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Enhancing transdermal drug delivery for Rheumatoid arthritis: A review on penetration enhancers

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Abstract
One common inflammatory arthritis that affects extra-articular tissues such as the skin, lungs, and heart is called rheumatoid arthritis (RA). NSAIDs have a number of disadvantages despite being used for therapy on a regular basis. Transdermal medication administration has become a viable substitute, providing benefits over oral therapy such avoiding the gastrointestinal system and improving patient adherence. The stratum corneum (SC), the skin's outermost layer, presents a substantial obstacle to drug absorption, constantly. Penetration enhancers, which can be synthetic or natural, are used to get around this. By lessening the SC's barrier qualities, these substances aid medication penetration of the skin. Sesame oil, turpentine oil, tulsi oil, terpenes, isopropyl myristate (IPM), oleic acid, Transcutol (TR), sucrose fatty acid esters, 1-menthol, and ethanol are just a few of the penetration enhancers that are examined in this review with an emphasis on their potential to improve the efficacy of topical formulations for RA.

Keywords: Penetration enhancers, Rheumatoid arthritis, enhancing, transdermal, skin barrier function

Introduction

An autoimmune chronic condition is rheumatoid arthritis, characterized by a high degree of systemic inflammation that is chronic inflammatory condition that affects joints, notably the hands and feet. It occurs when the mechanism that protects the body, the immune system, turns on its own tissues in an attempt for immunity against illnesses as well as infections. This condition causes pain, edema, stiffness, and loss of function in the joints [1, 2]. Non-steroidal anti-inflammatory drugs NSAIDS such as indomethacin IND, celecoxib, etoricoxib, diclofenac (voltaren, cataflam, arthrotec), ibuprofen, naproxen, and meloxicam are now used in India to treat RA and disease modifying anti-rheumatic drugs, corticosteroids, biological DMARDS [2,3]. NSAIDS may cause side effects including gastrointestinal disturbances, ulcers, and increased risk of cardiovascular events. Transdermal administration of drugs is the most effective way to deliver NSAIDs in order to counteract their side effects when taken orally. Currently, transdermal drug delivery is becoming more widely recognized as an effective non-invasive drug administration technique. Convenient to use, less adverse effects, prolonged therapeutic activity, and increased patient compliance are some of its advantages. As shown in figure 1 the stratum corneum's SC) barrier function poses a difficulty to the drug delivery system (DDS); skin penetration enhancers are used in order to overcome this problem skin's limited permeability is the primary drawback to the development of transdermal products. Several novel compounds have been discovered as possible permeability enhancers for transdermal medication administration in an effort to overcome this barrier effect. The agents known as permeability enhancers are employed to temporarily decrease the skin's impermeability, and the Permeability enhancement is the degree to which a formulation efficiently improves the skin's or mucosa's permeability. [4, 14]

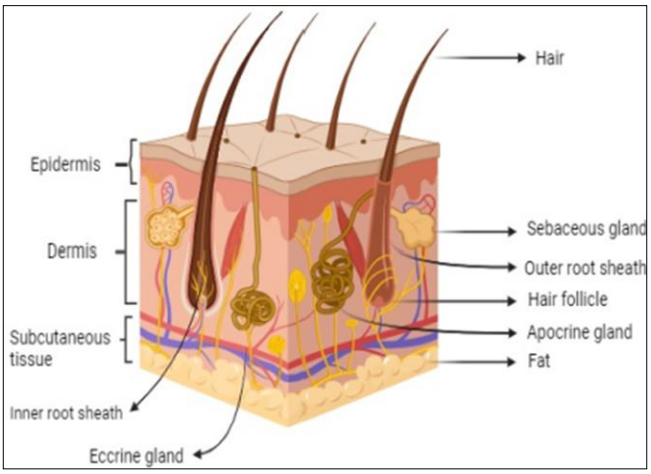

Fig 1: The structure of skin

Skin as an obstacle against drug penetration

The skin defends the internal organs since it is the body's largest organ. Muscles, ligaments, and also other underlying tissues from radiation and mechanical harm as well as external chemicals. Keratinized squamous epithelium makes up the epidermis, the skin's outermost layer. Highly vascular dermis is the next layer which is made up of a thick layer of tightly packed fibroelastic connective tissue that has numerous sensory receptors. It provides food and support to the epidermis. The hypodermis, or subcutaneous layer, is beneath the dermis and is made up of various amounts of adipose tissue. This low permeability is mainly caused by the skin's outermost layer, the stratum corneum, which functions as a rate-limiting lipophilic barrier that prevents water loss and facilitates the absorption of both chemical and biological pollutants. Hair follicles (HFs), the stratum corneum (SC), and tight junctions (TJs) in the interfollicular epidermis comprise the mechanical barriers of the skin.

Because atopic dermatitis and other skin conditions commonly disrupt mechanical barriers, skin issues have an impact on barrier function [5]. Similar to bricks and lipid mortar, the stratum corneum's lipids and proteins combine to create a complex structure that interlocks. In the stratum corneum, the two primary lipids are fatty acids and cholesterol. Ceramides are essential for the overall lipid matrix structure and stratum corneum's skin barrier function, particularly that of ceramides 2 and 5. Ceramides are closely packed in lipid layers due to the formation of strong hydrogen bonds across opposing amide head groups. This implies that the lateral orthorhombic chain organization of ceramide molecules is strengthened by a transverse arrangement. The lipid layers of the stratum corneum are strong, intact, and have barrier properties because of this hydrogen bonding [5, 6].

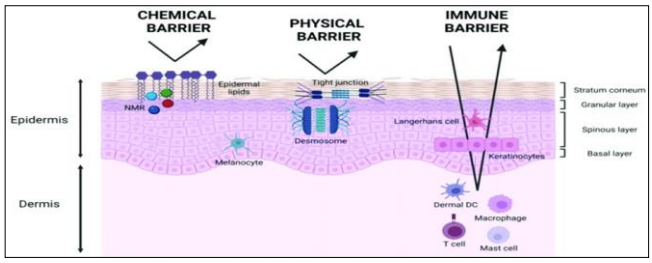

Fig 2: Barrier of skin

Penetration enhancers

Penetration enhancers act by making the skin less impermeable, which facilitates the intended drug's (penetrant) skin penetration [4]. Semisolid dose forms, such as creams and ointments, act as a transdermal delivery method, delivering drugs directly into the bloodstream. Proper medication permeation through skin is required. Penetration enhancers, often called sorption promoters or accelerants, may increase medication delivery through transdermal systems. Penetration enhancers interact with skin ingredients to increase medication efficacy or reduce barrier resistance. Penetration enhancers increase drug concentration in the vehicle, improve skin-formulation partitioning, and reduce skin thickness**.** This is efficient when used with cosolvents. A complicated concentration-dependent impact is exhibited by many permeation enhancers. Penetration enhancers utilized in Nano formulations include pyrrolidone (2-pyrrolidone, 2P), alcohols (ethanol, decanal), sulfoxides (DMSO), glycols (propylene glycol, PG), azones (laurocapram), surfactants, and terpenes [7, 8,].

Properties of permeation enhancers

1. These materials must to be biocompatible, i.e., they shouldn't irritate skin or cause allergies over the long term. Further, it shouldn't cause toxicity.
2. It should be compatible with the medication being administered.
3. It shouldn't have adverse pharmacological effects on the body.
4. It should be inexpensive with good solvent qualities.
5. It should be odourless, tasteless, and colourless.
6. It must possess both physical and chemical stability.
7. The method of action needs to be rapid, sustainable, and repeatable.
8. It shouldn't result in the unidirectional flow of endogenous materials and bodily fluids, and as soon as these substances are eliminated, Skin should return to its original barrier properties immediately [5, 9].

Classification of permeation enhancers

Major categories of permeability enhancers: enzymatic, vesicular, physical, synthetic, and natural [10].

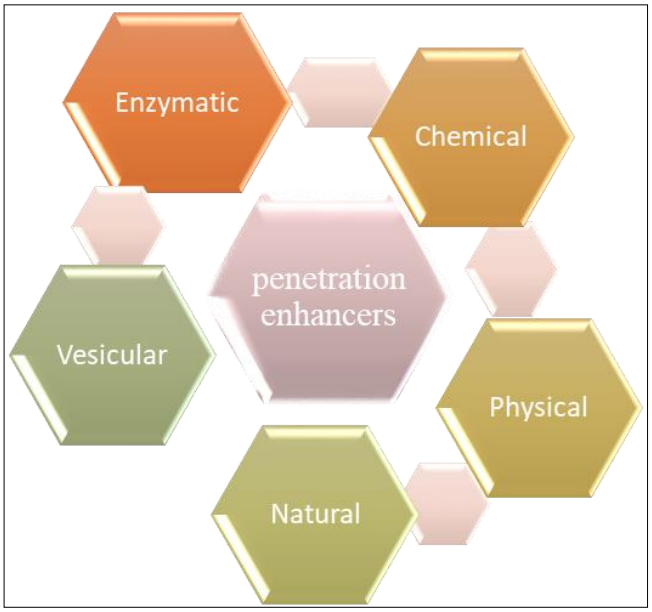

Fig 2: Classification of permeation enhancers

Physical permeation enhancers

Examples of useful skin current techniques are iontophoresis (which employs low-frequency ultrasound) and sonophoresis (which uses a small electric current of about 15 mA) [11].

Chemical permeation enhancers

These consist of substances including urea, azone, fatty acids, ethanol, and glycols etc. [12].

Natural permeation enhancers

Terpenes, fatty acid esters, essential oils, terpenoids, herbal extracts, and fatty acid glycols are examples of natural permeation enhancers [13].

Vesicular permeation enhancers

These are microscopic spheres of synthetic vesicles that might include active substances. Hydrophilic molecules will be present in the aqueous core of these vesicles, and lipophilic compounds will incorporate into the membrane made up of lipids that envelops the hydrophilic core. Vesicular carriers include liposomes, elastic vesicles, niosomes, Transethosomes (TEs), and ethosome synthetic vesicles. The vesicle walls of liposomes and niosomes are usually made up of phospholipid bilayers or synthetic surfactants [6, 14].

Enzymatic permeation enhancers

These compounds improve penetration by change the essential molecular proportion of the important stratum corneum lipids and inhibit key enzymes involved in the synthesis of epidermal lipids. Acetyl CoA carboxylase and HMGCoA reductase are two examples of these enzymes [10].

Investigated permeation enhancers in rheumatoid arthritis topical formulation

Table 1: The effectiveness of combining permeability enhancers with the active component

Drug molecule	Permeation enhancers	Therapeutic effect	Ref
Diclofenac	Sesame oil and turpentine oil	Sesame oil is not as effective as turpentine oil in enhancing penetration.	18
Ibuprofen	Transcutol (TR) and sucrose fatty acid esters	Transcutol was unable to improve the drug's skin penetration. The sucrose ester increased ibuprofen's skin penetration by 2.15 times.	25
Indomethacin	l-menthol	L-menthol improved the IMC solid nanoparticles' skin penetration.	27
Meloxicam	Isopropyl myristate (IPM) and oleic acid(OA)	Oleic acid improve penetration	33
Naproxen	Tulsi oil	Tulsi oil released the drug faster.	38
Celecoxib(CXB)	Propylene glycol (PG), Oleic acid (OA)	CXB release rate is increased by the OA/PG	42
Etodolac	Terpenes (anethole,carvacrol,and menthol)	Terpene anethole significantly increased etodolac absorption; carvacrol and menthol did not enhance etodolac absorption.	46
Sinomenine hydrochloride:	Ethanol	AS-TE enhance transdermal permeability and drug deposition	49

Sesame oil and turpentine oil (Diclofenac)

An NSAID that is useful in the treatment of RA is diclofenac. Diclofenac has a short half-life (4 h). Diclofenac has low bioavailability and poor dissolution due to its weak water solubility [15]. Dosage forms developed most recently are transdermal films/patches among the many transdermal drug delivery methods, and they are ideally suited for managing the chronic pain and inflammation experienced by individuals with arthritis. An ideal transdermal patch must be soft, elastic, and flexible. It also needs be adhesive that is sufficiently effective persist on the skin for the given duration of time. Several permeation enhancers can be applied to the skin in order to facilitate drugs pass through it more effectively. To enhance skin penetration, additional substances including alcohols, terpenes, and surfactants are employed [16,17]. Peng-Gang xu *et al* (2016) investigated as Sesame oil, turpentine oil, and penetration enhancers have been suede *vivo* permeation investigations of the diclofenac films were carried out into excised rat belly skin in a modified Franz diffusion cell. Drug permeability improved as enhancer concentration increased, and ex *vivo* drug permeation was higher in films containing penetration enhancers than in those without. It was evident that sesame oil did not have the same penetrating impact as turpentine oil. The highest percentage of permeation enhancers increased the percentage of drugs that penetrated when there was the best penetration. According to the study's findings, turpentine oil and sesame oil can help transdermal films containing diclofenac penetrate more easily, which is beneficial for RA. Turpentine oil acts more efficiently than sesame oil [18].

Transcutol (TR) and sucrose fatty acid esters (Ibuprofen

Ibuprofen (IBU) is a common popular and effective (NSAID) for administration of both acute as well as chronic musculoskeletal disorders. for topical administration to have a local effect where needed (in the joint, muscle), reduce systemic adverse effects, and provide faster pain relief than when taken orally.[19] When developing transdermal delivery systems, it is especially important to use an appropriate penetration enhancer to increase up the rate at which active pharmaceutical ingredients (API) pass through the membrane without affecting the skin or causing toxicity because of the skin's superior barrier properties.E.Csizmazia *et al*, (2011) [26] prepared transcutol (TR) and sucrose fatty acid esters offer a novel option because they are both skin-compatible and non-toxic. Transcutol [TR] insoluble in both polar and non-polar solvents makes it a helpful solubilizing agent for a variety of APIs Because of its humectant qualities, it can also promote the percutaneous penetration of different APIs [20, 21]. Moisture from the skin can be absorbed by TR, which raises the stratum corneum's (SC) water percentage and promotes its intercellular lipids to enlarge without changing the structure of the numerous bilayers. This lowers the diffusional resistance. Sucrose esters, or SEs, are a newer class of penetration enhancers. These non-ionic surfactants have polar groups that are fatty acids and polar head groups that are sucrose, a sugar replacement. SEs have been used in pharmaceutical manufacturing recently because of their broad range of HLB values, natural origin components, non-toxicity, biodegradability, and decreased barrier damage compared to other surfactants. For this reason, they are most appropriate for cutaneous and transdermal use [22,23]. *In vitro* drug release of all types of SEs varies based on the fatty acid chain's C atom number and Hydrophilic lipophilic balance (HLB)value. The potential of surfactant substances to increase skin penetration can be influenced by the specific type of substituents used, the chain's length, as well as the extent and range of unsaturation. It is well known that a surfactant's effect on membrane permeability is maximized when it has a linear alkyl chain with twelve carbon atoms. The C12 chain can penetrate the lipid bilayer and is moderately soluble in oil as well as water. Most efficient polyoxyethylene ether for IBU was discovered to be lauryl (C12) ether, which ensures excellent skin penetration into the deeper layers to effectively reduce pain and inflammation in musculoskeletal issues [24]. Excision of human epidermis and synthetic membrane were used in diffusion experiments to look into not only API release from the drug delivery system. Ibuprofen dispersion over synthetic membranes (*in vitro*) is proven by ibuprofen penetration by using hair-free mice- *in vivo* and evacuated human epidermis-ex *vivo*. Transcutol effectively increases the diffusion of ibuprofen; yet, it was unable to increase the drug's skin penetration. The sucrose ester increased ibuprofen's skin penetration by 2.15 times. sucrose laurate appears to be a suitable and useful ibuprofen penetration and permeability enhancer [25].

L-menthol (Indomethacin)

Indomethacin (IMC) is the most commonly administered NSAID for the treatment of pain, fever, and inflammation. The Biopharmaceutical Classification System (BCS) classifies indomethacin as a Class II medication; its log p and pka are 2.2 and 4.5, respectively [26]. The IMC inhibits

the enzyme cyclooxygenase (COX), which is necessary for the synthesis of prostaglandins from arachidonic acid. On the other hand, the suppression of COX by oral IMC delivery results in a reduction of the gastrointestinal tract's protection mechanisms and adverse reactions, like damage to the stomach mucosa. Moreover, studies have shown that an increase in the gastrointestinal system's direct stimulation by IMC associated with a decrease in resistive performance and was linked to the start of gastroduodenal mucosal injury. Noriaki Nagai *et al*. (2019) [28] evaluated A bead mill technique was used to crush 1% IMC with 0.5% methylcellulose and 5% 2-hydroxypropyl-β-cyclodextrin. The milled IMC was then gelled with or without Carbopol® 934, a permeation enhancer (N-IMC gel without menthol; N-IMC/MT gel with menthol). Furthermore, the N-IMC/MT gel's release of drugs, penetration into the skin, and percutaneous absorption were assessed. The transdermal formulations' particle characteristics, which ranged from 50 to 200 nm in size, remained constant when N-IMC gel and l-menthol were combined. Developed topical compositions including IMC solid nanoparticles and l-menthol, and found that the l-menthol addition improved the skin penetration of the IMC solid nanoparticles. *In vitro* research using a Franz diffusion cell, the N-IMC/MT gel showed better skin penetration than the N-IMC gel. Furthermore, the percutaneous absorption (AUC) of the N-IMC/MT gel was substantially higher than that of the N-IMC gels. On the other hand, there appeared to be less skin penetration of the N-IMC/MT gel at 4 ◦C, which inhibits all energy-dependent endocytosis. It was found that when l-menthol and IMC solid nanoparticles were combined, transdermal formulations containing both drugs had a greater rate of skin penetration. Furthermore, it has been demonstrated that the energy dependence of IMC solid nanoparticle skin penetration occurs. These results demonstrate the potential benefits of only employing solid nanoparticles (SNPs) by transdermal medication delivery [27].

Isopropyl myristate (IPM) and oleic acid (Meloxicam)

Nining Nining *et al*, (2023) [34] evaluated A nonsteroidal anti-inflammatory medication (NSAID) that particularly inhibits cyclooxygenase-2 (COX-2) is meloxicam (MX), a derivative of oxicam[28].The dose of MX for elderly patients with rheumatoid arthritis and ankylosing spondylitis may be treated for long-term treatment with a dosage as 7.5 mg per day. Drug distribution is restricted since the drug needs to gradually penetrate the stratum corneum barrier in order to enter deeper skin layers[29].Chemical penetration enhancers facilitate drug molecule flow by interacting with skin constituents[30].Esters and fatty acid groups were used as chemical penetration-promoting agents. Isopropyl myristate (IPM) is the most widely used and common ester penetration enhancer in commercial products. The drug can permeate the skin more deeply, moderate the rigid skin structure, and improve the fluidity of the skin by integrating the lipid layer. Because of its cis double bond, the fatty acid group oleic acid (OA) can improve drug penetration through the development of a permeable deficiency in SC lipids[31,32].This allows it to disintegrate into its own fat rather than spreading evenly across the skin's natural fats. When giving MX transdermally using matrix-type patches, it seems that OA can be employed to promote penetration as the MX penetrated from the IPM-MX and OA-MX patches demonstrated the greatest flux having a high diffusion flux [33].

Tulasi oil (Naproxen)

Guptha V *et al*, (2009) formulated Naproxen is (NSAID) that's efficient well for treating a variety of inflammatory conditions. Consistent with other NSAIDs, mainly prominent adverse consequence of peroral naproxen was gastrointestinal pain [34].Topical medication may be able minimize these potential side effects. The skin, one of the human body's largest available organs for topical administration, serves as the main delivery channel for topical pharmaceuticals. Without first penetrating the skin, a topical product cannot reach the site of action or go deeper into areas of inflammation. The drugs cannot be absorbed by the circulation and transmitted to the lower layers of the skin until it has reached the uppermost ones. When percutaneous absorption is at its rate-limiting phase, stratum corneum offers the most significant resistance to penetration. Drug permeation with the aid of the skin can be improved by chemical permeation enhancers as well as physical techniques such as mechanical disruption, electrical disruption, and chemical change. By improving the drug's partition coefficient with the aid of the skin & its thermodynamic activity in the vehicle, these kinds of compounds raise ski permeability [35].Chemical penetration enhancers alter the stratum corneum's barrier characteristics, increasing the medication's skin absorption capacity. The optimal penetration enhancer should not irritate the skin, be nontoxic, nonallergenic, compatible with medications and excipients, and be reversible. Conversely, the use of synthetic permeation enhancers has been associated with toxicity and skin discomfort. Natural substances are consequently being used as enhancers more and more due to their improved safety profile [36].In India, Tulsi, a plant in the Labiateae family, is revered and planted extensively. The leaf contains the triterpenoid ursolic acid, the phenylpropanoid rosmarinic acid, and the volatile oil eugenol. Two other active ingredients are caryophyllene and oleanolic acid. Seeds consists of fixed oils that are rich in linoleic and linolenic acid. In the Ayurvedic medicinal system, for many years, it has been utilized to treat a variety of ailments without causing any noticeable harm [37].The study looks investigated Tulsi oil's ability to increase penetration when preparing transdermal naproxen gels. While the precise mechanism of action is uncertain, it may change the features that characterize stratum corneum barrier to improve percutaneous penetration. To prepare several gel formulations, different quantities of Tulsi oil and naproxen were used. The findings demonstrated that the gel was easily spreadable, the drug concentration was consistent, and the pH ranged from 6.83 to 6.89. Formulations with Tulsi oil released the drugs more quickly than formulations without it, according to *in vitro* drug release tests. The optimal formulation was determined to contain 5% Tulsi oil [38].

Propylene glycol (Pg) and oleic acid (OA): (celecoxib CXB)

Mariane de cassia Lima Dante *et al*, (2017) evaluated A nonsteroidal anti-inflammatory medication called celecoxib (CXB) performs by specifically blocking cyclooxygenase-2's enzymatic activity. A potential treatment for skin inflammatory diseases and chemoprevention of skin cancer is CXB skin delivery. It is challenging to reach the stratum corneum, nevertheless, because it acts as a barrier to drug penetration [39]. To increase skin penetration and regulate

medication release, developed techniques like penetration enhancers and drug delivery systems, such as liquid crystalline systems. This study suggests delivering CXB to the skin via liquid crystalline glyceryl monooleate (GMO) systems. These substances offer sustained drug release and diffusion retardation because to their intricate matrix structure. When GMOs come into contact along with water, they transform into liquid crystalline phases, which improve penetration [40]. Additives including glycerol, ethanol, polyethylene glycol, and propylene glycol (PG) can be added to enhance medication release and skin penetration [41].The study evaluated the feasibility of GMO-W systems for CXB skin passage using polarized light microscopy and SAXS. Hexagonal and cubic phases are developed in systems of liquid crystals that contain Water and similar permeation enhancements, together with GMO. The production of crystalline liquid mesophases and the dependent on concentration phase at which CXB is formed are significantly impacted by the additions OA (oleic acid) and PG (propylene glycol), although these effects are independent of the main phase behaviour of the system. The CXB release rate is raised by the OA/PG interaction, whereas it is lowered by OA alone. The aerosol-ingested rat paw edema model's edema production is significantly reduced by the Liquid crystalline systems filled with CXBs, suggesting that the particular combinations may suitable for administration of celecoxib through the skin. Systems that contain CXB are more effective in the compared to the hexagonal phase, the cubic phase; this is because of the liquid crystalline structure and composition of the systems. Therefore, OA and PG alter CXB release and penetration in GMO-W cubic phase liquid crystalline systems, making them useful for administering CXB to the skin [42].

Terpenes (anethole, carvacrol, and menthol): (Etodolac)

Etodolac is a highly lipophilic anti-inflammatory drug that is frequently used to treat rheumatoid arthritis. The most common side effects of etodolac therapy are gastrointestinal problems, which are typically mild and transient. However, in some individuals, peptic ulcers and severe stomach bleeding may also develop [43].The most effective way to eliminate these side effects and attain high medication concentration at the application site seems to be by dermal application of etodolac. The most difficult part of using a transdermal delivery method is getting past the resistance of the stratum corneum (SC) to foreign substances. A penetration enhancer is required for certain medications in order for them to reach therapeutic plasma levels in the target tissue [44]. Terpenes are volatile oils that can be found organically and have many potential advantages. They have a reversible action on the lipids of SC, a high potential for percutaneous enhancement, limited percutaneous irritancy at low doses (1-4%), and strong evidence that they are not toxic, all of which indicate that they are clinically acceptable penetration enhancers. Moreover, it has been shown that a variety of terpenes can improve the lipophilic and hydrophilic medicines' percutaneous absorption [45].In order to improve the drug's percutaneous absorption; Cetin Tas *et Al.* (2006) evaluated hydrophilic gel formulations of etodolac utilizing sodium carboxymethylcellulose and terpenes such as menthol, carvacrol, and anethole. Studies conducted *in vivo* shown that the skin quickly absorbed and released etodolac. The etodolac absorption was considerably enhanced by the hydrophobic terpene anethole, indicating that hydrophobic terpenes efficiently impede lipophilic medication percutaneous absorption. But because menthol and carvacrol break the H-bond between ceramides, which loosens the lipid bilayer, they did not improve the absorption of etodolac. This might cause water to get into the lipids of the bilayer, increasing its hydrophilicity and hindering the drug's ability to penetrate the skin [46].

Ethanol: (sinomenine hydrochloride)

Sinomenine hydrochloride is a disease-modifying anti-rheumatic drug that is long-standing and in use in Chinese clinical settings to treat RA. It has a license from the Food and Drug Administration of China [47]. Sinomenine hydrochloride can have a first-pass effect and affect the stomach when taken orally. Because of stratum corneum's potent connection, no drug can move through the body. Drugs having a molecular weight of less than 500 Da and a log P of usually 3~5 are thought to get inside the body quickly and pass through the skin.7, 8 As nanotechnology progresses, nanocarrier is utilized in TDDS more frequently [48].Hui song *et al*, (2019) [50] developed a Transethosome (TE), which is derived from both ethosome and transferosome, has a higher entrapment efficiency (EE) for the water-soluble drug than any of the other two. It is also an edge activator, or penetration enhancer, with a high ethanol concentration. One type of nanocarrier with high ethanol content (20–50%) and significant deformation is the ethosome (E). Another use for ethanol is as a chemical penetration enhancer. In addition to having superior elasticity and penetration efficiency compared to the E group, TE and AS-TE that includes sodium deoxycholate can also successfully raise the entrapment efficiency of hydrophilic drugs. AS-TE, which can improve medication deposition and transdermal permeability for cellular damage in RA [49].

Conclusion

As a result of its benefits, the design of transdermal drug delivery has been expanding rapidly, which has encouraged numerous studies to include an increasing number of medications via this method. Penetration enhancers are used in order to improve the permeability of poorly absorbed drugs and hence retain their bioavailability, as skin acts as a barrier to drug penetration. In order to improve the development of a transdermal delivery system, this review article outlines the numerous chemical and natural permeation enhancers that can be employed. The stratum corneum, the skin's outermost layer, has a highly organized structure that can be disrupted by both natural and chemical penetration enhancers. They improve the penetration of drugs through the skin by modifying the lipid pattern. Drugs can enter the body more efficiently because to this method, which requires brief alterations to the lipid bilayers. Certain enhancers affect the proteins that connect skin cells. These interactions have the potential to alter the barrier qualities of the skin and promote drug transport. These enhancers facilitate medication absorption by their effects on intercellular proteins. Drugs, co-solvents are more able to partition into the stratum corneum when enhanced. Better medication administration through the skin results from this improved partitioning.

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