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Chemical and Physical Enhancers for Transdermal Drug Delivery

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1. Introduction

The application of preparations to the skin for medical purposes is as old as the history of medicine itself, with references to the use of ointments and salves found in the records of Babylonian and Egyptian medicine.(López-Castellano & Merino, 2010) The historical development of permeation research is well described by Hadgraft & Lane, 2005. Over time, the skin has become an important route for drug delivery in which topical, regional or systemic effects are desired (Domínguez-Delgado, et al., 2010). Nevertheless, skin constitutes an excellent barrier and presents difficulties for the transdermal delivery of therapeutic agents, since few drugs possess the characteristics required to permeate across the stratum corneum in sufficient quantities to reach a therapeutic concentration in the blood. In order to enhance drug transdermal absorption different methodologies have been investigated developed and patented (Rizwan et al., 2009). To date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin. These are termed 'Novel' due to recent development with satisfactory results in the field of drug delivery (Patel et al., 2010). Improvement in physical permeation-enhancement technologies has led to renewed interest in transdermal drug delivery. Some of these novel advanced transdermal permeation enhancement technologies include: iontophoresis, electroporation, ultrasound, microneedles to open up the skin and the use of transdermal nanocarriers (Díaz-Torres, 2010; Escobar-Chávez & Merino, 2010a).

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2. Chemical enhancers

Chemical percutaneous enhancers have long been used to increase the range of drugs that can be effectively delivered through the skin (López-Castellano & Merino, 2010). To date, a plethora of chemicals have been evaluated as enhancers, but their inclusion in topical or transdermal formulations is limited due to fact that the underlying mechanisms of action of these agents remain unclear. Although different chemicals are employed by the industry as percutaneous enhancers, some of which have several desirable properties, to date none has proved to be ideal. An ideal chemical penetration enhancer should have the following attributes (Barry, 1983; López- Castellano & Merino, 2010): a) It should be non-toxic, non-irritating and non-allergenic, b) It should work rapidly, and its activity and duration of effect should be both predictable and reproducible, c) It should exert no pharmacological activity within the body, d) It should work unidirectionally, e) When removed, the skin's barrier properties should return both rapidly and fully, f) It should be compatible with both excipients and drugs, and g) It should be cosmetically acceptable and, ideally, odourless and colourless.

2.1 Percutaneous penetration routes of drugs

There are three major potential routes of percutaneous penetration: appendageal, transcellular (through the stratum corneum), and intercellular (through the stratum corneum) (Figure 1). There is a weight of evidence that suggests that passage through the intact stratum corneum constititutes the predominant route by which most molecules penetrate the skin, as the appendageal route is characterized by a limited available fractional

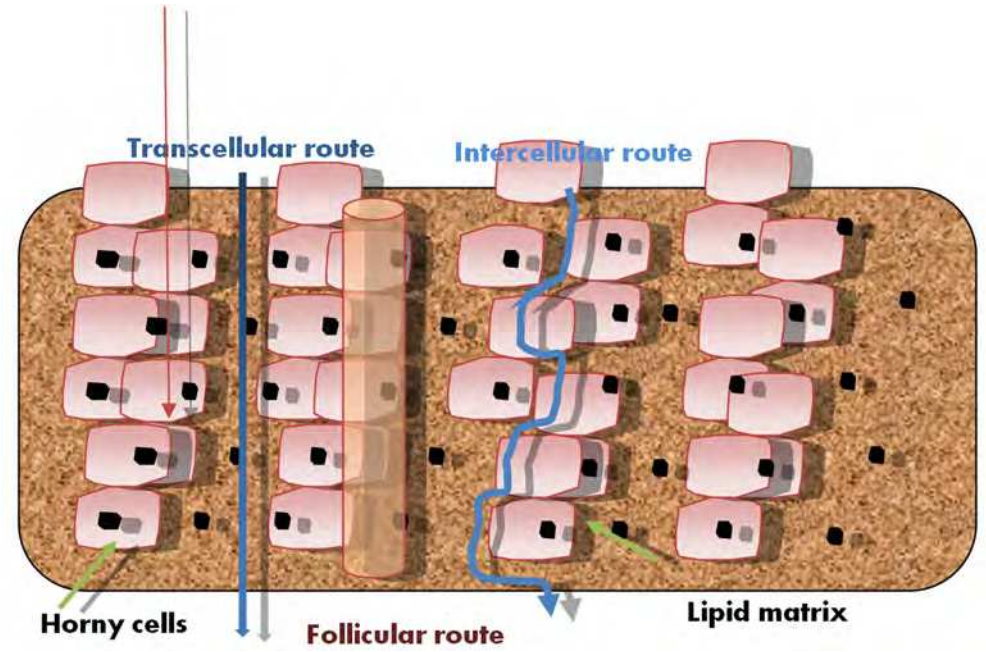

Fig. 1. Processes of percutaneous absorption

area of 0.1%. In this way, diffusion through the skin is controlled by the particular characteristics of the stratum corneum. In order to obtain a sufficient drug flux and, in turn, the therapeutical objectives in question, an alternative is to use chemical percutaneous enhancers. These substances alter some of the properties of the stratum corneum. (López-Castellano & Merino, 2010)

2.2 Direct effects on the skin due to the use of transdermal penetration enhancers

The lipid–protein-partititioning theory sets out the mechanisms by which enhancers alter skin lipids, proteins and/or partitioning behaviour (Barry, 1991): i) They act on the stratum corneum intracellular keratin by denaturing it or modifying its conformation, causing subsequent swelling and increased hydration; ii) They affect the desmosomes that maintain cohesion among corneocytes; iii) They modify the intercellular lipid domains to reduce the barrier-like resistance of the bilayer lipids. Disruption to the lipid bilayers can be homogeneous when the enhancer is distributed evenly within the complex bilayer lipids, but the accelerant is more likely to be heterogeneously concentrated within the domains of the bilayer lipids and iv) They alter the solvent nature of the stratum corneum, thus aiding the partitioning of the drug or a co-solvent into the tissue.(López-Castellano & Merino, 2010)

2.3 Indirect effects on the skin due to the use of transdermal penetration enhancers

Chemical enhancers can produce: *a)* Modification of the thermodynamic activity of the vehicle. The permeation of a good solvent from the formulation, such as ethanol, can increase the thermodynamic activity of a drug; *b)* It has been suggested that, by permeating through the membrane, a solvent can 'drag' the permeant with it, though this concept is somewhat controversial and requires confirmation; *c)* Solubilising the permeant within the donor, especially when solubility is very low, as in the case of aqueous donor solutions, can reduce depletion effects and prolong drug permeation.(López-Castellano & Merino, 2010)

2.4 Classification of percutaneous chemical enhancers

The classification of percutaneous enhancers is frequently based on the chemical class to which the compounds belong. Table 1 shows the principal classes of percutaneous enhancers.

CHEMICAL CLASS	COMPOUNDS
Water	Water
Sulfoxides and similar chemicals	Dimethyl sulfoxide, Dodecyl methyl sulfoxide
Ureas	Urea
Alcohols	Ethanol, Caprylic alcohol, Propylene glycol
Pyrrolidones and derivatives	N-methyl-2-pyrrolidone, 2-pyrrolidone
Azone and derivatives	Azone® (1-dodecylazacycloheptan-2-one)
Dioxolane derivatives	SEPA®
Surfactants (Anionic, Cationic, Nonionic, Zwitterionic)	Sodium lauryl sulfate, Cetyltrimethyl amonium bromide, Sorbitan monolaurate, Polisorbate 80, Dodecyl dimethyl ammoniopropane sulfate
Terpenes	Menthol, Limonene
Fatty acids	Oleic acid, Undecanoic acid

Table 1. Principal classes of percutaneous enhancers.

2.5 Determination of permeation enhancement

The great majority of studies of the effects of enhancers on skin permeability have been carried out by means of *in vitro* diffusion experiments in which various kinds of diffusion cells have been used. The most well-known of these cells are the Franz diffusion systems. These cells have two receptor compartments - donor and receptor (donor positioned above receptor) – between which the skin is placed. In general, the skin is pretreated with a solution of the chemical enhancer to be evaluated. The transdermal flux (J) of drugs can be estimated from the slope of the linear region (steady-state portion) of the accumulated amount of drug in the receptor compartment versus time plot. Permeation enhancing activity, expressed as enhancement ratio of flux (ER_{flux}), is determined as the ratio between the flux value obtained with the chemical enhancer and that obtained with the control. A number of variables can strongly influence the permeation enhancement of drugs. The most important are the skin used in the experiments, temperature, humidity, enhancer concentration, vehicle employed and degree of saturation of the drug in the donor and receptor compartments. (López-Castellano & Merino, 2010)

2.6 Uses in topical/transdermal formulations

Some examples of drugs delivered throughout the skin using chemical enhancer are shown in Table 2.

Drug	*Chemical enhancer*
Sodium salicylate (Hadgraft et al., 1985; Smith & Irwin, 2000); *Sodium naproxen* (Escobar-Chavez et al., 2005); *Ibuprofen* (Philips & Michniak,1995; Shen et al., 2007); *Nonivamide acetate* (Fang et al., 1997); *Meloxicam* (Zhang et al., 2009); *Flurbiprofen* (Ma et al., 2010); *Naloxone* (Xu et al., 2007); *Furosemide* (Agyralides et al., 2004); *Methotrexate* (Allan, 1995); *Sumatriptan succinate* (Balaguer-Fernandez et al., 2010).	Azone®
Sodium naproxen (Escobar-Chavez et al., 2005); *Sodium diclofenac* (Escribano et al., 2003); *Lidocaine* (Cazares-Delgadillo et al., 2005); *Testosterone* (Hathout et al., 2010); *Mometasone furoate* (Senyiğit et al., 2009); *Ketorolac* (Amrish et al., 2009).	Transcutol ®
Haloperidol (Vaddi et al., 2009); *Indomethacin* (Ogiso et al., 1995); *Leuprolide* (Lu et al., 1992).	Urea
Tizanidine hydrochloride (Mutalik et al., 2009); *Minoxidil* (Mura et al., 2009); *Metopimazine* (Bounoure et al., 2008); *Nortriptyline hydrochloride* (Merino et al., 2008; Escobar-Chavez et al., 2011).	Alcohols
Lidocaine (Lee et al., 2006); *Bupranolol* (Babu et al., 2008); *Propanolol* (Amnuaikit et al., 2005); *Acyclovir* (Montenegro et al., 2003).	Pyrrolidones
Tizanidine hydrochloride (Mutalik et al., 2009); *Daphnetin* (Wen et al., 2009); *Nitrendipin* (Mittal et al., 2008).	Fatty acids
Diclofenac (Kigasawa et al., 2009); *Nortiptyline hydrochloride* (Merino et al., 2008); *Verapamil hydrochloride* (Güngör et al., 2008); *Minoxidil* (Mura et al., 2009)	Terpenes
Retinol (Mélot et al., 2009); *Morphine* (Monti et al., 2001); *Arginine vasopressin* (Nair&Pachangula, 2003); *Insulin* (Pillai & Pachangula, 2003); *Enoxacin* (Fang et al., 1998).	Surfactants

Table 2. Examples of drugs delivered throughout the skin using chemical penetration enhancers.

3. Sonophoresis

Absorption of ultrasonic energy leads to tissue heating, and this has been used with therapeutic intent in many conditions. More recently it has been realized that benefit may also be obtained from the non-thermal effects that occur as ULTS travels through tissue. ULTS therapies can broadly be divided into ''high'' power and ''low'' power therapies where high power applications include high intensity focused ULTS and lithotripsy, and low power encompasses sonophoresis, sonoporation, gene therapy and bone healing. There are three distinct sets of ULTS conditions based on frequency range and applications: 1) High frequency (3–10 MHz) or diagnostic ULTS, 2) Medium frequency (0.7–3 MHz) or therapeutic ULTS, and 3) Low frequency (18 to 100 KHz) or power ULTS.

3.1 The ultrasound

The term ultrasonic refers to sound waves whose frequency is >20 KHz. The intensity (I, expressed in W/cm^2), or concentration of power within a specific area in an ULTS beam, is proportional to the square of the amplitude, p, which is the maximum increase or decrease in the pressure relative to ambient conditions in the absence of the sound wave. The complete relationship is: $I= p^2/2\rho c$, where ρ is the density of the medium and c is the speed of the sound (in human soft tissue, this velocity is 1540 m/s). The intensity is progressively lost when a sound wave passes through the body or is deviated from its initial direction, a phenomenon referred to as attenuation. In homogeneous tissue, the attenuation occurs as a result of absorption, in which case the sound energy is transformed into heat and scattered. The sound waves are produced in response to an electrical impulse in the piezoelectric crystal, allowing the conversion of electrical into mechanical or vibrational energy; this transformation requires a molecular medium (solid, liquid, or gas) to be effective. The ULTS beam is composed of two fields, the ''near field,'' in the region closest to the transducer face, and the ''far field,'' corresponding to the conical diverging portion of the beam (Figure 2). The parameters controlling this configuration of the ULTS beam are principally the frequency and the size of transducer.

3.2 Mechanisms of action

3.2.1 Cavitation effects

Cavitation is the formation of gaseous cavities in a medium upon ULTS exposure. The primary cause of cavitation is ULTS-induced pressure variation in the medium. Cavitation involves both the rapid growth and collapse of a bubble (inertial cavitation), or the slow oscillatory motion of a bubble in an ULTS field (stable cavitation). Collapse of cavitation bubbles releases a shock wave that can cause structural alteration in the surrounding tissue (Clarke et al., 2004) ULTS can generate violent microstreams, which increase the bioavailability of the drugs (Tachibana & Tachibana, 1999). Tissues contain air pockets that are trapped in the fibrous structures that act as nuclei for cavitation upon ultrasound exposure. The cavitational effects vary inversely with ULTS frequency and directly with ULTS intensity. Cavitation might be important when low-frequency ULTS is used, gassy fluids are exposed or when small gas-filled spaces are exposed. Cavitation occurs due to the nucleation of small gaseous cavities during the negative pressure cycles of ULTS, followed by the growth of these bubbles throughout subsequent pressure cycles (Tang et al., 2001).

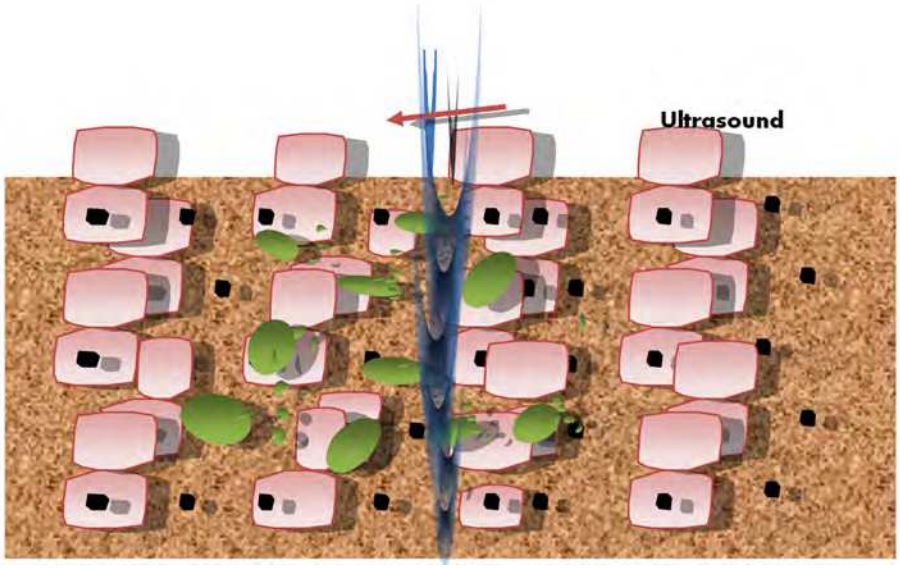

Fig. 2. Enhanced permeation by disruption of lipid barrier and cavitation by use of ULTS.

3.2.2 Thermal effects

Absorption of ULTS increases temperature of the medium. Materials that possess higher ULTS absorption coefficients, such as bone, experience severe thermal effects compared with muscle tissue, which has a lower absorption coefficient (Lubbers et al., 2003). The increase in the temperature of the medium upon ULTS exposure at a given frequency varies directly with the ULTS intensity and exposure time. The absorption coefficient of a medium increases directly with ULTS frequency resulting in temperature increase.

3.2.3 Convective transport

Fluid velocities are generated in porous medium exposed to ultrasound due to interference of the incident and reflected ULTS waves in the diffusion cell and oscillations of the cavitation bubbles. Fluid velocities generated in this way may affect transdermal transport by inducing convective transport of the permeant across the skin, especially through hair follicles and sweat ducts.

3.2.4 Mechanical effects

ULTS is a longitudinal pressure wave inducing sinusoidal pressure variations in the skin, which, in turn, induce sinusoidal density variation. At frequencies greater than 1 MHz, the density variations occur so rapidly that a small gaseous nucleus cannot grow and cavitational effects cease. But other effects due to density variations, such as generation of cyclic stresses because of density changes that ultimately lead to fatigue of the medium, may continue to occur. Lipid bilayers, being self-assembled structures, can easily be disordered by these stresses, which result in an increase in the bilayer permeability. This increase is,

however, non-significant and hence mechanical effects do not play an important role in therapeutic sonophoresis. Thus cavitation induced lipid bilayer disordering is found to be the most important cause for ultrasonic enhancement of transdermal transport.

3.3 Advantages and disadvantages of sonophoresis

Sonophoresis is capable of expanding the range of compounds that can be delivered transdermally. In addition to the benefits of avoiding the hepatic first-pass effect, and higher patient compliance, the additional advantages and disadvantages that the sonophoretic technique offers can be summarized as follows in Table 3.

Advantages	Disadvantages
Enhanced drug penetration (of selected drugs) over passive transport.	Can be time-consuming to administer.
Allows strict control of transdermal penetration rates. Permits rapid termination of drug delivery through termination of ULTS. Skin remains intact, therefore low risk of introducing infection. Less anxiety provoking or painful than injection	Minor tingling, irritation, and burning have been reported (these effects can often be minimized or eradicated with proper ULTS adjustment (Maloney et al., 1992). SC must be intact for effective drug penetration.
In many cases, greater patient satisfaction.	
Not immunologically sensitizing.	
Less risk of systemic absorption than injection.	

Table 3. Advantages and disadvantages of using sonophoresis as a physical penetration enhancer.

3.4 Applications of ultrasound

Table 4 summarizes the research on sonophoresis uses in the transdermal administration of drugs.

Anesthetics		
Research	**Outcome**	**References**
Topical skin penetration of lidocaine	Increase in the concentration of lidocaine transmitted into rabbit subdermal tissues when topical application was followed by use of ULTS	Wells et al., 1977.
Double blind, vehicle-controlled, crossover trial in healthy volunteers for lidocaine cream	No increase in absorption of lidocaine cream by using ULTS	McEnlay et al., 1985.
Trial in healthy volunteers for lidocaine oil	Other variables include differences in ULTS frequencies and drug concentrations.	Novak et al., 1964.

Skin lidocaine penetration	250 kHz induced the highest penetration of lidocaine.	Griffin & Touchstone, 1972.
Anesthetic effect of lidocaine in legs of hairless mice	ULTS in conjunction with a topical aqueous lidocaine solution was rapidly effective in inducing an anesthetic effect in the legs of hairless mice	Tachibana et al., 1993
Sonophoresis of topical benzocaine and dibucaine	No detectable increase in the rate of anesthetic penetration	Williams et al., 1990.
Administration of lidocaine hydrochloride trandermally on healthy volunteers applying 0.5 MHz ULTS.	0.5 MHz ULTS in sonophoresis for conduction anesthesia using lidocaine hydrochloride for a nerve block, it is more effective than the 1 Mhz that is widely used in clinical situations	Kim et al., 2007.
Permeation of procaine hydrochloride through cell monolayers applying therapeutical ULTS.	Extent and velocity of the permeation of procaine hydrochloride through MDCK monolayer can be controlled by sonophoresis	Hehn et al., 1996.
Analgesic and anti-inflammatory drugs		
Effect of intensity, mode, and duration of ULTS application on the transport of three non steroidal anti-inflammatory drugs (NSAIDs) across cellulose membrane and hairless rabbit-skin	Demonstrated the synergistic effect of temperature and ULTS operation parameters on drug transport of NSAIDs	Meshali et al., 2008.
Effect of an ULTS (1 MHz) on transdermal absorption of indomethacin from an ointment in rats	Intensity and duration of application play an important role in the transdermal sonophoretic delivery; intensity of 0.75 W/cm^2 for 10 min was most effective for delivering indomethacin	Miyazaki et al., 1992.
Study of the influence of ultrasound on percutaneous absorption of ketorolac tromethamine *in vitro* across hairless rat skin	A significant increase in permeation of ketorolac through rat skin was observed with the applied sonication at 3 W/cm^2 when compared with permeation at 1 and 2 W/cm^2.	Tiwari et al., 2004.
To determine if a ketorolac tromethamine (KT) gel solution could be administered *in vivo* via phonophoretic transdermal delivery using pulsed ULTS by examining its anti-inflammatory effects in a rat carrageenan inflammation model.	The transdermal application of KT gel using sonophoresis had significant anti-hyperalgesic and anti-inflammatory effects. These findings suggest that the transdermal administration of a KT gel using sonophoresis with pulsed ULTS might be useful for treating acute inflammation and pain.	Yang et al., 2008.
Application of ultraphonophoresis of 5% ibuprofen nurofen gel to affected joints of 20 patients.	Analgesic efficacy of transcutaneous 5% gel nurofen in osteoarthrosis.	Serikov et al., 2007.

Examination of therapeutic effects of sonophoresis with ketoprofen in gel form in patients with enthesopathy of the elbow.	Positive effects of sonophoresis using a pharmacologically active gel with ketoprofen were shown to be highly significant in assessments, objective (clinical examination) and subjective (interview). The pain symptoms in the elbow resolved in most of the patients.	Cabak et al., 2005.
Quantitative study of sodium diclofenac (Voltaren Emulgel, Novartis) phonophoresis in humans	Previously applied therapeutic ULTS irradiation enhances the percutaneous penetration of the topical diclofenac gel, although the mechanism remains unclear	Rosim et al., 2005.
Investigation of *in vitro* penetration and the *in vivo* transport of flufenamic acid in dependence of ULTS.	Using this *in vitro* model it is possible to compare the transdermal delivery of commercial flufenamic ointment in volunteers.	Hippius et al., 1998.
Antibiotics		
Effect of ULTS on the delivery of topically applied amphotericin B ointment in guinea pigs.	Amphotericin B content in the skin and subcutaneous fatty tissues was much higher when the drug was delivered in the presence of ULTS.	Rornanenko & Araviiskii, 1991.
Administration of tetracycline in healthy rabbits using electrophoresis and sonophoresis	It was found that the tissue levels of tetracycline administered with the modified methods of electro and sonophoresis increased with an increase in the current density or ULTS intensity, the procedure time and antibiotic concentration.	Ragelis et al., 1981.
Immunosuppressives		
Investigated the topical transport of Cyclosporin A using low-frequency US throughout rat skin	The enhanced skin accumulation of Cyclosporin A by the combination of low-frequency ULTS and chemical enhancers could help significantly to optimize the targeting of the drug without of a concomitant increase of the systemic side effects.	Liu et al., 2006.
Evaluation of the efficacy of low frequency sonophoresis (LFS) at 25KHz produced by a sonicator apparatus for treatment of alopecia areata, melasma and solar lentigo.	The study showed that LFS, a not aggressive technique, enhanced penetration of topic agents obtaining effects at the level of the epidermis, dermis and appendages (intradermal delivery), giving better results in the treatment of some cosmetic skin disorders.	Santoianni et al., 2004.

Anticancer drugs		
Application of a method using ULTS and nano/microbubbles to cancer gene therapy using prodrug activation therapy.	Dramatic reductions of the tumor size by a factor of four.	Aoi et al., 2007.
Investigation of competitive transport across skin of 5-fluorouracil into coupling gel under the influence of ULTS, heat-alone and Azone® enhancement.	Ultrasonication produced a decrease in percutaneous drug penetration. This effect was due to the diffusive loss of the hydrophilic substance 5-fluorouracil from the skin surface.	Meidan et al., 1999.
Insulin		
To determine if the 3x1 rectangular cymbal array perform significantly better than the 3x3 circular array for glucose reduction in hyperglycemic rabbits.	Using the rectangular cymbal array, the glucose decreased faster and to a level of -200.8±5.9 mg/dL after 90 min.	Luis et al., 2007.
To demonstrate ultrasonic transdermal delivery of insulin *in vivo* using rabbits with a novel, low-profile two-by-two ULTS array.	For the ULTS-insulin group, the glucose level was found to decrease to -132.6 ± 35.7 mg/dL from the initial baseline in 60 min	Lee et al., 2004.
The purpose of this study was to demonstrate the feasibility of ULTS-mediated transdermal delivery of insulin *in vivo* using rats with a novel, low profile two-by-two US array based on the "cymbal" transducer.	For the 60-min ULTS exposure group, the glucose level was found to decrease from the baseline to -267.5 ± 61.9 mg/dL in 1 h. Moreover, to study the effects of ULTS exposure time on insulin delivery, the 20-min group had essentially the same result as the 60-min exposure at a similar intensity.	Smith et al., 2003.
Corticosteroids		
Determination of the effect of ULTS on the transcutaneous absorption of dexamethasone.	A sonophoretic effect occurred with dexamethasone when its application saturated the skin.	Saliba et al., 2007.
To determine if ULTS enhances the diffusion of transdermally applied corticosteroids.	The effects of sonophoresed dexamethasone can be measured in terms of reduced collagen deposition as far down as the subcutaneous tissue but not in the submuscular or subtendinous tissue	Byl et al., 1993.
Comparison of effectiveness of 0.4% Dexamethasone sodium phosphate (DEX-P) sonophoresis (PH) with 0.4% DEX-P iontophoresis (ION) therapy in the management of patients with knee joint osteoarthritis	Significant improvement in total WOMAC scores was observed in 15 (60%) and 16 (64%) patients in the PH and ION groups respectively, indicating no significant difference in the improvement rate.	Akinbo et al., 2007.

Designing a sonophoretic drug delivery system to enhance the triamcinolone acetonide (TA) permeability.	The highest permeation of TA was observed under the ULTS treatment conditions of low frequency, high intensity, and in continuous mode.	Yang et al., 2006.
Cardiotonics		
The sonophoresis of digoxin *in vitro* through human and hairless mouse skin.	There was no enhancement of digoxin absorption across human skin by ULTS.	Machet et al., 1996.
Vasodilators		
Skin penetration enhancement effect of ULTS on methyl nicotinate in 10 healthy human volunteers.	ULTS treatment applied prior to methyl nicotinate led to enhanced percutaneous absorption of the drug	McEnlay et al., 1993.
Hormones		
Effect of permeation enhancers and application of low frequency (LUS) and high frequency ultrasound (HUS) on testosterone (TS) transdermal permeation after application of testosterone solid lipid microparticles (SLM).	Skin exposure to HUS or LUS before application of 1% dodecylamine for 30 min had no superior enhancement effect over application of either LUS or HUS alone. Application of drug loaded SLM offered skin protection against the irritation effect produced by TS and 1% DA.	El-Kamel et al., 2008.
Cicatrizants		
The effectiveness of sonophoresis on the delivery of high molecular weight (MW) hyaluronan (HA) into synovial membrane using an animal model of osteoarthritis (OA).	Synovial fluid analysis revealed increased absorption and fluorescence microscopy showed deeper penetration of both HA1000 and HA3000.	Park et al., 2005.
Calcein		
The skin permeation clearance of model hydrophilic solutes, calcein (MW 623) and-labeled dextrans [MW 4400 (FD-4) and MW 38000 (FD-40)], across the skin under the influence of ULTS.	Good correlations were observed between the $3H_2O$ flux and solute clearances and, unexpectedly, the slope values obtained from linear regression of the plots were consistent for all solutes examined.	Morimoto et al., 2005.
Oligonucleotids		
Assessment of the potential of low frequency ULTS (20 kHz, 2.4 W/cm^2) in delivering therapeutically significant quantities of anti-sense oligonucleotides into skin.	Microscopic evaluations using revealed heterogeneous penetration into the skin. Heterogeneous penetration led to the formation of localized transport pathways, which occupied about 5% of the total exposed skin area.	Tezel et al., 2004.
Stimulants		
The effect of low-frequency sonophoresis on fentanyl and caffeine permeation through human and hairless rat skin.	Discontinuous ULTS mode was found to be more effective in increasing transdermal penetration of fentanyl while transdermal transport of caffeine was enhanced by both continuous and pulsed mode.	Boucaud et al., 2001.

Calcium		
Manipulation of the Ca^{2+} content of the upper epidermis by sonophoresis across hairless mouse SC.	Sonophoresis at 15 MHz did not alter barrier function.	Menon et al., 1994.
Panax notoginseng		
Effect of a therapeutic US coupled with a Panax notoginseng gel for medial collateral ligament repair in rats.	This study reveals a positive ultrasonic effect of Panax notoginseng extract for improving the strength of ligament repair.	Ng et al., 2008.
Other applications *i)To study the mechanisms of penetration due to US throughout the skin*		
To demonstrate the calcein permeability through the localized transport regions (LTRs) from the exposure to the ULTS/ Sodium lauryl sulphate (SLS) system.	LTRs and the non-LTRs exhibit significant decreases in skin electrical resistivity relative to untreated skin, suggesting the existence of two levels of significant skin structural perturbation due to ULTS exposure in the presence of SLS.	Kushner IV et al., 2004.
To shed light on the mechanism(s) by which low-frequency ULTS (20 KHz) enhances the permeability of the skin.	Significant fractions (30%) of the intercellular lipids of SC were removed during the application of low frequency sonophoresis.	Alvarez-Roman et al., 2003.
Investigation of short time sonication effects of human skin at variable intensities and on the dynamics of fluorescein transport across the skin.	A short application of ULTS enhanced the transport of fluorescein across human skin by a factor in the range of 2–9 for full thickness skin samples and by a factor in the range of 2–28 000 for heat-stripped SC samples	Cancel et al., 2004.
Use of quantum dots as a tracer and confocal microscopy and transmission electron microscopy (TEM) as visualization methods, on low frequency sonophoresis.	ULTS significantly increased the frequency of occurrence of the otherwise scattered and separated lacunar spaces in the SC. A significant increase in lacunar dimensions was observed when 1% w/v sodium lauryl sulfate was added to the coupling medium.	Paliwal et al., 2006.
ii)Kelloids		
ULTS therapy with a water-based gel alone	"Complete flattening" of keloids in two young men when 1 MHz at 0.8 W/cm 2 was applied for approximately 4 minutes.	Walker, 1983.
iii) Tumours		
Optimization of ULTS parameters for *in vivo* bleomycin delivery	An effective antitumor effect was demonstrated in solid tumors of both murine and human cell lines.	Larkin et al., 2008.

Investigation of high-intensity focused ULTS (HIFU) exposure of (111) In-MX-B3.	The HIFU exposure shortened the peak tumor uptake time (24 vs. 48 h for the control) and increased the peak tumor uptake value (38 vs. 25 %ID/g for the control). The HIFU effect on enhancing tumor uptake was greater at earlier times up to 24 h.	Khaibullina et al., 2008.
Supurative wounds		
Treatment of suppurative wounds with ULTS.	sonophoresis of ethylenediaminetetra acetic acid with the quinoxaline antibiotic dioxidine was effective in accelerating wound purification an delimination of necrotic issues	Levenets et al., 1989.
Treatment of suppurative wounds with ULTS.	Sonophoresis of a 1% papain solution together with dimethyl sulfoxide was an effective method for treating purulent wounds and inflammatory infiltrates.	Matinian et al., 1990.

Table 4. Research on uses of sonophoresis to administer different drugs through the skin

4. Iontophoresis

Transdermal 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. During application of the current, the drug is repelled by the corresponding electrode and pushed through the stratum corneum. A substance can pass through the skin by electromigration, electroosmosis or passive diffusion. The latter of the three mechanisms is a result of changes caused by the electric field to the permeability of the skin, and its effects are negligible compared with those of the other two mechanisms. When ions are repelled by the electrode of the same charge and attracted by the electrode of the opposite charge is electromigration. When neutral substances are transported with the solvent flow is electroosmosis, which at physiological pH favours the movement from the anode to the skin.

The advantages and disadvantages that the iontophoretic technique offers are summarized in Table 5.

4.1 Mechanisms of action

Skin is a complex membrane and controls the movement of molecules across it in the presence of an electric field. Skin has an isoelectric point (pI) of 4–4.5. Above this pH, the carboxylic acid groups are ionized. Therefore, at higher pH values, the skin behaves as a permselective membrane which especially attracts cations that have been repelled by the anode, thus favouring the passage of molecules by electromigration (Merino et al., 1999). The movement of small sized cations (mainly Na+) generates a solvent flow that promotes the passage of non-charged molecules through the skin. This process is identified as electroosmosis (Delgado-Charro and Guy, 1994). Electrical mobility decreases with

molecular weight, and, as a consequence, the electroosmotic contribution becomes increasingly important for larger molecules (Guy et al., 2000). The dependence of iontophoretic flux on the intensity of the current applied has been clearly demonstrated by Faraday's law (Sage et al., 1992): where Ja is the flux (in moles per unit time), ta is the transport number, Za is the valence of ion a, I is the current applied (Amperes), and F is Faraday's constant (Coulombs/mol). The transport number, ta, is the fraction of the total current transported by a specific ion, and is a measure of its efficiency as a charge carrier: ta=Ia / I. It follows that knowledge of a compound's transport number allows the feasibility of its iontophoretic delivery or extraction to be predicted. The sum of the transport numbers of all the ions present during iontophoresis equals 1 (Σti=1), illustrating the competitive nature of electrotransport.

Advantages	Disadvantages
Enhance penetration of ionized and unionized molecules. Moreover, improving the delivery of polar molecules as well as high molecular weight compounds (e. g. peptides and oligonucleotides). Enabling continuous or pulsatile delivery of drug (depending on the current applied). Permitting easier termination of drug delivery. Offering better control over the amount of drug delivered since the amount of compound delivered depends on applied current, duration of applied current, and area of skin exposed to the current. Restoration of the skin barrier functions without producing severe skin irritation. Ability to be used for systemic delivery or local (topical) delivery of drugs. Reducing considerably the inter and intraindividual variability, since the rate of drug delivery is more dependent on applied current than on stratum corneum characteristics.	Can be time-consuming to administer. The actual current density in the follicle maybe high enough to damage growing hair. SC must be intact for effective drug penetration.

Table 5. Advantages and disadvantages of using iontophoresis as a physical penetration enhancer.

4.2 Types of iontophresis

4.2.1 Direct iontophoresis

Direct iontophoresis can be anodal if the drug is neutral or positively charged and cathodal if the drug is negatively charged. Although cations have better properties for iontophoresis, anions can also increase their transdermal drug flux with respect to passive diffusion.

4.2.2 Reverse iontophoresis

Reverse iontophoresis across the skin is a potentially useful alternative for non-invasive clinical and therapeutic drug monitoring. During current application, reverse iontophoresis

allows the movement of neutral and positively charged entities into the cathode while negatively charged entities move into the anode. The main problem with this is that skin contains some of the entities to be analyzed, which implies that there is a period of time within which it is necessary to withdraw skin reserves and after which it is possible to correlate extracted levels of the analytes with levels in the blood (Leboulanger et al., 2004).

4.3 Applications of iontophoresis

The most extended uses of iontophoresis are the treatment of palmoplantar hyperhidrosis and the diagnosis of cystic fibrosis. However, iontophoresis is also used for the topical delivery of others drugs such as lidocaine, acyclovir and dexamethasone. The only system commercially available at present is the fentanyl iontophoretic transdermal system. It is indicated for the shortterm management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization. Currently, the iontophoretic delivery of apomorphine for the treatment of idiopathic Parkinson's disease is being evaluated in human subjects. Peptide drugs including various series of amino acid derivatives and tripeptides, thyrotropin release hormones, LHRH and analogues, vasopressin and calcitonin can also be administered by means of this technique. One peptide that has focused the attention of researchers in the field of iontophoresis is insulin.

5. Electroporation

Electroporation is the phenomenon in which cell membrane permeability to ions and macromolecules is increased by exposing the cell to short high electric field pulses. The increase in permeability is attributed to the electric field induced "breakdown" of the cell membrane and the formation of nano- scale defects or "pores" in the membrane – and hence electro-"poration". Electroporation can be of two types - reversible and irreversible. In irreversible electroporation the electric field is such that the membrane permeabilization leads to cell death. This may be caused by either permanent permeabilization of the membrane and cell lysis (necrosis) or by temporary permeabilization of a magnitude which can cause a severe disruption of the cell homeostasis that can finally results in cell death, either necrotic or apoptotic. In reversible electroporation the electric pulse causes only a temporary increase in permeability and the cell survives. The reversible electroporation mode has numerous applications in biotechnology and medicine both, *in vitro* and *in vivo*. Irreversible electroporation has applications in the food industry, for sterilization and in medicine for tissue ablation (Ball et al., 2010).

5.1 Mechanisms of transdermal electroporation

The theory postulates two paths for electroporation induced transdermal transport, through pores formed in the multiple lipid bilayers connecting corneocytes and through appendage cells. Small lipid-soluble molecules can partition into the SC, and then diffuse across the lipid bilayer membranes, but water soluble molecules, particularly charged molecules, cannot penetrate significantly by this route. High voltage pulsing (> 50V) creates aqueous pathways ("pore") through stratum corneum (SC) lipid bilayer membranes, and short pathway segments are formed across 5--6 lipid bilayer membranes which connect adjacent corneocyte interiors forming transcellular straight-through pathways. Moderate voltage (= 5

to 50V) pulses appear to electroporate cell linings of the appendages. Temperature is considered to play a role in the permeabilization.

5.2 Advantages and disadvantages of electroporation for transdermal drug delivery

The advantages and disadvantages that the electroporation technique offers are summarized in Table 6.

Advantages	Disadvantages
Enhanced drug penetration (of selected drugs) over passive transport. Allows strict control of transdermal penetration rates. Versatility: electroporation is effective nearly with all cells and species types (Sung et al., 2003). Efficiency: a large majority of cells take in the target DNA or molecule (Huang et al., 2005). Permits rapid termination of drug delivery through termination of electroporation. The procedure may be performed with intact tissue (Heller et al., 1996). Less anxiety provoking or painful than injection. In many cases, greater patient satisfaction.	Cell damage: If the pulses are of the wrong length or intensity, some pores may become too large or fail to close after membrane discharge causing cell damage or rupture (Murthy et al., 2004). The transport of material into and out of the cell during the time of electropermeability is relatively nonspecific (Murthy et al., 2004).
Not immunologically sensitizing.	

Table 6. Advantages and disadvantages of using electroporation as a physical penetration enhancer.

5.3 Applications of electroporation

The field of skin electroporation is made of two aspects. The first deal with electroporation in a conventional sense in relation to the cells of the skin and the second is unique and relates to transdermal effects. The concept of transdermal electroporation may be traced to fundamental research on the breakdown of flat lipid bilayer membranes. Prausnitz et al., (1993) addresses the fact that transdermal transport normally occurs primarily through the intracellular lipids organized in bilayers. Small molecular weight lipophilic drugs can be effectively delivered by passive transdermal delivery. However, the stratum corneum does not permit passage of polar/hydrophilic molecules and macromolecules. The paper suggests that microsecond to millisecond electroporation type pulsed electric fields applied across the skin produce, in a manner similar to that found in studies on flat lipid bilayers, trans bilayer aqueous pores. It reports that electroporation produces transient structural changes in the skin resulting in an up to four orders of magnitude increase in transdermal mass transfer flux of polar molecules in human skin *in vitro* and animal skin *in vivo*.

6. Microneedles

The use of microneedles is another method for bypassing the stratum corneum barrier, which have been introduced as a form of transdermal drug delivery. They can penetrate the

upper layer of the skin without reaching the dermis, to be an efficient method to deliver drugs transdermally in an almost painless method. The drug diffuses across the rest of the epidermis into the dermis where it is absorbed into the blood circulation. Nowadays different types of microneedles have been designed by other researchers as well, varying in their materials of fabrication, shapes, dimensions, modes of application, etc. (Chabri et al., 2009).

6.1 Microneedle types and their methods of transdermal delivery

Microneedles are available as both solid and hollow microneedles made of various materials (Figure 3). Till date, five methods of transdermal delivery mediated by microneedles have been attempted (Gill & Prausnitz, 2007): *Poke with patch approach*: It can be inserted into the skin to pierce the stratum corneum and create micro conduits through which drug can enter into the lower layers of the epidermis (Henry et al., 1998). *Coat and poke approach:* It involves coating the drug to be delivered around the surface of the microneedle. By inserting the microneedles through the skin, the drug coating dissolves off in the skin fluid and the dissolved drug diffuses through the skin into the blood microcirculation. The coating methods are used to roll coating, spray coating and dip coating (Gill & Prausnitz, 2006). *Dip and scrape:* The dip and scrape method involves placing the array in contact with the drug solution and then scraping multiple times across the skin to create microabbrassions (Mikszta et al., 2002). *Dissolving microneedles:* It is referred to microneedles made from a biodegradable polymeric material with the drugs encapsulated inside them. In this method, the drug is released in a controlled manner as the microneedle dissolves off when inserted into the skin (Lee W. J et al., 2007). *Injection through hollow microneedles:* This occurs where the microneedles are designed with holes at the centre or with side openings through which drugs are microinjected into the lower layers of the skin and then diffuses across the viable skin until it reaches the blood vessels in the dermis (Griss & Stemme, 2003).

Solid microneedles: These are easier to fabricate, have better mechanical strength and sharper tips as compared to hollow microneedles (Rhoxed et al., 2008a). Solid silicon microneedles have been widely used for the transdermal drug delivery studies (Donnelly et al., 2009; Haq et al., 2009). However, silicon is expensive, not biocompatible and brittle. Therefore it breaks easily during the penetration across skin (Chen et al., 2008). Polymer has been used as an alternative material because it is a cheaper and stronger material which could reduce tissue damage (Fernandez et al., 2009). Polymer increases the bluntness of the microneedle tip due to the low modulus and yield strength of polymer. Polymer microneedles have a main limitation with its mechanical properties which could cause needle failure during the penetration across skin (Park et al., 2007). Bevelled tip microneedles have been fabricated using biodegradable polymers (Park, 2004). Metal is the third material used to manufacture microneedles. It is mechanically strong and relatively cheap to produce.

Hollow microneedles*:* The purpose of this type of microneedles is to deliver drugs through the bore at the needle tip. This reduces the sharpness of needle tip which affect the penetration of this needle into skin. These issues have been resolved recently including openings at the side in the microneedles rather than at the bottom (Roxhed et al., 2008). These microneedles have their tip closed initially; however they can be opened on insertion into the skin where the tip dissolves in the high saline solution in the interstitial fluid. The tips can also be opened as a result of applied pressure. It has been proposed the use of

rotary drilling and mechanical vibration as methods to enhance insertion of hollow microneedles and the fluid infusion flow rate (Wang et al., 2006).

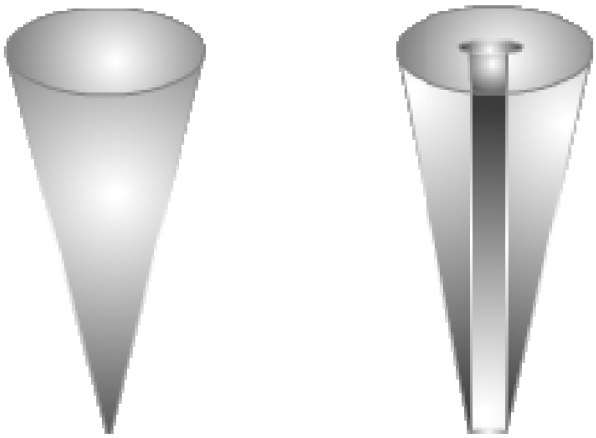

Fig. 3. Two dimensional view of hollow and solid microneedle.

6.2 Microneedles manufacturing

The methods that have been adopted for microneedle fabrication include wet etching, deep reactive ion etching (DRIE) (Teo et al., 2005), microinjection moulding (Sammoura et al., 2007), isotropic etching, isotropic etching in combination with deep etching and wet etching respectively, dry etching, isotropic and anisotropic, photolithography, thin film deposition (Moon & Lee, 2003), laser cutting (Martanto et al., 2004), and inclined LIGA process (Perennes et al., 2006). Studies have shown that factors such as microneedle geometry, coating depth on solid microneedle and skin thickness affect the drug delivery efficiency using microneedles (Al-Qallaf et al., 2009a; 2009b). To ensure that both the insertion and delivery occur at the right location, they should be sharp enough and at least 100μm in length (Stoeber & Liepmann, 2000).

6.3 Microneedles applications

Vaccination against virus: Researchers have recently presented microneedle patches as a better alternative for immunization. The vaccine can be coated unto microneedle array and presented as a simple patch which can allow patients to immunize themselves without the necessity for intense medical training (Stoeber & Liepmann, 2005). *Cutaneous fluid extraction and glucose monitoring:* A prototype of a disposable microneedle based glucose monitoring devices has been designed in which, the fluid extraction chamber attached to the microneedle can be connected to a sensing device which measures and indicates the glucose concentration in the body (Zimmermann et al., 2003). *Acne treatment:* The treatment is limited by the low rate of penetration of drugs through the stratum corneum. So, experiments have been carried out by applying the TheraJectMAT™ dissolving microneedles containing API in a GRAS matrix to the surface of human skin with acne (Kwon, 2006). *Delivery of nanoparticles:* It was showed that the delivery of particles of 1μm in

diameter is enhanced when the skin is pre-treated with microneedles by adopting the poke with patch approach. Therefore, it seems to us that the delivery of micro and nano-particles is important in order to facilitate controlled/ delayed delivery after the drug is inserted into the skin (McAllister et al., 2003). *Insulin delivery:* Microneedles have been shown to deliver insulin with a significant biological effect as the blood glucose concentration was reduced by substantial amount using microneedles.

7. Nanocarriers

Nanocarriers are so small to be detected by immune system and they can deliver the drug in the target organ using lower drug doses in order to reduce side effects. Nanocarriers can be administrated into the organisms by all the routes; one of them is the dermal route. The nanocarriers most used and investigated for topic/transdermal drug delivery in the pharmaceutical field are liposomes, dendrimers, nanoparticles and nanoemulsions (Table 7).

Nanocarrier	Size	Preparation Methods	Characteristics	References
Nanoparticles	10-1000 nm	In situ polymerization, emulsification-evaporation, emulsification-diffusion, emulsification-diffusion by solvent displacement	Solid or hollow particles wich have entraped, binded or encapsulated drugs.	Domínguez-Delgado et al., 2011; oppimath et al., 2001
Solid lipid nanoparticles	50-1000 nm	High-pressure homogenization.	Similar to polymeric nanoparticles but made of solid lipids.	Almeida & Souto, 2007
Inorganic nanoparticles	<50nm	Sol-gel technique	Nanometric particles, made up of inorganic compounds such as silica, titania and alumina.	García-González, 2009
Liposomes	25 nm-100 µm	Sonication, extrusion, mozafari method	Vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments.	El Maghraby et al., 2008
Dendrimers	3–10 nm	Polymerization	Macromolecular high branched structures.	Menjoge et al., 2010
Quantum dots	2-10nm	Colloidal assembly, viral assembly, electrochemical assembly.	Made up of organic surfactants, precursors and solvents.	Rzigalinski & Strobl, 2009
Lipid globules	1-100 nm	Emulsification espontaneous systems.	Multicomponent fluid made of water, a hydrophobic liquid, and one or several surfactants resulting in a stable system.	Dan et al., 2010

Nanocarrier	Size	Preparation Methods	Characteristics	References
Lipid microcylinders	<1 μm	Self emulsification	Self organizing system in which surfactants crystallize into tightly packed bilayers that spontaneously form cylinders	Dodla & Bellamkonda, 2008
Lipid microbubbles	<2 μm	Sonication	Gas filled microspheres stabilized by phospholipids, polymers or low density proteins.	Tartis et al., 2008
Lipospheres	0.2-100 μm	Melt method, multiple microemulsion, cosolvent method	Solid lipid core stabilized by a monolayer of phospholipids molecules embedded in the particle surface.	Fang et al., 2007
Ethosomes	<400 nm	Cold method, hot method	Non invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation.	Elsayed et al., 2006
Aquasomes	60-300 nm	Self-assembling of hydroxyapatite by co-precipitation method	The particle core is composed of noncrystalline calcium phosphate or ceramic diamond, and it is covered by a polyhydroxyl oligomeric film.	Rojas-Oviedo et al., 2007
Pharmacosomes	<200 nm	Hand-shaking method, Ether-injection method	Pure drug vesicles formed by amphiphilic drugs	Jin et al., 2006
Colloidosomes	200 nm – 1.5 μm	Self-assembly of colloidal particles at the interface of emulsion droplets	Hollow capsules with elastic shells.	Rossier-Miranda et al., 2009
Niosomes	10-1000 nm	Self-assembly of nonionic surfactant	Bilayered structures made of non-ionic surfactant vesicles.	Hong et al., 2009
Nanoemulsions	20-200 nm	High-pressure, homogenization, microfluidization, phase inversion Temperature.	Submicron emulsions o/w or w/o	Elnaggar et al., 2009

Table 7. Examples of Nanocarriers used for transdermal drug delivery

7.1 Liposomes

Liposomes are hollow lipid bilayer structures that can transport hydrophilic drugs inside the core and hydrophobic drugs between the bilayer (Bangham, 1993). They are structures made of cholesterol and phospholipids. They can have different properties depending on the excipients included and the process of their elaboration. The nature of liposomes makes them one of the best alternatives for drug delivery because they are non-toxic and remain inside the bloodstream for a long time. Liposomes can be surface-charged as neutral, negative or positive, depending on the functional groups and pH medium. Liposomes can encapsulate both lipophilic and hydrophilic drugs in a stable manner, depending on the polymer added to the surface (Rodriguez-Justo & Morae et al., 2011). There are small unilamellar vesicles (25 nm to 100nm), medium-sized unilamellar vesicles (100 nm and 500nm), large unilamellar vesicles, giant unilamellar vesicles, oligolamellar vesicles, large multilamellar vesicles and multivesicular vesicles (500 nm to microns). The thickness of the membrane measures approximately 5 to 6 nm. These shapes and sizes depend of the preparation technique, the lipids used and process variables. Depending on these parameters, the behavior both *in vivo* and *in vitro* can change and opsonization processes, leakage profiles, disposition in the body and shelf life are different due to the type of liposome (Rodriguez-Justo & Morae et al., 2011).

Liposomes preparation techniques follow three basic steps with particular features depending on safety, potential scale up and simplicity: 1) Lipid must be hydrated, 2) Liposomes have to be sized and 3) Nonencapsulated drug has to be removed. The degree of transdermal drug penetration is affected by the lamellarity, lipid composition, charge on the liposomal surface, mode of application and the total lipid concentrations (Cevc & Blume, 1992). Some examples of drugs delivered throughout the skin by using liposomes are melatonin (Dubey et al., 2007b), indinavir (Dubey et al., 2010), amphotericin B (Manosroi et al., 2004), methotrexate (Dubey et al., 2007a), ketoprofen (Maestrelli et al., 2005), estradiol (Essa et al., 2004), clindamicyn hydrochloride and lignocaine (Sharma et al., 1994).

7.2 Dendrimers

Dendrimers are monodisperse populations that are structurally and chemically uniform. They allow conjugation with numerous functional groups due to the nature of their branches. The amount of branches increases exponentially and dendrimers growth is typically about 1 nm per generation (Svenson & Tomalia, 2005). The dendrimers classification is based on the number of generations. After the creation of a core, the stepwise synthesis is called first generation; after that, every stepwise addition of monomers creates the next generation. This approach allows an iterative synthesis, providing the ability to control both molecular weight and architecture.

The kind of polymer chosen to construct the dendrimer by polimerization is very important with regard to the final architecture and features. In addition, the use of branched monomers has the peculiarity of providing tailored loci for site-specific molecular recognition and encapsulation. Notably, 3D and fractal architecture, as well as the peripheral functional groups, provide dendrimers with important characteristic physical

and chemical properties. In comparison with linear polymers, dendritic structures have "dendritic voids" that give these molecules important and useful features. These spaces inside dendrimers can mimic the molecular recognition performed by natural proteins. Furthermore, dendrimers have a high surface-charge density due to ionizable groups that help them to attach drugs by electrostatic forces, regardless of the stoichimetry. This dendrimer-drug association provides drugs with better solubility, increasing their transport through biological membranes and sometimes increasing drug stability. The number of molecules that can be incorporated into dendrimers is related to the number of surface functional groups; therefore, later-generation dendrimers are more easily incorporated into dendritic structure. However, not all the functional groups are available for interaction due to steric volume, molecule rotation or stereochemistry effects. Dendrimers can have positive and negative charges, which allows them to complex different types of drugs (Kabanov et al., 1998). The main problems with this kind of transdermal carrier are poor biodegradation and inherent cytotoxicity (Parekh, 2007). In order to reduce their toxicity, dendrimers have been linked to peptides and which are formed from amino acids linked via peptide-amide bonds to the branches of dendrimers in the core or on the surface. When they are bio-transformed, dendrimer-peptide systems produce amino-acid derivatives. Finally, the synthesis of these structures is less expensive and purification does not present any difficulty (Niederhafner et al., 2005). Due to their form and size, these molecules can carry drugs, imaging agents, etc. Dendrimers interact with lipids present in membranes, and they show better permeation in cell cultures and intestinal membranes (Cheng et al., 2008). Dendrimers also act like solubility enhancers, increasing the permeation of lipophilic drugs; nevertheless, they are not good carriers for and hydrophilic drugs.

7.3 Nanoparticles

Nanoparticles are smaller than 1,000 nm. Nowadays, it is possible to insert many types of materials such as drugs, proteins, peptides, DNA, etc. into the nanoparticles. They are constructed from materials designed to resist pH, temperature, enzymatic attack, or other problems (Huang L. et al., 2010; Wei et al., 2010). The nanoparticle technology can be divided into three stages: first generation (involves those nanoparticles that had only one component in their structure and these delivery systems are able to transport drugs in the blood until they reach the target), second generation (implies nanoparticles made of one main component and additional substances and these complexes are able to cross barriers and reach difficult targets such as the brain) and third generation is represented by nanoparticles that can be made of nanoparticles with one main component combined with a second component to reach a specific target (Cui et al., 2005; Herffernan & Murthy, 2005). Moreover, nanoparticles can be classified as nanospheres or nanocapsules (Figure 4). Nanospheres are solid-core structures and nanocapsules are hollow-core structures (Yoo et al., 2005). Nanoparticles can be composed of polymers, lipids, polysaccharides and proteins (Goswami et al., 2010; Li et al., 2009). Nanoparticles preparation techniques are based on their physicochemical properties. They are made by emulsification-diffusion by solvent displacement, emulsification-polymerization, in situ-polymerization, gelation, nanoprecipitation, solvent evaporation/extraction, inverse salting out, dispersion polymerization and other derived from these one.

a) b)

Fig. 4. a) Nanospheres and b) nanocapsules.

7.4 Nanoemulsions

Nanoemulsion 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). They can be stable (methastable) for long times due to the extremely small sizes and the use of adequate surfactants. Nanoemulsions can use hydrophobic and hydrophilic drugs because it is possible to make both w/o or o/w nanoemulsions (Sonneville-Aubrun, et al. 2004). They are non-toxic and non-irritant systems and they can be used for skin or mucous membranes, parenteral and non parenteral administration in general and they have been used in the cosmetic field. Nanoemulsions can be prepared by three methods mainly: high-pressure homogenization, microfluidization and phase inversion temperature. Transdermal delivery using nanoemulsions has been reduced due to the stability problems inherent to this dosage form. Some examples of drugs using nanoemulsions to transdermal drug delivery are gamma tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin and nimesulide (Shakeel & Ramadan, 2010).

8. Conclusions

Transdermal drug delivery has several potential advantages over other parenteral delivery methods. Apart from the convenience and noninvasiveness, the skin also provides a "reservoir" that sustains delivery over a period of days. Furthermore, it offers multiple sites to avoid local irritation and toxicity, yet it can also offer the option to concentrate drugs at local areas to avoid undesirable systemic effects. However, at present, the clinical use of transdermal delivery is limited by the fact that very few drugs can be delivered transdermally at a viable rate. This difficulty is because the skin forms an efficient barrier for most molecules, and few noninvasive methods are known to significantly enhance the penetration of this barrier.

In order to increase the range of drugs available for transdermal delivery the use of chemical and physical enhancement techniques have been developed in an attempt to compromise skin barrier function in a reversible manner without concomitant skin irritation. Recently, several alternative physical methods have emerged to transiently break the stratum corneum barrier and also the use of chemical enhancers continues expanding. The projectile methods use propelled microparticles and nanoparticles to penetrate the skin barrier. Microneedle arrays are inserted through the skin to create pores. "Microporation" creates arrays of pores in the skin by heat and radio frequency ablation. Also, ultrasound has been employed to disrupt the skin barrier. All these methods have their own advantages

and drawbacks, but a reality is that new developments are expected in the future to make these methods even more versatile.

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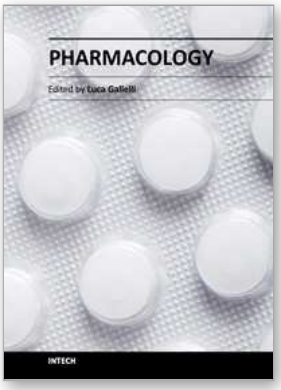

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The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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