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MICRONEEDLE PATCHES FOR TRANSDERMAL DRUG DELIVERY: A REVIEW

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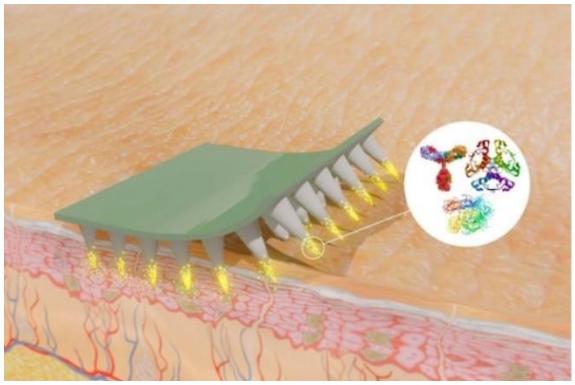
ABSTRACT

Most medicines cannot penetrate the skin at therapeutically useful rates, which has significantly hindered the success of transdermal drug delivery. It has recently been suggested that using micron-scale needles to increase skin permeability can significantly improve transdermal delivery, particularly for macromolecules. Microneedles of various sizes, forms, and materials have been created using the instruments of the microelectronics industry. Solid microneedles, which have been demonstrated to enhance skin permeability to a wide variety of molecules and nanoparticles in vitro, have been the focus of the majority of drug delivery investigations. Oligonucleotide delivery, insulin-induced blood glucose reduction, and protein and DNA vaccine-induced immune response stimulation have all been shown in in vivo experiments. In these investigations, needle arrays have been employed as drug carriers that release medication into the skin from a microneedle surface coating or to puncture holes in the skin to enhance transport by diffusion or iontophoresis. It has also been demonstrated that hollow microneedles can microinject insulin into diabetic rats. The ratio of microneedle fracture force to skin insertion force, or margin of safety, was determined to be ideal for needles with a small tip radius and a thick wall in order to address practical uses of microneedles. Human volunteers reported no pain when microneedles were put into their skin. All of these findings point to microneedles as a potentially useful technique for delivering medicinal substances into the skin for a variety of potential uses.

1. INTRODUCTION

Since methods created for the computer industry can now precisely create nano-scaled geometries, the fields of microelectronics and micromachinery are finding increasing usage in the medical area. The creation of microneedles for dermal and transdermal drug delivery that is, the delivery of medications into and through the skin, respectively is one use for these procedures. Microneedles are needle-like structures that can reach lengths of up to 1 mm and sizes in the micron size range. In order to facilitate (trans) dermal drug distribution, these structures are employed to puncture the epidermis.



1.1 Overview of transdermal drug delivery systems

These days, researchers can create microneedles with or without a bore, in a variety of sizes, shapes, and materials. Microneedles have been used to collect biological samples through the skin and to deliver drugs (trans) dermally. Microneedles' primary benefit is its non-invasive, painless skin piercing capability. Microneedles can also be included into "lab-on-a-chip" systems, which combine hollow microneedles with microsensors, micropumps, or both technology. These methods can be used to track the health of people with conditions like diabetes. The creation of minimally invasive, fully automated modules for continuously extracting and analyzing biological fluid and directly responding to the analytical results by delivering medications is the ultimate goal of "lab-on-a-chip" techniques. However, there are currently no (trans) dermal medication delivery devices available on the market that use microneedles. Following a brief overview of (trans)dermal drug delivery, this paper discusses several microneedle manufacturing processes and variables that affect skin penetration, including applicator use and microneedle shape. The various (trans)dermal drug delivery methods for solid and hollow microneedles are next explained. The topic of microneedles' (trans)dermal delivery of particular medication classes vaccines and therapeutic proteins is next covered. Finally, prospects are offered for the therapeutic application of microneedle-

based (trans)dermal medication delivery.[1]

1.2 Limitations of traditional transdermal methods

1.2.1 Drug Properties & Skin Barrier (Physicochemical Restraints)

- **Molecular Size of Drugs**

Generally speaking, therapeutic dosages of medications with a molecular weight more than 500 Daltons cannot be administered via the stratum corneum using conventional transdermal drug delivery systems (TDDS).

- **Dosage and Potency of Drugs**

The total amount of medicine that can pass through is restricted by the barrier. As a result, conventional patches are only appropriate for extremely powerful medications, usually those with a daily maximum dosage of less than 10 mg.

- **Solubility and Lipophilicity**

The medication must be sufficiently soluble in both hydrophilic and hydrophobic phases, necessitating a particular balance, usually indicated by a logP value in the range of 1 to 3 (or 1 to 5). There are restrictions on medications with low or extremely high partition coefficients.

1.2.2 Topical and Patient-Related Issues

- **Allergy and Skin Irritation**

Patient discomfort and non-compliance may result from the patch's ingredients (drug, adhesive, and enhancers) causing skin irritation, erythema, and itching at the application site.

- **Adherence and Beauty**

In addition to causing physical discomfort, prolonged patch adherence may jeopardize the prescribed dosage schedule if the patch comes off or is applied improperly.[2]

2. Microneedle Technology

2.1 Types of microneedles: solid, hollow, coated, dissolving

2.1.1 Solid Microneedles

Solid microneedles form microchannels and holes in the stratum corneum. In order for the drug to eventually migrate to the skin through the temporary microchannels, a drug formulation patch is subsequently applied to the skin. Using the "poke-and-patch" method, solid microneedles are made to administer drugs to the skin. This method allows pharmaceuticals in drug-loaded patches to be transferred by iontophoresis or diffusion,

depending on whether an electric field is provided. An alternate method is "coat and poke" when the stratum corneum is first treated with drug-coated microneedles. Since there is no drug reservoir on the skin's surface, the entire drug to be administered is found on the needle's surface with this method. The second tactic is also known as "dip and scrape," in which the microneedles are submerged in a solution of a medication or therapeutic substance, then scraped across the skin's surface, leaving the medication or therapeutic substance in the microchannels the microneedles created.[3,4,5]

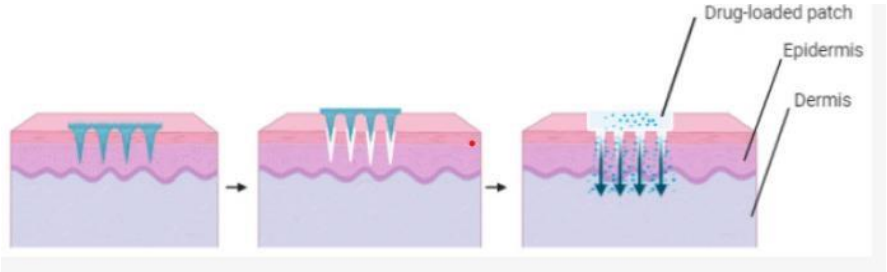


Figure 1: Transdermal patch application after the skin's microchannel pores are created using a solid microneedle device.

According to the literature, the first microneedle was created for in vitro intracellular administration and imprinted into a silicon wafer. According to reports, these microneedles were introduced into nematodes and cells to improve gene transfection and molecular absorption. Microneedles were subsequently created for use in transdermal medication administration. There are now several types of solid microneedles available. Solid silicon microneedles with the following measurements were created by Narayanan and Raghavan (2017) for optimal transdermal drug delivery: average height: 158 μm, base width: 110.5 μm, aspect ratio: 1.43, tip angle: 19.4°, tip diameter: 0.40 μm. Martin et al. (2012) demonstrated in a groundbreaking study that sugar mix solutions may be used to create sugar glass microneedles in a vacuum at a low temperature. The microneedles had the right amount of structural rigidity to effectively pierce human skin. According to a prior study by Cha et al. (2014), polydimethylsiloxane (PDMS) was micromolded to create a microneedle array of polylactic acid (PLA, a biodegradable polymer). A microneedle porous titanium array (TPMA) created by a process called modified metal injection molding (MIM) was demonstrated in another study. For two hours, TPMA was created at 1250 °C. Since TPMA's surface contained only titanium and oxygen, its biocompatibility could be guaranteed. The fact that TPMA can pass through the skin's surface without breaking or cracking was also underlined. The main idea behind microneedles is that they create tiny pores that help carry

medications straight to the epidermis or upper dermis with little damage to the skin's layers. The membrane barrier can then be broken down, allowing drugs to reach the systemic circulation through subepidermal blood vessels. Microneedles come in a variety of materials and shapes and range in height from 25 to 2000 μm. Microneedles for medical applications have been made from a range of materials, such as silicone, glass, metals, and non-biodegradable and biodegradable polymer polymers. The main factors that determine the strength, adaptability, and permeability of microneedles are their materials, which should be carefully selected based on the intended use. Numerous materials, including ceramics, metals, silicon, glass, and carbohydrates, can be used to make microneedle devices. The production of microneedles for transdermal medicinal delivery has investigated a number of materials with desirable properties, including enhanced biocompatibility and high mechanical strength. Metals, silicon, glass, ceramics, and polymers like carbohydrates are among them. Using FDA-licensed medical devices made of relatively inexpensive metals like titanium, stainless steel, and nickel, metal microneedles exhibit high mechanical strength and are simple to manufacture. Metal microneedles can be made by laser cutting, wet etching, metal electroplating, and laser removal techniques. Silicon is a material that is frequently utilized to make microneedles because of its exceptional qualities. Silicon is the main component used in micro-electromechanical systems (MEMS) because of its high mechanical strength and biocompatibility. Glass-based microneedles are excellent options for drug delivery applications due to their inertness, affordability, and speed of production. For many years, drug delivery has made use of ceramic materials. Drugs can be absorbed and diffused through porous ceramic microneedles as soon as they are inserted into the linked pores. The microneedles' inherent porosity allows them to fill medications without the requirement for an extra processing step. Microneedles made of carbohydrates such maltose, chitosan, trehalose, and starch can be created via micromolding. Micromolding and drawing lithography are frequently used in the production of microneedles based on carbohydrates.

There are several ways to create polymeric microneedles at room temperature, including as low-energy graph lithography, micro-injection, and tempering. Arrays of polymeric microneedles are very useful for administering DNA, proteins, medications, and vaccinations. With a network structure of polymer crosslinking and hydrophilic qualities, polymer-based microneedles can dissolve and swell. Microneedles can be made to deliver medications in a variety of ways using the materials covered above.[3,6,7,8]

2.1.2 Hollow Microneedles

Drug delivery from the patch reservoir to the microcirculation is made possible by hollow microneedles, which have a dosage capacity of up to 200 μL. This device functions similarly to a standard hypodermic syringe in many aspects. The tips of hollow microneedles have holes that can be filled with a medication solution. When the medication is injected into the tissue, it is instantly released into the epidermis or higher dermal layer. Hollow microneedles can also be used to transport large molecular weight molecules including proteins, oligonucleotides, and vaccines. Hollow microneedles are extremely difficult to make, and those with a high aspect ratio don't have the same internal support system as solid needles, which could lead to failure if implanted wrongly. Stress from improper handling of the patch assembly or unit during insertion and removal may cause the needles to fracture and fail. The majority of microneedle manufacturing techniques aim to reduce microneedle height and offer a more advantageous safety margin.[9,10,11]

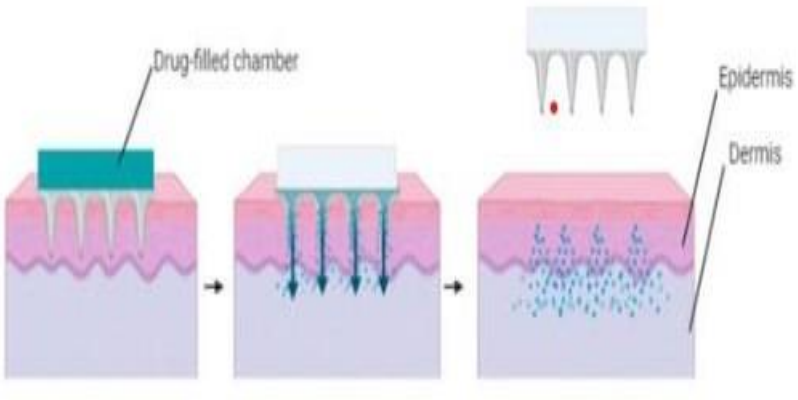


Figure 2: Hollow microneedles are used to illustrate poke and flow. Figure 3: Hollow microneedles are used to illustrate poke and flow.

Drugs can be delivered to the skin or other tissues through a particular pathway made possible by hollow microneedles. Similar to hypodermic needles, hollow microneedles help deliver liquid medications under pressure. Generally speaking, microneedles have the potential to develop into a very sophisticated medical device and monitor for skin penetration and corneal barrier rupture to the stratum corneum, which permits drug distribution into working skin layers and the drainage of bodily fluids. Only hollow MNs have made it to the market for medical devices, despite years of research and a variety of MN forms. The creation of porous ceramic microneedles that can administer medications at room temperature has advanced over the last few decades.[12,13,14]

2.1.3 Swellable and Dissolvable Microneedles

Swellable or dissolvable polymers are a new surface method in microneedle manufacturing. During the manufacturing process, the medication to be delivered is trapped inside the needle. The polymer that forms the needle's architecture breaks after it has penetrated the stratum corneum, releasing the medication that was confined. The advantage of dissolving microneedles inside the skin basically lowers the chance of needlestick injuries after application.

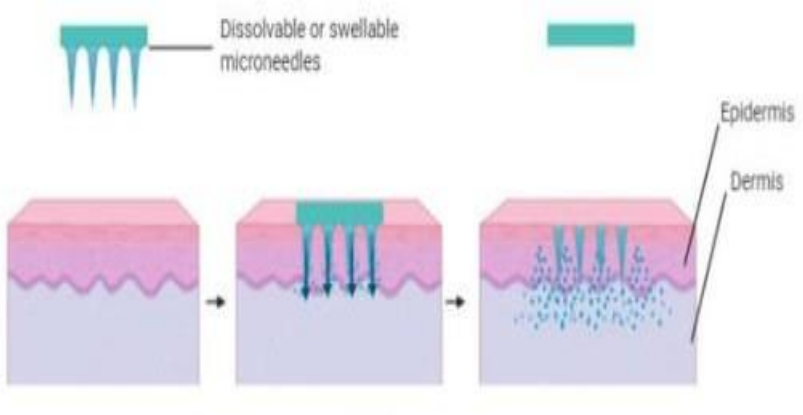


Figure 3: shows how to poke and release using swellable or dissolving microneedles.

According to Mikszta et al. (2009), swellable microneedles, microneedles that swell following skin puncture are more sophisticated and aim to get beyond the dissolvable microneedles poor yield limitations. The structure of swellable microneedle patches is based on a hydrogel, whose hydrophilic properties efficiently draw moisture from the surrounding tissue, causing the microneedle core to enlarge and create pores into which the medicinal material can spread. Using the baseplate as a drug reservoir that can transport the underlying microcirculation through the inflated microneedle structure is the strategy's primary advantage. Table 4 shows some recent developments in dissolving and swelling microneedle instruments with a wide range of medications and polymers. They are especially adept at eliminating interstitial fluid, which is a very inventive way to use the swelling mechanism.[15,16]

2.1.4 Microneedles with Coating

Sharp, micrometer-sized needle shafts that are fixed to a base substrate and have a medicine and water- soluble, inactive excipients applied to their surfaces make up a coated microneedle array. Coated microneedles are continuously being tested for the skin administration of various active materials, including peptides, viruses, small molecules, and microparticles. The

quality of coatings, the reproducibility of the coating process, and the effectiveness of drug administration are important considerations when using coated microneedles for drug delivery. In one investigation, immersing the microneedle patches in a coating solution allowed for the coating of both the base substrate and the complete array of microneedles. By employing particular coating techniques to restrict coatings to microneedle shafts exclusively, another study found increased delivery efficiency and decreased medication waste. A sharp, insoluble solid microneedle coated with active ingredients and water-soluble inactive excipients makes up a coated microneedle. When placed into the skin and subjected to interstitial fluids, the use of hydrophobic coating material facilitates the microneedle detachments. The excipients in the microneedle coating are dissolved by the interaction with aqueous interstitial fluids, and the detachment process subsequently takes place on the microneedle surface. The interstitial solubility of the coated excipients determines the rate of medication release within the skin. When the coating detachment process from the microneedle surface is finished, it is crucial to remove the microneedles from the skin. The activity of coated microneedles is shown in Figure.[17,18,19]

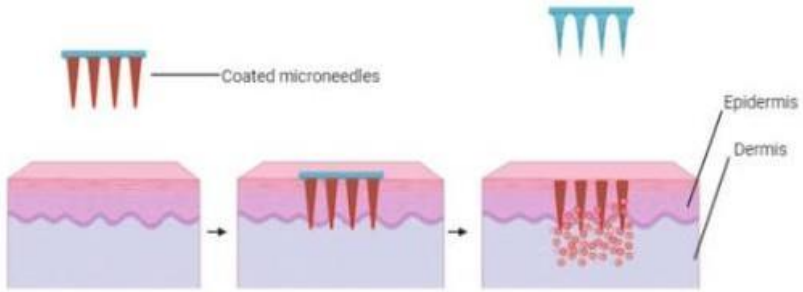


Figure 4: Coated microneedles are used to demonstrate "poke and release."

A micron-scale dip-coating technique can be used to coat single patches, arrays, or many microneedle patches. The microneedle array is submerged in a coating and removed at an ideal pace to create the microneedle coatings. According to the study, the microneedles' manual withdrawal speed from the coating solution was maintained at roughly 2 mm/s for film processing and 0.35 mm/s for pocket filling. Fluorescence or bright-field microscopy were then used to assess the coating uniformity. As previously said, despite being an outdated technique, dip-coating is still crucial for coating microneedles because of its simplicity of usage. However, the microneedle array substrate may be impacted by surface tension (which is common on the micron size) and its consequences, capillary and viscous forces, which could result in an unknown or reduced amount of medicine. In a different investigation, a thin

drug formulation film with a solution layer of about 200 μm was produced by uniformly applying the coating fluid to the surface of a roller with a diameter of 10mm. The cut-off device was then linked horizontally to the microneedles. The microneedles' tips were 50 μm shorter than the device's top. The roller revolved at a linear speed of 0.3 cm/s and was situated at the top of the apparatus. The coating fluid adhered to the microneedles' tips while they rotated. The produced microneedles were frozen after being vacuum-dried.

Additionally, the paper described a dip-coating method using microneedle plates and 3D produced fittings. Before being 3D printed, the desired fixtures and microneedle plate were initially developed using Auto CAD software (Autodesk, Mill Valley, CA, USA). The polylactic acid microneedles and the solvent were separated using a polyformaldehyde plate. A computer-connected microscope was used to carefully monitor and regulate the microneedle shafts as they were dipped into the reservoir to create the coated microneedles device. The portable holder descended at a rate of 10 mm per minute during the fabrication process until it came into contact with a coating solution from a reservoir. After being submerged, microneedles were moved at a constant 10 mm/min. After disassembling the fixtures, the coated microneedles were examined under a microscope, vacuum-dried, and frozen.[20,21,22]

3. Mechanism of Action

The diffusion mechanism is followed while administering the medication topically. The skin is momentarily disturbed in the microneedle drug delivery device. To administer enough medication to provide the necessary therapeutic response, a microneedle device is created by arranging hundreds of microneedles in arrays on a tiny patch, similar to a typical transdermal patch on the market. It avoids the barrier layer by penetrating the stratum corneum. The medication is applied directly to the epidermis or higher dermis layer, where it enters the systemic circulation and, once it reaches the site of action, exhibits a therapeutic reaction.[23]

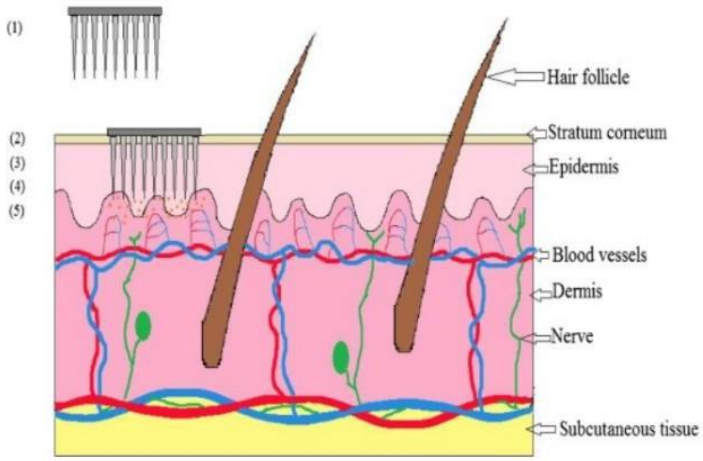


Figure 5: Delivery of drug from transdermal route [skin]

- Penetration: The stratum corneum and epidermis are penetrated by a variety of micron-sized needles, which are usually 1–100 um in diameter and hundreds of um in length.[24]
- Bypass of the Barrier: This penetration makes microscopic holes (microchannels) big enough to let the medication reach the skin's viable layers (upper dermis and/or epidermis), where it can act locally (for localized treatment) or be absorbed into the systemic circulation (for systemic delivery).
- Drug Delivery: Depending on the type of MN, one of the techniques listed below is used to distribute the medication into the skin.[23]

4. Advantages and Applications

Compared to traditional transdermal patches and hypodermic injections, microneedles have the following major advantages:

- Minimal Invasiveness and No Pain: They cause little to no pain and no bleeding because they pierce the stratum corneum but avoid the nerve fibers in the deeper dermis layer. Patient compliance is significantly increased as a result.
- Bypassing the Stratum Corneum: They enable the transdermal administration of hydrophilic medications and macromolecules (such as proteins, peptides, and nucleic acids) that are unable to passively penetrate the skin by overcoming the skin's strong barrier function.
- Self-Administration: Patients can effortlessly self-administer the medication thanks to the patch-based design, which streamlines the administration procedure.[25]
- Preventing First-Pass Metabolism: Similar to other TDD systems, they transport the medication straight into the bloodstream, preventing first-pass metabolism in the liver and

gastrointestinal breakdown, which increases bioavailability.

- Enhanced medication Stability: The medication is contained in a stable, solid form for some formulations (such as solid-state coated or dissolving MNs), which frequently removes the need for a cold chain for shipping and storage.[26]
- Decreased Biohazardous Waste: The sharp waste that comes with traditional needles is totally eliminated by dissolving MNs.[27]

MNs are appropriate for a variety of biomedical applications due to their efficiency and adaptability:

- Vaccine Delivery (Vaccination): MN patches are a particularly efficient way to provide vaccines, such as those for measles and influenza. The epidermis and upper dermis' abundance of immune cells boosts the immunological response (immunogenicity).[28,29]
- Pain management: Analgesic medication used locally.
- Diabetes Management: Used for minimally invasive glucose monitoring and insulin administration.[30]
- Systemic administration of therapeutic peptides, proteins, and hormones for the management of chronic diseases.
- Cosmetics/Dermatology: MNs administer medications and cosmeceuticals (such as those for wrinkles, acne, scars, and hair loss) straight into the targeted skin layer for targeted treatment.[31]
- Chemotherapeutics or immunotherapies are delivered locally to tumors in or under the skin as part of cancer therapy.[32]

5. Preclinical and Clinical Evaluation

- **In vivo studies**

The Gazi University Ethics Committee gave its approval to the animal study (approval number: G.U.ET-20.021). The study used Wistar Albino rats weighing between 300 and 350 g. Throughout the investigation, the animals were kept in regular laboratory settings at a temperature of 25 ± 2 C with a 12-hour light:12-hour dark cycle. One intraperitoneal dose of streptozotocin (STZ) (60 mg/kg) caused diabetes. Just prior to injection, STZ was dissolved in freshly made 0.01 M citrate buffer pH 4.5. Five days later, a glucose meter was used to assess blood glucose levels from tail vein blood samples in order to confirm diabetes. Rats were classified as diabetics if their fasting blood glucose levels were 300 mg/dL or more (Wang et al. 2012, Bulboaca et al. 2019). The mice were split into

four groups at random: subcutaneous (0.3 IU insulin), 1 mm MN (0.3 IU insulin), 2 mm MN (0.3 IU insulin), and control (no therapy applied). Each rat's dorsal portion was used an animal hair clipper to shave prior to the testing. The animals fasted for six hours during the experiment and had unlimited access to water and food (standard pellets). To release insulin, MNs coated with insulin were gently rolled against the skin for one minute. A glucose meter was used to assess the blood glucose levels after blood samples were drawn from the tail vein at prearranged intervals.[33]

- **In vitro studies**

The paddle over disc method was used for in vitro drug release investigations. Dry films of a given thickness were cut into circles, weighed, and adhered to a adhesive-coated glass plate. After that, the apparatus was calibrated to 32°C ± 0.5°C and the plate was submerged in a 500 mL phosphate buffer (pH 7.4). After that, the paddle was positioned 2.5 cm away from the glass plate and run at 50 rpm. Samples (5 mL aliquots) were taken out at the proper intervals for up to 12 hours, and a double beam UV-visible spectrophotometer (Elico SL159, Hyderabad) was used to measure the drug content at 264 nm. The mean value was computed after the experiment was conducted in triplicate. Permeation enhancers such as oleic acid and tween 80 were added to the F17, F9, and F5 formulations based on physicochemical characterization and drug release patterns. Pig ear skin was used in ex vivo diffusion trials for each of the six formulations.

- **Microscopic images of transdermal patches**

An electronic microscope equipped with a digital camera was used to view microscopic images of each formulation in order to assess the uniform dispersion of drug and polymer as well as the surface of the films that were created.

- Transdermal patches were assessed for their physicochemical properties in addition to microscopic analysis. The thickness The manufactured transdermal films' thickness was measured at five distinct locations using a screw gauge with the least count, and the average was computed using an SD.
- A strip of film was repeatedly folded at the same spot until it began to break in order to assess the folding endurance of patches. It is calculated as the number of times the film is folded in the same spot until it breaks or shows visible cracks.
- Variation in weight : Ten randomly chosen patches were weighed independently in order to subject the patches to weight variation. It was determined what the average was.

- Homogeneity of drug content: To extract the drug from the patch, each patch from several formulations (1 cm2, or 25 mg of drug) was dissolved in phosphate buffer (pH 7.4) and constantly agitated for a full day using a magnetic stirrer. Following filtering and phosphate buffer dilution, the percentage of drug concentration was determined using spectrophotometry at a wavelength of 264 nm.[34]

6. Conclusion and Future Directions

Numerous compounds have been successfully delivered transdermally in a variety of forms and configurations. The range of drugs that can be successfully administered transdermally can now be greatly expanded. This will significantly boost the market for transdermal delivery, which will become increasingly important as the number of innovative medications keeps growing. Small-scale clinical trials have demonstrated the appealing features of microneedle-based devices, including low discomfort, minimal invasiveness, mild inflammation, if any, and complete skin regeneration in a matter of hours. Closure delivery systems may become important in the monitoring of non-invasive medicinal medicines and analytes. Further development may also make advantage of microneedle technologies. Focus group assessments identify critical areas for technological improvement that the Microneedles Ideology needs to investigate. This guarantees that every patient will use repeatable microneedles and that the insertion was successful. In order to commercialize their unique microneedle-based solutions, a significant number of small and large industrial firms are presently conducting clinical trials. Future studies will address any regulatory concerns pertaining to the use of microneedle devices and create strategies to guarantee dependable, inexpensive methods of producing microneedles in large quantities. Overall, the market for microneedles appears to have a bright future due to the basic modern knowledge feed industry's explosive rise. It is anticipated that technological advancements based on microneedles would eventually improve disease detection, diagnosis, and treatment while simultaneously improving the health-related quality of life for patients all over the world.

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