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Review

Micro-scale devices for transdermal drug delivery

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ABSTRACT

Skin makes an excellent site for drug and vaccine delivery due to easy accessibility, immuno-surveillance functions, avoidance of macromolecular degradation in the gastrointestinal tract and possibility of self-administration. However, macromolecular drug delivery across the skin is primarily accomplished using hypodermic needles, which have several disadvantages including accidental needle-sticks, pain and needle phobia. These limitations have led to extensive research and development of alternative methods for drug and vaccine delivery across the skin. This review focuses on the recent trends and developments in this field of micro-scale devices for transdermal macromolecular delivery. These include liquid jet injectors, powder injectors, microneedles and thermal microablation. The historical perspective, mechanisms of action, important design parameters, applications and challenges are discussed for each method.

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1. Introduction

Transdermal drug delivery systems encompass a wide array of non-invasive or minimally invasive technologies for delivering drugs and vaccines across the skin without needles (Barry, 2001; Prausnitz et al., 2004; Schuetz et al., 2005). Key advantages of transdermal delivery include easy accessibility of skin, which aids in high patient compliance, avoidance of the gastrointestinal tract and the ability to achieve sustained release. The transdermal route has distinct advantages over traditional routes of drug administration, namely the oral route which has poor macromolecular bioavailability, or injections which are limited by pain, accidental needle-sticks, and possible side effects due to transiently high plasma drug concentration (Kermode, 2004; Mitragotri, 2005). These advantages of transdermal delivery coupled with a boom in the rate of macromolecular drug discovery have led to significant advances in transdermal device development over the last decade.

Skin has evolved to be a highly effective barrier around the human body (Scheuplein and Blank, 1971). This has made it very challenging to deliver large molecular weight hydrophilic drugs such as proteins and peptides. The outermost layer of skin, stratum corneum, is primarily composed of dead corneocytes embedded in lipid layers (Elias, 1983). This brick and mortar like arrangement offers a substantial barrier to small hydrophilic compounds as well as to essentially all high molecular weight drugs. Molecules which are successful in crossing stratum corneum may enter the blood circulation via diffusion (Flynn et al., 1974). The rate of diffusion depends on molecular weight as well as concentration gradient, making it even more difficult to deliver large molecules in a time controlled manner, as macromolecules diffuse slowly and may have limited solubility in aqueous medium. This has limited the number of drugs delivered with passive methods to highly lipophilic molecules under 500 Da (Prausnitz et al., 2004). Therefore, there is a need for methods and devices to deliver hydrophilic and high molecular weight drugs in a controlled and reproducible fashion.

Technologies used by transdermal devices can be divided into passive or active methods based on whether an external source of energy is used for skin permeation enhancement. Passive methods include use of chemical enhancers, emulsions and lipid assemblies as well as biological methods such as peptides (Schreier and Bouwstra, 1994; Karande et al., 2004; Prausnitz et al., 2004; Schuetz et al., 2005; Chen et al., 2006; El Maghraby et al., 2006). Chemical methods are relatively easy to incorporate into transdermal patches and can be used to deliver varying dosage amounts by changing the application area. However, these methods may have a lag time up to hours and thus cannot be easily adapted for rapid onset or time varying delivery which may be needed for drugs such as insulin.

Increasing numbers of academic and industrial researchers are focusing on transdermal devices with active mechanisms for skin permeation (Brown et al., 2006). A similar trend is seen in the type of systems that have entered the transdermal market in the last decade, and those under clinical development (Gordon and Peterson, 2003; Brown et al., 2006). These active methods of skin permeation enhancement include jet injectors, iontophoresis, electroporation, ultrasound, microneedles, powder injection, ablation and tape stripping (Burkoth et al., 1999; Prausnitz et al., 2004; Mitragotri, 2006; Prausnitz et al., 1993; Mitragotri et al., 1995; Bashir et al., 2001; Doukas and Kollias, 2004; Kalia et al., 2004; Karande et al., 2004; Habash et al., 2006; Arora et al., 2007). Active methods increase transport across the skin typically by using an added driving force for drug transport or by physically disrupting the barrier. This enables delivery of many hydrophilic drugs and macromolecules. In addition, active methods also offer more control over delivery profile, thus resulting in shorter delays between application and drug reaching systemic circulation compared to passive methods. Also, the device and application parameters can be adjusted to better match individual's skin properties (Tezel et al., 2001; Davis et al., 2004; Baxter and Mitragotri, 2005).

For the same reasons, devices using active methods can have additional requirements including power supply, possible feedback/sensor mechanism to adjust the rate of delivery and user interface for parameter control (LaVan et al., 2003). This stretches the challenges of active device development beyond simply breaching the permeability barrier of skin and into varying engineering fields of microelectromechanical systems (MEMS), micro fluidics and embedded software (Grayson et al., 2004; Ekinci and Roukes, 2005). It is this complexity of implementation of active permeation methods into devices that makes this task challenging.

In addition to the complexity of device fabrication and integration, issues related to maximizing delivery efficiency while minimizing undesirable reactions require significant research and development efforts. Over the last decade, great progress on this front has been made with the advent of devices which have at least one working parameter in micrometer range and are collectively referred to as micro-scale devices in this review. Operation at micron scale is important because micron-sized breaches in the stratum corneum barrier are large enough to let most drugs through, since most drugs are of nanometer dimensions. At the same time, they are small enough that they appear to be safe, well tolerated by patients and allow rapid skin recovery post-administration. Such micro-scale devices include liquid jet injectors, solid powder injectors, microneedles and thermal microporation devices. We discuss their mechanisms of permeation enhancement, the current devices using each method, health effects and future directions for device development.

2. Liquid jet injectors

Liquid jet injections employ a high-speed jet to puncture the skin and deliver drugs without the use of a needle. Research on jet injectors began in the early 1930s with Arnold Sutermesiter, an engineer who noticed accidental injections of diesel oil into the hands of workers when small leaks occurred in high-pressure lines (Bremseth and Pass, 2001). Since then, two main classes of liquid jet injectors have been developed. These are single-dose jet injectors, known as DCJIs (disposable cartridge jet injectors) and MUNJIs (multi-use-nozzle jet injectors) (Mitragotri, 2006). Some DCJIs are only partly disposable while others are fully disposable. MUNJIs did not have any disposable parts and were introduced for rapid mass immunization. Their use, however, was discontinued in the wake of reports of spread of hepatitis B in the 1980s due to their use. The cause of outbreak was thought to be cross contamination due to splash back of interstitial liquid from the skin onto the nozzle (Canter et al., 1990). The focus of most studies on jet injectors since then and those discussed in this review therefore is on liquid DCJIs.

2.1. Mechanism

The basic design of commercial liquid jet injectors consists of a power source (compressed gas or spring), piston, drug-loaded compartment and a nozzle with orifice size typically ranging between 150 and 300 μm (Mitragotri, 2006). Upon triggering the actuation mechanism, the power source pushes the piston which impacts the drug-loaded compartment, thereby leading to a quick increase in pressure (Schramm and Mitragotri, 2002). This forces the drug solution through the nozzle orifice as a liquid jet with velocity ranging between 100 and 200 m/s. A schematic of injection process is shown in Fig. 1. The jet is turbulent in nature and the diameter of the jet is comparable to that of the orifice but increases with distance traveled. Upon impinging on skin, the jet punctures through the skin and initiates hole formation. The formation of a hole is believed to be due to a combination of skin erosion and fracture and is completed during the first few hundred microseconds (Baxter and Mitragotri, 2005). As the jet progresses deeper in the skin, velocity decreases until it does not have sufficient energy to continue hole formation. This completes the first phase of injection i.e. unidirectional skin puncture and is followed by the second phase, multidirectional jet dispersion from the end point of penetration. Further, the dispersion of liquid from this point appears to be approximately hemispherical, whose shape is governed by jet power (Schramm-Baxter and Mitragotri, 2004).

2.2. Design parameters

The depth of penetration and shape of liquid dispersion is governed by the orifice diameter and jet exit velocity. Nozzle diameters between 31 and 559 μm and exit velocities between 115 and 200 m/s have been used in experimental studies (Baxter and Mitragotri, 2005, 2006). An increase in penetration depth is reported both with increasing nozzle diameter at constant exit velocity and increasing jet exit velocity at constant diameter, when injection volumes were kept constant. Increasing diameter also increased size of dispersion. More recently, jet power (P_o) has been suggested as a combined parameter for describing dependence of jet penetration depth and dispersion on velocity and nozzle diameter. Jet power is calculated as:

$$P_o = \frac{1}{8}\pi\rho D_o^2 u_o^3$$

where D_o is nozzle diameter, u_o is exit velocity and ρ is liquid density. Penetration depth increased from 0.2 mm at a power of 1 W to 2.8 mm at a power of 62.4 W. With increasing power, the shape of liquid dispersion at the end of hole also changed from resembling a lower hemisphere with end of eroded hole as center to an upper hemisphere with end of hole lying at the top of hemisphere (Schramm-Baxter et al., 2004). With variation in jet parameters, it is possible to span the full thickness of skin and control the depth where the bulk of drug solution is being delivered. The percent completeness of injection, defined as the percent of drug solution delivered across the skin, also increased linearly from near zero at a power of 1 W to >90% at a power of ~30 W, beyond which the delivery remained constant at or above 90%. Other factors which may affect penetration depth but need further investigation include mechanical properties of skin, injection volume and stand-off distance. The stand-off distance is defined as the distance which the liquid jet travels after leaving the injector's orifice until it makes contact with the skin.

2.3. Applications

MUNJIs have been used for mass immunization programs for diseases including measles, smallpox, cholera, hepatitis B, influenza and polio (Weniger, 2003). DCJIs have been used for delivery of several proteins. Most work has been done on delivery of insulin (Weller and Linder, 1966; Lindmayer et al., 1986) and growth hormones (Verhagen et al., 1995; Bareille et al., 1997; Agerso et al., 2002; Dorr et al., 2003), while erythropoietin (Suzuki et al., 1995) and interferon (Brodell and Bredle, 1995) have also been delivered. Insulin administration by jet injectors led to a faster delivery into systemic circulation, possibly due to better dispersion at the injection site. However, the acceptance of jet injectors has been low due to variable reactions at the site of administration (see Section 2.4 below).

To counter the challenges faced by traditional jet injectors, a novel pulsed microjet has been developed (Arora et al., 2007). This new approach focuses on minimizing pain and bruising by minimizing injection volumes and depth of penetration. The actuation mechanism is based on a piezoelectric transducer and offers strict control over delivery volumes and injection velocity. The high velocity (>100 m/s) of microjets allowed their entry into skin, whereas the small jet diameters (50–100 μm) and extremely small volumes (2–15 nl) limited the penetration depth (~200 μm). The efficacy of this design was confirmed by delivering therapeutic doses of insulin in a rat model.

2.4. Safety

The acceptance of conventional jet injectors has been mixed due to variable reactions at the administration site. Some reports state no difference in level of pain compared to that experienced by hypodermic needles (Sarno et al., 2000), but others have reported higher levels of pain (Jackson et al., 2001). Variable reports in local reactions further augmented this fact, with some researchers reporting absence of local reactions (Resman et al., 1985) while others have reported significantly more reactions including pain, bleeding and haematomas (Houtzagers et al., 1988). It has been shown that the depth of penetration and percent delivery decrease with increasing Young's modulus (i.e. mechanical strength) of skin (Baxter and Mitragotri, 2005). Commercial injectors come with very limited choice of settings and owing to the person-to-person variability in skin's mechanical properties, variability in patient response may be due to the failure of this "one size fits all" approach of current devices. Future devices such as pulsed microjets are being designed to address these problems by offering superior control over injection profile.

3. Powder injectors

Powder jet injectors deliver vaccines or drugs in dry powdered form into superficial layers of skin. The terms biolistic injectors and gene guns have also been commonly used for these injectors, with the latter term used exclusively for DNA delivery (Peachman et al., 2003; Kendall, 2006). The early work on injecting solid micro-particles in biological samples was reported by Klein et al. (1987), who demonstrated transfection of plant cells with DNA and RNA using nucleic acid-coated tungsten particles. Since then, researchers have explored the potential of this technique for applications in protein delivery, gene therapy as well as traditional and DNA vaccination (Sarphie et al., 1997; Burkoth et al., 1999; Chen et al., 2000, 2001b, 2002).

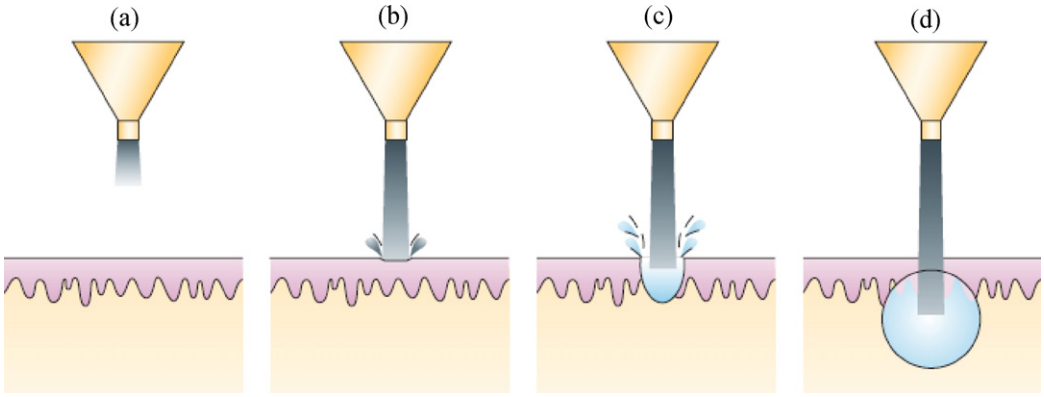

Fig. 1. Schematic of drug delivery using liquid jet injector (Mitragotri, 2006): (a) formation of liquid jet, (b) initiation of hole formation due to impact of jet on skin surface, (c) development of hole inside skin with progress of injection, (d) deposition of drug at the end of hole in a near spherical or hemispherical pattern (spherical pattern shown).

3.1. Mechanism

Basic design of solid jet injectors include compressed gas as the power source, a drug compartment containing particulate drug formulation, and a nozzle to direct the flow of particles (Kendall et al., 2004a; Mulholland et al., 2004). The drug compartment is closed with diaphragms on either side, which are typically few microns thick. Upon triggering the actuation mechanism, compressed gas from a storage canister expands and pushes against the diaphragms, sequentially rupturing them. The flow of gas carries the drug particles with it. The particles then exit through a nozzle and impinge on skin (Fig. 2). Upon impacting on the skin, particles puncture micron-sized holes into stratum corneum by virtue of their momentum. Some particles are contained in stratum corneum while a significant percent reach the viable epidermis for the desired therapeutic effect.

Another design used for studying powder injection mechanisms is light gas gun, which uses an accelerating piston for imparting desired particle velocity (Crozier and Hume, 1957). Upon triggering the actuation mechanism, the piston accelerates and carries the particles with it. A deceleration mechanism forces the piston to slow down and makes the particles leave the surface of piston. The particles are ejected and impact on target tissue surface.

3.2. Design parameters

Key parameters in determining particle delivery across the stratum corneum are impact velocity, particle radius and particle density. The particles constitute of powdered preparation of drugs or vaccines and range between 10 and 20 μm. For DNA vaccination, coated metal particles between 0.5 and 3 μm have been used. A much broader range of particle sizes (0.5–52.6 μm) and densities (1.08–18.2 g/cm^3) have been studied for injector development (Kendall et al., 2004a). For studying correlations between particle properties and skin penetration, a combined parameter, namely particle impact parameter, has been defined as $\rho v r$, where ρ, v and r are particle density, impact velocity and radius, respectively. Particle impact parameter represents momentum per unit cross-sectional area of the particle. Depth of penetration and fraction of particles penetrating stratum corneum were found to be directly proportional to this parameter. At a fixed value of particle impact parameter, an increase in particle radius corresponds to a decrease in particle velocity at constant density and resulted in a decrease in penetration depth. For a given set of particle properties, velocity of particles can be controlled by varying gas pressure (200–900 psi). Since keeping particle impact parameter uniform is necessary for targeting specific skin layers, various internal contour designs have been studied for achieving narrow velocity profiles. This has led to optimization of internal sections of the injector, namely driver tube and shock tube through which the carrier gas flows before reaching the nozzle (Kendall, 2002; Kendall et al., 2004b). A recent study has revealed a correlation between epidermal cell death and particles delivered per unit area of target tissue, making particle payload another important parameter (Raju et al., 2006).

3.3. Applications

Solid jet injectors have been studied for delivery of DNA encoding for viral and bacterial antigens using coated gold microparticles (Morel et al., 2004; Matthews et al., 2007a,b). Induction of humoral and cell mediated immune response against influenza, hepatitis B and rabies has been shown in mice (Chen et al., 2000; Lodmell et al., 2000; Chen et al., 2001a,b, 2002). Protection against tumors has also been demonstrated by injecting DNA coated gold micro-particles and DNA encapsulated in polymeric particles (Han et al., 1999, 2000, 2002; McKeever et al., 2002; Frelin et al., 2003). An extensive review of preclinical DNA vaccination studies using solid jet injector systems in large animal models (swine and non human primates) has been published by Fuller et al. (2006). Clinical efficacy in humans has been demonstrated by induction of cell mediated and humoral immune response against hepatitis B using DNA coated gold micro-particles (Chen et al., 2000; Roy et al., 2000). Phase I clinical studies for delivery of DNA vaccine against influenza showed humoral response (Drape et al., 2006). Another human clinical study used cross-immunization regime with primary immunization using powder injector followed by intradermal injection as booster, and showed cell mediated response against malaria (McConkey et al., 2003).

3.4. Safety

Human clinical trials have reported painless delivery at the time of injection with DNA vaccines being well tolerated (Tacket et al., 1999; Roy et al., 2000; McConkey et al., 2003; Rottinghaus et al., 2003; Roberts et al., 2005; Drape et al., 2006). Post injection symptoms have been reported to develop quickly after the injection and include mild erythema, hyper-pigmentation, flaking and discoloration at the injection site. In some cases, transient sensations of mild tingling, tightening or burning have also been reported. Most symptoms disappeared within the first month except mild discoloration, which has been reported to persist for up to 6 months.

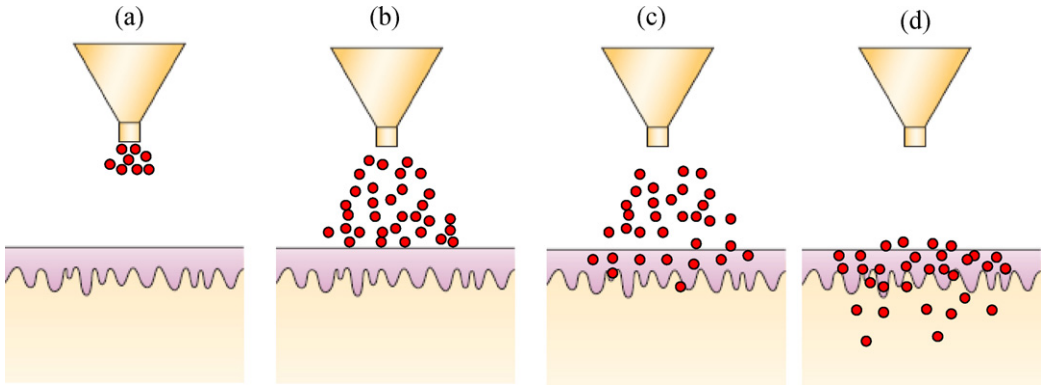

Fig. 2. Schematic of drug delivery using powder injector (modified from Mitragotri (2006)): (a) ejection of particles from nozzle, (b) impact of particles on skin surface, (c) penetration of particles across stratum corneum, (d) completion of delivery. Particles which penetrate into the skin are mostly distributed in stratum corneum and viable epidermis.

4. Microneedles

Microneedles, as the name suggests, are micron-scale needles that are employed for transdermal vaccination and drug delivery (Reed and Lye, 2004). The recognition that very small needles may be sufficient for transport across the 10–20 μm-thick stratum corneum was first proposed in the 1970s (Gerstel and Place, 1976) but progress was delayed largely due to lack of techniques to fabricate such small structures. The first work on use of microneedles for transdermal drug delivery was reported in the late 1990s (Henry et al., 1998). Established techniques of the microelectronics industry are now being adapted and expanded upon for microneedle fabrication. Earlier designs of microneedles had silicon as the fabrication material due to easy adaptability to microelectronic fabrication processes. Current designs emphasize metal and polymeric microneedles.

Four different types of microneedle designs have been developed, which include solid microneedles that pierce the skin to make it more permeable, solid microneedles coated with dry powder drugs or vaccines for dissolution in the skin, microneedles prepared from polymer with encapsulated vaccine for rapid or controlled release in the skin, and hollow microneedles for injections (Matriano et al., 2000; Cormier and Daddona, 2003; Prausnitz et al., 2003; Prausnitz, 2004; Reed and Lye, 2004; Prausnitz, 2005; Prausnitz et al., 2005; Birchall, 2006; Coulman et al., 2006; Sivamani et al., 2007). Metals used in solid microneedles include stainless steel, titanium and nickel-iron. Polymeric needles use engineering plastics, biodegradable polymers and water-soluble polymers such as polycarbonate, polylactic-coglycolic acid, and carboxymethylcellulose, respectively.

4.1. Mechanism

The mechanism of action depends on the microneedle design and is summarized in Fig. 3. All types of microneedles are typically fabricated as an array of up to hundreds of microneedles over a base substrate. Solid microneedles can either be pressed onto the skin or scraped on the skin for creating microscopic holes, thereby increasing skin permeability by up to four orders of magnitude (Mikszta et al., 2002; McAllister et al., 2003). This is followed by application of drugs or vaccines from a patch or topical formulation. Residual holes after microneedle removal measure microns in size and have a lifetime of more than a day when kept under occlusion, but less than 2 h when left uncovered (unpublished data).

The second strategy is to have vaccines or drugs encapsulated in a dry coating onto solid microneedles (Matriano et al., 2002; Gill and Prausnitz, 2007). This coating can dissolve within 1 min after insertion into skin, after which the microneedles can be withdrawn and discarded. As an alternative to using insoluble metal or polymer microneedles, complete microneedles have been fabricated out of biodegradable or water-soluble polymers. Model drugs have been encapsulated within PLGA microneedles for controlled release over hours to months (Park et al., 2006) and, more recently, within water-soluble carboxymethyl-cellulose, polyvinyl-pyrrolidone and maltose for rapid release within minutes (Ito et al., 2006b; Kolli and Banga, 2008; Lee et al., 2008; Sullivan et al., 2008). The final approach consists of using hollow microneedles to puncture the skin followed by infusion of liquid formulation through the needle bores in a manner similar to hypodermic injection (Gardeniers et al., 2003; Wang et al., 2006).

4.2. Design parameters

Microneedle design is constrained by a number of parameters. First, microneedles must be capable of inserting into skin without breaking. While metals are typically strong enough, polymers must be selected to have sufficient mechanical strength. Microneedle geometry is also important, where sharpness of tip strongly affects the force required for microneedle insertion into skin. Other parameters, including microneedle length, width and shape all influence force required for microneedle fracture (Davis et al., 2004; Park et al., 2005). Typical microneedle geometries vary from 150 to 1500 μm in length, 50 to 250 μm in base width and 1 to 25 μm in tip diameter.

Microneedles can also be designed to minimize pain. Initial studies showed that specific microneedles of a couple hundred microns length were reported painless (Kaushik et al., 2001; Mikszta et al., 2002). More recently, a detailed study has shown that microneedle length strongly affects pain, where a 3-fold increase in needle length (i.e. 500–1500 μm) increased pain 7-fold (i.e. from 5% to 35% of the pain caused by a hypodermic needle) (Gill and Prausnitz, 2008). Increasing the number of microneedles (620 μm long) 10-fold from 5 to 50 increased pain by a factor of three. Other geometrical parameters did not influence pain significantly.

Fabrication methods for microneedles need to be designed appropriately. As single-use, disposable devices, manufacturing costs should be kept low. Lithographic etching and micro-molding methods are typically used and are expected to have mass production costs well under US $1.00 and possibly as low as US $0.10 per device. Fabrication methods also need to avoid denaturing of vaccines and drugs and have therefore emphasized room temperature

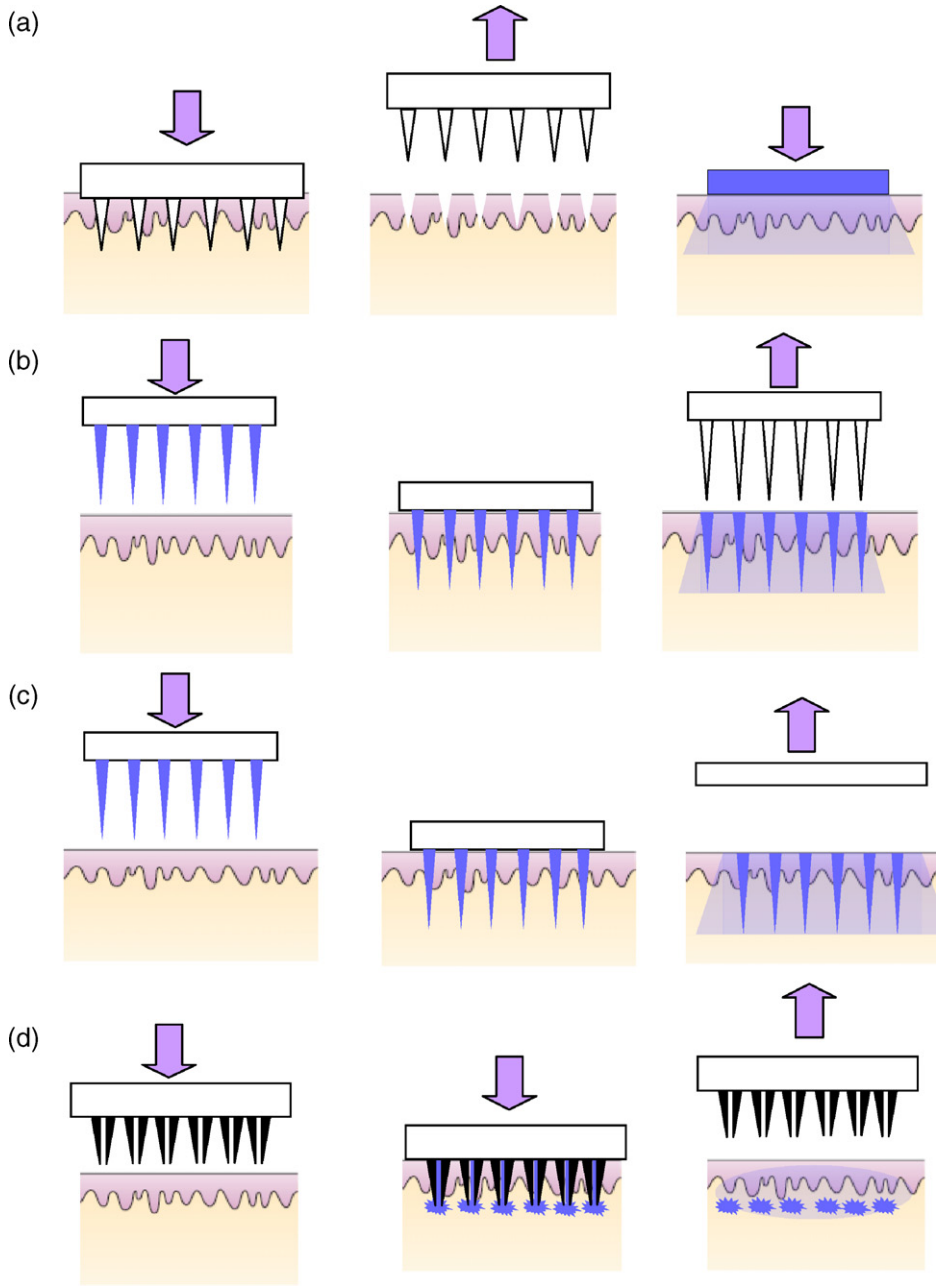

Fig. 3. Schematic of drug delivery using different designs of microneedles: (a) solid microneedles for permeabilizing skin via formation of micron-sized holes across stratum corneum. The needle patch is withdrawn followed by application of drug-containing patch, (b) solid microneedles coated with dry drugs or vaccine for rapid dissolution in the skin, (c) polymeric microneedles with encapsulated drug or vaccine for rapid or controlled release in the skin, (d) hollow microneedles for injection of drug solution.

processing with aqueous solvents and GRAS excipients (Prausnitz et al., 2003; Prausnitz, 2005; Prausnitz et al., 2005).

4.3. Applications

Microneedles have been studied *in vitro*, in animals and in humans for a variety of applications. Microneedle piercing has been shown to increase skin permeability by orders of magnitude to a variety of compounds ranging from low molecular weight tracers to proteins, DNA and even nanoparticles (Mikszta et al., 2002; McAllister et al., 2003). A recent study reported on delivery of naltrexone, which is used to treat alcohol and opioid addiction, at therapeutic levels in normal human subjects using this approach (Wermeling et al., 2008). Solid microneedles have also been coated with a number of different compounds, including low molecular weight drugs, proteins, DNA, virus particles and micro-particles (Gill and Prausnitz, 2007). Human clinical trials by Zosano Pharmaceuticals (Freemont, CA, USA) had completed Phase II clinical trials for delivery of parathyroid hormone from coated microneedles at the time of writing this review. Dissolving polymer microneedles have similarly encapsulated various compounds, including erythropoietin and enzymes that were shown to retain activity after encapsulation and even after at least 2 months of storage at room temperature (Ito et al., 2006a; Lee et al., 2008; Sullivan et al., 2008). Hollow microneedles have been shown to deliver insulin to rodent models and modulate blood glucose levels (Gardeniers et al., 2003; McAllister et al., 2003). Recent work in human subjects has demonstrated insulin delivery to control blood glucose levels in diabetic human subjects and lidocaine delivery to induce local anesthesia in normal human subjects (unpublished data).

Vaccine delivery via microneedles has attracted considerable attention. For example, administration of influenza vaccine via microneedles elicited immune responses comparable to or better than intramuscular injections in mouse model (Alarcon et al., 2007). Human clinical trials on influenza vaccination using hollow microneedles have completed Phase III and have been submitted as the basis for registration in Europe through collaboration between Becton Dickenson (Franklin Lakes, NJ, USA) and Sanofi Pasteur (Lyon, France) (Dean et al., 2005). Other vaccine studies include administration of ChimeriVax™-JE for yellow fever, plasmid DNA encoding hepatitis B surface antigen, and recombinant protective antigen of *Bacillus anthracis* (Mikszta et al., 2005, 2006). In all these studies, microneedles generated immune responses at least as strong as those generated by subcutaneous or intramuscular injections. Studies also demonstrated dose sparing ability of microneedles, where lower antigen dosage via microneedles elicited immune response comparable to higher antigen doses via alternate routes, i.e. subcutaneous and intramuscular injections (Matriano et al., 2002; Widera et al., 2006). Recently, a device which uses an electrically active microneedle array to cause electroporation in the skin has effectively enhanced DNA vaccination (Hooper et al., 2007).

4.4. Safety

Although data has not yet been published from ongoing human clinical trials, their progression through Phases II and III suggests an acceptable safety profile. Other data from animal and human studies have been published and generally report no significant adverse reactions to microneedles. More specifically, no infections caused by microneedles have been reported (Matriano et al., 2002; Cormier et al., 2004; Widera et al., 2006). In addition, skin irritation has been reported to be mild and transient when it exists at all (Lin et al., 2001; Matriano et al., 2002; Mikszta et al., 2002; Gardeniers et al., 2003; McAllister et al., 2003; Martanto et al., 2004; Wang et al., 2006), and bleeding is generally not associated with use of microneedles (Mikszta et al., 2002; McAllister et al., 2003; Martanto et al., 2004; Davis et al., 2005; Dean et al., 2005; Mikszta et al., 2005; Alarcon et al., 2007). As discussed above, a variety of microneedle designs have been reported to be painless in human subjects. Additional studies are needed to fully assess safety.

5. Thermal ablation

Use of thermal energy for surgical removal of selected tissue has been reported by medical practitioners as early as Hippocrates (460–370 BC), who used hot iron rods for cauterization of wounds (Karpozilos and Pavlidis, 2004). In modern medicine, thermal ablation generally refers to tissue removal due to high temperature induced by various energy sources. Percutaneous thermal ablation for tumor targeting is well established but does not use devices with micron-sized operating dimensions and is discussed elsewhere (De Sanctis et al., 1998; Van Rhoon and Wust, 2005). More recently, devices with micro-scale ablation elements have been developed for controlled removal of stratum corneum and thus thermally microporate the skin for enhanced transdermal drug delivery.

5.1. Mechanism

Thermal ablation of skin that selectively removes stratum corneum without damaging deeper tissues is achieved through careful control of skin surface temperature over short duration of time. A schematic of this process is shown in Fig. 4. By heating the skin surface briefly (e.g. $\ll$1 s), heat penetration is largely limited to stratum corneum, with local temperatures up to hundreds of degrees Celsius, while deeper viable tissue remains much cooler and structurally intact (Bramson et al., 2003). Formation of micropores of 30 μm diameter and 70 μm depth and absence of necrosis in surrounding tissue has been reported using selective ablation techniques (Bramson et al., 2003). In another study, micropores exhibiting an elliptical geometry of 80 μm width, 300 μm length and 40–50 μm depth were formed corresponding to the geometry of ablation elements (Sintov et al., 2003).

One mechanistic hypothesis is that bound water in the stratum corneum must be heated beyond its boiling point, upon which the water vaporizes (Apitz and Vogel, 2005). This sudden increase in volume of water blasts micro-craters locally in stratum corneum. In this way, thermal treatment of the stratum corneum triggers a mechanical event that actually causes tissue ablation. Other experiments suggest that temperatures much higher than boiling point of water are needed for extensive tissue ablation and that stratum corneum combustion is mechanistically responsible (Park et al., 2008).

5.2. Design parameters

The temperature, duration, and localization of thermal energy applied to the skin are all critical design parameters. Skin should be heated well above 100 °C and possibly up to many hundreds of degrees Celsius. Because skin heating is done for a very short time and extreme temperature gradients exist within skin (e.g. >10,000 °C/mm), it has been difficult to make precise measurements of skin temperature. To localize heating within the stratum corneum, thermal pulses are applied typically on the millisecond time scale or shorter. Longer pulses lead to heating of deeper skin tissue, which can cause undesirable damage to living tissues. Heating should also be localized to specific areas on the skin surface. Since it would generally be undesirable to ablate large areas on the skin surface for safety reasons, heating elements measuring just microns in size have been used. By employing an array of these micro-heaters, large area of skin can be treated for drug delivery, but only small spots of stratum corneum area are ablated within the treated area.

One approach to achieving controlled heating in this way involves a two-dimensional grid of wires having micron-scale resistors between each of the nodes. Using such a device, a brief surge of electric current through the network causes the resistors to suddenly heat up due to ohmic resistance. The electrodes cool down as soon as the current is turned off. This transiently heats the skin surface and ablates stratum corneum. PassPort™ system fabricated by Altea Therapeutics Corp. (Atlanta, GA, USA) (Banga, 2006) is based on this concept. A prototype of this device used an array of 80 μm diameter tungsten wires (72–75 wires/cm^2) as resistive elements for producing focused short bursts of thermal energy for ablation of stratum corneum (Bramson et al., 2003).

Another approach involves an array of electrodes that are activated one by one or through a feedback mechanism to briefly pass radiofrequency (RF) current into the skin. The resulting heat generated within the stratum corneum selectively heats this tissue for localized ablation. One such handheld device based on RF energy is ViaDerm™ which has been developed by TransPharma Ltd. (Israel) (Levin et al., 2005). The device employs a disposable array of stainless steel micro-electrodes (100 μm length and 40 μm diameter; 200 electrodes/cm^2) mounted on a polycarbonate body. The activation of device is governed by pressure as the device is pressed on skin at the site of application. Repeated applications of up to 250 and 380 V for *in vivo* and *in vitro*, respectively, were used at a frequency of 100 kHz for duration of 1 ms each.

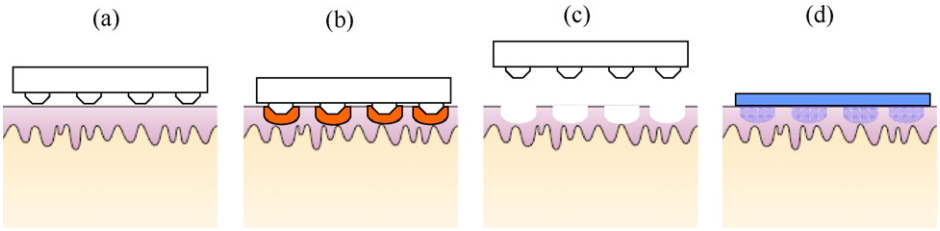

Fig. 4. Schematic of drug delivery using thermal ablation: (a) micro-electrodes are pressed against the skin, (b) skin is ablated via heating due to RF energy or resistive heating in the electrodes, (c) after removing the ablation device, (d) micropores formed are covered with drug patch for delivery.

5.3. Applications

ViaDerm™ has been extensively tested *in vitro* for delivery across porcine skin and *in vivo* on pigs and Sprague-Dawley rats for delivery of testosterone, grainsetron hydrochloride, diclofenac sodium and plasmid DNA (Sintov et al., 2003; Levin et al., 2005; Birchall et al., 2006). The studies consisted of either topical application of model drug or application of transdermal drug patch post ablation. Following *in vivo* testing, a number of human clinical studies have been reported for ViaDerm™ TransPharma Medical (2008). Delivery of grainsetron was tested over a period of 24 h in human clinical trials. A steady increase in plasma grainsetron levels for up to 12 h after patch administration followed by maintenance of a constant level till patch removal at 24 h was reported. Phase I human clinical trials were conducted for delivery of hPTH [1–34], a peptide fragment of human parathyroid hormone, as an anabolic treatment for osteoporosis. The study was carried out over a period of 7 days with daily administration of hPTH [1–34]. Absence of drug accumulation or degradation of hPTH [1–34] and drug bioavailability of 40% has been reported. In addition, ViaDerm™ system is currently in Phase I/II clinical trials for hGH delivery. A human clinical study has also been performed for delivery of insulin TransPharma Medical (2008).

Thermal ablation by PassPort™ system has been tested for administration of adenovirus vaccine with approximately 120-fold increase in reporter gene expression in various mice strains (Bramson et al., 2003). More recently, delivery of interferon $\alpha 2\beta$ has been shown with passive and iontophoretic patch in rat model (Badkar et al., 2007). The device has also been tested for delivery of influenza antigens, tetanus antigen, erythropoietin and fentanyl citrate in preclinical studies. Human clinical trials are currently underway for transdermal delivery of basal levels of insulin, hydromorphone HCl, fentanyl citrate, and apomorphine HCl Altea Therapeutics (2008).

5.4. Safety

Thermal ablation devices have shown acceptable safety profiles. In a recent human clinical trial for evaluating safety, administration sites were examined and results quantified using Draize irritation index for irritation on a scale of 0–8 and Visual Analogie Scale (VAS) for pain on a scale of 0–100. Draize index was 0.75 while VAS score was 5, confirming low degree of erythema and pain. Similar results have been reported in clinical trial for grainsetron delivery, where no irritation was detected after 24 h patch application. Slight erythema has been reported for use of prototype for PassPort™ system (Badkar et al., 2007).

6. Conclusions

The concepts which form the basis of transdermal micro-devices discussed here were discovered and first described several decades ago. The literature reviewed here strongly indicates that our fundamental understanding of device design parameters and how they affect device interaction with skin has significantly advanced over the last decade. These advances have resulted in novel device designs with increased therapeutic potential and minimal patient discomfort. Ongoing challenges include increasing therapeutic potential still further for some of these devices. Overall, promising trends for the next generation of transdermal vaccination and drug delivery micro-scale devices have emerged.

Micro-scale disruption of skin using the devices discussed here offers several advantages. Micron-sized pores can deliver several therapeutic molecules over a broad molecular weight range in shorter duration of time. These microscopic holes are still small enough to limit undesired effects including pain, irritation and infection. Other advantages include better delivery control over physical and physiological impact on skin. Current disadvantages are big size of some devices and high cost for single use devices or difficulties in component re-use. Future challenges lie principally in device engineering for making devices more portable, affordable and give reproducible results across a wide range of subjects.

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