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Development of isolated panduratin A-loaded solid lipid nanoparticles as a transdermal delivery system for cosmeceutical products

Worranan Rangsimawong[1], Kusuma Jitsaeng[1], Sureewan Duangjit[1], Phaijit Sritananuwat[2] and Praneet Opanasopit[3]*

[1] Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[2] Division of Biopharmacy, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[3] Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand

***Corresponding author**: Worranan Rangsimawong worranan.r@ubu.ac.th*

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ABSTRACT

Panduratin A (PA), isolated from *Boesenbergia rotunda* (L.) Mansf., is a cyclohexenyl chalcone derivative with low water solubility, from which a suitable transdermal delivery system could be developed to improve skin penetration. Solid lipid nanoparticles (SLNs) are carriers for lipophilic drugs to penetrate the skin layers. Therefore, the objective of this study was to develop SLN containing PA as a transdermal delivery system. Cytotoxicity studies in skin cells, (normal human fibroblasts (NHFs) and human immortalized keratinocytes (HaCaTs),) were evaluated. The PA-loaded SLN formulations were formulated and characterized. From the results revealed that PA was not toxic to NHF and HaCaT cells at 1 µg/mL concentrations, indicating no cytotoxicity of skin cells. SLN formulation 0.1% w/v of PA-loaded SLN (SLN4) exhibited favorable properties such as the nanometer size, negative zeta potential, and the highest entrapment efficiency at 99.81%. The release and skin permeation study showed that PA from SLN4 was released from and permeated through skin better than oil (control) at all sampling times. In conclusion, PA has no skin cell cytotoxicity and is suitable to be used as a cosmeceutical ingredient. SLN4 plays a ideal role as a transdermal delivery system of PA, resulting from its suitable physicochemical properties and ability to permeate the skin.

Keywords: panduratin A; normal human fibroblast; human immortalized keratinocytes; solid lipid nanoparticles; transdermal delivery system

1. INTRODUCTION

Panduratin A (PA) isolated from *Boesenbergia rotunda (L.)* Mansf. is a potential natural nutraceutical that enhances skin hydration and barrier function based on cornified envelope formation and filaggrin processing (Woo et al., 2015). Moreover, PA in the range of 0.001–0.1 µM significantly reduces the expression of matrix metalloproteinase (MMP-1), known as a natural anti-aging agent, and induces the expression of type-1 procollagen at the protein and mRNA gene levels (Shim et al., 2008). However, PA is a prenylated cyclohexenyl chalcone with a molecular

weight of 406.5 g/mol and XlogP of 6 (PubChem, 2023), which implies low water solubility and leads to low oral bioavailability (Boonyarattanasoonthorn et al., 2023). Thus, methods to improve solubility and skin permeability should be developed to overcome this limitation.

The outermost layer of the skin, the stratum corneum, is the barrier that limits many drugs penetrating the skin (Menon et al., 1989). Percutaneous drug absorption depends on many factors, including daily dose, molecular weight, lipophilicity, and melting point. Ideally, the daily dose of a drug should be less than or equal to 20 mg per day, the molecular weight should be less than 500 Da, the logP value should be in the range 1–3, and the melting point should be less than 200 °C (Yu et al., 2021). Therefore, an effective transdermal delivery system for PA should also be developed to improve the skin permeability of PA.

Solid lipid nanoparticles (SLNs) have been used as alternatives to emulsions, liposomes, microparticles, and their polymeric counterparts for various application routes due to their ability to incorporate lipophilic and hydrophilic drugs, improved physical stability, low costs relative to liposomes, and easy scale-up and manufacturing potential (Mehnert and Mader, 2001; Uner and Yener, 2007). The colloidal nanocarrier system of SLNs consists of surfactant-coated, high-melting point lipid nanoparticles, including high-melting point glycerides and waxes, (Mandawgade and Patravale, 2008). A drug or active compound is incorporated by dissolving and dispersing the drug in the molten lipid before high-pressure homogenization, depending on drug solubility in the lipid matrix (Schubert and Müller-Goymann, 2005). Moreover, the small particle sizes of SLNs enable close contact with the stratum corneum, enhancing the number of encapsulated agents penetrating the skin (Mei et al., 2003). SLNs can also form occlusive films, enhancing drug permeation (Baroli, 2010). Hence, SLN might be able to encapsulate lipophilic PA into lipid nanocarriers, improving the skin permeation of PA and being suitable to be used in cosmeceutical products.

The objectives of this study were to develop SLNs containing PA as transdermal delivery systems. Cytotoxicity studies of skin cells, normal human fibroblasts (NHFs) and human immortalized keratinocytes (HaCaTs), were performed using MTT assay. In addition, the PA-loaded SLN formulations were formulated and characterized, and *in vitro* release and skin permeation also were evaluated.

2. MATERIALS AND METHODS

2.1 Materials

PA isolated from *B. rotunda* (L.) Mansf. was supplied by the Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Thailand. NHFs and HaCaT cells were obtained from the American-Type Culture Collection (ATCC), Rockville, MD, USA. Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), trypsin–ethylenediaminetetraacetic acid (EDTA), L-glutamine (Glutamax™), nonessential amino acids, and penicillin–streptomycin were purchased from Gibco BRL, Rockville, MD, USA. In addition, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) was purchased from Sigma, Aldrich, USA; cetyl palmitate from SABO SpA, Levate, Italy; polysorbate 80 (Tween 80) from the Namsiang Group in Bangkok, Thailand; and Lecithin from Acros, New Jersey, USA. All chemical agents were of analytical grade.

2.2 Cell viability study

NHF and HaCaT cells were cultured in DMEM supplemented with 10% FBS, 1% penicillin–streptomycin, 1% Glutamax®, and 1% nonessential amino acids, and incubated in humidified conditions (5% CO_2, 95% air, 37 °C) until they reached 70–80% confluence. NHFs (10^4 cells/well) and HaCaTs (5×10^3 cells/well) were seeded into 96-well plates and incubated until cell confluence was achieved. After removing the cell medium from the cell plates and washing with PBS, pH 7.4, PA solution was added and incubated for 24 h. The cell viability was measured by MTT assay. Cells were incubated with 0.5 mg/mL of MTT solution for 3 h and the formazan crystal was dissolved with DMSO. The absorbance was analyzed by a microplate reader (VICTOR Nivo™ Multimode Plate Reader, PerkinElmer, Pontyclun, CF72 8YW, UK) at 550 nm. The percentage of cell viability was calculated using Equation 1.

$$\% \text{ Cell viability} = \frac{\text{Absorbance of treated cells}}{\text{Absorbance of untreated cells}} \times 100 \quad (1)$$

2.3 Formulation of SLN

The SLN formulations were prepared using the de-novo emulsification method. The composition of the oil phase was PA (0.05–1.00% w/v), cetyl palmitate (3.00% w/v), and lecithin (0.12% w/v). Polysorbate 80 (0.80% w/v) was dissolved in water for the aqueous phase. The oil and aqueous phases were heated at 65 ± 5 °C. Then, the aqueous phase was added to the oil phase under magnetic stirring at 400 rpm for 5 min. A probe-type sonicator reduced the particle size of emulsions for 15 min. Due to the poor water solubility of PA, undissolved PA was present in a yellow crystal. SLN formulations were then filtered through a 0.45 µm filter to remove precipitated PA.

For the characterization of SLN formulations, particle size, and zeta potential were measured using a dynamic light scattering particle size analyzer (Zetasizer Nano ZS, Malvern Instrument, Worcestershire, UK) with a 4 mW He–Ne laser at a scattering angle of 173°. All measurements were performed in triplicate. For entrapment efficiency (EE), SLN dispersion was disrupted by isopropyl alcohol and centrifuged at 10,000 x g for 10 min. PA content in the supernatants was determined by high-performance liquid chromatography (HPLC) analysis, and the % EE was calculated using Equation 2.

$$\% EE = \frac{C}{C_i} x\ 100 \quad (2)$$

where C is the concentration of PA in the formulation, and C_i is the initial concentration of PA.

2.4 *In vitro* release and skin permeation study

An *in vitro* release study was performed by vertical Franz-type diffusion cells through a dialysis membrane (Molecular weight cut-off: 6–8kDa, Spectrum™ Spectra/Por™, Spectrum Laboratories, Inc., CA, USA). Approximately 12 mL of PBS, pH 7.4, and Tween 20 (5 g/L) were mixed with ethanol in the ratio of 1:1 to form the receptor medium and continuously stirred using a magnetic stirrer. The temperature was maintained at 32 ± 0.5 °C. Then, 2 mL of the formulation was added into the donor compartment,

and 500 of receiver medium was collected at 0.5, 1, 2, 4, 6, 8, 24, 48, and 72 h for HPLC analysis.

For the skin permeation study, abdominal porcine skins were taken from intrapartum stillborn animals from a local farm in Sisaket province, Thailand. This study was approved by an investigational review board (04/2565/IACUC, Animal Experimentation Ethics Committee, Ubon Ratchathani University). The subcutaneous layers were removed using medical scissors (600–700 µm skin thickness). The skin permeation study was performed by vertical Franz-type diffusion cells, as described earlier. A 2 mL sample of the formulation was applied to the skin. The receiver medium (500 µL) was collected at 24 h for HPLC analysis.

In this study, PA dissolved in cold-pressed coconut oil (oil) was used as the control for *in vitro* release and the skin permeation study.

2.5 HPLC analysis

PA was analyzed using an HPLC system (Thermo Scientific™ Dionex™ UltiMate 3000, Germering, Germany) equipped with a C18 HPLC column (VertiSep™ GES, 4.6 x 250 mm, 5 µm pore size, Vertical Chromatography Co., Ltd., Bangkok, Thailand) and monitored by a UV detector at 285 nm. Samples were dissolved in ethanol with a 50 µL injection volume and 1.5 mL/min flow rate. The solvent system, acetonitrile and phosphoric acid (0.1% v/v), was subsequently mixed using a linear gradient starting with 20% acetonitrile, reaching 80% for 60 min.

2.6 Data analysis

The data were presented as the mean ± standard deviation (SD). A statistically significant difference was analyzed by one-way ANOVA, followed by Tukey's post-hoc test. The significance level was set at $p<0.05$.

3. RESULTS AND DISCUSSION

3.1 Cytotoxicity study

PA containing 0.3 g/g of extract was used as the active compound in this study. As shown in Figure 1, PA was not toxic on fibroblast, or keratinocytes skin cells at concentrations of 1 µg/mL, and the viability of HaCaT cells increased after treatment with low concentrations of PA.

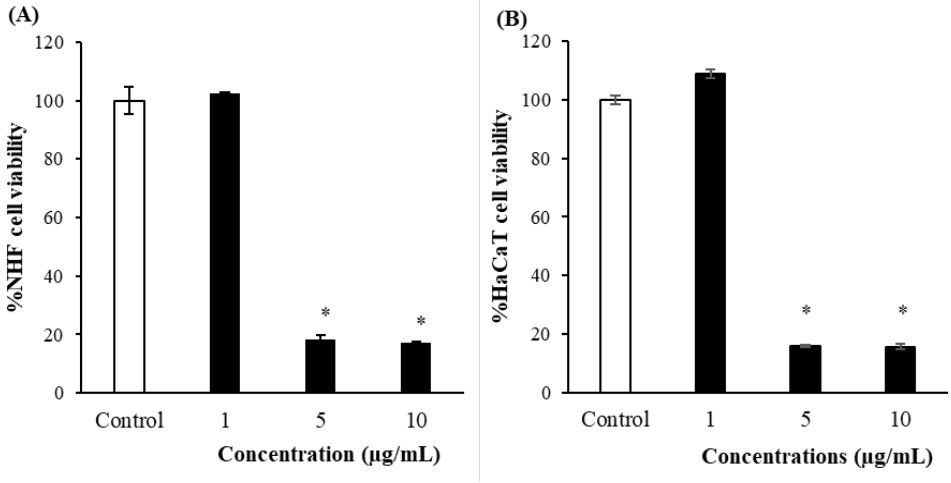

Figure 1. Percentages of (A) NHF and (B) HaCaT cell viability after treatment with PA
Note: data are presented as the mean ± SD (n = 3)
* indicates the significant difference from the control group (untreated cells) ($p < 0.05$)

According to Woo et al. (2015), *B. rotunda* extract and PA enhance skin hydration and barrier function by increasing cornified envelope formation and filaggrin processing, which are structures to prevent water loss from the body. The HaCaT keratinocyte differentiation process represents the formation of a cornified envelope (Woo et al., 2015). In addition, *B. rotunda* has been reported to accelerate human keratinocyte proliferation by activating ERK1/2 and PI3K/Akt kinases. This extract also possesses wound healing action through activating proliferation and survival pathways, representing potential therapeutic applications for skin regeneration. Therefore, as PA enhanced the viability of HaCaT cells, it indicated its potential use as a natural nutraceutical to enhance skin health function and its suitability for use as an active ingredient in cosmeceutical products.

3.2 PA-loaded SLNs

SLN solutions appeared clear white to yellow at 0.05 to 1.00% w/v PA concentrations. Increased PA concentration led to incomplete dissolution in the formulation, leading to increased particle size and sedimentation of insoluble compounds. SLN3–5 was successfully formulated as a white to yellow clear solution (Figure 2). The particle sizes and surface charges of SLN formulations were evaluated, as shown in Table 1. At PA concentrations of 0.05–0.2% w/v, these SLNs had significantly smaller particle sizes than the 1% PA-loaded SLN ($p<0.05$). The zeta potentials of all formulations showed negative surface charges. For the entrapment efficiency of the PA-loaded lipid nanocarriers, SLN3, SLN4 and SLN5 showed significantly higher PA entrapment than SLN1 and SLN2 ($p<0.05$), of which SLN4 had the highest % EE with good appearance (no coarse particles in the formulation). This suggested the capacity of the lipid nanocarriers to entrap PA, leading to the dissolution of PA for loading into SLNs.

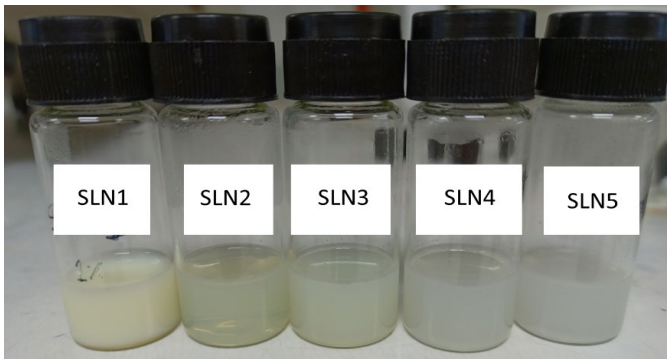

Figure 2. Appearance of SLN formulations

Table 1. Physicochemical properties of SLN formulations

Formulation	PA extract (% w/w)	Size (nm)	Zeta potential (mV)	% EE
SLN1	1.00%	174.80 ± 1.57	-26.20 ± 1.06	26.32 ± 1.50
SLN2	0.50%	70.37 ± 0.73*	-29.73 ± 0.40	46.86 ± 3.52
SLN3	0.20%	90.95 ± 0.92*	-32.03 ± 2.06	72.27 ± 11.59*
SLN4	0.10%	97.21 ± 1.29*	-32.07 ± 1.39	99.81 ± 9.19*
SLN5	0.05%	98.22 ±3.51*	-31.40 ± 1.97	94.97 ± 9.17*

Note: data present mean ± SD (n = 3)
* indicates significant difference from SLN1 ($p < 0.05$)

PA isolated from the *B. rotunda* ethanolic extract were cyclohexenyl chalcone derivatives (Eng-Chong et al., 2012), where chalcone is a compound of low water solubility that requires an effective topical formulation to improve skin penetration (Mattos et al., 2015). Nanocarriers have been developed to improve the stability, solubility, and activity of *B. rotunda* extracts, and their pure compounds. According to Atun and Handayani (2017), chitosan or alginic acid nanoparticles produced by the ethanol extract of *B. rotunda* exhibited a 197–877 nm size range of nanoparticles (+41.87 mV), where the zeta potentials depended on the components of nanoparticles, such as a positive charge for chitosan nanoparticles or negative charge for alginic acid nanoparticles (-82.10 mV).

The development of SLN formulations can provide distinctive properties, such as the capacity to improve the solubility of poor water-soluble drugs. They can also improve bioavailability, enhancing their targeting potential, cellular uptake, and their biological compatibility. SLNs are generally regarded as carriers with reduced toxicity (Silva et al., 2019). In addition, *B. rotunda* extract- loaded nanoparticles showed higher antioxidant activity than the starting material ethanol extract of *B. rotunda* (Atun and Handayani, 2017). In the case of skin hydration, a cornified envelope is well recognized as a marker of skin hydration and barrier function, with 1 µM PA (0.000041% w/v) markedly increasing the cornified envelope to 35%, compared to the non-treated control (Woo et al., 2015). This suggested that the concentration of PA in SLN4 was high enough to increase the marker of skin hydration. Therefore, successfully loading PA into SLN4 as a suitable lipid nanocarrier was evaluated in our study.

3.3 *In vitro* release and skin permeation study

As shown in Figure 3, SLN4 forcefully releases PA through the dialysis membrane higher than oil (control) at all sampling times. Although PA suspended in 50% ethanol was released entirely at 72 h (data not shown), a high percentage of ethanol is unsuitable for cosmetic products. Therefore, the aqueous and oil phase of SLNs were compatible with the biological system, making them potential candidates for nanocarriers based drug delivery of lipophilic drugs. Decreasing the drug mobility in a solid matrix and improving the absorption of a poor water-soluble drug from SLNs offers potentially beneficial effects to enhance the solubility and bioavailability of lipophilic drugs and release them far better than emulsions (Gupta et al., 2017; Rao et al., 2022). In this study, SLN4 exhibited high PA release into the receiver compartment, suggesting the ability to release an active compound after applying the formulation.

No PA was detected in any receiver medium up to 24 h. The amount of PA-loaded SLN4 that permeated through the skin was 7.51 µg at 24 h. The PA-dissolved in oil that did not permeate through the skin was found to deposit 1.47 µg into the skin at 24 h. These results indicate that SLN4 increased the permeability of PA through the skin. SLNs have beneficial properties for topical drug therapy, including biocompatible ingredients, drug release modifications, skin adhesion, and film formation with the subsequent hydration of the superficial skin layers. An occlusive film from intact SLNs on the top layer of the skin surface plays an important role in enhancing drug permeation (Baroli, 2010; Rangsimawong et al., 2016). In the case of PA-dissolved in oil, PA is a prenylated cyclohexenyl chalcone with a high logP value and low water solubility (Boonyarattanasoonthorn et al., 2023). The lipophilicity of the active compound is one of the factors that influence percutaneous absorption. Having high logP values (log P > 3) limits percutaneous drug absorption via the transdermal delivery route. Lipid nanoparticles for topical delivery are significant carriers of lipophilic drugs, having high log P values and a favourable molecular weight. SLNs are more effective at trapping and penetrating deep into the skin layers. The surfactant

mixtures and lipid in lipid nanoparticles play an essential part in drug encapsulation and preventing drug leakage throughout processing and delivery (Arora et al., 2017; Yu et al., 2021). Therefore, SLN4 is a suitable nanocarrier to deliver PA through the skin, presenting as a potential transdermal delivery system for cosmeceutical products.

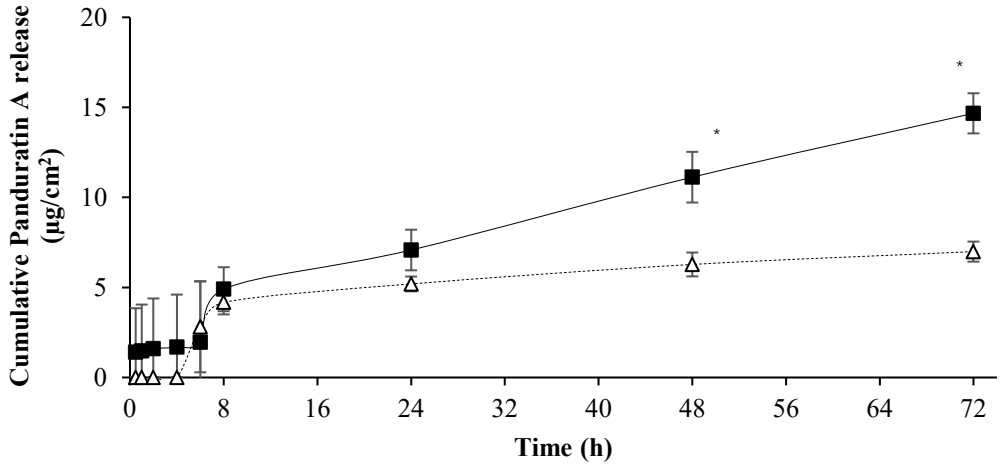

Figure 3. *In vitro* release profiles of PA from SLN4 (■) and oil (Δ) at 72 h
Note: data presents mean ± SD (n = 3)
* indicates a significant difference from oil ($p < 0.05$)

4. CONCLUSION

This study showed that PA is not toxic to keratinocyte and fibroblast cells at 1 µg/mL, indicating no cytotoxicity on skin cells. For SLN formulations, 0.1% w/v of PA-loaded SLN (SLN4) exhibited favorable properties such as the nanometer size and the highest entrapment efficiency. The release and skin permeation study showed that PA from SLN4 was released from and permeated through the skin better than from oil (control) at all sampling times. In conclusion, PA has no cytotoxicity on skin cells, making it suitable for use as a cosmeceutical ingredient. SLN4 plays an important role as a transdermal delivery system of PA, resulting from the suitable physicochemical properties and the ability to permeate the skin of nanocarriers.

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