ECORFAN Journal Bolivia 13[23]1-13: e21323113
Article

Formulation optimization and physicochemical characterization of polymeric nanocapsules for targeted dermal delivery in acne treatment

Optimización y caracterización fisicoquímica de formulación de nanocápsulas poliméricas para la administración dérmica dirigida en el tratamiento del acné

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Classification:

Area: Biology and Chemistry
Field: Life sciences
Discipline: Biomaterials
Subdiscipline: Other

https://doi.org/10.35429/EJB.2026.13.23.2.1.13
History of the article:
Received: March 09, 2026
Accepted: May 31, 2026

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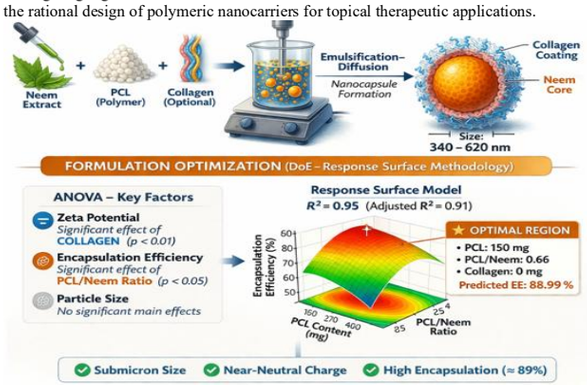
Abstract

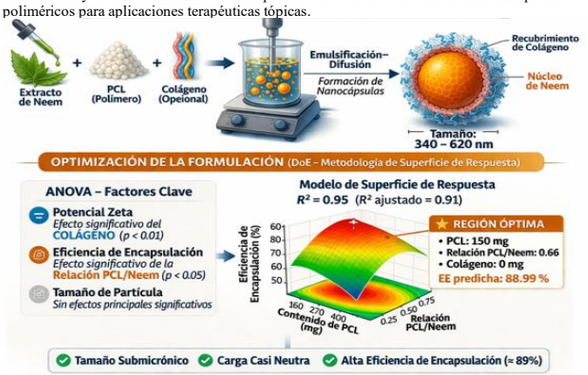
Polymeric nanocapsules based on poly[ε-caprolactone] were developed as a dermal drug delivery system for the controlled administration of neem bioactive compounds. The present study aimed to optimize formulation variables and evaluate their influence on key physicochemical properties including particle size, zeta potential, and encapsulation efficiency. Nanocapsules were prepared using the emulsification–diffusion technique and systematically varied in terms of polymer content, neem extract concentration, collagen functionalization, and polymer/drug ratio. Analysis of variance [ANOVA] revealed that collagen significantly influenced surface charge characteristics, while the polymer/neem ratio was identified as the dominant factor controlling encapsulation efficiency. Particle size was primarily governed by process-related physicochemical parameters rather than individual compositional variables. The optimized nanosystems exhibited submicron particle size distribution, near-neutral surface charge, and high drug loading capacity, suggesting their suitability for follicular targeting and localized dermal delivery. These findings highlight the relevance of formulation balance and surface functionalization in the rational design of polymeric nanocarriers for topical therapeutic applications.



Topical Nanoformulation, Acne Treatment, Dermal Drug Delivery

Resumen

Se desarrollaron nanocápsulas poliméricas basadas en poli[ε-caprolactona] como sistema de liberación dérmica de fármacos para la administración controlada de compuestos bioactivos del neem. El presente estudio tuvo como objetivo optimizar las variables de formulación y evaluar su influencia en propiedades fisicoquímicas clave, como el tamaño de partícula, el potencial zeta y la eficiencia de encapsulación. Las nanocápsulas se prepararon mediante la técnica de emulsificación-difusión y se variaron sistemáticamente en términos de contenido de polímero, concentración de extracto de neem, funcionalización con colágeno y relación polímero/fármaco. El análisis de varianza [ANOVA] reveló que el colágeno influyó significativamente en las características de carga superficial, mientras que la relación polímero/neem se identificó como el factor dominante que controla la eficiencia de encapsulación. El tamaño de partícula estuvo gobernado principalmente por parámetros fisicoquímicos relacionados con el proceso, más que por variables compositivas individuales. Los nanosistemas optimizados exhibieron una distribución de tamaño de partícula submicrométrica, una carga superficial casi neutra y una alta capacidad de carga de fármaco, lo que sugiere su idoneidad para la focalización folicular y la liberación dérmica localizada. Estos hallazgos resaltan la relevancia del equilibrio de la formulación y la funcionalización de la superficie en el diseño racional de nanotransportadores poliméricos para aplicaciones terapéuticas tópicas.



Nanoformulación tópica, Tratamiento del acné, Administración dérmica de fármacos

Area: Promotion of frontier research and basic science in all fields of knowledge

Citation: Chávez-Yuen, Wan Yin; Moreno-Cruz, Ana María; Piñón-Segundo, Elizabeth and Martínez-Pérez, Beatriz. [2026]. Formulation optimization and physicochemical characterization of polymeric nanocapsules for targeted dermal delivery in acne treatment. ECORFAN Journal Bolivia 13[23]1-13: e21323113.

Introduction

Acne is a common disorder experienced by up to 80% of people between the ages of 11 and 30 and up to 5% of older adults [Jacob et al., 2001]. Acne is caused and characterized by multiple factors, including: *Cutibacterium acnes* activity; increased sebum production; androgen stimulation; follicular hypercornification; an inflammatory response involving lymphocytes, macrophages, and neutrophils; and cytokine activation [Rivera, 2008].

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that primarily affects adolescents and young adults, although it can occur at any stage of life. Its etiology is multifactorial, involving a complex interaction between hormonal, genetic, microbial, and immunological factors [Tan & Bhate, 2015].

One of the key factors in the development of acne is the androgen-induced increase in sebum production, a process in which the sebaceous glands function as active endocrine organs responding to hormonal stimuli [Zouboulis, 2004]. This excess sebum, combined with follicular hyperkeratinization that obstructs the drainage of the pilosebaceous duct, creates a lipid-rich, hypoxic microenvironment conducive to the formation of open or closed comedones [Kurokawa et al, 2009; Williams et al., 2012].

Simultaneously, abnormal colonization by the bacterium *Cutibacterium acnes* occurs. This microorganism, typically a commensal of the skin microbiota, can become pathogenic under these favorable conditions, triggering the inflammatory processes characteristic of the pathology [Fitz-Gibbon et al., 2013; Dréno et al., 2018].

Cutibacterium acnes contributes to the inflammatory process by releasing lipolytic enzymes, proteases, and pro-inflammatory factors that stimulate the production of cytokines such as IL-1, IL-6, TNF-α, and chemokines. This triggers an innate immune response and localized inflammation, leading to the appearance of papules, pustules, and nodules. Furthermore, this bacterium has been shown to activate Toll-like receptors [TLR2] in keratinocytes and macrophages, amplifying the inflammatory response [Dréno et al., 2018].

The involvement of genetic factors and the skin microbiome in individual susceptibility to acne has also been identified. Additionally, certain external factors such as stress, a diet high in high-glycemic-index carbohydrates, comedogenic cosmetics, and some medications can exacerbate the condition [Melnik, 2011].

Among the most common topical treatments are retinoids [such as tretinoin, adapalene, or tazarotene], which work by normalizing follicular keratinization and reducing comedone formation. Topical antibacterial agents such as benzoyl peroxide and clindamycin are also widely used, reducing the bacterial load and providing some anti-inflammatory action [Zaenglein et al., 2016].

In moderate to severe cases, systemic treatments such as oral antibiotics [doxycycline, minocycline, erythromycin] are used. These act on *C. acnes* and have an anti-inflammatory effect. However, their prolonged use has raised concerns about the development of bacterial resistance, so their use should be limited. Another systemic option is the use of oral retinoids, especially isotretinoin, which has proven highly effective in reducing the size of sebaceous glands, sebum production, and inflammation. However, its adverse effect profile and teratogenicity require strict medical control [Layton, 2006].

In recent years, growing scientific interest has focused on the use of plant-derived bioactive compounds as safer alternatives or complementary agents in acne management. Phytochemicals such as terpenoids, flavonoids, phenolic compounds, and essential oils exhibit antimicrobial, antioxidant, anti-inflammatory, keratolytic, and sebum-regulating activities that may contribute to acne control [Ramsis et al., 2024]. However, the clinical application of these compounds is often hindered by physicochemical instability, low aqueous solubility, and limited dermal penetration. Therefore, the incorporation of natural actives into advanced drug delivery systems has emerged as a promising strategy to enhance therapeutic efficacy while minimizing systemic exposure.

Nanotechnology-based topical delivery systems have demonstrated significant potential in overcoming the limitations of conventional formulations by enabling targeted drug transport, controlled release, and enhanced follicular accumulation.

ISSN: 2410-4191.
RENIECYT: 1702902

Chávez-Yuen, Wan Yin; Moreno-Cruz, Ana María; Piñón-Segundo, Elizabeth and Martínez-Pérez, Beatriz. [2026]. Formulation optimization and physicochemical characterization of polymeric nanocapsules for targeted dermal delivery in acne treatment. ECORFAN Journal Bolivia 13[23]1-13: e21323113.
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Polymeric nanoparticles and nanocapsules can improve drug retention within the pilosebaceous units, reduce dosing frequency, and modulate drug release kinetics, thereby improving therapeutic outcomes in acne treatment [Reis et al., 2013]. Furthermore, nanoscale systems may enhance skin compatibility and reduce irritation through localized drug delivery and improved dispersion characteristics.

Among biodegradable polymers, poly[ε-caprolactone] [PCL] has been extensively investigated for dermal drug delivery due to its favorable biocompatibility, slow degradation rate, and ability to provide sustained release profiles. The physicochemical properties of polymeric nanoparticles, including particle size distribution, polydispersity index, zeta potential, and encapsulation efficiency, play a decisive role in determining their stability, dermal penetration capacity, and interaction with biological tissues [McNeil, 2005]. In addition, surface functionalization approaches such as collagen coating have been proposed to improve nanoparticle bioadhesion, modulate surface charge, and promote interaction with skin extracellular matrix components, potentially enhancing follicular targeting and dermal retention.

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From a formulation engineering perspective, the rational optimization of nanosystems requires the integration of statistical tools such as Design of Experiments [DoE] and Response Surface Methodology [RSM], which enable the systematic evaluation of formulation variables and their interactions. These approaches facilitate the development of predictive mathematical models capable of identifying optimal formulation conditions while reducing experimental variability and resource consumption.

Based on these considerations, the present study aims to formulate and optimize polymeric nanocapsules composed of poly[ε-caprolactone] incorporating neem extract as a plant-derived therapeutic agent and collagen as a surface functionalization component. Through physicochemical characterization and statistical modeling, this work seeks to elucidate the influence of formulation parameters on particle size, surface charge, and encapsulation efficiency, ultimately contributing to the development of advanced dermal nano-therapeutic systems for targeted acne treatment.

ISSN: 2410-4191.
RENIECYT: 1702902

Methodology

Preparation of Nanocapsules [PCL-Neem-Coll-NCs]

Polymeric nanocapsules were prepared using an emulsification–diffusion technique. The organic phase was composed of poly[ε-caprolactone] [PCL] and, depending on the experimental formulation [Table 1], neem extract dissolved in ethyl acetate previously saturated with water. Formulations intended as polymeric controls were prepared following the same procedure but without incorporation of neem extract.

The aqueous phase consisted of a 0.5% [w/v] polyvinyl alcohol [PVA] solution used as stabilizing agent. The organic phase was gradually added to the aqueous phase under high-shear homogenization at 10,000 rpm and maintained under stirring for 10 min to promote formation of a fine oil-in-water emulsion. Subsequently, deionized water was added to induce solvent diffusion and polymer precipitation, and homogenization was continued for an additional 5 min under identical conditions. The organic solvent and part of the aqueous phase were then removed under reduced pressure using a rotary evaporator to obtain a concentrated nanosuspension.

For collagen-functionalized formulations, an aqueous collagen solution [20 mL, 20 mg/mL] was added after nanocapsule formation and the dispersion was maintained under gentle magnetic stirring for 24 h to allow adsorption of collagen onto the particle surface. Formulations without collagen coating were processed identically but omitted this step.

Nanocapsules were recovered by centrifugation at 14,600 rpm, washed to remove residual stabilizer, and finally dried under vacuum prior to further characterization.

Physicochemical characterization of PCL-Neem-Coll-NCs

Particle size and polydispersion index Particle size and polydispersity index were determined by the dynamic light scattering technique using a Malvern Zetasizer Nano ZS90 [Malvern Instruments Ltd, UK] with a detection angle of 90° and a wavelength of 633 nm. One milliliter of each colloidal dispersion was diluted to 10 ml with distilled water to obtain a dilute dispersion.

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Z-potential evaluation of PCL-Neem-Coll-NCs

The zeta potential was determined using a ZS90 Nano Zetasizer, based on the electrophoretic movement of the particles in dispersion using polycaprolactone dispersions as a reference. This parameter indicates the degree of repulsion between adjacent particles. The measurements were performed in triplicate.

Quantification of Neem extract from PCL-Neem-Coll-NCs

Encapsulation efficiency [E.E.] was determined using the indirect method based on quantifying the unencapsulated active compound [Sotelo-Boyás et al., 2017]. Briefly, 2 ml of each colloidal dispersion was centrifuged at 14 600 rpm for 60 min, to separate the nanocapsules and the stabilizer by removing the supernatant. To the sediment obtained, 1 ml of cyclohexane was added to dissolve the unencapsulated ethyl acetate, but not to dissolve the polymeric barrier in the nanocapsules. The concentration of unencapsulated β-carotene was determined using a UV vis spectrophotometer at a wavelength of 275 nm. The measurements were performed in triplicate and the encapsulation efficiency was determined using the following relationship:

E.E. = [mg Neem added - mg Neem not encapsulated] / mg Neem added x 100 [1]

Experimental design, statistical analysis and response surface modeling

An empirical multilevel factorial design was employed to investigate the influence of formulation variables on the physicochemical characteristics of the polymeric nanocapsules.

The independent variables evaluated were poly[ε-caprolactone] concentration [X_1], polymer-to-bioactive ratio [X_2], and collagen concentration used as a surface functionalization agent [X_3]. The experimental matrix was constructed to explore the formulation space through systematic variation of these parameters.

Encapsulation efficiency [Y_1], particle size [Y_2], polydispersity index [Y_3], and zeta potential [Y_4] were considered as response variables. All experimental runs were performed under identical processing conditions and in randomized order to minimize experimental bias and improve reproducibility.

Response surface methodology [RSM] was applied to evaluate nonlinear effects and interaction terms between formulation variables.

The relationship between independent variables and the studied responses was described using a second-order polynomial model expressed as:

$$Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 \quad [2]$$

where Y_i represents the predicted response, β_0 corresponds to the intercept, β_1, β_2, and β_3 denote linear coefficients, β_{11}, β_{22}, and β_{33}represent quadratic effects, and β_{12}, β_{13}, and β_{23} describe interaction effects between formulation factors.

Regression coefficients were estimated using the least-squares method. Statistical significance of the model terms was evaluated through analysis of variance [ANOVA] at a confidence level of 95%. Model adequacy was assessed based on the coefficient of determination [r^2], adjusted r^2, F-value, and associated probability values. Response surface and contour plots were generated to visualize the influence of formulation variables and to determine the optimal formulation region.
All statistical analyses and graphical representations were performed using computational data analysis software and scientific plotting tools.

Optimization of nanocapsule formulation

An overall desirability function approach was applied to determine the optimal formulation conditions for polymeric nanocapsule preparation. This methodology enables simultaneous optimization of multiple response variables by transforming each response into an individual desirability function and combining them into a global desirability index.

The optimal formulation conditions were obtained by maximizing the overall desirability [D], defined as:

$$D = [d_1 \cdot d_2 \cdot d_3 \cdot d_4]^{1/k} \quad [3]$$

where d_i represents the individual desirability function corresponding to each response variable, and $k$is the total number of responses considered in the optimization process.

ISSN: 2410-4191.
RENIECYT: 1702902

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In the present study, encapsulation efficiency [Y_1], particle size [Y_2], polydispersity index [Y_3], and zeta potential [Y_4] were included in the optimization criteria. Encapsulation efficiency was maximized to enhance drug loading capacity, while particle size and polydispersity index were minimized to ensure nanosystem stability and uniformity. Zeta potential values were targeted within a near-neutral range to promote dermal compatibility and colloidal stability.

The optimal formulation region was determined by numerical optimization of the fitted response surface model, allowing identification of the combination of formulation variables that provided the highest overall desirability value.

Results and Discussion

Table 1 shows the batches of nanoparticles prepared according to independent variables and together with the quantitative results of dependent variables measured; namely, Particle Size [PS], Polydispersity Index [DI], zeta potential [ζ,] and Encapsulation Efficiency [EE].

Box 1

Table 1

Physicochemical characterization of PCL-Neem-Coll-NCs

Lote	PCL [mg]	Neem [mg]	Collag [mg]	Size particle [nm] *n=3*	Polidispersity index *n=3*	Z potential *n=3*	Encapsulation efficiency percentage *n=3*
1	75	0	0	410.67	0.154	-0.69	0
2	100	0	0	417.60	0.150	-0.43	0
3	150	0	0	391.37	0.212	-0.43	0
4	75	0	400	420.13	0.106	-0.65	0
5	100	0	400	380.60	0.168	-0.06	0
6	150	0	400	390.63	0.136	-0.16	0
7	75	50	0	463.43	0.097	-0.46	86.89
8	75	75	0	423.27	0.113	-0.71	70.30
9	75	100	0	434.33	0.140	-1.16	60.00
10	75	50	400	420.00	0.202	0.21	82.43
11	75	75	400	358.97	0.266	-0.12	58.36
12	75	100	400	361.80	0.239	-0.52	59.16
13	100	66	0	412.60	0.249	-0.75	85.90
14	100	100	0	405.97	0.155	-0.75	64.81
15	100	130	0	621.90	0.453	0.02	61.59
16	100	66	400	411.97	0.143	-0.64	90.28
17	100	100	400	409.23	0.135	0.01	56.73
18	100	130	400	558.23	0.193	-0.08	57.33
19	150	100	0	451.53	0.159	-0.52	89.65
20	150	150	0	457.10	0.098	-0.55	66.58
21	150	200	0	467.93	0.337	-0.71	63.70
22	150	100	400	411.87	0.075	-0.13	82.43
23	150	150	400	423.10	0.133	-0.09	65.80
24	150	200	400	448.77	0.182	0.13	60.99

Own elaboration

Particle size and formulation behavior

The developed polymeric nanocapsules exhibited mean particle sizes ranging from approximately 358 to 622 nm, depending on the polymer–drug ratio and collagen functionalization. Formulations containing moderate neem concentrations and intermediate PCL content [100–150 mg] showed more controlled particle size distribution [≈400–460 nm], whereas higher drug loading levels [Neem ≥130 mg] resulted in a marked increase in particle size [>550 nm].

This behavior can be attributed to the increased viscosity of the organic phase, reduced interfacial stabilization during solvent diffusion, and formation of larger emulsion droplets, which are typical phenomena in nanoparticle production by solvent displacement techniques [Mora-Huertas et al., 2010]. Similar trends have been reported in emulsification–diffusion systems, where excessive drug loading promotes droplet coalescence, delayed polymer precipitation, and consequently larger particle formation [Fessi et al., 1989; Kumari et al., 2010].

Importantly, particle sizes around 400–450 nm are considered highly suitable for follicular targeting in dermal delivery applications. Nanocarriers within this size domain may accumulate preferentially in hair follicles, enhancing local drug retention and therapeutic efficacy in acne treatment [Puglia et al., 2014; Lademann et al., 2007].

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ISSN: 2410-4191.
RENIECYT: 1702902

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Zeta potential and colloidal stability

Measured zeta potential values were generally between −1.4 and +0.3 mV, indicating that the developed nanosystems were mainly stabilized by steric rather than electrostatic mechanisms. This stabilization effect is likely associated with collagen surface functionalization, adsorption of non-ionic stabilizers, and hydration layers surrounding the polymeric shell.

Although absolute zeta potential values were relatively low, the absence of visible aggregation suggests that steric stabilization played a dominant role in maintaining nanosuspension stability. Similar findings have been reported for topical nanoformulations in which polymeric coatings or biopolymer adsorption provide sufficient stabilization even at near-neutral surface charge conditions [Honary & Zahir, 2013].

From a dermatological perspective, low surface charge may be advantageous, since highly charged nanoparticles can increase interaction with skin proteins and potentially induce irritation or inflammatory responses. Therefore, near-neutral zeta potential values may contribute to improved dermal compatibility of the developed nanocarriers [Puglia et al., 2014].

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Statistical analysis of formulation variables

A quadratic response surface model was applied to evaluate the influence of formulation parameters, including poly[ε-caprolactone] content, collagen concentration, and polymer-to-bioactive ratio, on the physicochemical characteristics of the developed nanocapsules.

The statistical significance of linear, quadratic, and interaction effects was assessed using analysis of variance [ANOVA].

Box 2

Table 2

ANOVA and regression coefficients of particle size

Factor	Coefficient	p-value	Significance
PCL	11.355	0.293	ns
Collagen	0.000	0.929	ns
Ratio	−0.004	0.526	ns
PCL²	−0.053	0.252	ns
Collagen²	0.000	0.929	ns
Ratio²	282.892	0.548	ns
PCL × Ratio	1.153	0.681	ns
Collagen × Ratio	−1.568	0.526	ns

$r^2 = 0.63$; $p > 0.05$.

Own elaboration

Analysis of variance [ANOVA] indicated that formulation variables did not exert statistically significant linear effects on particle size within the experimental domain evaluated [Table 2].

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The regression coefficient analysis revealed that particle size was not significantly affected by the individual formulation variables within the experimental domain studied, indicating that nanoparticle growth was mainly governed by physicochemical mechanisms associated with the emulsification–diffusion process rather than by compositional factors alone. In polymeric nanocapsule systems prepared by solvent displacement techniques, particle formation is typically controlled by transient supersaturation phenomena, interfacial tension gradients, and rapid polymer precipitation kinetics [Mora-Huertas et al., 2010].

The linear effect of polymer concentration did not show statistical significance [$p > 0.05$], suggesting that increasing the amount of poly[ε-caprolactone] within the evaluated range did not produce a proportional enlargement of the nanocapsules.

This behavior may be attributed to the fast nucleation stage occurring during solvent diffusion, which often leads to the formation of relatively stable nuclei that limit subsequent particle growth [Fessi et al., 1989; Kumari et al., 2010].

Similarly, the polymer-to-bioactive ratio did not present a statistically significant linear influence on particle size [$p > 0.05$], indicating that moderate variations in neem loading were insufficient to markedly alter droplet breakup efficiency or polymer precipitation dynamics. Previous studies have shown that, under controlled homogenization and solvent diffusion conditions, drug loading variations may influence encapsulation efficiency without substantially modifying particle size distribution [Mora-Huertas et al., 2010].

Collagen concentration also showed no significant linear contribution to particle size variation [$p > 0.05$], suggesting that surface functionalization occurred mainly after primary particle formation. Adsorption of macromolecules such as collagen onto preformed nanoparticles is generally associated with modifications in surface hydration and steric stabilization rather than with significant changes in core dimensions [Honary & Zahir, 2013].

Furthermore, the absence of statistically significant quadratic effects indicates that particle size did not follow a pronounced nonlinear response pattern within the explored formulation space. This observation supports the hypothesis that hydrodynamic conditions, solvent diffusion rate, and interfacial stabilization efficiency were sufficiently dominant to maintain particle dimensions within a relatively narrow range. Similar trends have been reported for polymeric nanosystems intended for topical drug delivery, where process parameters exert stronger influence on particle size than moderate compositional variations [Puglia et al., 2014].

Interaction terms between formulation variables were also statistically non-significant [$p > 0.05$], confirming that combined compositional variations did not generate synergistic or antagonistic effects on nanoparticle growth.

Overall, these statistical findings demonstrate that particle size in the developed nanocapsules was primarily controlled by process-driven physicochemical phenomena rather than by formulation composition alone, highlighting the robustness of the emulsification–diffusion technique in producing nanosystems within the submicron range suitable for dermal targeting applications [Shah et al., 2021].

Regarding the polydispersity index, statistical analysis revealed only moderate formulation influence, confirming that size distribution homogeneity was largely associated with emulsification stability and droplet breakup efficiency during nanoparticle formation. In colloidal systems prepared by solvent displacement, PDI is often considered an indicator of formulation robustness rather than a direct function of individual compositional variables [Mora-Huertas et al., 2010].

This interpretation is supported by the relatively low PDI values observed in optimized formulations, indicating reproducible particle formation conditions.

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Box 3

Table 3

ANOVA and regression coefficients of zeta potential

Factor	Coefficient	p-value	Significance
PCL	−0.039	0.468	ns
Collagen	0.000	0.684	ns
Ratio	0.000	0.878	ns
PCL²	0.0001	0.613	ns
Collagen²	0.000	0.684	ns
Ratio²	−1.234	0.618	ns
PCL × Ratio	0.0157	0.328	ns
Collagen × Ratio	0.0019	0.878	ns

$r^2 = 0.42$; $p > 0.05$.

Own elaboration

For surface charge behavior, ANOVA results [Table 3], demonstrated that the evaluated formulation factors did not significantly affect zeta potential values.

The regression coefficient analysis indicated that surface charge behavior of the developed polymeric nanocapsules was only marginally influenced by formulation composition within the experimental domain studied. Most linear terms associated with polymer concentration and polymer-to-bioactive ratio were not statistically significant [$p > 0.05$], suggesting that electrokinetic properties were predominantly governed by interfacial stabilization phenomena rather than by bulk formulation variables. In polymeric nanocarrier systems prepared by emulsification–diffusion methods, zeta potential is strongly dependent on surface adsorption processes, hydration layer formation, and steric stabilization effects rather than on variations in core composition [Mora-Huertas et al., 2010].

This behavior explains the relatively narrow range of ζ-potential values observed in the present study, which remained close to neutral values despite changes in polymer and drug concentrations.

Although collagen concentration showed a tendency to influence surface charge characteristics, its statistical contribution was not consistently significant across all regression terms [$p > 0.05$]. This suggests that collagen functionalization mainly contributed to steric stabilization through surface adsorption and formation of a hydrated biopolymeric shell rather than inducing strong electrostatic repulsion.

Similar observations have been reported in nanoformulations where macromolecular coatings modulate colloidal stability without producing substantial shifts in ζ-potential magnitude [Honary & Zahir, 2013].

The absence of significant quadratic effects further indicates that surface charge response did not follow a pronounced nonlinear pattern within the formulation space evaluated. This finding supports the hypothesis that the dominant stabilization mechanism was steric hindrance provided by polymeric chains and surface-bound biomolecules. In topical nanocarrier systems, steric stabilization is often sufficient to maintain dispersion stability even when electrostatic repulsion forces are limited [Puglia et al., 2014].

Interaction effects between formulation variables were also statistically non-significant [$p > 0.05$], indicating that combined variations in polymer concentration, bioactive loading, and collagen coating did not generate synergistic electrokinetic behavior.

Such results highlight that zeta potential in the developed nanosystem was primarily controlled by post-formation surface phenomena rather than by structural composition of the nanoparticle core.

From a dermatopharmaceutical perspective, near-neutral surface charge values may be advantageous, as highly charged nanoparticles can increase interactions with skin proteins and potentially induce irritation or inflammatory responses. Therefore, the electrokinetic profile observed in the optimized formulations supports their suitability for topical delivery applications [Shah et al., 2021].

Box 4

Table 4

ANOVA and regression coefficients of encapsulation efficiency

Term	Coefficient	p-value	Significance
PCL	0.062	0.930	ns
Collagen	3.20×10^{-6}	**0.022**	s
Ratio	−0.0016	**0.026**	s
PCL²	−0.0004	0.887	ns
Collagen²	0.0013	**0.022**	s
Ratio²	108.34	**0.038**	s
PCL × Ratio	0.073	0.719	ns
Collagen × Ratio	−0.656	**0.026**	s

$r^2 = 0.95$; $p > 0.05$.

ISSN: 2410-4191.
RENIECYT: 1702902

Chávez-Yuen, Wan Yin; Moreno-Cruz, Ana María; Piñón-Segundo, Elizabeth and Martínez-Pérez, Beatriz. [2026]. Formulation optimization and physicochemical characterization of polymeric nanocapsules for targeted dermal delivery in acne treatment. ECORFAN Journal Bolivia 13[23]1-13: e21323113.
https://doi.org/10.35429/EJB.2026.13.23.2.1.13

The regression coefficient analysis [Table 4], revealed that encapsulation efficiency was significantly influenced by collagen concentration and polymer-to-bioactive ratio, confirming that formulation composition played a critical role in determining drug loading performance of the developed polymeric nanocapsules.

The linear term associated with the polymer-to-bioactive ratio [p = 0.026] demonstrated a statistically significant effect, indicating that the balance between poly[ε-caprolactone] and neem extract governs the formation of hydrophobic domains capable of retaining the bioactive compound.

This behavior is consistent with previous studies reporting that encapsulation efficiency in polymeric nanosystems depends strongly on thermodynamic compatibility between the carrier matrix and the encapsulated molecule, as well as on the availability of sufficient polymeric structure to prevent diffusion losses during nanoparticle formation.

Collagen concentration also showed a significant contribution both as a linear [p = 0.022] and quadratic term [p = 0.022], suggesting the existence of nonlinear effects on encapsulation performance. This indicates that collagen does not simply act as an inert stabilizing component, but rather modulates interfacial properties and potentially influences the structural organization of the nanocapsule shell. The significant quadratic behavior further supports the presence of an optimal concentration range in which surface functionalization enhances system stability and drug retention.

Similarly, the quadratic effect of the polymer-to-bioactive ratio [p = 0.038] confirms that encapsulation efficiency follows a curved response pattern rather than a purely linear trend. This phenomenon is characteristic of nanocarrier systems prepared by emulsification–diffusion methods, where excessive drug loading may lead to partial saturation of the polymer matrix and increased drug leakage.

The significant interaction between collagen concentration and polymer-to-bioactive ratio [p = 0.026] highlights the synergistic role of surface functionalization and core composition in determining encapsulation behavior.

This interaction suggests that the influence of collagen becomes more pronounced at specific formulation ratios, reinforcing the concept that nanoparticle performance arises from a combined effect of bulk and interfacial formulation parameters.

In contrast, the absolute concentration of PCL and its quadratic term were not statistically significant [p > 0.05], indicating that within the experimental range evaluated, polymer amount alone was not the dominant factor controlling encapsulation efficiency. This finding suggests that the structural organization of the nanosystem and the relative proportion of components are more critical than total polymer content.

Overall, these statistical results confirm that encapsulation efficiency in the developed nanocapsules is governed by nonlinear formulation dynamics involving both core composition and surface characteristics, supporting the use of response surface methodology as a rational optimization strategy for dermal nanocarrier design.

Quadratic predictive model for encapsulation efficiency

Encapsulation efficiency [EE] was described using a second-order polynomial model based on coded independent variables:

$$EE = 31.6841 + 0.9958\,x_1 - 12.9796\,x_2 - 1.9493\,x_3 + 0.8814\,x_1^2 + 9.7952\,x_2^2 + 31.6841\,x_3^2 + 0.5055\,x_1x_2 + 0.4172\,x_1x_3 - 0.0576\,x_2x_3 \quad [4]$$

The coded variables were defined as:

$$x_1 = \frac{PCL-112.5}{37.5} \quad [5]$$

$$x_2 = \frac{Ratio-0.0995}{0.335} \quad [6]$$

$$x_3 = \frac{Collagen-200}{200} \quad [7]$$

The experimental ranges evaluated were 75–150 mg for PCL, 0.66–1.33 for the polymer-to-bioactive ratio, and 0–400 mg for collagen concentration.

The model showed a high predictive capability, with a coefficient of determination r^2=0.9547 and adjusted r^2=0.9144, indicating that approximately 95% of the variability in encapsulation efficiency was explained within the studied formulation domain.

ISSN: 2410-4191.
RENIECYT: 1702902

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https://doi.org/10.35429/EJB.2026.13.23.2.1.13

The quadratic model demonstrated that encapsulation efficiency was governed by a combination of linear, quadratic, and interaction effects among formulation variables, confirming the non-linear nature of nanocapsule formation by the emulsification–diffusion method. This type of multivariable behavior is commonly observed in polymeric nanocarrier systems, where drug loading depends on complex physicochemical interactions rather than on simple linear relationships [Mora-Huertas et al., 2010].

The polymer-to-bioactive ratio exhibited the strongest linear effect, with a negative coefficient [−12.9796], indicating that increasing the relative amount of neem extract with respect to poly[ε-caprolactone] reduced encapsulation efficiency. This trend is consistent with previous reports describing that excessive drug loading may lead to partial saturation of the polymer matrix and reduced drug retention capacity in polymeric nanocarriers [Kumari et al., 2010]. In solvent displacement systems, such behavior has been associated with competition between polymer precipitation and drug partitioning during nanoparticle formation [Fessi et al., 1989].

The presence of a significant quadratic term for the polymer-to-bioactive ratio [+9.7952] indicates curvature in the response surface, suggesting the existence of an optimal formulation region. Similar nonlinear relationships between formulation variables and encapsulation efficiency have been reported in response surface studies involving polymeric and lipid-based nanosystems [Shah et al., 2021].

These findings support the interpretation that both insufficient and excessive drug loading can negatively affect encapsulation performance. Collagen concentration showed a negative linear effect [−1.9493] together with a strong quadratic contribution [+31.6841], indicating that its influence on encapsulation efficiency was not purely linear. Although collagen was incorporated as a surface functionalization component, its effect on encapsulation may be related to modifications in interfacial properties and nanoparticle surface organization. Previous studies have shown that adsorption of biopolymers onto nanoparticle surfaces can alter interfacial tension, hydration layers, and overall colloidal behavior [Honary & Zahir, 2013].

Therefore, the observed nonlinear effect may reflect a balance between stabilization and increased interfacial hydrophilicity.

The interaction terms between formulation variables were of lower magnitude but contributed to describing the overall system behavior. In particular, the interaction between polymer concentration and the polymer-to-bioactive ratio suggests that polymer availability may partially influence the effect of drug loading on encapsulation efficiency. Similar interaction effects have been described in multivariate optimization studies of nanocarrier systems using response surface methodology [Shah et al., 2021].

Overall, the model indicates that encapsulation efficiency is controlled by a balance between hydrophobic core formation, interfacial stabilization, and polymer–bioactive compatibility.

The high predictive accuracy of the model supports the use of response surface methodology as a robust tool for the rational optimization of polymeric nanocarriers intended for dermal delivery of lipophilic phytotherapeutic compounds, in agreement with previously reported nanocarrier optimization strategies [Mora-Huertas et al., 2010].

Conclusions

The present study demonstrated the successful development and optimization of polymeric nanocapsules based on poly[ε-caprolactone] for the encapsulation of neem extract using an emulsification–diffusion technique.

The nanosystems exhibited suitable physicochemical characteristics for dermal drug delivery, including particle sizes within the submicron range, acceptable size homogeneity, near-neutral surface charge, and high encapsulation efficiencies.

Statistical analysis revealed that encapsulation efficiency was the most sensitive response variable to formulation composition, being significantly influenced by the polymer-to-bioactive ratio and collagen concentration, including their quadratic and interaction effects.

ISSN: 2410-4191.
RENIECYT: 1702902

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In contrast, particle size and zeta potential were not significantly affected by formulation variables, indicating that these parameters were mainly governed by process-related physicochemical mechanisms such as solvent diffusion dynamics, interfacial tension, and polymer precipitation kinetics.

The application of response surface methodology enabled the identification of a predictive quadratic model with high accuracy [$r^2 = 0.95$], confirming the presence of nonlinear behavior and a well-defined optimal formulation region. The desirability-based optimization approach identified an optimal composition characterized by high polymer content, low polymer-to-bioactive ratio, and absence or low levels of collagen, achieving encapsulation efficiencies close to 89%.

From a pharmaceutical perspective, the results demonstrated that efficient encapsulation of lipophilic phytoconstituents is primarily controlled by the balance between hydrophobic core formation and interfacial stabilization mechanisms. The findings highlight the importance of formulation design and statistical modeling in the rational development of nanocarrier systems.

Overall, the developed nanocapsules represent a promising platform for dermal delivery of plant-derived bioactive compounds, particularly for applications such as acne treatment, where controlled localization and retention of lipophilic agents are required. Future studies may focus on in vitro release behavior, skin permeation, and biological activity to further validate the therapeutic potential of the optimized nanosystem.

Declarations

Conflict of Interest

The authors declare no conflict of interest. They have no known competing financial interests or personal relationships that could have influenced the article reported on herein.

Author contributions

Chávez-Yuen, Wan Yin: Conceptualization, methodology, investigation, formal analysis, data curation, writing – original draft.

Moreno-Cruz, Ana María: Investigation and formal analysis [encapsulation efficiency determination].

Piñón-Segundo, Elizabeth: Supervision, validation, and manuscript review.

Martínez-Pérez, Beatriz: Conceptualization, supervision, project administration, funding acquisition, and manuscript review and editing.

Data and materials availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial Support

Wan Yin Chávez Yuen and Ana María Moreno Cruz express their gratitude for the support provided by the COMECyT scholarship for Master's Studies, numbers 2023BPC1-M-34645 and 2022BPC2-M1012, respectively. Beatriz Martínez Pérez, gratefully acknowledge Secretary of Science, Humanities, Technology and Innovation [SECIHTI] for the financial support provided through the monthly stipend of the National System of Researchers [SNII]. This work was supported by PAPIIT-UNAM [References IN220923 and IN226826].

Abbreviations

DLS	Dynamic Light Scattering
DoE	Design of Experiments
EE	Encapsulation Efficiency
PCL	Poly[ε-caprolactone]
PDI	Polydispersity Index
PVA	Polyvinyl Alcohol
RSM	Response Surface Methodology
X_1, X_2, X_3	Independent variables [PCL concentration, polymer-to-bioactive ratio, collagen concentration]
Y_1–Y_4	Response variables [encapsulation efficiency, particle size, polydispersity index, zeta potential]
ζ [Zeta potential]	Surface electrokinetic potential

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ISSN: 2410-4191.
RENIECYT: 1702902

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