A Review on Management of Rheumatoid Arthritis and Development of Transdermal Patches

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***Abstract*—Rheumatoid arthritis (RA) is a chronic, progressive, and systemic autoimmune inflammatory disorder characterized by persistent inflammation of synovial joints resulting in cartilage destruction, bone erosion, joint deformity, and functional disability. The disease mainly affects small joints of the hands and feet in a symmetrical pattern and is associated with severe pain, swelling, stiffness, and reduced mobility. Rheumatoid arthritis not only affects joints but may also involve extra-articular organs such as lungs, heart, eyes, skin, and blood vessels. The prevalence of rheumatoid arthritis is increasing globally, particularly among women, making it an important public health concern. Conventional treatment approaches include non-steroidal anti-inflammatory drugs, corticosteroids, disease-modifying anti-rheumatic drugs, and biological agents. Although these therapies provide symptomatic relief and delay disease progression, long-term administration often produces gastrointestinal irritation, hepatic toxicity, renal impairment, frequent dosing complications, and poor patient compliance.**

To overcome these limitations, transdermal drug delivery systems have emerged as a promising alternative approach for rheumatoid arthritis management. Transdermal patches deliver drugs through the skin into systemic circulation at a controlled and sustained rate. These systems provide several advantages including avoidance of first-pass metabolism, improved bioavailability, prolonged therapeutic action, reduced systemic side effects, and enhanced patient compliance. Various natural and synthetic polymers, permeation enhancers, plasticizers, and adhesives are utilized for the successful formulation of transdermal patches. Recent advancements such as microneedles, nano-carriers, hydrogel systems, iontophoresis, and sonophoresis have significantly improved transdermal drug delivery efficiency.

This review comprehensively discusses the etiology, epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of rheumatoid arthritis along with formulation aspects, evaluation parameters, challenges, recent advances, and future perspectives of transdermal drug delivery systems for rheumatoid arthritis therapy.

***Index Terms*—Rheumatoid arthritis, Transdermal patches, Autoimmune disorder, Controlled drug delivery, Anti-inflammatory drugs, Nanotechnology, Drug delivery system**

I. INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterized by persistent synovial inflammation and progressive destruction of articular structures [1,2]. It is one of the most common autoimmune disorders affecting approximately 0.5–1% of the global population. The disease is more prevalent in women compared with men and generally occurs between 30 and 60 years of age [2,5]. Rheumatoid arthritis primarily affects synovial joints including joints of the fingers, wrists, knees, elbows, ankles, and feet in a symmetrical manner. Continuous inflammatory processes eventually result in cartilage degradation, bone erosion, joint deformities, and loss of physical function.

The exact cause of rheumatoid arthritis remains unknown, but several genetic, environmental, immunological, and hormonal factors contribute to disease development [5,6,15,16]. Genetic susceptibility associated with HLA-DR4 and HLA-DR1 genes has been strongly linked with increased risk of rheumatoid arthritis. Environmental triggers such as smoking, stress, infections, obesity, and exposure to pollutants may activate abnormal immune responses in genetically predisposed individuals. The disease involves activation of T-cells, B-cells, macrophages, and inflammatory cytokines leading to chronic synovial inflammation.

Management of rheumatoid arthritis mainly focuses on reducing inflammation, relieving pain, preventing joint damage, and improving quality of life [8,21]. Conventional treatment includes oral non-steroidal anti-inflammatory drugs, corticosteroids, disease-modifying anti-rheumatic drugs, and biological agents. Despite therapeutic effectiveness, long-term oral therapy often causes gastrointestinal ulceration, hepatic toxicity, nephrotoxicity, frequent dosing requirements, and systemic side effects. Injectable formulations may also reduce patient acceptance due to pain and inconvenience.

Novel drug delivery systems such as transdermal patches have gained significant attention for overcoming limitations associated with conventional dosage forms [11,12]. Transdermal drug delivery systems are medicated adhesive systems designed to deliver therapeutic agents through the skin into systemic circulation in a controlled manner. These systems improve bioavailability, reduce dosing frequency, avoid hepatic first-pass metabolism, maintain steady plasma drug concentration, and enhance patient compliance. Therefore, development of transdermal patches for rheumatoid arthritis management represents a promising and innovative therapeutic strategy.

II. EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis is one of the most prevalent chronic inflammatory disorders worldwide. The global prevalence of rheumatoid arthritis is estimated to be approximately 0.5–1% of the total population [2,5]. Women are affected nearly three times more frequently than men due to hormonal and immunological factors. The disease commonly develops between the ages of 30 and 60 years, although it can occur at any age.

The prevalence and severity of rheumatoid arthritis vary among different populations and geographical regions. Developed countries generally report higher prevalence due to better diagnostic facilities and increased awareness. Genetic susceptibility, environmental exposure, dietary habits, and lifestyle factors significantly influence disease occurrence.

Smoking is considered one of the strongest environmental risk factors associated with rheumatoid arthritis [7,15]. Obesity, stress, infections, and occupational exposure to silica and pollutants may also increase disease risk. Family history of autoimmune disorders significantly increases susceptibility toward rheumatoid arthritis.

Rheumatoid arthritis imposes substantial social and economic burden due to chronic disability, reduced productivity, increased healthcare costs, and decreased quality of life. Early diagnosis and appropriate therapeutic intervention are essential for preventing severe joint damage and long-term complications.

III. ETIOLOGY OF RHEUMATOID ARTHRITIS

The exact etiology of rheumatoid arthritis remains unclear; however, several factors are involved in disease initiation and progression.

Genetic Factors

Genetic predisposition plays an important role in rheumatoid arthritis development. Human leukocyte antigen genes such as HLA-DR4 and HLA-DR1 are strongly associated with increased susceptibility toward rheumatoid arthritis. Individuals carrying these genes possess higher risk of autoimmune responses against synovial tissues.

Environmental Factors

Environmental triggers significantly contribute to disease progression. Cigarette smoking is considered one of the most important risk factors because it promotes inflammatory cytokine production and autoantibody formation. Infections caused by viruses and bacteria may also trigger autoimmune reactions.

Hormonal Factors

Hormonal imbalance contributes to increased prevalence of rheumatoid arthritis in females. Estrogen and other hormonal changes influence immune system regulation and inflammatory responses.

Immunological Factors

Autoimmune reactions represent the central mechanism involved in rheumatoid arthritis pathogenesis. Activation of immune cells including T-cells, B-cells, and macrophages results in release of inflammatory mediators leading to chronic synovial inflammation.

IV. PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

The pathophysiology of rheumatoid arthritis is strongly associated with activation of inflammatory cytokines including tumor necrosis factor-alpha, interleukin-1, and interleukin-6 [17,19,20].

The pathophysiology of rheumatoid arthritis is complex and involves multiple inflammatory and immunological processes. The disease begins when immune cells mistakenly identify synovial tissues as foreign antigens. Antigen-presenting cells activate T-lymphocytes which further stimulate macrophages and B-cells.

Activated immune cells release inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6 [17,19,20]. These cytokines increase vascular permeability and promote migration of inflammatory cells into synovial tissues causing swelling, pain, and redness.

Continuous inflammation results in thickening of synovial membranes and formation of pannus tissue. Pannus invades cartilage and bone causing erosion and irreversible joint destruction. Chronic inflammatory activity eventually produces deformities, reduced mobility, stiffness, and functional disability.

Rheumatoid arthritis may also produce extra-articular complications involving cardiovascular, pulmonary, ocular, and skeletal systems due to prolonged systemic inflammation.

V. CLINICAL MANIFESTATIONS

Rheumatoid arthritis presents with various articular and extra-articular manifestations depending on disease severity and duration.

The most common symptom is symmetrical joint pain involving small joints of the hands and feet. Morning stiffness lasting for more than thirty minutes is considered a characteristic feature of rheumatoid arthritis. Swelling, tenderness, warmth, and restricted movement occur due to synovial inflammation.

Patients frequently experience fatigue, weakness, fever, weight loss, and loss of appetite. Chronic inflammation may produce joint deformities such as ulnar deviation, boutonniere deformity, and swan-neck deformity.

Extra-articular manifestations include rheumatoid nodules, anemia, osteoporosis, pulmonary fibrosis, cardiovascular complications, vasculitis, and ocular disorders. Severe rheumatoid arthritis may significantly reduce quality of life and physical function.

VI. DIAGNOSIS OF RHEUMATOID ARTHRITIS

Diagnosis of rheumatoid arthritis is based on clinical examination, laboratory investigations, and imaging techniques.

Physical examination includes assessment of joint swelling, tenderness, pain, and range of motion. Laboratory investigations include rheumatoid factor, anti-cyclic citrullinated peptide antibodies, erythrocyte sedimentation rate, and C-reactive protein levels.

Radiographic imaging techniques such as X-ray, magnetic resonance imaging, and ultrasound are used for evaluating cartilage destruction and bone erosion. MRI and ultrasound help detect early inflammatory changes before radiographic abnormalities become visible. Early diagnosis and prompt treatment are essential for reducing disease progression and preventing irreversible joint damage [21,29].

VII. CONVENTIONAL TREATMENT OF RHEUMATOID ARTHRITIS

Conventional treatment strategies mainly involve use of NSAIDs, corticosteroids, DMARDs, and biological agents for controlling inflammation and preventing disease progression [8,9,31].

Treatment of rheumatoid arthritis mainly aims to relieve pain, suppress inflammation, prevent joint destruction, and improve quality of life.

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs such as diclofenac, ibuprofen, naproxen, and ketoprofen are widely used for reducing pain and inflammation. However, prolonged administration may produce gastric ulceration, bleeding, and renal toxicity.

Corticosteroids

Corticosteroids such as prednisolone and dexamethasone provide rapid anti-inflammatory action. Long-term therapy may lead to osteoporosis, hypertension, immunosuppression, diabetes, and adrenal suppression.

Disease-Modifying Anti-Rheumatic Drugs

DMARDs including methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine slow disease progression and reduce joint destruction.

Biological Agents

Biological agents such as infliximab, adalimumab, and etanercept target inflammatory cytokines involved in rheumatoid arthritis pathogenesis.

Despite therapeutic effectiveness, conventional therapies are associated with poor bioavailability, systemic side effects, frequent dosing, and poor patient compliance. Therefore, novel drug delivery systems such as transdermal patches have gained significant attention.

Transdermal Drug Delivery System

Transdermal drug delivery systems are medicated adhesive systems designed to deliver drugs through the skin into systemic circulation at a controlled rate [11,12,13].

Transdermal drug delivery systems are medicated adhesive formulations designed to deliver drugs through the skin into systemic circulation in a controlled manner.

The skin acts as a natural protective barrier against external agents. However, suitable formulation strategies and permeation enhancement techniques facilitate drug transport across the stratum corneum.

Transdermal patches provide several advantages compared with oral and injectable dosage forms including sustained release, improved bioavailability, avoidance of hepatic first-pass metabolism, and enhanced patient compliance [11,12,13,14]. These systems avoid hepatic first-pass metabolism, reduce gastrointestinal irritation, maintain prolonged therapeutic action, improve bioavailability, and enhance patient compliance.

Transdermal systems are particularly beneficial for chronic diseases requiring long-term therapy such as rheumatoid arthritis because they reduce dosing frequency and provide sustained drug release.

VIII. ANATOMY AND PHYSIOLOGY OF SKIN

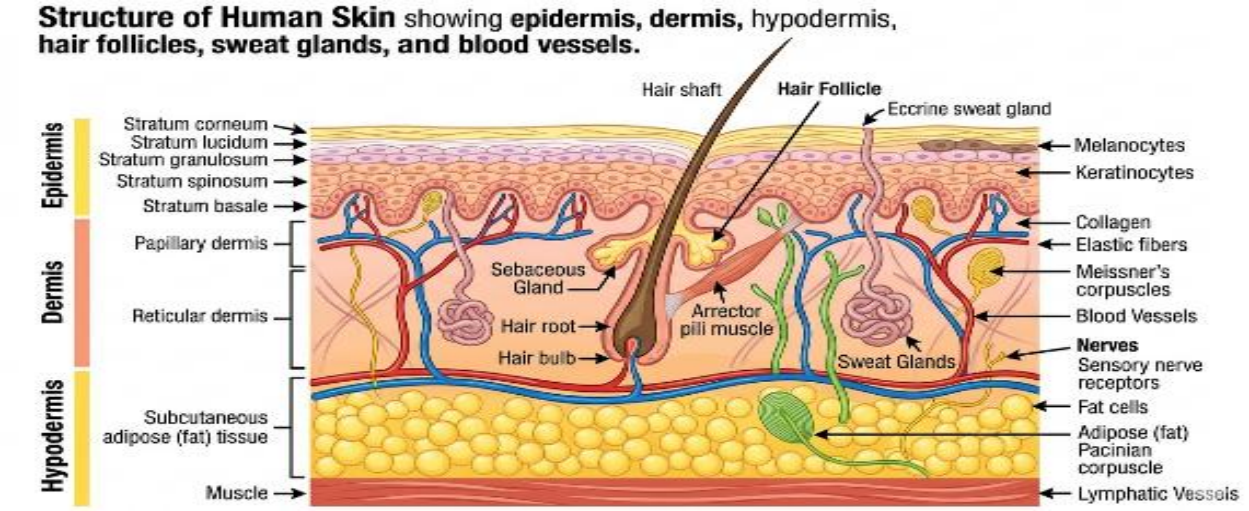
The skin acts as the major protective barrier of the body and plays a critical role in transdermal drug delivery [33,34].

The skin is the largest organ of the body and serves as a protective barrier against environmental damage. Human skin consists of three major layers namely epidermis, dermis, and hypodermis.

The epidermis is the outermost layer and contains the stratum corneum which acts as the principal barrier to drug permeation. The dermis contains blood vessels, lymphatics, connective tissues, sweat glands, sebaceous glands, and nerve endings. Drugs reaching the dermis enter systemic circulation through dermal blood vessels.

The hypodermis mainly contains adipose tissues and connective tissues that provide insulation and mechanical support.

Drug permeation through skin generally occurs through transcellular, intercellular, and appendageal pathways. Factors such as skin hydration, molecular weight, lipophilicity, and partition coefficient significantly influence transdermal drug absorption.



Mechanism of Drug Permeation through Skin

Drug permeation through skin mainly occurs according to passive diffusion principles and depends on physicochemical properties of the drug and integrity of the stratum corneum [47,48,51]. Drug permeation through skin mainly occurs by passive diffusion according to concentration gradient principles. The process involves adsorption of drug onto skin surface followed by penetration through the stratum corneum, diffusion across viable epidermis and dermis, and uptake into systemic circulation.

The stratum corneum represents the major rate-limiting barrier for transdermal drug delivery. Drugs with molecular weight below 500 Da and balanced lipophilic-hydrophilic properties are considered suitable candidates for transdermal delivery.

Chemical permeation enhancers such as alcohols, fatty acids, surfactants, and terpenes improve skin permeability by disrupting lipid organization within the stratum corneum [41,54,55].

Physical enhancement techniques including iontophoresis, electroporation, sonophoresis, and microneedles temporarily alter skin barrier properties and improve drug transport.

IX. TYPES OF TRANSDERMAL PATCHES

Different types of transdermal patches are developed depending on structural design and mechanism of drug release.

Reservoir System

Reservoir patches contain drug reservoir enclosed between backing membrane and rate-controlling membrane.

Matrix System

Matrix patches contain drug uniformly dispersed within polymer matrix. Drug release occurs by diffusion.

Drug-in-Adhesive System

These systems contain drug incorporated directly into adhesive layer.

Micro-Reservoir System

These systems combine properties of both matrix and reservoir systems.

Advanced transdermal technologies including microneedle patches and nano-carrier systems have significantly improved drug permeation and therapeutic efficacy.

X. COMPONENTS OF TRANSDERMAL PATCHES

Transdermal patches contain several formulation components necessary for controlled drug delivery.

Polymers

Polymers control drug release and provide structural integrity. Common polymers include hydroxypropyl methylcellulose, ethyl cellulose, Eudragit, and polyvinyl pyrrolidone.

Drug Substance

Anti-inflammatory drugs such as diclofenac sodium, aceclofenac, ketoprofen, and piroxicam are commonly used.

Plasticizers

Plasticizers improve flexibility and mechanical strength of patches.

Permeation Enhancers

Permeation enhancers increase drug penetration through the skin barrier.

Adhesives

Adhesives ensure proper attachment of patches to skin surface.

Backing Membrane

Backing membrane protects patch from external environment.

XI. METHODS OF PREPARATION OF TRANSDERMAL PATCHES

Several methods are used for preparation of transdermal patches.

Solvent Evaporation Method

Drug and polymers are dissolved in suitable solvent followed by casting into molds and drying.

Mercury Substrate Method

Polymeric solution is spread over mercury surface to form films.

Asymmetric Membrane Method
Special asymmetric membranes are prepared for controlled drug release.

Micro-Reservoir Method
Drug reservoir is dispersed within polymer matrix to obtain controlled release properties.
Selection of preparation method significantly influences mechanical properties, drug release characteristics, and therapeutic performance.

XII. EVALUATION PARAMETERS OF TRANSDERMAL PATCHES

Evaluation of transdermal patches is necessary for ensuring quality, safety, and effectiveness.
Thickness and weight uniformity tests help maintain consistency in formulation. Folding endurance determines flexibility and resistance toward mechanical stress.

Drug content uniformity ensures proper distribution of active pharmaceutical ingredient within the patch matrix. Moisture uptake studies evaluate formulation stability during storage.
In-vitro drug release studies determine release kinetics and diffusion behavior of drugs. Skin irritation studies are performed to assess safety and compatibility.

XIII. APPLICATIONS OF TRANSDERMAL PATCHES IN RHEUMATOID ARTHRITIS

Transdermal patches containing diclofenac, ketoprofen, and aceclofenac have shown improved therapeutic efficacy and reduced gastrointestinal complications in rheumatoid arthritis therapy [55,56,57].
Transdermal patches are extensively investigated for delivery of anti-inflammatory and analgesic agents used in rheumatoid arthritis treatment.
Diclofenac transdermal patches provide prolonged anti-inflammatory action with reduced gastrointestinal side effects. Ketoprofen and aceclofenac patches have also shown effective pain reduction and sustained therapeutic action.
Nano-carrier incorporated transdermal systems including liposomes, nanoemulsions, and solid lipid nanoparticles improve drug penetration and bioavailability.
Microneedle-assisted transdermal systems create microscopic channels within the skin facilitating efficient delivery of therapeutic agents without pain.

Recent Advances in Transdermal Technology
Recent advancements in pharmaceutical technology have significantly improved transdermal drug delivery systems.
Microneedle technology represents one of the most promising approaches for enhancing skin permeability. Microneedles create microscopic pores within the stratum corneum allowing efficient delivery of drugs.
Iontophoresis utilizes electrical current for enhancing transdermal transport of ionic drugs. Sonophoresis uses ultrasound waves to improve skin permeability.
Nanotechnology-based systems such as liposomes, transferosomes, ethosomes, dendrimers, and nanoparticles improve drug stability, penetration, and controlled release [57,58,60].
Hydrogel-based systems and smart patches capable of stimuli-responsive drug release are also being explored for rheumatoid arthritis therapy.

XIV. CHALLENGES IN DEVELOPMENT OF TRANSDERMAL PATCHES

Despite several advantages, development of transdermal systems faces multiple challenges.
The low permeability of the stratum corneum limits penetration of many drugs. Only potent drugs with low molecular weight and suitable lipophilicity are ideal candidates for transdermal delivery.
Skin irritation caused by adhesives, polymers, and permeation enhancers represents another major challenge. Variability in skin permeability among individuals also affects therapeutic performance.
Maintaining uniform drug distribution, adequate adhesion, mechanical strength, and long-term stability requires careful formulation optimization.

XV. FUTURE PERSPECTIVES

Future research in transdermal drug delivery systems focuses on development of smart patches capable of controlled and targeted drug release.
Integration of nanotechnology, biodegradable polymers, and advanced permeation enhancement techniques may further improve therapeutic effectiveness and patient compliance.

Personalized transdermal therapies and biologically targeted delivery systems are expected to revolutionize rheumatoid arthritis management in the future.

XVI. CONCLUSION

Recent advancements such as microneedles, iontophoresis, nano-carriers, and hydrogel systems have significantly improved transdermal drug delivery efficiency for rheumatoid arthritis management [58,59,60].

Rheumatoid arthritis is a chronic autoimmune inflammatory disorder associated with progressive joint destruction, pain, stiffness, and severe disability. Conventional oral and injectable therapies provide symptomatic relief but are frequently associated with gastrointestinal irritation, systemic toxicity, poor bioavailability, and reduced patient compliance.

Transdermal drug delivery systems have emerged as a promising alternative approach for rheumatoid arthritis management because they provide controlled and sustained drug release through the skin into systemic circulation. These systems avoid hepatic first-pass metabolism, improve bioavailability, reduce dosing frequency, minimize systemic side effects, and enhance patient convenience.

Different polymers, permeation enhancers, plasticizers, and advanced formulation strategies are utilized for successful development of transdermal patches. Recent advancements such as microneedles, nano-carriers, iontophoresis, sonophoresis, and hydrogel systems have significantly improved skin permeability and therapeutic effectiveness.

Future integration of nanotechnology, smart delivery systems, and biodegradable polymers may further enhance the effectiveness of transdermal therapy. Therefore, transdermal patches represent a safe, effective, patient-friendly, and innovative therapeutic strategy for management of rheumatoid arthritis with improved quality of life and therapeutic outcomes.

REFERENCES

[1] Firestein, G. S. and I. B. McInnes, "Immunopathogenesis of Rheumatoid Arthritis," *Immunity*, vol. 46, no. 2, pp. 183–196, 2017.

[2] J. S. Smolen, D. Aletaha, and I. B. McInnes, "Rheumatoid arthritis," Lancet, vol. 388, no. 10055, pp. 2023–2038, 2016.

[3] V. Kumar, A. K. Abbas, and J. C. Aster, Robbins and Cotran Pathologic Basis of Disease, 10th ed. Elsevier, 2020.

[4] H. P. Rang, M. M. Dale, and J. M. Ritter, Rang and Dale's Pharmacology, 9th ed. Elsevier, 2020.

[5] D. L. Scott, F. Wolfe, and T. W. Huizinga, "Rheumatoid arthritis," Lancet, vol. 376, no. 9746, pp. 1094–1108, 2010.

[6] P. K. Gregersen, J. Silver, and R. J. Winchester, "The shared epitope hypothesis," Arthritis Rheum., vol. 30, no. 11, pp. 1205–1213, 1987.

[7] D. Sugiyama, K. Nishimura, K. Tamaki, et al., "Impact of smoking on rheumatoid arthritis," Ann. Rheum. Dis., vol. 69, no. 1, pp. 70–81, 2010.

[8] B. G. Katzung, Basic and Clinical Pharmacology, 15th ed. McGraw Hill, 2021.

[9] L. L. Brunton, R. Hilal-Dandan, and B. C. Knollmann, Goodman and Gilman's Pharmacological Basis of Therapeutics, 13th ed. McGraw Hill, 2018.

[10] L. V. Allen, N. G. Popovich, and H. C. Ansel, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 10th ed. Wolters Kluwer, 2014.

[11] M. R. Prausnitz and R. Langer, "Transdermal drug delivery," Nat. Biotechnol., vol. 26, no. 11, pp. 1261–1268, 2008.

[12] Y. W. Chien, Novel Drug Delivery Systems, 2nd ed. CRC Press, 2018.

[13] B. W. Barry, "Novel mechanisms and devices to enable successful transdermal drug delivery," Eur. J. Pharm. Sci., vol. 14, no. 2, pp. 101–114, 2001.

[14] R. H. Guy and J. Hadgraft, Transdermal Drug Delivery. Marcel Dekker, 2003.

[15] D. Alpizar-Rodriguez and A. Finckh, "Environmental factors and rheumatoid arthritis," Clin. Exp. Rheumatol., vol. 35, suppl. 107, no. 5, pp. 32–39, 2017.

[16] M. Cutolo, A. Sulli, and R. H. Straub, "Estrogen metabolism and rheumatoid arthritis," Ann. N. Y. Acad. Sci., vol. 1069, pp. 131–137, 2006.

[17] I. B. McInnes and G. Schett, "Cytokines in rheumatoid arthritis," Nat. Rev. Immunol., vol. 7, no. 6, pp. 429–442, 2007.

[18] C. M. Weyand and J. J. Goronzy, "Immunopathogenesis of rheumatoid arthritis," Nat. Immunol., vol. 7, no. 4, pp. 291–297, 2006.

[19] M. Feldmann and R. N. Maini, "Role of cytokines in rheumatoid arthritis," Immunol. Rev., vol. 223, pp. 7–19, 2008.

[20] F. M. Brennan and I. B. McInnes, "Evidence for cytokines in rheumatoid arthritis," J. Clin. Invest., vol. 118, no. 11, pp. 3537–3545, 2008.
[21] D. Aletaha and J. S. Smolen, "Diagnosis and management of rheumatoid arthritis," JAMA, vol. 320, no. 13, pp. 1360–1372, 2018.
[22] E. M. Gravallese and G. S. Firestein, "Rheumatoid arthritis pathogenesis," Cell, vol. 186, no. 8, pp. 1554–1572, 2023.
[23] A. J. Silman and J. E. Pearson, "Epidemiology and genetics of rheumatoid arthritis," Arthritis Res., vol. 4, suppl. 3, pp. S265–S272, 2002.
[24] C. Turesson and E. L. Matteson, "Extra-articular features of rheumatoid arthritis," Nat. Rev. Rheumatol., vol. 3, no. 6, pp. 335–344, 2004.
[25] S. E. Gabriel, "Cardiovascular morbidity in rheumatoid arthritis," Am. J. Med., vol. 121, no. 10, suppl., pp. S9–S14, 2008.
[26] D. van der Heijde, "Radiographic imaging in rheumatoid arthritis," Best Pract. Res. Clin. Rheumatol., vol. 17, no. 5, pp. 715–730, 2003.
[27] K. Nishimura, D. Sugiyama, Y. Kogata, et al., "Meta-analysis of anti-CCP antibodies," Ann. Intern. Med., vol. 146, no. 11, pp. 797–808, 2007.
[28] M. Ostergaard, J. Edmonds, F. McQueen, et al., "MRI in rheumatoid arthritis," J. Rheumatol., vol. 32, no. 12, pp. 2462–2471, 2005.
[29] B. Combe, R. Landewe, C. I. Daien, et al., "Early rheumatoid arthritis management," Ann. Rheum. Dis., vol. 76, no. 6, pp. 960–977, 2017.
[30] K. G. Saag, R. Koehnke, and J. R. Caldwell, "Low-dose corticosteroids in rheumatoid arthritis," Ann. Intern. Med., vol. 124, no. 11, pp. 1067–1074, 1996.
[31] J. A. Singh, K. G. Saag, S. L. Bridges, et al., "American College of Rheumatology guideline for rheumatoid arthritis treatment," Arthritis Rheumatol., vol. 68, no. 1, pp. 1–26, 2016.
[32] R. Maini, E. W. St Clair, F. Breedveld, et al., "Infliximab therapy in rheumatoid arthritis," Lancet, vol. 354, no. 9194, pp. 1932–1939, 1999.
[33] A. C. Williams, Transdermal and Topical Drug Delivery. Pharmaceutical Press, 2003.
[34] H. A. E. Benson, "Transdermal drug delivery: penetration enhancement techniques," Curr. Drug Deliv., vol. 2, no. 1, pp. 23–33, 2005.
[35] D. Bhowmik, B. Chiranjib, and R. M. Chandira, "Recent advances in transdermal drug delivery system," Int. J. PharmTech Res., vol. 2, no. 1, pp. 68–77, 2010.
[36] R. Gupta and B. Rai, "Transdermal drug delivery system: a review," Int. J. Pharm. Sci. Res., vol. 3, no. 2, pp. 376–382, 2012.
[37] D. Patel, S. A. Chaudhary, B. Parmar, and N. Bhura, "Transdermal drug delivery system review," Pharm. Innov., vol. 1, no. 4, pp. 66–75, 2012.
[38] C. Puglia and F. Bonina, "Lipid nanoparticles as novel delivery systems," Int. J. Cosmet. Sci., vol. 34, no. 1, pp. 1–10, 2012.
[39] S. Mutalik and N. Udupa, "Formulation development of transdermal patches," Indian Drugs, vol. 41, no. 9, pp. 545–550, 2004.
[40] V. P. Shah, J. Elkins, and S. Y. Lam, "Evaluation criteria for transdermal systems," Pharm. Res., vol. 10, no. 4, pp. 387–390, 1993.