

Formulation and Evaluation of a Nanostructured lipid carrier Gel Co-loaded with Rutin and Quercetin for Acne vulgaris

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Abstract:

Rutin and Quercetin are naturally occurring flavonoids broadly found in vegetables, fruits, tea & medicinal plants. These bio functional flavonoids constituent are popular for their significant actions such as anti-inflammatory, antimicrobial, antioxidant, anti-tumour and cardioprotective antidiabetic. The purpose of this research was to formulate Rutin & quercetin encapsulated nanostructured lipid carriers gel formulation for acne reduce the unintended effects and to extended release. Methods: Rutin and quercetin encapsulated nanostructured lipid carriers gel were developed using fraction factorial design to assess the influence of procedure and composition variation. The NLCs gel were formulated by melt emulsification method. The prepared dosage form were eventually added into gelling system of Carbopol 940 for ease of application. The prepared gels was analysed for its anti-acne activity, biomarker estimation and anti-microbial studies. Results: NLCs presents average particle size is 175 ± 10 nm to 286 ± 23 nm and percentage entrapment in the range of 94 ± 0.3 to 98 ± 4.0 respectively. In vitro drug release study shows that the gel formulation can easily applicable to the skin and has better drug absorption and release and does not cause skin irritation. Conclusions: The findings demonstrates the formulated NLCs gel formulation showed a brilliant carrier for topical delivery of Rutin and quercetin, proving it gives release of drug in controlled manner, and ability to target skin disease.

Keywords: NLCs, in-vitro study kinetic modelling, Rutin and Quercetin, Good health and well-being.

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Introduction:

It is a multifactorial and inflammatory long term disease in pilosebaceous unit. In which hair follicles involved and also sebaceous gland. It is most prominent dermatological conditions globally, influencing all age groups population, but it is particularly common during adolescence¹. Epidemiological studies indicate that acne impact around 9.4 percent of the worldwide different age group people and approximately 85 percent of teenagers, with a considerable number of cases persisting into adulthood, especially among females. Although acne is not a life-threatening condition, its impact on quality of life is significant due to visible skin lesions, potential for permanent scarring, and associated psychological consequences such as anxiety, social withdrawal, and depression².

The disease predominantly influence region of the body with a high impact of sebaceous unit, involving the neck, chest, shoulders, face and upper back. practically, acne showed with a broad spectrum of wound which are broadly classified into inflammatory and non-inflammatory types. The closed comedones (white heads) and open comedones (black heads) come under the non-inflammatory lesions. Whereas papules, pustules, nodules, and cysts come under the category of inflammatory lesions. The magnitude of acne can

range from mild comedonal acne to extremity nodulocystic forms that may result in permanent scarring and post-inflammatory hyperpigmentation³. The pathology of acne vulgaris is complicated and includes the interaction of multiple biological processes. Four primary reasons are widely identified as central to the formation of acne: enhanced production of sebum, abnormal follicle keratinization, proliferation by *Propionibacterium acnes* (also known as *Cutibacterium acnes*), and redness⁴. These elements interact in a dynamic and sequential way rather than acting individually, which eventually results in the formation of acne wounds. One of the primary causes of acne formation is thought to be excessive sebum production. Androgenic hormones like testosterone and dihydrotestosterone are the main regulators of sebum production, which is a lipid-rich material made by sebaceous glands. Increased androgen levels during adolescence cause the sebaceous unit to become more active, which results in excessive sebum excretion. This lipid-rich atmosphere promotes bacterial growth and aids in follicular blockage⁴. An additional critical stage in the pathophysiology of acne is abnormal keratinisation of the follicular epithelium. Under normal physiological conditions, keratinocytes are shed from the follicular lining and expelled through

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the follicular opening. However, in acne-prone skin, there is hyperproliferation and abnormal differentiation of keratinocytes, leading to the accumulation of corneocytes within the follicle. This process results in the growth of microscopic comedones, that can progress in detectable comedones. This obstruction of the follicular duct further promotes the retention of sebum and cellular debris, providing favourable anaerobic atmosphere for bacterial growth. A major factor in the development of an inflammatory lesion from a non-inflammatory one is the colonisation of follicles by *Cutibacterium acnes*. This anaerobic gram-positive bacteria thrives in the lipid-rich environment of the sebaceous follicles⁵. It produces lipase enzymes that hydrolyze triglycerides in sebum and then convert free fatty acids, that are highly aggravating and pro-inflammatory. Furthermore, bacterial antigens trigger the host immune response, which in turn triggers inflammatory pathways and releases pro-inflammatory mediators like interleukins and cytokines like tumour necrosis factor (TNF)⁵.

It is now understood that inflammation plays a key role in the pathophysiology of acne, even in its early, subclinical phases. Both innate and adaptive processes are involved in the immune response to *Candida acnes*. These mechanisms include the activation of Toll-like receptors (TLRs), the production of reactive oxygen species (ROS), and the recruitment of inflammatory cells such neutrophils and macrophages. Tissue damage, follicular rupture, and the development of papules, pustules, cysts, and nodules are the outcomes of these processes. The onset and severity of acne are influenced by a number of endogenous and exogenous factors in addition to these fundamental pathogenic mechanisms. Sebum production and follicular activity are significantly influenced by hormonal imbalances, especially those involving androgens and IGF-1 (insulin-like growth factor-1). Another significant factor is genetic predisposition; studies show that those with a family history of acne vulgaris are more likely to develop acne. Furthermore, by affecting hormone levels, inflammatory responses, and skin barrier function, environmental and lifestyle factors like nutrition, smoking, stress, and pollution exposure can make acne worse⁶. Due to their influence on insulin and IGF-1 signalling pathways, dietary factors—particularly high glycaemic index meals and dairy products—have been linked to the development of acne. These pathways contribute to the development of lesions by stimulating keratinocyte growth and sebaceous gland activity. Similarly, it has been demonstrated that psychological stress exacerbates acne by triggering the release of stress hormones, which can raise inflammatory reactions and sebum production. By causing oxidative stress and follicular obstruction, lifestyle choices like smoking and using comedogenic cosmetics may exacerbate the illness⁷. Acne has a profound effect on a person's psychological and social well-being in addition to its physical symptoms. Reduced self-esteem, social anxiety, and poor interpersonal interactions can

result from visible facial lesions. Acne has been linked to despair and suicidal thoughts in extreme cases, underscoring the necessity for all-encompassing treatment that takes into account the psychological and physical elements of the condition. The treatment of acne is still difficult despite substantial research and improvements in our understanding of the condition. Antibiotics, benzoyl peroxide, and retinoids are the main topical medications⁸. Conventional therapy approaches target one or more of the major pathogenic causes. Hormonal therapy, oral antibiotics, isotretinoin, and physical therapies are examples of further systemic treatments. However, problems including side effects, antibiotic resistance, and lesion recurrence restrict these treatments' long-term efficacy. As a result, there is growing interest in new therapeutic strategies, such as drug delivery systems based on nanotechnology, which provide enhanced effectiveness, tailored action, and fewer side effects⁸. Understanding the fundamental role of skin microorganisms, epigenetic changes, and inflammatory signalling pathways in acne pathology has also been a focus of current research. These new discoveries have created new opportunities for the creation of individualised and focused treatment plans. Designing successful therapeutic strategies and enhancing patient outcomes require a thorough grasp of the complex nature of acne⁹.

In summary, hormone regulation, microbial colonisation, immunological response, and environmental variables all combine to cause acne vulgaris, a complicated dermatological condition. Research in dermatological and pharmaceutical sciences is crucial due to its high frequency, chronic nature, and substantial emotional impact. To overcome present obstacles and provide safer and more effective treatments for acne control, greater research into its underlying causes and treatment approaches is crucial¹⁰.

Materials and methods

Material

Rutin was purchased from CDH Pvt. Ltd., and quercetin was purchased from Yucca Ltd. Eucalyptus oil from Moksha Pvt. Ltd. Stearic acid and methyl parabenzoate were collected from CDH, New Delhi, India. Carbopol-940 gelling agent were obtained from CDH, new Delhi, which are of good grade used in this research.

Method

Rutin and Quercetin gel was developed according to the composition. Carbopol 940 was dissolved in distilled water and after that Rutin, Quercetin and RQ NLCs dispersion infused into polymeric gel using a high shear mixing at 1000rpm for 5min. The formulated NLC gel instantly neutralized with triethanolamine till pH becomes 5-6. The prepared gel was kept aside for 24h at ambient for equilibration¹¹.

Table 1: Optimized formula for formulation (loaded combination of Rutin, quercetin and

S.N	Formulation Code	NLC (suspension form) (ml)	Carbopol 940 (g)	Triethanol amine (ml)	Disodium EDTA (g)	Propylene Glycol (ml)	D.M. water (100 ml)
1	RQNLC	10	1.5	0.2	0.005	2.5	q.s
2	RNLC	10	1.5	0.2	0.005	2.5	q.s
3	QNLC	10	1.5	0.2	0.005	2.5	q.s

CHARACTERIZATION ORGANOLEPTIC

Physical properties

The gel's physical appearance was examined using both visual and common human senses. Colour, odour, and texture were among the organoleptic characteristics that were examined by rubbing the sample with the fingers¹².

Homogeneity

After being packaged in containers, each generated gel was visually inspected to ensure uniformity. Their appearance and the existence of any aggregates were examined¹².

Spreadability

The horizontal glass plate method was used to assess the prepared gels spreadability. One gram of nanostructured lipid carrier gel was sandwiched between two horizontal glass plates after a standard weight of five grams was fastened to the upper glass plate. The entire set stayed upright. It was noted how long it took for the plate to disengage from the other plate. The formula was used to determine the spreadability.¹².

Spreadability is equal to $M \times L/T$

M = Weight attached to the upper slide (g)

L = Glass slide length (cm)

T is the time in seconds.

pH determination

Standard solutions with pH values of 4.0, 7.0, and 9.2 are used to calibrate the pH meter prior to analysis. The glass electrode was submerged in the gel (50 g) following the calibration, and the pH was recorded¹⁴.

Viscosity

The viscosity of the NLC gel was determined utilizing the Brookfield viscometer. The gel was maintained at a steady 25°C. The Helipath T-bar Spindle No. 96F was attached to the viscometer and then incorporated in the beaker containing 50 g of NLC gel. The reading was recorded in centipoises (cps) and the instrument was started at various revolutions per minute¹⁶.

STABILITY STUDY

The stability study of RQNLCG gel was subjected to accelerated stability testing by storing samples at different temperatures such as 25°C (room temperature), 40°C (accelerated), and sometimes refrigerated conditions (4°C), with controlled

study, evaluations e.g, appearance, color, odor, pH, viscosity, spreadability, and entrapment efficiency are regularly monitored at predetermined intervals (e.g., 0, 1, 3, and 6 months). Changes in any of these parameters could indicate degradation or instability¹⁶

IN-VITRO DRUG RELEASE STUDY

The in vitro drug release profile of the nanostructured lipid carrier optimised gel formulations RQNLCG, RNLCG, and QNLCG was investigated using Franz diffusion cells. Approximately 1 g of gel, or 0.5 mg, was used to secure the dialysis membrane over the donor compartment. For the whole night, the dialysis membrane was submerged in pH 7.4 phosphate buffer. The receptor compartment was filled with the pH 7.4 buffer. The beaker was then placed over a magnetic stirrer, and the temperature and speed were maintained at 37±0.5°C and 100 rpm for the duration of the research. Samples (2 ml) were taken out at predetermined intervals and replaced with an equal volume of fresh buffer. A UV spectrophotometer was used to determine the drug content of the samples after the proper dilution at isobestic point 384 nm (Rutin and quercetin NLC gel), QNLCG at 371 nm, and RNLCG at 264 nm¹⁶.

EXTRUDABILITY

The gel formulas were put into ordinary collapsible aluminum tubes with caps, and the ends were crimped shut. The weights of the tubes was reported. Two glass slides were used to clamp the tubes. The cap was removed after the slides were covered with 500 g. The extruded gel's volume was weighed and measured. The percentage of the extruded gel was determined (>90% extrudability: Excellent, >80% extrudability: Good, and >70% extrudability: Fair)¹⁸.

Swelling Index

To determine the swelling index of the produced gels, 1 gram of gel was placed on porous aluminium foil in a 50 ml beaker filled with 10 ml of 0.1 N NaOH. Samples were reweighed, removed from beakers at different intervals, and left in a dry place for some time.¹⁹.

$$\text{Swelling index (SW\%)} = [(W_t - W_o) / W_o \times 100]$$

Result and discussions

Quercetin and Rutin loaded Several gelling agents,

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including Carbopol-940, were used to create the nanostructured lipid carrier (NLCs) gel. Feel aesthetic attractiveness, ease of spreadability, and compatibility with nanoparticulate dispersion. The gelling agent of choice was carbopol 940. For gelling, several concentrations of Carbopol 940 ranging from 0.50 to 1.5% were employed; the concentration that produced the best viscosity (0.7%) was selected for gel formation. The nanoparticle dispersion was mechanically stirred at 800 rpm while carbopol 940 was introduced. The Carbopol 940 was stirred until it dispersed. Triethanolamine (0.2 mL) was used to neutralize the Carbopol dispersion.

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All of the manufactured NLC gel formulations was confirmed to be devoid of any dispersed particle matter upon close visual inspection against a dark and white backdrop. It was discovered that every composition was transparent gel. It had a smooth, non-greasy texture. (Table 2).

Table 2: Physical characteristics of the drugs loaded NLCs-gel

S.N.	Formulation code	Parameters	Result
1	RQNLCG	colour	Orange in color
		texture	Smooth
		appearance	Pleasant
		odour	Odourless
		gritty	Non gritty
2	RNLCG	color	Slightly brownish in color
		texture	Smooth
		appearance	Pleasant
		odor	Odourless
		gritty	Non gritty
3	QNLCG	color	Orange in color
		texture	Smooth
		appearance	Pleasant
		odour	Odourless
		gritty	Non gritty

Homogeneity

Both formulations were correctly homogenized mixtures, as demonstrated by the uniformity of the

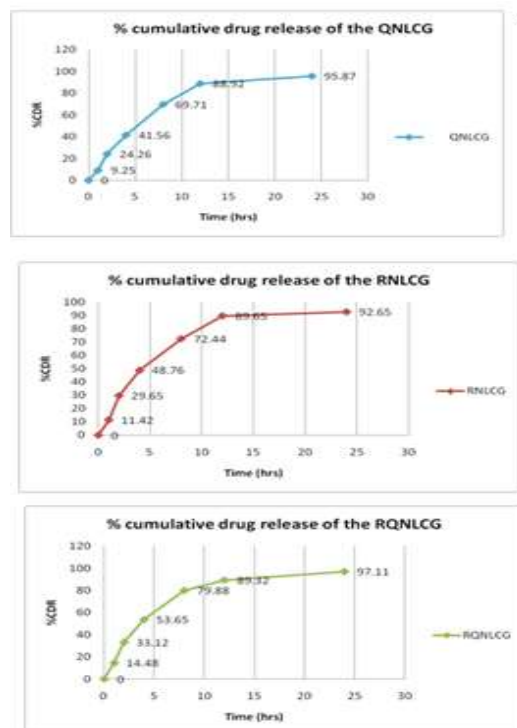
gel of the optimized formulation. For the medication to appropriate penetrate, this consistency was necessary. Results depicted in Table 3.

Table 3: Homogeneity of the drugs loaded NLCs-gel

S.N.	Formulation code	Parameters	Result
1	RQNLCG	Homogeneity	Homogenous mixture
2	RNLCG		Homogenous mixture
3	QNLCG		Homogenous mixture

In-vitro Drug Release Study

For assess the flow behaviour of the created NLC gel formulations—QNLCG, RNLCG, and RQNLCG—Research conducted for in-vitro drug release. For every formulation, the cumulative drug release profiles showed a steady and regulated release pattern over a 24-hour period. Of all the formulations, RQNLCG showed the highest cumulative drug release (97.11%) after 24 hours, indicating efficient drug diffusion from the nanostructured lipid carrier gel matrix. Additionally, QNLCG had a strong drug release profile with a cumulative release of 95.87%, while RNLCG displayed a somewhat lesser release of 92.65%. The consistent increase in drug release over time suggests that the medication has successfully integrated into the lipid matrix and that the formulation has controlled release qualities. The in vitro release data shown in Figure 1 and Figure 2.



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Figure:1 % Cumulative Drug release of the QNL CG, RNLCG and RQNL CG

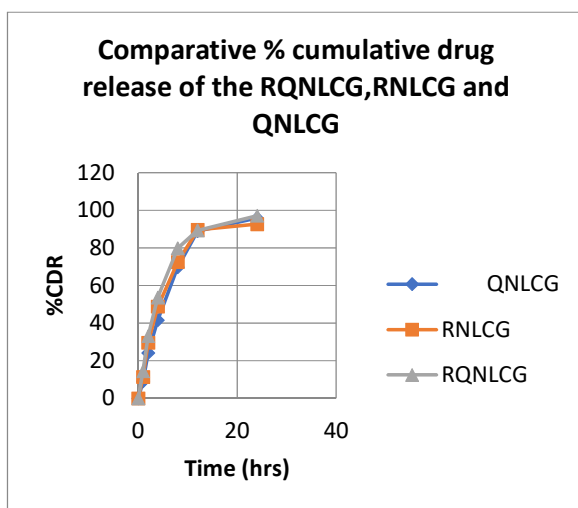


Figure 2: comparative graph of % cumulative drug release of RQNL CG, RNLCG and QNL CG

Spreadability

The spreadability parameter was designed to assess the uniform dispersion and ease of application of drug-loaded gel formulations across the skin's surface. The topical formulation's spreadability is crucial because it guarantees improved patient compliance, simple application, and consistent medication delivery.

Formulations RQNL CG, RNLCG, and QNL CG were found to have spreadability values of 0.498 ± 0.037 , 0.486 ± 0.028 , and 0.485 ± 0.061 , respectively showed in Table 4. Out of all the formulations, QNL CG had the lowest spreadability value and RQNL CG had the highest, indicating substantially improved spreading behavior. However, there was very little difference across the formulations, suggesting that their spreading characteristics were nearly the same.

Table 4: Spreadability of the drugs loaded NLCs-gel

S.N o.	Formulations	Parameter	Finding s
1	RQNL CG	SPREADABILITY	0.498 ± 0.037
2	RNLCG		0.486 ± 0.028
3	QNL CG		0.485 ± 0.061

pH determination

The gel compositions for topical administration were assessed by measuring their pH. Formulations RQNL CG, RNLCG, and QNL CG were found to have pH values of 6.95 ± 0.045 , 7.1 ± 0.056 , and 6.9 ± 0.021 , respectively showed in Table 5. All

formulations showed pH values close to the neutral range, according to the results.

Table 5: pH of drugs loaded NLCs-gel

S. No.	Formulations	Parameter	Findings
1	RQNL CG	pH	6.95 ± 0.045
2	RNLCG		7.1 ± 0.056
3	QNL CG		6.9 ± 0.021

Viscosity

For topical gel formulations, viscosity is a crucial factor since it affects the formulation's consistency, spreadability, drug release behaviour, and patient acceptance. The generated NLC gel formulations' viscosity investigation showed acceptable rheological properties appropriate for topical application. RQNL CG had the greatest viscosity value (9056 ± 11.25 cps) of all the formulations, followed by QNL CG (8964 ± 35.74 cps), while RNLCG had a relatively lower viscosity (8852 ± 22.57 cps) showed in Table 6. Differences in polymer concentration, lipid content, and the interaction between the nanostructured lipid carriers and gel matrix could be the cause of the formulations' small variations in viscosity.

Table 6 : Viscosity of drugs loaded NLCs-gel

S.N o.	Formulations	Parameters	Findings
1	RQNL CG	Viscosity	9056 ± 11.25
2	RNLCG		8852 ± 22.57
3	QNL CG		8964 ± 35.74

Swelling Index

The formulated NLC gel formulations' hydration capacity and water uptake behaviour were assessed using the swelling index study. Because it affects drug diffusion, consistency, bioadhesion, and release characteristics, swelling behaviour is a crucial feature for topical gels. The results showed that all formulations had appropriate swelling properties. Among the formulations, RQNL CG had the greatest swelling index value (90.42%), indicating better swelling behaviour and higher water absorption. RNLCG and QNL CG had swelling index values of 77.39% and 75.98%, respectively showed in table 7.

Table 7 : Swelling Index of optimized gel

S.No.	Formulation	Parameter	Results
1	RQNL CG		90.42

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2	RNL CG	Swelling Index	77.39
3	QNL CG		75.98

Drug Release Kinetic Model

To determine the release Mechanism and evaluate the regression coefficient various kinetic models fitted to in vitro drug release data. The mathematical model was utilized are Zero order, first order, Higuchi, Hixon crowell and krosmeier peppas model²¹. The value of R² (Regression coefficient) for QNLC gel, RNLC gel and RQNLC gel shown in Table 8.

Table 8: Drug profile of kinetic release model of optimized formulations QNL CG, RNL CG AND RQNLC G

S. N o.	For mu latio ns	zer o ord er Rel eas e (R ²)	fir st or de r ki net ic rel eas e (R ²)	hig uc hi kin eti c rel eas e (R ²)	korsm eyer kineti c releas e (R ²)	hixon Crow ell kineti c releas e (R ²)
1	QN LC G	0.973	0.981	0.975	0.999	0.998
2	RN LC G	0.941	0.989	0.993	0.995	0.996
3	RQ NL CG	0.889	0.997	0.990	0.997	0.981

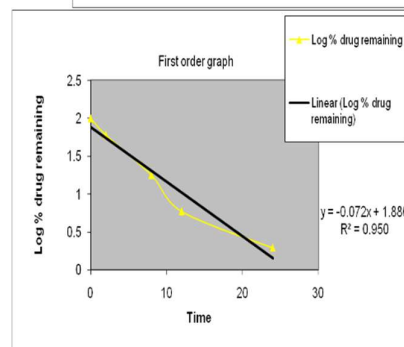
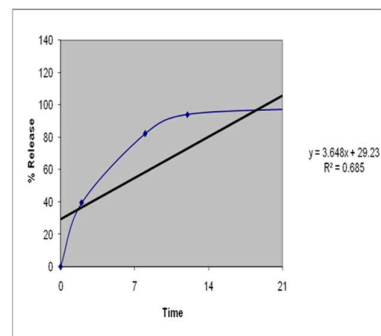


Figure :1 RQNLC zero order kinetic release model
Figure:2 RQNLC First order kinetic release model

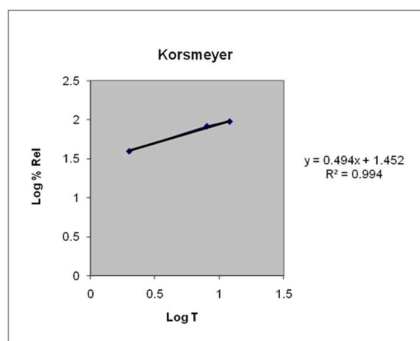


Figure:3 Korsmeyer kinetic release model for RQNLC

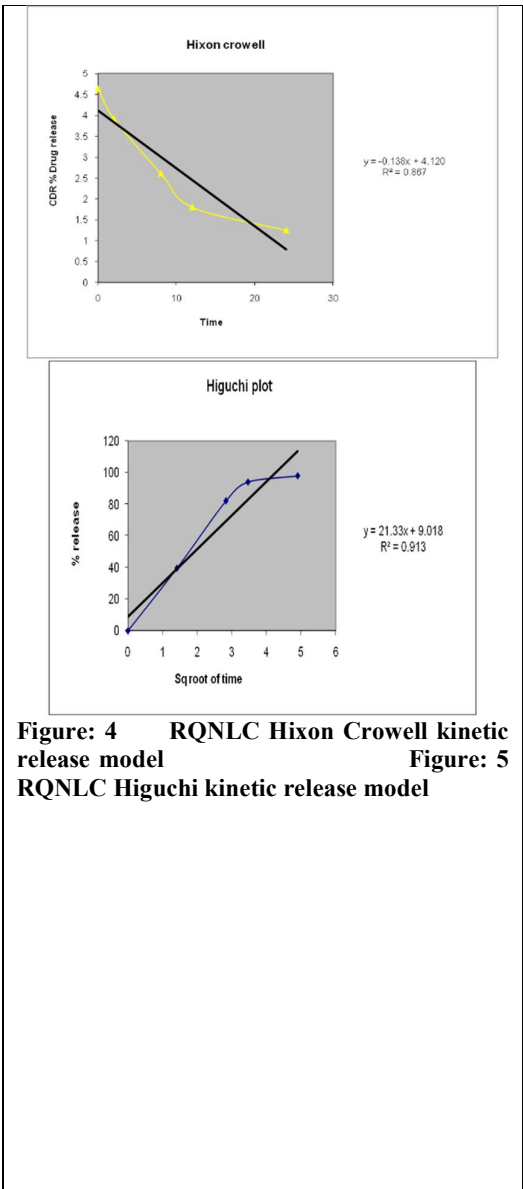


Figure 4: Drug Kinetic Release model of Optimized RQNLG gel

Extrudability

In the extrudability testing, the RQNLCG, RNLCG, and QNLG formulations all demonstrated good extrudability grades, indicating satisfactory extrusion properties. Of all the tested formulations, RQNLCG achieved the highest extrudability rating (86.18%), indicating better flow characteristics and easier application. While RNLCG shown somewhat lower extrudability (82.48%), QNLG also demonstrated notable extrudability (84.13%) showed in Table 9.

Table 9: Extrudability of RQNLG, RNLC and QNLG gel

Formulations	Weight of the formulation	Mass of gel extruded	Extrudability amount (percent age)	category
RQNLCG			86.18	Good
RNLCG			82.48	Good
QNLG			84.13	Good

RQNLCG	15.22	13.23	86.19	Good
RNLCG	15.63	12.11	82.39	Good
QNLG	15.93	13.41	84.15	Good

Transmission electron microscopy: Transmission electron microscopy was used to examine the dispersion morphology of the optimized NLCs (Joel, JEM-F200 Multi-purpose Electron Microscope). An optimized Rutin and quercetin NLCs dispersion was diluted with pre-filtered distilled water, then it was placed on copper grids, dried, and treated with 1% phosphotungstic acid for negative staining. The vesicle surface morphology of the formulation was then examined using a TEM at an accelerating voltage of 100 kV²⁰. The results showed in figure 5.

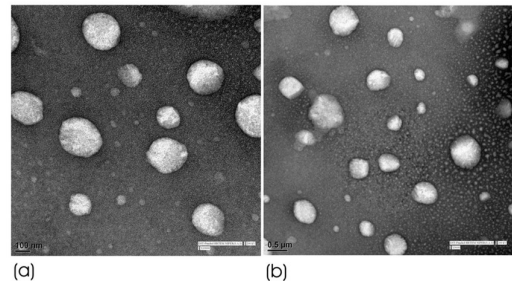


Figure 5: TEM image of optimized RQNLG Gel

Discussion

The objective of this study was to develop and refine a topical delivery system for nanostructured lipid carrier gel loaded with quercetin and rutin as a novel method of treating acne. The lipid surfactant ratio had an impact on the output variables during the optimisation process, which was directed using fraction factorial design and produced a stable nanocarrier with optimal entrapment efficiency. In order to improve the drug's permeability, it was beneficial to employ eucalyptus oil as a liquid and stearic as a solid lipid in the formulation of RQNLCs. Additionally, poloxamer 188 and Tween 80 were utilised as co-surfactants and surfactants, respectively. A weakly soluble medication can be made more soluble by increasing its penetration and improving its stability. RQNLC gel was created. When employed as a gelling agent, carbopol, a cross-linked copolymer of acrylic acid, is easily dispersed and unaffected by the viscosity of the gel when other ingredients (lipids and surfactants) are present. Carbopol is utilised for both the formulation's stability and the regulated release of medications from nanocarriers. Nanostructured loaded gel displayed a sustained release pattern, while in vitro diffusion of RQ NLCs gel shown higher release than drug-loaded gel. The release exponent "n" value of 0.6 in the release kinetics findings from the RQNLC gel demonstrated Krosmeier's kinetic release. This kind of diffusion

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demonstrates that both polymer relaxation and diffusion regulate drug release^{22,23}.

Conclusion:

The proficiency of NLC as gel for topical delivery was validated by the evaluation of optimized formulation. RQ-loaded NLC gel have shown brilliant characterization in context to zeta potential, particle size, viscosity, anti-acne and antimicrobial properties. This type of delivery system provide controlled release and shown good in vitro profiles. This research work concluded that RQNLC gel provide better application and good release. This is an great advancement in the management of acne. Optimized RQNLC depicted good physicochemical properties. This research study highlighted NLC loaded Rutin and Quercetin gel having great impact as antimicrobial and also reduce inflammation and best topical drug delivery route for acne management.

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