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A MINI REVIEW ON ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM

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Keywords:

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ABSTRACT: Currently, oral drug delivery and parenteral drug delivery are used for the treatment of various diseases. In the oral drug delivery system, due to the first-pass metabolism and acidic environment of the gastrointestinal route, the drug exposes to acids and enzymes present in the gastrointestinal tract, which may lead to degradation of the compound, which ultimately results in poor bioavailability of the molecule. On the other hand, the parenteral drug delivery system has its own disadvantages as it is invasive and needs skilled personnel for administration. To overcome these problems, the transdermal drug delivery system is introduced as a novel approach, and recently there is tremendous interest in transdermal drug delivery systems. A transdermal patch is a medicated adhesive patch winch that is placed onto the skin to deliver the appropriate dose of the drug through the skin and directly into the bloodstream. In this, transdermal patches are prepared for drug penetration through the skin layer (Stratum corneum barrier). To avoid the stratum corneum barrier, the microneedle-based transdermal drug delivery system is advantageous. Microneedles are classified into solid microneedles, coated microneedles, dissolving microneedles, hollow microneedles, and hydrogel-forming microneedles. This review provides information regarding transdermal drug delivery, a factor that can affect the transdermal delivery, ingredients used in the formulation of TDDS, drug penetration, different types of methods for formulations, and some advanced techniques such as microneedles.

INTRODUCTION: Recently, there is growing interest in the novel drug delivery system for existing drug molecules. The novel drug delivery system offers to increased safety and efficiency of a drug molecule and also improves patient compliance. Transdermal drug delivery systems (TDDS) are self-contained and discrete dosage forms. Another advantage of the TDDS is that the dose is reduced as compared to the oral route of drug delivery [1].

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The transdermal drug delivery system delivers the drug into systemic circulation through the skin at a controlled and predetermined rate. TDDS is a promising method for drug application as it reduces the first-pass metabolism of the drug in the liver. It gives controlled and sustained release of the drug with a short biological half-life. Transdermal patches are designed to follow zero-order kinetics and will be helpful in the treatment of the chronic condition. Due to the reduction in dose of the drug, it also decreases the side effect and toxicity and ultimately improves patient compliance [2].

An ideal drug candidate for transdermal drug delivery should require the following characteristics,

1. Molecular weight should be less than 500 Da.

2. Log partition coefficient preferably in the range of 1 to 3.

3. Potent molecule; dose less than 10 mg.
4. Aqueous solubility should be greater than 100 ug/ml.

2. Anatomy of the Skin: Skin is the largest organ of the body with surface area of 1.8m^2. Main function of the skin is to provide a protective barrier between the body and external environment against microorganisms, *etc*. [3]

Skin divided into three main regions

- Outermost layer – Epidermis (Stratum corneum)
- Middle layer – Dermis
- Innermost layer – Hypodermis

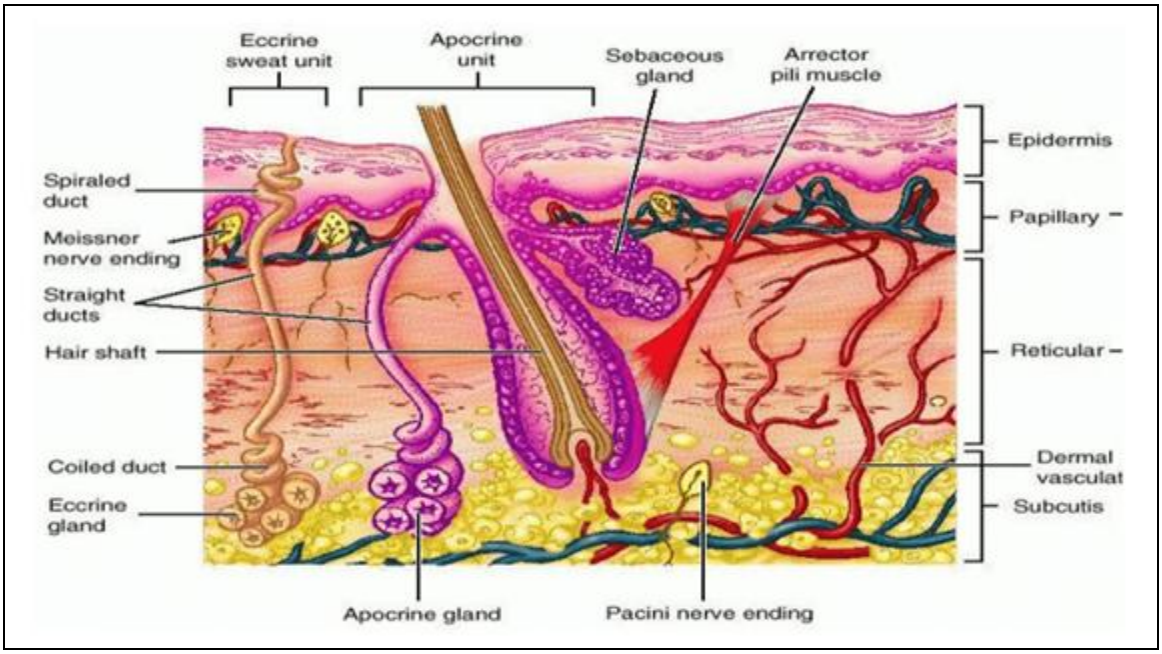

FIG. 1: STRUCTURE OF HUMAN SKIN

2.1. Epidermis: It is the outermost layer of the skin having a thickness of approximately 0.8 mm. It consists of multi-layered regions of epithelial cells and viable epidermis. The epidermis consists of keratinocytes (95% of cells) and other cells in epidermis layer including melanocytes, Langerhans cells, and Merkel cells.

The stratum corneum is the most superficial layer, which is directly in contact with the external environment and has barrier properties [4]. Keratinocytes in the basal layer divide into the stratum spinosum; stratum granulosum; and stratum corneum. Stratum corneum consists of metabolically active agents, such as mitochondria and ribosomes.

2.2. Dermis: It is 3-5 mm thick. The dermis is composed of collagenous (70%) and elastic fibers, which gives strength and elasticity to the skin. Blood vessels give nutrition to both dermis and epidermis. It also consists of nerves, macrophage, and lymphatic vessels [5]. The dermis is metabolically active and also plays an important role in regulating body temperature, for wound repair, to deliver oxygen and nutrients to the tissue and also remove the waste products.

2.3. Hypodermic / Subcutaneous Layer: It consists of a network of fat cells. It is between the skin and underlying tissues of the body that is muscle and bone. It provides protection against physical shock, heat insulation, and mechanical support of the vascular. It provides a store of high-energy molecules and carries the principal blood vessels and nerves to the skin. Fat cells present into the subcutaneous layer are approximately 50% of body fat [6].

3. Drug Penetration Routes: Two possible routes of drug penetration across intact skin are:

- Trans-appendageal pathway
- Trans-epidermal pathway

- Intracellular route
- Intercellular route

Trans-appendageal route; involved passage of molecules through sweat glands and across the hair follicles. Intracellular route; drug delivery through the route passes from corneocytes which have highly hydrated keratin creating a hydrophilic pathway. A drug passes through the corneocytes of stratum corneum [7]. Intercellular route; in intercellular pathways, the drug diffuses through the lipid matrix present between the cells.

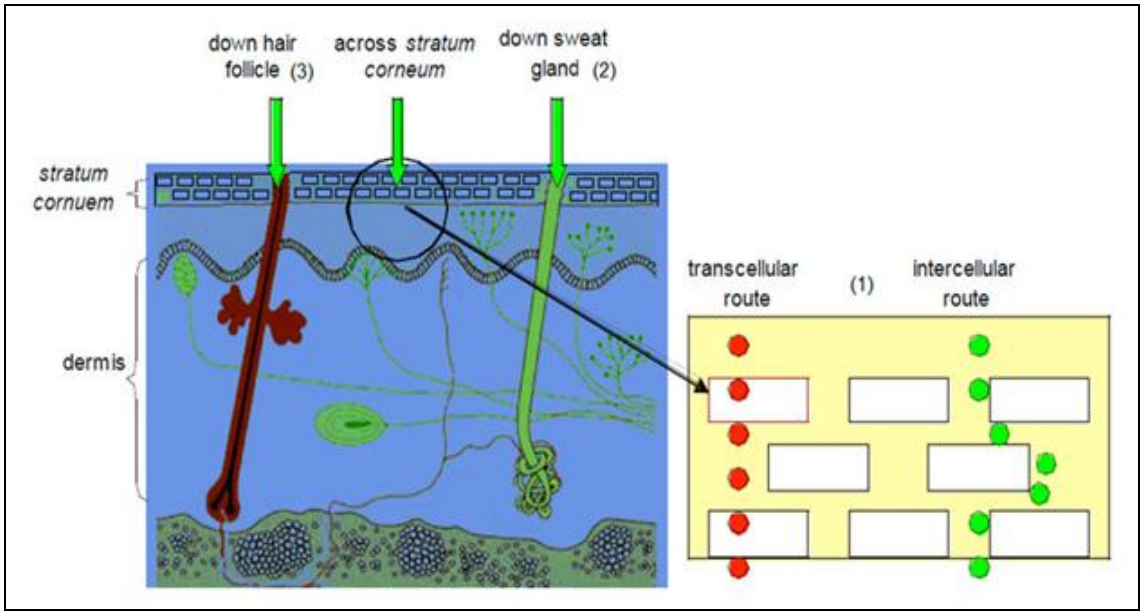

FIG. 2: POSSIBLE DRUG PENETRATION ROUTES ACROSS HUMAN SKIN

Transport through the Skin: Delivery of the topically applied drug molecules into the systemic circulation is a complex process via several routes. Initially, drug molecules are present in the skin layer. Diffusion and dissolution through the formulations is the initial step in delivery. After the passage through three potential routes mentioned above. Firstly, it can pass *via* the shunt routes.

In this case molecules will partition into sweat or sebum before diffusing against the outflow from the glands. The molecules are passed from the stratum corneum *via* an intracellular route or intercellular route. In the intracellular route, drug diffuses through the aqueous keratin in corneocytes and then intercellular lipids. In the intercellular route, drug diffuses via tortuous route within the lipid domain. After passing from the stratum corneum, molecules diffuse through the lower epidermal layer and then reach to the systemic circulation. The skin contains esterases, peptides and hydrolases, and because of this, skin is metabolically active and reduces the bioavailability of topically applied drugs. Route for the transport depends on the physicochemical nature of the drug.

4. Advantages of Transdermal Drug Delivery: Transdermal drug delivery system delivers the drug into systemic circulation through the skin so it avoids both the first-pass metabolism and also enzyme and pH deactivation into the gastrointestinal tract.

TDDS requires less amount of dose as compared to oral drug delivery so ultimately, it decreases dose-related side effects of the drug. Drug candidates with sustained plasma peak concentration are suitable for transdermal drug delivery. TDDS is easy and suitable for a drug molecule which is unstable in gastrointestinal tract. The drug which is having short half-life and narrow therapeutic window can also be given through TDDS. Therapy should be stopped at any point when drug shows adverse effects and it suitable for self-administration increasing patient compliance.

5. Disadvantages of Transdermal Drug Delivery: Large molecular size molecules are suitable candidates for transdermal drug delivery systems. The drug has sufficient aqueous and lipid solubility for penetration through the stratum corneum.

Ionic drugs cannot be delivered through transdermal drug delivery. Some formulation of the drug may cause irritation or allergic reaction at the site of application. High drug levels cannot be achieved in the blood through transdermal drug delivery. Adherence to transdermal patches for a long time is difficult.

6. Kinetic of Transdermal Permeation: Kinetic for skin permeation is important for the development of successful transdermal drug delivery [8].

Transdermal permeation of a drug involves the subsequent steps:

- Absorption by stratum corneum
- Penetration of drug through the epidermis
- Uptake of the drug within the dermal papillary layer

- The rate of permeation across the skin (dQ/dt) is given by, equation 1

$$dQ / dt = Ps (Cd - Cr)\ldots..1$$

- Where, P_s - Overall permeability constant of the skin tissue to the penetrant, C_d - Concentration of skin penetrant in the donor compartment (*e.g.,* on the surface of stratum Corneum), C_r - Concentration within the receptor compartment (*e.g.,* body)

$$Ps = Ks \times Dss / hs\ldots\ldots2$$

Where; Ks - Partition coefficient for the interfacial partitioning of the molecule which is penetrated from a solution medium onto the stratum corneum. D_{ss}- Apparent diffusivity of the penetrant molecule. h_s - Overall thickness of skin tissues.

As K_s, $D_{ss,}$ and h_s are constant under given conditions, the permeability coefficient (P_s) for a skin penetrate is often to consider to be constant. From Eq. 1, it is clear that a constant rate of drug permeation can be obtained only when (C_d>>C_r), *i.e.,* the drug concentration at the surface of the stratum corneum (C_d) is greater than the drug concentration in the body (C_r) then Eq.1 becomes, eq.3

$$dQ / dt = Ps \times Cd\ldots.3$$

And the rate of skin permeation is constantly provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be released from the device at a rate Rr, *i.e.,* either constant or greater than the rate of skin uptake Ra *i.e.,* Rr>> Ra.

Since Rr >> Ra, the drug concentration on the skin surface C_d is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s. *i.e.* C_d>>C_s. Therefore, a maximum rate of skin permeation is obtained and is given by equation 4.

$$(dQ / dt)\ m = Ps \times Cs\ldots\ldots4$$

From the above equation, it can seen that the utmost rate of skin permeation depends upon the skin permeability coefficient P_s and equilibrium solubility within the stratum corneum C_s. Thus skin permeation appears to be stratum corneum limited. The limited membrane flux (J) under steady-state conditions is described by equation 5.

$$J = (DCKo / w / h\ldots..5$$

Where, J - Amount of drug passing through membrane system per unit area per unit time. D - Diffusion coefficient of drug within the membrane. C - Concentration gradient across the membrane. K - Membrane/vehicle partition coefficient. h - Membrane thickness.

7. Factor Affecting on Transdermal Permeation:

7.1. Biological Factor:

7.1.1. Skin Condition: Intact skin structure itself act as a barrier, but different type of agents crosses that barrier *e.g.* acid, alkali, solvents like methanol, chloroform. Agent removes lipid structure and forming artificial pass way for passage of molecule.

7.1.2. Skin Age: Adult's skin is more permeable than older patients. Older patients have dramatical changes in the anatomy of skin that decreases penetration of the drug. In children, some type of drug shows side effects *e. g.* Potent steroids, boric acid, hexachlorophene because of greater surface area per unit body weight [9].

7.1.3. Blood Supply: Change in peripheral circulation affects the absorption of the transdermal drug delivery system.

7.1.4. Skin Metabolism: Skin metabolism affects the efficiency of the drug, which penetrates through

the skin. Skin metabolizes steroids, hormones, chemical carcinogens, *etc*., and decreases the bioavailability of that agents.

7.1.5. Regional Skin Site: Thickness of the skin, nature of stratum corneum, and density of appendages affects the absorption of the agent. This factors ultimately affect the penetration of drug.

7.1.6. Species Differences: Skin thickness, the density of appendages, and keratinization of skin which varies from patient to a patient; this can affect the absorption and permeation of drug.

7.2. Physicochemical Factors:

7.2.1. Skin Hydration: Permeability of skin increases when the skin comes into contact with water. Hydration is the most important for increasing permeation so the humectant is added into the formulation.

7.2.2. Temperature and pH: The diffusion coefficient decreases as the temperature decreases. Permeation of drugs increases with temperature variations.

Weak acids and weak bases dissociation depending on the pH and pka or pkb values. Penetration of unionized drugs determines by the drug concentration into the skin. Hence temperature and pH play an important role in the penetration of drug from skin [10].

7.2.3. Diffusion Coefficient: Penetration of drug depends on the diffusion coefficient of drug. The diffusion coefficient depends on the properties of the drug and diffusion medium.

7.2.4. Drug Concentration: Flux is directly proportional to the concentration gradient across the barrier. Concentration gradient will be higher if the concentration of drug is more across barrier.

7.2.5. Partition Coefficient (K): Optimum partition coefficient value is required for the good penetration. Drug with high K value and low K value are not suitable candidates for TDDS.

7.2.6. Molecular Size and Shape: Drug absorption is inversely proportional to the molecular weight. Small molecular weight drug molecules are suitable candidates for the TDDS.

7.3. Environmental Factors:

7.3.1. Sunlight: Because of sunlight, the outer layer of blood vessels becomes thinner, and it's lead to bruising.

7.3.2. Cold Season: In the cold season, the skin becomes dry, which can affect the hydration of the skin. So, to minimizing the effect on hydration, the moisturizers are used, which increases the water intake of the skin.

7.3.3. Air Pollution: Dust can fulfill the pores and increases the bacteria on the surface of the skin, which leads to acne and spots on the skin and affects the drug delivery through skin. A chemical pollutants can also affect the anatomy of the skin.

7.3.4. Effect of Heat on Transdermal Patches: Penetration of drug is directly proportional with the heat. The storage area for the transdermal drug delivery is the cool and dry place until their use.

8. Formulation of Transdermal Drug Delivery:

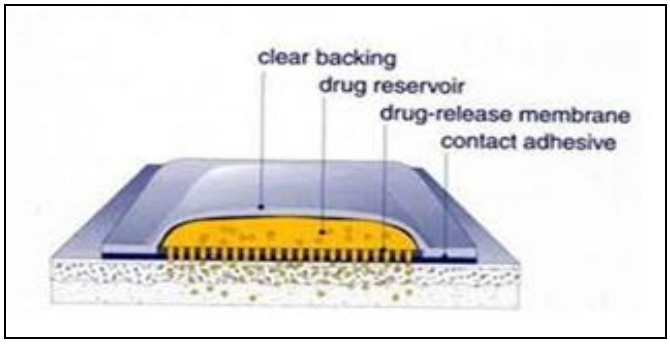

FIG. 3: COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

8.1. Drug Substance: Different types of drug properties should be checked before the selection of the drug. The molecular weight of the drug substance should be less than 1000 Daltons. For the penetration of the drug through the skin it should have an affinity for both lipophilic and hydrophilic phase [7]. The drug which is having a low melting point is a suitable candidate for TDDS. Drug dose should not be more than 50 mg/day. Molecules for the TDDS should be potent. The drug should be stable when it comes into contact with skin. The drug should not be irritant or allergic to the skin. A short biological half-life of the drug molecule is required. The drug should not follow a zero-order kinetic profile for transdermal drug delivery.

The drug is not get metabolized into the skin. The ideal dose for transdermal drug delivery is 10 mg/day.

TABLE 1: IDEAL PROPERTIES OF DRUG SUBSTANCE FOR TRANSDERMAL DRUG DELIVERY [8]

Parameter	Properties
Dose	Less than 20mg/day
Half life	< 10 hrs
Molecular weight	<400 Dalton
Melting point	<200°C
Partition coefficient	1 to 4
Aqueous Solubility	>1mg/ml
pH of the aqueous saturated solution	5-9
Skin Permeability Coefficient	>0.5×10 -3 cm/h
Skin Reaction	Non irritating and non-sensitizing
Oral Bioavailability	Low

8.2. Polymer Matrix: Polymers are the important components in the formulation of TDDS. Drug reservoir and drug-polymer matrix are coated or sandwiched in between the polymeric matrix. Multi-layered transdermal drug delivery can also be formulated. Backing layers are formulated by using a polymer that can prevent the wastage of drug molecule [12].

Different properties should be there for the polymer; the Chemical structure and molecular weight of the polymer is should be appropriate for proper drug release and drug diffusion. Polymer should be non-toxic in nature. Polymer should be chemically stable. Polymer should be easily formulate or easily available. Polymer should not be more expensive. The Amount of the drug should be stable into the polymeric layer that shows the drug-polymer compatibility. Previously, number of synthetic and natural polymers have been used by various researchers in the formulation of TDDS [8].

TABLE 2: DIFFERENT TYPES OF POLYMERS USED IN THE FORMULATION OF TDDS

Natural polymers	Synthetic polymers	Synthetic elastomers	Biopolymers
Zein, Gelatin, Shellac, Waxes, Chitosan, Natural rubber, Cellulose derivatives	PVA, PVC, Polypropylene, Polyacrylate, Polyurea, Polyamide, Polyethylene, PVP	Polybutadiene, Silicon rubber, Nitril acrylonitril, Neoprene, Hydrin rubber, Polyisobutylene	Polylactic acid, Collagen, Xanthan, Pullulane, Elastin, Gellan

8.3. Penetration Enhancers: Penetration enhancers are helpful to overcome the problems associated with the skin barriers for penetration of the drug and increase the penetration of the drug. Penetration enhancers increase the skin permeability of the drugs [13]. Penetration enhancers are required to have physical and chemical compatibility with drugs and excipients. Penetration enhancers should not cause any effect on body fluids and electrolytes. Penetration enhancers give controlled action of the drug. It should not cause toxic effects, irritating effects, and allergic reactions [14]. Penetration enhancers should not change the pharmacological effect of the drug. It should be economical, colourless, and odourless.

8.4. Backing Layer / Laminate: The backing layer protects the drug reservoir from the external environment, gives stability to the formulation, and also provides support. It should have elastic, flexible, and impermeable to drug diffusion to prevent drug loss. The backing layer is compatible with the drug, polymer, and excipients. It is fabricated with aluminium foil, polyethylene, polyester, polyvinyl chloride, heat-sealed layers, and polyurethane [15]. The chemical resistance of the material is taken into consideration for designing of the backing layer.

Prolong contact between the backing layer and excipients may cause the diffusion of the drug reservoir through backing layer so the compatibility study is taken into consideration. The backing layer with the high flexibility, good oxygen transmission, and high moisture vapour transmission rate is the most suitable backing layer for the TDDS [16] *e.g.*, Polyethylene and polyester film.

8.5. Adhesives: Adhesives should adhere to the skin when applied pressure from the finger and placed there for a prolonged time period. It maintains the patch in continuous contact with the skin. It should not be irritant, compatible with other ingredients and skin, and also easily removable. Pressure-sensitive adhesives are used because it maintains the contact of skin and transdermal system. It should adhere with applied finger pressure, exert a strong holding force. Polyacrylate, polyisobutylene, and silicon-based adhesives are frequently used in TDDS. The selection of adhesive is based on patch design and drug formulation. For

matrix systems, a peripheral adhesive and for reservoir systems, a face adhesive are selected. In drug-in-adhesive matrix systems, the selection is based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive [17].

8.6. Plasticizers: It provides flexibility and improves the brittleness of the polymer. When we added the plasticizers, which change the physical and mechanical parameters of the polymer, plasticizers loosen the tight polymer linkage by connecting themselves between the molecules of the polymer chains.

Plasticizer increases the elongation at break, toughness, and flexibility of the polymer while decrease the tensile stress, hardness, electrostatic charge ability, and glass transition temperature [18,] *e.g.*, Glycerol derivatives, phthalic acid esters, sebacic acid esters, oleic acid esters, alcohols, dibutylpthalate, triethylcitrate, poly-ethylene glycol.

8.7. Rate Controlling Membrane: Rate controlling membrane determines the rate at which drug is to be delivered from the dosage form. Different types of natural and synthetic origin polymers are used to formulate the rate-controlling membrane. *e.g.*, Chitosan, poly-2- hydroxyethyl methacrylate.

8.8. Release Liner: Release liner is a part of primary packaging and prevents the loss of drug from the polymer matrix and gives protection to the patch from the outside environment. Release linear may be occlusive (*e.g.*, polyethylene, PVC) or non-occlusive (paper fabric). Polyester foil and metallic foil are frequently used for the release liner in TDDS [19].

8.9. Other Excipients: Various solvents such as methanol, chloroform, triethylcitrate, polyethylene glycol, propylene glycol *etc*., are used as permeation enhancers and also dissolve the drug and polymers [20].

9. Various Methods for Preparation of TDDS:

9.1. Asymmetric TPX Membrane Method: A prototype patch are fabricated with the heat-sealable polyester film (type 1009, 3m). In this, a concave membrane having 1 cm diameter will be used as the backing membrane. Drug sample dispensed into concave membrane and covered by TPX (poly-4-mthl-1-pentene) and sealed by adhesive [21].

9.2. Circular Teflon Mould Method: It is a solvent evaporation technique or solvent casting method. An appropriate ratio of polymer solution and organic solvent are taken in this method. The drug is dissolved in the half amount of the same organic solvent (In different concentrations). In that solution, the Di-N-butyl phthalate is added as a plasticizer. Stir the solution for 12 h and pour the solution into the circular Teflon mould. The solvent is allowed to evaporate for 24 h. Before evaluation, the dried film is stored for 24 h at 25°C in a desiccator containing silica gel to eliminate aging effects. These types of films are to be evaluated within one week of preparation [22].

9.3. Mercury Substrate Method: The drug is dissolved in the polymer solution. The plasticizer is added into the above solution. Stir the solution for 10-15 min to formulate a homogenous dispersion. Then pour the solution into a levelled mercury surface, which is covered with an inverted funnel to control solvent evaporation [22].

9.4. IPM Membranes Method: The drug is dispersed into a mixture of water, and propylene glycol contains carbomer 940 as a polymer. Stir the solution by magnetic stirrer for 12 h. Dispersion is to be neutralized. Made a viscous mixer of the solution by adding triethanolamine into the neutralized solution. Buffer pH 7.4 can be maintained for formulating solution gel. The formed gel will be incorporated into the IPM membrane for the formulation of TDDS [23].

9.5. EVAC Membranes Method: For the preparation of the target transdermal therapeutic system; 1% carbopol, reservoir gel, polyethylene (PE), ethylene-vinyl acetate copolymer (EVAC) membranes are used for the rate-controlling membranes.

If the drug is insoluble in water, then propylene glycol is used for the preparation of gel. After the drug is dissolved in propylene glycol the carbopol resin will be added into the solution and neutralize by adding 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on the sheet of a backing layer covering the specified area.

A rate-controlling membrane is placed over the gel and the edges are sealed by heat to obtain a peak-proof device [24].

9.6. Aluminium Backed Adhesive Film Method: Aluminium backed adhesive film method is suitable when unstable matrices are formulated in the TDDS because of a greater loading dose (more than 10 mg). Chloroform is used as a solvent for the preparation of this film because most of the drug and adhesives are soluble in chloroform.

The drug is dissolved in chloroform followed by addition of adhesive material and dissolved it. Custom made of aluminium former is lined with the aluminium foil and blanked off with tightly fitting cork blocks [25].

10. Types of Transdermal Patches:

10.1. Single layer Drug-in-adhesive: In this system, drug and excipients are inclusive with skin adhesive, which serve as formulation foundation as a single breaking layer [3]. The rate of drug release depends on the diffusion phenomenon.

The rate of release of drug is expressed as:

$$dQ / dt = Cr / (1 / Pm + 1 / Pa)$$

Where, C_r = Drug concentration in reservoir compartment, P_a = Permeability coefficient of adhesive layer, P_m = Permeability coefficient of rate controlling membrane

10.2. Multi-Layer Drug-in-Adhesive: In this system, drug and excipients are incorporated with adhesive but both layers of adhesive are separated by single-layer membrane. The released of the drug occurred through diffusion phenomenon [3].

The rate of release of drug is governed by the following equation;

$$dQ / dt = (Ka /r \times Da / ha) \times Cr$$

Where, K_a/r = Partition coefficient for the interfacial partitioning of the drug (reservoir layer to adhesive layer).

10.3. Drug Reservoir-in-Adhesive: In the reservoir system, inclusion of liquid compartment containing drug solution/suspension between the backing layer and semipermeable membrane followed by adhesive layer and release liner [7].

10.4. Drug Matrix-in-Adhesive: This system is designed by the inclusion of semisolid matrix having the drug in solution or suspension form which is in direct contact with the release liner [7].

The rate of release of drug is governed by the following equation:

$$dQ / dt = A \times Cp \times Dp \times 1/ 2/ 2t$$

Where, A = Initial drug loading dose dispersed into the polymer matrix, C_p = Solubility of the drug, D_p = Diffusivity of the drug in the polymer

11. Technologies for Developing/ Types/ Formulation of TDDS

11.1. Membrane Permeation – Controlled System: In reservoir systems, the drug is enclosed between a rate-controlling microporous or nonporous membrane and an impermeable backing laminate. The drug is dispersed uniformly into the solid polymer matrix and suspended in a viscous liquid medium for making a paste or semisolid form. The release rate of the drug is determined by the abrasive rate, permeability, diffusion, and thickness of the membrane. Zero-order kinetic is followed by reservoir system. The whole system is supported on the impermeable metallic backing. The intrinsic rate of drug release from membrane permeation controlled system type of drug delivery system is defined by the following equation:

$$dQ / dt = Cr / (1 / Pm + 1 / Pa)$$

Where; C_r – Drug concentration in reservoir compartment, P_m – Permeability coefficients of adhesive layer, P_a – Permeability coefficient of rate-controlling membrane. This system is a multilaminate process. Products consist of three substrates hold together by using two layers of drug which contains adhesive. Firstly, the drug is processed into the physical /chemical form required for incorporation into the system. Then the drug adhesive components and excipients are mixed with a solvent to form a uniform solution. These adhesive compositions are deposited as a thin film on moving substances rate, which are subsequently dried to remove solvent from the system. In this system, the five-layer product consists of release linear, contact adhesive, control membrane, drug reservoir and backing substrate. The above lamination is then printed and cut into the final

dosage form. Patches are packed separately into the aluminium foil [26].

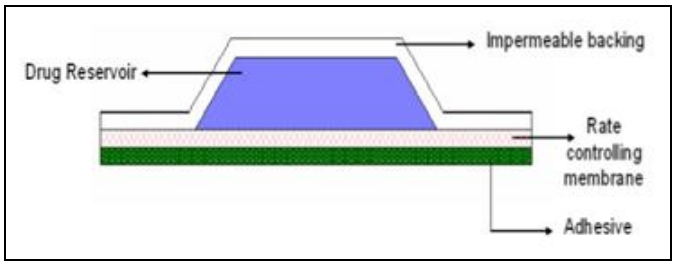

FIG. 4: MEMBRANE PERMEATION CONTROLLED SYSTEM

11.2. Matrix-dispersion System: The drug is dispersed homogeneously and uniformly into a hydrophilic or lipophilic polymer matrix. This polymer disk which contains drugs is fixed onto an occlusive base plate into a compartment fabricated from a drug-impermeable backing layer [27]. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference and forms a strip of adhesive film in a matrix dispersion system.

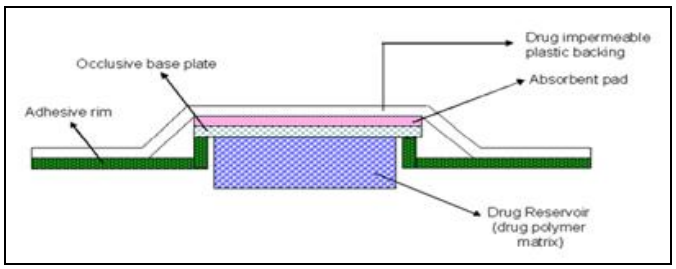

FIG. 5: MATRIX-DISPERSION SYSTEM

11.3. Drug-in-Adhesive System: The drug reservoir is formed by dispersing the drug homogeneously into an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting method or by melting the adhesive (in the case of hot-melt adhesives) onto the impervious backing layer [26]. Layers of non-medicated adhesive polymer are applied on the top of the system.

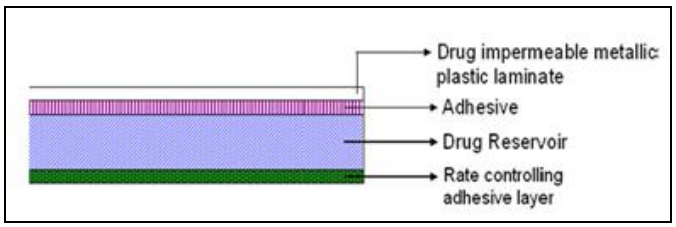

FIG. 6 DRUG-IN-ADHESIVE SYSTEM

11.4. Micro Reservoir Systems: This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug into an aqueous solution of water-soluble polymer and then dispersed the solution homogeneously into a lipophilic polymer which forms thousands of unleachable, microscopic spheres of drug reservoirs [26]. Unstable dispersion is stabilized by using cross-linking of polymers.

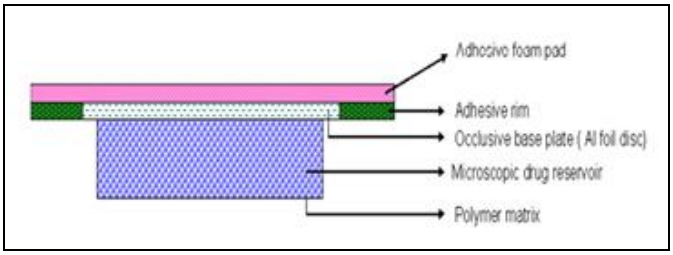

FIG. 7: MICRORESERVOIR SYSTEMS

12. Recent Advanced Techniques for Formulating TDDS:

12.1. Structure-Based Drug Permeation Enhancement Techniques:

12.1.1. Microfabricated Microneedles: These are the devices which is having the features of both the hypodermic needles and transdermal patch. That can deliver the drug effectively across the membrane. The systems consist of a drug reservoir and some projections (microneedles) extending from the reservoir. This system helps in penetrating the drug through the stratum cornea and epidermis for the delivery of drug [28].

12.1.2. Microneedles: Microneedles are very tiny and sleek devices for the delivery of drugs [7]. Microneedles are manufactured by different technologies like silicon etching technology and micro-mechanical system manufacturing (MEMS) technique. Microneedles are not penetrated deep into the skin layer to reach up to the nerve endings into the anatomy of the skin, and thus, there is no pain sensation during the microneedle's insertion into the skin [29].

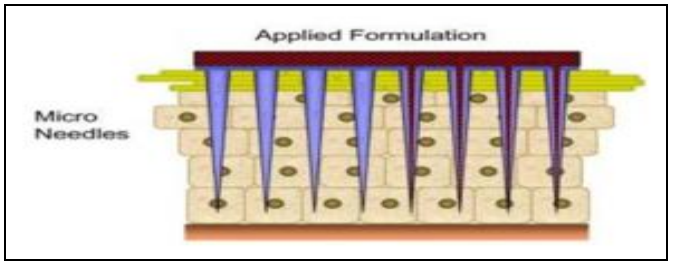

FIG. 8: MECHANISM OF ACTION OF A MICRO-NEEDLE ARRAY

12.1.3. Macroflux: These are devices having an area of around 8cm as well as 300 micro projections per cm^2 with the length of individual micro projection less than 200µm. Three types of Macroflux have been designed. They include:

12.1.3.1. Dry-Coated Macroflux System: This is used for short period drug delivery which contains micro projection array coated with medicament (drug) that is adhered to a elastic polymer adhesive backing.

12.1.3.2. D-TRANS Macroflux System: This is also for short duration administration that consists of a micro-projection array combined with reservoir of drug.

12.1.3.3. E-TRANS Macroflux System: This is a demanded delivery that involves a micro projection array combined with an electro transport system.24

12.1.4. Metered-Dose Transdermal Spray (MDTS): It is a liquid preparation for topical use. Prepared by a vehicle that is volatile cum non-volatile in nature, which contains the completely dissolved drug or medicament into a solution. MDTS gives sustained release and better permeation through skin [5]. MDTS is improving the delivery of drug without skin irritation because of its non-occlusive in nature. Simple administration of drug improves the acceptability and dose flexibility.

12.2. Electrically-based Drug Permeation enhancement techniques:

12.2.1. Iontophoresis: Iontophoresis involves providing the limited current (few milliamperes) to skin as per certain area using the electrode. Electrodes remain in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as an example to produce the sweat in diagnosis of cystic fibrosis and iontophoretic delivery of lidocaine is considered to be a good for rapid onset of anaesthesia [30].

12.2.2. Ultrasound: In this technique, there is a mixing of drug substances with a coupling agent (usually with gel, cream, or ointment) that transfer ultrasonic energy from the system to the skin. Ultrasonic energy ruptures the lipids present in the stratum cornea and allows the drug to penetrate through skin barriers [7].

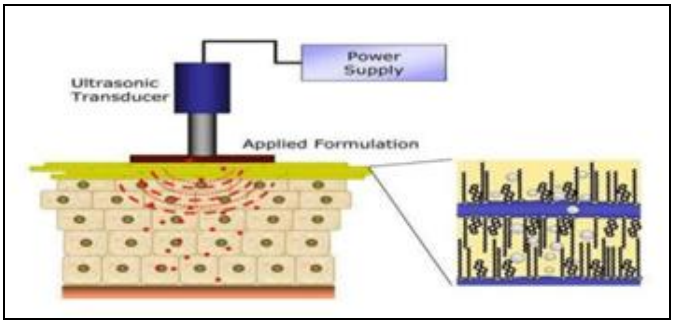

FIG. 9: THE BASIC PRINCIPLE OF PHONOPHORESIS SHOWING ULTRASOUND PULSES ARE PASSED THROUGH THE PROBE INTO THE SKIN, FLUIDIZING THE LIPID BILAYER BY THE FORMATION OF BUBBLES CAUSED BY CAVITATION

12.2.3. Photomechanical Waves: Photomechemiical waves develops the transient channels. That channels lead a possible permeation mechanism for high permeation of the drug through the stratum corneum [31].

12.2.4. Electroporation: In this method, short and high voltage electrical pulses are applied to the skin thus, the diffusion of the drug is improved and increases the permeability of the drug. The electrical pulses are useful to form fine pores in the stratum cornea, through which the transportation of drugs occurs. For the safe and painless administration of the drug through the skin, the electrical pulses introduced by electrodes to reserved that electric field in the stratum cornea [31].

12.2.5. Electro-Osmosis: Porous membrane has some charge on it. A difference in the voltage is applied to the porous membrane; because of charges present in the membrane a bulk fluid or volume flow takes place without concentration gradients, this process is known as electro-osmosis [32].

12.3. Velocity Based Drug Permeation Enhancement Techniques

- **A.** Needle-Free Injections
- **B.** Intraject
- **C.** Implaject
- **D.** Jet Syringe
- **E.** Iject
- **F.** Mini-ject

12.4. Other Drug Permeation Enhancement Techniques:

12.4.1. Transfersomes: This device penetrates the skin barrier along with the skin moisture gradient.

Transfersomes carriers create a drug deposition in the systemic circulation that is having a high concentration of the drug. Transfersomes contain a component that can decrease the stability of lipid bilayers and thus leading to deformable vesicles [33].

12.4.2. Medicated Tattoos: Med-Tats is a modification of a temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of the drug in children and other unconscious patients.

12.4.3. Skin Abrasion: This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substances. For example, one approach is used to creates micro channels into the skin by damaging the impermeable outer layers by using sharp microscopic metal granules is generally known as microscissuining.

12.4.4. Controlled Heat Aided Drug Delivery (CHADD) System: It increases the transfer of drug substance to the systemic circulation by applying heat to the skin that increases the temperature of the skin layer. It leads to an increase in microcirculation and permeability into the blood vessels. CHADD system consists of a small unit that is used for heating purpose, which is placed on the top of a conventional patch device. The limited intensity of heat is generated for a small duration of time because of oxidation reaction into the unit.

12.4.5. Laser Radiation: This involves the exposure of the skin to the laser beam. That results in the removal of the stratum cornea without damaging the epidermis, which remains in contact with it. Removal of the stratum cornea by this technique increases the delivery of lipophilic and hydrophilic drugs.

13. Evaluation of Transdermal Films: The evaluation of transdermal patches is performed to check the quality and reproducibility. Various evaluation tests include

13.1. Thickness of the patch: The thickness of the drug-loaded patches is measured at different points by using a digital micrometer to determine the thickness of the prepared patch.

13.2. Weight uniformity: The patches are dried at 60°C for 4 h before. The area which is specified of the patch is to be cut in different parts of the patch and weigh it on a digital balance. The average weight of the all sections and standard deviation values are to be calculated from the individual weight and the weight uniformity is calculated [34].

13.3. Folding Endurance: A strip of a specific area is cut into the appropriate size and repeatedly folded at one place till it breaks from that point. How many times the film will be folded at that point without breaking of the patch that number gives the value of the folding endurance [35].

13.4. Percentage Moisture Content: The prepared films are weighed individually and placed into a desiccator containing fused calcium chloride at room temperature for 24 h. After that the films are weighed again and percentage moisture content is calculated using below mentioned formula:

$$\text{Percentage moisture content} = [(W_i - W_f)/ W_f] \times 100$$

Where; W_i – Initial weight of film & W_f – Final weight of film

13.5. Percentage moisture uptake: The weighed films are kept in a desiccator containing a saturated solution of potassium chloride with maintaining 84% RH. After 24 h, reweigh the films and calculate the percentage moisture uptake by the below-mentioned formula:

$$\text{Percentage moisture content} = [(W_i - W_f)/ W_f] \times 100$$

Where; W_i – Initial weight of film & W_f – Final weight of film

13.6. Drug content: The selected area of patch is to be dissolved in a suitable solvent in specific volume. Then, the solution is filtered through a filter medium and analysis should be done for the drug content with the suitable method such as UV or HPLC technique.

13.7. Polariscopic examination: This test is useful to examine the drug crystals from transdermal patch by polariscopic. A specific surface area of the patch is kept on the slide and observe the drug crystals for drug particles characterization *i.e.* crystalline form or amorphous form of drug in the patch.

13.8. Shear adhesion test: This test is performed for the evaluation of cohesive strength of an adhesive polymer. It is changed as per different

factors *i.e.* molecular weight, the degree of cross-linking, type and amount of tackifier added.

An adhesive coated tape is placed onto a stainless-steel plate; a specific weight is hung up from the tape and pulled it in a direction of parallel to the plate. Shear adhesion strength is determined by measuring the time taken to pull the tape off the plate [7]. The more the time taken to pull the tape from plate, greater is the shear strength.

13.9. Peel Adhesion Test: In this test, the force which is required to abolish an adhesive coating from a substrate is referred as a peel adhesion.36 For that a single tape is applied to a stainless-steel plate or a backing membrane depends on the patch formulation and then tape is pulled away from the substrate at a 180° angle and the required force to pull the tape is measures.

13.10. Tack Properties: Tack is the ability of polymer to adhere a substrate with the pressure of little finger, it's important for transdermal systems that applied at site of action with little figure pressure. Tack is depending on molecular weight, composition of polymer and tackifying resins which is used in the polymer.

13.10.1. Thumb Tack Test: This is the subjective test in which evaluating the patch by pressing the thumb in to the adhesive. By the experience observations are taken into consideration.

13.10.2. Probe Tack Test: In this test, the tip of probe with defined surface roughness are come into contact with adhesive and when the bond is formed between the adhesive a probe, removal of probe away from the adhesive with the fix rate of speed which break the bond in between [37]. The force which is required for breaking the bond is recorded as tack and that is expressed in grams

13.10.3. Rolling Ball Tack Test: This test involves measurement of distance travelled by a stainless steel along with upward face of adhesive. The diameter of ball is 7/16 inches and that ball released on inclined tract which having angle 22.5℃. The distance travelled by the ball is more it means the polymer is less tacky. Distance travelled by ball is determines the tackiness of polymer and that distance is measured in inches. It gives the softness of adhesive polymer.

13.10.4. Peel Tack or Quick Stick Test: It is the force required for breaking of the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 90° which is having speed 12 inches/minute. The value of force is placed in grams/inch or ounces/inch [38].

13.11. Flatness Test: The film is cut into the longitudinal strip from the different portion of film. Three strips are taken from the film. The length of each strip is measured it gives some variation in length because of non-uniformity in flatness. That is measured by determining percentage constriction. 0% constriction that means the film is 100% flatness.

13.12. Percentage Elongation Break Test: The percentage elongation break is calculating by noting the length of the patch just before the breaking point. The percentage elongation is determined from the below-mentioned formula:

$$\text{Percentage elongation break} = [(L_f - L_i)/ L_i] \times 100$$

Where, L_f – Final length of each strip, L_i – Initial length of each strip

13.13. Skin Irritation Study: Skin irritation study and sensitizing testing is performed onto the healthy rabbits (average weight 1.2 to 1.5 kg).For that clean the dorsal surface of the rabbit and after that remove the hair from that part [39]. Again, clean that shaved surface by using the rectified spirit and the test formulations/patches are applied over the skin. The applied patch is removed from that area after 24 h and the skin is observed by different parameters and classified into 5 grades which is depends on severity of skin injury.

13.14. Stability Studies: The stability studies procedure is followed according to the ICH guidelines. The formulation is placed at 40°C and 75% RH for 6 months. From that sample, the degradation of the drug is calculated by using the drug content.40

13.15. *In-vitro* Release Studies:

- **Paddle Over Disc Apparatus (USP Apparatus 5):** This method is suitable for the USP paddle dissolution apparatus. Transdermal system is not attached to a disc or cell. It's rested at the bottom of the vessel

which contains a dissolution medium at 32±0.5°C.

- **Cylindrical Apparatus (USP Apparatus 6):** This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder here, the patches are immersed in dissolution medium at 32±0.5°C.
- **The Reciprocating Disc (USP Apparatus 7):** In this method, patches attached to holders oscillate in small volumes of medium. This apparatus is useful for system delivers low concentration of drug [41]. In addition, paddle over-extraction cell method also be used for the *in-vitro* release study.

***In-vitro* Skin Permeation and Release Kinetics Studies:** The design and development of transdermal patch is affected by *in-vitro* studies. *In-vitro* studies help in the finding out of the route of skin permeation, the rate of drug transfer through skin and entered into the systemic circulation. Methodology used for this study allowed flexibility in using the model in addressing different factors involved in preliminary or feasibility studies in the development of transdermal patch.

13.15.1. Franz Diffusion Cell: *In-vitro* skin permeation study of transdermal patches can be performed using Franz diffusion cell (most commonly used). By using 1.0cm^2 as an effective permeation area and 10 ml as a receptor cell volume. The temperature for this study is maintained at 32℃ ± 1℃. The receptor compartment is filled with 10 ml PBS and this solution is continuously stirred in a magnetic stirrer at 100 rpm/min. The skin is fixed properly on a receptor compartment in that the stratum corneum side of the skin is to the donor compartment [42]. After the predetermined time intervals the samples are withdrawn by the sampling port of the diffusion cell for the 24 h and then samples are analysed. The receptor phase is immediately fulfilled with equal volume of fresh diffusion buffer which is having maintained temperature.

13.15.2. Horizontal-Type Skin Permeation System: After the Franz diffusion cell, this system is most commonly used for permeation study of drug through skin [43]. Horizontal type skin permeation system having the receptor and donor compartment has a capacity of 3.5 ml of PBS solution and constantly rotated by the rpm set of star head magnets at 600rpm and membrane area for this is about 0.64cm^2. By using a thermostat, the temperature is controlled throughout the experiment.

13.15.3. Flow Diffusion Cell: The advantage of diffusion cell apparatus is that this is used for the drug having lower solubility in the receptor compartment. Fully automated cell is used in this system and directly connected to the HPLC. They have the donor chamber which is having large capacity to allow appropriate loading of the applied compound and also low volume (0.3ml) receiving chamber. That ensures rapid removal of penetrating through the skin at relatively low pumping rates [44].

13.16. *In-vivo* Studies: The different types of variables that are not taken into consideration during *in-vitro* study [45]. Following factors are taken into consideration while selecting transdermal *in-vivo* system:

The Rate Limiting Process: Solubilisation of drug or drug diffusion in the vehicle, partitioning from the different vehicle, diffusion of drug through the test membrane or partitioning, and removal by the receptor phase.

- The intrinsic diffusivity and apparent diffusivity of the permeate.
- The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery, and receptor phase.
- The predominating route of diffusion into the experimentation and the relative extents of the drug binding.
- The intrinsic barrier potential of the membrane and the effects that vehicle components may have on different types of retardative properties. Hydration of the membrane and penetration enhancers are important in this process.

13.17. *In-vivo* Studies of Transdermal System can be Performed by using Following Model:

13.17.1. Animal Models: For *in-vivo* studies, small scale of animals are generally preferred because of

availability and economic consideration. In humans, more time and resources are required for the study [46]. The different types of animal species are used in *in-vivo* study *i.e.*, mice, rat, guinea pig, hairless mouse, hairless rat, hairless dog, cat horse, goat, rhesus monkey, miniature pig, squirrel, chimpanzee, *etc*. The most preferably used animal for the *in-vivo* study in the rhesus monkey. Different types of experiments have been carried out to determine a perfect fit animal model for the best prediction and results of the behaviour of the device.

13.17.2. Human Volunteers: During the clinical phases in the development of transdermal drug delivery is the collection of all pharmacokinetic and pharmacodynamic data from involved human volunteers. That data is required to evaluate any toxic effects generate during the application of transdermal formulations.

The determination of percutaneous absorption in humans can be performed by labelling of the drug by C14 radioisotope and it measures the radioactivity in excreta but it required very much attention about to know how much amount resides into the body and how much excrete by other routes which is not defined. The method is given approximately results, the absolute result however, it has some limitations [47]. To overcome that limitations, other methods developed for the study, which was defined as:

13.17.2.1. Reservoir Technique: In this study, short exposure of radiolabelled compound to the skin with the removal of upper layer of skin (stratum corneum) by using tape stripping. The analysis is done for the determination of the content of the compound into the layer of skin. This method is helpful for the determination of the amount of drug penetrate over a long time period.

13.17.2.2. Mass Balance Technique: In this technique, the application site is covered with an occlusive chamber but this chamber is being replaced by another new chamber after a limited time period and washing is given at the time of replacing of chamber [48]. Radio-labelled compound were used and the different parameters are checked *i.e.*, chambers, washings, faces and urine of the patients. Advantage of this technique is it include achievement of mass balance between the applied dose and the excretion levels.

13.17.2.3. Biophysical Models: These models are physiologically based pharmacokinetic models. Models are based on well-known anatomical and physiological data thus represent an accurate information of drug disposition in various organs and tissues [49]. These models are based on steady state mass balance equation and Fick's second law of diffusion.

CONCLUSION: Transdermal drug delivery system has been a safe, effective and economical drug delivery system. Due to the recent advances in technology and transfer of drug through the skin without rupturing the skin membrane transdermal drug delivery system receive more acceptance. It promises worldwide acceptance for adminis-tration of drug through skin for different classes of drug. Different methods are used to prepare patches by using basic components of TDDS. After preparation of the transdermal patches, they are evaluated under different parameters such as physicochemical parameters, in vitro permeation studies, skin irritation studies and stability studies. Future developments of TDDS will be more promising and may offer a lot of advantages.

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