Iranian Journal of Pharmaceutical Sciences
2025: 21 (1): 271- 281
https://journals.sbmu.ac.ir/IJPS

Research Article

OPEN ACCESS

Anti-Acne Gel of Quercetin Loaded Niosomes

Pratiksha Labade[a], Ashlesha Pandit[a*], Prafulla Chaudhari[a]

[a] *Department of Pharmaceutics, JSPM's Rajarshi Shahu College of Pharmacy and Research, Tathawade, Pune-411033, India.*

Received: August 30, 2024 **Last Revision:** February 26, 2025 **Accepted:** March 09, 2025 **Available online:** July 26, 2025.

Abstract

We aimed to create a gel to treat acne. It contains quercetin-loaded niosomes. The thin film hydration method formulated quercetin-loaded niosomes made of cholesterol, maltodextrin, and span 60. The best batch of niosomes showed entrapment efficiency (97.10±0.10%), particle size (62.37±2µm), zeta potential (-43.4±6mv), and polydispersity index of 0.0554. The best batch (F7) was composed of quercetin (50 mg), Span 60 (180 mg), cholesterol (20 mg), maltodextrin (120 mg), hydration time (120 s), and hydration volume (30 ml). Further, F7 was subjected to a sonicator to reduce the particle size to 593.5±2.0 nm. Niosomes with spherical shapes were evenly dispersed, as shown by SEM analysis. Next, using a cold mechanical technique, quercetin niosomes loaded gel was prepared using carbopol 940. Gel exhibited a pH of 6.4, a high viscosity of 12,500 cP, quercetin diffusion through goat skin (93.56±2.19% within six h), and a zone of inhibition against *Cutibacterium acnes* (5.2± 0.9 mm). In conclusion, niosomal gel loaded with quercetin was thus shown to be a viable delivery strategy to treat acne.

Keywords: Acne, Niosomes; Quercetin; Gel; Niosomal gel; Propionibacterium acnes.

1. Introduction

A common skin issue, acne vulgaris, is frequent worldwide [1]. Chronic sebaceous follicle inflammation is the source of a dermatological condition that manifests as inflammatory papules and nodules [2]. Acne is caused by the sebaceous glands being hypersensitive to a typical amount of androgens in the blood. Sebaceous glands and hair follicles in the middle layer of the skin are breeding grounds where *Cutibacterium acnes* (*C. acnes*), a normal skin resident, worsens the inflammation [3]. The condition, which interferes with normal skin functioning by causing itching and soreness, is thought to afflict 10% of adults and 85% of teenagers [4]. The proliferation of a bacterium formerly *Propionibacterium acnes* (*P. acnes*), which is now known as *Cutibacterium acnes*, is its main cause [5]. Additional bacteria, like *Corynebacterium* species, *Malassezia* species, and *Staphylococcus epidermidis* [6, 7, 8], may also be present on the skin and add to the total complexity of acne development [9]. Acne can be caused by various reasons, such as bacterial infection, cosmetic use, stress, follicular epidermal hyperproliferation, and excessive sebum production due to clogging of sebaceous glands [10]. Specifically, the initial stages of inflammation are influenced by a gram-positive anaerobic bacteria called *Candida acne* [11]. During puberty, 5-alpha reductase converts testosterone to the more potent dihydrotestosterone (DHT) due to androgens, which bind to certain receptors in the

*** Corresponding Author**:
Ashlesha Pandit, Professor, Department of Pharmaceutics, JSPM's Rajarshi Shahu College of Pharmacy and Research, Tathawade, Pune-411033, India.
E-mail: ashleshapandit@jspmrscopr.edu.in.

Cite this article as: Labade P., Pandit A., Chaudhari P. Anti-Acne Gel of Quercetin Loaded Niosomes. Iran. J. Pharm. Sci., 2025, 21 (1): 271- 281.
DOI: https://doi.org/10.22037/ijps.v21i1.46120

sebaceous glands and promote sebum output [12]. Because of the increased hyperproliferation of the follicular epidermis, sebum is retained. Once swollen follicles burst, pro-inflammatory chemicals are released into the dermis, causing inflammation [13]. *Malassezia furfur*, *C. acnes*, and *Staphylococcus epidermis* induce inflammation and stimulate the development of follicular epidermal tissue [14].

Currently, using natural products, mainly plant-based, to treat acne is on the rise. One such natural phytochemical is quercetin, which is mainly a polyphenol component found in broccoli, citrus fruits, grapes, berries, and cherries. It has been demonstrated that quercetin exhibits antimicrobial effects against *C. acne* [15]. Derivatives of quercetin exhibited greater antimicrobial or antibacterial action against gram-negative bacteria than gram-positive bacteria [16]. Antioxidant [17], anti-tumoral [18], anti-inflammatory [19], antimicrobial [20], antibacterial [21], and antiviral [16] qualities have been observed for quercetin. An essential player in the immune response to bacterial infections such as *C. acnes* is toll-like receptor 2 (TLR-2). Quercetin inhibits TLR-2 synthesis, which may limit the immune system's ability to identify C. acnes and, as a result, lessen the inflammatory response [22]. TLR-2 receptors are found on the skin's surface, and bacterial infections in the body that cause inflammation are identified [23]. Moreover, it functions within the bacterial body to prevent DNA supercoiling, which stops bacterial development [24]. The application of quercetin to treat acne can be made by various conventional topical medicines abundantly available on the market. However, skin membranes (mainly the structure of the stratum corneum) act as barriers that affect these products with less therapeutic action [25]. Because of this problem, the successful drug delivery to target an affected skin area is niosomes. The elastic nature of the niosome easily gets transported through the skin. Furthermore, the small size, high surface area, and flexible nature of niosomes help to deliver the drug to the target site [26].

Niosomes (non-ionic surfactant vesicles) are formed by combining non-ionic surfactant and cholesterol to get tiny lamellar structures [27, 28]. Because of their amphiphilic character, the non-ionic surfactants in aqueous fluids create a closed bilayer vesicle with energy, either heat or physical agitation [29, 30]. Niosome vesicles are delivered through gel due to easy applicability, adherence to the skin, and higher retention on the skin due to its semisolid nature [26]. Herein, carbopol 940 is a crosslinked polyacrylic acid polymer carbomer. It is non-toxic and non-irritating, providing high viscosity and forming clear gel [31].

The literature exhibited anti-acne niosome gel using betel leaf essential oil to boost stability and trans follicular penetration of the gel [27]. Similarly, niosomal nanocarriers of quercetin were formulated for enhanced skin delivery to study anti-tyrosinase and antioxidant activity [32]. Likewise, antiacne activity using topical niosomal gel was explored, which contained a combination of benzoyl peroxide and tretinoin [33]. Because of this literature, the current investigation explored the potential of niosome-encapsulated quercetin to treat acne. Because quercetin is lipophilic, adding it to niosomes was thought to improve the stratum corneum's permeability and characteristics by reducing transepidermal water loss and smoothing the skin by restoring skin lipids. Therefore, the current study aimed to create a gel containing quercetin-loaded niosomes to treat acne.

2. Material and Methods

Quercetin was procured from P. C. Chem, Mumbai, India. The chemicals used during the study were of analytical grade.

2.1. Preparation of quercetin niosomes

Quercetin niosomes were formulated using the thin film hydration method with minor modifications [34, 35]. The preliminary study established the quantity of quercetin to be loaded into niosomes. The ingredients maltodextrin, span 60, cholesterol, and quercetin were added in the mixture of chloroform: methanol (1:1) and organic solvent (20 ml) and finally subjected to rotary evaporator (Equitron Medica Instruments Mfg. Co., India). The composition of formulations is shown in **Table 1**. The organic solvent was vaporized at low pressure (500 mm Hg) by applying a vacuum and rotating the flask continuously at 150 rpm at 56ºC till the formation of dry film [36]. The portion-wise hydration of the film was done with a phosphate buffer of pH 7.4. The vesicles were allowed to hydrate and mature by rotating the flask at 40ºC for a predetermined period. The hydrated niosomes dispersion formulations were kept in glass vials at 4ºC till further use [37].

Table 1. Formulation of niosomes

Batch (code)	Quercetin (mg)	Span 60 (mg)	Cholesterol (mg)	Maltodextrin (mg)	Hydration Time (sec)	Hydration Volume (ml)	Particle Size (µm)	Entrapment Efficiency (%)
F1	50	180	20	120	80	20	108.5±0.3	68.48±0.16
F2	50	180	20	120	90	20	96.24±0.3	71.97±0.6
F3	50	180	20	120	120	20	90.99±0.1	86.45±0.8
F4	50	180	20	120	105	30	84.87±0.2	90.52±0.2
F5	50	180	20	120	120	10	96.23±0.3	93.70±0.42
F6	50	180	20	120	105	20	76.46±0.3	92.45±0.43
F7	50	180	20	120	120	30	62.37±0.3	97.10±0.10
F8	50	180	20	120	90	10	52.03±0.1	94.68±0.25
F9	50	180	20	120	90	30	39.73±0.2	75.76±0.24
F10	50	180	20	120	105	10	38.13±0.3	90.33±0.10

2.2. Characterization of niosomes

2.2.1. Particle size

The particle size of niosomes was determined using a plane-polarized light microscope [Metzer Optical Instruments Pvt. Ltd.] [38].

2.2.2. Entrapment Efficiency

The entrapment efficiency of drug-loaded niosomes was determined after separating an unentrapped drug, which was performed by cooling centrifugation (Remi, C-24DL) at 12,000 rpm for 30 min at 4°C [39]. UV spectroscopy quantified the amount of the drug at 256 nm (UV spectrophotometer/1800 Shimadzu, Japan). Lastly, equation (1) was used to determine the entrapment efficiency [39, 40].

$$EE\ [\%] = \frac{Total\ amount\ of\ drug\ added - free\ drug\ in\ supernatent\ x\ 100}{Total\ amount\ of\ drug\ added} \quad (1)$$

2.2.3. Scanning electron microscopy

The surface appearance of the best batch of niosomes was examined using scanning electron microscopy (SEM). The formulation was secured using double-sided adhesive tape on an aluminum stub. A vacuum evaporator covered the formulation with gold-palladium (Au/Pd). At 25 kV accelerating voltage, the morphology was analyzed using an electron microscope (SEM Quanta-200-EDX system, ICON labs, Mumbai) fitted with a digital camera [40, 41]. Further, the surface characteristics of the chosen formulation of quercetin niosomes were noted using a scanning electron microscope.

2.2.4. Sonication of niosomes

The dispersion of niosomes (best batch) was sonicated at ultrasonicator (Ultrasonic Probe Sonicator, PCI Analytics, India) to get small and uniform size vesicles [39] using three cycles with 5 min break and one cycle run for 30 s to reduce the size. The sonication caused bubble formation, which affected lipid membranes [42].

2.2.5. Measurement of zeta potential and polydispersity index (PDI)

Colloidal properties of the niosomal formulations were studied in terms of particle size and PDI using a zeta sizer (SZ-100, Horiba Scientific). The homogeneity of vesicles was examined using PDI. Niosomes (0.1 ml) was diluted with phosphate buffer pH 7.4 to 100 ml. The instrument was operated at 25ºC and 90ºC scattering angle [35]. A stable formulation was indicated by a value larger than ± 30 mV [38, 42].

2.3. Preparation of niosomes gel formulation

Niosomes were further transformed into the gel using a cold mechanical process. Carbopol 940 was used as a gelling agent due to its hydrophilic and bioadhesive qualities. Niosomes (4.8 g) was covered with carbopol 940 (2%), shaken with a mechanical stirrer for 30 min, and left to swell overnight. Triethanolamine and methylparaben were added to the niosomal gel to attain pH and preservative action. The bath sonication method was used to get rid of the air bubbles. Similarly, the control gel was prepared by directly adding quercetin to the gel (without niosomes F0) [43].

2.3.1. Characterization of gel formulation

2.3.1.1. Drug content

Gel (10 mg) was added to 100 ml methanol, sonicated for 10 min, filtered (membrane filter 0.45 µm), and the filtrate was analyzed by UV spectrophotometer (1800, Shimadzu, Japan) at 256 nm to quantify quercetin [44].

2.3.1.2. Determination of pH

The dispersion's pH was measured using a digital pH meter (LAB MAN Scientific Instrument, India).

2.3.1.3. Viscosity measurements

Viscosity was measured using a Brookfield viscometer (LVDVE, USA) with spindle 64 running at 60 rpm. An appropriate container filled with gel was set beneath the viscometer. The spindle was lowered and submerged into the gel until the spindle shaft reached an immersion mark [38, 45].

2.3.1.4. Texture profile analysis

Firmness, tackiness, and work of adhesion are a few characteristics that can be used to assess the spreadability of the formulation [44]. A texture analyzer (Brookfield Engineering Corporation, USA) was used to examine each of these attributes using the following parameters: a probe sample holder (TA3)/100 was filled with sample, where the following parameters were applied: test type set at compression mode, a tapered cone with the target value of 10 mm, trigger force of 2.0 g and lowering and return speed of 0.5 mm/s [46].

2.3.1.5. In-vitro diffusion study

Franz diffusion cell assembly with 20 ml capacity (DBK Instruments, India) was used to get in vitro drug release. The receptor compartment of the cell was filled with diffusion medium pH 7.4 phosphate buffer solution (diffusion medium). Niosomes, control gel (without niosomes), and niosomal gel, each containing 390 mg (equal to 4 mg of quercetin), were studied by placing on the dialysis membrane-135 (LA398-1MT, molecular weight cut off 12 to 14 kD, HiMedia Laboratories Pvt. Ltd., India), flat width of 33.12 mm which was previously soaked in phosphate buffer pH 7.4 for 24 h. It was positioned between two compartments. The magnetic stirrer at 100 rpm was used to stir the diffusion medium at 37±0.5°C. Further, 1 ml of the aliquot was taken out at predetermined intervals and reintroduced with the same media volume. The aliquots were analyzed by UV spectrophotometry (1800, Shimadzu, Japan) at 256 nm to quantify quercetin [39, 47].

2.3.1.6. Ex-vivo study

Fresh abdominal goat skin was used to perform an ex vivo study, free of visible damage. After gently rinsing the skin with buffer to get rid of any dirt, the hair of the skin was gently removed with scissors [45]. Franz diffusion cell (20 ml) (DBK Instruments, India) was used where the skin was positioned between the two cell compartments with an effective diffusional area of 3.14 cm^2. Niosomal gel (390 mg) and control gel (390 mg) (without niosomes), both containing equivalent to 4 mg of quercetin, were put on the skin of the donor compartment. A pH 7.4 phosphate buffer solution was introduced into the recipient compartment, which was continuously stirred at 50 rpm and maintained at 37±0.5°C. At predefined intervals of 30 min, 1 ml aliquots were removed from the receiver compartment and replaced with an equal volume of fresh phosphate buffer solution. The sample was subjected to spectrophotometric analysis at 256 nm [48]. By determining the steady-state flux (Jmax) and examining the proportion of drug diffused, the ex vivo permeation of quercetin across the membrane was investigated. Jmax was determined using the following equation (2):

$$\text{Jmax} = \left(\frac{\text{dQ}}{\text{dt}}\right)/\text{A} \qquad (2)$$

Where DQ/dt - Skin permeation rate, which is the slope of the cumulative amount of permeated quercetin vs. time, A = the effective diffusion area of the skin (3.14cm^2).

2.3.1.7. Antimicrobial assay

The microbial strain *Cutibacterium acnes* (MTCC 1374) was used to test the antimicrobial sensitivity of quercetin-loaded niosomes, quercetin niosomal gel, and control gel (without niosomes) using the cup plate method. Samples were tested against *C. acnes* using medium Muller-Hinton agar, wherein a 7 mm diameter was bored and filled with the above samples (2.5 mg/ml). The plates were incubated for 48 h at 37°C. The

antimicrobial capability of samples was assessed by measuring the size of the zone of inhibition [38, 49].

3. Results and Discussion

3.1. Preparation of niosomes

Quercetin-loaded niosomes were formulated using the thin film hydration technique. The vesicle-forming capacity of sorbitan monostearate (Span 60) and cholesterol were studied, varying the parameters of hydration time and hydration volume (**Table 1**). Here, the role of cholesterol was to stabilize the vesicles. Maltodextrin was incorporated into niosomes to enhance the stability of vesicles and provide flexibility to surfactant and cholesterol [37]. F7 niosomes formulation was selected as the best batch by considering the smallest particle size and maximum entrapment efficiency.

3.2. Characterization of niosomes

3.2.1. Particle size

Particle size of niosomes (F1 to F10) was ranged from 38.13 to 108.5 µm (**Table 1**). Here, by decreasing hydration time, the particle size was found to be decreased. The change in hydration time was a strategy to control nanovesicle size. The particle size of batch F7 was found to be 62.37±0.3 µm.

3.2.2. Entrapment Efficiency

The entrapment efficiency of quercetin niosomes was 68-97% (**Table 1**). Furthermore, the lipophilicity of quercetin (log P=1.82±0.32) contributed to the high entrapment efficiency. Furthermore, the addition of cholesterol in the niosomes enhanced the hydrophobicity of the bilayer. Thus, enhancement in drug entrapment was observed within the bilayers and, thus, fewer drug leakage, ultimately resulting in high entrapment efficiency [48]. Since formulation F7 displayed the highest entrapment efficiency (97±2.2%) than other batches, it was considered the best batch [39].

3.2.3. Scanning Electron Microscopy

A scanning electron microscopy image of F7 revealed spherical-shaped, uniform-size isolated vesicles of niosomes (**Fig. 1**). These results revealed the uniform loading of quercetin and process parameters.

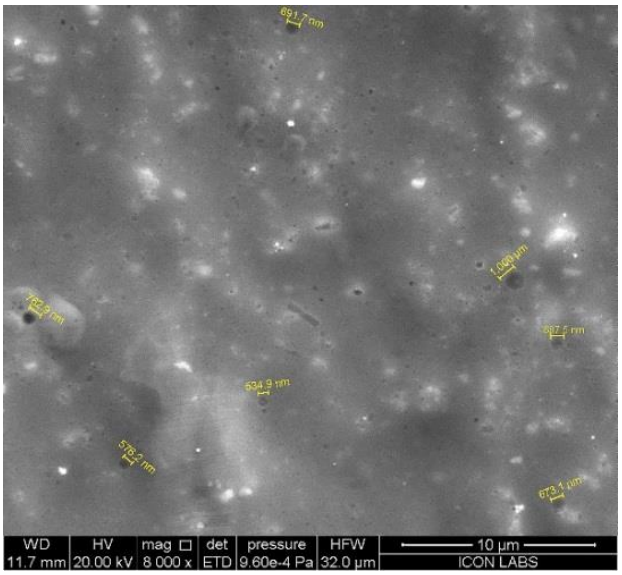

Figure 1. SEM image of niosomes

3.2.4. Polydispersity index, particle size, and zeta potential

The polydispersity index (F7) was found to be 0.0554, which specified the uniformity of particles in a dispersion medium. Particle size (**Fig. 2a**) of the F7 batch of niosomes was found to be 62.37±0.3 µm prior to sonication, while it showed a reduction in particle size after sonication to 593.5±2.4 nm. Thus, the small size of niosomes favored easy penetration through paracellular pathways into the skin through the skin's pores to sebaceous glands and hair follicles where acne lesions typically persist. Niosomes designed for anti-acne applications should ideally have a particle size between 300 - 700 nm [38]. This size range effectively targets sebaceous follicles within the skin, which are the primary sites of acne development. The ultra-sonication of niosomes reduced the size and contributed to a large surface area [50]. Further, the zeta potential (**Fig. 2b**) of the F7 formulation was found to be -43.4 mV due to the presence of maltodextrin [49], which represented the stability of the dispersion. Thus, the agglomeration was prevented due to strong electric charges on the surface of the particles. The adequate charge of quercetin was represented as a numerical value of zeta potential that helped the mobility and thus hindered aggregation of particles [51]. Thus, phase separation was not observed due to the high zeta potential value. Further, negative zeta potential imparted electrostatic repulsion amongst vesicles, which further prohibited agglomeration of vesicles [52].

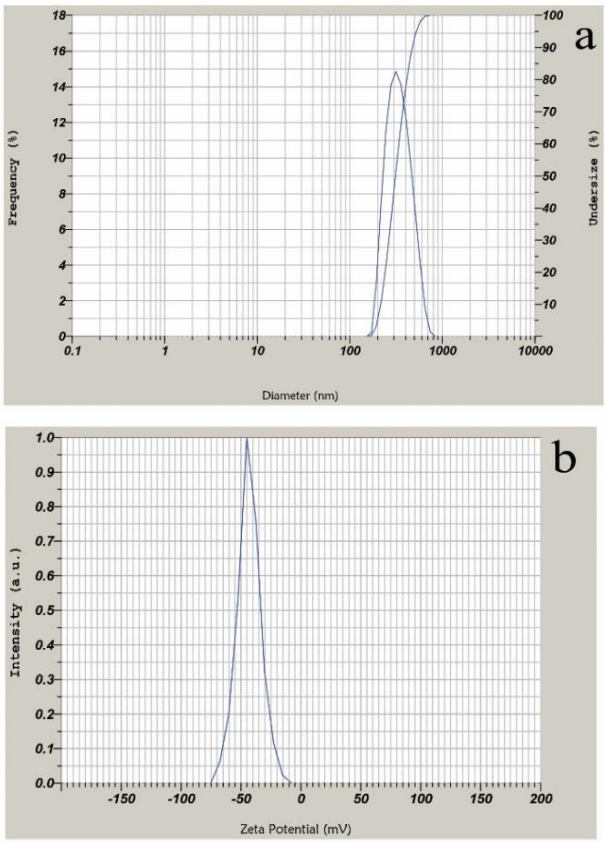

Figure 2. Characterization of niosomes (a) Particle size and (b) Zeta potential

3.2.5. Characterization of gel formulation

The actual niosomal gel photograph is shown in **Fig. 3** (c).

3.2.5.1. Drug content and pH of the gel

The niosomal gel showed a pH of 6.4, attuned to the skin's pH [53]. Thus, irritation upon application of the niosomal gel to the skin was avoided [54]. However, skin pH is normally acidic (between 4 and 6). The acidic pH of the stratum corneum layer of the skin is essential for optimal functioning of the skin's natural barrier system. A shift or increase in the skin's pH inclines the skin to several inflammatory and infectious dermal infections, such as acne vulgaris [55].

3.2.5.2. Viscosity measurement

Niosomal formulation displayed a maximum viscosity of 12500 cP [53]. Span 60 increases the viscosity of niosomal gel as it forms a stabilizing network within the gel and prevents niosomes from moving freely, thus increasing resistance to flow [54]. Thus, the more viscous the formulation, the more adherence to the target skin surface. The low-viscosity gels (viscosity of less than 15,000 cP) were preferred to treat skin disorders like acne [56]. The more viscous gel helps to retain the acne on the skin surface.

3.2.5.3. Spreadability of gel

The spreadability of gel is a measure of how easily it can be applied to the skin. It is a combination of rheological properties, including its viscosity, structure, and visco-elasticity of gel. A gel with good spreadability is well distributed on the skin, which further adheres to the skin and shows a good effect [46]. The work of adhesion at the load versus time profile is the maximum peak force attained throughout the compression cycle. It was calculated as the ratio of the area under the tackiness curve to the area under the firmness curve. Niosomal gel (**Fig. 3a**) and control gel (**Fig. 3b**) showed the following values: the tackiness values were 205 and 100g, respectively, and firmness was found to be -97 and -50 mm, respectively. Niosomal gel showed less viscosity, as indicated by the less steep curve in **Fig. 3b**, which depicted better spreadability. The spreadability of the formulation is inversely related to the viscosity. The spreadability of the niosomal gel was found to be 20.5±1.45 g cm/s. The lower viscosity of niosomal gel was the presence of vesicles of niosomes [57].

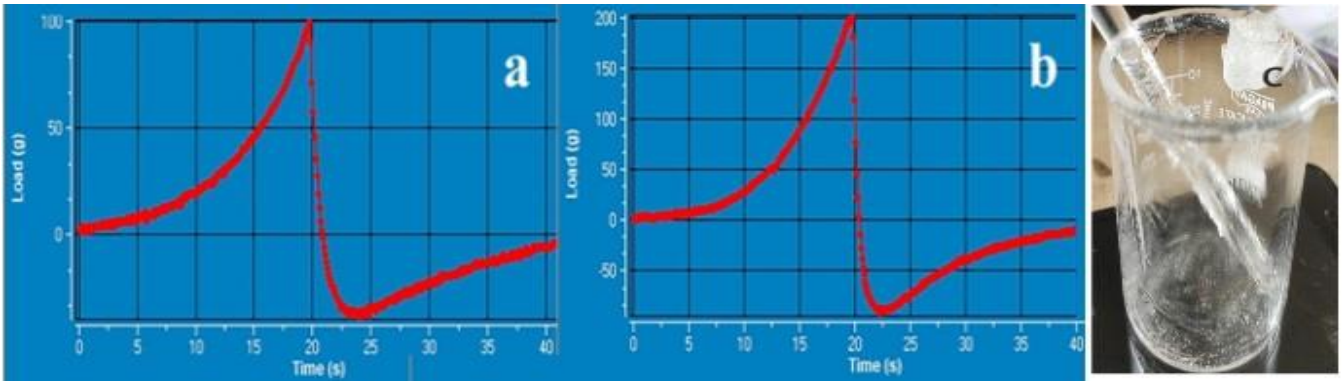

Figure 3. Texture analysis of (a) niosomal gel, (b) control gel; (c) actual photo of formulation of gel

3.2.5.3. Spreadability of gel

The spreadability of gel is a measure of how easily it can be applied to the skin. It is a combination of rheological properties, including its viscosity, structure, and visco-elasticity of gel. A gel with good spreadability is well distributed on the skin, which further adheres to the skin and shows a good effect [46]. The work of adhesion at the load versus time profile is the maximum peak force attained throughout the compression cycle. It was calculated as the ratio of the area under the tackiness curve to the area under the firmness curve. Niosomal gel (**Fig. 3a**) and control gel (**Fig. 3b**) showed the following values: the tackiness values were 205 and 100g, respectively, and firmness was found to be -97 and -50 mm, respectively. Niosomal gel showed less viscosity, as indicated by the less steep curve in **Fig. 3b**, which depicted better spreadability. The spreadability of the formulation is inversely related to the viscosity. The spreadability of the niosomal gel was found to be 20.5±1.45 g cm/s. The lower viscosity of niosomal gel was the presence of vesicles of niosomes [57].

3.2.5.4. In vitro drug diffusion of niosomal gel

The rate at which quercetin diffused from the niosomal gel demonstrated the delivery process of the medication. The drug diffusion was 99.1% after six hours (**Fig. 4**). According to the results of drug diffusion (as shown in **Fig. 4**), niosomes and niosomal gel exhibited higher and longer behavior of drug diffusion than control gel (without niosomes). Quercetin niosomal gel resulted in a noticeably slower diffusion profile than niosomes within six hours. The drug was released faster (99.15±0.13% within six hours) through niosomes, while it was comparatively slower initially in the case of niosomal gel (98.34±0.36% within six hours). The initial quick diffusion of quercetin from the exterior portion of the niosomal gel was rapid, followed by a slower rate [58]. The viscous nature of gel and the entrapment of quercetin in the bilayer structure of niosomes exhibited a slower drug diffusion profile. Thus, drug diffusion was retarded by the following barriers: the first barrier was the niosomal bilayer, and the second barrier was the carbopol gel matrix. However, such a type of delayed behavior was beneficial for transdermal delivery. Initially, the fast drug diffusion caused saturation of the epidermis, while later, gradual slow diffusion of the drug was used to attain a high concentration gradient, thus successfully delivering the drug at the target site [38, 59].

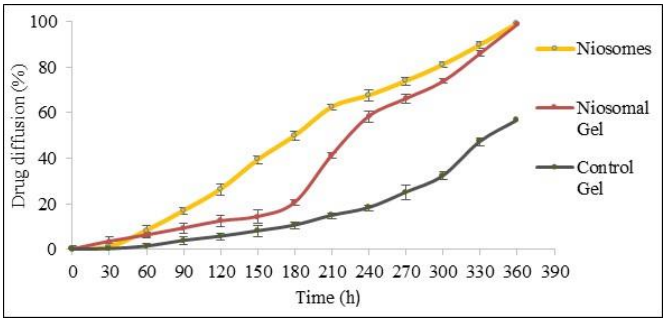

Figure 4. In vitro drug release of niosomes, niosomal gel and control gel

3.2.5.5. Ex-vivo permeation study

Nanoparticles with a diameter of 5–7 nm can penetrate through the intercellular route, while nanoparticles with a diameter of 36 nm can penetrate through the aqueous pores. Niosomes with particle size within the 200-300nm range are required for optimal skin permeation. This nano-sized range favors penetration through the skin's stratum corneum, enhancing drug delivery efficacy [26]. Ex-vivo permeation study through the goat skin exhibited the transport of control gel (without niosomes) and quercetin niosomal gel, as shown in **Fig. 5**, which represented 62.84±1.34% within six hours and 93.56±2.19% within six hours. Earlier, similar results were obtained for the permeation of quercetin [32].

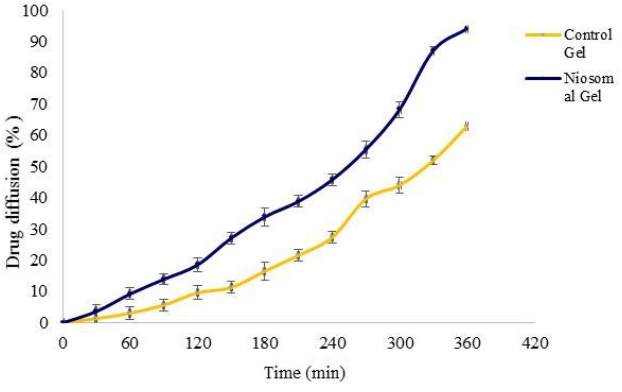

Figure 5. Ex-vivo study of control gel and niosomal gel

Herein, treatment of acne favors drug permeation till deep into the skin in the middle layer at the hair follicles and sebaceous glands. Herein, niosomes enhanced the residence time of the drug in the epidermis, potentially enhancing its permeation. The quercetin niosomal gel (93.56±2.19% till six hours) penetrated the skin faster than the control gel (62.84±1.34% till six hours) due to the small vesicle size of niosomes.

Additionally, the niosomal gel significantly showed greater diffusion than the control gel [59]. Considering flux, the niosomal gel depicted more diffusion (0.0032 µg/cm^2/min) than the control gel (0.00089 µg/cm^2/min) within six hours of diffusion study. Thus, the niosomal gel demonstrated a 3.2-fold improvement over the control gel. This may be due to lipid-based vesicles (niosomes), encapsulated drugs and facilitated penetration through the membrane, and improving solubility of poorly soluble drugs. The lipid bilayer of the niosome fused with the skin lipid layer facilitated drug transportation, enhancing flux.

3.2.5.6. Antimicrobial activity

Quercetin-loaded niosomes, quercetin niosomal gel, and control gel (without niosomes) revealed 5.6±1.2, 5.2±0.9 and 3.9±0.6 mm zone of inhibition against *C. acnes* (**Fig. 6**). Niosomes represented better antimicrobial activity as compared to control gel. Herein, improved drug penetration was attributed to better permeation through the medium due to small niosomes and better diffusion through the medium compared to the control gel without niosomes. This resulted in a larger zone of inhibition than the control gel. However, adding niosomes into a gel further reduced the permeation of the drug compared to niosomes, which was revealed in less zone of inhibition [60, 61].

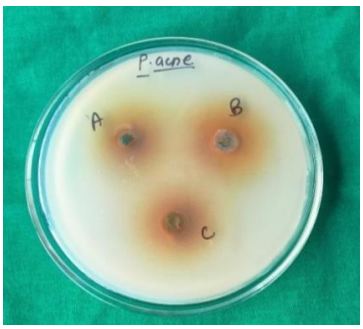

Figure 6. Zone of inhibition against *Cutibacterium acnes* of A: control gel, B: quercetin loaded niosomes C: quercetin niosomal gel

4. Conclusion

Quercetin-loaded niosomes were prepared for the treatment of acne. Niosomes favored the permeation of the drug and enhanced the residence time of the drug in the epidermis. Due to the small vesicle size, quercetin niosomal gel penetrated the skin faster than the control gel. Further, niosomes exhibited better antimicrobial activity against *Cutibacterium acne* than the control gel. Thus, due to their small vesicle size, niosomes proved beneficial in targeting deep-seated skin infection acne. In conclusion, the anti-acne gel of quercetin-loaded niosomes was considered to have a successful delivery.

Acknowledgements:

The authors thanked P. C. Chem Mumbai, India, for providing quercetin.

Conflict of Interest

The authors declared no conflict of interest.

Athors Orcid numbers:

Ashlesha Pandit: 0000-0001-5966-3229
Prafulla Chaudhari: 0000-0002-6805-9661

Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

References

1. Alanazi MS, Hammad SM, Mohamed AE. Prevalence and psychological impact of Acne vulgaris among female secondary school students in Arar city, Saudi Arabia, in 2018. *Electron. Physician*. (2018) 10(8):7224-7229.
2. Geng R, Sibbald RG. Acne vulgaris: Clinical aspects and treatments. Adv. FSkin & Wound Care. (2024)1; 37(2):67-75.
3. Motosko CC, Zakhem GA, Pomeranz MK, Hazen A. Acne: a side- effect of masculinizing hormonal therapy in transgender patients. Br. J. Dermatol. (2019) 1; 180 (1):26-30.
4. Wadhwa K, Kadian V, Puri V, Bhardwaj BY, Sharma A, Pahwa R, Rao R, Gupta M, Singh I. New insights into quercetin nano-formulations for topical delivery. Phytomed. Plus. (2022) 1; 2 (2):100257.
5. McLaughlin J, Watterson S, Layton AM, Bjourson AJ, Barnard E, McDowell A. *Propionibacterium acnes* and

acne vulgaris: new insights from the integration of population genetic, multi-omic, biochemical and host-microbe studies. Microorganisms. (2019) 13; 7 (5):128.
6. Fournière M, Latire T, Souak D, Feuilloley MG, Bedoux G. Staphylococcus epidermidis and *Cutibacterium acnes*: two major sentinels of skin microbiota and the influence of cosmetics. Microorganisms. (2020) 7; 8 (11):1752.
7. Ramasamy S, Barnard E, Dawson Jr TL, Li H. The role of the skin microbiota in acne pathophysiology. Br. J. Dermat. (2019) 1;181(4):691-9.
8. Kutlu Ö, Karadağ AS, Wollina U. Adult acne versus adolescent acne: a narrative review with a focus on epidemiology to treatment. An. Bras. Dermatol. (2023) 98 (1):75-83.
9. Dessinioti C, Katsambas AD. The role of *Propionibacterium acnes* in acne pathogenesis: facts and controversies. Clinics in Dermatology. (2010) 28 (1), 2-7.
10. Qidwai A, Pandey M, Pathak S, Kumar R, Dikshit A. The emerging principles for acne biogenesis: a dermatological problem of puberty. *Hum. Microbiome J.* (2017) 1; 4:7-13.
11. Lim HJ, Kang SH, Song YJ, Jeon YD, Jin JS. Inhibitory effect of quercetin on *propionibacterium acnes*-induced skin inflammation. Int. Immunopharmacol. (2021) 1; 96:107557.
12. Makrantonaki E, Ganceviciene R, Zouboulis CC. An update on the role of the sebaceous gland in the pathogenesis of acne. Dermatoendocrinol. (2011) 1; 3(1):41-9.
13. Tanghetti EA. The role of inflammation in the pathology of acne. J. Clin. Aesthet. Dermatol. (2013) 6(9):27.
14. Alexeyev OA, Dekio I, Layton AM, Li H, Hughes H, Morris T, Zouboulis CC, Patrick S. Why we continue to use the name *Propionibacterium acnes*. Br. J. Dermatol. (2018) 1; 179(5).
15. Kawabata K, Mukai R, Ishisaka A. Quercetin and related polyphenols: new insights and implications for their bioactivity and bioavailability. Food funct. (2015) 6(5):1399-417.
16. Nguyen TL, Bhattacharya D. Antimicrobial activity of quercetin: an approach to its mechanistic principle. Molecules. (2022) 12; 27(8):2494.
17. Zhang M, Swarts SG, Yin L, Liu C, Tian Y, Cao Y, Swarts M, Yang S, Zhang SB, Zhang K, Ju S. Antioxidant properties of quercetin. In Oxygen transport to tissue XXXII. Springer US. (2011) 283-289.
18. Almatroodi SA, Alsahli MA, Almatroudi A, Verma AK, Aloliqi A, Allemailem KS, Khan AA, Rahmani AH. Potential therapeutic targets of quercetin, a plant flavonol, and its role in the therapy of various types of cancer through the modulation of various cell signaling pathways. Molecules. (2021) 1; 26 (5):1315.
19. Saeedi-Boroujeni A, Mahmoudian-Sani MR. Anti-inflammatory potential of Quercetin in COVID-19 treatment. J. Inflamm. (2021) 18:1-9.
20. Osonga FJ, Akgul A, Miller RM, Eshun GB, Yazgan I, Akgul A, Sadik OA. Antimicrobial activity of a new class of phosphorylated and modified flavonoids. ACS omega. (2019) 30; 4(7):12865-71.
21. Jaisinghani RN. Antibacterial properties of quercetin. Microbiol. Res. (2017) 2; 8(1):6877.
22. Lim HJ, Kang SH, Song YJ, Jeon YD, Jin JS. Inhibitory effect of quercetin on *propionibacterium acnes*-induced skin inflammation. Int. Immunopharmacol. (2021) 1; 96:107557.
23. Vijay K. Toll-like receptors in immunity and inflammatory diseases: Past, present, and future. Int. Immunopharmacol. (2018) 1; 59:391-412.
24. Plaper A, Golob M, Hafner I, Oblak M, Šolmajer T, Jerala R. Characterization of quercetin binding site on DNA gyrase. *Biochem. Biophys. Res. Commun*. (2003) 27; 306(2):530-6.
25. Zhao L, Chen J, Bai B, Song G, Zhang J, Yu H, Huang S, Wang Z, Lu G. Topical drug delivery strategies for enhancing drug effectiveness by skin barriers, drug delivery systems and individualized dosing. Front. Pharmac. (2024) 16;14:1333986.
26. Budhiraja A, Dhingra G. Development and characterization of a novel antiacne niosomal gel of rosmarinic acid. Drug deliv. (2015) 18; 22(6):723-30.
27. Jufri M, Muthaharrah MU, Humairah EL, Purwaningsih EH. Stability of anti-acne niosome gels containing betel leaf (Piper betle L.) essential oil. Int. J. Appl. Pharm. (2017) 130-4.
28. Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. J. Adv. Pharm. Technol. Res. (2010) 1; 1(4):374-80.
29. Uchegbu IF, Florence AT. Non-ionic surfactant vesicles (niosomes): physical and pharmaceutical chemistry. Advances in colloid and interface science. 1995 Jun 27;58(1):1-55.
30. Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int. J. Pharm. (1998) 172, (1–2), 33-70.
31. A-sasutjarit R, Sirivat A, Vayumhasuwan P. Viscoelastic properties of Carbopol 940 gels and their relationships to

piroxicam diffusion coefficients in gel bases. Pharm. Res. (2005); 22(12):2134-40.

32. Banyi Lu, Yanting Huang, Zhongyun Chen, Jingyi Ye, Hongyu Xu, Wenrong Chen, Xiaoying Long. Niosomal nanocarriers for enhanced skin delivery of quercetin with functions of anti-tyrosinase and antioxidant. Molecules. (2019) 24(12): 2322.
33. I Handojo.The combined use of topical benzoyl peroxide and tretinoin in the treatment of acne vulgaris. Int. J. Dermatol. (1979) 18(6):489-96.
34. Yasamineh S, Yasamineh P, Kalajahi HG, Gholizadeh O, Yekanipour Z, Afkhami H, Eslami M, Kheirkhah AH, Taghizadeh M, Yazdani Y, Dadashpour M. A state-of-the-art review on the recent advances of niosomes as a targeted drug delivery system. Int. J. Pharm. (2022) 25;624:121878.
35. Mohanty D, Rani MJ, Haque MA, Bakshi V, Jahangir MA, Imam SS, Gilani SJ. Preparation and evaluation of transdermal naproxen niosomes: formulation optimization to preclinical anti-inflammatory assessment on murine model. J. Liposome Res. (2020) 1; 30(4):377-87.
36. Javani R, Hashemi FS, Ghanbarzadeh B, Hamishehkar H. Quercetin-loaded niosomal nanoparticles prepared by the thin-layer hydration method: Formulation development, colloidal stability, and structural properties. LWT. (2021) 1; 141:110865.
37. Mohanty D, Rani MJ, Haque MA, Bakshi V, Jahangir MA, Imam SS, Gilani SJ. Preparation and evaluation of transdermal naproxen niosomes: formulation optimization to preclinical anti-inflammatory assessment on murine model. J. Liposome Res. (2020) 1; 30 (4):377-87.
38. Budhiraja A, Dhingra G. Development and characterization of a novel antiacne niosomal gel of rosmarinic acid. Drug deliv. (2015) 18; 22(6):723-30.
39. Abdelkader H, Ismail S, Kamal A, Alany RG. Preparation of niosomes as an ocular delivery system for naltrexone hydrochloride: physicochemical characterization. Die Pharmazie- Int. J. Pharm. Sci. (2010) 1; 65(11):811-7.
40. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes. A review on niosomal research in the last decade. J. Drug Del. Sci. Tech. (2020) 1;56:101581.
41. Elmi N, Ghanbarzadeh B, Ayaseh A, Sahraee S, Heshmati MK, Hoseini M, Pezeshki A. Physical properties and stability of quercetin loaded niosomes: stabilizing effects of phytosterol and polyethylene glycol in orange juice model. J. Food Eng. (2021) 1; 296:110463.
42. Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. J. Adv. Pharm. Technol. Res. (2010) 1; 1(4):374-80.
43. Shirsand SB, Para MS, Nagendrakumar D, Kanani KM, Keerthy D. Formulation and evaluation of ketoconazole niosomal gel drug delivery system. Int. J. Pharm. Investig. (2012) 2(4):201.
44. Lin YK, Hsiao CY, Alshetaili A, Aljuffali IA, Chen EL, Fang JY. Lipid-based nanoformulation optimization for achieving cutaneous targeting: Niosomes as the potential candidates to fulfill this aim. Eur. J. Pharm. Sci. (2023) 1; 186:106458.
45. Ravalika V, Sailaja AK. Formulation and evaluation of etoricoxib niosomes by thin film hydration technique and ether injection method. Nano. Biomed. Eng. (2017) 1; 9(3):242-8.
46. Pandit AP, Omase SB, Mute VM. A chitosan film containing quercetin-loaded transfersomes for treatment of secondary osteoporosis. Drug Deliv. Transl. Res. (2020) 10:1495-506.
47. Khazaeli P, Pardakhty A, Shoorabi H. Caffeine-loaded niosomes: characterization and in vitro release studies. Drug Deliv. (2007) 1; 14(7):447-52.
48. Barot T, Rawtani D, Kulkarni P. Development, characterization and in vitro–in vivo evaluation of Farnesol loaded niosomal gel for applications in oral candidiasis treatment. Heliyon. (2021) 1; 7(9).
49. Owodeha-Ashaka K, Ilomuanya MO, Iyire A. Evaluation of sonication on stability-indicating properties of optimized pilocarpine hydrochloride-loaded niosomes in ocular drug delivery. Progress Biomat. (2021)10:207-20.
50. Van der Koog L, Gandek TB, Nagelkerke A. Liposomes and extracellular vesicles as drug delivery systems: A comparison of composition, pharmacokinetics, and functionalization. Adv. Healthc. Mater. (2022) 11(5):2100639.
51. Dubey A, Prabhu P, Kabrawala H, Ghate V. Niosomal gel of adapalene: its formulation, physicochemical properties and evaluation for mild-acne. Adv. Biomed. Pharma. (2015) 2(1):22-31.
52. Goyal MK, Qureshi J. Formulation and evaluation of itraconazole niosomal gel for topical application. J. Drug Deliv. Ther. (2019) 25; 9(4-s):961-6.
53. Waqas MK, Sadia H, Khan MI, Omer MO, Siddique MI, Qamar S, Zaman M, Butt MH, Mustafa MW, Rasool N. Development and characterization of niosomal gel of fusidic acid: In-vitro and ex-vivo approaches. Des. Monomers Polym. (2022) 31;25(1):165-74.

54. Zaid Alkilani A, Hamed R, Abdo H, Swellmeen L, Basheer HA, Wahdan W, Abu Kwiak AD. Formulation and evaluation of azithromycin-loaded niosomal gel: optimization, in vitro studies, rheological characterization, and cytotoxicity study. ACS Omega. (2022) 25;7(44):39782-93.
55. Prakash C, Bhargava P, Tiwari S, Majumdar B, Bhargava RK. Skin Surface pH in Acne Vulgaris: Insights from an Observational Study and Review of the Literature. J Clin Aesthet Dermatol. (2017) 1;10(7):33–39.
56. Moammeri A, Chegeni MM, Sahrayi H, Ghafelehbashi R, Memarzadeh F, Mansouri A, Akbarzadeh I, Abtahi MS, Hejabi F, Ren Q. Current advances in niosomes applications for drug delivery and cancer treatment. Materials Today Bio. (2023) 23, 100837.
57. Goyal, G, Garg, T, Malik, B, Chauhan, G, Rath, G, Goyal, AK. Development and characterization of niosomal gel for topical delivery of benzoyl peroxide. Drug delivery, (2015) 22(8): 1027-1042.
58. Han SB, Kwon SS, Jeong YM, Yu ER, Park SN. Physical characterization and in vitro skin permeation of solid lipid nanoparticles for transdermal delivery of quercetin. Int. J. Cosmet. Sci. (2014) 36(6):588-97.
59. Kajbafvala A, Salabat A, Salimi A. Formulation, characterization, and in vitro/ex vivo evaluation of quercetin-loaded microemulsion for topical application. Pharm. Dev. Technol. (2018) 14; 23(8):741-50.
60. Chellathurai BJ, Anburse R, Alyami MH, Sellappan M, Bayan MF, Chandrashekharan B, Chidambaram K, Rahamthulla M. Development of a polyherbal topical gel for the treatment of acne. Gels. (2023), 9(2):163.
61. Azeem M, Hanif M, Mahmood K, Ameer N, Chughtai FR, Abid U. An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review. *Polym. Bull.* (2023) 80(1):241-62.