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From nanoemulsions to nanostructured lipid carriers: A relevant development in dermal delivery of drugs and cosmetics

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ABSTRACT

Recent advances in nanotechnology have led to the development of nano-scale drugs and delivery systems to improve drug therapeutic effectiveness. Between the end of '50 and the beginning of '60, the first colloidal systems in the nano-metric range were achieved by chance. Several research highlighted the usefulness of these nano-carriers as drug delivery systems to overcome biological barriers later on. Since few drugs are effective after their topical application, due to the barrier function of the skin, colloidal systems have being widely explored as carriers to improve drug skin permeation. In particular, a great deal of attention has been paid to delivery systems based on highly biocompatible and biodegradable components such as lipids and phospholipids. As a result, different types of nano-carriers such as liposomes, microemulsions, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been developed. This review will focus on the nano-carriers arising from the first colloidal systems consisting of water, lipids and surfactants, i.e. microemulsions and their consequent improvement through the development of SLN and NLC. The properties of these nano-carriers will be discussed along with their applications as skin delivery systems both in pharmaceutical and cosmetic fields.

1. Introduction

1.1. Background

Nanotechnology is a science devoted to creation, modification and utilization of materials, devices, and systems in the nano-meter size range. It exploits the physical, chemical, and biological properties of materials that improve or radically differ from those of bulk materials, just because they are on a nano-metric scale [1,2].

Nanotechnologies are already used in several commercial products and industrial applications such as electronics, foods, fuel and solar cells, batteries, chemical sensors, etc. Moreover, numerous applications of nanotechnology in the pharmaceutical and cosmetic have revolutionized the administration of drugs and cosmetics. Indeed, the use of nano-carriers have led to the definition of nanomedicine, a multidisciplinary subject area including many scientific disciplines, which has been defined as the application of nanotechnology for the prevention, treatment, diagnosis, monitoring, and control of biological systems [3]. The main nanomedicine research areas have been classified as:

- Nanotechnology-based diagnostics including imaging (molecular diagnostics, imaging with nanoparticles, biosensor etc.)
- Nano-pharmaceuticals (targeted drug delivery, nanotechnology-based drug, nano-pumps and nano-coated stents, etc.)
- Regenerative Medicine and Nano-surgery (nano-biotechnology scaffolds, nano-laser surgery, etc.)
- Nanorobotics (vascular surgery by nano-robots, nano-robots for detection and destruction of cancer, etc.)

Nano-carriers for medical application include several engineered constructs, assemblies, architectures, and particulate systems with distinct physicochemical characteristics, whose unifying feature is the size between 1 and 1000 nm (as commonly defined in pharmaceutical sciences). Diagnostic or/and therapeutic agents can be encapsulated, incorporated into such nano-carriers or covalently attached or adsorbed onto their surface. Different classes of nano-carriers such as liposomes, nanocrystals, lipid and polymeric

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nanoparticles, block copolymer micelles, gold nanoparticles, dendrimers, etc. have been used to improve drug and gene delivery, targeted therapy, diagnostics and some of them have already a routine clinical use [1,3].

Several studies have shown that nano-carriers are advantageous in several pharmaceutical and cosmetic applications and, above all, vesicular carriers, microemulsions, and lipid nanoparticles are the most studied and used. Microemulsions and lipid vesicles (liposomes) were described for the first time almost simultaneously in the 60s of the past century. Indeed, in 1959 Schulman et al. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions" while liposomes were discovered by Sir Alec Bangham in 1961 [4,5]. Successively, these colloidal carriers were proposed in topical drug delivery and lipid nanoparticles were developed starting from microemulsions. In this review, we will focus on the evolution from microemulsions to lipid nanoparticles, for dermal application in the pharmaceutical and cosmetic field.

To understand better the potential of these carriers as skin Drug Delivery Systems (DDS), at first, general issues regarding cutaneous permeation will be introduced. Indeed, the skin can offer several advantages as a route of drug administration although its barrier nature makes it difficult for most drug to penetrate into and permeate through it.

1.2. Skin anatomy and physiology

The skin is the largest organ in the human body and acts as a main target as well as a principal barrier for dermal and transdermal drug delivery. Indeed, because of its easily accessible large surface area, it has received a great research interest as a non-invasive alternative route to conventional oral or injectable administration of drugs. Indeed, drug delivery into/through the skin offers different advantages that include improved bioavailability of drugs that suffer the gastrointestinal environment and/or hepatic first pass effects, potential of delivering drugs for a prolonged period at a constant rate, reduced side effects, and improved patient compliance. However, percutaneous drug delivery is still challenging. Indeed, even now, there is the need to overcome individual variability among the different locations on the skin, and for the effective barrier that this organ forms between the organism and the environment. Definitely, the primary function of the skin is to act as a barrier in order to protect the human and mammalian body, thus, preventing invasion of pathogens and protecting from chemical and physical assaults, as well as from unregulated loss of water and solutes. This important role is due to the architecture of the skin, which is composed of three functional layers, namely epidermis, dermis, and hypodermis (also known as subcutaneous fat layer) [6].

The protective properties are provided by the epidermis, the outermost skin layer, in spite of its very low thickness, which varies from 0.02 mm from up to 5 mm depending on the location of the skin. The epidermis is a stratified squamous epithelial layer, containing keratinocytes organized in four main different strata (i.e. stratum corneum, granular layer, spinous layer, basal layer). The physical barrier is primarily localized in its uppermost layer, known as horny layer or stratum corneum (SC, 10–20 μm thick), consisting in 15–25 flattened, stackened, hexagonal, and cornified cells (corneocytes) embedded in lipid-enriched intercellular domains [6].

SC thickness varies greatly being particularly thick in the palms of the hand and soles of the feet. The SC barrier properties are partly related to its high density (1.4 g/cm^3), its low hydration (15–20%) in comparison with common body tissues (70%), and its low surface area for solute transport. The barrier properties are further supported by continuous desquamation of the horny layer with its complete turnover occurring every 2–3 weeks [6]. All SC cells originate in the deepest epidermal stratum, the basal layer, and undergo many morphologic, biochemical and physiological changes as they move from the basal lamina to the superficial skin layer under the pressure of the newly produced keratinocytes. In the epidermal basal layer, also melanocytes, Langerhans cells, and Merkel cells are present together with the keratynocites.

Corneocytes are mainly composed of insoluble packed keratins (70%) and lipids (~20%) enclosed in a cornified envelope, while the intercellular region consists of lipids and desmosomes, which allow corneocyte cohesion. The lipid intercellular domain consists of lamellar sheets composed of approximately equimolar concentrations of free fatty acids, cholesterol, and long chain ceramides. Below the SC is the viable epidermis (50–100 μm), which has an important function of regeneration of the SC [7].

The stratum corneum barrier function is not only dependent on one single component but also on its total architecture, described by Elias as the "bricks and mortar" model where the bricks are the corneocytes and the mortar refers to the lipid rich matrix (Fig. 1) [8].

The nucleated epidermis also contributes to the barrier through tight, gap and adherent junctions, as well as through desmosomes and cytoskeletal elements. During epidermal differentiation, lipids are synthesized in the keratinocytes and extruded into the extracellular domains, where they form extracellular lipid-enriched layers. The cornified cell envelope, a tough protein/lipid polymer structure, resides below the cytoplasmic membrane on the exterior of the corneocytes. Ceramides A and B are covalently bound to cornified envelope proteins and form the backbone for the subsequent addition of free ceramides, free fatty acids, and cholesterol in the lipid matrix of the SC. The lipids are organized as multiple lipid bilayers, which form regions of semi-crystalline gel and liquid crystals domains [7].

The dermis (1–2 mm) is directly alongside the viable epidermis and provides the mechanical properties of the skin. The dermis is made up of collagen, elastins and glycosaminoglycans, collectively called the extracellular matrix, as well as fibroblasts that extend the extracellular matrix. The highly vascularized dermis also contains the pilo-sebaceous glands, sweat glands, dermal adipose cells, mast cells and infiltrating leucocytes [9].

1.3. Percutaneous absorption

Dermal and transdermal drug delivery requires efficient penetration of active compounds through the skin barrier basically by a passive diffusion process. A molecule applied on the skin surface may use two diffusional routes to penetrate: the transappendageal and the transepidermal routes (Fig. 1). The transappendageal route includes transport via the skin shunts, i.e. sweat glands and hair follicles with associated sebaceous glands. Although these routes were traditionally considered of minor importance because of their relatively small area (0.1–1%), recent research has indicated that the pilo-sebaceous units may contribute significantly to topical drug delivery by acting as low resistance pathway for nanoparticles to enter the stratum corneum [10,11]. As known, this route has also been considered as potential transport route for ions and large polar molecules [7]. Moreover, the relative surface area of the shunts may be of greater significance in areas of the body such as the scalp, where the density and size of hair follicles are much greater than in other location on the skin such as on the back [12]. In addition, the hair follicles and sebaceous glands are associated with various dermatological disorders such as acne, alopecia, and several skin tumours. Therefore, there is a great interest in the pilo-sebaceous units as targets for localized drug delivery, as well as shunts for transdermal delivery, even if the specific role of the