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CURRENT TECHNOLOGIES TO INCREASE THE TRANSDERMAL DELIVERY OF DRUGS

VOLUME 2

PHYSICAL PENETRATION ENHANCERS: THERAPEUTIC APPLICATIONS AND DEVICES

Editor:
José Juan Escobar-Chávez

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Current Technologies to Increase the Transdermal Delivery of Drugs

(Volume 2)

Physical Penetration Enhancers: Therapeutic Applications and Devices

Edited by

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FOREWORD

Pharmaceutical knowledge has grown exponentially over the last 40 years. We now have a much clearer understanding of how drugs are absorbed into, distributed within, and cleared from the body.

The potency of agents with which we deal continues to increase, and our ability to unravel mechanisms of action proceeds. New drugs –in particular peptides, proteins and other biological response modifiers- are being developed and new challenges await pharmaceutical scientists. Controlled drug delivery represents a field that must keep pace with changing nature of chemotherapy. Tighter control of drug input into the body in both quantitative and temporal senses is crucial, and design *of new delivery systems* must respond to this demand for increased sophistication. For this purpose, scientists have used new technologies to improve the penetration rate of drugs. These technologies include physical and electrical methods that include iontophoresis (small direct current), sonophoresis (mainly by low frequency ultrasound energy), electroporation (by application of short micro to milli-second electrical pulses), radiofrequency (laser-generated stress), microneedles and also the use of nanocarriers alone or in combination with the use of the above mentioned physical enhancers. These biophysical techniques have many others therapeutical applications that include physiotherapy, gene delivery, DNA based vaccination, drug administration, diagnosis, dentistry, *etc*.

The development of technology has permitted the generation of devices that involve the use of physical enhancers for many of the mentioned therapeutical applications.

The objective of this book is to provide a general and an updated overview of the theoretical and practical aspects of iontophoresis, electroporation, sonophoresis, microneedles, radiofrequency and transdermal nanocarrier systems on the delivery of transdermal drugs. Such a generalized approach would be helpful in medicine, pharmacy, drug discovery, drug delivery, drug design and toxicological research.

The contributors to this text have been directed to emphasize updates on above mentioned technologies involved in therapeutic applications and devices. Authors were selected for their knowledge and reputation in their subject area, and for their ability to address objectively the topics of this book. I believe that they have performed this task effectively, producing a text

that will facilitate and optimize future developmental programs in pharmacy, medicine and pharmaceutical technology.

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PREFACE

"*Physical penetration enhancers: Therapeutic applications and devices*", is the second volume of the series "*Current technologies to increase the transdermal delivery of drugs*" from Bentham Science Publishers. This book provides an overview of main current physical enhancers in the therapeutical and pharmacy field. The importance of therapeutical applications of physical enhancers, and devices existing in the market will be addressed in each chapter. Exclusive chapters on Iontophoresis, Sonophoresis, Electroporation, Microneedles, Radiofrequency and more recently the use of nanoparticles in combination with the above mentioned physical enhancers, highlighting their main therapeutic applications will be included in this book.

Currently, there are no unique books available on therapeutical applications of physical penetration enhancers and currently devices in the market. Brief chapters and books describing only one of the physical enhancers or only one of the therapeutical applications (*i.e.*, transdermal drug delivery) of these enhancers are available to readers in some drug delivery or toxicology books. For these reasons, more detailed information about therapeutical applications (drug delivery, gene therapy, physiotherapy, skin disorders, vaccination, *etc.*) is now needed. This book presents a general overview of the theoretical and therapeutic aspects of iontophoresis, electroporation, sonophoresis, microneedles, radiofrequency and nanocarriers systems in combination with physical enhancers. Such a generalized approach would be helpful in medicine, pharmacy, drug discovery, drug delivery and toxicological research.

A comprehensive book which provides the basis and updated therapeutical research information is necessary. For this fact, this e-book will be an interesting option that could be used by students and academics of medicine, biopharmacy, pharmaceutical technology, design and development of drugs, pharmacology, by physicians, dermatologists, scientists and pharmaceutical R & Ds. The book also will be useful for medicine, pharmacy, pharmacology and pharmaceutical technology departments of different Universities all over the world.

In summary, this e-book reviews the therapeutical uses of physical enhancers such as iontophoresis, sonophoresis, electroporation, microneedles, radiofrequency and nanocarriers in combination with physical enhancers. After an introduction, definition, mechanisms of

action, the focus turns to the relevance of therapeutical applications studies and finally the different physical enhancer devices in the market.

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To my Family and all my personal affections.

CHAPTER 1

Physical Penetration Enhancers: An Overview

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Abstract: A number of physical methods for drug penetration enhancement and improve bioavailability of the stratum corneum (SC) such as micro-needles, heating, iontophoresis, electroporation, and ultrasound have also been evaluated in the last decade. On the other hand, nanotechnology has shown remarkable potential in target-specific delivery of drugs in the body. In this chapter, we discuss the role of overview about nanocarrier systems, physical enhancers and their possible combination in order to improve the passage of molecules through the organ systems. All these methods have their own advantages and disadvantages, nevertheless, novel developments are projected to be more adaptable to different needs.

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Keywords: Controlled release, Drug delivery, Nanocarrier systems, Nanomedicine, Nanoparticles, Nanopharmaceutics, Physical penetration enhancers, Synergism, Therapeutic applications.

1. INTRODUCTION

In order to improve the penetration ability of agents therapeutics into systemic circulation, numerous methodologies have been investigated, developed and patented such as physical enhancers: iontophoresis, electroporation, ultrasound, microneedles and radiofrequency [1 - 10]. Alternatively, nanocarrier systems are being used as drug transporter systems. In this review, the expression nanocarrier referred to nano-systems that are used for effective carriage of loaded drug to the target sites or cells such as nanoparticles (NP), nanoemulsions, nanosuspensions, liposomes, micelles, vesicles, dendrimers and transfersomes. In the case of NP, these are defined as nanospheres or nanocapsules which is different in the morphology and architecture. Nanospheres are prepared by a polymeric matrix and nanocapsules are made of an oil core delimited by a polymeric membrane [1].

Currently, in order to improve penetration of nanocarrier systems into organ systems, especially to increase the skin permeability of drugs, a number of methods have been developed including use of physical enhancers [10 - 15]. Particularly, the skin has become an important way of administration of therapeutics agents for dermal and transdermal drug delivery. Dermal and transdermal ways offer a viable non-invasive administration of drugs, and avoids the hepatic first-pass effect. Also, dermic drug delivery system localizes high concentrations of agent therapeutic at the site of action and consequently, decreasing the side effects [1].

Transdermal delivery involves increasing the penetration of a drug through the skin when a systemic effect is wanted. Though, the dermal and transdermal administration of drugs is influenced by on drug's physicochemical properties, for example, charge, solubility, diffusivity, molecular size, polarity and molecular weight [1]. This chapter reviews the combination of nanocarrier systems and physical enhancers in order to improve the delivery of therapeutic molecules in many ways. Additionally, potential therapeutically applications of these physical

enhancers are reviewed in this chapter.

2. PHYSICAL ENHANCERS

2.1. General Aspects of Physical Enhancers

An enhancer is a technique that modify the penetration facility of drug chemically or physically. With the intention of increase the penetration ability of drugs into organ systems, numerous methodologies such as physical enhancers have been investigated, developed and patented (*e.g.* iontophoresis, electroporation, ultrasound, microneedles and radiofrequency) [4]. Tabel **1** shows the principal characteristics of these techniques.

Table 1. Physical enhancers.

Physical Enhancers	Definition	Characteristics	Refs
Sonophoresis	Sonophoresis is the application of ultrasonic energy that temporarily improves skin permeability.	Sonophoresis functions at frequencies of 20 kHz-16 MHz and intensities up to 14 W/cm^2 (spatial average pulse average intensity, ISAPA) to enhance skin permeability.	[7]
Iontophoresis	Iontophoresis is the use of slight electric current in order to improve the transport of drugs, which consists of an anode and a cathode deposited on a surface (*e.g.* skin).	Iontophoresis uses an electric current of ~ 0.5 A/cm). A drug can pass through the surface by electromigration, electroosmosis or passive diffusion.	[8]
Electroporation	The electroporation technique consists of the application of a high electrical field pulses with the purpose to create nano-sized pores in a cell membrane and thus, increase the passage of ions and macromolecules through the skin.	Electroporation can be reversible and irreversible.	[4, 5]
Microneedles	Microneedles are used to open holes into the skin to create a pathway for the following delivery of drugs.	Generally, microneedles have a length of 100-500 μm.	[4, 5]
Radiofrequency	Radiofrequency ablation (RF) is a simple, safe, and effective therapy for chronic radiation proctopathy.	The frequency is between 10 kHz and 900 MHz.	[9]

According to physical enhancers, one of the main routes of drug administration is

CHAPTER 2

Iontophoresis

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Abstract: Transdermal administration offers an interesting alternative to oral and parenteral drug administration; nevertheless, skin is an important barrier for drug absorption. Iontophoresis, a technique that consist of the application of low current density across a membrane can facilitate drug entrance through it. Iontophoresis can be used for local effects on skin, nail, eye or ear and it can also be used for systemic delivery when applied through skin. In this chapter, the mechanisms involved in drug transport during iontophoresis application and factors affecting its efficacy are reviewed. Examples of the use of iontophoresis in different fields are presented together with the most recent research.

Keywords: Ear permeation, Electric current treatment, Electromotive drug delivery, Eye permeation, Iontophoresis, Iontophoretic devices, Low current treatment, Nail permeation, Physical permeation enhancement, Transdermal absorption.

1. INTRODUCTION

Epithelia general properties limit passive delivery of most compounds across

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José Juan Escobar-Chávez (Ed.)

them. To overcome this barrier limitation several passive and active strategies have been attempted to ensure safe delivery and to improve efficacy of drugs as well as patient compliance.

Passive procedures, as optimization of formulation or drug carrying vehicles to increase permeability, in general do not greatly enhance the drug permeation of molecules with molecular weights higher than 500 Daltons. Active methods such as sonophoresis, iontophoresis, electroporation and other techniques such as laser microporation and microneedless produce superior enhancement of drug transport through the membranes. These methods, physically or mechanically, facilitate the delivery of various lipophilicities and molecular weights drugs, including proteins, peptides, and oligonucleotides [1, 2].

Among the methodologies mentioned, iontophoresis is one of the best-known and represents a promising physical penetration method to enhance delivery of drugs, especially trough skin.

The application of low density electrical current, and voltage, through a membrane, called iontophoresis, promotes permeation of a therapeutic drug placed on the surface of the membrane.

Iontophoretic drug delivery through the skin offers several important advantages over more traditional dosage forms. First pass metabolism is avoided with iontophoretic transdermal administration and this technique usually increases patient compliance. Along with these advantages, iontophoresis provides additional ones:

- Delivery of both ionized and unionized polar drugs, that can have either low or high molecular weight.
- Continuous or pulsatile delivery of a drug can be selected, depending on the mode of current used.
- Permits ease ending of drug administration.
- Current mode, duration of the process and area of application, parameters that determine the amount of drug delivered, can be modified according to the needs.
- Easy skin recovery after application, since no severe irritation is produced.

- It can be used for systemic or local (topical) delivery of drugs.
- Inter and intra subject variability is considerably reduced compared with passive diffusion, since the rate of drug delivery is more dependent on applied current than on membrane characteristics.

Iontophoresis has been established as a safe, versatile and efficient enhancement technique and several iontophoretic devices have been marketed. Clinically, iontophoresis has been employed to deliver through skin fentanyl and lidocaine for pain relief [3, 4], pilocarpine to induce sweating (as a diagnostic test) [5], and tap water to treat hyperhidrosis [6]. Iontophoresis even has been used as a monitoring technique in diabetic patients, since it can be used to extract glucose from the skin [7]. Also, recently has seen an interest into the potential use of iontophoresis to deliver drugs through other membranes such as the nail and through the sclera and cornea, the two main barriers to eye drug delivery [8].

In this chapter basic concepts of iontophoresis will be discussed, examples of application of this delivery technique for drug application will be explained and currently existing iontophoretic devices for different treatments will be exposed.

2. MECHANISM OF ACTION AND THEORETICAL BASIS OF IONTOPHORESIS

During iontophoresis low density, and low voltage, current (less than 0.5 $mA.cm^{-2}$, 1-10 V) is applied through an electrical circuit which electrodes are placed on a membrane surface. This allows the propelled ions to pass through the membrane.

In the course of current application skin resistance is reduced. It may be due to micro- or nano-phores formation as a consequence of proteins and lipids, present in the stratum corneum, reorientation under the application of the electric field; or it may be caused by the ions flux into stratum corneum (either from beneath the stratum corneum or from the formulation on it). Local changes can also take place in hair follicles and sweat glands. As a result the originated pores, negatives in charge considering the permselectivity of skin at physiological pH, may have different diameters and structures. Nevertheless, after current cessation skin resistance is recovered so it can be considered that skin alterations under iontophoresis are reversible [9].

CHAPTER 3

Delivery of DNA-Based Vaccines with *In Vivo* Electroporation

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Abstract: Recent technological advances have re-established the value of DNA-based vaccines in tackling unmet medical needs. Such advances include the optimization of DNA plasmid constructs, the addition of novel molecular adjuvants into the formulations, and the development of *in vivo* delivery strategies such as electroporation (EP). The combination of DNA-based vaccines with the delivery platform of EP has enhanced the antigen expression by up to 1000-fold higher than DNA injection alone, resulting in greatly enhanced immunogenicity of DNA-based vaccines. Pre-clinical EP-enhanced DNA-based vaccination has elicited robust functional host immune responses to a myriad of disease targets resulting in protection from viral challenge or tumor growth, depending on the disease model. Significantly, the problems encountered in translating these responses to the clinic have been overcome, and equally impressive immune responses are being observed in human beings when DNA-based vaccination is married with EP, as was observed in a recent clinical trial. In this review we will cover the principles of EP in respect to enhancing DNA-based vaccination protocols targeting pDNA delivery to the muscle or skin, and discuss the top line results that have revealed for the first time clinical efficacy of DNA-based vaccine candidates.

Keywords: DNA-based vaccines, Electroporation.

1. INTRODUCTION

Thirty years ago Neumann *et al.* reported on the successful delivery of genes into

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cells in culture through the use of an electrical pulsing method [1]. This technique of gene delivery became known as electrotransfer or electroporation, and was quickly adapted to *in vivo* protocols to aide in the delivery of macromolecules, such as chemotherapeutics and plasmid DNA (pDNA), across the mammalian membrane of cells residing in a tissue rather than a culture dish. EP has been used in the clinic to efficiently deliver large molecule chemotherapeutics such as bleomycin in electrochemotherapy (ECT) [2], or high voltage irreversible EP (IRE) has proved efficacious at causing cancer cell death [3]. ECT and IRE have been reviewed in depth elsewhere [2, 3]. More recently, EP has been utilized to transfer nucleic acid constructs in gene therapy trials [4]. In this review we will focus on the use of EP to enhance the delivery of pDNA to elicit robust immune responses in DNA-based vaccination protocols.

1.1. DNA-based Vaccination: The Concept

Conceptually and experimentally, DNA-based vaccination is a very attractive platform. The vaccine construct is not an inactivated or attenuated version of a pathogen, or a pathogen-associated protein. The construct is designed to be a blue print of the antigen(s) of choice, which following nuclear delivery can be read by the host's own machinery, initiating its manufacture, processing and presentation. The major advantage of DNA-based vaccines over inactivated virus or viral protein-based vaccines is their ability to drive the generation of both T cell and B cell responses. This in conjunction with ease and speed of design and manufacture [5], and the stability of pDNA at room temperature, are some of the favorable traits associated with this technology [6]. Additionally, modern day genomics allows for customization of the vaccine, so scientists can marry molecular biology techniques with their understanding of the immune system to develop vaccines that encode novel antigens and/or combinations of antigens. DNA-based vaccination has the potential to harness the power of the immune system to tackle multiple unmet medical needs, such as HIV, RSV, Influenza, and various cancers.

1.2. DNA-based Vaccination: The Early Years

The first DNA-based vaccination studies were reported in the early 1990's, when multiple groups demonstrated the induction of immune responses following naked

injection of pDNA into mouse muscle [7 - 9]. It was demonstrated that *in vivo* transfection of mouse muscle cells with pDNA encoding target infectious agent-associated antigens could drive robust T cell and antibody responses against the pathogens, and importantly protect against future challenge. For example, Ulmer *et al.* reported that *in vivo* transfection with pDNA encoding influenza A nucleoprotein raised a protective immune response against subsequent challenge with a heterologous strain of influenza A virus in mice [9]. Such studies demonstrated that vaccination of small animals with naked pDNA could protect against infectious agents or halt tumorigenic growth [9, 10].

However, historical attempts in the 1990's to translate these pDNA vaccine successes into large animal models or humans ended in disappointment [11, 12]. The robust immune responses observed in mice could not be replicated in non-human primates (NHPs) or humans. One of the major reasons cited for this was the inefficiency of the delivery of the pDNA into the host's cells. This appeared to be less of an issue for small animal studies that often compensated for this by using very high (dose by body weight) doses and by forced cellular transfection through hydrodynamic pressure.

1.3. DNA-based Vaccination: The Delivery

Even though the excitement associated with DNA-based vaccination waned during the first few years of this century, investigators that remained in the field focused their attention on further defining pDNA's interaction with the innate immune system, how and what adjuvants could be used in combination, and maybe most importantly, understanding how the use of certain modalities could enhance the delivery and cellular uptake of large (several kbp's) pDNA molecules. Platforms developed to enhance *in vivo* pDNA delivery included ballistic devices, polymers, bacteria, sonoporation and electroporation [6, 13 - 19].

As mentioned above, EP has been successfully employed to assist in the delivery of nucleic acids into cells, both *in vitro* and *in vivo*. EP achieves this by inducing transient perturbation in the cell membrane and an electrical gradient that permits entry of large molecules, such as pDNA vaccines, into the cell. Studies have described an increase in tissue gene expression by 100-1000 fold when reporter

CHAPTER 4

Sonophoresis: Therapeutical Uses and Devices

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Abstract: The administration of drugs in the skin using ultrasound is recognized like sonophoresis. The ultrasound is dating back to the fifties for high frequency (HF) and low frequency (LF). It has been investigated over the past two decades. Clearly, the use of ultrasound to drug delivery (DD) recently gained importance, thereby increasing patents and new commercial devices.

This chapter shows the important findings in sonophoresis. Particular attention is focused into therapeutical applications including transdermal drug delivery (TDD), gene therapy, sport medicine and sonophoretic devices.

Keywords: Physical enhancers, Skin, Sonolysis, Sonophoresis, Sonophoretic devices, Sport medicine, Ultrasound.

1. INTRODUCTION

Applications of ultrasound were used as an imaging technique. In the decade of the twenties, ultrasound (US) showed that could generate modification in human's

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organisms, thus began the US treatment [1].

The use of ultrasound in tissue generates heat thereof due to absorption of energy, allowing the use under different conditions. Recently it has been studied that the same benefit is obtained without thermal application by US.

US treatments could be divided as low and high frequency, LF covers the applications as phonophoresis, gene and physiotherapy, and last but not least important it can be used for bone healing.

The application of US has been used for many years in the medical field.

US have 3 different arrangement applications. These are shown in Table **1**.

Table 1. Set of US conditions based on frequency (F) range.

Ultrasound types (frequency ultrasound)	Range of frequencies (KHz)
Low	20-100
Medium	0.7-3.0
High	3.0-10.0

Table 2. Principal applications of US.

Relevant Applications of Ultrasound
(i) For diagnosis in medicine.
(ii) For physical therapy (0.1- 15 MHz) the application of higher frequencies restricts the action to more superficial layers in to the skin.
(iii) In sport medicine. It can reduce healing times in fresh fractures or injuries in almost 30 -38% (<0.1 W/cm^2).
(iv) For transdermal, ocular and ungual/transungual DD, ocular permeability enhance through changes in the structure of the cornea (20kHz).
(v) In surgery, practice patterns, traditional delegation of use and involving procedures (5-10 MgHz).
(vi) In gene therapy increases plasmid transfection through the formation of short pores in the plasma membrane.
(vii) For the treatment of tumors. US is used to treat a variety of solid tumors with the advantage that this technique have a fewer complications after treatment.

The principal medical applications of US are shown in Table **2**. Initially US was

investigated for the treatment of skin conditions [2, 3] and swelling of joints [4]. Lately is of interest to use it for TDD [5] and gene therapy [6].

In recent years, reviews with important information on a lot of aspects of sonophoresis have been published [7 - 15]. This chapter displays a well-run view of therapeutic, pharmaceutical applications of US and sonophoretic devices. This Approach is justified because of the information available by US uses.

2. THE US

US is an energy that spreads [16,17]. Path propagation is parallel to oscillation direction as observed in Fig. (**1**).

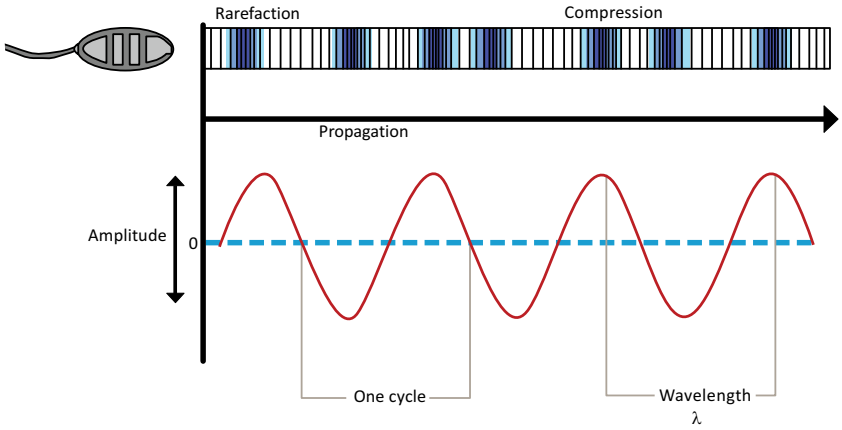

Fig. (1). Representation of sound wave propagation.

The concentration of energy within a specific area in an US ray is called intensity (I). The intensity is decreasingly when US pass into the body, this is called attenuation. Tissue attenuation occurs for the absorption and sound force that are converted to warmth and scattered [13, 18] (Fig. **2**).

Other experimental variables [17] that are important in sonophoresis are shown in Table **3**.

Duty cycles are common at 10%, 25%, 50% or continuous application [19 - 28]. US is frequently used in pulsating as it lowers the effects of warming related by US. Various horn-to-skin spaces are utilized in sonophoresis studies, ranging from placing the US horn skin contact about 4 cm [28, 29]. Treatments vary over time,

CHAPTER 5

Radiofrequency as Physical Approach for Transdermal Penetration Enhancement, Non-Surgical Skin Procedures, Orthopedics and Chronic Pain

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Abstract: This review provides a summary of studies on the use of radiofrequency to overcome the skin barrier in order to evaluate its therapeutic potential, primarily in the fields of drug delivery and gene therapy. Other applications in non-surgical dermatologic procedures, orthopedics and treatment of chronic pain are also addressed. Additionally, this chapter includes a description of common devices used in some of the fields described and information of risks, safety and cost of treatments in the area of medical skin procedures.

Keywords: Chronic pain, Dermatology, Drug delivery, Gene therapy, Non-contact, Non-invasive, Non-surgical, Orthopedics, Radiofrequency, Therapeutics.

1. INTRODUCTION

Radiofrequency (RF) is a versatile technology commonly employed to generate therapeutic intensities of heat in order to produce structural and biological responses. RF ablation methods were first introduced as a minimally-invasive procedure in the field of neurology, and it has been expanded to other domains to treat tumors in the lung, some types of ventricular arrhythmias, varicose veins,

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endovenous ablation, treatment for Barret's esophagus, uterine fibroids, healing of bone tissue and skin lesions [1]. It is recently used as promising non-invasive strategy for transdermal penetration and gene delivery enhancement, orthopedics, sleep apnea and chronic pain [2 - 5]. The term non-invasive refers to non-surgical methods and does not involve penetrating the body as by incision or injection.

The principle mechanism of RF is electroconductive heating, also referred as ohmic heating or resistive heating. This term is defined as the passage of electrical current (either DC or alternating current) through a material which functions as an electrical resistance in which heat is generated.

One of the biggest challenges in drug delivery is the ability to transport the therapeutic agents into the body safely and reliably. Skin, the largest soft membrane tissue covering the body is an ideal target for certain treatments including gene therapy. However, the stratum corneum (SC), the outermost layer of the epidermis forms a barrier to protect underlying tissue, impeding the passage of therapeutic molecules. There are several penetration enhancement strategies that would increase the number of drugs available for transdermal administration without having safety issues. Vehicle-based drug which does not change the SC properties such as vesicles and particles [6], pro-drugs [7], and synergistic system [8, 9], or chemical penetration enhancers, representing a good strategy as absorption accelerants [10]. Another interesting approach is physical and electrical methods that temporarily diminish the barrier of the skin by accelerating the absorption of molecules to enhance either drug flux or gene expression [11]. Those may include iontophoresis [12, 13], electroporation [14], microneedles [15], laser techniques [16] and radiofrequency [2, 17, 18]. RF technology assists the percutaneous penetration of actives (including peptides and gens) by removal of the outermost layer of the skin by using an alternating electrical current preferably from 100 to 500 KHz. The flow of this current through the tissue produces ions to collide one another which results primarily in localized heat creating transitory micro-pathways across the SC and epidermis, increasing the passage of hydrophilic compounds across the skin. The risk of discomfort or painful sensation is minimal as the microchannels created do not reach ending nerves [19].

Non-contact RF is shown to be an effective alternative in the field of dermatology and cosmetics. It is called non-contact RF because the active electrode does not touch directly the tissue surface. Only few scientific data on the relevancy of this technique regarding its impact on structural changes of skin tissues has been communicated. Many clinical studies considering the RF procedures as safe, tolerable, of rapid recovery and effective for skin treatments have been carried out. However, such trials are commonly obtained from non-randomized and non-comparative data using subjective means of evaluation, showing modest results [20, 21].

Non-contact RF has also been employed in orthopedics as an effective tool for controlled heating of tissues (above physiological temperature) to generate structural and biological effects. Tendon diseases for instance represent an important (30%) proportion of rheumatologic consultations in day-to-day consultations [22]. RF energy works to shrink and tense ligaments and articular capsule tissue in a controlled manner [23]. Actually, hydrogen bonds of collagen molecules may break at supraphysiologic temperatures, which collapse the molecule allowing connective soft tissue to shrink. Some symptoms of tendinopathies coming from irritation of nociceptors may be treated by bipolar RF by inducing degeneration of nerve, and delay of newly developed sensitive afferent fibers into treated tissues [24]. RF energy applied above supraphysiologic temperatures may also induce an anticipated response, similar in time and nature of the wound healing responses of thermal and surgical damages, following a predictable sequence of events that contributes to inflammation [23].

This chapter presents experimental and clinical data of therapeutic applications of non-invasive RF to enhance primarily transdermal drug delivery. Furthermore, the effectiveness of this technique in cutaneous gene delivery, as well as in areas such as non-surgical dermatology, orthopedics and chronic pain is also discussed. To conclude, the description of devices used in the mentioned fields and the relationship between cost, risks and safety of different dermatological procedures is described.

CHAPTER 6

Microneedles

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Abstract: Transdermal drug delivery is a well-accepted route of administration for therapeutical drugs. Skin is the largest area human body organ, however, the substantial barrier property of the skin stratum corneum limits practical value of transdermal route of drug administration. It has been proved that microneedle array devices can overcome the barrier characteristics of the stratum corneum and enhance the delivery of therapeutic medicines through skin. This chapter focuses on looking at the microneedle-mediated transdermal drug delivery for therapeutical applications. The definition of microneedles, enhancement mechanisms and devices in research or in the market are also depicted.

Keywords: Definition, Devices in research or in the market, Mechanisims of action, Microneedle, Therapeutical applications.

1. INTRODUCTION

Transdermal drug delivery (TDD) is convenient for the delivery of active pharmaceutical ingredients. The transdermal route offers some advantages compared with other noninvasive routes of drug delivery, such as the circumvention of first-pass hepatic metabolism, increased compliance and potential for controlled release. However, the clinical application of transdermal drug delivery has been limited because of the extremely low permeability of drugs through the stratum corneum [1].

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Microneedle array devices with sub-millimeter needle-shaped structures was expected to overcome obstacles of the outermost skin layer, the stratum corneum. The concept of microneedles, piercing through the stratum corneum and increasing markedly drug skin permeability without stimulating sensory nerve endings and causing pain was first put forward by Gerstel MS and Place VA in 1976 [2]. And Henry *et al.*, demonstrated the proof of the concept experimentally in 1998 for transdermal drug delivery [3]. Since then, hundreds of preclinical studies have been reported. Microneedle technology has shown great effectiveness in promoting the penetration of macromolecules, hydrophilic substances, vesicles and nanoparticles. Recently, numerous types of microneedles have been clinically examined across a range of applications, including drug and vaccine delivery. The aim of this chapter is to give an overall picture of the main features of microneedles used for transdermal and topical drug delivery. The definition of microneedles, enhancement mechanisms, therapeutical applications and devices in research or in the market are depicted.

2. DEFINITION OF MICRONEEDLES

Microneedles are a kind of drug delivery device for the use in the percutaneous administration of a drug for local therapy or systemic therapy. Microneedles can be defined as solid or hollow according to its structure. The device generally comprises a multiplicity of micron sized needles which are attached to a base support. The typical height is range from 100 to 1000 μm (*e.g.* Fig. **1**). A variety of materials have been evaluated for the fabrication of microneedles, such as silicon, metal, ceramics and polymers [4, 5].

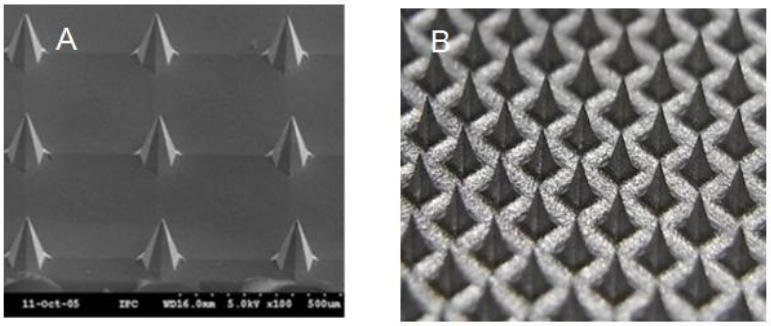

Fig. (1.1). A. Solid silicon microneedles, **B.** Solid metal microneedles (from author's lab).

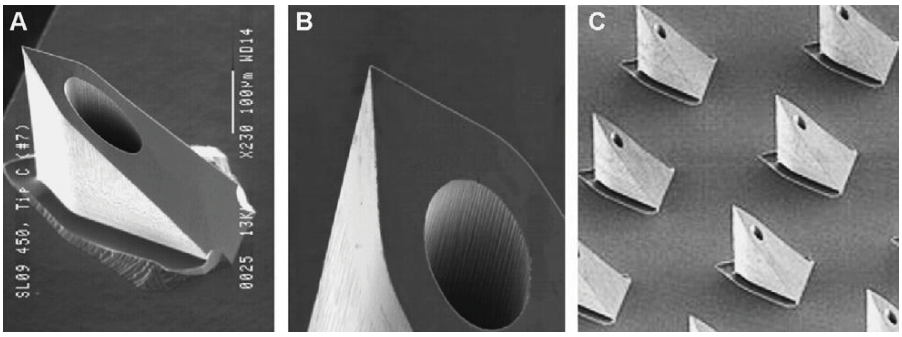

Fig. (1.2). Hollow silicon microneedles. (**A**) A single microneedle, (**B**) the microneedle tip, and (**C**) a microneedle array (Reprinted with permission from [6]. Elsevier (2009).

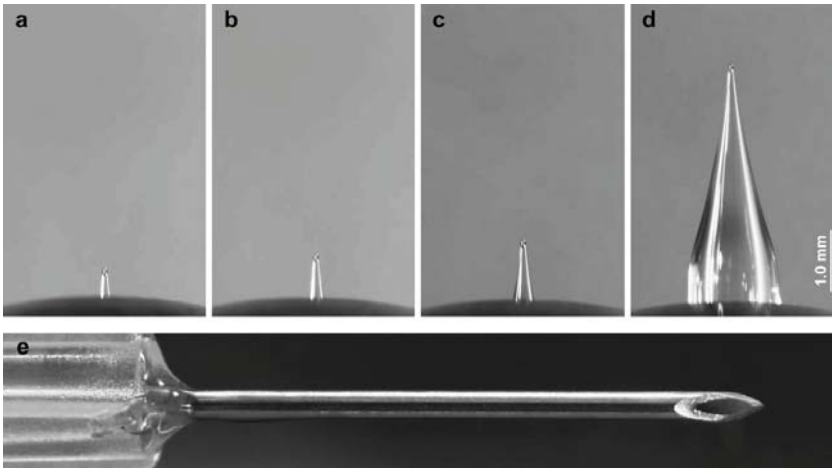

Fig. (1.3). Hollow microneedle used for intradermal infusion. Microneedles length (**a**) 0.5mm, (**b**) 0.75 mm, (**c**) 1 mm and (**d**) 4 mm, (**e**) Hypodermic needle (26-gauge). All images are obtained under bright field microscopy at the same magnification. (Reprinted with permission from [7]. Elsevier (2011)).

In addition, different terms have been reported in the literature base on the geometry or application of the needle, such as micropile [8], microstructure [9], microprojections [10, 11], micron sized lancets [12], microdevices [13], *etc* [14 - 18]. Despite of use of different terms, all these microneedles were for the same purpose, namely to pierce stratum corneum to form hydrophilic pathways by minimally invasive method without contacting the nerves of the skin to avoid bleeding or pain. Human volunteers have reported that a microneedle array having 5 × 10 arrays of 620 μm long stainless steel needles was not painful upon insertion [19]. Another study in 18 human volunteers reported that microneedle insertion

CHAPTER 7

Nanocarrier Systems with the Use of Physical Enhancers

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Abstract: At present, nanotechnology has acquired great importance. One of the fields where nanotechnology has been used with great success is medicine. This has allowed the emergence of a branch of nanotechnology called nanomedicine. Nanomedicine has been used by all known routes of administration (oral, intravenous, transdermal, *etc.*). Topical/transdermal route is one of the most used routes to administer formulated drugs in nanocarrier systems (nanoparticles, liposomes, dendrimer, transfersomes, nanoemulsion, *etc.*) in combination with the use of physical enhancers (microneedles, iontophoresis, sonophoresis, *etc.*). This route has great potential to deliver drugs, but the stratum corneum, which is the most external layer of the skin, confers properties of permeability to this organ.

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In order to modify the skin barrier properties and use the skin as a route to administer drugs into the body, some interesting strategies have been developed in last decades, such as the use of chemical and physical enhancers and even the combination of these enhancers with nanocarrier systems. For this reason, this chapter mainly emphasizes the applications of the 3 main physical enhancers (ultrasound, iontophoresis and microneedles) with nanocarriers for administering drugs by topical/transdermal routes, where they have been more widely used.

Keywords: Nanocarriers, Physical enhancers, Transdermal drug delivery.

1. INTRODUCTION

At the present time, nanotechnology has tremendously influenced all fields where it has been used. In the field of medicine has revolutionized many of the concepts existing up to date; for that reason, the emergence of a new hybrid concept between nanotechnology and medicine, is known as nanomedicine [1]. This new branch of medicine has changed the concept we had of treatment and diagnosis of diseases [2]. On this scale of nanometers, it is possible to treat a disease at the level of cellular organelles and adequately, control its progression. The drug path at the nanoscale is carried out by a modern version of a vehicle that protects the drug from action of the immune system, changes of pH, and it is made for the desired site of action. These so-called nanoscale vehicles are known as nanocarriers (Fig. **1**).

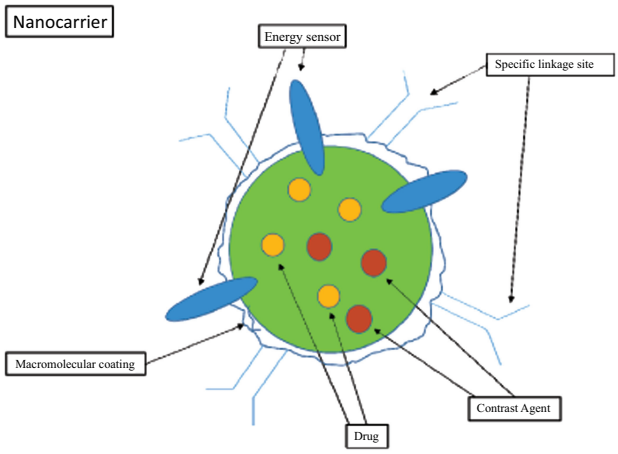

Fig. (1). Schematic representation of an ideal nanocarrier.

2. DEFINITION AND GENERALITIES OF NANOCARRIER SYSTEMS

Nanocarriers are colloidal drug delivery system in the neighborhood of 1 to 1000 nm. These systems are very tiny and they are compared to some body structures [3]. Nanocarriers are nanosized particles and they are made of different macromolecules to be able to be administered by different routes. Nanocarriers can be administered *via* different the routes. The size of nanocarriers, let them be undetectable for the immune system; for that reason, they are the perfect tool to fight again a lot of illnesses and carry the drug directly in the target organ. This fact, helps to avoid side effects and increases the effectiveness of the drug [4 - 8].

The nanocarriers have become an interesting option to deliver drugs, gene therapy [9], for increasing the bioavailability of poorly soluble drugs [10] with low permeability or for percutaneous administration. Chemicals that were unlikely to be administered, now with nanocarriers may be used in therapeutic applications [11]. There are drugs that were not feasible to use as therapeutic agents due to their low bioavailability, and by the need of high concentrations to exert a pharmacological effect with the possibility of leading to toxic levels. But now by mean of nanocarriers their application is possible.

The nanocarriers can be made with a lot of substances, for example, polysaccharides [12], natural or synthetic polymers [13], lipids [14], proteins [15], amino acids [16] and inorganic compounds (Fig. **2**). The use of different materials for nanocarriers makes these systems to have great physicochemical, pharmacological and toxicological properties. This variety of materials permits that nanocarriers can be loaded with a wide range of drugs with different physicochemical and pharmacological characteristics.

These nanostructures can be made to be very specific for the intended purpose; for example, it can be placed on the surface of these systems folic acid [17], since it is known, that many of cancers have an over expression of folate receptors. This strategy helps nanocarriers to link to the site of action and they will be joined to these receptors, making them much more targeted release of the drug directly to the tumor.

Therapeutic dose concepts used in traditional pharmacology, will change

Glossary

Cavitation = formation of vapour cavities in a medium upon ultrasound exposure.

Dendrimers = monodisperse populations those are structurally and chemically uniform. They allow conjugation with numerous functional groups due to the nature of their branches.

Electroporation = phenomenon in which cell membrane permeability to ions and macromolecules is increased by exposing the cell to short high electric field pulses.

Gene delivery = is a therapeutic technique, in which a functional gene is inserted into a patient's cells to correct a genetic defect or to provide the cells a new function.

Iontophoresis = consists of the application of a low density current and low voltage (typically 0.5 A/cm^2) *via* an electrical circuit constituted by two drug reservoirs (anode and cathode) deposited on skin surface.

Liposomes = are hollow lipid bilayer structures that can transport hydrophilic drugs inside the core and hydrophobic drugs between the bilayer.

Microneedles = is a drug delivery device for use in the percutaneous administration of a drug for local therapy or systemic therapy.

Nanoemulsions = are isotropic dispersed systems of two non-miscible liquids, normally consisting of an oily system dispersed in an aqueous system (o/w nanoemulsion), or an aqueous system dispersed in an oily system but forming droplets or other oily phases of nanometric sizes (100 nm).

Nanoparticles = is a small object that behaves as a whole unit in terms of its transport and properties.

Physical penetration enhancers = Enhancement technologies that increase the passage of drugs throughout the skin.

Radiofrequency = is a versatile technology commonly used to generate therapeutic levels of heat by using various forms of alternating current.

Reverse iontophoresis = convenient non-invasive method for extracting substances through skin, allowing this way sampling body fluids to monitor them efficiently.

Sonolysis = therapy that involves administration of microbubbles with ultrasound, but without the administration of a thrombolytic drug.

Sonophoresis = absorption of ultrasonic energy that has been used with therapeutic intent in many conditions.

Transcorneal iontophoresis = delivery of a high concentration of drug to the anterior segment of the eye: cornea, ciliary body, aqueous humors and lens.

Ultrasound = a form of mechanical energy that is propagated from one point to another by the interaction between neighboring oscillating particles.

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José Juan Escobar-Chávez

Dr. Escobar-Chávez (Doctor of Chemical Sciences, University of Mexico, Mexico) is a professor at the Faculty of Chemistry and Pharmacy; University of Mexico. He joined the faculty in 1998. He has completed two postdoctoral researches with one year in each of them, one in abroad at the University of Valencia, Spain, in the Department of Pharmacy and Pharmaceutical Technology and the other at national level in Universidad Nacional Autónoma Metropolitana-Xochimilco in the Department of Biological Systems. He also made a doctoral stay at the University of Geneva, Switzerland, at "Centre de Recherche et d'Enseignement Interuniversitaire, Pharmapetides".

His research interests are in the Topical and Transdermal delivery of drugs and include the use of the tape stripping technique to quantify the pass of drugs, the use of TEWL and ATR/FTIR to show the changes of skin as a result of the use of chemical enhancers, the use of physical enhancers as iontophoresis, sonophoresis, solid and polymeric biodegradable microneedles and electroporation in the administration of transdermal drugs. Development and characterization of mucosal and ocular delivery systems and application of nanotechnology in transdermal drug delivery are others major research interests. He is author of 10 book chapters. He also is editor of the book "Current Technologies to Increase the transdermal delivery of drugs" from Bentham Science Publishers. He has 20 publications in indexed journals of high international impact in the area of Pharmacy and Pharmaceutical Technology. He has two patents of transdermal technological developments. He won the 2014 CANIFARMA prize awarded by the National Chamber of Pharmaceutical Industry in Mexico. He has been reviewer of many recognized journal of Pharmacy, Pharmaceutical technology and Dermatology. He teaches analytical chemistry, biopharmacy, analysis of drugs, and pharmaceutical technology at FES Cuautitlán-UNAM and he is involved in pharmacy curriculum development.