

Study on Topical Transdermal Delivery System Based on Oil-in-Water Nanoemulsion

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論 文 名 : Study on Topical Transdermal Delivery System Based on Oil-in-Water Nanoemulsion
(Oil-in-Water 型ナノエマルジョンに基づく局所経皮送達システムに関する研究)

区 分 : 甲

論 文 内 容 の 要 旨

Transdermal delivery systems, as non-invasive drug administration strategies, offer several advantages, including the avoidance of first-pass metabolism, enhanced local therapeutic effects, and improved patient compliance. These systems hold great promise in the treatment of skin diseases and tissue repair. However, the stratum corneum, as the primary barrier of the skin, significantly limits the permeation of exogenous substances. This presents a particular challenge for the stable delivery of hydrophobic drugs, which often exhibit low solubility and poor bioavailability.

Considering the hydrophobic nature of the stratum corneum, one might initially expect the outermost phase of a transdermal formulation to be oil-based, which naturally leads to the idea of a multiple emulsion system such as oil-in-water-in-oil (O/W/O). However, multiple emulsions are often plagued by poor structural stability and low drug loading capacity, limiting their clinical utility. In response to this challenge, this study adopts a more stable and practical approach by developing and optimizing an oil-in-water nanoemulsion (O/W-NE) system.

The formulation was designed to improve drug penetration, targeting, and therapeutic efficacy through model validation. A well-dispersed O/W-NE with an average droplet size of ~100 nm was established, incorporating glycerin as a safe penetration enhancer. The system demonstrated high drug encapsulation efficiency, reduced burst release, and good skin affinity. Ceramide-loaded nanoemulsions were evaluated in a sodium dodecyl sulfate (SDS)-induced skin barrier damage model, showing effective skin repair. Additionally, dihydrotestosterone (DHT) was used as a model drug in a transdermal-induced androgenetic alopecia (AGA) mouse model, confirming follicular targeting and regulation of the hair growth cycle.

Overall, this nanoemulsion-based platform significantly enhances the transdermal delivery and efficacy of hydrophobic drugs. Through systematic design, it enables prevent burst release and versatile applications, offering a promising strategy and delivery vehicle for both skin disease treatment and animal model development.

Chapter 1 outlines the background, objectives, and overall research strategy of this study.

Chapter 2 presents a review of previous studies relevant to this research.

Chapter 3 focuses on the development, optimization, and characterization of the O/W-NE. Through formulation screening and adjustment of preparation conditions, an O/W-NE with an average droplet size of approximately 110 nm was successfully developed, demonstrating long-term stability at 4 °C and favorable drug encapsulation efficiency. The results further indicated that, compared to conventional emulsions, the addition of glycerin to the aqueous phase enhances the structural stability of the system, improves droplet uniformity, and mitigates burst release. These features highlight the potential of the O/W-NE as a promising carrier for drug delivery.

Chapter 4 investigates the *in vitro* safety and transdermal performance of the nanoemulsion system. The biocompatibility of the nanoemulsion was first evaluated through cell viability assays and *in vivo* skin irritation tests in animal models, confirming its suitability for transdermal application. Both *ex vivo* skin and *in vivo* studies in mice were employed to examine the permeation behavior, demonstrating that smaller droplet size and the addition of an appropriate concentration of glycerin significantly enhance the transdermal delivery efficiency of the O/W-NE.

In Chapter 5, the reparative effect of ceramide delivered via an O/W-NE system on SDS-induced skin barrier disruption is systematically evaluated. An SDS-induced mouse model was established to mimic common skin disorders such as eczema and xerosis. Ceramide-loaded O/W-NE (CER-NE) was applied transdermally, resulting in reduced erythema, dryness, inflammation, and epidermal thickening. CER-NE effectively restored skin barrier function. This study demonstrates a promising strategy for delivering ceramide to stimulate epidermal differentiation and stratum corneum regeneration, with potential applications in epidermal therapy and regenerative medicine.

In Chapter 6, to address the limitations of conventional AGA modeling methods—such as low efficiency, systemic side effects from injections, and skin irritation from ethanol-based delivery—an O/W-NE was applied for the transdermal delivery of DHT to establish a mouse model of AGA. Results showed that conventional methods were less efficient, poorly targeted, and often caused adverse effects. In contrast, the O/W-NE model provided a more stable and reproducible system, with varying model severity depending on delivery efficiency. This confirmed the superior follicular targeting capability of O/W-NE and their potential for delivering actives to skin appendages. The established model offers a valuable platform for further therapeutic investigations and expands the application of O/W-NE systems in androgen-related disease modeling and treatment.

Chapter 7 summarizes the key findings of this study and provides perspectives on the future application of O/W-NE in transdermal delivery of hydrophobic drugs, treatment of skin disorders, and the development of localized disease models.