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Needle-Free Injection Technology: Revolutionizing Drug Delivery

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KEYWORDS

Needle free delivery; Transdermal; Jet-injectors; Microneedles; Electroporation; Sonoporation.

ABSTRACT:

In recent years, considerable research has been dedicated to revolutionizing drug delivery methods, ensuring safe and effective administration within the human body. The primary aim of innovative needle-free injection technology is to advance transdermal drug delivery by offering a swift, dependable, painless, cost-effective, and efficient therapeutic approach. Transdermal drug delivery stands as one of the most significant and intricate methods following the oral route. Numerous pharmaceutical treatments, including vaccines, macromolecules, medications, and biopharmaceutical products, find their optimal application in transdermal administration. Within this technology, multiple techniques have been developed, with some still in the developmental stage, to enhance the delivery of therapeutic agents via this pathway. These techniques encompass jet injectors, microneedles, electroporation, iontophoresis, sonoporation, microchips, and laser microporation. Leveraging the fundamental principles underlying these techniques and considering the physicochemical properties of the therapeutic agent, they can be effectively employed to administer a diverse range of medicinal substances swiftly and safely, garnering regulatory approval. These technologies represent a substantial improvement in patient compliance compared to conventional injectable therapies. The ultimate objective of transdermal drug delivery using this technology is to mitigate skin resistance, ensuring the timely and precise delivery of therapeutic agents to the appropriate site, thereby achieving the optimal concentration across the skin necessary to elicit the desired therapeutic effect.

1. Introduction

Recently, lots of novel innovativeresearch work is carried out for drugdelivery to provide medications in a safe and effective manner to our body. Development of novel techniques such as needle-free injection technology (NFIT), delivers the medication effectively inside the skin without pain (Harrison, 2010). Primarily NFIT is related with the transdermal drug delivery system (Kalia et al., 2013). Thisnovel NFIT is rapidly gaining importance and acceptance from patients in treatment therapy. Under this technology various products, devices cometo the market such as jet injectors, microneedles. Jet injector was mostly used by diabetic's patients suffering from diabetes mellitus Type-I, as they require rapid administrations of insulin (Stewart and Darlow, 1994). They are also applicable for vaccine delivery through skin (Nestle et al., 2009). To avoid pain, trouble at injection site needle syringe was replaced by needle-free injection systems. Besides, microneedles and jet injectors, there are also other methods by which therapeutic agent were delivered inside the skin without the use of a needle. These methods are electroporation (Weaver et al., 1995), iontophoresis (Wu et al. 2007) and sonoporation (Liang et al., 2004).

These drug delivery techniques have been developed and adopted to deliver a huge number of therapeutic agents through skin based on their potency and physicochemical characteristics. The main objective behind the development of needle-free technology is to administer medications in a safer, effective, relatively non-invasive or minimally invasive way (Gratieri et al., 2013; Kalia et al., 2013).According to World Health Organization (WHO), it was estimated that about one-third of immunization are unsafe in a low-resource region, which are held by fewer numbers of qualified medical practitioners due to reuse of needles, unsterilized needles, dangerous infections, accidental needle sticks injuries(Miller and Pisani, 1999). To obtain better compliance of treatment by patients, such techniques are going to prove fruitful. Here, we provide

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the overview of some novel needle free technologies which are designed for transdermal drug delivery.

2. Needle Free Injection Technology

2.1 Jet injectors

Jet injectors represent a groundbreaking facet of needle-free injection technology (NFIT) that has made remarkable strides in modern medicine. These devices operate on a simple yet ingenious principle: instead of using a needle to penetrate the skin, they employ high-pressure systems to force a fine stream of medication or vaccine through the skin's surface. This innovative approach not only eliminates the fear and pain associated with traditional injections but also offers numerous advantages.

Jet injectors have gained prominence in various medical applications. Notably, they have been a game-changer for individuals with diabetes mellitus Type-I, who require frequent and swift insulin administration. Jet injectors provide a virtually painless and convenient means of delivering insulin, significantly enhancing the quality of life for these patients.

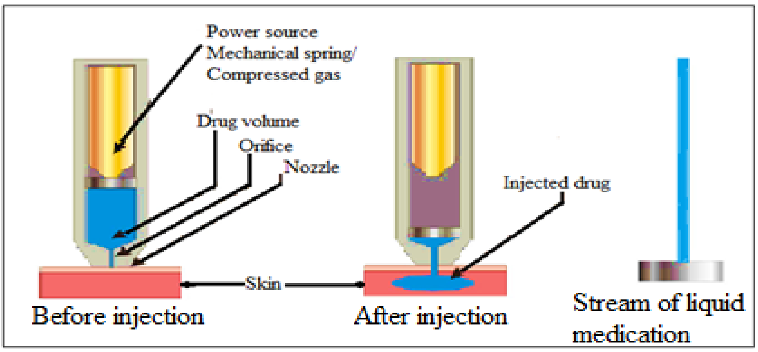

Figure 1 Depicts diffusion of drug through skin by using jet injection device

Moreover, jet injectors have proven instrumental in vaccine delivery. They offer a rapid and efficient way to immunize individuals without the need for needles. This feature is particularly valuable in regions with limited access to healthcare resources, where unsafe injection practices can lead to infections and other health hazards.

The technology behind jet injectors continues to evolve, with ongoing research aimed at enhancing their precision and effectiveness. As part of the broader NFIT landscape, jet injectors exemplify how innovation in drug delivery can revolutionize patient care, making treatments more accessible, comfortable, and efficient.

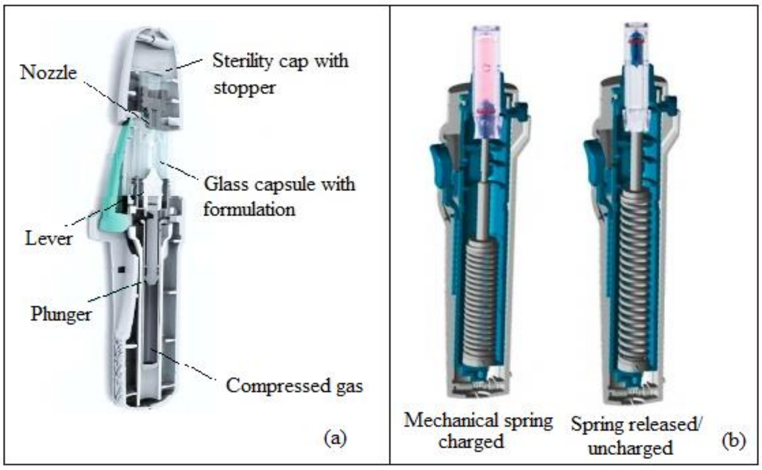

Figure 2 Needle-free jet injection device (Jet injectors) (a) Sumavel™ DosePro™ (Zogenix, Inc.; Brandesetal., 2009) (b) Stratis® (Pharmajet, Colorado, USA)

Table 1Jet injection devices on the market having FDA clearance

Company	Product	Power source	Drug product
Bioject	Biojector® 2000	Compressed gas	Liquid

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	Zetajet™	Spring actuated	Liquid
Injex Pharma	Injex 30	Spring actuated	Insulin
	Shireen Porejet	Spring actuated	Hyaluronic acid
Pharmajet	Stratis®	Spring actuated	Liquid
Antares Pharma	Tjet®	Spring actuated	Growth hormone
	Medi-jector®	Spring actuated	Insulin
European Pharma Group	Insujet™	Spring actuated	Insulin
Zogenix Incorporation	Sumavel™DosePro™	Compressed gas	Sumatriptan

2.2 Microneedles
Mironeedles are microstructered fabrications and is a mostpromising technology for transdermal delivery of therapeutic agent. It consistsof pointedprojections fabricated into arrays that createdrug delivery pathways through the skin.Microneedles are potential for delivery of microgram levels of highly potent drugs (Kim et al. 2012), vaccines(Hansen, 2010),peptides and high valueformulations of proteins.Medicinal agents can be deposited inside dermis or epidermis without reaching pain sensitive nerve endings (Bariya et al., 2012). Microneedles arenon-invasive technique of transdermal drug delivery.Dimension of Microneedles ranges from 25µm to 1000 µm in length. The human epidermis varies in depth across the body; it is approximately 1500 µm deep (McAllister et al, 2003). Various kinds of microneedles are developed such assolid microneedles, drug-coated microneedles (Gill and Prausnitz, 2007), drug-impregnated dissolvable microneedles (Lee et al.) and hollowmicroneedles for deliveryof liquid drug formulations (Prausnitz, 2004).Now-a-days microneedles are used for delivery of insulin (Bora et al., 2008; Martano et al. 2004), DNA Vaccineand Proteins (Prausnitz, 2004).

Microneedles were fabricated by using various materials such as silicon, metals including stainless steel (Gill et al. 2007; Martanto et al. 2004), titanium, nickel and ceramics (Omatsu et al. 2010; Jung et al. 2008; Bystrova et al. 2011). Polymer can be used; non-degradable polymers such as polycarbonate (Jin et al. 2009), polymethyl methacrylate and biodegradable polymers such as poly-lactic-co-glycolic acid (PLGA), polyglycolic acid (PGA) and polylactic acid (PLA) were used for fabrication of microneedles (Park et al. 2005).Transportation of drugs across the skin usually occurs by simple diffusion mechanism. In order to increase permeability and bio-availability of drug, various enhancement techniques were used in combination with microneedles. These techniques include iontophoresis (Lin et al. 2001; Vemulapalli et al. 2008), radiofrequencies and electroporation (Hooper et al. 2007; Prausnitz et al. 2008).

2.2.1Solid microneedles
Solid microneedles used for pore formation in the skin. The medicinal agents can be applied to the skin surface over the pores by using a drug-loaded patch; Sharp microneedles penetrate inside the skin to make holes through which drugscan be transported. Solid microneedles usually fabricated by using materials such as ofsilicon, metal, glass and plastics.Solid microneedlestechnique was developed fifteen years ago (Sachdeva and Banga, 2011) and used to deliver insulin(Martanto et al., 2004) as well asgenetic vaccines (Wermeling et al. 2008).

2.2.2Drug-coated microneedles
Drug-coated microneedles were used not only as piercing structures, butalso as vehicles to carry and deposit drug inside the skin. Various techniques by which drug can be coated on the fabric structure of microneedle are Layer-by-layer coating techniques (Saurer et al. 2010; DeMuth et al. 2010);spray coating by use of atomizer (McGrath et al. 2011).

2.2.3Drug-impregnated dissolvable microneedles
As consequences to thedrug-coated microneedles and recent advances in polymer sciences, it can be possible to infuse or dissolve drug completely into the polymer. Polymer microneedles were designed in such way that completely dissolve medicinal agent in the skin. Biodegradable polymer prevents bio-hazardous waste, toxic effects after its use.Drug-impregnated dissolvable microneedlesare safe composed ofinert, water-soluble materials, such as polymers and sugars whichdissolve in the skin after insertion. This type of microneedles increases the permeability of drug. Drug-impregnated dissolvable microneedles were fabricated mostly by solvent casting (Lee et al. 2008), micromold drawing method (Jung et al. 2011)and ultrasonic welding method (Min et al. 2008; Park et al. 2007).

2.2.4 Hollow microneedles
Hollow microneedles provide a well-defined conduit for delivery of drug into the skin, arrays of hollow microneedles carries drugs instantaneously into the body using simple diffusion mechanism. These are capable of injectingvery small volumes of liquid (Wang et al. 2006; Roxhed et al. 2008). Use of biocompatiblematerials makes it relatively safe and potential to deliver medication across the skin.Hollow

microneedles were fabricated by laser cutting techniquefrom stainless steel sheets using an infrared laser (Gilland Prausnitz, 2007). Hollow microneedles assisted drug delivery also useful for controlling the drug release rate from skin, release profile of drug important in increasing the transdermal delivery of large molecular compounds and to provide useful information for designing an effective hollow microneedle system.

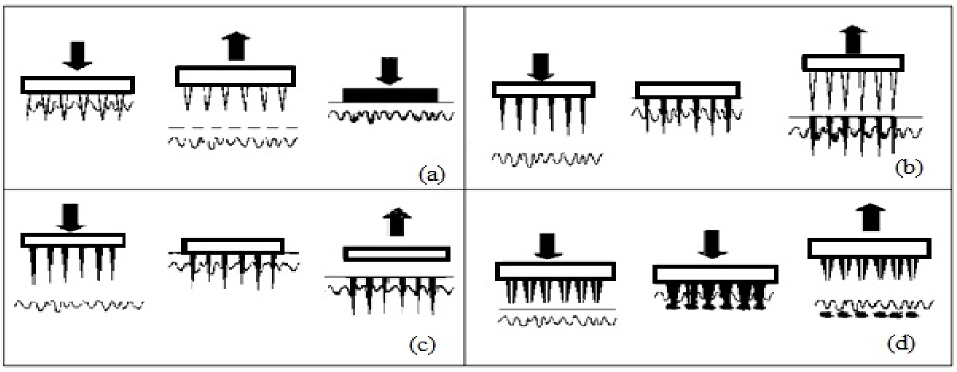

Figure 3Schematic representation of various microneedle designs for transdermal drug delivery: (a) Solid microneedles, (b) Drug coated microneedles, (c) Drug-impregnated dissolvable microneedles (d) Hollow microneedles

Table 2 Microneedles on the market having FDA clearance

Name of technology	Company	Type of microneedle	Drug Product
Macroflux®	Alza	Coated microneedle	Vaccines, Proteins
VaxMat®	Theraject	Dissolvable microneedle	Vaccines
OnVax®	BD	Solid microneedle	Vaccines
MicroJet®	NanoPass	Hollow microneedle	Vaccines
h-patch®	Valeritas	Dissolvable microneedle	Insulin
Micro-Trans™	Valeritas	Solid microneedle	Vaccines, Proteins

2.3 Electro-poration

Electro-poration is the latest technique of drug delivery known to createa transient pores in the cell membraneby using a high-voltage electric pulse (Prausnitz et al. 1993; Weaver et al. 1995). Skin is an interesting part of our body, resistance of a stratum corneum of skin acts as the barrier for drug deliverywhich decreaseswithin less than 1 µs upon application of high-voltage electric pulse (Weaver et al., 1999).These changes werereversible and did not alter the viability of the skin. These techniques work by disrupting or modifying the lipid structures of intact skin due to transmission of short duration of high-voltage electric pulse.Thereby create transient aqueous pathways or pores(channels)in the lipid region of the stratum corneum. Through these pores drug products in aqueous solutions can surpass the skin barrier. Furthermore effect of electroporationcan be enhanced by application of ultrasound, facial and corporal electroporation. Electroporation technique plays an important role in the enhancementof permeation of highly charged macromolecules across the stratum corneum and to achieve a biological response by attaining therapeutic concentration of drug inside the skin (Pliquett, 1999).

For transport of drug across the stratum corneum by electroporation technique, the corresponding voltage applied is in the range of 0.3-1.0 V per bilayer,but stratum corneum composed of 100 bilayer membranes in a series. Electroporation, i.e. electrical breakdown or disruption of the skin membrane's structure requires applied voltage nearlyin the range of 30-100V (Pliquett et al. 1995; Prausnitz et al. 1993).These structural changes are reversible, during the application of voltage.Resistance of the skin membrane decreases graduallyand causes the creation of transient pores which having size less than 10 nm and having short life approximately µs to second (Weaver et al. 1999). Transient pores are responsible for the transportation of drug across the skin membrane and are higher forelectroporation than iontophoresis.

Electroporation increases the permeability of charged moleculesdue to electrophoresis and enhanced passive diffusion mechanismduring high voltage pulses(Vanbever et al.1996; Pre'at et al. 1999).Higher skin permeabilityis achieved during the pulse and drug transportation occurs after pulsing and last for hours

which is important in an *in*-vitro studies. Evidencesfor the contribution of enhanced post-pulseincreased transport seen with neutral molecules and drugswhich are added after application of the pulses (Vanbever et al. 1998).

This technique of drug delivery is a non-invasive, user-friendly method. Electroporation has found applications in (a) gene delivery(Mir et al., 1999),(b) delivery of proteins and macromolecules (Lombry et al., 2000), (c) introduction of plasmids or foreign DNA into living cells forgene transfections, (d) insertion of proteins intocell membranes, (e) enhancing drug delivery forchemotherapy of cancerous cells,(f) delivery of macromolecules, at least 40 kDa (Pre'at et al. 2004). Electroporation ishighly reproducible, non-invasive technique shows promising future.

2.4Iontophoresis

The main objective of iontophoresis drug delivery system is to increase the delivery rate of ionic therapeutic agent. Iontophoresis involves the application of a mild electric potential gradient in order to create a flow of current from the device into the skin. The passage of current necessitates the conversion of an electron flow into an ion flow at the electrode interface hence; iontophoresis is ideally suited to facilitate the transport of hydrophilic ionisable molecules, which are not good candidates for passive transdermal delivery (Kalia et al., 2004). Iontophoresisstill remains challengingtask for delivery of ionic agentslike proteins and peptides.

An iontophoretic system for drug delivery consists (a) Power supply, source of electric current(nearly 0.5 mA/cm^2)usually battery operated and with control electronics (b) Two reservoir system with an electrode, one is an “active”reservoirsystem consisting of ionic therapeutic agent other is “return” reservoir systemwhich consists of an electrolyte serves to complete the electric circuit (Godin and Touitou, 2003).This, system works when the active and return reservoir systems placed on the skin surface. The ionic current flows via active reservoirsystem and below the skin to the return reservoir system, and back through the skin into the return reservoir. At the return reservoir, it is transformed back into the current to complete the circuit at the opposite side of the current source (Godin, 2003). The mechanism followed by iontophoresis for flux (transport of drug molecule across the biological membrane) is convective transport due to electro-osmosis (EO) and electro-migrations (EM). Anions are delivered exclusively from the cathode (Kalia et al., 2004) and cations delivered from the anode by electro-osmosis transport mechanism (Pikal, 1990).

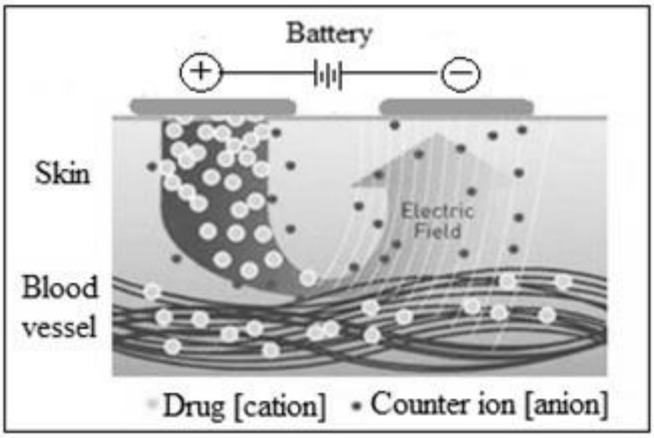

Figure 4Depicts active iontophoresis

Iontophoresis improves the delivery of polar molecules as well as macromolecules. It has ability to deliver drugs either systemically or topically by reducing inter and intra-individual variability (Ceve G, 2003). Iontophoresis is not novel technique of drug delivery but it one of the most important technique for transdermal delivery of hydrophilic ionisable molecules. Iontophoresis has found application (a) for delivery of antibiotics into the eye, (b) for treatment of patients suffering from hyperhidrosis of the palms, feet, and axillaeby using anticholinergic compounds. Recently,it can be used as tool for diagnosis of vascular diseases when used in combination with laser Doppler.

2.5 ***Sonoporation***

Sonoporation is also known as Cellular Sonication or Sonophoresis. The ultrasonic frequencies were used for modifying the structural integrity of the cell plasma membranein order to enhance permeability of the cell membrane. Sonoporation now-a-days emergedas a promising technique with a broad range ofpotential applications such as ultrasound-mediated gene transfer

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(Newman and Bettinger, 2007), uptake of RNA (Cheon, et al. 2009) and DNA into the cell (Zarnitsyn and Prausnitz, 2004), use of lowfrequency ultrasound for enhancement of membrane permeabilityfor a drug, including high molecular weight proteins (Guzman et al. 2002), used in insulin delivery (Tachibana, 1991) and also used in physical therapy.

Sonoporation is a process which exponentially enhances the absorption of topical compounds into the epidermis, dermis by enhancing the permeability of cell membrane.Sonoporationtechnique works by stimulation ofmicro-vibrations which are generated by use of ultrasound waves.The drug is mixed with a coupling agent like gel, cream, ointment which transforms ultrasonic energy from the ultrasoundtransducer to the skin. Transport of drug across the cell membrane by using sonoporation enhanced due to the process of cavitation and microstreaming (Bommannan et al. 1992).

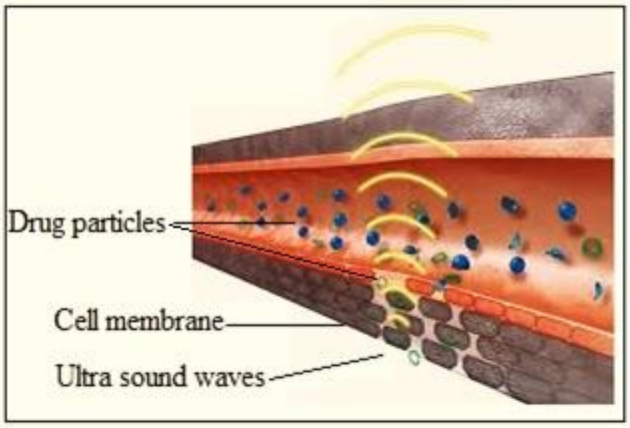

Figure 5Transport of drug across the cell membrane

2.5.1 ***Cavitation Sonoporation***

Ultrasound-induced cavitation during sonoporation is known to enhance transdermal drug delivery for local, regional, and systemic treatment.Cavitation is the formation of cavities in a body organ or tissue, the activity of cavitation generally decreases for increasing ultrasound frequency; sonoporation has been demonstrated for low ultrasound frequency 20-100 kHz. For in-vivo lithotripsy shock waves (ultrasound) required in megahertz frequency nearly 1-2 MHz for 2 min.There are two types of cavitation "inertial" and"non-inertial" (Junru and Nyborg, 2008). Formerly inertial cavitation, known as "transient"cavitation, whereas non-inertial cavitation known as "stable" cavitation. Low frequency sonophoresis (20-100 kHz) used for inertial cavitation external to skin and highfrequency sonophoresis (>.7 MHz) used for cavitation to internal skin, thus cavitation by sonoporation plays important role in increasing skin permeability.

2.5.2 ***Microstreaming Sonoporation***

A progressive increase in sound wave creates a radiation force when the momentumtransported by the ultrasound waves changes with position in the medium known to produce microstreaming, which is unidirectionalflow in fluid as result of presence ofultrasound waves.The primary reason for microstreaming isultrasound reflections and other distortions which occurred during wave propagation(Shi, 2001). Shear stresses developed by microstreaming will affect on the abutting tissue structures.Microstreaming is important when the surrounding medium is fluid or biological medium.Potentialapplication of microstreaming is atool for identifying the difference inbetween liquid blood and clots or soft tissue for diagnosis of haematoma (Le, et al. 2000).

As consequences in development of sonoporation technique moderate intensity ultrasound assisted by encapsulated microbubbles (EMB) can be used in in-vitro and in-vivo targeted drug delivery (Tachibana, 1999). Sonoporation is a fruitful technique for delivery of therapeutic compounds in safer, invasive mannerto specific target cells.

3. Other emerging technology

Lot of research has been ongoing to find immensely potential system for drug delivery of potent medicinal agent in safer, painless and cost beneficent manner. Drug delivery is a most essential aspect ofmedical treatment. Pharmacological action of medicinal agent can be achieved by attaining therapeutic concentration at the targeted site at right amount of a drug and at the right time. For successful transdermal drug delivery of key parameter is increasing permeability as well as

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bioavailability across the cell membrane. Recent advances and development of novel technologies such as microchip and laser microporation used to potentiate the transcutaneous drug delivery.

3.1 *Microchip*

Microchip is designed to control rate as well as the time release of molecule from the fabricated device.Release ofdrug molecule in continues or pulsatilemanner can be possible by this system.The microchip composed of a substrate having multiple reservoirs. These multiple reservoirs are responsible retainingtherapeutic agent in the form of solid,liquid, or gel.This substrate are capped with conductive membrane serves as anode such as gold (Merchant, 1998) and finally wiredto circuit which controlled by microprocessor. Reservoirare etched into substrate by chemicaletching or ion beam etching techniques, about100-1000 reservoirs can befabricated on a single microchip. This microchip works by an electrochemical reaction between cathode (surface of the microchip) and anode surface (Frankenthal and Siconolfi, 1982). Each reservoir which filled with atherapeutic agent released at open ends of thereservoirs and then sealed with a waterproofmaterial. On application of electric voltage nearly 1volt causes anode membrane to dissolves due to an electrochemical reaction. This allows the material to diffuse from inside toexternal surrounding fluid. Each reservoir present on the microchip is get activated due to controlled circuit and openedindividually, allowing complex release patterns of drug. Microchip has been used as subdermal implant in controlled release of drug at right time and at right place (Langer et al. 1999).

3.2 *Laser microporation*

Laser microporation is an advanced technique utilizes laser energy for creation of micropores in the skin membrane. Lasers were used for drug delivery (Grunewald et al. 2011) by removing the upper skin layers that create micropores (aqueous channels). Therefore it enhances the permeability of drug by increasing diffusion mechanism. Laser microporation works by emitting infrared light which correspond to water molecules and responsible thermal ablation. At increasing temperature the biological changes occurs in the skin surface coagulation (60-65 ^{0}C, drying (90-100 ^{0}C) and vaporisation (>100 ^{0}C). Vaporisation of skin lead to formation micropores in the skin but it destruct the tissues of skin in order to reduce this destruction cold ablation i.e. exposing skin for shorter duration of time to laser pulses (Jih and Kimyai-Asadi, 2008). Pore density and depth of laser microporation play a key role in improving drug delivery (Baron, et al. 2003).

The practice of laser microporation for drug delivery is limited to fewer drug products as it is recent technique, less number of studies published till date. Furthermore, application of this technique found to be (a) in delivery of small molecules having molecular weight less than 50Da and possessing certain physico-chemical properties and potency (Bachhav et al. 2010),(b) in delivery of macromolecules(Fang et al. 2004)which having large molecular weightsuch as proteins, hormones(Zech et al. 2011)and insulin delivery etc.

4. Conclusion

Transdermal is the second most signicant route after oral for drug deliveryof low molecular weight highly potent compounds, small molecules, peptides, proteins and genes, biopharmaceuticals. This huge range of therapeutic agent can be used as potential candidates for transdermal delivery and administered with the help of novel innovative technologies. They can be used for systemic or local delivery.As transdermal route is restricted for certain drug product of high doses makes them challenging to deliver by this route. To overcome the certain problems associated with conventional transdermal drug delivery system, novel NIFT for Transdermal drug delivery proves to be fruitful. Use of basic principle of novel technologies enables them to achieve ultimate goal of development of safer, effective and cost efficient drug delivery.

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