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Development of a novel single-use microneedle design platform for increased patient compliance

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Abstract

Microneedles (MN) skin patches are novel medical devices in micron scale with a needle array which offers an alternative drug delivery system to conventional methods. MN patches are applied onto the skin reaching the dermal layer where the drug molecules are released at a specific rate. There is a lack of knowledge surrounding some determinant factors required to define an efficient MN application into the user skin. The aim of the project is to determine the optimum application parameters to fabricate a polymeric MN patch and to design a disposable single-use MN applicator with enhanced usability.

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Keywords: microneedle patches; PLGA; self-applicator; atomised spray; sterilization; state-of-art review.

1. Introduction

The aim of the project is to develop a dissolvable microneedle (MN) patch integrated with a mechanical transducer built into the backing layer in order to enhance its applicability for patients [1,2,3].

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This robust integrated patch will provide accurate and consistent control of insertion depth irrespective of different application rates, application forces and moreover, different thumb or finger sizes thereby, minimising operational errors. The overall purpose of the project is to improve the patient compliance with this novel drug delivery application system. Therefore, the key objectives of this project are:

1. Fabrication and characterization of polymeric MN using spray technology already established in Cork Institute of Technology (CIT)/University College Cork (UCC) research group (Ireland).
2. Assess the effect of process conditions and sterilisation on the MN properties.
3. Establish the key parameters that contribute to efficient and consistent insertion of MN.
4. Design and develop a low cost single use applicator that eliminates inconsistencies associated with manual application.
5. Integrate the applicator and MN array into a single unit, taking factors such as fabrication, sterilisation, use and disposal into consideration.
6. Test prototypes of the new applicator design and compare its performance with manual and existing multi-use applicator designs to establish which insertion technique enables the most reliable self-application of MN arrays.

This study briefly summarises the methodology of the proposed work and also reviews key elements of the project. The key project elements includes: MN overview, materials selection, MN design and fabrication process, sterilisation considerations, MN applicator design, characterization methods and finally the factors related to the clinical compliance.

Nomenclature

GPa	GigaPascals
MPa	MegaPascals
kGy	KiloGray
m/s	Meters per second
$pJ/\mu m^2$	PicoJules per square micrometres

2. Methodology

The project will involve the fabrication of polymeric microneedle patches by atomized spray technology, characterization of MN under different conditions and processes, the integration of both MN patch and applicator, their validation and verification so as to construct and perform testing of the prototype based on the proposed design. The proposed MN patch system will consist of two integrated parts: 1) a dissolvable MN layer constructed from poly-lactic-glycolic-acid (PLGA) which will be of suitable mechanical strength to breach the stratum corneum (SC) and 2) an applicator which will be built into the backing of the MN layer to provide an effective and controlled application. Each polymeric MN patch composed of PLGA will be fabricated by applying the polymer onto poly-dimethylsiloxane (PDMS) moulds using atomized spraying technology. PDMS moulds are provided by Tyndall Institute in UCC. Relevant factors for the optimisation of the fabrication process, such as nozzle height, flow rate, polymer concentration, polymer type will be assessed due to their influence on the physical and mechanical properties of PLGA. The MN will be sterilised using gamma radiation with a dose of 29.1-29.7 kGy, adhering to U.S. Food and Drug Administration (FDA) guidelines (BS EN 556-2:2015). The effects of sterilisation on the physiochemical and mechanical properties will be analysed by different characterization techniques. The design of the MN applicator will involve different phases, starting with the study of the influence of the MN geometry on the insertion force, fracture/buckling failure forces and other factors that influence the MN performance. Using Finite Element Analysis modelling (FEA), skin and MN behaviours will be predicted so as to optimise insertion parameters and needle array parameters such as array density, base plate diameter and the resulting insertion force. Computer-Aided Design (CAD) modelling will facilitate design of an optimised MN applicator and visualise the integrated system before manufacturing of the parts. The applicator design will follow the current regulations, such as FDA regulations and EU regulations (MEDDEV regulations) that classify the potential designs as a Class IIa or IIb device

depending on how long the MN patch takes to dissolve in the skin and if the applicator will remain with the MN patches after application. Finally, validation and verification of the integrated system will be done so as to ensure its effective usability, where ex-vivo pig skin studies will be performed in UCC. A variety of software packages will be used in this project: CES Edupack will be used to research into materials and their properties; FEA modelling will be performed with Abaqus and CAD modelling with SolidWorks and Abaqus; statistical analysis will be performed using Minitab, SPSS and Gpower.

3. Project review

3.1. Microneedle overview

MN skin patches are novel medical devices consisting of an array of needles less than 2 mm in height. MN mediated transdermal delivery is an interesting route of administration for the systemic delivery of drugs and offers an alternative approach compared to the conventional parenteral methods. Conventional drug delivery methods such as intravenous (IV), intramuscular (IM), and subcutaneous, sublingual (SD) administration are used extensively in medical practice, with an estimated 16 billion injections administered worldwide in IV drug administration. Despite efficacy and worldwide use, IV, IM and subcutaneous drug delivery systems are associated with patient pain, phobia, anxiety, hazardous waste and needle pricks across adult and pediatric populations alike [6,7] . Medicated MN patches are presented as an alternative to the complications associated with hypodermic needles. Delivering pharmacological molecules in a minimally invasive manner by applying the medicated patch to the skin, this method offers an effective delivery system which is pain-free, biologically safe without biohazard waste, patient friendly and self-directed in its application. Other important considerations include avoidance of the harsh gastrointestinal problems (pH, enzymatic degradation, hepatic metabolism) with using this systemic delivery system and long term storage with the avoidance of long cold storage trains [8]. Therefore, from an ethical perspective, MN are a desirable option.

3.2. Microneedle design

There are four main MN types; solid, coated, dissolvable and hollow MN as can be seen in Fig. 1. Solid MN create micropores from their application to the skin which is subsequently followed by applying a drug solution layer where the formulation enters the temporary formed pores [3]. This mode of action is referred to as “poke and patch”. Coated MN are solid MN coated with the drug. The drug dissolves from the solid MN into the skin and the solid MN are removed from the skin (“coat and poke” approach). Dissolving MN are made from biodegradable materials which dissolve in the skin releasing the drug. This is termed a “poke and release” method. Finally, hollow MN are similar to conventional hypodermic needles but shorter in length where the drug liquid formulation is injected into the skin (“poke and flow” approach).

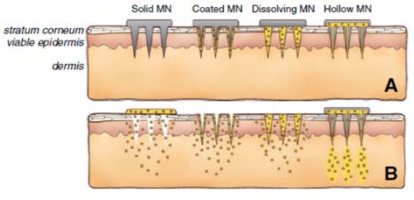


Fig. 1. Different types of micro-needle design [3].

a)



b)

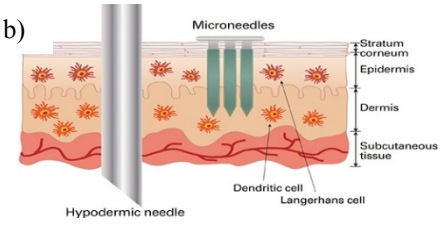


Fig 2. (a). An estimation of mean epidermal cell nuclei of 8.6 microns [10]; (b) Comparison between conventional intramuscular injection by hypodermic needle and MN. [11].

All MN patches, irrespective of the MN type, are applied onto the outer layer of the skin, the epidermis. It is composed by keratinocytes, melanocytes, Langerhans cells and Merkel cells. As an overview of the epidermis, it is divided in 5 or 4 layers depending on the part of the body: SC, stratum lucidum, stratum granulosum, stratum

spinosum, and stratum basale. The MN patches work by breaching the SC, which is composed of 10 to 30 layers of flattened corneocytes (10-20 microns in depth), which are mostly lipid secretions and keratin. The main function of the SC is to act as a repellent barrier or to regulate water level in the body, protecting deeper layers from microbial infection and mechanical and chemical stresses. An illustration of skin layer can be seen in Fig. 2. The MN structure penetrates this epidermis layer, and then the upper layers of the dermis, second skin layer, without reaching the abundant amount of pain sensitive nerve endings. These nerve endings are mechanoreceptors and thermoreceptors with the primary aim to provide the sense of touch and heat, and they are responsible of the sensation of pain. The dermis layer is located approximately 40 microns from the skin surface and is also where the blood capillary system lies which is responsible for transporting the drug around the body. According to some studies, the Young Modulus of the skin varies between 4.6 MPa and 20 MPa for mechanical tests, but this factor is dependent of the age, and it affects the insertion force of a MN into the skin. This same study explains that the skin stretching decreases almost 4 MPa from one neonate to an elderly adult, the same effect can be seen for the elasticity modulus, reducing from 70 MPa in a child to 60 MPa in an elderly adult [9]. Skin parameters will be evaluated in order to build a valid FEA model that represents the intended target population. Findings of current MN patches studies will be investigated in order to understand the factors that determine the optimal conditions for insertion into the skin, such as needle height, tip radius, base diameter, needle angle and array density. Extensive research has been performed investigating different MN heights. MN heights in the range of 500-600 microns have been found to be optimal reducing pain, bleeding and possibility of infection [3, 13]. Also, it has been found that microneedle insertion is facilitated with smaller tip diameters, bigger distance between MN in the MN array, and the octagonal pyramidal MN shape, and is independent on the number of needles in the patch [14,15,16].In this study, dissolvable MN in the range of 500-600 microns will be fabricated.

3.3. Microneedle material

Solid MN are mainly made of metal, silicon, ceramic or polymers. However, biodegradable materials such as polymers, sugars and more recently bioceramics can be employed to fabricate the dissolving microneedle structures. The drug is formulated into the biodegradable material [17]. In this study, the material selected for construction of the MN is PLGA, what is a copolymer composed of lactic and glycolic acid repeat units. PLGA is a FDA approved material which is non-toxic, biocompatible and safe to use. PLGA is commonly used in the biomedical field for sutures, fracture fixation, oral implants and drug-delivery due to its diverse properties. Some of the physical properties associated with PLGA can be seen in Table I. The physical properties of PLGA can change depending on the initial molecular weight (MW), lactic-glycolic acid ratio (LA:GA), size of the device, exposure to water (surface shape) and storage temperature. PLGA typically has an amorphous structure with disordered polymer chains. The glass transition temperature (Tg) ranges from 45 to 55 ºC. It is dependent on the lactic acid content and on the degradation time, and it is dependent on the copolymer composition as well as on the MW. However, there are some semi-crystalline PLGA materials, with 35-55% crystallinity. The Tg will influence the mechanical strength of the polymer and also, the stability of the material on storage. The Young Modulus for the PLGA is 2GPa with 3-10 % polymer elongation (tensile properties) and it is almost a constant with independence of the LA:GA ratio, and Tg. Also, the MW and polydispersity index can affect the mechanical strength of the material, but LA:GA ratio does not affect the mechanical strength, nor elongation, but it does have an effect in the degradation time and in the Tg.

Table 1. Properties and fabrication of biodegradable polymer materials [18].

Polymer	Modulus (GPa)	Elongation (%)	Solvent	Cristallinity (%)	Degradation Time (Weeks)	Applications
Poly(D,L-lactide-co-glycolide) 85/15	2.0	3-10	Ethyl acetate, chloroform, acetone, THF	Amorphous	5-6	Interference screws, suture anchors, ACL reconstruction
Poly(D,L-lactide-co-glycolide) 75/25	2.0	3-10	Ethyl acetate, chloroform, acetone, DMF, THF	Amorphous	4-5	Plates, mesh, screws, tack, drug delivery
Poly(D,L-lactide-co-glycolide) 50/50	2.0	3-10	Ethyl acetate, chloroform, acetone, DMF, THF	Amorphous	1-2	Orthopedic implants, drug delivery
Poly(L-lactide-co-glycolide) 10/90	-					

These are important characteristics which have implications for the application of the MN into the skin to ensure that the MN did not break on impact. PLGA is biodegradable through the hydrolysis of its ester bonds along the backbone forming labile by-products (alcohols and acids) which can be easily metabolised in the body. The degradation kinetics of the polymers is dependent on the lactic-glycolic acid ratio and the molecular weight. Therefore, the drug release can be tailored (over 1-6 months) as a result on the chemical composition of the copolymer selected. The material can encapsulate molecules of virtually any size such as chemical and protein drugs. PLGA is a polymer that can be easily processed e.g. solvent casting and thermal processing methods. The polymer can cast into any shape using solvents such as chlorinated solvents, tetrahydofuran, acetone and ethyl acetate [18, 19]. Understanding the properties of PLGA is important in order to select the right copolymer for this study: PLGA is an attractive material and it is a perfect candidate for the fabrication of MN for transdermal use as a result of its mechanical, biodegradation and casting characteristics, as it has been shown in recent studies [17]. Chen et al. have fabricated successfully MNs patches composed of embeddable chitosan MN and poly(L-lactide-co-D,L-lactide) (PLA) as a supporting array for the delivery of encapsulated antigens to the skin, being a proper material for this purpose [20].

3.4. Fabrication process

A wide range of MN fabrication processes have been researched. These include micro moulding, thermal drawing, injection moulding process, centrifugation [3, 21, 22]. In this study, the dissolving MN will be fabricated by micro-moulding methods. Moulds are fabricated using a hydrophobic material, PDMS. The process for preparing the moulds involves pouring a PDMS solution over a master structure coated with platinum and then by curing the polymer overnight at room temperature. Once moulds are cured, they are peeled from the master structures and used as master structures for the creation of MN patches [3]. The polymeric MN will be prepared using an atomized spray technique. Recent studies demonstrated that MN can be fabricated with polymeric materials creating an amorphous content using single formula sugars, with either a novel laminate-layered or horizontally-layered dissolving MN arrays, by adapting the spraying method [21]. Polymeric MN have been already fabricated by CIT's research group being orthogonal shaped MN with sharp tips.

3.5. Sterilisation

Sterilisation of the prototype is an important consideration. McCrudden et al. studied the considerations in the sterile manufacture of hydrogel MN arrays with some model drugs. Results showed that no measurable bioburden was detected in any of the prepared devices and endotoxin levels were below the FDA limits (20 endotoxin units/device). The hydrogel-forming MN were not affected by gamma irradiation (25 kGy) in terms of their physical properties or drug capabilities. However, sterilisation process decreased the drug concentration of the MN patches [23]. In this study, the PLGA MN will be sterilised according to the FDA guidelines using gamma radiation. The effect of the sterilisation process on the polymer characteristics will be studied and new routes of approach may be taken.

3.6. Applicator design

To allow a reproducible and repeatable delivery of the drug, MN should be inserted into the skin in a controlled and reproducible manner. This demands the use of an applicator such as a manual (thumb pressure actuator or applicator system) or mechanical (spring-loaded mechanism or piston driven) system which is either for a single use or multiple use [17]. Our research will focus in the design and building of a MN applicator which will be integrated into the MN backing layer. An investigation into the relevant key factors for the clinical use of MN patches (with or without applicator) must be considered as these are an important part of the established regulatory requirements, these includes [8]: 1) Effective, uniform and repeatable MN application to overcome any variations in skin properties; 2) Controlled depth of penetration of the MN into the skin so as to prevent introduction of microbial contamination and to avoid potential infections; 3) Sufficient mechanical strength to breach the SC without

fracturing the MN structures on the patch; 4) Easy and safe to use as well as being pain-free if an applicator is utilised [17]; 5) Ease of sterilisation; and 6) Maintain proper physical stability and physical integrity during storage and application. There are several designs commercially available for the use of solid or hollow MN only (3M, Zosano® Pharma, MicroCor™, Adminpatch®, Micronjet®, BD Soluvia™, MTS-Rollers™, see in Fig. 3.) but commercial applicators for the administration of dissolvable MN are not available at the moment. It has been shown that manual impact insertion devices result in low penetration efficiencies (56%) with high inter and intra-individual variation compared to mechanical impact insertion devices. This was attributed to the variations in applied force which were below optimum insertion conditions [5]. This supports the need for an applicator device to assist in the insertion of the MN patch. However, it must also be noted that there are a number of disadvantages associated with existing applicators for solid and hollow MN such as: 1) additional application system required by the patch; 2) large cumbersome and awkward devices; 3) re-sterilisation for multiple use; 4) risk of infections and 5) clogging of MN in the case of hollow MN in its re-use. There are also other designs currently under research that include vibration and electrical driven mechanisms [25]. The use of thumb pressure actuation directly onto the base plate of the MN patch is complex and with high inter and intra-individual variability. Electrical driven devices which possess adjustable forces are more stable over time and more suitable for multiple use compared to manual or spring induced forces [25]. However, for single use, a mechanical driven applicator could be better from an economic point of view. In the last year, there were publications proving the effective use of integrated systems (built-in insertion mechanism into each patch) which are designed with spring loaded mechanism, with two concentric rings, and a push-plate, for solid MN with the intended use of penetrating different skin models in one-handling step [2]. This proof-of-concept study ascertained that their integrated applicator-assisted insertion method resulted in 80% penetration efficiency on a foam material (skin model) compared to manual applicator methods due to the force distribution onto the pushing plate and that the puncture efficiency has a factor three times higher when applying thumb pressure on the patch base plate directly.

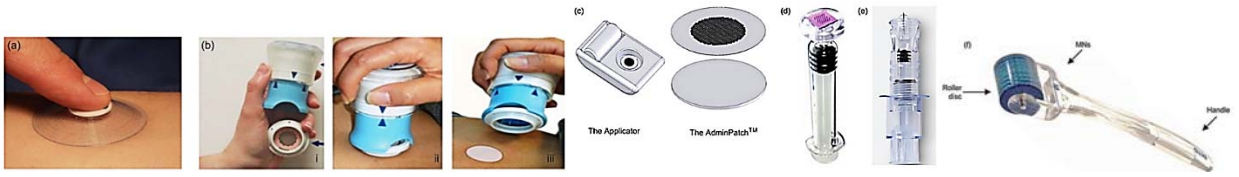


Fig 3. MN applicators from different companies. (a) MicroCor™ applicator; (b) Zosano's Macroflux®; (c) AdminPatch®; (d) MicronJet®; (e) BD Soluvia™ .Adapted from BD (2009); (f) MTS-Rollers™ applicator. (Adapted for review publication [24].

The same study also showed that the use of an impact-insertion applicator improves the efficiency and reproducibility for a high-density MN path. In this study, spring loaded and push-plate mechanisms will be investigated. The applicator and its parts can be fabricated with methods such as 3D printing, plastic injection, or with conventional machining, all available in CIT.

3.7. Characterisation methods

In order to characterise the fabricated polymeric MN and to set the applicator specifications, the methods used will include a qualitative scoring system, imaging using optical light microscopy and scanning electron microscopy (SEM) and some methods to determine the physical and structural features of the patches (the shape, size and number of micro-needles produced on a patch). Chemical analyses will determine the chemical structure (Raman spectroscopy) and the chemical phases present (crystalline/amorphous (differential scanning calorimetry (DSC)). The mechanical properties (tensile strength and compression) will be determined using an Instron Dynamic testing machine. Also a number of artificial skin models will be examined by using ex-vivo pig skin studies in order to understand the influence of MN geometry and applied force versus penetration depth. It is important to note that CIT research team in collaboration with UCC have developed expertise in the area of drug delivery, in particular

microneedle systems, as well as established effective analytical skills in analysing micro-systems and their performance in in-vitro and ex-vivo settings [26].

3.8. Modelling

The information from the skin studies in literature will provide the basic knowledge about micro properties of skin that can be used in simulations to assess the parameters of MN geometry that underpin insertion. This modelling will be performed using Abaqus FEA software. By simulating the behaviour of a MN patch insertion in a skin model, a greater understanding of the insertion parameters will be ascertained. This understanding will provide meaningful information in order to create a feasible applicator integrating both MN patch and MN applicator for enhancing user application and, ensuring an effective insertion. Using a virtual model of the skin together with a model of MN and applying the rate-dependent out-of-plane hyperplastic properties of the SC and dermis layers, it will be possible to establish the optimum parameters for the design of the MN applicator (insertion parameters, needle array parameters, such as array density, base plate diameter versus array area, insertion force). This approach of predicting the response of a model is cost-effective and time-saving [13] Some studies have already shown through modelling, that hyperestatic moduli from a micro-indentation of individual skin strata is rate-dependent, which enables extrapolation of stiffness properties for high velocities (greater than 1m/s) and the characteristic fracture energies can be lower than the reported values in previous studies (10 pJ/μm2 against >100 pJ/μm2). Also, it showed that at higher velocities (around 10 m/s) the energy accumulated in the top skin layers causes fracture before stress waves transmit any deformation to the material. It is important to highlight that penetration energy is proportional to the skin inflammation, tolerability and acceptability related to the MN insertion. [13].

3.9. Clinical compliance

One of the key objectives of the project is to design an applicator with certain settings so as to enhance usability. Norman et al. performed a clinical study that investigated the pain threshold associated with a patch application against intramuscular injection, the results showed that patients rated the patches 1.5 on average while the injection was rated 15, on a scale one in 100 [4]. The same study also proved that there was increased usability and patient acceptability for solid microneedle patches with an applicator. Other clinical studies showed that the use of MN technology was positive however there was much concern over the variability involved with the application [27]. Finally, a study performed so as to compare the pain and sensory response between silicon microneedle patches and single-blinded insertions of a hypodermic needle demonstrated that the MN caused significantly less pain and were more comfortable than the hypodermic needles [28].

4. Conclusions

A preliminary literature review and project review has been performed. PLGA is an attractive material with high possibilities for the fabrication of MN structures. There is a huge potential market for the use of MN patches as a drug delivery system which offers solutions to problems associated with the conventional routes. The proposed design after performing this study is a single use, disposal MN patch with an integrated applicator to meet the needs of the end-user and to enhance its application.

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