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MICRONEEDLE: AN ADVANCED TECHNOLOGY OF TRANSDERMAL APPLICATION

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ABSTRACT

It is difficult to deliver the drugs having large molecular weight, the macromolecules (proteins, peptides) and the hydrophilic drugs by transdermal route. Now-a-days significant efforts are in progress to spread out the scope of the transdermal delivery system to include these hydrophilic molecules and macromolecules by designing specialized delivery technology. The concept of utilization of microneedles is one of the major advancement in transdermal drug delivery system. Microneedles are like conventional needles fabricated in micron range (100-1000 µm) of solid silicon/or hollow drug filled metal or polymer needles, devoid of pain upon insertion, because it does not pass the stratum corneum to reach the nerve endings. It can deliver a large number of molecules with greater flux and in a controlled manner. The mechanism for delivery is not based on diffusion as it is in other transdermal drug delivery products. Instead, it is based on the temporary mechanical disruption of the skin and the placement of the drug or vaccine within the epidermis, where it can more readily reach its site of action. Microneedles technology has the potential to revolutionize therapeutics by enabling the delivery of biopharmaceuticals. The review covers the advancement in transdermal drug delivery technology with a special emphasis to microneedle technology.

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INTRODUCTION

Transdermal Drug Delivery System (TDDS) has proven its efficacy to deliver the medicaments at a controlled rate through the intact skin to the blood circulation. TDDS can be effective both for acute as well as chronic illness like in pain and

trauma, motion sickness, cardiovascular diseases as well as in hormone therapy. It offers many advantages over conventional dosage forms; like it can bypass the hepatic first-pass metabolism thereby improving the half-life of the drug and reduced the frequency of administration. It is

easier to administer and as because it is painless unlike injections, it improves patient compliance, especially in case of pediatric and geriatric patients. It can maintain a constant blood level for prolonged time period with minimal inter and intra-patient variability. Self medication is possible and termination of medication is possible at any moment. [1, 2]

Approximately more than 30 products used in transdermal route have been approved for sale in the US and more than 10 API have been taken for approval for the global use. In recent years, a few transdermal products have been approved by the US FDA. IONSYS (Fentanyl ionophoretic), a product by Alza Corporation was approved in 2006 for management of pain. Emsam, a product by Bristol-Myers Squibb (Princeton, NJ, USA) was approved in 2006 for major depressive disorder. Fentanyl generic by Watson Pharmaceuticals was approved in 2007 as an analgesic. Neupro, by Schwarz Pharma (Mequon, WI, USA) was approved in 2007 for Parkinson's disease. Exelon, by Novartis (East Hannover, NJ, USA) was approved in 2007 for dementia [3].

There are certain criteria in drug's physicochemical property so that a drug can be able to penetrate the skin membrane for the effective TDDS, and thereby the medicament can easily reach to the target site [4]. The required criteria for a drug which make it suitable to formulate in TDDS are Low molecular weight (less than 500 Daltons), Low dose (daily dose in few mg), Narrow therapeutic window, Moderate solubility, Short half life, Low melting point (less than 200°C) having moderate lipophilicity with a log P value in between 1-3 and permeability coefficient greater than $0.5X10^{-3}$ cm/hr.

It is difficult to deliver the drugs having large molecular weight, the macromolecules (proteins, peptides) and the hydrophilic drugs by this route. Now-a-days significant efforts are in progress to spread out the scope of the transdermal delivery system to include these hydrophilic molecules and macromolecules by designing the so-called *active* patches that use a variety of technologies for skin-flux enhancement.

ADVANCEMENT IN TRANSDERMAL TECHNOLOGY:

Transdermal drug delivery is a noninvasive, user-friendly delivery method for therapeutics. However, its clinical use has found limited application due to the remarkable barrier properties of the outermost layer of skin, the stratum corneum (SC). Physical and chemical methods have been developed to overcome this barrier and enhance the transdermal delivery of drugs.

Iontophoresis: it enhances the transport of low molecular weight, ionized molecules across the biological membrane under the influence of an electric current. Chien et al. [5] suggested that delivery of larger molecules such as insulin, a protein drug and vasopressin, a peptide drug, can be successfully delivered through the intact skin by applying a non-invasive iontophoretic drug delivery.

Sonophoresis: in this technique the enhancement of migration of drug molecules through the skin occurs due to ultrasonic energy. There is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum corneum, which allows the medicament to permeate via biological barrier. Majority of studies on sonophoresis includes delivering the steroidal anti-inflammatory drugs (hydrocortisone).

Phonophoresis: Other technologies that scientists have investigated include use of chemical permeation enhancers or application of magnetic fields,

Magnetophoresis : The effect of magnetic field on diffusion flux of drug substance was found to enhanced with increasing applied strength [4].

Photomechanical Waves

Photomechanical waves significantly led to the stratum corneum highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

Electroporation

In this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of

drug is improved with the increasing permeability. Enhanced transport for low molecular weight ionized molecules Delivery of larger molecules such as heparin and oligonucleotides. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea. No safety concerns and less clinical data on safety.

Electro-Osmosis

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

OTHER SKIN FLUX ENHANCEMENT TECHNIQUES ARE AS FOLLOWS:

Transfersomes-

This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

Medicated Tattoos-

Med-Tats is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

Skin Abrasion-

This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules are generally known as Microscissuining.

Controlled Heat Aided Drug Delivery (CHADD) System-

It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consist a small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

Laser Radiation-

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum corneum without damaging the epidermis which remains in contact with it. Removal of the stratum corneum by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

More recently, considerable interest has arisen regarding microporation technologies that create micronsized *microchannels* or *micropores* in the skin by using technologies such as laser ablation, thermal or radiofrequency ablation, or mechanical microneedles [6]. Researchers have described these minimally invasive technologies as third-generation technologies that will have a significant impact on medicine [7].

Scientists use microneedles for drug delivery in a variety of application modes. One method inserts microneedles in the skin to create microchannels, followed by the application of a patch from which the drug then diffuses into the skin via the microchannels. Scientists typically use solid microneedles for this scenario. Alternatively, another application delivers the drug via hollow microneedles using pressure or other driving mechanisms. A third application coats the drug directly onto solid microneedles or incorporates it inside the microneedles during fabrication. The flux of small compounds like calcein, diclofenac methyl nicotinate was increased by microneedle arrays. In addition, microneedles also have been tested to increase the flux of permeation for large compounds like fluorescein isothiocynate-labeled Dextran, bovine serum albumin, insulin and plasmid DNA and nanospheres. In microneedle devices, a small area (the size of a traditional transdermal patch) is covered by hundreds of microneedles that pierce only the *stratum corneum* (the uppermost 50 µm of the skin), thus allowing

the drug to bypass this important barrier (Figure 1). The tiny needles are constructed in arrays to deliver sufficient amount of drug to the patient for the desired therapeutic response.

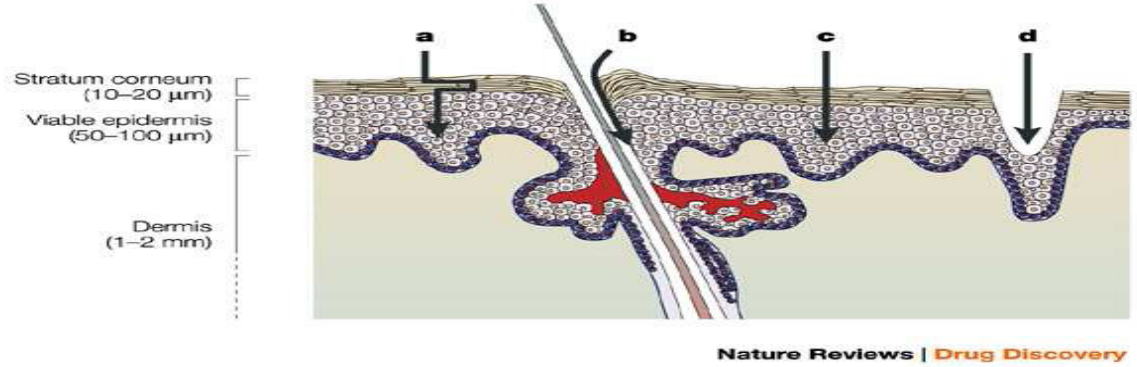

Fig.1 Drug delivery into the skin through microneedle

Most important advantages of microneedles over hypodermic needles is that, they are not responsible for any pain on the insertion of the needle [10] and contrasting other transdermal devices they can deliver a large number of molecules with greater flux and in a controlled manner [11].

Microneedles do not reach the nerve endings and are therefore painless upon application. Several studies, performed in human subjects using both solid and hollow microneedles, have demonstrated that microneedles 150-to-200 µms long, with well designed geometry, are painless upon insertion [12].These recommend an effortless, convenient and painless delivery and that's why having a good patient compliance [13]. Microneedles are generally coated projections with drug in micron range(100-1000 µm) of solid silicon/or hollow drug filled metal or polymer needles which go through the stratum corneum to provide a direct and controlled release route to the underlying tissues. [13, 14]

These microneedle concepts were first proposed in the 1970s [15]. In literature microneedles were first proposed by Hasmi et al for intracellular delivery and gene transfection [16]. Micro-electromechanical system(micromachining) are used for making microneedles from a various ranges of substrate materials like silicon, metal, polymer, titanium, glass and sugar. Microneedles may have various shape and structures like pyramidal, spiked, candle like and spear shaped structure [17].

Hollow like hypodermic needle; solid— increase permeability by poking holes in skin, rub drug over area, or coat needles with drug. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system. Hollow microneedles could be used to remove fluid from the body for analysis – such as blood glucose measurements – and to then supply microliter volumes of insulin or other drug as required [18]. Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training. Very small microneedles could provide highly targeted drug administration to individual cells.These is capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled.

TYPES OF DRUG MOLECULES USED:

It is very important to determine or select the type of drug molecules that can be delivered properly by the microneedles. Microporation of the skin by these needles creates microchanneles, which are hydrophilic pathways, with a diameter of around 50µm. Thus it may deliver drug molecules of large size and even small particulate carrier system. Most importantly it may deliver water-soluble molecules and macromolecules as the pathways are hydrophilic. Therefore it will expand the scope of delivering hydrophilic drug in terms of transdermal microneedles. Although skin

microporation will expand the scope of transdermal delivery to hydrophilic drug molecules, it seems that it will still be restricted to potent drug molecules. Literature reports investigations into the delivery of a number of drug molecules via microporated skin, including antibodies, anthrax vaccine, antisense oligonucleotides, calcein, desmopressin, docetaxel, erythropoietin, human growth hormone, insulin, interferon alpha-2b, methyl nicotinate, methotrexate, naltrexone, nicardipine, ovalbumin, and several other vaccines, genes, and drug molecules [6, 38]. Microneedles are used for the delivery of contraceptives, anti -cardiac drugs, analgesic, anti-infectives, local anaesthetics [19]. Model drugs which are delivered by the microneedles are calcein [20], diclofenac [21], methyl nicotinate [22], desmopressin [23], bischloromethyl nitrosurea [24], bovine serum albumin [25].These are also used for the gene therapy for treating cutaneous malignancies, alopecia, genodermatoses [26].

MATERIALS THAT ARE USED TO FABRICATE MICRONEEDLES:

A variety of materials have been used for the preparation of microneedles, are silicon, metal and polymer.

Silicon:

First microneddles were made up of silicon, because fabrication of sharp and hard microneedles with them was a lot easier as they had greater mechanical strength [27].These microneedle arrays of silicon are fragile and can provoke immune response which may neutralize the effect of the drug potentially [28]. Besides these fabrication with silicon needs costly processing of clean room and microfabrication technique. Also, silicon is brittle, and these needles may potentially break in the skin.

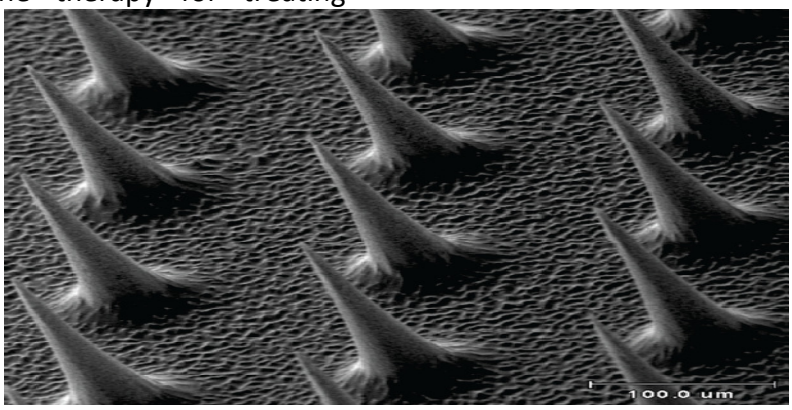

Fig.2 Solid silicon microneedles

Metal

These are having good mechanical strength; cost is comparatively low and they are already approved by the FDA. Metals that used for the fabrication of microneedle are stainless steel, titanium, nickel, iron [30]. Titanium is generally used for its biocompatible characteristic [31].

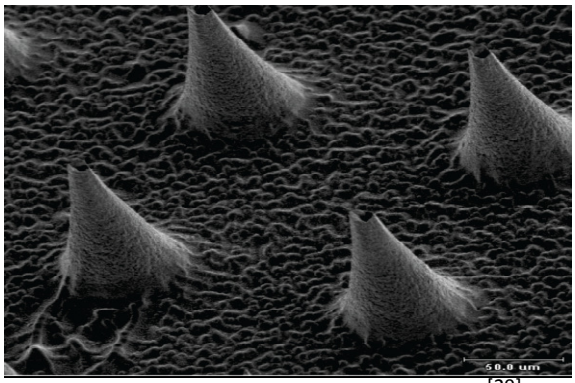

Fig.3 Hollow metal microneedles [29]

Polymer

In case of polymer both engineering plastics (polycarbonate, paralyne) and biodegradable polymers (polylactic and polyglycolic acid) are used because these are highly cost effective i.e. low cost of many bulk polymers and various modification of the needle can be done. Biodegradale polymers are used owing to the chance of microneedle breaking off in the skin [32].

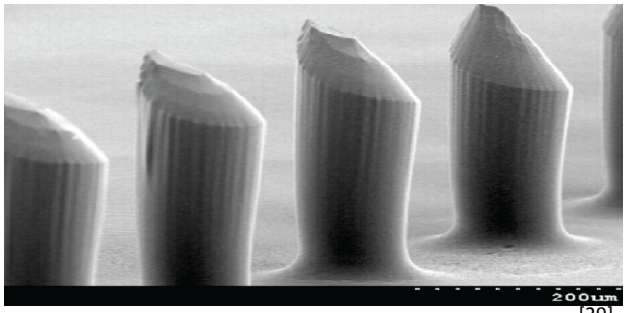

Fig.4 Biodegradable polymer microneedles [29]

Glass

Applications also have used glass to fabricate microneedles for the variety in designs and geometries. These are physically capable for the insertion in the tissues and they are having large drug loading capacity and one can see that how much amount is delivered after its use.

TYPES OF MICRONEEDLES

Various types of needles have been fabricated as well, for example: solid (straight, bent, filtered), and hollow. Solid microneedles could eventually be used with drug patches to increase diffusion rates; solid-increase permeability by poking holes in skin, rub drug over area, or coat needles with drug. Hollow needles could eventually be used with drug patches and timed pumps to deliver drugs at specific times. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system. Hollow microneedles could also be used to remove fluidfrom the body for analysis – such as blood glucose measurements – and to then supply microliter volumes of insulin or other drug as required. The hollow needle designs include tapered and beveled tips, and could eventually be used to deliver microliter quantities of drugs to very specific locations. The researchers demonstrated that an array of 400 microneedles can be used to pierce human skin delivering drug macromolecules. Very small microneedles could provide highly targeted drug administration to individual cells. These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled.[33]

OPTIMAL LENGTH

At the recently concluded annual meeting of the Controlled Release Society in Copenhagen, Denmark, researchers reported using microneedles varying in length from 50 to 900 µm. Under ideal conditions, the desired target site in the skin should dictate microneedle length. Microneedles generally do not penetrate the skin for their entire length, and scientists

need to consider this fact in their development. They also should consider the location of any target cell type; for example, vaccines target langerhan cells that are found in the stratum basale layer. Some researchers have suggested [34] that successful microneedles-mediated delivery requires precise targeting to dendritic cells in viable epidermis or dermis, which is a thin layer of cells 30 to 120 µm in humans that is located from 10 to 20 µm under the surface of the skin. They also have indicated that 65µm-long microneedles can achieve this delivery. Vaccine-delivery studies by other scientists, however, also have used much longer microneedles (greater than 500 µm) successfully, and this aspect may need further research to understand fully what role microneedle length may play in drug and vaccine delivery. For drug-delivery studies, the author makes a further distinction between delivery to systemic circulation for which blood circulation is under the epidermis, ~150 µm from the skin surface, and delivery to deeper skin tissue for topical or localized indications. The author's drug-delivery studies have generally used 500µm-long microneedles that penetrated the skin to an average depth of about 160 µm, as observed by histological sectioning and confocal microscopy, and that effectively enhanced drug flux through skin. Studies reported in the

literature have indicated that increasing microneedles length may result in increased drug delivery [35]. Disposal of microneedles is another aspect that scientists need to consider for commercialization. Even though microneedles are not likely to cause needle-stick injuries due to their shorter length, this risk or the risk of abuse may increase when increasing the length of the microneedles in a patch. The major advantage of microneedles over traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10-15 µm of the skin. microneedles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.

DELIVERY OF DRUG VIA MICRONEEDLES

Like the other transdermal delivery, here the delivery of the drug via microneedles is not based on the mechanism of diffusion through the skin. Instead, it can deliver large number of molecules with a greater flux by temporary mechanical disruption of the stratum corneum (uppermost 50µm of the skin) and finally placement of the drug in the epidermal layer of the skin; from there it can reach the site of action quickly. Stratum corneum, the main barrier of the transdermal route is overcome by microneedles. The skin is composed of three separate layers: epidermis (upper layer, ranges from 50-150µm), dermis and hypodermis. Upon piercing the skin, microneedles creates micro channel on the skin and direct the drug molecules to the viable epidermis (living but painless, highly diffusing layer), not to the dermal layer where nerve endings and capillaries may cause pain on insertion of needles. That's why drug molecules can readily diffuse towards dermis and can enter the main blood stream. Hence, transdermal drug delivery in terms of microneedle recommends a suitable delivery for macromolecules.

Encapsulation of the biomolecules (drug) has been done within the microneedles and then it is inserted into the skin, where the needles dissolve within minutes and releasing the trapped drug at desired site. In case of microneedles made up of biodegradable polymer, there is no need to remove the needles.

In such type of devices, a definite area is spread with hundred of microneedles, which puncture the stratum coneum of the skin and allow the drug to pass this important barrier. The arrays of the minute needles deliver desired amount of drug to the site for the intended therapeutic effect. [40].

SOME DELIVERY STRATEGIES

There are various strategies have been developed for the application of microneedles as transdermal device. These are as follows:

Poke with patch approach: Here the array of solid microneedles at first pierces the skin and then the drug patch is applied on the treated site. Drug is then passed through the skin by diffusion.

Coat and poke approach: It involves the coating of the entire drug to be delivered on the surface of the needles and here after the insertion of the needles the drug will release by dissolution.

Biodegradable microneedles: In this case the drug is encapsulated within the biodegradable polymeric needle and after the insertion of the microneedle the drug will release in a controlled fashion.

Hollow microneedles: Here the drug is injected through the needle with the help of a hollow channel.

Dip and scrape: This is the approach where the array of needles is at first dipped into the drug solution and then rubbed on the skin surface, leaving the drug within the microabrasions on the skin. Generally blunt tipped needles are used for this approach, length rages from 50-200 µm.

APPLICATIONS OF MICRONEEDLE TECHNOLOGY

- It may prove useful for immunization programs for the mass vaccination or administration of antidotes in bioterrorism incidents because it needs minimum medical training to apply them.
- Very small microneedles could provide highly targeted drug administration to individual cells.
- Fabrication of microneedles on a silicon substrate because of their small size, thousands of needles can be fabricated on a single wafer. This leads to high accuracy, good reproducibility, and a moderate fabrication cost.

 Microneedles are capable of local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled [42]
 Hollow microneedles could be used to remove body fluids for analysis such as blood glucose measurements and to supply micro liter volumes of insulin or other drug as required [43].
Microneedles can deliver, molecules to cells in culture, into localized regions of tissue inside the body, and across the skin into the circulatory system.
The delivery of membrane–impermeable molecules into cells is needed for a broad variety of applications in molecular and cell biology. Molecules of interest include peptides, proteins, oligonucleotides, DNA, and a variety of other probes that alter or assay cell function.
Drug delivery targeted to a precise region in the body can reduce side effects, minimize the dose of a costly drug, or provide a means of delivery to a location that is difficult to treat [44]. Two novel devices that deliver drugs to specific regions of tissue inside the body. Microfabricated neural probes have been used to deliver drugs into neural tissue of guinea pigs *in-vivo* [45], while simultaneously monitoring and stimulating neuronal activity. Microprobes have also been inserted across vessel walls of normal and atherosclerotic rabbit arteries *in-vitro.* [46]
microneedles have been designed in such a way that by decreasing the size of hypodermic needles, insertion pain and tissue trauma experienced by patients can be reduced.
Also, the combination of these needles with micropumps and other devices can yield more sophisticated needles that can potentially deliver drugs in a more controlled manner [47].

CONCLUSION

The intact skin is not sufficiently permeable to the majority of drugs. The enhancement of skin flux is done by number of ways like iontophoresis, sonophoresis, phonophoresis, magnetophoresis etc. microneedle is a novel approach for transdermal drug delivery. It is a convenient, painless less invasive and can be used for administering macromolecules like proteins, peptides, hormones, antibiotics as well as hydrophilic drugs are also potentially be delivered through skin via microneedles. In contrast to oral delivery, microneedles avoid first pass effect and offer the benefit of immediate cessation of drug administration in case of an adverse effect or overdose. Very small microneedles could provide highly targeted drug administration to individual cells. Hence it could be suggested that microneedles provide a powerful new approach to transdermal drug delivery and represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications.

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