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Review article

Dermal and transdermal delivery of pharmaceutically relevant macromolecules

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ABSTRACT

The skin offers an attractive way for dermal and transdermal drug delivery that is why the drug still needs certain qualities to transcend the outermost layer of the skin, the stratum corneum. The requirements are: drugs with a maximum molecular weight of 1 kDa, high lipophilicity and a certain polarity. This would restrict the use of a transdermal delivery of macromolecules, which would make the drug more effective in therapeutic administration.

Various studies have shown that macromolecules without support do not penetrate the human skin. This effect can be achieved using physical and chemical methods, as well as biological peptides.

The most popular physical method is the use of microneedles to create micropores in the skin and release the active agent in different sections. But also, other methods have been tested. Microjets, lasers, electroporation, sonophoresis and iontophoresis are also promising methods to successfully deliver dermal and transdermal macromolecules. Additionally, there are different penetration enhancer groups and biological peptides, which are also considered to be interesting approaches of enabling macromolecules to travel along the skin.

All these methods will be described and evaluated in this review article.

Contents

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1. Introduction

The skin is the largest organ in the human body [1,2] and performs a lot of physiological functions. It operates as a barrier to microorganisms, toxins, ultraviolet radiation, it is an active organ of metabolism, sensation, temperature regulation and immunology and it prevents human beings from water and electrolyte loss [3]. Skin offers a painless and compliant interface for topical and systemic drug administration [3]. The main barrier of the skin is the outermost layer, the Stratum corneum (SC) [4], which has to be overcome in dermal and transdermal drug delivery. The requirements for these types of drug delivery are: small drug molecules with a maximum molecular weight of >1 kDa and a high lipophilicity. Therefore, SC is a particularly decisive barrier when it comes to the administration of pharmaceutically relevant macromolecules. The dermal and transdermal delivery of these macromolecules is highly challenging for dermato-pharmaceuticals.

Drug delivery can involve various approaches, formulations, technologies and systems for the transport of a pharmaceutical compound in the body which would result in the safe onset of the therapeutic effect [5].

Transdermal drug delivery is an attractive alternative to oral administration or by injection [6–9]. It has an advantage over oral applications because it bypasses the gastrointestinal tract and avoids the first-pass side-effect. Dermal applications also have advantages over injections, because they are painless and can be self-administered.

In particular, the challenge is the dermal administration of appropriate macromolecules such as heparin (for example used in pain relieve ointment), hyaluronic acid (for example as a filler or as vehicle for dermal drug delivery [10]) and vaccines [11,12] There is still no direct evidence that heparin and hyaluronic acid derivatives penetrate the skin from semisolid formulations.

Transdermal drug delivery has been in clinical use since 1981 [13]. One benefit is that the drug release can be extended over a longer period, sometimes hours or even days. The skin works as a drug reservoir while minimizing gastrointestinal incompatibility and potential toxicological risk [14].

After nearly four decades of extensive study, the success of this method of administration is still sporadic, with only a few transdermal formulas available on the market, all of which are based on low molecular weight lipophilic drugs [16] (see Fig. 1).

The development of dermal and transdermal products for macromolecules is hindered by the low skin permeability of the macromolecules. It has succeeded in overcoming these challenges due to advances in physical and chemical technologies [17], such as sonophoresis, lasers, chemical penetration enhancers, etc.

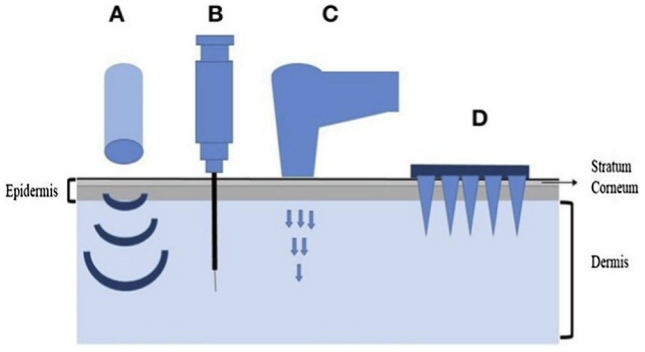

Fig. 1. Delivery methods (A) Sonophoresis, (B) Intradermal Injection, (C) Microjet injection, (D) Microneedle patch [15].

2. Physical methods

2.1. Microneedles

One of the most published physical methods involves the penetration of macromolecules and vaccines by using microneedles (MNs). Various studies used different MN types for their experiments.

In a review from 2003, Prausnitz [18] published the different kinds of MNs. They distinguished solid MNs from hollow MNs and described the differences between their delivery mechanisms. Hollow MNs operate on a "poke and flow" principle [19] and give the option of transporting drugs through the interior of well-defined needles by diffusion or by pressure-driven flow [18]. Solid MNs function according to different principles. They work with the "poke and patch", "poke and release", "coat and poke" or the "dip and scrape" concepts [18,19] which can be used for a wide range of applications (see Fig. 2).

Andar et al. [20] used the poke and patch delivery mechanism. They compared the enhanced permeation after MN-treatment and untreated skin, in *vitro* and reported a MN-assisted transdermal delivery of Gas vesicle nanoparticles (range of ~200–400 nm).

Davidson et al. [13] coated the MN with a drug solution which included Insulin (5.8 kDa) as a model drug. They investigated how the geometry of MNs affects the level of permeability in skin and the magnitude by bypassing the SC. They examined both penetration depth and center-to-center spacing and declared them as the most significant factors. In general, larger, longer and more densely packed MNs resulted in greater skin permeability (see Tables 1 and 2).

Li et al. [21] created a treatment of maltose MNs to create microchannels for human IgG (150 kDa) as model molecules. Therefore, the authors examined various things like the needle length, the number of needles and the effect of donor concentration. The ability of the needles to dissolve in the skin upon insertion, was noteworthy because they created micro-scale conduits for the percutaneous transport of macromolecules (see Figs. 3–5).

Demir et al. [22] analysed the delivery of macromolecules using disposable polymeric (sodiumalginate) MNs. This method offered the possibility to lower the risk of biohazardous sharps and cross contamination. The model drug was bovine serum albumin (66 kDa).

Donelly et al. [23] studied the mechanical properties of MNs prepared from a hydrogel-forming formula and the microneedle-deformation during the injection-process. They also used Insulin as model drug. They produced MNs swelled in skin to produce continuous, unblockable conduits from patch-type drug reservoirs to the dermal microcirculation, this allowed prolonged transdermal drug administration.

Pierre et al. [24] devised a schedule on the possibility of intradermal delivery using MNs, their geometry, length and materials (silicon, polymers, metal, glass). They examined both coated and uncoated MNs with a wide range of drug molecules (insulin among others) with a low oral bioavailability which benefited of their technology. The simple self-application of MNs, the lack of pain and the possibility of a controlled release of drugs all favour patients' compliance in the tests.

Banks et al. [25] also used a solid MN with the poke and patch principle. They tested whether non-specific COX inhibition (diclofenac) could extend pore lifetime in hairless guinea pigs following MN treatment. They concluded, that it is an effective method of extending pore lifetime and may have clinical implications, for example increasing patients' compliance with therapy.

Vaccination is another field of usage for MNs. In a review from 2015 Arya et al. [27] summarized the vaccination challenges and