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Review

# Recent Advances in Lipid-Based Vesicles and Particulate Carriers for Topical and Transdermal Application

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ABSTRACT

In the recent decade, skin delivery (topical and transdermal) has gained an unprecedented popularity, especially due to increased incidences of chronic skin diseases, demand for targeted and patient compliant delivery, and interest in life cycle management strategies among pharmaceutical companies. Literature review of recent publications indicates that among various skin delivery systems, lipid-based delivery systems (vesicular carriers and lipid particulate systems) have been the most successful. Vesicular carriers consist of liposomes, ultradeformable liposomes, and ethosomes, while lipid particulate systems consist of lipospheres, solid lipid nanoparticles, and nanostructured lipid carriers. These systems can increase the skin drug transport by improving drug solubilization in the formulation, drug partitioning into the skin, and fluidizing skin lipids. Considering that lipid-based delivery systems are regarded as safe and efficient, they are proving to be an attractive delivery strategy for the pharmaceutical as well as cosmeceutical drug substances. However, development of these delivery systems requires comprehensive understanding of physicochemical characteristics of drug and delivery carriers, formulation and process variables, mechanism of skin delivery, recent technological advancements, specific limitations, and regulatory considerations. Therefore, this review article encompasses recent research advances addressing the aforementioned issues.



## Introduction

The pharmaceutical drug delivery market is expected to grow from $1048.1 billion in 2015 to $1504.7 billion by 2020, with a compound annual growth rate of 7.5%.[1] Conventionally and till to date, the oral route retains a major share of this drug delivery market. However, the oral route is becoming increasingly unpopular for variety of drugs and disease conditions, particularly due to the recent technological advancements in drug delivery arena (such as improvement in manufacturing processes, fabrication of functionalized polymers, and evaluation techniques) and emerging demand for a more localized delivery to minimize side effects. In this regard, skin delivery provides an attractive alternative to oral drug delivery.[1] Skin delivery can be broadly differentiated into dermal (topical) and transdermal drug delivery. Dermal delivery is the application of drug directly at the site of action (skin surface), resulting in higher localized drug concentration with reduced systemic drug exposure.[2] On the other hand, transdermal delivery transports the drug across skin surface to the systemic circulation for achieving therapeutic levels. Both topical and transdermal applications have successfully delivered variety of drugs.[1,3-5] This is also evident from the fact that skin delivery which was valued around $9.44 billion in 2013 is expected to reach $11.21 billion by 2018 with higher compound annual growth rate compared to the oral route. The main driving force for the increasing interest in the skin delivery could be attributed to the increasing incidences of chronic skin diseases, demand for targeted and patient compliant delivery, highly competitive oral drug delivery market, and growing interest among pharmaceutical companies in life cycle management strategies.[1,2,6]

However, despite growing interest in the skin delivery, the greatest challenge for the researchers is to overcome the inherent limitation of drug absorption imposed by impervious stratum

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corneum, the outermost layer of the skin.[6,7] Researchers have tried various approaches to either disrupt or weaken the stratum corneum to improve skin delivery. The first major approach to overcome the skin barrier is the use of chemical enhancers such as azones, glycols, ethanol, terpenes, and so on.[6,8] They facilitate drug transport by partially fluidizing skin lipids and increasing drug partitioning. A second approach is to use physical enhancement methods, such as sonophoresis (ultrasound), electroporation, magnetophoresis, microneedles, thermal ablation, microdermabrasion, and iontophoresis.[7,9-12] This approach bypasses the stratum corneum and delivers the drug directly to the target skin layer. Both of the aforementioned approaches have shown successful delivery for variety of drugs.[11,13] However, physical approaches are mostly painful, expensive, and lack patient compliance while chemical permeation enhancers can cause skin irritation and permanent skin damage.[6] Finally, the third approach is the use of drug delivery systems like nanoparticles, microparticles, and lipid-based delivery systems. These systems can increase skin transportation by improving drug solubilization in the formulation, drug partitioning into the skin, and by fluidizing the skin lipids.[6] Among the various studied drug delivery systems, lipid-based delivery systems have shown a great potential for both topical and transdermal delivery, especially in the last few decades.[14]

Lipid-based delivery systems are composed of biocompatible and biodegradable lipids that can be utilized for controlled release, targeted delivery, and drug protection. The first commercial product utilizing lipid-based delivery system was marketed in 1988 for antimycotic agent, econazole.[15] Since then, several reports are published indicating the success of these delivery systems.[6,14,16-19] Based on the recent literature review for skin application, majority of the lipid-based skin delivery systems are classified into vesicular carriers and lipid particulate systems. Vesicular carriers comprise liposomes, ethosomes, ultradeformable liposomes, and other specialized novel vesicular carriers. Due to the limited success of conventional liposomes in the skin delivery, majority of the recent research are predominantly focused on polymeric liposomes (PLs) and elastic liposomes like ultradeformable liposomes and ethosomes. Lipid particulate systems have also gained popularity in the recent past. Among this class, lipospheres, solid lipid nanoparticles (SLNs), and more recently nanostructured lipid carriers (NLCs) have been successfully utilized for skin delivery. Table 1 provides a brief summary of various lipid-based delivery systems.

The lipid-based delivery systems can be tailored to target various skin conditions depending on the delivery system selected, formulation composition, manufacturing processes, and process variables. However, fabrication of these delivery systems requires understanding of process and formulation variables, mechanism of skin delivery, knowledge of physicochemical characteristics, recent technological advancements, and specific limitations. To address these needs, this review article focuses on lipid-based delivery systems (specifically vesicular and lipid particulates) with emphasis on recent research, advancements, and challenges. Also, acknowledging that the literature provides only a limited review on lipid-based delivery systems for unique areas like transcutaneous immunization (TCI), vaccine delivery via the skin, and cosmeceuticals, we have attempted to encompass these areas within the limited scope of this review article. Furthermore, it is also imperative to understand the associated regulatory implications for achieving commercial success of these delivery systems for skin application. However, because literature review of past decade provides little information of this subject, the regulatory aspects and U.S. Food and Drug Administration (FDA) standpoint for lipid-based delivery systems are also covered in this article.

## Skin Anatomy and Physiology

The skin is the largest organ of the human body. The total surface area of the skin of an average male adult is approximately 2 $m^2$.[35] The major functions of the skin include protection against mechanical stresses, prevention of excessive water loss; facilitating transpirational cooling, and preventing absorption of foreign bodies. Anatomically, skin is composed of 3 main distinguishable layers, namely epidermis, dermis, and subcutaneous (SC) "fat" tissues (Fig. 1).[36]

### *Epidermis*

The epidermis is divided into 2 regions: the nonviable epidermis (the stratum corneum) and the viable epidermis. It consists of 70% water and keratinizing epithelial cells responsible for synthesis of the stratum corneum.[37] The epidermis does not contain any blood vessels and hence molecules permeating across the epidermis must cross the dermal-epidermal layer to enter the body's systemic circulation.

The stratum corneum is the outermost layer of the skin and is involved in skin homeostatic and protective functions. The stratum corneum is the final product of epidermal differentiation with approximately 10-20 μm thickness and is considered as metabolically inactive.[37] It consists of 10-25 layers of dead, elongated, fully keratinized corneocytes, which are embedded in a matrix of the lipid bilayers. It typically resembles "Brick and Mortar" type structure, where corneocyte from hydrated keratin of the skin resembles Bricks embedded in a Mortar, comprising of extracellular lipid components.[38] The extracellular lipid is constituted of 2 lamellar phases with predominant crystalline phase and the subpopulation of liquid lipid phase.[39] Lipids that constitute the extracellular matrix of the stratum corneum have a unique composition and are very different from the lipids that constitute most biological membranes.

The viable epidermis is present below the stratum corneum and is approximately 50-100 μm thick.[40] It is different from the stratum corneum because it is physiologically more closely akin to the other living cellular tissues and contains many metabolizing enzymes. The viable epidermis is involved in the generation of stratum corneum and metabolism of the foreign substances. It is also involved in the immune response of the skin due to the presence of Langerhan cells (LCs).[41]

### *Dermis*

The dermis is a supportive, compressible, and elastic connective tissue protecting the epidermis. It is composed of fibrous proteins (collagen and elastin) and an interfibrillar gel of glycosaminoglycans, salts, and water. Blood and lymphatic vessels, nerve endings, hair follicle, sebaceous glands, and sweat glands are embedded within the dermis. Extensive vascular network in the dermis plays a crucial role in skin nutrition, repair, immune responses, and thermal regulation.[37] The hair follicles and sweat ducts form a direct connecting path from dermis to the skin surface, bypassing stratum corneum and henceforth involved in providing appendageal route of skin permeation.[42]

### *Subcutaneous "Fat" Tissue*

The SC fat tissue located below the dermis is composed of the cells that contain large quantities of fat, making the cytoplasm lipoidal in character.[37] The collagen between the fat cells provides the linkage of the epidermis and the dermis with the underlying structures of the skin. The main function of SC fat tissue is to act as a heat insulator and shock absorber.