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THE ROLE OF PERMEATION ENHANCERS IN TRANSDERMAL DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Transdermal drug delivery systems (TDDS) have revolutionized the way therapeutic agents are administered, offering improved patient compliance, controlled release rates and avoidance of the first-pass effect. However, the bioavailability of these systems is often limited by the skin's natural barrier function, which hinders the permeation of medicinally active ingredients. Permeation enhancers play a crucial role in overcoming this limitation by increasing the permeability of the skin, thereby enhancing the bioavailability of transdermally delivered drugs. This review aims to provide a comprehensive overview of the role of permeation enhancers in TDDSs, including their mechanisms of action, classification, and applications. The review also discusses challenges along with opportunities that surround using things that help medications permeate through skin devices. Improving efficacy along with safety is definitely what permeation enhancers are working for when it comes to topical delivery systems.

KEYWORDS

Transdermal drug delivery system, Permeation enhancer, Skin devices, DMSO and Topical delivery.

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INTRODUCTION

Transdermal drug delivery systems are patches that are applied topically and release drugs at a predetermined, controlled rate for systemic effects. Therapeutic amounts of pharmacological chemicals can now be injected via the skin into the bloodstream for systemic effects to transdermal drug delivery systems, or TDDSs[1]. Transdermal drug delivery systems offer several benefits over traditional delivery methods, including better patient compliance, a predicted and regulated rate of

transport and the avoidance of the first pass effect[2]. The amount and degree to which a medicinally active ingredient penetrates systemic circulation and becomes accessible at the primary site of action is referred to as bioavailability. The best bioavailability is obtained with intravenous injection; partial medication absorption and first-pass metabolism cause lower rates when taken orally[3]. Transdermal patches are pharmaceutical preparations that cross the epidermal barrier and deliver medications straight into the bloodstream. It works well for the delivery of medications with brief biological half-lives. Transdermal patches are simple to apply and remove. When it comes to chronic conditions like hypertension, when long-term dosage is necessary to maintain therapeutic medication concentration, this method of drug delivery is more relevant[4]. A set of physicochemical procedures known as a drug delivery system (DDS) regulates the movement and release of pharmacologically active substances into cells, tissues, and organs so that the active substances can work as effectively as feasible[5]. The drug reservoir in this transdermal drug delivery system is enclosed in a compartment made of a rate-controlling polymeric membrane and a drug-impermeable backing layer. The drug particles are either suspended or distributed in the solid polymer matrix within the drug reservoir compartment[6]. An additional method of administering medications through the skin layer is transdermal drug delivery. Before the medication reaches its target location, it passes through the skin and enters the bloodstream, where it circulates throughout the body[7,8]. Compared to alternative administration methods, the transdermal medication delivery approach offers a number of advantages. Examples include the capacity to avoid first-pass metabolism in the liver, avoid the digestive tract and administer continuous dosages of medication for a prolonged length of time. Other methods of administering drugs, such intravenous, can hurt and raise the risk of infection[9].

TDDS

Often referred to as "patches," transdermal drug delivery systems are discrete, self-contained dosage forms intended to administer a therapeutically appropriate dose of medication through intact skin (Wokovich *et al*, 2006). The majority of transdermal drug delivery systems that are sold commercially fall into one of three categories: reservoir systems, matrix systems with or without a rate-controlling membrane. The adhesive, the rate-controlling membrane, and the drug reservoir are the three main parts of the reservoir system. Before the medication and other excipients in the reservoir may enter the skin, they must pass through the rate-controlling membrane[10]. TDD is a painless way to apply a drug formulation to healthy, unbroken skin in order to deliver medication systemically[11,12]. Without building up in the dermal layer, the medication first enters the stratum corneum before moving on to the deeper layers of the epidermis and dermis[13]. The medicine can be absorbed systemically via the dermal microcirculation once it reaches the dermal layer[14,15]. TDD is superior to other traditional drug delivery methods in several ways. It can offer a non-invasive substitute for parenteral methods, avoiding problems like needle fear[16].

TYPES

In the Reservoirs system, the medication is kept in an impermeable reservoir that is closed on one side. There is an adhesive surface for application on the skin on the opposite side. Certain patches have the medication dissolved in a gel or liquid. This makes it possible to employ liquid chemical enhancers like ethanol and create simpler formulations. Usually, they consist of four layers:

A backing membrane that is impermeable;

The drug reservoir itself

A semi-permeable membrane that could serve as a barrier with a rate limit

The layer of adhesive[17]

The Matrix System: The medication is incorporated into an adhesive polymer matrix by the matrix

patch, which releases the medication into the skin continually.

The amount of medication contained in the matrix and the region of the skin where the patch is applied determine the drug's dosage.

The active component in a matrix patch is dispersed equally over the patch.

A patch divided in half will have half the surface area and half the dose delivered in an hour.

Compared to the reservoir system, the matrix patch has a lower risk of inadvertent overdose and less opportunity for misuse[18].

SKIN

With a surface area of 1.7 m2, the skin is the largest and most accessible organ in the body, making up 16% of an average person's total body mass[19-21]. The skin's primary purpose is to act as a barrier of defense between the body and the outside world, keeping out germs, toxins, allergies, ultraviolet (UV) radiation, and water loss[22]. The three primary sections of skin are the outermost layer, known as the epidermis, which contains the stratum corneum; the middle layer, known as the dermis; and the innermost layer, known as the hypodermis[23,24].

Epidermis

The epidermis is divided into four layers: stratum granulosum, stratum spinosum, stratum germinativum, and stratum corneum, which is the epidermis's most distant layer[25]. SC is around 15 µm thick, made up of keratinized corneocyte layers separated by an intercellular lipid domain[26]. The lipid domain between cells is made up of neutral lipids, ceramides, triglycerides and free fatty acids. The remaining components include phospholipids, glycosphingolipids, and cholesterol, all of which are necessary for desquamation. The corneocytes in the lipid-protein matrix form a brick wall structure. Corneodesmosomes hold the thick, overlapping corneocytes together, and they are encased in a complex lipid matrix. These contribute to the intact skin's tightness and impermeability, acting as a primary permeability barrier for hydrophilic molecules with molecular masses greater than 200-350 Da[27].

Dermatis

The dermis is a hydrophilic deposit measuring 0.1-0.5cm thick. The dermis is a network of elastin and collagen fibers embedded in a mucopolysaccharide matrix that contains blood vessels, lymphatic and nerve endings, pilosebaceous units, and sweat glands. The connective tissue's collagen fibers provide support, while elastic tissue provides flexibility. The dermis does not significantly limit substance transfer (but it may pose a considerable barrier for very hydrophobic medicines)[28]. Blood vessels in the dermis domain remove chemicals that pass through the epidermis layers, keeping the concentration difference between the dermis and the skin surface that facilitates penetration. Furthermore, sebum glands, sweat glands, and hair follicles stimulate the dermis region, resulting in a "shunt" pathway that favors a few permeants.

Hypodermis

The skin's innermost layer is known as the hypodermis, or subcutaneous layer. It acts as an absorber for any shocks directed at the body and improves insulation[29]. Connective tissue, adipose tissue (fat cells), fibroblasts, blood vessels and macrophages are all cells that make up the hypodermal layer.

IDEAL PROPERTIES

TDDS's ideal characteristics include The perfect TDDS should have the following characteristics: A minimum melting point of less than 200 c; a shelf life of up to two years; the optimal partition coefficient needed for the drug's therapeutic action

Avoiding medication metabolism in the first pass;

Not interfering with stomach or intestinal fluids;

Patch size should be less than 40cm.

Because the drug is infused steadily over an extended period of time, the negative effects of intermittent dosing are avoided. The painless, non-invasive, and straightforward application increases patient compliance. The drug is able to achieve more stable and controlled blood levels for a longer period of time. The characteristics are similar to intravenous infusions. This method works well for administering medications with short half-lives,

limited therapeutic windows, and low oral bioavailability.

When the patch is removed, the medication is stopped[30].

LIMITATIONS OF TDDS

Large-molecule drugs are difficult to absorb; local irritation may occur at the application location. The medication molecule's ideal size is between 80 and 100 Daltons.

Transdermal administration is not appropriate for hydrophilic medications.

The skin's ability to act as a barrier varies depending on the patient.

High drug levels cannot be achieved in blood or plasma using TDDS[31].

THE SKIN PERMEATION MECHANISM

Three possible routes exist for drug molecules in touch with the skin's surface to penetrate: via the sweat ducts, through hair follicles and sebaceous glands (referred to as the shunt or appendageal route), or directly through the stratum corneum. The lack of an appropriate experimental model that would allow for the separation of the three paths has further compounded the argument among scientists over the years over the relative relevance of transport across the stratum corneum vs the shunt or appendageal route. *In vitro* studies typically use hydrated skin or epidermal membranes, causing the swelling that comes with moisture to seal off appendages. The pre-steady state permeation of polar molecules and the flux of big molecules were suggested to be caused via a follicular shunt channel by Scheuplein *et al*. The horny layer lipid structure, permeation and DSC studies are the basis for the mechanisms of action of several penetration enhancers. According to the study, every penetration enhancer interacted with the lipid structure of the stratum corneum, upsetting its arrangement and increasing its fluidity, which made it easier for medications to penetrate. Numerous accelerants also had effects on intracellular protein; OA and Azone worked best when dissolved in a polar co-solvent such as PG. The solvating impact of enhancers on protein helices may accelerate intracellular drug transport, which could explain the decreased size and widening of T4 following accelerant administration. Water is a powerful penetration enhancer in dry tissue and alters the diffusional resistance of intracellular contents in response to skin moisture. Tiny polar accelerators, such DMSO and its derivatives, can build up in the tissue's intercellular and protein areas, which will improve drug distribution into the skin and result in higher fluxes[32].

ROUTES OF PERMEATION ENHANCERS

Physical permeation enhancers

Physical permeation enhancers include iontophoresis, electroporation, ultrasound, laser radiation, pressure waves, and magnetophoresis. Iontophoresis involves using a low-level electric current to improve the penetration of a topically applied medicinal drug, either directly to the skin or indirectly through the dose form[33-48].

Electroporation

Electroporation delivers high voltage pulses across the skin for a fraction of a second, forming new aqueous channels in the stratum corneum for drug diffusion[34].

Ultrasound

Ultrasound also known as sonophoresis, is the use of ultrasonic radiation to increase transdermal transport of solutes, either concurrently or through pretreatment[48].

Laser radiation and photomechanical waves are commonly used in therapeutic therapies for decades and pressure waves have recently been shown to improve skin permeability[49-61].

Magnetophoresis

Magnetophoresis uses a magnetic field as an external driving force to increase the diffusion of a diamagnetic solute over the stratum corneum. These methods have limitations, including regulatory limits on the amount of current that can be utilized in humans and the irreparable damage such currents can cause to the skin's barrier qualities[62,63].

Thermophoresis

Thermophoresis is a homeostatic process that maintains skin surface temperature at 32°C, which has been shown to improve the distribution profile of topical medicaments. For every 7 to 8°C increase in skin surface temperature, flow increases by 2 to 3 times[64-67].

Vasodilation

Vasodilation of subcutaneous blood vessels is also significant in improving transdermal transport of topically applied chemicals. In vivo delivery of nitroglycerin, testosterone, lidocaine, tetracaine and fentanyl from transdermal patches with linked heating devices has been demonstrated to increase as a result of the raised temperature at the delivery site[68-71].

Microneedle-based devices

Microneedle-based devices have been used for percutaneous drug administration, with devices consisting of a drug reservoir and several projections that extend from it. Needleless injections are a painless method of giving medications to the skin, avoiding safety, pain and terror concerns associated with using hypodermic needles[72-75]. Radio frequency treatment exposes skin to high frequency alternating current, creating heat-induced microchannels in the membrane similar to laser radiation. The Viaderm device is a hand-held electronic device made up of a microprojection array and a medication patch[76-80].

Carriers and vehicles

Carriers and vehicles include micro- or nanocapsules, nanoemulsions, submicron emulsions, miniemulsions, solid lipid nanoparticles (SLNs) and vesicular carriers[81-92].

Liposomes

Liposomes are concentric biomolecular layers that can encapsulate medicines and have various applications, including skin distribution, gene delivery and cutaneous vaccination[93-118].

CHEMICAL PERMEATION ENHANCERS

Dimethyl sulphoxide (DMSO) is a potent aportic solvent used in pharmaceutical science to treat systemic inflammation. It is colorless, odorless, and hydroscopic and can cause issues like erythema and wheal of the stratum corneum. Dimethylacetamide and dimethylformamide (DMF) are also potent aportic solvents, but they can cause irreversible membrane damage. DMSO can also remove lipids, increasing the horny layer's permeability. Pyrrolidones have been used to improve the permeation of various compounds, but their use in a matrix-type transdermal patch has been limited[119]. CPEs in TDDSs operate as SC modifiers without causing skin injury, resulting in increased drug penetration. According to Morrow *et al,* utilizing chemical permeation enhancers is one of the most common methods for changing the SC. Figure No.3 depicts various chemical permeation enhancers and discusses their mode of action as well as toxicity profile.

Water

Water is a traditional method for improving transdermal medication delivery, with the human skin having 15-20% water and two states: bound water and residual water[120]. Water molecules increase fluidity in the cholesterol-stiffened domain and facilitate interactions between head groups, which is how hydration conditions boost the transport of lipophilic medicines. However, water has no effect on SC modification, raising the question of what causes the SC layer modification[121-123].

Alcohol

Alcohols are the most prevalent CPEs used in transdermal drug delivery, typically used as co-solvents with water[124]. Alcohols are short-chain solvents that can extract SC lipids when used at optimal concentrations for lengthy periods of time. The effect of ethanol on estradiol skin penetration was studied using the human skin sandwich flap model. Long-chain alcohols have also been shown to improve penetration, with 1-butanol being the most efficient booster of levonorgestrel across rat skin[125-132]. Transcutol (TC) is a hydrophilic CPE with skin-like solubility properties, commonly used in transdermal and topical formulations due to its propensity to improve penetration. Recently, penetration enhancer-containing vesicles (PEVs)

have received attention as carriers for improved transdermal medication delivery. Studies have shown that PEVs improve *ex vivo* drug transport of both diclofenac forms and sodium naproxen in pig skin[133-135]. The effects of penetration enhancers on human cadaver skin include the penetration of saturated TQ solutions using various permeation enhancers, such as Azone, oleic acid, and Transcutol. These enhancers may provide enough TQ flux and produce TQ reservoirs, which may be useful for releasing medication at a consistent rate[136].

Sulfoxides

Dimethylsulphoxide (DMSO) is a widely used penetration enhancer among sulfoxides, enhancing intercellular keratin penetration. In vitro studies show that 15-30% of DMSO can penetrate human skin within 2 hours. However, DMSO is metabolized in the body, and its high doses can cause side effects like erythema, scaling, contact urticaria, stinging and burning sensations[137-142]. Dimethylformamide (DMF) and dimethylacetamide (DMAC) are similar aprotic solvents with similar structures, but they can induce irreversible membrane damage. New structural equivalents, such as decyl methyl sulphoxide (DCMS), work on human skin in a concentration-dependent and reversible manner[143].

Azone

Azone, a transdermal penetration enhancer, is a chemical fusion of cyclic amide and alkyl sulfoxide, resulting in low irritancy and being hydrophobic but soluble in most organic solvents. It interacts with the skin's surface lipid, generating a'soup spoon' shape[144]. Azone's usefulness is concentration-dependent, with its effectiveness being concentration-dependent. It has been found to improve the penetration of naproxen, form ion pairs with anionic medicines, and synergize with salicylic acid. It also has been found to provide adequate flow and form thymoquinone reservoirs in the skin[145-152].

Surfactants

Anionic surfactant

Anionic surfactants, such as soaps and sodium lauryl sulphate (SLS), bind to epidermal proteins, increasing hydration intensity[153-155]. Studies show that SLS increases tissue water content and irritation, while SLS enhances skin penetration of ketotifen and lorazepam[156,157]. Low-frequency ultrasound combined with an anionic surfactant increases polar chemical penetration. These surfactants also have a reversible action, as skin tissues revert to their standard form upon removal[158].

Cationic surfactants

Cationic surfactants, which are often quaternary ammonium compounds, have a positive charge on the hydrophilic head group and bulky lipophilic hydrocarbon groups. CTAB and BKC are well-known cationic surfactants used in transdermal formulations to improve the absorption of many medicines, such as diazepam, haloperidol, and methyl nicotinate[159-161]. Cationic surfactants cause penetration by swelling the SC and reacting with intercellular keratin. Due to the substantial side effects, these substances were not tested *in vivo* for penetration augmentation.

Non-ionic surfactants

Non-ionic surfactants, such as Tween and Brij series, are used to promote penetration and improve membrane fluidity, making them safer than ionic surfactants. They provide fewer unpleasant sensations and are often used in permeation investigations[142-163]. Biosurfactants, primarily carbohydrates, triglycerides, and organic acids, are used to reduce surface and interfacial tensions and offer advantages over synthetic surfactants such as biodegradability, decreased toxicity, greater surface and interfacial activity, higher selectivity and better safety[164,165]. Microbial surfactants, such as glycolipids and lipopeptides, are extensively researched and used in transdermal drug administration as permeation enhancers to promote medication transport across the skin[166-171].

NATURAL PERMEATION ENHANCERS (NPEs)

NPEs are a relatively new type of penetration enhancer in the pharmaceutical business. Because of its advantages, such as low cost and improved safety profile, additional research is needed in this field to produce stable transdermal formulations

including natural permeation enhancers (NPEs) that can be scaled up for commercial transdermal medication products[172].

Papain

Papain has been isolated from Carica papaya. It's an endocytic plant cysteine protease[173]. Papain, a proteolytic enzyme, was investigated *in vitro* and *in vivo* for its ability to permeate low-molecular-weight heparin. The combination of LMWH with papain was discovered to be a novel method for improving orally administered heparin absorption and thus bioavailability[174].

Piperine

Piperine is produced from mature fruits of Piper nigrum and Piper longum[175]. Piperine was investigated for the *in vitro* permeation of aceclofenac across human cadaver skin, and Fourier transform infrared technology was used to check the possible mechanism, which revealed that piperine enhances aceclofenac transdermal permeation via a biphasic mechanism involving partial extraction of SC lipid and interaction with SC keratin[176].

Capsaicin

Capsaicin, a prominent alkaloid among capsaicinoids, is generated only in capsicum fruits of the genus capsicum and belongs to the Solanaceae family[177]. The permeation-enhancing characteristics of capsaicin for naproxen were investigated, with azone serving as the standard enhancer and capsaicin being compared to it. Prior to the trial, a different amount of the chosen booster was applied to the skin. The outcomes were evaluated between a formulation containing 3% capsaicin and a commercially available naproxen gel formulation. It was discovered that when the skin was treated with azone and capsaicin, penetration increased and capsaicin also altered the SC layer. As a result, it was discovered that capsaicin improves naproxen penetration through SC, implying that capsaicin is a capable skin enhancer, similar to the well-known enhancer azone[178].

Fragrant myristica

M. fragrans was tested as a penetration enhancer in a transdermal gel formulation containing diclofenac sodium, the target medication. Methanolic, chloroform, and n-hexane extracts of M. fragrans were utilized as penetration enhancers instead of the synthetic enhancer Triton X. In both *in vivo* and *in vitro* investigations, methanol and chloroform extracts were found to have a higher percentage cumulative release (%) and thus better penetration than the synthetic enhancer[179].

Essential Oil

Essential oils are natural products produced from aromatic plants and contain a combination of aromatic-smelling volatile chemicals, notably terpenes, terpenoids, and phenylpropanoids[180]. They can be recognized as a natural alternative to synthetic skin penetration enhancers because of their promising penetration-enhancing activity[181]. Essential oils, as penetration enhancers, aid in the distribution of medicinal molecules into the skin by interacting with intercellular lipids through a variety of physical mechanisms including enhanced disorder, phase separation, and fluidization. Because they are rapidly absorbed by the skin, they are also easily expelled by the body via urine and feces. As a result of their superior safety profile in contrast to other penetration enhancers, their use is on the rise[182]. Essential oil as skin permeation enhancer. Penetration enhancers interact with tissue components to reduce barrier characteristics by partitioning into the SC while causing minimal harm to the underlying skin cells. D-limonene and 1, 8-cineole have been found to affect permeant diffusivity via altering SC lipid[183].

Eucalyptus oil

Eucalyptus oil can be extracted from several Myrtaceae species, including Eucalyptus citriodora, Eucalyptus dives, Eucalyptus globulus, Eucalyptus polybractea and Eucalyptus radiata. The oil is extracted from eucalyptus leaves using steam distillation. When coupled with 70% (w/v) isopropyl alcohol and 10% (v/v) eucalyptus oil, the oil improved chlorhexidine penetration (2% [w/v]) into the dermis and lower layer of the epidermis compared to the chlorhexidine/isopropyl alcohol solution alone[184].

RECENT TECHNIQUES FOR IMPROVED TRANSDERMAL DRUG DELIVERY

Structure-Based Enhancement Methods

Microneedles

Microneedles are a relatively new method for transdermal medicine delivery that forms a physical route through the upper epidermis, increasing skin permeability. Microfabricated microneedles are a cross between hypodermic needles and transdermal patches. This technology involves the implantation of micron-sized needles into the skin's surface. It only eliminates or creates pores in the SC region, thus there is no discomfort because nerve fibers are located in the skin's deeper layers. Furthermore, the medicine's travel distance will be reduced .Microneedles are tiny, slender devices created by silicon etching and micro-mechanical system manufacturing (MEMS) processes. There have been numerous delivery systems that have used microneedles for TDDS.

Macroflux

This approach employs a titanium microprojection array to create a superficial route through the epidermal barrier layer. The microprojection patch's basic component is a titanium disk with a polymeric adhesive backing. The titanium disk is 8cm 2 and is composed of a series of small titanium tooth-like microprojections coated with medicinal chemicals. There are up to 300 microprojections per cm, each measuring less than 200im. They only penetrate the stratum corneum, a thin layer of dead cells, and create 'holes'--microchannels that transfer large molecules to the epidermis' deeper layers. The titanium microprojections are too small to cause any pain. This approach enables the painless and needle-free transdermal delivery of high-molecular-weight drugs such as insulin, peptidic hormones, and vaccines. Patients can get medicine for up to twelve weeks using this new strategy.

Metered Dose Transdermal Spray (MDTS)

It is a topically applied liquid preparation in the form of a solution made up of a volatile or non-volatile vehicle in which the medicament is completely dissolved. The use of MDTS leads to a sustained degree of medicine penetration through the skin. The MDTS could provide the following benefits: Its non-occlusive nature increases delivery capability while reducing skin irritation. Increased acceptance Flexible dosing simple manufacturing.

Electrically Based Enhancement Techniques

Iontophoresis

In iontophoretic delivery systems, the drug is applied to the skin beneath the active electrode. A current of less than 0.5mA is passed between the two electrodes, successfully repelling the medication away from the active electrode and into the skin. Pilocarpine can be utilized to induce sweat in the detection of cystic fibrosis, and lidocaine iontophoretic administration is regarded to be a useful approach for quick anesthetic onset.

Ultrasound

The use of ultrasound at an adequate frequency significantly enhances transdermal drug transport over a skin system no larger than a wristwatch, a process known as phonophoresis or sonophoresis. It combines ultrasonic and topical pharmaceutical therapy to deliver therapeutic drug concentrations to targeted skin sites. The drug is coupled with a coupling agent, which is often a gel but can also be a lotion or ointment, to convey ultrasonic energy from the device to the skin. This involves rupturing the lipids in the stratum cornea, which allows the medication to get through the biological barrier.

Photomechanical Waves

Photochemical waves act by altering the lacunar system, resulting in the formation of temporary channels across the stratum corneum via the permeabilization mechanism.

Velocity-based Enhancement Techniques

Needle-free injections

Intraject: Implaject Jet Syringe Iject, Mini-ject, Cross-jet and Jet Syringe.

RECENT ADVANCEMENT IN TDDS

A study of the controlled delivery kinetics of ibuprofen in transdermal patches. They used chitosan (CS)-based materials such as composites with poly (lactic acid) (PLA) granules, films, and freeze-dried scaffolds, as well as hydroxypropylocellulose blends. Furthermore,

biopolymer matrices showed excellent adhesion to PLA microspheres and hydroxyapatite (HAp) particles. Ibuprofen (IBU) release kinetics from acquired films are described. A trial on giving co-encapsulated medications via transdermal patch. This work describes a detailed examination of the co-encapsulation of drugs with different lipophilicity, olanzapine and simvastatin, and their transdermal distribution in a formulation containing nanostructured lipid carriers (NLC). They found that the external medium in the NLC dispersion has a significant impact on penetration. He also discovered that using NLC had a synergistic impact with certain permeation enhancers, resulting in high flux augmentation ratios (48 and 21 respectively, for olanzapine and simvastatin) relative to the drugs in solution. The resulting compositions can be described as non-irritant.

Transdermal patch performance is being improved through drug-loaded nanofiber research. In their study, electrospin ibuprofen (IBU)-loaded composite nanofibers were used. Cellulose acetate and poly(vinyl pyrrolidone) (CA/PVP) were mixed to make uniform nanofibers. Research into the physicochemical properties of CA/PVP mixtures indicated that adding enough PVP enhanced the electrospinnability of the original CA solution. Physical state detections of IBU in medicated CA/PVP nanofibers revealed that the nanofibers were uniformly distributed in an amorphous state. Furthermore, CA/PVP nanofibers have excellent water vapor permeability, which may increase the breathability of transdermal patches. They concluded that electrospun drug-loaded CA/PVP nanofibers had enormous promise for improving the thermodynamic stability and breathability of transdermal patches and may be used to create new types of transdermal drug delivery systems (TDDS). Investigation of diclofenac sodium-loaded solid lipid nanoparticles (SLNs). Guggul lipid was used as the primary lipid component, and physical properties, permeability profile, and anti-inflammatory effect were studied. The SLNs were produced using the melt-emulsion sonication/low temperature solidification method, then tested for physical characteristics, in vitro drug release, and accelerated stability before being converted into gel. The gels were compared to a commercial emulgel (CEG) and a plain carbopol gel containing drug (CG) in terms of drug penetration and anti-inflammatory effects *in vitro* and *in vivo*. The SLNs remained stable, with acceptable physical features. They determined that the physicochemical properties of the major lipid component dictate the characteristics of SLN. The SLN made of guggul lipid has good physical properties and adequate stability. It also exhibited a regulated drug release profile and a good permeability profile. A study of microneedle arrays that generate hydrogels. They used crosslinked polymers to build unique microneedle arrays. Crosslinked polymers absorb skin interstitial fluid quickly upon skin insertion, producing continuous, unblockable hydrogel conduits from patch-type drug reservoirs to the dermal microcirculation. It was observed that such microneedles, which can be manufactured in a number of patch sizes and geometries, are easy to sterilize, resist hole closure while in place, and can be completely removed from the skin. They demonstrated that this technology has the potential to overcome the limitations of current microneedle designs and significantly expand the types of medicine that can be given transdermally, with benefits for industry, healthcare professionals, and, ultimately, patients.

FUTURE PROSPECTS

Transdermal delivery has generally been employed to provide low-molecular-weight medicines, which are mainly lipophilic and have great potency. The latter attribute remains an obvious benefit in the selection of medication candidates; nevertheless, the technology under development allows for the consideration of many other small molecules, peptides, and proteins with quite varied properties as possibilities for percutaneous administration. Furthermore, in addition to challenging conventional concepts of feasibility, they can improve bioavailability and modify delivery kinetics. Sustained release of medicine from

dissolvable microneedles has the potential to be a viable technology for skin delivery due to long-term drug delivery and a reduction in the number of microneedles.

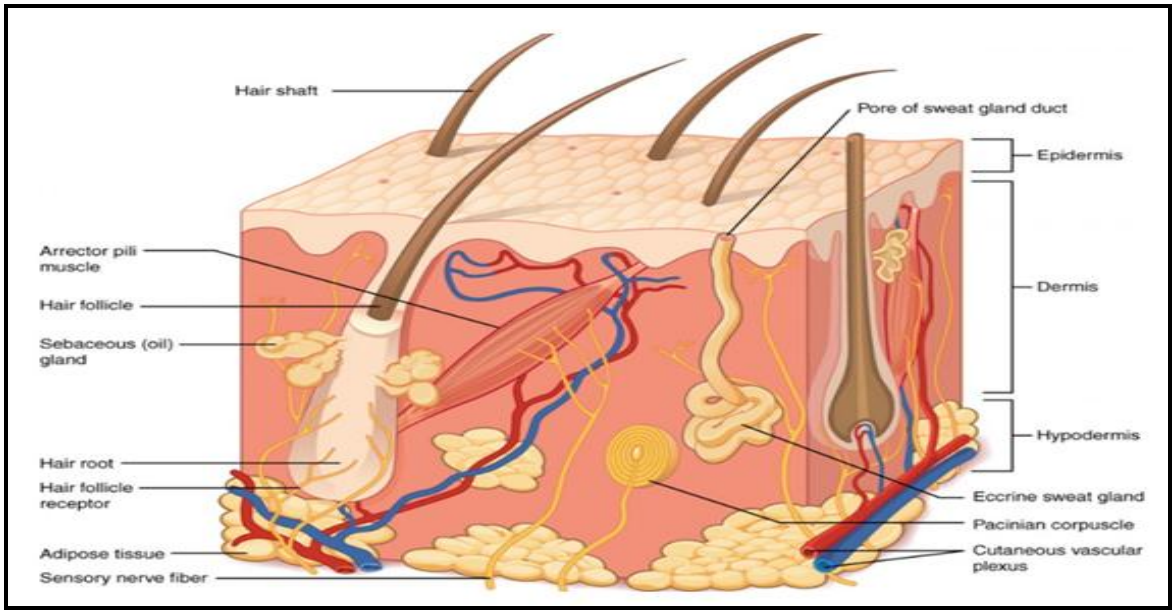

Figure No.1: Schematic representation of the skin layer

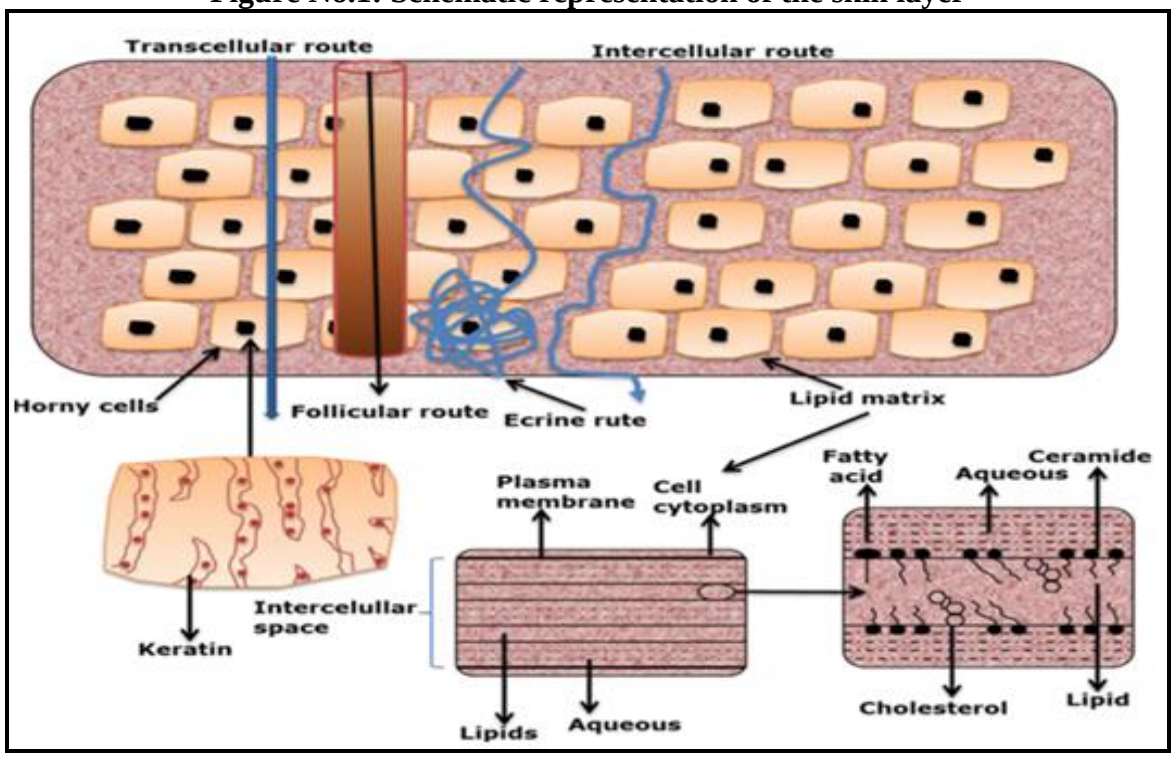

Figure No.2: A diagram of the stratum corneum, including intercellular and transcellular penetration channels

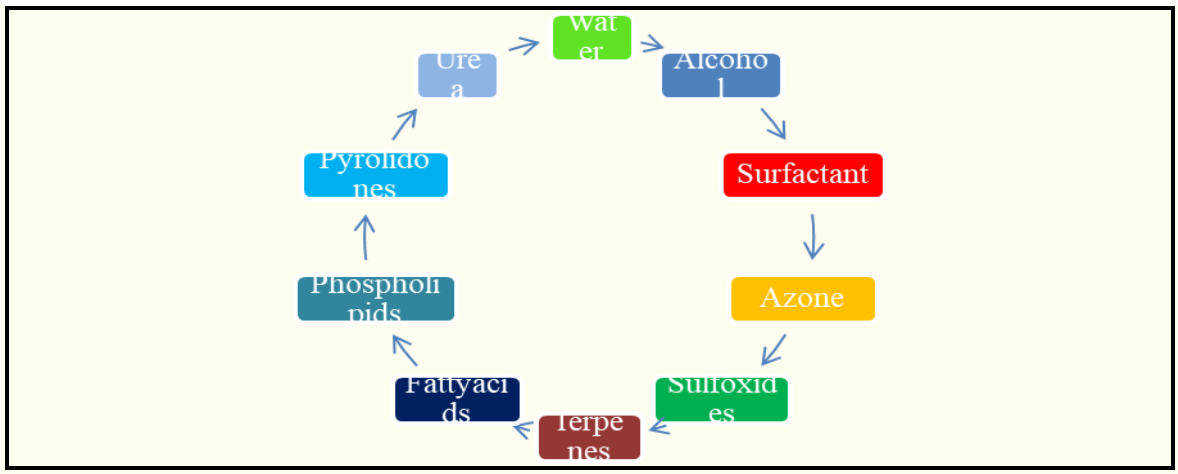

Figure No.3: Various types of chemical permeation enhancers used in TDDSs

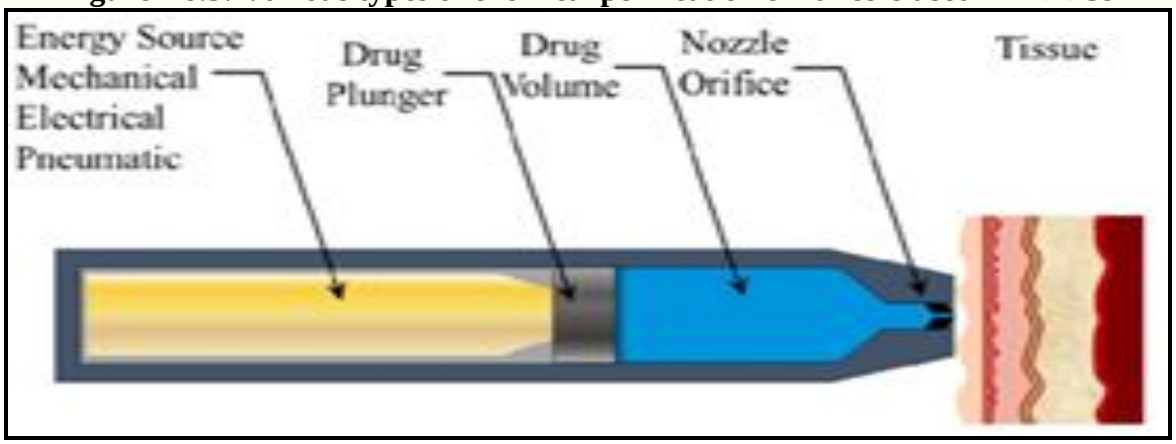

Figure No.4: Implant jet injections

CONCLUSION

Transdermal drug delivery systems (TDDS) represent a significant advancement in the field of pharmacology, offering a non-invasive and effective method for administering medications directly through the skin. This innovative approach has garnered attention for its numerous advantages, which include enhanced patient compliance and the ability to bypass first-pass metabolism, a process where the concentration of a drug is significantly reduced before it reaches systemic circulation. By delivering drugs transdermally, patients can experience more consistent therapeutic effects, as the medication is absorbed directly into the bloodstream, leading to improved bioavailability. One of the primary benefits of TDDS is the convenience it offers to patients. Traditional methods of drug administration, such as oral or injectable routes, can be cumbersome and may require strict adherence to dosing schedules. In contrast, transdermal patches or gels can provide a steady release of medication over an extended period, allowing for less frequent dosing and reducing the burden on patients to remember to take their medication. This ease of use can lead to better adherence to treatment regimens, ultimately improving health outcomes. Moreover, by avoiding first-pass metabolism, TDDS can enhance the efficacy of certain medications that would otherwise be significantly metabolized by the liver before reaching systemic circulation. This characteristic is particularly beneficial for drugs with narrow therapeutic windows, where precise dosing is critical for achieving the desired therapeutic effect without causing toxicity.

Despite these advantages, several challenges persist in the development and application of transdermal drug delivery systems. One significant limitation is the difficulty in delivering large-molecule drugs, such as peptides and proteins, through the skin. The stratum corneum, the outermost layer of the skin, acts as a formidable barrier to the penetration of larger molecules, which can hinder the effectiveness of TDDS for certain therapeutic agents. Researchers are actively exploring various strategies, such as the use of chemical enhancers, microneedles, and iontophoresis, to improve the permeability of the skin and facilitate the delivery of larger molecules.

Another challenge is the variability in skin permeability among individuals. Factors such as age, skin condition, hydration levels, and even genetic differences can influence how effectively a drug is absorbed through the skin. This variability can lead to inconsistent therapeutic outcomes, making it difficult to predict the efficacy of transdermal systems across diverse patient populations. As a result, personalized approaches to TDDS may be necessary to account for these differences and optimize drug delivery for individual patients.

In conclusion, while transdermal drug delivery systems offer a promising and effective alternative to traditional drug administration methods, ongoing research and development are essential to address the challenges associated with large-molecule drug delivery and individual variability in skin permeability. By overcoming these obstacles, TDDS has the potential to revolutionize the way medications are administered, leading to improved patient outcomes and enhanced therapeutic efficacy.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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