A Comparative Study of Micro-needle Patches and Hydrogel Patches for Acne

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Abstract

The current study's objective is to compile the various preparation and characterization techniques for hydrogel and microneedle patches with respect to the treatment of acne and to arrive at which one produces the best outcome. An inflammatory condition called acne vulgaris affects the sebaceous unit of the hair follicle. Usually persistent, it gets better on its own. Stress, smoking, youth, and comedogenic substances including halogens, androgens, corticosteroids, and pore-clogging cosmetics can all contribute to increased acne formation and severity. In addition to topical treatment methods consisting of ointments, gels, and creams, hydrogel patches report to be efficacious since they can stick to the affected area for a longer duration of time, and hence prolonged action of the incorporated drugs is possible. Hydrogel patches prevent secondary infection, owing to their hydrocolloid adhesives property. Microneedle (MNs) patches are a type of topical and advanced dosage form which falls under this type of formulation used for better efficacy in the treatment. This system with a network of microscopic needles makes a pathway for therapeutic compounds, including (bio) macromolecules, small molecules, and nanoparticles, to travel through the skin.

Keywords: Acne, Hydrogelpatches, Microneedle patches, Formulations, Comparison

1. Introduction

Acne is a long-lasting inflammatory skin condition characterized by nodules, papules, pustules, and comedones. It is a widespread issue that many teenagers face. Increased sebum production and inflammation are two factors in the multifactorial etiology of acne. Pilosebaceous follicles are colonized by Propionibacterium acnes, which play a significant role in the inflammatory response [1].

There are different types of acne which are **Comedones** (whiteheads or blackheads) or papules, which are the most common types of acne lesions or clogged pores, which are the first category of acne. Because the clogged pores remain beneath the surface or are known as closed comedones, **whiteheads** are white lumps. **Blackheads**, on the other hand, are open comedones that have a blackish hue on the skin's surface. However, the air's reaction with too much oil, not dirt, is what gives the object its black color. **Pustules** (pimples) are pus-filled lesions that are white or yellowish in color and red at the base. Acne nodules are more severe acne lesions that cling to the deeper skin layers, are uncomfortable and leave scars. Additionally, cysts are like nodules in that they are painful, pus-filled tumors that can induce scars [2].

2. Acne treatment

Teenagers are frequently affected by acne, hence many scientists are focussing on various acne treatment solutions. The term "acne patch" refers to a recent advancement in topical acne therapy. But till date, no reports were identified on acne patches. Consequently, this review is focussed to compare the different types of acne patches which are shown in **Table.1** [3].

Table.1 Acne treatment based on the severity of acne

TYPE&AVTIONS	**CLINICAL OUTCOMES**
I- MILD	Acne that is open and closed, with inflammation pimples and pustules on occasion.
II-NORMAL	Moderate Papules and Pustules, mostly on the Face
III-INTENSE	There are numerous papules and pustules on the chest and back, as well as a few inflammatory nodules on occasion.
IV -EXTREME	Very Bad Numerous sizable, uncomfortable nodules and pustules

Acne is commonly treated with topical medications, systemic medications, physical therapy, laser therapy, and photodynamic therapy. For mild to moderate acne, topical treatment is the norm. Retinoids, the cornerstones of topical acne treatment are antibacterial like benzoyl peroxide and antibiotics. A topical therapy might irritate the local region while preventing future sores [4]. Because they have the unintended side-effect of drying up the skin, gels, pledges (medicine pads), washes, and solutions are frequently used on oily skin. While lotions, creams, and ointments can be applied to dry skin, there is a higher chance that they will cause irritation.

In the early days of topical medication, patches were frequently employed as the transdermal delivery mechanism, including nicotine patches for smoking reduction and cessation aids,

scopolamine patches for the treatment of motion sickness, and fentanyl patches for the treatment of pain. Drug candidates that are suited for transdermal distribution have been identified over time, for use in cosmetics, for instance [5].

3. Treatment for acne with patches

There are several types of patches for delivering transdermal routes, There major 3 types of patches for Acne are as follows and shown in **Fig.1** [6].

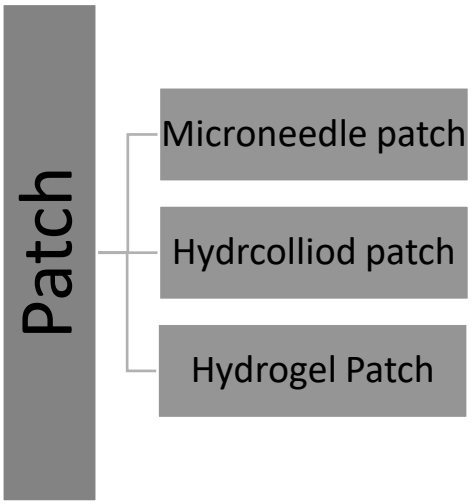

Fig.1 Title Treatment for acne with patches

4. Hydrogel patches

Hydrogels are explained in an enormous way by investigators over decades. Hydrogel, a cross-linked, Hydro-swelling macromolecule network produced by the simple reaction of one or more monomers, is the most well-known of these [7].

It is a polymeric substance, according to another explanation, that can expand and can store enormous amount of water inside its structure without dissolving in it. Hydrogels have sparked in the light over the last fifty years because of its potential in a wide range of applications. Because of their high-hydro content, they have flexibility that is very similar to that of natural tissue [8]. The ability of hydrogels to intake water is because of its hydrophilic functional groups linked to the gel's polymeric structure, whereas their resistance to disintegration is due to cross-links between network chains. Many organic and synthetic materials fit the definition of hydrogels [9].

Hydrogels are two- or multi-component systems made of water that fill the gap between macromolecules and 3D network of polymer chains. In an equilibrium state, these structures can hold varying amounts of water depending on the properties of the polymer(s) used as well as the type and density of the network joints; usually, in the hydrated form, the mass fraction of water in a hydrogel is much higher than the mass fraction of polymer [10]. To get considerable amounts of swelling in real life, it is typical to use synthetic polymers that are hydro soluble in their uncross-linked condition. To make hydrogels, several "traditional" chemical procedures can be applied.

Due to its special qualities, the creation of hydrogel-based patches has recently received a lot of attention. Most hydrophilic polymers used to create hydrogels can store a significant quantity of water, up to 1,000 times their dry weight, ranging from 10 to 20% [11]. Hydrogels are a good dosage form for topical use due to the significant amount of water they contain, which plays a critical role in the suppleness and moisturization of the skin. Either synthetic or natural polymers can be used to create these hydrogel patches. The regulated drug delivery provided by hydrogel base patches over a predetermined period increases their significance and acceptability which is shown in **Fig.2** [12].

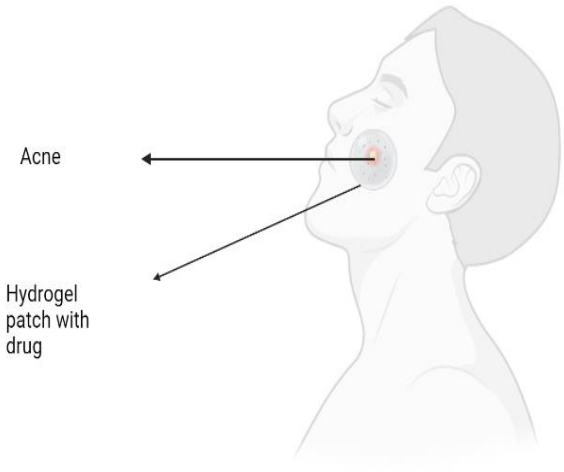

Fig.2 Hydrogel acne patch on the spot

5. Preparation of Hydrogel patches

According to the sources we read, there are numerous ways to prepare the hydrogel patch for acne treatment.

Pectin/gelatin dispersion combinations were created and refined to create the hydrogel patches, as shown below. A particular weighted quantity of pectin powder was first dissolved into the water to produce pectin polymeric dispersion (2-6%, w/v) in millipore water. To achieve the highest clarity and total hydration of the pectin, the powder was sifted into mechanically stirred water that was being agitated at a high rate (300 rpm). After adding the powder, the speed was reduced to 50 rpm and left for a night. The pectin dispersion was then filtered four times through pharmaceutical-grade cellulose Durapore membrane filters with reducing nominal pore sizes: 5, 1.2, 0.8, and 0.4 m, with a SS (Stainless steel) barrel, base, Filter support screen, Top Cap, and Tubing Adapter. EtOH was added to the filters before filtration to increase the stability of the pectin and reduce its microbial charge. The filtrate was collected and put into polycarbonate bottles. The rate of filtering was set to very low values (Typically 10 mL/min) to promote more interaction between the product and filters.

Before adding gelatin powder, the pectin dispersions (Purified) were kept at 60 °C and magnetically agitated (300 rpm). The resulting polymer mixture was then filtered through a disposable sterile syringe filter (0.22 m pore size) to eliminate air bubbles created during the stirring and filtering procedures, and the filtrate was then held under a vacuum for 15 minutes at 60ºC. Each of the 24 multiwell culture plates' 2.4 cm diameter dishes were then filled with two millilitres of the degassed dispersion. Gelatin is frequently completely dissolved in 30 minutes (Corning Incorporated, The hydrogel patches were created in two steps, with gelatin and pectin triggering the ionic and thermal gelation processes, respectively. The first stage involved keeping the polymeric dispersion-containing multiwell culture plates at 5 °C for 24 hours. The hydrogel patches were created in two steps, with gelatin and pectin triggering the ionic and thermal gelation processes, respectively. The first stage involved keeping the polymeric dispersion-containing multiwell culture plates at 5 °C for 24 hours. The patches underwent a second gelation by being coated with 2 mL of a (Barium chloride) BaCl2 1.5% (w/v) solution after initial gelatin gelation led the patches to partially consolidate. After the gelation had finished (3 hours), barium chloride was withdrawn using a pipette, and prepared patches were then kept in BaCl2 0.5% (w/v).[13] In this approach for making hydrogel patches, barium chloride was used to crosslink the polymers utilising the thermal gelation method. The following are the three methods for inserting medications into the patches:

Method #1 involved adding gelatin/pectin polymeric dispersion mixture that was held at 60 C and swirled magnetically in the rpm of 300 with a drug powder that had been coarsely pulverised (with a mortar and pestle) at a concentration (Conc)of 5 mg/mL.

Method #2 involves preparing gelatin/pectin polymeric dispersion mixture at 60 °C and 100 L/mL, then mixing the dissolved drug solution with the appropriate solvent. The drug was solubilized in a suitable solvent at a concentration (Conc) of 50 mg/mL.

In **Method #3**, Using a Nikon SMZ 1500 Stereomicroscopy equipped with a digital camera, the testosterone-loaded patches analysed microscopically after being administered to the developing patches after being initially dissolved in a BaCl2 solution that was being used as a gelling agent [13].

The assessments and findings based on this method of hydrogel patch preparation were as follows:

5.1. *In vitro* release studies

Testosterone was released from the hydrogel *in vitro* utilising a dissolving test of transdermal patches and a paddle apparatus with an extraction cell for solid oral dose forms (Ph. Eur. VII Ed.). The cell's core forms a hollow with a diameter of 27 mm and a deep of 2.6 mm to retain the hydrogel patch. A 3.14 cm2 release surface is produced by covering the cell with a cover having a 20 mm central opening. The cell's cover is facing up, and it is positioned at 25.0 2.0 mm from the paddle blade at bottom of the vessel. The test performed in sink circumstances, at 100 rpm and 32.0 0.5 C, used water/dry ethanol solution (80/20 w/w), as the dissolution medium. At regular intervals, 2 mL of the sample was withdrawn out of the vessel and replaced with the amount of brand-new dissolving medium. A UV-vis spectrophotometer was used to calculate the drug concentration in the samples. To produce a drug calibration curve in the dissolving media, an 80/20 water/ethanol solution was utilised as the blank (max = 249.0 nm, r = 0.9991). Outcomes are displayed as the average of three measurements, and an error is indicated by the standard deviation (SD) [13].

6. Transdermal hydrogel patch with triclosan:

The equation was extracted from a citation in the text,

Triclosan (TS) bacterial inhibitor, Transcutol (TC) triclosan 'solvent SPA and dihydroxy aluminum amino acetate (DDA) Emollient, stabilizing agent, emulsion stabilizer, gelling agent, Polyacrylic acid Emulsifying, stabilizing, and emulsion-stabilizing agents, Tartaric acid Agent of acidifying, Glycerin is a cosolvent, emollient, humectant, and antibacterial preservative, Carboxymethylcellulose (CMC, sodium salt) (CMC, sodium salt) enhancing agents viscosity; stabilizing agent [14].

A polymer is typically utilized as a hydrogel basis to create hydrogel patches because of its hydrophilic and drug-release capabilities. Sodium polyacrylate (SPA) and carboxymethylcellulose serve as the polymer matrix (CMC, sodium salt). Transcutol CG (TC, diethylene glycol monoethyl ether) is one of several other compounds that exist in addition to those mentioned above [15]. TC has a high solubilizing capacity, is non-toxic, and is biocompatible with skin, making it a possible transdermal permeation enhancer. According to reports, it can also boost topical application chemical skin accumulation without also improving transdermal penetration. Specifically, the rate of the cross-linking reaction must be modest and the compaction process cannot be finished before the fluid gel from the polymer is put into the film in order to achieve a semi-solid thin layer [16]. This approach is known as in situ gelations. Hydrophobic antibacterial triclosan diffuses effortlessly through the lipid skin layer. The patch can be effective on both the skin underneath and the skin around it, according to the results of the *in vitro* antibacterial test. It has been demonstrated that adding TC to this patch formulation increases the amount of triclosan that accumulates in the skin without also increasing transdermal penetration. Additionally, it has been demonstrated that this patch sticks effectively to facial skin and that it may be removed from the skin without hurting [17]. Therefore, it can be inferred that the patch model used in this study can be used to treat acne on the facial skin [18].

The assessment study was carried out by the cited literature, and after the drug passed the stability test, it assessed the drug release,

The accelerated stability test is used, by way to conduct a 6-month stability test on the transdermal patch at the following temperatures and relative humidity levels: 40°C and 75°RH to confirm the presence of the stability potential of the drug in the best-optimized formulation.[19] A diffusion study was used to measure the concentration of active components released after being stored for 6 mo. Visual observations were also done as part of the stability test. Shape, clarity, smoothness, homogeneity, viscosity, uniformity, and flexibility are all aspects of visual observation [20].

According to the findings of these tests, the hydrogel transdermal patches had a stable pH after 6 months of storage. At 40C/75% RH, the total amount of released pharmaceuticals remained steady for 6 mo, while the full drug release curve only slightly changed at 72 h. Visual observation was also done, and the optimized transdermal patch's visual attributes—particularly its shape, transparency, smoothness, homogeneity, viscosity, and flexibility—did not alter during the analysis [21]. The improved transdermal patches ATR curve holds steady while being stored under accelerated pressure settings.

6.1. The following technique provides information about liposomal-loaded hydrogel using DOE,

Reverse phase evaporation was used to create (Cryptotanshinone)CPT-loaded niosomes. Diacetyl phosphate (0.1 mg), Cryptotanshinone (dissolved in 1 ml of anhydrous ethanol), and chloroform were also added to a dry fifty ml RBF. To form an organic phase, the mixture then sonicated, period of 30 seconds at 80 W. Dropwise additions of phosphate buffered saline (PBS) solution which containing Tween 80 were made to the organic phase (pH 7.4). The mixture was sonicated at 50 W for an additional 10 minutes to form an emulsion [22]. Following that, the organic solvent was removed by a rotary evaporator running under vacuum at 50 °C and 15 rpm. The light-yellow solution of niosomes was discovered, and they were left for a night at 4°C for growth before being employed for analysis [23].

Design-Expert V8.0.6 was employed to produce niosomes with the best entrapment efficiency and lowest size of the particle. A 3-factor, 4-level central composite design (CCD) was used for the optimization, and Table S1 lists the variables and results. The volume ratio of chloroform to PBS, the molecular weight of CPT, and the molar ratio of cholesterol to Tween 80 were the three variables that were set. Each factor was given four different levels, and each variable was analysed at five different coded levels (1.68, 1, 0, + 1, + 1.68) each. The molar ratio of cholesterol to Tween 80 ranged from 0.5 to 4, and the combined weight of both compounds was kept at 71.2 mg. CPT had a molecular weight that varied between 0.2 and 0.6 mg. Chloroform was added to PBS at a volume ratio of 1-4 while keeping the overall volume constant at 22 ml. The evaluation of CPT-loaded liposomes particle size (Y1) and encapsulation effectiveness (Y2) is then given below **Table.2** [24].

S. No.	Size (nm)	Polydispersity index	Zeta potential (mv)	EE (%)
1	147.3 ± 0.71	0.12 ± 0.009	− 28.20 ± 1.50	67.12 ± 0.50
2	145.5 ± 1.62	0.127 ± 0.001	− 31.36 ± 3.22	70.78 ± 0.57
3	133 ± 0.84	0.125± 0.003	− 30.12 ± 1.57	69.68 ± 0.29
4	147.7 ± 1.25	0.145 ± 0.003	− 26.33 ± 2.44	63.29 ± 0.83
5	178.7 ± 2.14	0.205 ± 0.183	− 27.73 ± 2.65	45.22 ± 1.23

Table.2 Studies on the EE, Zeta Potential, and particle size persistence of the enhanced Cryptotanshinone-loaded niosomes.

Size Of the nanoparticles, Pdi Index, Zeta Potential Measurements, PH, Rheology, and other methods were later used to evaluate this research. Skin irritation, *in vitro* cytotoxicity, *in vivo* anti-acne activities and penetration mechanism investigation, statistical analysis, *in vitro* CPT release.

In this study, a novel topical delivery system for the treatment of acne was created using 3DP-CPT-NH. Niosomes with optimized CPT loading demonstrated good CPT encapsulation efficiency. When 3DP-CPT-NH was being created, the formulated CPT-NH demonstrated noticeable printability, allowing for easy customization of the drug doses, size, thickness, or area using a semi-solid extrusion process [25]. It was found that the *in vitro* release behaviour of 3DP-CPT (Cryptotanshinone)-NH adhered to the Korsmeyer model. accelerated skin

hydration, sizable inter-corneocyte SC gaps, and altered lipid bilayer architecture may all be contributing factors to the positive benefits of the study, which included improved transdermal performance and CPT (Cryptotanshinone) deposition in the epidermis. More importantly, it efficiently lessened acne without causing skin irritation. Overall, 3DP-CPT (Cryptotanshinone)-NH is a strong and promising topical administration technique with a tonne of potential for the usage of personalised acne treatments [22].

6.2. The following procedure involves creating proniosomes using the slurry approach.

(TRT) Tretinoin, which is derived from vitamin A, it is a well-known retinoid that is used to treat psoriasis, cutaneous lupus erythematosus, skin cancer, and acne (Laszlo & Fenske, 1998). Topically applying vitamin A reduces wrinkles, speeds wound healing, and protects the skin from UV (ultra violet) rays. Topical TRT prevents follicular unit obstruction and manages pilosebaceous unit keratinization. [26]. As a result, (TRT) Tretinoin is the most effective treatment for comedonal acne. Despite their effectiveness in treating acne, some people find the side effects of retinoids, such as TRT (all-trans-retinoic acid) and the retinoic acid acidified version of vitamin A, intolerable. Retinoids can irritate the skin, especially when they used for first time [27].

In 20 ml of dichloromethane, accurately weighed cholesterol, surfactants, and TRT (Tretinoin) (**Table.3**) were dissolved. Sorbitol's weight to overall content ratio (surfactant: cholesterol content) was 1 g/mol. A rotary evaporator flask of 100 ml was filled with sorbitol powder, and a vacuum was applied until the powder was dry and free-flowing. In the rotary evaporator flask, the organic solution was combined with the dry powder, which was composed of determined amounts of TRT (Tretinoin), surfactant, and cholesterol were dissolved in dichloromethane. The water bath was kept at 40 2 C [22]. The vacuum was maintained while the spinning speed was set to 100 rpm until the dichloromethane was gone. The free-flowing proniosomal powder was then removed and refrigerated at 8 degrees Celsius. To create the noisome dispersion, the proniosomes were hydrated in 100 ml of distilled water at 60 C [28].

	Transdermal patch	**Hypodermic needle**	**Microneedle**
Description	The skin will be covered with a sticky patch.	With a small hole at the end of a fine, hollow tube with a sharp point	On the surface of a tiny patch, needles aligned at the micron scale.
Onset of action	Less	More	More
Pain	NO	YES	NO
Bioavailability	Less	Enough	Enough
Patient compliance	Better	Reduced	Better
Self-administration	YES	NO	YES
Mechanism of drug delivery	Drug must pass the stratum corneum barrier, which causes big molecules to diffuse poorly.	immediately inserting a drug into the dermis	Drug applied to the epidermis directly without passing through the stratum corneum, increasing permeability

Table.3 Comparison of the medication delivery methods using transdermal patches, hypodermic needles, and microneedles.

Characterization of the generated properly hydrated TRT proniosomal dispersions

- Transmission Electron Microscope (TEM)
- Vesicle size analysis
- Entrapment efficiency
- In-vitro release studies
- Differential scanning calorimetry (DSC)
- Data analysis

7. TRT-based proniosomal hydrogel preparation

A potential formula N8 with 0.025% TRT contains an appropriate vessel size, the maximum entrapment effectiveness, and a high percentage of drug released after 5 h was chosen based on the characteristics given above and the outcomes of the major impacts of the adopted factorial design. By mixing 1% (w/w) Carbopol 934 into the chosen N8 hydrated proniosomal formulation while stirring magnetically at 800rpm, N8G created. Up until the carbopol was distributed, stirring was continued. A solution of triethanolamine was used to neutralize the dispersions. For comparison, a hydrogel formulation containing 0.025% TRT (Tretinoin) dispersion (TG) was created [28].

Following this **skin irritation** test was carried out as followed,

The study followed the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutics for Human Use Guidelines for Good Clinical Practice and the Helsinki Declaration (Declaration of Helsinki-Current, 2013). (European Medici Association, Good Clinical Practice Guidelines). This study included ten healthy people ranging in age from 23 to 40. After being educated on the study's procedures, all volunteers provided written informed permission before the operation began. Each participant was given a single dose of 0.3 g of all formulation (N8G, TG, and the product which were marketed) over a 5 cm2 surface area on the forearm [29]. Completion of 6 hours, the test specimen was rinsed with tap water, and any visible changes, such as erythema, were noted (redness). The vision of Researchers Draize (Campbell & Bruce, 1981), the mean erythemal ratings (ranging from 0 to 4) were recorded, with 0 indicating no erythema, 1 indicating a little erythema, 2 indicating a moderate erythema, 3 indicating a moderate to severe erythema, and 4 indicating severe erythema.

7.1. Clinical assessment of the chosen formulas

7.1.1. Study participants

The study was carried out selecting Twelve participants in all were chosen for the trial because they had clinically proven acne vulgaris lesions on their faces.

When the number of papules, closed comedones, and open comedones decreased at the follow-up, an improvement for each treatment was noted. Any decrease in the count of lesions was estimated in accordance with the amount and severity of lesions counted during the initial check and was treated as a percentage reduction [30]. Each group of patients had their weekly means and standard deviations of this percentage% reduction determined, which were then taken for additional statistical analysis of each lesion type and the overall lesion

count. Using a student t-test with a p50.05. significance level, the % change between the marketed product and N8G was compared.

The proniosomal encapsulation of TRT offered the benefit of resolving solubility and skin irritancy issues. In comparison to commercially available products, Acne patients using N8G (hydrated proniosomes made with 0.025% TRT, Span 60, and a Span60:cholesterol molar ratio of 3:1) showed advantage in reducing the amount of both open and closed comedons, papules, and acne lesions overall. The improved stratum courneum stratum penetration of the TRT may be responsible for this superiority [31]. The outcomes of this study demonstrate, possibility of TRT(Tretinoin)-loaded proniosomes as a topical medication delivery method for accelerating TRT's effectiveness in treating acne while minimizing its side effects.

These were the various ways to prepare hydrogel patches, and we'll now look at microneedle patches.

8.Microneedle Patch

Microneedle (MNs) patches are a type of topical, transdermal patch that contains tiny needles composed of a substance. This system with a network of micrometre needles establishes a pathway through the skin for the transportation of a variety of therapeutic compounds, including (bio) macromolecules, small molecules, and nanoparticles (vesicles) [32]. These microneedle patches are designed to only pierce the epidermis, not the dermis, and to avoid damaging the neurons. These patches were made to be painless and simple to use because they are typically applied at home [33].

The most popular methods for administering medication through the skin are topical creams and hypodermic needles. Patients are less likely to tolerate using pointy needles due the pain it produces, and creams have a lower efficacy or bioavailability. Skin serves as the primary impediment for the topical drug administration [34]. The three main layers of skin are the dermis, which is the thickest layer, the middle epidermis, and the stratum corneum, which is the outermost layer. Only certain types of molecules, such as lipophilic and low molecular weight medications, can penetrate the stratum corneum layer, which serves as a primary barrier [35]. Numerous challenges arise while developing topical formulations because of the layer's very poor permeability.

Researchers have looked at microneedles (MNs) for transdermal medication administration and for eliminating the drawbacks of the existing methods. A microneedle device (MNs) has a number of little pointy needles that are applied to the skin. The problems with transdermal patches and hypodermic needles prompted the creation of the microneedle (MN) drug delivery system, which is seen as hybrid of the two[36]. The fundamental problem with transdermal delivery technology is that many drugs cannot exert their therapeutic effects because they cannot penetrate the skin quickly enough. Researchers' advanced method, microneedles, allows Hydrophilic, High-Molecular-weight compounds to enter and cross the stratum corneum. When drugs are administered via a microneedle (MN) device, more drug molecules can permeate the skin due to the drug molecules' ability to enter and cross through the stratum corneum layer[37]. The technology's distinguishing traits include a quicker beginning of response, Better Patient Compliance, Self-Administration, Increased Permeability, and Efficacy shown in **Table.3**.

8.1. Types of microneedles:

Microneedles can be broadly divided into two categories. These come in two varieties: hollow and solid.

1. Solid microneedles: Also known as arrays of projections, solid microneedles are applied prior to the administration of a medicine and then removed to create holes in the stratum corneum. These can be utilised by sticking needles into the skin for a predetermined amount of time. By coating with the medication, solid microneedles can be made, which can subsequently be injected into the skin. The medicine will still be deposited into the skin membranes after the removal of the microneedle-containing device. When implanted into the skin, erodible microneedles disintegrate, making it simple to load the medicine into them[38].
2. Hollow microneedle - Research on tissues from human cadavers has shown that the skin itself, not the microneedles, is the main barrier to fluid flow to the skin via them. By using a micropipette puller to remove type 1 borosilicate glass pipettes that had been fire-polished, hollow microneedles were created. A beveler was then used to bevel the drawn needles at a 300-degree angle, creating hollow microneedles with an oval-shaped hole. Because of the needle's Oval shape, the effective radius of the needle starting point could be calculated by averaging the lengths of the needle tip opening's long and short axes[39].
3. Coated microneedles have also been tested in the sclera of human cadavers, demonstrating quick delivery of BSA and sulforhodamine in under 30 seconds. The medication immediately dissolved from the needle into the dermis when it was put into the skin of a dead pig using microneedles encased with vitamin B, calcium, and 1 um BasO4 microparticles[40].
4. It has been demonstrated that calcein can be delivered to human cadaver skin using poly-lactide-co-glycolide microneedles in a controlled release manner right below the dermal-epidermal junction. These needles could regulate time for periods ranging from hours to months, depending on the encapsulation formulation[41].

9. Drug delivery method:

There are numerous methods for transdermal medication administration using microneedles, including the following:

The poke-and-patch method, Microneedles that break down naturally (i,e Biodegradable microneedles), Microneedles with holes (i,e Hollow microneedles), Dipping and scraping, The coat-and-poke method

The ***"poke with patch"*** method entails piercing the skin with a variety of solid microneedles before applying the medication patch to the area being treated. Diffusion or, if an electric field is introduced, iontophoresis may transport a medication patch over skin[33].

9.1. Biodegradable microneedles: The drug is enclosed in biodegradable, polymeric microneedles, which are then inserted into the skin to deliver the medication in a regulated manner[42].

9.2. Hollow microneedles: This technique includes injecting medication using a hollow-bored needle. This method resembles an injection more so than a patch[43].

9.3. Dip and scrape: This technique involves dipping tiny needles into a medication solution first, then scraping the needles across the skin to leave the medicine behind in the tiny abrasions they cause. To induce microabrasions, the arrays were repeatedly scraped across the skin of mice while immersed in a medication solution[44].

9.4. Coat and poke method: In this method, the medicine is coated on the needles before being poked into the skin to release it through disintegration. The needle itself is coated with the full medicine that will be administered[45].

10. Mechanism of drug delivery

Drugs are administered topically through the diffusion mechanism. Using microneedles to administer medication causes temporary skin injury. An MN device is made by arraying hundreds of microneedles (MNs) on a tiny patch to deliver enough medication for eliciting the required medicinal response.It bypasses the barrier layer by slicing through the stratum corneum[46]. The medication is instantly injected into the Epidermis or Upper Dermis layer, where it travels to the site of action and triggers a therapeutic response.

To circumvent issues with oral delivery, API molecules are slowly transported from the skin's surface into the body via the transdermal route. Patients often approve of this method since, in some cases, using a patch instead of popping a tablet is more practical and effective. Although the transdermal patch market has a value of $6.23 billion in 2019, the value in 2021 was $ 7.22 billion, the lack of APIs that can be delivered transdermally (fewer than 20 in total) is the largest issue[47]. Additionally, factors influencing ACTIVE PHARMACEUTICAL INGREDIENT penetration rate include age, race, application place, and dermis condition.

This route of administration is ideal for ACTIVE PHARMACEUTICAL INGREDIENTS s with low molecular masses (less than 400–500 Da), balanced lipophilicity (log p 1-3), and low melting points. In addition, a few milligrams of an API dose that produces a therapeutic response and a strong pharmacological potential of APIs are necessary[48]. Because they are excessively hydrophilic, drugs with log p values 1 cannot effectively reach the stratum cornea SC. Contrarily, medications with log p values > 3 are extremely hydrophobic and quickly become stuck in the SC's intercellular lipids following topical application.

Although blood circulation is close to the dermis's surface, it can be difficult to distribute Hydrophilic Medications, Charged Molecules, Peptides, Proteins, and Nucleic acids since the skin is made to keep out unwanted substances. Both the lipid matrix structure and the mechanical qualities of the skin, i.e., those aspects of it that are affected by environmental factors, determine how complex the drug entering process into the skin is (humidity and temperature)[49]. In-depth investigation on physical and chemical techniques for therapeutic drug delivery has been conducted in order to circumvent the SC's barrier function, establish regulated drug release, and increase the efficacy of current formulations for transdermal administration. These techniques include Electroporation, Sonophoresis, Laser or Chemical Enhancers which produce nanometer-scale perturbations in the SC to facilitate drug molecule transit, as well as Iontophoresis, which propels hydrophilic medicines through sweat glands and hair follicles. The delivery of chemicals like macromolecules into the skin is still a very difficult task shown in **Fig.3**[50].

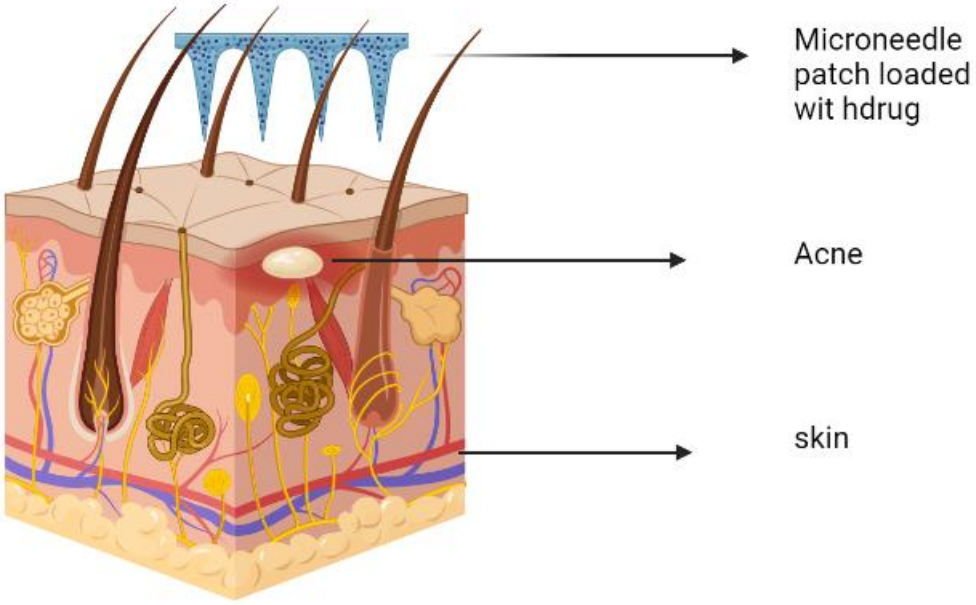

Fig. 3 Microneedle acne patch

Microneedles (MNs) can be used to transport micro drug molecules, macromolecules, or nanoparticles in addition to ACTIVE PHARMACEUTICAL INGREDIENTs which will not passively pass through the stratum cornea SC. Most importantly, the content of the medication molecules does not limit their application[51].

11. ***Preparation of microneedle patches has many different types of methods they are as follows***, Micro Electromechanical Systems (MEMS), Laser Cutting, Laser Ablation, Micro molding method (Solvent Casting), Atomized Spraying method, Droplet-Born Air Blowing method (DAB), Pulling Pipettes, Additive Manufacturing (AM), Fused Deposition modeling (FDM), Stereolithography, Digital light processing, Two-Photon-Polymerization (2PP), Microneedle coating techniques, Dipcoating, Gas-jet Drying, Spray coating, EDHA(electrohydrodynamic atomization), Piezoelectric inkjet printing[48].

11.1. Will see the development and design of Antimicrobial Microneedles.

There are various types of microneedles, including solid, hollow, coated, dissolvable, degradable, and expandable MNs. Hollow MNs can infuse fluids and support suspension. After being inserted into the skin, dissolving MNs entirely dissolve, encasing the medication in a polymeric matrix[52]. MN systems for degradable polymers are frequently created by encasing the medicine in a degradable MN matrix or having embedded micro- or nanoparticles. After absorbing interstitial fluid, swellable or crosslinked MNs expand and discharge their payloads. In general, solid MNs are made of silicon, polymers, or metals like titanium and stainless steel. Drugs are not naturally present in solid MNs, but they can be used as a pretreatment to increase the skin's permeability[37]. Drugs may be coated utilising a variety of methods on the surface of solid MNs in addition to pretreatment.

It has also been recommended to use coated solid MNs to treat contagious illnesses like viral warts. The integrated materials as well as geometrical features like form, length, and tip

radius affect the mechanical properties and functionality of polymeric MNs. In addition to using nanofillers, photo-polymerization can be used to cross-link the polymer matrix and increase the stiffness of polymer-based MNs[53]. The polymer composition and molecular weight are crucial variables for adjusting the mechanical strength of MNs (for example, the poly (lactic acid): poly (glycolic acid) ratio in poly(lactic-co-glycolic acid)). Future delivery methods for bioactive compounds with antibacterial properties look promising using polymeric MNs. Antimicrobial MN patches can be applied directly to target sites to fight diseases or to distribute antimicrobial drugs there[54].

There are three methods for incorporating the microbial agents into microneedle patches, they are explained in this below **Fig.4**,

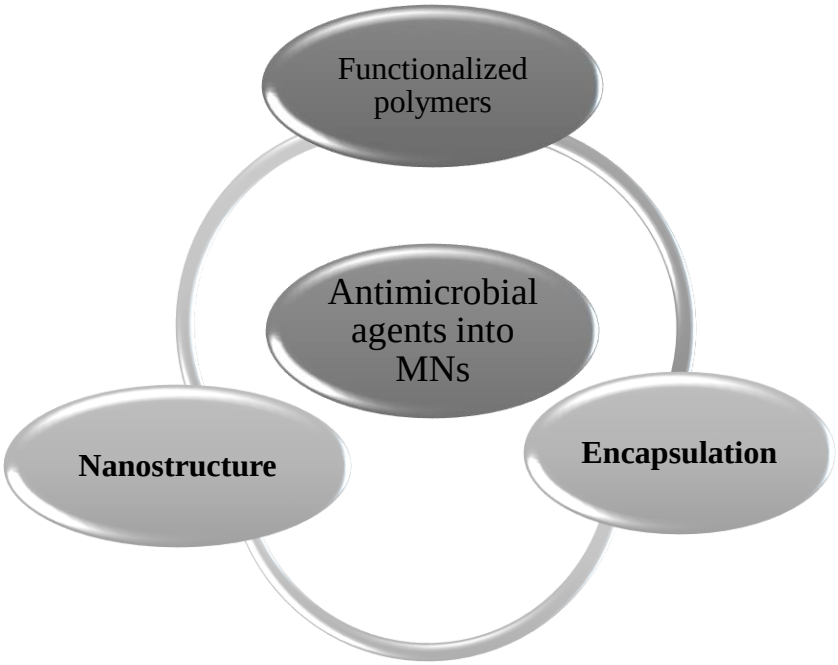

Fig. 4 Methods for incorporating the microbial agents into microneedle patches

12. Microneedle patch containing poly (ionic liquid)-based microneedles

Develop MN patches with salicylic acid that are based on ACTIVE PHARMACEUTICAL INGREDIENT poly (ionic liquid) (API PIL) (SA). The poly (ionic liquid)-based MNs are created by straightforward Photo-Crosslinking an Imidazolium-type ionic liquid (IL) monomer in MN Micro-Molds. These MNs are subsequently anion swapped with salicylic acid anions (SA)[55]. The transdermal treatment of P. acnes infection with synthetic SA-loaded PIL poly (ionic liquid)-MNs has demonstrated therapeutic efficacy both *in vitro* and *in vivo*. These poly (ionic liquid)-based MNs with active pharmaceutical components can enlight acne treatment, suggesting potential applications for skin ailments.

Ionic liquid (IL) monomers are used to create a family of polymers called poly (ionic liquids), which have highly stable physical and chemical characteristics. Because of their Cationic functional groups, such as Imidazolium Pyrrolidinium, Quaternary Ammonium, etc., PILs poly (ionic liquids) have also demonstrated intrinsic antibacterial characteristics. PILs poly (ionic liquids) can engage with the Electronegative Bacterial cell walls through Coulomb interactions, and their lipophilic alkyl chains can disrupt and demolish the hydrophobic

bacterial cell membranes, which ultimately causes the death of the bacteria. Recent reports suggest that the solubility, bioavailability, and/or biological characteristics of active pharmaceutical ingredients (APIs) in Ionic liquid (IL) form, where IL Ionic liquid serves as both a carrier and a medicine, may be enhanced. Electrostatic interactions between PIL cations and API anions have been employed as an unique drug loading technique[56].

12.1. Preparation of 3-hexyl-1-vinylimidazolium bromide (Im-C6)

Equimolar amounts of 6-bromo-1-hexane and 1-vinylimidazolium were reacted for 24 hours at room temperature to create Im-C6. The item was then washed three times with ethyl acetate and diethyl ether. 1H NMR (400MHz, D2O,): 7.77 (s, 1H), 7.57 (s, 1H), 7.102–7.162 (m, 1H), 5.77 (d, 1H), 5.40 (d, 1H), 4.23 (t, 2H), 1.89 (s, 2H), 1.29 (s, 7H), and 0.84 (s, 3 H). 13C NMR: 128.34, 122.72, 119.37, 109.28, 102.54, 49.92, 30.30, 28.95, 24.90, 21.56, and 13.27 (400 MHz, D2O). [M]+ calculated for C11H19N2, 179.15; found, 179.15. HRMS (ESI) m/z[56].

12.2. PIL-based microneedle patch preparation

The master mould was made of polydimethylsiloxane (PDMS) and had dimensions of 250 mm for the base, 600 mm for the height, and 15 15 arrays with a 550 mm tip-to-tip spacing. Through Photo-Crosslinking of monomers in the PDMS mould, Poly (ionic liquid)-based microneedle MN patches were created. Im-C6 (20 mol%), hydroxyethyl methacrylate (HEMA, 80 mol%), HCPK (photoinitiator, 1 wt% of the total weight), and PEGDA (2.5 wt%, as a crosslinker) were combined and homogenized using an ultrasonic machine[57]. The slurry was then diluted with 65 weight percent (wt) of deionized water. The diluted water solution underwent a 5-minute ultrasonic treatment. As soon as the cavities in the mold were filled, the mixture was cast into them. Then, the solution-filled master mould (1.0 cm) was degassed in a vacuum oven for 30 min. at room temperature. The MN patches (also known as poly (ionic liquid)-MNs) were subjected to UV irradiation (wavelength of 250 nm) for 25 minutes before being gently removed from the mould. The produced micro needle MN patches were vacuum-dried for 24 hours at room temperature before usage[56].

The resulting poly (ionic liquid)-MNs were immersed in a saturated sodium salicylate solution for three days to make sure that every Br anion was entirely swapped for a salicylic acid anion. Before use, all of the MN patches were then vacuum-dried for 24 hours at room temperature. To remove any remaining sodium salicylate that had attached to the surfaces of the MN patches, three washes with deionized water and methanol were performed. The patches for Minnesota were given the designation SA-PIL-MN. After being applied for three days, the SA-PIL-MN patches were submerged in a saturated sodium salicylate solution as a reusability test[58]. The used SA- poly (ionic liquid)-MNs were sonicated in deionized water before being cleaned. depends on the frequency of switching a saturated sodium salicylate solution.

After preparing the MNs, the prepared MNs were characterized by several studies, and they are as follows,

Salicylic acid release in PBS in a laboratory setting, Salicylic acid ex-vitro study of drug transdermal distribution, MN patches based on PIL that have antibacterial properties bacterial morphological alterations, blood lysis test, Evaluation of cytotoxicity, *in vivo* anti-acne trials, statistical investigation[59].

This particular method tells that, by combining PIL with microneedles, the study offers a simple but efficient method for treating acne infections. Salicylic acid section could be delivered into the skin's micro-channels using painless microneedles because salicylic acid anions were loaded onto poly (ionic liquid)-MN via electrostatic interactions between salicylic acid anion and imidazolium cation[60]. PIL-strong MN's mechanical properties allowed for the maintenance of drug delivery for seven days. Another model of P. acnes-induced inflamed acne infection in mice was created using a topical approach. It should be mentioned that microneedles expedited salicylic acid's transdermal efficacy and improved the therapeutic impact[61]. Experiments using skin tissue and immunohistochemical examinations of acne-affected skin using TNF-, IL-8, and MMP both produced the same outcome. This study is the first to systematically examine the effects of transdermal medication delivery using PILs, microneedles, and salicylic acid to treat acne. It also offers recommendations for developing novel, potent treatments for topical skin diseases[62].

13. Objectives for the preparation of microneedles are:

1. Define skin healing responses to solid microneedle insertion to assess skin permeability and estimate the pharmacokinetics of medications delivered through permeabilized skin[63].
2.To identify barriers to fluid flow into the skin from hollow microneedles, investigate the effect of hollow microneedle-based infusion settings on skin conductivity and discomfort[43].
3. To evaluate security and effectiveness of systemic therapeutic effects in people with type 1 diabetes, measure Pharmacokinetic Parameters, Pain, Irritation, and User preference for Microneedle (MN)-based insulin delivery[64].
4. Applying lidocaine to the skin will allow you to evaluate the safety and effectiveness of local therapeutic effects[65].

A wide range of delivery devices that can access intradermal cells include microneedles. While some microneedle patches use the skin's moisture to dissolve the vaccine into the intradermal layer, others employ small needles coated with the vaccine. A different kind of tool is a hollow microneedle, which uses tiny needles connected to a standard syringe. Preclinical research holds out a lot of hope for use in many vaccinations[66].

14. Comparison between Hydrogel and microneedle patches

We have discussed the comparison between Hydrogel patches and microneedle patches below in **Table.4**.

HYDROGEL PATCH	MICRONEEDLE PATCH
In essence, hydrogels are three-dimensional network structures made from a select group of natural and synthetic polymers. Because of their porous structure, they can hold and convey a considerable amount of water. Cross-linked hydrophilic polymer networks with a lot of water make up hydrogel. The hydrogel was created for several medicinal	Microneedle (MNs) patches are a type of transdermal patch that deliver drugs topically using a substance with tiny needles. To transport different therapeutic chemicals through the skin, including (bio) macromolecules, small molecules, and nanoparticles, this system with a micrometre needle arrangement creates a

uses due to its high-water content, which makes biocompatibility advantageous. Because hydrogels can be modified chemically in several ways, their construction offers a novel mechanism for delivering tiny chemicals, proteins, cells, and tissue regeneration. **ADVANTAGES** The advantage of low toxicity for microbial cell entrapment in hydrogel beads. pH variations could be detected by environmentally sensitive hydrogels. Hydrogels have good transport properties. Hydrogels are biocompatible. Easy to modify. **DISADVANTAGES** Hydrogels are expensive. Hydrogels causes thrombosis at anastomosis sites. Because hydrogels are non-adherent, a second dressing may be necessary to keep them in place. Hydrogels' mechanical strength is minimal. Difficulty in sterilization.	transportation pathway (vesicles). Microneedles (MNs) have been investigated for transdermal medication administration and for overcoming the drawbacks of existing methods. The topical method of drug administration makes use of the diffusion process. Using microneedles to administer medication causes temporary skin injury. An MN device, which consists of hundreds of tiny needles arrayed on a tiny patch, delivers just the right amount of drug to achieve the desired therapeutic effect. **ADVANTAGES** You can administer a lot of macromolecules. On the skin, the active pharmaceutical ingredient is easily administered. without being impacted by first-pass metabolism. Simple administration and quick drug distribution that can be focused on a particular location. high tolerability that does not result in skin edema or erythema. **DISADVANTAGES** The potential for "bouncing off" on the skin surface. Potential effects of the external environment, such as skin moisture, on medication delivery. Repeated injections could cause vein collapse. Skin layer differences between individuals may contribute to the penetration. The depth of the particles may vary. When the patch is removed, the microneedle's tip may break out and remain inside the skin.

Table.4 Comparison between hydrogel patches and microneedle patches

Conclusion

As we came to conclusion part, we conclude our review of Hydrogel patch and Microneedle patches by comparing both patches formulations and its properties. Hydrogels have the advantage of low toxicity is that microbial cells can be trapped inside hydrogel beads. Hydrogels have biocompatible properties, Hydrogels are simple to formulate. Microneedles have advantage of administering wide variety of macromolecules, they play important role in not resulting in skin edema and erythema, they are difficult in preparation. In present and future Hydrogels and Microneedles are very useful and effective way of treating acne in teenagers and adults. They are easy to handle, easy to clean, and they can be administered or applied without aid of physician. These both patches have present and future scopes in their own ways.

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