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Non-aqueous self-double-emulsifying drug delivery system: A new approach to enhance resveratrol solubility for effective transdermal delivery

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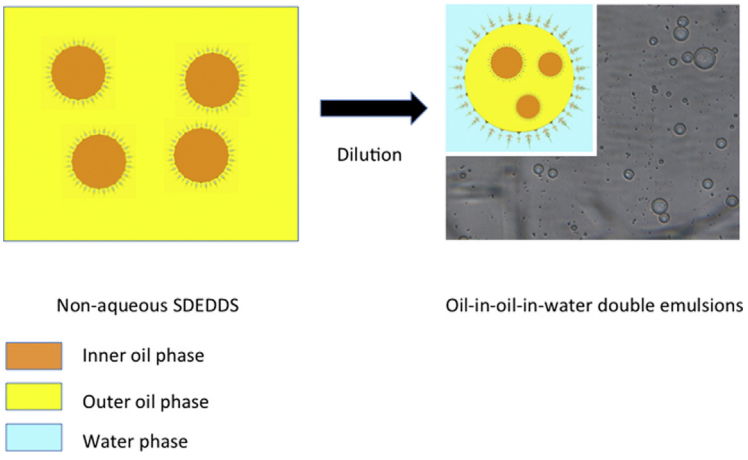
HIGHLIGHTS

- The non-aqueous SDEDDS could improve *trans*-resveratrol solubility through formulations optimization.
- The SDEDDS could release the oil phase to form fine oil-in-oil-in-water emulsions, with a sustained release of *trans*-resveratrol.
- *trans*-Resveratrol from SDEDDS will be higher than the drug permeation from the free form aqueous solution.

GRAPHICAL ABSTRACT



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ABSTRACT

trans-Resveratrol, a naturally occurring polyphenol has attracted considerable interest for its beneficial potentials for human health. However, the biological effects of *trans*-resveratrol appear strongly limited by its low solubility, which is a barrier to the development of therapeutic applications. Herein, we developed a novel formulation, non-aqueous self-double-emulsifying drug delivery systems (SDEDDS) by formulating mixtures of hydrophilic surfactants and oil-in-oil (O/O) emulsions, which could improve *trans*-resveratrol solubility through formulations optimization. SDEDDS can spontaneously emulsify to oil-in-oil-in-water double emulsions in the mixed aqueous solution, with drugs encapsulated in the internal oil phase of the double emulsions. We employed non-aqueous SDEDDS to improve the skin retention of *trans*-resveratrol solubility, a polyphenol drug with poor solubility. The optimized *trans*-resveratrol-SDEDDS was found to be stable up to 3 months under 30 °C and 40 °C. *In vitro* transdermal studies revealed that *trans*-resveratrol from SDEDDS will most likely be higher than the drug permeation from the same dose of the free form aqueous solution. These studies demonstrated that non-aqueous SDEDDS might be a promising strategy for topical delivery of poor solubility drug.

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1. Introduction

Resveratrol is a natural non-flavanoid polyphenol mainly found in grapes, mulberries, cranberries, peanuts and plants of the *Cassia quinquangulata* family [1], with the *trans*-resveratrol isomer being more biologically active [2]. Many studies have demonstrated that resveratrol has a wide range of pharmacological properties, which has been shown to be a cardio-protective effect, chemopreventive activity, anti-diabetic activity and against neurodegenerative disorders [3–5]. However, more attention has been paid to the topical application of resveratrol in various physiological and pathological conditions, such as anti-inflammatory [6], antimicrobial [7] and antiviral disorders [8] and skin cancer [9]. It was demonstrated that resveratrol targets IκB kinase in blocking the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate-induced nuclear factor-κB (NF-κB) activation and cyclooxygenase-2 (COX-2) expression in mouse skin *in vivo* [10]. Resveratrol protected dorsal skin of volunteers against repetitive ssUVR-induced sunburn and suntan [11]. From here, there is a great interest to increase resveratrol concentration into the epidermis. However, exploitation of resveratrol health promoting effects is challenging due to its very limited transdermal following topical application, caused by its poor biopharmaceutical properties, namely low solubility [12]. However, transdermal of resveratrol was closely related to the formulation [13]. Therefore, a proper carrier should be carried out to facilitate delivery of resveratrol for cosmetic or therapeutic purposes.

Oil-in-oil (O/O) emulsions were first reported in 1965 by Molau. The simple emulsions are binary system, whereby the dispersed droplets contain smaller droplets of a similar polarity and immiscibility phase [14]. The structural properties of this kind of emulsions have been proved controlled release of a component from the inner phase [15]. O/O emulsions offer possible reservoir formulation, which could be used for dermatological application or as reservoir systems in controlled release devices [16]. This leads to a number of potential applications in the fields of medicine, pharmacy, cosmetics and separation processes. Besides, a vegetable oil–alcohol system has been prepared by Xu et al. as a drug delivery system to solve solubility of drug [17]. However, the disadvantage was that because these emulsions are insoluble in water, the emulsions must be sheared at high speed to disperse and release the active materials.

Self-double-emulsifying drug delivery system (SDEDDS) has gained advantage for their ability to incorporate hydrophilic drugs. Upon mild agitation followed by dilution in aqueous media, the system could form fine double emulsions [18]. However, traditional SDEDDS only could encapsulate water-soluble drug and some of fat-soluble drug. Hence, a non-aqueous SDEDDS, which combines the benefits of a traditional SDEDDS and O/O emulsion, was considered. The non-aqueous SDEDDS is a multiple system after dilution, being comparable to water-in-oil-in-water emulsions. In this case it is an oil-in-oil-in-water dispersion. This SDEDDS type used the fact that for a number of poor soluble drugs like *trans*-resveratrol, the solubility in inner oils (polar organic solvents) is higher than their solubility in outer oils. Unfortunately, these dosage forms often contain large amounts of surfactants. However, chronic application of surfactants in high doses could disturb some physiological processes [19].

Our aim was therefore to improve *trans*-resveratrol solubility and skin retention by developing a non-aqueous self-double-emulsifying formulation. Furthermore, In addition, we aimed to design *trans*-resveratrol loaded self-double-emulsifying drug delivery system (*trans*-res-SDEDDS) with the lowest surfactant content possible, while maintaining high *trans*-resveratrol incorporation capacity and improving skin retention.

2. Materials and methods

2.1. Materials

trans-Resveratrol (purity ≥ 98.93%) was supplied from Shanghai DND Pharm-Technology Co., Inc. (Shanghai, China); polyglyceryl-10 laurate (P10) was purchased from Heyi Food Technology Co., Ltd. (Shanghai, China); Transcutol® CG was purchased from Gattefosse (SAINT-PRIEST Cedex, France); polyglycerol polyricinoleate (PGPR) was purchased from Esterol Sdn Bhd (Shah Alam, Malaysia); PEG-30 Dipolyhydroxystearate (P135) was supplied by Croda (UK); Cremophor® A6, A25 and polyglyceryl-2 dipolyhydroxystearate (PGPH) were purchased from BASF SE (Ludwigshafen, Germany); caprylic/capric triglyceride (ODO) was purchased from Zhengtong Chemical Co., Ltd. (Henan, China); grape seed oil, evening primrose oil, olive oil, coconut oil, aloe oil, avocado oil, corn oil, soybean oil, hydrogenated castor oil were purchased from Guangzhou Boyi Trading Co., Ltd. (Guangzhou, China); polyoxyethylene (23) lauryl ether (L23) and polyoxyethylene (21) stearyl ether (O/100G) were purchased from Lipo Chemicals Inc. and Croda (Shanghai, China), respectively; polyoxyethylene (40) stearate (S40) was supplied from Nanjing Well chemical Co., Ltd. (Nanjing, China); sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan monooleate (Span 80), polyoxyethylene sorbitan Monooleate (Tween 80), polyoxyethylene sorbitan monostearate (Tween 60), polyoxyethylene sorbitan monolaurate (Tween 20), polyethylene glycol 400 (PEG 400), ethanol, glycerol, propylene glycol (PG) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China); rhodamine 123 (Rh123) was purchased from Acros organics (New jersey, USA); Chromatographic methanol was purchased from Merck (Germany). All other chemicals used were of analytic grade and commercially available products.

2.2. Preformulation studies

2.2.1. Solubility studies

The solubility of *trans*-resveratrol was determined in various excipients, including surfactants and oils by the shake flask method [20]. An excess amount of *trans*-resveratrol was added to each cap vial containing 2 g of the excipients. Vials were then shaken in a water bath shaker maintained at temperature 5 °C above the melting point until equilibrium (48 h). The mixtures were then centrifuged at 6000 rpm for 10 min (Beckman coulter, Allegra X-22R). The supernatants were collected for analysis. The quantitative of *trans*-resveratrol was performed on a High Performance Liquid Chromatography (PE200, PerkinElmer, USA). The column used was ZORBAX SB-C18, 5 μm, 4.6 × 150 mm (Agilent technology, USA). The mobile phase consisted of acetic acid-methanol (60:40, v/v). The sample injection volume was 20 μL and mobile phase was at a flow rate of 1.0 mL/min. A good linearity was achieved with a correlation coefficient of 0.9997 over the concentration range of 0.1–25 μg/mL. Each value was expressed as the mean ± SD ($n = 3$).

2.2.2. Drug-excipients chemical compatibility

Accurately weighed amounts of *trans*-resveratrol (5 mg) and each of selected excipients (2 g) were placed in 5 mL amber colored glass vials and mixed thoroughly. Closed vials containing blends were stored in stability chambers at 30 °C/65% RH, 40 °C/75% RH and 60 °C/75% RH for 14 days. A pure *trans*-resveratrol sample alone was also kept under similar conditions. Triplicate samples of drug-excipients blends were analyzed after 14 days by validated HPLC method.

2.2.3. Immiscibility studies

The Immiscibility of outer phase oil with inner phase oil is an important factor that determines the O/O emulsions can be formed.