Journal of Controlled Release 247 (2017) 86–105

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Topical and cutaneous delivery using nanosystems

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ARTICLE INFO

Article history:
Received 27 August 2016
Accepted 20 December 2016
Available online 23 December 2016

Keywords:
Topical delivery
Cutaneous delivery
Nanosystems
Nanoparticles
Colloidal nanocarrier systems

ABSTRACT

The goal of topical and cutaneous delivery is to deliver therapeutic and other substances to a desired target site in the skin at appropriate doses to achieve a safe and efficacious outcome.
Normally, however, when the stratum corneum is intact and the skin barrier is uncompromised, this is limited to molecules that are relatively lipophilic, small and uncharged, thereby excluding many potentially useful therapeutic peptides, proteins, vaccines, gene fragments or drug-carrying particles. In this review we will describe how nanosystems are being increasingly exploited for topical and cutaneous delivery, particularly for these previously difficult substances. This is also being driven by the development of novel technologies, which include minimally invasive delivery systems and more precise fabrication techniques. While there is a vast array of nanosystems under development and many undergoing advanced clinical trials, relatively few have achieved full translation to clinical practice. This slow uptake may be due, in part, to the need for a rigorous demonstration of safety in these new nanotechnologies. Some of the safety aspects associated with nanosystems will be considered in this review.

Contents

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http://dx.doi.org/10.1016/j.jconrel.2016.12.022
0168-3659/

1. Introduction

There has been great interest in nanosystem facilitated delivery of therapeutic, diagnostic, prophylactic or cosmetic substances into the skin, in which the goal is to overcome the skin barrier in a controlled manner to reach targets in various skin layers, including the stratum corneum, as well as deeper tissues, or systemically. On the other hand, nanomaterials are also applied directly to the skin, for example, when titanium or zinc oxide is used as sunscreens. Here, the intention is not to penetrate the stratum corneum, but to deliver the nanomaterials so that they remain on the skin surface. In this review, we will examine some of the various nanosystems currently in use, with particular reference to their ability to penetrate the skin barrier. Table 1 summarises the scope of the field of topical and cutaneous delivery using nanosystems and Table 2 gives a more detailed summary of the properties of some of the nanodelivery systems to be discussed later in this review. The range of particulate nanosystems under investigation is illustrated in Fig. 1. Some of the applications of topically applied nanodelivery systems for treatment of skin disorders are listed in Table 3.

2. The stratum corneum barrier problem

The skin plays a major role in protecting the body from the surrounding environment by providing a highly efficient barrier to the penetration of exogenous molecules and micro-organisms, and maintaining homeostasis by preventing excessive loss of water [38]. A simplified representation of human skin containing its major structures and cell types is illustrated in Fig. 2. Although the location of the barrier within the skin was long debated, Scheuplein showed conclusively in 1966 that it largely resided in the stratum corneum [39], due to its unique structure, most simply described as a series of layers of flattened corneocytes surrounded by a lipid envelope. The most likely route taken by a substance in penetrating the stratum corneum is *via* a tortuous pathway through the lipids surrounding the corneocytes (intercellular route) [40], although the transcellular route though the corneocytes may be viable under certain circumstances [41]. The stratum corneum is also traversed by pilosebaceous units (hair follicles and associated sebaceous glands) and sweat glands. While the average follicular orifice area on the human skin surface is only about 0.1% of the total surface area [42], under some circumstances these appendages may be potential routes of entry into the skin [43], as we shall discuss later.

Table 1
Scope of the field of topical and cutaneous delivery using nanosystems.

Nanosystem use	Dermatologicals, vaccines, diagnostic agents, cosmetics
Target sites	Surface, Skin, Systemic
Product range	Nanoparticles, nanoemulsions, nanovesicles
Chemical adjuncts	Formulation enhancers, Skin pretreatment
Physical adjuncts	Electrical, sound, electromagnetic, physical, other technologies
Efficacy	Able to facilitate cargo penetrating in sufficient quantities?
Safety	Major area of concern from regulators and consumers

The fundamental question facing those who seek to develop formulations for topical or transdermal delivery is; how can a particular active be made to overcome the formidable stratum corneum barrier, so that it can be delivered to the site of action in sufficient quantities to achieve a desired therapeutic effect, with the least possible adverse effects? The range of substances that are suitable for diffusion through the stratum corneum is generally limited to those that are relatively small (<~500 Da), lipophilic (log 1–3) and water soluble [44]. Given the generally low permeation rates for most molecules, they must also be highly potent [45]. Clearly, there is a vast array of attractive prospects for topical application such as peptides, proteins, vaccines, nucleotide fragments or powerful cancer therapeutics that do not fit these criteria. This dilemma has been a major factor in the interest in nanodelivery systems that could expand the range of active molecules that are available for therapeutic or other purposes.

3. Solid nanoparticles (NPs)

In the early 1900s, Ehrlich introduced the concept of drug targeting using a delivery system he called '*Zauberkugeln*' (Magic Bullets) [46]. This was put into practice in the 1950s and 1960s with the development of miniaturised delivery systems, focusing initially on polyacrylic beads for oral delivery, with the first nanoparticles for vaccination purposes appearing in the late 1960s [47]. By 1978, the field was sufficiently advanced for the first review article on nanoparticles as new drug delivery systems to be published [48]. In 1994, nanoparticles were defined for pharmaceutical purposes in the Encyclopaedia of Pharmaceutical Technology as "solid colloidal particles ranging in size from 1 to 1000 nm. They consist of macromolecular materials and can be used therapeutically as drug carriers, in which the active principle (drug or biologically active material) is dissolved, entrapped, or encapsulated, or to which the active principle is adsorbed or attached" [49]. Later developments saw the use of nanoparticles for intravenous cancer therapy, with Brasseur et al. reporting an enhanced efficacy of actinomycin D absorbed on polymethylcyanoacrylate nanoparticles against an experimental subcutaneous sarcoma [50], taking advantage of their enhanced permeability and retention effects [51]. The first commercial nanoparticle product containing a drug appeared on the US market in 2005. This contained an injectable suspension of human serum albumin nanoparticles containing paclitaxel (Abraxane®, Abraxis BioScience, now Celgene Corporation, Los Angeles, CA, USA) and was indicated for the treatment of metastatic breast cancer [52].

The first reported topical applications of nanoparticles were to the eye, when Li et al. treated albino rabbits with polymeric nanoparticles encapsulating progesterone in 1986 [53]. However, it was not until the end of the 20th century that reports on the application of nanoparticles to skin for vaccination [54] and vitamin A delivery [55] appeared in the literature. In the short time since, the topical application of a range of nanomaterials has been investigated. Of interest in this review are such materials as quantum dots, metal particles (gold, silver and beryllium), metal oxides (TiO_2, ZnO, carbon nanotubes and organic fullerene derivatives [1,56–64]. These are relevant because, as we have already seen, nanosystems are not only potential drug delivery vectors, but some have also been suspected of causing harmful effects on the skin. For instance, it has been proposed that surface-coated quantum dots could be used to carry drugs into the skin [65]. Similarly, drug-coated particles could be targeted to appendages such as hair follicles, where their payloads could be released slowly into local sites or into the systemic circulation [66]. Conversely, the unwanted penetration of