REVIEW ARTICLE

SKIN PORT: A NOVEL ROUTE FOR DRUG DELIVERY

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ABSTRACT

The transdermal route is considered an efficacious and innovative route in drug delivery and is attaining the consideration of pharmaceutical scientists for the last two dacades. For a successful transdermal drug delivery system (TDDS), a drug must infiltrate through the skin to underlying tissues and circulation without any drug accumulation in skin layers. The passage of therapeutic quantities of drug substances through skin into the general circulation for their systemic effects is facilitated by TDDS. Major problem that TDDS faces is dermal barrier. Attempts have been made to overcome this barrier to facilitate the passage of drug through skin for its therapeutic effect. This review aims to present the analysis of published research work to investigate the permeation of various drugs through skin port using different permeation enhancers.

KEY WORDS: Drug delivery; Skin port; Permeation enhacncers.

This article may be cited as: Akhlaq M, Hussain A, Bakhsh S, Shakoor A, Khan AM, Iqbal S, Kiran S. Skin port: a novel route for drug deliver. Gomal J Med Sci 2014; 12:176-84.

INTRODUCTION

The transport of drug into targeted tissues with an attempt to avoid systemic adverse effects is known as percutaneous delivery. Stoughton provided the concept of percutaneous absorption of drug[1] for the first time. Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Transdermal drug delivery (TDD) means placing a drug on the skin in the form of a patch, cream or lotion wherein the drug permeates across the skin and enters the bloodstream[2] which depends on some factors i.e. nature of the skin barrier, the balance between physicochemical properties of the membrane and the drug, application time, skin site, skin condition, effect of vehicle on stratum corneum, properties and types of formulations and finally the technologies available to facilitate the transdermal transport.[3] The drug absorbed after transdermal application is detected by various means i.e. by measuring blood levels of a particular drug, detecting urinary excretion of drug and its metabolites and by the clinical response of patient to drug.[4]

The term Transdermal Drug Delivery System (TDDS) includes all drug formulations which are administered by topical and controlled drug delivery into general systemic circulation. TDDS patches of various size and shape have been designed and marketed for the treatment and prevention of systemic diseases. The drug delivered topically undergoes sequential absorption i.e. first drug is released from TDDS, absorbed through skin's first barrier stratum corneum, then epidermis and dermis into blood circulation and transported to targeted site to achieve therapeutic effect. For ideal and successful TDDS, the drug must penetrate through skin to underlying tissues and blood circulation without any drug accumulation in skin layers. Although TDDS are a new drug delivery system and need approval for being safe and effective.[5] These should scientifically support in vitro and in vivo claims for controlled release formulations and assure reproducibility both in vitro and in vivo. TDDS appears to reach a practical stage although introduced more than 200 years ago. It would be wise here to distinguish between transdermal and topical delivery. If it is suspected cutaneous pain and/or osteoarthritis, in the former case we are dealing with topical delivery and in the latter, "locally enhanced topical delivery (LETD)" according to Cross and Roberts' notation. Hence transdermal drug delivery involves the continuous administration of therapeutic molecules through the skin. Transdermal drug delivery route has become FDA approved and most successful drug delivery system now a-days since 1st TD patch in 1981.There is gradual increase in number of TDDS products and it seems likely to continue for the future.[6]

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ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

TDDS has become viable and successful dosage form due to clinical benefits, strong market, regulatory precedence and industry interest.[7] The advantages of transdermal delivery over other delivery systems are as follows:

- Skin represents a relatively large and readily accessible surface area for absorption and prevents overdose or undesirable effects.[8]
- Reduced gastric ADRs and increased tolerability.
- First pass metabolism (liver metabolism) of drug is avoided.
- Reduced pharmacokinetic peaks and troughs i.e. peak plasma concentration of drug.
- Suitable for drugs with short half life, high lipophilicity and narrow therapeutic index.[9]
- Increased duration of action.
- Easy to apply and remove in case of toxicity.
- Drug absorption is unaffected by pH, enzymatic activity and drug-food interactions.
- Reduced dosing or administration frequency and increased patient compliance.[10]
- Improved drug stability and solubility, reduced lag time and increased the rate of delivery.
- Targeted drug delivery of vaccine by targetting the potent epidermal Langerhans and dermal dendritic cells that generate a strong immune response at much lower doses than deeper injection.[11]

LIMITATAIONS OF TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS)

- Permeation rates are different and depend on age, race, site of application and individuals and also skin diseases.
- Drugs with higher molecular weight (>500 Da) i.e protein/peptide are poor candidates for TDDS because they can not cross stratum corneum.
- Difficult in delivering hydrophilic drugs like peptides and macromolecules including new genetic treatment employing DNA or small-interfering RNA (siRNA).[12]

DYNAMICS TRIGGERING ERRATICISM

With the passage of time, knowledge has increased about drug and skin properties and the processes that control skin permeation.In late 1960 and early 1970 scheuplein and Blank developed some rules for skin permeation that were regularly updated by other scientists.At end it was reported that epidermis (chemical composition, application site and morphology) controls skin permeation and the rate and extent of absorption which can be modified by modifying this barrier by physical or chemical means. The factors that affect the permeation of the skin barrier can be divided into physiological and physicochemical variables. Few important factors include variables of the skin age, skin condition, and the area of the skin treated the thickness of the skin barrier phase, blood flow and species variation.[13] The conditions for drug delivery may be controlled i.e. skin hydration, skin temperature and donor or receptor pH.

PHYSIOLOGIC AND PATHOLOGIC FACTORS

Species variation: Due to difference in physiological structure and biochemical structure of animal and human skin, difference in permeability is observed. Epidermis lipid content composition is also different and is thought to be responsible for difference in permeability.Although appendageal openings per unit area in an animal skin are usually higher than in human skin, but this is not an underlying reason for permeability differences.

Age, gender and race: Adult skin is less permeable than infants. Thickness and integrity of the epidermis affect the skin permeability. In most immature infants, epidermis has less keratinization and is only one or two cell thick making it barely detectable. Epidermis permeability of older infants is less than that of preterm infants.[13] Premature infants of (26-30 weeks gestation) have little thinner epidermis while the full-term infants (37-40 weeks gestation) show a histological epidermal layer that is thicker than that of the aged (50-76 years). It is usually observed that poorly developed epidermis of low birth weight or premature babies is converted into developed epidermis within four weeks after the birth.[14]

These changes are observed when skin undergoes aging process i.e. dryness of epidermis is increased, sebaceous gland activity is decreased (resulting in decrease in amount of surface lipids), dermal-epidermal junction is flattened and skin capillary network shows atrophy resulting in a gradual attenuation of blood supply to the viable epidermis.

Physiological and pathological conditions of skin: Lipid film: The skin surface has a protective layer, a lipid film that not only prevents removal of moisture from skin but also maintains barrier functions of epidermis.

- Pathologic injuries to the skin: Permeability can be increased by injuries that disrupt the continuity of stratum corneum permeability
- Cutaneous Drug Metabolism: Viable epidermis contains catabolic enzymes that may render

a drug inactive by metabolism and thus affect topical bioavailability of the drug e.g. Testosteron is 95% metabolized.

- Regional Variation: Variability in permeation rate is caused by differences in the nature and thickness of barrier layer of skin.[15] Thus rate of percutaneous absorption varies at different sites of body because skin has different thickness throughout the body i.e the eyelid is approximately 0.02 inches and palm and sole about 0.16 inches.[16]

Effect of hydration: Under normal conditions water content of the SC is 5-15% but epidermis can contain water content up to 50% when hydrated. Transdermal permeability is increased by hydration of stratum corneum which can be achieved by covering or occluding the skin with plastic sheet leading to sweet and condensed water vapor causing hydration.[15]

Skin temperature and blood flow rate: Rate of penetration and hence skin permeation is increased by increase in skin temperature. This may be due to:

- Thermal energy required diffusivity.
- Solubility of drug in skin tissues.
- Increased vasodilatation of skin vessels.

Skin condition: When the barrier function is disrupted the penetration rate is greately affected by skin condition leading to increased loss of diffusive water. Skin barrier function is characterized by transepidermal water loss (TEWL). Different factors can increase skin permeability such aschemical (e.g. solvents detergents, acids and alkalies), physical (e.g. weather, sunlight, and occlusion) and pathological factors (e.g. mechanical damage, pathological factors). Epidermis is removed from skin by tape stripping technique. Rate limiting step of human skin permation was investigated by using estradiol as model drug. It was reported that more resistance was provided to drug permeation by the full thickness skin (SC/E/D) than the stripped full thickness skin (E/D).[17] Skin is delipidized by mixtures of polar and non-polar solvents resulting in a substantial reduction of the barrier function of the skin. In another report, it was found that only 1-2% of hydrocortisone penetrated from areas of normal skin but 78-90% of hydrocortisone penetrated through stripped skin sites.[13]

Physicochemical factors affecting skin permeation: At site of action, therapeutic drug concentration is not achieved due to barrier properties of the skin and physicochemical properties of drug (concentration, lipid solubility, etc) causing insufficient transport of vehicle through the skin. The physical and chemical properties of a compound have a decisive influence on its penetration through the skin. It include; physical state, concentration, particle size, molecular size /molecular weight, water solubility, liposolubility /log P (octanol/water), ionization, and chemical structure: binding properties.[18]

Physical state: Liquids and solutions of substances penetrate more readily than dry particulates. Permeation of volatile liquidsinto the skin may becontrolled by the degree at which the liquid is evaporated away from the skin's surface. Other states include concentration, Particle size and Polymorphism.[18]

Molecular size /weight: Molecular size plays a prominenent role in membrane permeation. Whether molecular weight (MW) or molecular volume (V) is a better forecaster of flux (J max) or permeation coefficient (*Kp*), but in recent years simpler and less error-proned molecular weight is preferred. Absorption of molecules through normal human skin rapidly falls on a molecular weight increases over 500 Dalton A and molecular weight of lower than 100 improves epidermal uptake.[19]

Water solubility: It is observed that for sufficient permeation of substance to skin, the substance must be sufficiently soluble in water i.e dermal uptake of substance is low if water solubility is below 1 mg/l, is low to moderate if water solubility is between 1-100 mg/l and is moderate to high if water solubility is between 10-10,000 mg/l.But dermal uptake for substances will also be low if water solubility is above 10,000 mg/l and the Log P value below 0 because the substance may be too hydrophilic to cross the lipid rich environment of thestratum corneum.

Liposolubility /Log P (octanol /water): Permeation is also affected by lipophilicity or Log P_{ow} value of substance.A Substance must have good lipophilicity to cross the epidermis i.e. if a substance has Log P_{ow} values below 0, it will have poor lipophilicity that will limit penetration into the stratum corneum and hence dermal absorption while substances with Log P_{ow} values below –1 are not likely to be sufficiently lipophilic to cross the stratum corneum; therefore dermal absorption is likely to be low. If Log P_{ow} values lie between 1 and 4, it favors dermal absorption (values between 2 and 3 are optimal) particularly if water solubility is high. When value is above 4, the rate oftransfer between the stratum corneum and the epidermis limit the the rate of penetration but uptake into the stratum corneum will be high. If value of Log P_{ow} becomes above 6 then the rate of transfer between the epidermis and the epidermis will be slow and it will limit absorption across the skin leading to slow uptake into the stratum corneum itself. Intramolecular interactions i.e. electronic conjugation, interactions between polar groups, steric and hydrophobic effects affect lipophilicity markedly.

Ionization: Substance in highly ionized form proton acids have poor penetration in skin, where *Kp* for the neutral form [*Kp*(N)] is very much larger than *Kp* [*Kp*(I)] for the ionized form; factors of around 10,000 being found for a number of chromone carboxylic acids. The situation is not clear for proton bases. It seems that not only the neutral forms of thebases can permeate human skin[20] but ermeation can also be affected by nature of the vehicle and the dilution factor of the substance whether polar or non-Polar and it was observed that penetration was increased by non-polar carriers.[21]

Chemical structure: binding properties: When substances bind to skin components i.e certain metal ions particularly Ag, Cd, Be and Hg ions, acrylates, quaternary ammonium ions, sulphonium salts and heterocyclic ammonium ions, an anticipated slight reduction in uptake of chemicals through skin could be observed with these groups for the same reason i.e quinines, acid chlorides, dinitroor trinitro benzenes, halotriazines, and alkyl sulphide.

Effect of drug concentration: It was commonly observed that drug flux increases as drug concentration increases. At saturated solution (solubility), the drug shows maximum flux (J max) because no higher concentration can exist in formula than the higher concentration found at that concentrated solution. The activity of solid is unity at solubility, which is also the activity of dissolved material. Thus Jmax from all saturated solutions should be same because all saturated solutionshave the same thermodynamic activity.

Effect of vehicle: Vehicles are capable of altering the character of the epidermis to some extent when applied to the skin. For example, skin hydration is caused by increase in water which in turn decreases the barrier function. Thus skin hydration and lower skin barrier is produced by vehicle with large percentage of water together with other volatile solvent as explained for various drugs asaspirin, ketoprofen, naloxone, E2b, imipramine hydrochloride,[22] 5-FU and AZT. Vehicles that are good solvents for skin lipids, when permitted to remain in contact with the skin, will extract lipids thereby facilitating permeation such as EtOH.[23] Another effect includesfluidization of the structure of the intercellular lipids in the SC leading to increased permeation through skin which may be induced by solvent. An increase in the skin permeation rate is observed by using EtOH as a vehicle for aspirin,[23] 5-FU[24] and naloxone. It was well established that ethanol acts as CPE by mechanism of lipid extraction and 'fluidization' of SC lipid domains.Effect of 100% of EtOH onpercutaneous absorption of ketoprofen atfix concentration was observed and it was concluded that permeation rate was low initially then was followed by enhancement. Some studies also state that EtOH has been used as a vehicle due to its solvent drag mechanism based on the assumption that water molecules from viable epidermis are dragged by EtOH in SC. Ketoprofen-thermodynamic activity is increased by a mixture of EtOH and water thereby increasing permeability of ketoprofen through the SC. EtOH causes stabilization of the lipid bilayer increasing EtOH lag time.[25] It was also found that EtOH at concentration of 50% increases flux of highly polar drugs (i.e. mannitol and urea) through hairless mouse SC due to formation of new pores.[26] EtOH produced higher flux of hydrophilic drug (i.e. naloxone) at concentration of 66% than at other concentrations (i.e. 33% and 50%). FT-IR was used to screen the effects of EtOH and it indicated that as concentration of EtOH was increased peaks became broader showing increase in lipid bilayer fluidity by EtOH.[27] EtOH at very high concentration (i.e. 75%), increased flux of all drugs (i.e. estrone ammonium sulfate, hydrocortisone, estrone and E2b) mainly through pore pathways.[26] Propylene glycol (PG) is not only non volatile and hydrophilic but also good solvent for both lipophilic and hydrophilic drugs and is widely used as CPE. Flux of lipophilic drug (e.g. oestradiol) is increased by increasing PG content in SC that increases drug solubility in skin and finally flux from PG co-solvent. Flux of other drugs e.g. naloxone[27] and 5-FU was also studied by using combination of PG and water from 0 to 100% and it was observed that not only the drug solubility increases as PG concentration increases but also permeability coefficient and flux of drug in the PG/water increases as PG content in thewater increases. Higher flux of 5-FU was provided by PG at 80% than at the other percentages while higher flux of naloxone was provided at 50% and 66% PG in water (12.23 and 12.27 mg/cm^2/hr respectively) that was greater than at 100% PG (4.49 mg/cm^2/hr). [28-30]

Different types of membranes used for in vitro permeation studies: Literatures have shown that different types of membranes ranging from excised human skin to animal skin have been usedfor in vitro study of TDDS. Animal skin and other model membranes have been widely utilized in percutaneous absorption studies because of much difficulties arising in availability of excised human skin. Generally pig, rat, and rabbit skin has been widely used as they offer similar barriers the diffusion of a wide range of molecules forpenetration through human skin. Although animal skins may provide barrier and diffusion properties similar to human skin, yet they cannot replicate fully the complex nature of human skin and the *stratum corneum* barrier in particular.[31] In an attempt to reduce such issues, several researchers have developed artificialskin equivalents. Silicon membranes (PDMS) have also been used as artificial skin equivalents in a variety of percutaneous research work and some correlation between silicon membrane and skin can be drawn under very limited

conditions. Polymeric membranes like poly-alkylene carbonatemembrane[32] and celluloseacetate membranes have also been reported in percutaneous absorption studies in addition to these silicon membranes. A comparative study has been performed in rats, rabbits and man using radio labeled (^{14}C or ^{35}S) compounds e.g. haloprogin, N-acetylcysteine, cortisone, testosterone, caffeine and butter yellow to evaluate their percutaneous absorption.The results indicated that skin permeability decreases in the following order: rabbit> rat> pig and >man. Rabbit skin was used to study permeation of Flurbiprofen because literature review has reported that rabbit skin indicate higher permeability than rat, pig and even human skin.

PERMEATION ENHANCERS

A chemical that is capable of modifying the barrier to skin penetration by reversibly damaging or by altering the physicochemical nature of the stratum corneam to reduce its diffusional resistance is called "penetration enhancer" or Chemical Permeation Enhancer (CPE). They are also referred to as absorption promoters or accelerants. These are the chemical compounds that increase permeability of stratum corneum to attain higher therapeutic levels of the drug.[33-35] Ideal characteristics (limitations) of chemical penetration enhancers[33] are as follows:

- They should have complete and rapid reversible effects.
- They should ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should work unidirectional, i.e. they should prevent loss of endogenous materials from body allowing only therapeutic agents to pass into skin.
- Barrier properties should return to normal both rapidly and fully when removed from body
- They should be readily incorporated into the delivery system.
- They should be odorless, tasteless and inexpensive.
- Some CPE produce complex effects that depend on concentration e.g. increase of ADRs with increase in concentration of CPE and decrease with decrease in concentration of CPE.[32]

MECHANISM OF ACTION OF PERMEATIN ENHANCERS

Menon valuable research about mechanism of action of CPE provided an understanding of the properties and structure of epidermis.[36] CPE act on three major sites associated with lipid bilayer by various mechanisms of action which are as follows:

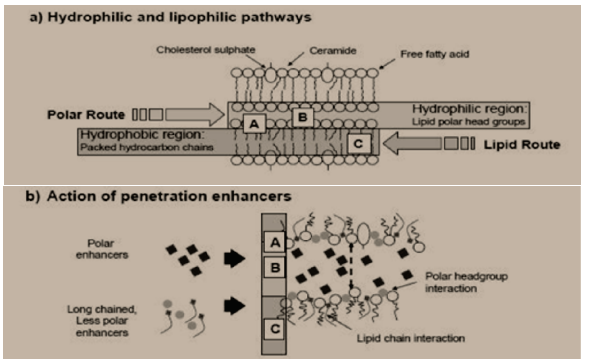

Figure 1: Schematic presentation of the proposed mechanism of action of CPE.[37]

1. Interaction with the polar head groups of the lipids (Site A).
2. Interaction in the aqueous domain of the lipid bilayers (Site B).
3. Interaction with the lipid alkyl chain (Site C). Cornified cell envelope and intercellular junctions are sites where CPEs can interact. Some CPEs may also cause lipid extraction.[7]

Action at site A: Various CPE interact with polar head of lipid group (Fig. 1, site A) through hydrogen and ionic bondings, disturb the hydration spheres of the lipids and subsequently alter head group interaction and upset the packing order at the head region.This disturbance further causesa decrease in the retarding action which this domain imposes on the diffusion of polar penetrants. A second response of above CPE effect may be to increase the volume of the aqueous layer so that more water enters the tissue. Thisexpansion (swelling) provides a greater cross-sectional area for polar diffusion (site B) and a larger fractional volume of 'free' water as distinct from the structured water at the lipid interface. This modification may also happen with simple hydration process. Thedisturbance of the interfacial structure will now tend to alter the lipid tails packing such that lipid hydrophobic route becomes more disordered and more easily traversed by a lipid-like penetrant (site C).[7-37]

Direct influence at site B: A number of enhancers can also act directly in the aqueous domain (Figure1, Site B) by increasing the solubility of this site (aquous domain) for the permeant. Solvents such as propylene glycol PG and ethanol are believed to act in this way.[21] High concentration of solvents such as dimethylsulphoxide, propylene glycol or ethanol in a vehicle or device penetrates into aqueous regionof the tissue becoming a better solvent for molecules such as hydrocortisone and oestradiol. Various reports show that the underlying mechanism of B site interaction of these solvents

is that they modify the skin permeability by altering the solubility parameter of the skin.[21] As a result, the partitioning of the drug from the vehicle into the SC increases because operational partition coefficient now favors an elevated drug concentration in the skin. The solvent then diffuses out into the dermis followed by the drug diffusing down its concentration gradient.[37]

Action at the lipid domain site C: Some CPE's can insert themselves directly between the hydrophobic tails of the lipid bilayers (Fig. 1, site C). As a result they are able to disturb lipid packing, increasing lipid fluidity and drug permeation allowing easier diffusion for lipid penetrants. In some cases, this lipid disturbance is also associated with some disturbance in polar head groups causing permeation of solutes in this region.In other words it can be said that this alteration in lipid packing can reflect back to provide an element of disorder at the polar head group region of the intercellular domain promoting polar route permeation. From various researches done in order to determine the mechanism for this disruption of lipid hydrophobic tails, it was concluded that this ability of CPE to disturb lipid alkyl chain packing is releated to their structural features i.e their long saturated alkyl chain with optimal carbon atoms 9-14 and polar head.It was also observed that C 18 was optimal carbon number for saturated long fatty chains i.e oleic acid.[37-39]

New technologies for understanding mechanism and screening of new chemical enhancers, scientists use only CPE that has established safety and efficiency in practice because many CPE interact with each other and with skin in complex manner. Recently, some new technologies (i.e. XDR, FTIR, etc) have been developed to show the mechanism of action of CPE at molecular level and even ultrastructural changes in CPE.[38]

EXAMPLES OF PERMEATION ENHANCERS

A concise description of various permeation enhancers used in transdermal drug delivery studies is given below:

Alcohols: Among alcohols, Ethanol is the most commonly used as vehicle and permeation enhancer for TDDS. For TD and topical DS ethanol, methanol and isopropyl alcohol have been used in a range of gels, creams and patches. Alcohols especially more polar members, are solvents that can cause skin irritation by delipidizing the membrane by causing extraction of intercellular lipids and disrupting the epidermis resulting in reducedbarrier function of the epidermis.[42] Methanol has been studied in various articles to evaluate its effects. Some alcohol-containing vehicles due to the solvent nature of alcohol act on sebum within the follicle and have been shown to enhance transfollicular delivery of drug molecules.[43] Various studies were coducted to study the mechanism of permeability enhancement of isopropyl alcohol (IPA). IPA was found to fluidize the epidermis and disrupt the bilayer structure of the intercellular lipids. Ethanol has dual functions, it acts as a solvent and as a permeation enhancer. Various mechanisms have been identified and reported for ethanol to act as CPE. Ethanol is also reported to increase transdermal permeation by mechanism of extracting large amount of SC lipids in some studies.[9] Ethanol is found to directly affect skin; it alters tissue solubility properties with consequent increase in drug partitioning into epidermis.[21] Ethanol increases permeation of triethanolaminesalicylate from a hydrophilic emulsion base and ketoprofen from its gel-spray formulation. To increase permeation of methyl paraben, ethanol acts as a vehicle for menthol. It is also evident from other studies that ethanol increases permeability of flurbiprofen, indomethacin, isosorbide dinitrate, zalcitabine, didanosine, zidovudine, cyclobarbita and ibuprofen.The main factor that affects this permeability is the percentage of ethanol expressed as volume fraction of ethanol (v_e vol/vol). Permeation of fluoxetin was decreased when volume fraction of ethanol was increased from 65-95% vol/vol. Similar results were also obtained with estradiol when ethanol volume fraction was modified. Underlying mechanism for decrease in permeability with increase in volume fraction of ethanol is that when voume of ethanol is increased, thedrug solubility increases which inturn decreases drug activity and finally drug partitioning and permeation into the skin.[44] It has been used as two co-solvent systems in combination with TCP and with water for drugs ibuprofen, zidovudin, didanosine, zalcitabine, regafur and alclofenac. As the volume fraction of ethanol in the two cosolvent systems was increased, permeation rate of zalcitabine, didanosine, and zidovudine was also increased and it reached a maximum at 50–60% v/v of ethanol.[30]

Propylene glycol: Propylene glycol (PG) is water soluble and viscous liquid, containing two hydroxyl groups. To distinguish it from β-propylene glycol (isomer propane-1, 3 diol), PG is also called as α-propylene glycol. PG is colourless, clear, nearly odorless and hygroscopic solvent. It is widely used in pharmaceutical and cosmoceutical industries becaue it has been proved efficient for transdermal drug delivery system. It is not only used as solvent and preservative but also as permeation enhancer in transdermal drug delivery system.

PG has been commonly used as solvent and CPE for several drugs in a variety of pharmaceutical formulations. It has been studied alone and also in combination with various other permeation enhancers. Shine et al[43] studied several glycols e.g. fatty acids, diethylene glycol and triethylene glycol as CPE. It was concluded from one study that per-

meation of highly lipophilic antiestrogen drug was increased by propylene glycol due to lauric acid in it. A number of studies have been reported that PG increases not only drug partitioning but also its permeation.[44] In one case, permeation of 5-FU was much increased with urea analogues in presence of PG as vehicle. It was found to increase flux of piroxicam, methotrexate[45] 5-FU and cyclosporine-A when used in combination with azone.Similarly flux of estradiol was also 10 times increased when PG was used along with 5% oleic acid. Enhanced flux of 5-FU was observed with a saturated solution of terpenes in a PG-water cosolvent system.[44] Although PG increased permeationof ketoprofen, verapamil HCL and heparin sodium, but it inhibited ketoprofen flux at higher concentration. PG at concentration of 80% in combination with terpenes showed increased terpene activity and maximum flux.[44] Similarly permeation of caffeine through mouse skin was also evaluated. It was observed that flux of caffeine was increased upto 13-fold and 16-fold by PG in combination with terpenes.[46] Flux of acelofenac was also found to be increased by higher concentrations of PG in combination with ethanol.[47] Various mechanisms are suggested to be responsible for its action as CPE. Few important mechanisms stated are that it competes for solvation sites of polar head groups of lipid bilayers of epidermis and thus increases the partitioning of drug into epidermis. Differential Scanning Calorimetery results have shown that PG may also interact with a-keratin and produce similar and broader transitions that increase with increase in concentration of PG.[7] It was also suggested that PG may also increase lipid fluidity by producing slight changes to two other major lipid transitions. Various other studies have also reported same mechanism for action of PG as CPE i.e. PG interact with epidermis keratin, occupy its hydrogen bonding sites and solvates this keratin. Another mechanism states that PG enters the tissue in larger amount and increases intracellular diffusion of drugs when used in combination with azone.

Polyethylene Glycol as solubility and permeation enhancer: Polyethylene glycol (PEG) is also known as poly (ethylene oxide) (PEO), polyoxyethylene (POE) and carbowax (trade name). It is one of the commercially important types of polyether. PEG, PEO or POE refers to an oligomer or polymer of ethylene oxide. PEO and PEG are liquids or low-melting solids depending on their molecular weights.

Polyethylene glycol is odorless, non-toxic, neutral, nonvolatile, lubricating and nonirritating. PEG is soluble in water, benzene, methanol, dichloromethane and is insoluble in hexane and diethylether. It produces non-ionic surfactants, when couled to hydrophobic molecules. It also contains toxic impurities i.e 1,4-dioxane and ethylene oxide. It causes nephrotoxicity if applied to damaged skin. Polyethylene glycol (PEG) is a condensation polymers of ethylene oxide and water having general formula $H(OCH_2CH_2)_nOH$, where "n" is the average number of repeating oxyethylene groups that typically range from 4 to about 180. These are available over a wide range of molecular wight's i.e. 300 g/mol to 10,000 g/mol. Simply it can be stated that PEG has a tendency to be referred to as oligomer and polymer having molecular mass below 20,000 g/mol. PEGs with molecular weights of 1500±20000 are usually used for the manufacture of solid dispersions and solutions. Their average molecular weight is indicated by the number included in the names of PEG e.g. a PEG with n=9 would have an average M.W. approximately 400 Da and would be labeled as PEG 400. As MW of PEG increases, viscosity also increases. PEG is most commonly used as a good solvent and CPE. The main factor influencing the performance of a solid dispersion is drug/carrier (PEG) ratio in a solid dispersion. If the percentage of PEG is very high, it can cause complete absence of crystallinity of the drug leading to greater increase in solubility and thus release rate of drug while if drug percentage is very high, it forms small crystals within dispersion leading to decreased molecular dispersion.[48-50]

Solubilization power of any solvent system gives a quantitative estimate of the solubilization potential of the co-solvent. Solubilization power of various co-solvents was determined and it was found to vary as ethanol>glycerol>PG>PEG 400 in water and ethanol>PG>glycerol>PEG 400 in buffer. The polarity of the solvent varies as glycerol>PG>ethanol>PEG 400 as shown by the dielectric constants of the solvents. It was assumed that as it appears that solubility of drug is not affected by co-solvent polarity factor only, there must be other important factor that governs the solubility of drug i.e ability of solvent to form hydrogen bonds with the hetero-atoms in the drug molecule.Same results and observations were also reported by Seedher and Bhatia.[51] Although PEG has been used as co-solvent but solubility enhancement with it was least. Researchers also tried different ratios of PEG to increase solubility of drug dispersion i.e 1:1 and 2:1 PEG 8000: drug solid dispersions. It was found difficult to prepare solid dispersion using PEG 400 because it led to the formation of sticky mass that was difficult to dry. This solid dispersion solubility was studied in water and PB (pH 7.4) and it was concluded that it showed higher solubility in water when used in combination with buffer. The total increase in aqueous solubility due to the combined effect of solid dispersion and buffer (146-486 µg/ml) was 3.33 times where 146 µg/ml shows aqueous solubility and 486 µg/ml shows PB solubility. Various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid, and capric acid) and anionic surfactant (polyoxyethylene-2-oleyl ether,

polyoxy ethylene-2-stearate ether) were studied by Lee[43] to see their effects on the release of triprolidone.

Water as a penetration enhancer: Free water present within the tissue acts as penetration enhancer and modifies solubility of drug in epidermis thus altering its partitioning from vehicle into membranes.[50] Penetration of both hydrophilic and lipophillic permeants is increased by hydration of epidermis. Increased hydration of epidermis leads to swelling and opening of epidermis compact structures causing an increase in drug penetration.[51]

Other CPE are glycerides, pyrrolidones, sulfoxide and similar compounds, Fatty acids and esters, essential oils, terpenes and terpenoids, polyvinyl alcohol and urea which were used in various topical and transdermal formulations.

CONCLUSION

TDDS has become viable and successful dosage form due to its clinical benefits, strong market value, regulatory precedence and industry interest clinching that the system might be the most efficient and the safest dosage form for drug delivery in upcoming clinical span.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.