Improving the bioavailability of coenzyme Q10

From theory to practice

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ABSTRACT: Coenzyme Q10 (CoQ10) is a natural substance that is present in all human cells and plays a fundamental role in converting energy from carbohydrates and fatty acids, while it is also a very effective antioxidant. CoQ10 is insoluble in water and is poorly absorbed in the gastrointestinal tract. Its use in functional food is therefore very limited. Yet by modulating the formulation its bioavailability can be modified significantly. One of first successful strategies was to use an emulsion system. Absorption has been further improved by increasing the solubility in water, such as in inclusion complex of CoQ10 with β-cyclodextrin, Q10vital - used widely in the food industry where bioavailability reaches over 400 percent the bioavailability of crystalline CoQ10.

INTRODUCTION

Coenzyme Q is 2,3-dimethoxy-5-methyl-6-polyisoprene parabenzoquinone, also known as ubiquinone. It is naturally present in all membranes of living cells (1). The predominant form in most mammalian cells is Coenzyme Q10 with a tail, composed of 10 five-carbon isoprenoid units. It plays a central role in the mitochondrial respiratory chain as a carrier of electrons from complex I and II to complex III, a key part in the oxidative phosphorylation process, and it is responsible for converting energy from carbohydrates and fatty acids into an energy-rich biological molecule - ATP - which drives cellular machinery and synthesis (2). Apart from its essential role in energy conversion, CoQ10 is also a very effective antioxidant. Its antioxidant properties were discovered over 40 years ago (3) and were studied extensively *in vitro* and *in vivo*. Ubiquinoles can react with oxygen free radicals preventing damage to biologically important molecules as well as the peroxidation of lipids and are also capable of functioning synergistically with other antioxidants. A key advantage of CoQ10 lies in its presence in the mitochondria, the main source of free radicals (oxidative stress). For this reason, it can be more effective than other antioxidants which are more evenly distributed throughout a cell. Intracellular synthesis is the major source of CoQ10. Mevalonate is one of the precursors of CoQ10, which is also included in the biosynthesis of cholesterol. Various types of food provide an additional source of CoQ10 to the body, yet these sources contribute just 3-5 mg CoQ10 per day in people's diets in Western countries (4). The highest concentration of CoQ10 is found in tissues with high energy conversion such as the heart, kidney and liver (1, 5). Only 5-10 percent of total CoQ10 is located in cytosol, while there is about 50 percent in mitochondria, making it very accessible to free radicals that are mainly formed during the oxidative phosphorylation process (6). It is mostly present in a reduced form (ubiquinol), except in the lungs and brain where the oxidised form is predominant (5) (Figure 1).

CLINICAL ASPECTS

The efficiency of CoQ10 biosynthesis decreases progressively with increasing age (1). CoQ10 deficiency has also been observed in various medical conditions (7) and in people with specific lifestyles (i.e. vegetarians, smokers) or drug therapies. As CoQ10 shares its biosynthesis pathway with cholesterol, this process is significantly weakened in people using statins, cholesterol-lowering drugs. Statins competitively restrict the conversion of HMG-CoA into mevalonate, a cholesterol precursor, but unfortunately mevalonate is also the precursor of a dozen other end-products, including CoQ10 (8). The vital role of CoQ10 has been established in various clinical aspects by a number of preclinical and clinical trials. Cardiovascular disease is the leading cause of morbidity and mortality in the Western world and there is evidence to support the therapeutic value of CoQ10 as an adjunct to standard medical therapy for congestive heart failure (9). Oral CoQ10 has been shown to improve functional capacity, endothelial function and left ventricular systolic function in advanced chronic heart failure without any side effects. The use of CoQ10 is also suggested as an adjuvant therapy for angina and hypertension. Further, clinical trials suggest that supplemental CoQ10 can slow the functional decline in various neurodegenerative disorders, such as Huntington's disease, Friedreich's ataxia and particularly Parkinson's disease (10). A deficiency of CoQ10 is also common with migraine patients and the preventive treatment of migraine headaches has been studied successfully (11). The supplementation of CoQ10 can improve the tolerability of cancer treatments (12), although further investigation is needed. In individual cases, the partial or complete regression of cancer has also been observed in relation to CoQ10 supplementation (13). In addition, the beneficial effect of CoQ10 is also reported in many other conditions (14).

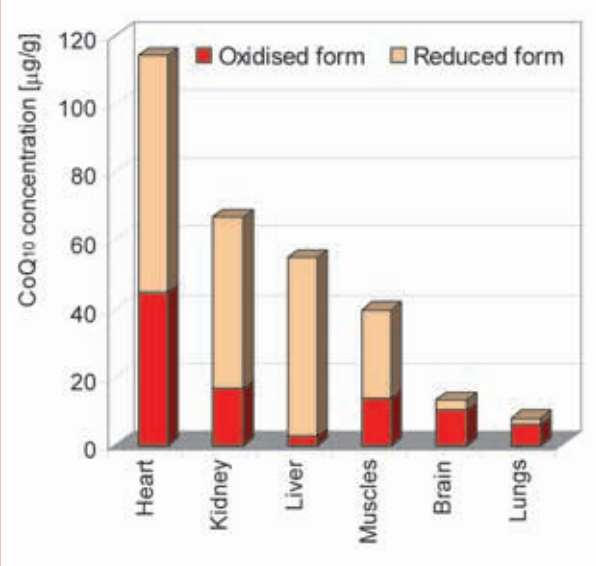


Figure 1. Distribution of CoQ10 in human tissues (5)

ABSORPTION AND METABOLISM

CoQ10 is a crystalline powder that is insoluble in water due to its lipophilicity. It has a relatively high molecular weight (M_r= 863) and its solubility in lipids is also limited so it is very poorly absorbed in the gastrointestinal tract (15). Absorption follows the same process as that of lipids and the uptake mechanism appears to be similar to that of vitamin E, another lipid-soluble nutrient (16). While the absorption of supplemental CoQ10 can be enhanced with a fatty meal, gastric digestion does not appear to be an important factor for products based on pure CoQ10 (16). Emulsification and micelle formation is required for the absorption of fats.

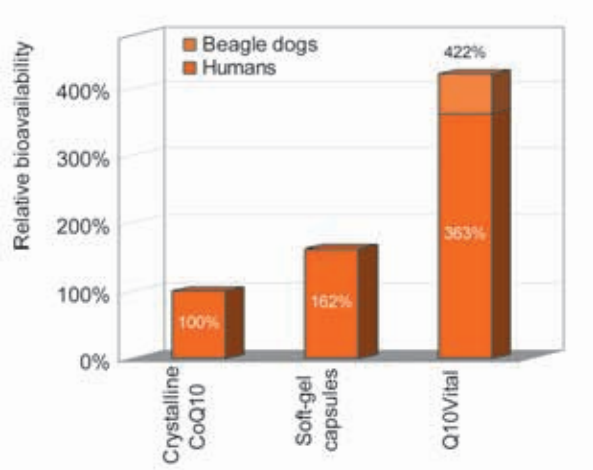
For CoQ10, this process is chiefly facilitated by secretions from the pancreas and bile in the small intestine (16). A general rule is that the higher the dose that is orally administered, the lower is the percent of the dose absorbed (16).

Data on the metabolism of CoQ10 in animals and humans are very limited (16). A study with ^{14}C-labelled CoQ10 in rats showed most of the radioactivity in the liver 2 hours after oral administration when the peak plasma radioactivity was observed, but it should be noted that CoQ9 is the predominant form of coenzyme Q in rats (17). It seems that CoQ10 is metabolised in all the tissues, while a major route for its elimination is biliary and faecal excretion (16). After the withdrawal of CoQ10 supplementation, the levels return to their normal levels within a few days, irrespective of the type of formulation used (18).

PHARMACOKINETICS AND BIOAVAILABILITY

Some reports have been published on the pharmacokinetics of CoQ10. The plasma peak can be observed 2-6 hours after oral administration, mainly depending on the design of the study (16-20). In some studies, a second plasma peak was also observed at about 24 hours after administration, probably due to both enterohepatic recycling and redistribution from the liver to circulation (16). *Tomono et al.* used deuterium-labelled crystalline CoQ10 to investigate pharmacokinetics in human and determined an elimination half-time of 33 hours (19). Bioavailability is the degree to which a drug or other substance becomes available to the target tissue after administration (21). By definition, intravenously administered drugs have 100 percent bioavailability while decreased bioavailability can be observed when medication is administered via other routes. When orally administered, the substance has to pass the intestinal wall and then travels to the liver through portal circulation.

Figure 2. Relative bioavailability of three forms of CoQ10* (20, 27, 30)



*adopted from three separate studies and recalculated with crystalline CoQ10 as a reference product: a) Single-dose (SD) bioequivalence study of CoQ10 in soybean oil suspension (soft-gel capsules) and crystalline CoQ10 as a reference (human volunteers, 100 mg CoQ10) (27); b) SD bioequivalence study of water-soluble Q10Vital and soft-gel capsules as a reference (human volunteers, 60 mg CoQ10) (20); c) SD bioequivalence study of water-soluble Q10Vital and soft-gel capsules as a reference (beagle dogs, 30 mg CoQ10) (30)

These processes form part of the 1st pass metabolism and allow a drug to achieve systemic circulation. Insufficient time for absorption in the gastrointestinal tract is usually reflected in low bioavailability (22). This is very common for orally administered compounds with poor water-solubility, such as Coenzyme Q10. High inter- and intra-individual variations of bioavailability can often be observed in such cases. Several physiological factors influence the bioavailability of drugs, such as sex, age, genetic phenotype, physical activity, health of the gastrointestinal tract and various disorders, type of administration (fed or fasted state), interactions with food etc. Relative bioavailability is one of the measurement tools used to assess the bioequivalence between two formulations of the same drug and is usually calculated as a test vs. reference ratio of the area under the curve (AUC), derived by the integration of the plasma concentration-time relationship after a single oral dose.

IMPROVING THE BIOAVAILABILITY OF CoQ10

The importance of how drugs are formulated for bioavailability is well known (22). In order to find a principle to boost the bioavailability of CoQ10 after oral administration, several new approaches have been taken and different formulations and forms have been developed and tested on animals or humans.

Reduction of particle size

The obvious strategy is reduction of the particle size to as low as the micro- and nano-scale. Nanoparticles have been explored as a delivery system for various drugs and an improvement of the oral bioavailability of drugs with poor absorption characteristics has been reported (23); the pathways of absorption and the efficiency were affected by reduction of particle size. This protocol has so far not proved to be very successful with CoQ10, although reports have differed widely (24, 25). The use of the aqueous suspension of finely powdered CoQ10 in pure water has also only revealed a minor effect (18).

Soft-gel capsules with CoQ10 in oil suspension

A successful approach was to use the emulsion system to facilitate absorption from the gastrointestinal tract and to improve bioavailability. Emulsions of soybean oil (lipid microspheres) could be stabilised very effectively by lecithin and were utilised in the preparation of soft gelatine capsules. In one of the first such attempts, *Ozawa et al.* performed a pharmacokinetic study on beagle dogs in which the emulsion of CoQ10 in soybean oil was investigated; about two times higher plasma CoQ10 level than that of the control tablet preparation was determined during administration of a lipid micro sphere (18).

Although an almost negligible improvement of bioavailability was observed by *Kommuru et al.* with oil-based soft-gel capsules in a later study on dogs (26), the significantly increased bioavailability of CoQ10 was confirmed for several oil-based formulations in most studies (15, 18, 27-29), revealing the importance of the composition of formulations in addition to solubilisation in an oily base. Both the type of oil used and additives have important effects on the absorption. *Schulz et al.* showed a 40 percent increase in the bioavailability of CoQ10 in commercially available soft-gel capsules with soyban oil in comparison to capsules with rice bran oil; in both cases, the bioavailability of CoQ10 was higher than for crystalline compound (64 percent and 17 percent increases, respectively) (29).

Weis et al. tested various soybean oil dispersion formulations on healthy human volunteers; based on AUC_{48h} values, a 62 percent increase in bioavailability was reported for CoQ10 in soybean oil (Figure 2) (27). Interestingly, almost no increase in bioavailability was observed when a micelle forming agent was used alone or in combination with a liposome forming agent as an additive to soybean oil (27). In several cases the dispersion of CoQ10 in oils has been mixed with (mostly inorganic) inert powder materials such as silica to obtain greasy powders to facilitate dispersion in aqueous media and

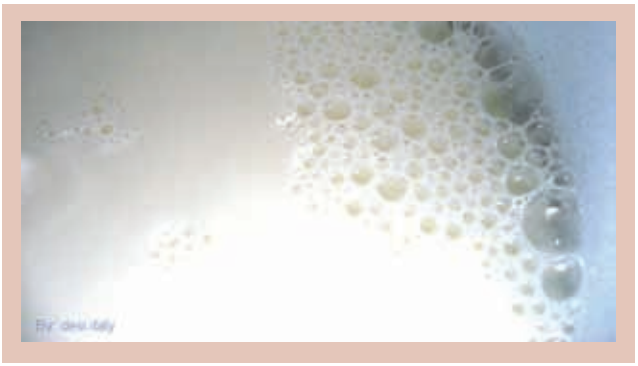
to enable the preparation of corresponding finished dosage forms for reconstitution, e.g. sachets. Such forms and preparations, which in aqueous media in fact form emulsions and not solutions, have often been misleadingly declared "water-soluble".

Novel forms of CoQ10 with increased water-solubility

Facilitating drug absorption by increasing its solubility in water is a common pharmaceutical strategy (22) and has also been shown to be successful for Coenzyme Q10 (15, 20, 30). Different approaches have been developed to achieve this goal, with many of them producing significantly better results over oil-based soft-gel capsules in spite of the many attempts to optimise their composition. Examples of such approaches are use of the aqueous dispersion of solid CoQ10 with tyloxapol polymer (31), formulations based on various solubilising agents, i.e. hydrogenated lecithin (32), dispersions of CoQ10 beadlets in a gelatine matrix coated with starch-based granules (33), and complexation with cyclodextrins (34). Among the latter, β-cyclodextrin is found to be the most promising and it is already commonly used in the food industry and as a drug carrier system due to its proven safety, round-the-world approval and easy accessibility. The impact of this strategy can be presented with an example of such a product, an inclusion complex of CoQ10 and β-cyclodextrin (Q10Vital) (34). This form of CoQ10 is available in liquid or powder form and has been determined to be stable, well-soluble in diverse aqueous media, without taste or odour, and therefore very attractive to the food industry which then immediately used it to fortify various food products across the world, such as diary products (e.g. milk, yoghurt, kefir etc.), fruit nectar, syrup and other beverages, honey, tea, as well as a food supplement in a variety of formulations like effervescent tablets, capsules, syrups etc. The bioavailability of CoQ10 in Q10Vital has been evaluated in pharmacokinetic studies on healthy human volunteers (20) and beagle dogs (30). In both cases, the pharmacokinetic parameters were determined after single-dose (SD) oral administration and compared to a reference commercially available soft-gel capsules with CoQ10 in soybean oil as optimised formulation. The study on humans showed a statistically significant 120 percent increase of the bioavailability for liquid Q10Vital form (20). When combining this data with Weis' pharmacokinetic study of CoQ10 in soft-gel capsules based on soybean oil (27), the bioavailability of Q10Vital reaches 363 percent of the bioavailability of crystalline CoQ10 (Figure 2). While the study on humans was performed in fasting conditions, even better results were observed with dogs where Q10Vital was administered with food (30). The study showed a 160 percent increase in bioavailability over the reference soft-gel capsules, representing 422 percent of the bioavailability of crystalline CoQ10 (Figure 2). Studies also indicate that the bioavailability of Q10Vital can be further improved by using it as a food additive (20). That is because the appropriate matrixes reduce its pH sensitivity, stabilise its solutions in the gastrointestinal tract and thereby improve its *in vivo* absorption. In addition to Q10Vital, improved bioavailability is also reported for some of the other forms of CoQ10 with improved water solubility (15).

CONCLUSIONS

Coenzyme Q10 is a natural substance that is found in all human cells. Apart from its fundamental role in the oxidative phosphorylation process, which drives cellular machinery and synthesis, it is also a very effective antioxidant. Intracellular synthesis is a major source of CoQ10 but this process weakens with increasing age and in some medical conditions. While food provides an additional source of CoQ10 to the body, it can hardly compensate for this deficiency. The use of functional food fortified with CoQ10 can significantly reduce this problem. CoQ10 is a lipophilic compound with a relatively high molecular weight, insoluble in water and its solubility in lipids is also limited. Due to these properties, the enrichment of most food products is not easily achievable and the absorption of CoQ10 in the gastrointestinal tract is very poor. A significant modification of the



bioavailability of CoQ10 has been enabled by the development of new forms and formulations. The first successful strategy was to use an emulsion system to facilitate absorption. A good example of this solution is soft gelatine capsules with a CoQ10 suspension in soybean oil, where increased bioavailability of CoQ10 of about 60 percent was measured. Further improvement has been achieved by increasing the solubility of CoQ10 in water, such as in the Q10Vital form, where the bioavailability of CoQ10 could reach over 420 percent of the bioavailability of crystalline compound. Further, the modified physical properties have made this form very attractive to the food industry, which then immediately used it as a CoQ10 fortifier in various food products like milk, yoghurt, fruit nectar, syrup, honey, tea etc. The bioavailability is also significantly enhanced with most of other forms of CoQ10 that feature improved water solubility.

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