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Dissolving Microneedles in Therapeutics: A Smart Approach to Minimally Invasive Drug Delivery

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ABSTRACT

Current developments in the field of transdermal drug delivery have placed the dissolving microneedles (DMNs) technology on the path to changing the landscape of taking medicine as an aspect of painless, self-administered, physio-minimally invasive, and contrasted to normal subcutaneous or intramuscular injections. In this review, the DMN systems evolution is followed, and the formation of these systems as drug carriers to multifunctional platforms that can be used in various types of diseases has been outlined. The importance of fabricating DMNs through techniques (micromolding, droplet-born air blowing, and drawing lithography) is discussed in detail considering attaining structural integrity and fast dissolution. The incorporation of biocompatible materials as polymers, e.g., hyaluronic acid, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), carboxymethyl cellulose (CMC), and chitosan (CS), is considered in terms of maximizing the mechanical strength aspects, rate of dissolution. Skin penetration efficiency, bioavailability of the drug, and stability in the physiological environment are covered by performance testing. Although DMNs hold great potential for clinical benefits such as increased patient compliance and decreased risk of infection, there are still concerns about large-scale production and formulation standardization and regulatory acceptance. These are the obstacles that have to be considered in the process of successful translation of DMNs into routine work.

1. INTRODUCTION

The delivery of therapeutic agents through the skin using transdermal methods remains the preferred method because it combines ease of use with non-intrusive application to cross both the gastrointestinal system and first-pass metabolism. The effectiveness of skin-based drug delivery has historically been restricted by the stratum corneum skin layer acting as a barrier

to drug absorption. Microneedles (MNs) represent an advanced technology for improving drug absorption through the skin(1). The protein/peptides/macromolecules bypass the GIT and show better bioavailability while administered as transdermal drug delivery(2). The microneedles consist of sub-millimeter projections (up to 1500 μm in length) that penetrate the stratum corneum while settling into lower skin layers yet not extending into deeper pain receptors. The purpose of microneedles is to deliver drugs through the skin without pain while preventing substances that do not naturally penetrate the skin. Since then, the volume of investigational research concerning MNs has expanded remarkably; more than 4000 patents and scholarly articles have been introduced, with the count of such still having an exponential increase (3).The patent for the first percutaneous MN drug delivery device was filed by Gerstel and Place in 1967(4). Solid microscale needles originated from an invention by Gerstel and Place that received a patent from the United States Patent and Trademark Office in 1976. Following its expiry towards the end of the 1990s (and following the development of complementary new technologies in microscale manufacturing of MEMS devices), a new interest was developed in MN research, and microneedles were to become the new hope of transdermal drug administration(5).In 2006, Dr. Desmond Fernandes developed the first MN device to be commercially available on the market(6). This device was to form the modern-day Dermaroller. The main application that the device will be used on is commercial healthcare and the use of solid MNs. Microneedling (sometimes called "percutaneous collagen induction" or "needle dermabrasion") is an experimental dermatological treatment that has been used, around the same time, to treat scars(7). The cosmetic procedure has, in turn, changed to employing 13 mm needles mounted on a roller with topical formulation vitamin (A, C, and E) compounds to foster rapid healing and improvement of skin as well as collagen generation(8).Manufacturing processes have advanced in microfabrication to achieve precise and controlled production of microneedles. Various types of microneedle arrays are available for delivering drugs into the skin, which include solid, hollow, coated, dissolving, and hydrogel-forming microneedles (9–12) (Fig.1).

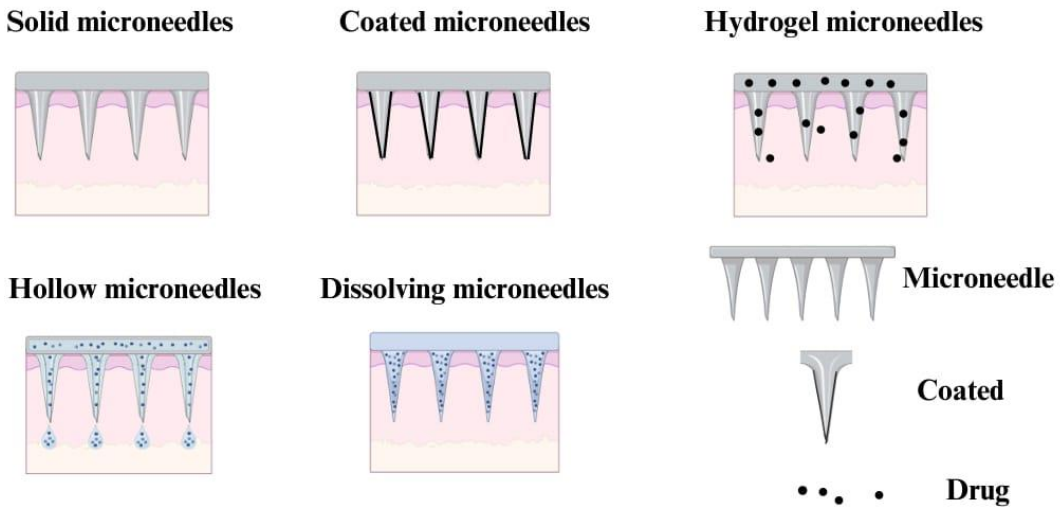

Fig.1.Types of Microneedles

Among all microneedle types, Dissolving Microneedle (DMNs) arrays represent an especially engaging device for biologic delivery. Degradable MNs, also known as dissolving MNs (DMNs), function in a "poke and release" fashion(13).The arrays consist of biocompatible materials (i.e., water-soluble polymers with sugars) and the drug of interest and maintain enough mechanical strength to penetrate skin before dissolving with interstitial fluid (ISF) to release the drug(14–16).The majority of dissolving microneedles reported in literature require skin insertion time exceeding five minutes for complete dissolution. To shorten this time, the arrowhead microneedles were developed to divide from their shaft structure immediately after insertion. The microneedles embed themselves in skin tissue rapidly, followed by complete dissolution inside the skin tissue (17). After dissolving the microneedle arrays, the skin patch can be removed with just a small amount of biohazardous waste (18). The delivery of drugs through dissolving microneedles enables minimally invasive infusion and avoids all disposal risks that needles present to healthcare staff. Additionally, dissolving MNs can improve the chemical stability of vaccination antigens and encapsulated medications, negating the need for cold storage(19,20).

Research interest in this technology has grown significantly because it shows promise for revolutionizing drug delivery methods of vaccines and hormones as well as peptides and small molecules. The field of transdermal drug delivery received a new direction thanks to dissolving microneedles, which present groundbreaking improvements among drug delivery methods.The following discussion evaluates dissolving microneedles through basic operation principles together with benefits and usage cases as well as the barriers that need resolving to reach fulfilment.

2. Polymers used in DMNs

The development of microneedles requires selecting an appropriate polymer since this selection determines the needle strength and their ability to penetrate skin along with their drug release properties. Different polymers have production applications in making polymeric microneedles, and they exhibit various properties (21). The structural integrity of water-soluble polymers decreases when drug encapsulation happens since they lack the strength of non-dissolvable materials like silicon and copper. The insertion ability of microneedles into the body depends on their water resistance properties and structural strength. Researchers investigate the combination of polymers and materials in order to improve performance characteristics. The selection process for target tissue between transdermal and non-transdermal applications remains vital because these tissues are part of sensitive medical devices. The choice of polymers must be made with caution because their resistance levels depend on moisture in the environment. The subclassifications of dissolvable microneedles include, (Fig.1)

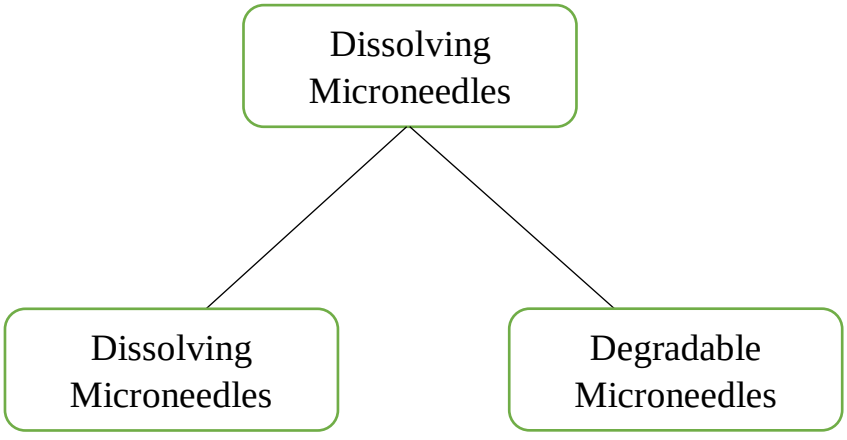

Fig.2.Subclass of Dissolving Microneedle(22)

Table 1: Comparison of characteristics of Dissolving Microneedles

Type	Characteristics	Positive (pros)	Negative (Cons)	Reference
Dissolvable microneedles	Water-breaking polymers form these patches, which will dissolve after placement into the skin.	Minimize the risk of infection and reduce medical waste, No need of needle removal from skin.	Limited Drug Loading Capacity, Not Suitable for Large Molecules, Stability & Storage Issue	(23)
Degradable microneedles	The polymers in these devices consist of materials which naturally break down inside the body.	Biocompatible and Can provide controlled release, Avoids needle disposal issues	Higher cost, Slow and Unpredictable Degradation,	(24)

The matrix selection becomes a necessary factor during DMN production. Fabrication of DMNs should include proper selection of polymers. In order for the mechanical strength of DMNs to be enhanced through these modifications, they lead to lower whole-system effects. Scientists mixed two or more polymers to improve both mechanical stability and drug activity in the final products. Scientists incorporate excipients into the polymer along with multiple matrix polymers to develop DMNs. HA, PVA, PVP, protein, and several types of carbohydrate compounds are widely used for making DMNs (25–27). The controlled-release delivery through the skin requires polymer microneedles to stay within the skin tissue for multiple days to reach its effectiveness of sustained delivery for months(28,29).

2.1. Hyaluronic acid (HA)

Hyaluronic acid (HA) resulted from being first isolated in 1934, and its drug delivery was continued with much study because of its biocompatibility, degradation, and also due to its nature of being water-soluble(38,39).Human skin contains hyaluronic acid as an extracellular matrix substance, which functions as a non-sulfated glycosaminoglycan. The substance exhibits excellent biological compatibility and is biodegradable and non-immunogenic in addition to its water-dissolving nature(16).The healing properties of HA remain optimal in dermis part metabolism because the molecule maintains high levels of skin moisture. On the basis of MW, HA can be classified into 5 groups(40): Very High Molecular Weight HA (MW: >6 x 103 kDa), High Molecular Weight HA (MW: >1 x 103 kDa), Moderate

Molecular Weight HA (MW: 250–1000 kDa), Low Molecular Weight HA (MW: 10–250 kDa), and Oligomer HA (MW: <10 kDa). Differing MWs lead to the altered penetration into the skin, as HA with low MW will penetrate more deeply into the layers of the skin. In some studies, it was reported that HA 10 kDa has good mechanical properties, and on the other hand, HA with MW greater than 50 kDa will exhibit side effects like immunosuppression in vivo, and HA less than 50 kDa is pro-inflammatory (41). The tissue hydration functions alongside pain reduction while supporting healing processes that HA delivers. Medical establishments utilize this material for three purposes, which are beauty procedures, skin tissue restoration, and arthritis treatment. DMNs made with HA possess a high level of mechanical strength together with swift breakdown in bodily fluids that enables deep tissue penetration(30).Among the numerous ways of applying HA into DMNs, one can present fabricating insulin-contained DMNs, the doses of which were 0.13, 0.25, and 0.44 IU. The DMNs were analyzed in terms of stability under different temperatures and also reduction of blood sugar in Wistar rats in vivo. After 1 month of storage, it was established that 90% of the insulin will be retained in DMNs at -40, 4, 20, 40, and 49°C, and these values point towards the fact that DMNs-HA preserved insulin at these temperatures long-term. Moreover, these DMNs showed the same efficacy compared to SC insulin injections(42).High molecular weight HA exhibits both anti-inflammatory properties together with immunosuppressive effects and low molecular weight. HA leads to inflammatory repair and induces temporary blood vessels(31)**.**

Polymer	Type	Characteristics	Reference
Hyaluronic Acid (HA)	Natural	Biocompatible, hydrophilic, enhances skin penetration.	(30,31)
Chitosan (CS)	Natural	Biodegradable and suitable for both control and sustain release of microneedles	(32)
Silk fibroin	Natural	Biocompatible, mechanically robust, suitable for controlled release	(33)
Carboxymethyl Cellulose (CMC)	Synthetic	Hydrophilic, biodegradable, used for drug stabilization.	(34)
Polycaprolactone (PCL)	Synthetic	Biodegradable, suitable for sustained drug release	(35)
Poly(lactic-co-glycolic acid) (PLGA)	Synthetic	Biodegradable, used in controlled-release microneedles	(24,36)
Polyvinyl Alcohol (PVA)	Synthetic	Offers good mechanical strength, controlled dissolution	(37)

Table 2: Various types of polymers used in the preparation of Dissolving Microneedles

2.2. Polyvinyl pyrrolidone (PVP)

The water-soluble polymer PVP belongs to N-vinyl amide polymers, demonstrating excellent properties. There are various pharmaceutical grades used in PVP, as shown by the two extreme values (the least K of 12 and the greatest of 120). The K value of PVP represents the difference in viscosity and the difference in molecular weight (MW) that will rise with a greater K value. PVP is also biocompatible with good mechanical properties sufficiently realized to generate DMNs(43).PVP does not need high temperatures and organic solvents in the fabrication of DMNs; thus, it can be used to ensure the stability and encapsulation of heat-sensitive active protein substances(44).Combination with other polymers might also be used in PVP, like 20% w/w PVA and 20% w/w PVP, to provide active substances of DMNs(45). An example of a protein that has been developed with PVP as DMNs includes collagen. Sun et al. took PVP as a carrier in the system with MW 10 kDa and added a plasticizer, PEG. The dissolution time of these DMNs after applying them on human and porcine skin was 5 min. The fluorescent imaging outcomes indicated that the DMNs entered the human skin and accumulated the collagen in the papillary layer of the dermis. The observation is of benefit to aesthetic enhancement, wound healing, and immune illness(46).In 2017, Lee et al. presented a blend of two types of PVPs with various MWs to achieve good mechanical properties characteristic of DMNs that contain insulin. The PVPs employed were the PVP 360, which has the MW 360 kDa, and PVP 10, which has the MW 10 kDa. In the case of tests on diabetic rats, CMC was incorporated into the backing layer to ensure that the DMNs would be more flexible to enable transdermal application. The findings indicated that compared with the use of subcutaneous (SC) injection, DMNs effectively transported insulin in the body and maintained blood glucose at normal levels among the rats up to 4 h following the injection(47).

2.3. Polyvinyl alcohol (PVA)

The water-soluble synthetic polymer named polyvinyl alcohol (PVA) demonstrates excellent safety qualities and high biocompatibility. The physical structure of PVA contains advanced water absorption properties together with thermal stability features, which makes it perfect for combining with other polymers during drug-loading DMN production (48).The melting point of PVA is 280°C, and this material is dissolved in water. There are 3 grades of PVA with respect to viscosity: high viscosity (MW ¼ 200 kDa), medium viscosity (MW ¼ 130 kDa), and low viscosity (MW ¼ 20 kDa). The procedure for DMN fabrication is influenced by various PVA aqueous solution concentrations. When used as a drug encapsulation agent, the PVA system enables high drug loading magnitude and controlled drug product release behavior. The use of PVA as a matrix system by itself contains various detrimental aspects. Manufacturers need alternative polymers with stronger mechanical properties since PVA does not sufficiently navigate the stratum corneum to deliver drugs through the skin. The drug release rate becomes delayed due to the poor water solubility of the drug materials. The production process of DMNs requires several combined polymers as matrix materials to guarantee both shape stability and microneedle dissolution.Research by Cole et al. (2017) demonstrated how PVA yielded the best results from their investigation of four polymers used to create DNA vaccine-delivery DMNs. In 2016, PVA was employed with Chu et al. to create an inactivated influenza vaccine H1N1 in DMNs. It was low-viscosity PVA that was PVA with MW 20 kDa. DMN's drying procedure was performed under three conditions, i.e., lyophilization at 24 h and air-drying at

either 25 or 45°C. Based on the findings of the study, one of the methods of drying that was preferred was lyophilization, which increased the potency of inactivated influenza vaccines. Moreover, DMN storage was also done at 4 temperatures, which were 4, 25, 37, and 45°C at 3 months, and the outcomes indicated that the DMNs were thermostable at the given temperatures. During the experiments on mice, the hemagglutination inhibition (HAI) titer was used as the efficacy measure of the influenza vaccine, and it was found that the HAI titer of the mice exposed to DMNs under the same storage conditions of 45°C within a month of the preparation of the DMNs did not differ compared to the mice exposed to newly prepared DMNs. This meant that PVA was effective in the formulation process of inactivated influenza vaccines that were successful and heat stable as well(49).In 2018, the bevacizumab humanized monoclonal antibody was also transformed to MNs form, which was previously allowed to treat cancer in the form of intravenous fluids. PVA having the MW of 9-10 kDa, when integrated with bevacizumab, formed the system of DMNs by Courtenay et al. Having been administered to mice, bevacizumab was released through DMNs and could last in plasma 7 days following a single administration of DMNs. Also, bevacizumab was concentrated in lymphatics in vivo and manifested the prospect of being applied as a tumor therapy in lymphoma(50).

2.4. Carboxymethyl cellulose (CMC)

CMC is a natural polysaccharide. The polymeric material CMC possesses water solubility with low viscosity as well as film-forming ability along with elastic behavior and non-cytotoxicity and clinically safe substances when dissolved(9,51). The drug release from CMC occurs slowly while maintaining drug delivery control. The research team achieved this target by first forming drug-CMC particles and then placing CMC particles inside DMNs(52).Multiple research works prove that CMC acts as a substance that enhances drug release while improving cumulative drug delivery. CMC forms the base of DMN delivery systems that serve as protein drug stabilizers and enable vaccine and nucleic acid distribution together with biologically active drugs.

2.5. Chitosan (CS)

The manufacturing process of chitosan (CS) begins when chitin undergoes N-deacetyl group removal. Free amino groups exist only in CS among all natural polysaccharides, thus making it the basic member of this group. The skin dissolves CS-containing drugs that were previously stored as active substances because CS possesses powerful adsorption properties alongside its free amino groups(53).The microneedle system constructed by Chen and the microneedle system and dissolvable patch were implemented by Chen and colleagues that allow long-lasting intradermal administration of antigens. The hydrophilic polymer patch helped to give skin penetration assistance and easily dissolved. The MNs with chitosan stayed in the skin, fully releasing the model antigen, ovalbumin, over a period of 28 days. Experiments with animals proved that this system has a prolonged antibody persistence of up to 18 weeks, proving that using MN as a carrier had an added value of having a continuous antigen exposure (54).Mei-chin et al. developed chitosan-based microneedle patches to deliver in a long-term transdermal manner large, water-soluble molecules such as BSA. In this sustained release phenomenon, chitosan was very important as it was biocompatible, biodegradable, and hydrophilic, resulting in a gradual release of 95 percent BSA in a span of 8 days. Noteworthy, the action of entrapping the protein in chitosan had no harm to the structure of the protein, which proves that the manufacturing process was non-destructive on sensitive biologics(55).

3. Fabrication methods of DMNs

There are various ways of manufacturing DMNs, including micromoulding, droplet-born air-blowing, centrifugal lithography, photopolymerization and drawing lithography. A great deal of physical and chemical factors can influence DMNs, the stability and effectiveness of drugs present in DMNs during preparation and storage(9,44).

3.1. Droplet-born air-blowing method

The DAB method provides a rapid yet mild approach to make DMN available for production. Microneedle drug content depends on the interaction between the dropper pressure and duration timing. A solidification process using air pressure sets the right characteristics for microneedles through droplet solidification while maintaining drug stability without needing heat or light exposure (24). The droplet-born air-blowing method needs two facing plates where a polymer solution drop gets arranged based on array designs. The two plates start controlled movement once they achieve contact. Air blows change the polymer into solid form, which leads to microneedle creation when the two dish plates achieve their widest distance. Advanced methods based on the original technique allow the production of dissolvable microneedle patches by performing multiple pillar interactions during drying cycles (CCDP process)(56). The scientific production of DMNs through the DAB methodology generated effective therapeutic results. The research group of Hong et al. developed facial wrinkle-treatment DMNs through their droplet-born air-blowing method while using HA-based materials. The research revealed that DMNs developed by this particular procedure achieved delivery effectiveness and controlled drug concentration levels. Through their work, Kim et al. (2013) designed insulin delivery DMNs utilizing this production technique that achieved lower insulin activity loss beyond conventional protocols. Results from Park et al.'s (2020) study mirrored those of their research.

3.2.Micromolding (solvent casting) method

Micromolding is the most commonly used method, which is easy in its approach and cheap; thus, it can mass produce (57,58). In this case procedure, molds are prepared in the preferred architecture of MNs (in reference to master molds), and subsequently from these molds, one may produce additional molds that are subsequently used as positive master templates(13).In the process, the concentrated polymer drug solution or melted polymer was poured into the mother mold. Next, remove air from the polymer drug dispersion to fill the microholes progressively, followed by drying under any given conditions(31,59). Micromolding can be subcategorized into three processes, i.e., hot embossing, injection, and solvent casting(9). The least complicated of these approaches is the solvent casting method since high temperatures are not needed, which have the ability to destroy active substances that are sensitive to heat (proteins and peptides). Under this technique, the active substance in the form of a polymer solution is cast into the PDMS mold, and another procedure is performed. and exuded out as vacuum or centrifugation to occupy small spaces in the molds. The procedure will culminate in drying and removal of MNs in the molds (56,60).The solvent-casting micromolding technique falls into two categories in the development process, i.e., one-step and two-step casting.

3.2.1. One-stepcasting

The DMNs manufacturing process can be done in a single straightforward process referred to as one-step casting micromolding, whereby the polymer solution is combined with the active substance, after which it is cast into the PDMS mold, followed by centrifuging or vacuum drying(29). Nevertheless, a few other studies indicated that a minimal amount of the active substance (8 percent only) is condensed in the needles and preparedto be delivered. In the

meantime, the active substances on the baseplate will fail to dissolve in the skin, and hence they will take minimal action, and drugs involved will simply go to waste(61).The one-step casting method was adopted to prepare DMNs containing bevacizumab (BEV) peptide using a 20 w/w PVA. A mixture of PVA and BEV was filled in silicone molds having 19 X 9 pyramidal needles. The molds were dried at room temperature for 48 h and were cooled in a vacuum for 15 min. Following their in vitro permeation testing, about 8.7 ± 0.9 percent of the entire BEV could be released by the DMNs. The author decided that only BEV found in needles was complete enough to be delivered, but BEV in the baseplate was not delivered. This, unlike in previous studies done by the author using ibuprofen, involved the permeation of a tiny amount of ibuprofen on the baseplate, during which the microchannel was passed through before closing over the skin. The writer suggested the necessity to alter this one-step process to a two-step process to produce DMNs(50).

3.2.2. Two-step casting

The path to eliminate the issues regarding one-step casting is the creation of a method where the active substance will be concentrated solely at the tip of the MNs/needles, called the two-step casting(50,61). So in this technique, two polymer mixtures are made; the first solution has polymer and active substances, and the second solution will have only blank polymer that does not have the active substances. The first polymer mixture to be used in the water will be filled into the molds that are made of PDMS and dried, and the second polymer mixture that will be applied to the first mixture will be placed so that only the active substance will exist in the needle. Such an approach will minimize the wastage of drugs, as the drugs held in the baseplate will not be wasted(61).As an example of a peptide, exenatide was incorporated into the DMNs system via two-step casting(62).Lysozyme was also incorporated into the system using two-step casting as an active ingredient in the production of DMNs via micromolding (63).

3.3.Drawing lithography

The acceptable production results of drawn 3D microstructures heavily depend on the polymeric material's viscosity levels during its glass transition phases(64).During the manufacturing glass transition step, the essential drawing lithography procedure depends on the viscosities displayed by polymers. Three-dimensional microneedles emerge through polymer material deformation by elastic extension that starts from shock wave application until the stretching phase terminates(65).The baseplate contains drawing pillars that accept melted polymer material that extends into needles through vertical plate movement. Materials need exact temperature control during both curing and gentling microneedle structures as a part of the production process(66). Assuming the role of hydrolysis, the enzyme maltose-glucoamylase functions by splitting down ordinary safe molecules of maltose, thus releasing biomolecules encased inside. The controlled viscosity within DMNs depends on the regulator because it functions vitally during glass transition.Different microneedle structures can be made by adjusting maltose viscosity through drawing lithographic production, but strict process control is needed to preserve microneedle integrity. The advanced manufacturing technique eliminates traditional challenges by establishing quick manufacturing procedures that do not use molding techniques(65). The steel supporting post directs the stretchable fabrications of biodegradable PLGA thermoplastics during microneedle production at defined stretching velocities. The quick failure of the top part of the material produces the structure needed for making microneedles. Changes in temperature and the speed of fracture control the shape of microneedles immediately after cooling finishes.The material properties require close monitoring to stop any changes that result from heat treatment during this operating step(43,67).Magnetorheological drawing lithography represents the method that Chen and

colleagues used to create flexible microneedle arrays. A flexible substrate uses deformed curable magnetorheological fluid drops to create its one-step product. Envisioning the procedure required one hour and 90°C heat to produce the MN that boosted calcium protein delivery to rabbit skin(68). Lee et al. produced microneedle cuff (MNC) devices to serve medical drug delivery functions into blood vessel media and tunica adventitia. The drug delivery capabilities of microneedle cuffs exceed those of perivascular devices because these needles directly access tissue layers to provide slow medication release, which reduces intimal hyperplasia (IH)(69).

3.4.Centrifugal lithography

The polymer material moves along centrifugal force lines to create pillar-shaped needles when processed through centrifugal lithography systems(70). When a viscous hyaluronic acid (HA) droplet rested on solidified HA material, subsequent application of centrifugal force assisted by a non-adhesive film allowed formation of the first layer. Two sequential steps in the process involved adding another HA droplet to the initial layer, followed by repeating the centrifugation process(71).The result was a set of intricate needles with the appearance of wine glass shapes and a durable collar section at the plate base but a raindrop-formed tip. The practical use of this technology is restricted by the demands for specific mechanical properties of materials and active pharmaceutical ingredients (APIs), which can be effectively integrated and administered. The material loss that happens to the outer plate generates waste of active pharmaceutical ingredients. The industrial production application of centrifugal lithography remains restricted because of its single-step manufacturing approach, but its current usages are limited(70).

3.5.Photopolymerization

Photosensitive monomer polymerization occurs through microneedle molds as they activate liquid substances at normal ambient temperatures. The polymer solution transforms instantly from liquid form to solid because it does not require organic solvents when exposed to UV light. The rapid manufacturing process requires no supplementary drying operations because of its quick methodology. The same effects on medication stability and activity that exist during two-step casting can occur when UV radiation is present here too(14). Researchers at Sullivan et al. invented an innovative procedure for photopolymerization at room temperature, which preserves biomolecules and vaccine stability (72). The production of DMNs often utilizes high water-soluble polyethylene pyrrolidone (PVP) because of its water solubility properties(14). Adding microneedle molds to in-situ polymerization of monomers leads to DMN production(72).

3.6. Atomized spraying method

This is the process in which an atomized spray is created, and this atomized spray is created by a nozzle connected to an air source and a formulation of liquid. To dissolve MNs, the formulation is placed in PDMS molds, which are left to rest at room temperaturefor 2hs(73).This technique greatly lowers problems of liquid surface tension and viscosity and looks after total and uniform filling of the mold.Also the parameters of the spraying procedure and layering sequence may be changed to create microneedles with a specific layered shape, which may be designed to suit a particular drug delivery performance. The atomized spraying process is flexible, lendsitself to high-volume production, and can be performed in modest conditions, which has made this process compatible with a wide variety of drugs and biologics, including products that are heat- and environmentallysensitive(74).

3.7.Computer Aided Design (CAD) drawings

The designs employed in this study were finally sketched up with the help of AutoCAD (AutoCAD 2020, Autodesk Inc., San Rafael, CA) software. The microneedle structure was constructed using the circles with a distance of 600 µm between the needles (center of one circle to the center of the next). The cylindrical-type dissolving microneedles were fabricated by drawing a circle with a diameter of 90.9 µm with the software, which was maintained and repeated 60 times in order to create a structure of the needle type. To prepare the cone-like dissolving microneedles, it is important to provide a circle diameter of a current of 90 M was drawn, and the current was repeated 20 times. Then followed that by 50 10, 20, and 30 um, and each diameter was repeated 10 times and totaled to 60 repetitions to make the microneedle structure. 6 dissolving lines (2 mm long each) at an interspace of 600 m were printed in one pass. The serpentine mechanism was chosen to fill the circles with the help of the VMTools (Virtual Machine) software. After designing everything, all of it then was to be changed from a 'dxf' to a 'prg' so as to form the toolpath file, which is readable by the aerosol jet printer. The micro needles were printed by depositing the formulation at a surface where the microneedles were located, after which another printing was done on the next layer(73).

Table 3 : Prons and cons of Fabrication method

Method	Prons	Cons	Reference
Droplet-Born Air-Blowing	Mold-free,simple setup, No UV/heat (gentle process), Scalable	Poor shape uniformity, Limited control over dimensions	(75)
Micromolding (Solvent Casting)	Widely used, Compatible with many polymers, High drug loading	Long drying time, Risk of voids/shrinkage, Crystallization of drug	(38)
Drawing Lithography	Sharp, high-aspect ratio needles, No mold needed, Customizable height	Technically complex, Time-consuming, Low scalability	(36)
Centrifugal Lithography	High uniformity, Precise geometry, Scalable with automation	Requires centrifugal setup, Limited material options	(76)
Photopolymerization	High precision (e.g., DLP, 2-photon), Rapid prototyping, No drying step	UV may degrade drugs, Limited to photopolymers, High equipment cost	(36)
Atomized spraying method	Uniform Coating and Drug Distribution,Minimizes Material Wastage	Equipment Cost and Complexity,Clogging and Maintenance Issues	(77)

4.Evaluation of DMNs

The safe and reliable development of microneedles depends heavily on the essential practice of characterization methods. Basic techniques frequently serve to examine microneedle features according to the following list.

4.1.Scanning electron microscopy (SEM)

SEM technology determines microneedle morphological features through measurements of height with base diameter measurements as well as tip diameter measurements and the needle gap size. The stage required for vision enhancement receives a gold solution application before affixing the microneedle patch(13).

4.2. Mechanical characterizations

The evaluation enables the identification of the mechanical strength of prepared microneedles to resist the various forces in preparation, transport, storage and use.

4.2.1.Axial force test

The axial force test stands as the most widely used method that subjects both the MN array base and the needles' points to vertical force distribution(78).The fundamental goal of this essential mechanical evaluation is to determine the breakdown force of needles. The estimation range provided by the needle insertion force measurement stands as the essential information because it determines the failure forces for needles. The test is recognized as the safety point within the field (24).Several axial force investigations, including various tools and computation techniques, have determined the failure forces within MNs. The force and displacement data underwent calculation to determine failure through the work of Davis et al. (ScopeTest1, Endura TEC, Minnetonka, MN, USA)(79).

4.2.2. Insertion test

The insertion test provides a more important and precise measurement than the axial force test does. Various kinds of skins, including human and rat as well as pig, underwent examination under this test. The strength of MNs to deliver drugs across skin surfaces makes them advantageous tools. The assessment of needle-drilled holes in skin samples must be performed for essential purposes because numerous mechanical tests exist that simulate needle fracture force. Under laboratory conditions, Donnelly et al. studied the skin surface of a deceased piglet using digital microscopes after inserting a moveable cylindrical probe with an MN attached to it. The material testing equipment served to determine transverse compression load according to the methodology described by Jun et al. The researchers from Khan et al. used a texture analyzer to study how different MN pressures affected how deep they would penetrate into newborn pigskins. Researchers operated a texture analyzer to conduct insertion tests on three Caucasian male human skin samples, according to Davis et al. OCT technology was utilized to examine the penetration depth of MN implants in human skin during a different research study(2).

4.3.*In-vitro* test

A diffusion cell apparatus is used to test permeation of drugs through the skin. The pig ears utilized in the research were taken at the local abattoirs when the animals had just been killed using an electric current. Previous treatment of the ears was not performed; instead, the ears were brought to the laboratory in a cooling box. The pig ears were in the laboratory. It was cleaned thoroughly using distilled water, and its hair was taken out of the outer portion of the pig ear with the help of electrical hair clippers. The entire skin of the external region of the pig ear was delicately removed and separated from the underlying cartilage with the help of a

scalpel, and fat over the skin was taken to a depth of 1.2 mm and mounted in permeation cells positioned between the donor and receptor sides, and cumulative permeation curves of microneedle-treated and untreated skin were compared(80).

4.4. *In-vivo* test

Invivo experiments are usually conducted on hairless rats who are put under appropriate anesthesia. Variables like transepidermal water loss (TEWL) are assessed prior to the microneedling and after it with instruments including the Delfin Vapometer. The microneedles that are tested and studied are used in varied diseased conditions. This can be used in lieu of local or systemic therapy for normal patients or to deal with unconscious/agitated patients with abnormal behavior(80).

4.5. Skin penetration test

The optical coherence tomography (OCT) was used to evaluate the penetration of microneedles into the skin. Penetration was studied by use of neonatal porcine skin. Skin was preserved in the form of -20°C between experiments. Skin was thawed under PBS at 37°C for 30 min immediately before analysis and shaved with a disposable razor. Skin was added, SC side upwards, onto a sheet of dental wax to maintain support, followed by insertion of DNA-free microneedles into the skin by hand with manual pressure applied, after which they were held in place, within the skin, at 30 s intervals. After insertion, needle images are seen. Measurements of the penetration were carried out utilizing an EX1301 OCT microscope (Michelson Diagnostics Ltd., UK). 2D images of microneedles penetrating differently into the skin were then analyzed by ImageJ software (National Institutes of Health, USA)(81).

5.Applications of dissolving microneedles in drug delivery

Table 4 : The table represents various diseases, the corresponding drugs delivered using DMNs and the type of dissolving microneedle utilized

Disease	Drug / payload	Types of DMNs	Description	Reference
Influenza	Influenza vaccine	Sugar-based DMNs	The skin absorption of vaccine occurs rapidly through DMN devices made from trehalose or similar sugars because they dissolve quickly.	(82)
Diabetes Mellitus	Insulin	Polymer-based DMNs	The release of insulin through DMNs is controlled when PVP serves as the polymer base	(83)
Hypertension	Metoprolol	Carbohydrate-based DMNs	The DMNs based on carbohydrates dissolve when they are inserted into the skin leading to metoprolol delivery through the transdermal pathway.	(43)
Osteoporosis	Teriparatide	Hyaluronic acid-based DMNs	The vasodilation system using hyaluronic acid DMNs dissolves to release teriparatide efficiently into the skin tissue.	(84)
Tuberculosis	Rifampin	Gelatin-based DMNs	The gelatin-based DMNs enable direct passage of rifampin to enter the systemic circulation by dissolving them.	(13)

HIV/AIDS	Antiretroviral Drugs	Chitosan-based DMNs	The use of chitosan-based DMNs represents a biocompatible system to administer antiretroviral treatments.	(85)
Melanoma	Chemotherapeutic Agents	Silk fibroin-based DMNs	Local chemotherapy delivery becomes possible through DMNs made from silk fibroin materials which break down over time.	(3,86)
Acne Vulgaris	Clindamycin	Polyvinyl alcohol (PVA)-based DMNs	PVA-based DMNs dissolve in order to release clindamycin directly into acne lesion areas	(87)
Hair Loss (Alopecia)	Minoxidil	Maltose-based DMNs	DMNs containing maltose dissolve quickly which improves the delivery of minoxidil to hair follicles.	(77)
Antimicrobial skin infections	Antibacterial agents	Carbohydrate/polymer DMNs	It achieves direct antimicrobial effect, prevents oral side effects and predisposes higher patient comfort in the sites of infection	(88)
Ocular (Anterior/Posterior Eye)	Cyclosporine A (CsA)	PVP-based dissolving MN patches	Facilitates quick trans-scleral administration to the back of the eye, crosses the tear barrier, and increases bioavailability towards uveitis	(89)
Nucleic Acid Therapies	DNA/RNA constructs	Polymeric dissolving MNs	Guards unstable nucleic acids, enhances stability and delivery to the inside of the cells, evades enzyme degradation	(89)
Infantile Hemangioma	Propranolol hydrochloride	HA and PVP DMNs	Administering propranolol topically might enhance drug local levels, reduce the frequency administration, improve patient compliance	(90)
Chronic Pain	Lidocaine	CMC-based DMNs	The dissolution process of Carboxymethyl cellulose DMNs generates localized anesthetic effects.	(91)

6.Challenge associated with DMNs

The utilization of dissolving microneedles (DMNs) encounters multiple barriers which affect their effectiveness and large-scale production and medical approval process. Several hurdles affect the effectiveness of DMNs since they encompass mechanical issues alongside pharmacological complications, manufacturing complications, skin interaction factors, patient usability requirements, and regulatory needs.

6.1. Mechanical strength and penetration efficiency

DMNs manufactured from polyvinyl alcohol (PVA) frequently demonstrate low mechanical strength since this makes the devices prone to fracturing during insertion. The material brittleness appears as research studies show higher aspect ratios reduce structural strength, which causes increased breakage rates when performing drug delivery tasks(3).The effectiveness of skin penetration by DMNs directly depends on how their needles have been designed. A poor needle design prevents drugs from delivering correctly because it does not penetrate the skin deeply enough(92).

6.2. Drug loading and delivery constraints

Each DMN medication delivery system has the ability to release only minimal doses with a maximum volume of micrograms per skin unit. One model with thirty-six needles released a drug amount of 1.44 micrograms of sulforhodamine B. The restricted delivery quantities restrict their usefulness in therapeutic applications needing high doses(43)(2).The storage stability of biologic molecules and macromolecules encapsulated in DMNs remains a concern because they tend to degrade during fabrication or storage periods. The storage time of 60 days leads to activity loss of lysozyme. Drug delivery systems require stable drugs at all times for successful delivery(43).Transition times of DMNs are brief when incorporated; however, these rates do not match standard medication release profile(30).

6.3. Manufacturing challenges

The fabrication methods, including micromolding and photopolymerization, need exact specifications to achieve uniform needles with stable drug encapsulation. The penetration depth together with drug release effectiveness depends on the needle size and space between needles(92).The use of DMNs faces challenges regarding drug sterilization because standard procedures utilizing gamma radiation or ethylene oxide break down proteins and vaccines, thereby restricting the medicines selectable through this delivery method(43). Industrial-scale production of drug-infused microneedles faces obstacles because advanced precision manufacturing techniques, including micromolding, require much more cost alongside extensive complexity(30).

6.4. Skin interaction challenges

The way DMN penetrates into the skin depends on skin elasticity together with hydration levels and hair density. Research demonstrates that about 67% of DMNs are unable to properly penetrate the skin through hairy areas but achieve better penetration through bare skin models. The materials from DMNs produce skin irritations that cause redness and swelling and allergic reactions when in contact with application spots(43). The stratum corneum may sustain damage after multiple treatments as micro-scarring occurs along with stratum corneum injury. The wide range of skin thickness in patients requires specific treatment protocols because standard drug calculations become less accurate (92).

6.5. Patient usability challenges

Extension of use time (≥2 hours) for DMN patches hampers patient compliance among some people because of their need for a longer treatment duration. Problems with self-administration include both improper method of application angle and uneven pressure, which can result in drug release failure and needle breakdown(2).The low intrusiveness of DMNs fails to overcome needle phobia in certain patients because of psychological barriers(30).

6.6. Regulatory and clinical barriers

The FDA/PMDA has not approved any dissolving microneedles because standard guidelines are missing for essential characteristics such as mechanical strength, dissolution rate and drug release profile measurements(30)(92). A deficiency of pharmacokinetic data from clinical studies reduces the effectiveness of dose optimization along with safety evaluations for therapeutic approaches based on DMN(92).

6.7. Economic barriers

High development costs occur because DMN development demands expensive research and development time alongside profound material development as well as extensive testing needs. The competition for DMNs arises from established transdermal delivery systems such as patches along with hypodermic injections unless the new system proves superior through enhanced patient experience combined with better therapeutic outcomes(30).

6.8.Temperature-dependent stability

Thermal Degradation: For biologics (such as proteins and extracellular vesicles), high temperatures (>40°C) hasten polymer breakdown and medication instability. For instance, EVs generated from human adipose stem cells in DMNs only remained active for more than six months when kept below 4°C(93).

6.9.Humidity sensitivity

DMNs are composed of water-soluble polymers (such as hyaluronic acid and polyvinyl alcohol); they are very hygroscopic. Premature disintegration or swelling may result from exposure to ambient humidity, which might impair medication delivery and compromise mechanical integrity. Because moisture absorption destabilizes the microneedle matrix as well as encapsulated medicines, non-vacuum storage circumstances make this problem worse. The desiccant wrapping and humidity-controlled storage spaces are two examples of solutions(3,94).

7.Merits

7.1.Stability and storage

By improving the chemical integrity of vaccination antigens and encapsulated medications, these microneedles may often eliminate the requirement for cold storage. This feature is especially advantageous for delicate biologics and vaccinations(95).

7.2.Self administration capability

By making self-administration simple, these microneedles improve accessibility and lessen reliance on medical specialists(92,96)

7.3.Safety and reduce risk of infection

Although they dissolve upon insertion and leave no sharps waste behind, dissolving microneedles provide a reduced danger of cross-infection. Patients as well as healthcare providers are safer thanks to this feature(92).

7.4.Rapid and Uniform Dissolution

Polymer DMN based on PVP/PVA may dissolve easily into the interstitial fluid of the skin, in a range of 100-150 seconds, guarantees immediate drug release and little delay to the user. This fast dissolution is independent of various geometries of needles and there is a consistent performance of the same(97).

7.5.Minimally Invasive and Painless Drug Delivery

DMNs invade the stratum corneum without accessing pain receptors and this makes the process almost painless when compared to the traditional hypodermic needles. This aspect is particularly useful in the affected children and patients with phobia to needles since it enhances patient compliance and acceptance of therapies(98)

8.Demerits

8.1.Limited depth of delivery

Compressed tissue might accumulate in certain types of skin and block microchannels, which decreases the ability of pharmaceuticals to penetrate. The implementation of TDD technology brings multiple built-in drawbacks, which Minnesota does not have exclusively. The use of compressed tissues can result in skin redness and discomfort together with swelling and skin irritation that can lead to site infection at the application area(99).

8.2.Mechanical and Structural drawbacks

8.2.1.Inferior mechanical strength: The penetration strength of DMN devices usually remains inferior to metals and ceramics, which makes it difficult for them to effectively penetrate the stratum corneum(100).

8.2.2.Risk of breakage: When inserting DMNs into the skin, they can break easily, leading to difficulties in drug delivery together with skin retention of broken needle pieces(101,102).

8.3.Skin releated adverse effects

Drugs might leak from the delivery system, or the needles might have difficulty pierced through the skin at oblique angles(99,103).

8.4.Variability in Penetration Depth

The depth of drug penetration into the skin may also vary due to differences in penetration with different individuals, due to differences in the thickness and elasticity of different skins(2,104).

8.5.Potential for Skin Injury and Inflammation

It is typically safe, though careless insertion or excessive insertion pressure (particularly on the more advanced designs, such as micropillar-integrated DMNs) can cause the likelihood of skin injury, inflammation or even inadvertent insertion of the support structures(105).

9.Patents and clinical trails

The data provided in clinicaltrials.gov until the end of December 2021 show that the number was 148 clinical trials with microneedle technology, of which 7 percent of clinical trials used DMNs (82). As an illustration, Micron Biomedical, Inc. was involved in DMN testing with the measles and rubella vaccines; the testing was finished on 31 December 2022 (NCT04394689). This was phase 1 and 2, which have been done on various ages starting as young as 9 months, infants, as well as old as 40 years (NCT0439468904394689 2020). Other than this company, there are various other companies working by developing products of DMNs to provide biological products like Dissolvable Microneedle Chip (BioSerenTach, Phase 1 clinical trial), MIMIX (Vaxess Technologies, Phase 1 clinical trial), and SkinJect patch (SkinJect, Inc., Phase 1/2 clinical trial)(82).

Table 5 : Some Patent List of Dissolving Microneedle

Patent No	Invention	Formulation	Year of Invention
US2020197286A1	Successful administration protein/peptide using impregnation of microparticle	Microparticle: epidermal growth factor, poly(lactic-co-glycolic-	2020

	carrying protein in a soluble microneedle	acid), PVA DMNs system: Oligo-HA, Sodium CMC, trehalose, glycerin, hydrogenated castor oil-40, water	
KR20230116976A	Honeycomb heating of nanocomposte and a hydrophilic polymer to make soluble microneedle of increased strength in terms of the mechanics involved in it	Nanocomposite biopharmaceuticalamino clay: magnesium phyllosilicate and liraglutide/ teriparatide Polymer: PVA	2023
CN115708869A	A preparation process able to preserve the activity of the and a process that provides a microneedle patch vaccine that is made of polypeptide	Soluble matrix: HA 3-5 WDa and PVP 4-6 WDa	2023
CN116036003A	Soluble microneedle patch to stimulate skin healing and method of preparing the same	Dextran, trehalose, HA, water	2023

Table 6 :DMNs product on market

Product name	Active ingredient	Application site	Duration (hour)	Ref
Self-Dissolving Microneedle Patches	Collagen, Peptides, Caffeine	Facial skin	4	(Schminkles 2023)
Acropass Trouble Cure	Arginin, Palmitoyl oligopeptide, Niacinamide, Sodium hydroxide, Ferulic acid, Sodium Hyaluronate	Facial skin	2	(Acropass 2023)
Dissolving Microneedle Eye Patches	Acetyl Hexapeptide-8, Undaria Pinnatifida, Extract and Corallina Officinalis Extract, Heptatpeptide-7 Icelandic Complex	Skin under the eye	2	(Iceland 2023)
Acropass Soothing Q	Caffe Oil Deca, Peptide-9, Licorice, Tea tree Leaf Oil, Niacinamide	All skin	2	(Acropass 2023)
Needrop	Niacinamide, Astaxanthin, Collagen, Haematococcus bullpialis, Arbutin, Placenta, Ceramide, Dilauroyl, Glutamate lysine Na, Glycyrrhizic acid, Vanilyl butyl, Retinol derivatives, Vitamin C derivatives	Skin under the eye	5	(Nissha 2023)

10. Trends and Prospectives

10.1. Nucleic Acid Delivery: New research emphasizes that DMNs are an efficient method of administering all types of nucleic acid-based therapeutics, and 83 percent of preclinical trials achieved similar efficacy or better than other administration methods(106). This is especially the case for vaccines (e.g., viral and cancer vaccines) and gene-silencing drugs.

10.2. Advances in Fabrication and Drug Delivery: Recent studies also show how dissolving microneedles (DMNs) can be created with more effective application than the conventional technique of 3D printing, making it possible to change the shapes and easily produce them. The innovations improve drug loading, rates of dissolution, and the versatility of use, including veterinary and complex applications of drug deliverance(97).

10.3. Dual-Drug and Sustained-Release platforms: In a 2025 study, bimodal dissolving microneedles, which consisted of a nanoparticle coating that delivered diclofenac and dexamethasone co-delivery, were proposed. This platform obtained significant amounts of drug loading, released extended and efficient penetration (in excess of 90 percent into the stratum corneum), and extended treatment levels in vivo over 72 hours. This is a breakthrough based on setting limitations that were ineffective in loading in the drug area and ensuring that the combination therapy is possible and potential might be achieved, particularly in chronic diseases such as osteoarthritis(107).

11.Conclusion

Dissolving microneedles (DMNs) are an innovative breakthrough in transdermal delivery, providing an alternative approach that neither injects the drug into the body nor causes pain or insertion. The fact that they penetrate the stratum corneum barrier and are dissolved upon administration wipes away issues of biohazardous waste and device recovery; this makes them specifically appealing to clinical and self-administered treatments. These microstructures are made of biodegradable polymers, which help them breach the epidermal layer to allow targeted delivery, which would contribute to major drug bioavailability and compliance in patients. DMNs are about to achieve immense growth and wider clinical use, especially in vaccines, cosmetics, and chronic disease treatment. With the development in polymer science and manufacturing, DMNs provide a more scalable platform of precision and pain-free. In the future, it is possible to combine novel polymers, intelligent materials, and adaptive systems with fabrication and modeling for greater precision, safety, and effectiveness of DMNs.

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Author Contribution

Kavin Kamaraj- Conceptualization, Methodology, Writing-original draft, Writing-review and editing.

Kavitha Rajendran- Project administration, supervision, Writing-review and editing.

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The authors declare no competing interest.

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