

Review Article

Advanced Topical Drug Delivery Systems of Essential Oils

*Shamselalah Abuelgasim Habib Allah**, *Meka V N S Kiranmai*, *Elnazir Abakar Hassan*, *Prasanna Kumar Desu*, *A Anka Rao*, *Sivadasu Praveen*, *Amareswarapu V Surrendra*

K L College of Pharmacy, Koneru Lakshmiah Education and Foundation, Vaddeswaram, Guntur-522503, Andhra Pradesh, India.

ARTICLE INFO

Article history:

Received 05 February 2022

Received in revised form 21 February 2022

Accepted 07 March 2022

doi.org/10.38111/ijapb.20210801002

Keywords:

Essential Oils, limitation of barriers, Types of TDDS, Different applications, TDDS..

ABSTRACT

Goal of this overview, the article is to keep you up to date on the latest developments in the Medication delivery system by employing the topical route of administration. The most recent study focused on advanced tactics and procedures for administering local treatment to the skin and its components in the form of Nano emulsions. Devices such as iontophoresis Electroporation magnetophoresis limiting barriers skin and skin layers, as well as liposomes, Aerosols, microneedles, aquasomes, sticky important oils, and others. This information can be used as a foundation for improving and upgrading current approaches and technology.

Introduction

The administration of medications to the human body has been used to treat illness for a very long period. Topical shipping is the administration of a drug-comprising system to the skin to feast intrathecal problems like zits or the subcutaneous manifestation of a systemic disorder like psoriasis, including purpose of limiting pharmacological or biological consequences. Semi-solid composition out of its forms conquer arrangement on topical distribution due to other effects of the drug on the skin's surface or within the skin. Foam, sprinkle, oils, attended powders, solvents, also alike cared adherent arrangements have all been utilised successfully [1]. Transportation with a vehicle. Delivering medicine at a specified place one of the most challenging elements to create is topical components. An excellent topical formula should establish a stalwart chemical climate in an acceptable distribute hamper, allowing for the coexistence of numerous compounds with distinct, if not incompatible, physicochemical features. When employing a topical treatment, there must be contact with the environment of the skin, which might affect the cost about releasing chemicals in order to accomplish optimal skin absorption. The additive each-other must have more bodily consequences on the core, just like searing, blocking, or moisturising. Science has brought a deeper grasp due to all science, and what the drug did for body even what the body did for

drug like tablets feast zit. This knowledge has guide us for advancing a modern transport structure which can improve topical formulation efficacy, tolerability, and category acceptability [1-4].

Topical medicine delivery benefits from a cooperative's ease of delivery and cop-out of presystemic metabolism. A downside is the deficiency or decrease absorption cost, as well as cosmetic considerations. Some of these obstacles might be overcome with new drug transmission automation expertise and permeation boosts. There are a few crucial points to consider as you finish developing a topical dermatological product. You've certainly worked with parenteral or oral drugs before, beside that a several challenges and concerns that are specific to the development of topical preparations with essential oils. A topical system should be aesthetically pleasing as well as physically and chemically stable, which may require the use of a large number of excipients. The chemicals should make it easier for drugs to penetrate the pores layer, which is an elaborate filigree with a PH of roughly 7-5.5. As a result, the formulation's PH may vary after it is attached to the

* Corresponding author. Tel.: +249912319200.

E-mail address: shamselalah9@gmail.com



surface layers. Over skin dermatologic factors that are successful are those that meet the product's destination form and are:

1. Physicochemical properties indestructible with a long shelf life.
2. Removes the medicine out of device then injects it through the surface layers needed for the therapeutic dose.
3. Is patient tolerable with ornamentally based.
4. Use only FDA-approved excipients that are appropriate for the disease state.
5. Is simple to follow and well-suited to the intended packing and storage.
6. Can be created with industrial scale. Almost every improvement project hits roadblock at some point.

The projects are critical to be ready to foresee issues. Avoid them as much as able to be done, there also to understand how deal with the ones that it may will happen. Because it removes gastrointestinal trespassing and presystemic medication metabolism, yeast has confirmed favourable end outcomes in contrast to oral drug delivery machines. The most significant disadvantage of TDDS is that it comes into contact with the stratum carenum surface, which allows only lipophilic capsules with a high molecular weight to get across. To improve medication penetration in between stratum carenum, liposomes, transferosomes, and ethosomes are now employed. Ethosomes vesicles are discovered to take a far further productive in handing over medicine through the pores layers ethosomes, also known as bar hydro alcoholic solution or liposomes, are asymptomatic drug delivery transporter which allow tablets to penetrate the buried pores of a skin and finally enter systemic circulation. For effective cutaneous distribution, drugs must be appropriately entrapped within ethosomal membranes. Vesicles, ethosomal medicine transport scheme is a modernization approach that is handily to make, in addition to security and efficacy.

Ethosomal is employed to supply numerous medication molecules such as acyclovir ointment, bacitracin enzyme, testosterone hormone, insulin injection, and others due to its more defined pores layer penetration, improved medicine shipping, multiplied medicine artifice effectivity, and so on. As a result, ethosomal drug transportation machines have been a popular inquiry and improvement topic for new treatments [5].

Essential oils and their use in medicine:

One of the biggest manners to love integral oils is thru topical apply or utilize of necessary oils on the pores and skin and body. We employ so multiple topical product each day like lotions, soaps, creams, skincare products, cleanser, the listing goes on and on. It come into view, essential oils can achieve multiple of the same tasks as these different topical products. Essential oils can cleanse, moisturize, soothe, nourish and more, however the pleasant parts are that they offer a safe, herbal way to do so. Because quintessential oils are appropriated from the ground, they supply a natural way to supervise our bodies. Once you research about the many topical uses for indispensable oils, it is effortless to look why they are such a helpful part of any day-by-day movements or lifestyle. However, you are new to vital oils, or simply don't have a lot of trips the use of oils topically, you would possibly be wondering, what are the benefits of topical use? Just identify a few benefits:

1. Great benefits for the skin.
2. Affords soothing, calming, warming, cooling, or energizing emotions for the body
3. Let's in the consumer to target specific areas of the physique. [6]

Perhaps one of the largest an awesome advantage of topical software is that it can assist to encourage healthful searching skin. Whether you choose to enhance the incidental pores and pores and skin flaw or defect, limit the look of hyper pigmentation, clear away skin texture, or absolutely provide you pores and skin a blooming hoist, topical use of indispensable oils probates a safe, herbal way to care for the skin. If you ever fear about toxins and synthetic fillers that may be lurking in your industrial skincare products, using pure quintessential oils gives a protected way to naturally care for your skin. In addition to get a healthy skin, using vital oils topically can additionally furnish the whole physique with benefits. Different integral oils keep chemical components that make them beneficial for calming, soothing,

or enjoyable the body, muscle tissues or joints. Other fundamental oils can produce a warming or cooling sensation on the body. Using some fundamental oils also with the aid of applying them on chest and neck. When it comes to be topical application it's handy to relieve tension, soothe or rub down stressful areas, promote clear breathing. As with any crucial oil utility method, there are unique protection pointers that will assist us to safely revel in using fundamental oils topically. While integral oils are herbal and safe, we have to observe these safety tips to keep away from sensitivity or irritation. As we use secure application practices, we will be able to see how our physique reacts to each person quintessential oil and will soon learn how to use crucial oils topically to reap benefits every oil offers. To achieve a protection topical use of integral oils, it's very important factor to remember it is dilution. Dilution did not affect the efficacy or benefits of critical oils however expanded its absorption into the skin an additionally can assist defend sensitive or delicate skin from becoming irritated. There is normally vital oils desires dilution like, cassia, cinnamon, clove, oregano and thyme. The fantastic way to dilute a fundamental oil is with a carrier oil. A provider oil refers to a base oil, usually a pure vegetable oil that carriers the fundamental oil to the desired vicinity on the pores and skin or body and helps to increase absorption in the skin. For first the use of we have to practice a small quantity of oil 1-2 drops and wait to see the body reaction and then extended dose. To protect the body from inflammation due to use indispensable oil we ought to carry out a sensitivity check earlier lab test before using and avoid sun light and UV light after applying. In additional essential oils will not apply on certain areas like, eyes and the skin around it, inside nose, genitals and injured or broken or damaged skin [7].

Topical application for essential oil:

The best places to apply essential oils to collect the awesome advantages are, on face by adding a few drops from oils on ointment or face cleanser or on coconut oil to treat wrinkles, hyper pigmentation and improve skin moistening. For temples, forehead, base of the skull and neck to promote relaxation and good feeling. In abdomen applying it to improve the digestion and avoid discomfort able. On legs, arms and back after work

or physical activity as massage. Also, on chest for clear breathing and treating the chest disorder as asthma and viral or bacterial infections. Lastly on bottoms of the feet because this area has big bores for absorption. Otherwise, there is some examples of essential oils and their medical uses: Coriander used to reduce the appearance of blemishes, Geranium used as aromatherapy facial to beautify the skin, Marjoram used to help target tired and stressed area, Melaleuca used occasional skin irritation, Peppermint rub on temples after wake for energy, Rosemary applying on scalp and abundant looking head of hair for massage, Sandal wood adding on hot water and wash for relaxation, Wild Orange used as inhaler adding with peppermint of energy, Ylang-ylang apply on neck to treat uplifting effect, *Arborvitae* for repel of insects, Basil to reduce feeling of a tension, Black Pepper for stimulating wake up, Cardamom to promote clear breathing, Cilantro on fingernails and toenails for cleaning and healthy, Clary Sage during menstrual cycle on abdomen for muscle relaxation [8].

Types of topical dosage forms used to deliver essential oils

The exterior topical is distributed, flooded, and any other way disassemble over tissue for coping disordered areas, whereas an inner topical is enforced on the tissue layer conjunctiva mucosa through oral use, by vagina, and in rectal tissue as nearby activeness. Because skin is thick and complex, chemicals travelling via a climate will pass through the epidermis or every domestic or extracellular opening according to their exterior. All of them will even break through stratum carenum, dermal papillae or capillary partitions inside blood flow and lymphoid canals, where all of them then eliminated out of the pores and surface layer thru blood or lymph stream. Crossing the skin membrane is, without a doubt, a difficult phenomenon and research mission. Physiological variables like as thickness, moisture, and temperature can all influence the topical drug transport computing device [9]. Inflammation and the PH of the skin Topical medication delivery methods come in a variety of shapes and sizes, as well as diverse formulations:

1. Creams

Creams are emulsions of water and oils, it is categorised into two, first one is oil in water (o/w) like vanishing lotions which it can spread barring issue and do no longer go away the pores and pores and skin greasy or sticky, and the second one is water in oil (w/o) like cold creams which they are Increasingly lubricated and softening. They are carrying softeners or protectives, both of those can element influence allergies [10].

2. Ointments

Ointments are semi-solid hydrocarbon preparations (petrolatum, mineral, oil, etc.).

Hydrocarbon (synthetic). Ointments have a rugged softening reaction, which made them easy thru hard skin diseases. They also have an occlusive effect, which increases the permeation due to diligent drugs along with enhances effectiveness particularly on thickens, hardened skin. Ointments provide a defensive layer over a skin e.g., ease on housewives' appendages, aggravation skin inflammation. They are oiled, gummy, and absorb skin excretion, making them unsuitable for moist bawling rash, bushy spaces, and skin crudity for redness, and they contain no water and don't need a preservative [11].

3. Pastes

Pastes are a mixture between powder and ointment. The addition of powder enhances consistency (water proofers). As we are curative

reckless, which like, a possessive an ointment basis which they allow as long as skin water proofers are chosen. The addition of powder ratio with ointment will improve a viscosity as regards to construction, fabricating pastes much arduous to rub hence. This feature comes in handy when you don't want to apply a bothersome preparation to your ordinary pores and skin (e.g., enthralling paste for treating psoriasis).

4. Lotions

Lotions is a term that is now used loosely to refer to any liquid preparation in a room. Which medical medications are suspended or dissolved, whether they are inert or energetic Lotions are oil on water emulsions contain a huge level of water motives substance that donate a damp steadfastness for the preparation. The majority of them were drenched and hydro plus alcoholic solutions, with minor quantities from alcohol mixing with for helping in the solubilisation contain assiduous substances or the vaporization about a diluent via a skin layer. They are non-sticky and drying, and they are alcoholic. Emulsion lotions frequently do not dry, depending on the water content of the textile fabric (more water and/or a lot less oil means faster drying). Lotions are essential for big regions and are particularly good considering unshaven spaces, pores and skin prostrate towards redness zit, and intertriginous spaces [12].

5. Gels

Gels are clear formulations with ethers alcohol, cellulose polymers, and carbineer suspended inside water and combination between water and alcohol in ratio. As far as closed to pores of skin, gels liquefy, hard, or chuck a slim flick about effective drug. Gels were beneficial inner bushy places also were cosmetically biddability, but they tend to be drying. [13] Layers of the skin

The skin organ described as a biggest part on human skeleton, accounting for around 10 percent of total skeleton weight [14]. A pores and skin's basic obligation via simulate obstacle contact human formation with atmosphere. UV radiation, microorganisms, allergies, and chemicals, as well as water and nutrition loss, are all protected by this barrier. Furthermore, the pores and skin are involved in a variety of functions, including heat ordinance, metabolic function, or lastly systolic and diastolic pressure conduct. The skin is in addition a vital sense organ, transmitting information about the surroundings such as temperature, pressure, and unpleasant stimulation (pain). The epidermis, dermis, and subcutaneous tissues are the three essential regions of human pores and pores and surface layers. Hair cavity, eccrine or apocrine secretion buckets are among many appendages linked with the pores and pores and skin. From a skin and skin layers impregnation standpoint, the epidermis' outermost layer, the stratum carenum, provides the necessary barrier and, as a result, drawing shut this form is crucial to constructing the most beautiful transdermal or topical sedate transport methods. The epidermis tissues, also known as an excited sheet, is made up from 10 to 20 micrometres about low-hydration, low-consistency cellular mobile sheets. Even though those sheets in between 10 to 15 cells thick, which act as a basic membrane [15]. The epidermis sheet is known similarly having a block built-looks shape, beside cubes inside array (a "Mortar") via intercellular fats [16]. An epidermis intercellular fats specific composition or skeletal configurations inside many lamellate sheets surrounded by perpetual fat region are key via a stratum corneum' membrane properties [17]. There are three types of permeants that can be used on the pores and skin Possible routes at some stage in the epidermis: across an adjunct (a), by way of the squames (b) transcellular ways, also

via an origin sheet (c) intercellular path. Those tracks are no longer at the same time exclusive, with most compounds permeating the pores and pores and skin through aggregate of pathways primarily in particular primarily based on the physicochemical residences of the pervading fragments [18]. At the same time an intercellular fats bilayers engage absolutely a little vicinity via an epidermis, whose furnish just over going course via the stratum carenum [19]. Numerous periods via lookup have tested a magnitude as concerns that pathway via sedate penetration thru an epidermis [20]. The couple of fat and antipodal particles were in a position for transferring via those intercellular way however a volume or range about spreading were specifically structured above a physicochemical home about a durable.

An impregnating approach include a chain from methods interesting up along a launch about an impregnate (a medicine) via a dose structure (agent), accompanied across means of using talent of the utilization of the use of the diffusion into and with the aid of ability of Genius of the stratum carenum, then petitioning inside a much-drenched epidermal atmospheres or absorb inside further tissues and hold via conceivable of any use of performance of the cutaneous circulation. These strategies are particularly hooked up over a dissolved or absorptivity about a penetrant internal every ambient. As a result of this massive flexibility in passably of a different sedate particle, general techniques are improved for accelerate medicine penetration across stratum corneum, some of them have been discuss in this review articles.

Limitations of barriers in topical drug delivery system

Skin consists of a different barrier which are limitation the transmission of topical drug delivery device through the layers, this impediment publications researcher to discover a suitable mechanism to help the topical pills to penetrate the pores and pores and skin and bypass via the blood circulation to the web page of action. There are many barrier boundaries in pores and skin includes:

1.1. Interfollicular Epidermis

1.1.1. Stratum carenum

The initial barrier protects the skin from the elements, and the vast majority of pills are extremely important for the absorption process when using passive diffusion. Corneocytes that were associated with Corneodesmosomes or TJ balances are included. Or fats found between cells

Corneocytes are keratinocytes that have reached the end of their differentiation. They were identified by the absence of cellular nuclei and organelles, a collection of cytokeratin filaments grouped, at the lower back

of others, by flagging, and the immediacy of an inflexible membrane enveloping them. The CE developed unique proteins like as involucrin, loricrin, short proline-rich protein, filaggrin, envoplakin, periplakin, and

others such cysteine protease inhibitors that use transglutaminases to remove liked. Desmoplakin, desmoglein1, desmocollin, and Corneodesmosin are among the proteins that make up corneodesmosomes.

Corneodesmosins are supplied with extracellular area beyond laminae frame on a grained phone sheet, where it's subsequently pooled inside desmosomes, whatever then converted to corneodesmosomes step by step.

Corneodesmosome degeneration is necessary for corneocyte desquamation and, as a result, for an orderly delivery of epidermis. Lipid lamellae are tightly packed lipid layers that line the extracellular space of

the SC. Free fatty acids, also ceramides or cholesterol, and free fatty acids were used for making them. A long and quick periodicity phases of crystalline lamellar exist, with repeat distances of 13nm for the long and 6nm for the short. Aside from that, lateral packing is crucial. The healthy skin has a dense orthorhombic packing with the most SC lipids, whereas the subpopulation has a less dense hexagonal packing. Filaggrin, CE-proteins, and Corneodesmosin are some of the amazing aspects of which including exposed for being absorbed thru pores and skin membrane activity. Due to filaggrin conversion, the victims of ichthyosis vulgaris had a defective barrier characteristic. Under mechanical strain, filaggrin-deficient animals have increased exuviation and antigen penetration. Finally, skin PH has an impact on a number of variables that regulate epidermal fence character. Proteolytic required about exfoliating or enzymes involved in fat amalgamation are examples. However, at deeper layers, such as TJs, pH is critical for environs bending about particles, also hence choice cooperation. Thus, an addition towards has immediate physical and chemical effects over administered medicine or sedate delivery device, shifts for PH due to drug transport can used for manipulating skin obstacle activity, however they can as well lead to adverse event [21].

1.1.2. Tight intersection

Tight connections are a constant impediment in the epidermis' granular layer of the epidermis. They serve as a second barrier for molecules passing via the paracellular route from the backyard to the interior. TJs in on a dermis provide an obstacle for particles about unusual size, among Biotin-SH (556 Da) being the smallest measured molecule. TJs, particularly Claudine's, can restrict the passage of chemicals in a charge-selective manner depending on their combination. As a result, ions like chloride, sodium, and calcium are less likely to flow through the cell membrane. The appearance of cloudiness in the human epidermis is the most common symptom. These are Claudine's that tighten barriers. TJs also consist of number from cross proteins, including cingulum or aberrant protein kinase C, therefore required about revetment, law, or signalling, establishing TJs cells seem to be signalling stage. The significance via TJs for the pores and body surface layers is once demonstrated separately vital to claudin-1 busted mouse on date of birth according to the extreme water leakage [22].

1.1.3. Basal Lamina

At a dermo-epidermal interface, the basal lamina was districted on a basic issue due to lode basal. It's a unique combination of matrix proteins and carbohydrates. Laminas and collagens, as well as proteoglycans like hyaluronic acid or perlecan, are important components. Those components made of an across-linked mat-like structure with a variety of comparable molecules, which is essential for the optimal setup of the dermis and, as a result, for barrier configuration. Acute pemphigoid disease is caused by autoantibodies that are funnelled to include. It was originally found that fatness of the BM is surprisingly decreased in atopic dermatitis. Generally, nettles are the degree for that a BM may it allowed an obstacle. A BM's lattice formation shows there is a commute from essences within two skin layers stratum corneum or dermis has been slowed. Inside inner-outside obstacle investigations, however, an expected transfer for proteins among the dimension about around eight Nano meter is considerable reduced. Likewise, a BM prevented the corridor from other molecules, such as the canker virus. Similarly, it has been claimed that the Basal Membrane

performs the rate-choosy obstacle in spite of bigger molecules due to its robust bad cost [23].

1.2. Hair Cavities

Hair cavities were a type of intricate structure that can be found throughout the human body. With the exception of glabrous skin HFs are subjected to cycles in which a new piece of antigen is introduced. The relaxation phase, the increase phase, the catagen degenerate part, also the telogen or exogen episode. A preponderance from Hair Cavities were into antagen, whereas just a small percentage are in catagen or telogen. Even though the world is changing, the uptake of components with the help of HFs has been demonstrated and HFs are largely from the inside out. The employment of HFs to transport drugs causes a significant halt. There are two types of human antagen HFs. most important limitations obstacle-building the TJs are continually existing among a hollowed out under for HF's outer root sheath's lower central phase. During These TJ-containing layers are incorporated in the infundibulum with the help of a non-stop SC. to the epidermis' SC The blend, on the other hand, is slightly different [24].

1.3. Glands

Skin glands, in general, are protected by barriers. Because the inside-outside flux course of cutaneous glands is no longer suitable for drug administration, certain techniques, such as iontophoresis, can be used to induce absorption into glands. Because TJs are present in glands, increased transepidermal drug delivery via TJ barrier modifying enhancers, for example, may also reduce gland barriers. As a result, this could result in side effects such as increased or decreased sweat glide or lipid release via sebaceous glands [25].

1.3.1. Sebaceous Glands

Multicellular exocrine glands that terminate in the hair shaft are known as sebaceous glands. They've done it. Claudin-1, claudin-4, claudin-7, tricellulin, and ZO-1 are TJ proteins that have been found. The TJs in the sebaceous gland constitute a barrier to anti-desmoglein-1 single chain administered intradermally. Mouse skin has a fickle divide and definition. Outside of the TJ, holocrine secretion occurs. Barrier. Claudin-1 knockout causes TJ barrier leaking in sebaceous glands, as well as incomplete plasma membrane degradation and nuclei holocrine secretion [26]

1.3.2. Sweat Glands

A TJ barrier is built into sweat glands. The existence of ultrastructure on the ultrastructural level. TJs that create a barrier in sweat glands of human skin were first discovered in the nineteenth century. The 1970s and 1980s. Occludin, claudin-1, claudin-3, claudin-4, claudin-5, claudin-6, claudin-7, claudin-8, claudin-9, claudin-10, claudin-11, claudin-12-10b and claudin-15, as well as ZO-1 and ZO-2, are found in human pores and skin, with different expression patterns depending on gland location. Claudin-1 is rarely found in barrier-forming TJs, but claudin-3, claudin-10, and claudin-15 appear to be more common. Only claudin-3, claudin-4, and claudin-10 are present in mouse skin. TJ leakage is seen in Claudin-3 knock-out mice, which is thought to be related to a decrease in sweat retention in the lumen of the top sweat gland_ less sweat. Because of a missense mutation, humans possess a lot less claudin-10b in their sweat glands. Experiments in 3D life modelling sweat secretion found that a deficient TJ stand formation perturbs paracellular sodium transport in the CLDN10B gene, which causes anhidrosis. Patients with Alzheimer's disease have less sweat and lower claudin-1, claudin-3, and claudin-15 expression [27].

1.4. Blood Vessels

The vasculature is the last barrier between the pores and the skin. A one-cell thick endothelial cell layer provides the configuration between the surrounding tissue of the pores and skin and the human vascular system, completing up in the papillary loops of the superficial arteriovenous plexus shut through to the dermo epidermal junction in the top dermis. The function of endothelium in the pores and skin is similar to that of endothelium in the rest of the body: it diligently acknowledges pressure, shear forces, osmolarity, heat, chemokines, and cytokines using rules of penetrability and evacuation of also productively managed vasodilation or constriction. In addition to route effects on permeability, such as inflammatory stimuli, the pores and skin vasculature has a physiological significance: it is the primary effector of thermoregulation by opening up vascular loops that are ordinarily closed under resting conditions. In summary, the blood vascular device of the skin must be considered in conjunction with the epidermal components of the pores and skin barrier for an assessment of the total pores and skin barrier performance [28].

Approaches for improving the skin absorption of topical medication delivery systems

To promote drug molecule penetration through the skin, those diligent approaches entail providing external power to act as an applied pressure and/or acting to lessen the surface composition of the pores and skin. Recent progress has been made in these areas. Accuracy arranging, figuring, chemical arrangement, and fabric science advancements have resulted in the creation of devices for delivering medication to the skin in order for producing the applicable medicinal event [29]. The following is a list of current topical medicine administration strategies or gadgets.

1. Ultrasonography (phonophoresis and sonophoresis)

Ultrasonography refers to an application of sonographic power to facilitate the topical patches transfer of solvent beside by chance in turn through the use of a pre-treatment method and is also known as Sonophoresis or Phonophoresis. On exposure to ultrasound, the advance mechanism in the back of the expand in pores and skin possibilities is produced, leading in the formation of gaseous cavities within the intercellular lipids, resulting in the separation of the skin's subcutaneous layer. Ultrasound, also known as Sonophoresis, is a technique that increases the absorption of topical mixtures into the epidermis, dermis, and skin adjuncts quickly. Ultrasound waves excite micro-vibrations inside the skin dermis, which improve the regular kinetic electricity of molecules that make up topical methods, resulting in sonophoresis. It's commonly used in sanatoriums to give medicines via the skin [30].

2. Radiofrequency

It entails exposing the skin to a high-frequency alternating current of one hundred kHz, which exposes the production of warmth-induced micro channels in the skin's membrane, similar to when laser radiation is utilised. The number and depth of the tiny channels produced by the device are used to manage the cost of medicine transportation. Which is based on the homes of the device's microelectrodes [31].

3. Magnetophoresis

Magnetophoresis is a way to software utility of magnetic field that is effective in enhancing medication penetration in the route of the herbal borders. It has been demonstrated that magnetophoresis guides to accelerate transdermal drug transfer in both in vitro and in vivo studies are a powerful

method for drug penetration enhancement. To be magnetic kinesis and much more amazing drug partitioning into the stratum corneum [32].

4. Iontophoresis

Iontophoresis is a method of increasing drug absorption into the pores and pores and skin using software from an electric driven current. The capsules are placed under an electrode that has the same frequency as the medication, and the response electrode that is antithetical through alteration to the medicine is arranged on an impartial web page over bod shell. The flow about atoms through all pores and layers is aided by electrical strength. The principle of like fees repels all special and contrasting value attracts [33].

5. Electroporation

By using brief and powerful electric pulses that briefly penetrative the telephone tissue layer, electroporation is utilised to assist deliver medicines or genes into the cell, allowing transfer of molecules that would otherwise not be transferred via a mobile membrane. As soon as an atoms starts transferred are a cytotoxic drug or a genome, which method is called electrochemotherapy, and the eletrotransfere is DNA. Even yet, further medical data on the approach's safety and efficacy is forced to verify an intended marketable command [34].

6. Photomechanical waves and laser radiation

The effects of lasers on organic tissue layer have been widely corroborated in scientific treatments for decapods. Dermatological disorders are routinely treated with lasers. For example, laser radiation is employed to destroy the target cell over a 300nm time span to treat acne and offer facial reanimation. The SC is ablated as a result of the pores and skin being exposed to laser light in such a controlled and direct manner. Without causing considerable harm to the epidermis beneath it has been demonstrated that removing the skin's subcutaneous layer increases the transfer of lipophilic and hydrophilic medications [35].

Topical Drug Delivery Systems with a Twist

Every advanced current medicine administration strategies are explained in the following sections:

1. Foams that can be sprayed

Aerosol foams have been increasingly popular as topical treatments for a variety of skin disorders, such as acne vulgaris. The foam's auto foundation can be liquid or semi-solid, with the same physicochemical properties as typical carrier vehicles such as creams or gels, and lotions, or may have ideal features such as dampen, rapid searing performs, and elevated drug bioavailability. An arrested of aerosols are disseminated by releasing foams from the gas-pressurized container. The type of elements and the dosage container that are chosen to fulfil the specific therapy requirements determine the depth, globule extent, flexibility, viscosity, density, resolution, mobile nature, and unfold incapacity of the product. The form bubbles can also be used as cleansers on big hairy areas as in chest area and back and also face because they are easier to apply.

2. Liposomes

Liposomes are artificially manufactured lipid bilayer vesicles that are widely utilised as cars in prescribed capsules and cosmetics for controlled drug delivery to specific sections of the pores and pores skin or its layers. Liposomes are spherical vesicles with a membrane made up of amphiphilic lipids (lipids that are hydrophilic on one side and lipophilic on the other),

enclosing an aqueous core, similar to the bilayer membranes found in living cells. Because liposomes provide an amphiphilic environment, hydrophilic properties in their aqueous core and lipophilic components in their lipid bilayer could be encapsulated. This unique twin launch function permits the transfer of two various types of components as soon as they are applied to the skin, each with its own set of consequences for pores and skin permeability. This may also enhance the desired therapeutic outcome [36, 37].

3. Nano Emulsions

Nano emulsions are a type of emulsion that can be either w/o or o/w. The dispersion like water is used to identify and characterise water type formulations. When blended, the droplets are quite minute. Nano emulsions have a unique need that must be met. Other thermodynamic prerequisites, such as certain thermodynamically circumstances, specialised assembling techniques, or that surfactants may stabilise the tiny droplets, will no longer develop naturally in addition to the Nan emulsions. Because Nano emulsions are effective at delivering lipophilic coalesce through the pores layer, they could exist a viable vehicle to use in zit for increasing the permeation the energetic chemicals into a lipophilic environment of the pilosebaceous unit. Furthermore, Nano emulsion particles will no longer clog pores and may have other therapeutic benefits, such as improved hydration and skin viscoelasticity.

4. Polymer

Formulations have benefited greatly from the use of polymers. Huge particles made

Up by monomers (repeated formational components) which are bonded together by coordinate chemical bonds. Hall of molecules are the assembling blocks of innate products such as amber and paper, as well as organic ide, with both adaptable has fuelled pharmaceuticals industry developments that meet a wide range with therapeutic needs. In dermatology, for example, novel acyclic – acid polymers that transform into a gel in the presence of water by trapping water in microcells have been developed. Hydrophilic chemicals can remain in solution inside these aqueous microcells, while water- insoluble forms can act disseminated in dispersed systems. The finished product is a durable same like gel device which are simple to employ and delivers the occupied substance as soon as it is applied to the skin. Other excipients, such as moisturisers and emollients, can also be added to these polymer-based gels to improve therapeutic outcomes. This innovative polymer-based gel science, which is well-known for its efficacy and tolerability, is used in recently announced anti-zit preparations which mix clindamycin 1 percent and benzoyl peroxide 5 percent. One of the polymer types utilised in topical solutions is widely used in the development of better pores and skin delivery mechanisms.

5. Dendrimer

Dendrimers have lately been employed in cutting-edge Trans dermally and topically drug delivery schemes, resulting in enhanced remedy solubility, also controlled medicine release. Derivatives, drug polymers coalesces, and drug release all amount of viscosity that is generated. The ability to work with highly specialised dendrimer formulations for certain applications is a feature of dendrimer solutions. Dendrimer as a transdermal and topical drug transport building block has been found to boost antiviral drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and antibacterial,

antihypertensive, and cytotoxic medications. Ketoprofen and diflunisal, two NSAIDs, have been studied as possible skin patches scheme using Poly amidoamine. The Poly amidoamine device which found to have quicker transdermal drug delivery than formulations that did not contain dendrimers. In vivo studies in mice indicated persistent pharmacodynamics replications and 2.73-fold greater bioavailability over the course of twenty-four hours for certain dendrimer-containing drug solutions.

6. *Micro sponges*

It is a one-of-a-kind technique that allows for the controlled launch of topical dealers.

Microporous beads with a diameter of 10-25 microns and a charge of energetic mediums. If enforced to the pores and layers surface, the MDS releases its full complement of extended ingredients over time and in response to various stimuli such as rubbing, as seen Cosmetics, OTC skin care, sun blockers, and convention drugs are all examples of this. These are physiologically inactive molecules made by synthetic resins that can retain an active ingredient in amount equal to their own weight. The particles also preserve the entrapped active component from deterioration in the body and the environment. Microsponges can be used in a diversity of preparations, but gels are one of the most popular. When dispatched on the skin, micro sponges gradually release the active ingredients.

7. *Emulsifier-free formulation*

For dermatological and class products, emulsifier-free formulations are becoming more popular. The additives-free preparations are easy for use, they are well suited for oil-water emulsions, giving a fluxing fabric through a smooth skin sensation and dispersion ease. Emulsions, which are a component with two or over, substances which they have no longer mixable of one to another, are used in the majority of cosmetics and skin care products. According to the second rule of thermodynamics, they are innately unstable as a conclusion. As a consequence, surfactants such emulsifier agents are needed to stabilise the components and give a lengthy expire date. Likewise, these marketer surfactants emulsify and resist the herbal substances when dispatched to the skin. Epidermis lipoid are lipids found in the epidermis. As a result, the pharmaceutical company has been working on generating free surface-active agents of emulsions as an alternative for traditional preparations by employing stabilisers just like microporous emulsifiers and secure molecules. Sufficiently impervious merchandise due to a cosmetically first-class looks.

8. *Buckminsterfullerenes*

Buckminsterfullerene's are carbon-based compounds that appear a dented sphere and have a wide range of biological capabilities. Fullerenes are magnificent energetic molecules found in the elements of pores and skin care products because of their capacity to quench oxygen's reactive species (ORS). It means that fullerenes move through the pores and skin. Intercellular as quickly as they come into touch with the skin, as opposed to passing through cells¹². As a result, a fullerene must be utilised to "trap" the molecule. When active chemicals are applied to the skin, they are released into the dermis. Furthermore, fullerenes are thought to be powerful antioxidants in and of themselves. Fullerenes are well tolerated, according to the literature, and they show significant potential in dermatologic and cosmetic applications [40, 41].

9. *Dynamic Foams*

Pharmaceutical dynamic foams aren't novel; in fact, they've been used on skin surface therapy for more than three decades. Foam formulations, on

the other hand, have become increasingly fashionable, more than a hundred illness people filed worldwide in the last ten years alone. It has been announced that foam machinery would be used to administer a variety of diligent topical mediums, such as sunscreens, antibiotics, steroids, antiviral, and antifungal agents. Much as topical foams have a number of advantages, including better patient acceptance, the fundamental cause for their speedy adoption is that they work. In the very competitive dermatological market, as classy, attractiveness, and cosmetically pleasing autos, they deliver a substitute, potential system approach. Although there are numerous records demonstrating the certain form of topical foams, a little medical evidence to show that foams are superior to other topical autos just like ointment and creams for medication transmission [42].

10. *Lipid Nanoparticles in Solid Form*

Lipid and solid nanoparticles (NLS) have proven to be an effective sedate transmission technology for a wide range of drugs. Their total achievement when dispatched over skin surface which is not completely investigated due to the intricacy of their composition and structure. Drugs can be directed systemically to the dermis's vasculature, locally to the pores and skin layers, or externally to the skin, according to theory. As a result, the therapeutic aims of the topical transport car must be considered when designing it. It is critical for deciding a sample of medicine release through the SKN formulation to comprehend drug permeation behaviour. The manufacturing method of the vehicle has been linked to a wide range of one-of-a-kind drug release patterns [43].

11. *Ethosomes*

The ethosomes are vesicular carriers that carry hydro alcoholic or fatty acids.

Glycolic/hydro/alcoholic Phospholipid with an extremely high concentration. Phospholipids such as, hydrogenated PC, Phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, Phosphatidic acid (PA) phosphatidylcholine (PC) alcohol (ethanol or isopropyl alcohol), water, and propylene glycol can all be found in ethosomes (or another glycol). Such a formulation allows for the passage of high concentrations of energetic components through the skin. The ratio of water to alcohol or water to alcohol-propyl can be changed to control drug transport. Soya phospholipids, such as phospholipon90, are among of the most coveted phospholipids. That's often used at the concentration of between 0.5 to 10% w/w. lipid profiles in scope of concentrations which is start from 0.1 to 1% they also can be combined on the recipe. Ethanol and isopropyl alcohol are two types of alcohol that can be used. Propylene glycol and transcitol are two glycols that are commonly used. Not ionized surface agents like PEG-alkyl ethers they also was included with the phospholipids by those formulations. Macrocyclic lipids such as coco alkyl amines, cetrimide, and others can also be introduced. The final product's alcohol percentage might in duration from 20% until 50%. The content of anhydride modified portion glycol and alcohol mixture can also vary between 22 and 70% [44].

12. *Microneedles*

For medications and immunizations that have been deemed ineffective via other routes, the needle or syringe compound they turn a go-to transfare technique, and it has been optimised as a commodity size product all over the world. As a result, it's no surprise that the needle structure we're all too familiar with is the main point of the first micro device for drug delivery:

Microneedles. Rather than harming the epidermis, microneedle therapy rejuvenates the pores and skin. These microneedle units are made using micromolding, microfabrication, micro sculpting, and a combination of these technologies. Microneedles has a numeral of conceivable advantages for thickness people, doctors, and also pharmaceutical industry as compared to alternative transportation techniques. The word "needle-phobes" refers to a group of people, particularly children. In addition, many patients, just like diabetic patient, are dependent upon a few injections every day. The application of treatment substances for a skin surface is involved in many other ailments, and the onset of a pandemic is one of them. Microneedles are said to be painless and remove the skin's natural barrier. Would entail mass immunizations. Microneedles have been developed as a remedy to the challenges caused by needle-based injections. This technological expertise will contribute in the creation of modern and enhanced instruments that are minor, less expensive, painless, and much useful in the number of biomedical and different uses. ALZA Corp. recently launched Macro flux, a microneedle technology that may be used with a pill reservoir and with arid covering the drug upon the micro projection batch, with the final being good for subcutaneous immunisation.

13. The Skin Abrasion

A top layer is directly eliminated or disrupted using the abrasion approach.

Permeation of topically applied medications is facilitated by the pores and skin. Apart of those instruments are built of dermatologist-developed methods for skin surface show up e.g. microdermabrasion, those who recycled to treat zits, blemish, hyperpigmentation, and different skin imperfections. Microscissuining are the procedure that uses sharp microscopic metal grains to erode the skin's impermeable outer layers, resulting in micro channels. Carlisle Scientific is now working on the microscissioner, a pen-like portable technology. Med Pharm Ltd, on the other hand, freshly developed the D3S dermal abrasion instrument for the delivery of arduous-to-articulate medicines including hydrophilic with little molecular weight compounds and bio pharmaceuticals. In vitro studies have shown that injecting angiotensin into the kidneys is effective. Pores and skin increase 100-fold in contrast to untreated human skin. According to histology research on human skin, the epidermis findings are resolvable and balmy.

14. Cyclodextrins

Cyclodextrins have a hydrophilic base and lipophilic characteristics. Cavity in the heart Many lipophilic water-soluble medicines can be combined with cyclodextrins to generate water-soluble inclusion complexes. Lipophilic particles on a bathed elaborate medium fight about arrange through chamber, while sedate particles on a central hole of an aqueous solution which is as an energetic balance added to separate sedate particles. Due to their size and hydrophilicity, cyclodextrins and drug/cyclodextrin complexes can only pass lipophilic biological barriers in modest concentrations, such as healthy skin. In general, cyclodextrins improve topical drug transport due to enlarging medicine accessibility on a fence exterior. From a Cyclodextrins cavity, sedate particles division into a lipophilic barrier at surface. As a result, drug transport from aqueous Cyclodextrins alternatives is controlled by diffusion. In which a presence of water, seems the cyclodextrins may only improve skin surface medicine transfer [45].

15. Aquasomes

Aquasomes are a new type of transportation system that has been invented recently. As peptide and protein transporters, they're carving out a niche. This is a three-layered self-assembled Nano particulate service system. They have a solid monocrystalline core that is lined in the company of poly hydroxyl macromolecule and biochemical an operative small particle which were occupying on it. Structural stability is ensured by the robust core. The carbohydrate coating, on the other hand, serves as a protective layer. Dehydration is avoided by taking this supplement. And the biochemically agile molecules were balanced. Aquasomes' ability to support the configuration integrity of bioactive compounds has led to speculation that they could be used as a delivery vehicle for peptide-based medications. The shipping machine is now operational. Insulin, haemoglobin, and a variety of antigens have all been successfully shipped [46].

Conclusion:

As a result of our current review, it appears that alternate medication delivery systems for critical oils are now focusing on discrete research initiatives. For ill people, inventing non-compulsory innovative medicine shipping gadgets of essential oils for topical administration based on the aforesaid aspects is highly important. Researchers are concentrating their efforts on medication delivery systems via the transdermal channel. Because of the numerous benefits and greatest use, the New Year is regarded as one of the best components. Returning to nature and avoiding chemical components pave the way for further advancement in this subject. Using new units and modern-day techniques in transdermal drug shipping of essential oils is until now on an inopportune platform due to marketable for optimising extraordinary transport through the top-notch merchandise for the public.

Acknowledgements

Authors are thankful to the Registrar, Koneru Lakshmaiah Education Foundation, Guntur, India. for providing necessary facilities and actions towards the fruitful completion of this manuscript.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

References

1. Lee, A.Y. Molecular Mechanism of Epidermal Barrier Dysfunction as Primary Abnormalities. *Int. J. Mol. Sci.* 2020, 21, 1194.
2. Basler, K.; Bergmann, S.; Heisig, M.; Naegel, A.; Zorn-Kruppa, M.; Brandner, J.M. The role of tight junctions in skin barrier function and dermal absorption. *J. Control. Release* 2016, 242, 105–118.
3. Yokouchi, M.; Kubo, A. Maintenance of tight junction barrier integrity in cell turnover and skin diseases. *Exp. Dermatol.* 2018, 27, 876–883.
4. Patzelt, A.; Ledermann, J. Recent advances in follicular drug delivery of nanoparticles. *Expert Open. Drug Delivery.* 2020, 17, 49–60.

5. Ishida-Yamamoto, A.; Igawa, S.; Kishibe, M.; Honma, M. Clinical and molecular implications of structural changes to desmosomes and corneodesmosomes. *J. Dermatol.* 2018, 45, 385–389.
6. Cangkrama, M.; Darido, C.; Georgy, S.R.; Partridge, D.; Auden, A.; Srivastava, S.; Wilanowski, T.; Jane, S.M. Two Ancient Gene Families Are Critical for Maintenance of the Mammalian Skin Barrier in Postnatal Life. *J. Investing. Dermatol.* 2016, 136, 1438–1448.
7. van der Velden, J.J.; van Geel, M.; Nellen, R.G.; Jonkman, M.F.; McGrath, J.A.; Nanda, A.; Sprecher, E.; van Steensel, M.A.; McLean, W.H.; Cassidy, A.J. Novel TGM5 mutations in acral peeling skin syndrome. *Exp. Dermatol.* 2015, 24, 285–289.
8. Karim, N.; Phinney, B.S.; Salemi, M.; Wu, P.W.; Naeem, M.; Rice, R.H. Human stratum corneum proteomics reveals cross-linking of a broad spectrum of proteins in cornified envelopes. *Exp. Dermatol.* 2019, 28, 618–622.
9. Monash, S.; Blank, H. Location and reformation of the epithelial barrier to water vapor. *AMA Arch. Derm.* 1958, 78, 710–714.
10. Rancan, F.; Giulbudagian, M.; Jurisch, J.; Blume-Peytavi, U.; Calderon, M.; Vogt, A. Drug delivery across intact and disrupted skin barrier: Identification of cell populations interacting with penetrated thermoresponsive nanogels. *Eur. J. Pharm. Biopharm.* 2017, 116, 4–11.
11. Parhi, R.; Suresh, P.; Patnaik, S. Physical means of stratum corneum barrier manipulation to enhance transdermal drug delivery. *Curr. Drug Deliv.* 2015, 12, 122–138.
12. Sklar, L.R.; Burnett, C.T.; Waibel, J.S.; Moy, R.L.; Ozog, D.M. Laser assisted drug delivery: A review of an evolving technology. *Lasers Surg. Med.* 2014, 46, 249–262.
13. Asfour, M.H. Advanced trends in protein and peptide drug delivery: A special emphasis on aquasomes and microneedles techniques. *Drug Deliv. Transl. Res.* 2020.
14. Del Rio-Sancho, S.; Lapteva, M.; Sonaje, K.; Bohler, C.; Ling, V.; Boehncke, W.H.; Kalia, Y.N. Targeted cutaneous delivery of etanercept using Er: YAG fractional laser ablation. *Int. J. Pharm.* 2020, 580, 119234.
15. Kezic, S.; Jakasa, I. Filaggrin and Skin Barrier Function. *Curr. Probl. Dermatology.* 2016, 49, 1–7.
16. McLean, W.H. Filaggrin failure-from ichthyosis vulgaris to atopic eczema and beyond. *Br. J. Dermatology.* 2016, 175, 4–7.
17. Kawasaki, H.; Nagao, K.; Kubo, A.; Hata, T.; Shimizu, A.; Mizuno, H.; Yamada, T.; Amagai, M. Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J. Allergy Clin. Immunology.* 2012, 129, 1538–1546.
18. Thyssen, J.P.; Jakasa, I.; Riethmuller, C.; Schon, M.P.; Braun, A.; Haftek, M.; Fallon, P.G.; Wroblewski, J.; Jakubowski, H.; Eckhart, L.; et al. Filaggrin Expression and Processing Deficiencies Impair Corneocyte Surface Texture and Stiffness in Mice. *J. Investig. Dermatology.* 2020, 140, 615–623.
19. Niehues, H.; Schalkwijk, J.; van Vlijmen-Willems, I.; Rodijk-Olthuis, D.; van Rossum P. Epidermal equivalents of filaggrin null keratinocytes do not show impaired skin barrier function. *J. Allergy Clin. Immunology.* 2017, 139, 1979–1981 e1913.
20. Kezic, S. Loss-of-function mutations in filaggrin gene and malignant melanoma. *J. Eur. Acad. Dermatology. Venereal.* 2018, 32, 193.
21. Proksch, E. pH in nature, humans and skin. *J. Dermatology* 2018, 45, 1044–1052.
22. Sharma, S.; Kaur, T.; Malhotra, S.K.; Rai, J.; Chaudhary, S. Correlation of Vitamin D3 Levels and SCORAD Index in Atopic Dermatitis: A Case Control Study. *J. Clin. Diagnostic. Res.* 2017, 11, WC01–WC03.
23. Marenholz, I.; Rivera, V.A.; Esparza-Gordillo, J.; Bauerfeind, A.; Lee-Kirsch, M.A. Association screening in the Epidermal Differentiation Complex (EDC) identifies an SPRR3 repeat number variant as a risk factor for eczema. *J. Investig. Dermatology.* 2011, 131, 1644–1649.
24. Catunda, R.; Rekhi, U.; Clark, D.; Levin, L.; Febbraio, M. Loricrin downregulation and epithelial-related disorders: A systematic review. *J. Dtsch. Dermatology. Ges.* 2019, 17, 1227–1238.
25. Moosbrugger-Martinz, V.; Jalili, A.; Schossig, A.S.; Jahn-Bassler, K.; Zschocke, J.; Schmuth, M.; Stingl, G.; Eckl, K.M.; Hennies, H.C.; Gruber, R. Epidermal barrier abnormalities in exfoliative ichthyosis with a novel homozygous loss-of-function mutation in CSTA. *Br. J. Dermatology.* 2015, 172, 1628–1632.
26. Muttardi, K.; Nitoiu, D.; Kellsell, D.P.; O’Toole, E.A.; Batta, K. Acral peeling skin syndrome associated with a novel CSTA gene mutation. *Clin. Exp. Dermatology.* 2016, 394–398.
27. Rice, R.H.; Durbin-Johnson, B.P.; Ishitsuka, Y.; Salemi, M.; Phinney, B.S.; Rocke, D.M.; Roop, D.R. Proteomic Analysis of Loricrin Knockout Mouse Epidermis. *J. Proteome Res.* 2016, 15, 2560–2566.
28. Boczonadi, V.; Maatta, A. Functional Analysis of Periplakin and Envoplakin, Cytoskeletal Linkers, and Cornfield Envelope Precursor Proteins. In *Methods in Enzymology*; Elsevier: Amsterdam, the Netherlands, 2016; Volume 569, pp. 309–329.
29. Takeda, M.; Nomura, T.; Sugiyama, T.; Miyauchi, T.; Suzuki, S.; Fujita, Y.; Shimizu, H. Compound heterozygous missense mutations p.Leu207Pro and p.Tyr544Cys in TGM1 cause a severe form of lamellar ichthyosis. *J. Dermatology.* 2018, 45, 1463–1467.
30. Has, C. Peeling Skin Disorders: A Paradigm for Skin Desquamation. *J. Investig. Dermatol.* 2018, 138, 1689–1691.
31. Leclerc, E.A.; Hucheng, A.; Mattiuzzo, N.R.; Metzger, D.; Chambon, P.; Ghyselincq, N.B.; Serre, G.; Jonca, N.; Guerrin, M. Corneodesmosin gene ablation induces lethal skin-barrier disruption

- and hair-follicle degeneration related to desmosome dysfunction. *J. Cell Sci.* 2009, 122, 2699–2709.
32. Grubauer, G.; Elias, P.M.; Feingold, K.R. Transepidermal water loss: The signal for recovery of barrier structure and function. *J. Lipid Res.* 1989, 30, 323–333.
 33. Sajic, D.; Asiniwasis, R.; Skotnicki-Grant, S. A look at epidermal barrier function in atopic dermatitis: Physiologic lipid replacement and the role of ceramides. *Skin Thera. Lett.* 2012, 17, 6–9.
 34. Kihara, A. Synthesis and degradation pathways, functions, and pathology of ceramides and epidermal acylceramides. *Prog. Lipid Res.* 2016, 63, 50–69.
 35. Bouwstra, J.A.; Honeywell-Nguyen, P.L.; Gooris, G.S.; Ponc, M. Structure of the skin barrier and its modulation by vesicular formulations. *Prog. Lipid Res.* 2003, 42, 1–36.
 36. Misra A, Pal R, Majumdar SS, Talwar GP, Singh O. Biphasic testosterone delivery profile observed with two different transdermal formulations. *Pharm Res* 1997; 14:1264-8.
 37. Thacharodi D, Rao KP. Rate-controlling biopolymer membranes as transdermal delivery systems for nifedipine: Development and in vitro evaluations. *Biomaterials* 1996; 17:1307-11.
 38. Mukhopadhyay A, Mukhopadhyay B, Basu K. Circumvention of multidrug resistance in neoplastic cells through scavenger receptor mediated drug delivery. *FEBS Lett* 1995; 276:95-8.
 39. Nanda A, Khar RK. Pulsed mode constant current iontophoretic transdermal delivery of propranolol hydrochloride in acute hypertensive and normotensive rats. *Indian Drugs* 1998;35:274-
 40. Rao MY, Vani G, Chary BR. Design and evaluation of mucoadhesive drug delivery systems. *Indian Drugs* 1998; 35:558-65.
 41. Murthy NS, Sathesh M. Enhancer synergism of propylene glycol and PEG -400 in terbutaline sulphate transdermal drug delivery systems. *Indian Drugs* 1997; 34:224-6.
 42. Tatapudy H, Madan PL. Benzoyl peroxide microcapsules I. preparation of core material. *Indian Drugs* 1995; 32:239-48.
 43. Kshirsagar NA, Gokhale PC, Pandya SK. Liposomes as drug delivery system in leishmaniasis. *J Assoc Physicians India* 1995; 43:46-8.
 44. Kshirsagar NA, Bodhi PV, Kotwani RN. Targeted drug delivery in visceral leishmaniasis. *J Par Dis* 1997; 21:21-4.
 45. Banerjee G, Nandi G, Mahato SB, Pakrashi A, Basu MK. Drug delivery system: Targeting of pentamidines to specific sites using sugar grafted liposomes. *J Antimicrobial Chemotherapy* 1996;38:145-148.
 46. Sharma D, Chelvi TP, and Kaur J, Ralhan R. Thermosensitive b liposomal Taxol formulation: Heat-mediated targeted drug delivery in murine melanoma. *Melanoma Res* 1998; 8:240-4.