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Review on Microneedles – An Innovative approach to Transdermal drug delivery

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Abstract:
With the advancement in recent technologies in the field of pharmaceutical research arena based on drug discovery and drug delivery, development of microneedles has proven to be an excellent and a merely suitable substitute which serves as an efficient tool for delivery of drugs through the skin in a sustainable and stable manner. Microneedle drug delivery is a newly developing dosage form which is still in its infant stage in our country, but it need to be explored as it serves as a connecting link between transdermal patches (TDP) and hypodermic needles. It also overcomes the disadvantageous properties of both the dosage forms. In particular, these current advances provide opportunities for developing advanced drug delivery systems for personalized transdermal medicines. Oral administration and hypodermic syringes are today's most commonly used delivery methods. However, they pose several disadvantages, such as painful side effects of using hypodermic syringes or the problem associated with oral administration, such as drug bioequivalence. Transdermal patches pose numerous advantages as an alternative method, as they provide controlled release of medicine to the patient in a minimally invasive manner. However, they cannot permeate large molecules to pass the SC (the top layer of skin), thereby limiting the medical application to patients. MNs have been proposed to overcome this limitation and provide the transdermal delivery of large molecular weight proteins. Microneedles either in the form of patches or an array, have been observed as a potential carrier for the delivery of numerous macromolecular drugs for the effective transdermal delivery.Though its has not been commercialised in a huge way in our country so the purpose of research and presentation is to create an awareness and better understanding of microneedles, which can be proven to be landmark discovery in delivery of drugs for the treatment of various diseases through the skin.

Keywords: Microneedle(MN), Subcutaneous(SC), Transdermal delivery of protein(TDP), Tramsdermal delivery of drug(TDD), Drug delivery (DD). Phosphate Buffer Saline (PBS). Micromoulding

Introduction: [1], [2]

Microneedles are one of the recently developed drug delivery systems which is similar to traditional needles but the difference is these are fabricated on the micron scale and the size ranges from 1100 microns in length and 1 micron in diameter. These are defined as micro-scale needles, arranged on a transdermal patch. These are the microstructure system composed of micro sized array projection coated with a drug or the needles itself made up from the drug. These are considered as a combination of hypodermic needles as well as transdermal patches and effective enough to overcome the limitations being possessed by these two systems. Micro needles have been formulated as a novel drug delivery carrier for effective transdermal delivery, as these have been developed by fabrication, done by involving the tools of microelectronics so that the penetration up to hundred microns deep into the skin can be achieved in a painless manner. Stratum corneum is the limiting barriers for the transport of several drugs and it will be bypassed by the use of microneedles. These are mainly arranged in the form of arrays. Micro needle arrays have been developed based on etching method used by microelectronics industry to develop arrays of micron-sized needles. Various reports have shown to prepare silicon or metal micro needles, and also by using dextrin, maltose, glass. It is also a patch system which will be used for transdermal delivery. As the success of transdermal delivery is limited by the fact that most of the drugs are insufficient in reaching the layers of the skin at the desired therapeutic rate. Thereby, the use of micro needle patches to enhance the skin permeability has been put forward and was found to be efficient in increasing transdermal delivery specifically for macromolecules.

The first report related to the development of microneedles for topical delivery was published in late 1990s, where the use of micro needles was emphasized in puncturing the skin for the enhanced permeability of the drug “calcein” (molecular weight 623 Da) across the human skin by four folds in vitro. Since then, a lot interest has been developed in this field both in terms of micro needle fabrication and drug delivery. The first micro needle system comprises of a drug reservoir and projections which are extending from the reservoir to penetrate the stratum corneum and epidermis to deliver the drug. This technique has been observed to improve the transdermal delivery of a variety of molecules like anthrax vaccine, β-galactosidase, calcein, bovine serum albumin, desmopressin, diclofenac, erythropoietin, methyl nicotinate, ovalbumin, plasmid DNA, insulin.

1.1 Different Drug Delivery Routes and their disadvantages: [3]

Numerous forms of DD routes are currently being used, which include, oral administration (gastric, colonic, enteric, etc.), hypodermic injections (e.g., intra-venous, intra-muscular, intra-cranial, sub-cutaneous injections, etc.), inhalation (pulmonary) and TDD (skin appendages). Oral administration and hypodermic injections are the most common delivery methods with approximately 80% of drugs administered orally. However, several difficulties associated with oral dosage forms exist, e.g., pH changes within the body causing degradation to drugs, enzymatic activity, variable transit time, side effects and first pass metabolism. The main disadvantages of using hypodermic injections is the resultant infection, pain caused during application, patient fear, anxiety and patient incompetence.

A good alternative that can overcome such problems is transdermal delivery of drugs (TDD), which can resolve issues such as by-passing first-pass metabolism (thus eliminating harmful metabolites whilst increasing bioavailability), and patient compliance. Transdermal delivery includes the applications of gels, creams, ointments and more recently transdermal patches. One transdermally delivered drug that is commonly used is nicotine, first developed in 1984 by Jarvikand Rose to help smokers give up smoking. However, there are disadvantages associated with TDPs, for example, the prevention of large molecules from bypassing the SC, the outermost layer of the skin, which is the rate limiting barrier. TDPs are applicable for molecules that are traditionally smaller than. Thus the most suitable drug delivery system which overcome the disadvantages of all other drug delivery system is proved to be use of microneedle technology.

1.2 Development in the research of microneedles over the ages: [4], [5], [6],[7],[8],[9]

Methods that have been employed to solve the short comings of both TDPs and hypodermic injections are ultrasound, MNs, iontophoresis, electroporation, chemical enhancers, and others. These techniques can overcome the protective SC barrier as they allow the passage of large molecular compounds such as proteins and DNA. MN technology in particular has grown over the past 15 years and can permit drugs to bypass the SC layer by the insertion of micron sized needles that

create micro channels through the SC. The MNs are small enough in length to avoid touching nerve endings of a patient, thereby, causing little or no pain. Furthermore, MN technology has shown to be more advantageous in comparison to the other TDD techniques, such as the ability to deliver large molecular molecules that are larger than 500 Da and the versatility in the application to allow solid or liquid formulations to be developed for disease specific applications.
There are numerous journal papers that have reviewed different types of drug delivery technologies and specific drug deliveries. A number of review papers have also discussed specific technologies, e.g., various methods to fabricate MNs, or the devices that are currently being used or are likely to be used in clinical trials. Indeed one can safely assume that the most significant aspects of MNs research have been discussed in review or research papers. However, one issue that is obvious is that there is little attempt to quantify the trend in the progress of MN technology. In other words, it is not clear how slow or fast the rate of progress is the development the MNs based methods are. It is also not clear from the existing literature what method one could use to quantify the trends and, if the trend could be quantified reliably given that the MNs based research is still relatively new as compared to most other TDD methods. This review paper will look into assessing these gaps in the literature by using a time series analysis of the journal papers found in Scopus, using a time series analysis tool namely, 'autoregressive integrated moving average (ARIMA) model (also known as univariate Box-Jenkins analysis) to look at the future trend patterns in the number of publications based on several key word searches. Quantifying and predicting past and future trends are important to determine the market values of these products as there is a growing interest to produce MN's to a commercial quality and scale. The program IBM SPSS Statistics version was used to produce the time series analysis tool and analyse the data from Scopus. The ARIMA model was created by omitting 2014 data as it is currently incomplete, therefore the analysis will give an indication of the trend till 2013. For the completeness of the paper, we discuss other relevant issues as well as follows.

1.3 Significance of Microneedle Drug delivery system:

- Although there are several commercially available TDPs, they are limited by the SC which includes overcoming the mass transfer resistance TDPs administer drugs via passive diffusion There are mechanisms for the storage of drugs on TDPs. A drug is either stored in a reservoir or incorporated into the transdermal patch fabric, whereby it is transported across the skin via a concentration gradient. Although these methods have shown to be applicable for a variety of drug formulations, they are still limited by the drug molecules that can permeate through the SC barrier. As mentioned earlier, MNs have been proposed as an alternative delivery method to TDPs and hypodermic syringes as they have shown to overcome the various short comings previously outlined.[10]
- Indeed, it has been illustrated by and other researchers that MN research is a promising field of research to be pursued more extensively as it can be used to overcome the skin's natural defensive barrier, the SC in both adults and children.[11]
- The rate of release of the drug depends upon the controlling membrane of the TDP and therefore ensuring a consistent drug release profile can be uncertain which is overcome by use of MN technology [12]
- MNs have been made possible to make due to the technological advances that have occurred in the last 20 years. Since the independent invention of the hypodermic needle in the mid 1850's hypodermic needles, or syringes, have been the most common form to administer biotherapeutics. [13]
- MN use has the advantage of simple patient administration of drugs with minimal invasiveness to the patients. The MNs would only permeate the SC and not the nerve receptors, consequently, the patients would feel little or no pain, though longer microneedles can also be used where deeper delivery of the drug is desired. Therefore, the development of MNs is important as it has the potential to overcome numerous disadvantages posed by the traditional DD systems.[14]
- Increasing Permeability of Skin: The use of MN as a drug delivery system is an important development as the potential to allow a wider scope of molecules to be transdermally delivered through the skin is greatly increased.The amount of drug that is delivered can also be increased. However, an understanding of the permeability of skin would need to be established in order to determine how to increase drug content. It is important to look at skin thickness when investigating increasing permeability of skin, as increasing skin permeability is important for transdermal drug delivery.[15]
- The invention of the MN can overcome this factor as the needles bypass the SC layer, which is the rate dependent layer and can allow large molecular weight proteins to pass into the blood stream. A well-known method to quantify the drug

release through skin is the use of Franz diffusion cells, and therefore have been used in literature extensively to calculate the permeability of skin.[16]

1.4 Other technologies in conjunction with microneedles for drug delivery:

There have been multiple papers outlining various methods conducted to analysedifferent techniques to increase the permeability of skin. They can be categorised into chemical and physical enhancing techniques, some of which include, thermal ablation, sonophoresisand electroporation an individual enhancement technique cannot possess all the desired properties to facilitate the transport of drugs transdermally. [17]

There are several physical methods that have been used in conjunction with MN technology to increase skin permeation. One such example is the use of sonophoresis with MNs. It is a technique which allows molecules to permeate through the barrier of the skin more readily as ultrasonic waves create micro-vibrations on the skin. [18],[19]

1.5 Advantages: [20-23]

Microneedles(MN) have been developed in ways that enable them to share advantages of both hypodermic needles and transdermal patches to deliver drugs through the skin at therapeutically desirable quantities. The combinatorial design of such MNs has overcome the limitations of the hypodermic needles (pain and risk associated) and transdermal patches (limited by the transport barrier provided by stratum corneum). MNs have the advantages of delivering small quantities of high-potency medication through the skin to minimize the pain factor and allowing precise tissue localization for drug delivery. Moreover, large active pharmaceutical molecules can be administered without causing pain using MNs as they only puncture the epidermal skin layer. They can also be used for biological analysis (via skin blood contact). Due to minimal invasiveness they offer the advantage of fast healing at the injection site (local skin area) with low risk of microbial infection. MNs also have the added benefit of rapid penetration of drugs directly into the blood circulation system (compared to skin diffusive approaches), subsequently avoiding the first pass effect of the liver and the digestive enzymes of the gastrointestinal tract. Furthermore, a selection of active and functional molecules (small molecules, e.g., calcein, and large molecules, e.g., proteins) and vaccines are well tolerated through controlled MN delivery. While this technique is termed pain-free, it is also minimally invasive without long-term oedema or erythema.A rapid onset of drug delivery can be accomplished by coupling MNs with an electrically controlled micro-pump which can effectively determine the rate of drug delivery as compared with other drug delivery approaches.To improve patient's compliance which is difficult to be achieved for vaccine delivery through transdermal drug delivery system.

1.6 Disadvantages [20-23]

There is immense potential for the use of these micron-sized needles for transdermal drug delivery enhancement.
A number of challenges also have to be addressed including irritation, microbial contamination and the delivery of therapeutically relevant concentrations of drugs.
There is also a limited choice of appropriate biomaterials, lack of mechanical strength, poor control of drug delivery, and limitation of drug loading dose.
Potent drugs requiring low doses and vaccines seem to be the drugs most likely to be delivered in therapeutically useful concentrations.

1.7 Applications in drug delivery

Most bio therapeutic agents and vaccines are injected by the use of hypodermic needle due to the advantage of providing a low-cost, rapid and direct way to deliver almost all types of molecules into the body. However, self-medication is difficult to achieve. Though oral delivery can overcome this problem, but various drugs cannot be given by this route due to poor absorption and drug degradation in the gastrointestinal tract and liver. Thus, an attempt has been made to modify the needles, by shrinking it to micron size in order to make it efficient for drug delivery and also improving the patient compliance and safety. As a micron-scale device, a microneedle should

be capable enough to deliver the drug as well as to avoid pain, fear and the need for expert training to administer. [24]

Microneedle allows precise tissue localization of delivery, such as within the skin, the suprachoroidal space of the eye, and the cell nucleus. Most applications of microneedles studied till now have emphasized mostly to drug and vaccine delivery to the skin. Conventional transdermal drug delivery system is limited by the barrier nature of the stratum corneum. Various chemical, biochemical and physical methods have been studied to enhance the skin permeability. [24]

Chemical and biochemical methods developed so far do not found to be broadly effective for delivery of bio therapeutics and vaccines across the skin. While physical methods have greater promise for delivery of macromolecules, they typically involve the use of sophisticated devices that are relatively large, costly and require training to use. Microneedles, in comparison to all the methods, can be prepared as a low-cost patch that is simple for patients to apply for delivery of bio macromolecules, macromolecules like insulin, growth hormones, immunobiologicals, proteins and peptides. [25]

Microneedles can also be employed for targeted vaccine delivery to antigen-presenting cells in the skin. [25]

Other applications of microneedles have also been such undergo development like drug delivery to the eye, especially via the suprachoroidal space, has received recent attention. [10]

Microneedles have been used to deliver molecules into cells and their nuclei, among other laboratory applications. [26]

Microneedles have also gain prominent attention in the field of cosmetics and various cosmeceuticals have been used for the treatment of acne, pigmentation, scars and wrinkles as well as for skin toning. [26]

Table 1: Drug formulated in Microneedle formulation along with its application [24], [25], [26]

Drug	Transdermal system	Application
Anti-restenosis	Micro needle patches	Targeted drug delivery in atherosclerosis[10]
Insulin	Micro needle patches	Reduced glycerol level up to 80% within 4 hrs.[11]
Desmopressin	Microneedles	Enhanced bioavailability, in the treatment of enuresis.[10]
Immunization (Antigen)	Microneedle array patch system	Effective immunization[10]
Vaccination(Influenza vaccine)	Microneedle patches	Enhanced immune response as compared to intramuscularinjection.[11]
Insulin	Fabricated arrays of solid microneedles	Increases insulin transdermal delivery to lower the blood glucose level by 80%.[12]
Lidocaine Hydrochloride	Microneedle array	Repeatable and robust penetration across stratum corneum and epidermis.[12]

Table 2: Some of the microneedle marketed formulation

Market product	Description	Manufacturer
AdminPen™	Microneedle array-based pen-injector device	AdminMed
AdminPatch™	Microneedle array	AdminMed
Macroflux®	Microneedle array	MacrofluxR Corporation Inc.
Microcore®	Dissolvable peptide microneedle patch	Corium
Microjet®	Intradermal microneedle injection system	NanoPass

Microneedles have also undergoing further research to have use in clinical implications to make them a better system to be effective in therapies, vaccinations and other useful applications in the field of pharmaceutics [27].

1.8 Future Prospects of microneedle-based DRUG delivery technologies: .[28],[29].

Research into MN devices is in its fourth decade already. Given the time span and amount of published data, it is somewhat surprising to see the relatively small number of commercial MN-based pharmaceutical products, and MNbased vaccines in particular. The main reason is probably the fact that until recently, fabrication methods for MN arrays were not mature enough to be the basis of a robust and reproducible industrial process, needed in the pharmaceutical environment. Hence, the interest of the pharmaceutical industry in the research of MN devices was somewhat limited. Recently, however, with the introduction of microelectronic- and laser-based state-of-the-art methods into MN research, it has become possible to develop production methods that have the potential of scalability and translation of laboratory settings into a good-manufacturing-practice environment. Therefore, it can be expected that enormous efforts invested in design and fabrication methods of MN devices will finally start giving more clinically relevant results in this decade. The other important reason that translation of MN-based vaccines into clinical use is still somewhat slow is the sole fact that in most cases, despite all the aforementioned disadvantages, traditional intramuscular or subcutaneous application of a vaccine results in a sufficient and reliable immune protection. The 100-year-long paradigm of needle- and syringe-based application of vaccines is simply not easy to put into question. However, the fact that current needle-and-syringe methods work fine may slow down an easy penetration of MN-based alternatives, but with further technological improvements, accumulation of data on efficacy and safety, and paying more attention to the patient's comfort, we are likely to see the introduction of a number of MN-based vaccines by the end of this decade. To conclude, research on MN devices for vaccine delivery was until recently more about solving the design and fabrication issues, while now focus is swiftly changing to the use and application of MNs for delivery of clinically relevant vaccines.

Literature Review:

Method of Findings:

SwarnlataSarafet. al., 2011. Studied and give the review regarding microneedles from micromachining to transdermal drug delivery. According to their review microneedles are produced by employing micromachining or micro electromechanical systems technology, which is used for manufacturing the integrated circuits. Microfabrication helps in fabricating the microneedles in various ranges of sizes and shapes with the desired strength for easy insertion into the skin. Microneedles combine the advantages of conventional injection needles and transdermal patches while minimizing their disadvantages. These are safer and painless alternative to hypodermic needle injections for various biomedical applications such as blood sampling and delivery of drugs especially for protein biotherapeutics and vaccines. They could also be used for targeting of the bioactive for treating skin cancers. Their review provides a detailed study about the different techniques in conjunction with MN technology for enhancement of skin permeation for the better delivery of drugs through transdermal routes along with its comparison between such techniques in order to differentitiate which technique is better. The review also suggest different types of microneedle and their mechanism of action. [30]

Maaden Koen van der, Luttg Regina et. al., 2015. Experimented and developed microneedle-based drug and vaccine delivery via nanoporousmicroneedle arrays which focus on the possibilities and constraints of porous microneedletechnologies for dermal drug delivery. They show preliminary data with commercially available porous

microneedles and describe future directions in the field of research. Drug delivery via hollow microneedles (a miniaturized form of hypodermic needles) is achieved by pressing a liquid drug formulation through the bore of the microneedle into the skin which consist of a drug formulation which is first loaded into the pores of a microneedle array Subsequently, the microneedles are pierced into the skin, and the drug diffuses from the microneedle matrix into the skin. As the microneedles are depleted of the drug, the drug diffuses from the drug reservoir (microneedlebackplate) via the microneedles into the skin. Hence, drug delivery via porous microneedles has elements of microneedle pretreatment (i.e., drug delivery is a diffusion-based process), with the major technical difference that porous microneedles remain inside the skin during drug delivery. Fluorescein, trypan blue, and fluorescently labeled nanoparticles of 30 nm are the materials which are used in the experiment. [31]

Cheung, K. Das, D.B., 2015. Microneedles for Drug Delivery: Trends and Progress This review looks at the various technologies developed in microneedle research and shows the rapidly growing numbers of research papers and patent publications since the first invention of microneedles (using time series statistical analysis). This provides the research and industry communities a valuable synopsis of the trends and progress being made in this field. Their review also gives detailed study of different delivery methods of microneedles for the effective delivery of different types of proteins and biomolecules and their probable outcome therapeutically and also its different method of fabrication. The article also focuses on theoretical explanation of different types of microneedle , its method of fabrication and its biomedical applications. [32]

Gittard Shaun D. et.al. 2009. Experimented on Fabrication of Polymer Microneedles Using a Two-Photon Polymerization and Micromolding Process. In this study polymer microneedles for transdermal delivery were created using a two-photon polymerization (2PP) microfabrication and subsequent polydimethylsiloxane (PDMS) micromolding process. The method involves solid microneedle arrays, fabricated by means of 2PP, and were used to create negative molds from PDMS. Using these molds microneedle arrays were subsequently prepared by molding eShell 200, a photo-reactive acrylate-based polymer that exhibits water and perspiration resistance. The eShell 200 microneedle array demonstrated suitable compressive strength for use in transdermal drug delivery applications. Human epidermal keratinocyte viability on the eShell 200 polymer surfaces was similar to that on polystyrene control surfaces. In vitro studies demonstrated that eShell 200 microneedle arrays fabricated using the 2PP microfabrication and PDMS micromolding process technique successfully penetrated human stratum corneum and epidermis. The results suggest that a 2PP microfabrication and subsequent PDMS micromolding process may be used to create microneedle structures with appropriate structural, mechanical, and biological properties for transdermal drug delivery of insulin and other protein-based pharmacologic agents for treatment of diabetes mellitus. [33]

Angira G. Purohit, et. al., 2014. Formulate and evaluate the coated microneedles for the treatment of hair loss. The goal of the study was to enhance permeation of drug with the aid of microneedles, thus reducing the concentration of alcohol and damage of scalp cells. Stainless steel microneedle roller (1 mm, 142 microneedles per roller) was purchased. Microsyringe was used to coat each individual needle present on the roller. Coated microneedles were studied for coating uniformity, in-vitro drug release and ex-vivo drug release. Drug release profile of coated microneedles was found to be comparable with marketed solution of minoxidil of the same strength. Accelerated stability study of one month at accelerated temperature and humidity condition showed insignificant rate of degradation. Method of fabrication is solvent evaporation technique using different polymers such as HPMC, PVP etc and alcohol. The main objective of the study is to show that coated microneedle formulations showed great potential in transdermal drug delivery systems. Alopecia presented common problem in both the genders. It was also learnt that various areas on scalp presented differences in drug permeation due to differences in concentration of fat cells under the skin. As minoxidil was the most commonly used drug for topical application to promote hair growth, the same was chosen for the study. [34]

Venisettyet. al., 2014. Fabricate the microneedle molds and polymer based biodegradable microneedle patches in lab scale. The research work aims to design microneedle molds in a novel way and fabricate and characterize biodegradable polymer based micro-needle patch utilizing polymer casting. Methods include fabrication of polymer patch involved

two steps, one is to fabricate microneedle array mold and the other is to prepare biodegradable polymeric microneedle patch using the molds. Molds are prepared by manually piercing the mixture of resin and hydrate (emseal) using needles having micro tips and patches are prepared using polymer solution. Characterization of microneedle patch was done using scanning electron microscope and skin piercing ability was understood from histological studies of the rat skin. The micro-needles on the patch were found to be uniform in size and shape, with concentric circular features, the size of the microneedle tip was found to be between 20-50 µm and base around 200 µm and the shape was found to be conical with sharp tip. The micro-needles showed good penetration in to the skin which was observed by the histological studies performed using rat skin. The present study demonstrates that the microneedle molds can be prepared using resins and microneedles can be developed using polymer casting method. The developed microneedles showed comparable structural features with those reported in the literature. These microneedles possessed good mechanical strength and can pierce the rat skin. [35]

Ahmad Rita Haj. et. al., 2015. Reviewed about the microneedle coating techniques for transdermal drug delivery. In this review, it describes several processes to coat MNs. these include dip coating, gas jet drying, spray coating, electro hydrodynamic atomisation (ehda) based processes and piezoelectric inkjet printing. Examples of process mechanisms, conditions and tested formulations are provided. As these processes are independent techniques, modifications to facilitate MN coatings are elucidated. in summary, the outcomes and potential value for each technique provides opportunities to overcome formulation or dosage form limitations. While there are significant developments in solid degradable MNs, coated MNs (through the various techniques described) have potential to be utilized in personalized drug delivery via controlled deposition onto MN templates.The study also focuses on different designs of microneedles and their mechanism of action in efficient delivery of drugd through transdermal route in the form of different types of microneedles. Apart from that different types of coating techniques also illustrated in the review article.Subsequently its biomedical application also elucidated elaborately. [36]

NejadHojatollahRezaei. et. al., 2017. They developed a facile, low-cost and cleanroom-free technique for the fabrication of microneedles using molds created by laser ablation. Microneedle mold with high aspect ratios is achieved on acrylic sheet by engraving a specific pattern of crossover lines (COL) using CO2 laser cutter. Ablating COL pattern on the acrylic sheet creates a sharp conical shape in the center of the design. We have shown that a variety of microneedle shapes with different heights and tip angles can be easily achieved by changing the number and the length of the COL. Polydimethylsiloxane (PDMS) microneedles were fabricated by casting the PDMS on the mold. The resulted PDMS microneedles are oxygen plasma treated and then silanized. Another PDMS layer is casted on PDMS microneedles and detached after curing. The silanization prevents those two layers of PDMS from bonding to each other and makes them easily detachable. After detachment of the PDMS mold of microneedles, the mold is used to fabricate degradable polyvinyl alcohol microneedle patch suitable for transdermal drug delivery. The release kinetics of the needles are also shown and discussed in order to prove the applicability of the needle. [37]

KuoShyh-Chyi. Chou Yukon., 2004. Developed anovel method to fabricate polymeric hollow microneedles with sharp tips by a proprietary photolithography and molding process. This process can be employed to fabricate a multi-layer structure that consists of a microchannel layer, a supporting layer and many polymeric hollow out-of-plane microneedles on the supporting layer. The structure was fabricated monolithically, and won't be out of shape after high temperature/high pressure vapor test. It can be used for biomedical applications such as drug delivery, blood sensing and printing tip array. It also determine the microneedles for blood extraction by numerical simulation. Furthermore, this array of needles was coated with polydimethylsiloxane (PDMS) to make an inverse mold. The typical dimension of microneedles is the bore diameter of 50 µm and length of 600 µm. PDMS prepolymer was prepared by mixing the commercially available prepolymer and catalyzer (Sylgard 184 kit, Dow Corning) in a 10:1 w/w ratio. The mixture was degassed under vacuum to eliminate bubbles created during mixing. The PDMS inverse mold was cast from a polymeric hollow microneedles arrays master. PDMS was cured by baking for 4 h at 60 °C. After cooling to room temperature, the PDMS was peeled from the master. In this way the study came to a conclusion that the potential applications of the structure are analysis of blood, drug delivery and printing tip array. [38]

Lee IC. et. al., 2017. Developed a two-layer dissolving polymeric microneedle patches for insulin transdermal delivery in diabetic mice. Here, two-layer dissolving polymeric MN patches composed of gelatin and sodium carboxymethyl cellulose (CMC) were fabricated with a two-step casting and centrifuging process to localize the insulin in the needle and achieve efficient transdermal delivery of insulin. In vitro skin insertion capability was determined by staining with tissue-marking dye after insertion, and the real-time penetration depth was monitored using optical coherence tomography. Confocal microscopy images revealed that the rhodamine 6G and fluorescein isothiocyanate-labeled insulin (insulin-FITC) can gradually diffuse from the puncture sites to deeper tissue. Ex vivo drug-release profiles showed that 50% of the insulin was released and penetrated across the skin after 1 h, and the cumulative permeation reached 80% after 5 h. In vivo and pharmacodynamic studies were then conducted to estimate the feasibility of the administration of insulin-loaded dissolving MN patches on diabetic mice for glucose regulation. The total area above the glucose level versus time curve as an index of hypoglycemic effect was 128.4 ± 28.3 (% h) at 0.25 IU/kg. The relative pharmacologic availability and relative bioavailability (RBA) of insulin from MN patches were 95.6 and 85.7%, respectively. This study verified that the use of gelatin/CMC MN patches for insulin delivery achieved a satisfactory RBA compared to traditional hypodermic injection and presented a promising device to deliver poorly permeable protein drugs for diabetic therapy. [39]

Kim Yu chun. et. al., 2009. Formulate and coated the microneedles with inactivated influenza virus to improve vaccine stability and immunogenicity. Microneedle patches coated with solid-state influenza vaccine have been developed to improve vaccine efficacy and patient coverage. However, dip coating microneedles with influenza vaccine can reduce antigen activity. In this study, we sought to determine the experimental factors and mechanistic pathways by which inactivated influenza vaccine can lose activity, as well as develop and assess improved microneedle coating formulations that protect the antigen from activity loss. After coating microneedles using a standard vaccine formulation, antigenicity was reduced to just 2%, as measured by hemagglutination activity. The presence of carboxymethylcellulose, which was added to increase viscosity of the coating formulation, was shown to contribute to vaccine activity loss. After screening a panel of candidate stabilizers, the addition of trehalose to the coating formulation was shown to protect the antigen and retain 48–82% antigen activity for all three major strains of seasonal influenza: H1N1, H3N2 and B. Influenza vaccine coated in this way also exhibited thermal stability, such that activity loss was independent of temperature over the range of 4 – 37°C for 24 h. Dynamic light scattering measurements showed that antigen activity loss was associated with virus particle aggregation, and that stabilization using trehalose largely blocked this aggregation. Finally, microneedles using an optimized vaccine coating formulation were applied to the skin to vaccinate mice. Microneedle vaccination induced robust systemic and functional antibodies and provided complete protection against lethal challenge infection similar to conventional intramuscular injection. Overall, these results show that antigen activity loss during microneedle coating can be largely prevented through optimized formulation and that stabilized microneedle patches can be used for effective vaccination. [40]

Dillon Colin. et.al. 2017. Developed and characterise the dissolving microneedles for the transdermal delivery of therapeutic peptides. This study presents a dissolving MN system composed of polyvinylpyrrolidone (PVP) and trehalose to encapsulate active pharmaceutical peptides within the MN matrix. Rapid systemic delivery is then achieved once the needles have penetrated the SC and dissolved in the interstitial fluid of the skin. A variety of characterisation techniques were carried out to determine the optimum formulation. A model peptide, polymyxin B, was then incorporated into the MN system and delivered through porcine skin. In addition, the activity of the model drug was monitored during all stages of the formulation process. [41]

AntoVrdoljak. et. al., 2013. Gives a review about recent literature on microneedle vaccine delivery technologies. Vaccination using MN devices targets the skin's rich immune system, leading to better utilization of the antigen and resulting in superior immune response, often achieved using a lower vaccine dose than required by conventional delivery routes. However, despite the number of advantages and nearly four decades of research, the number of licensed MN-based vaccines remains limited to date. Nevertheless, it is to be expected that on the back of a number of recently developed scalable and robust MN-fabrication methods, more intensive translation into clinical practice

will follow. Here, we review the current status and trends in research of MN-related vaccine delivery platforms, focusing on the most promising approaches and clinically relevant applications. [42]

Luttge Regina. et. al., 2007. Developed new fabrication method consisting of lithographically defining multiple layers of high aspect-ratio photoresist onto preprocessed silicon substrates and release of the polymer by the lost mold or sacrificial layer technique, coined by us as lithographic molding. The process methodology was demonstrated fabricating out-of-plane polymeric hollow microneedles. First, the fabrication of needle tips was demonstrated for polymeric microneedles with an outer diameter of 250 mum, through-hole capillaries of 75-mum diameter and a needle shaft length of 430 mum by lithographic processing of SU-8 onto simple v-grooves. Second, the technique was extended to gain more freedom in tip shape design, needle shaft length and use of filling materials. A novel combination of silicon dry and wet etching is introduced that allows highly accurate and repetitive lithographic molding of a complex shape. Both techniques consent to the lithographic integration of microfluidic back plates forming a patch-type device. These microneedle-integrated patches offer a feasible solution for medical applications that demand an easy to use point-of-care sample collector, for example, in blood diagnostics for lithium therapy. Although microchip capillary electrophoresis glass devices were addressed earlier, here, we show for the first time the complete diagnostic method based on microneedles made from SU-8. [43]

Jiyu Li. et. al., 2016. Fabricate Ti porous microneedle array by metal injection molding for transdermal drug delivery. The research present a titanium porous microneedle array (TPMA) fabricated by modified metal injection molding (MIM) technology. The sintering process is simple and suitable for mass production. TPMA was sintered at a sintering temperature of 1250˚C for 2 h. The porosity of TPMA was approximately 30.1% and its average pore diameter was about 1.3μm. The elements distributed on the surface of TPMA were only Ti and O, which may guarantee the biocompatibility of TPMA. TPMA could easily penetrate the skin of a human forearm without fracture. TPMA could diffuse dry Rhodamine B stored in micropores into rabbit skin. The cumulative permeated flux of calcein across TPMA with punctured skin was 27 times greater than that across intact skin. Thus, TPMA can continually and efficiently deliver a liquid drug through open micropores in skin. [44]

Donnelly Ryan F. et. al., 2016. Gives a review on review on microneedle arrays as transdermal and intradermal drug delivery systems for materials science, manufacture and commercial development This review focuses on a range of critically important aspects of microneedle technology, namely their material composition, manufacturing techniques, methods of evaluation and commercial translation to the clinic for patient benefit and economic return. Microneedle research and development is finally now at the stage where commercialisation is a realistic possibility. However, progress is still required in the areas of scaled-up manufacture and regulatory approval. [45]

Conclusion:

- Microneedles can deliver a plethora of drugs and vaccines; the technology is not limited to any specific class of drugs.
- More than 70% of the products in development are patches incorporating solid or dissolvable needles, rest are hollow microneedle arrays which employ the use of a syringe.
- About 12 products based on microneedle technology are currently in clinical development, more than half of which are in phase II or a higher stage of development. In addition, there are a number of other products currently in preclinical trials.
- Many academic institutions are also exploring the use of microneedles for diagnostics, gene delivery and continuous drug monitoring purposes.
- Majority of these research projects are focused in developing micro needle products as easy-to-use wearable patches.
- With several new micro needle based therapeutic product launches by the end of this decade, we expect the overall market for micro needle based delivery devices to reach annual sales of 485 million units by 2030.

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