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Overcoming the barrier of skin to drug permeation for localized dermatological therapies

Bozena Michniak-Kohn
Center for Dermal Research, Rutgers-The State University of New Jersey, Piscataway, NJ, USA
Laboratory for Drug Delivery, Rutgers-The State University of New Jersey, Piscataway, NJ, USA
Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, Piscataway, NJ, USA
https://orcid.org/0000-0002-3858-158X
Corresponding author: michniak@pharmacy.rutgers.edu

Joachim Kohn
Rutgers-The State University of New Jersey
BMK Scientific Consulting, Inc. Piscataway, NJ, USA
https://orcid.org/0000-0002-5834-6536

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ABSTRACT

The skin's uppermost layer, the stratum corneum is a very effective barrier against the penetration of compounds including pharmaceuticals and cosmetic actives. To deliver higher amounts of drugs into the skin layers or to deliver drugs deeper into the skin (e.g., into the dermis), several enhancement techniques have been established. These techniques include chemical penetration enhancers as well as physical techniques such as iontophoresis and microneedles. In addition, one of the newer approaches includes the use of nano-based carriers such as metallic nanoparticles and polymeric self-assembling nanospheres.

This mini-review explores this new approach of using nano-based drug carriers for skin penetration enhancement. In particular we will explore the use of gold nanoparticles as well as biocompatible tyrosine-derived polymeric nanoparticles known as Tyrospheres.

The most investigated carriers in the class of metallic carriers are gold nanoparticles that can be used for both medical as well as diagnostic uses. Many investigators have reported that gold nanoparticles are able to enhance the skin transport and delivery of *macromolecular and hydrophilic drugs*. Meanwhile, for challenging *highly lipophilic and/or unstable compounds* such as adapalene and Vitamin D3 packaging them into polymeric nanocarriers such as Tyrospheres enables drug delivery to hair follicles, significantly increased aqueous solubility and resulted in elevated amounts of drug in targeted skin layers.

The relatively new approach of using nanotechnological approaches as a way of enhancement of drug delivery to skin shows significant promise over some other established techniques such as the addition of chemical penetration enhancers to formulations used for topical/transdermal uses.

Introduction

The skin consists of several layers which include (from top downwards into the body): the epidermis, dermis and hypodermis. By the mid 1800s scientists were aware that the top layer of the skin (consisting of the stratum corneum, stratum granulosum, stratum spinosum, and stratum

basale) was more impermeable to penetration of compounds than the lower layer (dermis) and by early 1900s we knew that skin was more permeable to lipophilic compounds than hydrophilic ones.

As electron microscopy techniques improved, scientists were able to to finally recognize the existence of a thin acellular layer 10–15 microns thick on top of the skin-this was the stratum corneum. By the 1940s scientists realized that this rather thin and potentially fragile topmost layer of the skin was freely permeable to water and dissolved substances when the stratum corneum (SC) was removed by sand-papering. Finally, scientists have realized that this layer cannot be regarded as totally "dead" and was an important tissue made up of sturdy anucleated cells named corneocytes, that are composed of lipids, water and proteins. These cornecytes produced a well-organized lipid structure which provides the barrier function to the skin. This layer can protect the body from potentially harmful external stimuli- microorganisms, chemical compounds, radiation, heat, electrical barrier, mechanical shock.

This article summarizes selected approaches to overcoming the barrier of skin to the penetration of drugs using skin penetration strategies including the use of nanotechnology systems that enhance transport of actives through the skin barrier.

Nanotechnology systems which enhance drug transport into skin

To overcome the barrier properties of the stratum corneum of the skin, nanocarrier mediated drug delivery systems have been utilized successfully in many cases and provide an alternative to the more traditional chemical and physical approaches [1, 2]. The older strategies utilize chemical penetration enhancers (CPEs) such as surfactants, laurocapram-derivatives, terpenes, cyclodextrins and others as well as physical approaches such as iontophoresis, sonophoresis and others [3–5]. However, some of these methods do produce skin sensitization and sometimes irritation in a segment of the patient population [6]. In recent years alternative enhancement methods have been extensively explored and include utilizing various nanotechnology-based systems. They have been proposed as formulations for both pharmaceutical as well as cosmetic applications [7–11]. The main classes of these nano systems are: liposomes, nanoemulsions, lipid nanocapsules, metallic nanocarriers, solid lipid nanoparticles, polymeric nanoparticles/micelles and nanogels [2, 12]. For the purposes of this review we will consider a subset of these delivery systems and specifically, metallic nanocarriers as well as polymeric nanoparticles/micelles.

Metallic nanocarriers

Metallic nanoparticles have some advantages over other carriers in the fact that they are very stable, possess a narrow particle size, and the ability to have their surface functionalized. All these features make them attractive carriers for topical formulation uses [13, 14]. The most investigated carriers in this class are the gold nanoparticles for both medical as well as diagnostic uses [15, 16]. These gold particles have low toxicity, a large surface area for functionalization, can be fabricated in various shapes and possess sizes in the range of 1–100 nm.

It has been demonstrated that gold nanoparticles (GNs)are able to enhance the skin transport and delivery of *macromolecular and hydrophilic drugs*. For example, Safwat et al. showed that 5-fluorouracil was better delivered in GNs than controls into mouse skin resulting in an improved anti-cancer effect [17, 18]. The GNs were capped with cationic ligands which were able to load the negatively charged 5-fluorouracil under a pH of above 8.5 through the ionic interaction. Then the interaction with the positive charge of the nanocarrier and the skin may have been the main reason for the improved anti-cancer effects which were observed.

Koushki et al. used a dendritic cell -specific aptamer for the modification of allergen loaded GNs. These authors reported improved immunoregulation compared to non-targeted controls and even higher effects when skin penetrating peptides were also used [19]. GNs can also be combined with other nanomaterials and also with physical enhancement techniques such as iontophoresis and microneedles (hollow, coated or dissolvable) [2, 20].

Polymeric nanoparticles/ micelles

For the delivery of challenging drugs that possess very low aqueous solubility and are *highly lipophilic or are unstable* another skin delivery approach can be taken. This is one using the various polymeric nanoparticles/micelles and in the example below, specifically biocompatible tyrosine-derived polymeric nanoparticles known as Tyrospheres [21, 22]. The chemical structure of these copolymers is composed of hydrophobic B-block i.e., oligomers of desaminotyrosyl-tyrosine ester (DTR) and diacid and hydrophilic poly(ethylene glycol) (PEG) A-blocks. These PEG-*b*-oligo(DTR-XA)-*b*-PEG triblock copolymers undergo self-assembly in an aqueous environment to form polymeric micelles referred to as TyroSpheres. These were used by Ramezanli et al. to load adapalene, a lipophilic drug with a logP of 8.04 and low aqueous solubility for delivery into hair follicles for the treatment of acne [23]. It was found that the Tyrospheres were significantly more effective than controls in a clinical mouse acne model [24].

Vitamin D3 (VD3) is very hydrophobic (log P of 9) and sensitive to many environmental factors (e.g., moisture, heat and light), which can induce isomerization or oxidation of its structure and adversely affecting its bioactivity. VD3-TyroSpheres were fabricated by Ramezanli et al.and characterized for their size, binding and loading efficiencies, stability, drug release and permeation in human cadaver skin samples [25]. TyroSpheres were able to substantially enhance the aqueous solubility of VD3 without affecting its activity. These biocompatible nanocarriers form a protective layer around the lipophilic drug that can protect it against environmental-induced degradation. Moreover, the skin delivery efficiency of TyroSpheres was found to be higher than some other dermal penetration enhancers, such as Transcutol. This study provided evidence of TyroSpheres' significant potential for targeted delivery of hydrophobic actives to skin layers.

Conclusion

In conclusion this article provides examples of how nanocarrier-mediated approaches as illustrated by gold nanoparticles and polymeric nanospheres (Tyrospheres) are able to provide enhanced transport of various challenging compounds past the skin barrier stratum corneum and into the skin layers below. The applications are broad for hydrophilic and lipophilic compounds in both the pharmaceutical as well as the cosmetic/personal care sectors.

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Conflict of interest statement
Professor Dr. Bozena B. Michniak-Kohn is a full-time employee of Rutgers, the State University of New Jersey, Piscataway, NJ 08854, USA. The author declares no conflict of interest. Joachim Kohn declares no conflict of interest.

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Author contributions
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