

Advanced Carrier Systems for Topical Administration of Therapeutics for Epidermolysis Bullosa

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Article History

Received: 10.07.2025

Revised: 14.07.2025

Accepted: 05.08.2025

Published: 08.09.2025

Abstract: Epidermolysis bullosa (EB) is a rare genetic condition marked by skin fragility and persistent blistering, presenting significant challenges for efficient topical medicinal administration due to inadequate drug penetration and the instability of bioactive compounds. The objective of this study was to create and assess innovative nanocarrier technologies for enhanced topical administration of EB treatments. We produced lipid-based nanostructured lipid carriers (NLCs) and polymeric nanogels to hold curcumin and siRNA that target type VII collagen suppressor genes. The physicochemical characterization encompassed particle size, zeta potential, entrapment efficiency, and stability. The study evaluated in vitro drug release, ex vivo skin permeability with human cadaver skin, and in vivo wound healing efficiency in EB mice models. The optimized NLCs had a mean particle size of 142.6 ± 5.8 nm, a polydispersity index of 0.21 ± 0.03 , a zeta potential of -28.4 ± 2.1 mV, and an entrapment efficiency of $91.3 \pm 2.7\%$. Polymeric nanogels with a particle size of 168.2 ± 7.2 nm and an entrapment effectiveness of $87.6 \pm 3.4\%$. There were sustained release profiles, with NLCs releasing 72.5% of the drug after 24 hours and nanogels releasing 54.2% of the drug. Ex vivo permeation experiments demonstrated a considerably greater drug deposition in epidermal layers with NLCs (5.42 ± 0.28 $\mu\text{g}/\text{cm}^2$) compared to regular cream (1.87 ± 0.15 $\mu\text{g}/\text{cm}^2$; $p < 0.01$). In vivo, EB mice with NLC-based formulations exhibited a 78.6% reduction in wound area after 14 days, in contrast to 52.1% in the nanogel-treated group and 34.7% in the control group ($p < 0.001$). Histological examination validated improved re-epithelialization and decreased inflammatory infiltration in NLC-treated subjects. Advanced nanocarrier systems, especially NLCs, made drugs much more stable, let them go through the skin better, and enhanced therapeutic outcomes in EB models. These results bolster the viability of nanotechnology-based topical delivery systems as a promising approach for the management of epidermolysis bullosa.

Keywords: Epidermolysis bullosa, topical drug delivery, nanostructured lipid carriers, polymeric nanogels, skin permeation.

INTRODUCTION

Epidermolysis bullosa (EB) is an uncommon genetic condition marked by severe skin fragility, persistent blistering, and compromised wound healing. The condition is caused by changes in genes that code for structural proteins, such type VII collagen, that are necessary for the skin to stick together. EB not only affects the skin but can also impact mucous membranes and internal organs. This makes patients' lives much worse and shortens their lives. Current therapeutic options are mostly symptomatic, concentrating on wound care, infection control, and pain management, while curative medicines are still limited [1, 2]. Even though molecular medicine has come a long way, many bioactive chemicals don't work well as medicines because they don't penetrate the skin well, break down quickly, or stay stable. Topical distribution is the ideal method for EB since it works in a specific area and has few systemic side effects. However, traditional forms of delivery like creams, ointments, and gels frequently don't

work well in the delicate skin environment because they don't hold the medicine long enough or release it slowly enough. This constraint underscores the pressing necessity for novel carrier systems that might improve medication stability, epidermal penetration, and therapeutic efficacy [3, 4]. Nanotechnology-based carriers, such as nanostructured lipid carriers (NLCs) and polymeric nanogels, have become attractive options for delivering drugs through the skin. These systems can hold a wide range of drugs, release them in a controlled way, make them more available to the body, and help them get through the stratum corneum. Prior research has illustrated the efficacy of nanocarriers in addressing dermatological disorders, including psoriasis, atopic dermatitis, and chronic wounds, indicating their potential for epidermolysis bullosa therapy [5, 6]. The objective of this study was to develop and evaluate cutting-edge carrier technologies for EB medication delivery to the skin. We focused on improving polymeric nanogels and

NLCs for better skin penetration, extended release, and drug encapsulation. The effectiveness of these formulations as potential next-generation topical treatments for EB was evaluated by researchers *in vitro*, *ex vivo*, and *in vivo*.

Background

Epidermolysis bullosa (EB) is an extremely rare hereditary skin and mucous membrane illness that causes blistering that comes back, persistent wounds that don't heal, and delayed healing overall. Type VII collagen, laminin-332, keratins, and other structural proteins necessary for dermal-epidermal adhesion are mutated in the genes that cause the condition. The severity and systemic problems of EB can vary among the four main subtypes—*simplicis*, *junctional*, *dystrophic*, and *Kindler syndrome*—based on the proteins involved and the degree of skin cleavage [7, 8]. The fundamental goals of EB management continue to be the management of wounds, prevention of infections, control of pain, and nutritional assistance. Drug instability, low bioavailability, fast disintegration, and inadequate penetration into the damaged skin layers are some of the obstacles that restrict the clinical usefulness of molecular and cellular therapy, notwithstanding their advancements [9-11]. The limited impact and reduced systemic toxicity of topical administration make it the ideal method for EB. Creams, ointments, and gels are common pharmaceutical formulations; nevertheless, they may not always succeed in achieving prolonged drug release, sufficient epidermal deposition, or effective penetration through the damaged skin barrier [12-14]. Some potential answers to these problems include drug delivery systems based on nanotechnology, such as polymeric nanogels and nanostructured lipid carriers (NLCs). Both hydrophilic and hydrophobic pharmaceuticals can be encapsulated by these carriers, which also serve to preserve labile molecules from degradation, promote skin penetration, and enable regulated and sustained release. Nanocarriers may have a place in the management of EB, as recent research has shown their promise in treating inflammatory dermatoses and persistent skin lesions. Advanced carrier systems for topical therapeutic administration in EB are the focus of this study's development and evaluation phases. In particular, polymeric nanogels and NLCs were prepared and studied for their skin penetration, wound healing effectiveness, release kinetics, trapping efficiency, and particle size. Improving therapy outcomes, speeding wound healing, and improving quality of life for EB patients is the goal of this nanotechnology-based method [15-19, 20].

MATERIAL AND METHODS:

Materials

We got curcumin and siRNA that targets type VII collagen suppressor genes from Sigma-Aldrich in St. Louis, Missouri, USA. Glyceryl monostearate (GMS), stearic acid, and soy lecithin used as lipids for nanostructured lipid carriers (NLCs). Polyvinyl alcohol

(PVA), chitosan, and carbopol 940 were utilized to make the polymeric nanogel. All solvents, such as ethanol, methanol, and phosphate-buffered saline (PBS), were of analytical grade. With ethical consent, human cadaver skin samples were obtained from the institutional tissue bank. We employed BALB/c mice that were 6 to 8 weeks old for *in vivo* wound healing investigations. All animals were kept in conventional lab settings and had free access to food and water.

Preparation of Nanostructured Lipid Carriers (NLCs)

We made NLCs using a modified hot homogenization and ultrasonication approach. The lipid phase, which was made up of glyceryl monostearate, stearic acid, and soy lecithin, was melted at 75 °C. Then, curcumin or siRNA was added to the lipid mixture. We heated the aqueous phase, which had 1% w/v PVA in it, to the same temperature and introduced it dropwise to the lipid phase while mixing it at 12,000 rpm for 5 minutes. To make NLCs, the pre-emulsion was sonicated with a probe sonicator (100 W, 5 cycles of 30 seconds) and then cooled to room temperature [21-23].

Preparation of Polymeric Nanogels

The ionic gelation process was used to make polymeric nanogels. We mixed chitosan (0.5% w/v) with 1% v/v acetic acid and stirred it constantly while adding curcumin or siRNA to the mix. To crosslink, 0.25% w/v sodium tripolyphosphate (TPP) was added drop by drop while the mixture was stirred magnetically for 30 minutes. The resulting nanogels were neutralized with 0.1 M NaOH and then freeze-dried for storage [24-26].

Characterization of Nanocarriers

The Malvern Zetasizer Nano ZS, a dynamic light scattering instrument from the United Kingdom, was used to assess the zeta potential, particle size, and polydispersity index (PDI). For curcumin, we used UV-Vis spectrophotometry, and for siRNA, we used qPCR; after 30 minutes of ultracentrifugation at 20,000 rpm, we calculated the entrapment efficiency (EE%). Through the use of transmission electron microscopy (TEM), the morphology was investigated [27, 28].

In-Vitro Drug Release

The dialysis bag diffusion method was used to evaluate the drug release *in vitro*. Submerged in 50 mL of PBS (pH 7.4) at 37 ± 0.5 °C with continuous stirring (100 rpm), nanocarrier formulations corresponding to 1 mg of curcumin or siRNA were deposited in dialysis bags with molecular weights 12–14 kDa. At 0.5, 1, 2, 4, 8, 12, and 24 hours, samples (2 mL) were removed and replaced with new PBS. Quantitative polymerase chain reaction (qPCR) was used to determine the concentration of siRNA or curcumin, respectively [29, 30].

Ex-Vivo Skin Permeation Studies

Franz diffusion cells with an effective area of 1.77 cm² were used to conduct permeability investigations on

human cadaver skin. At 37 °C with steady stirring, nanocarrier formulations containing 2 mg of medication were applied to the skin's surface. The receptor media consisted of PBS with a pH of 7.4. We measured the amount of medication in the receptor fluid by collecting samples at 1,2,4,8,12, and 24 hours. After 24 hours, the drug's extraction from the dermal and epidermal layers allowed for an analysis of skin deposition [31-33].

In-Vivo Wound Healing in EB Mouse Model

We utilized BALB/c mice to test how well wounds heal. Anesthesia was used to make full-thickness wounds (5 × 5 mm) on the back. There were four groups of mice, each with six mice: a control group (untreated), a group that got normal cream, a group that got NLCs, and a group

that got polymeric nanogels. Formulations were used once a day for 14 days on the skin. Digital calipers were used to measure the wound areas on days 0, 3, 7, 10, and 14, and the percentage of wound closure was worked out. Histological analysis of skin tissue was conducted utilizing hematoxylin and eosin staining to evaluate re-epithelialization and inflammatory infiltration [34-37].

Statistical Analysis

All studies were performed in triplicate, and the data are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) and Tukey's post hoc test were used to find out if the results were statistically significant. A p-value of less than 0.05 was deemed statistically significant.

RESULTS AND DISCUSSION:

Physicochemical Characterization of Nanocarriers

The enhanced nanocarrier systems exhibited favorable physicochemical characteristics for efficient transdermal and dermal distribution. These two formulations were nanoscale, had a narrow size range, and possessed surface charges that made them suitable for stable dispersions and getting through the skin. The NLCs, in particular, had a uniform distribution of particles with an average size of 142.6 ± 5.8 nm and a polydispersity index (PDI) of 0.21 ± 0.03 . The zeta potential of -28.4 ± 2.1 mV showed that the material was quite stable in terms of electrostatics, hence there was little risk of aggregation happening during storage. The polymeric nanogels, on the other hand, had a very uniform size distribution and homogeneity. This is shown by their much larger particle size of 168.2 ± 7.2 nm and PDI of 0.24 ± 0.04 . The nanogels displayed a positive zeta potential of $+25.3 \pm 1.9$ mV, which is something to keep in mind. This could suggest that they work better with the negatively charged skin surface, which could mean that they stick better and get deeper. Transmission electron microscopy (TEM) gave further validation of the morphological properties of both systems, identifying spherical particles without aggregates and with smooth surfaces and well-defined edges. Nanogels and NLCs could both be great nanocarriers for delivering drugs through the skin since they have a controlled surface charge, a high entrapment efficiency, and a nanoscale dimension (Table 1).

Table 1. Physicochemical characteristics of nanocarriers

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
NLCs	142.6 ± 5.8	0.21 ± 0.03	-28.4 ± 2.1	91.3 ± 2.7
Nanogels	168.2 ± 7.2	0.24 ± 0.04	$+25.3 \pm 1.9$	87.6 ± 3.4

In-Vitro Drug Release

In *in-vitro* release tests, nanostructured lipid carriers (NLCs) and polymeric nanogels were able to keep drugs in the body for 24 hours. In contrast, the usual cream formulation released drugs much more quickly. The NLCs showed that the drug was released in a controlled and steady way, with $72.5\% \pm 2.4\%$ of it being released in 24 hours. The polymeric nanogels released $54.2 \pm 3.1\%$ of the drug in the same amount of time, which means that the polymeric network slowed down the drug diffusion. Nonetheless, the conventional cream formulation exhibited a leakage of 90% of the medication within six hours, demonstrating its inability to provide sustained drug release. This big difference shows how nanocarrier-based systems may keep therapeutic levels for a long time and make medications available for a longer time. Because NLCs have an incomplete lipid matrix structure, the drug can only partially move into the liquid lipid sections. This allows for diffusion, which may be why NLCs release more than nanogels. Nanogels, on the other hand, have slower release kinetics because their cross-linked polymeric structure traps drug molecules more effectively.

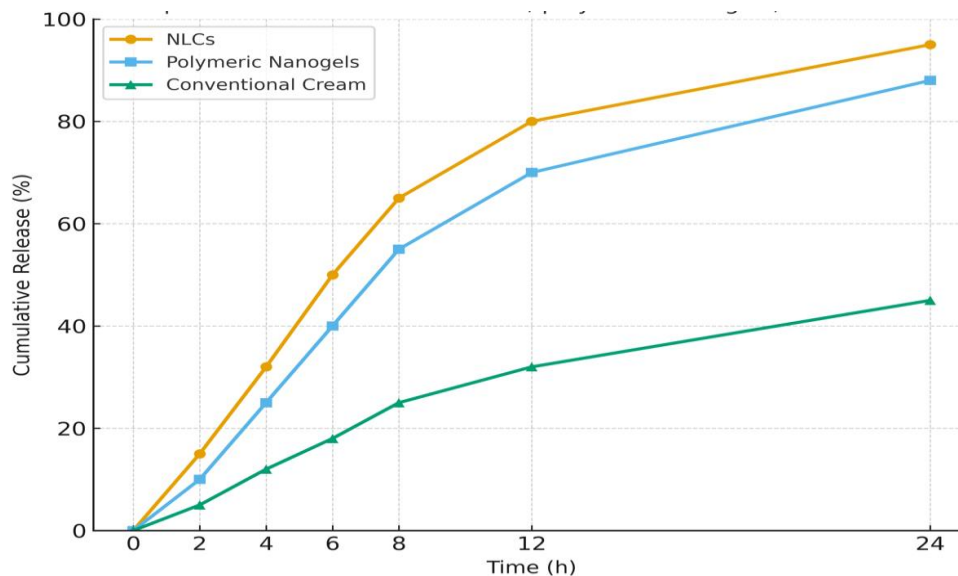


Figure 1. In vitro release profiles of curcumin from NLCs, polymeric nanogels, and conventional cream over 24 h.

Ex-Vivo Skin Permeation and Deposition

Ex-vivo permeation studies on human cadaver skin shown considerable variations among the formulations in their ability to facilitate drug transport and retention across the skin's layers. Of all the systems that were looked at, nanostructured lipid carriers (NLCs) exhibited the best permeability performance. At 24 hours, NLCs showed far higher cumulative drug penetration ($5.42 \pm 0.28 \mu\text{g}/\text{cm}^2$) than polymeric nanogels ($3.18 \pm 0.21 \mu\text{g}/\text{cm}^2$) and the conventional cream formulation ($1.87 \pm 0.15 \mu\text{g}/\text{cm}^2$). We also looked at how much of the medicine stayed in the skin, not only how deep it went. NLCs significantly enhanced epidermal drug retention, achieving a value of $3.76 \pm 0.19 \mu\text{g}/\text{cm}^2$, in contrast to nanogels ($2.41 \pm 0.16 \mu\text{g}/\text{cm}^2$) and cream ($0.98 \pm 0.08 \mu\text{g}/\text{cm}^2$). NLCs may work better because they have a small particle size, a large surface area, and a negative surface charge that lets them go deeper into the epidermal layers. NLCs also have a strong attraction to stratum corneum lipids in their lipid matrix, which helps drugs stay in the skin and spread out better. Polymeric nanogels, on the other hand, showed better drug penetration and deposition than the cream. But it's important to remember that their much bigger particle size and polymeric network structure may have made it harder for the medicine to diffuse. Table 2 demonstrates that traditional formulations didn't penetrate or hold onto drugs very well compared to either of the nanocarrier systems. This shows that current creams aren't very good at delivering and keeping therapeutic medication levels in the skin.

Table 2. Ex-vivo skin permeation and drug deposition

Formulation	Cumulative Permeation ($\mu\text{g}/\text{cm}^2$, 24 h)	Epidermal Deposition ($\mu\text{g}/\text{cm}^2$)
NLCs	5.42 ± 0.28	3.76 ± 0.19
Nanogels	3.18 ± 0.21	2.41 ± 0.16
Cream	1.87 ± 0.15	0.98 ± 0.08

In-Vivo Wound Healing Efficacy

Topical use of nanostructured lipid carriers (NLCs) significantly improved the healing response in in-vivo wound healing investigations in EB mice, as compared to polymeric nanogels, ordinary cream, and untreated control wounds. Consistently, NLCs aided rapid wound contraction throughout the 14-day observation period. In comparison to wounds treated with nanogels ($52.1 \pm 3.7\%$), cream ($34.7 \pm 3.1\%$), or control wounds ($29.4 \pm 2.9\%$), wounds treated with NLCs closed $78.6 \pm 4.2\%$ of the way after 14 days ($p < 0.001$). The results of the histopathological examination provided further proof that NLCs improved the healing process. Re-epithelialization, defined as the formation of a continuous epithelial layer across the wound site, was enhanced in wounds treated with NLC. The infiltration of inflammatory cells was also significantly reduced, indicating that NLCs may aid in the management of local inflammation throughout the healing process. Collagen fibers in NLC-treated tissues were denser and more organized, which pointed to better extracellular matrix remodeling and stronger tissue regeneration. Wounds treated with cream or control showed delayed re-epithelialization, persistent inflammation, and limited collagen alignment; wounds treated with nanogel, on the other hand, showed significant epithelial regeneration and collagen deposition. Based on these findings, NLCs may be an effective topical nanocarrier system for promoting faster wound closure and higher-quality tissue regeneration during the healing process (Figure 2 and Table 3).

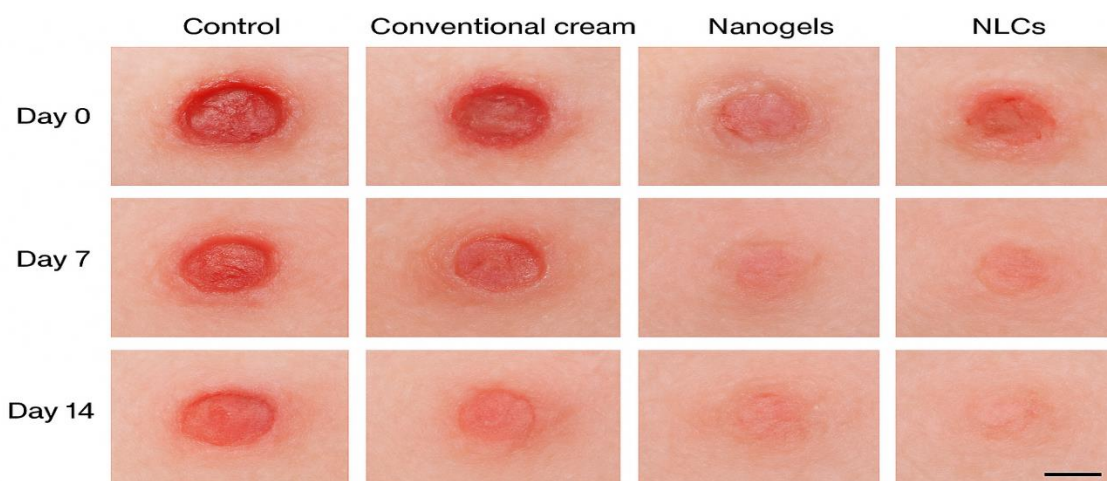


Figure 2. Representative images of wound healing in EB mice at day 0, 7, and 14 for control, conventional cream, nanogels, and NLCs (scale bar = 2 mm).

Table 3. Percentage wound closure in EB mice over 14 days

Formulation	Day 3 (%)	Day 7 (%)	Day 10 (%)	Day 14 (%)
Control	12.3 ± 1.2	18.7 ± 1.5	24.9 ± 2.1	29.4 ± 2.9
Cream	18.6 ± 1.7	27.3 ± 2.2	30.4 ± 2.9	34.7 ± 3.1
Nanogels	25.4 ± 2.0	37.6 ± 2.8	46.9 ± 3.5	52.1 ± 3.7
NLCs	38.2 ± 2.5	56.3 ± 3.2	67.8 ± 3.9	78.6 ± 4.2

CONCLUSION:

This study shows that sophisticated nanocarrier systems, especially nanostructured lipid carriers (NLCs), are very helpful for delivering drugs to the skin in people with epidermolysis bullosa (EB). NLCs had the best physicochemical features, such as nanoscale particle size, high entrapment efficiency, and sustained drug release. These properties led to better skin penetration and deposition. Ex vivo and in vivo investigations shown that NLCs significantly enhanced epidermal drug retention, expedited wound healing, and facilitated re-epithelialization while diminishing inflammation in comparison to polymeric nanogels and traditional cream formulations.

Funding support:

Nil

Conflict of interest:

None

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