

Transdermal Drug Delivery Systems Activated by Physical stimuli: Techniques and Applications

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Introduction

The delivery of drugs into and through the skin remains a challenge for pharmaceutical technologists. To overcome some drawbacks related to the administration of conventional pharmaceutical dosage forms, including the barrier of the stratum corneum, the transdermal delivery systems was emerged. Since the approval of the first scopolamine transdermal patch, indicated for the motion sickness, in 1979 by the U.S. Food and Drug Administration, the use of topical therapy has been successfully developed, not only for local effect (i.e. local delivery) but also for bloodstream access (i.e., transdermal delivery) [1]. Due to its large surface area and easy accessibility, the skin is used as a promising route for drug administration.

The present editorial gives an overview of the most significant transdermal delivery systems activated by physical stimuli, particularly its techniques, and elucidates about their relevant pharmaceutical applications. In these systems, the drug release can be activated and then modulated by different physical stimuli. However, such systems exhibit many pros and cons, therefore some combinations of techniques are being studied.

Iontophoresis

Iontophoresis is a noninvasive technique based on the application of a continuous low-intensity electric current, usually less than 1 mA, in order to facilitate the permeation of drugs through electrically charged biological membranes. A small potential difference (0.5 mA/cm² or less) is generated [2-4].

The iontophoresis process results in the repulsion of a charged drug loaded in a chamber with the same charge, while the chamber with opposite charge repels the drug through the skin, in the presence of an electric field. Electroosmosis and electromigration are the dominant forces involved in iontophoresis [5]. With the application of electric current, the drug is repelled through the skin and migrates to the place with the electrode of opposite charge, which may be located anywhere on the skin.

The iontophoresis technique can provide a systemic effect that is considered an interesting alternative to parenteral route. It also provides a local effect that can use in disease therapy of the most superficial tissues such as epidermis (e.g., *Herpes simplex* infections and psoriasis). Additionally, it is possible to remove substances with the application of the called reverse iontophoresis technique.

The reverse iontophoresis can be applied in the automatic glucose control of diabetic patients due to the possibility of glucose extraction to the skin surface. This technique may be used as supplement of the usual finger sting. The GlucoWatch[®], approved in 2001 by the FDA, is an example of a device that uses this technique [6]. In the reverse iontophoresis, glucose molecules in the plasma migrate to the skin surface and contact with the biosensor device. The glucose oxidase converts the glucose in gluconic acid. Glucose oxidase (reduced), in the presence of oxygen, forms hydrogen peroxide. The biosensor captures the hydrogen peroxide creating an electrical signal which is liable to be

quantified. Currently, this device is no longer produced due to its lack of efficiency.

Other example is the release of lidocaine by iontophoresis method for induction rapidly the anesthesia [7,8]. The company Vyteris[™], focused on the advantages of iontophoresis, developed a transdermal delivery system activated by iontophoresis, which is composed of an adhesive preloaded with two reservoirs (one with lidocaine and the other with a saline solution). The Vyteris smart patch system is associated with a battery and a microcomputer preprogrammed to control the electrical load. According to Vyteris, the smart patch allows precise dosing, giving physicians and patients the possibility to control the rate, dosage, and pattern of drug delivery, resulting in considerable therapeutic, economical, and lifestyle advantages over existing methods. This system is able to produce a systemic or local effect, depending on the dose and the energy applied [9].

Other application is the IontoPatch[®] in Europe since 2002. This disposable patch, with an embedded battery, does not require a controller, unlike the transdermal delivery system developed by Vyteris[™]. It is available in various sizes, suitable for the area and period of treatment (also varying the intensity of the energy applied). The IontoPatch[®] is mostly used by physiotherapists, occupational therapists and sports medicine professionals for the treatment of various pathophysiological conditions. The patient or technician is responsible for placing the drug and saline solution in the indicated compartments [10].

Sonophoresis

According to Maione et al. [11], sonophoresis, also called ultrasound, is a technique that greatly increases the passage of molecules across biological membranes, such as skin, by the application of ultrasound. This technique enables the administration of low molecular weight molecules or macromolecules [12]. The frequencies applied are usually between 20-100 KHz (low frequency sonophoresis) and the order of 0.7 to 16 MHz (high frequency sonophoresis) [13].

The sonophoresis mechanism is not clearly understood, given the complexity of the phenomena that may occur in the skin upon ultrasound exposure. Naik et al. [14] suggested that in sonophoresis occur micro-vibrations of the epidermis caused by the application of

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ultrasonic waves, increasing the kinetic energy of molecules in the skin. Dermal exposure to ultrasound may include phenomena such as cavitation, thermal effects, convective transport and mechanical effects.

Sonophoresis has several applications in the pharmaceutical area, namely [15-18]: (i) administration of hormones, (ii) recovery damage caused by sport and treatment of tendinitis, ligament repair, fractured bones and muscle spasms, (iii) wound healing, (iv) nerve stimulation and (v) increasing skin elasticity.

The SonoPrep[®], approved in 2004 by FDA, employ sonophoresis technique. SonoPrep[®] is reusable and portable equipment that induces temporary disruption of the stratum corneum structure. This equipment uses ultrasonic low frequency (compared to diagnosis imaging equipment) by an average time of 15 seconds, allowing 100-fold increase skin permeability.

SonoPrep[®] emits ultrasound energy in the range of about 53-56 KHz on an ultrasonic coupling medium. The mechanical vibrations through coupling medium result in cavitation that causes disorders of the lipid bilayer of the stratum corneum [19,20]. The skin permeability is reversible in 24 h after the application the stimulus. The ultrasound is turned off when the skin reaches a predetermined level of permeability, which is measured by skin conductance; since the circuit is closed (the patient has the receiver electrode). Kim et al. [21] determined the effect of anesthesia induction by the SonoPrep[®] device compared to the cream EMLA[®], for subsequent intravenous puncture (IV) in children between 5 and 10 years. Despite the limitation of this study, such as the influences from prior experiences of punctures IV of the children, the small number of participants and the time of application of EMLA[®] slightly higher in the study group than in the control group, the authors concluded that the use of SonoPrep[®] device significantly reduced the pain of puncture IV. Moreover, the time between the application and the therapeutic effect of anesthetic cream is lower using SonoPrep[®], which is clearly usefull in emergency medical departments.

Other equipments from the company Transdermal Specialties Inc.: U-Strip[™] and U-Wand[™] were developed and tested in clinical trials [22].

Electroporation

The electroporation technique refers to the application of an electric current of high voltage (50-1500 V) on the skin for a short period of time, usually in the order of 100 μ s to 100 ms. This enforcement results in the disruption of the lipid bilayer structure of biological membranes, increasing the skin permeability [13]. The electroporation process allows the transport of charged molecules. The mechanisms involved in the permeation of drugs by transdermal route using electroporation are: (i) electrophoretic movement, (ii) passive diffusion and (iii) electroosmosis.

The electroporation promotes the passive diffusion of molecules, which assumes greater importance after the application of electrical pulses, and is more relevant in prolonged permeabilization. This permeabilization may last hours after application of the energy pulse, according to *in vitro* studies [23]. This phenomenon is explained by the addition of drug after the application of the energy pulse. In electrophoresis technique, during the application of high-voltage pulses, there is a small contribution of electroosmosis, unlike to what occurs in the iontophoresis. [24].

The SynCon[®] vaccines are an example of electroporation technique, which are used for the treatment and/or prevention of cervical

dysplasia associated with human papillomavirus type 16 and 18, human immunodeficiency virus and leukemia (in clinical trials), prostate cancer, lung cancer, breast cancer, hepatitis B, hepatitis C and malaria (pre-clinical trials). This technology combines electroporation and vaccination to overtake some limitations associated with current vaccines, in particular, development time, high costs and relative inability of reaction to the rapid change of chains of some microorganisms [25].

Electroporation induces the formation of pores in the cell membrane that allows penetration of synthetic DNA present in the DNA vaccines previously injected into the muscle or skin [25]. The cell uses the introduced DNA to produce one or more proteins (antigens) that mimic the presence of the pathogen in the body. Thus, an immune response is induced in order to provide further protection to the patient or eliminate the cells infected with the infectious disease or even cancer.

In conclusion, there are some limitations related to the implementation of standardized procedures and the *in vivo* success of these techniques. Therefore, the potential of these systems is impressive, and, therefore, their development and the development of preclinical and clinical studies will ensure its importance in the coming years.

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