A GENERAL REVIEW OF THE MANUFACTURING OF 3D PRINTED TRANSDERMAL MICRONEEDLE PATCH/CHIP BY USING SLA PRINTER

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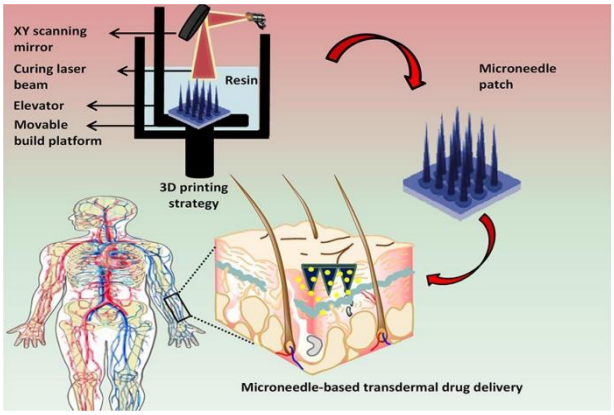
ABSTRACT: -

Transdermal drud delivery system (TDDS) is the best and easy self-management system. It interacts with the skin and delivers the drug in a controlled manner into the systemic circulation. This reduces side effects associated with oral therapy, such as first-cycle liver damage metabolism, GIT irritation, etc. Skin infusion enhanced technology has been developed to improve skin bioavailability of drugs.In recent years 3D printing has attracted great interest in the pharmaceutical field as a promising tool for the on-demand manufacturing of patient centred pharmaceutical forms. microneedles as TDDS having extensive attention due to their distinguished property, including improved patient compliances and self-administration, compared to traditional parenteral administrations.Microneedle technology potential in controlled drug delivery which has got rising attention from the inventory investigation & clinics. MNS can pierces through the stratum corneum layer of the skin into the epidermis, evading the interaction with nerve fibres; microneedle patches have been fabricated using various types of materials & application process. 3D printing gives the prototyping and manufacturing flexibility to produce the microneedle patches in single step manner with high level of shape complexity and duplicity. This review aims to go through recent successes in 3D printing MN based patches. In this regard, after the evaluation various types of MNS & fabrication technologies and elaborates their advantages, limitations & applications as controlled drug delivery systems. We will study different 3D printing approaches applied for MNs patches fabrication.

Graphical abstract



Key words: Microneedle aspects; Types of Microneedles; Materials and methods of manufacturing; CAD of microneedle patch; manufacturing process of microneedle patch; limitations; Advantage and disadvantages; Evaluation properties.

Introduction

Over the eras, in the pharmaceutical plot, the notion of a '' one- size- fits- all medication'' has been revised to make room for individual drugs, primarily due to the spread of three-dimensional printing(3DP). This technology allows the manufacturing of pharmaceutical forms with customized shapes, pills, release characteristics, and pharmaceutical combinations. The asked object is produced in a level-by-level manner by rewording a computer- backed design(CAD) model into a solid prototype. Between the advantages conferred, in addition to adding patient compliance and adherence to treatment, this approach reduces fabrication costs and enables the on- point product of drugs, potentially performed in hospitals and chemists(1). It is scritical to probe an optimal system for medicine delivery in agreement with the characteristics of the medicine. Oral administration is a simple and accessible medicine delivery system because the patient can tone-administer the medicine; however, its operation to biopharmaceuticals is grueling (Homayun etal. 2019). Injections affect high bioavailability and rapid-fire onset of medicine action. still , moxie is needed for administration and case compliance is low(Prausnitz 2017). thus, the ideal medicine delivery system should be as simple as oral administration and should parade high bioavailability as with injection(2).The multiple advantages of transdermal medicine delivery which provides advanced bioavailability of the medicine delivered into the body through the skin, better patient compliance, controlled medicine release, minimum gastric mucosal vexation, and inhibition of first- pass metabolism the biggest challenge is the rigid and non-permeable structure of the stratum corneum(SC), confining the passage of the substance through the skin. Only low-molecular weight lipophilic medicines are allowed to pass through the SC subcaste. colorful transdermal medicine delivery strategies such as ultrasound, iontophoresis, electroporation, colorful nanocarrier- loaded creams, and transdermal patches have been explored to overcome this issue. however, the limitations of these strategies have fostered the demand for new advancements. Microneedles(MNs) conforming to micron-sized needles in arrays represent a promising approach for the development of transdermal medicine delivery systems that could overcome the rigid structure of the SC subcaste. Because of their small size, MNs pierce the skin easily and non-invasively, avoiding contact with dermal jitters and blood vessels, thereby adding skin permeability, with minimal implicit pitfalls of skin injury and impurity. In addition MNs allow small medicine molecules, macromolecules and nanoparticles to pass through the SC subcaste and directly reach the systemic rotation. In addition to these parcels, cost- effectiveness, high case compliance and effective storehouse conditions are other outstanding parcels(3). (4)Additive manufacturing, generally known as 3D printing,(5) provides crucial advantages over traditional manufacturing approaches, including the capability to fabricate complex geometrical products, the ease of substantiated pharmacotherapy for cases, low cost, substantiated boluses, product of case- specific bias, and fabrication with high tunability and complexity.(6),(7)

Microneedles aspects:

Although the microneedle design varies depending on the delivery system, type of microneedle, and action of the drugs to be delivered, maximum patches have certain common features. A typical microneedle has the shape of a phased sharp tip with a length of 150 – 1500 μm, a range of 50 – 250 μm, and a tip consistency of 1 – 25 μm(Waghule etal. 2019).[8] Microneedles are generally made of soul, silicon, polymer, glass, or ceramic. The medicine is generally placed in or on the microneedle tip, which is fixed to the base substrate underneath to form an array. The microneedle array is attached to the patch backing for ease of use; this backing includes a skin adhesive for better contact with the skin.

Classification of microneedles:

Skin microneedles are generally divided into four types(Figure 1). Solid microneedles are mainly produced from metal and silicon that give strong mechanical tapes and do not contain medicines. therefore, after the operation of microneedles, it is necessary to spread the medicine further within the urban sections. In contrast, when using coated microneedles, the drug is administered to the skin surface at the same time with the app. After dissolving the microneedles, the drug can be incorporated into the biodegradable matrix, with no sharp waste after using the microneedle. Hydrogel microneedles deliver drugs slowly because the medicine is present in all areas Same as the tip about the microneedle and patch background. carbon the plots of microneedles vary by type, suitable the model must be chosen according to the micronails .Drug dose, onset of action, delivery time, delivery effectiveness packaging, sharps waste and patch life.

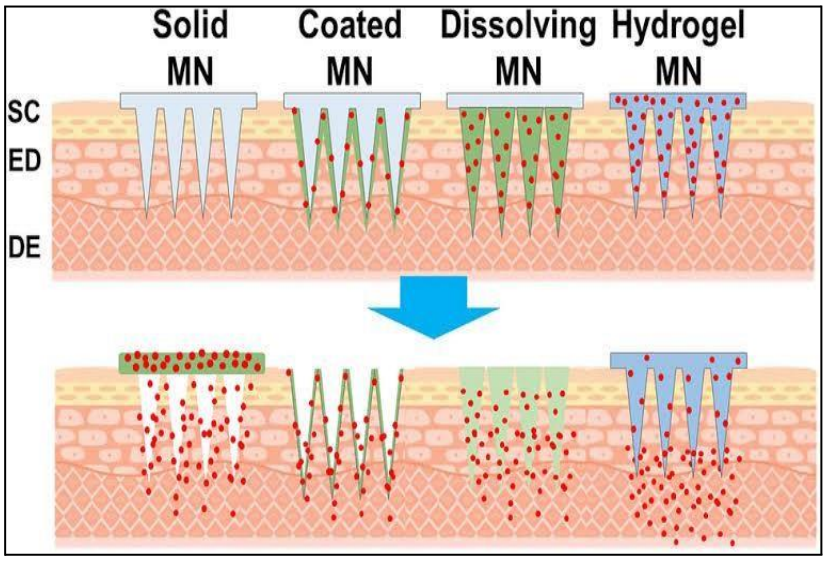


Fig.(1)

Solid microneedles

Solid microneedles are a group that includes the microscale tapered sharp tips consisting of a single material without some drugs or excipients, when, applied to the skin, the formation of

micron-sized pores are formed on the surface of the skin (fig. 2).. When the drug is placed on the treated area, it passes through the stratum corneum, which is the largest barrier of the skin, through these pores; it is easily transferred to the capillaries in the epidermis, which increases its bioavailability drug (Henry et al. 1998)[9].The substance can be formulated as a standard transdermal patch or topically applied to the skin - (Hoang et al. 2015)[10]. Medicines can be delivered over and extend the time by adding reagents that keep the pores open for a longer time (Brogden et al. 2013)[11].

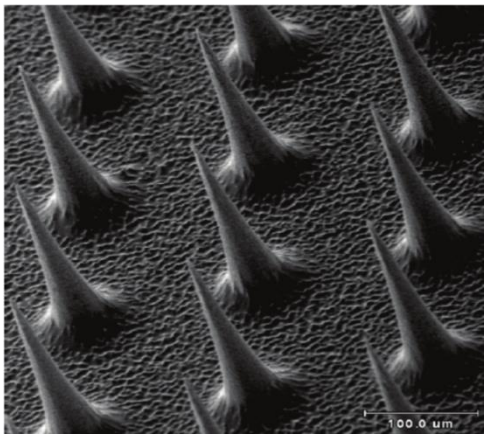


Fig.(2a) solid microneedles

Coated microneedles,

The surface of the solid microneedles is covered with a water-soluble matrix so that the medicinal substance quickly dissolves into the skin after the microneedle is inserted **(**Figure 2b) (Haj-Ahmad et al. 2015; Jiang et al. 2007)[12]. The coating composition must form a film on the surface with a microneedle and maintain adhesion during storage and skin application. To achieve this goal, the viscosity of the preparation must be sufficient.The place where the covering product is placed must be considered received. Usually, only investment in medicine is beneficial at the end where the microneedle goes into the actual skin. In the case of dip coating, the area covered by the drug can be trolled by adjusting the depth of the microneedle included in the coating composition (Gill et al. 2007a; Gill et al. 2007b; Shakya et al. 2019)[14],[15]. The area covered by the drug can be determined by adjusting the surface tension of the coating compound that controls the coating spread microneedles. In the coated microneedles, the medicine can be delivered quickly and dissolves in the skin, so the effect of the drug begins quickly. The thickness of the coating can be increased several times coating by composition; however, it is not suitable as a medicine dosing because it requires a high dose due to dosage limitations.

(Chen et al. 2017; Waghule ja ai. 2019).

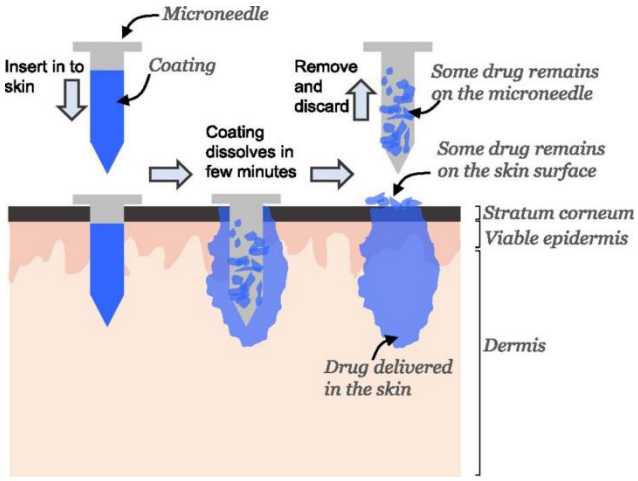


Fig.(2b) coated microneedle

Dissolvable microneedles

The microneedles themselves can be water soluble or biodegradable materials that contain drugs and have sufficient mechanical force to penetrate the skin (Figure 2c) (Sullivan et al. 2010)[16]. During Solvent microneedle insertion there is no sharp debris on the skin because it tears, dissolves, or breaks down on contact with skin liquid (Edens et al. 2015; Hirobe et al. 2015; Quinn et al. 2015). Soluble microneedles are mainly produced using a water-soluble biodegradable polymer through the solvent cast method. Biodegradable cellulose-based polymers such as carboxymethyl cellulose (CMC) and methyl cellulose Lulose, are often used. Saccharides (e.g. sucrose) are also contained in microneedles; they promote degradation of the preparation and stabilization of biomolecules (Mistillis et al. 2015; Raphael et al. 2016)[17]. In this formula, the nozzle containing the drug must be compatible along with the drug, provide mechanical strength, and have a viscosityis is low enough to fill the microscale mold space well without air bubbles. The substrate contains No drug should have a higher viscosity than the tip, vol be a mechanically weak or water-insoluble material (Prausnitz 2017). Several short-term studies have been conducted recently. extending the usage time of the microneedle chip in particular microneedle tips quickly from the bottom substrate without the ends completely dissolving in the skin. He et al. reported a microneedle patch capable of rapid differentiation classification after cutting the skin. Mechanically the heating force of the microneedle was adjusted by swinging drip with a microneedle (Li et al. 2019a). In addition, the tip of the microneedle was detached within 2 min from a basic substrate that consisted of a prefabricated material (He et al. 2019b). Jun et al. evolved to be addition-sensitive microneedles for instant microneedle separation after application to the skin (Jun et al. 2018)[18]. A small single wall was drawn on the side of the microneedle base; structurally, this allowed rapid mechanical removal of the tip basis. As with soluble and coated microneedles, this system is disadvantageous for large doses; research is being conducted to increase the number of drugs that can be incorporated into these microneedles.

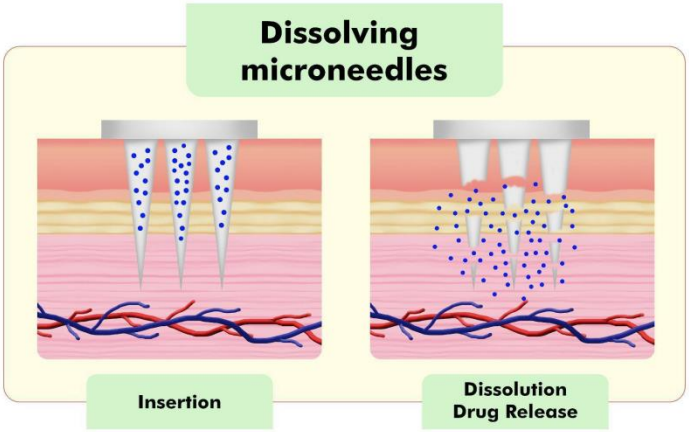


Fig.(2c) Dissolvable microneedles

Hydrogel microneedles:

The hydrogel microneedles contain the drug in all regions from the tip of the microneedle, the lower substrate, and the background of the chip and is released slowly when the patch is applied to the skin (Figure 2d). Microneedle patches mainly consist of hydroge,l and when they meet liq to the skin, they are moistened but not dissolved (Al Sulaiman et al. 2019; Li et al. 2020; Yu et al. 2015)[19]. The medicine contained in the hydrogel is administered through the skin diffusion (Migdadi et al. 2018; Courtenay et al. 2020)[20]. Because the drug can be added to the entire microneedle patch, this system is suitable for high-dose administration; however, the disadvantage is that the application time of the patch is long due to the slow speed of drug delivery.

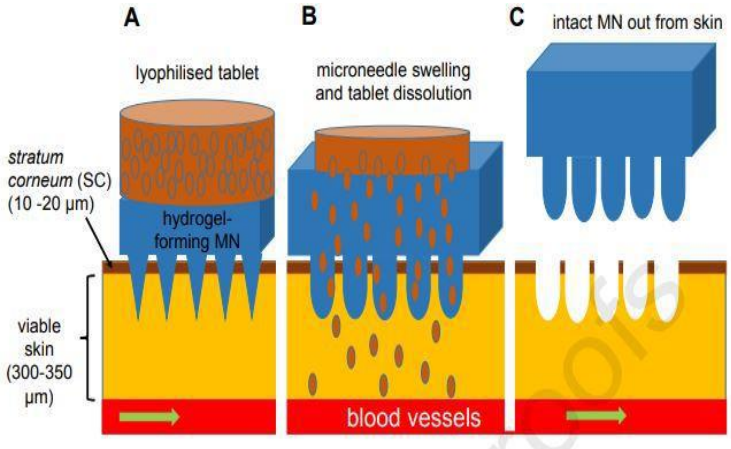


Fig (2d) **Hydrogel microneedle**

Materials and methods:

Materials

The material used in the manufacture of the MN chip was surgical Guide Class 1 biocompatible resin (Holiday lab). The resin is noncytotoxic, nonsensitive and nonirritant and complies with ISO 10993-1:2018 [21]. The surgical guide requires post-treatment to achieve biocompatibility and optimal mechanical properties. In addition, this material is autoclavable, which is an important feature for medical use. In addition, 99% isopropyl alcohol was used to wash the printed parts according to the resin manufacturer's instructions.

MN Computer Aided Design (CAD):

The structural design of the MN was modeled using Solidworks 2019 software and was inspired by the single-plane inclined pin design. The length of the MN was 450 μm, the inner diameter (β) was 100 μm, the outer diameter (α) was 232 μm, and the slope angle (θ) between the side surface and the chamfered plane was 45°, (figure . 3). This MN was evaluated in detail in [22].

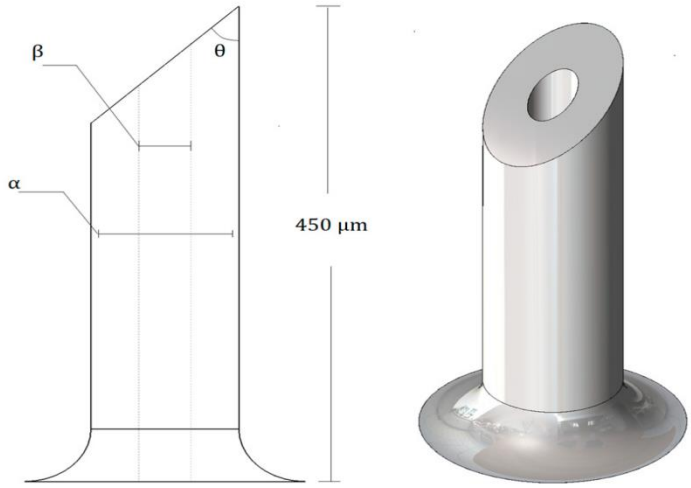


Fig.(3.)

This relatively simple MN structure allows adequate load distribution throughout the structure, allowing to penetrate the skin without structural damage

MN Patch Computer Aided Design (CAD):

The design of the MN upgrade was performed using Solidworks (version 2020-2021 SP5.0, Dassault Systemes) software. The chip consists of 25 MNs (see Figure 4) arranged in 5 columns and 5 rows with dimensions of 10 mm × 8 mm × 0.5 mm. The dimensions of MNs are in the range of dimensions used for MN design in this work, with lengths from 150 μm to 1500 μm and widths from 50 μm to 250 μm[23]. Different authors have previously used this number of microneedles in patches for transdermal drugs with promising results [24,25,26].

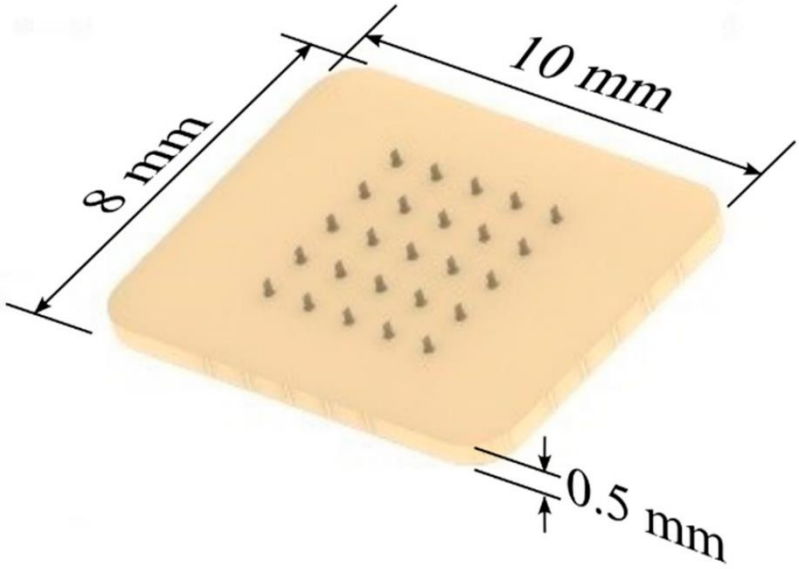
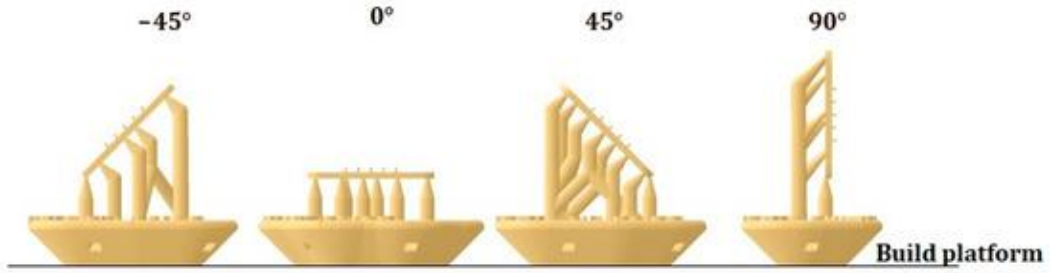


fig.4 Microneedle patch CAD model

The beveled tip design ensures that the most visible part of the MN penetrates the skin initially, allowing a microperforation that gradually expands as the MN is punctured, preventing the needle from clogging during the process.

MN Patch Manufacturing Process:

The 3D- printed transdermal patch was manufactured using Form2 SLA technology with a Class 1 resin evaluated according to ISO 10993- 1. The MN patch was modeled in SolidWorks and exported to Preform, the 3D printing preparation software. In this software, we configured the printing angle, support s, raft, and layer consistency. The printing angles of the corridor were −45 °, 0 °, 45 °, and 90 ° for the constitution platform, i.e., the angle between the plane of the patch base and the plane of the constitution platform(see Figure 5). The supports were generated manually with a touchpoint size of 0.30 mm and a viscosity of 1. The raft type was configured as a full raft with a thickness of 3 mm. Thinner layers reduce the stair- step effect, achieving better print quality on the part's exterior. For this reason, the chosen consistency was the minimum allowed by the form 2 printer with surgical resin. .



Fig(.5) printing angles concerning the build platform

After printing, the microneedle chip was immersed in 99% isopropyl alcohol for different periods (2, 4, 6, 8 and 10 min) to determine the optimal time for the process (Figure 6B). To do this, the process was repeated three times at different times; Washing for 2 min was not enough to remove excess resin. It was then placed in an ultrasonic cleaner for 10 min (Figure 6C); this is necessary because the patch eventually prints it with extra resin. After cleaning the chip with alcohol, it was left to dry for approximately 20 mins before the curing process (UV radiation) in Curing Mode for 30 mins at 60°C (see Figure 6D).

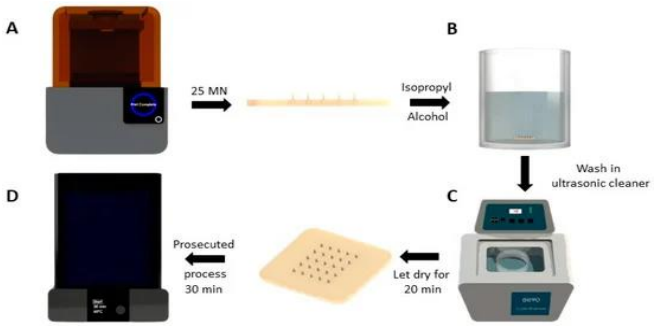


fig.(6) MN patch manufacturing process.

This method uses the ability of 3D printing to produce small structures to make micrometers of order efficient, repeatable and precise. A total of eight patches were printed, and further research is awaited to evaluate the printed details of the patches .

Limitations and perspectives:

Microneedles are a transdermal drug delivery system that is rapidly growing in exploration owing to the benefit of increasing patient access to drugs by replacing other routes of administration. Microneedles have been proven to improve medicinal stability and drug delivery efficacity through nonclinical and clinical studies. However, microneedles as a tool for drug delivery have limitations.

Limited medicine dose : Because of their small size, microneedles can deliver only a limited number of medications. Thus, their operation is delicate when a large cure or nonstop release of medicine is needed. To overcome this limitation, immediate limitations can be overcome by applying several patches at once or periodically changing the microneedle patch. However, for expanding the scope of microneedles in drugs, exploration is demanded on adding the medicine cure that can be incorporated in the microneedles.

Solubilization technology for poorly soluble drugs : It is an essential technology for solving the problem of small- dose microneedles. Principally, sufficient drug solubility in an waterless result is needed to apply the drug to a microneedle. However, because several drugs show low water solubility, only a small portion of the drugs can be delivered(Kearney etal. 2019)[27]. adding the solubility of a poorly soluble drug allows a large dose of the medicine to be contained in the same expression, enabling the objectification of advanced quantities of medicines in microneedles of limited size.The use of prodrugs for adding solubilization is a representative method for solubilizing inadequately answerable medicines. In addition, there has been a harmonious exploration on perfecting the solubility of inadequately answerable

medicines using surfactants or liposomes, swab medication of the medicine, pH adaptation, and nanoparticle control technology.

Sustained drug-releasing technology :Till date, exploration of microneedle- grounded medicine delivery has concentrated on demonstrating rapid-fire dissolution of medicine phrasings from microneedles into the body. Therefore, although microneedles are effective for single medicine administration, they have limitations in nonstop medicine delivery. To demonstrate sustained medicine release using microneedles, divisible microneedles have been developed. Since Chu et al. First developed divisible microneedles(Chu etal. 2011)[28],colorful studies on divisible microneedles have been conducted for minimizing the patch- wearing time through fleetly separating the expression from the microneedle.(Choi etal. 2018; Li etal. 2019a, 2019b). In addition, exploration is being conducted on introducing a sustained-release expression technology for enabling long- term medicine delivery of medicines separated from the microneedle into the body. Li etal. have developed a divisible microneedle to release contraceptive hormones and maintain their situations within the remedial range for roughly a month(Li etal. 2019a, 2019b). Through exploration of expression technology for long- term medicine delivery, colorful medicines can be applied to microneedle patches, and colorful incrementally modified medicines can be developed by enabling effective medicine delivery. In addition, it is necessary to develop an tenacious patch that does not beget toxin when wearing a microneedle patch for a long duration.

Fabrication technology: Microneedle master molds are primarily manufactured by deep reactive ion etching for fabricating the small microneedle tips, the size of which ranges over several knockouts of micrometres with high delicacy and reproducibility. Because the instrument and conservation are precious, the hedge to enter the field of microneedle exploration is high, and the technology of mass product has been limited to certain companies.

3 D printing : As the technology for 3D printing advances, microneedle manufacturing has been conducted using entry- position 3D printers. Because the price and conservation of 3D printers are affordable, they can be fluently employed for colorful operations. CAD software enables the design of new shapes of microneedles. 3D printing can significantly dock the product development time due to rapid-fire fabrication and revision of the prototypes. However, there is still a limit to the accoutrements that can be used, and the low resolution of entry level 3D printers remains a problem. Although there are high- resolution 3D printers, the instrument price is high. Nonetheless, 3D printing studies have continued to overcome the limitations. It is anticipated that the 3D printing technology will enable us to produce customized microneedle patches depending on individua lsymptoms.

Regulations :Currently, the licensing of microneedle products is reused for each operation rather than for a specific microneedle system(product-specific blessing). thus, the licensing of

microneedle products is delayed, which is a factor circumscribed in the commercialization of microneedles. To address this problem, a microneedle- grounded licensing regulation, including the shape, expression, sterilization, and packaging of the microneedle, must be defined. Through the junction of cGMP and quality control, a microneedle licensing system grounded in quality by design should be established to promote the commercialization of microneedle products as pharmaceuticals

.Convergence with digital technology : Current microneedles are designed as simple patches for delivering medicines; however, in the future, they can be developed as digital drugs through emulsion with information technology. Confluence systems that provides information on the medicine-loading quantum, patch- changing time, or rate of controlled medicine release can be developed.confluence technology can maximizie the medicine delivery operation of microneedles and diversifying the products.

Advantages& Disadvantages:

Advantages	Disadvantages
Improve drug delivery Drugs are delivered directly into the body through the stratum corneum. The onset of drug action is rapid An accurate drug dose is delivered by controlling microneedle formulations Microneedles avoid first pass metabolism. It is effective for vaccine delivery because of the abundance of immune cells in the dermis. Improve safety and patient compliance Microneedles are painless and safe because of their small length and size. The need for expertize is reduced for patch application. Microneedle patches reduce or eliminate biohazardous sharp waste. Improve the manufacturing process and cost saving The optimized solid-state formulation of the microneedles does not require a cold-chain system. Microneedle patches, which encompass the functionality of the drug, needles, and syringe, reduce the overall size of the drug package.	Drug dose is limited due to the small size of the microneedles. Temporary inflammation and allergy can occur. Sophisticated technologies are needed for manufacturing microneedle patch with a reproducibility. Microneedle patches need a storage container to hold the microneedle patches hygienically without damage during distribution from the manufacturers to the patients. When the solid microneedles are applied, some parts of the microneedles can be broken or remain in the skin.

Evaluation of the transdermal MN patches:

The developed patches were evaluated by performing the following tests.

a. Thickness: A Screw gage was used to determination the thickness of 10 selected patches. The thickness was measured at 5 different locations. Then average was calculated (Mounika et al., 2014).

b.uniformity of weight: Uniformity of weight was calculated by weighing the patches on a digital balance. The test was performed on 5 patches, and the average weight was calculated (Mounika et al., 2014).

c. Moisture content: For moisture content, a desiccator with fuzed calcium chloride was used. Patches to be evaluated were initially weighed and placed in a desiccator for 24 h. After 24 h, patches were reweighed and moisture content was calculated by subtracting the final weight from the initial weight with respect to the initial weight (Mounika et al., 2014).

d.moisture uptake: To maintaining 84% humidity in the desiccator, Potassium Chloride solution was placed in Desiccator. Weighted patches were placed in the above desiccator for 24 h. After 24 hrs, the patch was reweighed, and % uptake moisture was calculated by subtracting the final weight from the initial weight with respect to the initial weight (Mounika et al., 2014).

e.Enfolding endurance : Folding endurance was determined by folding the patch several times at the same time and at the same place till the patch broke. The number at which a patch folds without breaking gives the value of folding endurance (Mounika et al., 2014).

f.Water vapor transmission (WVT) rate:A glass vial is used as a transmission cell in which Calcium Chloride is placed, which acts as a desiccant. A film which to be evaluated was placed over the cell. This cell was weighed and placed in a desiccator filled with Potassium Chloride solution (saturated solution) to maintain the 84% RH.The glass vial was removed from the desiccator and reweighed after 24 h for a period of 72 h. The WVT rate was determined by the below formula (Mounika et al., 2014).

$$WVT = \text{Final Weight} - \text{Initial Weight Area}$$

g.Drug content determination: Approximately 100 ml solution of Phosphate buffer with pH 7.4 was used to perform this test. A patch with dimensions of 1 cm × 1 cm was cut and added to a buffer solution. Stirred the solution with a magnetic stirrer for 5 h, filtered the solutions, and drug content analysis was performed with dilution at 240 nm wavelength by using a spectrophotometer (Mounika et al., 2014).

h. In vitro drug release study: A glass diffusion cell was used to perform this test in which the receptor compartment had a capacity of 20 ml and the donor compartment had a capacity of 2 ml. The orifice had a diameter of 4 mm. The patch was placed over a semipermeable membrane attached to the diffusion cell. A solution of phosphate buffer with pH 7.4 was placed

i.In vitro skin permeation study: Franz prolixity cell were used in this study. The abdominal skin of the rat was fixed between the two chambers, which were the patron cube and the receptor cube.The receptor cube had a capacity of 20 ml and was filled with7.4 pH phosphate buffer.The patch was fixed to the skin. This setup was mounted on a stirrer. The receptor cube, Which was filled with Phosphate buffer, was stirred with a glamorous stirrer(temperature 32 Â±0.5 Â°C). The samples were taken out at different time intervals and the medicine content was analysed using spectrophotometer. After each sample pullout, an equal volume of buffer result was replaced every time. The graph between accretive quantum of medicine percolated and time was colluded(Mounika etal., 2014).

j.Skin irritation test : A skin irritation test was performed to check that the expression is free from any skin vexation. mainly Wistar rats were named for this study. One day before the trial, hair on The reverse of the rats were removed by trimming. 5 groups were prepared each of 6 rats per group and were treated one time in a day over a period of 7days.Group 1-Normal, Group 2- control(operation of commercially available expression), Group 3 â€“0.8 v/v waterless result of Formalin(Formalin was used as a standard irritant with attention of0.8 v/v.), Group 4-blank transdermal patch(without medicine), and Group 5-Transdermal patch with a medicine. The operation point will be estimated on the 8th day by the same investigator for erythema and edema(Oza etal.,2013).

k. In vivo studies Wistar albino rats(adult joker) were named, Which were importing an average of 230 to 250 g. These were kept at 25Â± 1- C and 55 Â± 5 RH with 12- hour alternate light and dark cycles. All the rules were followed as per the beast ethics commission guidelines.
The rats were placed in polypropylene coops with 4 rats in each pen and had free access to laboratory food(Ubaidulla etal., 2007, Patraetal., 2017).

l.Pharmacokinetic evaluation of patches on animals : Adult rats (Wistar Albino species) were selected for the bioavailability study, and the superficial skin was examined for any abnormality on the skin surface of the rats. Only 230 to 250 g weight of rats were selected, and shaving on the dorsal side was performed. Rats were kept under observation before application of the transdermal patches to avoid any unwanted effects of shaving. Rats were kept completely fasted during this period of time. Three groups were prepared. Group I was administered with the drug Carvedilol orally (5 mg/kg), Group II was administered the F6 formulation and group

III was administered the F7 formulation. The blood samples were taken out at various time intervals i. e. 2, 4 8 and 24 h. Before the analysis was done, plasma samples were centrifuged by centrifugation and stored in vials at −70 °C. The drug plasma concentration was measured using reverse-phase HPLC method. Chromolith column was used (column length: 100 × 4.6 mm, 2 µm), flow rate was 1.5 ml/min, Methanol: Acetonitrile: Phosphate buffer pH 3.0 (45:25:30 v/v) was used as a mobile phase. The injection volume of the sample was 10 µL. and retention time was 5.5 min.(Alexander et al., 2012, Gannu et al.,2007, Alkilani et al., 2015, Zsikó et al., 2019)

M.Efficacy in rats against hypertension: Initial blood pressure (BP) of rats was measured using a MUROMACHI MK2000ST with a non-invasive tail cuff and a digital BP display method. Initially, normal BP was measured. which was normal; Hypertension was induced by injecting Physostigmine 15 µg/kg/day intravenously for 2 weeks. Hypertension was induced after 14 days, and a mean BP of 150 mmHg was selected. Four groups (n = 5) were prepared for the rats. Group 1- no treatment (control), group 2- treated with Carvedilol 5 mg/kg orally, group 3 was treated with Carvedilol transdermal patch of Formulation F6 and group 4 treated with transdermal patch of formulation F7. BP of rats was recorded at various time intervals (1, 2, 4,6,10, 24 Hrs) (Fröhlich et al., 2015).

Conclusions:

The MN chip for transdermal drug delivery was fabricated from a biocompatible resin using an SLA 3D printer. The plugged internal holes were remarked by micro-drilling. The print quality was good because the appearance of the chip closely matched the geometry of the CAD model, indicating that this microneedle fabrication method has a significant contribution to device manufacturing. The simulation confirmed its dimensions, and the material was resistant to MN penetration into the skin. No structural deformations or irreversible damage was observed in the simulation when the force required to pierce the skin was used. The main goal is to increase penetration without causing pain. It may be difficult for the patient to insert the needle first and then the patch. The biggest problems associated with microneedling technology are skin allergies, redness and irritation.

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