Regulatory Considerations and Commercialization of 3D Printed MN Mediate Vaccine Delivery

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelors of Pharmacy (Honors)

Department of Pharmacy
Brac University
September 2020

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

No animal or human trial was carried out for completion of this project.

Abstract

3D printing or additive manufacturing is a process first introduced at 1980s. Since then, it showed great achievements in fabricating complex structures with ease in sectors such as industry as well as medical and pharmaceutical sectors. Creation of complex structures such as scaffolds, patient specific implants and MNs are few example of 3D printing in medical and pharmaceutical sector. Although the setup of 3D printer and workstation is costly, novel techniques and development of novel biomaterials are showing promising future of 3D printing in pharmaceutical sectors. Over the past decade, the benefits of a MNs in TDD and several applications and benefits of MN were found out. In this review article, commercialization of 3D printing MNs were brought into lime light along with the probable cost, regulatory affairs and consequences of mass production of 3D printed microneedle.

Keywords: Additive Manufacturing, 3D printing, TDD

Dedication

I want to dedicate this project to my respectable supervisor Dr. Md. Jasim Uddin, Assistant Professor in Department of Pharmacy, Brac University for his continuous guidance throughout my project.

Acknowledgement

I would like to proceed by thanking the Almighty who is the source of our strength and knowledge which have enabled me to complete this project with full diligence.

I would like to express my deepest gratitude and appreciation to my project supervisor, Dr. Md. Jasim Uddin (Assistant Professor, Department of Pharmacy, Brac University), whose expertise, ample time spent and consistent guidance in every step have helped me to accomplish this project efficiently. I would like to thank him for his great advice and patient behavior throughout this phase whenever I encountered difficulty.

I would also like to express my sincere gratitude to Dr. Eva Rahman Kabir (Professor and Chairperson, Department of Pharmacy, Brac University) who has been a constant source of inspiration for me.

Finally, I would also like to thank my parents for their support and words of encouragement which motivated me to work harder to overcome the difficulties.

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List of Acronyms

MN	Microneedle
CAD	Computer-Aided Design
TDD	Transdermal Drug Delivery
NSAID	Non-Steroidal Anti-Inflammatory Drug
PVP	Polyvinylpyrrolidone
PVA	Polyvinyl Alcohol
DLP	Digital Light Processing
3DM-Cast	Three Dimensional Model-Cast
AM	Additive Manufacturing
3DP	3-D Printing
FDA	Food and Drug Administration
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CBER	Center for Biologics Evaluation and Research

Chapter 1

Introduction

1.1 3D Printing

The 3D printing process builds a three-dimensional object from a computer-aided design (CAD) model, usually by successively adding material layer by layer, to put simply, 3D printing is a method of making 3D objects originating from a digital file. 3D printing or 'additive manufacturing' covers different technologies which serves a computer-generated sample to generate an object by means of precise handling of devices (Economidou, Lamprou, and Douroumis 2018a). Three dimensional originates from a liquid-based stereo-lithography process from the late 1980s (Chua, Yeong, and An 2017). It has transformed earlier prototypes and hence as a result, it found usefulness in many fields other than medical. Briefly, it is a process in which a digital version of 3D object is built using computer aided design (CAD) software such as SolidWorks, AutoCAD, ZBrush, Blender, FreeCAD, Meshmixer, and SketchUp (Tappa and Jammalamadaka 2018).

Not only that, objects or object components developed via CAD, can be downloaded via the internet, and ultimately printed locally or even at home via 3D printer. Thus the idea of sharing a developed map for MNs can as well deduce cost of production, keeping in mind that the reproducibility of 3D printers are extremely high (Ligon et al. 2017). In the last decade, among many findings that are presented into pharmaceutical and biomedical market, the most innovative and influential is believed to be three- dimensional printing (3DP) as this method is known as an adaptable tool of precise manufacturing of numerous devices. This method serves as a technology for developing many things such as, novel dosage forms, tissues engineering, organ engineering, disease modeling etc. (Jamróz et al. 2018). This technology has been in use for more than thirty years in the automobile and aeronautical

industries but the use of this technology was restricted only to 3D printing of anatomical models for scholastic training purposes in case of medical field. It is only due to latest developments in research and generating novel biodegradable materials that has made use of additive manufacturing in medical and pharmaceutical fields flourish. Nowadays, 3D printing technology has wide-ranging applications in the clinical field and is swiftly expanding as it has transformed the healthcare system by modifying implants and prostheses, building surgical aids personalized to the patient, and printing tissues and living scaffolds for use as regenerative medicine. Table 1 displays the applications of this technology in several sectors (Tappa and Jammalamadaka 2018).

Table 1: Application of 3D printing in various sectors

No.	Sector	Application
1.	Industry	• Manufacture of Prototypes and spare parts for automotive and aeronautical industry • Surgical scaffolds
2.	Medical	• Surgical models such as dental fixtures, bridges, and crowns. They are used for educational purpose as well. • Modified implants and prostheses which are patient specific. • Customized tissue engineering and regenerative medicine.
3.	Pharmaceutical	• Tailored transplants for drug delivery • Patient specific dosages form designing • Microneedle devices.
4.	Food	• Additive manufacturing of cakes, cookies, candies, and other desserts
5.	Fashion	• Accessories such as jewelry, clothes, shoes
6.	Household	• Household objects such as bowls, plates, cups

Increasing demand for tailored pharmaceutics and medical devices made the impact of 3D printing rise rapidly over past few decades, in fact, 3D printing has become a powerful tool serving as a tool of precise manufacturing of patient specific dosage forms, tissue and disease modeling. The present accomplishments include drug delivery systems with enhanced release characteristic, modifiable and personalized dosage forms, implants which corresponds to specific patient anatomy and also composed of cell based materials for regenerative medicine (Jamróz et al. 2018). 3D technology has wide range of applications in medicines. Few examples of these applications are maxillofacial surgery, orthopedics, spinal surgery, neurosurgery, cardiac surgery, transdermal drug delivery and various other disciplines (Tappa and Jammalamadaka 2018). The suitability of numerous printing technologies has been researched over the past for the direct or indirect printing of MN arrays or for the adjustment of their surface by coating with drugs for transdermal drug delivery (Economidou et al. 2018a). Medical scientists envisioned the unique prospects of 3D printing to fundamentally alter how patients are treated, aiming in taking modern therapeutics from the massively produced to the customized (Chia and Wu 2015). Additive manufacturing has plentiful applications and has earned much interest in the world of medicine. Minor time consuming attribute of this technology has contributed to their increased applications upon patients. There are several different fabricating processes involved in this technology. Depending on process, additive manufacturing can be classified into four broad categories which include extrusion printing, material sintering, material binding, and object lamination. These classifications are briefly described in Table 2 (Tappa and Jammalamadaka 2018). In case of medical field, patients can benefit from this technology as anatomical models ease understanding of pathology and procedure by patient which results in better patient– doctor understanding and greater patient satisfaction (Tack et al. 2016).

Table 2: Types of 3D printing

Extrusion Printing	Fused Deposition Modeling (FDM)
	Bioprinting
Material Sintering	Selective Laser Sintering (SLS) [3]
	Electron Beam Manufacturing (EBM)
	Stereolithography (SLA)
	Continuous Liquid Interface Production (CLIP)
Material Binding	Binder Jetting/Inkjet
	Polyjet
Lamination	Laminated Object Manufacturing (LOM)

Approval of 3D medical devices can be provided by FDA through abbreviated pathways such as emergency use pathways, compassionate use exemption pathways. For example, when a new born baby in 2013, suffering from tracheobronchomalacia was at risk, emergency-use exemption pathway was used to approve an anatomically specific tracheal splint to save the baby's life (Alhnan et al. 2016). The world demand for 3D printers and related materials and software is projected to increase by ~20% per year. There will be an enhanced demand for printing materials, related to the increased installed base of 3D printers. Polymers such as acrylonitrile-butadienestyrene, polylactic acid and nylon were initially employed in 3DP, and continue to be simply applied, with some growth in the institution of metals. The most rapid growth will be observed in the medical and dental market, with especially good opportunities anticipated in dental applications (Choonara et al. 2016). Even though there are many 3D printer technologies, but not all are amenable to pharmaceutical manufacturing. The

technologies hold great promise for pharmaceutical manufacturing. Pharmaceutical manufacturers can adopt this technology to manufacture specialty products such as microparticles, implants, and intrauterine contraceptives, which require high precision and quality. Regardless, there are some technical and regulatory challenges that need to be addressed by pharmaceutical companies (Rahman et al. 2018).

1.2 Microneedle: A short overview

Microneedle patches are arrays of tiny needles that painlessly pierce the skin to deliver medication into the body. Biocompatible microneedles are usually fabricated via molding of a master structure. Microfabrication techniques used for fabricating these master structures are costly, time intensive, and require extensive expertise to control the structure's geometry of the structure, despite evidence that microneedle geometry is a key design parameter (Johnson and Procopio 2019). Nowadays, polymer microneedles (MNs) have become a novel device in the field of clinical medicine and health due to the fact that traditional injection and extraction devices every so often appear painful and troublesome for patients (Yao et al. 2019). After the first MN reported for the drug delivery in 1971, MNs have been developed over 4 decades. Compared to the traditional drug delivery system, MNs have been demonstrated to be safe and successful enough to deliver various drugs (He et al. 2019). Over the last 20 years transdermal microneedles (MNs) have paved the way for the delivery of various active substances across the skin (Pere et al. 2018). Microneedle patches (MNPs) have been proposed to improve vaccination in developing countries and are the subject of increasing research in academia and industry (Shuliang Chen, Peter Novick 2017). Along with that select studies have demonstrated the feasibility of microneedle mediated oral mucosal vaccination, but they have only begun to explore the broad functionality of microneedles (Das C Hansen KC and Tyler JK 2017). Methods which are used to alter the outer layer of the stratum corneum can be classified into two categories. They are passive and

active methodologies. Passive methods involve use of drug, vehicle interactions and alteration of formulation to modify the stratum corneum and are relatively easy to integrate into TD patches such as chemical enhancers and emulsions. Embedding microfluidic architectures with microneedles enables fluid management capabilities that present new degrees of freedom for TDD (Yeung et al. 2019). Figure 1 describes the active and passive methods of TDD.

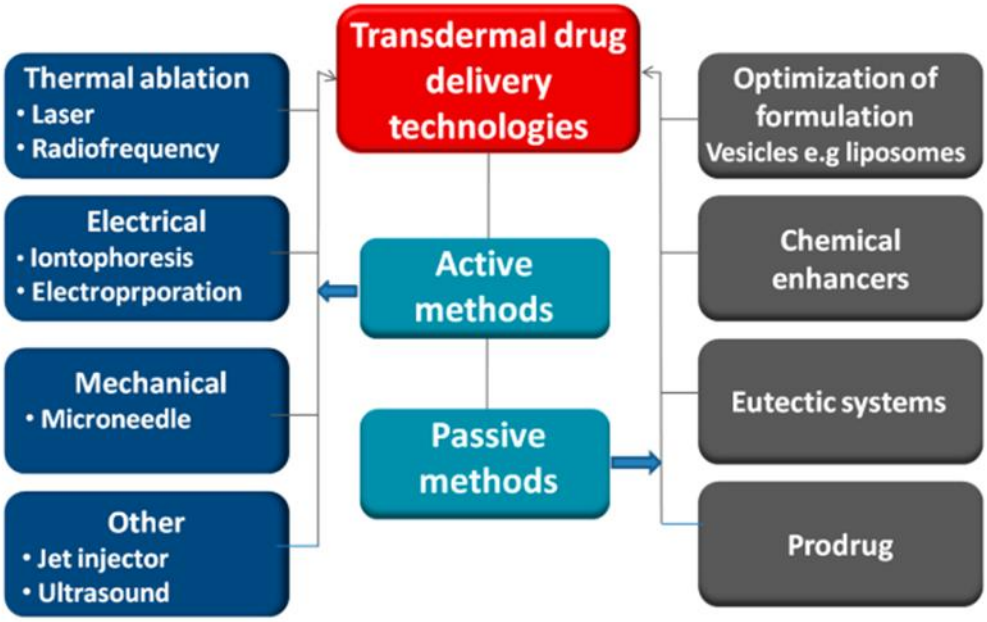

Figure 1: Methodologies for enhancing transport of drug across the skin

Notably, microneedles may be more effective to deliver macromolecules through the skin than traditional patches, due to its microstructure. Recent advances in high-resolution 3DP techniques fabricating small and tiny structures accelerate the application of 3DP in manufacturing the microneedles. While traditional microfabrication techniques are limited to the microneedles with simple geometries, new 3DP technology enables to fabricate microneedles having more sophisticated and complex geometries (Park et al. 2019). 3D printing comprises of various distinct manufacturing techniques. An overview of the main technologies that have or expected to present an impact on the evolution of TDD or in other

words, major established 3D printing technologies used for preparation of microneedle are Inkjet printing, Photopolymerisation-based technologies, Fused deposition modelling (Economidou, Lamprou, and Douroumis 2018). Currently only one microneedle device is approved by the FDA. Soluvia, a device with a single microneedle, has been approved to deliver the Fluzone influenza vaccine. Another device, MicronJet with four microneedles, has been granted FDA clearance (Walsh, Allen, and Desai 2015). Apart from them, other techniques used for microneedle preparation are summarized in Table 3.

Table 3: Types of MN

Type of MN	Manufacturing technique
Solid MN	
Silicon MNs	Most well-known methods are 3D laser ablation, silicon dry-etching process, Isotropic etching, Dicing a silicon substrate and then acid etching and many more.
Metal MNs	Wet etching, Metal electroplating are well known methods
Polymer MNs	Photolithography
Ceramic MNs	Ceramic micro molding and sintering lithography are used.
Coated MNs	Process mostly involves dipping or spraying the microneedles with an aqueous solution of high viscosity to hold more formulation during drying. A surfactant, the active agent and a stabilizing agent is added beforehand. Newer methods are being discovered recently.
Dissolving MNs	Micro molding

Hollow MNs	Newer methods of synthesis of Hollow MN are being developed recently. Most well-known established methods are, Micro-electromechanical systems (MEMS) techniques-laser micromachining, deep reactive ion etching of silicon, wet chemical etching and micro-fabrication and many more.

As a trendy field in pharmaceutical and biomedical research, MNs applications are constantly evolving, even though they are based on very well-established techniques. The number of molecules administered by MNs is also increasing, with insulin and vaccines administration being the most investigated. Furthermore, MNA are being used to deliver cells and applied in other organs and tissues like the eyes and buccal mucosae (Guillot et al. 2020).

1.3 Microneedles in patient compliance

Microneedle or TDD systems might be the solution sought by patients and physicians towards a simple, self-administrative, pain-free pharmaceutical therapy that will simultaneously circumvent the drawbacks of traditional administration routes such as needle phobia, pain or digestive issues (Economidou et al. 2018a). Microneedles is a novel approach for transdermal delivery of drug substances, vaccines or macromolecules which cannot be administered orally due to their poor absorption or enzymatic degradation in the gastrointestinal tract and liver (Scoutaris, Ross, and Douroumis 2016). 3D printed MNs can effectively penetrate the superficial epidermis and thus might reduce the risk of skin damage without pain sensation (Uddin et al. 2020).

MNs can be used for several purposes such as Skin recovery process, get rid of skin irritation and infection and also has application such as Oligonucleotide delivery, Vaccine therapy, Peptide delivery, Hormone delivery, Cosmetics, Lidocaine delivery, Pain therapy Ocular

delivery, Cancer therapy (Waghule et al. 2019). Cost-effective, well tolerated and simplicity has made MN become progressively utilized over the last several years. Also, its outstanding capability to treat localized areas of disease has encouraged various studies on its future potential in focal diseases of inflammation, dyschromia, and photodamage (Ehrlich 2017). Conditions such as abnormal (keloid and hypertrophic) has no satisfactory single modality therapy to-date except few available options which are often futile, agonizing, potentially hazardous, and require involvement of health care professionals. Due to which a self-administered microneedle device based on drug-free physical contact for inhibiting abnormal scars is reported. Unlike many existing treatment options, microneedle treatment is based on physical contact. It can be categorized as a class I/II medical device. This eliminates reliance on the usage of toxic chemicals to inhibit abnormal scars, thereby mitigating against accompanying contraindications (Yeo et al. 2017). Several dissolving macromolecules were recently utilized to blend with bioactive protein for the production of drug-loaded microneedles. The loaded drug or protein can be released from the microneedles within several minutes after penetrating into the skin. Since the whole microneedle is composed of macromolecules, the amount loaded can be enhanced. Moreover, the whole production procedure requires neither high temperature nor any organic solvents, so that the loaded protein remains bioactive. In addition, there is no need to deal with needle waste as with conventional injection because the macromolecule microneedles spontaneously dissolve within the penetration site (Chen et al. 2017). Novel design of the polymeric microneedle array, with side-open holes in the conical section and integrated reservoir has been proposed which is suitable to be integrated into various categories of micropumping devices operating in the range of 10–100 kPa of outlet pressure (Bodhale, Nisar, and Afzulpurkar 2010). Microneedles investigated are significantly less painful than the hypodermic needle with microneedle pain scores varying from 5 to 40% of the hypodermic needle. Microneedle

length has the strongest effect on pain, where a three-fold increase in length increases the pain score by seven fold. The number of microneedles also affected the pain score, where a 10-fold increase in the number of microneedles increases pain just over two-fold. Microneedle tip angle, thickness and width did not significantly influence pain (Gill et al. 2008). On the other hand, typical injections with hypodermic needles can cause pain and discomfort for patients with possible damage to veins and bruising. In this context, microneedles (MN) have gained significant research interest for innovative drug delivery and monitoring methods (Taylor et al. 2020). In near future, it would be possible to deliver vaccine using MN as several antigens with different sizes (e.g., tetanus, diphtheria, hepatitis B, polio, and influenza) are currently under investigation for their loading ability into the ceramic npMNAs and the subsequent release in vitro and into ex vivo human skin (van der Maaden et al. 2015).

This review paper highlights the possible chances as well as drawbacks regarding commercialization of microneedles. Along with that, it summarizes current situation of regulatory authorities regarding 3D printed MN as well as other 3D printed medical devices.

Chapter 2

Commercial aspects of using 3D printing for microneedle preparation

2.1 Cost of microneedle preparation using 3D printing

Microneedles (MN), a highly efficient and versatile device, have attracted extensive scientific and industrial interests in the past decades due to prominent properties including painless penetration, excellent therapeutic efficacy and relative safety and most important of all, low cost (Yang et al. 2019). 3D printing of MN takes it up a notch as this technique neither requires complex and expensive manufacturing facilities nor expertise in microfabrication (Krieger et al. 2019). Cost-effectiveness of the 3D printing is suggested in only 7 % of the selected publications of a review paper while other publications do not agree and conclude that the technology is not cost effective along with that several authors refer that the complexity of cases can provide an answer to the additional cost of surgical guides. The growing economic pressure on healthcare makes it crucial for researchers to study cost related to new technologies and techniques. More cost-effectiveness studies related to 3D printing would be needed to evaluate the acceptability of the technology, both for complex cases and for routine cases using 3D printing. Few data on it could be found in the literature which is not sufficient enough. The production cost of 3D-printed parts depends heavily on the manufacturing facility and even though cheap desktop 3D-printers allow cheap 3D models and guides, but have less quality approvals and controls compared to the commercial manufacturers as a result of which they fail to meet high quality standards. Furthermore, the reported costs of self-printed parts differ among authors, with few mentioning direct preparation costs such as CT, MRI, multiple prints and computer or the time cost involved in designing the model but the heterogeneity of these printed parts prevents more in-depth analysis. Therefore, we would encourage future research to present the data in a much more

transparent and objective way, and to make the first steps into cost-effectiveness calculations (Tack et al. 2016). Some factors to consider during 3D printing are given below:

Table 4: Factors to consider during 3D printing cost

Factors	
Object Weight	Printer lifetime
Printing time	Daily usage
Electricity Tariff	Repairs cost
Printer power	Other cost
Filament cost	Failure rate
Printer purchase	Total cost

Microneedle devices are cost-effective and can be self-administered at the user's convenience (Yeo et al. 2017). In a clinical study comparing with the molded microneedles, it was found that the 3D printed ones had better high frequency performance (such as for EMG), and the molded microneedles performed better for low frequency signals (such as for EEG) (Soltanzadeh 2019).

Another important benefit offered by 3D printing is the ability to produce items cheaply. Traditional manufacturing methods remain less expensive for large-scale production; however, the cost of 3D printing is becoming more and more competitive for small production runs. (Lee Ventola 2014). Many novel biodegradable microneedles such as PVP K30-based biodegradable microneedle arrays offer an added benefit of eliminating needle delivery-based associated pain and chances of infection, thereby would prove to be more patient compliance (Shah and Choudhury 2017). However, the material and manufacturing costs are too high to produce disposable items (Lin and Jiang 2019). According to the

findings of a US Centers for Disease Control and Prevention-funded study a microneedle patch measles vaccine is less costly compared with traditional subcutaneous (SC) measles vaccines. In a study, among a hypothetical population of 1 million children using the MN patch compared with old syringe-and-needle administration a spreadsheet-based incidence-of-measles vaccination model was used to estimate costs of a 2-dose measles vaccination program. It is to be noted that cost effectiveness was estimated assuming MN vaccines would be more heat stable and require less expensive cool chains when used in the field and cost of measles vaccination was found to be $0.95* (range $0.71–$1.18) for the first dose delivered via microneedle patch, compared with $1.65 (range $1.24–$2.06) for the first dose delivered by SC vaccination. Microneedle patch vaccination was estimated to cost $1.66 per measles case which is significantly less compared to SC vaccination which was estimated $2.64 per case averted. Finally, it was estimated total costs of the vaccination program were $1.5 million compared with $2.5 million, respectively (Centers and Control 2016). Although a less-invasive influenza vaccine technology such as the MNP has many potential advantages, its economic value will depend on price and, if self-administered, the percentage of people who successfully administer the MNP (Anon 2015). Use of microneedle patch technology in measles vaccination programs potentially reduces costs and extends vaccine coverage in hard-to-reach communities. Acceptability of new technology relative to the conventional vaccine-delivery method is one of the key elements of cost-effectiveness of the microneedle patch (Adhikari et al. 2016). In another experiment, hydrogel microneedles were manufactured by high-precision digital light processing (H-P DLP) additive manufacturing system which performed multifunctional tasks such as drug delivery and detection with minimally invasion. Critical parameters and mechanical properties of MNs were measured and analyzed to find a balance between precision and stiffness and were found out that these properties are affected by exposure time of each layer. Optimized printing parameters

provided a balance between precision and stiffness (Yao et al. 2019). Novel cost effective methods of MN production are being developed. For example, in another recent experiment, feasible and cost-effective customization of the design to increase skin penetration of MNs was successfully achieved by 3D-printing of master molds using a desktop DLP 3D printer. Deviating from the typical geometries of MNs, pyramidal or conical, researchers are enabled to produce various geometries and test their effectiveness as robust and sharp MNs. The tanto blade-inspired designs proved to be effective for skin penetration without pre-mature fracture as the fracture force was higher than the insertion force (El-Sayed, Vaut, and Schneider 2020).

Microneedle (MN)-based devices have gained significant interest as a strategy to overcome the skin's formidable barrier: the stratum corneum. This approach provides a less invasive, more efficient, patient friendly method of drug delivery with the ability to incorporate various therapeutic agents including macromolecules (proteins and peptides), anti-cancer agents and other hydrophilic and hydrophobic compounds (Ali et al. 2020). While several reviews have discussed microneedle-based cosmetic and drug delivery applications, there is a gap in understanding the effect of material of construction of microneedles on drug stability and potential for large-scale manufacture (Bhatnagar et al. 2019). With novel techniques, the cost of producing 3D printed microneedles decreases in great extent. Hence further research is needed in order to develop techniques of 3D printing that reduces cost of production of MNs. Novel techniques such as implementation of stereolithography printed MNs will open new horizons for transdermal drug delivery and reduce the cost of production due to the low cost of the printers, printing inks and fast fabrication times (Windmill, Lamprou, and Douroumis 2019).

2.2 Scope of transdermal drug delivery using microneedle in medical field

Transdermal administration of drugs has been gaining popularity due to its multiple benefits. It avoids the first-pass metabolism of drugs and offers better patient compliance compared to hypodermic, intravenous, or intramuscular delivery routes owing to its painless nature (Badnikar et al. 2020). Up until now, the field of TDD, has been one of the safest and most efficacious ways of delivering medications across the skin, and is still becoming a favorable option of delivery of drug through skin. This is mainly because skin proposes an accessible and suitable site for the administration of medications and also because TDD is a straightforward method of delivering drugs as it involves systematical administration of drugs (Alkilani et al. 2015). The efficiency of transdermal delivery of cosmetic ingredients is often limited by the outer layer of the skin, known as the stratum corneum, which can prevent diffusion of the cosmetic ingredients through the skin. A polymer microneedle array that dissolves in the skin can enhance the permeability of the skin to cosmetics (Park et al. 2015). In case of anti-aging treatment, collagen can be delivered transdermally up to the dermis layer for its cosmetic/ pharmacological effect. The approach may be useful for the transdermal delivery of proteins and other macromolecules for localized effect within the skin layers (Cho Lee 2019; Kathuria et al. 2016). MNs can overcome problems associated with hypodermic needles as the MN fabricated is not only long enough to reach blood vessels but also sharp enough for minimally invasive blood extraction (Li et al. 2013). Over the counter drugs such as analgesics can be delivered using MN patches which can be developed using 3D printing. The large size MN patches shows fast onset and sustained delivery of LD through skin, potentially useful to increase the application scope of topical LD for pain management and other analgesics (Kathuria et al. 2016). Although many advantages of dissolvable MNAs have been documented through in-vitro and in-vivo studies, regulatory approval and subsequent clinical applications of MNAs necessitate precise control of

deliverable dosage and delivery rate. The delivery rate and amount are dictated by the MNA material, needle geometry, and the array configuration. These requirements translate into the need for high-accuracy, reproducible, and scalable (high-throughput) fabrication techniques applicable to relevant dissolvable materials (Bediz et al. 2014). Vaccination through dermal route using MN can offer important advantages such as dose sparing, pain-free immunization and avoidance of needle stick injuries. Furthermore, it can extend the vaccination coverage in developing countries by potentially offering improved vaccine stability, reduction of vaccine wastage and of burden on trained personnel (Leone et al. 2017). In another experiment, a 3D printed microheater integrated drug-encapsulated microneedle patch system for drug delivery is presented. The ink solution comprised of polydimethylsiloxane (PDMS) and multiwalled carbon nanotubes (MWCNTs) with mass concentration of up to 45% is prepared and used to print crack-free stretchable microheaters on substrates with a broad range of materials and geometric curves. The adhesion strength of printed microheater on microneedle patch in elevated temperatures are measured to evaluate their integration performance. Assessments of encapsulated drug release into rat's skin are confirmed by examining degradation of microneedles, skin morphologies, and released fluorescent signals. Results and demonstrations established creates a new opportunity for developing sensor controlled smart microneedle patch systems by integrating with wearable electronics, potentially useful in clinic and biomedical research (Bhrigu K Lahkar and Büyükçolpan 2019).

TDD by MNs can also outclass traditional ways of TDD if their advantages are taken alone into comparison. MNs made of polymer has several benefits over hypodermic needles such as it can elicit a higher immunogenic response, can inhibit microbial entrance at the injection site, can be administered at home by unskilled caregivers, diminishing the requirement of practice or healthcare personal to push the drug and getting rid of the needle safely, have the capacity to improve the shelf life of drugs, have the capability for high loading capacity and

have flexibility in material composition that permits smart drug delivery systems (Luzuriaga et al. 2018). In a research, using additive manufacturing, a dual-function MN array was invented on personalized curved surfaces for TDD, which was used to deliver diclofenac and was found out that a significantly higher amount of diclofenac was transferred through skin by this needle compared to intact skin, implying that MN could be used for better delivery of NSAID (Lim, Ng, and Kang 2017). Recently in a study the use of the high-resolution 3D printing technique was used for the robust and seamless integration of MNs with a chamber or delivery systems, for biomedical applications, circumventing the need for laborious and complex fabrication techniques. A reservoir of 2 cubic millimeter volume topped with hollow MNs with inner diameter and height ranging from 80 to 120 μm and from 200 to 400 μm, respectively, was fabricated. It can be further integrated with actuation and pumping mechanisms for drug delivery in future work (Moussi et al. 2020). Other than that, in another experiment use of direct 3D printing via Two-Photon Polymerization (2PP) lithography was done to fabricate ultra-sharp polymer microneedles specifically designed to perforate the guinea pig RWM (Round Window Membrane) (Nicholas Dias, Yung Peng 2017).

In a study, gene gun or intramuscular injection was used to deliver DNA vaccine encoding hepatitis C virus which already showed to induce strong in vivo functional T-cell responses in mice and was followed by in vivo electroporation. This method of cutaneous DNA delivery by means of MNs was compared with two other delivery methods. They were (1) intramuscular DNA delivery using hypodermic injection and (2) cutaneous delivery using gene gun. The first method is widely used in animal studies but is generally ineffective in humans while the second one can be effective in humans. The study shows that delivery of a NS3/4A-expressing DNA plasmid into the skin using coated MNs can provoke CTLs specific response for hepatitis C virus. Notably, it was found that CTL priming using MNs was similar to gene gun at similar doses, which indicates that immune responses generated using

MNs may be sufficient enough for DNA vaccine applications (Gill et al. 2010). Instances of using light-based 3D-printing as an approach for producing drug-delivery methods have been reported, mostly in the form of microneedles as medical devices – a salient example being that of the successful delivery of an influenza vaccine utilizing microneedle arrays (Hwang et al. n.d.). Although the use of microneedles for drug delivery as well as vaccination through the intradermal route has been reported to enter Phase III clinical trials, the use of microneedles for vaccination has yet to enter that stage. Therefore, additional research has to be performed, so that the delivery of vaccines by microneedles enters the final stages of clinical trials and eventually become fully commercialized. Thus, needles and syringes could be eventually and potentially replaced by microneedles leading to greater vaccination rates (Greve and Jorgensen 2016).

The growing demand for patient-compliance therapies in recent years has led to the development of transdermal drug delivery, which possesses several advantages compared with conventional methods. Delivering protein through the skin by transdermal patches is extremely difficult due to the presence of the stratum corneum which restricts the application to lipophilic drugs with relatively low molecular weight. To overcome these limitations, microneedle (MN) patches, consisting of micro/miniature-sized needles, are a promising tool to perforate the stratum corneum and to release drugs and proteins into the dermis following a non-invasive route (Jamaledin et al. 2020). A comprehensive approach to fabricate novel dissolving MNAs with undercut microneedles for effective multicomponent cutaneous vaccination is already demonstrated. The manufacturing approach strategically combined 3D laser lithography with nanoscale resolution and micromolding with mechanically flexible molds that allow direct removal of undercut MNAs. Reproducible fabrication of dissolvable MNAs with undercut microneedles incorporating multiple cargos was achieved using different biocompatible and water-soluble polymers, and these MNAs successfully delivered

biocargos to murine and human skin microenvironments. Importantly, cutaneous vaccination with antigen-loaded MNAs elicited more potent antigen-specific cellular and humoral immune responses than traditional immunization by intramuscular injection (Balmert et al. 2020).

2.3 Materials needed for Microneedle preparation

3D printing for MNs was first investigated in 2007 by Ovsianikov et al. while using a lithography-based multiphoton polymerization printing method, since then, the ability to print biocompatible and biodegradable materials from conventional 3D printing methods, such as stereolithography (SLA), FDM™, Selective Laser Sintering (SLS), CLIP, and Digital Light Processing (DLP) has been the focus of numerous studies (Farias et al. 2018). The use of 3D laser stereolithography to create master prototypes, with replication by soft-embossing is a significant advance in the field of microneedle manufacture. Microneedle design can be based primarily upon structural and functional modeling. Novel geometric features such microneedle open channels connected to microfluidic reservoirs that are directly rendered from CAD drawings go way beyond what is possible by subtractive fabrication methods (Rad et al. 2017). Such as, a manufacture process for 3D printed polymer MN coated with iron by sputter deposition has been developed. This process combines the flexibility of 3D printing in terms of shape and dimensions with the functional properties of a magnetic metal layer (Kavaldzhiev et al. 2017). However, unfortunately most researchers have focused on the biomedical applications of microneedles so far compared to fabrication process. For making cost effecting and less time consuming MNs, more research is required (Chen et al. 2018). The only materials that are approved by FDA for synthesis of MN up until now are PVP and PVA (Y. Chen et al. 2020). MN can be manufactured using polymers, metal or silicon, ceramic, silica glass and carbohydrate (Waghule et al. 2019). Among them biocompatible and biodegradable polymers are most safe but are cost effective. Over the past years MN's have

been synthesized using numerous polymeric materials such as poly-lactic-co-glycolic acid, poly-L-lactic acid, poly-glycolic acid, poly-carbonate, (PLGA), poly- dimethylsiloxane, carboxymethyl cellulose, maltose, dextrin and galactose have all been used to fabricate MN (Donnelly et al. 2011) and some other materials such as Amylopectin (Price 2008), polyvinylpyrrolidone and polyvinyl alcohol (Sullivan, Murthy, and Prausnitz 2008). Biodegradable 3D printed PLA microneedles are an emerging class of novel transdermal drug delivery systems (Karagoz 2020). Biocompatible and biodegradable material-based dissolving, coated, and swellable MNs have the potential to deliver a range of therapeutics transcutaneously, and therefore, the data from the recent phase I clinical trial using dissolving MNs are exciting. Further testing in the clinic and a clear path to regulatory approval including the establishment of a guideline for appropriate quality controls is needed in order for MNs to reach their full potential as drug delivery modalities (Tarbox et al. 2018).

In terms of MN printing technology, it is noted that vat printing is a common approach, which prints 3D objects with photopolymerization, i.e., to expose liquid polymers to ultraviolet or visible light to turn liquid into solids. The advantage of vat printing is high resolution, which is necessary to obtain MNs with sharp tips for skin penetration. Compared with moulding, however, vat printing also has its disadvantages. First, the candidate materials are limited to photocrosslinkable polymers while a variety of materials can be used for moulding method. Second, the photocurable polymer solutions contain photoinitiators, which can be a concern because of their potential toxicity (G. Chen et al. 2020).

Chapter 3

Regulatory affairs of 3D printed Microneedle

By definition, regulatory approval is the process of approving a medicinal product or medical device for use in humans. Up until now, there is no approved MN vaccine available in market according to regulatory authorities. They also revealed the evidence necessary to approve these products which consist of manufacturing MN aseptically or employing final sterilization procedures. Up until now, 3D printed MNs were manufactured on small scale which is why scaling up the production would require considerable amount of thought. Consideration would often depend on number of conditions such as for silicon MN clean room conditions are required. Also, large scale manufacture of 3D printed MN would require a company sufficient initial investment as large scale of production of 3D printed MN has not been done yet and hence there are no established manufacturing equipment. New range of quality control tests will now also become necessary. Most likely the first regulatory rules that will be set for 3D printed MN would also be followed for production of next 3D printed MN. Other factors such as packaging of 3D printed MN would also be required. Overall, from a regulatory perspective, 3D printed MN that is coated with drugs would rather be seen as a new dosage form than a device (Greve and Jorgensen 2016). According to regulatory authorities, the likely considerations and potential requirements from a regulatory standpoint that must be addressed for MNs to be accepted for clinical use are summarized in Table 5. Whether MNs will be accepted as a drug delivery system, consumer product, or medical device is a question that comes in mind at first. If MNs are to be considered closer to a traditional hypodermic injection than a transdermal patch, regulatory authorities are likely to request that the device is rendered sterile prior to use. Aseptic manufacture would be expensive as they will most like involve sterilization techniques such as moist heat, microwave heat or even gamma radiation.

As mentioned before, sufficient initial investment is required for large scale manufacture of 3D printed MN if any manufacturer wishes to commercialize them for protein, peptide and antibody based therapies. Stability of the formulation and potential immunological effects will be of particular concern for regulatory affairs (Kirkby, Hutton, and Donnelly 2020).

Table 5*: Regulatory standpoint that must be addressed for MNs clinical use*

Factors
Sterility of the MN dosage form
Uniformity of content
Packaging
Potential for MN re-use
Disposal procedures
Deposition of MN material into skin
Ease and reliability of MN application
Assurance of MN insertion
Potential immunological effects

An interviewee with regulatory expertise also noted that there is currently no formal guidance or precedent for supervised group self-administration of a vaccine using MN patch in the United States. Oral typhoid vaccine has been approved for self-administered at home, but this involves taking a capsule rather than applying a patch to the skin (Jacoby et al. 2015). Very few studies have been conducted with few FDA approved MN based device such as regulatory approved hollow MN device, MicronJet, for pDNA delivery to human skin in an effort to combine the favourable transfection efficiencies previously witnessed with liquid delivery (soak and poke approach) with the finite dosing that can be achieved using a hollow MN delivery system. This study exemplified, for the first time, the use of hollow MNs for

efficient vectorless delivery and expression of pDNA in human skin and proposes hydrodynamic delivery as the mechanism for enhanced gene expression, even with a 'standard' injection volume. Hydrodynamic gene delivery has not previously been observed in human skin tissue. The approved MicronJet hollow MN system ensures accurate delivery of a finite dose of exogenous DNA into the skin and provides more efficient and reproducible gene expression compared to solid MN delivery strategies. The delivery method provides potential advantages over other chemical and physical gene delivery methods with respect to cost, simplicity and flexibility of dosing and therefore could be the basis for future nucleic acid based immunotherapies and vaccines. More studies like this are needed to set up regulatory requirements for MN devices (Dul et al. 2017). This is because, once regulatory hurdles are overcome and manufacturing processes developed, optimised and validated to current good manufacturing practice standards, the benefits for patients, and ultimately for the industry, will be considerable (Donnelly and Douroumis 2015). The large-scale manufacturing of MNs will require automated quality QCT in place at each stage of the production line. There are strict regulations and pharmacopoeial standards that a drug product would need to meet in order to be deemed appropriate for release for human use. However, no pharmacopoeial standards will be elaborated for MN-based products until a range of MN products are marketed, since such tests are derived from those approved by the regulatory authorities as part of a manufacturer's submitted dossier. Thus, the regulatory specifications will ultimately be significantly influenced by the first MN drug delivery products to be marketed, early industry adopters of the technology thus having the advantage of determining the quality standards that later MN products will need to meet (Lutton et al. 2015). Not only MN, the drugs to be delivered by MN or MN patch need regulatory approval as well. Not all drugs are suitable for patch delivery. The only drugs that can be used are those that can penetrate the skin, that are sufficiently potent to be active and that meet a clinical need. Untill

2015, nearly two dozen molecules have been approved by the regulatory authorities for transdermal administration and have reached the market (Pastore et al. 2015). Materials used to build MN also plays significant role in regulatory approval process. A number of approaches have been investigated for fabricating metal MNs, such as electroplating (palladium), photochemical etching (titanium), and laser cutting (stainless-steel). Metals such as stainless-steel (e.g. hypodermic needles) have been in medical use for decades. Essentially, the use of such materials will effectively reduce the regulatory path of approval, compared with that required for non-approved material, such as silicon (Donnelly, Raj Singh, and Woolfson 2010).

Recently in a study it was showed that no bio burden was detectable in any of the MN or lyophilized wafer formulations investigated and that endotoxin levels were very low. However, regulatory authorities may require additional assurances beyond cGMP manufacture in order to guarantee patient safety. Moist and dry heat sterilisation destroyed all formulations, while gamma irradiation damaged the model protein and altered the appearance of, and release profile from, dissolving ibuprofen sodium-loaded MN arrays. Notably, hydrogel-forming MN prepared from super-swelling polymers were completely unaffected by gamma irradiation in terms of physicochemical properties and release profiles of both small and macromolecular model drugs (McCrudden et al. 2014). Up until now, MNs have been approved by the Food and Drug Administration (FDA) for delivery of vaccines and pharmaceutical through the epidermis in clinical setting only (Lopez-Ramirez et al. 2020). PLGA poly(lactide-co-glycolide) is another successfully used biodegradable polymers approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) due to its biodegradability and biocompatibility for MN synthesis (Battisti et al. 2019). In the recent years, there have been substantial industrial activities in the area of MN devices. At present, a number of MN-based devices are being designed and developed by

different companies. This include: Becton-Dickinson (BD) Technologies (USA), Zosano Pharma (USA), Microneedle Therapy System (USA), Sanofi Pasteur MSD (USA), Valeritas (USA), Nanopass Technologies (Israel), 3 M (USA), Rodan + Fields (USA), Vaxxas (Australia), Corium (USA) and, more recently, Lohmann Therapie- Systeme AG (Germany/USA), the world's largest transdermal patch manufacturer (Duarah, Sharma, and Wen 2019).

Another important thing to consider is the approval of 3D printing process. 3D-printed pharmaceuticals are patentable in nature; their regulatory control also plays an important role. The FDA is currently approving 3D printed medical devices through the 510(k) regulatory process. In 2016, draft guidance has been issued by US FDA on the Technical Considerations for Additive Manufactured Devices for the manufacturer of 3D printing-based devices. However, it is still questionable whether FDA will consider just the 3D printed product or the 3D-printer or both of them. Thus, the approval of first 3D-printed pharmaceutical product does not assure that next upcoming products will also be approved. For effective product evaluation and approval, regulatory agencies are working on to understand the effect of 3D geometric design, material attributes, and 3D printing process parameters on the performance of 3Dprinted solid dosage forms. Regulatory bodies also felt the need of mechanistic models for 3D printing processes which can be utilized as predictive tool for product performance in different disease and patient conditions. It is expected that current research on 3D printing with regulatory requirement can bring the most effective and safer pharmaceutical product (Singhvi et al. 2018). FDA has formed a guideline regarding 3D printing in medical device guidance agenda. Pharmaceutical manufacturers have always been a part of the 3D printing discussion until Aprecia Pharmaceutical won the first regulatory approval (FDA) for manufacturing antiepileptic dosage form used to treat epilepsy, using the novel process to make the personalized medicine in system. Aprecia is the global leader and pharmaceutical

manufacturing industry, which has fabricated the world's first and only FDA-validated, commercial technology for 3D printing. Nonetheless, transfer of such technology to pharmacies, physicians, and hospitals with 3D printers, leading to personalized therapies for patients is still a big challenge for the manufacturers. Although this technology holds great promise, it does bring with it a number of unpredictable risks (Warsi et al. 2018).

To conclude, currently no regulatory requirements are defined for MN array-based products as this technology is very innovative. This also applies for 3D printed microneedle. But in coming years this issue will have to be addressed in the when companies intending to commercialize MN patches will apply for marketing authorization. Unlike conventional transdermal patch systems, which is only applied to the surface of the skin, MNs breach the stratum corneum barrier and often penetrate into the viable epidermis and dermis. Since MNs breach outermost protective layer of the skin, a series of novel scientific/ regulatory questions rises, which needs to be answered for getting approval. Getting approval from a regulatory perspective would become easier if MN is considered as a new dosage form instead of a special type of the preexisting transdermal patch systems (Larrañeta et al. 2016).

Chapter 4

Challenges to overcome

Advancement in additive manufacturing has brought the prospect of personalized dose a step closer. However, the most common question everyone has in mind now is that can regulatory bodies and current legal framework handle the uncertainty of this boldly marching technology? Regulatory bodies have been thinking about the benefits of 3D printing and its future potential. However, implementing the current regulatory affairs might delay their introduction in market. There are few questions that would require answers such as which regulatory pathway will the innovators take to approach such non-traditional devices? Will the regulatory process comprise the 'pharmaceutical ink', and also 3D printer as the end product? Currently FDA is planning to make a short term guidance document that consists of regulation that might aid to cope up with this evolving technology so that in future, regulatory approval of novel 3D printed product does not take much time to get approved. This is evident as FDA is working on developing a sound understanding of 3D printing through its own research inside two of its own laboratories, the FDA's Office of Science and Engineering Laboratories (OSEL), the Laboratory for Solid Mechanics and FDA's Functional Performance and Device Use Laboratory. But currently, FDA's planned guidance on 3D printing fell to the "B-list" in its 2015 medical device guidance agenda and due to which a clear regulatory pathway regarding 3D printed products is likely to take some time. In the market, approximately eighty-five 3D printed medical devices and implantables have gained FDA clearance and they have been approved by means of several pathways of FDA approvals such as 510 (k), PMA, de novo, HDE, etc. Up until, all approved 3D printed medical devices and implantables gained FDA approval through the Premarket Notification - also called PMN or 510 (k) pathways. All of these products highlights the fact that 3D printed product is substantially equivalent to a legally marketed device. Such a regulatory approach

can also be implemented for MN TDD patch if they are seen as dosage form. (Alhnan et al. 2016). Because, in recent years, (MN) transdermal patch have gained interest among patients and doctors as well. Most likely the reason behind this is MN can produce pores in stratum corneum which allow big molecules such as insulin, melanostatin or erythropoietin into the skin. These big molecules usually do not cross the skin. Current fabrication techniques of MN do not allow fabrication of MN onto curved surfaces due to which results in improper insertion of MN into the skin. As a result, non-uniform drug delivery through MN can occurs and it could lead to a major obstacle in getting regulatory approval for 3D printed MN. To potentially overcome these limitation (Table 6), Lim et al. established a method that requires DLP printer to fabricate MN using a high resolution castable resin 3DM-Cast. The fabricated MN, after evaluation and analysis, showed results in which MN showed to penetrate skin fully. Another advantage of additive manufacturing of MN was that it can be used to alter geometry of MN for better delivery of drugs. Coating of MN with drugs offer another challenge regarding deposition of drug in MN but that challenge can be tackled with 3D printer with a piezoelectric driven material jetting function as it allows deposition of specific amount of drug onto MN. Other than accurate dosing, this technology allows user to retain the superior mechanical strength of existing MNs. Another experiment that showed to overcome these challenges was done by, Gittard et al. and Doraiswamy et al. They used high resolution printer like 2PP to generate MN which have extremely fine tip and allows good penetration of skin (Lim et al. 2018).

Chapter 5

Conclusion

Despite the fact that MNs are becoming a convenient tool in multiple sectors of Pharmaceutics such as TDD of vaccine, hormones, proteins, treating conditions such as keloid and hypertrophic scars, patient compliance dissolving MN, the cost of mass production of MNs on depends on several factors such as, equipment cost of 3D printer and associated workshop, purpose of MNs and materials for 3D printing of MNs. On the other hand, the uses of biodegradable MNs can dismantle the risks of safely disposing needles after use. MNs can be made out varieties of materials, which are of course, approved by FDA. Despite that, using novel biodegradable materials can prove to be cost effective in 3D printing of microneedle.

The promising scopes of MNs on healthcare field is shining day by day with novel inventions, experiments and research. However, the use of 3D printed MNs in large scale commercialization is still a costly step and is not cost effective. It is mainly due to set up cost of 3D printers and workstation, along with less popularity of MNs as TDD that still large scale commercialization is not very much seen for MNs. Nevertheless, the increase in uses of MNs on future due to its great patient compliance might result cost effective production of 3D printed microneedles. As reviewed in this article, novel fabrication technologies can also reduce the cost of 3D printing MNs to a greater extent. Therefore, combination of all the aforementioned factors can lead to fulfilment of all the promising fields of MNs which would also benefit under developed, developing, as well as hard to reach countries. Development and approval of 3D printed microneedles by regulatory authorities will aid in building the framework for approval of 3D printed devices. The ease and benefits of 3D printing will then become feasible for producing microneedles and will help in patient compliance, removal of needle phobia and pave a path in future development of other 3D printed medical devices.

Chapter 6

Future Direction

From a pharmaceutical point of view, 3D printing is a technology that holds huge potential in future. Already many attempts were made to scale up 3DP manufacturing technique of medicinal devices and some proved to be successful as well. The only limiting factor is that more research is needed now to make 3DP techniques industrially feasible for dosage form formulation. Currently, there is only one FDA approved 3D printed dosage form on the market and in future this number might increase if the manufacturer ensures that the printable products comply with the current manufacturing and control standards for the medical products and devices. Numerous research has already been done that shows this technology to be promising for pharmaceutical industry and therefore it is very much desirable that appropriate regulatory requirements are established soon for this technology to develop further and aid in patient satisfaction (Jamróz et al. 2018). So far, it can be concluded that, MN methods may prove a cost-effective, efficacious, and patient friendly alternative of TDD as MN are capable of penetrating skin for exchange of small drugs, macromolecules, nanoparticles, or fluid extractions (Alkilani et al. 2015). Table 7 contains some recently developed TDDS products.

Table 6: Some recently developed/to be launched TDDS product

Serial	Product's usage	Product's description
1	Smoking therapy	Reduces smoking habit by nicotine administering
2	PAQ	Delivery of insulin for type-II diabetics
3	Dermo-patch	Skin spot correction treatment
4	Energizing eye patch	Cosmetic patch for skin rejuvenation
5	Beauty patch	A printed bio-battery for energy efficiency

3D printed MN are relatively new and since there are still relatively few FDA approved MN devices, number of challenges must be addressed before MN become widely available including considerable planning and standardization. This will aid in establishing and addressing MN device regulatory considerations. Issues such as product sterility; the potential for accidental reuse of certain MN modalities (e.g., solid MN), appropriate packaging and manufacturing aspects and the potential for undesired immunological effects should be addressed by FDA along with the choice of appropriate biomaterials for preparation of MNs (Ita 2015). By ensuring that the FDA quality experts realize the full benefit of this technology, they can encourage manufacturing of 3D printed medical devices such as 3D printed MN in large scale, whilst providing meaningful and appropriate regulatory oversight. So far, the FDA has reviewed and regulated 3D printed products under the existing regulations. Extensive cross-centre collaboration within the Agency with individual centres forming specific work groups has led FDA initiate several internal regulatory science and research project such as CDER, CDRH, CBER. The CDER works directly with the stakeholder to identify 3D printing scientific issues, the CDRH has published guidance and previously held public workshops to obtain input regarding this technology. Currently, FDA is focused to establish a common framework which will allow manufacture of wide range 3D printed products such as 3D printed MN under existing regulations (Khairuzzaman 2018).

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