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Research article

Formulation and Characterization of Myricetin Solid Lipid Nanoparticles (SLNs) via Ultrasonication Method

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ABSTRACT

Background: Myricetin is a flavonol flavonoid with promising neuroprotective and antioxidant activities. However, its therapeutic application is severely limited by poor water solubility and a low dissolution rate. This study aimed to enhance the solubility and formulation stability of myricetin by developing a Solid Lipid Nanoparticle (SLN) delivery system**.**

Methods: Myricetin-SLNs were prepared via the ultrasonication method using Tween 80 as a nonionic surfactant. Lipid screening was conducted using Imwitor 491, Dynasan 118, and Apifil at concentrations of 2%, 4%, and 6%. The selected lipid (Apifil at 2%, 3%, 4%, and 5%) was melted at 100 °C, homogenized with the aqueous phase using a magnetic stirrer at 2000 rpm for 1 hour, cooled to 35°C, and subjected to probe ultrasonication at 35 kHz for 5 minutes. The SLNs were characterized using a particle size analyzer and a UV-Vis spectrophotometer to evaluate storage stability, particle size, polydispersity index (PDI), entrapment efficiency, zeta potential, and DPPH free radical scavenging activity.

Results: Lipid screening revealed that Apifil-based formulations provided superior physical stability compared to Imwitor 491 and Dynasan 118. The optimized formulation, F7 (containing 2% Apifil), yielded the smallest particle size of 105.5 ± 0.70 nm, a highly homogeneous PDI of 0.232, a zeta potential of -20.52 mV, and the highest entrapment efficiency at 73.56%. Furthermore, F7 demonstrated strong antioxidant activity with an IC_{50} value of 38.77 ppm, compared to pure myricetin (14.44 ppm).

Conclusion: The formulation of myricetin into Solid Lipid Nanoparticles using 2% Apifil via ultrasonication effectively minimizes particle size and maximizes entrapment efficiency. Although it exhibits lower long-term storage stability at room temperature, it successfully preserves potent antioxidant activity, offering a promising approach for health sciences and advanced drug delivery applications.

INTRODUCTION

Myricetin is a flavonoid compound belonging to the flavonol subclass, characterized by hydroxyl substitutions at the 3, 5, 7, 3′, 4′, and 5 positions. This was demonstrated in a study by Qu (2006), where myricetin inhibited free radicals by 71.5% with an IC_{50} value of 9 µg/mL using the DPPH assay.

Although myricetin can be utilized as an active pharmaceutical ingredient, it suffers from poor solubility and low bioavailability. Low solubility and permeability impede the absorption process of poorly water-soluble drugs, thereby affecting their pharmaceutical availability under the Biopharmaceutics Classification System (BCS). Myricetin is classified as a BCS Class II drug, meaning it possesses high permeability but low solubility. Since solubility directly influences a drug's bioavailability, this

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limitation is highlighted by studies showing that the bioavailability of quercetin—a typical flavonoid—is less than 17% in rats (Yao, 2014) and even lower at approximately 1% in humans (Chan, 2003). Drugs with low solubility consequently exhibit a low dissolution rate, leading to incomplete absorption and poor bioavailability (Shargel and Yu, 2005).

To overcome myricetin's solubility issues, several methods have been employed, such as liposomes (Landi-Librandi et al., 2011), microemulsions (Zhang et al., 2010), solid dispersions (Wang, 2012), and β-cyclodextrin inclusion complexes (Wang et al., 2008). In a study by Hong (2014), myricetin was formulated into a nanosuspension via ultrasonication, which effectively enhanced its solubility. This approach yielded a physically stable formulation with particle sizes ranging between 300–500 nm and significantly improved bioavailability in rats.

Researchers continue to develop nanotechnology as a viable drug delivery system to enhance the water solubility and bioavailability of poorly soluble drugs. Additionally, it can be utilized to evaluate biodistribution within specific tissues, thereby establishing a toxicokinetic profile (chaulandu, 2012). One of the most frequently used types of lipid-based nanoparticles is the Solid Lipid Nanoparticle (SLN) (Bonifácio, 2014). The advantages of SLNs include enhancing the solubility and oral bioavailability of poorly water-soluble drugs (Hu, 2016), while remaining free from cytotoxicity, and offering targeted as well as controlled drug release characteristics. The primary components of SLNs are biologically safe lipids or lipid-group compounds (biodegradable and biocompatible), which heavily influence the resulting physicochemical characteristics, stability, and release profile (Qian et al., 2011).

One method used to prepare SLNs is ultrasonication, which breaks down particles into the nanoscale using ultrasonic waves specifically acoustic waves with a frequency greater than 20 kHz that generate a cavitation effect (Nakahira, 2007). The ultrasonication technique is widely used in nanoparticle fabrication, particularly for SLNs, because it is a simple and effective method that does not require organic solvents. However, a major drawback of this method is a wider particle size distribution that can extend into the micrometer range. Metal contamination caused by the sonication probe is also a challenge in this technique. To address these limitations, high-speed stirring (homogenization) is integrated at elevated temperatures above the melting point of the solid lipid. This study was conducted to formulate SLN preparations using the ultrasonication method with myricetin as the active pharmaceutical ingredient, combined with specific types of solid lipids and surfactants. Characterization of the myricetin-SLNs includes particle size, particle size distribution, solubility, zeta potential, UV-Vis spectrophotometry, and stability.

METHODS

Design and Samples

The initial stage of preparation involved lipid screening using Imwitor 491, Dynasan 118, and Apifil at concentrations of 2%, 4%, and 6%. The selected lipid (Apifil at 2%, 3%, 4%, and 5%) was melted at a temperature of 100 °C. The aqueous phase, consisting of Tween 80 and demineralized water, was added gradually into the melted lipid phase and homogenized using a magnetic stirrer at 2000 rpm for 1 hour. The temperature was incrementally decreased to 35 °C, after which myricetin was added. The mixture was then subjected to ultrasonication at a frequency of 35 kHz for 5 minutes.

Table 1. Ingredients

Ingredients		F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid Lipid(%)	Imwitor 491	2	4	6	-	-	-	-	-	-
	Dynasan 118	-	-	-	2	4	6	-	-	-
	Apifil	-	-	-	-	-	-	2	4	6
Surfactant (%)	Tween 80	20	20	20	20	20	20	20	20	20
Demineralized Water *Ad* (ml)		50	50	50	50	50	50	50	50	50

Research instrument and data collection

The equipment used in this study included a particle size analyzer and a UV-Vis spectrophotometer. The materials used were myricetin, lipids (Imwitor 491, Dynasan 118, and Apifil), Tween 80, demineralized water (*aquademineralisata*), and 1,1-diphenyl-2-picrylhydrazyl (DPPH).

The storage stability was evaluated via visual observation to assess physical stability and precipitate formation at room temperature over a 2-week period. The myricetin-SLN formulation that yielded the smallest particle size was evaluated for its stability at room temperature over a 2-week storage period, with observations conducted on a weekly basis.

For the antioxidant assay, a 157 ppm DPPH solution was prepared. The myricetin standard solutions were prepared at concentrations of 1.94, 3.88, 7.75, 15.5, and 31 ppm. Meanwhile, the SLN formulation samples were prepared at concentrations of 3.125, 6.25, 12.5, 25, 40, 60, and 80 ppm within 10 mL amber volumetric flasks using ethanol as the solvent. From each concentration, a 1 mL aliquot was mixed with 1 mL of the DPPH solution and 3 mL of ethanol, followed by incubation during the predetermined operating time (OT). The absorbance of each mixture was measured using a UV-Vis spectrophotometer at the maximum absorption wavelength of 516 nm.

Data Analysis

The percentage of DPPH free radical scavenging activity was calculated to determine the antioxidant capacity. The percentage of inhibition was evaluated using the following formula:

$$\%\text{Inhibition} = \frac{\text{Absorbance of Control} - \text{Absorbance of Sample}}{\text{Absorbance of Control}} \times 100\%$$

The antioxidant activity against DPPH is expressed as the IC_{50} value, which represents the concentration of the test compound required to achieve 50% free radical scavenging.

RESULTS

The initial characterization and optimization involved matrix screening across nine base formulations using different solid lipids. The formulation composition matrix is detailed in Table 1. Based on the screening, advanced evaluations were conducted on the selected core formulations utilizing Apifil as the solid lipid base, as presented in Table 2.

Table 2. Composition of Selected Myricetin-SLN Formulations

Formula	Myrisetin (%)	Apifil (%)	Tween 80 (%)	Demineralized Water
F7	0,02	2	20	Add 50 ml
F8	0,02	3	20	Add 50 ml
F10	0,02	4	20	Add 50 ml
F11	0,02	5	20	Add 50 ml

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DISCUSSION

Critical experimental conditions that require careful consideration include the magnetic stirring speed and the concentration of each lipid used, which were evaluated based on visual stability over a 4-week period. In this study, myricetin was utilized as the active pharmaceutical ingredient to formulate the Solid Lipid Nanoparticles (SLNs). Additional excipients included the lipids Apifil, Dynasan, and Imwitor 491, with Tween 80 employed as the surfactant.

The lipid Apifil yielded a superior particle size distribution and physical stability compared to Imwitor 491 and Dynasan. The latter two lipids tended to solidify more readily at room temperature due to agglomeration, which triggered substantial particle growth within a few days. This phenomenon occurs because of an increase in the partial glyceride content, such as monoglycerides (Jenning et al., 2000; Souto et al., 2013). This was further confirmed during the lipid screening process: formulations containing Imwitor 491 at 2% (F_1), 4% (F_2), and 6% (F_3), as well as Dynasan at 2% (F_4) and 4% (F_5), exhibited instability by the second week. In contrast, formulations with Apifil at 2% (F_7) and 4% (F_8) remained stable up to the fourth week. Although Dynasan at 6% (F_6) maintained stability through the fourth week, visual observations of its turbidity and viscosity indicated that it would likely produce larger particle sizes.

The observed instability was also influenced by the Hydrophilic-Lipophilic Balance (HLB) between the lipid and the surfactant, as an optimal HLB facilitates the rapid formation of nanoemulsions in water. Dynasan possesses long hydrocarbon chains and lacks functional polar groups, resulting in a large molecular size. Consequently, it cannot penetrate the hydrocarbon region on the surface of Tween 80, which hinders nanoemulsion formation and leads to rapid phase separation (Boonme, 2013).

Tween 80 was selected as the surfactant at a concentration of 20% because it is a nonionic surfactant characterized by its non-toxic, non-irritating nature, and its ability to effectively reduce the interfacial tension between oil and water (Cristina, 2013). Furthermore, it can produce nanoparticles within the targeted nanoscale range of less than 200 nm. Tween 80 features an unsaturated hydrophobic chain; generally, a longer hydrophobic chain in a surfactant exerts a greater positive influence on the water solubility of a drug. Tween 80 also provides steric stabilization to the particles, preventing the nanoparticles from agglomerating with one another (Shi, 2002; Libo et al., 2011).

Table 3. Particle Size Distribution and PDI Characterization

Formulation Code	Particle Size (nm)	Polydispersity Index (PDI)
F7	105.5 ± 0.70	0.232
F8	209.1 ± 10.88	0.744
F10	187.0 ± 0.87	0.430
F11	113.3 ± 0.76	0.749

Particle size is the most critical characteristic in a nanoparticle delivery system. The use of surfactants directly influences the particle size, polydispersity index (PDI), and the stability of the resulting SLN emulsion. Surfactants function as stabilizers by occupying the interface between the droplets and the external phase, thereby forming a physical barrier around the particles to prevent coalescence, keeping the two immiscible liquids separated, and reducing the intermolecular attractive forces within each liquid (Ansel, 2008). In alignment with these experimental findings, F_7 utilized a surfactant concentration higher than its lipid content. Conversely, F_8, F_9, and F_{10} did not exhibit this trend, which was likely due to the occurrence of agglomeration.

In lipid-based drug delivery systems such as SLNs and nanoliposome formulations, a PDI value of 0.3 or below is considered acceptable and indicates a homogeneous population (Badran, 2014; Putri, 2017). As shown in Table 3, the resulting polydispersity index for F_7 was 0.232, demonstrating that the myricetin-SLN formulation was a reasonably homogeneous dispersion. In contrast, a polydispersity index greater than 0.5 indicates high heterogeneity (Avadi et al., 2010), which was observed in formulations F_8 and F_{11}.

Zeta potential represents the electrical charge on a particle's surface, which can influence physical stability within a solution through electrostatic forces between particles; hence, it serves as a measure of the repulsive forces between particles (Qi et al., 2004). Most aqueous colloidal systems are stabilized by electrostatic repulsion; the stronger the repulsive forces, the less likely the particles are to coalesce and form aggregates. In this study, the zeta potential was measured exclusively for F_7, as it was the only formulation that met the ideal criteria across multiple characterization parameters. The myricetin-SLN formulation (F_7) exhibited a zeta potential of -20.52 mV over three replicates, suggesting a lower long-term stability profile. According to Rosli (2015), a colloidal dispersion system with a zeta potential value of approximately ± 30 mV is considered a stable formulation. A high positive or negative zeta potential value will cause nanoparticles to repel each other, thereby preventing the tendency toward aggregation. Consequently, nanoparticle stability is fundamentally characterized by its zeta potential.

Table 4. Entrapment Efficiency of Myricetin-SLN Formulations

Formulation	Entrapment Efficiency	Active Ingredient Content (mg)
F7	73.56% (0.7356)	19.2 mg
F8	28.89% (0.2889)	20.8 mg
F10	40.19% (0.4019)	19.8 mg
F11	42.46% (0.4246)	20.0 mg

The purpose of evaluating the entrapment efficiency is to determine the capacity of the lipid matrix to entrap the active ingredient and to assess the efficiency of the preparation method used. Factors that influence the drug loading capacity within lipids include the solubility of the drug in the molten lipid, the miscibility of the liquid drug within the liquid lipid, and the physical and chemical structures of the solid lipid matrix (Uner & Yener, 2007). If the active ingredient does not completely dissolve in the molten lipid, a portion of it will be excluded from the lipid matrix and dissolve into the external medium. The evaluation of entrapment efficiency revealed that formulations with a higher lipid content generally yielded better entrapment efficiency. This occurs because a larger lipid composition provides a greater matrix volume, resulting in a higher entrapment efficiency value; an increase in Apifil offers more

crystalline spaces for the active ingredient to be incorporated into the SLNs (Qingzhi Li, 2009). This trend was demonstrated by F_8, F_{10}, and F_{11}, where a higher lipid concentration led to a greater entrapment efficiency. However, F_7 exhibited the highest entrapment efficiency overall. This was likely because the 2% Apifil concentration allowed for the optimum entrapment of the active ingredient, achieved complete miscibility within the matrix, and provided the highest absorption capacity.

The storage stability was evaluated via visual observation to assess physical stability and precipitate formation at room temperature over a 2-week period. Precipitate formation was observed in the SLNs stored at room temperature. This phenomenon occurs because elevated temperatures increase the kinetic energy of the droplets, thereby facilitating interparticle coalescence and agglomeration. Inappropriate storage temperatures disrupt Brownian motion, which is further exacerbated by incomplete drug entrapment within the lipid matrix, alongside structural differences among the active ingredient, surfactant, and lipid.

This instability is driven by several factors, notably because Tween 80—a nonionic surfactant containing polyoxyethylene groups—is temperature-sensitive, which consequently impacts the thermodynamic stability of the system. As the temperature rises, nonionic surfactants become increasingly lipophilic due to the dehydration of the polyoxyethylene headgroup. This dehydration leads to an increase in the interfacial tension between the oil and water phases, resulting in a turbid and unstable nanoemulsion appearance. However, the observed precipitate was reversible, as it could be redispersed upon agitation.

The antioxidant activity analysis of myricetin demonstrated a decrease in absorbance, indicating the scavenging of DPPH free radicals by myricetin. This reduction in absorbance is attributed to the presence of phenolic compounds, which exhibit antiradical activity due to their functional groups, particularly the hydroxyl (-OH) groups. These groups react radically with DPPH, thereby reducing the absorption intensity at the maximum wavelength of DPPH (Zheng, 2010).

The pure myricetin showed an IC_{50} value of 14.44 ppm over three replicates, which is categorized as a very potent antioxidant activity. The antioxidant assay was also performed on the optimized formulation (F_7), which met the ideal nanoparticle characterization criteria. F_7 yielded an IC_{50} value of 38.77 ppm, which is classified as a potent antioxidant activity. This decrease in activity, who noted that antioxidant capability in a sample can decline due to environmental oxidation, such as exposure to excessive heat during the active ingredient mixing process. Furthermore, the reduction in scavenging activity is influenced by the incorporation and dilution of the active ingredient with other excipients within the SLN matrix.

CONCLUSION

Based on the research findings, it can be concluded that myricetin Solid Lipid Nanoparticles (SLNs) can be successfully prepared using the ultrasonication method. However, the myricetin-SLNs exhibited physical instability by the second week, characterized by phase separation and the formation of a reversible precipitate. The characterization of myricetin within the SLNs using the optimized lipid, 2% Apifil (F_7), yielded the smallest particle size of 105.5 ± 0.70 nm, a zeta potential of -20.52 mV, an entrapment efficiency of 73.56%, and potent antioxidant activity with an IC_{50} value of 38.77 ppm.. .

CONFLICTS OF INTEREST

No conflicts of interest were disclosed by the writers of this work

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