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Review on 3-D Printed Microneedle System as a Novel Approach for Transdermal Drug Delivery

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Abstract

The procedure of forming digital file from three dimensional solid objects is called 3D printing.3D printing technology is utilised in the field of fashion, food, art, human anatomy, biochemistry and biology. 3D printing is utilised in the field of drug delivery system e.g. pellets, patches, tablets, microneedles etc. 3D printed micro-needles are very safe to use and can be prepared easily with less time required whereas conventional microneedles are taking time to prepare and sterilization and high-tech equipment's to prepare the patch. We can make the personalized patch with different size, shape (such as round, cone, cylindrical), length, array format, patch area etc.

- **INTRODUCTION**

3D printing is otherwise called added substance producing. The procedure of forming digital file from three dimensional solid objects is called 3D printing. Basically, the additive process is utilised to created 3D printing objects(Ligon et al., 2017). In this process, by setting down progressive layers of materials an object is built. Anyone of these layers can be seen as a delicately cut level cross-segment of the destined article. It procured an effect as a standard device in the car, aviation, and customer merchandise enterprises (Kreiger et al., 2015).

3D printing technology is utilised in the field of fashion, food, art, human anatomy, biochemistry and biology.This technology are utilised in building measuring device, to visualise molecules and for teaching anatomy (AbouHashem et al., 2015). The applications of 3D printing in various fields are given below:-

2. APPLICATION OF 3D PRINTING

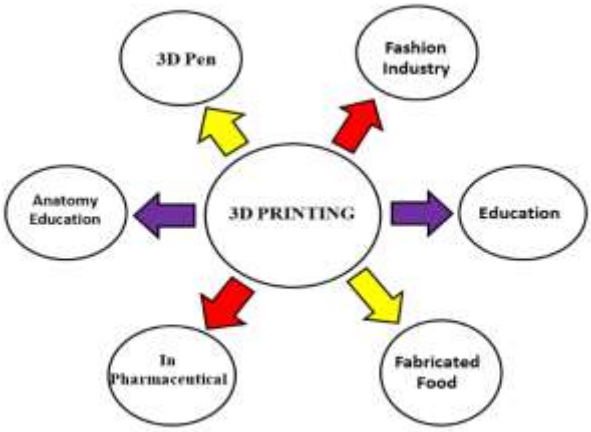


Fig.1. Application of 3D printing

2.1 Education: Utilizing 3D printing, scientists have made counterfeit models to define proteins, DNA, hybridization, crystal unit cells, nanostructures, complex orbital structures, steric communications, and energy surface models, among different themes. In spite of the utilization of these new models, the diminished hazardous pace of current innovation implies that models can take from a few minutes to hours to finish the creation of models that happen outside of ordinary class times(Bernard & Mendez, 2020).

2.2 3D pens: - Another energizing option in contrast to standard 3D printers is 3D pens. These gadgets radiate a slim layer of plastic by melting the string or by utilizing light to clean the monomer blend, much like to marketable 3D printers. This free structure measure has been acknowledged by some in expressions of the human art community, yet the absence of precision makes applications in science teaching and different fields is troublesome (Bernard & Mendez, 2020).

2.3 Fashion industry: 3DP is utilized in the fashion business to create models, high fashion exercises, and modified items that give customers a cooperative open door driven by decision.Nike has utilized SLS to create models and to make lightweight end plates connected to the Vapor Laser Talon and Vapor High Agility football spikes.

High fashion style creators are likewise utilizing 3DP to convey in manners that arising innovations can be utilized to configuration new form. London designer Catherine Wales uncovered her Project DNA assortment of corsets, masks, and 3D caps at the Arnhem Mode Biennale in the Netherlands(Vanderploeg et al., 2017).

2.4 Anatomy education: -3D printing, in the course of recent many years, has been utilized effectively in an assortment of clinical fields, including education. In anatomy, excellent 3D printed writings of cadaveric material have as of late been delivered for instructive purposes.

3D bones are printed and acquainted with understudies in anatomy education. This has been accomplished through various strides for the orientation community between the two-participatinguniversities. The venture was a continuation of the existing partnership between the two universities in the field of biomedical schooling. It utilizes assets and framework (3D surface scanners, printers, bone collections, and so on), just as aptitude in the two universites, empowering the creation of excellent scanners and printing and expanding the number and variety of osteological tests(AbouHashem et al., 2015).

2.5 Food industry: -There is a developing business sector interest for personalized food items, a large number of which are at present designed and made by exceptionally trained artists. The expense of a set number of pieces is high. 3D food printing likewise called Food Layer Manufacturing(J. Sun et al., 2015).

Fabricated foods generally composed of many ingredients such as proteins, lipids, simple as well as complex carbohydrates and emulsifier which can be interact with each other and capable to modify the final food characteristics(Pulatsu & Lin, 2020)

Food printing incorporates 3D (3DP) printing and advanced gastronomy procedures to personalized food pieces in bulk in shape, shading, taste, texture, and amount of healthy food.

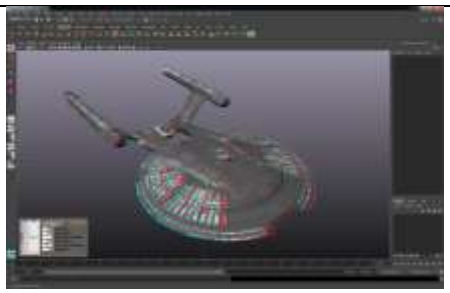
3DP is an advanced controlled automated building process that makes a layer of solidforms with layers and uses phase change or compound responses to tie layers together. Computerized gastronomy is the utilization of food measure information in the production of food with the goal that our food information can beyond taste to coordinate all parts of gastronomy(J. Sun et al., 2015).

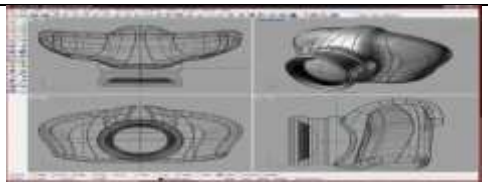
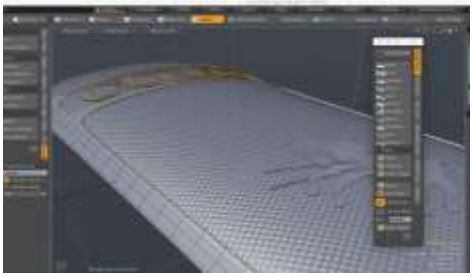
2.6 Drug discovery:-The utilization of this innovation in the field of medication conveyance has been researched and as of late embraced with the FDA's approval of a 3D printed tablet, Spritam (levetiracetam), which keeps on supporting the capacity of 3D printing to make complex and personalized simulation structures(Kazi & Jasvi, 2016). The advantages of utilizing extra production methods as measurement structure incorporate the capacity to precisely control the distribution of the active pharmaceutical ingredient (API) segment inside the dosage form, produce complex geometries, apply an insignificant store for API, diminish squander and consider quicker computational execution(Jamróz et al., 2018).To get ready for the limit of the limit with respect to every person. Business motivations related with drug printing incorporate distantly chains of complex, slow, and costly customary supply chains, limiting production waste and stock, and permitting singular rating structures without the requirement for high-volume production(Prasad & Smyth, 2016).

3. SOFTWARE USED IN 3D MODEL (table form)

In order to make good use of the 3D printer, models must be made into a 3D modeling system that is ultimately sent to the printer to be printed as a visual. There are various types of modeling software used in the 3DP industry(L. Sun & Zhao, 2017). These programs range from a basic system to furthering a system.

Table 1:- list of various software name, structure and there uses.

Serial No.	Software Name	Uses	Structure
1	Maya https://www.autodesk.com/products/maya/overview?term=1-YEAR&support=null	It is applicable for advanced users and professionals. It is beneficial because of its procedural effects and powerful world and character creation tools. It is primarily marketed at animation professionals, Maya is useful for many aspects of 3D modeling, especially in terms of mathematically smooth surfaces and shapes.	
2	3DS Max https://www.autodesk.com/products/3ds-max/overview?term=1-YEAR&support=null	It is applicable for advanced users and professionals. Another program that focuses on animation, 3DS Max offers some great 3D modeling features such as shading tools, parametric mesh modeling, and polygon modeling.	

3	Inventor https://www.sculpteo.com/en/glossary/inventor-definition/	It is applicable for advanced users and professionals. Tailored specifically for product design and engineering applications and loaded with tools for simulation and manufacturing. Inventor 3D CAD software offers professional-level 3D mechanical design.	
4	Rhino3D https://www.rhino3d.com/	It is applicable for advanced users and professionals It is very powerful and full of features for modeling, analysis, rendering, 3D capture, CAM, and 3D printing.	
5	Modo https://www.foundry.com/products/modo	It is applicable for amateurs to professionals. Its Procedural modeling and artist-friendly tools for modeling, animation, texturing, and rendering.	

A separate program falls under the category of computer-aided drug design (CAD). CAD is used in various industries and is very important in 3DP. Since you have the 3D model, the subsequent stage is to set up your 3D printer file. This is called slicing(Jain et al., 2018).

3.1 Slicing: From 3D Model to 3D Printer Slicing is partitioning a 3D model into hundreds or thousands of horizontal layers and is finished with slicing programming. Some 3D printers have

an underlying slicer and let you feed the raw.stl, .obj, or even CAD record. At the point when your record is cut, it's fit to be taken care of to your 3D printer. This should be possible through USB, SD, or the web (C. Guo et al., 2019).

Additionally, there are other terms to be familiar with(Gokhare et al., 2017):

- Slicer (also called slicing software): software used in the majority of 3D printing processes, converting 3D objects to specific printer instructions.
- Fused deposition modeling (FDM): a 3D printing process that uses an ongoing filament of a computer-controlled, thermoplastic material to create a printed shape for objects.
- Parametric 3D printing: refers to the model being defined by individual parameters (specific lengths, heights, and widths, which are editable during and after the modeling process.
- G-Code: a standard programming language for 3D printers that contain commands to move parts within the printer.

3.2 Advantages and disadvantages of 3D printing

Table 2:- list of Advantage and Disadvantage of 3D printing technology.

Advantage of 3D printing (Berman, 2012; Gokhare et al., 2017; Kalaskar, 2017)	**Disadvantage of 3DP**(Berman, 2012; Gokhare et al., 2017; Kubáč & Kodym, 2017)
✓ Faster production ✓ Rapid prototyping ✓ Easily accessible ✓ Flexible design ✓ Better quality ✓ Print on demand ✓ Tangible design and product testing	✓ High energy consumption ✓ Limited material ✓ It is very expensive technique ✓ Restricted build size ✓ We can use only some materials ✓ 3D printers are not common to

✓ Strong and lightweight parts ✓ Cost- effectives ✓ Faster design and production ✓ Minimizing waste ✓ Environmental friendly ✓ Less waste production ✓ Advanced healthcare ✓ Risk reduction	used ✓ Injuriousdischarges ✓ Too much dependence on plastic ✓ 3D printers are moderate ✓ Production of perilous weaponry ✓ Copyright encroachments ✓ Manufacturing job losses

4. Scope of 3D printing in drug delivery

3D printing is utilised in the field of drug delivery system e.g. pellets, patches, tablets, microneedles etc.

4.1 Film

(Jamróz et al., 2017)worked on the orodispersible film with the help of 3D printing technology based on hot-melt extrusion. The group prepared an orodispersible film of a poorly soluble drug using a fused deposition modeling technique. The developed film had the added advantage of giving a higher dissolution rate.

(Jamróz et al., 2017)used the aripiprazole as a drug model with cyclodextrins, polyvinyl alcohol as a polymer to fabricate oro-dispersible films. Fused deposition method was found to be aappropriate method for the production of aripiprazole containing oro-dispersible films with easy reform shape and drug content.

(Ehtezazi et al., 2018)developed a make a fast-dissolving Ibuprofen, paracetamol oral film by FDM.

(Tagami et al., 2019)reported a mucoadhesive Catechin film by a hot-melt extrusion method.

(Wang et al., 2017)made an active 3D patch of tetracycline hydrochloride by the electrohydrodynamic (EHD) printing technology.

4.2Tablet: -

(Khaled et al., 2014)they prepared the controlled release bilayer tablets of Mucinex by using the Extrusion printer. They prepared the 2 layers of tablet, the first one for immediate release and the second layer for the sustained release.

The first layer composition is HPMC2208, PAA, methocel K100M were used for sustained release hydrophilic matrix and second layer polymer composition is HPMC2910, MCC, SSG were used as an immediate release and Mucinex used as a active ingredient and other solvent with analytical grade for this experiment.

The result of this demonstration is successful and we get a hope for future to make a personalized care and treatment with least cost.

4.3 Pellets: -

(Awad et al., 2019)they prepared the pellets for multiple drug (paracetamol and ibuprofen) for controlled release pattern with the help of Selective laser sintering 3DP technique.They used the paracetamol and ibuprofen as active ingredient for loading and ethyl cellulose, kollicoat (for instant release), PVA, PEG,used as a polymer and span 80 used as a binder and other solvent used as analytical grade.

SLS 3DP was effectively used to make mini-printlets in two distinct measurements, 1 mm to 2 mm. Previously Paracetamol was used as the model medication and ethyl cellulose was used as the primary polymer grid.

Double miniprintlets for multi-drug treatment were likewise created, fusing paracetamol and ibuprofen in various layers. Like the single miniprintlets, the double miniprintlets were imprinted in two distinct sizes, 1 mm and 2 mm. The double miniprintlets were set up in two diverse configurations, wherein one medication was scattered in Kollicoat IR, a polyvinyl liquor/polyethylene glycol unite copolymer with immediate release characteristics, and the other

medication was scattered in ethyl cellulose.In this work, we showed that smaller than usual printlets arranged utilizing SLS 3DP offer a novel drug delivery approach with high flexibility and power over the drug content and release properties.

4.4 Microneedles: -

(Pere et al., 2018)work on theinsulin skin delivery with the help of 3D printed microneedles. They use the stereolithography technique for the preparation of polymeric microneedle patches for the delivery of insulin by transdermal delivery. They prepared microneedles in a cone shape.

They used insulin solution for loading active ingredient and xylitol, trehalose, mannitol, class-1 resin as a polymer and other solvents were of analytical grade.

They use the inkjet printing for the coating layer of xylitol, trehalose, mannitol for accurate and reproducible. And the result of this experiment is a 3D printing stereolithographic procedure was presented for the creation of microneedle designs for insulin transdermal delivery.

5. Innovation of 3D printing technology: -

Table 3:- list of invention of 3D printing technology.

Sr. No.	**Year**	**Machine name**	**Reference**
1	1980	Dr. Kodama for his first tries in quick prototyping in 1980. He was the pioneer in added substance fabricating method and presented stereolithography which utilized photosensitive resin polymerized with the guide of UV light.	(Bala et al., 2016)(Pravin & Sudhir, 2018)
2	1983	Charles (Chuck) Hull, invented SLA machine	(Bala et al., 2016)
3	1984	Alain Le Méhauté, Olivier de Witte and Jean Claude André reported their patent for the stereolithography	(Kazi & Jasvi, 2016)
4	1986	The 1st patent was given for stereo lithography	(Bala et al., 2016)

		apparatus (S.L.A)	
5	1987	SLA-1, was introduced and sold in 1988	(Bala et al., 2016)
6	1987-89	Carl Deckard documented a patent in the US for the Selective Laser Sintering (SLS) RP measure. This patent was given in 1989.	(Bala et al., 2016) (Pravin & Sudhir, 2018)
7	1989	Scott Crump filed a patent for Fused Deposition Modeling (F.D.M)- the proprietary innovation	(Bala et al., 2016)
8	1993-99	Significant parts in 3Dprinting thought of different methods like ZCorpbinder jetting from MIT and Arcam MCP innovation and Selective Laser Melting.	(Bala et al., 2016)
9	1996	Sanders Prototype (later Solid-scape) and Z Corporation were set up	(Bala et al., 2016)
10	1997	Arcam was established	(Bala et al., 2016)
11	1998	Objet Geometries launched	(Bala et al., 2016)
12	2000	MCP Technologies (a set up vacuum projecting OEM) presented the S. L. M innovation	(Bala et al., 2016)
13	2002	Envision Tech was founded	(Bala et al., 2016)
14	2009	The main economically accessible 3D printer in kit form and dependent on the RepRap idea was offered available to be purchased.	(Bala et al., 2016)

6. Machines and their features utilised in 3D printing

Table 4:- list of 3D printer and there features.

Techniques/ma	Characteristic features	Advantages	Disadvantages	Reference

chine				
Binder deposition method	The essential 3D printing innovation utilized for drug creation is inkjet affirmation on powder beds. Inkjet printers splash details of medications or fasteners in little drops at exact rates, movements, and sizes onto a powder bed. The fluid detailing inside the printer may contain a cover in particular, and the powder bed may contain the dynamic fixing (API) with extra excipients. On the other hand, APIs can be flown onto powder beds as arrangements or nanoparticulate suspensions. Binder Jetting is an added substance fabricating measure in which a fluid restricting specialist is specifically kept to join powder particles. Layers of material are then attached to frame an item**.**	1. full colour options 2. No warping and shrinking of product in different temp.	1. low part strength 2. less accurate material jetting	(Kunchala & Kappagantula, 2018)
Direct write: - Direct-Ink-	It is an expulsion based added substance fabricating strategy	**1.** no entrapment of particles in	**1.** low accuracy	(Zhang et al.,

Writing (DIW)	intensely used in meso-and small sizes. In DIW, the fluid stage "ink" is apportioned out of little spouts under controlled stream rates and stored along carefully characterized ways to manufacture 3D designs layer-by-layer. Utilizations a PC controlled translational stage that moves an example producing gadget to accomplish, layer-by-layer, 3D microstructure.	pores 2. high fabrication speed	2.easy to sag and collapse during printing	2015)
Fused deposition modelling (FDM)	FDM printers utilize a thermoplastic fiber, which is warmed to its softening point and afterward expelled, layer by layer, to make a three-dimensional article. FDM was the method protected by Scott Crump, prime supporter of Stratasy ltd and was created because of the constraints found in inkjet printing. It involves the softening, expulsion, and layer by layer testimony of materials that after cementing	1. low cost 2. fast and acceptable strength	1. nozzle clogging 2. limitation in usable material	(Long et al., 2017)

	bring about items with foreordained constructions.			
Inkjet printing	Mix of dynamic drug fixings and excipients are definitely splashed on the substrate as beads dependent on two procedures, that is, nonstop and drop on interest. In persistent jet printing, the flood of drops are consistently sprinkled on the substrate or digressed towards the waste line when not being used. Nonetheless, in drop on interest technique, the necessary number of drops are sprinkled on the substrate and shut when not out of luck.	1. high resolution 2. control in drop size and ejection rate	1. high viscous bio-inks can't be used 2. weak mechanical integrity of the construct	(Y. Guo et al., 2017)
Material extrusion	Material Jetting forms objects in a comparative technique to a 2-dimensional ink jet printer. Numerous materials can be utilized in one cycle and the material can be changed during the form stage. Material is streamed onto the form stage surface in drops, which are framed utilizing a swaying spout.	1. Accuracy 2. Good surface finishes.	1. Build process is slow 2. Limited no. of wax like materials	(Chaunier et al., 2018)

	The material is expelled from mechanically incited spouts. Dissimilar to cover streaming, which requires a powder bed, expulsion techniques can print on any substrate. Normal kind of expulsion printing is intertwined fiber creation (FFF), likewise known by the reserved name: melded affidavit modeling™ (FDM®).			
Extrusion method	Material is expelled from the mechanized nozzle onto the substrate. As in powder bed statement, it doesn't have powder bed and need higher help material. The materials that can be expelled are liquid polymers, suspensions, semisolids, glues.	1. wide range of material choice 2. good mechanical properties	1. limited material for thermoplastic 2. viscosity and temperature of materials	(Hwang et al., 2018)
Pen based 3D method	This is a refreshed adaptation of expulsion procedure as hand-held gadget to plan wanted designs which are generally deficient. Likewise, theresearchers are thinking about its significance in surgeryfor affidavit of 3D	1. very low cost 2. easy to use	1. extruder in human controlled	(Kara et al., 2006)

	designs materials.In this interaction, the layer by layer gathering is physically controlled with hand held gadget.			
Powder bed fusion method	It includes the combination or restricting of low liquefying point with high dissolving point covers. The laser shaft supplies the warmth needed for the limiting. It is a quick interaction, yet nearly more mind boggling than expulsion technique. The Powder Bed Fusion measure incorporates the accompanying usually utilized printing strategies: Direct metal laser sintering (DMLS), Electron shaft liquefying (EBM), Selective warmth sintering (SHS), Selective laser dissolving (SLM) and Selective laser sintering (SLS).	1. wide material choice 2. low cost and minimum support	1. long print time 2. weak structure property	(S. Sun et al., 2017)
Selective laser melting	It is a fast prototyping, 3D printing, or added substance fabricating (AM) procedure intended to utilize a powerful	1. no support material is required	1. low mechanical strength	(Wei et al., 2019)

	thickness laser to soften and meld metallic powders. To many, SLM is viewed as a subcategory of specific laser sintering (SLS). The SLM cycle can completely liquefy the metal material into a strong three-dimensional part not at all like SLS.	2. good material property	2. not suitable for large objects	
Stereolitho-graphy	Stereolithography includes presenting fluid tars to bright or other high-fuel light source to instigate polymerization responses. The procedure utilizes photopolymerizable crude material. An illustration of medication conveyance application is 3D printing of photopolymerizable hydrogels	**1.** fine control over pore shape and size 2. ability to fabricate complex geometries	1. slow process 2. required supportive material	(Manapat et al., 2017)
Sheet lamination method	It is an automated laser-cutting and sheet-by-sheet assembly of products. This process is quick and inexpensive although it has lower solution and more useful than most printing methods.	1. multi material layers possible 2. Faster print time, but post processing will be required.	1. limited material options available 2. Hollow part are difficult to produce in some type of SLM**.**	(Bhatt et al., 2019)
Direct energy deposition	In this interaction the crude materials are dissolved by a	1. reduce material waste	1. low build resolution	(Miedzinski, 2017)

method	laser or electron shaft fuel sources as they are stored. This strategy utilizes the material that can't be expelled like powder or other crude materials.	2. easy material change	2. no support structures	
Thermal inkjet printing	Thermal inkjet printer comprise of miniature resistor, when current is instigated, this warmth, warms up the watery ink liquid which changes over it into fume structure that moves out of a nozzle bringing about bead structure. This procedure requires high temperature that may corrupt the warmth delicate material.	1. high resolution 2. accuracy 3. wide range of material	1. May damage post processing. 2. delicacy of the 3D printed features	(Hoath, 2016)
Zip dose	This procedure was created by MIT in late 1980's. Give a customizedportion notwithstanding the conveyance of high medication stacked with high crumbling and disintegration level by assembling profoundly permeable material. This procedure is utilized for forming a tablet with high portion and fast	1. high drug load 2. use highly porous material 3. wide range of products	1. requires access to small amount of liquid 2. costly	(West & Bradbury, 2019)

	deterioration.			

8. Concept of transdermal drug delivery: -

Transdermal therapeutic systems are characterized as independent, self-discrete dosage forms, which when applied to the unblemished skin convey the medication at a controlled rate to the systemic circulation. A simple patch that you stick onto your skin like a bandage, which act as a passive diffusion of medication across the skin as the delivery mechanism. TDDS are dosage form intended to convey a remedially powerful measure of medication across a patient's skin(Brown et al., 2006).

Advantage of TDDS: -

- ✓ Avoid first pass metabolism
- ✓ Improve patient compliance
- ✓ Prolong time of action
- ✓ Reduce frequency of dosing
- ✓ Uniform drug level in plasma
- ✓ Increase therapeutic efficacy

TDD isn't in every case normally achievable. The significant restriction of this route comes from the nature of the skin boundary itself. The external most layer of the skin, the Stratum Corneum plays the dominant role in the impermeability of the obstruction, being extremely thick and significantly low in hydration (15–20%)(Economidou et al., 2018).

The first transdermal system, Transdermal SCOP was authorized by FDA in 1979 for the avoidance of nausea and vomiting associated with level(Prausnitz & Langer, 2008). Most transdermal patches are intended to deliver the active ingredient at a zero-order rate for a time of a few hours to days following application to the skin. This is particularly profitable for prophylactic treatment in chronic conditions(Mehta, 2004).

9. Concept of MNs drug delivery: -

Back in 1976, microneedles were first discovered and till 2000s the innovation employed to produce needles of micron measurements was not comprehensively accessible. The microneedles are empty needle like structure having a size ranging from microns and length measures up to 1micrometer that is adequate to permit going of a liquid and solid medication through the microneedle. The empty shafts can be straight, for example extended from base to tip, and having atleast one or more opening on the sides from the lateral side of the needle instead of having only opening at the tip(Prausnitz, 2004).

Microneedles can be installed inside transdermal drug delivery. Microneedles are invented to pass through the epidermis layer till a profundity of 70–200 micrometer, because of short and thin structure of the microneedle they are not able to pass to nerves through the dermis layer that's gives the painless delivery of active pharmaceutical ingredients (APIs) of small and higher molecular weight. 47 In comparison of other transdermal drug delivery microneedles are more capable in delivering accurate amount drug at site of action(Hao et al., 2017).

Advantages of microneedles(Sivamani et al., 2007)**: -**

• Large molecules can be managed

• Painless administration of the active pharmaceutical ingredient.

• First-pass metabolism can be avoided

• Faster recovery at injection site than with a hypodermic needle

• No trypanophobia.

• Ease of administration of drug.

• Decreased microbial penetration as associated with a hypodermic needle, the microneedle penetrates only the epidermis layer of skin.

• Specific skin region can be focused for wanted medication conveyance improved medication efficacy may bring about portion decrease

• Good tolerability without long-term oedema or erythema

• Rapid medication conveyance can be accomplished by coupling the microneedles with different technologies

Disadvantages of microneedles(Indermun et al., 2014)

Cautious utilization of the gadget might be expected to keep away from particles 'skipping off' the skin surface. The thickness of the stratum corneum and other skin layers fluctuates among people and so penetration depth of particles could change as well

• The outer climate, similar to hydration of the skin, could influence delivery.

• Repetitive infusion may fall the veins

• The tip of the microneedle may sever and stay inside the skin on expulsion of the fix

9.1 Types of microneedles based on drug delivery

9.1.1Solid microneedles

As the name suggests, it is entirely solid and work by creating the hole in Stratum Corneumof the layer of skin. As the medication are coated on the upper surface of solid microneedle, it deliveredatthe site of action by puncturing the stratum corneum layer of skin and would be removedafter the delivery and whole process of drug delivery is shown in. It alsoincreases the permeability of skin by creating hole on skin layer so that applied drug caneasily reaches the site of action with minimal loss and less amount of time. The size of solidmicroneedle varies between 750-1000μm in length and comparison with hypodermic needle formulated a PLA composed microneedle of size of 600micrometre to increase the delivery of small molecule drugs across the skin(Prausnitz, 2004)(Hao et al., 2017).

Materials used for the formulation of Solid Microneedle(Chen et al., 2018)**: -**

Silicon: Manufacturing solid microneedle using silicon is costly and has disadvantage of being brittle and have possibility of breaking down in skin.

Metal: Microneedle formulated using metals are generally have good mechanical strength and manufacturing cost is also low. Various metal involved during the formulation of solid microneedle are stainless steel, gold, platinum, titanium, nickel, iron, etc.

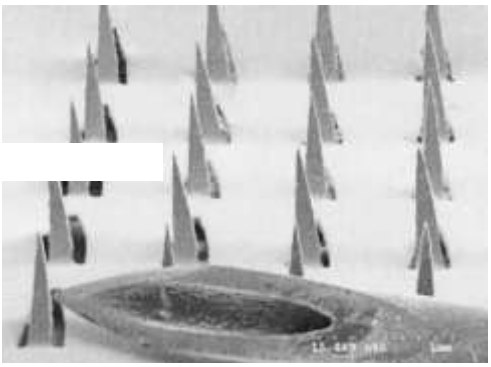


Fig.2 Figure illustrating relative comparison of solid microneedle with hypodermic injection.

Biodegradable materials such as PCCP [Poly (di(carboxylatophenoxy) phosphagene)] consisting of phosphorus-Nitrogen provides potent adjuvant activity and also overcomes the limitation of metal and silicon made solid microneedles.

9.1.2 Coated Microneedles

Coated Microneedle are those which consists of coating of drug on its surface. This microneedle allows the diffusion of drug from surface to deep epidermal layer of skin. But due to coating it increases the thickness of the microneedle and can influence the penetrating ability of microneedle. Despite this limitation, the coated microneedle found great utility in vaccine delivery across the skin(Prausnitz, 2004)(Hao et al., 2017).

9.1.3 Dissolving / degradable microneedle

Dissolving or Degradable microneedle patch is manufactured with the help of soluble/degradable polymer materials with drug / molecules with tangled in polymeric matrices. Drug is released form patch through the dissolving or biodegradable of the polymer & rate of drug release is organised by the dissolving or degradable amount of polymer media of microneedle. Dissolving

or degradable microneedle patch can be employed for alter deliveryof protein(Hao et al., 2017)(Prausnitz, 2004).

Material used: Polycarbonate, PVP, PLA, PLGA, PGA, PVP etc. Other materials like fast-dissolving sweeteners and also various polysaccharides have been searched to formulation of the dissolvable microneedles. Another mucoadhesive polymer such as Gantrez AN-139 can also be used due to advantage of withstanding higher compression pressure(Chen et al., 2018).

Advantage(Kwon et al., 2017)(Waghule et al., 2019)**: -**

- Transferring large doses of drug.
- Dissolving microneedles have been developed for vaccine delivery.
- The best choices for long-term therapy with improved patient compliance.

Disadvantage(Kwon et al., 2017)**: -**

- It's hard to get a deliver a fixed amount of drug.

9.1.4 Hollow Microneedle

As the solid microneedle dramatically increases the skin permeability, still there is need of some more controlled and reproducible drug delivery system. In this scenario, Hollow Microneedle found its application as it provides more accurate and controlled drug delivery. Hollow microneedles are hollow inside their shaft and have various advantages such as option of delivering both high and low molecular weight drug in according to need of body, possibility of pressure driven movement of drug instead of passive movement and reduces the chance of cross contamination of surrounding with deliverables. Various type of hollow microneedles are fabricated for transdermal drug delivery such as Metal Hollow Microneedles made of metal, Silicon hollow microneedle made up of silicon and of glass microneedle(Prausnitz, 2004)(Hao et al., 2017).

Method of manufacturing: -

Hollow MNPs can be created from metal through metal electro-deposition joined with master shape, in which master shape is made by means of the strategies referenced in Section 3.1 and after sputtering a conductive seed layer onto the master shape, metal is electrodeposited into the master shape to frame the hollow MNs. In addition, metal hollow MNs can be manufactured by means of two phase Electro-deposition, in which the hollow design is created by twice electro-deposition.

Silicon hollow MNPs can be created by dry etching or a mix of dry and wet etching (Chen et al., 2018; Sivamani et al., 2007).

Advantage(Kwon et al., 2017)(Waghule et al., 2019)(Sivamani et al., 2007)**: -**

- Hollow microneedles have been developed for vaccine delivery.
- It is used for high molecular weight compounds such as proteins, vaccines, and oligonucleotides.
- Drug flow rate and release pressure can be adjusted.
- Capable of administering a large dose.

Disadvantage: -

- Dependent on the flow rate of the microneedle.
- Can formation of clogged.

10. Fabrication microneedles: -Manufacture of microneedles are cut from stainless steel sheets utilizing an infrared laser. The ideal microneedle shape and measurements are first drafted in AutoCAD programming. Utilizing this plan laser energy is utilized to cut the microneedles. A cutting rate of 2 mm/s and air cleanse at a steady pressing factor of 140 kPa is utilized. Microneedles are either set up as in-plane needles or as out of the plane microneedles Laser cutting(Sivamani et al., 2007).

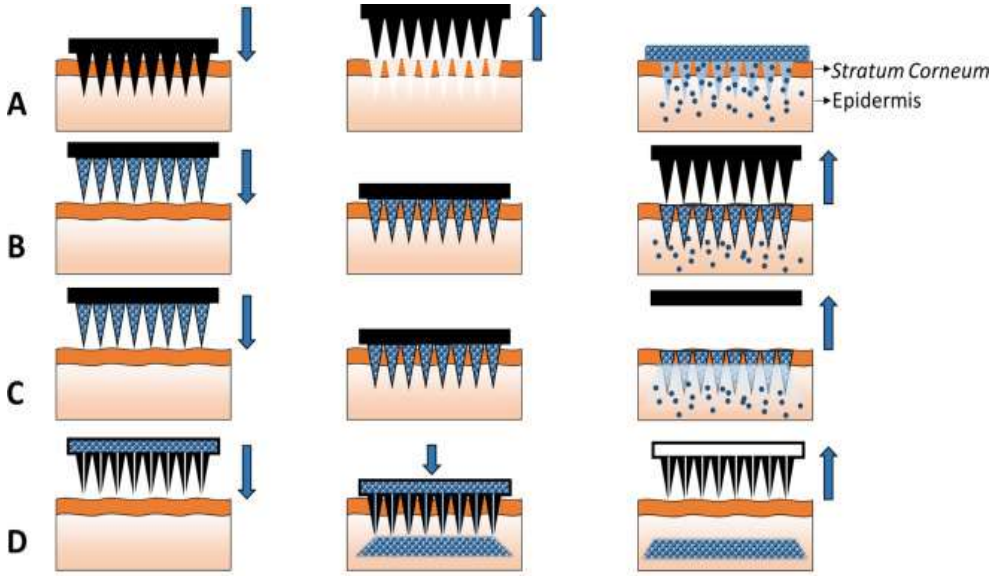


Fig.3: Systematic representation of drug delivery through different types of microneedles.

[A. Solid Microneedle B. Coated Microneedle C. Dissolvable Microneedle

D. Hollow Microneedle]

S. no.	Type	Material	Fabrication method
1	Solid	Stainless-Steel	Infrared laser cutting
2		Stainless Steel	Wire electrical discharge machining
3		Tungsten	Deep reactive ion etching
4		Titanium alloy	Ion sputtering deposition
5		Tantalum	Twisted light with spin
6		Silicon	Photolithography + etching
7		Palladium	Two stage electrodepositions
8		Hafnium oxide	Atomic layer deposition + master mold

9	Hollow	Silicon	Dry etching
10		Silicon	Combination of dry and wet etching
11		SU-8	Photolithography
12		Glass	Drawn-glass micropipette
13	Dissolving	Fibroin	Solvent casting+vacuum
14		Maltose	Melt casting
15		Gelatin	Solvent casting + centrifiugation
16		Hyaluronic acid	Solvent casting
17		Alginate	Solvent casting + centrifiugation

10.1 Benefits of microneedle prepared by 3D printing over conventional preparation techniques: -

3D printed micro-needles are very safe to use and can be prepared easily with less time required whereas conventional microneedles are taking time to prepare and sterilization and high-tech equipment's to prepare the patch.

We can make the personalized patch with different size, shape (such as round, cone, cylindrical), length, array format, patch area etc. The same was mentioned by(Bhatnagar et al., 2018; Jamróz et al., 2018).

It'simproves the penetration power of MNs patch. Whereas conventional preparation of MNs patch is very difficult to relay impossible to make a personalized MNs patch because in take so much time to formulate patch (Ita, 2017).

In conventional techniques we need different product and procedure for making different type of patch such as solid MNs, Hollow MNs, and dissolving MNs whereas in 3D printing technology we need just one technology with help of a computer software and printer(Bariya et al., 2012).

In conventional techniques for preparation of MNs we need metal and different tech such as infrared laser for the cut needle structures from stainless steel sheets and form a Solid micro-needles patch, and electrodeposition combined with master mold to form a Hollow microneedles patch(Chen et al., 2018), in dissolving microneedles we use Centrifugation, vacuum and pressure are adopted the MN structure(Chen et al., 2018). After the cutting and successful formation of MNs, then manually bending needle at 90° out of the plane of the sheet. whereas 3D printing technology need a computer software and 3D printer to prepare a MNs on sheet we just need an extrusion of polymeric solution and start the preparation of MNs(Bariya et al., 2012).

3D printed MNs are very safe to use and easy to remove and it not causing pain because it prepared by bio-degradable polymer which is non-toxic for us. Whereas conventional prepared MNs cause pain and burning in site of administration and some time it can cause the inflammation due to metal and stainless steel(Cheung & Das, 2016). Polymers used in microneedle drug delivery(Park et al., 2005).

11. Published literatures of microneedle drug delivery by 3D printing technology: -

Sr. no	dosage form	Drug	Polymer	3DP technology	Reference
1	Micro-needles	Insulin	mannitol and xylitol (drug carriers), Class I resin (polymer)	Stereolithography, inkjet print	(Pere et al., 2018)
2	Micro-needles	Computational	Trimethylolpr	Continuous	(Johnson et

		design of microneedles	opane triacrylate, Polyacrylic acid, photopolymerizable, derivatives of polyethylene glycol and polycaprolactone	Liquid Interface Production	al., 2016)
3	Micro-needles	Biodegradable polymer microneedles	polylactic acid, PVA	fused deposition modelling	(Jamróz et al., 2017)
4	Micro-needles	insulin delivery	photopolymeric resin,	Stereolithography, inkjet printing	(Economidou et al., 2019)
5	Micro-needles	Biodegradable polymer	Hydrogel, PVP, PDMS	Stereolithography 3D printing (Objet Eden350, Stratasys, Ltd., Edina, MN, USA).	(Foundation et al., 2015)
6	Micro-needles	Cisplatin, retinoic acid, rapamycin	PVC, PVA, PEG	Stereolithography, inkjet dispensing	(Bhatnagar et al., 2018)

7	Micro-needles	Besifloxacin	PVA, PVP K-30	Poly-jet 3D printer	(Yao et al., 2020)
8	Micro-needles	Hydrogel based	PEG400DA, Phenylbis phosphine oxid	Digital light processing	(Yao et al., 2020)

Conclusion and future prospect of 3D printing

3D printing technology successfully worked on various field, but in pharmacy 3D printing technology has very excellent growth in a various formulation such as bilayer tablets, multiple compartment capsules, pellets, films, and patches. In microneedles patch, 3D printing technology has very exponential power to produce a better patch with less time and less material.

3D fabricated MNs patch can we used as a personalized patch with a change in their size, shape, needles size, and their location from the sheet. We can administer drugs in different layers of skin by changing the degree of the attached microneedle. Recently, we have several 3D printers to use the formulation of MNs patch as we read above but, in those printers, if we add the outer accessories with the 3D printer so it improves the efficacy and production rate. For example, if we can add isotropic shrinkage technique with 3D printing technology so it will call a print-and-shrink fabrication technique which allows the creation of complex shape polymeric needles. And we have several issues with FDM and inkjet printer but we can cure by working and optimizing those printers.

Future work includes improving the FDM 3D printer's nozzle configuration to upgrade the goal without raising the expense altogether or building up a method that will take into consideration more adaptable MNs. By upgrading the resolution, more characterized shapes can be made, which would bring down the measure of time required for etching. With the headway of 3D imprinting in industry, especially late business dispatches of 3D printed items, this technique gives a versatile manufacturing of MNs. This novel formulation method has shown the capability

of fast prototyping MNs at low expenses, overcoming any issues between additive manufacturing and inactive medication delivery (Jamróz et al., 2017).

Because of the cheap in cost, pain free, short manufacturing time, well biocompatibility, and medication conveyance execution properties of 3D constructed MNs, it is energizing to adjust MNs to the market. We hope to apply 3D printed MNs with properties above to clinical use in future(Yao et al., 2020).

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