Types of microneedles and dissolving microneedle patches in cosmetics for acne and wrinkle improvement

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ABSTRACT:

MNs are micron-scale needles put on the bottom of a patch that allow a passage of the stratum corneum and so increase diffusion into the skin. This review article examines with the types of the microneedle devices present and the use of dissolving microneedle in various cosmetic related problems such as acne and wrinkle improvement. It briefly reviews about the ROS responsive MNPs to improve the interactions of the antibiotics with bacteria. An API poly ionic based microneedle patches containing salicylic acid are developed for the treatment of acne. A review of the study which was done utilising a combination of peptides, antioxidants, and marine complexes to attack key causes of skin wrinkles utilising Hyaluronic acid-based Microneedles was discussed.

Keywords: microneedle patches, dissolving microneedles, stratum corneum

1.Introduction

Anti-aging cosmetics are mostly designed as semisolid formulations for topical use, such as creams or gels. Topical use of these products is simple, practical, and risk-free. This method employs a newly developed administration route method that eliminates past drawbacks as discomfort, anxiety of patient, administration of small doses, and various adverse effects. Unfortunately, efficacy of these formulations is decreased due to the barrier function provided by skin, which restricts active component penetration.[1] To address skin penetration concerns with dermal extracellular matrix components, filler injection was proposed as a treatment method with greater rejuvenating benefits as compared to standard topical formulations. However, this is an expensive, intrusive, and frequently painful procedure that may result in systemic allergies and should only be conducted by a competent healthcare expert. [2-3] Despite the limitations of these tactics, innovative technologies are still required to boost the penetration of cosmetic components while limiting their losses. Microneedles (MNs) have evolved as a non-invasive and effective alternative technology for cosmetic applications in this vein. [4-5] MNs are micron-scale needles put on the bottom of a patch that allow a passage of the stratum corneum and so increase diffusion into the skin. All microneedles are an array of extremely tiny needles in various shapes and heights in micro size, they prevent contact with the skin's proprioceptors, resulting in a painless injection. The Georgia Institute of Technology research team led by Mark Prausnitz published the first study on microneedles in 1998. The paper showed that microneedles could pierce the stratum corneum of human skin and were therefore ideal for the transdermal administration of medicinal substances. MNs have been examined as a platform for the administration of a variety of medications and vaccinations, as well as cosmetics, due to their self-application and less intrusive nature.[6] The target surface for transdermal medication absorption into the circulation is the epidermal layer.[7] Lipophilic substances of low molecular weight (<500 Da) have been shown to easily pass the epidermal layer; however, pharmaceutical bio-macromolecules and other biomolecules such as nucleic acids or proteins have a more difficult time reaching deeper layers of skin. However, if the therapeutic drugs are accepted, they have a relative benefit in terms of improved physiological activities since they do not undergo hepatic first-pass metabolism. Oral and parenteral methods would be alternatives for providing

these bioactive pharmaceuticals in nano-size formulations without abandoning the benefits of self-administration, mobility, and pre-planned dose for chemically or enzymatically stable therapeutic agents. However, newly created biological agents with high molecular sizes, for example, demand more feasible ways for circumventing the 500 Dalton restriction. Not only is a tape-stripping or abrasive skin preparation pad used to promote skin penetration in experimental and clinical treatments, but ultrasound, microneedles, iontophoresis, low-frequency sonophoresis, and electroporation have all been researched to deliver therapeutic chemicals through the skin. Among all Microneedles (MNs) have been widely researched during the last decade.[8]

To support this assertion, both passive and active ways of increasing transdermal distribution of target compounds have been used.[9] Optimized medication formulation or carrier application in passive approaches frequently results in limited transfer of bio-macromolecules. Active physical or mechanical modalities, on the other hand, provide excellent permeability through skin, even for substances of greater molecular weights. For example, multiple microneedles with varying needle lengths (from 100 to 1100 m) and needle densities per cm^2 have been developed for various applications. Notably, local application of a Microneedle containing needle with a length of 100-700 m can create micro-sized channels in the stratum corneum, resulting in easier transport of target molecules to the target areas. According to histology research, the stratum corneum has an average thickness of roughly 10 μm. Furthermore, the synthesis and delivery of various medications into the deeper layer of cutaneous tissue use the same geometrical factors, such as needle side wall thickness, needle height, tip radii, and aspect ratio.[10-11]

2. Types of MN devices:

2.1 Solid and coated microneedles:

Solid Micro needles are often constructed of metals such as gold, nickel, and titanium, and silicon, ceramic, and non-degradable polymers with great durability to generate holes inside skin, increasing drug penetration at the site of application.[12] Petchsangsai et al constructed a microneedle array which is homemade. A microneedle array was made by cutting and arranging 9 acupuncture needles on a silicon matrix. They found that compared to electroporation and sonophoresis alone, utilising an externally applied insertion force of around 10 N improved the transport of hydrophilic macromolecules in MNs.[13] Notably, the volume of distribution over 24 hours was increased higher by combining MN devices with sonophoresis, simultaneous electroporation-sonophoresis and electroporation procedures than by using the MN system alone. Solid MNs can be coated with drug-loaded biodegradable polymers using a variety of techniques including as dip coating, drop coating, spray coating, and layer by layer coating to improve the rate of delivery.[14] Many biomolecules have been dipped and coated on to microneedles for easy transdermal administration including proteins, viruses, and DNA. To get reliable treatment results, the coating process should produce a uniform, thin layer of biocompatible material that is loaded with drugs on the solid MN. Furthermore, coated-MNs enable many drugs delivery options in a single-treatment operation for each and every needle in different drug solutions. In a separate investigation, Kapoor et al created solid polymeric microneedle patch which is loaded with approximately 250 grams of peptide A on 1.27 cm^2 patch comprising 316 needles. He claimed that this technology is able to deliver the target protein in a manner similar to subcutaneous injection. The investigation further claimed that the coating method would stabilise peptide A, improve the function of protein, minimise total dose of peptide loading on Microneedle patch making it a non-intrusive route to peptide transdermal administration. [15-17]

2.2 Dissolving microneedles:

Dissolving MNs, as contrast to solid MNs, are made from drug-loaded encapsulated polymers which are biodegradable such as polyvinyl, carbohydrates and polyesters.[12] Whereas the rigidity of solid

MNs increases the potential of breakage and subsequent skin discomfort such as irritation caused by shattered needles, although less potent than solid MNs, dissolving microneedles can nonetheless penetrate the skin.[16] In comparison to coated MNs, dissolved MNs regulate drug release during matrix degradation, increase drug loading, and solve the uniform coating process problem.[17-18] In comparison to solid and coated MNs, dissolving MNs can give the correct quantity of therapeutic dose.[19] This type of microneedles has gained popularity because they are convenient to the user and may be used using the "poke and release" approach.[36] Dissolving microneedles are typically created by pouring polymeric solutions into moulds which are further vacuum dried at room temperature. When the dissolving microneedles are used the curative ingredients progressively penetrate into the skin as the dissolving microneedles degrades through dehydration or edoema. This type of microneedle's main benefit is that it may deliver the agent in a single use without occluding the channel, which prevents microchannel healing.[37]

Castilla-Casadiego et al previously developed a dissolving chitosan-based Microneedle for administering meloxicam as pain reliever in cattle. Meloxicam which is a nonsteroidal anti-inflammatory medication that inhibits COX-2 and prostaglandin E2 activity. They also discovered that the microneedle patch could effectively supply meloxicam for approximately one week.[20] In another work, Ramalheiro et al. created quickly dissolving polyvinylpyrrolidone and poly vinyl alcohol microneedles for administration of rapamycin in treatment of psoriasis. Rapamycin release from dissolving MNs inhibited NK cell activation and suppressed inflammation. In, invitro, the medication which was loaded is continuously delivered for two weeks.[21-22] Psoriasis is a persistent cutaneous illness characterised by hyperkeratosis and aberrant dermal layer thickness.

Detachable (separable) MNs, which are part of dissolving MNs, are known to avoid issues caused by a potential immune response after needle deterioration because of long-term replenishment inside epidermal layer. The subtypes of these microneedles are capable of swiftly delivering a suitable dosage of particular medications to target sites. The backbone of these microneedles are formed of non-biodegradable substances, whereas tips are pointed and are made of biodegradable scaffolds.[12] Pukfukdee et al. created a solid matrix of separable hyaluronic acid-polyvinylpyrrolidone-maltose for

cell transport into cutaneous tissue. In this regard, murine melanoma cells (B16-F10) are encapsulated and discovered that the administration of melanoma cells into the hypodermic area via cell-loaded needles was effective.[23]

2.3 Hallow microneedles:

Hallow MNs are a different method for hypodermically delivering huge quantities of compounds with a high molecular weight such proteins, nucleic acid, and antibodies. Metals such as stainless steel, ceramic, gold, titanium, and other non-degradable polymers are used to construct hollow MNs.[24] The drug loaded MNs should be evaluated for their physical properties, content, release rate and cytotoxicity of drug. The backbone of these MN's should be described in terms of shape, mechanical properties, and skin permeation quality. The safety of these MNs is analysed by cutaneous tissue irritation, infection and discomfort.[25-27] Tofacitinib citrate, a JAK inhibitor, was distributed intradermally by Cárcamo-Martnez et al. using hollow MN arrays made of Gantrez® S-97 and 10% PEG. outcomes were evaluated to hollow MN system and often topical administration. They stated that the hallow microneedles allows for a delayed loading of the drug and a lower delivery rate.

2.4 Swellable microneedles:

Swellable microneedles are types of microneedles which inflate after being exposed to cutaneous interstitial fluid. Swellable MNs, like other MN kinds, create microchannels on the skin. Hydrophilic polymers having large swelling capacity, such as acrylate derivatives and polyethylene glycol, are employed to construct swellable MNs.[24] The hydrophilicity of the microneedles can be improved by various techniques. Chew et al for example, increased the hydrophilicity of PEGDA polymer by cross-linking with HA and using ultraviolet irradiation. The coating with photo-curable compounds further improved MN attachment capacity. According to their findings, the produced matrix expanded swiftly in less than 10 minutes, releasing 90% of the loaded medication in the aqueous phase. In this current microneedle fabrication procedure, this technique enables more concentration drug loading and an effective delivering rate of drugs. Yang et al. previously developed swellable microneedles to promote the granisteron sustained release, an inhibitor of serotonin receptor 5HT3, to reduce nausea

post chemotherapy. When the enterochromaffin cells, also known as Kulchitsky cells, are exposed, serotonin is produced, and the vagus nerve is stimulated, which results in vomiting.[25]

2.5 Smart microneedles:

As the MN delivery system developed, it became necessary for professional self-health administration ways to have exact control release of drug, high drug absorption efficacy, and correct selective cell distribution with significantly less adverse consequences. Thus, responsive drug delivery platforms known as "smart MNs" were developed, allowing for the modulation of the pace, quantity, and timing of transdermal cutaneous drug delivery in response to external, endogenous, or multiple triggers. In this technique, smart microneedles are composed of various materials which are responsive i.e., Thermal and pH responsive materials.[25] In drug delivery till now, variable thermosensitive materials having a lower critical solution temperature which are insoluble in high temperatures or a higher critical solution temperature that is which are soluble in high temperatures are employed. Examples of substances that have been utilised to deliver medication to the desired location include polypeptide, elastin, NIPAM, carbohydrate based and Pluronic metal nanoparticles, polyacrylic acid-co-acrylamide, carbon nanoparticles, hydrogels, PEG based block copolymers etc. [26] Because different cellular regions and portions of the body have varied pH levels, biomaterials that can react to physiological or acidic environments have been created. pH-responsive materials have acidic or alkaline groups which have a Pka value ranging between 3-10 and the ionisation takes place by electrostatic interactions when the pH of the environment changes. [27] PAA, poly L-lysine, block copolymers, poly amidoamine modified derivatives of different substrates such as mesoporous silica, chitosan, pH-sensitive bonds between applied materials such as ionic nanostructures such as calcium phosphate, and hydrazine links etc. have all been used as pH-responsive materials for drug delivery.[28]

The smart Micro needle fabrication technique, which consists of three phases that result in microneedle matrix phase transition or shape-shifting (shrinkage, swelling, and leakage) and selective release of drugs. The following are the steps:

(I) the endogenous environmental changes in PH, temperature, or osmotic pressure

(II) Exogenous stimuli such as UV, NIR, electricity, magnetic field, and ultrasound cause dynamic bond cleavage, isomerization, reduction, or ring-opening between structural materials utilised in MNs. [29]

Figure 1: Before needling into skin

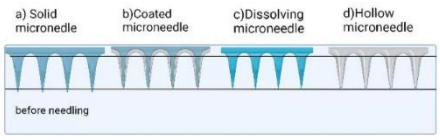
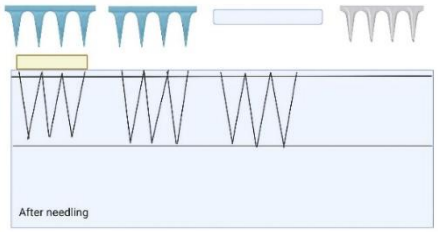


Figure 2: After needling into skin



3. Mechanism of MN patch:

Microneedle-based medication delivery devices can transport micrograms of tiny molecules or peptides to hundreds of milligrams of high-value protein compositions. The distribution process is not reliant on diffusion, as in other transdermal medication delivery systems. The medicine is encapsulated within the microneedles, which are subsequently injected into the skin as biomolecules. tiny region is covered by hundreds of microneedles that only puncture the stratum corneum, allowing the medicine to overcome this key barrier. The small needles are designed in arrays to deliver enough medicine to the patient to get the appropriate therapeutic response. The technique of microneedle delivery is based on mechanical rupture of the skin and administration of the medication within the epidermis, where it may more easily reach its designated site of action. The medication, such as biomolecules, is captured within the microneedles, which are subsequently introduced into the skin and the drug is released into the

bloodstream. Within minutes, the needles disintegrated, releasing the encased medicine at the desired point of delivery. [30-31]

4. MN patches for acne:

Acne is a typical inflammatory skin condition that affects the sebaceous glands of hair follicles.[32] One of the primary causes of acne is an inflammatory reaction, and bacteria in hair follicles, particularly Propionibacterium acnes (P. acnes), which grows in huge numbers and in turn produce lipases that breakdown locally stored sebum.[33] This process results in the formation of acne lesions, the production of free fatty acids, the chemotaxis of inflammatory cells, and the release of inflammatory mediators . Acne therapy necessitates the use of both local antibacterial and anti-inflammatory treatments. Antibiotics and nonsteroidal anti-inflammatory medications (NSAIDs) such as salicylates have been used to kill germs and manage local inflammation in skin lesions; however, due to the skin barrier, different transdermal techniques are required to facilitate drug entry into the lesion site. [34,39]While oral antibiotics and isotretinoin exhibit greater therapeutic efficiency, they frequently carry the risk of teratogenicity and damaging the intestinal microflora. Enhancing the direct contact between antibiotics and P. acnes is necessary to boost the antimicrobial impact, since an in vitro study revealed that P. acnes might create a biofilm inside follicles.[40]

Microneedle (MNs) technology is a new minimally invasive acne treatment procedure that has evolved in recent years. MNs can increase self-healing and speed skin metabolism, minimising the appearance of acne scars and acne. The majority of anti-acne MNs described in the literature were microneedles rollers or fractional radio frequency microneedles. They are also known as solid microneedles (SMNs) since they are formed of monocrystalline silicon or metal. Despite this, the SMNs are drug-free and must be administered after use. Furthermore, they must be operated by professionals.[41] Dissolving microneedles (DMNs) differ from SMNs in that they are constructed of hydrophilic polymer materials and are loaded with active chemicals. Furthermore, DMNs are disposable, preventing cross-infection, and may be self-administered by patients, boosting safety and convenience.[42] DMNs loaded with medications of varying polarity or molecular weight can be produced by optimising polymer materials

and solvents. These have several uses in the medicinal and cosmetic industries.[43] In order to administer a range of therapeutic compounds, such as small molecules, biomacromolecules, and nanoparticles, microneedle patches are transdermal drug delivery devices made up of arrays of micrometre-sized needles.[44] Since the depth of the needles may be changed to just pierce the epidermis without damaging dermal neurons, patients can administer MNs at home in ease.[45]

An ROS responsive microneedle patch was developed to improve the interaction of antibiotics with the bacteria used for the treatment of acne. The microneedle was made from a drug loaded reactive oxygen species ROS responsive poly vinyl alcohol matrix to provide on-demand medication release and minimise adverse effects. in inflammatory tissues, the ROS level under pathological circumstances could surpass 500 m, which is significantly greater than the ROS level in normal tissue (1–15 m).[46] In order to effectively limit bacterial growth, the ROS-responsive microneedles were able to release medication into the infected follicle in a sustained way after passing through the epidermis. A base containing methacrylated hyaluronic acid and diatomaceous earth (DE) was used to support MNs. This base may absorb pus as well as other purulent exudates and debris to aid healing and maybe prevent recurrence in the future. Adsorption-capable ROS-responsive MN patches can efficiently transfer antimicrobial therapeutics into dermis to quickly and easily eradicate P. acnes.

An API poly ionic based microneedle patches containing salicylic acid are developed for the treatment of acne. By creating microchannels in the epidermis that are bigger than molecular dimensions but smaller than holes made by hypodermic needles, MNs transfer medications (or vaccinations) through the skin. Unfortunately, germs can enter through these pathways and cause illnesses. Developing intrinsic antimicrobial MNs is thus preferred to prevent infections caused by bacteria at the insertion site.[47] Poly ionic liquids which are a kind of polymer made from ionic liquid monomers that have great physical and chemical stability.[48]Furthermore, due of their cationic functional groups, such as quaternary ammonium pyrrolidinium and imidazolium, poly ionic liquids have demonstrated inherent antibacterial capabilities.[49] These can engage with bacterial cell walls which are electronegative via coulomb interactions, and the disruption and degradation of hydrophobic bacterial cell membranes by lipophilic alkyl chains is done results in killing bacteria.[50] Recently, it was revealed that active

pharmaceutical ingredient in ionic liquid form, in which IL works as both carrier and medication, might increase its solubility, bioavailability, and (or) biological characteristics.[51] A unique drug loading approach involves electrostatic interactions between PIL cations and API anions. To treat acne infections, create salicylic acid loaded and inherently antibacterial PIL-based MN patches.[52]

Addressing the poor solubility, irritation of skin, and low permeability of azelaic acid (AZA) in commercial formulations, a co drug approach based on matrine (MAT) was used to develop antiacne dissolving microneedles. In 1996, FDA authorised azelaic acid, a natural organic dicarboxylic acid, for the topical treatment of acne. When compared to other available antiacne medications such as antibiotics, contraceptives and isotretinoin. Azelaic acid is safer, and no antimicrobial resistance has been discovered. However, due to Azelaic acids low solubility and skin irritation problems it not only complicated to prepare a formulation but also can reduce patient compliance. Currently azelaic acid formulations include a twenty percent azelaic acid cream and a fifteen percent of azelaic acid gel. Both of these formulations linked to skin adverse responses with a ubiquity of 5 - 10%, including stinging, burning, and dryness. Furthermore, due to the barrier effect of the stratum corneum, the effective medication penetration rate for most topical therapies is quite low. Matrine, a legume alkaloid, has a nonsteroidal anti-inflammatory medication action and can be used to treat inflammatory skin conditions. MAT has been used to treat disorders that cause stinging and itching. Furthermore, the antibacterial action of MAT against Staphylococcus aureus and Staphylococcus epidermidis has been documented. Both together played a crucial role in preventing acne by microneedle patches. [53-56]

5. Microneedle patches for wrinkles:

Skin appearance, which is a fundamental sign of age, is destined to alter as we age. As a result, the phrase "aged skin" refers to the consequences which are age related which occur during a lifetime, such as wrinkles, loss of elasticity and firmness a decrease in moisture holding capacity, and uneven pigmentation. Extrinsic factors that contribute to skin ageing include cellular metabolism, hormones, genetics and metabolic processes, as well as prolonged light exposure, ionising radiation, pollutants, toxins, chemicals. Indeed, extrinsic factors are estimated to account for 80% of the apparent indicators

of skin ageing, leaving just 20% for intrinsic causes. [57] Wrinkles visible lines or folds in the skin are the earliest indicators of ageing skin and are among the most serious skin occurrences. While leathery or wrinkled skin makes people appear old, smooth, and supple skin removes years from their looks. Currently therapeutic options for skin wrinkling include topical medications such as creams and serums, injections, microdermabrasion, and chemical peels. Antiwrinkle treatments and procedures, like as BT which is botulinum toxin injection and hyaluronic acid fillers, are popularly known to improve crow's feet wrinkles. Microneedles (MNs) are a collection of sub milli meter sized needles (50-900μm) that penetrate the stratum corneum (SC) and allow treatments to be delivered into the epidermis. They produce short-term, micron-sized holes in the skin without causing dermal nerves to activate. In addition, use in the pharmaceutical market, the potential of Microneedles (for ex: dissolving microneedles) for cosmetic appeal has been recognised. HA based material for microneedles has gained a lot of attention among microneedle scaffolds because of its good biocompatibility and non-immunogenicity, as well as its viscoelastic qualities enabling easy manufacture and long shelf life.[58] The ability of HA MNs to distribute active proteins and peptides effectively has opened new avenues for reaching targeted skin care results. HA Microneedles provides a subtle and discreet way to transport bioactive compounds deep into the skin while keeping them intact and active. A study was done utilising a combination of peptides (e.g., acetyl octapepetide3, arginine/lysine polypeptide, palmitoyl tripeptide5), marine complexes (e.g., seaweed extracts) and antioxidants to attack the key causes of skin wrinkling utilising HA based MNs. The MNP effects on the skin, including antiwrinkle, hydration, density and skin thickness was examined using human volunteers in twelve weeks of monocentric clinical trials. The product is made up of adenosine, a natural marine compound derived from seaweed extracts, and a blend of bioactive peptides such as acetyl octapeptide3, palmitoyl tripeptide5, and arginine/lysine polypeptide. By preventing the release of acetylcholine, encouraging the synthesis of key dermal structural proteins like collagen and elastin, and reducing and neutralising free radicals, it combats the main causes of skin ageing. These actions also increase the skin's resistance to damaging external stressors (aggressors). Additionally, the combination was administered utilising HA based dissolving microneedle technology, overcoming the impermeability of human skin and supplying

hyaluronic acid to support the structure of glycosaminoglycans (GAGs). Although the primary goal of hyaluronic acid-based microneedle was to deliver active ingredients by penetrating the stratum corneum, HA itself is an enhancer of skin texture and appearance by preserving skin's capacity to retain water as well as its suppleness and viscosity. In a multi-targeted manner, the study assessed the effectiveness and safety of hyaluronic acid-based microneedle patches that were loaded with minerals and active peptides. participants underwent wrinkle depth measurements. Before and after using the product, the average wrinkle depths were 363±146μm and 287±166μm. Improvements in wrinkle depth were seen in all participants, ranging from 3% to 83%. For each participant, improvements in wrinkle depths are displayed. Transdermal distribution using microneedles provides a practical method for administering active substances. The microneedle patch administration technique is painless, simple, minimally invasive and can be self-administered without the need for a trained health expert and offers controlled release of active ingredients.[59]

6. Conclusion:

The microneedle patch is an appealing transdermal active ingredient delivery method. Microneedles containing active compounds are injected into the skin and self-dissolve, allowing the active substances to be delivered through the newly established channel. There are various advantages to using a dissolving microneedle patch for transdermal medication administration. The administration and removal of the microneedle patch is basic, non-invasive, and painless. Individuals might opt to self-treat using cosmetic microneedle patches at home. Moreover, the microneedle patch might be combined with other targeted compounds, allowing for the coadministration of multiple active components by transdermal delivery. In conclusion the microneedle patches have a good impact in treating the acne and wrinkles and delivering various drugs bypassing the stratum corneum effectively without causing any pain or discomfort to the patient. To conclude the microneedle patches have shown to work effectively when compared to the traditionally available topical formulations for various cosmetic related problems such as acne and wrinkles.

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