26.5% and 12.5% for the physical mixture and pure compound, respectively.

A disintegration test was not performed. However, observing the dissolution of the tablets, solid dispersion tablets disintegrated faster into smaller granules, which was not achieved with the physical mixture or pure drug. This provides larger surface area for drug dissolution and faster release. Enhanced disintegration and, subsequently, dissolution for the tablets prepared from solid dispersion could be attributed to the manufacturing process, which allows a structural rearrangement of CoQ_{10} crystals within the matrix made from Eudragit polymers during solvent evaporation.

Subsequent drying and grinding produced excellent CoQ_{10}–Eudragit granules that allowed ease of compression without the need for binders or granulation during tablet preparation. This is evident from the DSC and PXRD data shown in Figs 3 and 4. Figure 3 shows the representative x-ray diffraction patterns for the pure CoQ_{10}, physical mixture, and the solid dispersion. Eudragit L 100-55 is an amorphous polymer and does not reveal any x-ray diffraction patterns. As seen from the x-ray diffraction plot, major peaks for the physical mixture and pure drug were retained. This should reflect no change in the crystallinity of the drug. A decrease in the intensity of the peaks with the physical mixture is only due to a lower loading of the drug per unit weight of the physical mixture. The characteristic crystalline peaks of CoQ_{10} were also observed for the polymer–CoQ_{10} solid dispersion. Even though main peaks were retained, there was an apparent change in their intensity. For example, looking at the area from 9° to 12°θ, intensity of the

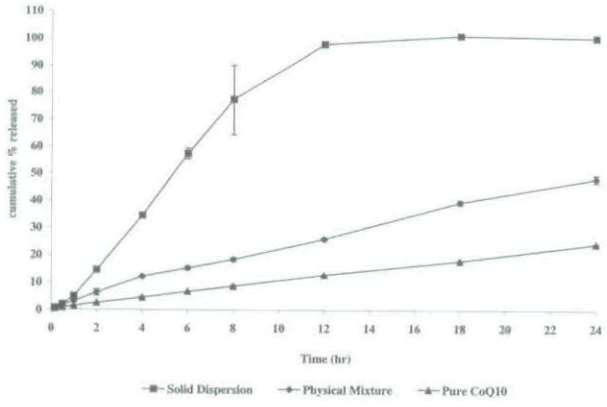

Figure 2. Dissolution profiles of the solid dispersion, physical mixture, and pure CoQ_{10} tablets containing an equivalent of 100 mg of CoQ_{10}.

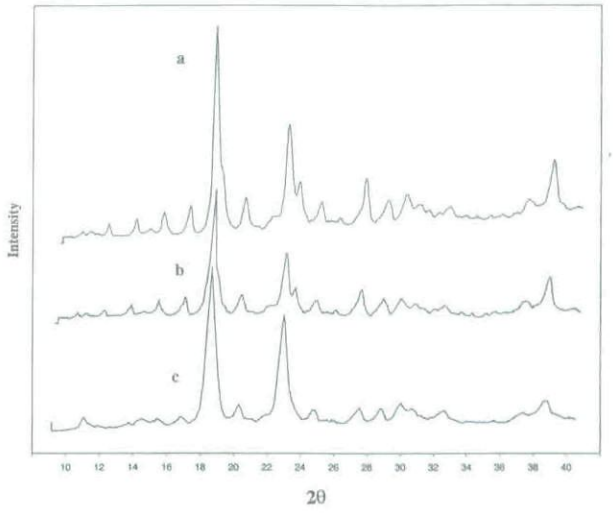

Figure 3. X-ray diffraction patterns of (a) pure CoQ_{10}, (b) physical mixture, and (c) solid dispersion.

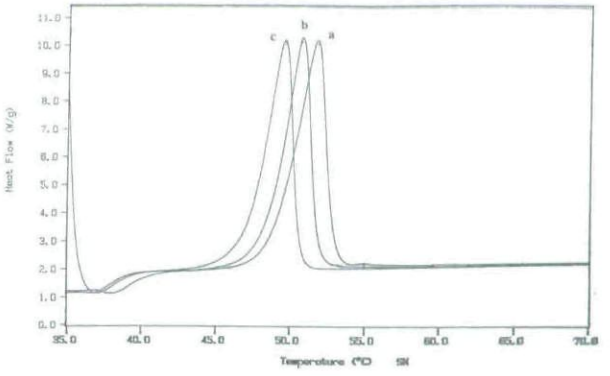

Figure 4. DSC curves of pure (a) CoQ_{10}, (b) physical mixture, and (c) solid dispersion.

peak at $\theta = 11.4°$ was increased and the peak at $\theta = 11.7°$ disappeared. Furthermore a new peak appeared at $\theta = 5.7°$. This is due to the process utilized in the preparation of solid dispersion. Slow solvent evaporation allows drug crystals to pack and rearrange themselves within the polymer network. This may or may not be associated with a change in the crystallinity. Since we are measuring powder crystallinity using PXRD, it is logical that such changes would be reflected in the crystalline pattern of the solid dispersion. This was not possible with the physical mixture and the pure drug, which were provided as powder and were not subjected to the same treatment and manufacturing processes as was the solid dispersion.

This was further supported by the DSC data given in Fig. 4, which shows the representative DSC curves for the pure CoQ_{10}, physical mixture, and the solid dispersion. Pure powdered CoQ_{10} showed a melting endotherm at 51.7°C, which was shifted slightly to 49.6°C for the solid dispersion with no change in enthalpies or heat capacities. This reflects the interaction between the CoQ_{10} and the polymer described earlier, which may not be associated with a change in the crystallinity of the drug.

Dissolution Photostability of Coenzyme Q_{10}

CoQ_{10} is a light-sensitive compound (3,9,26). To ensure its stability against photodecomposition throughout the dissolution experiments, a photostability experiment was performed as described earlier. The fluorescent light (typically 400–800 fc) provides a reasonable simulation to natural light and is widely used in photostability testing (2).

The degradation profiles of the CoQ_{10} micellar solution exposed to fluorescent and UV light are given in Fig. 5. After a period of 24 hrs, 100% of the compound was retained for the sample maintained at 37°C in the dissolution vessel at ambient light conditions. Fluorescent lamps were used as the light source in the laboratory with no exposure to any external light source. For the samples stored at 440 fc, 880 fc, and UV light, only 43.7%, 15.7%, and 8.3% remained after 24 hrs at each stress condition, respectively. As given in the graph, photostability of CoQ_{10} is dependent upon the amount of light exposure. Further, it readily decomposes upon exposure to UV irradiation.

Similar results were obtained for the photostability of solid state ubiquinone, where the percent

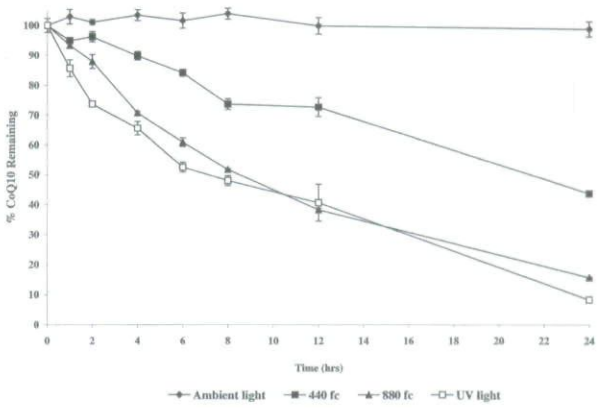

Figure 5. Photostability of CoQ_{10} in the simulated dissolution conditions.

degradation decreased with increasing wavelength, reaching a maxima at 350 nm and no degradation at a wavelength greater than 450 nm (23). Relative amount of light exposure at the surface of the dissolution apparatus and sample vials in the stability chamber can be obtained using a camera equipped with a photometer (Minolta® model ∝5XI, Osaka, Japan). In a photometer, the degree of lens opening (aperture size) is given as a numerical value, termed F-stop or F-number. F-stop is inversely related to the actual aperture size and is directly proportional to the amount of light exposure per unit time (27). Using a shutter speed of 1/15 as a unit time, F-stop values at the surface of the dissolution vessels and sample vials stored at 440 and 880 fc were 4.5, 13, and 22, respectively. Thus, stability of the samples throughout the dissolution experiments were maintained by low exposure to fluorescent light.

CONCLUSIONS

Solid dispersion of CoQ_{10} with Eudragit L 100-55 provides an alternative solid formulation to the existing dosage forms. The solid dispersion obtained demonstrated an extended-release property with an improved dissolution over the physical mixture or the pure CoQ_{10}. This may be advantageous in the development of a bioavailable sustained-release solid formulation. Dissolution medium with low percentage of added surfactants can be obtained by combining different glycerides and solubilizing agents. A combination of 4%

Labrasol and 2% Cremophor EL distinguished the dissolution patterns of the prepared formulations and provided sink condition with eight times the solubility of a conventional 30 mg CoQ_{10} tablet. Coenzyme Q_{10} was photostable throughout the dissolution experiments with no detected decomposition products.

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