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New Approaches in Topical Delivery Through Using Various Permeation Barrier Enhancers

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Abstract: Topical delivery of drug is an appealing ways of conservative way in administrating for systematic therapeutics. Human skin is refractive to most molecules, particularly hydrophilic ones, in spite of the existence of trans-barrier route. Overcoming the logical obstacle of skin transportation has become one of issue to design delivery systems of transdermal drug. The crucial of preserving this protective barrier after breaching nano-sized (5 nm - 10 μm) skin surface is for purposes of transdermal drug delivery. Alternatively, sufficient deformable and stable nano-sized carriers can help in achieving controlled and reliable drug delivery across skin barrier. Their ability to act as drug carriers on, in and ideally below skin barrier(s) must be preserved. A proper design of self-regulating, ultra-adaptable and stable hetero-aggregates can overt spontaneously and deliver drugs through primary skin barrier and minimizing the cutaneous drug clearance; this grants deep/targeted deposition and prolonged action of the carrier-transported drugs. Therapeutic products based on ultra-adaptable self-regulating, nano-sized (~100nm) carriers are under development. In meantime, there is tremendous potential to overcome the skin barrier in enhancing transport of drug molecules offered by chemicals. However, single chemicals are limited in their efficiency to interfere low concentration's skin barrier and will cause skin irritation at most for high concentration's skin barriers. However, chemical mixtures made up by many components resulted in supplying lofty potency to permeate the skin in contrast with single chemicals that not necessary cause irritation. This write-up is an overview on systems of chemical mixtures' employed synergistic offering a better process of enhancing permeation of skin.

Key words: Self-regulating · Ultra-adaptable · Stable hetero-aggregates · Multicomponent mixtures · Synergistic mixtures

INTRODUCTION

Oral delivery is the simplest and most appropriate method in transporting drugs particularly when reiterated or when need a regular administration [1]. However, the benefit is unacceptable for drugs that are made up by peptide and protein and delicate towards degradation of enzymes within gastro- intestinal stream. Protein and peptide-based drugs derived from therapeutic spectrum's fraction, in primary caused by advanced acceleration to understand interactions of protein chemistry and drugs. In terms of the number of approved products, transdermal delivery is successful controlled release technologies, which are on the market [2]. A successful development and marketing of transdermal delivery systems (TDS) for several drugs has been led by the feasibility of transdermal route of systematic drug delivery. There will be many more types of drugs be included in the list of

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successful TDS formulations. In present, a number of drug classes are under investigation in identifying their potential for TDS development. There is a rate-limiting step in delivering most of the drugs which is penetration of stratum corneum and a considerable activity towards different percutaneous penetration enhancement technologies has been led by this step [3]. A study on chemical penetration enhancement has been done most extensively and a leading role had been expected to happen in the introduction of more TDS goods. After oral administration, it experiences an extra-ordinary first-pass metabolism and is eliminated quickly with a biological half-life of 2 h [4, 5]. The properties of drugs in term of physicochemical, pharmacokinetic and pharmacological make it well suited for TDS development. Ogiso *et al*. [6] illustrate higher skin permeation *In vitro* and in vivo, with the use of penetration enhancers in rabbits. A drug reservoir acts as a solution or gel within the impermeable backing laminate and a rate controlling membrane is consist in reservoir-type TDS. Both microporous (e.g. polypropylene) or nonporous polymeric membrane (e.g, ethylene vinyl acetate copolymer with a particular drug permeability) can be as the rate controlling membrane. There is a thin layer of drug/enhancer compatible, a pressure sensitive adhesive polymer, on the outer surface of the polymer membrane which acts in providing intimate contact of TDS with skin surface [7, 8]. Using this technology, a numbers of TDS have been successfully developed and being approved by FDA for marketing, e.g, Transderm-Nitro EstradermTM, DuragesicTM [9, 10]. The aim for the present investigation was to evolve a reservoir-type of TDS by chemical mixtures employed with synergistic which give better enhancement of skin permeation. In order to optimize transiting process of mixtures chemicals from a reservoir-type TDS through skin as permeation barrier, the skin penetration enhancer was investigated.

Permeation Enhancement's Chemical Methods

Chemical Permeation Enhancers: A number of chemicals can pair with skin in a reaction and interfere with the structure of highly lipid bilayer in forming a prime obstacle in diffusing of exogenous molecules. The surveillance can act as guidance for the study on chemical agent in improving transportation through the skin. A study has been done to identify the ability of 300 chemicals that acts as enhancers in skin permeation or penetration in increasing the drug molecules transportation within human skin. Recently, almost all study investigates the approach for advantages that they offer on physical methods of transdermal drug permeation enhancement which represented by permeation enhancers. They are low-cost and uncomplicated to formulate, flexible-design, easy to apply and give freedom for self-administration of the patient. At last, active therapeutic can be reacted together with chemical enhancers and become a topical gel or cream, or a sticky route of skin that will be used at any body's part in a continuous systematic delivery of drug. Generally, a broad group with varied functional groups of chemical is contained in permeation enhancers and act by varied mechanisms to enhance drug transport. We are using 'chemical enhancers' term in this review to incorporate chemicals with a wide range as discussed in Section 3 same with a number of system that is complex arise of combination of particular chemicals (in the presence of therapeutic or not) like colloids, eutectic mixtures, inclusion complexes, vesicles and microemulsions as discussed in Section 5. Chemical enhancers display broad excipient effects range towards the prime use of participation in permeabilizing the skin too. These also including drug solubility's improvement, aesthetic traits' improvement like smell, texture, color, acts as preservatives, fillers and emulsifiers, but they are not limited to these. This review's purpose is to aim the chemical enhancers' prime stake as agents of skin permeabilization.

Chemical Permeation Enhancers' Action Mechanism: Enhancers in permeation can improve the transportation of drugs within the skin with group with varied mechanisms. These may affect the structure of skin with an action at corneocytes or intercellular lipids, stratum corneum's dead cells directly. They also may be categorized into groups of two by the acts at skin's intercellular lipids [11]. By creating drug diffusion route in permeating through, they can extract the lipids or by partitioning themselves into lipid bilayers, they can disrupt and caused fluidization of the highly ordered lipid lamellae [11-13]. With the presence of chemical enhancers, lipid extraction and fluidization can happen via various mechanisms [12]. In alternate, skin transport of a drug can be improved using chemical enhancers by enhancement of the formulation's thermodynamic activity, like source of formulation of drugs with high saturation. During prior literature, various modes of action for penetration enhancers and several scientific perspectives have been discussed considerably [14, 15]. Plus, enhancement of individuals' discussion can be explained by strong mechanism's references on their action.

Chemical Permeation Enhancers' Category: Traditionally, enhancers of chemical were sorted primarily by the structures than mechanism for skin's action. They are classified based on benefits that are practical only because the enhancers in permeation may react with skin with varied mechanisms which are not easy to explain. Different chemical in same group may have different mechanism reaction on skin due to the properties of individual physic-chemicals. Discussion below explained the accepted group of enhancers in permeation in broad categorized by the structures of the chemical.

Water: Water is the enhancer of natural penetration used extensively [16]. The important part to determine the penetration enhancement of drugs is by knowing the stratum corneum's hydration state. Usually, increased number of stratum corneum's hydration improves transdermal flux of for many drugs. Water contributes in fostering delivery of transdermal that has been widely reviewed in the world [16].

Hydrocarbons: Some of hydrocarbons such as halogenated alkanes, alkanes, mineral oil and squalene were applied to increase permeation of varied drugs as vehicles or penetration enhancers through skin [17]. The enhancers of permeation function in general by making a stratum corneum's partition to disrupt the bilayer structure of ordered lipid. An experiments' series have been done to study the used of alkanes in skin permeation with variety length of the chain (9-18 atoms), resulted in shorter alkanes (5-6 atoms) have the largest caffeine's permeation enhancement while longer alkane (9-10 atoms) have the largest enhancement in skin permeation for diazepam and propranolol [17, 18]. Squalene enhanced sodium diclofenac's permeation while mineral oil enhanced chlorododecane and methyl to act as enhancer of permeation for timolol maleate [19]. Some of the hydrocarbons' effects on permeation of skin by varied drugs have been discussed by Buyuktimkin *et al*. [15].

Alcohols: Usually, alcohols played many purposes like solvents, penetration enhancers or vehicles to improve drug's transdermal delivery. Alkanols, polyglycols, glycerols and glycols are included also. Alcohols may improve the permeation of skin with variety of mechanisms such as improvement of drug partition into skin, extracting of lipids and proteins, formulation's solubility of drugs and swelling of the stratum corneum [15, 20-24].

Acids: In this category, fatty acids are the chemicals studied by most people [14, 21-23]. These chemicals also enhanced skin's drug molecules transportation with varied mechanisms such as lipid bilayers' partition and disruption of the domains sequence, enhancing partition of drug of stratum corneum also formation of drugs and lipophilic complexes [25, 26]. Usually, acids' purposes are vehicles or solvents however they also may play function as enhancers in permeating the vehicle system or the solvent [15]. One of the examples in this category is oleic acid which studied widely as enhancers in permeation [27, 29].

Amines: Enhancement of skin permeation of varied drug groups was a success and can be categorized into acyclic, tertiary, secondary, primary and cyclic. Amines may improve permeation of skin by partitioned it into lipid bilayers or enhancing skin's drug partition [11, 15, 23].

Amides: There is a large chemical's class formed by cyclic and acyclic amides acts in enhancing permeation [15]. First is azone as enhancer of synthetic permeation with its analogues following by the pyrolidones which are most widely amides that being studied [30, 31]. Usually, functions of amide are solvents and the action is done with improved drug's activity of solvent or enhancing partition of drug in the skin. Urine substances along with the analogues that are also in the class is typically functions in enhancing the permeation of solvents and give different skin's effects depends on the chosen system of the solvent however react through disruption of skin lipids in general.

Esters: Some studies used esters of fatty acids and resulting in enhancement of permeation in the skin with an extensive drugs variety [11, 15, 23, 24]. Most extensively studied ester is isopropyl myristate. Esters generally react through self-division among stratum corneum's domains of the ordered lipid [15, 20].

Surfactants: An extensively surfactants' variety were vigorously acted as enhancers in permeating the skin [15, 35, 36]. These were including many categories like non-ionic, cationic, anionic and zwitterionic. Surfactants are typically functions together a system of solvent or solvent while the action is based on balancing of lipophilic and hydrophilic, length and charge for lipid tail [11]. In this category, two surfactants which are non-ionic and anionic have been focused extensively in the study [37, 38].

Essential Oil, Terpenes and Terpenoids: In study of drug delivered transdermal, terpenes have become a choice in demand of enhancers in permeating [39-41]. In the class, a restriction of different chemicals and how it affects particular terpene on skin is based on the properties of its physicochemical, the lipophilicity in specific. Generally, combination of non-polar groups and little terpenes are superior as enhancers in permeating the skin [15].

Sulfoxides: Chemical that has been primarily deeply investigated in a study is dimethyl sulfoxide for its function as enhancers in permeating. Originally, its function is as solvent in improving division of drug within the skin; but some of the research found dimethyl sulfoxide's function and the derivatives for system of solvent that acts as enhancers [15, 21, 23].

Lipids: Enhancement of skin permeation for vehicles, micellar systems and microemulsions is usually performed by phospholipids [42, 43]. There is no appreciable effect of phospholipids on interaction of stratum corneum as single molecules. But, it may enhance partitioning of encapsulated drug through fusion of stratum corneum's lipid bilayers and disrupt the structure of ordered bilayers with structures of self-assembled like micelles or vesicles [15, 21].

Miscellaneous: Rather than enhancers of classical chemical permeation analyzed above, there are some group of chemical examined on the capability in improving drug's skin transportation. Various types of drug with different hydrophobic with complexes of inclusion can be formed by cyclic oligosaccharides such as cyclodextrins thus increasing the partition and solubility of the stratum corneum [44-97]. It has been showed those amino acids along with the derivatives such as thioacyl derivatives can improve transdermal drug permeation. Oxazolidinones and alkyl amino esters also functions successfully to enhance the permeation [15]. There is new chemical category have been investigated in enhancing permeation which is enzymes. It was shown that medicinal leech and papain enzymes achieved a success in enhancing drug's transdermal delivery [15, 98]. In some studies, ketone also can improve permeation of skin for steroidal drugs. Generally, it is a success of variety of drug transdermal enhancement with the aid of macrocyclic ketones that have more than 11 carbon atoms [15]. Lastly, it is proposed that schemes of metabolic intervention affect the components of stratum corneum's synthesis while the homeostasis is being used as enhancer in permeating the skin [21].

Chemical Permeation Enhancers' Limitation

Effectiveness: There is a crucial restriction for permeation capability of the chemicals in enhancing skin transportation in most study of transdermal literature which is they cannot achieve the desired skin disruption [36]. Their permeation through stratum corneum is poor while the activity of stratum corneum's top layers is limited. The activities decrease in line with the decreasing of concentration across the stratum corneum. Thus, the drug molecule's candidate results in weak transdermal delivery. Generally, there are variety of different mechanisms can be used by chemical enhancers to disrupt skin. Some investigators achieved a success in identifying the physicochemical forces that can determine enhancer's activity for skin's permeation [99-103]. Physicochemical correlation parameters like partition coefficient, polar forces, solubility, charge and hydrogen bonding ability permits one in evolving quantitative structure activity correlations (QSAR) in linking the structure of chemical to enhance the permeation on potential of skin disruption. By depending with those relationship, one may create an enhancers of permeation which significantly more affective for the permeabilization capability of the skin rather than conservative chemicals. SEPA (2-n-nonyl-1,3dioxolane) and azone (1-dodecylazacycloheptan-2-one) can be as examples for "synthetic" enhancer in permeation process and being used from molecular properties knowledge in the skin permeabilization design [104]. In designing enhancers that is potent acts as lipid fluidizers or lipid extractors with the use of dispersion and polar forces, hydrogen bonding and division coefficient used for quantitative correlations [11]. In specific, it is found that was basically unattainable in creating permeation enhancers to extract lipid which are safe and potent since same properties of molecular chemicals take responsibility in extracting lipid also in denaturing the protein that consequence with irritation of skin. A very high partition coefficient of permeation enhancers was discovered in functioning to fluidize high influence lipid however they are weak to be soluble in aqueous formulations which directly bound the applied functions [11].

Safety: There is also other difficulty use chemical to enhance transdermal transportation which is the ability in causing irritation of skin. Generally, ability in causing skin disruption gives the scales for the enhancers' ability in penetration that caused irritation of skin which is proportional to it [11]. The term irritation can be used in describing any negative and unpleasant impact comes from chemicals when it interacts with constituents of skin

and also includes swelling, dermatitis, erythema, local inflammation, or any other deleterious reactions. The common restriction for enhancers of chemicals arise skin's action mechanism. Enhancers for potent permeation are excellent to disrupt the corneocytes or stratum corneum's lipid bilayers that are highly ordered. This is as presentation for stratum corneum as the biggest obstacle in transportation in drug molecules' to diffuse however it is dead in physiological. Potent enhancers in permeation are competent to disrupt the stratum corneum but they are unable to control the superficial layer's activity thus might make diffusion with the viable epidermis located under the stratum corneum. Within feasible epidermis, enhancers for penetration may do an interaction with keratinocytes, epidermis's living cells thus cytotoxicity occur. There are difficulties in creating enhancers in permeation in controlling the exclusively stratum corneum's effect. For outcomes, it is difficult to hit an ideal equivalence of potency and safety for enhancers of chemical [11].

Chemical Mixtures' Opportunities: There are some opportunities offered by chemical mixtures in overcoming the limitations of individual chemical enhancers. Compared to individual chemicals, chemical mixtures can offer superior potency via diverse techniques. Single mixture's components may lead to disruption of skin via complementary or same mechanisms thus causing a synergistic and energetic impact in enhancing the permeation. As example, two chemical enhancers combination will work together where one of them reacts with lipids while another one acts at corneocytes which may overt the intercellular hydrophobic along with permeation of drug molecule in hydrophilic route. Similarly, component of a mixture may level up stratum corneum drug molecule's partition while another part may design pathway of diffusion with disruption of lipid bilayer or corneocytes. There is also example showed that enhancers can give synergistic or additive behavior when one of the enhancer stabilizes the drug and keep it from skin metabolism while other enhancer form pathways of diffusion for drug permeation. The chemical mixtures also can produce a synergy of potency and safety beyond of the exhibiting synergistic effects in enhancing transportation of drugs [36]. There is a way that is potent and safe in designing chemical permeation enhancers which intend to end the relationship of epidermis's activity and also stratum corneum's activity. There is high potency of permeation enhancers in having a lofty disruptive activity of stratum corneum whereas safety demands for enhancers of permeation that having a few or none viable epidermis's activity. It is extremely difficult yet unlikely to achieve the decouple mechanism of single chemicals' skin diffusion. Anyway, the chemicals combined offer a special opportunity to achieve decoupling. Chemicals mixture can be created since they consists of high-rise cell and activity in lipid bilayer by disrupting stratum corneum that already dead. When the diffusion of the mixture's components happen from epidermis to the stratum corneum, mixture's concentration and composition changed cause by the contrast in coefficient of partition along with two components' diffusion rates of stratum corneum across epidermis. Mixture's results of epidermis may be believed to be protected when having little ability of disruption. The theory is practical in creating a combination in showing a composition and concentration of the stratum corneum with a totally different epidermis composition and concentration. Mixture's activity can be connected with components' composition along with the concentration, thus mixtures' action can be decoupled. It is possible to design a formulation which has very high potential of stratum corneum's disruption make them become potent and the scarce range in ability to disrupt in the epidermis made it become protected [36].

Chemical Permeation Enhancers' Synergistic Mixtures Synergy: Several studies have indicated some mixture of chemicals done a synergistic interaction and induce the enhancement in permeating the skin more in contrast with single component that being inducing permeation enhancers [23, 34, 36]. Chemicals synergy may be used in creating potent enhancers of permeation controlling the effectiveness of individual enhancers' limitation. Alternately, definition of synergy in respecting of enhancement in permeating acquired from each component in a mixture. From experimental studies of mixture of 5000 different chemical enhancers, it is reported that the induction of the enhancement to formulate is connected with process of synergistic interaction with enhancers of chemicals [60].

Synergistic Chemical Mixtures Groups: Inducement of skin permeation enhancement can be done by chemical mixtures with different mechanisms those are complex but usually not directly explained. There is an easy classification way for mixtures of synergistic depend on how the mixtures were created by their single parts. For several cases, like vesicles, a single chemicals consisted by mixture can assemble by themself in forming well-structured of complex secondary and enhance skin permeabilization. In alternate, chemicals can affect others

by individual at structure of skin. There is commentary below discussed on groups of chemical mixtures which are differ from each other but similarly, functions in enhancing permeability of skin until an extensive drug range.

Mixtures of Solvent: A number of classical enhancers in permeating including solvents like glycols, fatty ester, fatty acids, water and alcohols functions during primary state. Mixture consists two or more solvents is the most extensively formulation strategies investigated in facilitating transportation of drugs through the skin. The mechanism of the systems in increasing transdermal flux may include i) thermodynamic activity's changes (e.g. by raising solvent's saturation level while level up its tendency of escaping) or ii) interacts specifically with stratum corneum, by level up the ability of the drug to be soluble in the stratum corneum (i.e. facilitating drug partition across the vehicles and skin) or with many types of transportation for route alteration (i.e. the polar and nonpolar route) of stratum corneum [34, 61]. Several studies on propylene glycol have been done extensively for its function as a co-solvent [34]. Some reports have reported on the enhancement of synergistic extracted in propylene glycol-fatty acids mixture [62, 63], fatty acids' ester or alcohols' ester [64, 65], also alcohols [63]. Clebopride's ability to permeate the skin from an isopropyl myristate:diethylene glycol monoethyl ether (60:40) binary mixture was more 80-fold than isopropyl myristate alone (Rhee *et al*. [66]). While Krisnaiah *et al*. [67] investigated on the solutions consists of various ethanol:water effect towards ondansetron hydrochloride's permeation of skin and discovered 60% v/v water:ethanol synergistic mixture resulted in largest permeation of skin *In vitro*.

A study by Panchagnula *et al*. [68] focused on combination of binary for propylene glycol, ethanol and water in term of capability purpose in enhancing naxolone's enhancement of transdermal permeation while discovered it is acceptable that therapeutically relevant naloxone's concentrations may be extracted with an ethanol:propylene glycol (67:33) mixture. The combination of solvent derived from glycerol monocaprylate and isopropyl myristate (10:90) proved permeation's pentazocine's enhancement with synergistic, place for solvent system's combination flux which has more 4- fold than single isopropyl myristate [69]. Drugs' transdermal flux with high number of lipophilic like anti-estrogens may improve incredibly with lauric acid:propylene glycol's combination (10:90) [70]. This formulation causes an extraordinary permeation enhancement cause by mutual process of enhancement between two chemicals along with the stratum corneum's fluidization process of synergistic lipid. Short chain alkanols-isopropyl myristate binary combination proves that there is difference between enhancements in estradiol transdermal flux in contrast with single alkanol [71]. Isopropyl alcohol-isopropyl myristate 1:1 combination enhanced estradiol flux by 35-fold through comparison with aqueous formulations. Tegafor's process of permeation within mouse's excised hairless of mouse has improved with tricaprylin:ethanol binary combination (60:40) [72]. N-methyl pyrrolidone:isopropyl myristate binary combination (75:25) is important to enhance flux of lidocaine through skin of human while indicated both 4-fold over 100% over 100% n-methyl pyrrolidone and 25-fold over 100% isopropyl myristate enhancemement [73]. A system of mixed solvent isopropyl myristate pyrrolidone and menthol:n-methyl pyrrolidone being filed in proving transdermal delivery of formoterol fumarate's synergistic enhancement [74]. An isopropyl palmitate:triethylene glycol monomethyl ether's binary system may enhance delivery of estradiol by 60-fold in contrast with single components [75]. The binary solvent mixtures' skin permeation enhancement can be enhanced by involving in third component into the mixture. As example, estradiol and acyclovir's permeation enhancement of a ternary mixture derived from propylene glycol, lauroylcholine and oleic acid better in contrast with corresponding binary system's sum [62].

Fang *et al*. [76] investigated on the system's effect for ternary solvent composed by isopropyl myristate (IPM), ethanol and triethanolamine towards permeation of skin for basic, neutral and acidic drugs *In vitro* using hairless skin of rat. The system for binary enhancer consisted by ethanol and isopropyl myristate made marked improvement of the drug penetration test. Larger effect on enhancement was discovered at acidic drugs during addition of binary system and triethanol amine. While, an improvement of isopropyl myristate and ethanol's binary system which is approximately 14-180 fold is happen when menefamic acid is added into it. It was also proved that selected ternary system of cis-oleic acid solvent with careful, dimethyl isosorbide and propylene glycol is effective in enhancing the nifepidine flux through mouse skin with less hair [77].

Permeation Enhancers' Mixtures in a Vehicle: High concentration of enhancers in permeation in solvent's condition give a chance in exerting strong effects on structure of skin, while enhancing the drug molecules'

transdermal flux. Some system contain specific advantages for some weak drugs' solubility to formulate aqueous solutions, they also sources on safety effect cause by deep induced irritation on skin's living layers. Some drastic effects can be cause by top-level of solvents that have big influences on the skin. There will be harm on demosomes and protein-like bridges which leads intercellular lipid's fissure while splits squames of stratum corneum. Solvents can make an entry to corneocyte to disrupt the keratin thus create vacuoles [61]. It is practically difficult for solvents or solvents mixture for transdermal patches employment or formulation of topical. It is possible for permeation enhancers of chemical to be formulated in a co-solvent which is passive, gel or cream base vehicles. Vehicles contribution in such system on permeating the skin is normally little or insignificant. An extensive study have been accumulated a point that convinced the mixtures of permeation enhancers are better in term of their ability in permeating in contrast to single chemicals. For example, there are permeation enhancer combinations of different or same groups of chemicals [15, 22, 23, 34]. Transdermal flux of zidovudine through skin of rat can be enhanced by combination of oleic acid and cineole synergistically [78]. Combination of isopropyl myristate and dibutyl adipate which are two ester derivatives indicates effect of synergetic on transdermal delivery that has been increased [15]. N-(2-mercaptopropionyl) glycine improves prazosin delivery with the presence of alcohols and esters [15]. Ethanol and n-lauroyl sarcosine aqueous solutions improved the fluorescein flux across corpse skin of human by 47-fold [13]. Ethanol and menthol work in synergetic is important to improve the tetracaine flux through mouse skin *In vitro* and resulted in the most powerful anesthesia's effectiveness for a study in human volunteer, lowest amount of duration for anesthesia onset and highest time for anesthesia [79]. *In vitro* dapiprazole base (DAP-B) permeation rate across skin with less hair of mouse was significantly improved by linoleic, linolenic and arachidonic acid mixture [80]. Furosemide's *In vitro* skin delivery was significantly enhanced with azone and oleyl alcohol combination as enhancers of permeation [81]. Propylene glycol and azone combination was able to level up percutaneous fluxes of lorazepam and clonazepam across human skin [82]. We have taken some studies from the past which explored on chemical mixtures' synergistic behavior in increasing permeability of the skin [80, 81, 60, 83]. A sodium lauryl sulfate, a cationic surfactant which is dodecyl pyridinium and chloride anionic surfactant combination was 2- to 3-fold greater in contrast of single surfactants to level up the electrical conductivity of skin - a skin permeability measurement [83]. In similar, phenyl piperazine and sodium laureth sulfate combination influenced more for 4- to 6-fold to increase permeabilization of skin in contrast of the single components [81]. This combination was effective to level up the *In vitro* permeability of skin of drug candidates like low molecular weight heparin, leutinizing hormone releasing hormone (LHRH), oligonucleotides and methotrexate [81]. Span 20 and sodium lauroyl sarcosinate combinations were competent enough to deliver sufficient leuprolide acetate's doses in therapeutic way which it is a synthetic analogue of LHRH in vivo in the model of large mouse [81].

Eutectic Mixtures: Transformation to oily state with high concentration in ambient temperature into solid drugs showed an increase of permeability of skin cause by an activity with high thermodynamic of their transport [84, 85]. The higher the skin lipid's solubility and lipophilicity, the lower the drug's melting point. In result, melting point decrease indirectly leveling up the function of transdermal permeating [86]. In literature, some eutectic systems of active drug have been studied together with skin permeation enhancer. The system arousing interest because of two mechanisms provided on how active drug's skin permeation through skin can be improved. At first, a formation of low melting mixture with the drug improved the partition in the skin. The action on the skin occurred in a split of second to disrupt the structure and improve the permeation of the drug. This mechanism's synergy can be exploited with the selection of right enhancer of permeation for the enhancer-drug combination. Ibuprofen and terpenes formulation together with fatty acids and propranolol formulation's eutectic system achieve a success to prove drug transdermal permeation improvement [87, 88]. Kang *et al*. [89] proved that lidocaine's permeation across the skin of snake can be enhanced by lidocaine:menthol eutectic system. While Kaplun-Frischoff and Touitou study resulted in enhancement of testosterone's permeation through skin of human corpse during combination of it and menthol in eutectic formulation [90].

Vesicles: Vesicles can be defined as colloidal particles consisted with concentric bilayers derived with amphiphilic molecules' self- assembly. It has obtained the importance as agent in both skin permeation enhancement and drug carrier in transdermal delivery of drug [42, 43]. Based on single or grouped molecules in vesicles' constitution, they may be categorized in a number of various groups. The vesicles' composition gives impact

on physicochemical characteristics like charge, lamellarity, size, bilayer elasticity and thermodynamic phase [91]. These physic- chemical characteristics give very great impact on the vesicles' behavior and also their effectiveness to improve transdermal delivery of drug [92-106]. As discussed in the literature, some mechanisms work as mediator with the vesicle-skin interaction. The interactions may happen whether in stratum corneum's deeper layers or at the surface of the skin based on the deformability or elasticity of the vesicles [107-113]. Synergistic interaction of the vesicles' components and between skin constituents with vesicles' interaction gain faith in having responsibility to give better vesicular system's enhancement in permeating the skin [114, 115]. There is similar mechanism which makes it looks quite alike for interaction of many systems of vesicles composed by more than one component and the stratum corneum. Therefore, the systems of chemical mixture been categorized depends upon the constituents in contrast with mechanisms for skin to interact. In the literature, some different of vesicles in term of types are reported. Liposomes contained lipids like phospholipids and cholesterol are normally worked by drug encapsulation of their core and level up in depositing of stratum corneum [96, 116-118]. There is a statement by Mezei and Gulasekharam on concentration of skin's triamcinolone acetonide which was noticed more 4- to 5-fold during liposomes' delivery in contrast with it was formulated normally [119]. Econazole and progesterone also received similar observations. Some of other study has discovered the information on skin's improvement for liposomes' drug deposition [120-123]. It is shown that assisting skin-lipid for dermal delivery has higher efficacy in contrast for delivering phospholipid vesicles. There is a limitation or liposome which focused on low level of effectiveness for drug delivery into deeper skin layers [124], but some studies reported the transportation of the particles through the skin [101, 125]. The composition of niosomes are non-ionic amphiliphiles as surfactants that having functions alike with liposomes [105, 126-128]. Some scholars reported niosomes' quality to improve drug permeation across the stratum corneum [126, 129, 130]. Currently, Paolino *et al*. reported those niosomes assembled derived of cholesterol, span 80 and new non-ionic surfactant alpha,omega-hexadecyl-bis-(1-aza- 18-crown-6) (Bola-surfactant) which is important in showing an improvement for percutaneous permeation in respect to ammonium glycyrrhizinate of unloaded Bola-niosomes and aqueous drug solution's physical mixture [131]. Niosomes that were derived of dicetylphosphate, span 60 and cholesterol has higher efficacy level that are able to increase the permeation of skin of frusemide through skin of mouse in contrast with chemicals formulated traditionally [132]. Generally, niosomes and hydrophobic drug delivery are well suited in contrast with hydrophilic drugs. A new type of vesicle systems, ethosomes is primarily constructed of ethanol, phospholipids and water [115, 133, 134]. It is documented that ethosomes is effective in transporting the molecules systematic circulation across the skin. Elsayed *et al*. [124] have explored the function of ethosomes in both *In vitro* and in vivo studies for various drug deliveries across skin such as testosterone, erythromycin, sotalol, propanolol, minoxidil, zidovudine, ketotifen, azelaic acid, trihexyphenidyl, sodium salicylate, ammonium glycyrrhizinate, cannabidiol and acyclovir. Currently, Rao *et al*. reported that fenasteride's transdermal flux are higher from ethosomal formulations with 2- to 7-fold in contrast with the aqueous formulations [135]. While Dubey *et al*. [136] documented methotrexate' transdermal flux through skin of human corpse may be improved with an ethosomal solution formulated consists of 45% of ethanol and 3% of phospholipids. An ultra-deformable hydrophilic lipid vesicle, transfersomes are presumed through skin significantly gradient of transdermal water activity. Transfersomes contained an edge activator and phospholipids that level up the bilayers' deformability and often stand as surfactant's individual chain like sodium deoxycholate, sodium cholate, dipotassium glycyrrhizinate, Span 60, Tween 20, Span 65, Tween 60, Tween 80 or Span 80 [137-145]. Various aspects of activators effects for transfersome's nature have been widely explored in some studies [145-148]. It was shown that ultra-deformable succeed in transporting a range of varied drugs through the skin such as 5- fluorouracil [149], tetracaine [150], lidocaine [150], methotrexate [144], cyclosporine A [151], diclofenac [153], insulin [152, 153], triamcinolone acetonide [154,55], hydrocortisone [156], levonorgestrel [157], dexamethasone [157], estradiol [158], dipotassium glycyrrhizinate [160], zidovudine [161] and low molecular weight heparin [159].

Microemulsions: Microemulsions are firmly established and clear isotropic mixtures of water, surfactant and oil while it usually combined with a co-surfactant [162]. They are simple and cheap in formulating, contain lofty of thermodynamic stability thus enhance process of solubilizing hydrophilic and also hydrophobic drugs. Some outstanding commentary consists of examples of a wide circumscription of microemulsions served the transdermal delivery of drug with an extensive variety of drugs [162-166]. Microemulsions offer permeation

enhancement based on the surfactant, co-surfactant and oil selection as well as mixture's relative concentration and composition. Usually, representative of oil phase is acids like ester or oleic acids like isostearylic isostearate, isopropyl palmitate, glycerin triacetate, isopropyl myristate or terpenes like medium chain triglycerides or limonene. While phase for surfactant normally posed with lipids with normal formulation like distearoylphosphatidyl choline, dioleylphosphatidyl ethanolamine and phosphatidylcholine. Other surfactants have also been used like Span 20, Tween 20, plurol isostearique, Tween 80, plurol oleique and Azone. Generally, the use of microemulsions'co-surfactants also consists of alcohols with long chain like dodecanol, decanol and octanol [162]. Every microemulsions' single parts are competent enough to enhance the transdermal drug delivery but their presence have synergistic enhancement as consequence which is important to level up drug molecule's transdermal flux. Gupta *et al*. [167] reported that 5-Fluorouracil's transdermal flux, drug of antineoplastic which raising 2- to 6- fold of isopropyl myristate:sodium bis(2-ethylhexyl) sulfosuccinate::water's microemulsion in contrast with same drug's aqueous solution. While Changez *et al*. [168] investigated on tetracaine hydrochloride's transdermal flux of microemulsion for n-propanol: water: lecithin: isopropyl myristate. It is stated that microemulsions improved the permeation ability in skin of mouse to tetracaine hydrochloride with 20- to 25-fold depends on microemulsion's composite. A function for microemulsions is it can improve in disrupting the structure of skin-lipid or by enhancing the stability of drug when being formulated. Ascorbic acid's stability in some microemulsion has been studied by Gallarate *et al*. [169]. As oils, they used cetearyl octanoate or isopropyl palmitate while as surfactants, cocoamide propylbetaine and dodecylglucoside thus for co-surfactant, they used 2-ethyl- 1,3-hexanediol. In microemulsion systems, ascorbic acids' stability against oxidation indicated a better result in contrast with the same element of aqueous formulations. Besides, Zhu *et al*. [170] made a statement on permeation for penciclovir's skin in formulating a microemulsion consist of water:ethanol:Cremorphor EL:oleic acid which is more 3.5-fold in contrast with a commercial cream.

Inclusion Complexes: Definition for inclusion complexes is they consist of arrangement of cages for molecular chemicals which are able in encapsulating core's drug molecule that is active. Cyclodextrins are the agents in forming the complexes of inclusion investigated widely the most [44-49]. Generally, it is believed that cyclodextrin inclusion complexes can enhance the stability of drug by avoiding oxidation, degradation or hydrolysis and enhancing solubility of drug. A number of studies have reported the cyclic oligosaccharides' action; in specific beta-cyclodextrins to level up the permeability of the skin of drugs consist of hydrophilic. As example, Masson *et al*. [50] described cyclodextrins can functions to enhance in permeating by drug transportation across the bulk formulation and biological membranes' lipophilic surface, place of partition for drug molecules towards lipophilic membrane from the complex. It is documented about the increasing of estradiol's absorption in the stratum corneum resulted of the increased availability of drug to the surface of the skin cause by complexion of inclusion (De Paula *et al*. [51]). Jug *et al*. [52] recommended cyclodextrins to create drug's complexes of inclusion while transports the molecules of the drug towards surface of the obstacle, place in dissociating the complex and permeating the drugs through membrane layer. As example, beta-cyclodextrin can sustain tixoxortol 17-butyrate 21-propionate's ability to maintain stable at 40 °C for a month [171]. Apart of supplying drug's stabilizing pocket, cycoldextrins and permeation enhancers may collaborate in synergistic to enhance the skin absorption. Adichi *et al*. [172] proved that an O-carboxymethyl-O-ethyl-beta-cyclodextrin (CME-beta- CyD) and prostaglandin E1 (PGE1)'s inclusion complex ointment base supplemented of propylene glycol:fatty alcohol with a 1-[2-(decylthio)ethyl]azacyclopentane- 2-one (HPE-101) permeation enhancer in improving PGE1's transdermal flux through skin with less hair of a mouse with generally 100-fold in contrast with single PGE1 and generally 10 times for combination of PGE1-HPE-101. There may be arising of complication on cyclodextrin and enhancers such as quaternary ammonium salts while lower on skin's side effect on toxic but remain in sustaining the capacity in permeating the skin while resulting a synergy relationship of potency and safety [173]. Some research described synergistic properties of traditional enhancers of permeation with cyclodextrins [48,174,175].

CONCLUSIONS

Chemical mixtures employed by synergistic systems offer a way in overcoming several limitations of single chemicals to improve transdermal delivery of drugs. Chemicals combination also can be used to either enhance the permeation enhancers' safety and potency. From previous research, synergistic systems' arrangement was restricted with experimental screening methods' low throughput. In the future, the novel synergistic system

arrangement need to improve with the high number of screening platform of throughput availability and logical arrangement proposition depending on enhanced interactions' understanding on chemicals and skin constituents. Moreover, synergistic chemical arrangement is unlimited nowadays for uncomplicated empirical mixtures of conventional enhancers of permeation however a design including system with high level of complexity is acceptable like inclusion complexes, microemulsion and vesicles.

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