Recent studies on increasing transdermal delivery systems of skin medicinal products

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Abstract. The last decade has shown a growing interest in the topical use of natural substances, as an alternative to oral or systemic therapy, being proposed and investigated various classical and modern release systems capable of transporting and releasing the active substance more efficiently, thus optimizing its action therapeutic. Transdermic administration is an attractive alternative that reduce the oral administration of drugs or hypodermic injections. The biggest challenge for transdermic delivery systems is that only a limited number of drugs can be administered this way. Using current methods of administration, approved transdermic drugs have molecular weights that are close to several hundred Daltons, exposing the octanol-water partition coefficients that promote lipid formation, which requires the application of milligram doses per day. For more than a decade, research into the percutaneous pathway to facilitate hydrophilic absorption of drugs has been particularly difficult, and transdermic absorption of peptides and macromolecules, including the new genetic treatment using low-interference DNA or RNA, has created huge challenges. In this regard, this article highlights the progress of world medicine for different approaches to formulations, such as: iontophoresis, electroporation, thermal ablation, microneedles, non-cavitative ultrasound, microdermabrasion, the use of combinations of chemicals to enhance skin absorption and so on, in order to improve the skin penetration of topical pharmaceutical forms.

1.   Introduction

The last decade has seen an increased interest in the topical use of natural substances as an alternative to oral or systemic therapy, with various classical and modern delivery systems being proposed and investigated, capable of transporting and releasing the active substance more efficiently, thus optimising its therapeutic action.

Transdermal administration is an attractive alternative that attempts to reduce the need for oral administration of drugs or hypodermic injections [1]. For thousands of years, humans have applied substances with therapeutic effects to the skin and nowadays modern transdermal solutions have been developed. The first transdermic system came in the form of a three-day

patch that delivered the amount of scopolamine needed to address vestibular disorders and has been approved for use in the United States since 1979 [2]. Ten years later, the success of the nicotine patch in transdermic application has greatly increased the prestige of the transdermal drug delivery process in medicine and the media. There are currently 19 systems used for percutaneous delivery drugs such as fentanyl, lidocaine, estradiol and testosterone; combination systems with more than one contraceptive and hormone replacement drugs; iontophoresis for pain relief therapy and ultrasound delivery systems. From 1979 to 2002, a new patch was authorized every 2 years on average. Between 2003-2007, this rate has tripled as a new transdermic drug delivery system is created every 7 months.

Transdermal administration has many advantages over oral administration. It is mainly used to protect the liver against premature drug metabolism. Transdermal administration also has important advantages over subcutaneous injections, which causes pain, produces medical waste, and carry a risk of transmitting diseases (especially in developing countries) from reused needles. Furthermore, transdermic systems are non-invasive and can be administered without medical intervention. They can be delivered long term (more than a week) and they also improve patient compliance and are generally less expensive.

Transdermal absorption is a complex process influenced by a large number of factors that depend on the nature of the active substance and the pharmaceutical formulation used in topical administration. One biggest challenge for transdermal delivery systems is that only a limited number of medicines can be administered by this route. Using current delivery methods, approved percutaneous drugs have molecular weights approaching hundreds of Daltons and exhibit octanol-water partition coefficients that favor lipid formation, requiring milligram doses per day. The study of transdermal routes to facilitate hydrophilic drug delivery has been a particular challenge, and transdermic transport of macromolecules and peptides, including new gene therapies using low-interfering DNA or RNA, has led to impressive challenge [3].

From a global perspective, the development of transdermal drug delivery systems is divided into three generations. The first-generation systems that gave rise to most patches today were carefully selected drugs that penetrate the skin in small or negligible amounts at therapeutic rates. The second generation further advances small molecule drug delivery by increasing skin permeability and the driving force for transdermic pharmaceutical preparations transport. The third generation allows for the percutaneous delivery of small-molecule drugs, macromolecules and virus-based vaccines [4], designed to penetrate the stratum corneum of the skin.

In this regard, this article highlights the progress of world medicine for different formulation approaches such as: iontophoresis, electroporation, thermal ablation, non-cavitational ultrasound, use of combinations of skin-enhancing chemicals, use of microacoustics and so on, with the aim of improving skin penetration of topically applied pharmaceutical formulations.

2. First generation transdermic transport systems

First-generation of transdermic drug transport systems account for the majority of clinically used transdermal patches. Significant advancements in patch technology and public acceptance have enabled the near-term growth in the market for first-generation transdermic patches. However, the rate of growth is steadily declining due to the practice of systems that have been exhausted. The next study is based on a new generation of small molecular weight, lipophilic and low dose effective patches. In general, their transdermic administration should be more efficient than oral administration due to their lower oral bioavailability. The first

generation of transdermic transport methods were primarily limited by the barrier, the outer layer of the skin, the stratum corneum, which is 10 to 20 μm thick. Another variation from traditional transdermic patches in first-generation systems is the application of a liquid spray or gel to the skin, which, through evaporation or absorption, can produce small lipophilic substances in the stratum corneum [5]. For example, testosterone gels have been used for many years, and transdermal estradiol sprays are also approved for use.

3.   Second generation of transdemic transport systems

Second-generation of transdermic drug transport systems demonstrate the need for improved skin permeability to diversify drug delivery. The ideal indicator is to increase skin solubility by reversibly disrupting the structure of the stratum corneum and providing a driving force for transport across the skin, while avoiding damage to internal tissues. However, traditional chemical amplification methods, iontophoresis and non-cavitational ultrasound, have encountered difficulties in achieving a balance between increased delivery to the stratum corneum and protection of deeper tissues. Thus, second-generation transport systems have achieved clinical breakthroughs by improving the transport of small molecules for dermatological, cosmetic, or other systemic applications, but with minimal impact on delivery of macromolecules [1], [2], [3].

4.   Third generation transdermic transport systems

Third-generation of transdermic drug transport systems is expected to have a major impact on drug delivery. This orientation allows for a stronger impact on the stratum corneum barrier, and therefore more efficient transdermal delivery, while protecting deeper tissues. In this way, new chemical enhancements, electroporation, ultrasonic cavitation and, more recently, microneedling, thermal ablation or microdermabrasion [6] have been shown to be effective in the formation of macromolecules in human clinical settings, including vaccines and therapeutic protein. These advances are made possible by the emergence of new techniques for localising action in the stratum corneum and the recognition that the safety offered by this localisation is capable of transforming these aggressive approaches into medically acceptable ones.

5.   Improved transdermal transport of active substances

Given the need to increase skin permeability, second-generation transport strategies have been directed towards the development of indicator chemical substances [7]. This approach is logical in expanding the traditional pharmaceutical instruments, as the main focus is on designing new formulations of chemical excipients. Many powerful chemical agents disrupt the highly structured intracellular lipid formation found in the stratum corneum. Inserting amphiphilic molecules into these bilayers disrupts molecular packing, and extraction of lipids with solvents or surfactants creates size packing defects in lipid nanoparticles. Liposomes, dendrimers, and microemulsions [8] have also been used as chemical potentate for supramolecular structures, which can not only increase skin permeability but also increase solubilization for drug absorption. The supramolecular size generally prevents their penetration into the skin, thereby localizing the action to the stratum corneum. These approaches have successfully improved the delivery of small molecule products, especially for dermatological and topical cosmetic applications. A new formulation that improves liposome deformation is currently undergoing clinical trials for insulin delivery. Another transdermic delivery method that has been used is the use of prodrugs [9]. The addition of cleavable chemical groups that increase the lipophilicity of the drug can facilitate drug transfer on the skin. One prodrug

approach is based on the linking of two drugs of similar or different small molecular sizes, where linking reduces their hydrophilicity, but at the expense of increasing their molecular weight. Because the prodrug's approach is based on changing the structure of the drug and not the structure of the skin, the prodrug can avoid skin irritation. Progress in this area has been hampered by the complexity of designing small molecule prodrugs and also by the need for prodrug approval as a new chemical entity by the US Food and Drug Administration (FDA).

5.1. Iontophoresis. Iontophoresis has, for more than a hundred years, studied the enhancement of the transdermic delivery system through the typical application of a low-voltage direct current [10]. In order to increase the permeability of the skin, iontophoresis uses an electrical driving force that promotes the transport of pharmaceutical preparations through the stratum corneum. Highly charged drugs move by electrophoresis, while weakly charged drugs can move by electroosmotic water flow generated by the preferential migration of mobile cations relative to fixed anions in the stratum corneum [11]. Because iontophoresis does not primarily alter the skin barrier, it is primarily suitable for small molecules that carry charges and large molecules up to several thousand Daltons.

5.2. Enhancement chemical combinations. Recent studies have shown that the use of appropriate combinations of chemical enhancers may lead to problems with the balance between enhancement and stimulation, based on the assumption that certain combinations of enhancers are particularly effective when present in specific formulations. This approach allows a targeting strategy that increases the permeability of the skin in the stratum corneum, avoiding irritation of deeper tissues where the composition becomes diluted or even altered. Researchers in the field are intensively investigating finding such experimentally rare combinations and therefore benefit from high performance screening. One such study was conducted examining nearly 500 pairs of different chemical stimulants formulated for more than 5000 compositions [12]. In this case an increase in permeability was identified but with low potential for skin irritation. The results of the in vitro screening were validated by in vivo administration of a peptide (leuprolide acetate) to hairless rats. It was shown that these combinations of chemical growth agents can enhance the delivery of macromolecules, whereas individual enhancers often fail [13].

5.3. Biochemical enhancers. More recently, peptides have been investigated as skin penetration enhancers, and a large class of peptides has been scanned. A synthetic peptide with 11 aminoacids has been revealed to contributes to the transdermal increase in insulin of diabetic rats [14]. Additionally, the analysis suggested an efficient transdermal pathway through hair follicles. Using the same method, cyclosporine was covalently attached to a cell-penetrating polyarginine-heptamer-peptide, leading to an increase in local absorption and inhibiting skin inflammation [15]. In these examples, through the chemistry of peptides, the high specific bioactivity allowed the delivery of drugs through the skin.

5.4. Electroporation. The practice of short high-voltage electrical pulses is known as a method of reversible disruption of cell membranes. Although electric fields measured in milliseconds during electroporation provide the electrophoretic driving force, electroporation diffusion can last up to hours, enhancing transdermal delivery of small drugs, vaccines, peptides and DNA. More recently, electroporation has highlighted a mouse skin peptide vaccine model that produces a strong cytotoxic T lymphocyte response [16]. The electric field applied during

electroporation initially targets the stratum corneum because its electrical resistance is higher than that of the deep tissue. However, after electroporation of the bilateral corneal lipid layers of the stratum corneum, the resistance dropped rapidly and the electric field was correspondingly more distributed to deeper tissues containing sensory and motor neurons. Although electroporation has been studied in animals, this approach to transdermic drug delivery in humans has been limited due to the complexity of ultrasonic cavitation device design.

5.5. Cavitation ultrasound. Concurrent to heating, ultrasonic waves generate cavitation and vibration, sometimes causing bubbles in the ultrasonic pressure field to collapse. Cavitation only occurs under certain conditions, unlike ultrasonic heating or imaging equipment. The possibility of transdermal drug delivery stems from the fact that cavitation bubbles concentrate ultrasound energy, allowing efficient targeting of the site of bubble activity [17]. Cavitation ultrasound is currently approved for enhanced transdermal delivery of lidocaine [18] and has been studied in animals for the transport of insulin, heparin, tetanus toxoid vaccines, and other compounds [17].

5.6. Microneedles. A simple way to permeabilize the stratum corneum is to penetrate inside it, using very short needles called microneedles. In the last decade, microneedles have been developed and used to introduce drugs into the skin using minimally invasive methods. The sturdy microneedles painlessly penetrate the skin, increasing the skin's permeability to a variety of small molecules, proteins, and nanoparticles, comparable to sustained-release patches. Alternatively, the drug is stored in microneedle capsules that can rapidly control the release of peptides, insulin or vaccines into the skin.

The design and construction of microneedles is currently in progress. Original manufacturing methods focus on low-cost production methods to obtain FDA-approved devices, metal and polymer microneedles, commonly found in other manufacturers. The surface of the microneedles was covered with various compounds, including proteins, small molecules, DNA and viral particles [20]. Microneedles are made from water-soluble polymers containing various compounds in the needle matrix. After a few minutes, these microneedles dissolve into the skin, leaving no medical waste behind after use.

Clinical animal trials have also been performed, demonstrating the release of parathyroid hormone from microneedles with covered surface [21]. At the same time, the delivery of vaccines using microneedles has been investigated. Animal studies have shown that live attenuated virus, inactivated virus and DNA vaccines, can be delivered for Japanese encephalitis, hepatitis B and anthrax using solid or open-hole microneedles.

5.7. Thermal ablation. Thermal ablation uses heat to selectively perforate the skin surface in the micrometer range. Instantaneous heating of the skin surface at temperatures of hundreds of degrees for durations ranging from microseconds to milliseconds, thereby transferring heat to the skin surface without spreading the temperature to the living tissue deep below [22]. This process protects the tissue from pain. Animal studies have demonstrated that thermal ablation can deliver many different compounds, such as human growth hormone and interferon a-2b [22], [23]. Skin heating is achieved using radio frequency heating products. Skin injury by producing microscopic holes caused by the thermal ablation procedure, was well tolerated.

5.8. Microdermabrasion. One way to disrupt the stratum corneum barrier is to use microdermabrasion or simply using abrasive paper. Microdermabrasion is a method of modifying and removing skin tissue for dermatological and cosmetic purposes. This abrasive mechanism associated with micron-scale blasting has been demonstrated increased skin permeability to drugs, including 5-fluorouracil [24], suggesting a potential application in the delivery of topically applied drugs.

5.9. Non-cavitational ultrasound. Ultrasound is recognized as a skin permeability enhancer when anti-inflammatory agents are massaged into the skin and, the use of ultrasonic heating can enhance the effect [25]. Ultrasound uses oscillating pressure waves at frequencies too high for the human ear to hear. Pressure gradients, along with ultrasound-related oscillations, act as a driving force to facilitate drug transfer into the skin, disrupt the structure of stratum corneum lipids, and increase permeability. The use of more aggressive non-cavitating ultrasound conditions is limited by heating associated tissues that do not target the stratum corneum and can affect deeper tissues.

6. Future perspectives and conclusions

Future prerspectives for first-generation of transdermic delivery systems technology will continue to provide small molecule drugs, especially those currently administered orally or by injection. Second-generation enhancer chemicals should be used as formulation excipients in the form of dermatological creams and ointments or systemic patches for small-molecule drugs. These issues have little impact on the delivery of drugs and hydrophilic macromolecules, as the most potent chemical stimulants diffuse through the stratum corneum, irritating deeper tissues. Advances in third-generation chemical enhancer combinations and their biochemical approaches offer strategies for better targeting, but are still in the research and development phase.

The second generation followed the physical improvement of the iontophoresis procedure, which now has an important clinical impact, especially for rapid and localised administration on the skin. Using electronic control of drug administration rates, iontophoresis has a special property, which can be an advantage through the possibility of patient-controlled dosing. Iontophoresis does not substantially overcome the influence of the skin barrier when administering macromolecular or vaccines, except in combination with other methods of increasing skin permeability. Also, in the context of physical therapies, non-cavitational ultrasound has been used for transdermal administration of anti-inflammatories, but appears to be unsuitable for delivery of large compounds.

The third generation brings physical enhancement through the use of cavitational ultrasound or electroporation, which allows transdermal delivery to result in nanoscale disruption of the stratum corneum. Cavitation ultrasound has been accepted for transdermic transport of lidocaine and may be authorized for peptides and other small molecules in the future. The effective application of cavitational ultrasound is limited by the need for complex devices to improve skin permeability at the nanoscale, and thus generally cannot be applied to macromolecule or vaccine delivery. Skin can also be disrupted, at the micron scale, through the physical use of third generation microneedles, thermal ablation or microdermabrasion. All these methods are subject to special clinical study, as they are capable of releasing not only small molecules, but also macromolecules or vaccines. Unpublished clinical results suggest that these methods may be safe and effective. A new type of microneedles, produced to deliver vaccines, is in regulatory approval for use in Europe, and new advanced clinical trials of microneedles and thermal ablation products are underway.

To increase the diffusion capacity of the drug, in the case of rapid administration, it is preferable to use microneedles with active action on macromolecules, combined with iontophoresis which creates an additional driving force. In general, transdermic drug transport offers a compelling opportunity to address the low bioavailability of oral drugs and the pain associated with injection. These technological advances can penetrate the stratum corneum of the skin while protecting deeper tissues, placing transdermal drug delivery methods in a leadership position for medical research.

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