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Permeation Enhancers for Transdermal Drug Delivery: Strategies and Advancements Focusing on Macromolecules

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Abstract: ***The various transdermal drug delivery methods allow medications to cross the biological barriers and enter the bloodstream to elicit the desired pharmacological response. The relevant article focuses on the numerous biological and other macromolecule-based permeation enhancers, including carbohydrates, protein-peptides, and lipids, used in transdermal drug delivery. Although the focus of the study is on the role of macromolecules, as well as their mechanisms and modes of action for efficient transdermal drug delivery, it also concentrates on recent developments in various permeation enhancement techniques. Transdermal administration of weakly permeable medications with shorter biological half-lives typically utilises permeation augmentation techniques and agents, which should not have any explicit toxicological implications or incompatibility within the formulations. In this review, the limelight has been given to the promising permeation enhancers of the current scenario, which consist of various macromolecules.***

Keywords: Permeation Enhancer, Macromolecules, Stratum Corneum, Enhancement Methods, Biomolecular Transdermal Delivery, Paracellular Pathway.

I. INTRODUCTION

Permeation enhancers play a vital role in the drug delivery through the transdermal system by penetrating across the different skin barriers and getting absorbed into the systemic circulation, which is essential for the drug to show its therapeutic action [1]. The movement of a drug through a biomembrane can be either active or passive. Permeation of gases, liquids & solutes through the membrane requires activation energy to move through the matrix of the barrier materials [2]. Some drugs utilize the transporter molecules for their influx or efflux (Fig. 1).

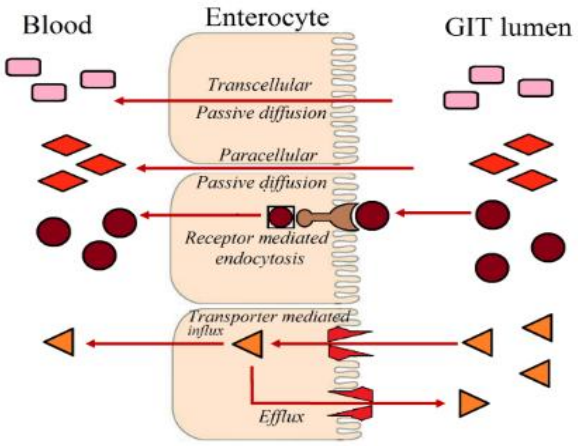

Figure 1: Drug Permeation Mechanisms Through Bio-Membrane

Different types of permeation enhancers are used in the formulations to help and facilitate the process. These substances or methods influence the stratum corneum, the rate-limiting layer of the skin and the outer layer of skin cells, to increase drug permeability. The literature review presented that several macromolecular agents can enhance the rate of permeation, which has diversified structure and categorised under distinguishable safety, efficacy and tolerability by utilizing the skin electroporation technique [3,4]. Proline, Sarcosine, Alanine, -Alanine, and Glycine are great candidates for usage as permeation enhancers due to their high biodegradability and low toxicity [5]. Peptide bonds join together many amino acids to form PPs (Proteins and Peptides). Studies have focused on developing novel technologies to overcome biological barriers by incorporating PPs as permeation enhancers. The results of this study demonstrated the excellent selectivity, efficacy, and lack of adverse effects of these macromolecules. Proteins and peptides (PPs) have gradually become more appealing medicinal molecules [6]. Methods used for essential oils, which are efficient permeation enhancers. Examples include eucalyptus, peppermint, and turpentine oil [7]. The monoterpene cyclic ether 1,8-cineole, which is present in eucalyptus oil, is an efficient skin penetration enhancer that can improve the penetration of both lipophilic and hydrophilic substances. They play various roles, ranging from support vehicles to permeation enhancers. Constituents, such as macromolecules consisting of peptides and proteins, have a diversified structure and are categorised under distinguishable safety, efficacy, and tolerability.

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These macromolecules play a vital role in enhancing the permeation rate by stabilized skin electroporation technique [8].

II. SELECTION OF ENHANCERS

Permeation enhancers are used to promote drug absorption through the skin by increasing skin permeability. These are the underlying causes of the transfer of the ionised drugs like timolol maleate and impermeable drugs like heparin [9]. Enhancers and promoters are substances that make it easier for drugs to cross biol membranes. They act by disrupting the stratum corneum, interacting with the barrier proteins and improving drug partition within the bio-membrane. By adopting any one of the pathways mentioned above, the inherent permeation rate can be substantially increased with a recognisable magnitude of solute eluting out of the membrane [10]. These enhancers are primarily used with hydrophilic drugs that have trouble interacting with the lipid structure of the bio-membrane. They work by interacting with both the polar and lipid parts of the membrane [10,11]. Their primary functions are based on three different mechanisms, which are discussed earlier: protein modification, lipid disruption, and partitioning promotion. In the process of lipid disruption caused by the enhancers, the stratum corneum's structure is altered, making it suited for drug penetration (e.g., azoles, fatty acids, and alcohols). When partitioning, various solvents alter the subcutaneous lipid layer's partition coefficient in favour of non-permeable medicines by interacting with and opening up dense protein structures in the corneocytes (e.g., dimethyl sulphoxide, ethanol), as shown in (Fig. 2) [11]. The enhancers ought to be perfect and compatible with the prescribed medication. The enhancers must be biocompatible; they shouldn't be irritative or trigger an allergic reaction when used over time or in small doses. The promoter must be inert, which means that it must not have any adverse pharmacological effects when ingested. It should also offer stability, both chemical and physical, to the formulation involved[12].

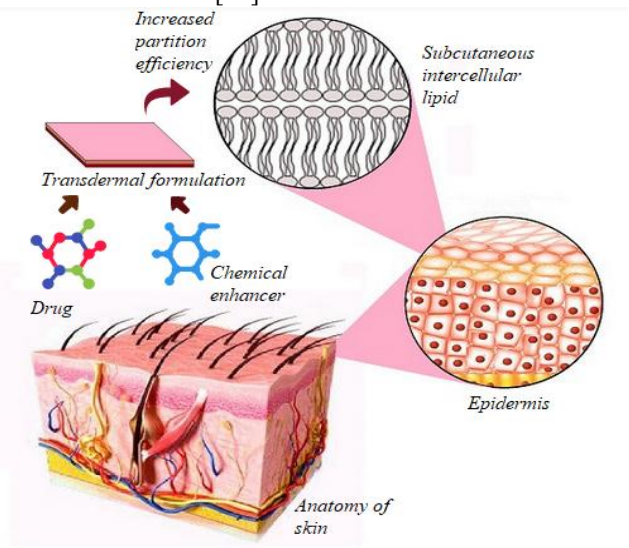

Figure 2: Effect of Permeation Enhancer on Drug Permeation in Transdermal Drug Delivery.

III. VARIOUS PERMEATION ENHANCEMENT MECHANISMS

Permeation enhancers have complicated modes of action. According to Barrys lipid protein partitioning (LPP) theory, that the enhancers shows their effect through one or more of the following three fundamental mechanisms: (a) interfering with epidermal keratin, (b) disrupting the highly organised structure of the lipids in the corneum layer and (c) enhancing drug partitioning into the skin. The Intercellular keratin may become denaturized, and an irreversible biological process can be observed. The change in enhancers causes the keratin site inside the corneum layer to become highly irritated. Therefore, it would probably be simpler to treat the skin irritation induced by an enhancing agent if it diffuses with the intercellular lipid of the SC[13]. Extractors, which remove lipids from the SC and fluidizers, which partition the lipid bilayers of the SC and fluidise them, are the two main kinds of lipid disruptors. Lipid fluidizers often outperform lipid extractors as they have less of an impact on the SC's natural composition[14]. The extent to which the lipid fluidizers' activity was increased was significantly influenced by amphiphilicity. These enhancers are physically connected to the lipid part of SC, have a polar head and one to two hydrophobic chains in common. Long amphiphilic enhancer chains can cut through the intercellular lipids of the SC, and their polar heads can interact with the polar lipid region via H-bonds and Van der Waals forces. The lipid packing's standard form would be significantly altered by the combined activity, allowing low selectivity medications to be more widely distributed [15].

Although the LPP theory proposed a basic framework for the principles behind permeation enhancement, it failed to explain the precise efficacy of an enhancer with respect to a particular medication or class of pharmaceuticals. The exact activity of the enhancer will likely depend on its physicochemical properties, as well as the penetrant. The possibility of complex formation between drugs and enhancers may be a significant factor in the breakdown of the transdermal barrier. For instance, Drakuli et al. established a modelling technique to demonstrate the creation of complexes between various medicines and terpenes, and they also suggested their various behaviours throughout the transdermal penetration process shown in (Fig. 3)[16].

The majority of recent studies have sought to understand better the connection between the enhancers' structural makeup and their efficacy in transdermal augmentation. However, it has been demonstrated that there is no direct correlation between skin irritation and increased permeability. Studies on the association between structure and irritation, as well as the causes of the enhancer's irritation, are crucial[17].

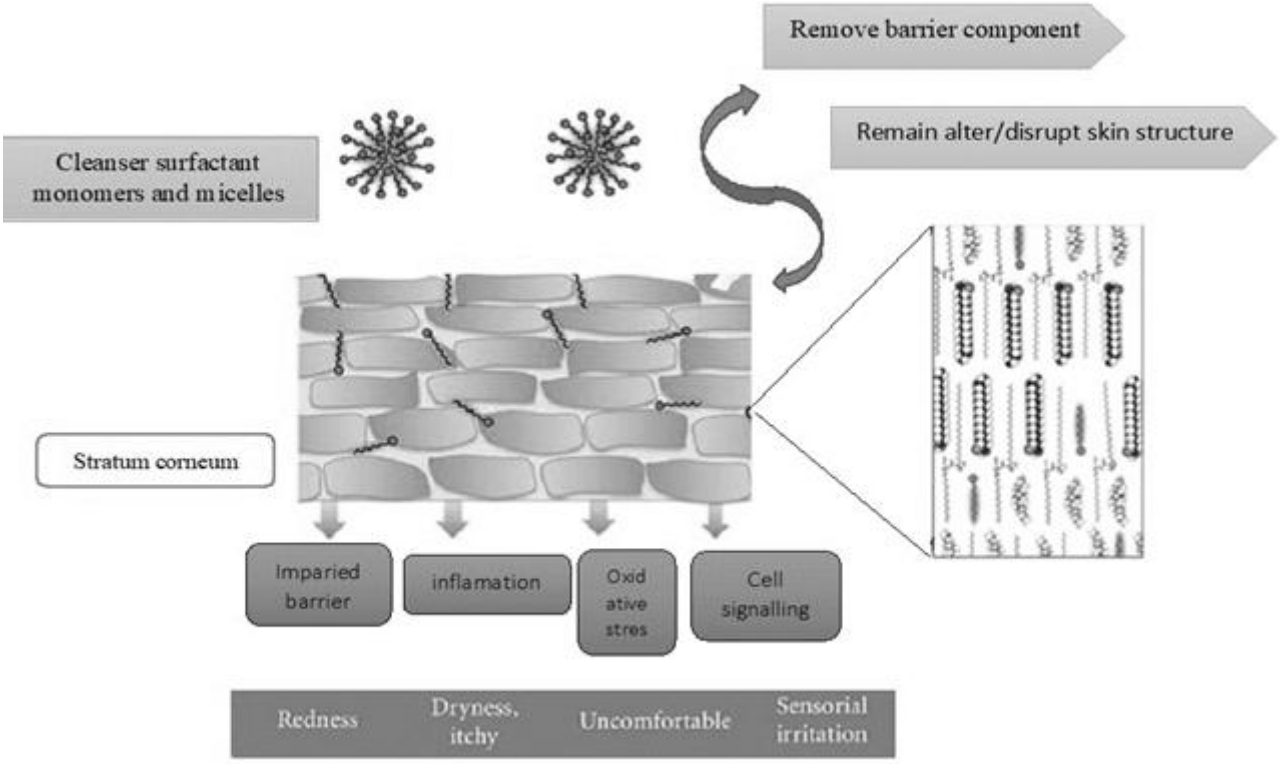

Fig 3: Behaviourial Mechanisms of Macromolecular Enhnacers.

IV. TYPES OF ENHANCERS

Several enhancement methods are currently in use to improve the permeability of medications, broad classifications of the enhancers are shown in (Fig. 4). The most prevalent types involve the use of chemical, physical, natural, bio-macromolecular and drug vehicle-based approaches [18].

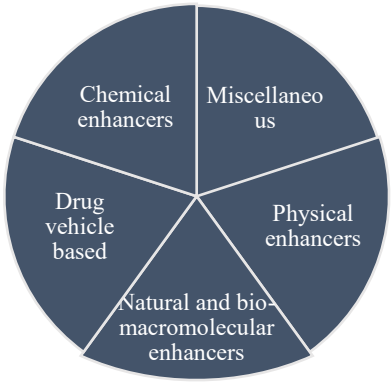

Figure 4: Types of Enhancers

4.1. Natural and Bio-Macromolecular Enhancers:

Natural materials are used to enhance the permeability of transdermally delivered medications, enabling various types of pharmaceuticals to pass through the stratum corneum. To employ these as enhancers, they must be non-toxic, safe, pharmacologically inactive, non-irritant, and non-allergenic[19]. By their molecular weight and by an apparent negative correlation between the enhancement ratio and the compound's molecular weight, i.e Sharma et al. reported that the use of aloe vera gel improves the in-vitro skin permeability of compounds[20]. The Aloe vera gel's derivatives can permeate the skin, even though they depend on the co-additives and molecular weight of the gel. The pull effect of the complexes that likely formed between the enhancers contained in the aloe gel is used to characterise the aloe gel's potential to enhance permeation, but further research is required to corroborate the results obtained from the postulated mechanism of action[21]. According to Nan et al., natural transdermal permeation enhancers (TPEs) are considerably safer than synthetic TPEs. In this work, Ledum palustre L. essential oil (EO) are used as a TPE. var. Gustav N. Busch is employed to improve permeability. The result summarises that the main constituents of the essential oils used are cuminaldehyde (CU), p-cymene (CY), 4-terpineol (TE), and sabinene (SA). Among these constituents, cuminaldehyde has the most significant effect on permeation enhancement in the study. CU improved the permeation rate of DNP by enhancing the mobility of the stratum corneum in in vivo skin erythema analysis [22]. Different natural oils have been shown by Lakshmi et al. to enhance the penetration of medications through the skin due to their diverse features, including [natural origin, sufficient penetration enhancer, and partitioning action] in the skin [23].

Sharma et al. reported that aloe vera gel increases the in vitro skin permeation of compounds, depending on their molecular mass, and by an apparent inverse correlation between the enhancement ratio and the molecular weight of the compound.

The constituents present in Aloe vera gel penetrate through the skin, and this process depends on the molecular mass and co-additives.

The pull effect of complexes that are likely produced between the chemical and enhancer contained in the aloe gel is used to characterise the aloe gel as having the potential to enhance permeation, however, the conclusions we reached from the suggested mechanism of action require further research and confirmation (Table 1) [24].

Table 1: Natural Biochemical Products as Potential Drug Permeation Enhancers

Permeants	Herbal Extracts [Surfactant]	Skin
Mefenamic acid	Aloe vera	Porcine ear skin
carvedilol	Glycyrrhizi	rat epidermis
oxybutynin	Aloe vera	Porcine ear skin
Gentamicin	Quillaja	Shed snake-skin
quinine	Aloe vera	Porcine ear skin

According to various surveys, the polyarginine heptamer is shown to be connected to the drug by converting it into a prodrug, and a synthetic peptide is obtained through phage display screening, a technique equivalent to the utilisation of molecules like 11-amino acids. Secondly, Magainin is another peptide that has a natural pore and acts as a biochemical stimulant[25]. By use of trehalose and a glycerol-free method of cryopreservation, Stefanic et al. reported that Bioactive promoters of cryopreservation RBCs act by the colloidal apatite nanoparticles. By adding the apatite nanoparticles to the medium where the RBC cryosurvival is increased by 91%, which can be compared to the use of glycerol in the FDA-approved cryoprotection[26]. Proline, Sarcosine, Alanine, -Alanine, and Glycine are examples of amino acid derivatives that indicates considerable potential enhancers because of their high biodegradability and low toxicity [27]. Peptide bonds connect many amino acids to create PPs (Proteins and Peptides). Due to the significant need for oral administration in clinical applications, various studies have focused on developing novel technologies as permeation enhancers to get beyond GI barriers of PPs. The usage of proteins and peptides (PPs) as medicinal molecules has steadily increased due to their high selectivity, effectiveness, and lack of adverse side effects compared to small molecular drugs[28]. Applying essential oils, such as eucalyptus, peppermint, and turpentine oil, has also been suggested as a method of improving penetration. [29]. The monoterpene cyclic ether 1,8-cineole, which is present in eucalyptus oil, is an efficient skin penetration enhancer that can improve the penetration of both lipophilic and hydrophilic substances. They serves a variety of purposes, from being permeation enhancers to support vehicles. The classification of biological macromolecules as shown in (Fig. 5) [30].

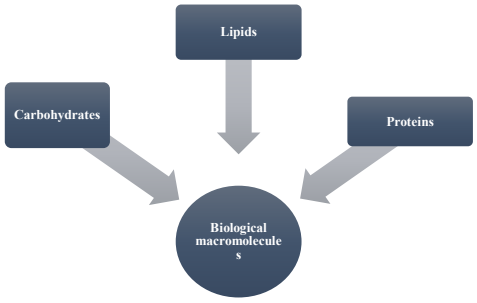

Figure 5: Classification of Biological Macromolecules.

Beyond their fundamental nutritional value, bioactive compounds in food may also offer health advantages. Many of these are intricate natural compounds with low intestinal permeability and/or low water solubility. Peptides, carbohydrates, lipids, and sophisticated organic compounds are a few of these. Although development factors pertaining to safety, efficacy, and cost-effectiveness differ between the two, there is a significant overlap in the methods used to permit oral delivery of pharmaceutical and nutraceutical goods, the classification of various biological macromolecules[31].

4.1.1 Carbohydrate:

Recent studies show that polysaccharides have great potential as transdermal permeation enhancers. The charge and hydration of polysaccharides allow them to react with the skin and promote drug penetration. Additionally, polysaccharide-based nanotechnology enhances the efficiency of drug utilisation. Various diseases are currently treated using polysaccharide-based transdermal drug delivery devices, exhibiting promising future applications. The most current knowledge on these excellent materials will be thoroughly discussed by reviewing various studies [32]. The use of chitosan as a transdermal drug delivery, which is formulated by nano-spray drying technique, where it gets conjugated with 5-fluorouracil to modify the skin by the help of microwaves [33]. Hexadecyl-D-glucopyranoside, a compound created by connecting D-glucose to cetyl alcohol via acetylated glucoside, is synthesised, and its capacity to stabilise microemulsions was examined. Carbohydrate lyotropic liquid crystals are utilised as stabilisers. [34]. The use of mucoadhesive nanoparticles is done as a carrier for trans-nasal insulin administration due to their large surface area, which can produce a high conc gradient, and given topically in the form of patches at a controlled and predetermined rate, using the modified starch and 1,4-cis polybutadiene nanoparticles to develop a novel polymer matrix system [35]. CPEs (Chemical permeation enhancers) are used either alone or in combination, significantly improve the penetration of Vitamin C and its derivatives in topical treatments. Phospholipids, amino acids, terpenes, and fatty acids exhibit permeation-enhancing effects whether they are given alone or with other CPEs. Non-ionic surfactants perform as CPE more effectively when used alone.[36]. Cysteine protease, also referred to as papain, is an enzyme that is generated from plants and may help decrease fibrosis because of its collagenolytic action. Its hydrophilic, high molecular weight, and protein composition—which is prone to breakdown—make it challenging to use as a medicine to reduce fibrosis, as it needs to be applied topically to permeate the stratum corneum barrier. The aim is to develop a papain-loaded, penetration-enhanced propylene glycol (PG) liposome drug delivery system for the treatment of fibrosis [37]. The understanding of topical, ophthalmic, and transmucosal drug delivery methods is expanding due to the utilisation of cyclodextrins in nanotechnology for non-invasive drug administration.

The capacity of DMN made of carbohydrate biopolymers to transport both high- and low-molecular-weight pharmaceutical compounds over the skin. These newly developed DMNs must be strong enough to penetrate the skin and dissolve there fast to achieve good medicine penetration [38]

4.1.2. Proteins:

Various surveys indicate that the unmatched by regularly utilised CPEs, amino acid-based enhancers offer a unique combination of potency, adaptability, and safety. The combination of various modes of action, such as improving drug solubility or increasing skin permeability, is made possible by their structural plasticity. Due to the demand for oral alternatives to parenteral distribution. The oral distribution of macromolecules, including peptides and proteins, is constrained by pre-systemic breakdown and insufficient gut wall penetration. However, some protein-based macromolecules operate as permeation enhancers, as demonstrated in **(Table 2)** [39]. M Tomita et al propose an absorption-enhancing mechanism of EDTA, caprate, and decanoyl carnitine in Caco-2 cells, as a result, C10 increases the intracellular calcium level by an interaction with the cell membrane, independent of cell polarity, resulting in contraction with actin microfilament [40]. According to Susanne M. Krug et al., sodium caprate is a macromolecular-based permeation enhancer that acts across the tricellular tight junctions of cells and has drug-enhancing properties. Caprate is based on increased permeability in tricellular cell contacts, which is mediated by the reversible removal of tricellulin from the tricellular tight junction. S. Zainuddin et al. propose a Chitosan-Based Oral Drug Delivery System for Peptide, Protein, and Vaccine Delivery. As a result, Chitosan-based drug formulations have gained attention for their ability to serve as a carrier and enhancer for the oral delivery of peptides and vaccines. Laffleur et.al investigated the effect of permeation enhancers of both ionic & non-ionic origin on peptide through the procaine abdominal skin. Tripeptide(Leu-Gly-Gly) is evaluated because of its toxicity behavior. The permeation study is carried out in franz diffusion cell. Tween 20 is used as a permeation-enhancing agent. Janusova et al. investigated several amino acid derivatives, including proline, sarcosine, alanine, β-alanine, and glycine, for enhancing the permeation of a transdermal system attached to a hydrophobic chain via an ester link. Among these proline derivatives of amino acids, one is found to be more efficient for enhancement purposes than the others. L-proline, a derivative of proline with a higher absorption capacity, confirms this. In vivo transdermal absorption studies in rats are carried out. Maher et al. studied the intestinal permeation enhancer, which is investigated through various strategies to improve the oral delivery of therapeutic peptides. Several permeation enhancers are tested in the intestinal delivery model; however, it is observed that enhancers related to the delivery system for oral peptides display poor action. The various protein-based macro enhancers shown in **(**Table 2**)** [41].

Table 2: Protein-Based Enhancer and Their Mechanism

	ENHANCER	MECHANISM
PROTEIN PEPTIDE	Citric acid	Chelating agents, paracellular
	EDTA	Chelating agents; paracellular[134]
	Sodium caprate (C10)	Multimodal[135]
	Sodium carprylate (C8)	Multimodal
	SNAC/5-CNAC	Transcellular
	Chitosan	Transcellular[136]

4.1.3. Lipids:

Lipid-based drug delivery is one of the most promising delivery systems for several drugs with poor solubility and bioavailability after administration through various routes of administration. Recent surveys indicate that the use of phospholipid-containing liposomes as vesicular macrocarriers for topical drug administration offers multiple benefits, including regulated drug release, localised drug deposition in skin layers, decreased systemic absorption, and fewer adverse effects from the medication. Lower serum levels and urine excretion of the medication provided evidence for localised skin deposition of drug-loaded liposomes [42]. Further, chemicals with high solubility and low permeability can be administered via a range of lipid dispersions, including solid lipid nanoparticles, water-in-oil microemulsions, reverse micelles, oily suspensions/solutions, and multiple emulsions. One of the best formulation techniques is called a lipid-based formulation (LBF). The development of the self-micro emulsified drug delivery system (SMEDDS) (Neoral®, Novartis) and approval of oral cyclosporin in a rough oil-in-water emulsion pre-concentrate (Sand immune®, Novartis, Switzerland) highlighted the potential of LBFs to enhance oral absorption of poorly soluble macromolecules. On the other hand, they are more frequently utilised to increase the water solubility of lipophilic small compounds from the Biopharmaceutics Classification System (BCS) Classes II and IV. Excipients employed in lipid-based formulations have solubilizing qualities as well as the capacity to increase the intestinal permeability of macromolecule's . For instance, Oleic acid (OA) (18:1) is a naturally occurring unsaturated fatty acid that is a popular and FDA-approved chemical permeation enhancer. OA encourages the formation of lipid domains in the SC and alters them, which acts by weakening the lipid bilayer's barrier function, allowing cargo molecules to pass through to the deeper epidermal layers. The fluidity of the lipid bilayer within the liposome is increased by the addition of pyrrolidone derivatives, according to Chong-Kook Kim et al. They hypothesised that this activity may be related to the potential of pharmaceuticals to promote transdermal absorption[70]. Novotny et. In this study, Transkarbam 12 (T12) is taken as an enhancer due to its low toxicity and highly active nature. A dual mechanism is considered for T12; the first step involves the decomposition of the polar head of the carbamate in SC lipids, and the second step consists of the reaction of the active enhancer, dodecyl 6-amminohexanoate.

Pradhan et al. studied the Box-Behnken design of calcipotriol (cp), focusing on the development and design of nanostructured lipid carriers filled with nanogels for the treatment of psoriasis. In this, he studied the mean zeta potential, particle size, and percentage entrapment efficiency by taking Carbopol 931 gel to obtain a CP-rich nanogel (CPNG) formulation. To generate a brand-new class of lipids containing heterocyclic head groups and oleyl hydrophobic chain domains, S. Marepally et al. designed and synthesised. Highly efficient transdermal penetration enhancers are the new compounds described in this paper. This article describes the synthesis of a new family of chemical penetration enhancers, such as 1, 1-Di-((Z)-octadec-9-en-1-yl), (Z)-1-(Octadec-9-en-1-yl)-pyrrolidine (5-membered cyclic ring with tertiary amine, Cy5T), and others. Five-membered cyclic pyrrolidinium iodide, (Z)-1-, with a tertiary amine (Octadec-9-en-1-yl)-piperidine, 1, 1-Di-((Z)-octadec-9-en-1-yl), a six-membered cyclic ring with a tertiary amine, and piperidium iodide (6-membered cyclic ring with quaternary amine, Cy6). First, we examined how well these lipids enhanced chemical penetration in vehicle formulations for drugs such as melatonin, ß-estradiol, caffeine, -MSH, and spantide II. The list of essential oils based on macro enhancers(Table 3)[43].

Table 3: Various Macro Enhancers of Essential Oils with Their Place of Application.

Essentials oils	Drugs	Place of application
Eucalyptus, turpentine oils, peppermint	5-fluorouracil	excised human skin
Rosemary, lilacin,ylang, peppermint oils	aminophylline	human skin
Basil oil	labetolol hydrochloride	rat abdominal skin
turpentine oils, tulsi	flurbiprofen	rat skin
mentha oils, citronella	trazodone hydrochloride	mouse epidermis
Ajuput, cardamom, melissa, orange, niaouli, myrtle oils	estradiol	hairless mouse skin

4.2.Chemical enhancers[CEs]

CEs are frequently referred to as "absorption promoters." The ideal chemical enhancers should be "pharmacologically inert," "nonirritating," "nontoxic," and "allergent," have a rapid onset of action, be reasonably priced, and be acceptable from a cosmetic standpoint (Table 4). These enhancers cross a partition, diffuse into the skin, and interact with its constituent parts. By altering and interacting with the intracellular route, solubility, or by partitioning of the subcutaneous layer, respectively, they improve the rate of drug permeation. These substances penetrate the subcutaneous layer directly between the hydrophobic lipid tails and alter the packing of lipids, which leads to lipid fluidity and speeds up drug absorption. The solutes interact with the polar heads in the aqueous region in the lipid portion of the intercellular bilayers. Which are regarded as secure [44]. Mainly, Franz Cells are used to investigate in vitro drug permeation properties. It has some advantages, like handling of specific tissues, samples are not collected continuously, and for analysis, a smaller amount of drug is required[45] These cells system requires a selection of specific receptor medium which regulates the sink conditions or the rate of solubilization in the patch. Danielsen et al. proposed an inquiry into new chemical enhancers through in silico screening of CE in a skin model, where they conduct simulation-like, coarse-grained molecular dynamics in a skin lipid matrix. Permeation enhancers have recently been added to formulations to improve the movement of therapeutic macromolecules like sulforhodamine and FITC-insulin-B across the intestine. In this study, Dimethyl palmitoyl ammonio propanesulfonate (PPS), a novel permeation enhancer, was chosen for its high potential and low toxicity behaviour. Microscopic tests showed that the model medications are penetrating through both trans and paracellular routes when PPS is present and found that this better penetration is causing an increase in relative bioavailability[46]. Kováčik.et.al. proposed in his study that there is interaction between CE and its components to temporarily lower the permeability barrier without endangering cells. However, it can alter the formulation's significance to enhance drug delivery. By varying the amounts of azone and tween 80, Levamisole hydrochloride transdermal absorption is studied by Chen et al. in relation to the effects of various azone dispersion states. The in vivo permeation investigation on rat skin showed that there has been a noticeable improvement in permeation through the rat skin. There is a solubilizer called Tween80. Tween's addition helps reduce the distribution of azone in the skin, thereby lowering the permeability of transdermal drugs. Curikova et al. sought to learn more about the impacts of permeation enhancers using a stratum corneum model. In this study, the transdermal membrane is produced by the accumulation of ceramide, stearic acid, and cholesterol sulfate. Skin permeation enhancers are tested in vitro using theenhancers N-dodecyl azepan-2-one (azone) and (s)-N-acetylproline dedecyl ester (L-pro2). Kang et al. investigate two terpene enhancers—carvone and eucarvone—and conduct a study using the in vitro permeation method. The study is conducted in two phases of skin—one of normal skin and the other of pretested skin. For the permeation study, haloperidol in propyleneglycol is used. According to Ren et al., a study was conducted to evaluate the qualities of indapamide and the effectiveness of other enhancers using rat abdominal skin. The permeation investigation is undertaken using a two-chamber diffusion cell and is performed in vitro to demonstrate the synergistic efficacy of binary and ternary combinations of various permeation enhancers. There are both binary and ternary combinations of hexylamine and chembetaine, as well as sodium laureth sulphate, decyl trimethyl ammonium bromide, and chembetaine. Several chemical permeation enhancers were explored by Whitehead et al. to demonstrate permeability. Binary and ternary combinations of various permeation enhancers are used in in vitro experiments to demonstrate the synergistic activity. Hexylamine and chembetaine are binary combinations, while sodium laureth sulfate, decyl trimethyl ammonium bromide, and chembetaine are ternary combinations. Park et al. studied chitosan-coated liposomes for enhanced transdermal resveratrol delivery by studying the zeta potential of the liposomes.

Moreover, the Franz diffusion cell and an animal skin are employed in the experiment. The liposomes are more stable when chitosan is used. To improve chemical permeability, Teixeira et al. combined two different types of local anaesthetics—ropivacaine hydrochloride and tetracaine—using lysine as a surfactant. The capacity of ropivacaine hydrochloride to increase permeation is greater. Yang et al. used chemical permeation enhancers (CPEs) in this investigation to increase the therapeutic efficacy of tiny compounds that permeate the tympanic membrane. To demonstrate the synergistic action, sodium dodecyl sulphate (SDS), limonene (LM), and bupivacaine hydrochloride are combined. The formulation's nomenclature, an in vitro investigation of hydrogel drug release, and the synergistic interactions between three chemical permeation enhancers are all examined using isobolographic analysis. The concentration-response curve for single CPEs, combinations of two CPEs, combinations of three CPEs, and the impact of CPE combinations on the peak effect all entail synergistic interactions among CPEs. Isobolographic analysis and combination studies are primarily used to observe the high synergistic effects between SDS, LIM, and BUP. The combination study of CPEs is also accountable for the peak influence on drug flux. Ameen.et.al. Investigated the feasible transdermal delivery of dimethyl fumarate(DMF) through skin permeation by taking different concentrations of each enhancers using Propylene glycol(PG)[47].

Tabel 4: Different Chemical Enhancers and Their Class

Classes of enhancer	examples
Fatty acids and derivatives	Acids :,lauric acid ,caprylic acid ,oleic acid Esters (monoglycerides) :glyceryl monooleate,glyceryl monocaprylate
surfactant	Anionic : sodium lauryl sulfate Cationic : alkyl dimethylbenzyl ammonium chloride Nonionic : polysorbate 80[85]
Terpenes ,terpenoids and essential oils	Monoterpenes : D-limonene ,menthol
Glycols and derivatives	Glycol : propylene glycol Ether : transcutol
Amide	Azone and derivatives
alcohols	Ethanol,butanol ,propanol
pyrolidines	n-methyl-2-pirrolidone
phospholipids	phosphatidylcholine
sulfoxides	Dimethylsulfoxide

4.3.Physical enhancement technique

Physical techniques should be combined with carriers to successfully deliver transdermal drugs since they are accurate and dependable in enhancing drug absorption. like phonophoresis, electroporation, iontophoresis, and photomechanical waves. Certainly, Iontophoresis is a process that uses electric current to make drugs more permeable when applied topically. Biotech materials like peptides and oligonucleotides are created during the delivery of hydrophilic drugs that are used in transdermal iontophoresis. Such delivery techniques were employed in the treatment of skin conditions such (cancer, dermatitis, scars). Methods like phonophoresis utilise ultrasonic energy to enhance the penetration of various active substances into the skin. There is a distinct improvement in transdermal absorption at low frequency regimes (20 kHz to 100 kHz) compared to induced high-frequency ultrasound application. The method of transdermal skin permeation involves the development of gaseous cavities, which disrupts the lipids of the stratum corneum and permits the medicine to pass through the skin. Ponophoresis of papain and hypotensive medications are used to treat eye diseases. Another electrical enhancement technique, called electroporation, allows for the implementation of high-voltage, brief (microsecond) pulses that are transdermal. This technique works by creating temporary substitute pores that serve as channels for electric pulses, enabling the delivery of macromolecules from the cell's outermost layer to its intracellular components. It was applied for a very brief period of time (100 ns to 1 s), increasing the penetration rate in the stratum corneum and the cell membrane[48].

There are other enhancement techniques used for permeation-enhancing purposes, such as: a) **Film hydration method**.Oskuie et al. (2018) aimed to study the development of an atypical liposome and ethosome vesicular system using turpentine as a skin enhancer for the improvement of fluconazole skin permeability. Here, Fluconazole is loaded into liposomes and ethosomes, and the structure of the formulation is confirmed by scanning electron microscopy.In vitro, ex vivo, and anti-fungal effects of liposomes and ethosomes, as well as the effect of penetration enhancers, are studied and compared with those of the free drug [98].Kahraman et al. (2018) aimed to examine the combination of nanomicelles with terpenes.This study reveals that the combination of these two is mainly used for enhancing purposes in topical drug delivery systems [49].b)**supersaturated system**. Moser et.Al,. In this study, supersaturation is used for the enhancing purpose of lipophilic compounds, specifically a levendustin derivative, LAP.The in vitro study is carried out using excised pig skin [49].c)**ultra filteration**.Wicker et al. (1996) studied the enhancing permeability of pectinesterase (PE) in ultrafiltration by using cations.The addition of cations and the higher pH release of PE increase permeation [49].Bellara et.In this study, a gas-liquid twin-phase system is used to overcome concentration polarisation in the ultrafiltration technique.Hollow fibre membranes are used for experimental work. Albumin and polysaccharide derivatives, such as dextran, are used as test media.Albumin shows reduction when gas-liquid twin phase cross flow is used[49].d) **by modulating bio availability**.Guo et.al 2019 ; deals with the study of oral delivery of nanocrystls(NCs)by permeation of the mucus, transepithelial transport system and the bioavailability study. For experimental work, spherical and rod-shaped NCs (SNCs, RNCs, FNCs) are experimented with. Fluorescence resonance energy is introduced in it.Results show that the shape of particles has the best influence on mucus permeation studies.Besides all these NCs and RNCs, they show good absorption capacity.The oral bioavailability shows an AUC0-24 h for RNCs of 1.44-fold and 1.8-fold, which is greater than the values of SNCs and FNCs, respectively. Further, Ezzat et al. (2019) studied the design, in vitro, and in vivo study for the drug catechin using chitosomes to improve oral bioavailability.They aimed to study the chitosan-tethered liposomes for enhancing purpose. Nanocarriers, optimised by the ethanol injection method, were used in physiochemical, ex-vivo,

and in-vitro studies involving Wistar albino rats.

Significant results are shown in the ex-vivo intestinal permeation study.Lee et al. (2017) studied the improvement in the bioavailability of apigenin that occurs when friedelin is co-administered. The presence or absence of friedelin is studied in Caco-2 cells and also in single pass rat intestinal perfusion model. The increased bioavailability of apigenin is confirmed by its oral administration with friedelin. There is an increased peak concentration due to apigenin, as indicated by the elimination half-life and the area under the curve (AUC) of the plasma concentration vs. time graph. The skin acts as a barrier, forming a layer of corneocytes filled with keratin and attached to a lipophilic matrix.Bile salt which consists cholic acid conjugates of taurine, glycine, chenodeoxycholic acid, emulsifies dietary fat and fasten the lipolysis process. It carries the lipid products via unstirred water layer in the intestinal mucosa by the micellar solubilization. By the decrease of binding property of bile salt hydrophilicity increases. Ewoud et al. (1989) studied the comparative presence of low bile salts in rabbits and rats (≤ 5 mM). Bile salt having the capacity to increase the drug intake to an appropriate extent. However, the results of secondary bile show effects like co-carcinogenic & co-mutagenic that can be developed in the pharmaceutical formulation which contain bile salts[50].

Another enhancement technique used to enhance permeability is spray freeze drying (SFD). Henry et.al.2011studiedIn a higher in-vitro dissolution performance of solid dispersion system, compounds which acts as in oleanolic acid in spray freeze drying, polyvinyl pyrrolidone-40 of bcs class 4 acts as a stabilizer, sodium caprate as kinetically stable penetration enhancer and wetting agent. In BCS class IV compounds, the absorption characteristics exhibit a consistent significant inter-animal variability in oral bioavailability of commercial oleanolic acid and formulations done by the SFD process. In self-microemulsifying drug delivery systems (SMEDDS), drugs with poor permeability during GI absorption can be enhanced by SMEDDS, as seen in BCS class 4 drugs. Four distinct permeation enhancers from the polymeric nanofiber are examined in-vitro by Mehta et al. Nanofibers that help cover the outside of contact lenses are created using electro-hydrodynamics. Triphasic release is demonstrated in an in vitro research. Fickian diffusion procedure considered release studies [50].

V. RECENT ADVANCEMENTS:

Many techniques are available for various macromolecular permeation enhancers, that may be used in transdermal drug delivery. Among these, KIM et al. proposed a study that ocular penetration enhancers impart novel mechanisms based on nanotechnology to improve various drug delivery methods already in use. [51]. Zyl.et.al. Investigated various enhancers which contains essential fatty acids (EFAs) for the study of transdermal delivery of flurbiprofen, evening primrose oil, vit F and used in a cream based formulation and discussed the skin delivery outputs by indicating the presence of flurbiprofen in the stratum corneum. Nanda et al. investigated the anti-inflating effectiveness of amlodipine using a rabbit model generated by carrageenan; in this case, the effect of sulphobutyl-ether-beta-cyclodextrin on corneal permeability is investigated. Due to the increased dissolution, it was found that the sulphobutyl-ether-beta-cyclodextrin increased both the drug's penetration and release rates [52]. Pramanik et al. Purposed that anti-inflammatory activity and ocular delivery of dexamethasone hydrogel system can be benefited by incorporating kaolin which can protect the mucosa by adhering it and by absorbing viruses and toxins. When it is applied, there is a complete disappearance of the HPMC film in the rabbit eye within 2 hours. Hence, though kaolin promotes ocular permeation, HPMC films.[53]. Mohapatra.et.al. Studied a model drug on a sheep cornea by using the mechanism of kinetical permeation. Here, a matrix film was prepared from hydroxypropyl methylcellulose, which contains triethanolamine as a plasticiser and benzalkonium chloride (BZC) as a preservative, using the solvent casting technique. Models like korsmeyer-peppas models and Higuchi are used and also the use of FTIR and XRD was done which indicates that in the film growth of the diclofenac is inhibited, and there is an enhancement of the drug permeation rate in the ocular tissue by the enhancement of the concentration of triethanolamine with the presence of benzalkonium chloride[54]. Mohapatra.et.al. Studied the statistical moment theory of diclofenac potassium kinetic permeation in cornea to distinguish the steady and non-steady state. Using docking analytical calculations to study the binding of HPMC-DCP reveals the interaction between the drug and excipient at the molecular level. The study shows an enhanced permeation rate in the cornea, and an anti-inflammatory action is observed after the application of H2 film[55]. Mohapatra. et.al Studied and evaluated the triethanolamine effect as a plasticiser in an ex vivo study showing thermodynamic characteristics by using diclofenac potassium in a Hypromellose matrix film. These are used to study enthalpy, entropy, activation energy, and free energy estimation of permeability, diffusibility, and partitioning. The transformation and growth of the crystal nature in the drug are observed in the amorphous state, and there is an intermolecular hydrogen bonding[56].

Mohapatra.et.al. Evaluated the permeation of diclofenac potassium in the trans-corneal as a temperature parameter using HPMC matrix film, which contains triethanolamine and benzalkonium chloride as a plasticiser and preservative, respectively. There was a crystalline to amourphous transition state and a molecular dispersion observed between the diclofenac potassium and HPMC[57]

Studies of skin permeation typically involve percutaneous absorption at the outset. They enable the identification of various formulation parameters essential for drug permeation through the skin. In vitro study conditions of drug permeation under the skin can be used to validate the predictions of human study by percutaneous absorption and which can be used to reduce the future prospective studies [58-60].

VI. CONCLUSION

The current work summarises the potentiated permeation profiles of challenged drugs by permeation enhancers in the transdermal drug delivery system, focusing on macromolecules and recent techniques. This review identifies enhancers that are reliable, effective, and compatible with preparations for drug delivery. The studies relate the stratum corneum as a rate-limiting membrane, where corneocytes form a matrix barrier, and drugs must utilise a macromolecular carrier for their influx and efflux activity. Several amino acid- and lipid-based macro enhancers possess potency and safety features superior to those of other enhancers. Their structural versatility enables the combination of multiple mechanisms, to facilitate the drug permeation. In some other cases, the potential pulling action of complexes created by natural macro enhancers, such as aloe gel, increases permeability, which is typically utilised by the lipid portion of the biomembrane. Several enhancement techniques are here discussed to increase the permeability of drugs. The most common types are physical, chemical, natural, bio-macromolecular, and drug-vehicle-based methods. Techniques such as phonophoresis, electroporation, iontophoresis, and photomechanical waves enhance the permeation rate of various active constituents. Literature demonstrates that these methods disrupt the lipid on the surface of the skin, allowing the drug to enter the stratum corneum. This review indicates that the use of natural products, peptides, and other complex biomolecules shows great promise as permeation enhancers in a future scenario for providing novel modifications.

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