IJBPAS, March, Special Issue, 2025, 14(3): 593-623

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

ADVANCES IN PERMEATION ENHANCERS: MECHANISMS AND APPLICATIONS

PATIL PJ[*1] AND KARMARKAR RR[2]

1: M.G.V.'S Pharmacy College, Panchavati, Nashik- 422003, Maharashtra, India

2: M.G.V.'S Samajshri Prashantdada Hiray College of Pharmacy, Malegaon. District-Nashik, Maharashtra, India

[*]**Corresponding Author: Mrs. Patil Poonam Jaykar; E Mail: poonampatil969@gmail.com**

Received 25th Dec. 2024; Revised 9th Jan. 2025; Accepted 21st Feb. 2025; Available online 15th March 2025

https://doi.org/10.31032/IJBPAS/2025/14.3.1071

ABSTRACT

To enhance the bioavailability and absorption of drugs, scientists have created compounds referred to as "permeation enhancers." These molecules are specifically designed to simplify passage of drugs through biological barriers like stratum corneum. Functions of these enhancers include increasing skin pliability, modifying lipid structures, interacting with intracellular proteins, and enhancing drug partitioning. Formulation optimization is crucial in the development of these enhancers, with polymers and nanoparticles playing a key role. Scientists employ various mechanical and chemical techniques, like electroporation, sonophoresis, laser ablation, microneedles, mechanical abrasion, thermal ablation, iontophoresis, pressure augmentation, hyperthermia, and nanotechnology, to rise drug penetration into body. Chemical permeation enhancers encompass surfactants, fatty acids, esters, alcohols, terpenes, azone, sulfoxides, nonsteroidal anti-inflammatory drugs (NSAIDs), lecithin, chelating agents, hydrotropes, penetration-enhancing polymers, and cyclodextrins. Natural permeation enhancers like essential oils (e.g., peppermint, lavender, and eucalyptus) find application in topical formulations to improve absorption of active substances by skin. Careful formulation design is imperative to ensure both efficacy and safety. The use of permeation enhancers represents diverse and evolving field, subject to ongoing research efforts aimed at expanding drug delivery options and enhancing therapeutic outcomes.

Keywords: Permission enhancer, stratum corneum, absorption

INTRODUCTION:

The largest organ in the human body, the skin, acts as a barrier to keep water within and hazardous environmental elements out **[1]**. Because of its protective barrier function, skin is a major barrier to the absorption of drugs. There have been several attempts to devise methods to get drugs through stratum corneum (SC), which is impermeable **[2]**. For medications to be effectively delivered dermally or transdermal, it is necessary to overcome this barrier **[3]**. The medicine is absorbed through the stratum corneum, dermis, epidermis, and finally bloodstream during the percutaneous absorption process, which is facilitated by a concentration gradient between the drug and the skin **[4-6]**.

Penetration means increasing the ability of a medicine, chemical, or other material to pass through a biological barrier such as the skin, mucous membranes, or cell membranes by using a substance or compound known as a permeation enhancer **[7-8]**. These boosters are used to raise the bioavailability of medications, the efficiency of topical applications, or the absorption of diverse chemicals **[9]**.

To the penetrating molecule, the skin acts as a passive barrier **[10]**. Even though it has the highest penetration resistance, the stratum corneum is where percutaneous absorption reaches its limiting stage **[11]**. Substances known as penetration enhancers temporarily lower the skin's permeability, allowing penetrants to be absorbed more easily **[12-13]**. These materials should be affordable, odorless, tasteless, colorless as well as compatible with medicine and excipients. When the enhancer is removed, the skin should rapidly resume its barrier function to prevent forfeiture of electrolytes, fluids, and other endogenous materials. There is no such thing as a perfect penetration booster. Yet numerous enhancers have been tried and true in clinics and labs, displaying many of these characteristics. The effects of various amplifiers on transdermal penetration of various drug moieties are being studied by researchers. This review aims to classify penetration-improving substances and explain their mechanism of action to help choose the right ones for transdermal absorption of medications.

Permeation enhancers play a pivotal role in pharmaceutical and cosmetic formulations by augmenting the penetration of active compounds through biological barriers, such as the skin or mucosal membranes.

Understanding the mechanisms and significance of these enhancers is paramount for optimizing drug delivery systems and improving therapeutic outcomes **[13]**. By modulating the physicochemical properties of the barrier and/or the drug molecules themselves, permeation enhancers can enhance solubility, disrupt lipid structures, or alter

membrane fluidity, ultimately facilitating drug permeation. Moreover, they can mitigate enzymatic degradation and efflux mechanisms, thereby prolonging drug retention within the target site. Mechanisms of permeation enhancers are crucial for the development of novel formulations with enhanced bioavailability, reduced side effects, and improved patient compliance.

Therefore, research endeavors focusing on permeation enhancers hold immense promise for advancing the field of pharmaceutical and cosmetic sciences, ultimately translating into enhanced efficacy and patient care. Overall, writing a review on permeation enhancers is necessary for advancing our understanding of drug delivery science and promoting the development of more efficient and safer therapeutic interventions **[14]**.

This review indicates that alpha-bisabolol possesses several characteristics that make it a promising candidate for enhancing drug permeation across biological barriers.

Its amphiphilic nature allows it to interact with both hydrophilic and lipophilic components of biological membranes, thereby potentially disrupting the barrier integrity and facilitating the passage of drugs or active compounds. Additionally, alpha-bisabolol exhibits anti-inflammatory and skin-soothing properties, which can contribute to reducing barrier resistance and improving drug penetration. Studies have also suggested that alpha-bisabolol may modulate the expression of proteins involved in tight junction formation, further enhancing paracellular transport.

Furthermore, its low cytotoxicity and biocompatibility make it an attractive option for incorporation into pharmaceutical and cosmetic formulations. However, further research is warranted to fully elucidate the mechanisms underlying its permeation-enhancing effects and to optimize its formulation and dosage for various applications. Overall, alpha-bisabolol holds promise as a natural and safe permeation enhancer, with the potential to improve the efficacy of drug delivery systems and enhance the therapeutic outcomes of pharmaceutical and cosmetic products.

Mechanism of permeation enhancer

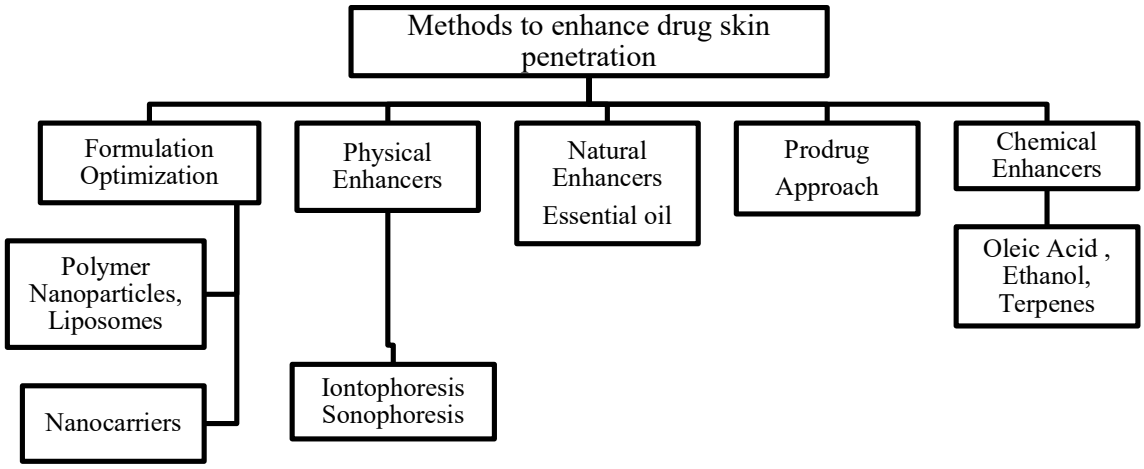
It's common knowledge that penetration enhancers make it easier for drugs to pass through the skin. But the precise mechanics of it is only partially understood how penetration enhancers work **[14]**. The following mechanisms, or combinations thereof, may be responsible for the actions of skin penetration enhancers: Solvent action is the initial proposed mechanism.

1. The penetration boosters make the skin and tissue components more pliable or easily soluble.
2. The second mechanism postulated is that enhancers interact with intercellular lipids, causing the highly structured

lamellar structure to be disrupted and so boosting the diffusivity of medicines from lipid domain.

3. The third theory proposes that enhancers promote drug penetration within corneocyte layer by interacting with intracellular proteins.
4. The fourth theory proposes increasing the stratum corneum's partitioning of medications, co-enhancers or co-solvents. The latter three steps are explained by the LPP theory, which stands for lipid-protein partitioning **[15]**.

Methods to progress drug skin penetration



Formulation optimization

Polymers and nanoparticles are crucial in the development of permeation enhancers for delivery of drug **[16]**. Polymers enhance the permeation of pharmaceuticals through biological barriers like skin, mucous, or cell membranes **[17-18]**. Nanoparticles play a flexible role in these systems, providing benefits and activating pathways for improved permeation and delivery **[19-21]**. Nanocarriers, such as liposomes, are essential components in permeation enhancer formulations, encapsulating, protecting, and transporting drugs and enhancers, enhancing efficacy and reducing side effects **[22-23]**. Liposomes are microscopic vesicles with a central water core and a bilayer or bilayers of lipids. Overall, nanoparticles and nanocarriers play vital roles in improving drug delivery and delivery **[24]**. In some of diverse ways, it is utilized to improve the efficiency as well as the durability of permeation enhancers:

a) Controlled Release: The production of "controlled-release" medication delivery systems can be accomplished with help of

polymers. It is possible to regulate the rate at which an active component is released from polymeric matrices if pharmaceuticals and permeation enhancers are first encapsulated within those matrices. This results in a therapeutic effect that is maintained throughout time **[25-27]**.

b) Enhanced Adhesion (enhanced adhesion): Adhesion of drug delivery system to skin is absolutely necessary for transdermal administration of drugs. It is possible to add polymers into adhesive layers in order to strengthen the system's adhesion to the skin and ensure that drugs and enhancers are distributed effectively **[28]**.

c) Protection and Stabilization: Polymers can protect sensitive medications and permeation enhancers from environmental variables such as moisture and oxygen, which can damage them. Polymers can also stabilize the drugs and permeation enhancers. In addition to that, they lend the formulation a higher level of physical stability **[29]**.

d) Controlled Release of Permeation Enhancers: Polymers can be employed to control release of permeation enhancers by themselves. This is referred to as the controlled release of permeation enhancers. Because of this, the augmentation of drug penetration may be more precisely controlled and maintained **[30-31]**.

e) Enhanced Skin Penetration: Polymers have ability to interact with stratum corneum of the skin and change its characteristics, hence increasing the skin's receptivity to the absorption of drugs. They have ability to alter microscopic structure of skin, which in turn facilitates permeability.

f) Muco-adhesion: In mucosal drug administration, certain polymers are engineered to stick to mucous membranes. This improves drug and enhancer retention while also making absorption easier. **[32]**

g) Enhanced Permeability: The ability of certain polymers, when paired with permeation enhancers, to intensification permeability of drug molecules through biological barriers. Modulating the barrier characteristics of the mucosal or skin tissues is the means by which this goal can be accomplished **[33]**.

h) Matrix Systems: Polymers can be utilized to construct matrices for use in systems that distribute drugs topically. These matrices have the ability to regulate the release of medicines and other substances that enhance penetration over time **[34-35]**.

i) Patch Formulations: Polymer matrices are frequently used in transdermal patches; these matrices house the active substances as well as the enhancers. Polymers are used to regulate release of drugs, improve adherence, and shield formulations from the effects of the surrounding environment **[36-37]**.

j) Hydrogels: Hydrogels which are constructed of water-absorbing polymers, are utilized in a number of drug delivery applications, with transdermal and mucosal delivery. Hydrogels are used in delivery of drugs through mucosal and transdermal routes. They have the ability to make the environment more humid and to enhance the rate at which medicines and enhancers are released **[38-40]**.

k) Targeted Delivery: When combined with permeability enhancers, functionalized polymers containing ligands or targeting molecules can accomplish site-specific drug delivery. This can be done to achieve site-specific drug delivery **[41-42]**.

Physical permeation enhancers

It is also known as physical methods or techniques, are approaches used to improve the penetration or permeation of drugs, compounds, or other substances through biological barriers. These methods involve the application of physical forces or technologies to improve delivery of therapeutic agents. Some common physical permeation enhancers include **[43-47]**.

a) Iontophoresis: It is technique that uses a low-level electrical current to drive charged molecules, including drugs, across biological barriers. It is often used in transdermal drug delivery for conditions such as pain management and local anesthesia **[48-50]**.

By passing a small electrical current through an iontophoretic chamber containing an electrically charged active drug and its carrier, iontophoresis is a non-invasive system that increases skin penetration of pharmaceuticals **[51]**. It is iontophoretic device that houses the iontophoretic chamber. The quantity of drug molecules absorbed through the skin can be significantly affected by the delivery system's composition and the medication's release characteristics. Organic solvents and surface-active compounds can alter skin permeability, which in turn can enhance percutaneous absorption. The two most important methods for increasing the flow of medicine through the skin are electro repulsion and electroosmosis. A positively charged chemical is repelled from skin by positively charged chamber, whereas a negatively charged chemical is repelled from skin by negatively charged cathode. This allows for effective delivery of chemical. In presence of an electric field, two primary modes of mass transfer are referred to as electromigration and electroosmosis, respectively. The process is predicated on the idea that opposite charges attract one another and involves dissolving the drug in an electrolyte that surrounds an electrode with a polarity that is analogous to that of the drug. Iontophoresis makes use of a very mild current, and as a result, patients

report feeling very little or nothing at all during the process **[52]**.

b) Electroporation: It is a method that uses brief bursts of high-voltage electric current to transiently open up cell membranes, resulting in the creation of pores through which medicines and other compounds can be introduced. The potential of electroporation as a method for transdermal medication administration is clearly demonstrated by this research. The use of electroporation to enhance the efficiency and expand the variety of substances that can be transdermal administered has revolutionized the delivery of medicines in both laboratory and living organism settings. It could be a good substitute for invasively delivering macromolecules (up to 40 kDa) and delivering them quickly and/or pulsatilely through the skin **[53-54]**.

The utilization of electroporation in conjunction with various other physical enhancers is expected to result in the production of data that is both helpful and fascinating. As a result, the attempts to investigate electroporation as a method of transdermal drug delivery will likely be increased.

The reader needs to be aware that there is multiple chemical, biochemical, and physiological processes involved in electrically aided drug delivery, and that there is overlay in systems elaborate in transport via electroporation **[55-56]**.

It is one of physical and chemical ways that can be used to transfer genes and drugs. It is superior in a number of ways, although having a number of deficiencies as well. It is still the approach of choice in various circumstances, as demonstrated by the vast body of relevant scholarly research. In the not-too-distant future, further innovations are anticipated that will make this method even more flexible. It is necessary to perfect both the pulse protocol and the electrode design in order to minimize the most significant detrimental consequence, which is muscular contraction. This method is used in gene therapy and certain drug delivery applications **[57]**.

c) Sonophoresis:

Sonophoresis, also known as phonophoresis, is process of using ultrasound at a frequency that is optimal for purpose of considerably enhancing the delivery of medications through skin **[58]**. This method was initially implemented in physiotherapy and sports medicine, but later it was adapted for use in research on transdermal drug administration **[59]**. On the other hand, it has been demonstrated that a low frequency (less than 20 kHz) rather than therapeutic ultrasound (less than 1 MHz and higher) results in a thousand times greater enhancement **[59]**. It has been suggested that the enhancement achieved using a combination of ultrasound and chemical enhancers may be superior than that achieved using either enhancement

approach separately **[60]**. The process of sonophoresis involves the use of ultrasonic waves to advance skin's ability to absorb drugs. The stratum corneum can be made more permeable to drugs by use of mechanical vibrations produced by ultrasound **[61-63]**.

d) Microneedles:

Microneedles are tiny, minimally invasive needles that create micro-channels in the skin, allowing for improved drug delivery **[64]**. They can be used for transdermal drug administration and have applications in vaccines and diabetes management. Microneedles have several advantages over transdermal drug delivery techniques, most significant of which is improved skin permeability achieved by avoiding the stratum corneum **[65]**. A trans-epidermal delivery system that causes minimum pain is paired with penetration augmentation techniques such as physical and chemical procedures in order to boost flow of permeation. Deeper penetration of the skin is achieved by employing these techniques **[66-67]**. To improve the physical properties of topical drug administration, many approaches can be employed, such as iontophoresis, sonophoresis, and electroporation. The stratum corneum can be disrupted or new pores and microchannels can be created in the skin using these methods **[68]**. When these methods are used in conjunction with microneedles, the permeability of medications across the skin is five to ten times greater than when microneedles are used alone.by the administration of a large number of active components, macromolecules, antibodies, genes, proteins, and peptides with the use of microneedle delivery. In the near future, microneedle systems will be able to treat cancer, diabetes, Alzheimer's disease, and cardiovascular problems with tailored medicine delivery, skin-sealable administration, and less intrusive immunization conveyance **[69-70]**.

e) Laser Ablation:

Laser ablation techniques involve use of lasers to create micropores in skin, enabling enhanced drug delivery through the treated area. Laser ablation (LA) is gaining popularity as an alternative to surgical resection for specific cancers, aiming to reduce suffering and improve outcomes **[71]**. However, challenges include accurate applicator placement and treatment planning. New HTP tools and monitoring tools are gaining attention and clinical acceptance for improving safety and outcomes. Recent developments include the use of new lasers with different wavelengths and modes of operation, improved understanding of laser-tissue interactions, and advancements in targeting nanoparticles to tumor cells **[72]**. To realize these technologies, further improvements and translation for clinical use require

interdisciplinary collaboration. Mass spectrometry imaging has also gained interest in biomedical questions, particularly in metallomics **[73-75]**.

f) Mechanical Abrasion:

Mechanical abrasion methods, such as dermabrasion or microdermabrasion, involve the physical removal of stratum corneum. This enhances drug penetration and is often used in cosmetics and dermatology. A simulation of dentin demineralization was performed in EDTA solution for 13 hours as part of a study that investigated the responses of silver and fluoride with dentin **[76]**. According to the findings, silver phosphate was produced alongside the mineral phase, and fluoride interactions with dental hydroxyapatite led to the formation of fluoro-hydroxyapatite crystals as well as a substance with properties similar to calcium fluoride. The rapid discoloration was caused by silver ions that attached themselves to the collagen in the dentin and formed a protective coating. The silver-based dentin, also known as SDF, was able to profoundly penetrate dentin, with the largest concentration occurring on the surface of the dentin. Brushing the surface with a mechanical tool can remove some of the silver compounds there, but it is not nearly as effective on demineralized dentin **[77]**.

g) Thermal Ablation:

Thermal ablation methods, such as radiofrequency and laser-induced thermotherapy, use heat to disrupt or penetrate biological barriers. These methods have applications in skin rejuvenation and medical treatments. Thermal ablation, a method of selective removal of the superficial layer of skin (SC) through microsecond heat pulses, is a potential alternative to mechanical abrasion, tape-stripping, or chemical therapy **[78]**. This method allows for the apoptosis of cells and the formation of microchannels or pores, allowing for the delivery of various medications via transdermal delivery. Lasers for thermal skin ablation have gained interest due to their ability to control the depth of the ablated skin. Ultrasound can impact tissues and cells through cavitation and heat radiation, with the temperature rise and thermal effect directly proportional to the absorption coefficient of the medium **[79]**. Radiofrequency ablation involves inserting a thin needle electrode into the patient's skin, resulting in the formation of microchannels and increased drug transport across the skin. However, these methods have drawbacks, such as difficulty in regulation, reproduction, and skin irritation **[80]**.

h) Enhancement:

The application of mechanical pressure to the skin, as in massage or compression

devices, can improve penetration of topical agents. It is used in physiotherapy and sports medicine **[81]**.

i) Hyperthermia:

Hyperthermia involves the application of heat to the skin or tissues. It can increase blood flow and permeability, potentially improving drug delivery to the affected area **[82]**.

j) Nanotechnology:

Nanoparticles, as discussed earlier, are another form of physical permeation enhancers. They can interact with biological barriers at the nanoscale and improve drug penetration.

Physical permeation enhancers offer advantages in terms of non-invasiveness, localized drug delivery, and the potential for improved bioavailability. The precise use, the compound's composition, and safety and patient comfort factors all play a role in determining the method of choice. Careful consideration of the medication delivery scenario at hand is required when choosing from among various physical modalities, each of which has its own benefits and drawbacks **[83]**.

Chemical permeation enhancers

Biological barriers include the skin, mucous membranes, and cell membranes; chemical permeation enhancers boost the ability of medications, chemicals, and other substances to penetrate or permeate these barriers **[84]**. These chemical enhancers function by interacting with the barrier to make it more permeable **[85]**. Chemical permeation enhancers are widely used in pharmaceuticals, cosmetics, and various other applications. Here are some common types and examples of chemical permeation enhancers:

a) Surfactants:

The term "surfactants" refers to a class of chemicals that are able to lower the surface tension of various biological barriers. Surfactants are already present in an extensive variety of chemical formulations used in medicine, cosmetics, and agriculture. Many transdermal drugs have had their penetration rates increased in recent years with application of surfactants. High penetration barrier across stratum corneum layer of outermost layer of skin limits transdermal method of administration to a limited variety of drugs and makes it impractical to do so very frequently. Surfactants have power to change permeability properties of various biological membranes, including skin. In stratum corneum, they can make the lipids more soluble. In order to know whether a surfactant molecule can cross the stratum corneum's lipid lamellae, it is important to know its partitioning behavior and how well it dissolves in water. Surfactants with different hydrophobic and hydrophilic properties have been studied and tested as permeation enhancers. Improving drug

distribution is the driving force for this study. In order to improve the rate of permeability, many surfactants are utilized. These include sodium lauryl sulfate, tween, span, and sorbitan monopalmitate **[86-87]**.

b) Fatty Acids and Esters:

Fatty acids and their esters are known for their ability to disrupt lipid structures in cell membranes, enhancing the penetration of drugs. Oleic acid is often used in transdermal drug delivery **[88]**.

c) Alcohols:

Alcohols can enhance drug penetration by troublemaking lipid organization in stratum corneum. Examples include ethanol and isopropyl alcohol **[89]**.

d) Terpenes:

Essential oils contain terpenes, which are natural substances. They improve drug penetration by causing disruptions to the skin's lipid composition. Skin penetration enhancers (PEs) **[90]** derived from terpenes, which are abundant in plants, show a lot of promise. There have been at least 28 terpenes studied and used as TDDS Pes. The most popular ones are nerolidol, menthone, limonene, menthol, and 1,8-cineole. Synthetic polyethylene glycol (PE) has lower enhancing activity than natural terpenes for both lipophilic and hydrophilic chemicals. The interaction between these terpenes, the majority of which include oxygen, and the lipids in the skin dictates how efficient they are as PEs. Both the terpenes and the medication molecules' lipophilicity impact the enhancing effect. A low boiling point and a chain structure may increase the penetration augmentation impact of amphiphilic terpenes, which already has a high effect. When compared to chemical skin PEs, natural terpenes seem to be safer because to their less irritancy potential. The following are some examples: menthol, α-bisabolol, limonene, cineole, Anethole, Borneol **[91-92]**.

Terpenes, which are often isolated from medicinal plants, are finding more and more use as penetration enhancers (PEs) in various formulations used in the pharmaceutical industries. In comparison to synthetic polyethylenes (PEs), these volatile chemicals, which are made up of atoms of carbon, hydrogen, and oxygen, are generally regarded as being safer. According to a number of studies, the penetration of hydrophilic and lipophilic substances is enhanced by the presence of naturally occurring terpenes.

Terpenes are absorbed through the skin, which increases their level of diffusion across the lipids that separate the cells. Altering structure of keratin and disrupting packing of hydrophobic lipids in stratum corneum (SC) are two other uses for these agents. It was shown that there was a positive link between the uptake of terpene and SC partition coefficient **[93]**.

e) Azone:

Azone, also known as 1-dodecylazacycloheptan-2-one, is a synthetic permeation accompaniment commonly used in transdermal drug delivery **[94]**.

f) Sulfoxides and Sulfoxide Derivatives:

Dimethyl sulfoxide (DMSO) and its derivatives can enhance drug penetration through skin and mucous membranes. DMSO is used in topical formulations for its penetration-enhancing properties **[95-96]**.

g) Ibuprofen and Salicylates:

Some NSAIDs, such as ibuprofen, and salicylates, like salicylic acid, can act as permeation enhancers themselves and are used in topical formulations **[97]**.

h) Lecithin:

Lecithin, a naturally occurring phospholipid, can be used as a permeation enhancer, particularly in liposomal formulations **[98]**.

i) Chelating Agents:

Chelating agents, such as ethylene-diamine-tetraacetic acid (EDTA), can disrupt the tight junctions between cells, enhancing permeability of mucous membranes **[99]**.

j) Hydrotropes:

Hydrotropes are compounds that advance solubility of poorly water-soluble drugs, making them more amenable to mucosal or transdermal delivery **[100]**.

k) Penetration-Enhancing Polymers:

Certain polymers PEG and PVP, can be used to improve penetration of drugs and are sometimes classified as chemical permeation enhancers **[101]**.

l) Cyclodextrins:

Inclusion complexes formed by cyclodextrins and pharmaceuticals enhance the solubility and translocation of the former through various biological membranes. Many things must be considered before settling on a chemical permeation enhancer, including the type of medicine or molecule that needs to be given, the intended use, any necessary safety measures, and any applicable regulations. Careful formulation design is necessary to optimize the use of these enhancers while ensuring efficiency and protection of product **[102]**.

Natural permeation enhancers

Natural permeation enhancers, such as essential oils, are compounds derived from plant sources that have been used traditionally and in modern applications to improve the penetration or permeation of drugs, compounds, or other substances through biological barriers. One of the many medicinal uses for essential oils-volatile, fragrant molecules derived from plants-is to improve the absorption of other medicinal substances **[103]**. Here are some essential oils that are used as natural permeation enhancers.

a) Lavender Essential Oil: The soothing and relaxing effects of lavender oil are well-known. It has been applied topically to improve the skin's ability to absorb specific

chemicals. It can also have anti-inflammatory effects, which can be beneficial in topical formulations **[104]**.

b) Eucalyptus Essential Oil: Eucalyptus oil contains compounds that can increase skin permeability and improve the absorption of topical formulations. It is often used in products like ointments and creams **[105]**.

c) Peppermint Essential Oil: Peppermint oil has a cooling and refreshing sensation and can improve penetration of active essentials through skin. It is used in various topical products for pain relief and skin care.

d) Tea Tree Essential Oil: Tea tree oil is recognized for its antimicrobial properties and is often used to enhance the penetration of other antimicrobial or anti-inflammatory compounds in topical applications.

e) Rosemary Essential Oil: Rosemary oil is believed to improve circulation and can potentially enhance delivery of drugs through skin or mucous membranes.

f) Lemongrass Essential Oil: Lemongrass oil is sometimes included in formulations to enhance the permeation of other active ingredients. It has a fresh, citrusy aroma.

g) Ginger Essential Oil: Ginger oil may have properties that can improve skin permeation. It is often used in products for pain relief and relaxation **[106]**.

It's important to note that while natural permeation enhancers like essential oils can offer advantages in terms of being derived from natural sources and having various therapeutic benefits, their use should be carefully considered. Safety, skin sensitization, potential allergic reactions, and interactions with other compounds in a formulation should be evaluated. The specific essential oil chosen may depend on the application, the intended effect, and the compatibility with the active ingredient. The effectiveness of natural permeation enhancers can vary depending on the specific essential oil, the formulation, and the desired outcome. In many cases, essential oils are used in combination with other excipients or techniques to optimize their permeation-enhancing properties.

With their 'Generally Regarded As Safe' rating from USFDA, natural terpenes have advantages over more conventional enhancers including alcohols, Azone®, fatty acids, sulfoxides, and pyrrolidones. In addition to their excellent penetration-enhancing properties, they also have minimal systemic toxicity and low skin irritancy.

Sesquiterpenes are pretty big molecules that are separated from the parts of essential oils that have higher boiling points. Researchers looked into how well sesquiterpenes which were picked because they are safe and don't irritate the skin can get into it. They used the water-loving drug 5-fluorouracil as a test drug.

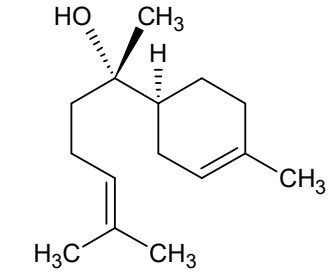
Particular sesquiterpenes involved following: **[107]**

- Hydrocarbons: β-caryophyllene, (+)-longifolene, (+)-β-cedrene and (+)-aromadendrene
- Alcohols: (−)-guaiol, (−)-isolongifolol (synthetic derivative), (+)-cedrol, (−)-α-bisabolol, farnesol and nerolidol;
- Others/miscellaneous: (+)-cedryl acetate and β-caryophyllene oxide which are together synthetic derivatives.

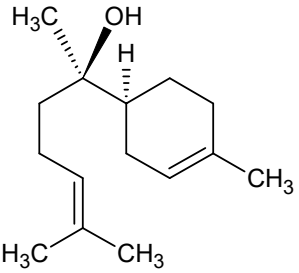
The cyclic compounds (−)-isolongifolol, (−)-guaiol, and (+)-cedrol exhibited weakest boosting effects of alcohols studied because they lacked distinct hydrocarbon tails, which made them less effective at disrupting the lipids. Given its status as a monocyclic alcohol, (−)-α-bisabolol displayed intermediate activity and would fit more snugly into lipid domain. Most effective enhancers were nerolidol and farnesol, which are acyclic alcohols with properties that can disrupt lipid packing **[108]**. By comparing their structures, we found that the enhancer activity was dramatically increased when the alcohol was changed from primary to tertiary. We are concentrating on α-Bisabolol as an enhancer of permeation.

Some aromatic plants, such as Eremanthus erythropappus, Smyrniopsis aucheri, and Vanillosmopsis species, have subsequently been found to contain the sesquiterpene alcohol α-bisabolol, which was first discovered in Matricaria chamomilla (Asteraceae) in the 1900s **[109]**. It has been determined that there could be four potential stereoisomers of α-(-)-bisabolol. There are several cosmetic and dermatological items that include bisabolol **[110]**. The term α-(-)-bisabolol is usually suggested when bisabolol is mentioned. German chamomile, sage, Vanillosmopsis sp., Myoporum grassifolium, and other plants can be hydro distilled to produce α-(-)-bisabolol, which is also called levomenol. The percentage of α-(-)-bisabolol in Matricaria chamomilla is up to 50%, whereas in S. runcinata it is up to 90%. Candeia wood (Eremanthus erythropappus) is another little investigated source of α-bisabolol that could contain as much as 85% of the compound **[111]**.

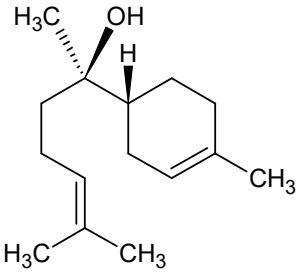
Bisabolol, with the molecular formula $C_{15}H_{26}O$, is a sesquiterpene alcohol. Its alternative names include alpha,4-dimethyl-alpha-(4-methyl-3-pentenyl)-3-cyclohexene-1-methanol. Bisabolol has a subtle, floral scent **[112]**. At 12 Torr, its boiling point is 153°C, and it has a comparatively low density of 0.93. The liquid is colorless. Because of its high oxidation potential, bisabolol is a lipophilic compound. Though soluble in ethanol, it almost insolubilizes in water. Mainly bisabolol-oxide A and B are byproducts of oxidation. Synthesized version of α-(±)-bisabolol is typically a combination of the less common enantiomer α-(-)-bisabolol **[113]**.



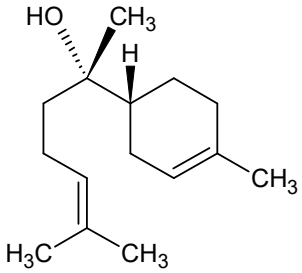
(–)-α-Bisabolol



(–)-epi-α-Bisabolol



(+)-α-Bisabolol



(+)-epi-α-Bisabolol

Applications

In most cases, an increase in melanin is to blame for the darkening of skin that occurs in hyperpigmentation. Hyperpigmentation can be produced by number of different reasons with inflammatory skin conditions, allergic and irritating contact dermatitis. Hyperpigmentation of epidermis and dermis has been linked to an increase in melanogenic enzyme activity or the number of melanocytes. Production of a-melanocyte-stimulating hormone (a-MSH) is known to require the cAMP response element (CRE). Two assays, a cAMP response element luciferase reporter assay and a melanin test, were used to determine whether or not a-bisabolol had a depigmenting impact. The data showed that a-bisabolol counteracted the effects of a-MSH on CRE activation. Similarly, substance reduced the melanin concentration caused by a-MSH **[114]**. Melanin synthesis is catalysed by the enzyme tyrosinase. Many studies have demonstrated that a-MSH promotes tyrosinase gene expression via activating MITF (Microphthalmia-associated transcription factor) gene expression. Scientists examined the impact of α-bisabolol on the a-MSH-induced MITF and tyrosinase gene expression and discovered that it had an effect, indicating that a-bisabolol hinders melanogenesis through the reduction of intracellular cAMP levels **[115]**.

Although there are benefits to administering medications via the percutaneous route compared to intravenous or oral routes, the stratum corneum acts as an architectural barrier to topical and transdermal drug

distribution. Use of penetration enhancers is common practice for lowering stratum corneum permeability. Because of their non-toxicity, extensive usage for transdermal distribution, and all-natural composition, these are GRAS. The α-blocker dapiprazole is used topically on the eyes to treat chronic uncomplicated glaucoma, prevent miosis before surgery, and reverse pharmacologically-induced mydriasis. Lower dosages, maintained plasma levels and more patient compliance are all potential benefits of transdermal administration compared to oral methods in patients with various diseases. The permeability coefficient of dapiprazole was dramatically increased when tested in the presence of terpenes such γ-limonene, α-bisabolol and terpinolene compared to other vehicles. Changes in bisabolol's activity show how different functional groups affect a compound's pharmacological profile **[116]**.

The sesquiterpene alcohol α-bisabolol, which is present in essential oils, has been discovered to possess anticancer properties in relation to pancreatic cancer. Akt activity was inhibited and apoptosis was promoted in pancreatic cancer cell lines by α-bisabolol therapy. Additionally, the therapy significantly reduced tumor growth in xenograft nude mouse models placed subcutaneously and peritoneally **[117]**. The compound α-bisabolol derivative effectively reduces pancreatic cancer cell proliferation and apoptosis, inhibiting tumor growth and reducing pancreatic cancer dissemination to peritoneal nodules. It suppresses AKT expression, indicating an anticancer effect, making it a promising new anticancer drug for pancreatic cancer **[118]**.

The apoptotic induction, cell cycle arrest, suppression of cell migration and invasion, and activation of the P13K/AKT signaling pathway are the mechanisms by which α-Bisabolol exerts its anticancer effects in human non-small cell lung carcinoma cells **[119]**.

Other applications

The optically active sesquiterpene alcohol (−)-α-bisabolol is made by distilling the essential oil of plants like Matricaria chamomilla and Vanillosmopsis erythropappa. (−)- α- Bisabolol's antibacterial and gastroprotective properties, along with its subtle floral aroma, have attracted a lot of attention from the economic community **[33]**. Using a modified single sucrose-gap approach, the researchers analysed changes in the properties of compound action potentials (CAPs) in the peripheral nerve systems of mice to determine the pharmacological effects of (-)-α-bisabolol **[34]**. Dementia and cognitive decline in the elderly are symptoms of Alzheimer's disease (AD), a neurodegenerative illness that can be fatal. This work looks into the effects of α-bisabolol on Aβ25-35 caused

neurotoxicity in PC12 cells, namely its anti-amyloidogenic and anti-apoptotic capabilities. The therapy decreases the tendency for Aβ aggregation and the intensity of fluorescence, according to the results **[120]**.

Preclinical models of chronic pain were examined for the antinociceptive and anti-inflammatory effects of (-)-α-bisabolol alone and in combination with β-cyclodextrin (βCD). Swiss mice were given BIS, BIS-βCD, or vehicle treatment and their spinal cord was examined. Results indicate BIS and BIS-βCD decrease mechanical and thermal hyperalgesia, TNF-α production, and IBA-1 expression. Complexation of BIS in βCD lowered therapeutic dose, indicating BIS as a viable chronic pain therapy molecule **[121-123]**.

CONCLUSION:

Substances that improve a drug's permeability to biological barriers include permeability enhancers. To develop efficient medication delivery systems, optimization of formulation is essential. Some methods that can increase physical penetration include iontophoresis, microneedles, electroporation, sonophoresis, and electroporation. In treatment of cancer, diabetes, Alzheimer's disease, and cardiovascular issues, microneedle devices provide targeted medication delivery, self-sealable administration, and less invasive immunization. Because it reduces discomfort and speeds up recovery, laser ablation is a preferred choice for treating some tumors. Chemical substances that can improve the rate of penetration include terpenes, esters, surfactants, fatty acids, synthetic polyethylenes (PEs), chelating agents, hydrotropropes, and PEs. Essential oils and other natural penetration enhancers offer medicinal qualities, however there are concerns about their use due to skin sensitization, allergies, and chemical interactions. Terpenes like α-Bisabolol have several possible applications, a low toxicity level, and are GRAS classified, making them attractive choices for drug permeation. These chemicals have great potential for transdermal drug administration, but further study and clinical trials are essential to determine their full potential.

REFERENCES:

[1] Fahad D, Mohammed MT. Oxidative stress: implications on skin diseases. Plant Arch. 2020;20(2):4150-7. https://doi.org/10.7314/apjcp.2014.15.2.561

[2] Basler K, Bergmann S, Heisig M, Naegel A, Zorn-Kruppa M, Brandner JM. The role of tight junctions in skin barrier function and dermal absorption. Journal of Controlled Release. 2016 Nov 28; 242:105-18. https://doi.org/10.1016/j.jconrel.2016.08.007

[3] Phatale V, Vaiphei KK, Jha S, Patil D, Agrawal M, Alexander A. Overcoming

skin barriers through advanced transdermal drug delivery approaches. Journal of controlled release. 2022 Nov 1; 351:361-80. https://doi.org/10.1016/j.jconrel.2022.09.025

[4] Higaki K, Amnuaikit C, Kimura T. Strategies for overcoming the stratum corneum: chemical and physical approaches. American Journal of Drug Delivery. 2003 Sep; 1:187-214. http://dx.doi.org/10.2165/00137696-200301030-00004

[5] Sala M, Diab R, Elaissari A, Fessi H. Lipid nanocarriers as skin drug delivery systems: Properties, mechanisms of skin interactions and medical applications. International journal of pharmaceutics. 2018 Jan 15;535(1-2):1-7. https://doi.org/10.1016/j.ijpharm.2017.10.046

[6] Bolzinger MA, Briançon S, Pelletier J, Chevalier Y. Penetration of drugs through skin, a complex rate-controlling membrane. Current opinion in colloid & interface science. 2012 Jun 1;17(3):156-65. https://doi.org/10.1016/j.cocis.2012.02.001

[7] Sohi H, Ahuja A, Ahmad FJ, Khar RK. Critical evaluation of permeation enhancers for oral mucosal drug delivery. Drug development and industrial pharmacy. 2010 Mar 1;36(3):254-82. https://doi.org/10.1080/03639040903117348

[8] Nicolazzo JA, Reed BL, Finnin BC. Buccal penetration enhancers—how do they really work? Journal of controlled release. 2005 Jun 20;105(1-2):1-5. https://doi.org/10.1016/j.jconrel.2005.01.024

[9] Aungst BJ. Absorption enhancers: applications and advances. The AAPS journal. 2012 Mar;14(1):10-8. https://doi.org/10.1208/s12248-011-9307-4

[10] Nielsen JB, Benfeldt E, Holmgaard R. Penetration through the skin barrier. 2016; 49:103-11. https://doi.org/10.1159/000441549

[11] Moss GP, Gullick DR, Wilkinson SC. Predictive methods in percutaneous absorption. Springer Berlin Heidelberg; 2015 Jul 1. http://dx.doi.org/10.1007/978-3-662-47371-9

[12] Prakash D, Singh AP, Katiyar NS, Pathak K, Pathak D. Penetration enhancers: adjuvants in transdermal drug delivery system. World Journal of Pharmacy and Pharmaceutical Sciences. 2016Feb28;5(5): 35376. http://dx.doi.org/10.20959/wjpps20165-6654

[13] Kovacik A, Kopecna M, Vávrová K. Permeation enhancers in transdermal drug delivery: Benefits and limitations. Expert opinion on drug delivery. 2020 Feb 1;17(2):145-55.

https://doi.org/10.1080/17425247.2020.1713087

[14] Schroeter A, Eichner A, Mueller J, Neubert RH. Penetration enhancers and their mechanism studied on a molecular level. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Modification of the Stratum Corneum. 2015:29-37. http://dx.doi.org/10.1007/978-3-662-47039-8_3

[15] Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. Drug delivery. 2016 Feb 12;23(2):564-78. https://doi.org/10.3109/10717544.2014.935532

[16] Ghasemiyeh P, Mohammadi-Samani S. Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. Drug design, development and therapy. 2020 Aug 12:3271-89. https://doi.org/10.2147%2FDDDT.S264648

[17] Luiz MT, Di Filippo LD, Alves RC, Araújo VH, Duarte JL, Marchetti JM, Chorilli M. The use of TPGS in drug delivery systems to overcome biological barriers. European Polymer Journal. 2021 Jan 5;142:110129. http://dx.doi.org/10.1016/j.eurpolymj.2020.110129

[18] Cuggino JC, Blanco ER, Gugliotta LM, Igarzabal CI, Calderón M. Crossing biological barriers with nanogels to improve drug delivery performance. Journal of Controlled Release. 2019 Aug 10; 307:221-46. https://doi.org/10.1016/j.jconrel.2019.06.005

[19] Kou L, Bhutia YD, Yao Q, He Z, Sun J, Ganapathy V. Transporter-guided delivery of nanoparticles to improve drug permeation across cellular barriers and drug exposure to selective cell types. Frontiers in pharmacology. 2018 Jan 26; 9:27. https://doi.org/10.3389/fphar.2018.00027

[20] Toy R, Roy K. Engineering nanoparticles to overcome barriers to immunotherapy. Bioengineering & translational medicine. 2016 Mar;1(1):47-62. https://doi.org/10.1002%2Fbtm2.10005

[21] Raj S, Khurana S, Choudhari R, Kesari KK, Kamal MA, Garg N, Ruokolainen J, Das BC, Kumar D. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. In Seminars in cancer biology 2021 Feb 1 (Vol. 69, pp. 166-177). Academic Press. https://doi.org/10.1016/j.semcancer.2019.11.002

[22] Yu YQ, Yang X, Wu XF, Fan YB. Enhancing permeation of drug

molecules across the skin via delivery in nanocarriers: novel strategies for effective transdermal applications. Frontiers in bioengineering and biotechnology. 2021 Mar 29; 9:646554. https://doi.org/10.3389/fbioe.2021.646554

[23] R Khan N, S Harun M, Nawaz A, Harjoh N, W Wong T. Nanocarriers and their actions to improve skin permeability and transdermal drug delivery. Current Pharmaceutical Design. 2015 Jun 1;21(20):2848-66. https://doi.org/10.2174/1381612821666150428145216

[24] Lombardo D, Calandra P, Barreca D, Magazù S, Kiselev MA. Soft interaction in liposome nanocarriers for therapeutic drug delivery. Nanomaterials. 2016 Jun 25;6(7):125. https://doi.org/10.3390/nano6070125

[25] Kaur G, Grewal J, Jyoti K, Jain UK, Chandra R, Madan J. Oral controlled and sustained drug delivery systems: Concepts, advances, preclinical, and clinical status. InDrug targeting and stimuli sensitive drug delivery systems 2018 Jan 1 (pp. 567-626). William Andrew Publishing. OI:10.1016/b978-0-12-813689-8

[26] Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. Journal of controlled release. 2022 Jan 1;341:132-46. https://doi.org/10.1016/j.jconrel.2021.11.025

[27] Malvey S, Rao JV, Arumugam KM. Transdermal drug delivery system: A mini review. Pharma Innov. 2019; 8:181-97.

[28] Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021 Sep 29;26(19):5905. https://doi.org/10.3390%2Fmolecules26195905

[29] Rastogi V, Yadav P. Transdermal drug delivery system: An overview. Asian Journal of Pharmaceutics (AJP). 2012;6(3). https://doi.org/10.22377/ajp.v6i3.51

[30] Pandey SP, Shukla T, Dhote VK, Mishra DK, Maheshwari R, Tekade RK. Use of polymers in controlled release of active agents. In Basic fundamentals of drug delivery 2019 Jan 1 (pp. 113-172). Academic Press. https://doi.org/10.1016/B978-0-12-817909-3.00004-2

[31] Anselmo AC, Mitragotri S. An overview of clinical and commercial impact of drug delivery systems. Journal of Controlled Release. 2014 Sep 28; 190:15-28. https://doi.org/10.1016/j.jconrel.2014.03.053

[32] Sosnik A, das Neves J, Sarmento B. Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral

routes: A review. Progress in Polymer Science. 2014 Dec 1;39(12):2030-75. http://dx.doi.org/10.1016/j.progpolymsci.2014.07.010

[33] Yi-Qun Yu, Xue Yang, Xiao-Fang Wu, Y-Bin Fan Enhancing Permeation of Drug Molecules Across the Skin via Delivery in Nanocarriers: Novel Strategies for Effective Transdermal Applications Journal of Bioengineering and Technology. 2021; 9: 646554 1-70. https://doi.org/10.3389%2Ffbioe.2021.646554

[34] Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. Journal of controlled release. 2022 Jan 1;341: 132-46. https://doi.org/10.1016/j.jconrel.2021.11.025

[35] Sivasankarapillai VS, Das SS, Sabir F, Sundaramahalingam MA, Colmenares JC, Prasannakumar S, Rajan M, Rahdar A, Kyzas GZ. Progress in natural polymer engineered biomaterials for transdermal drug delivery systems. Materials Today Chemistry. 2021 Mar 1;19: 100382. http://dx.doi.org/10.1016/j.mtchem.2020.100382

[36] Shahid N, Siddique MI, Razzaq Z, Katas H, Waqas MK, Rahman KU. Fabrication and characterization of matrix type transdermal patches loaded with tizanidine hydrochloride: potential sustained release delivery system. Drug development and industrial pharmacy. 2018 Dec 2;44(12):2061-70. http://dx.doi.org/10.1080/03639045.2018.1509081

[37] Sharma PK, Panda A, Pradhan A, Zhang J, Thakkar R, Whang CH, Repka MA, Murthy SN. Solid-state stability issues of drugs in transdermal patch formulations. AAPS PharmSciTech. 2018 Jan; 19:27-35. https://doi.org/10.1208/s12249-017-0865-3

[38] Khan F, Atif M, Haseen M, Kamal S, Khan MS, Shahid S, Nami SA. Synthesis, classification and properties of hydrogels: Their applications in drug delivery and agriculture. Journal of Materials Chemistry B. 2022;10(2):170-203. https://doi.org/10.1039/D1TB01345A

[39] Sharma B, Bharti R, Sharma R. Controlled drug delivery: "A review on the applications of smart hydrogel". Materials Today: Proceedings. 2022 Jan 1; 65:3657-64. http://dx.doi.org/10.17758/IAAST.A1014

[40] Prajapati SK, Jain A, Jain A, Jain S. Biodegradable polymers and constructs: A novel approach in drug delivery. European polymer journal. 2019 Nov 1; 120:109191. http://dx.doi.org/10.1016/j.eurpolymj.2019.08.018

[41] Shukla T, Upmanyu N, Pandey SP, Sudheesh MS. Site-specific drug delivery, targeting, and gene therapy. In Nano architectonics in Biomedicine 2019 Jan 1 (pp. 473-505). William Andrew Publishing. http://dx.doi.org/10.1016/B978-0-12-816200-2.00013-X

[42] Majumder J, Taratula O, Minko T. Nanocarrier-based systems for targeted and site-specific therapeutic delivery. Advanced drug delivery reviews. 2019 Apr 1; 144:57-77. https://doi.org/10.1016/j.addr.2019.07.010

[43] Supe S, Takudage P. Methods for evaluating penetration of drug into the skin: A review. Skin Research and Technology. 2021 May;27(3):299-308. https://doi.org/10.1111/srt.12968

[44] Barua S, Mitragotri S. Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects. Nano today. 2014 Apr 1;9(2):223-43. https://doi.org/10.1016%2Fj.nantod.2014.04.008

[45] Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of Controlled Release. 2012 Nov 28;164(1):26-40. https://doi.org/10.1016/j.jconrel.2012.09.017

[46] Giannola LI, Sutera FM, De Caro V. Physical methods to promote drug delivery on mucosal tissues of the oral cavity. Expert Opinion on Drug Delivery. 2013 Oct 1;10(10):1449-62. https://doi.org/10.1517/17425247.2013.809061

[47] Dragicevic N, Maibach H. Combined use of nanocarriers and physical methods for percutaneous penetration enhancement. Advanced drug delivery reviews. 2018 Mar 1; 127:58-84. https://doi.org/10.1016/j.addr.2018.02.003

[48] Wang Y, Zeng L, Song W, Liu J. Influencing factors and drug application of iontophoresis in transdermal drug delivery: an overview of recent progress. Drug Delivery and Translational Research. 2021 Jan 23:1-2. https://doi.org/10.1007/s13346-021-00898-6

[49] Gupta DK, Ahad A, Aqil M, Al-Mohizea AM, Al-Jenoobi FI. Iontophoretic drug delivery: concepts, approaches, and applications. Advanced and Modern Approaches for Drug Delivery. 2023 Jan 1:515-46. http://dx.doi.org/10.1016/B978-0-323-91668-4.00016-2

[50] Hu L, Batheja P, Meidan V, Michniak-Kohn BB. Iontophoretic transdermal drug delivery. In Handbook of Non-

Invasive Drug Delivery Systems 2010 Jan 1 (pp. 95-118). William Andrew Publishing. https://doi.org/10.1517/17425247.3.1.127

[51] Garg T, Kumar Goyal A. Iontophoresis: drug delivery system by applying an electrical potential across the skin. Drug delivery letters. 2012 Dec 1;2(4):270-80. http://dx.doi.org/10.2174/2210304x11202040005

[52] Dhote V, Bhatnagar P, Mishra PK, Mahajan SC, Mishra DK. Iontophoresis: a potential emergence of a transdermal drug delivery system. Scientia Pharmaceutica. 2012 Mar; 80(1): 1-28. https://doi.org/10.3797%2Fscipharm.1108-20

[53] Bolhassani A, Khavari A, Orafa Z. Electroporation-advantages and drawbacks for delivery of drug, gene and vaccine. Application of nanotechnology in drug delivery. 2014 Jul 25: 369-97. http://doi:10.577/258376.

[54] Yarmush ML, Golberg A, Sersa G, Kotnik T, Miklavčič D. Electroporation-based technologies for medicine: principles, applications, and challenges. Annual review of biomedical engineering. 2014 Jul 11; 16:295-320. https://doi.org/10.1146/annurev-bioeng-071813-104622

[55] Singhal M, Kalia YN. Iontophoresis and electroporation. Skin Permeation and Disposition of Therapeutic and Cosmeceutical Compounds. 2017: 165-82. http://dx.doi.org/10.1007/978-4-431-56526-0

[56] Kwon S, Shin S, Do M, Oh BH, Song Y, Bui VD, Lee ES, Jo DG, Cho YW, Kim DH, Park JH. Engineering approaches for effective therapeutic applications based on extracellular vesicles. Journal of Controlled Release. 2021 Feb 10; 330:15-30. https://doi.org/10.1016/j.jconrel.2020.11.062

[57] Escobar-Chávez JJ, Bonilla-Martínez D, Villegas-González MA, Revilla-Vázquez AL. Electroporation as an efficient physical enhancer for skin drug delivery. The Journal of Clinical Pharmacology. 2009 Nov; 49(11): 1262-83. https://doi.org/10.1177/009127000934498 4

[58] Pahade A, Jadhav VM, Kadam VJ. Sonophoresis: an overview. Int J Pharm Sci Res. 2010; 3(2): 24-32.

[59] Seah BC, Teo BM. Recent advances in ultrasound-based transdermal drug delivery. International journal of nanomedicine. 2018 Nov 20:7749-63. https://doi.org/10.2147/ijn.s174759

[60] Sarheed O. Combination treatments of chemical enhancers with low frequency ultrasound for the

transdermal delivery of hydrocortisone. Can. J. Pure Appl. Sci. 2013 Oct; 7: 2463-73. https://doi.org/10.1517%2F17425247.2010.538679

[61] El-Kamel AH, Al-Fagih IM, Alsarra IA. Effect of sonophoresis and chemical enhancers on testosterone transdermal delivery from solid lipid microparticles: an in vitro study. Current Drug Delivery. 2008 Jan 1;5(1):20-6. https://doi.org/10.2174/156720108783331014

[62] Rao R, Nanda S. Sonophoresis: recent advancements and future trends. Journal of Pharmacy and Pharmacology. 2009 Jun;61(6):689-705. https://doi.org/10.1211/jpp.61.06.0001

[63] Ita K. Recent progress in transdermal sonophoresis. Pharmaceutical development and technology. 2017 May 19; 22(4): 458-66. https://doi.org/10.3109/10837450.2015.1116566

[64] Giri Nandagopal MS, Antony R, Rangabhashiyam S, Sreekumar N, Selvaraju N. Overview of microneedle system: a third-generation transdermal drug delivery approach. Microsystem technologies. 2014 Jul; 20:1249-72. https://doi.org/10.1007/s00542-017-3354-4

[65] Seetharam AA, Choudhry H, Bakhrebah MA, Abdulaal WH, Gupta MS, Rizvi SM, Alam Q, Siddaramaiah, Gowda DV, Moin A. Microneedles drug delivery systems for treatment of cancer: A recent update. Pharmaceutics. 2020 Nov 17;12(11):1101. https://doi.org/10.3390/pharmaceutics12111101

[66] Yu YQ, Yang X, Wu XF, Fan YB. Enhancing permeation of drug molecules across the skin via delivery in nanocarriers: novel strategies for effective transdermal applications. Frontiers in bioengineering and biotechnology. 2021 Mar 29; 9:646554. https://doi.org/10.3389/fbioe.2021.646554

[67] Mishra DK, Pandey V, Maheshwari R, Ghode P, Tekade RK. Cutaneous and transdermal drug delivery: Techniques and delivery systems. InBasic Fundamentals of Drug Delivery 2019 Jan 1 (pp. 595-650). Academic Press. http://dx.doi.org/10.1016/B978-0-12-817909-3.00015-7

[68] A Charoo N, Rahman Z, A Repka M, N Murthy S. Electroporation: an avenue for transdermal drug delivery. Current Drug Delivery. 2010 Apr 1;7(2):125-36. https://doi.org/10.2174/156720110791011765

[69] Saikumar Y, Saikishore V, Pavani K, Sairam DT, Sindhura A. Role of penetration enhancers in Transdermal

drug delivery system. Research Journal of Pharmaceutical Dosage forms and Technology. 2012 Nov 1;4(6): II. DOI: 10.5958/0975-4377

[70] Khare N, Shende P. Microneedle system: A modulated approach for penetration enhancement. Drug Development and Industrial Pharmacy. 2021 Aug 3; 47(8): 1183-92. https://doi.org/10.1080/03639045.2021.1992421

[71] Lin CH, Aljuffali IA, Fang JY. Lasers as an approach for promoting drug delivery via skin. Expert opinion on drug delivery. 2014 Apr 1;11(4):599-614. https://doi.org/10.1517/17425247.2014.885501

[72] Hsiao CY, Yang SC, Alalaiwe A, Fang JY. Laser ablation and topical drug delivery: a review of recent advances. Expert opinion on drug delivery. 2019 Sep 2; 16(9): 937-52. https://doi.org/10.1080/17425247.2019.1649655

[73] Parhi R, Mandru A. Enhancement of skin permeability with thermal ablation techniques: concept to commercial products. Drug Delivery and Translational Research. 2021 Jun; 11:817-41. https://doi.org/10.1007/s13346-020-00823-3

[74] Pozebon D, Scheffler GL, Dressler VL, Nunes MA. Review of the applications of laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) to the analysis of biological samples. Journal of Analytical Atomic Spectrometry. 2014;29(12):2204-28. https://doi.org/10.1039/D4JA00045E

[75] Becker JS, Matusch A, Wu B. Bioimaging mass spectrometry of trace elements–recent advance and applications of LA-ICP-MS: a review. Analytica chimica acta. 2014 Jul 4; 835:1-8. https://doi.org/10.1016/j.aca.2014.04.048

[76] Kim EK, Hovsepian RV, Mathew P, Paul MD. Dermabrasion. Clinics in Plastic Surgery. 2011 Jul 1; 38(3): 391-5. http://dx.doi.org/10.1016/j.cps.2011.05.001

[77] Sayed M, Tsuda Y, Matin K, Abdou A, Martin K, Burrow MF, Tagami J. Effects of mechanical abrasion challenge on sound and demineralized dentin surfaces treated with SDF. Scientific reports. 2020 Nov 16;10(1):19884. https://doi.org/10.1038/s41598-020-77035-9

[78] Stafford RJ, Fuentes D, Elliott AA, Weinberg JS, Ahrar K. Laser-induced thermal therapy for tumor ablation. Critical Reviews™ in Biomedical Engineering. 2010;38(1).

https://doi.org/10.1615/critrevbiomedeng.v38.i1.70

[79] Blackwell J, Krasny MJ, O'Brien A, Ashkan K, Galligan J, Destrade M, Colgan N. Proton resonance frequency shift thermometry: a review of modern clinical practices. Journal of Magnetic Resonance Imaging. 2022 Feb; 55(2): 389-403. https://doi.org/10.1002/jmri.27446

[80] Szunerits S, Boukherroub R. Heat: a highly efficient skin enhancer for transdermal drug delivery. Frontiers in bioengineering and biotechnology. 2018 Feb 15; 6: 15. https://doi.org/10.3389/fbioe.2018.00015

[81] Kaushik V, Keck CM. Influence of mechanical skin treatment (massage, ultrasound, microdermabrasion, tape stripping and microneedling) on dermal penetration efficacy of chemical compounds. European Journal of Pharmaceutics and Biopharmaceutics. 2021 Dec 1; 169:29-36. https://doi.org/10.1016/j.ejpb.2021.09.003

[82] Seynhaeve AL, Amin M, Haemmerich D, Van Rhoon GC, Ten Hagen TL. Hyperthermia and smart drug delivery systems for solid tumor therapy. Advanced Drug Delivery Reviews. 2020 Jan 1; 163:125-44. https://doi.org/10.1016/j.addr.2020.02.004

[83] Emeje MO, Obidike IC, Akpabio EI, Ofoefule SI. Nanotechnology in drug delivery. Recent advances in novel drug carrier systems. 2012 Oct 31;1(1). http:// DOI:10.5772/51384

[84] Hassan N, Ahad A, Ali M, Ali J. Chemical permeation enhancers for trans buccal drug delivery. Expert opinion on drug delivery. 2010 Jan 1;7(1):97-112. https://doi.org/10.1517/17425240903338758

[85] Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, Tripathi DK. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of Controlled Release. 2012 Nov 28;164(1):26-40. https://doi.org/10.1016/j.jconrel.2012.09.017

[86] Ghafourian T, Nokhodchi A, Kaialy W. Surfactants as penetration enhancers for dermal and transdermal drug delivery. Percutaneous penetration enhancers chemical methods in penetration enhancement: modification of the stratum corneum. 2015:207-30. http://dx.doi.org/10.1007/978-3-662-47039-8_13

[87] Pereira R, Silva SG, Pinheiro M, Reis S, Vale ML. Current status of amino acid-based permeation enhancers in transdermal drug delivery. Membranes. 2021 May 7;11(5):343.

https://doi.org/10.3390/membranes11050343

[88] Babu RJ, Chen L, Kanikkannan N. Fatty alcohols, fatty acids, and fatty acid esters as penetration enhancers. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Modification of the Stratum Corneum. 2015:133-50. http://dx.doi.org/10.1007/978-3-662-47039-8_09

[89] Dragicevic N, Atkinson JP, Maibach HI. Chemical penetration enhancers: classification and mode of action. Percutaneous penetration enhancers chemical methods in penetration enhancement: modification of the stratum corneum. 2015:11-27. https://doi.org/10.1159/000107575

[90] Kopecna M, Macháček M, Novackova A, Paraskevopoulos G, Roh J, Vávrová K. Esters of terpene alcohols as highly potent, reversible, and low toxic skin penetration enhancers. Scientific reports. 2019 Oct 10;9(1): 14617. https://doi.org/10.1038/s41598-019-51226-5

[91] Chen J, Jiang QD, Chai YP, Zhang H, Peng P, Yang XX. Natural terpenes as penetration enhancers for transdermal drug delivery. Molecules. 2016 Dec 11;21(12):1709. https://doi.org/10.3390/molecules21121709

[92] Fox LT, Gerber M, Plessis JD, Hamman JH. Transdermal drug delivery enhancement by compounds of natural origin. Molecules. 2011 Dec 16;16(12):10507-40. https://doi.org/10.3390%2Fmolecules161210507

[93] Furuishi T, Kato Y, Fukami T, Suzuki T, Endo T, Nagase H, Ueda H, Tomono K. Effect of terpenes on the skin permeation of lomerizine dihydrochloride. Journal of Pharmacy & Pharmaceutical Sciences. 2013 Sep 20;16(4):551-63. http://dx.doi.org/10.18433/J36890

[94] Jampilek J, Brychtova K. Azone analogues: Classification, design, and transdermal penetration principles. Medicinal research reviews. 2012 Sep;32(5):907-47. https://doi.org/10.1002/med.20227

[95] Trommer H, Neubert RH. Absorption Enhancers. Encyclopedia of Pharmaceutical Science and Technology, Six Volume Set (Print). 2013 Jul 1:1-7.

[96] Yang R, Wei T, Goldberg H, Wang W, Cullion K, Kohane DS. Getting drugs across biological barriers. Advanced Materials. 2017 Oct;29(37):1606596. https://doi.org/10.1002/adma.201606596

[97] Dąbrowska M, Starek M, Skuciński J. Lipophilicity study of some non-steroidal anti-inflammatory agents and

cephalosporin antibiotics: a review. Talanta. 2011 Oct 30;86: 35-51. https://doi.org/10.1016/j.talanta.2011.09.017

[98] Elnaggar YS, El-Refaie WM, El-Massik MA, Abdallah OY. Lecithin-based nanostructured gels for skin delivery: an update on state of art and recent applications. Journal of controlled release. 2014 Apr 28; 180: 10-24. https://doi.org/10.1016/j.jconrel.2014.02.004

[99] Lemmer HJ, Hamman JH. Paracellular drug absorption enhancement through tight junction modulation. Expert opinion on drug delivery. 2013 Jan 1;10(1):103-14. https://doi.org/10.1517/17425247.2013.745509

[100] Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL, Partapur MU. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Educ Res. 2012;2(1):32-67.

[101] Sivasankarapillai VS, Das SS, Sabir F, Sundaramahalingam MA, Colmenares JC, Prasannakumar S, Rajan M, Rahdar A, Kyzas GZ. Progress in natural polymer engineered biomaterials for transdermal drug delivery systems. Materials Today Chemistry. 2021 Mar 1; 19:100382. http://dx.doi.org/10.1016/j.mtchem.2020.100382

[102] Haimhoffer A, Rusznyak A, Reti-Nagy K, Vasvari G, Varadi J, Vecsernyes M, Bácskay I, Fehér P, Ujhelyi Z, Fenyvesi F. Cyclodextrins in drug delivery systems and their effects on biological barriers. Scientia Pharmaceutica. 2019; 87(4): 33. https://doi.org/10.3390/scipharm87040033

[103] Herman A, Herman AP. Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. Journal of Pharmacy and Pharmacology. 2015 Apr; 67(4): 473-85. https://doi.org/10.1111/jphp.12334

[104] Schmitt S, Schaefer U, Sporer F, Reichling J. Comparative study on the in vitro human skin permeation of monoterpenes and phenylpropanoids applied in rose oil and in form of neat single compounds. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2010 Feb 1;65(2):102-5.

[105] Aggarwal S, Agarwal S, Jalhan S. Essential oils as novel human skin penetration enhancer for transdermal drug delivery: a review. Int J Pharm Bio Sci. 2013 Jan;4(1):857-68.

https://doi.org/10.3390%2Fpharmaceutics15010190

[106] Rai VK, Mishra N, Yadav KS, Yadav NP. Nano emulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. Journal of controlled release. 2018 Jan 28; 270:203-25. https://doi.org/10.1016/j.jconrel.2017.11.049

[107] Fox LT, Gerber M, Plessis JD, Hamman JH. Transdermal drug delivery enhancement by compounds of natural origin. Molecules. 2011 Dec 16;16(12):10507-40. https://doi.org/10.3390%2Fmolecules161210507

[108] Cornwell PA, Barry BW. Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. Journal of pharmacy and pharmacology. 1994 Apr;46(4):261-9. https://doi.org/10.1111/j.2042-7158.1994.tb03791.x

[109] Kamatou GP, Viljoen AM. A review of the application and pharmacological properties of α-bisabolol and α-bisabolol-rich oils. Journal of the American oil chemists' society. 2010 Jan; 87:1-7. http://dx.doi.org/10.1007/s11746-009-1483-3

[110] Noriega P. Terpenes in essential oils: Bioactivity and applications. Terpenes and Terpenoids—Recent Advances. 2020 Oct 10. doi://10.5772/intechopen.93792

[111] Kim SK, Han GH, Seong W, Kim H, Kim SW, Lee DH, Lee SG. CRISPR interference-guided balancing of a biosynthetic mevalonate pathway increases terpenoid production. Metabolic engineering. 2016 Nov 1; 38:228-40. https://doi.org/10.1016/j.ymben.2016.08.006

[112] Santos KA, Gonçalves JE, Cardozo-Filho L, da Silva EA. Pressurized liquid and ultrasound-assisted extraction of α-bisabolol from candeia (*Eremanthus erythropappus*) wood. Industrial Crops and Products. 2019 Apr 1; 130:428-35. http://dx.doi.org/10.1016/j.indcrop.2019.01.013

[113] Mavandi RA. Agricultural and biochemical of german chamomile (*Matricaria chamomilla* L.). Research in medicinal and aromatic plants. 2020 Dec:135. https://doi.org/10.4103%2F0973-7847.79103

[114] Satyal P. Development of GC-MS database of essential oil components by the analysis of natural essential oils and synthetic compounds and

discovery of biologically active novel chemotypes in essential oils. http://dx.doi.org/10.1177/1934578X20933067

[115] Busca R, Ballotti R. Cyclic AMP a key messenger in the regulation of skin pigmentation. Pigment Cell Research. 2000 Apr;13(2):60-9. https://doi.org/10.1034/j.1600-0749.2000.130203.x

[116] Pan C, Liu X, Zheng Y, Zhang Z, Li Y, Che B, Liu G, Zhang L, Dong C, Aisa HA, Du Z. The mechanisms of melanogenesis inhibition by glabridin: molecular docking, PKA/MITF and MAPK/MITF pathways. Food Science and Human Wellness. 2023 Jan 1;12(1):212-22. https://doi.org/10.1016/j.fshw.2022.07.011

[117] Eddin LB, Jha NK, Goyal SN, Agrawal YO, Subramanya SB, Bastaki SM, Ojha S. Health benefits, pharmacological effects, molecular mechanisms, and therapeutic potential of α-bisabolol. Nutrients. 2022 Mar 25;14(7):1370. https://doi.org/10.3390%2Fnu14071370

[118] Seki T, Kokuryo T, Yokoyama Y, Suzuki H, Itatsu K, Nakagawa A, Mizutani T, Miyake T, Uno M, Yamauchi K, Nagino M. Antitumor effects of α-bisabolol against pancreatic cancer. Cancer science. 2011 Dec;102(12):2199-205. https://doi.org/10.1111/j.1349-7006.2011.02082.x

[119] Murata Y, Kokuryo T, Yokoyama Y, Yamaguchi J, Miwa T, Shibuya M, Yamamoto Y, Nagino M. The anticancer effects of novel α-bisabolol derivatives against pancreatic cancer. Anticancer Research. 2017 Feb 1;37(2):589-98. https://doi.org/10.21873/anticanres.11352

[120] Wu S, Peng L, Sang H, Ping Li Q, Cheng S. Anticancer effects of α-Bisabolol in human non-small cell lung carcinoma cells are mediated via apoptosis induction, cell cycle arrest, inhibition of cell migration and invasion and upregulation of P13K/AKT signalling pathway. J. BUON Off. J. Balk. Union Oncol. 2018 Sep 1; 23:1407-12. doi/full/10.1177/1934578X19850033

[121] Rocha NF, Rios ER, Carvalho AM, Cerqueira GS, Lopes AD, Leal LK, Dias ML, de Sousa DP, de Sousa FC. Anti-nociceptive and anti-inflammatory activities of (−)-α-bisabolol in rodents. Naunyn-Schmiedeberg's archives of pharmacology. 2011 Dec; 384:525-33. https://doi.org/10.1007/s00210-011-0679-x

[122] Aron de Miranda HA, Gonçalves JC, Cruz JS, Araujo DA. Evaluation of the sesquiterpene (−)-α-bisabolol as a novel peripheral nervous blocker.

Neuroscience Letters. 2010 Mar 12;472(1):11-5. https://doi.org/10.1016/j.neulet.2010.01.042

[123] Shanmuganathan B, Suryanarayanan V, Sathya S, Narenkumar M, Singh SK, Ruckmani K, Devi KP. Anti-amyloidogenic and anti-apoptotic effect of α-bisabolol against Aβ induced neurotoxicity in PC12 cells. European journal of medicinal chemistry. 2018 Jan 1; 143:1196-207. https://doi.org/10.1016/j.ejmech.2017.10.017