A Review of the Delivery System of Coenzyme-Q10 Based on Nanotechnology

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Abstract: Coenzyme-Q10 is an important electron carrier and antioxidant component participate in respiration process and universally present in human cells. A lot of researches indicated that the deficiency of coenzyme-Q10 may associated with many diseases in various organ. Although coenzyme-Q10 has been proved to be endogenous, its supply as food or drug can also alleviate or cure those diseases. For decades, researchers are trying to improve the method of coenzyme-Q10 intake facing the difficult brought by its low bioavailability as its lipophilic and unstable nature. Fortunately, recently introduced transport carriers prepared by nanotechnology with lipid as basic matrix have drawn increasingly attention. This paper summarized and classified several nano-carriers from recent reports, introducing their advantages, disadvantages and application in medicine.

1. Introduction
Coenzyme-Q10, the ubiquinone, is a universal component present in cellular membrane system, a non-protein co-factor which consists of a quinone ring and a 10-unit isoprene chain. It undertakes important electron carry function as part of electron transport system across inner mitochondrial membrane from which cells convert energy in carbohydrates into ATP that can be utilized in bio-process. To fulfill this purpose, coenzyme-Q10 circles between two forms, oxidized ubiquinone and ubiquinol, after accepting electron or reduced, by which H concentration gradient is created. Those biochemical features of coenzyme-Q10 reveal its biofunction: act as electron carrier in respiratory process such as accelerate ATP as well as energy production, promoting cardiovascular function, and as potential antioxidant (coenzyme-Q10H2), eliminating free radical protect the lipid membrane by prevent LDL oxidation. Other research also suggests that coenzyme-Q10 can improve endothelial function by increase NO bioavailability and strengthen non-specific immunity respond [1-2].

Fig. 1 The molecular structure of coenzyme-Q10
As an endogenously synthesized bioactive compounds, the deficiency of coenzyme-Q10 may be the natural decrease with aging or indicate certain disease, for example heart failure. However, such deficiency can be compensated by exogenous intake. There is research suggests that long-term intake of coenzyme-Q10 may alleviate the symptoms and be potential treatment for numerous disease, for example: heart disease, arteriosclerosis, hypertension, angina, arrhythmia, Parkinson’s disease, stroke-like episodes (MELAS) syndrome, and diabetes. Other function includes: membrane stabilizer, positive effect on calcium channels, and tumor regression effect. Some even recommend health people to intake coenzyme-Q10 to maintain health and prevent disease [2].

Because coenzyme-Q10 has wide variety of function and positive effect on heart, brain, neuron and other system with low incidence of side effect, coenzyme-Q10 as an over-the-counter supplement has drawn increasingly attention of food, cosmetic and medical industry.

Despite of its nature of being lipophilic, coenzyme-Q10 has limited oral bioavailability because of hydrophobicity and large molecular weight. The absorption of coenzyme-Q10, similar to the Vitamin E, mainly occur in the intestine. With chemical nature resemble lipid, coenzyme-Q10 firstly incorporates into chylomicron via lymphatics than it enters the circulation ready for the further utility. However, those process depends on the dissolution at the first place. As a result, solubilized coenzyme-Q10 will have better absorption, and taking up coenzyme-Q10 with fatty meal is recommended as digestion of lipid also promotes the digestion of coenzyme-Q10[3]. Other features effect the absorption of coenzyme-Q10 includes the reliance on multiple transporter and variation in permeability in GI tract [4].

Furthermore, coenzyme-Q10 has poor chemical stability as it has unsaturated double bond, when exposed to air, it also degrades easily due to sun light, UV light and heat.

To solve the problem of low bioavailability, bring by its hydrophobicity, many new technologies were invented to ameliorate the water solubility of coenzyme-Q10, meanwhile improve its stability to light, heat and oxygen, some example includes nanotechnology, emulsification, cyclodextrin complexation technique and chemical combination. Contrast to the others, the delivery carrier prepared using nanotechnology has extremely small to enable the pass of coenzyme-Q10 through the cell membrane and achieve the goal of target and controlled release. The nanocarrier also has higher encapsulation efficiency and load capacity which offer coenzyme-Q10 better stability and bioavailability.

Recently, via nanotechnology, delivery carrier like nano-complex, nanoemulsion, nano-liposome, nano-gel and solid lipid nanoparticles were prepared using material like starch, polysaccharide, lipid, and protein, in addition to the advantages of being manometer size carrier, those formulation are prior in the light of high biocompatibility, biodegradability and non-toxic property. Therefore, coenzyme-Q10 delivery carrier based on natural bio-macromolecules and nanotechnology has very broad application prospect [5].

2. Delivery system of coenzyme-Q10

2.1. Liposome

Liposomes are self-assembled by lipid (mainly phospholipids and cholesterol) to form a bilayer membrane structure with properties resembling the cell membrane. The micro-hydrophilic environment inside it can carry hydrophilic substances, while the hydrophobic substances can be carried in the hydrophobic cavity between the bilayer. Due to their unique structure and properties, liposomes have a broad application prospect in the fields of medicine, food and cosmetics. The liposome used for carrying functional active substances is quite micro in size even can reach the nanometer level. The thickness of the wall of vesicle structure of nanometer liposomes is usually only 5-7 nm. By solvent injection method, using lecithin as material, coenzyme-Q10 liposomes of particles sizes ranging from 150nm to 200nm were prepared, with encapsulation rate up to 96.2% [6]. The nanoliposome of coenzyme-Q10 prepared using soybean phospholipid as the material has particle size of 166.0nm and encapsulation rate of 93.2%. The samples could be stored for 3 months after freeze-drying and remains stable. Another method called Rapid Expansion of Supercritical Solutions (RESS) produced Coen-
zyme-Q10 nanoliposomes which has particles size only 20-40 nm while encapsulation rate more than 90% [8]. Compared to other nano-transport carriers, liposomes can penetrate the membrane easily and transport coenzyme-Q10 directly to the mitochondria thanks to their unique bilayer membrane structure. However, the nanoliposomes also have own defects, such as poor stability of the nanoliposome dispersion solution and limited resistance to acidic base hot oxygen and metal ions. Therefore, many researchers seek methods to improve the interfacial properties of nanoliposomes, such as adding polysaccharides or small molecules to modify nanoliposomes to increase their physical and chemical stability. Expect for the chitosan, sodium alginate is also a commonly used material in nanoliposome modify. Research shows that sodium alginate modified liposomes have significantly improved thermal stability, which remains stable when heating under 40 degree for five day. After digestion in a simulated stomach environment for two hours, the retention rate of coenzyme-Q10 for modified liposomes increases by 16% compared to that of non-modified liposomes, which means more coenzyme-Q10 could enter the small intestine, increasing the chances of absorption by the body [9].

2.2. Solid lipid nanoparticles
Solid lipid nanoparticles have been drawing increasingly interest since 90s in last century. Using solid lipid core as basement for delivery carrier, it usually prepared as spherical particles with average size between 50-500nm, with inner part incorporate lipid soluble active drug component. To maintain solid in room temperature, the oil phase matrix of solid lipid particles usually uses lipid with higher melting points. The term lipid here are defined broader, including: natural glycerin stearate, animal fat, long chain fatty acid, bee wax etc. To prepared the SLNs, firstly, the solid oil and active substances are melted by heating, and then mixed with water to form a water-in-oil emulsion according to certain proportion. Then it can be formed by cooling after ultrasound or high-pressure homogenization. Emulsifier are needed during this process to stabilize the lipid solid. Natural emulsifier which used widely includes lecithin, saponins, rhamnolipid, alkyl glycosides and so on. Those lipid matrix and emulsifiers, as their resources naturally occurred, give solid lipid nanoparticles well biocompatibility and biodegradability and reduce the possibility of acute and toxic reaction in vivo [5]. Solid lipid nanoparticles can be good carrier for coenzyme-Q10 due to its lipophilic property. Through the transport of solid lipid nanoparticles, the dispersion of coenzyme-Q10 in the water phase was increased from less than 0.1% to 1.0%, and the encapsulation rate of solid lipid particles of coenzyme-Q10 was very high, close to 100%. The effect of coenzyme-Q10 in vivo was evaluated by animal model experiments, and the results showed that the absorption rate of coenzyme-Q10 in solid lipid particles was about three times higher than that of direct oral coenzyme-Q10 [10]. Solid lipid nanoparticles loaded with coenzyme-Q10 were prepared by the method of high shear homogenization, with particle size of 152.4 nm, potential -13.67 mV, and transmission electron microscope observation showed that coenzyme-Q10 is in non-crystalline form in the solid lipid nanoparticles [11]. Despite the fact that many advantages present showed by solid lipid nanoparticles in their use as transport carrier of coenzyme-Q10, such as higher rate of encapsulation efficiency and higher load and bioavailability, solid lipid nanoparticles nevertheless have some demerits. For example, the lipid phase in the particles can stay in solid form only when it reaches certain degree of crystallinity, and its commonly ordered crystal form leaves limited space for coenzyme-Q10 loading, which can influence its encapsulation efficiency. During preservation, solid lipid crystal form experiences the transform from α type to β type and β’ type, with the crystallization becomes more and more order, squeezing the coenzyme-Q10 that was originally encapsulated in the solid lipid particles and even result in leakage.

2.3. Nano-structured lipid carrier
In order to remedy the deficiency of solid lipid particles, researchers have developed a new nano-transport carrier, named nano-structured lipid carriers, which can also be considered as the second generation of solid lipid particles. Nano-structured lipid carriers replace the original solid lipids with semi-solid or semi-liquid mixed lipids. In this way, lipids formed can be more disordered, leaving a
relatively larger space for coenzyme-Q10, which can lead to better encapsulation and avoid leakage during storage. The newly developed Ultra-small nano-structured lipid carrier has particles size only 80 nm, it has as many as 3 times loading capacity compared to the normal nano-structured lipid carrier [12]. Research has shown that nano-structured lipid carriers loaded with coenzyme-Q10 are more efficient in bioavailability and can effectively eliminate oxidative free radicals in the body. Since the main matrix of nano-structured lipid carriers and solid lipid nanoparticles are lipid, the metabolism in vivo after oral administration is considerable safe. The lipid digestion in human gastrointestinal tract can facilitate the formation of chylo micron of coenzyme-Q10, which can increase the bioavailability significantly, and produce fatty acid and energy at the same time. Nano-structured lipid carriers have very small particle size hence a good penetrating effect to the cell membrane, which can deliver bioactive substances into the pathological cells and promote their apoptosis. Nano-structured lipid carriers, which incorporate many advantages of solid lipid nanoparticles, nano-emulsion and liposomes, such as permeable, dispersibility, high encapsulation rate and high loading capacity, are a kind of nano-transport carriers with great development potential and application prospect.

3. Application of coenzyme-Q10 in the health products and medicine
Coenzyme-Q10 is a vital part in the electron transport system of aerobic respiration and a common antioxidant is ubiquitous in almost every cell in human. Its properties determine the fact that the deficiency of coenzyme-Q10 is associated with a range of diseases. Fortunately, the extra exogenous supply may alleviate or cure various type of disease in the same time. Newly developed coenzyme-Q10 carriers use lipid as fundamental component could facilitate such treatment.

Coenzyme-Q10 has a series of physiological benefits, including anti-oxidative activity, improving immunity, delaying senescence and enhancing myocardial function. For decades, fundamental research and clinical trials about coenzyme-Q10 have been carried out and deepen, theory study has also promoted the development of market. Since 2003, when Food and drug administration (FDA) of USA officially approved coenzyme-Q10 as a food additive, more than 200 health food and drug products have been put into market which contain coenzyme-Q10 as a functional component. According China's food and drug administration (document no. 566 in 2009), coenzyme-Q10 can only be used for health food, and the daily consumption shouldn’t exceed 50 mg. Recently, the ministry of health has accepted the application of coenzyme-Q10 as a new resource food. In the future, Coenzyme can be applied not only to health food, but also to common food. At present, the incidence of cardiovascular diseases such as hypertension, hyperlipidemia and coronary heart diseases increase with the increase of life standard. “Prevent first” has become a consensus. As a result, coenzyme-Q10 nanocarriers have great potential and prospect in the development and utilization of health food. In addition to improving the solubility, dispersion and stability of coenzyme-Q10, these nanocarriers can also be used to prepare different types of products with unique physical and chemical properties.

In the light of cardiovascular diseases, supply of coenzyme-Q10 has been proved have positive effect in many conditions. Researchers have prepared coenzyme-Q10-loaded liposomes to test on the rabbit with myocardial infarction. After the intracoronary infusion of Q10 liposomes, the irreversibly damaged fraction in myocardium of rabbits has reduced significantly [13]. Besides pharmaceutical administration, coenzyme-Q10 is also added into cosmeceutical preparations. There are many researches regarding its dermal effect: Jiang Xiao and others prepared coenzyme-Q10 loaded nanostructured lipid carriers via high pressure microfluidics technique. After a several of tests, this formulation has particle size 151.7nm, further drug loading experiment shown better light stability and prolonged release with epidermal accumulative uptake 10 times than coenzyme-Q10 emulsion [14].

Thanks to their minimal size, nano-structured lipid carriers or solid lipid nanoparticles are able to penetrate through the skin and reach to the deeper tissue. Furthermore, in a study use human dermal fibroblasts, nanostructured lipid carriers can significantly reduce cell viability under the condition with or without ultraviolet-A explosion. However, nano-structured lipid carriers loaded with reduced form coenzyme-Q10 can maintain cell’s viability regardless of the irradiated or radiated condition.
4. Conclusion
Coenzyme-Q10 can bring many advantages to human health if added as supplement for medical purposes and it has already been used in pharmaceutical and cosmetic industry. Newly research regarding the transport carrier with particle size falling into nanoscale provides potential method to overcome its inherent limit and improves its bioavailability. The liposome, solid lipid nanoparticles and nano-structured lipid carrier has demonstrated their ability and potential prospect in medicine, especially in the development of topical dermal formulation. The results of those study suggest better bio-tolerance, epithelial penetration, stability, higher encapsulation efficiency and so on. However, despite those advantages, the hiding problems cannot be ignored. First of all, the exist of cytotoxicity should not be underestimated as the impair to cell viability is reported in some papers. Additionally, there are some factors which may influence the characteristic of nanocarriers remain unclear, including the particles size, storage and preparation condition, delivery system in vivo and individual variations. The particle size cannot be too large, as it would affect its penetrability, neither could it be too small, otherwise the drug particle will be prone to uptake in other tissue and so cannot reach to the target site. Another problem is that those research only limited in the laboratory, needs future study on how to put those research achievements into large scale production. And further research could also focus on targeting therapy and improves coenzyme-Q10’s production, for example from animal, microbe or plant resource. All in all, delivery carrier of coenzyme-Q10 based on nanotechnology is a promising field that should be subjective to more specific research.

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