Review Article

A Novel Approach: Transdermal Gel

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ABSTRACT

The skin forms the body's defensive perimeter against what is in reality the biologically hostile environment we humans live in. The delivery of drug through skin has been beneficial for long time due to large surface area of skin which is exposed to vast number of circulatory and lymphatic networks and the routes is easy to access. A topical delivery is one that is applied directly to any external body surface and they are only for localized action. Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. However both topical and transdermal products are intended for external use. But topical products are intended for localized action on one or more layers of the skin whereas transdermal drug delivery systems use the percutaneous route for systemic effect. The delivery of drugs through the skin provides several important advantages over traditional oral and intravenous delivery routes. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through the skin at predetermined rate with minimal inter and intra patient variability. The discovery of TDDS is a major breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass hepatic metabolism has accelerated transdermal drug delivery research in pharmaceutics.

Keywords: Gelling agents, pecutaneous penetration of drug, penetration enhancers, transdermal drug delivery, transdermal gel

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INTRODUCTION

In pharmaceutical industry developing a controlled dosage form has become increasingly important. Therefore various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. has been developed. Transdermal delivery has been emerged as a novel tool over injectables and oral routes as it increases the patient compliance and avoids the first pass hepatic metabolism. In transdermal drug delivery system the drug is delivered in a controlled rate into systemic circulation through the skin [1,2]. The intact skin is used as a port to administer a drug in transdermal gels but skin act as a barrier to ingress the material, it only allows a small material to penetrate over a period of time into systemic circulation. The one way to deliver a sufficient amount of drug transdermally is in which the drug agent is applied to skin in a patch and another one is by incorporating a drug in a gel. From both patches and transdermal gels medicament is delivered in a controlled diffusion mechanism. Excitement dwindled to disappointment, when the limitations of the existing transdermal technology became evident. Factors such as local skin irritation associated with certain drugs, limitation on the dose of the drug to be delivered transdermally, lag time associated with the delivery of the drug across the skin and variation of the absorption rate based on a site of application, caused interest in transdermal technology to decline [3]. But many technology companies have generated additional clinical data that shows the

potential of advanced transdermal technology in spite of its limitations to cure so many diseases.

Advantages of transdermal gels over patches [4]

- Heat, cold, sweating and showering prevent the patch from adhering to the skin surface. Therefore a new patch has to be applied daily.
- If patch doesn't adhere after a first day, then doctor often give them various types of tapes and bandages to use, but none of them have proven to be satisfactory.
- The patches repeatedly fall off, therefore a patient has to increase the number of refills in a month.
- There are reports of loss of efficacy of patches due to unreliable adhesive properties.
- Patches pulled skin away which cause bleeding and inflammation. The skin beneath the skin patch becomes abraded and wet to tough. When patch is removed, skin get adhered to it and left an open sore.
- Most patches depend on concentration gradient of drug within the matrix or reservoir to drive active drug through skin. As a result, a high percentage of dose can remain within the patch when delivery get stopped or slow down.
- For elderly or patients with psychiatric disorders, the medication through patches also proves to be challenging as they rip them off which must be kept in place for hours or even days.

TRANSDERMAL GELS

Gels are semisolid systems in which a liquid phase is constrained within a three dimensional polymeric matrix of natural or synthetic gums in which a high degree of physical or chemical cross linking has been established. Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state [5]. The USP defines gel as semisolid system consisting of either suspension of small inorganic particles or large organic molecules within the liquid. Gels have higher aqueous component which allows greater dissolution of drugs, which in turn easily migrate the drug through a vehicle, compared to ointment and creams. Therefore, they are superior in terms of use and patient compliance [6]. Transdermal gels are designed to deliver a therapeutically effective amount of drug across a patient's skin. However both topical and transdermal gels are intended for external use. But topical gels are intended for localized action on one or more layers of the skin whereas transdermal gels use the percutaneous route for systemic effect. Gel formulations provide faster drug release as compared to the ointments and creams in which the drug is dispersed as fine particles, but dissolution is inadequate because of their limited water content. Gels have a higher aqueous component that permits greater dissolution of drugs, and also permit easier migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream bases. Gels are generally considered superior in terms of use and patient compliance.

Topical versus Transdermal gels [7]

Table1: comparison between topical and transdermal gels

Topical gels	Transdermal gels
➢ Topical delivery is designed to deliver drug into the skin for treating dermal disorders.	➢ Transdermal delivery is designed to deliver drug through the skin (percutaneous absorption) to the general circulation for systemic effect.
➢ Target site: • skin	➢ Target site: • Site other than skin • Must penetrate stratum corneum (10-15microns thick) to deliver drug to capillary beds between epidermis (50-150 microns) and dermis.
➢ These are developed to minimize flux of drug through skin while maximizing its retention in the skin.	➢ It is maximize the flux through the skin into systemic circulation and simultaneously minimize the retention and metabolism of drug in the skin.

Advantages of transdermal gels [8, 9]

1. Avoids the first pass hepatic metabolism
2. Drug delivery can be easily eliminated in case of toxicity.
3. Fewer side effects as there is reduced plasma concentrations of drugs.
4. Dosing frequency get reduced which increases the patient compliance.
5. Through transdermal gels drug is delivered in a steady rate over an extended period of time.
6. Conventional dosage forms follow a peak and valley pattern of drug release kinetics in blood and tissue. Transdermal drug delivery system is designed to release drugs at a predetermined rate and continuously avoiding unnecessarily high peaks and sub therapeutic troughs in plasma drug levels.
7. Increases the therapeutic value of many drugs as it avoids the problems associated with drugs e.g. GI irritation, nausea, vomiting, heartburn and increased appetite after oral therapy.
8. Provides ease of rapid identification of medication in emergencies, non-responsive patients, unconscious or comatose patients.
9. Equivalent therapeutic effect with lower dose of drug can be achieved than is necessary when drug is given orally.
10. Drugs that are degraded by enzymes and acids in the gastrointestinal system can be administrated by incorporating in transdermal gels.
11. Continuity of drug administration permitting the use of a drug with short biological half-life.

Limitations of transdermal gels

- Transdermal gels are unsuitable for drugs that irritate or sensitize the skin.
- Transdermal gels are not suitable for drugs which have very low or high partition coefficient. Drug should have favourable partition coefficient (logP 1-3).
- For heavy drug molecules (>500Da) it becomes to penetrate the stratum cornea.
- Transdermal gels are not favorable for drugs which are extensively metabolized in skin.
- Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drugs entry imposed by skin's impermeability.
- Many drugs with a hydrophilic structure permeate the skin too slowly are of less therapeutic effect.

Desirable properties of gels:

- It should be inert, compatible with other additives and non-toxic.
- It should be stable at storage condition.
- It should be free from microbial contamination.
- It should maintain all rheological properties of gel.
- It should be washable with water and free from staining nature.
- It should not affect biological nature of drug.
- It should be convenient in handling and its application.
- It should possess properties such as thixotropic, greaseless, emollient, non-staining etc.

Classification of gels [10]

1. On the basis of phase system:

- Two phase system: The gel may consist of floccules of small molecules rather than large molecules. The gel structure is not always stable in these systems. These gels may be thixotropic, semi-solid on standing and become liquid on agitation.
- Single phase system.

2. On the basis of chemical nature:

- Inorganic gel
- Organic gel

3. On the basis of structure:

- Physical gels: unstable at high temperature or in solvents.
- Chemical gels: not tough due to uneven temperature.
- Slide ring gels: in that polymer chains are covalently cross did not link nor attractively interacted rather they are interlocked.

ORGANOGELS [11]

Organogel, a viscoelastic system, is a semi-solid preparation which has an immobilized external apolar phase. Organogels are thermodynamically stable in nature and regarded as matrices for the delivery of bioactive agents. The thermodynamic behavior of the organogels results in the formation of fibrous structure because of

which organogels resides in a low energy state.

Advantages [12]

- They don't form semisolid preparation on standing.
- Organogels decreases the diffusion rate of drugs because the drug is dissolved in polymer and transported between chains.

Disadvantages

- When a gel stands for some time, it shrinks naturally and some of its liquid is pressed out, known as syneresis.

Properties of organogels

1. **Viscoelasticity-** Organogels are formed due to physical interactions among the gelator molecules. When the stress is increased, the physical interaction forces between the fibres starts getting weakened until the shear stress is more enough to completely disrupt the interactions amonst the fibres, when the organogels starts flowing.
2. **Non-birefringence-** The organogels when viewed under polarized light appears as dark matrix. This is due to the isotropic nature of organogels which does not allow the polarized light to pass through the matrix. This property of organogels of doesn't allow the polarized light to pass through the matrix is called non-birefringent.
3. **Thermoreversibility**When the organogels are heated above a critical temperature, they starts flowing as the organogels loses its solid matrix-like structure. This happens due to the disruption of the physical interactions amongst the gelator molecules attributed to the increase in thermal energy within the organogels. When the heated organogels are cooled, they revert back to the stable configuration as the physical interaction amongst the organogelators.
4. **Thermostability**- The organogels are inherently thermostable in nature. The stability of the organogels may be attributed to the ability of the gelators to undergo self-assembly, under suitable conditions, so as to form organogels. As the gelators undergo self-assembly, it results in the decrease in the total free energy of the system and renders the organogels as low-energy thermostablesystem. Due to the inherent thermostability of the organogels, they have been proposed as a delivery vehicle for bioactive agents and for cosmetic applications where a longer shelf-life is desirable.
5. **Chirality-** Thermoreversibility of the gels formed due to the formation of the selfassembled solid-fiber network which is associated with the chirality. In general, it has been found that a good solid-fiber gelator has a chiral center whereas chirality does not have any effect on fluid-fiber gelators. Due to the presence of chiral centres within the gelators, gelators form compact molecular packing which provides the thermodynamic and kinetic stability to the organogels.
6. **Biocompatibility-** Initially, organogels were formed by using various non biocompatibleorganogels which make the organogelsnonbiocompatible. Of late, research on organogels using various biocompatible constituents has opened up new dimensions for the use of the same in various biomedical applications.

HYDROGELS [13]

Hydrogels are water swollen polymer matrices, with a huge tendency to absorb water. Their ability to swell, under physiological conditions, makes them an ideal material for biomedical applications. The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic, carboxylic, amidic, primary amidic, sulphonic and others that can be found within the polymer backbone or as lateral chains. It is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers, or by producing interpenetrating networks (IPN) or semi-interpenetrating polymer networks (s-IPN) of hydrophobic and hydrophilic polymers.

Classification of hydrogels [14]:

Table 2: Classification of hydrogels

S.No.	Classification	Contents
1.	Source	Natural Synthetic
2.	Component	Homopolymer Copolymer Multipolymer
3.	Preparation Method	Simultaneous polymerization Crosslink of polymer
4.	Electric charge	Anion Cation Zwitter ion
5.	Physical structure	Amorphous Semi crystalline Hydrogen bonded
6.	Crosslink	Covalent bond Intermolecular foce

Advantages of hydrogels [15-17]

- Hydrogels possess a degree of flexibility very similar to natural tissue, due to their significant water content.
- Entrapment of microbial cells within Hydrogel beads has the advantage of low toxicity.
- Environmentally sensitive Hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
- Timed release of growth factors and other nutrients to ensure proper tissue growth.
- Hydrogels have good transport properties.
- Hydrogels are Biocompatible.
- Hydrogels can be injected.
- Hydrogels are easy to modify.

Disadvantages of hydrogels [18]

- Hydrogels are expensive.
- Hydrogels causes sensation felt by movement of the maggots.
- Hydrogels causes thrombosis at Anastomosis sites.
- The surgical risk associated with the device implantation and retrieval.
- Hydrogels are non-adherent; they may need to be secured by a secondary dressing.
- Hydrogels used as contact lenses causes lens deposition, hypoxia, dehydration and red eye reactions.
- Hydrogels have low mechanical strength.
- Difficulty in handling.
- Difficulty in loading.
- Difficulty in Sterilization.

GELLING AGENTS [19]

For the preparation of gels, polymers are essential as they give the structural network. Such polymers are known as gelling agents. There are many gelling agents. Some of the common ones are acacia, alginic acid, bentonite, Carbopols (now known as carbomers), carboxymethylcellulose, ethyl-cellulose, gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate (Veegum), methyl-cellulose, poloxamers (Pluronics), polyvinyl alcohol, sodium alginate, tragacanth, and xanthan gum. Though each gelling agent has some unique properties, there are some generalizations that can be made.

1. If the gelling agent is added to the dispersing medium in a haphazard manner, there is a tendency for the agent to "clump." The outer molecules of the gelling agent contact the medium first and hydrate forming a surface layer that is more difficult for the medium to penetrate. The clumps will ultimately hydrate, but it will take more time. A much more efficient manner is to sieve the agents onto the surface of the medium a little at a time as the medium is stirring. Using glycerin as a wetting agent will sometimes minimize clump formation.
2. Some gelling agents are more soluble in cold water than in hot water.

Methylcellulose and poloxamers have better solubility in cold water while bentonite, gelatin, and sodium carboxymethylcellulose are more soluble in hot water. Carbomers, tragacanth, and alginic acid gels are made with tepid water.

3. Some gelling agents (carbomers) require a "neutralizer" or a pH adjusting chemical to create the gel after the gelling agent has been wetted in the dispersing medium.
4. Most gelling agents require 24-48 hours to completely hydrate and reach maximum viscosity and clarity.
5. Gelling agents are used in concentrations of 0.5% up to 10% depending on the agent.
6. It is easier to add the active drug before the gel is formed if the drug doesn't interfere with the gel formation.

Gel forming substances

Gel forming polymers are classified as follows:

1. Natural polymer

a. Proteins

i. Collagen
ii. Gelatin

b. Polysaccharides

i. Agar
ii. Alginic acid
iii. Sodium or Potassium carrageenan
iv. Tragacanth

2. Semisynthetic polymers

a. Cellulose derivatives

i. Carboxymethyl cellulose
ii. Methylcellulose
iii. Hydroxypropyl cellulose

3. Synthetic polymers

a. Carbomer

i. Carbopol -940
ii. Carbopol -934
iii. Carbopol -941

b. Poloxamer

c. Polyacrylamide

d. Polyvinyl alcohol

4. Inorganic substances

i. Aluminium hydroxide
ii. Bentonite

5. Surfactants

i. Cetostearyl alcohol
ii. Brij – 96

DRUG TRANSPORT THROUGH SKIN [20,21]

The penetration of drug into viable epidermis and dermis is viable to achieve. But once transepidermal penetration has been achieved, the continued diffusion of drug into epidermis is likely to result in drug transfer into microcirculation of the dermis and then into general circulation. Topical products may unintentionally reach systemic circulation, it is usually in sub-therapeutic concentrations, and does not produce effects of any major concern except possibly in special situations, such as pregnant or nursing patient. On the other hand, transdermal drug delivery systems use the percutaneous route for systemic drug delivery, but the skin is not the primary target organ.

Percutaneous absorption

Percutaneous absorption involves the transfer of drug from the skin surface into the stratum corneum, under the aegis of concentration gradient, and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis and into microcirculation. The skin behaves as a passive barrier to diffusing molecules. Molecular penetration through the various regions of the skin is limted by the diffusional resistances. The total diffusional resistance (R_{skin}) to permeation through the skin has been described by chein as

$$\mathbf{R_{skin} = R_{sc} + R_e + R_{pd}}$$

R = diffusional resistance

sc = stratum corneum, e = epidermis

pd = papillary layer of dermis

The role of hair follicles and sweat glands must be considered. But there effect is minimized because less fractional area has been occupied by these appendages. In early stages through absorption, transit through these appendages is large, especially for lipid molecules and those whose permeation through stratum corneum is low.

The stratum corneum can be taken as passive diffusion membrane but not an inert system, it has affinity for an applied substance. The correlation between external and surface concentrations is given in terms of solvent membrane distribution coefficient Km. This is expressed as Fick's First Law of Diffusion:

$$\mathbf{J_s = \frac{K_m D C_s}{\delta}}$$

and

$$K_p = \frac{K_m}{\delta}$$

where,

$K_p$is the permeability coefficient

J_s is the steady state flux of solute

C_s is the concentration difference of solute across membrane

δ is the membrane thickness

K_m is the partition coefficient of the solute between the membrane and the bathing solution.

PERMEATION PATHWAYS OF TRANSDERMAL GEL THROUGH STRATUM CORNEUM [22, 23]

For some lipophilic drugs the principle barrier to permeation may reside in the essentially aqueous viable epidermis membrane, for most molecules the stratum corneum is the rate limiting barrier to delivery. There are essentially three pathways by which a molecule can traverse intact stratum corneum:

i. via the appendages (shunt routes)
ii. through the intercellular lipid domains
iii. transcellular route

These pathways are not mutually exclusive, and it is likely that most molecules will pass through the stratum corneum by a combination of these routes.

I. TRANSAPPENDAGEAL TRANSPORT (SHUNT ROUTE TRANSPORT)

The appendages (hair follicles, sweat ducts) offer pores that bypass the barrier of the startum corneum (SC). These openings onto the skin surface occupy only around 0.1% of the total surface. And hence their contribution to the total drug flux at pseudo-steady state is generally regarded as being insignificant. Eccrine sweat glands may be numerous in several areas of the body (e.g. the palms and soles), but their openings onto the skin surface are still very small. The opening of the follicular pore of the skin surface is larger than that of the eccrine glands, though they are less numerous. In addition to initial rapid drug delivery and the greater significance in vivo than in vitro, transappendageal transport may also be important for large polar molecules and ions that would transverse poorly across the bulk of the stratum corneum.

II. TRANSCELLULAR ROUTE

The transcellular pathway for a molecule to traverse intact stratum corneum is often regarded as providing a polar route through the membrane. Indeed, the cellular components that the solute diffuses through – predominantly highly keratin – do provide an essentially aqueous environment, and hence diffusion of hydrophilic molecules through these keratinocytes is rapid. However, the keratin filled cells do not exist in isolation and they are bound to a lipid envelope that connects to a intercellular multiply bilayered lipid domains. Thus, molecule crossing the intact stratum corneum via the transcellular route faces numerous hurdles. First, there is partitioning into the keratinocyte, followed by diffusion through the hydrated keratin. In order to leave the cell, molecule must partition into the bilayer lipids before diffusing across the lipid bilayer to the next keratinocyte. In traversing the multiple lipid bilayers the molecule must also sequentially partition into and diffuse across the hydrophobic chains and the hydrophilic head groups of the lipids, and there are estimated to be between 4 and 20 such lamellae between each keratinocyte.

III. INTERCELLULR PATHWAY

The intercellular SC spaces were initially dismissed as a potentially significant diffusion pathway because of the small volume they occupy. However, the physical structure of the intercellular lipids was thoughts to be significant factor in the barrier properties of the skin. The lipid lamella in the SC plays a key role in the barrier function of the skin. The major lipids are ceramides, cholesterol, and free fatty acids. Both diffusional and morphometric ducts have been presented to support lipid and polar pathways through the intercellular lipids of SC. Some studies proposed that penetration could occur across the SC by one of two parallel pathways: the lipoidal pathway and the pore pathway, with this barrier existing in series with an epidermal-dermal porous barrier. Extremely polar permeants are rate-limited by the pore pathway of the SC with its limiting permeability coefficient, whereas permeants with intermediate

polarity are transported by the lipoidal pathway and exhibit a lipophilicity-dependent permeability coefficient. However, some studies suggested thet the lipophilic solutes may be transported through both a polar and nonpolar pathway through the intercellular region. Finally, Menon and Elias interpreted that extra cellular lacuna domains were a potential pore pathway for penetration of polar and nonpolar molecules across the SC, the continuity of such a pathway is unclear.

IV. HAIR FOLLICLES AND SWEAT DUCTS

Possible routes of penetration through hair follicles could involve the hair fibre itself, through the outer root sheath of the hair into the viable cells of the follicles, or through the air filled canal into the sebaceous gland. In addition, the release of sebum by the sebaceous glands may provide a lipoidal pathway that may influence absorption by this route. The route for the sweat duct may involve diffusion through either the lumen or walls to below the epidermis and through the thin ring of keratinized cells. Dense capillary networks closely envelop the bases of both the hair follicles and sweat ducts, providing access to the circulation for most molecules reaching theses regions. In the hair follicle, for example the outer root sheath is thought to be of greatest importance for drug delivery, as this layer is continuous with the epidermis and is indistinguishable from it, which potentially allows for increased surface area for absorption beneath the surface of skin.

Factors Affecting Drug Permeation: [24, 25]

I. Properties of the Permeant

The capacity of a molecule to enter the skin depends on its ability to penetrate, consequently the hydrophobic and hydrophilic barrier layers of the skin. Permeation through SC depends on the following physiochemical parameters:

Partition

Drugs must partition into the lipophilic domain of the SC, then into the more hydrophilic mileu of the viable epidermis before reaching the systemic circulation. Therefore, drugs possess balanced lipid and water solubility in order to be systemically absorbed. Drugs that are too hydrophilic are unlikely to partition from the vehicle into SC, whereas drugs that are too lipophilic will have a high affinity for the SC and unlikely to partition into the viable epidermis.

Molecular Size

The molecular weight of a chemical is a good indicator of its molecular size, which in turn, is related to the diffusion coefficient. As drug diffusion through the skin is a passive mechanism, small molecules traverse the human skin more rapidly than larger molecules. Candidates for transdermal delivery generally have a MW≤ 500 Dalton.

Solubility/ melting point

Organic materials with high melting points and with high enthalpies of melting have relatively low aqueous solubilities at normal temperatures and pressures. Thus, there is a clear relationship between melting point and solubility, and there are several theoretical models available that predict solubilities from melting point data.

From intercellular permeation pathway it is clear that lipophilic molecules tend to permeate through the skin faster than more hydrophilic molecules. Thus, solubility within the intercellular lipids can be correlated with the permeability coefficient.

Ionization

Considering the nature of the stratum corneum barrier to transdermal delivery, residing largely within the lipid bilayer domains, it is widely believed that ionisable drugs are poor transdermal permeants. Indeed, many of the arguments against using weak acids and weak bases that will dissociate to varying degrees depending on pH of the formulation (and on tha pH of the stratum corneum) are founded in the pH-partition hypothesis.

According to hypothesis, which was developed for absorption of drugs through the gastrointestinal tract, only the unionized form of the drug can permeate through the lipid barrier in significant amounts.

II. Physiochemical properties of drug delivery systems:

1. Release characteristics: Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depend on the following factors:

a) Whether the drug molecules are dissolved or suspended in the delivery system.
b) The interfacial partition coefficient of the drug from the delivery system to skin.
c) pH of the vehicle.

2. Enhancement of transdermal permeation: Majority of drugs will not penetrate the skin at rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancer into the system.

III. Physiochemical and pathological conditions of skin:

1. Reservoir effect of horny layer: The horny layer especially is deeper layer can sometimes act as a depot and modify the transdermal permeation of drugs. This effect is due to irreversible binding of a part of the applied drug with the skin.
2. Lipid film: The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.
3. Skin hydration: Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to accumulation of sweat. Increased hydration appears to open up the dense closely packed cells of the skin and increases its porosity.
4. Regional variation: Differences in nature and thickness of the barrier layer of skin causes variation in permeability.
5. Pathological injuries to the skin: Injuries that disrupt the continuity of the SC increases permeability due to increased vasodialtion caused by removal of the barrier layer.
6. Skin temperature: Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of thermal energy required for diffusivity.
7. Cutaneous self-metabolism: Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and the topical bioavailability of the drug is gently reduced.

PENETRATION ENHANCEMENT [26]

To increase the penetration of drug across stratum corneum, penetration enhancers are used. Some of the desirable properties of penetration enhancers are:

- They should be non toxic, non irritating and non allergic.
- The activity and duration of action of penetration enhancers should be predictable and reproducible.
- They should not have any pharmacological action in the body.
- The penetration enhancers should work unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogeneous material from the body.
- The penetration enhancers should be compatible with drugs and excipients.

Types of penetration enhancers

1. Chemical penetration enhancers
2. Physical penetration enhancers

Chemical penetration enhancers: Chemical penetration enhancers involves the use of chemicals to allow the entry of poorly penetrating molecules to across the skin' barrier. Substances reported to render the stratum corneum more permeable include alcohols, polyalcohols, pyrrolidones, amines, amides, fatty acids, sulphoxides, esters, terpenes, alkanes, surfactants and phospholipids.

Physical penetration enhancers: In this physical and electrical methods are used as penetration enhancers. This includes the iontophoresis, phonophoresis, electroporation and photomechanical waves.

Mechanism of action of penetration enhancers [27]

There are so many ways by which penetration enhancers increases the penetration of drug. They can act by their direct action on skin or by modifying the formulation. Mechanism of action of penetration enhancers which directly act on skin are:

i. They directly act on stratum corneum intercellular keratin, denature it or modify their confirmation by causing swelling and by increasing hydration.
ii. They act on desmosomes which maintain the cohesion between corneocytes.
iii. They cause the disruption of the lipid bilayer and the enhancer gets heterogeneously concentrated within the domains of bilayer lipids.

iv. They alter the solvent nature of the stratum corneum to modify partitioning of the drug or of a cosolvent into the tissue.

The above mechanisms of action are of peneteration enhancers which effect the stratum corneum and increases the penetration of drug by causing pilid disruption, protein modification and by promoting partitioning of drug. In addition, the indirect mechanisms of actions of enhancers are:

i. By modifying the thermodynamic activity of the vehicle. Rapid permeation of a good solvent from the donor solution, such as ethanol, leave the permeant in a more thermodynamically active state than when the solvent was present—even to the point of supersaturation.

By solubilising the permeant in the donor (e.g. with surfactants), especially where solubility is very low as with steroids in aqueous donor solutions, can reduce depletion effects and prolong drug permeation.

REFERENCES

1. Kshirsagar NA. Drug delivery systems. Indian Journal of Pharmacology 2000;32:S54-S61.
2. Lieberman, A Herbert, Rieger MM, Banker GS. Pharmaceutical Dosage Forms: Disperse Systems. 2nd ed. Informa health care USA: Inc. New York; 1996. 405-411.
3. KR Vinod, P Sravani, D Bandi, BB Teja. Transdermal drug delivery System-overcoming challenges of popular drug delivery system. International Journal of Pharma World Research 2010;1(3):1-14.
4. Wokovich AM, Prodduturi S,Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. European Journal of Pharmaceutics and Biopharmaceutics Aug 2006;64(1):1-8.
5. en.wikipedia.org/wiki/Gel.
6. Swarbrick J, Boylan JC. Encyclopedia of Pharmaceutical Technology. New York; Marcel Decker; 2001.169.
7. Mehta R. Topical and Transdermal Drug Delivery: What a Pharmacist Needs to know: 2004 Feb 9 [cited by 21]; available from: www.inetce.com/articles/pdf/221-146-04-054-h01.pdf
8. Keleb E, Sharma Rakesh K, Mosa EB, Z aljahwi A. Transdermal Drug Delivery Systems- Design and Evaluation. International Journal of Advances in Pharmaceutical Sciences 2010;1:201-211.
9. Loyd Allen V. Transdermals: Skin as a part of Drug Delivery System. International Journal of Pharmaceutical Compounding 2010;13(5).
10. Gupta S, Singh Ravindra P, *et al*. Organogel. A viable alternative for existing carrier system. IJCP, 2004, 1-4.
11. Sahoo S, Kumar N, Bhattacharya C, Sagiri SS, Jain K, Pal K *et al*. Organogels: Properties and Application in Drug Delivery. Designed Monomers and Polymers 2011; 14:95-108.
12. Gupta S, Singh Ravindra P, Sarkar A, Panchal H, Pandey D.Organogel:A viable alternative for existing carrier system. International Journal of Comprehensive Pharmacy 2011;5(2):1-5.
13. Ganji F, Vaseghani-Farahani E. Hydrogels in Controlled Drug Delivery Systems. Iranian Polymer Journal 2009;18(1):63-88.
14. Dumitriu S. Polymeric biomaterials. 2nd ed. New York: CRC Press: 2002. 1-17.
15. Todd Hoare R, Daniel Kohane S. Hydrogels in drug delivery: Progress and challenges. Polymer 2008 jan 19;49:1993-2007.
16. Peppasa NA,Buresa P, Leobandunga W, Ichikawab H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm 2000 jul;50:27-46.
17. Qiu Yong, Park Kinam. Environment-sensitive hydrogels for drug delivery. Adv Drug Delivery Rev 2012 sep 13;64:49–60.
18. Ratner BD, Hoffman AS, Schoen FJ, Lemons JE. Biomaterials Science: An introduction to materials in medicine. 3rded. New York: Published by academic press; 1996. 60-64.
19. Componding gelling agents. 1996; Available from: http://pharmlabs.unc.edu/labs/gels/agents.htm
20. Potts Russel O, Hadgraftjonathan H. Transdermal Drug Delivery. 2nd ed. United States of America: Marcel Dekker, Inc; 2004. 1-8.
21. Aulton ME, Taylor KMG. Pharmaceutics – The science of dosage form design. 2nd ed. China: Churchill Livingstone: 2002. 571-578
22. Tortora Gerard J, Reynolds Grabowski Sandra. Principles of anatomy and physiology. 9th ed. Canada: John Wiley and Sons; 2000. 140-151.
23. Adrian Williams C. Transdermal and Topical drug delivery. New York: Pharmaceutical Press; 2003. 30-33.
24. A Heather, Benson E, C Watkinson. Topical and Transdermal Delivery: principles and practice. Canada: John Wiley and Sons; 2012.
25. GhoshTapash K, R Bhaskara. Theory and Practice of Contemporary Pharmaceutics. United States of America: CRC Press LLC; 2000. 431-435.
26. PathanInayat B, Setty CM. Chemical penetration enhancers for transdermal drug delivery systems. Tropical journal of pharmaceutical research 2009 aug; 8(2): 173-179.
27. Singlavikas, Sainiseema, Singh gurpreet, Rana AC, Joshi Baibhav. Penetration enhancers: A novel strategy for enhancing trandermal drug delivery. International research journal of pharmacy 2011 dec 19; 2(12): 32-36.