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Review Article

TRANSDERMAL DRUG DELIVERY SYSTEM

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Presentation:

Because of ongoing advances in innovation and the capacity to apply the medication to the site of activity without breaking the skin film, transdermal course is turning into a generally acknowledged course of medication organization. In the course of the most recent two decades in excess of 35 Transdermal fix items have been affirmed in US.(1) The primary target of transdermal medication conveyance framework is to convey drugs into fundamental flow into the skin through skin at foreordained rate with insignificant bury and intra quiet variety. The improvements of TDDS is a multidisciplinary action that incorporates basic plausibility concentrates beginning from the choice of medication atom to the exhibit of adequate medication motion in an ex vivo and in vivo model pursued by creation of a medication conveyance framework that meets all the stringent needs that are explicit to the medication particle (physicochemical, strength factors), the patient (solace and corrective intrigue), the maker (scale up and manufacturability) and most significant economy.(2)

Definition:

Transdermal medication conveyance framework can convey the medications through the skin entry to fundamental dissemination at a foreordained rate and keep up clinically the successful fixations over a delayed timeframe.

A basic fix that you stick onto your skin like a cement wrap, which use aloof dissemination of medications over the skin as the conveyance component.

A transdermal fix is characterized as cured cement fix which is put over the skin to convey a particular portion of prescription through the skin with a foreordained rate of discharge to venture into the circulation system. Today the most well-known transdermal framework present in the market principally dependent on semipermeable layers which were called as patches. (3)

Potential favorable circumstances of TDDS:

• Avoidance of gastro intestinal inconsistency
• Provides use of medications with short natural half lives
• Improving physiological and pharmacological reaction
• Avoiding the change in medication levels Inter and intra tolerant varieties
• Maintain plasma convergence of powerful medications
• Termination of treatment is simple anytime of time
• Ability to convey tranquilize all the more specifically to a particular site
• Provide reasonableness for self-organization
• Enhanced helpful viability (4)

Hindrances of TDDS:

- Transdermal conveyance isn't reasonable for conveyance of enormous portions of medications.
- It can't regulate drugs that require high blood levels.(5)
- Drug which may cause bothering or sharpening are not given by this course.
- This course is constrained when the medication is widely utilized in the skin and when atomic size is extraordinary enough to keep the particles from diffusing through the skin28.
- For a medication, which doesn't have a positive o/w segment coefficient this course can't be utilized. Starting with one site then onto the next on a similar individual, from individual to individual and with age the boundary elements of the skin changes which upsets transdermal medication infiltration. (12)

Well known USES:

- Hormonal patches

o estrogen patches are some of the time endorsed to treat menopausal manifestations (just as post-menopausal osteoporosis) and to transgender ladies as a kind of hormone substitution treatment.

o contraceptive fix (showcased as Ortho Evra or Evra) and

o Testosterone CIII patches for the two men (Androde) and ladies (Intrinsa).

- The hostile to hypertensive medication clonidine is accessible in transdermal fix form[7]

- Emsam, a transdermal type of the MAOI selegiline, turned into the principal transdermal conveyance operator for an upper endorsed for use in the U.S. in March 2006.[8]
- Daytrana, the main methylphenidate transdermal conveyance framework for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), was affirmed by the FDA in April 2006.[9]
- 5-Hydroxytryptophan (5-HTP) can likewise be managed through a transdermal fix, which was propelled in the United Kingdom in mid 2014.[10]
- Rivastigmine, an Alzheimer's treatment prescription, was discharged in fix structure in 2007 Under the brand name Exelon(11)

Transdermal course and medication conveyance prospects:

SKIN:

The biggest organ: The skin is the biggest organ of the human body which covers a surface region of around 2 sq.m. what's more, gets around 33% of the blood course through the body. 5 It fills in as a porousness hindrance against the transdermal retention of different substance and natural specialists. It isolates the hidden blood dissemination organize from the outside condition. (13)

Life structures and PHYSIOLOGY OF SKIN:

The human skin is a multilayered organ made out of numerous histological layers. Skin is most open organ in body. Its real capacities are; security of major or essential inside organs from the outer impacts, temperature guidelines, control of water yield and sensation. The skin of a normal grown-up body covers roughly surface region of two square meters and gets around 33% of the blood circling through the body.

Human skin contains three particular yet commonly ward tissues as given underneath:

A) The stratified, vascular, cell epidermis,

B) Underlying dermis of connective tissues

C) Hypodermis

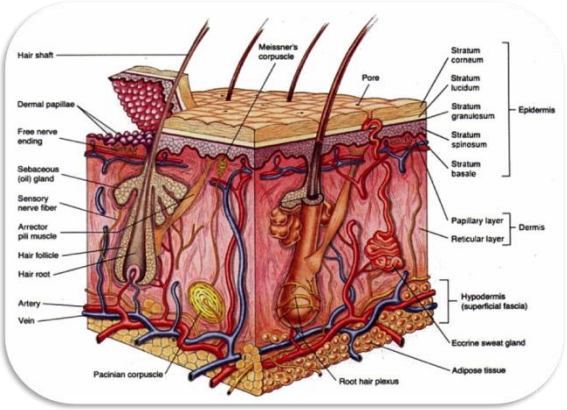

FIG. 1: SCHEMATIC REPRESENTATION OF SKIN AND ITS APPENDAGES

A) Epidermis- The epidermis is a stratified, squamous, keratinizing epithelium. The multilayered epidermis varies in thickness ranges from 0.8-0.06 mm. 90% epidermal cells are keratinocytes arranged in five layers & produce keratin protein. 8% melanocytes are presents. Langerhans cell arises from red bone marrow & migrates to epidermis, where they constitute small fraction of epidermis cells.

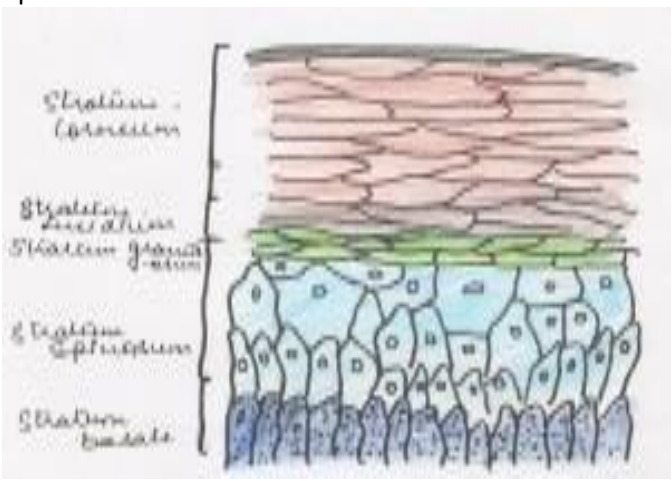

FIG. 2: SCHEMATIC REPRESENTATION OF ANATOMY OF EPIDERMIS

Five layers of epidermis:

a) Stratum Corneum
b) Stratum Lucidum
c) Stratum Granulosum
d) Stratum Spinosum
e) Stratum basale (14)

B) Dermis- It is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves.

C) Hypodermis- The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. The hypodermis layer is composed of loose connective tissues and its thickness varies according to the surface of body. (16)

Percutaneous Absorption: Before a topically applied drug can act either locally or systemically, it must penetrate through *stratum corneum*. [17]

Percutaneous absorption of drug molecules is of particular importance in transdermal drug delivery system because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general once drug molecule cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily.[18] The release of a therapeutic agent from a

formulation applied to the skin surface and its transport to the systemic circulation is a multistep process (figure 5) which involves:

- Dissolution within and release from the formulation
- Partitioning into the skin's outermost layer, the *stratum corneum* (SC)
- Diffusion through the SC, principally via a lipidic intercellular pathway.

Partitioning from the SC into the aqueous viable epidermis, diffusion

- **Physiological & pathological conditions of skin:**

1. Reservoir effect of horny layer: The reservoir effect of horny layer which is deeper layer 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 temperature: Increase in skin temperature increases the rate of skin permeation this is due to availability of energy required for diffusivity.

4. **Regional variation:** Differences in nature and thickness of the barrier of skin cause variation in permeability

5. **Pathological injuries to the skin:** Injuries that disrupt the continuity of the stratum corneum, increases permeability due to increased vasodilatation caused by removal of the barrier layer.

6. **Cutaneous self-metabolism:** Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and thus the topical bioavailability of the drug

7. **Skin barrier properties based on different age groups:** The pH of skin surface of new borns is higher than those in adult skin. The skin surface of the newborn is slightly hydrophobic and relatively dry and rough when compared to that of older infants. Stratum corneum hydration stabilizes by the age of 3 months. Whereas, There are changes in the physiology of aged skin (>65 years). The corneocytes are shown to increase in surface area which may have implications for stratum corneum function due to the resulting decreased volume of intercorneocyte space per unit volume of stratum corneum. The moisture content of human skin decreases with age

8. **Race:** Racial differences between black and white skins have been shown in some anatomical and physiological functions of the skin although data is relatively sparse. In black skin, increased intracellular cohesion, higher lipid content and higher electrical skin resistance levels compared to whites have been demonstrated.

9. **Body site:** Skin structure varies at different sites of body. Genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arms and legs. Intermediate permeability for most drugs is found on the trunk of the body.

10. Penetration enhancers used: Low permeability of drugs across the skin can be improved by the development of penetration enhancers. According to Chien et.al., penetration enhancers or promoters are agents that have no therapeutic properties of their own but can transport the sorption of drugs from drug delivery systems onto the skin and/or their subsequent transdermal permeation through skin.(22)

COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Polymer matrix/ Drug reservoir
2. Drug.
3. Permeation enhancers
4. Pressure sensitive adhesive (PSA)
5. Backing laminate
6. Release liner
7. Other excipients like plasticizers and solvents(23)

1. Polymer matrix/ Drug reservoir: Polymers are core part of TDDS. It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status. Polymers used in TDDS are classified as:

- Natural polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- Synthetic elastomers: e.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.
- Synthetic polymers: e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.(24)

2. Drug : Some of ideal properties of drug & some factors to be consider during preparation of TDDS are as follows:

- Drug has to be potent
- Drug should be Highly lipophilic (ideal log PO/W ≈ 2)

- It must be low molecular weight (ideally below 500 Dalton)
- It should have low melting point (ideally below 150 °C)
- Sufficient solubility in water at pH 6 to 7.4 (e.g., ≈ 0.05 to 1mg/ml if target delivery rate is in the mg range per day)
- Suitable pKa (determines solubility of the un-ionized form at physiological pH)

3. Permeation enhancers: Chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. They improve the permeability by interacting with structural components of stratum corneum. Ideal properties of permeation enhancers-

1. They should be non-irritating, nontoxic & non allergic.
2. They should not bind to receptor site i.e. not showing any pharmacological activity.
3. They should be cosmetically acceptable with an appropriate skin feel. (25)

4. Pressure sensitive adhesive (PSA)- Pressure sensitive adhesive helps to adhere transdermal patch the skin surface. It can easily remove from the smooth surface without leaving a residue on it. Ex-Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDS.

5. Backing laminate- Backing laminates are supportive material which is impermeable to drugs and also to permeation enhancers. They should chemically compatible with the drug, enhancer, adhesive and other excipients. Ex-vinyl, polyethylene and polyester films (26)

6. Release liner: Release liner is the primary packaging material that can protect the patch which will remove during application of patch to the skin. Release liner is made up of base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Release liner should be chemically inert & it should be permeable to drug, penetration enhancers & water.

7. Other excipients like plasticizers and solvents- Solvents used are chloroform, methanol, acetone, isopropanol and dichloromethane. Plasticizers used dibutylpthalate, triethyl citrate, polyethylene glycol and propylene glycol. (27)

Various diseases that can be treated by Transdermal Drug Delivery Systems:

Skin Disorders
Erectile Dysfunction
Menopause
Cardiovascular Disorders
Hypertension
Chronic Obstructive Pulmonary Disease
Neurological and Psychiatric Disorders
Parkinson's disease
Depression
Alzheimer's disease
Musculoskeletal Disorders

Transdermal delivery of drugs for Alzheimer's disease:

The first case of Alzheimer's disease (AD) was recorded in 1906 by Alois Alzheimer. Alzheimer causes mental and physical decline as a result of a progressive degeneration of neurological system, which progresses until death. While every part of cerebral cortex is involved, the occipital pole may be less affected in the great majority of patients. AD can be characterized by gross diffuse atrophy of the brain, along with the loss of neurons, neuronal processes, and synapses in the cerebral cortex and certain subcortical regions, resulting in degeneration of the temporal lobes, parietal lobes, parts of the frontal cortex, and cingulated gyrus. Accordingly, the affected people suffer from cognitive decline, memory impairment, difficulties in decision-making, and behavioral changes.

Cholinesterase inhibitors:

The deficiency of acetylcholine was known as the oldest hypothesis of causing the AD. Inhibition of the enzymes which degenerate acetylcholine is an effective therapy for pharmacological treatment of this neurological impairment. This therapy is associated with adverse events in the gastrointestinal system, and fluctuation of plasma level causes the symptoms linked to cholinergic hyperstimulation, which reduces the medication adherence of patients.(23,24). More recently, the technical principles underlying the development of transdermal drug delivery systems are summarized in Table 1.

Physostigmine:

Physostigmine was the first anticholinesterase documented as transdermal drug against treat AD. There may be some short-comings such as narrow therapeutic window, poor bioavailability, high first-past metabolic, and low user compliance of the oral and intravenous route of this drug that should be improved.[25,26] Levy *et al*. designed a formulation pad (3.6 cm × 3.6 cm) in 1986 which consisted of physostigmine in enhancer vehicle propionic acid and an ethylene/vinylacetate copolymer membrane with an adhesive on one side and an aluminum foil cover on its back.[27,28]

Consequently, physostigmine transdermal system was fabricated by Lohmann Therapie-Systeme GmbH that contained 30 mg active molecular in surface area 30.2

cm^2. The *in vitro* release revealed a stability of absorption from 8 h after administration over 22 h. A clinical study was carried out in a large number of participants (204 patients) with this patch; however, the plasma concentrations which were obtained (100 pg/ml) may not be efficient in the compensation for cholinergic deficiencies in affected brain areas and to produce benefits.[29] To enhance the permeation, a copolymer of non-ion surfactant polyethylene glycol was developed as a transdermal drug delivery for physostigmine with the 20% concentration of solution in the mixture of water/ethanol (80/20) and the amount of drug was 5.3 mg/cm^2. The area under the curve (AUC) over 24 h experiment was 245.2 ± 337.2 h.ng/ml, and the mean patch flux reached 4.6 ± 6.3 $\mu g/cm^2$ by rabbit test. This promising report enabled a possible carrier for functional agent on Alzheimer therapy.[20] There has a demand for further investigation of this innovative system for physostigmine.

Summary of transdermal drugs and techniques for cholinesterase inhibitors

Donepezil:

In the late 2008s, transdermal donepezil pharmaceutical dosage form has been evaluated. Among the cholinesterase inhibitors, donepezil is the most superior due to its high potency and selectivity for the enzyme in the central nervous system.[32] Valia *et al*. proposed two types of patches: A drug reservoir-in-adhesive and a drug matrix-in-adhesive A faster influx of functional substance was achieved with the second variant because the drug would migrate from reservoir into and through the adhesive layer. This novel system facilitated the controlled release by the correction of active surface of the patch which contacts directly to the skin.[33]

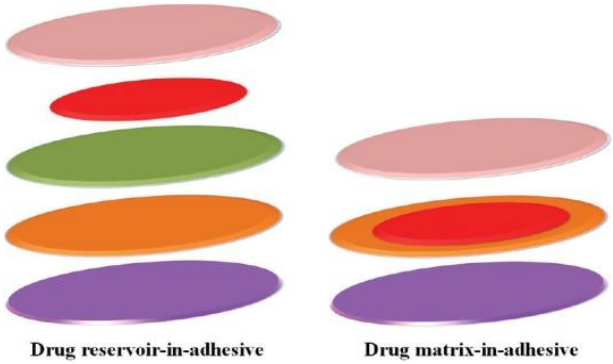

Fig.3: two types of patch for Alzheimer's disease)

Recent Technology Used in Transdermal Drug Delivery System:

Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979. In most patch designs, the drug is stored in a reservoir that is enclosed on one side with an impermeable backing and has an adhesive that contacts the skin on the other side.[30] There are some methods to apply simultaneously with the patch to reach a diffusion of the active substance such as iontophoresis, electroporation, ultrasound, and microscopy projection.[31]

1. Iontophoresis:

This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent19, 20. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-pertubation (for both charged and uncharged). Several iontophoretic systems are currently under commercial development including the Phoresor device developed by Iomed Inc. and the Vyteris and E-TRANS devices developed by Alza Corp.

1. Electroporation:

This method involves the application of high voltage pulses to the skin which has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect permeation rate include pulse properties such as waveform, rate and number. The technology has been used to enhance the skin permeability of molecules with differing lipophilicity and molecules such as proteins, peptides and oligonucleotides including biopharmaceuticals with molecular weights greater than 7kDA.23

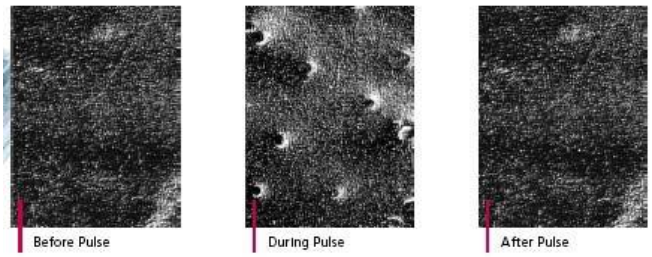

Fig. 4:

2. Microneedle-based Devices:

The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug. The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the

drug on the microprojection array24, the latter being better for intracutaneous immunization.

3. Abrasion:

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

4. Laser Radiation:

This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drug.

Transdermal Drug Delivery Systems Market Overview:

Global Transdermal Drug Delivery Systems Market was valued at $32,516 million in 2016, and is estimated to reach $61,689 million by 2023, growing at a CAGR of 9.5% during the study period. Transdermal drug delivery systems are an alternative to oral intravascular, subcutaneous, and transmucosal routes, wherein the drugs are delivered through the skin for therapeutic use. Rise in geriatric population and upsurge in number of patients suffering from chronic disorders are expected to drive the market growth. Moreover, increase in adoption of third-generation transdermal drug delivery systems, such as iontophoresis, boosts the market growth. However, disadvantages of these delivery systems, such as irritation at the site of application and edema, are expected to impede the market growth.

Growth in Asia-Pacific Region

According to a CADI Research Foundation, hypertension is the most prevalent disease in India. It is evident from the fact that the number of people with hypertension is projected to increase to 214 million in 2025 from 118 million in 2000. Hence, high incidence of cardiovascular disorders, such as hypertension, makes it an attractive market for transdermal drug delivery systems.

Recent Advancements

The market has witnessed development of new adhesives, molecular absorption enhancers, and penetration enhancers that are expected to enhance skin permeability, resulting in expansion of the range of drugs that are expected to be delivered through transdermal route.

For instance, new technology, such as micro needle-enhanced delivery, helps easy transportation of drug across the skin without the sensation of pain.

EVALUATION OF TRANSDERMAL FILMS

Interaction studies: Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation among other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable; thus, it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in thermal analysis, Fourier Transform Infrared spectroscopy, UV and chromatographic techniques by comparing their physicochemical characters, such as assay, melting endotherms, characteristic wave numbers, absorption maxima, etc. Other evaluation parameters are:

1. Thickness of the patch: The thickness of the drug-loaded patch is measured in different points by using a digital micrometer, and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.[6]

2. Weight uniformity: The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weighed in a digital balance.

The average weight and standard deviation values are to be calculated from the individual weights.

3. Folding endurance: A strip of the specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film can be folded at the same place without breaking gives the value of the fold ing endurance. [6]

4. Percentage moisture content: The prepared films are to be weighed individually and are to be kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films are to be reweighed to determine the percentage moisture content from the below-mentioned formula:[6] Percentage moisture content = [Initial weight - Final weight / Final weight] × 100.

5. Water vapor permeability evaluation: WVP can be determined with the foam dressing method, wherein the air-forced oven is replaced by a natural air circulation oven.[6] The WVP can be determined by the following formula: WVP = W / A (3) Where, WVP is expressed in gm/m2 per 24 h, W is the amount of vapor permeated

through the patch, expressed in gm/24 h, and A is the surface area of the exposure samples, expressed in m2 .

6. Polariscope examination: This test is to be performed to examine the drug crystals from the patch by a polariscope. A specific surface area of the piece is to be kept on the object slide and observed for the drug crystals to distinguish whether the drug is present as a crystalline form or an amorphous form in the patch.[6]

7. Shear adhesion: This test is to be performed for measurement of the cohesive strength of an adhesive polymer. An adhesive-coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape to affect it, pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken for removal, greater is the shear strength.

8. Peel adhesion test: In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. Molecular weight of the adhesive polymer and the type and amount of additives are the variables that determine the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then the tape is pulled from the substrate at a 180º angle, and the force required for tape removal is measured.[6]

9. Thumb tack test: It is a qualitative test applied for tack property determination of the adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

10. Percentage elongation break test: The percentage elongation break is to be determined by noting the length just before the break point. The percentage elongation can be determined from the below-mentioned formula: Elongation percentage = (L1 - L2) / L2 × 100 (4) Where, L1 is the final length of each strip and L2 is the initial length of each strip.

11. Quick stick (peel-tack) test: In this test, the tape is pulled away from the substrate at 90º at a speed of 12 inches/min. The peel force required to break the bond between the adhesive and the substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.[34]

SKIN PERMEABILTY KINETICS:

Fick's First Law of Diffusion

Percutaneous absorption of most drugs is a passive-diffusion process that can be described by Fick's first law of diffusion Q/dt = JT= PAΔC

JT is the total flux transported through a unit area of skin per unit time in steady state (µg/hr)

A is area of the skin

P is the effective permeability coefficient

ΔC is the drug concentration gradient across the skin

Rationale for Transdermal Drug Delivery (TDD):

Rationale for giving a drug Trans dermally has to be driven by an unmet medical need that can be met by this route, thus adding value to a drug therapy. For example, stable plasma level time profiles over extended time periods may reduce not only the dosing frequency, but possibly also side effects of the medication and daily doses that have to be administered by other routes. As transdermal drug administration is an easy, painless, and convenient mode of application, patient compliance for this route is in general high, especially in elderly and young people and patients groups who have difficulties swallowing or who are suffering from nausea or emesis.

In addition, transdermal patches may improve competitiveness of a pharmaceutical company in a large market segment. Known examples are nitroglycerin patches in the cardiovascular field, which were successfully introduced in the nitrate market more than 30 years ago, and recent introduction of Rivastigmine patches in the indication Alzheimer and dopamine agonist patches in the indications Parkinson's disease (PD) and Restless Legs Syndrome (RLS) [35].

General Aspects to be considered for TDD:

Before the drug is absorbed by the vascular network and/or lymphatic system in the dermis, it has to overcome some hurdles [36, 37]:

- Antigen presenting cells of viable epidermis reporting to the immune system like Langerhans cells and also cells filtering UV radiation or forming a barrier against chemicals
- Immune and inflammatory cells of the dermis which react on any mechanically or chemically induced irritation, like the mast cells. If the outermost skin layer has to be interrupted by microneedles or laser beams, location of nerve endings in the dermis has to be considered as well

In passive diffusion controlled systems the drug molecule can take different routes to cross the SC. The para- or intercellular tortuous route between the corneocytes is seen as the principal transport pathway for most lipohilic drugs. Following this route the drug has to diffuse through bilayers of ceramides, which are associated with free fatty acids (and their esters) and cholesterol. Structural properties of the paracellular lipid matrix fit the barrier needs of skin by being simultaneously robust and impermeable [38].

Physical Enhancement Techniques Tested in Clinical Studies for TDD:

Approaches to increase Trans epidermal drug transport rate may be subdivided in laser-, electrical-, structure-, and velocity-based techniques [41]..

Another advanced electrical approach is **microporation** of the biological barrier via an alternating current applied to an array of microelectrodes or filaments which are brought in contact with the skin [8]. This treatment creates local heat leading to cell ablation and transient creation of microchannels or pores typically 50 to 100µm in diameter. Target penetration depth of local heating is less than 100µm and pore number is typically in the range of 100 to 200cm². Microporation of the skin can be also achieved via application of short, solid microneedles or hollow cannulae, which penetrate the SC and epidermis up to the upper dermis, ideally without reaching pain-sensitive nerve endings in the dermis [42, 43]. This structure-based technique causes a minimally invasive and painless disruption of the skin barrier. Solid microneedles can be used to pierce the skin before the drug containing formulation is placed on the pretreated skin area ("poke and patch" approach), or the microneedles are coated with the drug before insertion and the drug remains in the skin on removal of the microneedle patch ("coat and poke" approach).

If the microneedles consist of dissolvable sugars or biodegradable polymers which are loaded with drug, they remain in the skin together with the drug and only their carrier system is removed from the skin ("poke and release approach").

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Considering today's experiences and progress in the transdermal field, it can be concluded that the future of transdermal drug delivery depends on:

- Development of passive and active transdermal drug delivery systems which meet unmet medical, patient, and drug needs
- Further improvement of skin pretreatment methods
- Development of on demand systems which combine a suitable technique with a tailor-made drug reservoir or formulation
- Progress made with appropriate techniques and approaches to overcome constraints of passive diffusion without compromising skin integrity

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