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The etiology, pathogenesis, treatment, and development of transdermal drug delivery systems for rheumatoid arthritis

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Rheumatoid arthritis (RA) is a long-term autoimmune disease that causes irreversible deformity of joints and disability of body parts. The symptoms include synovial tissue inflammation and cartilage and bone damage. To reduce the inflammation, therapeutic drugs are often used to target and limit the inflammation factor. Nonetheless, there are significant problems with the treatment such as a first-pass effect, gastrointestinal side effects, skin stratum corneum barrier, *etc*. Hence, a transdermal delivery system (TDDS) is applied for the treatment of rheumatoid arthritis as it increases the effectiveness of the drugs by overcoming the difficulties mentioned above. This paper reviews the research progress of transdermal drug delivery for the treatment of rheumatoid arthritis and explores the details of dosage forms such as gel, patch, drug microneedles, nanostructured lipid carriers and drug-loaded electrospun nanofibers, which provide numerous ideas for these dosage forms in RA treatment when using transdermal drug delivery methods.

1. Introduction

1.1. Introduction of rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a systemic and chronic autoimmune disease with symptoms such as synovial inflammation, damage to the joints, osteopenia, *etc*.[1] The pathophysiology of RA is accompanied by an imbalance of the immune system, which leads to the infiltration of inflammatory cells and dysregulation in the proliferation of synovial fibroblasts.[2] It causes damage to synovial tissue, cartilage, and joints. The prevalence rate of RA is up to 1% of the population but still it may affect millions of patients worldwide with an economic burden on the society.[3,4] RA can occur at any age and in a higher proportion of females than males.[5] RA can affect people at any age but with an increased incidence rate above 40 years old and in the geriatric age group.[6]

1.2. Genetic and environmental factors involved in the pathogenesis of RA

The pathogenesis of RA is not completely understood but can be related to genetic and environmental factors, or both.[7] Smoking, periodontitis, and the gut microbiome are the environmental risk factors associated with the genetic factors causing RA.[8] Smoking is considered another important triggering factor for RA.[9] Studies show that tobacco can stimulate antigen-presenting cells (ACPs) in the lungs and lead to the development of autoimmunity.[10,11] How environmental factors exactly contribute is yet to be evaluated; however, there might be hundreds of loci related to RA that can become mutated.[12,13] These loci can result in the overproduction of autoantibodies and activate B cells, T cells, and macrophages, causing the production of inflammatory factors.[14,15] In between these loci, the major histocompatibility complex (MHC) of genes is tightly linked to RA as it encodes the proteins, mainly those of MHC classes I and II, that will bind to the T cell receptor and activate it.[16] No wonder then that the types of loci that encode post-translational modification enzymes, co-stimulatory pathways, and intracellular regulatory pathways can cause abnormal immune activation or regulation.[2,17]

1.3. The involvement of inflammatory factors in immunopathogenesis of RA

These inflammatory factors lead to the damage of cartilage and bone and result in joint erosion. Synovial inflammation is

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very painful and directly linked to pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β).[18] These immunological reactions give rise to severe pathological conditions.[19] TNF-α can cause the abnormal expansion of fibroblast-like synoviocytes (FLS).[20] Then, it will lead to gene overexpression of cathepsin and matrix metalloproteinases (MMPs).[21] As a result, collagen and proteoglycan will start to break down and destroy the cartilage and bone.[22] A high level of IL-6 can lead to unusual activation of the Janus kinase (JAK)-signal transducer and the transcription pathway.[23,24] Then, it affects T cell proliferation, B cell survival, proliferation, and activation to worsen the inflammation.[25] The major pathophysiological pathways, including the major hallmarks of RA, are illustrated in Fig. 1.

2. Conventional treatment of RA

2.1. Therapeutic drugs used to treat RA

In the mild and medium stages of RA, herbal drugs, biologicals, and therapeutic drugs can be used as a treatment that can relieve pain and reduce joint dysfunction.[27–29] There are four main types of drugs for RA: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) or steroidal drugs, biologicals, and disease-modifying anti-rheumatic drugs (DMARDs).[25,30–32] NSAIDs and GCs are related to inflammation symptomatic relief but are unable to provide pathophysiological relief.[33] Therapeutic relief can be achieved using Janus kinase inhibitors such as baricitinib and tofacitinib.[34] These drugs are very effective, especially upon combining with either of the other anti-rheumatic drugs, or more specifically with monoclonal antibody drugs such as sarilumab and golimumab.[35,36]

2.2. Mechanism of action of NSAIDs to decrease inflammation in RA

NSAIDs are commonly used in the early stages of RA for pain-killing and anti-inflammation purposes,[37] for example, naproxen, ibuprofen, diclofenac, even aspirin, *etc*. Conventional NSAIDs are non-selective cyclooxygenase (COX) inhibitors, which can inhibit both COX-1 and COX-2, whereas selective COX-2 inhibitors are celecoxib, valdecoxib, parecoxib, *etc*.[38,39] These drugs can effectively counteract the reaction of

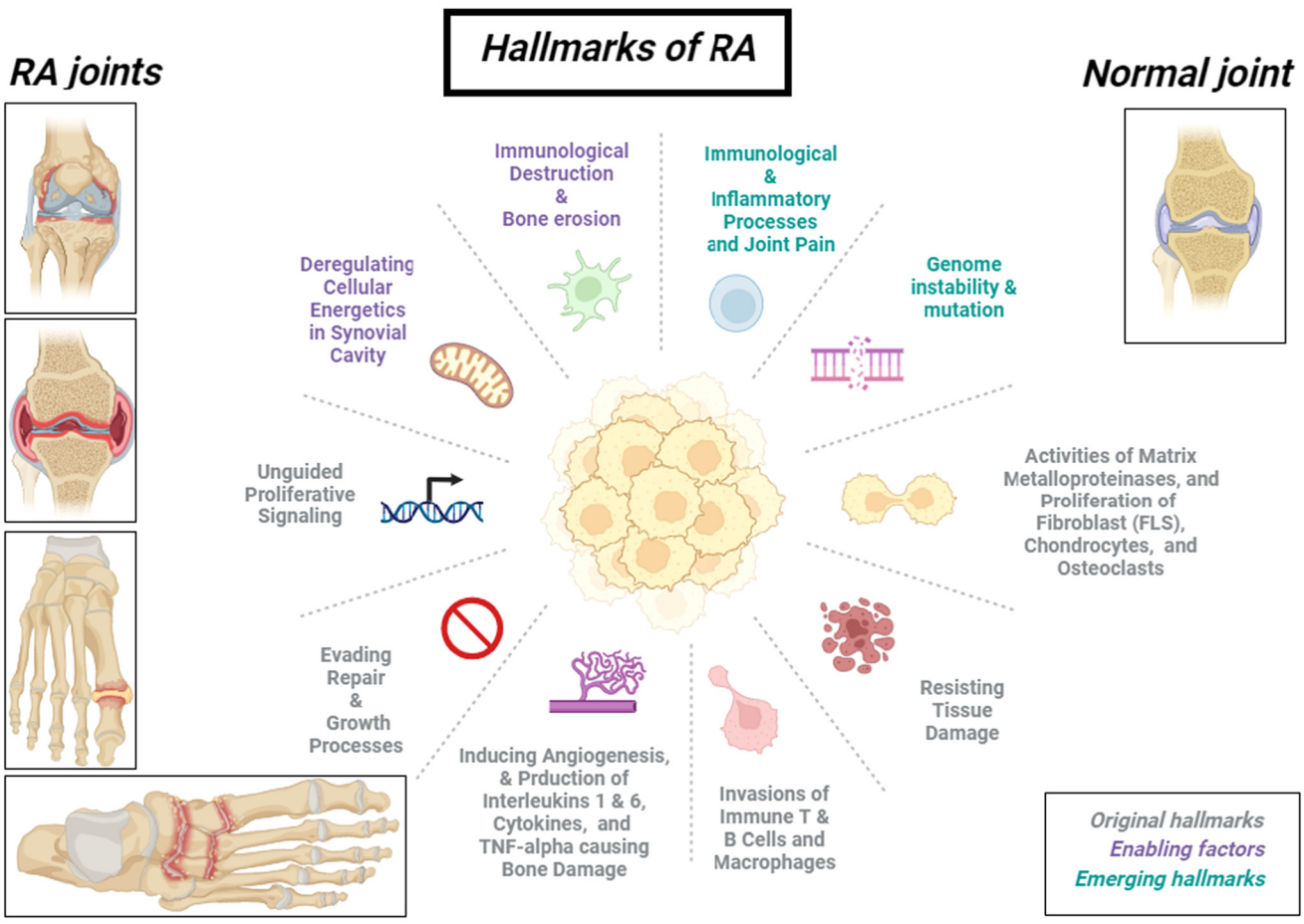

Fig. 1 The immuno-pathophysiological pathways of RA. The major hallmarks of RA involve genetic cues leading to the inflammatory processes. Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[26]

converting arachidonic acid to inflammatory prostaglandins without affecting the levels of beneficial prostaglandins.[40] However, selective COX-2 inhibitor drugs might lead to some cardiovascular complications as an adverse effect.[41] Most of NSAIDs are organic acids with an aryl group and low pK_a values. Due to these characteristics, NSAIDs can locate and stay in the inflammation areas with their characteristic lower pH conditions.[37] As a result, the production of prostaglandins, which cause inflammation and pain, can be reduced.[40,42]

2.3. Mechanism of action of GCs to decrease inflammation in RA

GCs are drugs that contain steroidal hormones such as prednisone, dexamethasone, *etc*.[43] Due to the lipophilic structure of GCs, they can pass through the plasma membrane of the cells and bind with the GC receptors (GRs). After the GC/GR complex forms, it is transported to the nucleus and limits conformational changes after binding with the negative GC-responsive element (GRE) in the nucleus to suppress the gene transcription of immune proteins.[44] Moreover, the GC/GR complex can interact with transcription factors such as nuclear factor-κB (NF-κB). In this way, GCs can inhibit the transcription of some pro-inflammatory cytokines that are produced by the monocytes and macrophages, including IL-1β, IL-6, and TNF-α, which are related to RA.[45–47]

2.4. DMARDs for RA treatment

DMARDs are a group of first-line medications for RA treatment.[48] DMARDs are further classified into a traditional class – "conventional synthetic DMARDs" (csDMARDs),[49] biological DMARDs (bDMARDs),[35,50] and targeted synthetic DMARDs (tsDMARDs).[51,52] The csDMARDs are commonly used for treating synovial inflammation and reducing joint damage.

2.4.1. An overview of methotrexate and leflunomide as csDMARDs. Methotrexate (MTX) is the most common csDMARD used in RA treatment.[53] There are several other csDMARDs commonly used in the treatment of RA, such as leflunomide, hydroxychloroquine, sulfasalazine, *etc*.[54–56] MTX is a folate analogue and enters into the cell by binding to the folate receptor as it contains an amino group, a methyl group, and a pteridine ring. MTX after being metabolized, attains a polyglutamate (derivative) form (MTX-glu). While MTX-glu is a substance mediating purine metabolism, which can increase the adenosine level in blood, while adenosine itself can bind with the adenosine A2 and A3 receptors, which can lead to the inhibition of the secretion (and production) of pro-inflammatory cytokines and therefore it may relieve patients from the inflammatory symptoms.[57]

Leflunomide has been found to target the dihydroorotate dehydrogenase (DHODH),[58] which is an enzyme responsible for the biosynthesis of pyrimidine.[59] The drug inhibits the DHODH enzyme and interferes with the oxidative conversion of dihydroorotate to orotate. This causes the decreased secretion of inflammatory cytokines, which is desirable for treating RA.[59]

2.4.2. An overview of bDMARDs. The bDMARDs are biological substances that are developed and produced through biological processes using organisms as sources.[35,49,60] The bDMARDs used in the treatment of RA include anti-TNF, and anti-IL-6 drugs, b-cell antigen (CD20-targeting antibody), and selective T cell co-stimulatory modulators.[61,62] These biological agents can target and limit intercellular signaling eliminating biosynthesis, or reducing the functionality of specific inflammatory factors.[23,35] While TNF-targeting drugs that include infliximab, adalimumab, etanercept, abatacept, golimumab, and certolizumab can block TNF-α binding to its receptors,[63–65] IL-6 receptor inhibitors, such as tocilizumab and sarilumab, are modified human anti-IL-6 receptor monoclonal antibodies that target and bind to the IL-6 receptor on the cell surface.[35] The selective T cell co-stimulatory modulator abatacept can reduce joint damage, RA activity, and pain, and can inhibit the activation of T cells, which can relieve inflammatory reactions.[66–68] The B cell targeting drug rituximab, which is a chimerical monoclonal antibody, targets the CD 20 molecules on the B cell surface, which can ultimately reduce the number of B cells in the RA patient.[69–71]

2.4.3. An overview of tsDMARDs. The tsDMARDs are low molecular weight inhibitors that can easily pass through the plasma membranes of the cell.[72,73] The tsDMARDs then bind to the molecule that responds to intercellular signaling, thus limiting the activity of the target substance.[74,75] For example, tsDMARDs can interrupt and block the JAK pathway, the NF-κB pathway, *etc*.[76–78] tsDMARDs include tofacitinib, baricitinib, upadacitinib, and peficitinib.[79–81]

2.5. The traditional drug delivery approaches to treat RA

The treatment of RA is aimed at preventing inflammatory processes and reducing the pain of patients.[76,80,82,83] The drug delivery systems used in this treatment are in the dosage forms of tablets, capsules, and injections but with certain limitations.[84–86] The major routes for administration of drugs for RA treatment are illustrated in Fig. 2. However, the oral method could, for instance, cause toxicities, adverse effects, low bioavailability, a first-pass effect, or be quickly eliminated by the liver and kidneys, while the IM/IV methods (or even intrathecal injections) may cause phlebitis, skin hypersensitivity, irritation, infections, damage to tissues, damage to vital organs, anaphylaxis, and even shock.[87–89] Considering the general limitations of the traditional dosage forms, transdermal drug delivery systems (TDDSs) are becoming the latest approaches to treating RA.[90–92] A desirable TDDS once developed can be used to avoid most of the side effects of traditional dosage forms, with the potential to enhance bioavailability.[93,94] This report reviews the research on the TDDSs developed to treat RA and discusses the various types of TDDSs used to treat RA.

3. Establishing the need for transdermal drug delivery systems

Drug delivery orally is the most desirable system for patients, especially those who require long-term consumption of thera-

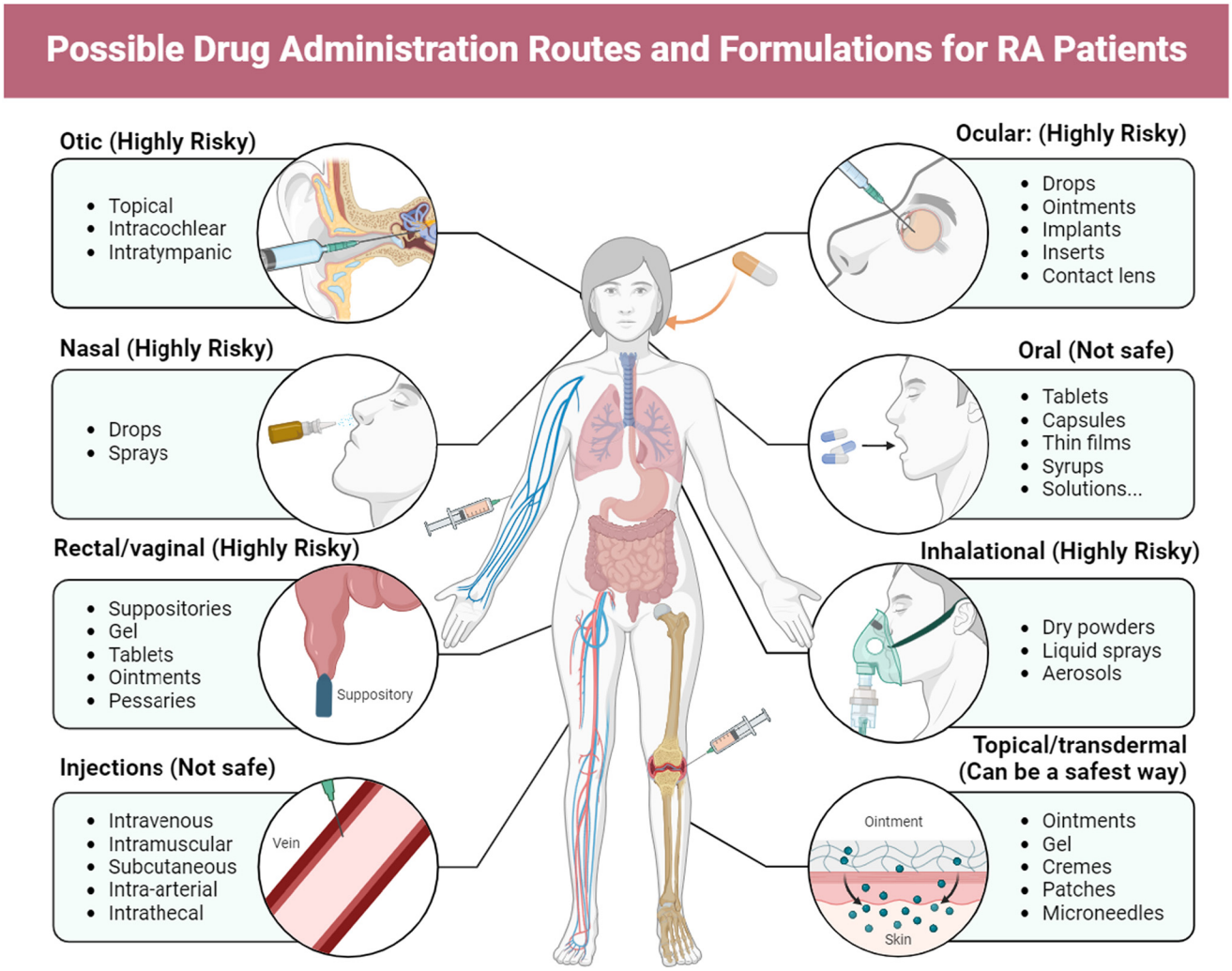

Fig. 2 Proposed drug administration routes and formulations to treat RA. Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[95]

peutic drugs. Therefore, it is the most usual method for the treatment of RA because of its low cost, convenience, safety, and flexibility. Moreover, injection is also one of the common ways involving intraarticular or subcutaneous methods to directly inject the drug into the joint area.[96–98] Injections can reduce certain limitations and adverse effects of the conventional oral route method, where drugs undergo gastrointestinal metabolism leading to poor bioavailability at the target joints.[99,100] On the other hand, the intra-articular injection can improve the drug's efficacy as it increases drug retention times in the joint and promotes more sustainable drug release.[87,101]

Most oral NSAID formulations are formulated to have low solubility, making them less bioavailable.[102–104] Nevertheless, methotrexate is the most commonly used csDMARD, and it has been shown to have a tablet dosage form with adverse effects as well as disadvantages of undergoing a first-pass effect, low bioavailability, and an effect on food consumption.[105–107]

bDMARDs are used through the injection method to treat RA efficiently; however, the injection method may cause injection site infection and an infusion reaction.[108–110] As a result, transdermal administration (TDDS) has become a high-profile development in the treatment of RA, as TDDS can bypass the first-pass effect and the gastrointestinal side effects of oral administration, as well as adverse effects of parenteral administration to reduce the risk of the injection method.[111–113]

Recently, ibuprofen gel and ketoprofen gels were developed as a type of TDDS dosage form for RA treatment.[94,114,115] Thus, the formulation development of an efficient TDDS for RA treatment has been attempted more frequently during the last decade.[90,116,117] This research area has added advancements to the existing technology, creating and testing novel excipients, and optimizing the preparation processes.[118,119]

4. Transdermal administration of drugs

Most of the drugs used in TDDSs should have a molecular weight of less than 600 Da. The drugs should possess unique heterophilic properties to undergo efficient transdermal delivery. The transdermal efficacy of the drugs for RA treatment can be enhanced by developing new chemical derivatives of the drugs with the desired molecular properties. Moreover, developing new technologies such as microneedles or adhesive patches that can lead to easy bypass of the stratum corneum can increase the diffusion coefficients and log *P* values of the drugs during the transdermal delivery.[120] The main barrier is the stratum corneum, since the subcutaneous layers of the skin already have very high diffusion coefficients, and log *P* values (from 1 to 3).[120] Considering these criteria, surges in transdermal RA treatments can be explored to develop novel TDDS approaches rather than continuing conventional therapeutic approaches for RA.

4.1. The skin as a barrier for the TDDS

The skin is the largest organ of the human body, as its surface area is around 1.5–2 m^2 and accounts for around 15% of a person's weight. The skin can be grouped into three areas: the epidermis, the dermis, and the subcutaneous layers, as shown in Fig. 3.[121] The skin protects the underneath parts of the body from heat, germs, chemicals, *etc*.

4.1.1. The epidermis of the skin. The epidermis forms a physical barrier to resist the external environment and block penetrations of external particles and drug molecules.[122] Most of the cells that comprise the epidermis basal layer are keratinocytes, which are cornified, granular, and spinous.[123] These cells divide and devote daughter cells to terminal differentiation, resulting in the creation of the stratum corneum (SC), which is the main interference or barrier layer when drugs cross the skin using a TDDS.[124] To address this, it is necessary to alter the compositional characteristics of the skin or to optimize the intercellular lipid arrangement for enhancing the transdermal bioavailability of the drugs.[123]

4.1.2. The dermis layer of the skin. The dermis layer is underneath the epidermis, which is around 0.5–5 mm thick. The composition of the dermis consists of the interstitial part and the cellular part. In the interstitial part, there are collagen fibers, elastic tissues, and other substances. In the cellular part, there are fibroblasts, mast cells, plasma cells, lymphocytes, dermal cells, dendritic cells, and histiocytes. Also, it contains blood and lymphatic vessels, hair follicles, sweat glands, *etc*.[124]

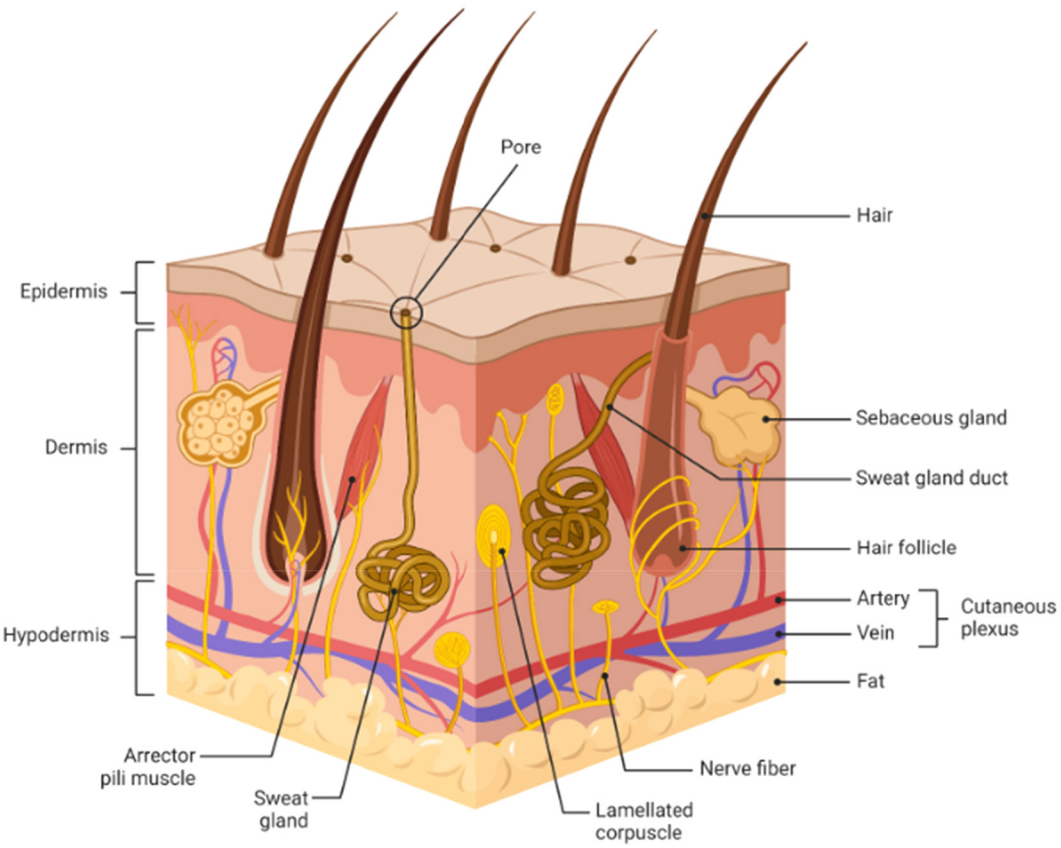

Fig. 3 Schematic representation of the skin. Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[115]

The dermis part is very important for the TDDS as the drugs are mostly absorbed by this part of the skin into the blood.[125]

4.2. The mechanism of transdermal drug absorption

The drugs can be absorbed by the skin *via* two pathways: the trans-epidermal route or the trans-appendage route.[92] Various advanced techniques involved to facilitate the transdermal penetration of drugs are microneedles, iontophoresis, the use of skin-permeable peptides, or use of mechanical force such as with a jet injector or through irradiation such as ultrasound, as shown in Fig. 4.[126] The trans-epidermal pathway can be chiefly subdivided into trans-cellular and intercellular, while the trans-appendage route can be chiefly subdivided into glandular and follicular routes.[127]

4.2.1. The trans-epidermal route. The trans-epidermal route involves delivering the drug through the corneocytes of the stratum corneum of the skin.[128] The route follows either trans-cellular (or intracellular), or paracellular (or intercellular) pathways for the transport of drugs.[129]

4.2.1.1. The trans-cellular or intracellular route. The trans-cellular route *via* keratinocytes and mature corneocytes can allow transport of hydrophilic, and heterophilic polar solutes.[130] As hydrated keratin is present in corneocytes, an aqueous environment is provided. However, the corneocytes are bound by lipid membranes, making further drug penetration challenging. Successful drug penetration involves unique and dynamic molecular properties of the drugs or small molecules. The drugs should be capable of undergoing repetitive geometric and polarity shifts to exhibit desired heterophilic characteristics for transdermal delivery.[92]

4.2.1.2. The intercellular pathway. The intercellular pathway favors lipophilic substances and non-polar drugs. The drug molecules are transported and diffused through the intercellular route, which is the lipid matrix. Subsequently, hydrophobic medications can penetrate the dermis through the lipid matrix, can be absorbed by the dermis, and can reach the bloodstream. Therefore, the intercellular route can be the main pathway for the absorption of lipophilic drugs.[59]

4.2.2. The trans-appendage route. The second route is the trans-appendage route that allows the penetration of the drug into skin layers through sweat/sebaceous glands and along the hair follicles.[127] The trans-appendage pathway means the substance is transported through the cavities lining the glands and hair follicles. Although this route can easily bypass the stratum corneum barrier, it still has to be considered a minor route as the percentage surface areas involved are relatively small in terms of the total area of the skin. However, it has been suggested as a possible route for large polar substances.[131–133]

5. Transdermal dosage forms for RA treatment

In this section, we have summarized various dosage forms used for the transdermal delivery of drugs for RA treatment.

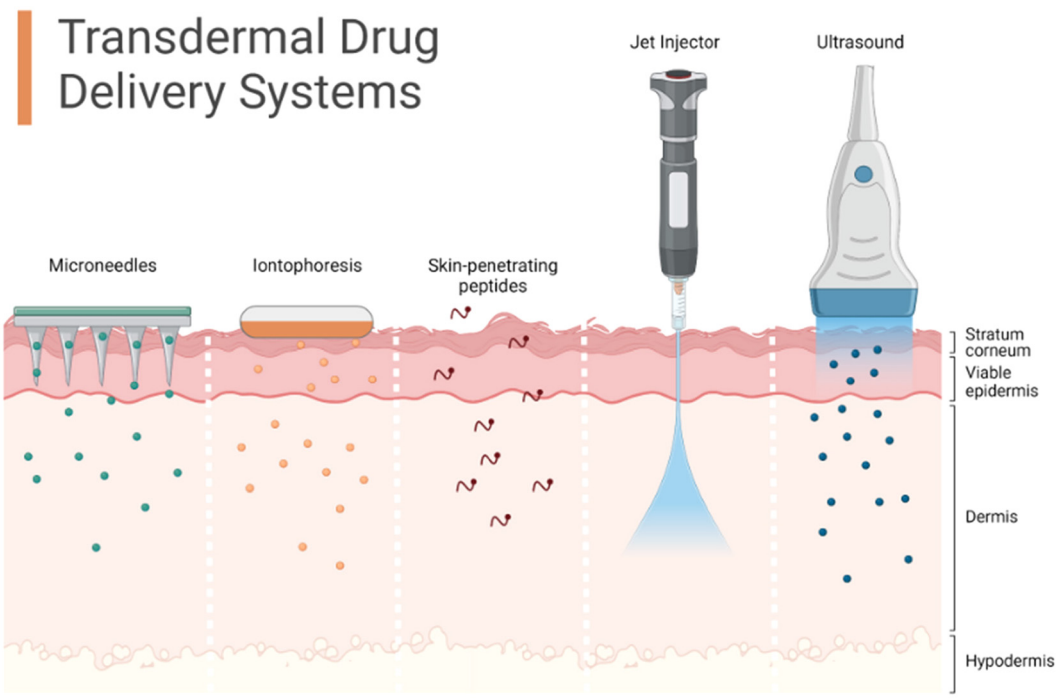

Fig. 4 Possible drug penetration routes across the human skin. Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[126]

There are several novel transdermal delivery systems, such as patches, microneedles, nano-structured lipid carriers, and drug-loaded electrospun nanofibers, which have great potential for future application in RA treatment.

5.1. Gels

Among the TDDSs used to treat RA, gels are the most common dosage forms. Gels are semisolids, comprising a three-dimensional network of structures that are widely used in food, cosmetics, biotechnology, and other industries. They are created by chemically or physically crosslinking polymers that include an additional hydrophilic or hydrophobic solvent phase.[134] Gel systems with various design technologies that exhibit distinct mechanical characteristics have been designed such as hydrogels, microemulsion gels and ethosomal gels. Gels can increase the transdermal bioavailability and effectiveness of anti-rheumatic medications.

5.1.1. Hydrogels. The application of hydrogels in the biomedical field is huge, especially *via* the TDDS.[135] Due to their porous nature, hydrogels can hold and retain a large amount of water inside their cross-linked polymeric cavities with tremendous efficiency.[136] Hydrogels are excellent carriers for drug delivery due to their permeability, biocompatibility, flexibility, and viscoelasticity. Hydrogels, mainly synthesized from hydrophilic polymers, can retain 100–1000-fold their dry weight in water. Due to the large amount of water enclosed within the hydrogel matrix, hydrogels are a suitable dosage forms in facilitating the drug molecules to penetrate the skin, while maintaining the skin's moisturization, and can be vital as a topical drug delivery carrier for RA treatment.[112]

5.1.2. Microemulsion gels. Microemulsion gels are transparent, colloidal drug carrier systems with thermodynamic stability and are widely used in TDDSs.[137] Microemulsions are isotropic mixtures of hydrophilic and lipophilic components that are formed spontaneously in the presence of surfactants/co-surfactants and stirring. Also, with their simple synthesis protocol and stability, they improve solubilization, biocompatibility, dispersion, and loading for both hydrophilic and lipophilic drugs, making them extremely useful drug carriers in a TDDS.[138,139] The surfactant and co-surfactant interfacial films stabilize the transparent dispersion of two liquid phases, *i.e.*, water and oil, in the microemulsion phase to form a gel.[140,141] And because of the low surface tension and small droplet size (less than 0.1 μm) of the dispersion, it can enhance the ability of a drug with poor solubility to achieve high absorption rates and permeation.

5.1.3. Ethosomal gels. Ethosomal gel is composed of phospholipids, ethanol (20–45% concentration), and water.[142] Due to the relatively high ethanol concentration, skin permeability is improved. As a permeation enhancer, ethanol can increase biological transportation and decrease side absorption, hence increasing bioavailability.[115,143] The mechanism of the ethosome is that ethanol reacts with the lipid molecule in the polar head group of the stratum corneum lipids, thus increasing fluidity and membrane permeability.[144] Besides, ethanol gives the vesicles soft and flexible characteristics, allowing drugs applied to these areas to more easily permeate deeper layers of the skin.[145]

5.2. Patches

The patch is a material with a multilayered three- or two dimensional design comprising four films: an impermeable film, a drug-containing matrix film, an adhesive film, and a peelable anti-adhesion protective film.[146] One of the key technologies used to fabricate patches is 3D-printing technology especially employing a fluid deposition model as shown in Fig. 5.[147] The patch has excellent administration compliance: nanocarriers can be mixed into the patch matrix layer to increase transdermal penetration performance.[115] The transdermal patch is a very comfortable and efficient dosage form as it is non-invasive and avoids the first-pass effect of the GI tract, which is the major adverse effect of oral drug administration. It delivers drugs through the skin that directly enter the blood circulation at a slow preset rate.[148] The preparation technology for patches, their structural elements, and the use of materials are improving day by day to enhance their effectiveness as TDDSs.

5.2.1. Transdermal patches loaded with drugs

5.2.1.1. Celecoxib patch. The NSAID celecoxib (CXB) is a selective COX-2 inhibitor, which is a sulfonamide molecule having adverse gastrointestinal effects and poor aqueous solubility. Researchers prepared a gel-based layered patch with a transdermal microemulsion as the base that included CXB drugs.[149] Use of a microemulsion can improve the skin penetration and lessen the adverse effects of the drug. In this instance, the microemulsion was composed of a co-surfactant Transcutol P, the surfactant Tween 80, and the oil phase triacetin. The pseudo-ternary phase was used to adjust the concentration of each component. Carbopol 934 was also added to the gel to increase its viscosity and adjust the skin contact and retention parameters. According to the *ex vivo* drug release study, the drug penetration rate of using a microemulsion gel is four times higher than that of conventional gel. Furthermore, the gel did not cause potential adverse effects to the skin, such as redness, rash, irritation, *etc*. Moreover, *in vivo* investigation showed that the test animal's inflammatory response had significantly decreased. In addition, compared to the commercial formulation, the drug concentration was enhanced with improvements in the retention period as well as overall bioavailability.[149]

5.2.1.2. Dexibuprofen patch. Dexibuprofen is an *S*-isomer of ibuprofen, which also contains the ability to be anti-inflammatory. However, dexibuprofen is forbidden for medication purposes due to its massive adverse effects, such as gastric ulceration, gastrointestinal bleeding, dyspepsia, anorexia, abdominal pain, heartburn, *etc*. However, researchers have created a transdermal patch based on a microemulsion that contains dexibuprofen that can lessen adverse effects and increase medication effectiveness.[150] The components of the microemulsion are water, a surfactant mixture consisting of Tween 80 and propylene glycol (2 : 1), and an oil phase made of ethyl oleate. The

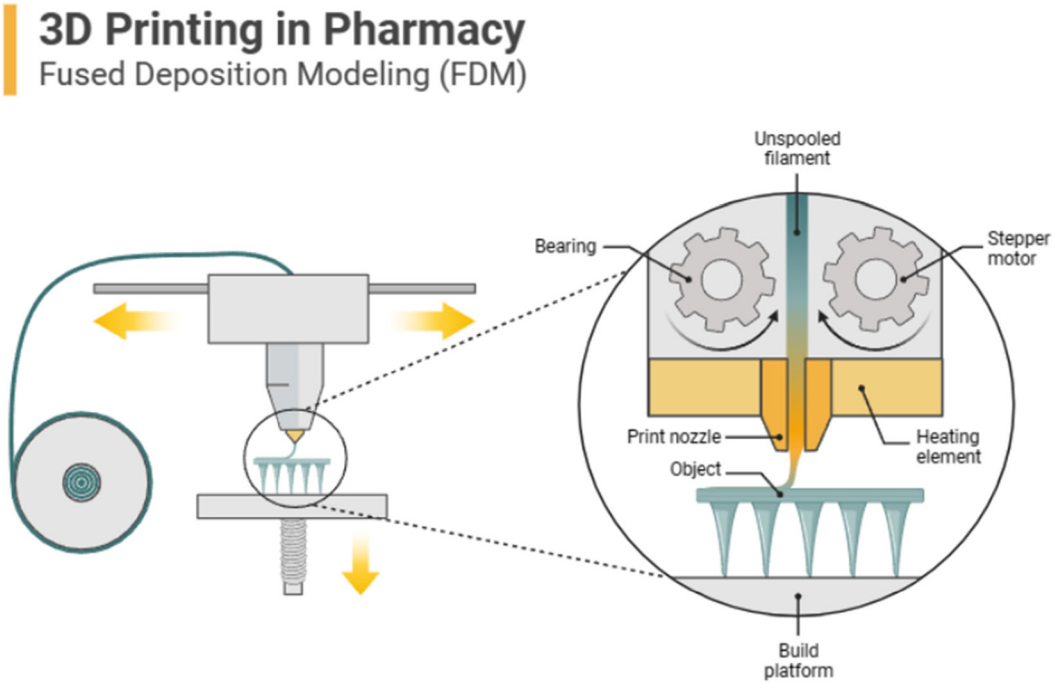

Fig. 5 Basic designs of a transdermal patch with 3D printing technology and using a fused deposition model. Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[147]

microemulsion has a pH of about 5.46, which is appropriate for skin penetration. Microemulsions are also stable chemically and physically. In addition, the *in vitro* release analysis shows zero-order release kinetics and up to 79.73% drug release in 24 hours. Cumulative drug permeation is observed to be up to 8174.45 μg cm^{-2}, which is a significant increase in skin permeability. Moreover, *in vivo* anti-inflammatory investigations demonstrate that a hind paw rat model exhibits an enormous reduction in swelling and inflammation with use of this patch.[150]

5.2.1.3. Diclofenac sodium patch. Diclofenac sodium (DS), an NSAID, is one of the most widely used analgesic drugs *via* the oral route, while leflunomide (LEF) is a DMARD used to block DHODH and hence lower the production of inflammatory cytokines. Although both DS and LEF are powerful anti-inflammatory drugs, they pose various gastrointestinal tract side effects such as dyspepsia, nausea, abdominal pain, oral or gut wall ulceration, and gastric bleeding.[151–154] Researchers have designed a transdermal DS/LEF patch with a microemulsion base gel matrix layer, which avoids the first-pass effect and lessens the gastrointestinal side effects of the orally administered drugs.[140] The microemulsion is formulated with isopropyl myristate (oil phase), Tween 80 (surfactant), and 1-pentanol (co-surfactant). After the microemulsion is prepared, it is combined with 1% (W/V) LEF and 1% (W/V) DS with respect to the oil and aqueous phases, respectively. The microemulsion pH value is around 4.7–6.55 and it is not irritable to the skin. The cumulative drug release profiles for LEF and DS after 24 hours are 77.36% and 89.90%, respectively, according to *in vitro* drug release assay. Furthermore, the patch demonstrates that improved drug penetration can be achieved at high concentrations of both surfactant and co-surfactant. According to an *in vivo* investigation, LEF/DS therapy reduces weight loss in arthritic rats. RA normally causes the loss of lean tissues, which constitute a major portion of the body mass, so RA can be linked to weight loss. In addition, histopathology analysis demonstrates that the gel patch with the LEF/DS microemulsion when applied to arthritic rats promotes recovery from inflammatory/fibrotic symptoms.[140]

5.2.2. Hydrogel patches. Ibuprofen is an NSAID that is widely administered *via* the conventional oral delivery method. The side effects of oral administration, such as the first-pass effect and the gastrointestinal effect, can be addressed with transdermal delivery. Scientists have created a hydrogel patch that can improve ibuprofen's transdermal delivery by using hydrogel-thickened nonionic microemulsions (HTMs) loaded with the medication.[155] The components of the microemulsion are a non-ionic surfactant (Labrasol® (18.81%)) and Solubilisant gamma® (28.22%), the oil phase (isopropyl myristate (5.22%)), ibuprofen (5%), xanthan gum (0.25%), and water that fills the remaining part up to the total volume required (100%). The viscosity, spread diameter, hysteresis area, and ibuprofen release rate were improved by the xanthan gum. As a result, the hydrogel patch can improve ibuprofen's use in the treatment of RA.[155]

6. Microneedles (MNs)

MNs are drug delivery forms that are less invasive and painless, having needle lengths ranging from 25 to 100 μm and pointer sizes also in the micrometer range.[118,156] MNs penetrate the SC skin-layer to create microchannels through which the drug can be directly injected into the upper dermis where the drug can diffuse further to enter the body's circulation. As the length of MNs is not sufficient to reach the skin thickness up to nerves or blood vessels in the dermis, they do not cause discomfort or pain.[116,157] Nonetheless, MNs are shown to carry and deliver small particles as well as macromolecules such as proteins and peptides.[158] The different types of MNs include solid MNs, hollow MNs, coated MNs, dissolving MNs, hollow MNs, degradable MNs, bio-responsive MNs, hydrogel MNs, and so on, as shown in Fig. 6.[159] Moreover, the hydrogel MNs and the dissolving MNs have become the latest research topic because of their extraordinary mechanical, skin-contact, drug penetration, and sustained drug release characteristics.

6.1. Dissolving microneedles (dissolving MNs)

Dissolving MNs are made from a water-soluble substance such as maltose, chondroitin, hyaluronic acid, *etc*.[113,160,161] The drug molecules are released into the skin by pressing the dissolving MNs against it. Since the MNs are composed of biocompatible and water-soluble substances, such as sugars and cellulose derivatives, they can be entirely dissolved within the skin over time. As a result, there will be no biohazardous remains on the skin.[116,162,163]

6.1.1. Delivery of TNF-α antibodies. Anti-TNF-α-Ab is an antibody towards the TNF-α biomarker, which is known as one of the inflammatory factors. Anti-TNF-α-Ab has demonstrated great therapeutic impact on RA. However, it causes systemic immunosuppression and concomitant side effects. Therefore, scientists have evaluated a dissolvable microneedle array for localized transdermal delivery of TNF-α antibodies.[164,165] The needles are made from carboxymethylcellulose (CMC) by using micro-milling or spin-casting fabrication methods, as CMC is a bio-dissolvable, mechanically robust, water-soluble polymer without causing any toxicity or irritation on the skin. Moreover, dimethyl sulfoxide (DMSO) is used as a penetration enhancer. After application to the skin, 75% of integrated antibodies are delivered to the skin microenvironment within 10–20 minutes. Experiments with mice show that IL-1β mRNA expression in the treated mice is reduced compared to that in untreated mice after 4 days. This demonstrates the therapeutic and physiologically active effects in an animal model.[164,165]

6.1.2. Delivery of tetramethylpyrazine. Tetramethylpyrazine (TMP) is an alkaloid that is extracted from Ligusticum, which is a Chinese medicine. TMP is one of the medications for RA treatment, as its pharmacological effects include platelet aggregation inhibition and anti-inflammatory effects. The main dosage forms of TMP are oral and injection. However, oral administration comes with various disadvantages, such as low bioavailability, gastrointestinal side effects, *etc*. In

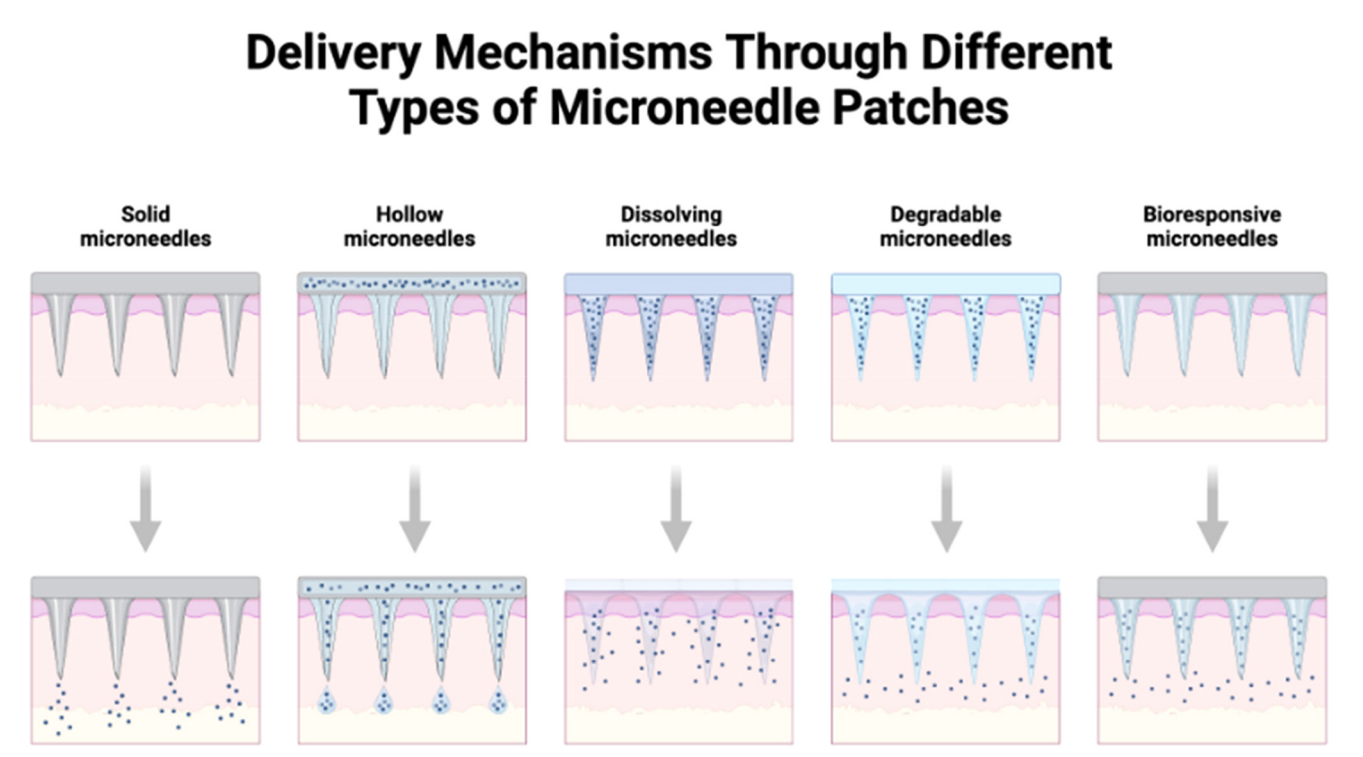

Fig. 6 Types of MNs such as solid MNs, hollow MNs, coated MNs, dissolving MNs, degradable MNs, bioresponsive MNs, hydrogel MNs, and so on. Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[159]

addition, chronic injections result in poor patient compliance. To address these challenges, scientists have designed a dissolving microneedle patch loaded with TMP.[160] Dextran (Dex) has been used to fabricate microneedles delivering 300 mg mL^{-1} Dex with a puncture efficiency exceeding 95%. Furthermore, compared to TMP cream, the dissolving MN patch containing TMP has demonstrated a longer-lasting drug release effect. The dissolving MN patch takes longer to equilibrate (7 hours) than cream (5 hours), according to the release curve. Through ELISA kit measurements, the concentrations of TNF-α and IL-1β were significantly reduced using the dissolving MN patch compared to treatment with cream and oral administration.[160]

6.2. Hydrogel microneedles (hydrogel MNs)

Hydrogel MNs comprise a cross-linked network of hydrophilic polymers. Hydrogel MNs patch, upon expanding, slightly penetrates on the skin surface, while in contact with the epithelium, can further penetrate to the stratum corneum. Then, they absorb tissue fluid and transport the drug through diffusion. Biomedical applications are increasingly being focused on hydrogel MNs due to their great biocompatibility, degradability, and non-toxicity.[93,166]

6.2.1. DTA6-loaded hydrogel microneedles. DTA6 is an aptamer, that is, a modified version of DTA. Since DTA6 is more stable and has strong binding affinity for the DEK protein, it can inhibit the release of inflammatory macrophages. DTA treatment has been shown to be efficacious in previous studies. However, DTA transportation treatment *via* articular injections and long-term injections leads to poor compliance in patients. Therefore, scientists created DTA6-loaded hydrogel MNs. The hydrogel MN is composed of hyaluronic acid that has been modified with methacrylate and was created using the micro-molding technique.[156] According to a study, a mouse group treated with DTA6 *via* hydrogel MNs shows better drug efficacy compared to a previously reported mouse group treated with DTA6 injections (refer to the discussion section of this reference). DTA6 *via* hydrogel MNs significantly reduced the levels of TNF-α and IL-6 in animal models, and bone and cartilage erosion is mostly reduced.[156]

6.2.2. Microneedles for MTX delivery. MTX is one of the most commonly used csDMARDs for the treatment of RA. Oral administration is the most common and convenient way to administer MTX. Nevertheless, MTX *via* the oral route has some drawbacks, such as intestinal absorption, nonlinear pharmacokinetics, and gastrointestinal side effects. To overcome these difficulties, researchers developed hydrogel MN arrays and a patch-like reservoir loaded with MTX (MTX-RV).[135] The hydrogel MNs were formed from polyvinyl alcohol (PVA) and a crosslinking agent (citric acid) (CA). MTX-RV is prepared by combining MTX with aqueous polymeric blends. In an *ex vivo* study, the MTX-RV-hydrogel MNs showed better control over the MTX permeation rate, thus delivering MTX more sustainably. Also, the pharmacokinetics showed that the C_{max} of MTX-RV-hydrogel MNs, which reached 35.1 ± 5.1 nM at 24 hours, thus demonstrating their steadier release of MTX compared to oral administration (57.4 ± 20.0 nM reached at 1 hour). Thus, avoiding the rapid release of MTX could reduce the side effects and improve the efficacy of MTX.[135]

7. Flexible liposomes (FLs)

Liposomes are lipid-vesicular, bilayer-shaped nanocarriers. As they contain both a hydrophilic head and a hydrophobic tail, they are used to deliver both hydrophilic and hydrophobic drugs.[167] Liposomes are mostly formed from phospholipids and cholesterol. They have high adaptability, as the formulation, surface charge, and properties, as well as the vesicle size, can be modified. FLs are a novel type of liposome that have edge activators that can improve the flexibility of the lipid layer. As a result, compared to rigid liposomes, they can disrupt the lipid barrier and penetrate deeper into the epidermis layers.[168] Also, they do not fuse with skin lipids and dehydrate on the skin's surface due to their osmotic concentration gradient.[169]

7.1. FLs for steroidal drug delivery

Researchers have designed dexamethasone (DEX)- and dextran sulfate (DS)-loaded flexible liposomes (DS-FLs/DEX) to treat RA *via* TDDSs.[170] DEX and DS are both anti-inflammatory and immunosuppressive GCs. In this design, DS-FLs/DEX are combined with hydrogels to provide a transdermal administration route. In the characterization study of DS-FLs/DEX, the penetration rate of DS-FLs/DEX was 5.4 times higher than that when using the regular liposome (DS-RLs/DEX) under the same pressure of 0.5 MPa. According to *in vitro* studies, the DS-FLs/DEX can achieve an initial burst release of 33% within the first 5 hours and maintain a steady release of 90% of DEX at 48 hours in a slightly acidic environment (pH = 6.5, inflammatory pH). In pharmacokinetics studies, the plasma half-life of the DS-FLs/DEX hydrogel is the longest among all the groups, which are DEX (oral), DEX hydrogel, DS-RLs/DEX, and DS-FLs/DEX. As the plasma half-life is prolonged, the bioavailability of DEX is improved. Nevertheless, *in vivo* studies show that the level of pro-inflammatory cytokines is lower with the application of DS-FLs/DEX compared to DS-RLs/DEX. As a result, DS-RLs/DEX and DS-FLs/DEX both have great potential for RA treatment.[170]

8. Electrospun and electrosprayed nanofibers (NFs)

Electrospun and electrosprayed nanofibers (NFs) are produced by electrospinning or electrospraying techniques where a polymer solution layer is coated over a backing layer, as shown in Fig. 7.[171] Due to their huge volume and surface area, the inter-woven fibers can more effectively deliver both hydrophilic and hydrophobic medicines. The drug release characteristics can be modified by altering the drug-to-polymer ratio, fiber diameter, and structure.[172,173]

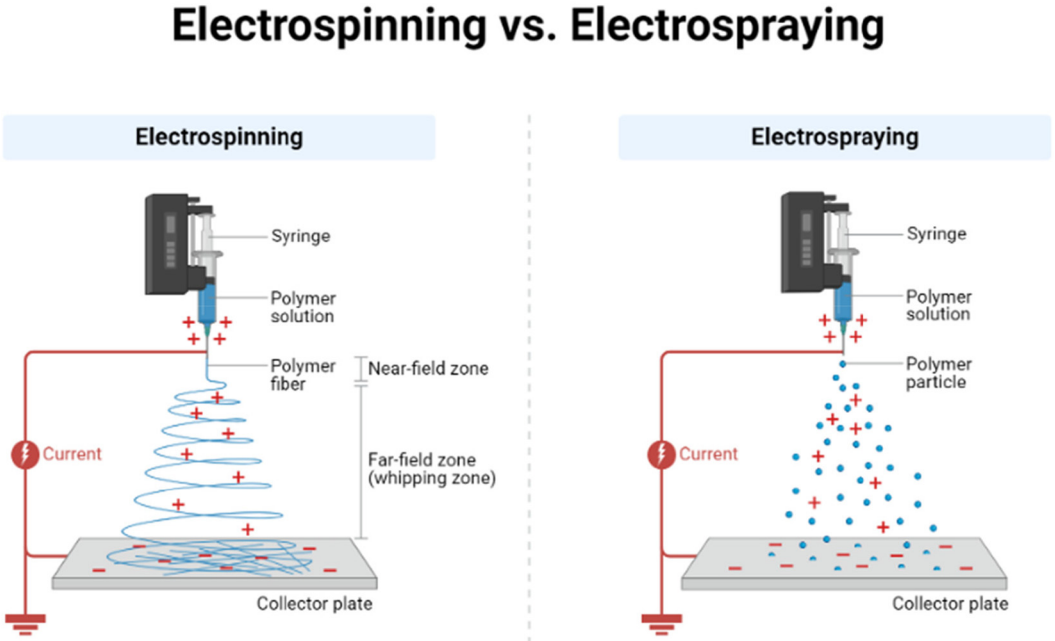

Fig. 7 A method of electrospinning and electrospraying by which DMAP, AAP, and HPβCD can be deposited to formulate patches with wound healing properties.[174] Declaration: The figure was adapted from the open-source platform of "Biorender" tools (or templates). Reuse of its tools or templates has been allowed by "Biorender" (therefore, copyright is not applicable) with relevant previous citations (if any) being incorporated.[171]

Researchers developed a novel drug delivery structure by using electrospun cyclodextrin NFs.[174] The inclusion complexes (IC) between NSAID and 2-hydroxypropyl-β-cyclodextrin (HPβCD) are used to create the NFs. The NSAIDs utilized in this situation are 4-aminoantipyride (AAP) and 4-dimethylaminoantipyrine (DMAP). Since HPβCD is non-toxic and biodegradable, it is an ideal material to create a biopolymer. After the fabrication is done, the DMAP/HPβCD-IC-NF and AAP/HPβCD-IC-NF forms a meshwork or a web-like layer of exceptional flexibility for biomedical applicability.[174]

The *in vitro* analysis indicates that there is excellent biocompatibility between DMAP/HPβCD-IC-NF and AAP/HPβCD-IC-NF. Cell viability was up to 100% 24 and 48 hours after the application of both DMAP/HPβCD-IC-NF (5 μg mL^{-1}) and AAP/HPβCD-IC-NF (5 μg mL^{-1}). Hence, sealing NSAIDs with electrospun nanofibers can improve their stability, and this technique also improves the cell survival, which promotes the growth of skin fibroblast cells. Also, both types of NF show excellent effects on the skin fibroblast group, with remarkable migration of the fibroblasts compared to fibroblasts without treatment. Although there are very few *in vivo* studies, addressing biocompatibility issues, but NSAIDs-HPβCD-IC-NFs can still be considered as potential candidates for RA treatment for further exploration.[174]

9. Conclusion

Rheumatoid arthritis (RA) is a chronic disease due to the dysfunction of the autoimmune system. The dysfunction causes secretion of inflammatory factors, which lead to cartilage damage and bone erosion. The conventional drug delivery systems that have been previously reported, such as oral and injection administration, have had their drawbacks and limitations shown in treating RA. In comparison, transdermal drug delivery systems (TDDSs) have certain advantages and efficacies, and have been proved safe in treating RA. This paper reviewed the ability of the TDDS and the drugs that are used in TDDSs for RA treatment. TDDSs can be used to improve the percutaneous penetration and solubility of drugs to attain sustainable drug release and reduce the systemic adverse reactions of currently available dosage forms. Thus, the skin-route bioavailability of the drug is enhanced and localized inhibition for the expression of IL-1β, IL-6, and TNF-α inflammatory factors is efficient. The use of synthetic materials to develop TDDSs in the context of treating RA will appeal to readers; nevertheless, a few studies have already mentioned TDDSs in detail or discussed the biological safety and feasibility of using TDDSs for RA treatment. The challenges of TDDSs are short-term and long-term skin damage due to toxic reactions, metabolic pathways, and the cytotoxicity of the active group when the drug enters the skin. Although the TDDSs used resulted in great performances in the RA animal models, more clinical data need to be tested in the future as the human pathological characteristics of RA are more complicated. There are numerous chemical substances and cells involved in the process of inflammation. Only a few currently targeted groups of chemicals have been used in TDDS technology. Histamine, bradykinin, E-selectin, and platelet β3 integrin-affecting drugs are some other examples of

the potential target group of chemicals to be used in developing different types of TDDSs. This article will appeal to acupuncture specialists, traditional Chinese medical practitioners, biologists, clinicians, chemists, and drug delivery specialists to develop novel skin-penetration and drug-bioavailability improvement technologies, such as microneedles and patch techniques, by designing further possible transdermal drug administration technologies. There are very few reviews specifically focusing on transdermal drug delivery systems to treat RA. This one will reveal broader opportunities for readers to design and develop sustainable and efficient TDDSs for RA treatment.

Author contributions

Mirza Muhammad Faran Ashraf Baig: initial draft writing, major re-writing, conceptualization, editing, review, and grammar revision. Chi Hin Kwan: initial draft writing, investigation and validation. Hongkai Wu and Sek Ying Chair: revision.

Data availability

The data have been appropriately cited. The data will be made available on request.

Conflicts of interest

The authors declare no competing interests including any of a financial or personal nature.

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