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Broad overview of engineering of functional nanosystems for skin delivery

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ABSTRACT

Nanotechnology involves the engineering of functional systems at nanoscale and it can be described as a collection of methods and techniques for processing materials to create products with special physicochemical properties. The rapid developments in nanotechnology have allowed the incorporation of therapeutic agents, actives for cosmetic, sensing agents into nanoparticles, for detection, prevention, and treatment of skin diseases. Nanoparticles promote the increase of penetration of drugs and many cosmetic chemicals across the skin. Nanoparticles offer many advantages as carrier systems since they can improve the solubility of poorly water-soluble drugs or actives such as phytocompounds, permeate the skin through different mechanisms, modify drug or actives pharmacokinetic and ultimately, improve their bioavailability. In this review, we discuss the recent advances of different types of nanoparticles for skin delivery over a period of 40 years. This review emphasizes approaches to overcome the drawbacks and limitations associated with the conventional systems and the advances and application that are poised to further enhance the efficacy of topical formulations with nanoparticles, offering the possibility of simplified dosing regimen that may improve treatment outcomes using these novel delivery nanosystems.

1. Introduction

The skin structure can be divided in three functional layers: epidermis (the outermost layer of skin) which is a stratified squamous keratinizing epithelial tissue that can be divided in *Stratum corneum* (SC), *Stratum granulosum* (SG), *Stratum spinosum* (SS) and *Stratum basale* (SB), from the exterior to the interior (Liuzzi et al., 2016); dermis and hypodermis (Fig. 1) (Bahamonde-Norambuena et al., 2015; Wickett and Visscher, 2006). In addition, in epidermis layer of the palms and soles there is another very thick layer called the *Stratum lucidum* (SL). The general structure of epidermis is represented in Fig. 1. SC is formed by nonviable corneocytes also named keratinized cells (Rajagopalan et al., 2016; Uchechi et al., 2014; Yukuyama et al., 2016). The keratinized cells contain neutral lipids (as cholesterol), ceramides and fatty acids (linoleic acid) playing an important role in the barrier function (Bahamonde-Norambuena et al., 2015; Liuzzi et al., 2016; Yukuyama et al., 2016). An important function of this stratum is to prevent water loss from deeper skin layers, which provide a softer skin surface under different atmospheric conditions (Liuzzi et al., 2016). Therefore, when water content decreases below a critical level desquamation of corneocytes occurs (Liuzzi et al., 2016). The cells on epidermis are keratinocytes (95%), Langerhans cells, melanocytes and Merkel cells (Ita, 2016).

Keratinocytes are also keratinized cells which migrate from the SB to the skin surface, by proliferation, differentiation and keratinization processes (Hirobe, 2014; Walters, 2002; Liliana and Sousa, 2008). They are columnar, cuboidal and mitotically active cells with a diameter of 6–8 μm (Hirobe, 2014; Walters, 2002). Some studies revealed that keratinocytes present acetylcholinesterases, which are responsible for the attachment of these cells (Grando et al., 1993; Walters, 2002).

The SL present several layers of flattened and compacted keratinocytes devoided of nuclei and cytoplasmatic organelles, being suggested that it was the skin's barrier layer responsible to the penetration of both ions and uncharged molecules (Walters, 2002).

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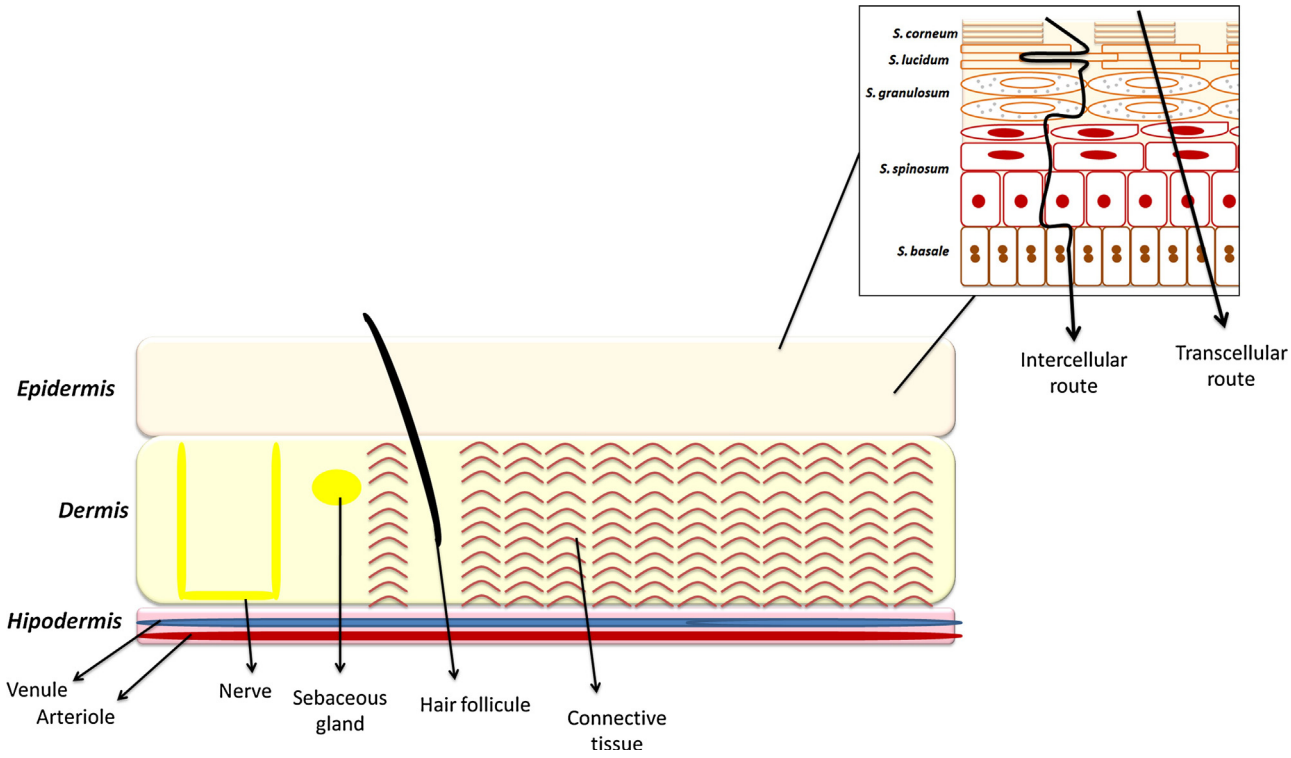

Fig. 1. Schematic representation of the general structure of the skin and, in detail, the structure of epidermis with intercellular and transcellular routes.

The SG is composed by 3–5 layers of keratinocytes and it consists in precursors of the SC intercellular lipids (phospholipids, cholesterol and glucosylceramides) (Bouwstra et al., 2002; Walters, 2002). Here, the Odland bodies which are flattened shape and lamellar bodies rich in lipids migrate to the cell membrane and in the interface between the SG and the SC. Then, it occurs fusion with the cytoplasmatic membrane and extrude their content into the intercellular space (Liliana and Sousa, 2008; Riviere and Monteiro-Riviere, 2005). When Odland bodies release the lipids, phospholipids are broken by co-secreted enzymes, converting the glucosylceramides to ceramides (Walters, 2002). Keratinocytes in SG are flattened and exhibit keratohyalin granules, that have profilaggrin (a precursor of filaggrin, which is responsible for aggregation, and alignment of keratin filaments). During the process of keratinization of the cells, proteins, lipids and the flatten cells are synthesized in the SC and this process generally takes 1 month (Walters, 2002). Langerhans cells, located in the SG, are dendritic immune cells with an important role in the immunological defense (Ita, 2016).

The SS is the largest layer in the epidermis. It is composed by several layers of irregular polyhedral keratinocytes with larger cytoplasm attached by desmosomes and Odland bodies (Riviere and Monteiro-Riviere, 2005).

The SB present melanocytes, Merkel cells and a single layer of keratinocytes (Liuzzi et al., 2016). Those cells are connected by desmosomes and by hemidesmosomes (to the basement membrane) (Walters, 2002). These keratinocytes present an expression of T-cadherin (Buechner et al., 2016). T-cadherin is a glycosyl-phosphatidylinositol-anchored member of the cadherin superfamily of adhesion molecules (Buechner et al., 2016). Moreover, the majority of the basal cells are stem cells (they present a large nucleus, cells organelles and tonofilaments – with keratin filaments), being responsible for the renewal of the cells in the epidermis (Walters, 2002; Scott and Banga, 2015). The desquamation of the epidermis occurs every 26–42 days (Scott and Banga, 2015). On the other hand, melanocytes are dendritic cells which are responsible for the production of melanin (by the melanosomes), mainly under exposition of ultraviolet (UV) rays (Riviere and Monteiro-Riviere, 2005). Cells have the ability to absorb and diffract this radiation (Riviere and Monteiro-Riviere, 2005). Merkel cells are tactile epithelioid cells associated with nerve endings (Riviere and Monteiro-Riviere, 2005).

Dermis is the principal structural support and mechanical barrier of the skin (Bahamonde-Norambuena et al., 2015). This layer is a matrix of dense irregular connective tissue, composed by collagen, elastin and reticular fibers in an amorphous ground substance of mucopolysaccharides (Bahamonde-Norambuena et al., 2015; Scott and Banga, 2015). Collagen is responsible of the durability and the regenerative properties of the skin. When this compound is below the normal concentration wrinkles and scarring appear (Scott and Banga, 2015). The principal cells in dermis are fibroblasts (FBs), also including dendritic (DCs) and mast cells (MCs) (Ita, 2016). Fibroblasts produce the compounds of the connective tissue while mast cells and macrophages are related to the immune and inflammatory responses (Walters, 2002). This layer also includes an extensive blood and lymphatic capillary network, sensory nerve endings, hair follicles, sweat glands and sebaceous glands (Bahamonde-Norambuena et al., 2015).

Sebaceous glands are responsible for the production of sebum (acidic mantle) that protect the skin and regulate the skin's pH ($pH \approx 5$) (Walters, 2002; Riviere and Monteiro-Riviere, 2005). Acidic mantle is a mixture of lipids presenting bacteriostatic and fungistatic activities (Riviere and Monteiro-Riviere, 2005). These glands also express T-cadherin as demonstrated in a recent study (Buechner et al., 2016). The T-cadherin is an atypical glycosyl phosphatidylinositol-anchored member of the cadherin superfamily (Buechner et al., 2016). Cadherins are transmembranar proteins which mediate the calcium-dependent intercellular adhesion. Members examples are E-cadherin (major type in the skin), T-cadherin, P-cadherin (Buechner et al., 2016). T-cadherins in