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FORMULATION AND CHARACTERISATION OF QUERCETIN NIOSOMES WITH VARIOUS CONCENTRATIONS OF SPAN 20 SURFACTANT

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ABSTRACT

Quercetin has low solubility, absorption and bioavailability which limits its practical use as a drug or supplement. Therefore, it is important to formulate a quercetin niosome system with various concentrations of span 20 as a surfactant. This investigation aimed to formulate and analyse a quercetin niosome preparation with span 20 variations to provide optimal quercetin solubility. Niosomes were prepared using various concentrations of span 20. In the present study, the quercetin niosome used the reverse phase evaporation (RPE) method. Quercetin niosome is characterised by its organoleptic properties, pH value, particle morphology comprising the particle shape and size, and encapsulation efficiency. Organoleptic observations of the quercetin niosome included a yellow colour, distinctive quercetin odour and thick consistency for all formulas. The pH remained within the physiological pH range of skin. Quercetin niosome morphology was close to spherical while the niosome particle size results were 2.13 µm (F1), 2.99 µm (F2) and 3.31 µm (F3). The quercetin niosome encapsulation efficiency results were 81.86 ± 0.47% (F1), 84.02 ± 0.26% (F2) and 88.24 ± 0.10% (F3). Quercetin niosome were successfully prepared using multiple span 20 concentrations below the cholesterol concentration characterised by the measurement results of organoleptic, pH, particle morphology and encapsulation efficiency.

Keywords: Quercetin; niosome; surfactants; span 20; RPE method

INTRODUCTION

Quercetin (3,3′, 4′, 5, 7-pentahydroxyflavone) is a naturally occurring flavonoid compound found in many vegetables, fruits and nuts. These compounds are found in apples, onions, tomatoes, broccoli, lettuce, black tea and green tea (Patel *et al*., 2018; Rothwell *et al*., 2013). A large number of important pharmacological activities of quercetin have been identified in recent years. Thus, interest in using quercetin as a medicinal or supplementary ingredient has grown rapidly. Quercetin has been reported to exhibit high antioxidant, antitumor, anti-inflammatory, antimicrobial, antibacterial and antiviral activity (D'Andrea, 2015; Gonta *et al*., 2020; Lesjak, 2018; Lin & Zhou, 2018; Pal & Tripathi, 2020a, 2020b, 2019; Wang *et al*., 2016; Xu *et al*., 2019). Additionally, it has also been reported to exhibit antithrombotic, anti-aggregatory and vasodilating activity (Chondrogianni *et al*., 2010; Chopra *et al*., 2000; Erlund *et al*., 2000).

However, the low solubility, absorption and bioavailability of quercetin limit its practical use as a drug or supplement, and thus a wealth of research has been conducted to address these issues (Praven, 2014; Sadeghi-Ghadi, 2020). Notably, various drug delivery systems have been developed to increase the water solubility of quercetin (Lesjak *et al*., 2018; Saik *et al*., 2020; Wang *et al*., 2016).

Non-ionic surfactant vesicles or niosomes, which are formulated with non-ionic

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surfactants in aqueous solutions with certain technology, were first used in the development of cosmetic preparations. Niosomes are typically multilamellar or unilamellar vesicles that have a closed double layer with hydrophilic cavities, both as internal and hydrophobic shells, as the outer layer to accommodate active substances (Chen *et al*., 2019; Ge *et al*., 2019).

Niosomes are composed of active medicinal ingredients, non-ionic surfactants and cholesterol or their derivatives. The active ingredients of the drug, both hydrophilic and hydrophobic, can be encapsulated in the niosome system. Notably, non-ionic surfactants, such as span 20, play a crucial role in forming good niosome systems (Barani *et al*., 2018).

The solubility of quercetin can be increased by several delivery systems such as liposomes (Gang *et al*., 2012; Goniotaki *et al*., 2004; Wong & Chiu, 2011), PEG-liposomes (Yuan *et al*., 2006), PLGA-PEG-EIMA nanoparticles (Khoee & Rahmatolahzadeh, 2012), nickel nanoparticles (Guo *et al*., 2009), LeciPlex (Date *et al*., 2011), nanoribbons (Han *et al*., 2012) and niosomes (Lu *et al*., 2019). Niosomes can improve the solubility of flavonoid components including myricetin, routine, festin, morin, breviscapine and quercetin (Lu *et al*., 2019). While many types of non-ionic surfactants can form niosomes (Cerqueira-Coutinho *et al*., 2016; Manosroi *et al*., 2003; Uchegbu & Florence, 1995), non-ionic surfactants with unsaturated hydrocarbon chains are less stable than non-ionic surfactants with saturated hydrocarbon chains such as span 20 (Abdelbary & El-gendy, 2008). Most recent studies have prepared quercetin niosomes using span 20 and certain cholesterol ratios of 1:1 and 2:1 (Elmowafy *et al*., 2020). However, these studies have not obtained optimal solubility results. Therefore, further research considering several concentrations of span 20 is required.

In the present study, we performed a niosome formulation using multiple span 20 concentrations below the cholesterol concentration. Quercetin niosome system is characterised by its organoleptic properties, pH value, particle morphology (particle shape and size) and encapsulation efficiency. In this particular research, quercetin niosome system manufacture was completed using reverse phase evaporation (RPE) method.

METHODS

Materials and instruments

The instruments used in this research included a 510 type pH meter by Eutech Instruments from Singapore, Hei-VAP core rotary evaporator by Heidolph from Germany, UV-1601 spectrophotometer by Shimadzu from Japan, FLEXSEM 100 scanning electron microscope (SEM) by Hitachi from Japan, S10H ultrasonic cleaner by Elma from Germany, magnetic stirrer by Mettler Toledo from Germany, and other glassware.

The materials used included quercetin by Sigma-Aldrich in U.S.A., sorbitan monolaurate span 20 HLB 8.6 by Sigma-Aldrich from U.S.A., cholesterol by Sigma-Aldrich from U.S.A., chloroform by Merck from Germany, distilled water and phosphate-buffered saline (KH_2PO_4 and NaOH) by Merck from Germany.

Formula optimisation

Niosomes with active ingredient quercetin were formulated using various concentrations of span 20 as a non-ionic surfactant and cholesterol as a stabiliser. We used multiple concentrations of span 20 with 1:1 ratio between surfactant and cholesterol. Chloroform was used as a solvent for cholesterol, and distilled water was used as a solvent for quercetin while phosphate-buffered saline was in a liquid phase (see Table 1). This optimisation is based on a recent study by Elmowafy *et al*. (2020) with slight modifications of multiple span 20 concentrations with 1:1 ratio of surfactant and cholesterol.

Quercetin niosome preparation

Quercetin niosomes were prepared using the RPE method according to Figure 1 (Moghassemi & Hadjizadeh, 2014). Quercetin, span 20 and cholesterol were carefully weighed using an analytical balance.

Cholesterol and span 20 were then dissolved in chloroform while quercetin was dissolved in distilled water and magnetically stirred. The quercetin solution was added to the mixture of span 20 and cholesterol which had been added to chloroform to produce a two-phase mixture and homogenised with a magnetic stirrer. The mixture was then sonicated for 16 minutes at a temperature of 4^0C to 5ºC to form a mixture. Phosphate-buffered saline with pH of 6.0 was added and sonicated for 12 minutes at a temperature of 4^0C to 5ºC until single phase was formed. The organic phase, i.e., chloroform, was removed using a rotary evaporator at a temperature of 40ºC and pressure of ±200 mmHg. Furthermore, the niosomes were heated in a water bath at 60ºC for 10 minutes until a certain consistency was obtained (Shegokar *et al*., 2011; Zarei *et al*., 2013).

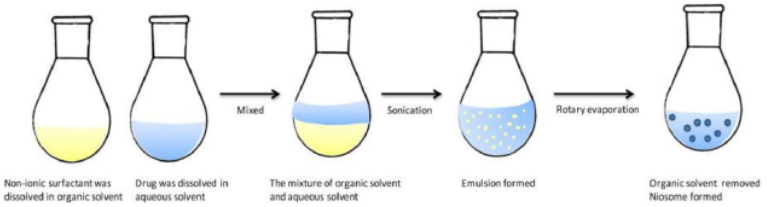

Figure 1. Reverse Phase Evaporation (RPE) method of noisome.

Quercetin niosome characterisation

Organoleptic

The organoleptic test was performed visually based on the respondents' assessments on the colour, smell and shape. A total of ten respondents, who were pharmacy students, participated in the testing. While other authors have measured the organoleptic preparation of drugs using this method (Płocica *et al*., 2013), we used a smaller number of respondents.

Determination of pH value

To determine the pH value, 10 mL of each quercetin niosome preparation formula was placed into a glass beaker and recorded using a 510 type pH meter. The pH meter electrode was washed with distilled water, and then dried with a tissue. The pH meter was standardised with a buffer solution of pH 6.0. Then, the electrodes were rinsed again with distilled water and dried. Determination of the pH value was performed using three replicates.

Particle morphology

Analysis on the particle morphology of quercetin niosome preparations included the assessment of niosome particle shape and diameter. The shape and diameter of the particles were tested using a FLEXSEM 100. First, 20 mL of the sample in each formula was dried using freeze dryer method. The dried sample was placed in an SEM holder. The holder was then inserted into the specimen chamber of FLEXSEM 100 for observation and image acquisition. Observations were made at 5000 and 25000 X magnification.

Determination of encapsulation efficiency

A 1 mL volume of the prepared niosome was dissolved in phosphate-buffered saline with pH of 6.0 at a ratio of 1:10. The aqueous suspension was centrifuged at 6000 rpm for 60 minutes. Up to 1 mL of the obtained supernatant was pipetted and placed into a 10 mL volumetric flask. Then, the volume was adjusted up to the limit line using phosphate-buffered saline. Thereafter, 1.0 mL of the solution was pipetted and added to the phosphate-buffered saline in a 10 mL volumetric flask. The volume was then adjusted up to the limit line using the pH 6.0 phosphate-buffered saline. Afterward, 1.0 mL of the solution was pipetted and added to phosphate-buffered saline with pH of 6.0 in a 10 mL volumetric flask, and filtered using filter paper. The solution was then measured

for absorption at a wavelength of 368 nm. Furthermore, the amount of quercetin that was either encapsulated or not using the niosome, i.e., encapsulate efficiency, was calculated using the standard curve equation via a UV-1601 spectrophotometer. The encapsulation efficiency of quercetin niosome can be calculated using the following formula.

Encapsulation efficiency:

$$\frac{\text{Drug encapsulated amount}}{\text{Drugs used in the formulation}} x\ 100$$

Data analysis

The pH and encapsulation efficiency values were expressed as mean ± standard deviation (SD) based on the three replicates of the test. The data obtained from the pH value and encapsulation efficiency testing of three formulas were analysed using one-way ANOVA statistical test ($\alpha = 0.05$). Further analysis was then performed using the honestly significant difference or HSD test. All tests were performed using SPSS 15 (SPSS Inc., U.S.A.).

RESULTS AND DISCUSSION

In the present study, quercetin niosomes were successfully prepared and characterised by measuring their organoleptic characteristics, pH value, particle morphology and encapsulation efficiency. The quercetin niosomes were formulated using the active ingredient quercetin, various span 20 concentrations, cholesterol, chloroform, CO_2-free distilled water and phosphate-buffered saline (Table 1). Formula 1 used a span 20 concentration of 7.74%, formula 2 used a concentration of 8.74% and formula 3 used a concentration of 9.74%.

Table 1. Quercetin niosome formula with various concentrations of span 20

No.	Materials	Functions	F1 (%)	F2 (%)	F3 (%)
1	Quercetin	Active ingredient	1.8	1.8	1.8
2	Span 20 (HLB 8,6)	Surfactant	7.74	8.74	9.74
3	Cholesterol	Stabilizer	9.94	9.94	9.94
4	Chloroform	Cholesterol solvent	39	39	39
5	Aquadest	Quercetin solvent	2.27	2.27	2.27
6	Phosphate buffer saline	Liquid phase	add 100	add 100	add 100

Note.
F1: Formula 1 with a surfactant concentration of 7.74%
F2: Formula 2 with a surfactant concentration of 8.74 %
F3: Formula 3 with a surfactant concentration of 9.74 %

The active ingredient, quercetin, has low solubility, absorption and bioavailability despite having many benefits as a medicinal and supplement ingredient. Thus, it is necessary to create a delivery system that can improve its properties—one of which is niosome preparations (Lesjak *et al*., 2018; Saik *et al*., 2020; Wang *et al*., 2016). Additionally, niosomes also have advantages in transdermal drug delivery such as sustained drug release, improved penetration and higher skin retention (Kumar & Goindi, 2014). Moreover, they are cheaper to prepare and more stable than liposome (Cerqueira-Coutinho *et al*., 2016).

Non-ionic surfactants such as terpenoids (Puras *et al*., 2014), polysorbate (Primavera *et al*., 2018), span (Barani *et al*., 2018), alkyl oxyethylene which usually contains C12 to C18 groups (Berlepsch *et al*., 2018; Tavano *et al*., 2013) and others are reported to have important roles in niosome preparations. Notably, span 20 can significantly increase the encapsulation efficiency of the drugs due to

the interaction between the drug and the span acyl chain (Barani *et al*., 2018). Cholesterol, when used in appropriate amounts, increases the stiffness and stability of the colloid formula, the transition temperature of the niosome gel fluid and the interaction with non-polar surfactant groups (Barani *et al*., 2019). Furthermore, chloroform functions as cholesterol solvent, distilled water is used to dissolve quercetin and phosphate-buffered saline in liquid phase functions as a pH stabiliser for niosome preparations (Moghassemi & Hadjizadeh, 2014).

This study used RPE method to developed quercetin niosome preparations. The experiments were performed by dissolving non-ionic surfactants and other additives in an organic solvent. However, the active ingredients were dissolved in polar solutions, e.g., water or PBS, and then added to the organic phase to form an emulsion under sonication. Organic solvents were evaporated using a rotary vacuum evaporator at 40^0C to 60ºC to form a niosome system (Jain & Vyas, 2006; Shegokar *et al*., 2011; Zarei *et al*., 2013). Compared to the thin film hydration (TFH) method, vesicles prepared using the RPE method can produce nanoparticles with uniform sizes and unilamellar or oligolamellar structures (Ge *et al*., 2019).

In the present study, the organoleptic characteristics of niosomes included a yellow suspension with a distinctive smell of quercetin and thick consistency. None of the formulas exhibited specific differences in terms of colour, odour or consistency because the quercetin concentration added to each niosome formula was similar, and span 20 did not affect the organoleptic properties of the niosomes. The results of pH measurements were 6.10 ± 0.10, 6.13 ± 0.06, and 6.16 ± 0.06 for formulas 1, 2 and 3 respectively. Thus, the three formulas had no specific differences in pH value. Notably, pH value affects the availability of the quercetin in molecular form. In their molecular forms, quercetin can penetrate easily. Additionally, it is expected that the pH of the preparation will not deviate greatly from the range of pH values for skin which ranges from 4.0 to 6.8 (Ge *et al*., 2019) so as not to irritate the skin (Table 2). Thus, it is very suitable for use as a topical drug model.

Table 2. Characteristics of quercetin niosome

No.	Characteristics		F1	F2	F3
1	Organoleptic	Color	Yellow	Yellow	Yellow
		Smell	Quercetin	Quercetin	Quercetin
		Consistency	Thick	Thick	Thick
2	pH Value*		6.10 ± 0.10	6.13 ± 0.06	6.16 ± 0.06
3	Particle morphology	Shape	Spherical	Spherical	Spherical
		Diameter	2.13 µm	2.99 µm	3.31 µm
4	Encp. efficiency*		81.86 ± 0.47%	84.02 ± 0.26%	88.24 ± 0.10%

Note.
*: The test was carried out for 3 replications indicated by ± Standard Deviation
F1: Formula 1 with a surfactant concentration of 7.74%
F2: Formula 2 with a surfactant concentration of 8.74 %
F3: Formula 3 with a surfactant concentration of 9.74 %

The niosome morphology observations for each formula were performed using a FLEXSEM 100 at magnifications of 5000 and 25000 X. An SEM is an electron microscope designed to describe the surface shapes of materials analysed using an electron beam. The main functions of SEM are related to finding topographic (surface characteristics), morphological (shape and size of the particles making up objects) and crystallographic information of the objects being analyzed. The working principle of SEM is associated with the wave property of electrons namely diffraction at small angles. Notably, samples

destined for SEM analysis must be solid. Since the niosome samples were in the form of a suspension, they had to be dried. Drying was performed using a freeze dryer. The working principles of the freeze dryer include freezing the solution, granulating the frozen solution and conditioning it in an ultra-high vacuum with moderate heating, so that the water in the preparation will sublimate and produce a solid preparation (Al Qtaish *et al*., 2020; Ge *et al*., 2019).

Based on observation results using SEM magnifications of 5000 and 25000 X for the F1, F2 and F3 groups, niosome shapes were spherical with average niosome particle diameters that were different for each formula i.e., 2.13, 2.99 and 3.31 µm for F1, F2 and F3 respectively (Table 2 and Figure 2). According to literature, the shape of niosome particles is spherical (Mehta *et al*., 2011). However, niosome sizes can vary widely from approximately 20 nm to 50 µm (Tangri & Khurana, 2011). Size and shape are very critical to the pharmacokinetics, bio-distribution, toxicity and stability of niosomes (Ge *et al*., 2019). This observation may be due to the effect of the strong affinity for drugs and niosomes to hold different lamellae together, thereby making the membranes more rigid (Kumar & Goindi, 2014).

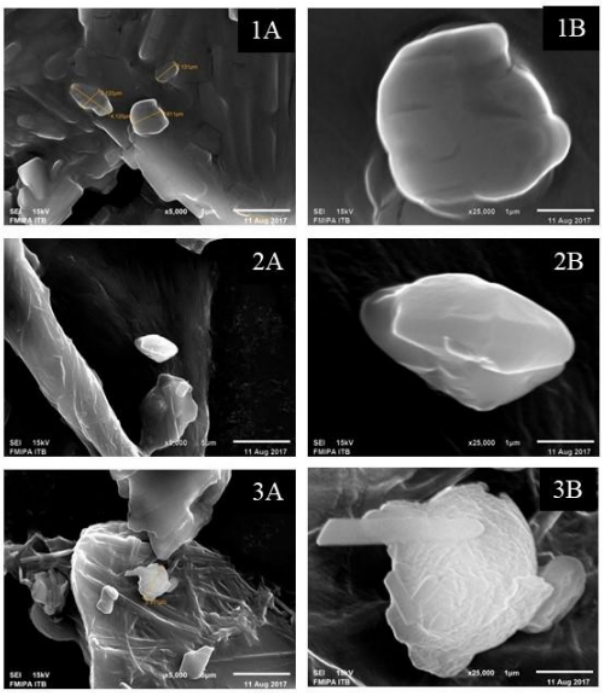

Figure 2. Particle shape and diameter of quercetin niosome particles tested using SEM instrument.

Note.

(1A) Formula 1 with magnification of 5000 X, (1B) Formula 2 with magnification of 25000 X, (2A) Formula 2 with magnification of5000 X, (2B) Formula 2 with magnification of 25000 X, (3A) Formula 3 with magnification of 5000 X, (3B) Formula 3 with magnification of 25000 X

The encapsulation efficiencies of the studied niosomes of F1, F2 and F3 were 81.86 ± 0.47%, 84.02 ± 0.26% and 88.24 ± 0.10% respectively (Table 2). These data indicate that increasing the concentration of span 20 can significantly increase the encapsulation efficiency of a niosome system. This could be attributed to the HLB value of span 20, i.e., 8.6, which could have heightened the hydrophobicity of the bilayer

domain and greatly increased the amount of quercetin loaded (Gilani *et al*., 2019). Increasing the amount of surfactant and keeping the amount of cholesterol constant can decrease the stiffness of the double layer and promote the niosomal form of drug leakage (Elmowafy *et al*., 2020), which is consistent with a previous study (Mali *et al*., 2013). Moreover, it is reported that an encapsulation efficiency of 75% to 90% is required to form niosomes of good quality (Dan, 2017).

CONCLUSION

Quercetin niosomes with various span 20 concentrations were successfully prepared and characterised by measuring their organoleptic characteristics, pH, PS and EE% values. Organoleptic observations of the quercetin niosome systems noted a yellow colour, typical quercetin odour and thick consistency among all formulas. The obtained pH values remained within the physiological pH range of skin for F1 (6.10 ± 0.10), F2 (6.13 ± 0.06) and F3 (6.16 ± 0.06). The quercetin niosome morphology results indicated shapes close to a complete sphere while the results for niosome particle size were 2.13, 2.99 and 3.31 µm for F1, F2 and F3 respectively. Moreover, the encapsulation efficiencies of quercetin niosomes were 81.86 ± 0.47, 84.02 ± 0.26 and 88.24 ± 0.10% for F1, F2 and F3 respectively. Notably, encapsulation efficiency exhibited significant differences between F1, F2 and F3. However, the encapsulation efficiency values of the three quercetin niosome formulas remained within the required range.

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