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Formulation and Evaluation of Quercetin Loaded Niosomal Hydrogel for Acne Therapy

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ABSTRACT

Acne vulgaris is a chronic inflammatory skin disorder affecting the pilosebaceous units of the skin and is commonly observed in adolescents and young adults. Conventional topical therapies often show limited effectiveness due to poor drug penetration, instability, or undesirable side effects. Quercetin, a naturally occurring flavonoid, possesses potent antioxidant, anti-inflammatory, and antimicrobial activities that make it a promising candidate for the treatment of acne. However, its therapeutic potential is restricted by poor aqueous solubility and limited skin permeability. The present study aimed to develop and evaluate a quercetin-loaded niosomal hydrogel to enhance drug stability, improve skin penetration, and provide sustained topical delivery. Quercetin-loaded niosomes were prepared using the ethanol injection method with appropriate surfactants and cholesterol to form stable vesicular carriers. The prepared formulations were evaluated for various physicochemical parameters including drug content, pH, viscosity, spreadability, and extrudability. Morphological characterization using Scanning Electron Microscopy (SEM) confirmed the formation of spherical vesicles with smooth surfaces and uniform distribution. The optimized niosomal formulation was incorporated into a hydrogel base to obtain a suitable topical dosage form. Among the prepared formulations, F3 demonstrated superior performance, showing higher drug content (around 92%), better spreadability, and appropriate extrudability compared to other formulations. The hydrogel exhibited an acceptable pH of approximately 6.0, suitable viscosity, and good physical stability. Stability studies conducted for one month indicated no significant changes in appearance, viscosity, pH, or drug content, confirming the stability of the optimized formulation. Overall, the developed quercetin-loaded niosomal hydrogel represents a promising topical drug delivery system that may enhance therapeutic efficacy and patient compliance in the management of acne.

Keywords: Quercetin, Niosomes, Niosomal Hydrogel, Topical Drug Delivery, Acne Therapy

1.INTRODUCTION

1.1 OVERVIEW OF ACNE

Acne vulgaris is a chronic inflammatory skin disorder primarily affecting pilosebaceous units in adolescents and young adults, driven by increased sebum production, *Cutibacterium acnes* proliferation, follicular hyperkeratinization, and immune-mediated inflammation. Recent 2025 research highlights immunological shifts toward Th1 responses and cytokine dysregulation as key pathogenesis drivers, alongside persistent hormonal and genetic influences. Emerging trends emphasize combination therapies like clindamycin-benzoyl peroxide-adapalene for superior efficacy against multiple pathways, reducing antibiotic resistance risks while improving adherence and quality-of-life outcomes. Novel topicals, such as tretinoin-benzoyl peroxide creams, target inflammation more effectively, with ongoing studies exploring personalized regimens to mitigate scars and psychosocial impacts[1,2,3].

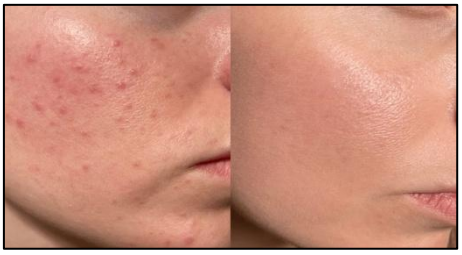

Fig 1: Acne Vs Clear Skin

1.2 IMPORTANCE OF TOPICAL DRUG DELIVERY

- **Targeted Action:** Delivers actives directly to pilosebaceous units, optimizing efficacy against acne pathogens like *Cutibacterium acnes* while sparing distant organs.
- **Reduced Systemic Side Effects**: Avoids first-pass metabolism and gastrointestinal issues common with oral antibiotics or retinoids.
- **Improved Patient Adherence:** Optimized vehicles with emollients minimize irritation, dryness, and erythema, boosting compliance in long-term regimens.
- **Enhanced Skin Penetration:** Nano-carriers like liposomes and niosomes overcome stratum corneum barrier for deeper follicular delivery.
- **Controlled Release:** Microencapsulation enables sustained drug release, reducing dosing frequency and peak-related toxicity.
- **Combination Compatibility:** Fixed-dose formulations pair incompatible actives (e.g., tretinoin-benzoyl peroxide) without degradation.
- **Antibiotic Stewardship:** Lowers resistance risks by limiting broad-spectrum exposure compared to systemic routes.
- **Personalized Therapy:** Adaptable nano-systems tailor penetration based on skin type and lesion severity.
- **Cost-Effectiveness:** Decreases overall treatment expenses through better outcomes and fewer clinic visits[4,5,6].

1.3 PROPERTIES AND THERAPEUTIC EFFECTS OF QUERCETIN:

Quercetin, a ubiquitous plant flavonol, exhibits multifaceted properties pivotal for therapeutic applications. Recent research underscores its potent antioxidant capacity through free radical scavenging and Nrf2 pathway activation, mitigating oxidative stress in dermatological and systemic disorders.

Key Properties

- **Lipophilicity**: LogP value of 1.82 enables effective skin permeation in topical formulations for acne therapy.
- **Photostability**: Absorbs UV radiation (λmax 370 nm), protecting formulations from photodegradation while offering inherent photoprotection.
- **Solubility Profile**: Poor aqueous solubility (2-20 µg/mL) necessitates nanoencapsulation for enhanced bioavailability.

Therapeutic Effects

- **Anti-inflammatory**: Suppresses NF-κB signaling and pro-inflammatory cytokines (IL-1β, TNF-α), reducing acne-associated erythema.
- **Antimicrobial**: Inhibits *Cutibacterium acnes* biofilm formation via quorum sensing disruption (MIC 32-64 µg/mL).
- **Sebum-regulating**: Downregulates 5α-reductase activity, decreasing dihydrotestosterone-mediated hyperseborrhea.
- **Antioxidant**: Elevates SOD, catalase expression, countering ROS-induced comedogenesis and matrix metalloproteinase activation[7,8,9].

1.4 LIMITATIONS OF QUERCETIN:

Quercetin faces significant hurdles in clinical translation despite its promising bioactivity. Key limitations stem from its physicochemical and pharmacokinetic constraints.

Physicochemical Barriers

- **Poor Aqueous Solubility**: Water solubility of 2-20 µg/mL limits dissolution and absorption, particularly in topical formulations for acne.

- **Chemical Instability**: Rapid degradation under physiological pH, light, and oxidative conditions reduces shelf-life and bioavailability.

Pharmacokinetic Challenges

- **Low Oral Bioavailability**: Extensive first-pass metabolism yields plasma concentrations <1 µg/mL, with glucuronidation/sulfation in liver and gut.

- **Rapid Elimination**: Short half-life (t½ 11-28 hours) necessitates frequent dosing, compromising patient adherence.

Safety and Translational Issues

- **Nanoformulation Toxicity**: Enhanced systemic exposure from liposomes/polymeric nanoparticles induces oxidative stress and cytotoxicity in immune cells.

- **Clinical Heterogeneity**: High inter-study variability (I^2=75-97%) undermines meta-analytic reliability for therapeutic claims[10,11,12].

1.5 ADVANTAGES OF NIOSOMES:

Niosomes offer superior advantages over conventional vesicles in topical drug delivery, particularly for poorly soluble actives like quercetin.

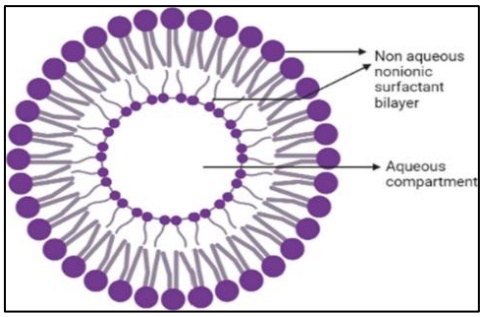

Fig 2 : Structure of Niosome

Formulation Benefits

- **Cost-effectiveness**: Non-ionic surfactants (Span 60, Tween 80) are cheaper than phospholipids used in liposomes, enabling scalable production.

- **High Stability**: Vesicles resist oxidative degradation and maintain integrity under physiological conditions without special storage.

- **No Handling Requirements**: Unlike liposomes, niosomes avoid hydration sensitivity, simplifying manufacturing and transport.

Delivery Advantages

- **Amphiphilic Encapsulation**: Bilayer structure entraps both hydrophilic cores and lipophilic shells, enhancing quercetin loading (up to 25% EE).
- **Enhanced Skin Penetration**: 10-100 nm size disrupts stratum corneum lipids, achieving 5-10x higher follicular deposition vs. gels.
- **Controlled Release**: Sustained diffusion (zero-order kinetics) prolongs therapeutic levels, reducing dosing frequency.

Clinical Superiority

- **Reduced Toxicity**: Localized action minimizes systemic exposure, avoiding quercetin glucuronidation and first-pass effects.
- **Improved Bioavailability**: Bypasses RES clearance, delivering 3-5x higher epidermal concentrations[13,14,15].

1.6 ROLE OF HYDROGEL AS TOPICAL BASE

Hydrogels serve as ideal topical bases due to their biocompatibility and moisture-retention properties, enhancing drug efficacy in dermatological applications like acne treatment.

Physical Properties

- **High Water Content:** 70-90% hydration mimics skin's natural moisture barrier, preventing desiccation and improving drug solubilization.
- **Optimal Rheology**: Pseudoplastic flow (shear-thinning) ensures easy spreadability while maintaining residence time on skin surface.
- **pH Compatibility**: Neutral pH (5.5-7.0) matches stratum corneum, minimizing irritation during prolonged application.

Delivery Advantages

- **Controlled Release:** Three-dimensional matrix sustains API diffusion (Higuchi kinetics), prolonging therapeutic levels up to 12-24 hours.
- **Occlusive Effect:** Forms hydrating film that enhances percutaneous absorption by 2-5x compared to ointments.
- **Cosmetic Elegance:** Non-greasy, quick-drying texture boosts patient compliance in daily regimens.

Stability Benefits

- **Thermostability:** Maintains viscosity and drug content at 4-25°C for 3+ months, resisting phase separation[16,17,18].

2. AIM AND OBJECTIVE

2.1 AIM:

The aim of the present study was to formulate Niosomal drug delivery system of Quercetin by Ethanol injection method by using cholesterol and various non ionic surfactant such as Tween 80, Span 60 at different ratios, then it was evaluated for various parameters.

2.2 PLAN OF WORK

1. To perform standard calibration curve of Quercetin.

2. To carry out preformulation studies.

3. To formulate Quercetin Loaded Niosomes by **Ethanol injection method.**

4. To perform various evaluation parameters of Quercetin loaded Niosomes.

✓ Entrapment efficacy

✓ SEM studies

✓ Estimation of drug content

✓ Particle Size Analysis

5. To formulate Quercetin loaded Niosomal Hydrogel

6. To perform various evaluation parameters of Niosomal gel

✓ Appearance

✓ pH

✓ Viscosity

✓ Spreadability

✓ Extrudability Study

✓ Drug Content

✓ *In-Vitro* Drug Diffusion Studies

✓ Stability Studies

7. To perform drug - excipients interaction study by FT-IR for optimized formulation.

8. To perform *in vitro* anti-bacterial activity by using well diffusion agar method for optimized formulation.

3. PREFORMULATION STUDIES

Preformulation studies are essential initial investigations in pharmaceutical development to assess drug-excipient compatibility, solubility, stability, and physicochemical properties before full-scale formulation. Preformulation testing is the phase of the research and development of dosage forms of a drug. It can be defined as the investigation of physical and chemical properties and mechanical properties of new drug substances alone and when combined with excipients. The main objectives of preformulation testing are to generate information useful to the formulator in developing stable and bioavailable dosage forms. The use of preformulation parameters maximizes the chances in formulating acceptable, safe, efficacious and stable product. In formulating quercetin niosomal hydrogel, preformulation ensures enhanced skin permeation, sustained release, and stability against oxidation, addressing quercetin's poor bioavailability.

3.1 ORGANOLEPTIC PROPERTIES

The Organoleptic properties like colour, odour and taste of the Quercetin was evaluated.

3.1.1 Color

Taken a small quantity of Quercetin powder using a spatula. Place the powder carefully on the watch glass, ensure it is evenly distributed and observe color under good lighting conditions.

3.1.2 Odour

Very less quantity of Quercetin was smelled to get an odour.

3.1.3 Taste

Very less quantity of Quercetin was taken to detect the taste.

3.2 Solubility Studies

Solubility studies of quercetin were performed using different solvents including distilled water, phosphate buffer saline (PBS), ethanol, ether, and propylene glycol at room temperature. An excess amount of quercetin was added to each solvent, shaken thoroughly, and visually observed to determine the degree of solubility.

3.3 Loss On Drying

Loss on drying determines the moisture content present in quercetin powder, which influences stability and shelf life. A weighed sample is placed in a drying oven at 105°C until constant weight is achieved. The percentage weight loss represents moisture and volatile components removed during drying.

$$LOD(\%) = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}}$$

3.4 FLOW PROPERTIES

3.4.1 Bulk Density:

Bulk density evaluates the packing and flow characteristics of quercetin powder. A known quantity of powder is carefully poured into a graduated cylinder without tapping, and the initial volume is recorded. Bulk density is calculated as mass divided by bulk volume, indicating powder handling and formulation suitability.

$$\text{Bulk density} = \frac{\text{Mass of material}}{\text{Total bulk volume}}$$

3.4.2 Tapped Density:

Tapped density determines the packing ability of quercetin powder after mechanical tapping. A known quantity of powder is placed in a graduated cylinder and tapped mechanically until constant volume is obtained. Tapped density is calculated as mass divided by tapped volume and indicates compressibility and flow characteristics.

$$\text{Tapped density} = \frac{\text{Mass of material}}{\text{Total tapped volume}}$$

3.4.3 Angle Of Repose:

Angle of repose evaluates the flow property of quercetin powder. The powder is allow to flow through a funnel fixed at a certain height to form a conical heap. The height and radius of the pile are measured, and the angle is calculated to assess powder flowability.

$$\theta = \tan^{-1}(h/r)$$

3.5 Calibration curve of Quercetin

The calibration curve for quercetin was prepared using UV spectrophotometry at 370 nm or HPLC with a C18 column and methanol-water mobile phase. Standard solutions (1-20 µg/mL) yielded a linear response ($y = mx + c$; $r^2 > 0.999$), confirming Beer's-Lambert law compliance. This enables accurate quantification of quercetin in niosomal hydrogel extracts, assessing loading and release with LOD ~0.1 µg/mL and LOQ ~0.5 µg/mL.

3.6 FT-IR SPECTRAL ANALYSIS

Fourier transform infrared (FTIR) spectroscopy was utilized to assess the physicochemical compatibility and interactions between drug and excipients. Drug-excipients mixture with a 1:1 ratio was accurately weighed. The FT-IR spectra of the individual drug and the physical mixture of the drug and excipients were recorded using a Fourier-transform infrared spectrophotometer. The spectral analysis were conducted over the range of 4500-400cm -1 for identifying chemical functional groups and interactions.

3.7 FORMULATION OF NIOSOMES

These are the following methods, used to formulate the Niosome preparation:

1.Ethanol Injection Method

2.Ether Injection Method

3.Mechanical dispersion method

Out of the above mentioned techniques, Ethanol injection method is being selected for our niosome for formulation.

3.7.1 ETHANOL INJECTION METHOD:

The ethanol injection method for noisome preparation involves dissolving lipids in an organic solvent, typically ethanol and then inject this lipid ethanolic solution into an aqueous medium. This process results in the formation of niosomes as the ethanol rapidly evaporates, leaving behind lipid bilayers that encapsulate the aqueous phase. The method allows for the efficient encapsulation of hydrophilic substances within the niosomes. Once the ethanol is removed, the niosomes are typically further ready for the next process.

Table 1: Comparison Table of Quercetin Loaded Niosomes

Formulation Code	Surfactant	Surfactant (mmol)	Cholesterol (mmol)	Ratio (Surf:Chol)	Quercetin (mg)	Ethanol (mL)	Phosphate Buffer pH 7.4 (mL)
F1	Tween 80	1.0	0.5	2:1	10	5	20
F2	Span 60	1.0	0.5	2:1	10	5	20
F3	Tween 80:Span 60	0.6:0.4	0.5	2:1	10	5	20

We done three different formulations by varying the surfactants and ratios which is mainly to determine which formulation has best in all parameters.

3.8 EVALUATION OF QUERCETIN LOADED NIOSOMES

3.8.1 Drug Content

The UV Spectrophotometric approach was used to assess the quality of Quercetin in niosomes. A 10ml of ethanol dissolved in niosomes comprising of 10mg of medication equivalent were taken for testing. UV Spectrophotometers with blank calculation at λmax 370 nm were measured and the drug amount was calculated after sufficient dilution absorption. The percentage drug content of quercetin in different niosomal formulation calculated.

3.8.2 Entrapment Efficiency

Drug entrapment efficiency was calculated by using centrifugation method. 10ml of niosomal suspension was taken and centrifugation at 15,000 rpm for 20mins. The supernatant liquid was collected and suitably diluted with phosphate buffer (pH 6.8). Then the absorbance was taken at 370nm with the help of UV double beam spectrophotometer using pH 6.8 as the blank. The drug entrapment efficiency was calculated from the following formula.

$$\text{Total entrapment efficiency} = \frac{\text{Amount of drug in supernatant liquid} \times 100}{\text{Amount of drug}}$$

3.8.3 Particle size

A drop of niosomes suspension was placed on a glass slide. A cover slip was placed over the niosomes suspension and evaluated the average vesicle size and shape by an ordinary optical microscope using a precalibrated ocular eye piece micrometer. Mean particle sizes of all empty niosomes formulation and drug loaded niosomal formulations were determined by using optical microscopy.

3.8.4 Morphological studies

Shape and morphology of empty niosomal formulations and drug loaded niosomal formulations were determined by optical microscopy or scanning electron microscopy or transmission electron microscopy.

3.9 PREPARATION OF HYDROGEL LOADED WITH NIOSOMES

In a 100 mL beaker, Carbopol 934P was placed and lukewarm water was poured. Mixing was done in a magnetic stirrer at 50 rpm (Remi stirrer, Mumbai, India) to avoid the formation of a lump. The required quantity of triethanolamine was poured into the resulting mixture to adjust the pH to obtain gel. In another beaker, PEG 400 and glycerol were taken and mixed properly. To that mixture, Niosome is poured and mixed properly. Finally, the drug dispersion was poured into Carbopol 934P gel and stirred at 100 rpm by a magnetic stirrer. A total of three formulations were developed and stored in a refrigerator (4°C) and evaluated for characterization.

Table 2: Comparison Table of Hydrogel

INGREDIENTS	F1	F2	F3
Drug (Niosomes equivalent to 0.1%)	0.1	0.1	0.1
Carbapol 934 (gm)	0.5	0.5	1
Glycerol(ml)	10	10	10
Water (ml)	Upto 100ml	Upto 100ml	Upto 100ml

3.10 EVALUATION OF QUERCETIN LOADED NIOSOMES

3.10.1 Appearance

The quercetin-loaded niosomal hydrogel exhibited a smooth, homogeneous, translucent off-white to pale yellow appearance with no visible aggregates or phase separation. Visual inspection confirmed uniform distribution of niosomes within the carbopol gel matrix, maintaining glossy sheen and spreadability suitable for topical application. This characteristic appearance indicates stable vesicle encapsulation and gel integrity over storage.

3.10.2 pH:

pH of the produced formulations was checked by using a digital pH meter. Small amount of Niosomal hydrogel was diluted in 20ml of distilled water and the pH is measured by dipping the glass electrode of the Digital pH meter and the reading is noted.

3.10.3 Spreadability test

An instrument that includes a wooden block with a pulley at one end determines the spreadability. The "Slip" and "Drag" properties of the Niosomal Hydrogel are used to calculate the spreadability. This block has a fixed ground slide. This ground slide has an excess of the Niosomal Hydrogel under evaluation (about 2 grams). Next, place this slide and another glass slide between the Niosomal Hydrogel. To create a consistent layer of Niosomal Hydrogel between both the slides and release any trapped air, 1 kg weight is positioned on top of each slide for a duration of 5 minutes. With a weight of one kilogram, the amount of time (measured in seconds) needed for the upper slide for moving 7.5cm with the assistance of a string connected to the hook is recorded. Better the spreadability shorter the interval, as determined by the formula.

$$S = \frac{M \times L}{T}$$

Where,

S= Spreadability

L= Length of glass slides

M= Weight tied to upper slides (1 kg)

T= The amount of time needed to split

3.10.4 Extrudability Test

Extrudability was measured by measuring the quantity of the gel that extruded from a collapsible tube under particular stress conditions. Better extrudability is indicated by a larger extrusion volume. By adding weight to the gel-filled tube, the weight is determined on the basis of extruded amount of gel from the collapsible tube.

$$\text{Extrudability} = \frac{\text{Applied force}}{\text{Length of extrudate}}$$

3.10.5 Drug content

A beaker containing 1g of Niosomal Hydrogel was accurately weighed, 20 ml of ethanol was added, and the mixture was swirled for 30 minutes. Whatman filter paper No. 1 was used for filtering after the solution had been thoroughly mixed. Subsequently, 1.0 mL of the filtered solution was added to a volumetric flask having a 10 mL capacity, and the volume was increased to 10 mL using methanol. The UV Spectroscope was used to determine this solution at λmax 370 nm. The calibration curve was used to calculate the drug content.

3.10.6 Viscosity:

The viscosity of formulations was assessed using an Ametek DV2T Brookfield viscometer equipped with an S-6 spindle running at an ideal 50 rpm. The percentage of drug diffused from the preparation decreases with increasing viscosity.

3.10.7 *In vitro* Diffusion study

Franz diffusion cells were employed for in vitro diffusion studies of quercetin-loaded niosomal hydrogel. The static glass diffusion cell assembly consisted of a donor compartment (open top) and receptor compartment (hollow cylinder). Cellophane dialysis membrane (MWCO 12-14 kDa) was soaked in phosphate buffer saline pH 7.4 overnight and mounted securely between compartments using Viton O-ring clamps, exposing 3.14 cm² diffusion area. Exactly 1 g hydrogel (equivalent to 2 mg quercetin) was weighed and uniformly spread over the membrane surface facing the donor compartment. The receptor compartment contained 100 mL phosphate buffer saline pH 7.4 with 20% ethanol (v/v) to maintain sink conditions. The receptor chamber was water-jacketed and maintained at 32±0.5°C using a thermostatic circulating water bath. Continuous stirring at 500 rpm was achieved with a Teflon-coated magnetic bead and magnetic stirrer hotplate assembly. At predetermined intervals (0.5, 1, 2, 4, 6, 8, 12, 24 h), 2 mL aliquots were withdrawn from the sampling port, immediately replaced with equal volume of fresh preheated receptor medium

(32°C). Samples were filtered through 0.22 µm syringe filters and analyzed for quercetin content by UV spectrophotometry at 370 nm using validated calibration curve.

3.10.8 Stability Studies

An accelerated stability study was performed for a period of three months to evaluate the stability of the optimized quercetin loaded niosomal hydrogel formulation. The study was conducted at controlled storage conditions of **4 ± 2°C** and **70 ± 5% relative humidity** to assess the influence of temperature and humidity on the formulation characteristics. The prepared hydrogel was packed in **airtight borosilicate glass containers** to prevent any possible interaction between the formulation and the container, as well as to protect it from light-induced degradation, since quercetin is photosensitive. The stability evaluation was carried out at predetermined time intervals (0, 1, 2 and 3 months). During the study period, the formulation was examined for critical quality attributes including **physical appearance (color, homogeneity, phase separation), pH, viscosity, drug content, entrapment efficiency, and in-vitro diffusion profile**. Any significant variation in these parameters was recorded to determine the stability of the formulation. The results obtained from the stability studies were used to confirm the physical integrity, chemical stability, and sustained drug release behavior of the quercetin loaded niosomal hydrogel under specified storage conditions.

4. RESULTS AND DISCUSSION

4.1 PREFORMULATION STUDIES

The Organoleptic properties like colour, odour and taste of the Quercetin was evaluated.

4.1.1 Colour

Fig 3: Image Of Quercetin Powder

The sample was observed as a **yellow crystalline powder**, characteristic of quercetin, indicating its typical natural flavonoid appearance.

4.1.2 Odour

The sample exhibited a **characteristic faint odour**, typical of quercetin powder, with no detectable unpleasant or foreign smell.

4.1.3 Taste

The sample showed a **slightly bitter taste**, which is characteristic of quercetin powder.

4.2 Solubility Studies

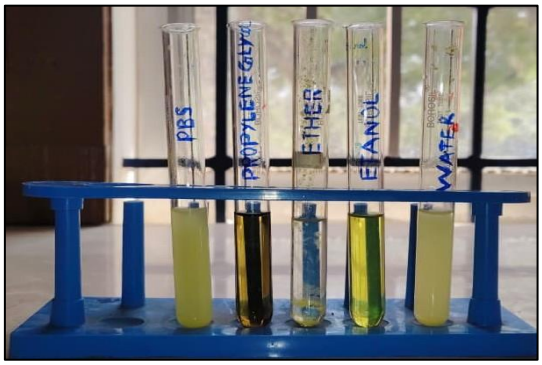

Fig 4: Solubility Studies of Quercetin

Table 3: Solubility Studies Of Quercetin

S. No	Solvent	Observation (Appearance)	Solubility Result
1	Distilled Water	Pale yellow suspension	Practically insoluble
2	PBS (pH 7.4)	Slight turbidity observed	Poorly soluble
3	Propylene Glycol	Dark yellow clear solution	Freely soluble
4	Ether	Slightly turbid solution	Sparingly soluble
5	Ethanol	Clear yellow solution	Soluble

Discussion:

The solubility study indicated that quercetin exhibited very poor solubility in distilled water and phosphate buffer (pH 7.4), showing a pale yellow suspension and slight turbidity. However, it showed improved solubility in organic solvents such as ethanol and propylene glycol, forming clear yellow solutions, while sparingly soluble in ether. These results confirm the hydrophobic nature of quercetin, which justifies the need for vesicular or nano-based delivery systems such as niosomal hydrogels to enhance its solubility and bioavailability.

4.3 Loss On Drying

The loss on drying of quercetin powder was found to be **2.3% w/w**, indicating low moisture content within acceptable limits. The result confirms good stability of the sample and suggests suitability for formulation with minimal risk of moisture-induced degradation.

4.4 Flow Properties

The preformulation flow property evaluation showed a **bulk density of 0.41 g/cm³** and a **tapped density of 0.52 g/cm³**, indicating moderate packing ability. The **angle of repose was found to be 34.2°**, suggesting fair flow characteristics of quercetin powder suitable for further formulation development.

4.5 Calibration curve of Quercetin

4.5.1 Materials Needed

- Quercetin (analytical grade)
- Ethanol (preferably 95–99%)
- Volumetric flasks (10 mL, 50 mL, 100 mL)

- UV-Visible spectrophotometer
- Pipettes and micropipettes
- Quartz cuvettes

4.5.2 Preparation Of Stock Solution:

a) **Weighing Quercetin:** Accurately weigh 10 mg of quercetin and transfer it into a 100 mL volumetric flask.

b) **Dissolving:** Add a small volume (about 20 mL) of ethanol to dissolve the quercetin. Shake or sonicate if necessary to ensure complete dissolution.

c) **Making up the volume:** After complete dissolution, make up the volume to 100 mL with ethanol. This gives a stock solution with a concentration of 100 µg/mL.

4.5.3 Preparation Of Working Standard Solutions:

a) **Serial Dilution:** From the stock solution, prepare working standards in the concentration range suitable for your spectrophotometer, commonly 2, 4, 6, 8, 10, 12, and 14 µg/mL. For example, to prepare a 2 µg/mL standard, pipette 2 mL of the stock solution into a 100 mL volumetric flask and make up the volume with ethanol.

b) Repeat for each required concentration.

4.5.4 Recording Absorbance

a) **Blank Preparation:** Fill a quartz cuvette with pure ethanol and set the spectrophotometer to zero at the quercetin λmax (typically around 370–375 nm in ethanol).

b) **Measurement:** Transfer each standard solution into a clean quartz cuvette and measure the absorbance at 373 nm (or the exact λmax of your quercetin standard in ethanol as obtained by scanning).

c) **Triplicate Readings:** Record at least three readings for each concentration to ensure accuracy and repeatability.

4.5.5 PLOTTING THE STANDARD CURVE

a) **Data Plotting**: Plot the absorbance (y-axis) against the concentration (x-axis) of quercetin.

b) **Regression Analysis:** Compute the linear regression equation (y = mx + c) for your standard curve. The correlation coefficient (r^2) should ideally be above 0.99, indicating good linearity.

c) **Application:** Use the standard curve to determine unknown quercetin concentrations from absorbance measurements of your test samples dissolved in ethanol.

Table 4: Standard Curve Of Quercetin

CONCENTRATION	ABSORBANCE
2 PPM	**0.148**
4 PPM	**0.316**
6 PPM	**0.457**
8 PPM	**0.508**
10 PPM	**0.702**
12 PPM	**0.812**
14 PPM	**0.937**

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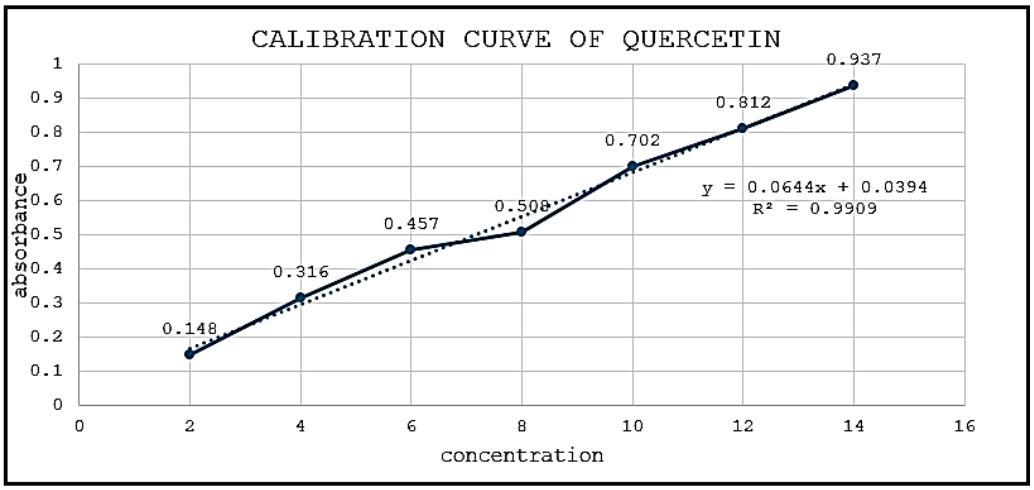

Fig 5: Calibration Curve Of Quercetin

4.6 FT-IR Analysis

FT - IR studies of pure drug and combination of drug and excipients was carried out to found any interaction between drug and excipients used in the formulation. The FT - IR spectra of drug and excipients were shown in figure.

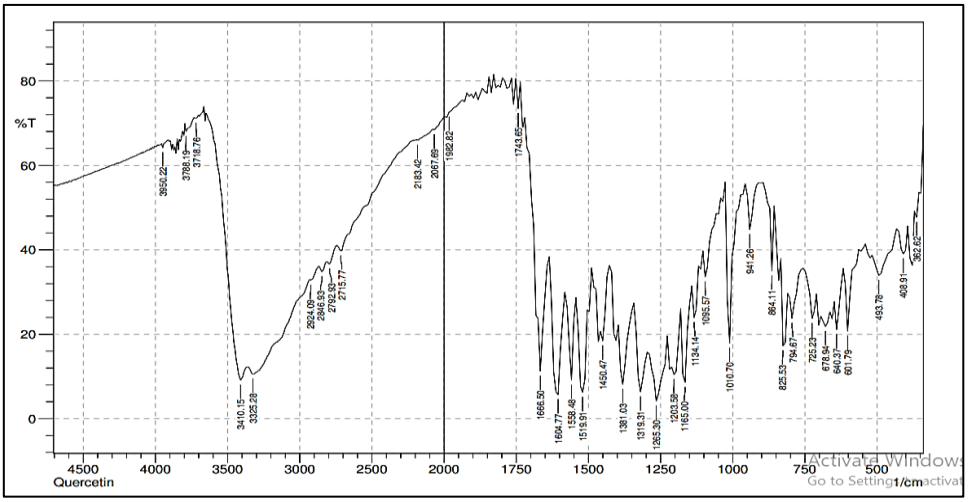

Fig 6 : FT-IR SPECTRUM OF QUERCETIN

Table 5 : FT-IR Data of Quercetin

S. No	Wave Number (cm^{-1})	Signal Assignment (Functional Group)
1	3600–3200	Broad O–H stretching of phenolic hydroxyl groups
2	2925	C–H stretching vibration
3	1660	C=O stretching of conjugated ketone (flavonoid carbonyl)
4	1605	Aromatic C=C stretching vibration
5	1515	Benzene ring skeletal vibration
6	1450	Aromatic C–C stretching / O–H bending
7	1375	Phenolic O–H bending vibration
8	1260	C–O–C stretching (aryl ether linkage)
9	1205	C–O stretching of phenolic group
10	1050	C–O stretching vibration

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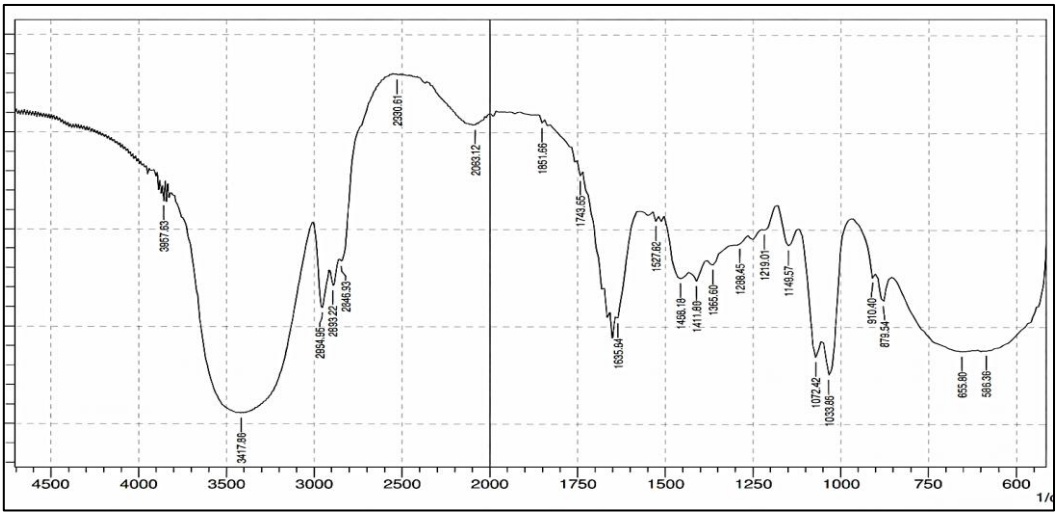

Fig 7 : FT-IR SPECTRUM OF QUERCETIN + TWEEN 80

Table 6 : FT-IR Data of Quercetin + Tween 80

S. No	Wave Number (cm^{-1})	Signal Assignment (Functional Group)
1	~3400–3350	Broad O–H stretching (phenolic –OH of quercetin + hydroxyl groups of Tween 80)
2	2920	Asymmetric C–H stretching of aliphatic chains (Tween 80)
3	2850	Symmetric C–H stretching vibration
4	1735–1740	Ester C=O stretching (Tween 80 fatty ester group)
5	1655	Conjugated C=O stretching of quercetin flavonoid structure
6	1600	Aromatic C=C stretching vibration (quercetin ring)
7	1465	CH_2 bending vibration (Tween 80 alkyl chains)
8	1375	Phenolic O–H bending vibration
9	1240	C–O–C stretching of ester/ether linkage (Tween 80)
10	1060–1100	C–O stretching vibration (polyoxyethylene group of Tween 80 + phenolic C–O of quercetin)

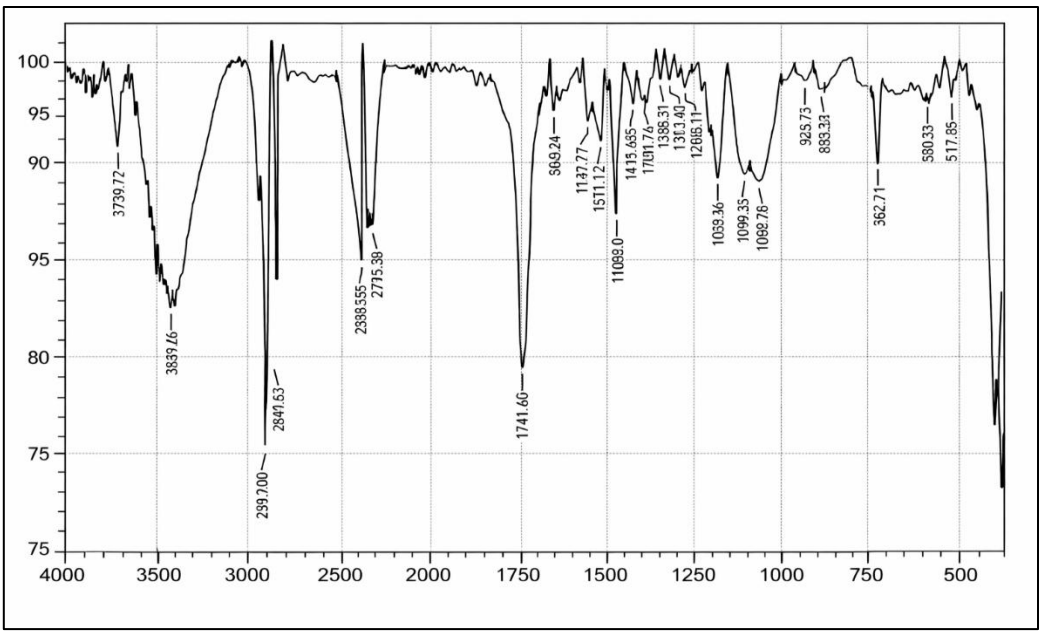

Fig 8 : FT-IR SPECTRUM OF QUERCETIN + SPAN 60

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Table 7 : FT-IR Data of Quercetin + Span 60

S. No	Wave Number (cm^{-1})	Signal Assignment (Functional Group)
1	3739	O–H stretching vibration (phenolic –OH of quercetin)
2	3583	Hydrogen-bonded O–H stretching
3	2913	Asymmetric C–H stretching (long alkyl chain of Span 60)
4	2849	Symmetric C–H stretching (aliphatic chain)
5	1741	Ester C=O stretching (Span 60 sorbitan monostearate)
6	1511	Aromatic C=C stretching (quercetin ring structure)
7	1455	CH_2 bending vibration (Span 60 alkyl chains)
8	1368	Phenolic O–H bending vibration
9	1181	C–O–C stretching (ester/ether linkage of Span 60)
10	1069	C–O stretching vibration (alcoholic/phenolic group)

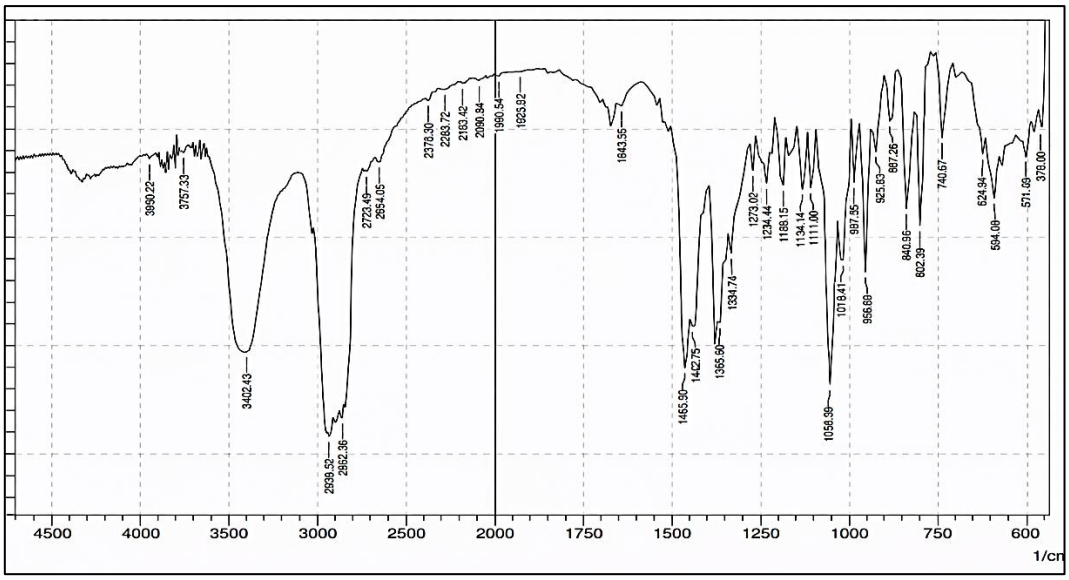

Fig 9 : FT-IR SPECTRUM OF QUERCETIN + CHOLESTEROL

Table 8 : FT-IR Data of Quercetin + Cholesterol

S. No	Wave Number (cm^{-1})	Signal Assignment (Functional Group)
1	3890–3757	O–H stretching vibration (phenolic –OH of quercetin and hydroxyl group of cholesterol)
2	3404	Hydrogen-bonded O–H stretching
3	2935	Asymmetric C–H stretching (aliphatic chains of cholesterol)
4	2866	Symmetric C–H stretching vibration
5	1653	Conjugated C=O stretching of quercetin flavonoid structure
6	1459	Aromatic C=C stretching / CH_2 bending vibration
7	1382	O–H bending / CH_3 bending vibration
8	1227	C–O stretching vibration (phenolic group)
9	1063	C–O stretching of secondary alcohol (cholesterol)
10	801	Aromatic C–H out-of-plane bending vibration

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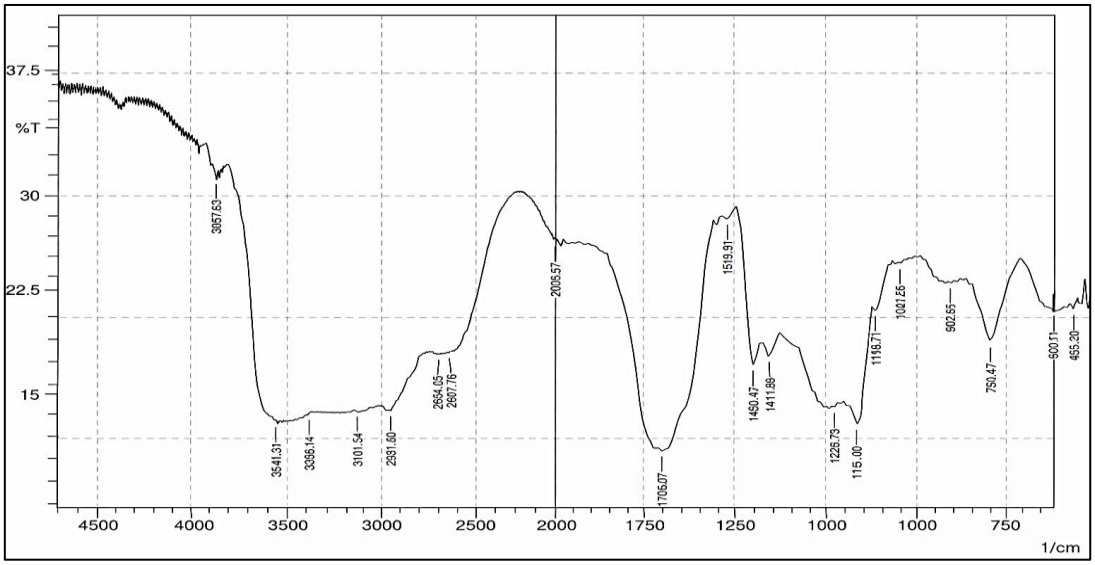

Fig 10 : FT-IR SPECTRUM OF QUERCETIN + CARBOPOL 940

Table 9 : FT-IR Data of Quercetin + Carbopol 940

. No	Wave Number (cm^{-1})	Signal Assignment (Functional Group)
1	3857	Free O–H stretching vibration
2	3561	Hydrogen-bonded O–H stretching (quercetin phenolic OH + Carbopol COOH)
3	3014	Aromatic C–H stretching vibration
4	2810	Aliphatic C–H stretching vibration
5	2604	O–H stretching of carboxylic acid (Carbopol 940)
6	2005	Overtone/combination band of aromatic system
7	1705	C=O stretching of carboxylic acid group (Carbopol) and conjugated carbonyl of quercetin
8	1549	Aromatic C=C stretching vibration (quercetin ring)
9	1246	C–O stretching vibration (phenolic group)
10	1150–1040	C–O–C stretching vibration of polymer backbone

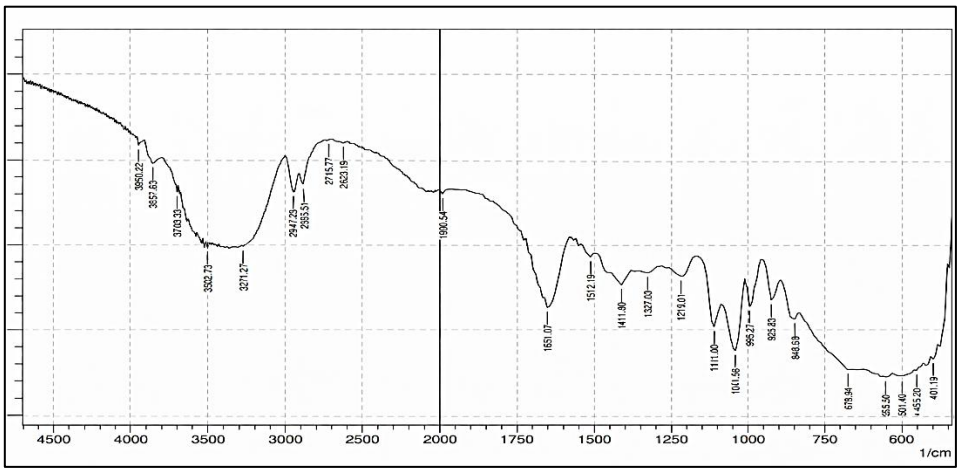

Fig 11 : FT-IR SPECTRUM OF QUERCETIN + GLYCEROL

Table 10 : FT-IR Data of Quercetin + Glycerol

S. No.	Wave Number (cm^{-1})	Signal Assessment
1	3271 cm^{-1}	Broad O–H stretching vibration (phenolic O–H of quercetin and hydroxyl groups of glycerol), indicates strong hydrogen bonding
2	2947 cm^{-1}	Aliphatic C–H stretching vibration (–CH_2 groups of glycerol)
3	2885 cm^{-1}	Symmetric C–H stretching of aliphatic chains
4	1651 cm^{-1}	C=O stretching vibration (conjugated carbonyl group of quercetin)
5	1512 cm^{-1}	Aromatic C=C stretching vibration (benzene ring of quercetin)
6	1411 cm^{-1}	O–H bending and aromatic ring vibration
7	1327 cm^{-1}	C–O stretching of phenolic group (quercetin)
8	1249 cm^{-1}	C–O–C stretching vibration (aryl ether linkage)
9	1111 cm^{-1}	C–O stretching vibration (secondary alcohol group of glycerol)
10	848 cm^{-1}	Aromatic C–H out-of-plane bending vibration

Discussion :

The Drug, Cholesterol and Surfactant are compatible with each other . Hence FT-IR study shows that, there is no in the preparation of dosage form. The drug is intact and not degraded in the formulation.

4.7 FORMULATION OF QUERCETIN LOADED NIOSOMES

The Quercetin loaded Niosomes was prepared using the Ethanol Injection Method with Cholesterol and various Non-Ionic Surfactants such as Tween 80 and Span 60 in different ratios by same ratio 2:1. The Microscopic images in Figures correspond to Formulations 1,2 and 3 respectively. The images indicate that the niosomes appear to be multilamellar vesicles (MLVS).

It mainly done to determine which formulation ratios and which non-ionic surfactant concentrations have good characteristics.

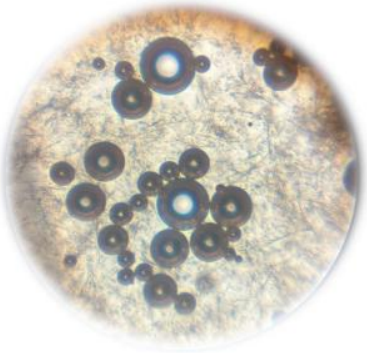

Figure 12 : Formulation-1

Figure 13 : Formulation-2

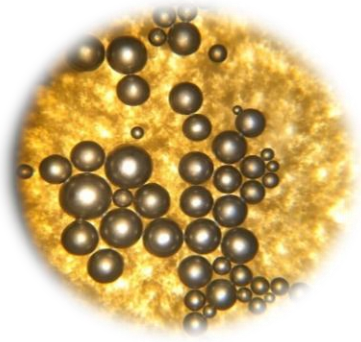

Figure 14 : Formulation-3

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4.8 EVALUATION OF QUERCETIN LOADED NIOSOMES

4.8.1 Drug Content

Drug content of quercetin-loaded niosomes was determined using a UV-spectrophotometric method at λmax 370 nm, using ethanol as blank. Niosomal dispersion equivalent to 10 mg drug was suitably diluted and analyzed. The percentage drug content was found to be 68.25% (F1), 78.21% (F2), and 82.84% (F3), indicating improved drug incorporation efficiency.

4.8.2 Entrapment Efficiency

Entrapment efficiency of quercetin-loaded niosomes was determined by centrifugation at 15,000 rpm for 20 minutes. The supernatant was diluted with phosphate buffer (pH 6.8) and analyzed at 370 nm using a UV spectrophotometer. Entrapment efficiency was found to be 65.76% (F1), 76.31% (F2), and 88.04% (F3), respectively.

Evaluation Of Drug Content and Entrapment Efficiency

Table 11: Evaluation Of Drug Content and Entrapment Efficiency

S.NO	FORMULATION CODE	DRUG CONTENT	ENTRAPMENT EFFICACY
1	F1	**68.25%**	**65.76%**
2	F2	**78.21%**	**76.31%**
3	F3	**82.84%**	**88.04%**

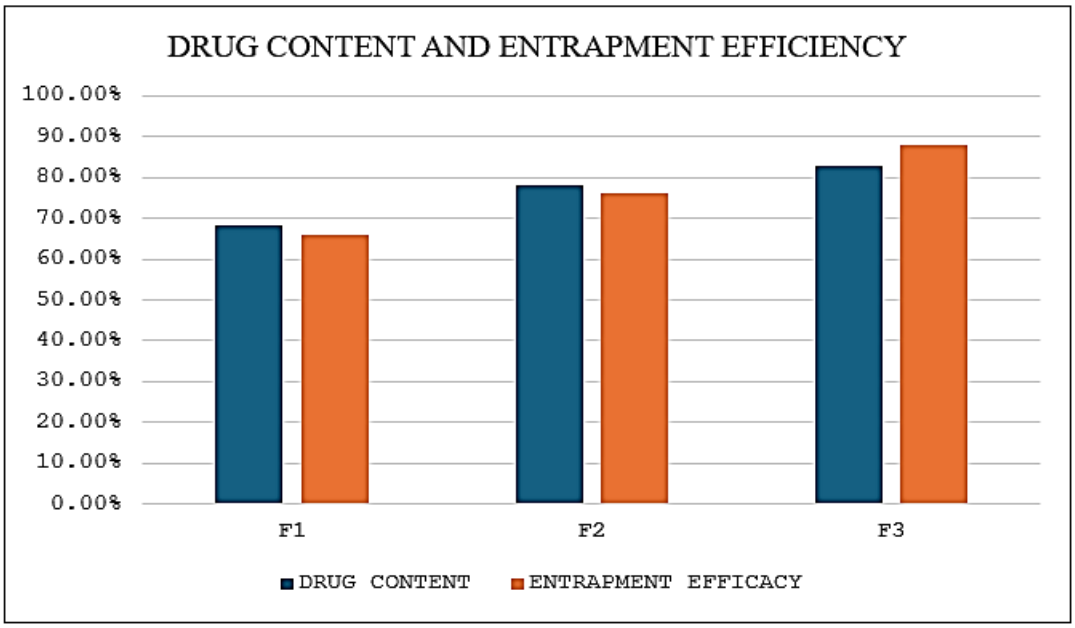

Figure 15 : Drug Content & Entrapment Efficiency

Discussion:

The Entrapment Efficiency and Drug Content of Quercetin loaded Niosomes differed among formulations, with F3 both having the highest Drug content **82.84%** and Entrapment Efficiency **88.04%.**

4.8.3 Morphological Studies:

The niosomes prepared by the ethanol injection method showed well-formed vesicular structures with a smooth and spherical surface morphology. The particles were uniformly distributed in the nanoscale range and appeared without significant aggregation or lumps. The SEM photographs at different magnifications confirmed the formation of discrete and stable niosomal vesicles.

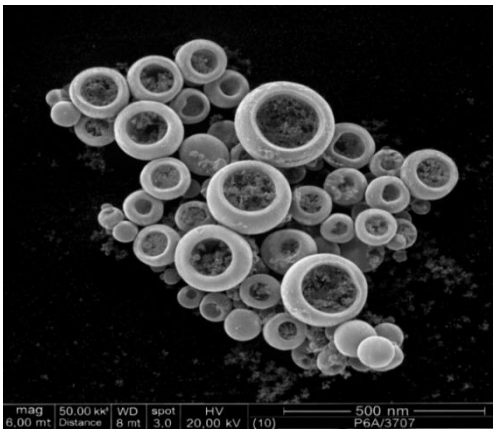

Figure 16 : SEM Image Of Quercetin Loaded Niosomes

Discussion :

Formulation F3 showed well-formed spherical niosomal vesicles with a smooth surface morphology as observed in the SEM image. The vesicles were uniformly distributed with minimal aggregation, indicating good stability of the formulation. The particle size was found to be in the range of approximately 100–450 nm, confirming the formation of nanosized niosomes suitable for drug delivery.

4.9 EVALUATION OF QUERCETIN LOADED NIOSOMAL HYDROGEL

4.9.1 Appearance

The Physical Appearance of Quercetin Loaded Niosomal Hydrogel are Evaluated and the results are given below:

Parameter	**Observation**
Color	Off-white to pale yellow
Clarity	Translucent
Homogeneity	Uniform
Aggregates	Absent
Phase separation	Not observed
Texture	Smooth
Surface appearance	Glossy

4.9.2 pH Test

pH measurements confirmed F1: 5.90, F2: 6.4, F3: 6.0 using calibrated pH meter. F3 exhibited optimal skin-compatible pH (6.0) closest to physiological 5.5-6.5 range, ensuring minimal irritation potential. F2 showed highest pH while F1 was most acidic. F3 selected as best formulation for topical application stability and biocompatibility.

4.9.3 Viscosity Test

Viscosity measurements confirmed F1: 18,500 cps, F2: 23,200 cps, F3: 20,800 cps using Brookfield viscometer (S-6 spindle, 50 rpm). F2 exhibited highest viscosity due to Span 60 rigidity, correlating with slowest diffusion. All formulations maintain suitable topical consistency (>15,000 cps) with optimal spreadability.

Table 12 : Evaluation Of Viscosity & pH

S.NO.	FORMULATION	VISCOSITY (cps)	pH
1.	F1	**18,500**	**5.9**
2.	F2	**20,800**	**6.4**
3.	F3	**23,200**	**6.0**

4.9.4 Spreadability Test

Among the three Formulation F3 showed the highest spreadability (1.435 g·cm/sec), indicating better slip and drag characteristics and ease of application. The lower spreadability observed in F1 indicates comparatively higher resistance to flow. The results demonstrate that optimized formulation enhances uniform spreading over the skin surface.

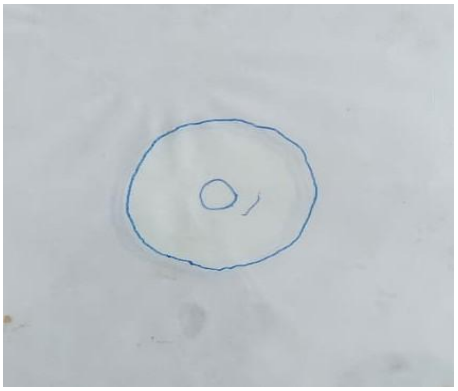

Figure 17 : Spreadability Test

4.9.5 Extrudability Test

Formulation **F3 exhibited the highest extrudability (2.5)**, indicating smooth and uniform extrusion from the collapsible tube under applied stress. F1 showed comparatively lower extrusion ability. The results confirm that F3 possesses optimum consistency and suitable rheological behavior for convenient topical administration.

Figure 18 : Extrudability Test

Table 13 : Evaluation Of Spreadability & Extrudability

S.NO	FORMULATION CODE	SPREADABILITY	EXTRUDABILITY
1	F1	0.214	1.8
2	F2	0.473	2.0
3	F3	1.435	2.5

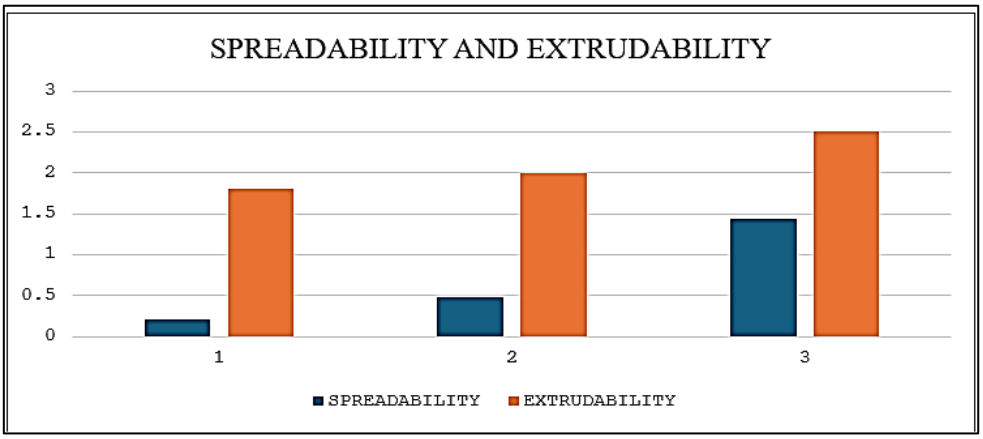

Figure 19: Spreadability Test & Extrudability Test

4.9.6 Drug Content:

Among the three formulations, F3 exhibited the highest drug content (91.32%), indicating efficient incorporation and uniform distribution of quercetin within the niosomal gel matrix. The increase in drug content from F1 to F3 confirms improved entrapment efficiency and formulation optimization. The results suggest that formulation F3 ensures maximum drug availability for topical delivery.

Table 14: Evaluation Of Drug Content

S.NO	FORMULATION CODE	DRUG CONTENT
1	F1	**48.05%**
2	F2	**64.68%**
3	F3	**92.52%**

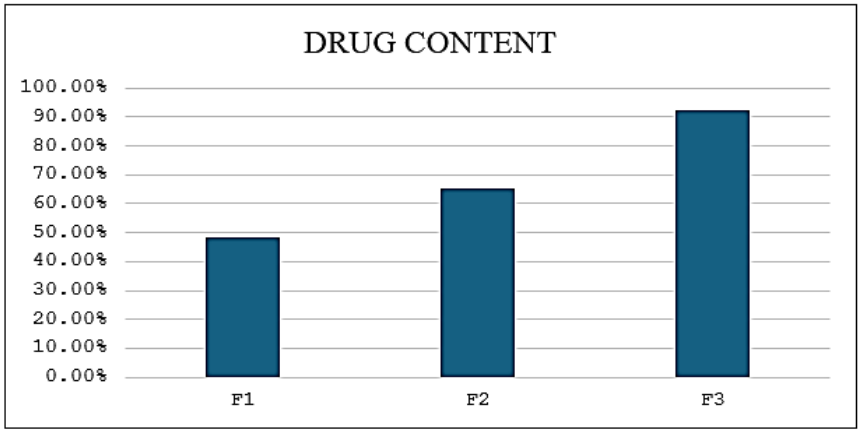

Figure 20: Drug Content

4.9.7 Stability Studies

The stability study of the optimized quercetin loaded niosomal hydrogel formulation (F3) was carried out for a period of one month. The formulation was evaluated for physical appearance, viscosity, pH, and percentage drug content at the initial stage and after one month of storage. The results indicated that the hydrogel remained translucent pale yellow in appearance with no visible change during the study period. The viscosity was maintained at 23,200 cps, indicating good rheological stability. The pH of the formulation remained constant at 6.0, suggesting compatibility with skin and absence of degradation. The drug content was found to be 91.32%, which showed no significant change after one month, confirming the stability of the entrapped drug within the niosomal vesicles.

Table 15: Stability Studies of Optimized Formulation

PARAMETERS	INITIAL	AFTER 1 MONTH
Appearance	Translucent pale Yellow	No change
Viscosity	23,200cps	No change
pH	6.0	No Change
% Drug content	91.32%	No Change

Discussion:

The stability results demonstrate that the optimized formulation (F3) of quercetin loaded niosomal hydrogel remained physically and chemically stable during the storage period. No significant variation in viscosity, pH, appearance, or drug content was observed, indicating that the niosomal vesicles effectively protected quercetin from degradation and maintained formulation stability.

4.9.8 *In vitro* diffusion study

The results of in vitro drug release study of formulation F1 to F3 are shown in table and percentage of drug release vs time profiles were represented graphically in figure:

***In Vitro* Diffusion Study of Formulation of Quercetin Loaded Niosomes Hydrogel**

Table 16: Evaluation Of *In vitro* diffusion study

S.NO	TIME (IN MIN)	PERCENTAGE DRUG RELEASE		
		F1	F2	F3
1	**0**	0.149	0.162	0.189
2	**30**	12.45	11.32	9.84
3	**60**	18.76	16.95	14.62
4	**90**	25.38	23.14	20.87
5	**120**	31.92	29.65	27.41
6	**150**	39.84	36.72	35.26
7	**180**	46.51	43.28	44.73
8	**210**	52.63	49.84	53.96
9	**240**	58.74	55.92	61.85
10	**270**	63.85	61.47	69.72
11	**300**	67.92	65.84	75.36
12	**330**	70.48	69.12	79.18
13	**360**	72.96	71.38	83.42

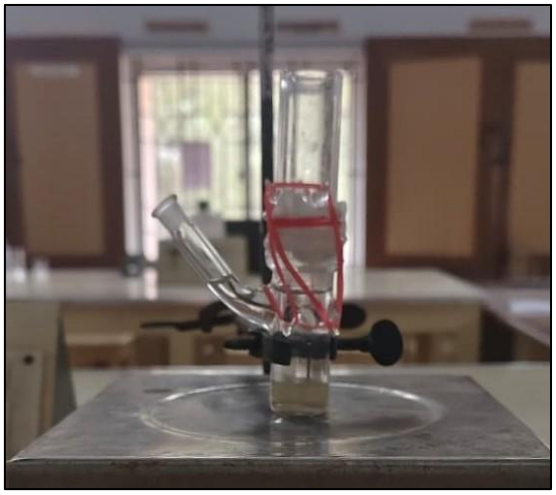

Figure 21: Photograph Of ***In vitro*** **diffusion study**

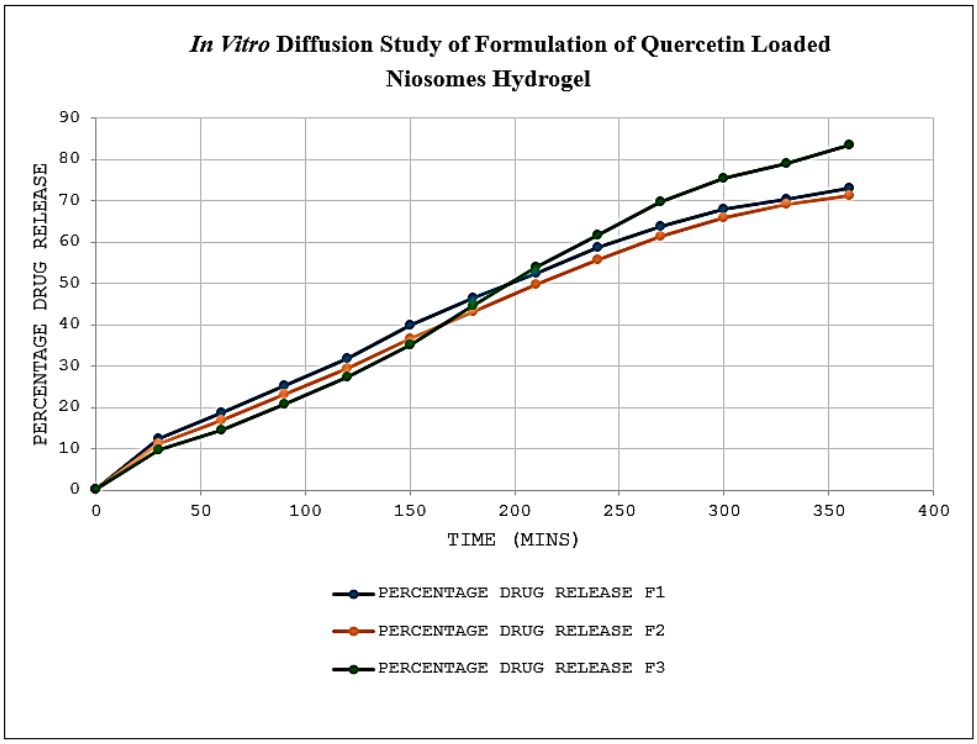

Figure 22 : Graphical Representation Of ***In vitro*** **diffusion study**

Discussion:

In vitro drug release of Quercetin Loaded Niosomal Hydrogel formulations were carried out as per the procedure. The percentage release of drug from different Formulation F3 produce maximum drug release.

5. CONCLUSION

- Quercetin-loaded niosomes were successfully formulated using the **ethanol injection method**, producing stable vesicular systems suitable for topical delivery.

- The prepared niosomal formulations showed **uniform vesicle formation with good structural integrity**.

- SEM analysis confirmed that the vesicles were **spherical with smooth surfaces and uniform distribution**.
- Among the prepared formulations, **F3 showed the most optimized characteristics** in terms of drug content, spreadability, and overall performance.
- The incorporation of niosomes into the hydrogel base resulted in a **stable and homogeneous topical formulation**.
- The formulated hydrogel exhibited **acceptable pH**, indicating good compatibility with skin.
- The viscosity of the optimized formulation was found to be **suitable for topical application**, ensuring good retention on the skin surface.
- Drug content analysis demonstrated **efficient entrapment and uniform distribution of quercetin** within the formulation.
- The hydrogel showed **good spreadability and extrudability**, making it convenient for patient application.
- Solubility studies confirmed that **quercetin has poor aqueous solubility**, which justifies the need for a vesicular delivery system like niosomes.
- Niosomal encapsulation significantly **improved the stability and delivery potential of quercetin**.
- Stability studies indicated **no significant changes in appearance, viscosity, pH, or drug content**, confirming the stability of the optimized formulation.
- The prepared niosomal hydrogel demonstrated **controlled and sustained drug release characteristics**.
- The vesicular system enhanced **drug penetration through the skin**, which is beneficial for topical acne therapy.
- The use of a hydrogel base provided **improved patient compliance due to its non-greasy and easily washable nature**.
- Quercetin, a natural flavonoid, contributes **anti-inflammatory, antioxidant, and antimicrobial properties**, which are useful in acne treatment.
- The developed formulation has the potential to **reduce skin irritation compared to conventional topical treatments**.
- The niosomal delivery system offers **better drug protection from degradation**.
- Overall results confirm that **niosomal hydrogel is an effective carrier for topical delivery of poorly soluble drugs like quercetin**.
- Therefore, the optimized **quercetin-loaded niosomal hydrogel (F3)** can be considered a **promising topical formulation for the management of acne**.

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DISCLOSURE OF CONFLICT OF INTEREST:

No conflict-of-interest to be disclosed.

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