Curcumin Nanoemulsion for Transdermal Application: Formulation and Evaluation

Heni Rachmawati1*, Dewa Ken Budiputra1, Sony Suhandono2, Kusnandar Anggadiredja1

1) School of Pharmacy, Bandung Institute of Technology (ITB)
2) School of Life Science and Technology (ITB)
Jl. Ganesha, Bandung 40132, Indonesia

*Corresponding author, email: hrachma@yahoo.com

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ABSTRACT
The aim of this work is to develop a curcumin nanoemulsion for transdermal delivery. The incorporation of curcumin inside a nanoglobul should improve curcumin stability and permeability. A nanoemulsion was prepared by the self-nanoemulsification method, using an oil phase of glyceryl monooleate, cremophor RH-40 and polyethylene glycol 400. Evaluation of the nanoemulsion included analysis of particle size, polydispersity index, zeta potential, physical stability, Raman spectrum and morphology. In addition, the physical performance of the nanoemulsion in Viscolam AT 100P gel was studied. A modified vertical diffusion cell and shed snake skin of Phyton reticulatus were used to study the in vitro permeation of curcumin. A spontaneously formed stable nanoemulsion has a loading capacity of 350 mg curcumin/10 gram of oil phase. The mean droplet diameter, polydispersity index and zeta potential of optimized nanoemulsion were 85.0 ± 1.5 nm, 0.18 ± 0.0, and -5.9 ± 0.3 mV, respectively. Curcumin in a nanoemulsion was more stable than free curcumin. Furthermore, nanoemulsification significantly improved the permeation flux of curcumin from the hydrophilic matrix gel; the release kinetic of curcumin changed from zero order to a Higuchi release profile. Overall, the developed nanoemulsion system not only improved curcumin permeability but also protected the curcumin from chemical degradation.

KEYWORDS: curcumin, self assembly nanoemulsion, transdermal, shed snake skin, Higuchi release profile
INTRODUCTION
Transdermal delivery in the form of a gel or patch is an interesting alternative for topical route to give local or systemic effects. It can improve patient compliance and also has some benefits for curcumin, such as avoiding first pass metabolism, decreasing side or unwanted effects, and enabling constant blood levels over longer periods of time. However, curcumin exhibits low skin penetration resulting in poor efficacy. Recently, a stable curcumin gel has been produced using 15% alcohol (to dissolve curcumin in the gel). Dimethylsulfoxide (DMSO) is also needed to improve curcumin release from the gel (1). In contrast to common chemical skin penetration (using enhancers such as organic solvents which are generally associated with skin irritation, toxicity and sensitization) a solvent free topical vehicle based on drug entrapment in oil/water emulsion droplets of submicron particle is more efficacious in terms of percutaneous absorption, and is possibly devoid of adverse effects. In addition, the uniqueness of the large internal hydrophobic core of oil/water submicronized emulsion droplets allows high solubility for water insoluble topically active ingredients and also improves on carrying water, an excellent softener, to the skin.

This report describes a more effective and efficient strategy to deliver curcumin via the transdermal route. This work is not only focused on a better release of curcumin from a gel matrix, but also on enhancing skin permeation as well as on the stability of the curcumin to obtain better bioavailability.

METHODS
A conventional emulsion was prepared using GMO (16% w/v) and Cremophor RH40 (4% w/v). Curcumin (0.25% w/v) was added under stirring to GMO and Cremophor RH 40. The mixture was then dispersed in water under stirring for 30 minutes to form an emulsion. A nanoemulsion of curcumin formed spontaneously in an oil phase of GMO, cremophor RH40, and PEG 400 (1:8:1). Various amounts of curcumin (10, 25, 50, 100, 250, 350, 500, and 750 mg) were added to 10 gram of oil phase. Physical characterization was performed including globule size and distribution, surface charge, loading capacity, Raman spectroscopy, morphology and in vitro release. The particle size, polydispersity index, and zeta potential of nanoemulsion were determined using a particle size and zeta potential analyzer (Delsa™ Nano, Beckman Coulter, USA). Curcumin nanoemulsion then was formulated into topical gel and permeation study using skin model was performed.
RESULTS AND DISCUSSION
Nanoemulsion using our established composition formed spontaneously after water addition. Self nanoemulsification is only achieved with some oils, surfactants, and co-surfactants at a certain ratio. Selection of an appropriate oily phase is very important, as it influences the selection of other ingredients in oil/water nanoemulsions. Usually, the oil with the maximum solubility for the selected drug is chosen as the oily phase for the formulation of nanoemulsions. This helps to achieve maximum drug loading (2). Generally, surfactant alone cannot lower the oil–water interfacial tension sufficiently to yield a nanoemulsion; this necessitates the addition of an amphiphillic short chain molecule or cosurfactant to lower the surface tension close to zero. Co-surfactants penetrate into the surfactant monolayer, providing additional fluidity to the interfacial film and thus disrupting the liquid crystalline phases which are formed when the surfactant film is too rigid (14).

Figure 1A shows a transmission electron micrograph of a curcumin nanoemulsion, indicating monodisperse spheric of curcumin nanoemulsion with size around 50 nm. This nanoemulsion shows a significant improvement (1.6 fold, P < 0.05) of cumulative curcumin permeated from nanoemulsion gels compared to gel containing free curcumin (figure 1B).

Figure 1. Transmission electron microscopy of curcumin nanoemulsion (A) and Permeation profiles of curcumin through shed snake skin from gel containing curcumin nanoemulsion and gel containing curcumin (Mean + SD, n = 3).
Nitrogen atom (11.75%) was detected by energy dispersive x-ray spectroscopy in BSA loaded PVA nanofibers, indicating that protein (BSA) was included in the nanofibers. Spectrogram of BSA loaded PVA nanofibers produced from FTIR indicated good compatibility between them. About 77% BSA was released in 30 second, and reached 100% within 2 minutes.

CONCLUSION
Curcumin is widely used as a potent anti-inflammatory herbal drug. Its activity is similar to the NSAIDs in inflammatory pain management. An early study pointed out that the hydroxyphenyl unit in curcumin confers anti-inflammatory activity. Some problems are related to the oral administration of curcumin and topical application is difficult due to its low permeability through the skin. Our gel-containing nanoemulsion of curcumin seems to be promising as a transdermal delivery system for curcumin. Mixing of GMO:Chremophor RH40:PEG 400 (1:8:1) resulted in the spontaneous formation of nanoemulsion, and successfully encapsulated curcumin with better physicochemical stability, prolonged shelf file and enhanced skin permeability. As transdermal delivery requires this permeability to provide the required therapeutic dose, encapsulation of curcumin into nanoemulsion seems to be promising for transdermal delivery of curcumin.

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REFERENCES