



Journal Homepage: -www.journalijar.com
**INTERNATIONAL JOURNAL OF
 ADVANCED RESEARCH (IJAR)**

Article DOI:10.21474/IJAR01/7109
 DOI URL: <http://dx.doi.org/10.21474/IJAR01/7109>



RESEARCH ARTICLE

TRANSDERMAL DRUG DELIVERY SYSTEMS: A MINI REVIEW.

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Manuscript Info

Manuscript History

Received: 15 March 2018
 Final Accepted: 17 April 2018
 Published: May 2018

Keywords:-

Transdermal, drug delivery, skin, stratum corneum.

Abstract

Skin has traditionally been used by various means to apply the medicaments for various purposes. Recent years have witnessed transdermal as a main route of delivery for various drugs which are difficult to deliver otherwise. Transdermal drug delivery offers several advantages mainly avoidance of first pass metabolism and gastric environment which would inactivate the drug. This review encompasses the basic anatomy of skin relevant to the transdermal route as a drug delivery and discuss in detail the various formulation strategies and permeation enhancement for better therapeutic effect. Finally, the review sums up with the current technologies in the market and also discuss the future direction.

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Introduction:-

Although drug delivery technology has made significant advances, oral route is still preferred even though it is not as effective as it should be for several drugs. These drugs are mainly those which has low solubility and high first pass metabolism (O'Driscoll and Griffin 2008; M. Shah 2017; Hu, Tang, and Cui 2004). To improve the drug delivery of these difficult molecules, several formulation strategies have been tried such as polymeric nanoparticles (Gaumet et al. 2008; Soppimath et al. 2001), solid lipid nanoparticles (M. K. Shah, Madan, and Lin 2014; Sanjula et al. 2009), liposomes (S. Moghimi and Szebeni 2003), dendrimers (Puri et al. 2009), nanocrystals (Muller and Keck 2004), solid dispersion (Khatri et al. 2018), self-micro emulsifying systems (Porter, Trevaskis, and Charman 2007). Another approach could be to change the route for the drug delivery which is through skin (Jain et al. 2017). Transdermal drug delivery has many advantages to offer over oral routes such as avoidance of first pass metabolism, avoidance of harsh gastric environment, patient compliance, easy to withdraw in case of unexpected situation, controlled and programmable delivery, easy to use and patient compliance for unconscious, vomiting and pediatric patients as well (Morales et al. 2017; Vora, Lin, and Madan 2013). This mini review covers the important characteristics of skin pertaining to the transdermal delivery of drugs and absorption pathways through skin. Most importantly, will enlighten the readers on the various methods of skin permeation enhancement available and focus more in details for transdermal drug delivery formulation strategies.

Human Skin:-

Anatomy and function:-

Skin is the largest organ of the human body, covering a surface area of 2 m² and receiving one-third of the total blood supply. It has important protective and homeostatic roles, and consists of epidermis, dermis and hypodermis which anchor the skin to underlying tissues. Each layer of the skin is physically and functionally distinct with

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appendages, including hair follicles, sweat ducts, and sebaceous glands, which account for 0.1% of the total human skin surface (Wang et al. 2005; Mills and Cross 2006).

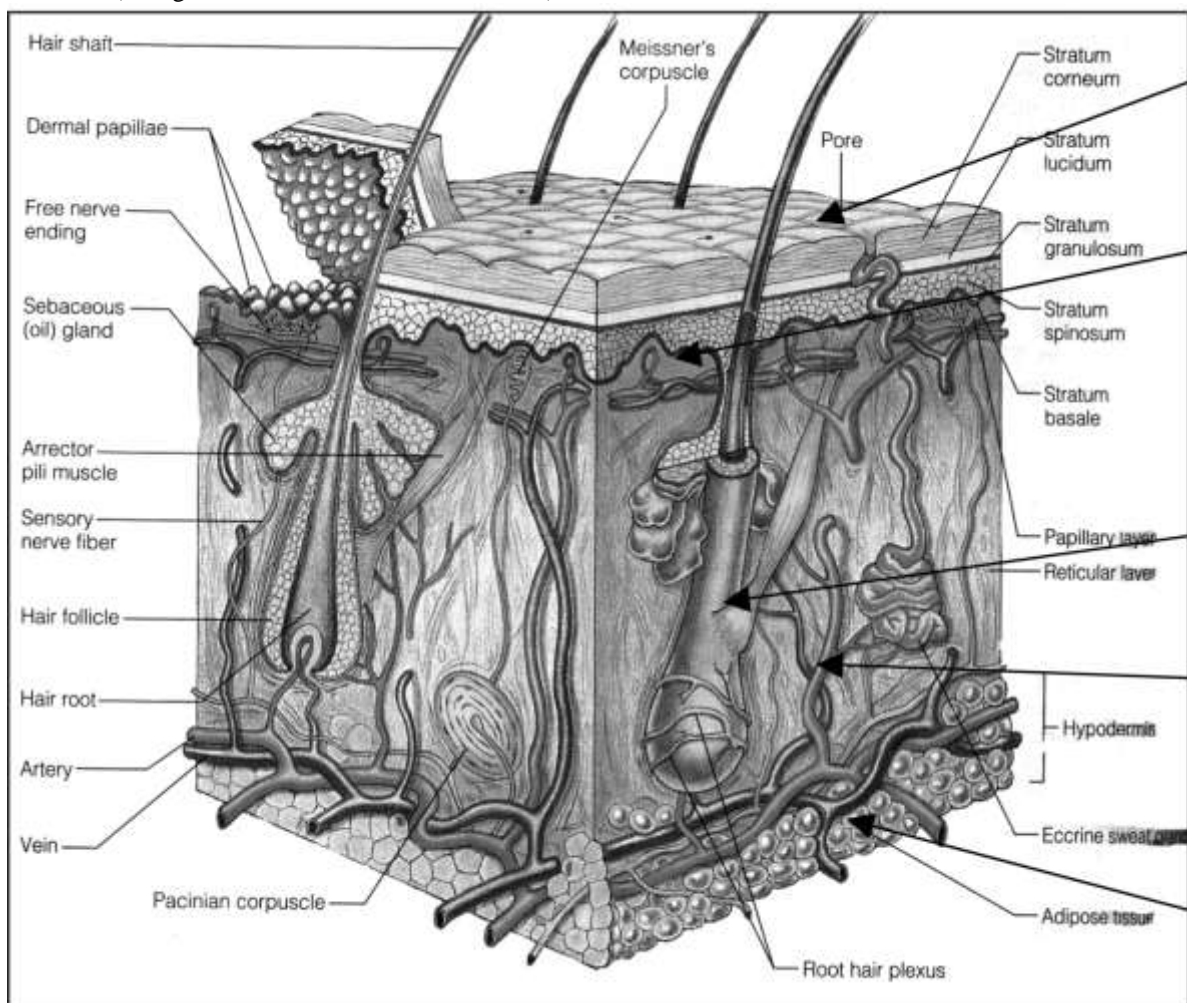


Figure 1:-Anatomy of the human skin. Adatped from (Brown et al. 2006)

The stratum corneum is the heterogenous outermost layer of the epidermis and is approximately 10-20 μ m thick. This non-viable epidermis is surrounded by intercellular lipids consisting of cholesterol, ceramides, and free fatty acids. It consists of 15-25 flattened, stacked, hexagonal and cornified cells and each cell is about 0.2-0.4 μ m thick, 40 μ wide, and undergoes a total turnover every 2-3 weeks. During desquamation, as the keratinocytes migrate towards the stratum corneum, phospholipids are replaced with sphingolipids which constitute the majority of the long chain, saturated fatty acids that create the lipophilic barrier. The dermis is vascularized and the thickest of all the skin layers, about 3-4 mm thick. It possess the sweat glands, hair follicles, nerve endings, and lymph vessels. It acts as the systemic absorption site for drugs and provides the nutritive, immune, and other support systems to the epidermis as well as regulates temperature, pressure, and pain sensation. The hypodermis or subcutis acts as a heat insulator, shock absorber, and energy storage region (Wang et al. 2005; Mills and Cross 2006). The detailed cross-section of the skin is shown in Figure 1.

Mechanical and barrier properties of stratum corneum:-

Normal skin is very permeable to most substances. The very thin (1-10% of the total), outermost skin part contributes over 80% to this transport resistance. The chief factor in this is the so-called horny region. This outermost stratum corneum layer is quite dry and is best suited for the purposes of a permeability barrier: it consists of one to two dozen flat and partly overlapping, largely dead cells (corneocytes) organized in columns or columnar clusters and coupled together with numerous desmosomes. Lipid material between corneocytes not only is ample but

also is highly organized and thus acts as extra intercellular 'glue' sealing the spaces between the cells in the skin (Gregor Cevc 1997).

It is, furthermore, important in this context that intercellular lipids in the horny layer mainly encompass the relatively non-polar substances, such as free fatty acids, cholesterol and cholesteryl esters, in addition to more than a dozen ceramides. Owing to the fairly long aliphatic chains of the latter, and due to the low overall lipid polarity in the skin, the inter-corneocyte lipids are tightly packed and at least locally appear as the lipid multi-lamellae. The latter, moreover, in many places adhere strongly to the corneocyte (envelope) membranes. All this contributes to the tightness and impermeability of the intact skin: it is hence very difficult to bring molecules with a high molecular mass. Generally, material transport across the skin increases only if the stratum corneum has been eliminated from the skin or after lipid extraction from the horny layer (G Cevc and Blume 1992).

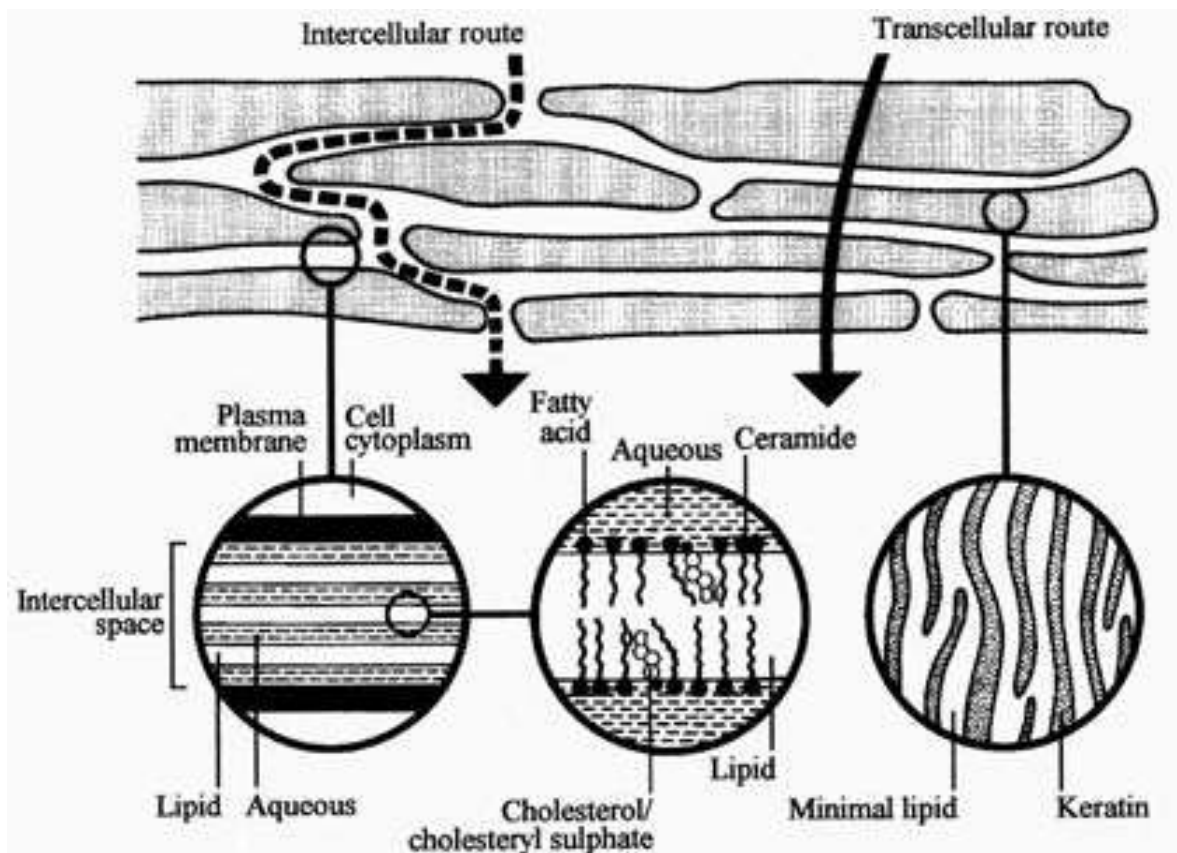


Figure 2:-Schematic representation of stratum corneum and its intercellular and transcellular pathways of drug permeation. Adapted from (H. Moghimi et al., n.d.).

Routes of skin penetration:-

Transport pathways: Drug molecules can cross cellular barriers either by moving across the cells (transcellular transport) or by passing between the cells (paracellular transport). The main physical barrier of the transcellular pathway is the lipid matrix of the membranes whereas that of the paracellular pathway is the intercellular tight junctions (Mills and Cross 2006). The two pathways are described in the following sections and schematically represented in Figure 2.

Transcellular transport (intracellular):-

Most common drugs traverse cellular barriers by transcellular pathways. These pathways require movement of solutes across and through cells and include passive diffusion, and carrier mediated and vesicular transport mechanisms (M. K. Shah, Madan, and Lin 2015). For passive diffusion there are two main potential mechanisms i.e. either the solute becomes distributed into the apical cell membrane and diffuses within the membrane to the basolateral side, or it diffuses across the apical cell membrane and enters the cytoplasm before exiting the cell across

the basolateral membrane. It has long been assumed that synthetic drugs pass cellular barriers by passive diffusion only, which would favour lipophilic drugs. However, there is accumulating direct and indirect evidence that the carrier-mediated membrane transport mechanism is not only a pathway for endogenous molecules (i.e. amino acids, oligopeptides, monosaccharides, water soluble vitamins, etc.) but also a transport route that can be used by xenobiotics. Integral membrane proteins present in the cell membrane serve as specific recognition sites for carrier-mediated transport. This transcellular pathway might be energy-consuming or not. If not, the term “facilitated diffusion” is generally used. Finally, large molecules can be transported by vesicular transport mechanisms, i.e. transcytosis. This implies receptor-mediated or adsorptive endocytosis at the apical cell membrane, followed by vesicle migration across the cell, and exocytosis at the basolateral membrane (Burton et al. 1993; Mills and Cross 2006).

Paracellular transport (intercellular):-

Paracellular transport, the tendency of a solute to follow the aqueous extracellular route, might be the primary pathway by which hydrophilic compounds of relatively low molecular weight cross epithelial and some endothelial barriers (Burton et al. 1993). Transport of larger hydrophilic molecules might be enhanced by modulation of junctional pores or addition of so-called drug absorption promoters. Translocation of solutes via the paracellular route takes place primarily by passive diffusion, namely by an energy-independent process characterized by solute movement in response to a chemical potential gradient. Because of ionizable side-chains in tight junction proteins, the junctional space has an electrostatic field with a negative net charge that might affect the paracellular flux of solutes via ionic interactions.

Polarized efflux systems:-

In recent years it has been found that the barrier function of the intestinal epithelium and of the blood brain barrier cannot be adequately described by a combination of metabolic and physical barriers alone. Another transport-limiting factor, which has only recently been appreciated, is the active efflux system (Burton et al. 1993). Efflux systems are present in cancer cells and represent the major barrier to the uptake of a wide variety of chemotherapeutic agents.

There has been much debate over the past decades on the route of penetration but experimental evidence suggests that, under normal circumstances, the predominant route is through the intercellular spaces. The diffusional pathlength is therefore much longer than the simple thickness of the stratum corneum (~20 µm) and has been estimated as long as 500µm. Importantly, the intercellular spaces contain structured lipids and a diffusing molecule has to cross a variety of lipophilic and hydrophilic domains before it reaches the junction between the stratum corneum and the viable epidermis. The nature of the barriers is thus very heterogeneous and it is perhaps surprising that diffusion through it can be described by simple solutions to Fick's laws of diffusion (Ho et al. 1995).

Methods of skin permeation enhancement:-

Due to rate-limiting barrier imposed by the stratum corneum, only drug molecules with certain characteristics such as (i) high potency (daily systemic dose should be ≤ 20 mg), (ii) molecular weight of less than 500 Daltons, (iii) log P in the range of 1-3, (iv) melting point less than 200 °C, (v) number of hydrogen bonding groups ≤ 2 , (vi) non-irritating potential, and (vii) non-immunogenic properties are able to passively permeate through the skin (Finnin and Morgan 1999).

Some of the common enhancement strategies that can be envisaged include

1. formulation effects – it has been observed that using a supersaturated solution which has chemical potentials greater than that of a saturated solution improves absorption. Moreover, some solvents can remove lipids from the stratum corneum.
2. removal of lipids - The barrier function is reduced when the lipids are modified in this way, although the effect has been shown to be reversible. Some topical and transdermal products contain high concentrations of solvents such as ethanol that may be capable of altering the lipid content of the skin.
3. lipid fluidization sometimes, if a formulation excipient permeates into the stratum corneum, it may intercalate into the structured lipids of the skin where it can disrupt the packaging. This effect leads them more fluid thereby increasing the diffusion coefficient of the permeant.
4. disruption of the skin lipids – the molecular characteristic that typifies an enhancer which disrupts the skin lipids is a polar head group with a long alkyl chain. Compounds such as the non-ionic surfactants have such properties.

5. solvent effect – some solvents or chemical compounds modify skin permeability by shifting the solubility parameter of the skin in the direction of that of the permeant. The solubility of the permeant in the outer layers will be increased and this, in turn, improves the flux. Propylene glycol, ethanol, transcutol[®], and N-methyl pyrrolidone are found to act in this way (Hadgraft 1999; Mehta J 2017).

Several physical and chemical means of assisting transdermal delivery have been explored so far (Bijal and Rakesh 2017). Some of the commonly used physical techniques include microneedles, needleless injectors, heat as a means of increasing skin permeation, iontophoresis, electroporation, sonophoresis, use of liposomes in transdermal applications and molecular absorption enhancement (Tanner and Marks 2008).

Several classes of the chemical enhancers (water, sulfoxides, azone, pyrrolidones, fatty acids, alcohols (along with fatty alcohols and glycols), surfactants, essential oils (including terpened and terpenoids), urea, phospholipids and certain solvents at high concentrations) have been identified as penetration enhancers (S Mansuri and B Vaghela 2014). However, their inclusion into topical or transdermal formulations is limited since the underlying mechanisms of action of these agents are seldom clearly defined (Williams and Barry 2004).

Transdermal drug delivery (TDD):-

The usage of intact skin as a portal of entry for drugs into the systemic circulation attracted tremendous interest after the introduction of the first transdermal patch containing scopolamine. Transdermal drug delivery is a viable administration route for potent, low-molecular weight therapeutic agents which cannot withstand the hostile environment of the gastrointestinal tract and/or are subject to considerable first-pass metabolism by the liver (Vora, Lin, and Madan 2013).

The release of a drug from the formulation applied to the skin surface and its subsequent transport to the systemic circulation involves several steps:

1. dissolution within and release from the formulation,
2. partitioning into the skin's outermost layer, the stratum corneum (SC),
3. diffusion through the SC, principally via a lipidic intercellular pathway, (i.e., the rate-limiting step for most compounds),
4. partitioning from the SC into the aqueous viable epidermis,
5. diffusion through the viable epidermis and into the upper dermis, and
6. uptake into the local capillary network and eventually the systemic circulation.

Therefore, an ideal drug candidate would have sufficient lipophilicity to partition into the SC, but also sufficient hydrophilicity to enable the second partitioning step into the viable epidermis and eventually the systemic circulation. For most drugs, except those possessing extreme lipophilicity ($\log K .5$), the rate-determining step for drug transport is o/w port across the skin is transit across the SC. However, from a drug delivery standpoint, it is far better that rate control resides within the delivery device in order to attain uniform input rates and reduce inter-individual variability (Kalia and Guy 2001).

A transdermal drug delivery system (TDDS) is thus a formulation or device (for example, a transdermal patch) that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose (Kalia and Guy 2001).

Developmental strategies and formulation development:-

The development of transdermal systems requires judicious selection of polymeric material whose diffusive characteristics will be such that a desirable permeation rate of a specific drug can be achieved. Therefore, understanding of diffusion in polymers and the mechanism of drug transport through them are important in controlled release analysis. The type of solute release is established by transport mechanism (Fickian or other). The solute size and polymer structure control the solute diffusion coefficient, and therefore, the magnitude of solute release.

In transdermal systems the release occurs by molecular diffusion that is related to molecular size and polarity of the drug, its solubility in the polymer phase, and the structure of the polymer. Control of solute diffusion coefficient may be achieved by controlling the degree of cross-linking, degree of branching degree of crystallinity, size of crystallites of the macromolecular carrier, and by adding adjuvants, which may slow down diffusional process either by hindering the diffusion or due to thermodynamic changes (Jain et al. 2017).

Design considerations of the transdermal therapeutics systems:-

To date there is no universal transdermal system design. Each system is formulated to meet specific biopharmaceutical and functional criteria, which dictate that the materials of construction, configuration of drug with the poor cosolvents, excipients, and enhancers are matched to optimize adhesive properties and drug delivery requirements. The success of formulation development may depend upon the proper selection of the transdermal technology or system design and its component. The main components of a transdermal patch are:

1. Liner- It protects the patch during storage. The liner is removed prior to use.
2. Drug - Drug solution in direct contact with release liner.
3. Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
4. Membrane – It controls the release of the drug from the reservoir and multi-layer patches and hence one of the most important component as well.
5. Backing – This component protects the patch from the outer environment.

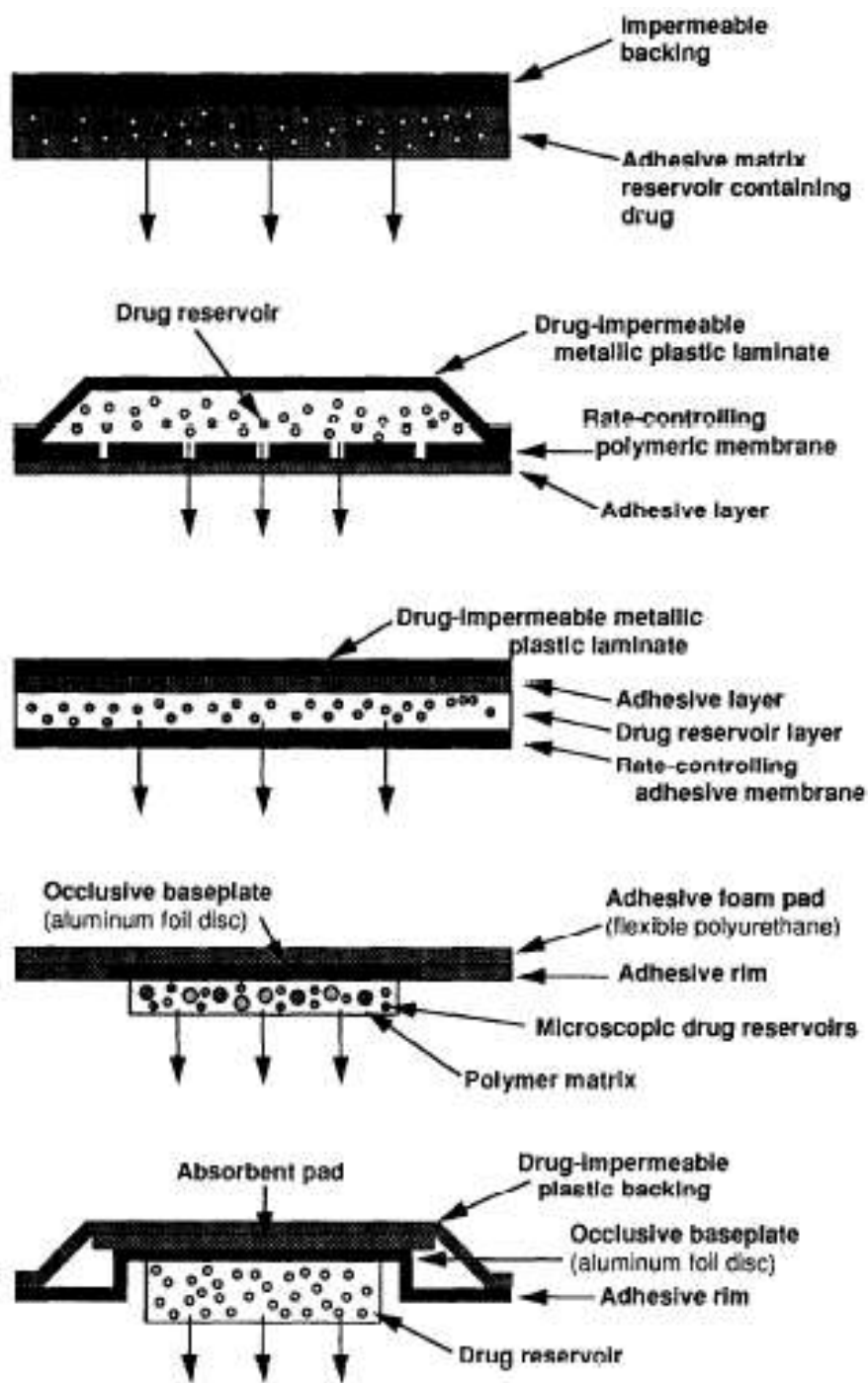


Figure 3:-Cross-sectional view of various transdermal delivery system designs. (a) PSA matrix device; (b) membrane-modulate TDS; (c) adhesive-controlled TDS; (d) micro-reservoir-type TDS; (e) matrix dispersion-type TDS Adapted from ("TRANSDERMAL DRUG DELIVERY SYSTEM," n.d.)

Pressure sensitive adhesive matrix type TDDS:-

The design is shown in Figure 3a. In this case, the drug reservoir itself is the adhesive. The rate of drug release is defined by Higuchi equation which can be used for drug release from a matrix-device. The adhesive (also known as pressure-sensitive adhesive (PSA) is physically and chemically compatible with the active ingredient as well as with

other excipients like enhancers and solubilizers. The most typical PSAs are acrylic, rubber or silicone adhesive. Efforts are made to obtain PSA which is non-irritant to the skin (Cilurzo, Gennari, and Minghetti 2012).

Adhesive diffusion-controlled TDDS:-

The adhesive layer can be used as a rate-controlling layer in reservoir device. Figure 3c shows a typical type of adhesive diffusion-controlled system. The drug reservoir is prepared by directly dispersing the drug in an adhesive polymer which is then spread by solvent casting or heating molding onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. In order to formulate an adhesive diffusion-controlled drug delivery system, a layer of nonmedicated, rate-controlling adhesive polymer with constant thickness should be spread onto it (Guyot and Fawaz 2000).

Membrane-modulated TDDS:-

The drug formulation is either totally or partially encapsulated in a drug reservoir compartment, which has a drug-releasing surface covered by a rate-controlling polymeric membrane. The polymeric membrane can be fabricated from a homogenous (or heterogenous) nonporous, microporous or semi-permeable polymeric membrane. Figure 3b shows a cross-section of a typical device under this category. Drug molecules are released across the membrane simply by diffusion through the pores among the polymers filled with solvent in a microporous membrane such as Millipore filters or Celgard[®] porous polypropylene, and through polymer itself in solution-diffusion membrane like one of silicone. The release rate from this type of TDDS can be tailored by modulating the partition coefficient and diffusivity of the drug molecules and the rate-controlling membrane and its thickness (Enscore, Osborne, and Shaw 1989).

Matrix-dispersion type TDDS:-

This is the simplest and the least expensive way to control the release of a drug to disperse it through an inert polymer matrix (shown in Figure 3e). In this group of TDDS, the drug reservoir is a homogenous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix. The release of drug molecules from this type of rate-controlled TDDS may be controlled at a rate preprogrammed by controlling the loading level as well as the solubility and/or the diffusivity of the drug in the polymer matrix (Higuchi 1961).

Microreservoir type TDDS:-

In this type of rate-controlled TDDS, the drug reservoir is a suspension of drug solid particles in an aqueous solution of a water-miscible polymer, such as polyethylene glycols. This forms a homogenous dispersion of many discrete, unextractable, microscopic drug reservoirs in a biocompatible polymer, such as silicone elastomers. The microdispersion is achieved by applying a high energy dispersion technique. Figure 3d shows the general design of this kind of the system. However, the device can be further modified with a layer of biocompatible polymer to obtain the desired drug release rate.

Current transdermal technologies and future direction:-

The transdermal market is dominated by HRT patches, but patches are also used for delivery of testosterone, nicotine, nitroglycerine, and analgesics (Marwah et al. 2016). '3M markets Minitran, which is the smallest daily nitroglycerin patch in the world while Noven's Vevelle-Dot is the world's smallest estradiol transdermal system (ERT) patch.' One of the pioneers in this field is Alza, which developed the first patch in the United States. Its brands include Duragesic, Estraderm, Transderm-Nitro, Tansderm-Scop, and Catapres-TTS[®] (ALZA Corporation, Mountain View, CA, USA). Several OTC products also have transdermal patches, including those used for delivery of nicotine, analgesics and cold and sinus remedies and travel/motion sickness (Tanner and Marks 2008).

A comprehensive review on the marketed products for transdermal drug delivery systems are discussed elsewhere (Marwah et al. 2016). Several other additions to the transdermal market have been; Synera, a local anaesthetic patch containing lidocaine and tetracaine.; the once-a-day product EmSam containing selegiline, a monoamine oxidase inhibitor, for the treatment of depression; IONSYS[™] (Janssen Pharmaceutica NV, Beerse, Belgium), a fentanyl iontophoretic transdermal system, this is the first needle-free, patient-activated analgesic system indicated for the short-term management of acute post-operative pain in adult patients during hospitalization. The TDS utilizes a process in which a low intensity electric field is applied. A dose of 40 µg fentanyl can be delivered in 10 min; Daytrana, a once-a-day patch containing methyl-phenidate for treatment of ADHD in children aged 6-12 years. Neupro (rotigotine transdermal system) for treatment of signs and symptoms of early-stage idiopathic Parkinson's

disease (Tanner and Marks 2008). Interestingly, novel formulation strategies such as nanoformulations delivered through a transdermal patch would be an interesting to explore further.

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