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Review Article

TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. The development of transdermal drug delivery systems is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of a drug molecule to the demonstration of sufficient drug flux in an ex vivo and/or in vivo model the fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale-up and manufacturability), and most important, the economy. This review article provides an overview of TDDS, its advantages over conventional dosage forms, drug delivery routes across human skin, penetration enhancers, various components of Transdermal patches, types of Transdermal patches.

Keywords: TDDS, Topical drug delivery, Types of transdermal patches.

INTRODUCTION

During the seventies, the newer forms of medication did not match rapid growth of new drugs. From eighties a sort of reverse trend is being witnessed. Research and Development activities have become far more vigorous in the field of novel drug delivery system, rather than in the research for newer drugs. The enormous cost, long drawn time and uncertainty about the reward have dampened the discovery of newer drugs. These novel drug delivery systems are developed by the application of the concepts and techniques of controlled release drug administration which cannot only extend the potent life of existing drug but also minimize the scope and expenditure of testing required for FDA approval and which make clinically already established drugs do their therapeutic best [1].

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and maintain the desired drug concentration. Many novel drug delivery systems have been developed e.g. Transdermal, Intrauterine, Intravaginal, and Implants etc. These drug delivery systems have added a new dimension of optimizing the treatment of several disease conditions by modifying various pharmacokinetics parameters. This drug delivery system releases the drug either by zero order kinetics or by first order kinetics or by both simultaneously.

Transdermal drug application has been well known since ancient times. Several ancient cultures used ointments, pastes, plasters and complex inunctions in the treatment of various symptoms or disease.

In 1877 Fleischer [1] declared that the skin is totally impermeable and this extreme view could not hold for long time. In 1957 Monash [1] proved a superficially located barrier in the skin as an obstacle to the penetration. These pioneering works were followed by extensive research ultimately proving that the stratum corneum was the main barrier to percutaneous absorption and substances/drugs cannot easily penetrate through it due to its nature. Transdermal drug delivery system releases the drug by zero (or pseudo zero order) or by first order or both kinetics and which maintain the drug level for prolonged period for desired action. Apart from this Transdermal Drug Delivery System is having various advantages and disadvantages discussed as

ADVANTAGES OF TDDS [2, 3]

1. Avoids hepatic first pass metabolism.
2. Maintains constant blood levels for longer period of time.
3. Improve bioavailability.
4. Decrease the dose to be administered.
5. Decrease side or unwanted effects.
6. Decrease gastrointestinal side effects.
7. Easy to discontinue in case of toxic effects.
8. Increase patient compliance.

DISADVANTAGES OF TDDS [2, 3]

1. Cost is high.
2. TDDS cannot deliver ionic drugs.
3. TDDS cannot achieve high drug levels in blood/plasma.
4. Cannot develop TDDS for drugs of large molecular size.
5. TDDS cannot deliver drugs in a pulsatile fashion.
6. Cannot develop TDDS, if drug or formulation causes irritation to skin.

SKIN [3, 4]

Structure of the Skin

Skin is most extensive and readily accessible organ in the body. Its chief functions are concern with protection, temperature regulation, control of water output and sensation. In an average adult it covers an area of about 1.73m^2 and receives one third of circulating blood through the body at any given time. The potential of using intact skin as the site of administration for dermatological preparations to elicit pharmacological action in the skin tissue has been recognized for several years. Until the turn of the century, the skin was thought to be impermeable. Skin is the complex organ and allows the passage of chemicals into and across the skin. The permeation of chemicals, toxicants and drugs are much slower across the skin when compared to other biological membranes in the body. The understanding of this complex phenomenon has lead to the development of transdermal drug delivery system, in which the skin serves as the site for the administration of systemically active drugs. Following skin permeation, the drug first reaches the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce their therapeutic action.

In discussing skin structure, we limit ourselves to those features of the membrane which are pertinent to drug delivery; in particular, we play special attention to the stratum corneum (SC), the outermost layer wherein skin's barrier function principally resides.

Microscopically, skin comprises two main layers: the Epidermis and the Dermis (~ 0.1 and 1 mm in thickness, respectively) (Figure 1). The dermal-epidermal junction is highly convoluted ensuring a maximal contact area. Other anatomical features of the skin of interest are the appendageal structure: the hair follicles, nails and sweat glands.

The epidermis is a stratified, squamous, keratinizing epithelium. The keratinocytes comprise the major cellular component (> 90%) and the responsible for the evolution of barrier function. Other cells present include Melanocytes, Langerhans cells and Markel cells, none of which appears to contribute to the physical aspects of the barrier.

The stratum corneum is usefully thought of as a "brick wall", with the fully differentiated corneocytes comprising the 'bricks', embedded in the 'mortar' created by the intercellular lipids. The corneocytes are flat, functionally dead cells, the cytoplasmic space of which is predominantly keratin. When the lamellar bodies of the upper granular cells extrude their contents, the flattened lipid vesicles fuse "edge-to-edge" and organize into extremely well ordered, multilamellar, bilayer shits. A layer of lipid covalently bound to the cornified envelope of the corneocyte has been suggested to contribute uniquely to this exquisite organization. Particularly noteworthy is that the intercellular lipids of the stratum corneum, in contrast to almost all other biomembranes, include no phospholipids, comprising rather an approximately equimolar mixture of ceramides, cholesterol and free fatty acids. These non-polar and somewhat rigid components of the stratum corneum's 'cement' play a critical role in barrier function.

On average, there are about 20 cell layers in the stratum corneum, each of which is perhaps 0.5 μm in thickness. Yet, the architecture of the membrane is such that this very thin structure limits, under normal conditions, the passive loss of water across the entire skin surface to only about 250 mL per day, a volume easily replaced in order to maintain homeostasis.

The link between skin barrier and stratum corneum lipid composition and structure has been clearly established. For example, change in intercellular lipid composition and/or organization typically results in a defective and more permeable barrier. Lipid extraction with organic solvents provokes such an effect. Skin permeability at different body sites has been correlated with local variation in lipid content. Moreover, most convincingly, the conformational order of the intercellular lipids of stratum corneum is correlated directly with the membrane's permeability to water. Taken together, these observations have led to the deduction that the stratum corneum has achieved such an excellent barrier capability by constraining the passive diffusion of molecules to the intercellular path (the corneocytes being simply too impermeable to allow efficient transfer from one side of the membrane to the other). This mechanism is tortuous and apparently demands a diffusion path length at least an order of magnitude greater than that of the thickness of the stratum corneum. Current opinion, then, is that the stratum corneum

is most convincingly viewed as a predominantly lipophilic barrier (this makes perfect good sense as it was designed to inhibit passive loss of tissue water in an aride environment), which manifests a high degree of organization, and which constrains permeating molecules to a long and convoluted pathway of absorption. These characteristics, therefore, dictate the permeability of the membrane and determine the extent to which drug of various physicochemical properties may be expected to transport.

The dermis, inner and larger (90%) skin layer, comprises primarily connective tissue and provides supports to the epidermis. The dermis incorporates blood and lymphatic vesicles and nerve endings. The extensive microvasculature network found in the dermis represents the site of resorption for drugs absorbed across the epidermis; i.e. at this point that transdermally absorbed molecules gain entry to the systemic circulation and access to their central target.

The dermis also supports skin's appendageal structure, specially the hair follicles and sweat glands. The pilosebaceous unit comprises the hair follicle, the hair shaft and sebaceous gland. The hair follicle is an invagination of the epidermis that extends deeper into the dermis. The lining of the lower portion of the hair follicle is not keratinized and presumably offers a lesser barrier to diffusion than the normal stratum corneum. With respect drug delivery, interest in these structures has centered upon the possibility that they may provide "shunt" pathway across the skin, circumventing the need to cross the full stratum corneum. While this is completely reasonable hypothesis, it is somewhat irrelevant from the practical standpoint because the follicles occupy relatively insignificant fraction of the total surface area available for transport (~0.1%). A similar argument can be made with respect to the sweat glands, which cover a considerably smaller total area than the follicles. As noted later, however, appendageal transport may assume a much more important role when specialized enhancing technologies are used to increase transdermal delivery.

In addition to relationship between rate of drug delivery to the skin and maximum achievable drug permeation across the skin, the choice of drugs to be delivered transdermally, clinical needs and drug pharmacokinetics are some of the important consideration in the development of transdermal drug delivery systems (TDDS). Schematic representation of drug levels in blood from P.O. and transdermal route of administration is shown in Figure 2. As can be seen from Figure 2, a TDDS is design to release drugs at a predetermined rate and continuously, avoiding unnecessarily high peaks and subtherapeutic troughs in plasma drug levels.

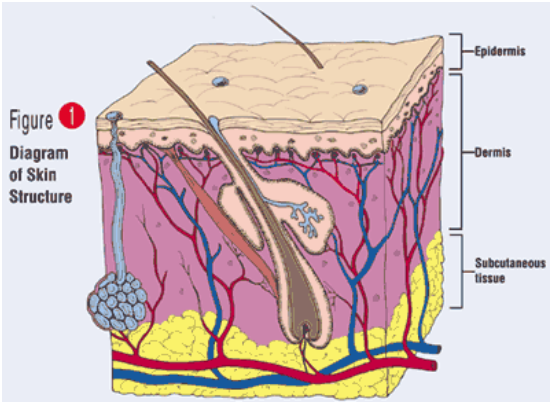

Figure 1: Skin Structure

TRANSPORT THROUGH THE SKIN [4, 5]

Skin is structurally complex and thick membrane. Molecules moving from the environment must penetrate the stratum corneum and any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, whereupon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex phenomenon and challenge in analysis.

A. ROUTE OF DRUG PENETRATION THROUGH HUMAN SKIN

When a molecule reaches intact skin, it contacts cellular debris, microorganisms, sebum and other materials. The diffusant then has three potential entry routes to the viable tissue, through the hair follicles with their associated sebaceous glands, via the sweat ducts or across the continuous stratum corneum between these appendages.

Electron photo-microscopic examination shows that intracellular region in stratum corneum is filled with lipid reach amorphous material. During cornification the lipid composition shifts from polar to neutral constituents. In the dry stratum corneum intracellular diffusion volume may be as high as 5% and least 1% of the fully hydrated stratum corneum. This intra-cellular volume is at least an order magnitude larger than that (approximate 0-2%) estimated for the intra-appendageal pathway, thus, intracellular diffusion could be significant.

Both the structured lipid environment between the cells and the hydrated protein, within a corneocytes plays major role in skin permeability, cell membranes are probably of only minor consequences (Figure 2 and 3). These figures illustrate two potential routes for drug permeation.

1. Intra cellular : between the cells and
2. Trans cellular: across lipid rich region.

At least for polar drugs, the transcellular route provides the main pathway during percutaneous absorption. Transappendageal route usually cannot contribute appreciable to the steady state flux and fractional area available for absorption is small. This route may be important for ions and large polar molecules, which cross-intact stratum corneum with difficulty.

B. EPIDERMAL BARRIER LAYER

The main barriers to absorption are the dead cells of the stratum corneum, restricting the inward and outward movement of drug substances and having high electrical resistance. The stratum corneum is a heterogeneous tissue, composed of flattened keratinized cells. The outer layers of these cells are less densely packed than those adjacent to the underlying granular layer. Therefore, the epidermal barrier becomes more impermeable in the lower part and this fact has lead to suggestion that a separate barrier exists at this level, the so called stratum corneum. These horny cells have lost their nuclei and are physiologically rather inactive [5].

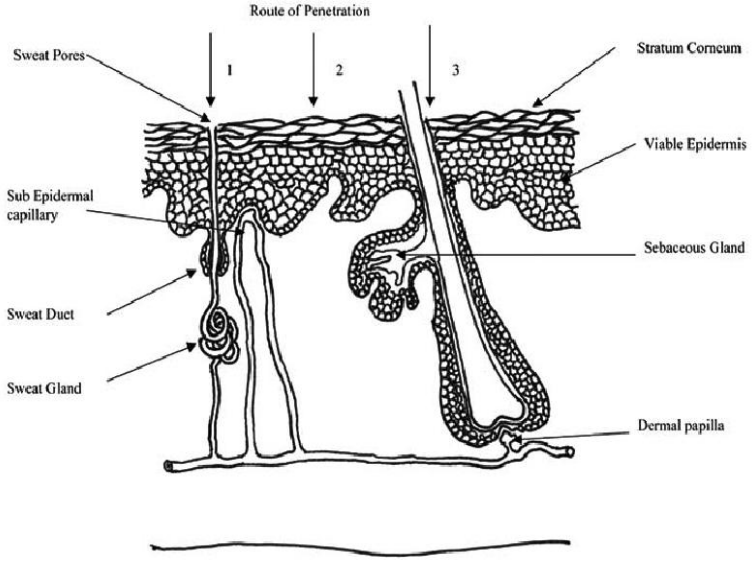

Figure 2: Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles.

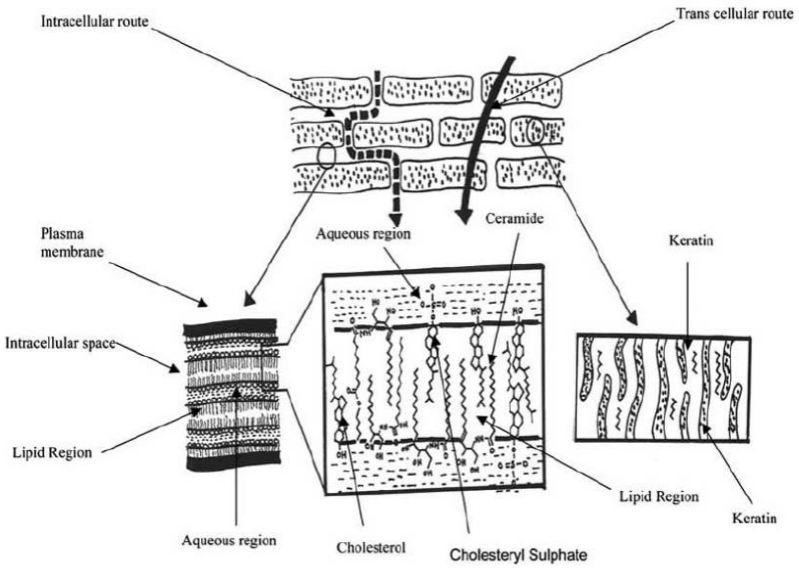

Figure 3: Diagrammatic representation of the stratum corneum and the intracellular and transcellular routes of penetration.

Analysis of penetration data, which are evident from controlled stripping experiments and the detailed picture of the stratum corneum, gained from electron microscopy support the idea that the barrier to penetration consists of the keratin-phospholipid complex in the dead and relatively dry cells of the entire stratum corneum.

Thus as molecules move from the environment into the skin, the rate limiting barrier i.e. the tissue that presents the greatest resistance to the movement of molecules, is the stratum corneum. Information is limited about the composition of the barrier. The main cellular components are proteins, lipids and water combined into an ordered structure. The composition of the stratum corneum is: cell membrane 5% (lipid & non-fibrous protein), cell contents 85% (lipid- 20%, α-Protein-50%, β-Protien-20%, non fibrous protein-10%), Intracellular material 10% (lipid and non-fibrous protein) [6].

When surface lipid offers little resistance to passage of compounds studies of lipid removal from the cutaneous surface indicate that lipid participate in epidermal water function. Onken and Moyer showed that barrier function is restored when extracted lipids are returned to the skin. Scheuplein has calculated the resistance of the skin to the passage of water from the sum of the tissue resistance [7].

$$RS = RSC + RE + RD$$

Where SC = Stratum Corneum

E = Epidermis; S = Skin; D = Dermis; R = Resistance

According to his calculations, the diffusional resistance of stratum corneum to water is approximately 103 times that of stratum corneum to water is approximately 103 times that of either the viable epidermis or superficial region of dermis. For certain material there may be second barrier to absorption at or near the dermoepidemal junction and not to penetrate into dermis. Because the stratum corneum is dead, it is usually assumed that there are no fundamental differences between in-vivo and in-vitro permeation.

C. EPIDERMAL RESERVOIR

The existence of depot or 'reservoir' within stratum corneum for topically applied materials has been suggested by Malkinson and Ferguson and investigated by Vickers in details. He applied small amount of flucinolone cream to the right forearm and occluded with saran wrap for 16 hour. After removal of saran area of skin for 9-11 days after initial application of steroid, vasoconstriction reappeared although no more steroids have been applied.

It was observed that applied diflorasone diacetate cream to the skin for 24 hrs. Later 37.5% of the applied dose have penetrated below the surface of the skin and could not be wiped off since only 1.1% of the dose was excreted in the urine and feces. It was concluded that 36.4% of the dose established a stratum corneum reservoir. Small but significant quantities of the steroid could still be recovered by skin swabbing as long as 22 days after the initial drug application.

Clinical and radiobiological studies suggest strongly that the depot reside in the stratum corneum and that is not just a surface film. It appears in the deeper portion of the stratum corneum. The presence of intact and normal stratum corneum is necessary for establishment of reservoir.

In general, those factors that promote percutaneous absorption also potentiate reservoir formation. If the temperature and humidity above the horny layer increases, the steroid store increases. The higher the bioavailability of the drug from the vehicle, the more pronounced is the reservoir [7].

D. EPIDERMAL DIFFUSION

Diffusion through the horny layer is purely passive process, which may be affected by physical factors as determined at ambient conditions. Percutaneous absorption to systematic circulation is more complicated process, epidermal diffusion is first phase and clearance from the dermis is the second. The latter depends on effective blood flow, interstitial fluid movements, lymphatic and perhaps other factors such as combination with dermal constituents. A passive diffusion has two main characteristics:

1. A delay period after the drug is placed on the surface, during which the membrane itself becomes charged with the penetrant.
2. A steady penetration after delay period, which lasts as long as the drug remains in the adequate supply on the surface and is removed from the lower surface. This steady rate is proportional to the concentration difference across the membrane. In case of adequately perfused skin, the rate may be considered equal to the concentration applied. The ratio of the steady rate to the concentration applied should be constant (termed as permeability constant). It is a measure of the permeability of the given skin to the drug in the given vehicle.

STRATUM CORNEUM AS THE TRANSDERMAL PENETRATION BARRIER

Stratum corneum mainly consists of the keratinized dead cells and water content is also less as compared to the other skin components. Once the dosage form is applied topically, the percutaneous absorption or transdermal permeation can be visualized as a composite of a series of steps [8].

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.

3. Finally through the papillary dermis and into the microcirculation.

The viable tissue layers and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid, so that, for the great majority of substances, diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium.

PERCUTANEOUS ABSORPTION [9]

Percutaneous absorption is defined as penetration of substances into various layers of skin and permeation across the skin into systemic circulations. The percutaneous absorption is a step-wise process and can be divided into three parts:

1. Penetration is the entry of a substance into a particular layer.
2. Permeation is the penetration from one layer into another, and is different both functionally and structurally from the first layer.
3. Absorption is the uptake of a substance into systemic circulation.

The stratum corneum is a wall-like structure with protein bricks and lipid mortar. The lipid matrix (Keratin phospholipid complex) of the stratum corneum plays a significant role in determining the permeability of substances across the skin. This is supported by the evidence from controlled stripping experiments, electron microscopy studies and also from the analysis of penetration and permeation data.

FACTORS AFFECTING TRANSDERMAL PERMEABILITY [9]

The principle transport mechanism across mammalian skin is by passive diffusion through primarily the transepidermal route at steady state or through transappendageal route at initially, non steady state. The factors, which affect the permeability of the skin mainly the stratum corneum, are classified into following categories:

1. Physicochemical properties of the penetrant.
2. Physicochemical properties of the drug delivery system.
3. Physicochemical and pathological conditions of the skin.

1. Physicochemical properties of the penetrant molecule

i. Partition co-efficient: Drug possessing both water and lipid solubilities are favourably absorbed through the skin. Transdermal permeability co-efficient shows a linear dependence on partition co-efficient. Varying the vehicle may also alter a lipid/water partition co-efficient of a drug molecule. The partition co-efficient of a drug molecule may be altered by chemical modification without affecting the pharmacological activity of the drug.

ii. pH condition: the effect of pH is mainly on the rates of absorption of acidic and basic drugs, unchanged form of drug has better penetrating capacity. Transport of ionizable species from aqueous solutions shows strong pH dependence.

iii. Drug concentration: Transdermal permeability across mammalian skin is a passive diffusion process and this depends on the concentration of penetrant molecule on the surface layer of the skin.

2. Physicochemical properties of the drug delivery system

a. The affinity of the vehicle for the drug molecules: It can influence the release of the drug molecule from the vehicle. Solubility in the vehicle will determine the release rate of the drug. The mechanism of drug release depends on whether the drug is dissolved or suspended in the delivery system and on the interfacial partition co-efficient of the drug from the delivery system to skin tissue.

b. Composition of drug delivery system: Composition of drug delivery system may affect not only the rate of drug release but also the permeability of the stratum corneum by means of hydration.

C. Enhancement of transdermal permeation: Release of the drug from the dosage form is less due to the dead nature of the stratum corneum. Penetration enhancers cause the physicochemical or physiological changes in stratum corneum and increase the penetration of the drug through the skin. Various chemical substances found to possess drug penetration enhancing property.

Lipophilic solvents	Surface active agents	Two component system
Dimethyl sulfoxide, Dimethyl formamide, 2-pyrrolidone	Sodium lauryl sulphate, Dodecyl methyl sulfoxide.	Propylene glycol, Oleic acid, 1,4-butane diol, Linoleic acid.

3. Physiological and pathological condition of the skin

a. Skin age: Foetal and infant skin appears to be more permeable than adult skin. Percutaneous absorption of topical steroids occurs more rapidly in children than in adults. Water permeation has shown to be same in adults and in children.

b. Lipid film: The lipid film on the skin surface is formed by the excretion of sebaceous glands and cell lipids like sebum

and epidermal cell which contain emulsifying agent may provide a protective film to prevent the removal of natural moisturising factor from the skin and help in maintaining the barrier function of the stratum corneum.

c. **Skin hydration:** Hydration of stratum corneum can enhance transdermal permeability. The rate of penetration of salicylic acid through skin with dry and hydrated corneum was measured when the tissue were hydrated, the rate of penetration of the most water soluble esters increased more than that of the other esters.

d. **Skin temperature:** Raising skin temperature results in an increase in the rate of skin permeation. Rise in skin temperature may also increase vasodilation of blood vessels, which are in contact with skin leading to an increase in percutaneous absorption.

e. **Cutaneous drug metabolism:** After crossing the stratum corneum barrier, some of the drug reaches the general circulation in active form and some of this in inactive form or metabolic form, because of the presence of metabolic enzymes present in the skin layers. It was reported that more than 95% of testosterone absorbed was metabolized as it present through the skin.

f. **Species differences:** Mammalian skin from different species display wide differences in anatomy in such characteristics as the thickness of stratum corneum, number of sweat glands and hair follicles per unit surface area.

g. **Pathological injury to the skin:** Injuries to the skin can cause the disturbance in the continuity of stratum corneum and leads to increase in skin permeability.

APPROACHES TO DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEM [10]

Various technologies have been developed to provide rate control over the release and transdermal permeation of drugs. They are discussed as

I. Membrane Moderate system:

The solid drug is dissolved in solid polymer matrix or suspended in an unleachable viscous liquid medium and encapsulated in shallow compartment modulated from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane (Figure-4).

The drug molecules are permeated to release only through the rate controlling polymeric membrane. The rate limiting membrane can be a microporous or non porous polymeric membrane with a known drug permeability property. To achieve an intimate contact of drug delivery system with the skin surface, a thin layer of a drug compatible hypoallergenic adhesive polymer may be applied. The rate of the drug release from the transdermal drug delivery system can be maintained by changing the polymer composition, permeability co-efficient or thickness of the rate limiting membrane and adhesive. The intrinsic rate of drug release from this type of drug delivery system is given as

$$dQ/dT = C_R/1/Pm+1/Pa$$

Where,

C_R= Drug concentration in the reservoir compartment.

Pa= Permeability co-efficient of the adhesive layer.

Pm= Permeability co-efficient of rate controlling membrane.

II. Adhesive diffusion control system:

In this system the drug directly dispersing the drug in the adhesive polymer and then spreading the medicated adhesive on reservoir layer formulate reservoir. On this a layer of non medicated rate controlled adhesive polymer of constant thickness is applied (Figure 5).

The rate of drug release of this type of system is defined as

$$dQ/dT = (Ka/r)X\ Da\ X\ C_R/\delta a$$

Where,

Ka/r = Partition co-efficient for interfacial partitioning of the drug form the reservoir layer to the adhesive layer.

Da = Diffusion co-efficient in the adhesive layer.

δa = Thickness of adhesive layer.

C_R = Drug concentration in reservoir compartment.

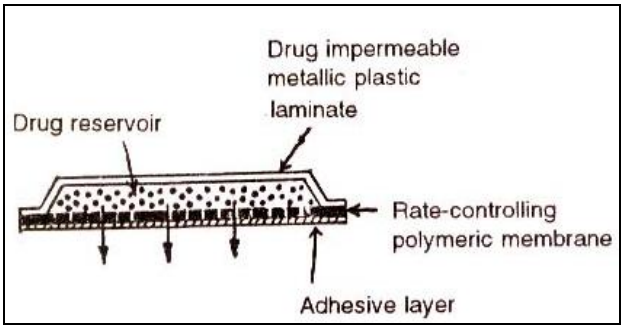

Figure-4: The cross sectional view of membrane moderate type TDDS.

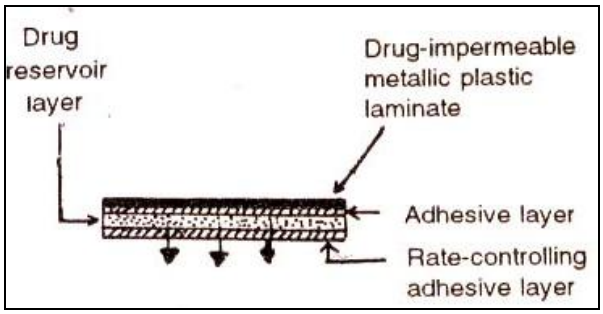

Figure-5: The cross sectional view of an adhesive diffusion type TDDS.

III. Matrix dispersion type system [10, 11]

In this system, the reservoir is formed by dispersing the drug homogeneously in a hydrophilic or lipophilic polymer matrix and then it is modulated into a medicated disc with the definite surface area and controlled thickness. This disc is then glued on to an occlusive base plate in a compartment fabricate from a drug impermeable plastic backing. The adhesive polymer is spread circumference to form an adhesive rim around the medicated disc (Figure 6).

The rate of drug release from this matrix dispersion system is defined as

$$dQ/dT = \sqrt{A^{*}Cp^{*}\ Dp/2t}$$

A= Initial drug loading dose dispersed in the polymer matrix, Cp & Dp are the solubility and diffusivity of the drug in the polymer respectively.

IV. Microreservoir system

In this system the drug reservoir is formed by first suspending the drug (solid form) in an aqueous solution of the water-soluble polymer and then dispersed homogeneously the drug suspension in lipophilic polymer by a high shear mechanical force. Cross-linking the polymer chain, to this a medicated polymer disc of constant surface area and defined thickness quickly stabilizes this dispersion (Figure 7).

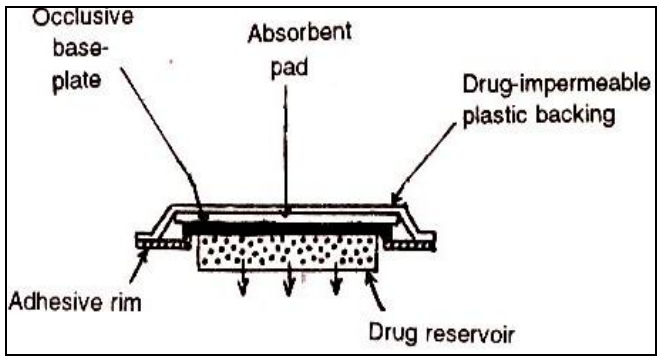

Figure-6: The cross sectional view of matrix dispersion type TDDS.

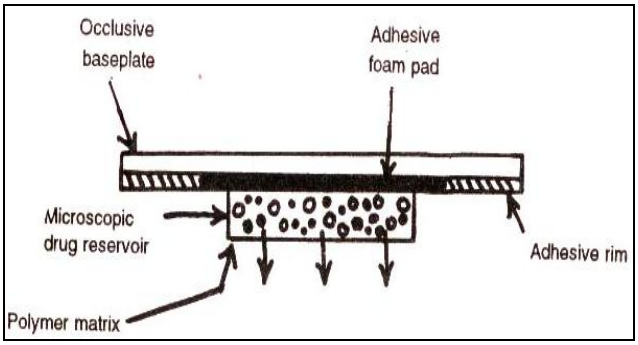

Figure-7: The cross sectional view of micro-reservoir type TDDS.

PENETRATION ENHANCERS [9]

The stratum corneum has long been considered a major barrier to penetration of topically applied chemicals. Studies have shown that most compounds have low permeability through skin.

There are three major limitations to the topical delivery of the drug [12]:

1. Most of the drugs permeate poorly across the stratum corneum.
2. If the drugs permeate across the stratum corneum, they are not easily retained the skin for localized therapy.
3. Many drugs are too irritating to the skin to deliver topically.

By permeation, one really means flux and one is concerned with problem of increasing flux across membrane. For any region within the membrane the flux, J, can be given by

$$J = -D\ \delta C/\delta X \text{ for flow in one dimension.}$$

Where,

D = diffusion co-efficient, = size, shape of permeant.

C = permeation co-efficient = thermodynamic origin.

X = special co-ordinate.

Therefore, enhancement of flux across the membrane depends on:

1. Thermodynamics (lattice, energies and distribution co-efficient)
2. Molecular size and shape
3. Reducing the energy required, making a molecular whole in the membrane and certain partial concepts like while evaporation and excipient interaction make useful system.

These are two kinds of enhancement measurements- The comparison of fluxes of the same molecule from two different vehicles and the comparison of fluxes of two different molecules from the same vehicle. The amount of increasing penetration is simply the ratio, R

$$R = J1/J2$$

Where,

J1 = flux from vehicle 1 (molecule 1)

J2 = flux from vehicle 2 (molecule 2)

Often these fluxes will not be at steady state since the membrane barrier properties will be changing with time if enhancement is occurring. For R to be true measure of the vehicle enhancement, drug should have same thermodynamic activity either by using saturated solutions or equal fractions of saturation. This in turn depends on activities of two drugs, which in turn depends on concentration and solubility.

For vehicle (mediated) induced penetration enhancement to occur, the energy for making diffusion holes must be altered. The process can take place if the solvent swells the

barrier but in case of skin, proteins and/or lipids must be altered to make it easier for a molecule to diffuse through the media. Surfactants can be used for polar molecule, which alters the proteins of stratum corneum and thus increase penetration. The more hydrophilic surfactant (ionic/zwitterionic) interacts strongly with the keratin and alter transport of less hydrophilic surfactant (long chain alcohol) interact weakly and do not alter the transport of polar molecule. For example urea has been reported to enhance skin permeation penetration and at high concentration denatures skin.

To alter fluid properties of stratum corneum lipids one must be to swell the lipid or increase the volume/molecule. The low permeability of the skin, relative to other biological tissues, is well known and it is perhaps this fact that has kept the skin as a minor part of entry of drugs. As compared to the oral or gastric mucosa, the stratum corneum is compact and highly keratinized. The lipid of the proteins of the stratum corneum as explained in 'Brick and Mortar' model provides a complex structure that is quite impermeable. To reduce the resistant of the stratum corneum and its biological variability, penetration enhancers can be defined as a chemical with the unique property in relation to skin that it reversibly reduced the barrier layer of the horny layer without damaging any viable cells. According to Chein et al. [1] Penetration enhancers or promoters are agents that have no therapeutic effect of their own but can transport the sorption of drugs from drug delivery systems onto the skin and/or their subsequent transdermal permeation through the skin. The penetration enhancers are the agents that increase the permeability of the skin. The penetration enhancers are the agents that increase the permeability of the skin or substances that reduces the impermeability of the skin.

Katz and Poulsen define a spectrum of properties, which such a material should ideally possess. An expanded list of desirable attributes is as follows [12- 14].

1. The enhancer should be pharmacologically inert and should possess no action of it as receptor sites in the skin or in the body in the amount or concentration used.
2. The material should not be toxic, irritant or allergic.
3. On application, the onset of action should be immediate and the duration of the effect should be predictable and suitable.
4. When the enhancer is removed from skin, the exposed tissue should immediately and fully recover its normal barrier properties.
5. The barrier function of skin should reduced in one direction only, so as to promote penetration into skin. Body fluids, electrolytes or other endogenous material should not be lost to the atmosphere.
6. The enhancer should have a good enhancement efficacy and be chemically and physically compatible with a wide range of drugs and pharmaceutical adjuvant.
7. The enhancer should be an excellent solvent for drugs, so that only minimal quantities of drugs are required.
8. The enhancer should spread well on the skin and possess a suitable skin feel.
9. The enhancer should be able to formulate readily into lotions, suspensions, ointments, creams, gels, aerosols and skin adhesives.
10. The enhancer should be inexpensive, odorless, tasteless and colorless to be cosmetically acceptable.

LIQUID-PROTEIN-PARTITIONING THEORY OF SKIN PENETRATION ENHANCEMENT [13]

The liquid-protein-partitioning theory of skin penetration enhancement suggests that accelerants usually act by one or more of three main mechanics, they can alter the intracellular lipid or intracellular protein domains of the horney layer and they may also increase partitioning into the skin of the a drug, a co-enhancer, water or any combination of this. The penetration enhancers can acts at different sites of intercellular domain of skin, which are shown in figure 8.

a. Molecular interaction for enhancer action within the intercellular domain

Interaction of Site A

Many penetration enhancers should react with the polar head groups of the lipid and modify hydrogen bonding and ionic forces. They will disturb the hydrogen spheres of the lipid and the subsequent alterations in head group interactions should upset the packing of the polar plane. This disruption may make the domain more fluid and so promote the diffusion in particular polar penetrants. A second response may be to allow more aqueous fluid to enter the tissue and so increase the water volume between lipid layers. These swallowing should provides a larger functional volume of 'free' water as distinct from structured water and hence increase the cross-sectional area available for polar diffusion (Site B). An important secondary feature is that disruption of interfacial structure will also alter packing of lipid chains. The lipid hydrophobic route thus becomes more disordered and more readily transversed by a lipid-penetrant (Site C).

Direct action at site B

An accelerant may affect the aqueous region in ways additional to those that alter bond interactions and thereby increase the water content. Thus, the enhancer may directly change the constitution of domain. For example, when vehicles or transdermal devices deliver high concentration of solvents such as propylene glycol, ethanol, the pyrrolidones or dimethyl-sulphoxide to the skin, the solubility ability of aqueous side may increase. Then the location may better dissolve molecules such as estradiol and hydrocortisone and the result is that the operational partition co-efficient now favors the development of a high drug concentration in the skin. A

complicating feature is that this solubilising effect may decrease the chemical potential of the drug in stratum corneum, temporary decrease in the driving forces for diffusion. When the solvent diffuses out of the stratum corneum into the viable epidermis, the drug follows at a relatively high flux as it diffuses down its new raised chemical potential gradient.

Action at site C (The lipid domain)

Many penetration enhancers, because of their structures, should insert between the hydrophobic tails of the bilayer, so upsetting their packing, increasing their fluidity and thus permitting easier diffusion of penetrants. These alterations in lipid packing can reflect back to provide some disorder in the polar head group region and so promote polar route penetration. Those enhancers with large polar head groups may also modify site 'A' directly.

Alteration at sites A & C will have a combined effect on amphiphilic penetrants. These will insert in a bilayer in a way similar to the lipid molecules and then more easily flex, rotate and in particular, diffuse laterally.

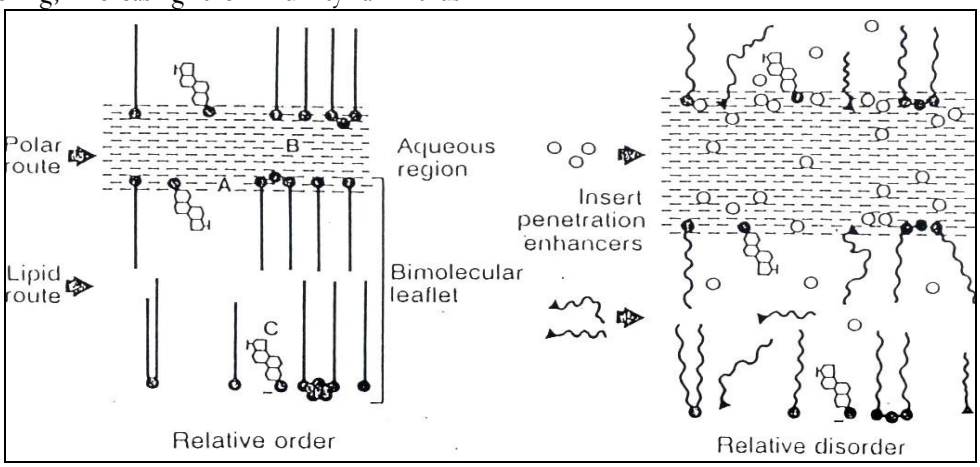

Figure-8: Molecular location for Enhancer action.

The intracellular route

For some specific penetrants, the intracellular pathway provides a significant route by enhancing interaction with lipid remains in the corneocytes. As regards a polar route, we should need to consider the keratin fibrils and the interactions with enhancers such as the aprotic solvents (e.g. DMSO, DMF and DMAc), the pyrrolidones and surfactants undergo with proteins. These mechanisms include interaction with polar groups, relaxation of binding forces and alterations in the conformation of the vehicles. Extensive interaction may form pore routes through the tissue.

Polymer selection for transdermal drug delivery system

The development of transdermal system requires judicious selection of a polymeric material or a series of polymers whose diffusive characteristics will be such that a desirable permeation rate of a specific drug can be obtained.

Following factors are taken into consideration during the selection of polymer:

1. Molecular weight and chemical functionality of polymer must allow proper diffusion and release of specific drugs. Increased polymer weight decrease drug diffusivity in polymers.
2. Polymer should not react with the drug.
3. The polymer and its degradation products must be non-toxic.
4. The polymer should not decompose on storage or during the useful life of device.
5. The polymer must be easy to manufacture and it should yield itself into desired product and should allow incorporation of large quantities of active component without deteriorating its mechanical properties.
6. Cost of polymers should not be excessive.

Natural polymers	Synthetic elastomers	Synthetic polymers
Gelatin	Neoprene	Polyethylene
Gum Arabic	Polysilozone	Polystyrene
Methyl Cellulose	Silicon rubber	Acetal co-polymer
Arabinogalactan	Chloroprene	Poly vinyl chloride
Starch	Hydrine rubber	Polyester
Shellac	Acrilonitrile	Polyamide
Proteins	Butyl rubber	Poly vinyl acetate
Natural Rubber		Ethyl vinyl acetate
Zein		Co-polymer

Table-1: Possible useful polymers for transdermal devices.

Polymers used in transdermal delivery are usually in the form of thin polymeric films or membranes with or without microscopic pores. They can be classified three categories.

1. Microporous films and membranes: These are systems with large pores of average diameter between 0.1 and 1.0μm. The pore pathway is tortuous and irregular and corrective transport is observed.
2. Microporous films: These systems have similar pores usually of a diameter between 100 Å and 500 Å and sometimes as high as 1 μm. The pore structure is the main parameter influencing permeation of the drug.
3. Non-porous films and membranes: These can be used for a variety of transdermal application. The polymer films have pores of molecular size usually between 10 Åand 100 Å. Effectively the spacing between micro molecular chains of the polymer becomes the controlling factor of controlled release of drug.

Selection of the drug for transdermal drug delivery system

Before the development of the transdermal drug delivery system of any drug various physicochemical properties pharmacokinetics and pharmacodynamic properties are taken under consideration. Typical requirement for transdermal delivery of drug includes

- Low molecular weight ranging from 500 to 1000.
- Low melting characters (150-200 ^{0}F).
- Aqueous solutions neither too acidic nor basic (between 5 and 9 pH units)
- Preferable lipid/water co-efficient i.e. partition co-efficient.
- The most important requirement of the drug to be delivered transdermally is demonstrated by need for controlled delivery, such as short half-life and adverse effects associated with other routes or complex oral route or IV dose regimen.
- Drugs, which get extensively metabolized in the hepatic, first pass effect.

Some commercial application

Though transdermal drug delivery is still a young science much has been accomplished as indicated by the number of transdermal products that have become commercially available science the first product ALZA'S transdermal scopolamine product for the prevention of motion sickness was introduced in 1981.

Drug	Product Name	Company
Scopolamine	Transdermal Scop^R	Alza Ciba
Nitroglycerine	Transdermal Nitro^R	Alba Ciba
Nitroglycerine	Nitro dur^R	Key Pharma
Nitroglycerine	Nitro disc^R	G.D.Searle
Clonidine	Catapress-TTS^R	Boehringer Inglheim Ltd

Table-2: Commercial transdermal products.

Gels – A Review

The term gel originated in the late 1800's as chemical attempted to classify semisolid substance according to their phenomenon – logical characteristics rather than their molecular compositions. At that time, analytical methods needed to determine chemical structure were lacking.

Gels were swollen networks possessing both the cohesive properties of solids and the diffusive transport properties of liquids. Elastically they tend to be soft and somatically they are highly reactive. They are semisolids being either suspension of small organic particles or large organic molecules interpenetrated with liquid. It is the interaction between the units of colloidal phase, inorganic or organic, which sets up structural viscosity, immobilizing the liquid continuous phase. Thus, get exhibit characteristics intermediate to liquids and solids.

According to Lerraine E. Pena [6] "gels are transparent to opaque semisolids containing a high ratio of solvent to gelling agent. When dispersed in an appropriate solvent, gelling agent merge or entangled to form three dimensional colloidal network structures. This networks limits fluid flow by entrapment and immobilization of the solvent molecules. The network structure is also responsible for a gel resistant to deformation and therefore its viscoelastic properties".

Classification [14]

The various types of gels are as follows

a) Hydrophobic Gels

The bases of hydrophobic gels (oleo gels) usually consist of liquid, paraffin with colloidal silica or alumina or zinc soaps.

b) Hydrophilic Gels

The bases of hydrophilic gels (hydro gels) usually consist of water, glycerol or propylene glycol gelled with suitable gelling agents such as tragacanth, starch, cellulose derivatives and magnesium-aluminum silicates.

Gels should be stored at temperature not exceeding 25^0C unless otherwise described. They should not be allowed to freeze. Substances that form aqueous gel or usually hydrophilic polymers capable of expensive solvation. At certain temperatures and polymer concentrations and in some cases with the addition of ions, a three dimensional network is formed.

Gels are divided into inorganic or organic gels. Bentonite magma is an example of in-organic gel. Organic gels typically contain polymer as a gel former.

Examples of organogels are plastibase (low molecular weight polyethylene) dissolve in mineral oil and dispersion of metallic stearates in oils. Solid gels with low solvent concentration are known as xerogels. Xerogels are often produced by evaporation of solvents, leaving gel framework behind. Example of xerogels include dry gelatin, tragacanth ribbons and acacia tears.
Pharmaceutical gels may be loosely categorized based on their network microstructure according to the following scheme suggested by faucci [16].

a. Covalently bonded polymer network with completely disordered structure.
b. Physically bounded polymer network predominantly discovered but containing ordered loci.
c. Well ordered lamellar, including gel mesophases formed by inorganic clays.

a) Covalently Bonded Structure

Covalently cross-lined gel networks are irreversible systems. They are typically prepared from synthetic hydrophilic polymer in one of two ways.

In first method of preparation, infinite gel network arises from the non-linear co-polymerization of two or more monomer species with the one being at least trifunctional. Both direction and position by which each polymer chain grows during the reaction is random, resulting in final microstructure of this gel being completely disordered. The gel point for co-polymerization between equimolar concentrations of two monomer species can be predicted, using modified Carothers equation:

$$X_n = 2/2\text{-}Pf_{av}$$

Where,
X_n = The number average degree of polymerization
P = The fractional conversion and
f_{av} = The average functionality of monomers involved
The gel point reaches when $X_n \rightarrow \infty$ {indicating that critical conversion for gelation (PG) is equal to $2/f_{av}$}

b) Physically bonded structure

Physically bonded gel networks are reversible systems. Factors such as temperature and ion additions can induce a transition between the sol and gel phases. These gels are formed primarily by natural organic polymers (proteins and polysaccharides) and semi synthetic derivatives. The particular organization of polymer chains in a junction zone depends on a chemical structure of the repeating unit. For example, sulfated polysaccharides (e.g. agar and carrageenans) that contain assortment sulfated galacatose residues from double helicles, two or more of which aggregate into multi-helicles functional zone. However, presence of few concomitant residues produces links that effectively block helix formation in large section of chains indicating that steric fit is critical to get formation.

Other zone junction requires the presence of multivalent ions to form a bridge between polymer chains. An egg box model was proposed by Pawel et al.[17] for the formation of calcium alginate gels, in which calcium cations are cooperatively bound between ionized carboxy groups located on the polyguluronate sequence of alginic acid. Locations are coordinated in the interstices of ordered segments of the polysaccharides chains.

Pharmaceutical Gel Application	Favorable properties
Dental	Highly thixotropic, optimal viscosity for filling fissure, adherent to enamel surface, optically clear, water soluble, oral digestible.
Dermatological	Thixotropic, good spreadability, greasless, easily removable, emollient, demulcent, non-staining, compatible with number of excipients (water soluble or miscible).
Nasal	Adherent, odourless, non-irritant, water-soluble.
Ophthalmic	Optically clear, sterile, mucomimetic, lubricating or non-sensitizing, water soluble or miscible.
Surgical and Medical Procedures	Lubricating, adherent to instrument surfaces, maximal contact with mucus.
Vaginal	Acid stable, adherent, does not liquefy at body temperature; slow dissolving, lubricating, greaseless and non-tacky, non-irritating.

Table-3: Required properties of pharmaceutical gels.

Gel formers	Gel forming concentration (%)	Required additives
PROTEINS		
Collegen	0.2-0.4	
Gelatin	2-15	
POLYSACCHARIDE		
AGAR	0.1-1.0	
ALGINATES	0.5-1.1	Ca^{2+}
	0.5-10	Na^{+}
K- Carrageenan	1-2	K^{+}
Gelium Gum (Low Acetyl)	0.5-1.0	Ca^{2+}
Glycerrhizin	2	
Gaur Gum	2.5-10	
Hyaluronic acid	0.25	Borate ion
Pectins (Low acetyl)	2.0	
Starch	0.8-2.0	Ca^{2+}
Tragacanth Gum	2-5	
SEMI SYNTHETIC POLYMERS		
CELLULOSE DERIVATIVES		
Carboxy Methyl Cellulose	4-6	
Hydroxy Propyl Cellulose	10-25	
Hydroxy Propyl Methyl	2-10	
Cellulose	2-10	
Methyl Cellulose	2-4	
SYNTHETIC POLYMERS		
Carbopol	0.5-2	
Polaxamer	15-50	
Poly acrylamide	4	
Poly vinyl alcohol	10-20	
INORGANIC SUBSTANCES		
Bentonite	5	
Aluminum hydroxide	5	
Hectorite	2	
SURFACTANT		
Brij	40-60	
Cetosterytl Alcohol	10	
Cetrimide	10	

c) Well Ordered Gel Structure

Under suitable conditions, certain silica, alumina and clay soils form rigid gels or lyogels. When clay belongs to smectite class, such as bentonite, hectorite and loponite, come into contact with water, they undergo interlayer swelling spontaneously followed by osmotic swelling to produce a gel. The plate like clay particles associates into a "cubic cardhouse" ordered structure, which is stabilized by repulsive forces, caused by interacting electrical double layer. Highly ordered lamellar gel microstructures are formed by certain mixture of surfactant and long chain fatty alcohols in water using small angle X-ray scattering (SAXS), an ordered lamellar stack lattice model was proposed for the gel formed by 10% w/w cetosteryl alcohol containing 0.5% cetrimide surfactant. In contrast, the microstructure of Brij 96 gel depends on the surfactant's concentrations. A hexagonal liquide-crystalline gel structure was detected by SAXS at concentration of 40-60% w/w in water, whereas extended lamellar structure was detected at higher concentration (70-80% w/w).

Table-4: List of gel forming substances

Gel forming compounds

Gel forming hydrophilic polymers is typically used to prepare liquid free semisolid dosage forms, including dental, dermatological, nasal, ophthalmic, recta and vaginal gels. Gels containing therapeutic agents are especially useful for application to mucus membrane and ulcerated or burned tissues, because their high water content reduces irritancy. Furthermore, gentle rinsing or natural flushing with body fluids, reducing the possibility for mechanical abrasion, easily removes these hydrophilic gels. Following table lists the favorable properties of pharmaceutical gels for particular applications.

CONCLUSION

Tansdermal drug delivery system is useful for topical and local action of the drug. The drugs which shows hepatic first pass effect and unstable in GI conditions are the suitable candidate for TDDS.

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