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

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Abstract: ***The various transdermal drug delivery method, allows medications to cross the biological barriers and enter the bloodstream to elicit 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. Though the focus of the study is on role of macromolecule, as well as their mechanisms and modes of action for efficient transdermal drug delivery, it also concentrates on the recent developments in various permeation enhancement techniques. Transdermal administration of weakly permeable medications with shorter biological half-lives typically makes use of the permeation augmentation techniques and agents, which should not have any explicit toxicological implications and incompatibility within the formulations. In this review, limelight has been given to the promising permeation enhancers of current scenario which consist of various macromolecules.***

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

I. INTRODUCTION

Permeation enhancers plays a vital role in the drug delivery through the transdermal system by penetrating across the different skin barriers and get absorbed into the systemic circulation which is essential for the drug to show its therapeutic action [1]. The movement of drug through bio-membrane can be of active or passive nature. 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).

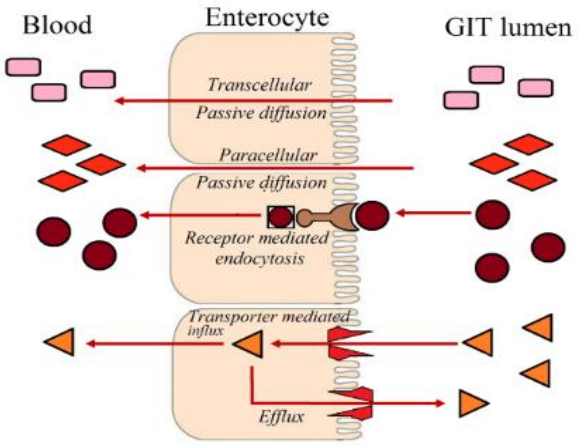

Fig 1: Drug Permeation Mechanisms Through Bio-Membrane

Different types of permeation enhancers are used in the formulations to help and facilitate the process. These substances or methods influence the corneum site, the rate-limiting layer of the skin and the skin's outer layer 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]. Many amino acids are joined together by peptide bonds to form PPs (Proteins and Peptides). Studies have concentrated on creating novel technologies to get beyond biological barriers by incorporating PPs as permeation enhancers. Result of these 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 of essential oils, which have been found to be 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 act various roles ranging for support vehicles as permeation enhancers Constituents like macromolecules consist of peptides and proteins, they have a diversified structure and categorised under distinguishable safety, efficacy and tolerability.

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These macromolecules plays 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 underline 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 bio-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 above-mentioned pathways 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 which makes them suited for drug penetration (e.g.,azones, 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 little doses. The promoter must be inert, which means that it must not have any negative pharmacological effects when ingested. It should also offers stability both chemical and physical to the formulation involved[12].

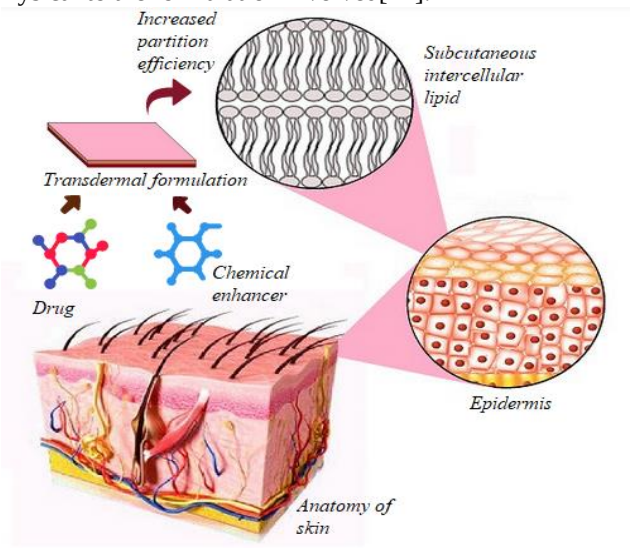

Fig 2: Effect of Permeation Enhancer on Drug Permeation in Transdermal Drug Delivery.

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 get denaturized and a irreversible biological process can be seen. The change in enhancers causes, the keratin site inside corneum layer would be highly irritated. Therefore, it would probably be simpler to treat the skin irritation induced by a enhancing agent if it diffuses with the intercellular lipid of the SC[13]. Extractors, which remove lipids from the SC and fluidizers, which partitions the lipid bilayers of the SC and fluidize 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 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 force. The lipid packing's normal form would be greatly 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 probably depend on its physicochemical properties as well as the penetrant and the possibility of complex formation between drugs and enhancers may be a major 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 better understand the connection between the enhancers' structural makeup and their efficacy in transdermal augmentation. However, it has been shown that there is no direct link between the skin irritation and the permeability increase effect. Studies on the association between structure and irritation as well as the causes of the enhancer's irritation are crucial[17].

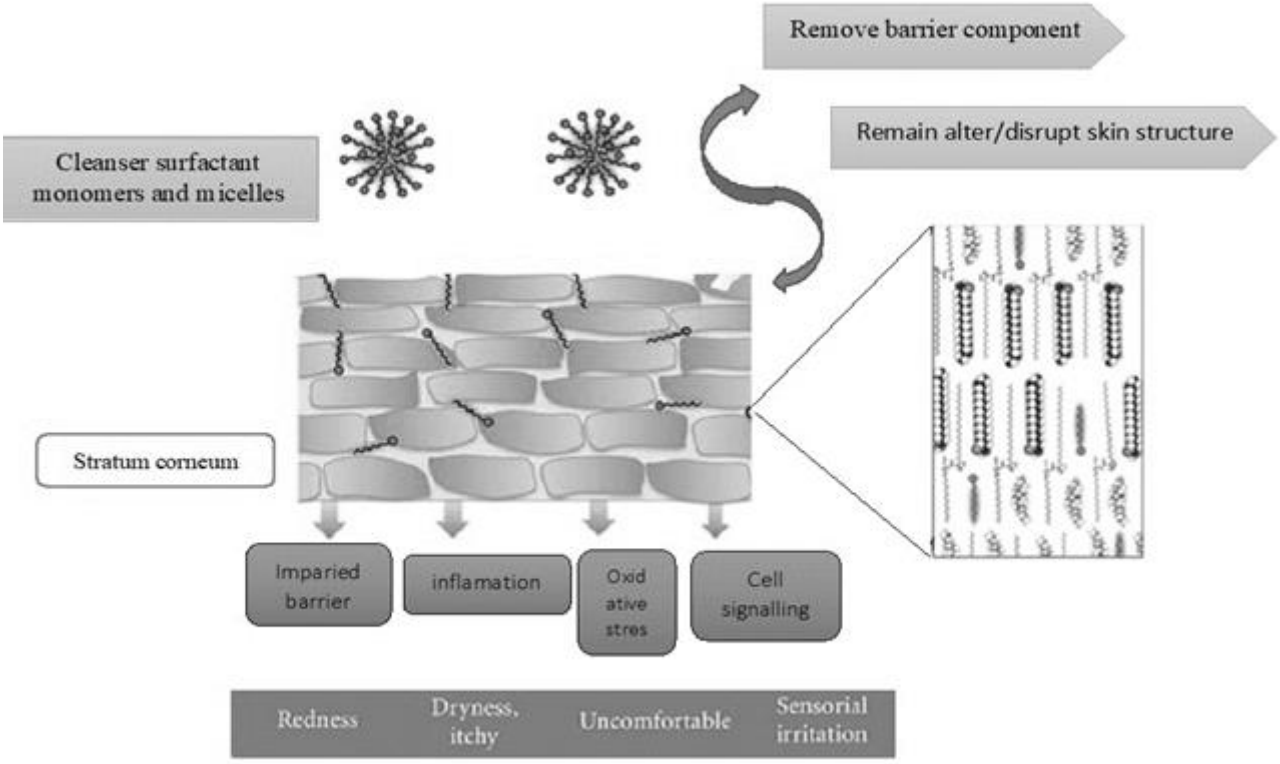

Fig 3: Behaviourial Mechanisms of Macromolecular Enhnacers.

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].

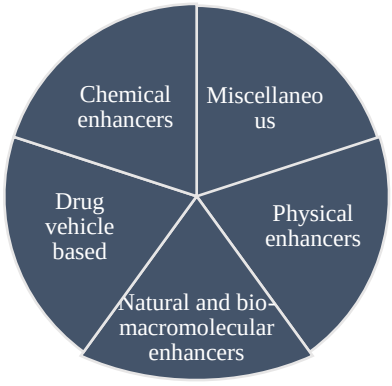

Fig 4: Types of Enhancers

4.1.Natural and Bio-Macromolecular Enhancers:

Natural materials are employed to increase the permeability of transdermally delivered medications, allowing different kinds of pharmaceuticals to pass through the stratum coreneum. To employ these as enhancers, they must be non-toxic, safe, pharmacologically inactive, non-irritant, and non-allergenic[19]. In accordance with 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 depends upon 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 are used to characterise the aloe gel's potential to enhance permeation, but further research is required to corroborate the results that 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 summarizes the main constituents of the essential oils used are, cuminaldehyde(CU), p-cymene(CY), 4-terpineol(TE) and sabinene(SA Above these constituent cuminaldehyde have more effect in permeation enhancement study. CU improved permeation rate of DNP by enhancing the mobility of 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 aloevera gel increases the in-vitro skin permeation of compounds depending on their molecular mass and by the apparent inverse co-relation between enhancement ratio and molecular weight of the compound.

The constituents present in the Aloe vera gel penetrates through the skin and moreover, this depend upon 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 has a 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 Bio Chemical Products as Potential Drug Permeation Enhancer

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 different surveys, the polyarginine heptamer shows that it is connected to the drug by turning it into a prodrug and a synthetic peptide is obtained by the phage display screening which is a equivalent technique to the utilisation of molecules like 11-amino acid. Secondly, Magainin is an another peptide that has a natural pore and act as biochemical stimulant[25]. By use of trehalose and a glycerol-free method of cryopreservation, Stefanic et al. reported Bioactive promoters of cryopreservation RBC acts 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 negative 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 macromolecule as shown in (Fig. 5) [30].

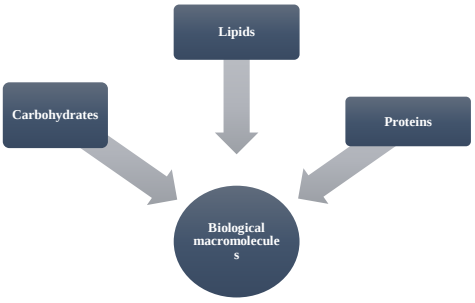

Fig 5: Classification of Biological Macromolecules.

Beyond of their basic nutritional worth, 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 shows that polysaccharides have a great potential as a transdermal permeation enhancers. Where, the charge and hydration of polysaccharides allows them to react with the skin and promote drug penetration. In addition, polysaccharide-based nanotechnology enhances drug utilization efficiency. Various diseases are currently treated by polysaccharide-based transdermal drug delivery devices and exhibit promising futures. 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-flurouracil 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 and can produces 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 assist to decrease fibrosis because of its collagenolytic action. Its hydrophilic, high molecular weight, and protein composition—which is prone to breakdown—make it difficult to use as a medicine to reduce fibrosis because it needs to be used topically in order to permeate the 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 because 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 DMN must be strong enough to penetrate the skin and dissolve there fast in order to achieve good medicine penetration [38]

4.1.2. Proteins:

Various surveys indicates 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 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 which acts across the tricellular tight junctions of cells, and have the drug-enhancing properties. caprate are 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 Chitosan-Based Oral Drug Delivery System for Peptide, Protein and Vaccine Delivery as a result Chitosan-based drug formulation has gained attention for their ability to serve as a carrier and an enhancer for 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. Tween20 is used as permeation enhancing agent. Janusova et.al, investigated some aminoacid derivatives like proline, sarcosine, alanine, β-alanine, glycine for enhancing the permeation of transdermal system which are attached with hydrophobic chain via ester link. Among these proline derivatives of amino acid is found more efficient for enhancement purpose than other derivatives It is confirmed by L-pro2 which is the derivative of procaline having more absorbing capacity. In vivo transdermal absorption studies in rats are carried out. Maher.et.al studied the intestinal permeation enhancer which is investigated through various strategies in order to improvement of oral delivery of therapeutic peptides. Several permeation enhancers are tested in the intestinal delivery model but relatively it is observed that the enhancers related to delivery system for oral peptides displayed 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. The recent surveys indicate about the use of phospholipid containing liposomes as vesicular macrocarriers for topical drug administration has various 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 . Taking a instance, Oleic acid (OA) (18:1), is a naturally occurring unsaturated fatty acid, is a popular and FDA-approved chemical permeation enhancer. OA encourages the formation of the lipid domains of the SC and changes them. Which acts by weakening the lipid bilayer's barrier function and lets cargo molecules 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.al, In this study Transkarbam 12(T12) is taken as enhancer due to its less toxicity and highly active nature. Dual mechanism is consider for T12, the first step is the decomposition of polar head of carbamate in SC lipids and second step involves the reaction of active enhancer of dodecyl 6-amminohexanoate.

Pradhan.et.al. Studied the Box-Behnken design of calcipotriol(cp) which focuses on development and design of nanostructured lipid carrier filled with nanogel for treatment of psoriasis. In this he studied the mean zeta potential, particle size and percentage entrapment efficiency by takin Carbopol 931 gel to obtain CP riched nanogel (CPNG) formulation. In order 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 melatonin, ß-estradiol, caffeine, -MSH, and spantide II. The list of essential oils based of 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 quick beginning of action, be reasonably priced & acceptable from a cosmetic standpoint **(**Table 4**)**. These enhancers pass across a partition, diffuse into the skin, and engage with its constituent parts. By altering and interacting with the intracellular route, solubility, or by partition 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 by altering 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 the in-vitro drug permeation property. It have some advantages like, handling of certain tissues, sample are not collected continuously and for analysis less amount of drug was 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 the inquiry on new chemical enhancers through the in-sillico screening of CE in a skin model, where he conducts simulation-like coarse-grained, molecular dynamics in a skin lipid matrix. Permeation enhancers are recently 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 pemeation is causing an increase in relative bioavailability[46]. Kováčik.et.al. proposed in his study that there is interaction between CE and its components in order to temporarily lower the permeability barrier without endangering cells. However, it can change the formulation's significances in order 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 over the rat skin. There is a solubilizer called Tween80. Tween's addition aids in reducing the distribution of azone in the skin, which lowers 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, two terpene enhancers—carvone and eucarvone—are taken and study is conducted using the invitro 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 is performed by considering the qualities of indapamide and the effectiveness of other enhancers by utilizing a rat abdomen skin. The permeation investigation is done by useing a two-chamber diffusion cell and are conducted in vitro to show the synergistic effectiveness 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. A number of 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 studing 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. In order 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 hydrogel drug release investigation, and the synergistic interactions between three chemical permeation enhancers are all investigated. Isobolographic analysis, the conc.-response curve for single CPEs, combinations of two CPEs, combinations of three CPEs, and the impact of CPEs combination on the peak effect all entail synergistic interaction 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 ponophoresis make use of ultrasonic energy to increase the penetration of various active substances into the skin. There is a distinct improvement in transdermal at low frequency regimes as (20 KHz f 100 KHz) as compared to the induced high frequency ultrasound application. The method of transdermal skin permeation involves the development of gaseous cavities, which leads to a disruption in 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), and transdermal pulses. This technique works by creating temporary substitute pores that serve as electric pulses that enable the delivery of macromolecules from the cell's outermost to its intracellular cells. 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 some other enhancement technique used for permeation enhancing pupose such as, a)**Film hydration method**.Oskuie et.al,2018 aimed to study the development of atypical liposome and ethosome vesicular system uses turpentine as a skin enhancer for the improvement of fluconazole skin permeability. Here Fluconazole is loaded with liposome and ethosome and the structure of formulation is confirmed by scanning electron microscopy.Invitro, ex-vivo and anti fungal,effect of liposome and ethosome and the effect of penetration enhancer are studied And compared with free drug[98].Kahraman et.al,2018 aimed to study the combination of nanomicelles with terpenes.This study results that the combination of these two are mostly used for enhancing purpose for topical drug delivery system[49].b)**supersaturated system**. Moser et.al,2001 In this study supersaturation is used for enhancing purpose of lipophilic compounds that is a levendustin derivative LAP.The invitro study is carried out by excised pig skin[49].c)**ultra filteration**.Wicker et.al,1996 studied the enhancing permeability of pectinesterase(PE) in ultrafilteration by using cations.Addition of cations and higher pH release of PE is increases the permeation[49].Bellara et.al, In this study gas-liquid twin phase system is used to surpass concentration polarization in the ultrafiltration technique.Hollow fibre membranes are used for experimental work. Albumin and polysacharide derivative 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 a spherical and rod shaped NCs(SNCs, RNCs, FNCs) are experimented. Fluorescence resonance energy is introduced in it.Results shows that shape of particles shows best influence for mucus permeation study.Besides all these NCs and RNCs shows good absorption capacity.The oral bioavailability shows auc0-24h for RNCs is 1.44-fold and 1.8-fold, which is than the value of SNCs and FNCs respectively . Further Ezzat et.al 2019; studied the design, invitro and invivo study for the drug catechin by using chitosomes for improving oral bioavailability.They aimed to study the chitosan-tethered liposomes for enhancing purpose. Nanocarriers are used which was optimized by ethanol injection method include physiochemical, ex-vivo study and in-vitro study by using wistar albino rats.

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Significant results shows in ex-vivo intestinal permeation study.Lee et.al 2017; studied the improved of bioavailability of apigenin takes place by the friedelin as a co-administration . The presence or absence of friedelin is studied in Caco-2 cells and also in single pass rat intestinal perfusion model. increased in bioavailability is confirmed by the oral administration of apigenin with friedelin. There is a increased peak concentration due to apigenin, the elimination half life and the AUC of the plasma concentration vs time graph . The skin as a barrier is impermeable as it forms a layering of corneocytes which is filled by 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 and 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 comparatively the presence of low bile salt in rabbits and rats(≤5mM). 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 for enhancing the permeability which is known to be 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 exhibits a consistent large inter-animal variableness in oral bioavailability by commercial oleanolic acid and formulation done by SFD process. In self-micro-emulsifying drug delivery system (SMEDDS) the drugs have poor permeability during GI absorption, as BCS class 4 drugs can be enhanced by SMEDD. 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 took release studies into consideration [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 the study that ocular penetration enhancers impart novel mechanisms based on Nanotechnology in order to improve the various drug delivery methods already being used. [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 2hrs. Hence though kaolin promotes the ocular permeation and 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 made of Hydoxypropyl methylcellulose which contains triethanolamine which is used as a plasticizer and BZC(benzalkonium chloride) which is used as a preservative and made by using 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 a enhancement of drug permeation rate in the ocular tissue by the enhancement of concentration of triethanolamine with the presence of the benzalkonium chloride[54]. Mohapatra.et.al. Studied the statistical moment theory of diclofenac potassium kinetical permeation in cornea to distinguish the steady and non- steady state. Using the docking analytical calculations of HPMC-DCP binding shows the interaction between drug-excipient at molecular level. The study shows a 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 plasticizer in a ex-vivo study showing thermodynamic characteristics by using diclofenac potassium in a Hypromellose matrix film. These are used to study the enthalpy, entropy, activation energy, free energy estimation of permeability, difusibility and partitioning. The transformation and growth of the crystal nature in the drug observed in the amorphous state and there is a 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 plasticizer and preservative respectively. There was a crystalline to amourphous transition state and a molecular dispersion observed between the diclofenac potassium and HPMC[57]

The studies of skin permeation are performed by involving percutaneous absorption in the beginning. They allow to identify various formulation parameters which are 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 summarizes the pottentiated permeation profiles of challenged drugs by permeation enhancers in the transdermal drug delivery system by keeping focus on macromolecules and recent techniques. This review identify enhancers that are reliable, effective and compatible with preparations for drug delivery. The studies relates stratum corneum as a rate limiting membrane, where corneocytes forms a matrix barrier and the drugs have to utilize a macromolecular carrier for their influx and efflux activity. Several amino acid and lipid based macro enhancers poses potency and safety features superior to other enhancers. Their structural versatility enables the combination of multiple mechanisms, to facilitate the drug permeation. On the other instances the potential pulling action of complexes created by natural macro enhancers like aloe gel, which increases permeability that typically utilised by 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. The techniques like phonophoresis, electropoation, iontophoresis, and photomechanical waves enhance the permeation rate of various active constituents. Litretures demonstrate that these methods disrupt the lipid on the surface of the skin allowing the drug into the stratum corneum. This review indicates the that use of natural products, peptides, and other complex bio molecules that shows a great promising permeation enhancers of future scenario for providing novel modifications.

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