A Novel Self-Microemulsifying System for the Simultaneous Delivery and Enhanced Oral Absorption of Curcumin and Resveratrol

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Abstract
The use of curcumin and resveratrol in combination has now become increasingly of interest because of their synergistic effects as therapeutic agents for various diseases, especially cancer. To overcome the poor oral bioavailability of both compounds and improve patient compliance, a novel self-microemulsifying formulation containing curcumin together with resveratrol was developed. Capryol 90, Cremophor EL and Labrasol were selected as the oil, surfactant and co-surfactant in the formulation, respectively, based on the solubility study of both compounds. More than 70% and 80% of curcumin and resveratrol, respectively, were released in 20 min. The formulation formed a fine oil in water microemulsion with droplet sizes in aqueous media of 15–20 nm. In addition, the formulation containing curcumin and resveratrol showed greater antioxidant activity than that of the formulations with individual compounds, while the cytotoxic activity against HT-29 of the co-formulation (IC50 = 18.25 μM; curcumin and resveratrol in the ratio 1:1) was less than the formulation with only curcumin (IC50 = 30.1 μM) and only resveratrol (IC50 = 25.4 μM). After oral administration to rabbits, the self-microemulsifying formulation containing curcumin together with resveratrol increased the total plasma concentrations of curcumin and resveratrol by 10-fold and 6-fold, respectively, compared to the unformulated combination. This study clearly demonstrated the potential use of the self-microemulsifying formulation for co-delivery, and enhanced oral absorption of poorly water-soluble natural compounds. In addition, the combination was found to produce synergistic antioxidant activity and cytotoxicity against HT-29 cells.

Introduction
Diferuloylmethane, commonly called curcumin, is a yellow pigment present in the rhizomes of turmeric (Curcuma longa L., Zingiberaceae). Curcumin exhibits antioxidant, anti-inflammatory, anticarcinogenic, and chemopreventive properties. In clinical studies, curcumin has been shown to prevent or treat various cancers in humans [1]. Resveratrol (3,5,4′-trihydroxystilbene) is a major component of grapes, wine, peanuts, and Polygonum cuspidatum Sieb. & Zucc. (Polygonaceae). It also has anticancer, antioxidant, and anti-inflammatory activities [2]. Recently, curcumin and resveratrol, two particularly important polyphenolic compounds, have been found to exhibit a synergistic anticancer effect against various cancer types, including colon cancer and hepatocellular carcinoma, and also in the treatment of diseases associated with oxidative stress [3]. However, both curcumin and resveratrol have low aqueous solubility and are rapidly metabolized. These problems result in poor oral bioavailability [4], which is an important restriction on their therapeutic usefulness. Many studies have indicated the importance of using self-microemulsifying drug delivery systems (SMEDDS) to improve solubility, absorption, and to increase the oral bioavailability of poorly water-soluble drugs [5]. SMEDDS are defined as isotropic mixtures of oils, surfactants, and co-solvents/co-surfactants that emulsify under conditions of gentle agitation, similar to those encountered in the gastrointestinal tract [6]. The spontaneous formation of an emulsion presents the drug in a dissolved form, and the resultant small droplet sizes provide a large interfacial surface area that enhances the rate and extent of oral absorption [7].

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