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PENETRATION ENHANCERS IN TRANSDERMAL DRUG DELIVERY SYSTEMS: A BRIEF REVIEW

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KEYWORDS:

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ABSTRACT

The transdermal route has been recognized as one of the highly potential routes of systemic drug delivery as skin is an important site of drug application for both local and systemic effects. Transdermal route provides the advantage of avoidance of the first-pass effect, ease of use and withdrawal (in case of side effects) and better patient compliance. However in skin, the stratum corneum is the main barrier for drug penetration. Penetration enhancement technology is a challenging development that would increase the number of drugs available for transdermal administration. Studies have been carried out to find safe and suitable permeation enhancers to promote the percutaneous absorption of a number of drugs. The present review includes the classification of permeation enhancers and their mechanism of action; thus, it will help in the selection of a suitable enhancer(s) for improving the transdermal permeation of poorly absorbed drugs.

INTRODUCTION:

Transdermal delivery constitutes one of the most important routes for new drug delivery system (NDDS). Transdermal delivery of drugs offers several advantages over conventional delivery including oral and injection methods. Transdermal delivery, that traditionally uses a patch containing drug substance pressed onto the skin, is non-invasive, convenient and painless, and can avoid gastrointestinal toxicity and the hepatic first pass metabolism. [1]

The skin is very effective as a selective penetration barrier. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis and into the blood circulation. The skin behaves as a passive barrier to the penetrant molecule. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption.

Penetration enhancers:

Penetration enhancers are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. Ideally, these materials should be pharmacologically inert, non-toxic, non-irritating, non-allergenic, compatible with the drug and excipients, odourless, tasteless, colourless, and in expensive and have good solvent properties. The enhancer should not lead to the loss of body fluids, electrolytes, and other endogenous materials, and skin should immediately regain its barrier properties on its removal. No single penetration enhancer can possess all the required properties. [2, 3] However, many enhancers exhibit many of these attributes, and they have been tested in clinics or in research laboratories. Several scientists are engaged in transdermal permeation studies using various enhancers for several drug moieties.

There are mainly three apprroaches for the penetration enhancement. [4]

    a. Chemical approach according to Barry[5]

    b. Biochemical approach

    c. Physical approach

A. Chemical Approach:

i. Alcohols: [6-12]

These include alkanols, alkenols, glycols, polyglycols and glycerols. Alcohols can enhance skin permeation by a variety of mechanisms such as extraction of lipids and proteins, swelling of the stratum corneum or improving drug partitioning into the skin or solubility of the drug in the formulation. Ethanol increases the permeation of ketoprofen from a gel-spray formulation and triethanolamine salicylate from a hydrophilic emulsion base. Propylene glycol promotes the flux of heparin sodium and verapamil hydrochloride and ketoprofen, but

at higher concentrations, it inhibits the flux of ketoprofen. Propylene glycol, in combination with azone, increases the flux of methotrexate, piroxicam, cyclosporin A.PG solvates the keratin of the stratum corneum, occupying the hydrogen bonding sites. When it is used in combination with azone, large amounts of glycol enter the tissue and promote intracellular diffusion of drugs. The flux of drug increased with increasing carbon chain length up to six carbon atoms in n-alcohols. These alcohols promote skin permeation of drugs by causing lipid extraction from the stratum corneum. Short chain glycerides, for instance, glyceryl monocaprylate enhances the partitioning of papaverine Short-chain glycerides are also effective as permeation enhancers (e.g., TCP). TCP is an excellent hydrophobic vehicle and promoted the permeability of tegafur combined with ethanol.

ii. Amines and amides: Urea, dimethyl acetamide, dimethyl formamide

Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism.[13]

iii. Cyclodextrines:

Cyclodextrins are the biocompatible substances that can form inclusion complexes with lipophilic drugs with resultant increase in their solubility, particularly in aqueous solutions [14]. An inclusion complex of piroxicam with β-cyclodextrin increased the drug flux three times across hairless mouse skin, and a similar complex of clonazepam with methyl-β-cyclodextrin improved its release profile from Carbopol hydrogel through cellulose nitrate membrane [15].

Cyclodextrins (in solution) forms a complex with enhancers like quaternary ammonium salts and shifts their critical micellar concentration to higher values, thereby decreasing the toxic effect of such enhancers. Transdermal absorption of alprostadil (AP) from its β-cyclodextrin complex and O-carboxymethyl-O-ethyl-β-cyclodextrin (CME-β-CD) complex was compared across hairless mouse skin. HPE-101 (1-[2-(decylthio)ethyl] azacyclopentan-2 one) was included as a permeation enhancer in both cases. Flux from the latter complex was 10 times higher than from the former one. It was concluded that a combination of CME-β-CD and HPE-101 enhances the topical bioavailability of the drug [16]. Complexation with cyclodextrins has been variously reported to both increase [17, 18] and decrease skin penetration. [19-23]

Loftsson and Masson concluded that the effect on skin penetration may be related to cyclodextrin concentration, with reduced flux generally observed at relatively high cyclodextrin concentrations, whilst low cyclodextrin concentrations resulting in increased

flux [24]. As flux is proportional to the free drug concentration, where the cyclodextrin concentration is sufficient to complex only the drug which is in excess of its solubility, an increase in flux might be expected. However, at higher cyclodextrin concentrations, the excess cyclodextrin would be expected to complex free drug and hence reduce flux. Skin penetration enhancement has also been attributed to extraction of stratum corneum lipids by cyclodextrins [25].

iv. Fatty acids: oleic acid:

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. The fatty acid extract of cod liver oil was found to be as good a permeation enhancer as oleic acid. The most effective transdermal penetration enhancer was palmitoleic acid, which resulted in a 640-fold increase in hydrocortisone flux through hairless mouse skin. Incorporation of pure cod liver oil in a PG vehicle did not improve the hydrocortisone permeability, suggesting that the unsaturated fatty acids have to be in the free form to be able to act as skin permeation enhancers. A 1- hr pretreatment of rabbit abdomen skin with 10% oleic acid in PG greatly enhanced the absorption of piroxicam from its gel [26].

v. Polyols: Propylene glycol:

PG promoted the flux of heparin sodium. [27] A saturated solution of terpenes in a PG-water cosolvent system enhanced the flux of 5-FU, terpene activity being dependent on PG content and with the maximum flux obtained from formulations containing 80% PG. Also, PG increases drug partitioning and drug permeation [28]. PG, in combination with azone, increases the flux of methotrexate [29], cyclosporin A [30], and 5-FU [31]. Flux of estradiol was 10 times higher when PG was used in conjunction with 5% oleic acid [31].

vi. Pyrrilidones: N-methylpyrrilidone, azones

Pyrrolidones and their derivatives have great potential to be used as transdermal permeation enhancers. The most common N-methyl-2-pyrrolidone (NMP) has been used widely to enhance the skin absorption of many drugs. By the use of NMP, the flux of the anti - inflammatory drug ibuprofen increased 16 times and that of flurbiprofen increased 3 times through cadaver skin. Kim and Chien [32, 33]. studied the effect of NMP on the skin permeation of the anti-HIV drugs zalcitabine, didanosine, and zidovudine using hairless rat skin at 37°C. Addition of 1% v/v of NMP in ethanol:tricaprylin (TCP) (50:50) cosolvent system could not significantly increase the permeation rate of these drugs. The influence of skin permeation of various enhancers prepared from 2-pyrrolidone containing a short alkyl group at the 1 position and a dodecyl group at the 3

position of the pyrrolidone ring was studied. The length of the short alkyl group at the 1 position considerably influenced the enhancing activity. 1-Propyl and 1-butyl-3-dodecyl-2-pyrrolidone showed the effective enhancement of penetration of indomethacin through the skin in 60 wt% ethanolic solution [34]. In general, 2-pyrrolidone enhances the transdermal permeation of caffeine through polar routes of skin by increasing its diffusivity and reduces the passage through the nonpolar route by decreasing diffusivity and partitioning.

Azone forms one of the major classes of percutaneous permeation enhancers. When azone was used in combination with PG, theflux of methotrexate[35]. and piroxicam[36] increased significantly. Azone is always more effective when used in combination with PG. PG promotes intracellular transport, while azone improves intercellular drug transport. Azone/PG increase penetration through the stratum corneum by affecting both the hydrophilic and lipophilic routes of penetration. Azone increases the fluidity of the lipid layer, while PG increases the water content of the proteinaceous region and helpsazone partition into the aqueous region. A combination of these two helps the penetration of hydrophilic drugs greatly. [37]

vii. **Sulfoxides: Dimethyl sulfoxide, decylmethal sufoxide:** Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aportic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic and is often used in many areas of pharmaceutical sciences as a "universal solvent". DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact uticaria, stinging and burning sensation.[38] The mechanism of the sulphoxide penetration enhancers is widely used to denature protein and, on application to human skin, has been shown to change the intercellular keratin conformation, from helical to ß sheet.[39, 40]

DMAC and DMF are similarly powerful aportic solvents. Southwell and Barry, showing a 12-fold increase in the flux of caffeine permeating across a DMF-treated human skin, concluded that the enhancer caused irreversible membrane damage.[41] DMF irreversibly damages human skin membranes but has been found in vivo to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay. [42, 43]

viii. Surface active agents: Cationic surfactants:

Surface active agents function primarily by absorption at interfaces and thus interact with biological membranes contributing to the overall penetration enhancement of compounds. Cationic surfactants are more destructive to skin tissue causing a greater increases in flux than anionic surfactants [44] Anionic surfactants may function by alteration of barrier function of the stratum corneum as a result of the removal of the water soluble agents that act as plasticizers [45]. Sodium lauryl sulphate has been implicated in reversible lipid modification with resultant disorganization of the stratum corneum and enhanced permeation [46]. In addition, non ionic surfactants are perforated to be able to emulsify sebum consequently altering partitioning potential of drugs in fever of enhanced permeation [47]. The permeation enhancement generated by these compounds may be dependent on the ability of the drug to partition between the free and bound and micelle form of enhancer.

ix. Terpenes: Eugenol

Terpenes and terpenoids are usually the constituents of volatile oil. Their chemical structure consists of repeated isoprene ($C_5 H_8$) units and is classified according to the number of isoprene units: Monoterpenes have two isoprene units (C_{10}), sesquiterpenes have three (C_{15}), and diterpenes have four (C_{20}). Terpenes may also be classified as acyclic/linear, monocyclic, and bicyclic. Terpenes are used as potential percutaneous penetration enhancers other than therapeutic applications such as its uses in antispasmodics, perfumery, carminatives, etc., The essential oils of eucalyptus, chenopodium and ylang-ylang have been found to be effective penetration enhancers for 5-flouorouracil transversing human skin in vivo [48, 49].

L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin [50] as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin [51, 52]. L - Menthol (present in a high proportion in peppermint oil) has been shown to increase the skin absorption of testosterone by forming a eutectic mixture with the drug, thereby lowering its melting point drastically from 153.7°C to 39.9°C, as reflected by differential scanning calorimetry (DSC) studies, increasing its solubility and hence its absorption. In further studies, menthol also has been shown to increase the absorption of ceramides and cholesteryl oleate. Menthol affects skin permeation by a dual mechanism: by forming a eutectic mixture with the penetrating compound, thereby increasing its solubility, and by altering the barrier properties of the stratum corneum [53].

The effect of three essential oils (eucalyptus, peppermint, turpentine oil) on the permeation of 5-fluorouracil (5-FU) were studied using excised rat skin. Eucalyptus oil was found to be the most

active, causing a 60-fold increase, while peppermint and turpentine oil showed 48- and 28-fold increases, respectively. Mode of action of these enhancers may be due to a combined process of partition and diffusion, the latter being dominant [54].

Some cyclic terpenes have also been investigated as penetration enhancers. Cineole, d-limonene, and α-pinene were studied using human cadaver skin for their absorption-enhancing effect on two neuroleptic drugs, chlorpromazine (CPZ) and haloperidol [55]. Permeation of haloperidol was increased by both cineole and d-limonene; α-pinene provided no change in its permeation profile. Coapplication of terpenes (1,8-cineole, menthone, limonene, nerolidol) with 5-FU, both at saturation, in a propylene glycol (PG)/water cosolvent system increased drug flux significantly [56]. Terpene activity depended on PGcontent, with maximum flux obtained with formulations containing 80% PG. A dual mechanism of permeation was proposed, one due to increased lipid disruption in the stratum corneum by terpenes and the second due to the increased drug partitioning contributed by the high PG content.

B. Biochemical approach:-

i. Synthesis of bio-convertible pro-drugs:

Prodrug may be designed to obtain an optimal partition coefficient for entering the skin barrier. After absorption and diffusion to the viable tissues, enzymes convert the prodrug to the active species. Many steroids have designed in this way. The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6-acyloxymethyl and 9-dialkylaminomethyl promoieties and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs, naltrexone, nalbuphine, buprenorphine, b-blockers and other drugs. Well established commercial preparations using this approach include steroid esters (e.g.betamethasone-17-valerate), which provide greater topical anti-inflammatory activity than the parent steroids.[57]

ii. Co-administration of skin metabolism inhibitors:

More interventionist approaches to drug delivery through human skin have also been proposed. Strategies that alter barrier homeostasis by interfering with any or all of the processes of synthesis, assembly, secretion, activation, processing, or assembling and disassembling of the extracellular lamellar membranes, could promote permeation.[58] synthesis inhibitor blocks temporarily the synthesis of ceramide, fatty material and cholesterol. This aspect is being increasingly investigated to increase the transdermal delivery of drugs that exhibit poor permeability across normal skin.fluvastatin increases the octanol/water partition coeffient of lidocaine hydrochloride by 50 times, the in vivo uptake increases only 2 fold.[59] Such an

approach would pose significant regulatory problems, not least of which would be issues related to increased xenobiotic or microbial access. The concept of interfering with barrier homeostasis on a relatively long timescale poses many clinical considerations and objections.

C. Physical approach:
i. IONTOPHORESIS:-

Iontophoresis is the facilitated movement of ions across a membrane under the influence of an externally applied small electrical potential difference (0.5 mA/cm 2 or less), is one of the most promising novel drug delivery system, which has proved to enhance the skin penetration and the release rate of a number of drugs having poor absorption/permeation profile through the skin [60, 61]. It is a localized, non-invasive, convenient and rapid method of delivering water soluble, ionized medication into the skin. It is gaining wide popularity in the area of pain relief as it provides a non invasive means of systemic administration of minute amount of drugs.

The mechanism of iontophoresis is based on the physical phenomenon that "like charges repel and opposite charges attract". The drugs are forced across the skin by simple electronic repulsion of similar charges. Thus, anionic drugs can cross the skin by using a negatively charged working electrode. Similarly, cationic drugs enter the skin more successfully when a positively charged electrode is used. While delivering a negatively charged drug across biological membrane, it is placed between the negative electrode (cathode), and the skin. The drug ion is then attracted through the skin towards the positive electrode (anode) by the electromotive force provided by the cell. In case of positively charged drug, the electrode polarities are opposite. Once the drug has passed through the outer barrier layer of skin, it reaches to its site of action by rapidly going into the circulation. The electric circuit is completed by the movement of endogenous counter ions from within the skin. In vitro iontophoretic studies conducted on peptides have shown an increase in the passive permeability of skin post iontophoresis. This shows, that the alteration of the skin barrier function due to current passage in vitro is, one of the mechanisms for enhanced permeability following iontophoresis.[62 - 64]

Mechanism of iontophoretic transport of drugs across the skin involves either diffusion, migration or electro-osmosis. Electro-osmosis is the bulk flow of fluid occurring in the same direction as the flow of counter ions when a voltage difference is applied across a charged, porous membrane. This flow involves motion of fluid without concentration gradient and is a significant factor affecting iontophoresis. At physiological pH, human skin has a slight negative charge and counter ions are usually cations. Therefore, flow occurs from anode to cathode electroosmotically thus, enhancing the flux of cationic drugs.

The potential of this technique has been exploited for the transdermal delivery of many drugs with poor penetration properties e.g., high molecular weight electrolytes such as proteins, peptides and oligonucleotides which are normally difficult to administer except through parenteral route. It also offers a great potential for the delivery of charged peptides used as drugs. Although iontophoresis has been able to achieve significant increase in the transdermal absorption of many drugs, it has not been able to show significant permeation of larger peptides like insulin. This has lead to many studies involving the use of various chemical enhancers (permeation enhancers) along with iontophoresis [65].

ii. SONOPHORESIS: ULTRASONIC ENERGY:-

Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the skin. Ultrasound has been used extensively for medical diagnostics and to a certain extent in medical therapy (physiotherapy, ultrasonic surgery, hyperthermia). Nevertheless, it has only recently become popular as a technique to enhance drug release from drug deliverysystems. A number of studies suggest the use of ultrasound as an external mean of delivering drugs at increased rates and at desired times. It was recognized in 1927 that ultrasound (ULTS) could produce lasting changes in biological systems, and this was the start of both safety studies, and of ultrasound therapy [66].

ULTS has been used in the medical field for several decades and can be divided into three major categories: [67]

     i) high frequency (2–10 MHz) or diagnostic ultrasound,

     ii) medium frequency (0.7–2 MHz) or therapeutic ULTS, and

     iii) low frequency (5 to 100 KHz) or power ULTS.

Mechanisms of Action: Its mechanisms were not clearly understood, reflecting the fact that several phenomena may occur in the skin upon ULTS exposure. These include:

     a) Cavitation effects.

     b) Thermal effects.

     c) Induction of convective transport.

     d) Mechanical effects.

a) Cavitation effects:

Cavitation is the formation of gaseous cavities in a medium ULTS exposure (Figure 4). The primary cause of cavitation is ULTS-induced pressurevariation in the medium. Cavitation involves either the rapid growth and collapse of a bubble (inertial cavitation), or the slow oscillatory motion of a bubble in an ULTS field (stable cavitation). Collapse of cavitation bubbles releases a shock wave that can cause structural alteration in the surrounding tissue [68]. Tissues contain air pockets

that are trapped in the fibrous structures that act as nuclei for cavitation upon ultrasound exposure. The cavitational effects vary inversely with ULTS frequency and directly with ULTS intensity. Cavitation occurs due to the nucleation of small gaseous cavities during the negative pressure cycles of ULTS, followed by the growth of these bubbles throughout subsequent pressure cycles. This cavitation leads to the disordering of the lipid bilayers and formation of aqueous channels in the skin through which drugs can permeate [69-71].

b) Thermal effects:

Absorption of ULTS increases temperature of the medium. Materials that possess higher ULTS absorption coefficients, such as bone, experience severe thermal effects compared with muscle tissue, which has a lower absorption coefficient [72]. The increase in the temperature of the medium upon ULTS exposure at a given frequency varies directly with the ULTS intensity and exposure time. The absorption coefficient of a medium increases directly with ULTS frequency resulting in temperature increase. A study [73] suggested the use of a new safety parameter, time to threshold (TT). TT indicates the time after which a threshold temperature rise is exceeded, and how long a piece of tissue can be safely exposed to ULTS, provided the safe threshold is known.

c) Convective transport: Fluid velocities are generated in porous medium exposed to ULTS due to interference of the incident and reflected ULTS waves in the diffusion cell and oscillations of the cavitation bubbles. Fluid velocities generated in this way may affect transdermal transport by inducing convective transport of the permeant across the skin, especially through hair follicles and sweat ducts. Experimental findings suggest that convective transport does not play an important role in the observed transdermal enhancement [74].

d) Mechanical effects: ULTS is a longitudinal pressure wave inducing sinusoidal pressure variations in the skin, which, in turn, induce sinusoidal density variation. At frequencies greater than 1 MHz, the density variations occur so rapidly that a small gaseous nucleus can not grow and cavitational effects cease. But other effects due to density variations, such as generation of cyclic stresses because of density changes that ultimately lead to fatigue of the medium, may continue to occur. Lipid bilayers, being self-assembled structures, can easily be disordered by these stresses, which result in an increase in the bilayer permeability. This increase is, however, non-significant and hence mechanical effects do not play an important role in therapeutic sonophoresis. Thus cavitation induced lipid bilayer disordering is found to be the most important cause for ultrasonic enhancement of transdermal transport [74].

iii. THERMAL ENERGY:-

Heat increases skin temperature that leads to increase in microcirculation and blood vessel permeability, thus facilitating drug transfer to the systemic circulation. Drug solubility, both in the patch formulation and within the skin increase with a rise in temperature. Zars, lnc [Salt Lake City,

UT, USA] has developed a technology that takes advantage of heat's ability to increase transdermal permeation. This technology is known as Controlled Heat-aided Drug Delivery (CHADD) system. CHADD system is a small heating unit that can be placed on top of a traditional patch. An oxidation reaction within the unit provides heat at a limited intensity and duration. [75]

iv. STRIPPING OF STRATUM CORNEUM:-

The abrasion technique involves the direct removal or disruption of the upper layers of the Skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g.,microdermabrasion) which are used in the treatment of acne, scars, hyper pigmentation and other skin blemishes. Microscissuining is a process which creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. In vitro data have shown that the application of the device can increase the penetration of angiogenesis into the skin 100- fold compared to untreated human skin. [75]

v. HYDRATION OF STRATUM CORNEUM:-

Water is the most widely used and safest method to increase skin penetration of both hydrophilic and lipophilic permeants. The water content of the stratum corneum is around 15 to 20% of the dry weight. Additional water within the stratum corneum could alter permeant solubility and there by modify partitioning from the vehicle into the membrane. In addition, increased skin hydration may swell and open the structure of the stratum corneum leading to an increase in penetration, although this has yet to be demonstrated experimentally. Hydration can be increased by occlusion with plastic films; paraffins, oils, waxes as components of ointments and water-in-oil emulsions that prevent transepidermal water loss; and oil-in-water emulsions that donate water. Of these, occlusive films of plastic or oily vehicle have the most profound effect on hydration and penetration rate. [76]

CONCLUSION:-

Skin permeation enhancement technology is a rapidly developing field which would significantly increase the number of drugs suitable for transdermal drug delivery, with the result that skin will become one of major routes of drug administration in the next decade. Research in this area has proved the usefulness of penetration enhancers in the enhancement of drug permeation through skin. The chemical penetration enhancement methods discussed in this review are promising. Focus should be on skin irritation with a view to selecting penetration enhancers which possess optimum enhancement effects with minimal skin irritation.

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