Coenzyme Q10: Novel Formulations

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Coenzyme Q10 (CoQ10) was first identified back in the fifties by two groups, Festenstein et al. (1955) and Crane et al. (1957). Its name was chosen due to the fact that it is an ubiquitous quinone present in all cells and that its chemical structure comprises a quinone group with a variable number of isoprenyl units, being ten in the case of humans. Its reduced form is known as ubiquinol and the oxidized one as ubiquinone. Both forms coexist and through sequential redox reactions serve to regenerate each other (Q cycle).

Keywords: Coenzyme Q10 ; ubiquinone ; mitochondria

1. Liposomes

Owing to its remarkable properties as an anti-fatigue, immunostimulating, and antioxidant molecule [1], CoQ_{10} is nowadays widely used as a functional food, drug, and health supplement. Clinically, it is also prescribed for cardiovascular disease, diabetes, viral hepatitis, cancer and many other patients [2]. However, as previously discussed, traditional CoQ_{10} formulations are not satisfactory, since they fail to increase CoQ_{10}'s low oral bioavailability. CoQ_{10}'s uptake is compromised due to its poor water solubility, instability to light, and thermolability [3]. For this reason, the development of alternative formulations has been a recurrent topic of study in the past few years. Numerous alternatives to the classic CoQ_{10} formulations have been proposed, like solid dispersion systems [4], nanoparticles [5], cyclodextrin inclusion compounds and microcapsules [6]. However, one of the most promising approaches has been the preparation of nano-liposomes with long circulating elements that improve the stability, prolong circulation times, and increase the bioavailability of CoQ_{10} [7]. The main drawback of this liposomal formulation is its high instability. As is widely known, lipid-based vectors are prone to aggregating and forming clustered complexes with larger dimensions [8]. Moreover, the encapsulation efficiency was hindered by the constant leakage of cargo through the lipid layers. In order to implement stability, the lyophilization of liposomes through a freeze-drying procedure was suggested. The lyophilized particles showed stable quality characteristics during long-term storage [9].

2. Self-Nanoemulsifying Delivery System

CoQ_{10}'s low gastrointestinal absorption and low oral bioavailability are a consequence of its low intestinal permeability and high molecular weight. Self-nanoemulsifying CoQ_{10} delivery systems have been developed to face the challenge of this drug's oral administration by increasing its dissolution in the gastrointestinal tract (GIT) [10]. Self-nanoemulsifying drug delivery systems (SNEDDS) can be defined as an isotropic and thermodynamically stable mixture of an oil, a surfactant, a co-surfactant, and a drug that forms nanoemulsion droplets of a reduced size (<100 nm) when subject to dilution in an aqueous medium under gentle agitation, similar to the gastric movements of the GIT [11]. The fundamental standard of these SNEDDS is that when the emulsion is formed in the GIT of the patient, the drug is presented in a solubilized form inside nano-sized droplets that provide a larger surface area for enhancing the drug's release and absorption [12]. This novel approach to increase CoQ_{10}'s dissolution and absorption has proven successful in recent studies, in which a daily intake of 100 mg of CoQ_{10} SNEDDS is proposed as a sufficient dietary supplement to compensate for low CoQ_{10} levels in patients suffering from various diseases [13].

3. Novel Lipid-Free Nanoformulation

As previously mentioned, several formulations have been developed to increase CoQ_{10}'s bioavailability: an oil solution and a suspension system [14], a lipid and surfactant-based emulsion [15], and a solid dispersion system [16]. However, the bioavailability of CoQ_{10} in these remains low. Thereafter, the next step forward was to develop lipid-free self-emulsifying drug delivery systems (SEDDS) [13], or nanoemulsions [17]. Traditional CoQ_{10} formulations make use of lipid-based delivery systems, because these present several benefits: they increase drug solubility in intestines, recruit lymphatic drug transport or modify enterocyte-based drug transport and disposition [18]. Nevertheless, many other factors like dispersion

rate, degree of emulsification, particle size or drug precipitation upon dispersion have a negative impact on the efficacy of lipid-based delivery methods. For this reason, novel studies have focused on the development of lipid-free nano-CoQ_{10} systems. One of the most promising approaches in the field achieved the development of CoQ_{10} nanoformulations with various surfactants but no other lipids. These nano-CoQ_{10} particles were modified with surfactants using hot high-pressure homogenization (HPH) [5]. Such surfactants were intended to alter cell membrane integrity and tight junctions [19] as well as inhibit efflux transporters like P-gp [20] so that permeability would be enhanced. Subsequent studies in rats demonstrated that the orally administered lipid-free nano-CoQ_{10} significantly improved CoQ_{10} bioavailability in comparison to common CoQ_{10} powder suspensions, mainly due to the action of surfactants. Thereby, lipid-free nano-CoQ_{10} complemented with surfactants like PEG40 hydrogenated castor oil (PHCO) or TPGS are a promising alternative for CoQ_{10}'s clinical application.

4. CoQ_{10}-Loaded Oleogels

As previously stated, CoQ_{10} is practically insoluble in aqueous solutions, therefore, its oral or intestinal absorption is slow and extremely inefficient. However, its bioavailability can be substantially modified by using an adequate formulation for its administration. Since CoQ_{10} is fat-soluble [21], its absorption is enhanced when taken with a meal having a high oil/fat content. In line with this, oil-based formulations, such as emulsions where CoQ_{10} is dissolved in an oil-dispersed phase, have proven to be successful for CoQ_{10} delivery. The research in the field indicates that solubilized CoQ_{10} formulations present a much higher bioavailability than non-solubilized powder-based CoQ_{10} products [22] meaning that a higher CoQ_{10} plasma concentration could be achieved using lower doses of solubilized CoQ_{10} formulations than those used with non-solubilized ones. Another factor supporting the use of solubilized formulations rather than traditional ones is the fact that mitochondrial and neurodegenerative disorders' patients commonly struggle to swallow [23][24]. Therefore, it is hard for them to deal with traditionally big CoQ_{10} tablets or powder-filled capsules. In light of this evidence, the research is now focused on developing formulations with CoQ_{10} solubilized either in liquid or jelly matrixes. Among the studies carried out in this direction, it is worth to point out the development of ethyl cellulose (EC)-oleogels for high-dose CoQ_{10} oral administration (1 g of CoQ_{10} per 5 g oleogel-disk) [25]. Medium-chain triglyceride (MCT) oil was used to dissolve CoQ_{10}, since it is known to be the only fat that people with the inability to absorb or digest conventional fats tolerate [26]. Moreover, two surfactants were evaluated to modulate the mechanical properties of the gels. SMS proved to be more convenient than lecithin, since it allowed a higher stability to oxidize the MCT oil and a better enhancement of CoQ_{10} stability while lowering the syneresis in the final oleogels. Moreover, SMS-containing oleogels showed higher thermal stability than lecithin-containing ones.

The novelty of the aforementioned study lies in the fact that the SMS-containing oleogels allowed loading exceptionally high doses of soluble CoQ_{10} in soft gel structures that reduce the swallowing discomfort for patients. Additionally, the number of dosage units per day could be reduced since each of these oleogels provides a high dose of CoQ_{10}. According to the authors, the CoQ_{10} dissolved in MCT was stable for 12 months when immobilized into the oleogels. Thereafter, neither storage nor distribution is a problem for the future translation of this formulation to the clinical practice.

5. Novel Water-Soluble CoQ_{10}

The use of CoQ_{10} as a functional food is full of promise, since its properties have the ability to beneficially influence body functions, promoting well-being and health as well as reducing the risk of diseases [27]. However, high lipophilicity of this molecule restrains its use as a food-enriching product, especially in aqueous-based preparations. To overcome this barrier, CoQ_{10}'s water solubility has been increased by encapsulating it in β-cyclodextrin inclusion complexes [28]. This novel patented formulation is available as Q10Vital and has proved to be stable and well-soluble in diverse aqueous media. A bioequivalence study has confirmed the improved bioavailability and efficacy of this novel CoQ_{10} material in comparison to the traditional soft gel capsules containing CoQ_{10} in soybean oil, which has been the most widely used formulation up to this moment in Europe [29]. According to that study's results, the mean plasma concentration of CoQ_{10} was highest in the individuals who consumed the liquid Q10Vital formulation, followed by those who took the Q10Vital powder. Moreover, the levels of CoQ_{10} were significantly lower in those who had soft gel capsules. The novel formulation presented higher standard deviations in pharmacokinetics assays owing to its sensitivity to individual pH differences, especially in the gastrointestinal tract. The acidic pH of such an environment may affect the interactions between the guest (CoQ_{10}) and the host (β-cyclodextrin) molecules. This inconvenience can be resolved by the co-administration of the formulation with an appropriate food matrix that reduces its pH sensitivity, stabilizes its solution in the GIT, and thereby improves its absorption [30]. All in all, CoQ_{10}/β-cyclodextrin complexes have proved to significantly increase water solubilization of CoQ_{10} and, hence, its gastrointestinal absorption. For this reason, this novel formulation,

either in its liquid or powder form, represents a more efficient CoQ_{10} delivery method for both the food and pharmaceutical industries.

6. Micellization of CoQ_{10} by Caspofungin

Since lipophilicity seems to be the main barrier for the parenteral delivery of CoQ_{10}, there is a rising interest in the development of water-soluble CoQ_{10} formulations. One of the most famous advances in the field was the formulation of micellar CoQ_{10} nanoparticles [31]. The formation of these hydrophilic particles was mediated by an FDA-approved drug, caspofungin (CF). Despite its moderate surfactant activity, CF successfully solubilizes CoQ_{10}, yielding micellar nanoparticles as a result. These nanoparticles were on average smaller than 200 nm in diameter, being therefore ideal for intravenous delivery, since such a reduced size allows for long circulating times and sufficient extravasation and tissue uptake [32][33]. The critical micelle concentration (CMC) is the parameter that reflects the stability of micelles following their dilution in blood. A CMC in the low millimolar range is desirable in drug-carrying compounds, since it indicates high stability after intravenous administration [34]. The CMC of these CF/CoQ_{10} particles is close to 50 µM, indicating that they are unlikely to dissociate rapidly upon injection. According to the authors of the study, the CF/CoQ_{10} formulation can be safely administered to mice via an injection, CoQ_{10} successfully reaching the desired tissues. The highest plasma CoQ_{10} concentration detected following intravenous CF/CoQ_{10} administration (8.6 mg/kg of body weight) was >160 times higher than the endogenous CoQ_9 level (CoQ_{10} being undetectable). The studied tissues (liver, kidney, heart, skeletal muscle, spleen, lung, and brain) also presented significantly higher CoQ_{10} levels after 10 daily intravenous doses of CF/CoQ_{10} (8.612 mg/kg of body weight). Nonetheless, further research on the uptake differences between tissues should be conducted.

Since both CF and CoQ_{10} are already extensively used in clinical practice and have favorable safety profiles, it is hypothesized that there should not be obstacles for CF/CoQ_{10} micelles' clinical development and approval for treatment of CoQ_{10} deficiencies and related diseases. However, patients' discomfort is the main drawback of this therapeutic strategy. As claimed by the authors of the study, CoQ_{10} uptake in organs was cumulative, the reason why several daily injections were required to reach the desired intra-organ CoQ_{10} concentration. Facing the prospect of several injections a day might be an ordeal for many patients [35], the reason why alternative administration procedures should be proposed for this therapy to be unconditionally appealing.

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