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Solubilization Effect of Anionic, Cationic and Nonionic Surfactants on Coenzyme Q10 Solid Dispersion

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ABSTRACT: Coenzyme Q10 (CoQ10) is an oil-soluble vitamin-like benzoquinone compound. Coenzyme Q10 plays a role in providing membrane stability, energy conversion and ATP production. It is also one of the important antioxidants in the body. The bioavailability of coenzyme Q10 is very low due to its low solubility in water and its large molecular mass. Among the solubility enhancement approaches, solid dispersions (SDs) are one of the most promising strategies. The use of suitable carrier and methodology plays a significant role in the biological response. In terms of a carrier, solid dispersions are classified broadly the third group. Surfactant-based SDs are called third-generation solid dispersions. To evaluate the surfactant effect on solubilization of CoQ10, three different surfactants of varying ratios between 1:1, 1:3 and 1:5 (w/w) were used namely sodium dodecylsulfate (SDS) (anionic), cetyl trimethyl ammonium bromide (CTAB) (cationic) and Pluronic F127 (non-ionic). CoQ10 solid dispersions were characterized in terms of particle size, polydispersity index, zeta potential, FTIR spectroscopy, DSC analysis, saturation solubility and in vitro dissolution studies. To compare dissolution rate, area under the dissolution curve (AUC), Mean Dissolution Time (MDT), mean residence time of the drug substance molecules in the dosage form (MRT), and dissolutio nefficiency % (DE%) were calculated. All the formulations showed improvement in the aqueous solubility, while the dissolution rate was increased only by Pluronic F127 ($p<0.05$). Among the surfactants, Pluronic F127-based SDs were found superior to other surfactants. The results revealed that surfactant-based SDs offered great success in improving the therapeutic efficacy of CoQ10.

KEYWORDS: Coenzyme Q10; solid dispersion; sodium lauryl sulfate (SLS); cetyltrimethylammonium bromide(CTAB); Pluronic F127.

1. INTRODUCTION

Approximately 40% of the marketed drugs have solubility problems. In addition, due to the low solubility of approximately 75% of newly synthesized drug molecules cannot pass from the preformulation stage to the clinical phases [1,2]. Therefore, solubility enhancement processes are crucial for human health and the pharmaceutical industry. Many methods have been developed so far for increasing the solubility of drugs. These methods are; reduction of particles to nano/micro dimensions, hydrotropy, use of various drug delivery systems, formation of polymorph and amorphous forms by applying crystal engineering, co-solvency, solid dispersions, liquisolid techniques, formation of water-soluble salt forms and inclusion complexing[3]. Among them, the solid dispersion (SD) method is one of the most effective and most applicable to scale-up[4].

Solid dispersion is a complex system formed by dispersing poorly water-soluble drugs in an inert solid carrier that is highly water soluble, using various methods. The SDs can be used to improve the bioavailability of poorly water-soluble drugs by increasing apparent solubility, dissolution rate, and/or long-term stability. There are different mechanisms to increase solubility and dissolution rate. These are;

i)drug is dispersed in the solid carrier at the molecular level, so it is easier to dissolve in the dissolution medium;

ii) agglomeration between particles is also eliminated due to the carrier in the structure;

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iii) drug is dispersed in the carrier amorph state by inhibiting crystallization in the solid state, and these systems can easily be dispersed and wetted in the medium by the dissolution of the carrier in the dissolution medium [5-7].

In the development of solid dispersion formulations, the choice of carrier influences the solubility, bioavailability, stability, and production of the formulation. Carriers must be pharmacologically inert, nontoxic, and chemically compatible with the drug. Solid dispersions are divided into 3 groups according to their carrier system and development of intellectual knowledge [8-10].

First-generation SDs: First-generation SDs are crystalline solid dispersions. In such systems, the drug is dispersed in the crystalline carrier a and crystalline mixture is formed. In these SDs, crystalline urea [11] and various sugars (D-fructose, D-dextrose,D,-mannitol and D-maltose) [12] are used. It is obtained by eutectic mixture. It is thermodynamically unstable and shows low emission profiles.

Second-generation SDs: These are solid dispersions produced to eliminate the problems seen in the first generation SDs. Therefore, crystalline structures such as urea and sugar are replaced by amorphous structures. In the second generation SDs, solubility, and dissolution rate increased by using amorph polymers such as PVP-based, cellulose-based, PEG-based, and acrylate-based polymers [9,13]. This is explained by the low thermodynamic stability of the amorph dispersions.

Third generation SDs: Third-class carriers are solid dispersions in which at least one surfactant is used as the carrier. Since surfactants are the most used structures for solubility enhancement, a high solubility increase is observed. 3rd generation SDs prevent precipitation during the shelf life and gastrointestinal tract, prevent nucleation and agglomeration and increase physical and chemical stability. For solubilization mechanism of the 3rd generationSDs, mechanism is mainly based on micellization [14]

Every cell contains Coenzyme Q10 (CoQ10, KoQ10; ubiquinol-10 and/or ubiquinone-10), which functions as a coenzyme in important enzymatic activities during cellular energy synthesis. Coenzyme Q10 functions as the electron transporter for the respiratory chain in mitochondria. Exposure to air, UV radiation, and high temperatures make CoQ10 sensitize chemical degradation. Additionally, it has extremely low oral bioavailability due to its large molecular size (863 Daltons), high lipophilicity (Log P= 21), and extremely low water solubility (0.7 ng/mL) [15-17].

In our study, solid dispersion formulations of Coenzyme Q10 which has the above-mentioned stability and solubility problem were developed. Surfactants were used as the carrier system in solid dispersions which are called third-generation SD carriers. Anionic (sodium dodecyl sulfate), cationic (CTAB) and nonionic (Pluronic F127) surfactants have been used to examine the effect of the ionic charge of the carriers on the physical properties and dissolution behavior of CoQ10.

2. RESULTS AND DISCUSSION

2.1. Preparation of solid dispersions

Solid dispersion was conceptually defined for the first time by Sekiguchi in 1961 and SDs can be described as a systems in which one or more drugs are dispersed in an inert carrier [10,11]. Solid dispersions are mainly used to increase the solubility and bioavailability of poorly soluble drugs[18], reduce particle size[19], transform the crystal structure of drugs into the amorphous form[20], mask taste[21], increase stabilization[22] and achieve rapid or slow release[14,23]. In our study, solid dispersions were prepared to increase the solubility and dissolution of CoQ10.

The most common methods in the preparation of solid dispersions are the fusion method, solvent evaporation method, spray-drying method, melt agglomeration, hot melt extrusion method etc. Especially for thermal-sensitive drugs, the most used method is the solvent evaporation method. Thus, the solubility of drugs can be increased without thermal degradation. In the our study, solvent evaporation method was used to prepare thermal sensitive CoQ10. Thereby, heat-related degradation was eliminated. By forming a homogeneous dispersion of the drug solution in acetonitrile and an aqueous solution of water-soluble carriers, the drug was dispersed homogeneously at room temperature. The evaporated SDs were kept in a desiccator with silica gel to completely dry over the night. Obtained SDs were tightly closed in containers and kept in the refrigerator [24,25].

In the improvement of solubility and/or bioavailibility of CoQ10, there has been many formulation have been developed such as dendrimer[26], liposomes[27-30], micelles[31], metal organic framework[32], solid lipid nanoparticles[30,33,34], nanostructured lipid carriers[35], nanoemulsion[28], protein nanoparticles[36], polymeric nanoparticle[37], self-nanoemulsifying drug delivery systems (SNEDDS)[38], nanocrystals[39,40] and solid dispersions[18,22]. Among them, SD was chosen because manufacturing is easy relative to the other systems.

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In the previous studies to increase the CoQ solubility by solid dispersion techniques, Poloxamer 407®[8], Poloxamer188® [22,41], PEG6000[22], Kolliphor HS-15®[22], Kollicoat IR®[22], Kollidon12®, Kollidon17®[22], Kollidon 30®[22], Kollidon 90®[22], Soluplus®[18,22], TPGS[22], Protein hydrolysates[42], poloxamer 407[43], polyethyleneglycol 3400[43], povidone K-30[43], HPMC 2910[43], Eudragit® L 100–55 [44], γ-cyclodextrin[45] has been used.

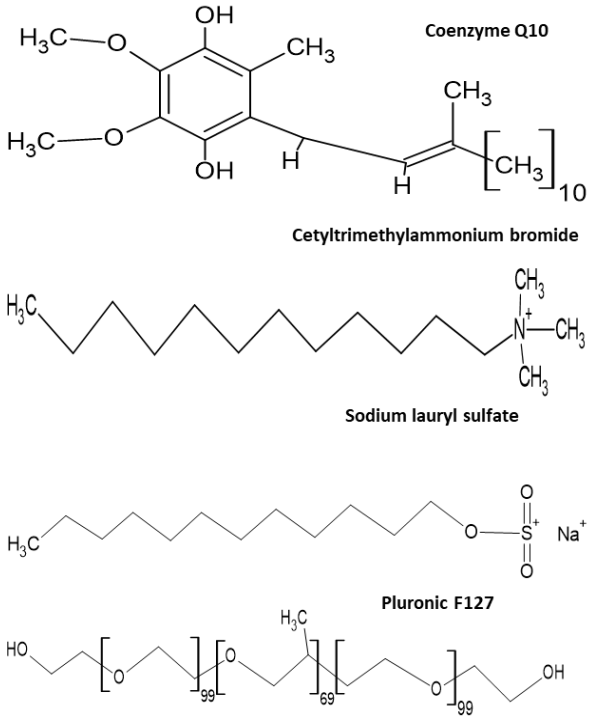

Figure 1. Chemical structure of drug and surfactants.

In our study, anionic (sodium lauryl sulfate), cationic (cetyltrimethylammonium bromide-CTAB), and nonionic (Pluronic F127) surfactants were used according to ionic charge (Figure 1). In the study, all surfactants increased the water solubility of Coenzyme Q10 in a certain amount (Figure 2 and 3). In terms of increasement solubility, formulations are listed as SSLS<SCTAB<SPluronic F127. In all formulations, solubility increases with increasing surfactant ratio as expected (Figure 3). The increase in solubility can be explained by the increase in wettability of CoQ10 and the micellization mechanism. Surfactants reduced the surface tension between the solubility medium and Coenzyme Q10 and increases wettability thereby solubility and bioavailibility [18,46]. Micelles are formed above the critical micelle concentration (CMC) at the certain temperature by surfactant molecules. Micellization is solubilization by micelles. In this study, solubility increased mainly by micellization. Because surfactant concentrations were selected above the CMC.

Sodium lauryl sulfate/ Sodium dodecylsulfate/SLS is an anionic surfactant found in many personal care products. SLS is a cheap and highly efficient foam generator. Surfactants like SLS, ammonium lauryl sulfate (ALS), and sodium pareth sulfate are utilized in many cosmetic products for their ability to cleanse and emulsify. They have a soap-like effect[47]. SLS is also used in biorelevant dissolution studies to ensure sink condition[48]. In the dissolution studies, SLS is used below the CMC, not to micellization effect. On the other way, SLS is generally used above the CMC in solubilizing poorly water-soluble drugs by micellization and preventing recrystallization[49]. For all that, a higher amount of SLS is considered toxic[50]. In this study, SLS was only investigated in terms of solubilization effect.

In our solid dispersion formulations prepared with SLS, the water solubility was increased from 0.802±0.174 to 81.118±0.559, 243.776±2.112, 327.532±5.276 µg/mL, respectively. One of the solubility enhancement mechanisms of solid dispersion is amorphization. After amorphization, solid dispersions can easily become recrystallized. To prevent recrystallization and maintain stability, Guan et al tried various cellulose derivatives and mixtures of surfactants. In the study, the solubility enhancement was obtained using Span 20, Tween 80 and SLS surfactants which are used as solubilizing and wetting agents. According to the results, SLS provided a very high solubility enhancement compared to other nonionic surfactants and had a very efficient role in the inhibition of recrystallizationcomparedtocellulosederivatives[51]. Inrecentstudies,

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SLS is generally used alongside a polymer. The in vivo bioavailability can be significantly enhanced by the solid dispersions obtained by the combination of SLS with dextrin[52], sodium carboxymethylcellulose (Na-CMC)[53], hydroxypropyl methylcellulose[54]by increasing dissolution rate and solubility.

CTAB is a cationic surfactant that has been used as an antibacterial and antifungal agent. In cationic surfactants, the hydrophilic headgroup carries a positive charge. Recent research has also demonstrated that CTAB can also be used for its anticancer effects' by activating p53 and 5'AMP-activated protein kinase signaling pathways, which encourage cancer cells to undergo mitochondrial apoptosis [55-57]. Detergent properties and emulsifying capacity of cations are quite weakand they are quite expensive. In the previous studies, CTAB is not used alone to enhance solubility/bioavailability but also give cationic charge/sterical stabilization [58,59]. In CTAB-based solid dispersion formulations, the water solubility capacity was increased from 0.802±0.174 to 226.899±6.595, 432.595±6.022, 589.768±0.559 µg/mL, respectively.

Nonionic surfactants are surfactants without ionic character. Today, they are frequently used in the production of cosmetics, creams and lotions. The most widely used nonionic surfactants are Poloxamers®. Poloxamers are synthetic triblock copolymer. Poloxamers consist of two blocks of polyethyleneoxide and one molecule of polypropyleneoxide(PPO) in the form of A-B-A. Its general formula is Poly(oxy-ethylene)x-Poly(oxy-propylene)y-Poly(oxy-ethylene)x. Poloxamers® can be used as a gelling agent, emulsification and solubilizing agent[60]. Poloxamers are available under various tradenames, including Pluronic®, Kolliphor® and Lutrols®. Commercially, Pluronic triblock copolymers are offered in a variety of grades, with varying physical properties and molecular weights. The classes are defined as L for liquid, P for pulp, and F for flakes based on their physical definitions. The poloxamers 188 (F-68), 237 (F-87), 338 (F-108), and 407(F-127) are frequently utilized. The copolymer PEO106-PPO70-PEO106, also known as Poloxamer 407 (P407) or Pluronic F-127 (PF-127), which was employed in our study, contains 70% ethyleneoxide, which improves/increases its hydrophilic feature. The copolymer PF-127 has a molecular weight of 12000 Da, a PEO/PPO ratio of 2:1, is non-toxic, has a low viscosity below 4 °C, and at body temperature, forms a semi-solid gel [61].

Pluronics has been proven significantly enhanced dissolution and solubility. The fast dissolving tablet formulation containing gliquidone-Pluronic F68 SDs enhanced bioavailability 1.8 times compared to the marketed tablet [62]. Using the Pluronic F127 and F68, atorvastatin, solid dispersions were prepared by melting method. According to the results, dissolution was increased significantly (93% within 30 min) and bioavailability was increased 2.25 and 4 times compared to Lipitor® and pure drugs, respectively [7]. In the preparation of Pluronic based solid dispersions, Pluronic F127 is the dominantly used carrier compared to others. Solubility enhancement properties of Pluronic F127 has been proven in many studies [8,63,64].

In PF-127-based formulations, the water solubility was increased from 0.802±0.174 to 157.753±11.251, 440.032±54.223, 1389.715±29.727µg/mL., respectively. When the dissolution rates of the 5:1 formulation prepared with PF-127 and pure CoQ10 are compared, it is seen that PF-127 also increases the dissolution rate as expected. Among all surfactants, the surfactant that increases the solubility and dissolution rate the most is Pluronic F127.The solubility of the prepared formulations was given in Figures 2 and 3.

In order to quantitatively compare the solid dispersion efficiencies, the stability constant Ks was calculated as indicated in Equation 1, as specified in Section 4.3 and the constants are given in Figure 3. The magnitude of this constan tindicates the effectiveness of the carrier solubilization and PF-127 has the highest value among them (Figure 3).

The increase in the solubility maybe results of micellization of the surfactants, the transformation of the drugi nto an amorphous state and inhibition of recrystallization, the increase in wettability and homogeneous dispersibility in the carrier. But the solubilizing effect is mainly result of the micellization abilities of surfactants. Micellization is directly related to the CMC of the substances. For this reason, surfactants with low CMC value form micelleforms more easily, resulting in increased solubility of hydrophobic substances. CMCs of surfactants are respectively SLS > CTAB > PF-127 (CTAB 1 mM, SDS 8.25 mM, F127 0.357 mM) [65,66]. The sizes of solid dispersion-based micelles were found around 183.4-165.6 nm. Size of micelles has been seen no correlation with CMC. But it is correlated with a solubilit yincreasement in terms of Ks (Figure 3). Also, zeta potential was changed according to ionic charge of surfactants. Their charge is correlated according to their polar headgroups. SLS is quite anionic, CTAB is cationic and Pluronic F127 is slightly anionic. Pluronic F127 lesser had a lower negative value than SDS. It was related to the nonionic properties of PF127 (Figure 4). It is suggested that Coenzyme Q10 is solubilized by forming micelles when solid dispersions come into contact with water. The micellization effect is in proportional with CMC value of surfactants. Because of the lowest values, Pluronic F127 has been found most effective carrier for Coenzyme Q10.

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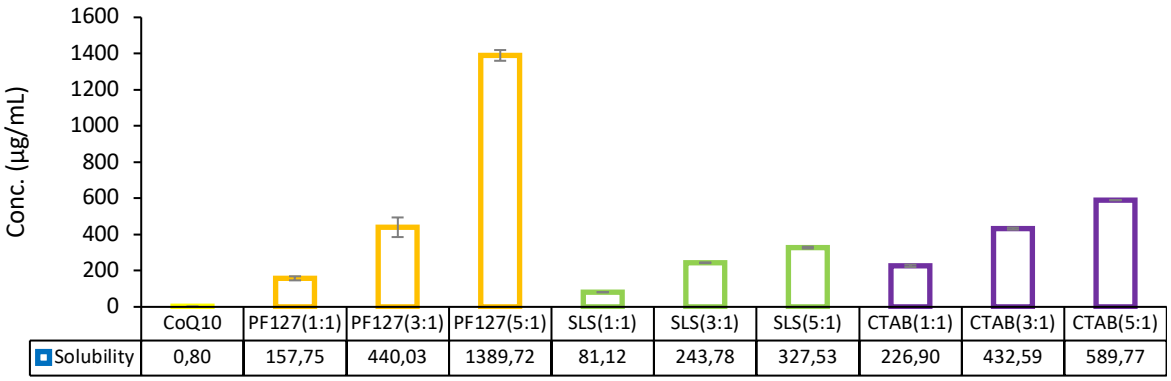

Figure 2. Solubility of pure drug and formulations (n=3)

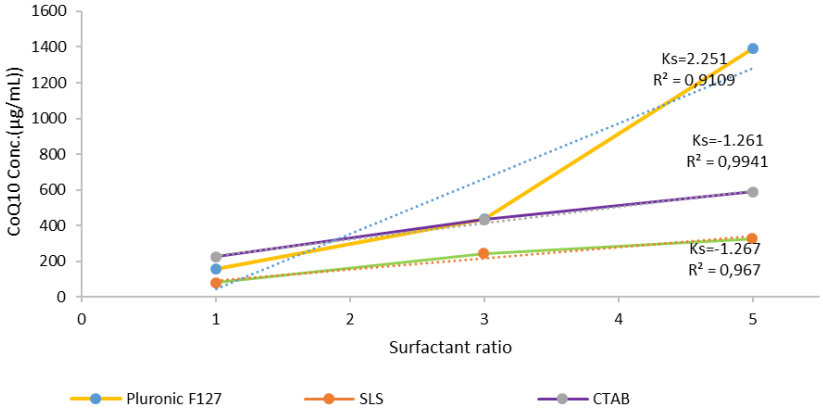

Figure 3. Solubility graphs of formulations.

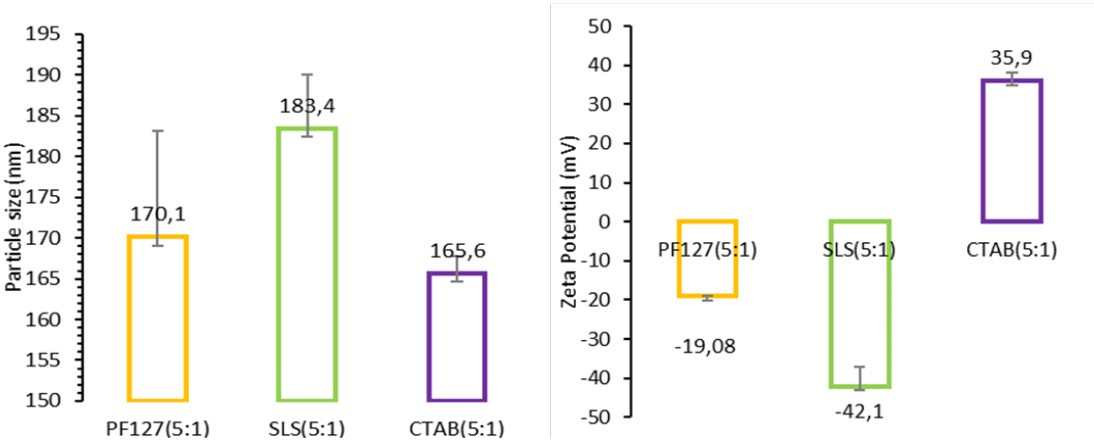

Figure 4. Particle size and zeta potential of formulations (5:1 ratio, Surfactant:Drug) (n=3).**2.2. DSC and FTIR studies**

In order to examine the interaction between the CoQ10 and excipients in the solid dispersions, DSC and FT-IR analyzes were carried out as indicated in Sections 4.5 and 4.6. The results obtained are shown in Figures 5 and 6. DSC and FT-IR analyzes were performed to examine the drug: excipient interactions of solid dispersions. Formulations with a ratio of 5:1 were used for comparison.

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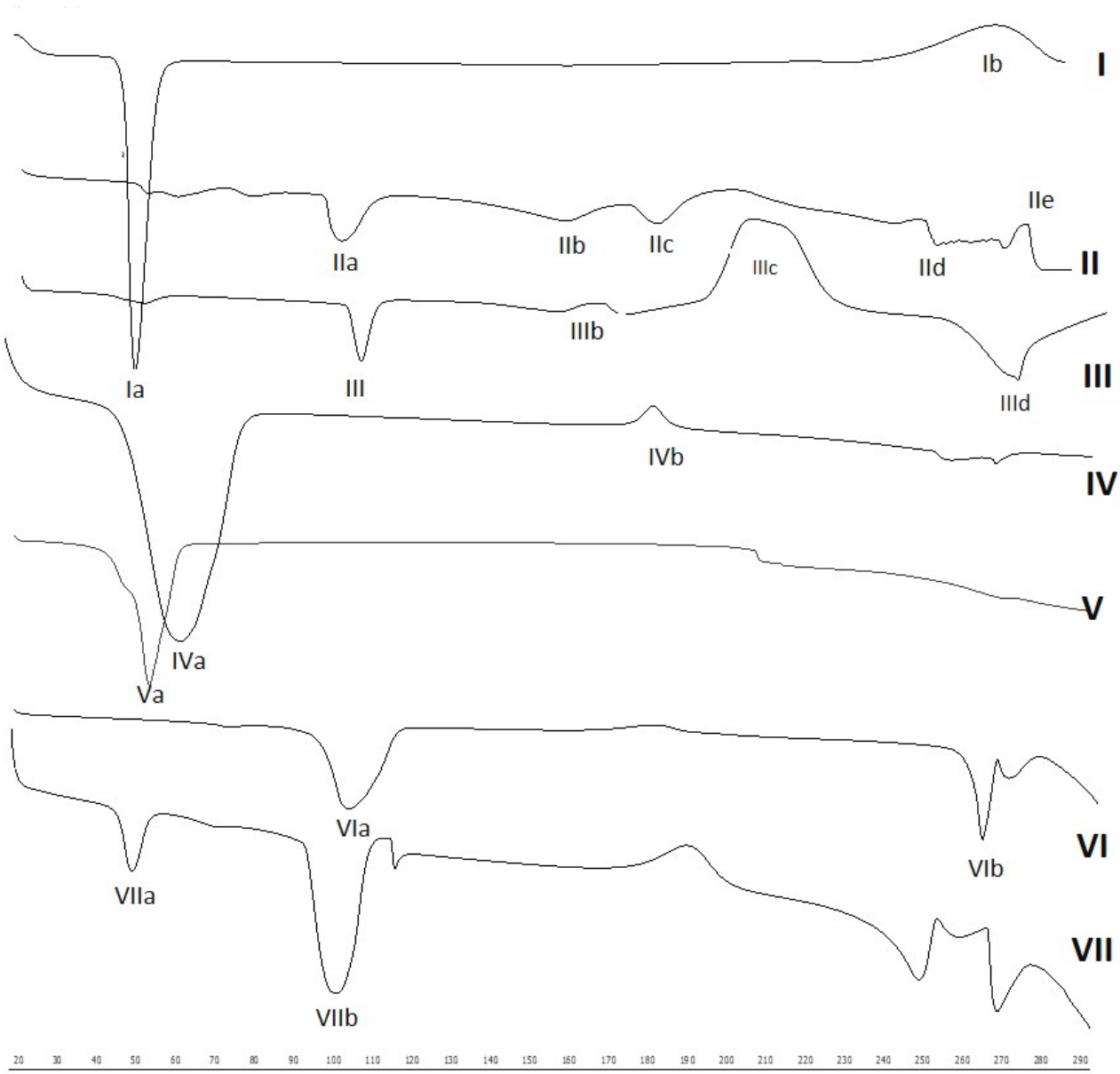

Figure 5. DSC thermograms (I:Coenzyme Q10, II:SLS, III:SLS:CoQ10 (5:1), IV: Pluronic F127, V: Pluronic F127:CoQ10 (5:1), VI: CTAB, VII: CTAB:CoQ10 (5:1).

When the DSC results are evaluated, the sharp end other micpeak is seen at 53°C (Ia) in CoQ10 thermograms and this peak belongs to the melting point of the substance indicating its crystalline nature [22]. The broad exothermic peak seen later at 273°C may be due to the destruction of some bonds or functional groups, structural depolymerization or destruction of polysaccharide chains. In the DSC graphs of SLS, end other mic peaks were observed at 107.29 (IIa), 165.35 (IIb), and 189.59 (IIc) °C and these are consistent with the literature[67]. But the characteristic melting point of the CoQ10 disappeared in the SLS-based SDs. This indicates that the drug has become amorphous. In evaluation of PF-127:CoQ10 (5:1) SDs thermogram, although the large end other micpeak of the surfactant occurs at 65°C (IVa), the peak of the drug is observed in the dispersion (Va). This peak also can belong to surfactant. The peaks of drug and surfactant may overlap because they are close. In CTAB:CoQ10 (5:1) solid dispersion, characteristic end other mic and exothermic peaks of CTAB and CoQ10 are observed even though their intensity decreases in the SDs (VII). The decrease in intensity may be due to amorphization, or it may be related to dilution due to the addition of other excipients.

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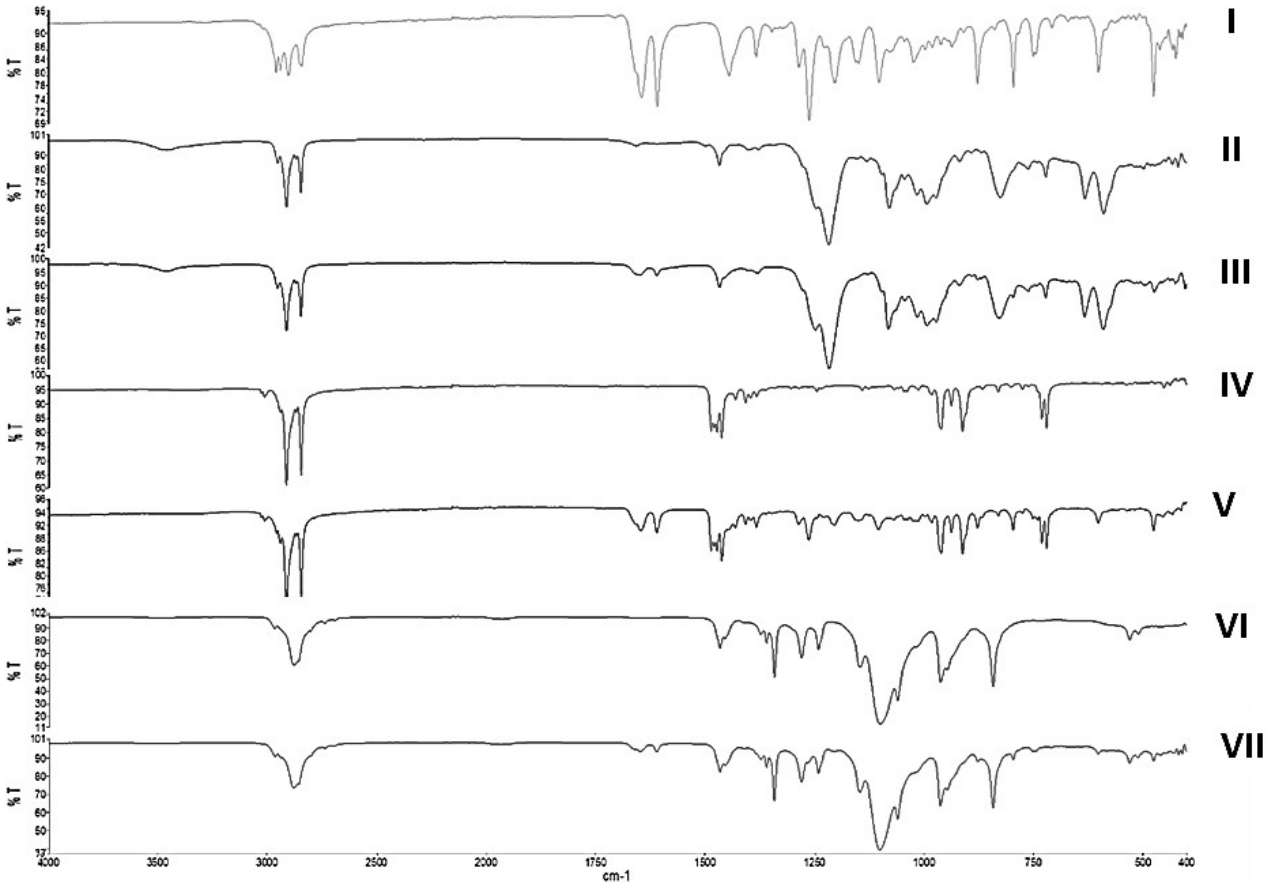

Figure 6. FT-IR results (I: Coenzyme Q10, II:SLS, III:SLS:CoQ10 (5:1), IV:CTAB, V:CTAB:CoQ10 (5:1), VI:Pluronic F127, VII: Pluronic F127:CoQ10 (5:1).

As it is mentioned above, amorphization is attributed to solubilization. However, thermodynamic instability makes them recrystallize. To prevent this, recrystallization inhibitors can be used to maintain this state. As it is seen in the thermograms, SLS was found most effective recrystallization inhibitor compared to other surfactants [51].

When the FT-IR spectra are examined, the peaks located at 1646-1610 cm^{-1} in the SLS:CoQ10 (5:1) SDs belong to the ketone carbonylpeaks of Coenzyme Q10. The peaks between 2944-2847 cm^{-1} are the peaks of C-H stretch bands belonging to CoQ10. Specific carbonyl peaks of Coenzyme Q10 in the solid dispersion are observed even though their intensity decreases. S=O tension band is observed between 1217 and 1246 cm^{-1} of SLS and it is also seen in theSDs.

In evaluation of PF-127:CoQ10 (5:1) SDs DSC thermogram, although the large endothermic peak of the PF-127 occurs at 65°C (IVa), the peak of the drug is also observed in the dispersion (Va). This peak also can belong to a surfactant or the peaks may overlap because of their close location. Inthe FT-IR spectra of PF-127:CoQ10 (5:1), specific carbonyl peaks of Coenzyme Q10 are observed even though their intensity decreases. The C-O voltage peak at 1099 cm^{-1} is dominantly available in the structure of PF-127 and PF-127-based SDs. The solid dispersion predominantly shows characteristic peaks of the surfactant. In solid dispersion, specific carbonyl peaks of Coenzyme Q10 are seen even though their intensity decreases.

In CTAB:CoQ10 (5:1) solid dispersion, characteristic endothermic and exothermic peaks of CTAB and CoQ10 are observed even though their intensity decreases in the SDs (VII). Thedecrease in intensitymay be duetotheamorphization of CTAB, or it may be relatedtodilutionduetotheaddition of otherexcipients. IntheFT-IR spectrum, specificcarbonylpeaks of Coenzyme Q10 areseeneventhoughtheirintensitydecreases. In CTAB:CoQ10 (5:1) soliddispersion, C-H stretchbendsbetween 2916 and 2848 $cm^{-1}$and C-H stretchbendsbetween 1486 and 1431 cm^{-1} of CTAB areobserved. Inthesoliddispersion, thepeaks of bothsubstancesareobserved.

When all the results are taken into consideration, peaks of the CoQ10 are seen except for the SLS SDs formulation. The decrease in their intensity indicates that the crystalline CoQ10 becomes semi-crystalline,

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indicating the moderate or no interactions between the drug and surfactant for the preparation of solid dispersion.

2.3. Dissolution rate studies

In the dissolution rate studies, 25% acetonitrile and 2% Tween 80 were used to ensure the sink condition. In the quantification method, the correct equation was obtained by the completed issolution of Coenzyme Q10 in this medium. In the dissolution rate studies, 2 mg of drug and drug-loaded SDs were subjected to the dissolution rate study for 24 hours (Figure 7).

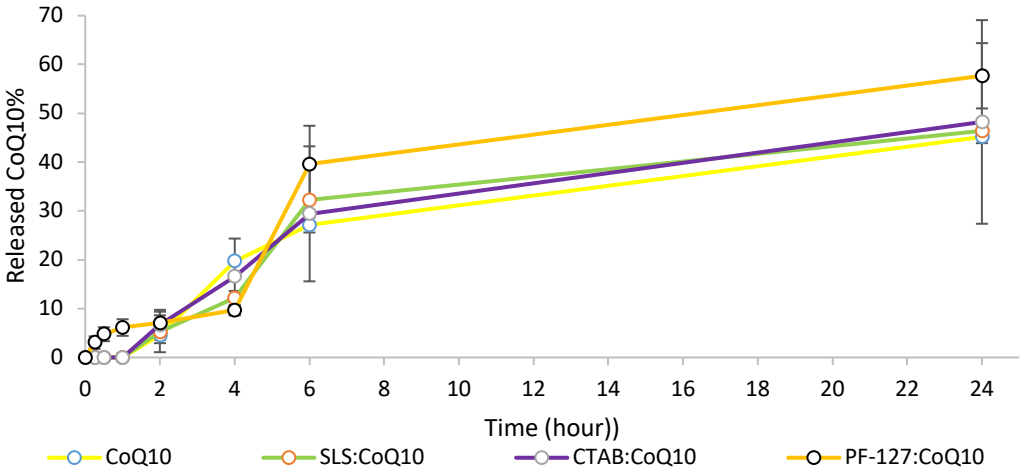

Figure 7. Dissolution of drugandformulations (5:1 ratio, Surfactant:Drug) (n=3).

Therearevariousmethodsfordissolution rate comparison, such as ANOVA-basedapproaches, ratio test procedures, multivariateconfidenceregionprocedures, model-dependentapproaches, bootstrap f2 method, ChowandKi'sMethod,andpairwiseprocedure[68]. Since the f2 similaritymethod, which is themostwidelyused, onlymeasuresthemean, it does not giveaccurateresults in results with high deviation [69]. For this reason, in our study, mean dissolution time (MDT), the mean residence time of the drug substance molecules in the dosage form (MRT), area under the curve (AUC) were calculated from the ratio test parameters. Theresultsaregiven in Table 1. High MRT andlow MDT indicatea slowerrelease rate. According to the average results, the highest MRT and lowest MDT in all formulations belong to pure CoQ10 but this value is not statistically significant ($p>0.05$). In addition, the AUC values of the CTAB and Pluronic F127-based formulations were statistically higher than the püre drug ($p<0.05$).

When Dissolution Efficiency (DE%) values were examined, an increase was observed in all formulations, but a statistically significant increase was found only in the Pluronic F127 formulation ($p<0.05$). This results is also compatible with the solubility enhancement effect surfactants. Pluronic F127 was found best in terms of solubility.

Table 1. Dissolution rate results (n=3)

Parameter	CoQ10	SLS:CoQ10	CTAB:CoQ10	PF-127:CoQ10
AUC	707.32±28.36	740.42±57.55	804.35±428.57	1048.57±233.83
MRT	10.21±0.20	10.40±0.24	10.06±1.66	9.23±0.73
MDT	8.39±1.03	7.21±0.33	6.99±2.11	7.20±0.81
DE%	29.50±0.012	30.85±2.40	33.51±17.86	43.69±9.74

The highest dissolution rate of Pluronic F127 is alsoc an be related to its lowest CMC value. Low CMC value also means good stability and micellization property for micelles. Therefore micellar structure remains without breaking when diluted with body fluids. Pluronic F127 has a good potential for micellization effect on the poorly soluble drugs. [70]

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3. CONCLUSION

In the study, various solid dispersion formulations have been developed to increase the solubility of poorly soluble Coenzyme Q10. While developing solid dispersion formulations, surfactants called third generation carriers were used by solvent evaporation technique. This technique is easy-to-operate, highly miscible and suitable for heat-sensitive drugs. While choosing the surfactants, formulations were formed by three type surfactants such as anionic, cationic, and nonionic according to their charges. Solubility studies showed that all surfactants have increased aqueous solubility of CoQ10. However, in the dissolution studies, Pluronic F127 has been found to be most potent surfactant significantly. Furthermore, FTIR and DSC results revealed that molecular interaction between the drugs and surfactants reduced drug crystallinity. In terms of crystallinity reducement, SLS was found best agent. As a result, our findings suggest that Pluronic F127 was the best candidate for increasing the solubility and dissolution rate of Coenzyme Q10. In further studies, Coenzyme Q10 loaded P-F127 based micelle formulations are developing by our groups.

4. MATERIALS AND METHODS

4.1. Materials

Cetyltrimethylammonium Bromide, Pluronic F127, and sodium lauryl sulfate was purchased from Sigma-Aldrich (Milwaukee, WI, USA). Coenzyme Q10 was purchased from Dibcr (Germany). All used solvents are HPLC grade.

4.2. Preparation of CoQ10 solid dispersions

CoQ10 SDs were prepared with different various surfactants bearing different ionic head group. In thepreparation of SDs, solvent evaporation method was used. Briefly, 10 mg of Coenzyme Q10 was dissolved in 4 mL of acetonitrile by sonication. After complete dissolution, the respective number of surfactants in different ratios (1:1, 1:3, 1:5) were dissolved in 0.5 mL distilled water and added to the drug solution mixing at 600 rpm to form solid dispersions. It was stirred under a fume hood for all night to evaporate the organic solvent and a solid mass was obtained. These dry solid dispersion formulations were then stored atthe 4-8 °C.

4.3. Phase solubility studies

The phase solubility studies were performed according to the method described by Higuchi and Connors[71]. Different amounts of SLS, CTAB and Pluronic F127 were used to prepare solutions in distilled water. An excess amount of CoQ10 and formulations were added to eppendorfs. The epperdorfs were placed and shaken at the 75 rpm and 37°C for 24 hours until they reached equilibrium. The 37 °C was chosen as a temperature to resemble the physiological temperature. After 24 hours, the excess amount of CoQ10 was ultracentrifuged at 25°C for 15 min at 13000 rpm (Hitachi CF-10, Japan) and then the samples were filtered through membrane filters (PTFE, Isolab, USA) with a diameter of 0.22 µm, diluted with acetonitrile, and analyzed by UV spectrophotometry at 274 nm (n=3).

In order to quantitatively compare the solid dispersion efficiencies, the stability constant K_s was calculated as shown in Equation 1. This constant indicates the effectiveness of the formulations.

$$Ks = Slope/(S_0\ (1 - Slope)) \quad \text{Eq.1}$$

S_o: The actual(intrinsic) solubility of the drug
Slope: Slope of the linear part of the phase solubility curve

4.4. Characterization of Solid Dispersions

4.4.1.Particle size distribution

When using surfactants, the solubilization mechanism is occurred throughthe formation micelles. For this reason, particle size, size distribution, and polydispersity indexes of SD formulation with the 1:5 drug:surfactant ratio were determined by dynamic light scattering (DLS) method using zetasizer (NanoSeries, Nano-ZS, Malvern Instruments, UK). Analyses were performed at 25˚C, equipped with a 4-mW He-Ne laser (633 nm). Hydrodynamic diameter (d.nm) was determined DLS at a scattering angle of 173°. Disposable zetasizer cuvettes were used for the measurement of nanoparticle suspensions and 3 replicates were made for each sample to obtain representative results.

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4.4.2.Zeta potential

The surface charge of the particles was automatically determined for the zeta-potential measurement using SD formulations with a 1:5 ratio by electrophoretic mobility on the zeta sizer (Nano Series, Nano-ZS, Malvern Instruments, UK) (n=3).

4.5.Differential scanning calorimetry (DSC)

Thermograms were obtained using Differential Scanning Calorimetry (DSC) equipment (Mettler-Toledo, Columbus, OH, USA) at 20°C/min between 20 and 300°C for compounds weighing between 2 and 10 mg. By contrasting the reference material (indium), the calorimetric behavior of the substance was examined. To exam interactions between the compounds, DSC thermograms of the drug, surfactants, and solid dispersions (5:1 surfactant:drug) were investigated.

4.6.Fourier transform infrared spectrophotometer (FTIR) analysis

IR spectra of drug, surfactants, and solid dispersions using 5:1 surfactant were taken. The measurement was made by placing a very small amount of sample on the diamond crystal of the device with the spatula tip.

4.7.Drug release studies

Drug release studies were carried out with a shaker water bath. In the study, formulation using surfactant at a ratio of 5:1 were used to compare. Pure CoQ10 or solid dispersions were put into the dialysis membrane (molecular weight cut off 12 000 Da, Spectrum Labs, CA, USA) by dispersed in 0.5-1 mL distilled water. These dialysis membranes were hydrated in ultrapure water 12 hours before starting the experiment and then transferred to the dissolution medium. The dissolution rate was carried out in 50 mL medium, at 37 °C, at 75 rpm. As a dissolution medium, PBS (pH 7.4) containing 25% (v/v) acetonitrile and 2% Tween 80 was used. Tween 80 and acetonitrile was added to ensure sink condition[29]. Samples in 1 ml volume were taken at 15., 30., 60., 120., 240., 360. minutes and 24. hours, respectively. The amount of fresh sample was replaced with fresh medium and analyzed spectrophotometrically at 275 nm (n=3).

Table 2. Equations of dissolution rate parameters.

Parameter	Equation
AUC, area under the dissolution curve	$AUC = \sum_{i=1}^{n} \frac{(t_i - t_{i-1})(y_{i-1} + y_i)}{2}$
MDT, Mean Dissolution Time	$MDT = \frac{\sum_{i=1}^{n} \overline{ti} \,.\, \Delta Mi}{\sum_{i=1}^{n} \Delta Mi}$
MRT, mean residence time of the drug substance molecules in the dosage form	$MRT = \frac{\int_0^t t\,(100 - y).\,dt}{\int_0^t (100 - y)\,.\,dt}$
DE, dissolution efficiency	$DE = \frac{\int_0^t y\,.\,dt}{y_{100}.\,t}.100\ \%$

n number of samplingpoints; t*i*th time point; $y_i$percentage of drugdissolved at time t_i; y percentage of drugdissolved at time t; $\overline{\overline{ti}}$ time at the midpoint between i and i–1; ΔM_iadditionalamount of drugdissolvedbetween i and i–1; k order of themoments of dissolutiontimes; y_{100} maximumpercentage of drugdissolvedoverthe time period 0−t

Various formulation parameters were tried to compare dissolution rates. For this purpose, the most used parameters, MDT, MRT and DE, were calculated with DDSolver software (Table 2) [68,72].

4.8. Statistical analysis

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SPSS (Version 20.0, Chicago, IL) was used for all statistical analyses. The mean value and standard deviation were calculated using descriptive statistics. Significant differences were considered when $p<0.05$.

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