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Original Research Article

Characterization and Penetration of Quercetin Spanlastic Gel with Span 60 as Vesicle Builder and Edge Activator of Brij 35 and Tween 60

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ABSTRACT

Aging is a process in which the skin undergoes degenerative changes caused by intrinsic and extrinsic factors. Quercetin has characteristics that demonstrate antioxidant potential. This research aimed to determine the effects of edge activators (EAs), namely, Tween 60 and Brij 35, on the characteristics and penetration of quercetin spanlastic gel with Span 60 as a vesicle builder. Spanlastic was made using the thin-layer hydration method and then formulated in an HPMC 4000 gel; its composition consisted of Span 60–Brij 35 (B1) and Span 60–Tween 60 (T1) at a ratio of 9:1. Characterization included particle size, the polydispersity index, entrapment efficiency, and drug loading. A penetration test was carried out in vivo on male balb/c mice with six samples, namely, F1 (quercetin spanlastic with EA Tween 60), F2 (quercetin spanlastic with EA Brij 35), F3 (quercetin spanlastic gel with EA Tween 60), F4 (quercetin spanlastic gel with EA Brij 35), K (quercetin gel), and R (gel base). Quercetin spanlastic F1 and F2 had a high entrapment efficiency of 94.48-99.06%, a drug loading of 0.142-0.158%, and a size of 841.2-1443.0 nm. F1 and F2 penetrated better than K and R, and F2 penetrated better than F1. Although quercetin spanlastic gel F3 and F4 also showed a good penetration ability, it was not as good as that of quercetin spanlastic F1 and F2. Spanlastic and spanlastic gel demonstrate potential which may be beneficial as innovative delivery systems.

Keywords: Quercetin, Spanlastic, Span 60, Tween 60, Brij 35, Penetration, Aging, Vesicle

Introduction

Aging (skin aging) is a process in which the skin undergoes degenerative changes, such as the appearance of fine lines, wrinkles, the thinning of the epidermis, uneven pigmentation, and a decrease in elasticity.[1] Aging can be caused by intrinsic factors (oxidants resulting from the body's natural metabolism) and extrinsic factors (pollution, UV radiation, and lifestyle). The impact of aging is generally unpredictable, prompting extensive research to identify anti-aging agents, one of which is quercetin. Quercetin is a flavone group compound with various pharmacological activities, including a strong antioxidant effect, as it contains three -OH groups in the C ring and 3',4'-catecol in the B ring.[2,3] Due to its strong antioxidant ability, quercetin is used as a potent anti-aging agent.[4] Quercetin has characteristics that may inhibit its effectiveness on the skin; that is, its structure is in the form of a nonpolar carbon ring, which makes it -difficult to dissolve in water (Biopharmaceutical Classification System (BCS) Class II), and it contains multiple hydroxyl groups, which hinder its penetration of the stratum corneum.[5,6,7]

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Therefore, an adequate delivery system is needed, including spanlastic, to facilitate the penetration of quercetin into the dermis layer of the skin. Spanlastic is able to increase the solubility of compounds entrapped in it because its structure is composed of non-ionic surfactants, namely, Span 60 as a vesicle builder (VB) and a hydrophilic surfactant as an edge activator (EA)[8]. Spanlastic has the characteristics of a membrane that is elastic and easily deformed when interacting with the skin membrane, so it can deliver more active molecules with a better flux than ordinary niosomes.[9,10] An edge activator (EA) is a component that has a high hydrophilic–lipophilic balance (HLB value) and provides deformability to vesicles by lowering the surface tension of the membrane, thereby changing the fluidity of the vesicles.[9] The composition of the VB and EA can influence the spanlastic characteristics and its effectiveness as a delivery system. In this study, two types of EAs were used: Brij 35 and Tween 60. These two types of EAs have different HLB values, carbon chain lengths, and molecular weights. This will affect the characteristics of the vesicles formed, such as their size and deformability. Size and deformability are two important factors in determining the penetration ability of spanlastic vesicles for topical use.

In this study, the thin-layer hydration is selected to form spanlastic considering the advantages of this method to increase the acceptability of the preparation, ensuring that it is not sticky, easy to clean, and able to provide a cooling effect when applied.[11] The antioxidant activity of quercetin as an anti-aging agent generally reach the dermis layer; thus, an in vivo penetration test was carried out on the back skin of balb/c strain mice (*Mus musculus*). The aim of this research was to determine the effect of different types of EAs and the effect of using a gel base on the penetration ability of quercetin spanlastic.

Materials and Methods

Materials

The following materials were used in this study: quercetin hydrate of pharmaceutical grade (p.g) (Tokyo Chemical Industry, Japan), Span 60 pro analysis (p.a) (Sigma-Aldrich, USA), Tween 60 p.a (Merck Schuchardt OHG, Germany), Brij 35 p.a (Sigma-Aldrich, UK), ethanol 96% p.a (Supelco, Germany), HPMC 4000 of p.g, methyl paraben p.a, propyl paraben p.a, propylene glycol p.a, rhodamine B (Merck, Germany), balb/c strain mice, and distilled water.

Method

Qualitative analysis of materials

A qualitative analysis was carried out on quercetin, Span 60, Tween 60, and Brij 35, covering organoleptic and FTIR spectra using FTIR-KBr (Perkin Elmer-Spectrum One, USA).

Quercetin spanlastic formula

The quercetin spanlastic formula can be seen in Table 1.

Table 1: Quercetin-loaded spanlastic formulas.

Material	Function	Components (%)	
		T1	**B1**
Quercetin	Active agent	10 mg	10 mg
Span 60	Vesicle builder	900 mg	900 mg
Tween 60	Edge activator	100 mg	-
Brij 35	Edge activator	-	100 mg
Ethanol 96%	Organic solvent	30 mL	30 mL
Aquadest	Aqueous solvent	10 mL	10 mL

Note: T1: Spanlastic formula with Tween 60 as Edge ActivatorT1: Spanlastic formula with Brij 35 as Edge Activator

Preparation of Quercetin spanlastic

Quercetin, Span 60, and EA (Brij 35 or Tween 60) were completely dissolved in 96% ethanol in a round-bottom flask. Then, the solvent was evaporated using a rotary evaporator (R-200, Büchi, Germany) (252 rpm, 55°C, vacuum) for 11 minutes until a thin layer was visible on the flask wall. Next, the thin layer was hydrated with distilled water using a rotary evaporator (252 rpm, 60°C, normal pressure) for 30 minutes until a cloudy spanlastic dispersion liquid formed. The spanlastic dispersion was sonicated 5x1 minutes and then allowed to stand for 2 hours at room temperature before being stored in a refrigerator at 2-4°C.[10]

Evaluation of quercetin spanlastic characteristics

Vesicle size and polydispersity index (PDI)

The vesicle size and spanlastic polydispersity index (PDI) were determined using a Delsa™ Nano C Particle Analyzer (Beckman Coulter, USA) with dynamic light scattering (DLS). If necessary, the sample was diluted with water until a good consistency was obtained in order to clarify the observation results. [10]

Entrapment efficiency and drug loading

A standard curve was created with quercetin working standard solution concentrations of 1, 15, 20, and 25 ppm, and the absorbance was observed at a wavelength of 373 nm using a Double-Beam Spectrophotometer UH5300 (Hitachi High-Tech, Japan). From the absorbance data, a linear regression equation was developed, $y = bx + a$, with the abscissa of the standard working concentration and the observed absorbance ordinate. Sample preparation for the % entrapment efficiency and % drug loading tests used the same method, namely, quercetin that failed to be trapped in vesicles was separated from the sample. A sample of 1.5 mL of quercetin spanlastic was centrifuged at 15,000 rpm using a Heraeus 3332 Fixed-Angle Rotor (Germany) centrifuge for 120 minutes at a temperature of 4°C. The clear supernatant was collected and then examined for absorbance at a wavelength of 373 nm. Next, the quercetin content in the supernatant was calculated as free quercetin, which was not trapped in vesicles. The amount of quercetin entrapped in vesicles was determined by reducing the total amount of quercetin in the formula from the amount of free quercetin.

Penetration study

For the penetration evaluation, six formulas were used, as listed in Table 2, consisting of formula F1, F2, F3, F4, K and R.

Preparation of K formula

The K formula consisted of a non-spanlastic quercetin gel that was prepared with HPMC 4000, developed in distilled water for 60 minutes, stirred using a magnetic stirrer until homogeneous, and then left to stand overnight. Next, a solution of methyl paraben and propyl paraben was prepared in propylene glycol, and a solution of quercetin and rhodamine B was prepared in 96% ethanol. The two solutions were mixed homogeneously in a gel base with a magnetic stirrer for 30 minutes. [11]

Preparation of quercetin spanlastic F1 (Tween 60) and F2 (Brij 35)

The preparation of the F1 and F2 formulas was the same as that of the quercetin spanlastic but differed in terms of the EA used (F1—Brij 35; F2—Tween 60); additionally, after Span 60, quercetin, and 96% ethanol were dissolved, rhodamine B was added as a marker, as it dissolves completely in 96% ethanol.[10]

Preparation of quercetin spanlastic gel F3 (Tween 60) and F4 (Brij 35)

HPMC 4000 was developed in distilled water for 60 minutes, stirred using a magnetic stirrer until homogeneous, and then left to stand overnight. Next, a solution of methyl paraben and propyl paraben in propylene glycol was added to the developed HPMC 4000 and stirred until a gel base homogeneously formed.[11] After that, quercetin spanlastic F1 (EA Tween 60) was added to obtain the F3 formula, and spanlastic F2 (EA Brij 35) was added to obtain the F4 formula.

Table 2: Formulas of F1, F2, F3, F4, R and K for penetration study

Material	Function	Components (%)					
		F1	F2	F3	F4	F5	F6
Quercetin-loaded spanlastic with EA Tween 60	Active agent	Equivalent to 0.025 quercetin		Equivalent to 0.025 quercetin		-	-
Quercetin-loaded spanlastic with EA Brij 35	Active agent		Equivalent to 0.025 quercetin		Equivalent to 0.025 quercetin	-	-
Quercetin	Active agent	-	-	-	-	0.025	-
HPMC 4000	Gelling agent	-	-	1.5	1.5	1.5	1.5
Methyl paraben	Preservative	-	-	0.18	0.18	0.18	0.18
Propyl paraben	Preservative	-	-	0.02	0.02	0.02	0.02
Propylene glycol	Cosolvent, humectant	-	-	15	15	15	15
Ethanol 96%	Cosolvent	-	-	10	10	10	10
Rhodamine B	Marker	0.1	0.1	0.1	0.1	0.1	0.1
Aquadestillata	Solvent	-	-	Ad 100	Ad 100	Ad 100	Ad 100

Note: F1, quercetin spanlastic with EA Tween 60; F2, quercetin spanlastic with EA Brij 35; F3, quercetin spanlastic gel with EA Tween 60; F4, quercetin spanlastic gel with EA Brij 35; K, quercetin gel; R, gel base.

Preparation of gel base (R Formula)
The preparation of the R formula was the same as that of the K formula but without the addition of the quercetin solution.

Preparation of experimental animals
This work received ethical approval from the Faculty of Veterinary Medicine Universitas Airlangga Animal Care Ethics Committee (No.2.KEH.082.07.2022). In this study, one group was used to test one formula, so there were six groups of experimental animals. Based on the resource equation approach, it was found that the number of experimental animals per group should be three.[12]
The inclusion criteria for this penetration test were male balb/c strain mice (*Mus musculus*), an age of 8 weeks old, a weight of 20-30 grams, no skin disease, and no wounds on the skin before or after hair removal. The exclusion criteria for the experimental animals were mice with skin disease, wounds, or bleeding on the skin or who died before the study began.
The animals, as shown in Figure 1, were acclimatized for one week under a 12-hour light–dark cycle. A cage housed 4 animals, each separated by a partition. The day before the penetration test, the mice's back hair was shaved over an area of 4x2 cm^2 with a hair clipper.

Penetration test
The skin of the mice that had been shaved was divided into two areas: area A, where the test sample was applied for 4 hours, and area B, where the sample was applied for 2 hours (Figure 1). In area A, 50 mg of the sample was applied. Two hours later, the same amount of sample was smeared on area B. After four hours in area A, the mice were sacrificed using the dislocation method, and then the skin was taken from each area and stored in an ultra-deep freezer. Furthermore, skin preparations were made and observed under a fluorescence microscope (Nikon H-600L, Japan), with a rhodamine red filter and a magnification of 100x. Observations included the fluorescence depth and intensity of the rhodamine B marker in the skin layers after 2 and 4 hours of application.
Data analysis
The organoleptic qualitative test data of the research materials, in the form of product descriptions, were compared with those in the literature and the Certificate of Analysis (CoA) for each material. Meanwhile, the results of the FTIR examination were analyzed for compatibility with the literature. Furthermore, the penetration test data, that is, the rhodamine B fluorescence data obtained for each penetration test sample formula after being applied for 2 or 4 hours, were analyzed via visual observations, assessing the luminescence depth and intensity in each skin layer.

Figure 1: Animal model for penetration test.A: area where the test sample was applied for 4 hours; B: area where the sample was applied for 2 hours

Results and Discussion

Characteristics of quercetin-loaded spanlastic

The characteristics of the quercetin-loaded spanlastic are shown in Table 3. The particle size, polydispersity index, entrapment efficiency, and drug loading characteristics were compared between the T1 and B1 formulas.

Quercetin spanlastic using EA Tween 60 (T1) and EA Brij 35 (B1) with a VB:EA ratio of 9:1 had good entrapment efficiency and drug loading percentages. T1 had greater entrapment efficiency and drug loading percentages than B1. This is due to the difference in the EA HLB values, with Tween 60 having a value of 14.9 and Brij 35 having a value of 16.9. An increase in the HLB value of the EA will increase membrane hydrophilicity and reduce vesicle interfacial energy, causing a greater risk of vesicle leakage and a decrease in the entrapment efficiency percentage.[10,13,14]

T1 had a larger particle size than B1 due to differences in the molecular weight of the EA used: Tween 60 has a higher molecular weight (1312 g/mol) than Brij 35 (1199.5 g/mol). The increase in the EA molecular weight is directly proportional to the increase in the size of the spanlastic vesicles formed.[13,15] The polydispersity index of T1 and B1 was less than 0.7, which means that the particle size distribution of both types of spanlastic was within a narrow range and that the size of the vesicles in the system was relatively homogeneous.[14,15]

Penetration test

The test samples used in the penetration test were quercetin spanlastic F1 and F2 and quercetin spanlastic gel F3 and F4, along with quercetin gel K and gel base R as the control formulas. The parameters observed were the rhodamine B fluorescence depth and intensity in the transversely cut mouse skin. The reddish-yellow glow in the microscope field of view in Figure 2 is the fluorescence of rhodamine B. In the K and R formulas, the glow was only observed in the stratum corneum area of the skin after 2 and 4 hours of application. This indicates that rhodamine B is unable to penetrate into the skin surface if the delivery system is not facilitated. In the F1 and F2 formulas, quercetin demonstrated an increased penetration ability, as indicated by the glow of rhodamine B in the epidermis layer of the skin 2 hours after application and deeper into the dermis layer 4 hours after application. The spanlastic system in the F1 and F2 formulas is able to facilitate quercetin penetration through two mechanisms.

Table 3: Characteristics of quercetin-loaded spanlastic using Tween 60 and Brij 35

Characteristics	**T1** **(mean ± SD)**	**B1** **(mean ± SD)**
VB:EA ratio	9:1	9:1
Particle size (nm)	1443.0 ± 56.5	841.2 ± 19.7
Polydispersity index	0.513 ± 0.034	0.322 ± 0.020
Entrapment efficiency (%)	99.06 ± 0.12	94.48 ± 2.36
Drug loading (%b/b)	0.158 ± 0.008	0.142 ± 0.005

In the first mechanism, spanlastic vesicles are moved via the osmotic gradient of water.[16] As spanlastic F1 and F2 use EAs with large HLB values, the spanlastic vesicles have good hydrophilicity and tend to be attracted to areas with a higher water content. The depth of skin penetration depends on the increase in the osmotic gradient of water, so this condition pushes the spanlastic vesicles into the deeper layers of the skin. The large HLB value of the EA also causes spanlastic to have good deformability and elasticity, and it is able to reduce the size of the vesicles when passing through small gaps such as pores or intercellular gaps without causing damage to the structure.[9,17] The second mechanism involves the spanlastic component, which is a surfactant; the spanlastic component is able to work as a penetration enhancer by modifying the intercellular lipid lamellar of the stratum corneum and reversibly increasing the pore size of the skin membrane, making it easier for the active ingredient to penetrate. Spanlastic vesicles F1 and F2 use non-ionic surfactants, thereby minimizing interactions with the skin, which tends to be negatively charged.[9,17]

Two hours after application, the glow of rhodamine B under the stratum corneum in F2 was stronger than that in F1. Then, 4 hours after application, it was observed that the glow of rhodamine B in the F2 formula could penetrate the skin into the lower dermis area approaching the hypodermis, while the F1 formula was only able to penetrate the top layer of the dermis. This shows that quercetin spanlastic with the EA Brij 35 is able to provide better delivery for topical penetration than quercetin spanlastic with the EA Tween 60. The penetration of spanlastic with a smaller size such as quercetin spanlastic with the EA Brij 35 supports the easy penetration of vesicles through small gaps such as pores and intercellular gaps.[10,18] Quercetin spanlastic with Tween 60 has a size above 1µm, so vesicle penetration cannot be maximized due to space obstructions. Meanwhile, Brij 35 has a shorter alkyl chain (C12) than Tween 60 (C18). The long alkyl chain structure of the EA Tween 60 provides stronger hydrophobic interactions with the VB, so the elasticity of the vesicles is lower than that of the EA Brij 35.[19] With quercetin spanlastic gel F3 and F4, the luminescence of rhodamine B only reached the epidermis layer of the skin 4 hours after application. At the same time, quercetin spanlastic F1 and F2 were able to penetrate the dermis layer of the skin. These results show that the penetration ability of the F3 and F4 formulas is not as good as that of the F1 and F2 formulas. The use of a gel base in the F3 and F4 formulas requires the quercetin spanlastic to be released from the gel base toward the skin surface before penetration. A polymer matrix such as HPMC is a hydrogel that can provide a controlled-release effect due to changes

in the water balance within the system.[20,21] To achieve the same skin penetration results, quercetin spanlastic in a gel takes a longer time than quercetin spanlastic without a base.
Spanlastic has been proven to be able to increase the penetration of quercetin into the skin, and the use of Brij 35 as an EA provides a better penetration ability than Tween 60; thus, it has great potential for further development as a quercetin delivery system for topical anti-aging products.

Conclusion
A spanlastic system with EAs Tween 60 and Brij 35 can enhance the penetration of quercetin into the skin. Quercetin spanlastic with Brij 35 as an edge activator increases quercetin penetration more effectively than that with Tween 60 as an edge activator. The use of spanlastic in a gel base slows down the process of quercetin penetration into the skin. Spanlastic and spanlastic gel demonstrate advantages and potential and, thus, may be beneficial in the future as innovative delivery systems.

Conflict of Interest
Authors declare no conflict of interest.

Authors' Declaration
The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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