CHAPTER I

INTRODUCTION

Nanoparticles are solid colloidal particles with the size ranging from 1 to 1000 nm (Lockman *et al.*, 2002). They could be classified into polymeric nanoparticles, nanocapsules, solid lipid nanoparticles, and nanogels (Date and Patravale, 2004). Nanoparticles made from lipid material or lipospheres represent an alternative coilloidal drug carrier system since 1990s period. This carrier combines the advantages but avoids the disadvantages of other traditional colloidal carriers such as emulsions, liposomes and polymeric microparticles. The proposed advantages include protection of incorporated labile drugs from degradation, controlled release capacity, low cytotoxicity, excellent tolerability and high entrapment efficiencies, especially for water-insoluble drugs. At the same time, this lipid-base nanoparticles also avoid the problem of organic solvent and biotoxicity of carrier (Mehnert and Mäder, 2001; Wissing, Kayser and Müller, 2004).

There are several methods to prepare the nanoparticles. High shear homogenization and ultrasound are initially used; however, dispersion quality is often compromised by the presence of microparticles. High pressure homogenization technique has also been used to produce nanoparticles (Mehnert and Mäder, 2001). However, this method requires high-torque mechanical mixing which can cause a potential damage to drugs. Sjöström and Bergenståhl (1992) produced nanoparticles by solvent-emulsification-evaporation method in which the organic solvent was requried.

Warm microemulsion technique is an alternative approach in the production of the nanoparticles that has been wildly employed (Igartua *et al.*, 2002). Lawrence

(2004) described microemulsions as thermodynamically stable, clear, fluid dispersions of oil and water stabilised by a surfactant or surfactants; usually in combination with a cosurfactant. Gasco (1997) firstly reported the preparation of nanoparticles from warm microemulsion by using dilution method. The warm microemulsion is added to a cold aqueous medium (2-3°C) in the range of 1:25 to 1:50 volume ratio of microemulsion to a medium and the precipitation of the lipid phase forming fine particles is obtained. The size of nanoparticles is affected by the composition of the microemulsion system, particularly the surfactant and co-surfactant used. However, due to the dilution step, achievable lipid contents forming particles are considerably low. Oyewumi and Mumper (2002) have recently developed method to produce small and stable nanoparticles from microemulsion systems. The process involves melting a pharmaceutically acceptable polymeric matrix material. Upon the addition of defined amounts of a suitable surfactant and water, a clear and stable oil-in-water (o/w) microemulsion is formed. Simple cooling of the warm microemulsion in the same container results in the formation of nanoparticles. This strategy has been reported to have advantages; since a variety of biocompatible ingredients can be used, well-defined and uniform nanoparticles may be reproducibly made without the use of expensive and/or damaging high-torque mechanical mixing, and no organic solvents are required. In addition, high entrapment efficiencies will be achievable, especially for water-insoluble drugs such as Coenzyme Q_{10}.

Coenzyme Q_{10}, also known as ubidecarenone, or Co Q_{10}, is a naturally occurring vitamin-like compound found in the inner mitochondrial membrane throughout the body, especially, in organs with high rate of metabolism such as the heart, kidney and liver. Coenzyme Q_{10} is a strongly lipophilic compound that exists in two-redox forms, namely ubiquinone and ubiquinol. The biological activity of Coenzyme Q_{10} results from its ability for reversible redox conversion (Crane, 2001). It plays an essential role in energy metabolism or cellular bioenergetics as a key

component of the mitochondrial electron transport systems for the production of cellular ATP (adenosine triphosphate), which is an integral part in the regeneration and rejuvenation of the skin. Coenzyme Q_{10} is also a lipid soluble antioxidant, capable of functioning synergistically with other antioxidants such as vitamin E and has membrane-stabilizing properties. The antioxidant activities of Coenzyme Q_{10} could make it useful as a treatment for aged skin. Coenzyme Q_{10} is approved for the treatment in cardiovascular disorder such as congestive heart failure and angina pectoris (Langsjoen and Langsjoen, 1998; Hoppe *et al.*, 1999). Recently, Narain *et al.* (2004) found that Coenzyme Q_{10} exerted an inhibitory effect on melanoma cells, which was related to the function of Coenzyme Q_{10} in the mechanism of apoptosis, the process of programmed cell death.

Several experiments on Coenzyme Q_{10} formulation are focused almost exclusively for improvement of drug bioavailability via oral route. The examples of Coenzyme Q_{10} oral formulation reported include solubilized system with blend of surfactant (Chopra, *et al.*, 1998), self-emulsifying systems (Kommuru *et al.*, 2001), solid dispersion (Nazzal, *et al.*, 2002), and nanoemulsified composite systems (Carli, *et al.*, 2005). However, oral administration is one of the least effective modes of Coenzyme Q_{10} delivery due to uncertainties of absorption and inactivation in the gastrointestinal system. In contrast, a topical delivery is more pharmacologically advantageous due to a more specific and directs delivery to the point of interest, resulting in a higher absorption/dosage ratio of Coenzyme Q_{10}. Moreover, due to its comfortable; the topical use will increase patient compliance. Narain *et al.* (2004) has developed liposome-encapsulated Coenzyme Q_{10}. However, Mehnert and Mäder (2001) suggested that liposome has some problem in chemical and physical stability that might lead to liposome aggregation and drug degradation during storage.

Incorporation of Coenzyme Q_{10} into the solid matrix of nanoparticles can protect them against chemical degradation (Müller, Radtke and Wissing, 2002).

Nanoparticles facilitate the topical delivery of drug to underlying tissues due to the small size of nanoparticles is in close contact with the stratum corneum that can increase the amount of encapsulated agents penetrating into the viable skin. These ultrafine particles also show an occlusive effect which promotes the penetration of active ingredients into the upper part of the epidermis. Moreover, due to their solid matrix, sustained drug release is possible. Furthermore, nanoparticles seem to be well suited for use on damaged or inflamed skin because they are based on non-irritative and non-toxic lipids (Dingler *et al.*, 1999; Jenning, Schafer-Korting, and Gohla, 2000; Mei *et al.*, 2003).

In this study, the nanoparticles carrier prepared from microemulsion technique was selected for incorporating Coenzyme Q_{10}. The formulations of microemulsion were prepared by varying the oil phase (matrix material) and the surfactant phase. The oil phase was the non-ionic emulsifying wax or Brij® 72. The composition of emulsifying wax was a combination of cetostearyl alcohol and one of the surfactants Tween® 20, Tween® 60, and Cetomacrogol 1000 at a weight ratio of 4:1. The non-ionic surfactants used to form microemulsion were Brij® 78 or Tween® 80. Solid nanoparticles were cured by cooling a warm microemulsion to room temperature in the same container. Various combinations of the microemulsion components (oil, surfactant and water phases) were tested with the aim of determining the optimal combinations of each ingredient. The different concentrations of Coenzyme Q_{10} (1-4 mg/mL) were loaded in the formulations containing different concentrations of oil and surfactant. The prepared formulations were characterized on the appearance, particle size and size distribution. The entrapment efficiency (%) of Coenzyme Q_{10}-loaded nanoparticles was then determined. The morphology, thermal analysis, the *in vitro* release profile and stability of Coenzyme Q_{10}-loaded nanoparticles dispersion, freeze-dried Coenzyme Q_{10}-loaded nanoparticles and Coenzyme Q_{10}-loaded nanoparticles in cream base were studied.

The aim of this research was to study the effect of various components on the preparation of nanoparticles from microemulsion. The lipophilic cosmeceutical, Coenzyme Q_{10}, was chosen for incorporation in the nanoparticles. The entrapment efficiency, the physicochemical properties, and the *in vitro* release profile were investigated. The stability of Coenzyme Q_{10}-loaded nanoparticles was performed in order to use the nanoparticles as a promising drug carrier in various applications, especially for topical delivery.

From this research, the preparation method of nanoparticles from microemulsion system will be achieved and used for increasing the solubilization and stability of Coenzyme Q_{10}. This Coenzyme Q_{10}-loaded nanoparticle could be incorporated in to various formulations for cosmetic and pharmaceutical application, especially for topical delivery.