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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
Transdermal patches are designed to deliver a therapeutically effective amount of drug across the skin membrane. In order to deliver therapeutic agents through the skin for systemic effects, the great physicochemical, morphological and biological properties of the skin are taken into consideration. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intra patient variations.

INTRODUCTION
Now each day several medication square measures administered orally however they're ascertained no more effective as desired therefore to upgrade such character TDDS was created. Drug delivery administered by the skin and attain a general impact of drug is named as transdermic drug delivery system. These square measures reasonably dose type which incorporates drug transport to cheap cuticle and doubtless dermal tissue of the skin regionally therapeutic impact. Whereas Associate in Nursing exceptionally important division of the drug is transported in general blood circulation. A transdermic dermal patch is characterized as a medicated adhesive patch that is about over the skin to deliver a selected dose of medication by the skin with a predestinate rate of unleash to achieve into the circulation system. "Transdermal drug delivery system is outlined because the locally administered medications, that once applied to the skin deliver the drug, through the skin at a preset and controlled rate". Medication square measure administered by varied routes like oral, parenteral, nasal, transdermic, rectal, intravaginal, ocular etc. Among all of them, oral route is commonest and in style however this route of administration has some drawbacks like initial pass metabolism, drug degradation in channel thanks to pH, enzyme etc.

The main objective of percutaneous drug delivery system is to deliver medicine into circulation into the skin through skin at preset rate with least put down and intra patient variation. Three presently percutaneous delivery is one among the foremost promising ways for drug application. half-dozen It reduces the load that the oral route normally places on the digestive tube and liver. It enhances patient compliances and minimizes harmful facet effects of a drug caused from temporary over dose and is convenience in percutaneous delivered medicine that need one-time decrepit application.

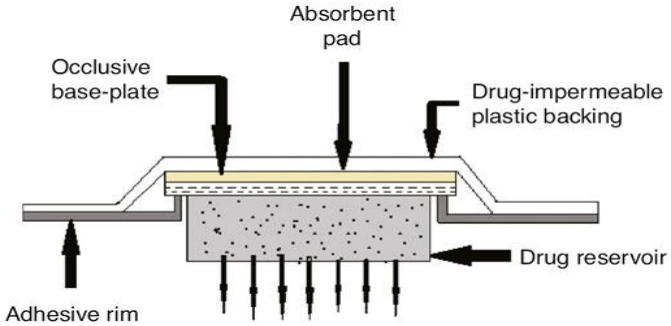

Fig. 1: Transdermal drug delivery system device.

Advantages of transdermal drug delivery system

- Transdermal drug delivery system avoids epithelial duct drug absorption difficulties lined by epithelial duct hydrogen ion concentration, protein activity and alternative orally administration of drug
- Avoidance of 1st pass metabolism.
- Avoidance of epithelial duct incompatibility.
- Minimizing undesirable aspect effects.
- Suitable for administration of drug having terribly short half-life and slender therapeutic window
- Transdermal drug delivery permits the dodging of epithelial duct absorption, with its associated pitfalls of protein and hydrogen ion concentration associated deactivation.

Disadvantages of transdermal drug delivery system

- Transdermal drug delivery system doesn't appropriate for delivery of ionic medicine.
- Only potent medicine square measure appropriate candidates for skin patch thanks to the natural limits of drug entry obligatory by the skin's solidness.
- It cannot deliver medicine in an exceedingly pulsatile fashion Properties that influence Transdermal Delivery
- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response

Anatomy and Physiology of skin

Skin is that the most in-depth organ of the natural covering a vicinity of regarding 2m2 on in a median human adult. This multi-layered organ receives around one third of all blood current through the body. With thickness of solely a metric linear unit, the skin separates the underlying blood circulation network from outside atmosphere.

Human skin contains of 3 distinct however reciprocally dependent tissues:

A. The stratified, vascular, cellular known as as "epidermis"
B. Underlying corium of connective tissues
C. Hypodermis

Epidermis

The epidermis is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts: the living or viable cells of the Malpighian layer (viable epidermis) and the dead cells of the stratum corneum commonly referred to as the horny layer 5

Stratum corneum

This is the outermost layer of skin also called as horny layer. It is the rate limiting barrier that restricts the inward and outward movement of chemical substances. The barrier nature of the horny layer depends critically on its constituents: 75-80% proteins, 5-15% lipids, and 5-10% ondansetron material on a dry weight basis. Stratum corneum is approximately 10 mm thick when dry but swells to several times when fully hydrated. It is flexible but relatively impermeable. The architecture of horny layer may be modeled as a wall-like structure with protein bricks and lipid mortar. It consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocytes are embedded in a lipid matrix which plays a significant role in determining the permeability of substance across the skin.

This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum Basale. In the Basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the Basale layer move outward, they itself alter morphologically and histochemical, undergoing keratinization to form the outermost layer of stratum corneum

Viable epidermis is further classified into four distinct layers

- ♣ Stratum lucidum
- ♣ Stratum granulosum
- ♣ Stratum spinosum
- ♣ Stratum basale

Dermis

Dermis is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of a matrix of connective tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water, and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all three layers and reach in systemic circulation.

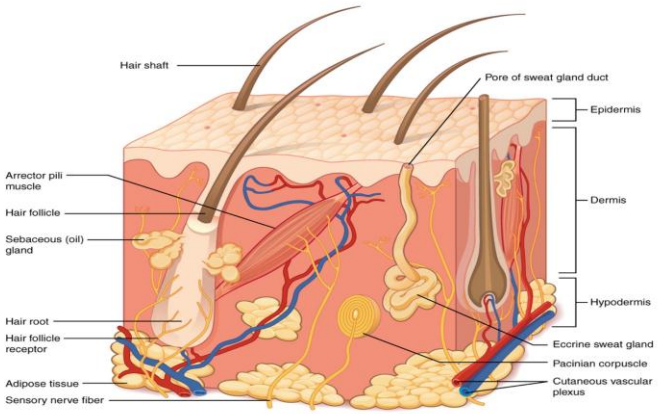

Fig. 2: Structure of skin.

Factors affecting transdermal permeation biological factor

- **Skin conditions**

The intact skin itself acts as barrier however several agents like acids, alkali cross the barrier cells and penetrates through the skin, many solvents open the advanced dense structure of stratum corneum Solvents like alcohol, chloroform take away supermolecule fraction, forming artificial shunts through that drug molecules will pass simply.

- **Skin age**

It is seen that the skin of adults and young ones are a lot of porous than the older ones however there's no dramatic distinction. Children shows cyanogenic effects thanks to the larger extent per unit weight. thus, potent steroids, boric acid, antibacterial drug have made severe aspect effects.

- **Blood supply**

Changes in peripheral circulation will have an effect on transdermic absorption.

- **Regional skin site**

Thickness of skin, nature of horny layer and density of appendages vary web site} to site. These factors have an effect on considerably penetration. Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So, skin metabolism determines efficacy of drug permeated through the skin.

- **Species differences**

The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

Physicochemical factors

1. Skin hydration

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.

2. Temperature and pH

The permeation of drug increases ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and PKa or PKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

3. Diffusion coefficient

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

4. Drug concentration

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier

5. Partition coefficient

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

6. Molecular Size and Shape

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

Basic components of transdermal drug delivery system

The components of transdermal drug delivery system include

1. Drug substance
2. Polymer matrix
3. Penetration enhancers
4. Pressure sensitive adhesive
5. Backing membrane
6. Release linear

1. Drug substance

For with success developing a stratum drug delivery system, the drug ought to be choosen with care. the subsequent area unit a number of the fascinating properties of a drug for stratum delivery.

2. Polymer matrix

Polymers area unit the backbone of stratum drug delivery system. System for stratum delivery area unit fictitious as multi superimposed compound laminates in which a drug reservoir or a drug compound matrix is sand witched between 2 compound layers, associate outer greaseproof backing layer that stops the loss of drug through the backing surface associated associate inner compound layer that functions as an adhesive, or rate controlled membrane.

3. Penetration enhancers

These area unit compounds that promote the skin permeable Ness by sterilization the skin as barrier to the flux of a desired penetrate.

4. Pressure sensitive adhesive

A Pressure Sensitive Adhesive (PSA) could be a material that helps in maintaining associate intimate contact between stratum system and therefore the skin surface. It ought to adhere with no more than applied finger pressure, be sharply and permanently tacky, exert a robust holding force. to boot, it ought to be removable from the sleek surface while not going away a residue e.g.: polyacrylamides, polyacrylates, polyisobutylene, silicone polymer based mostly adhesive. the choice of associate adhesive is predicated on varied factors, as well as the patch style and drug formulation. protein ought to be chemistry and biologically compatible and will not alter drug unharness. The protein is positioned on the face of the device or within the back of the device and increasing peripherally.

5. Backing membrane

The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through the top. They must be impermeable to drugs and permeation enhancers. E.g.: Metallic plastic laminate, Vinyl polyethylene and Polyester films, Aluminum foil, Foam pad.

Fig. 3: Basic components of TDDS.

6. Release linear

During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. It protects the patch during storage. A release coating layer is made up of silicon or Teflon.

Approaches in the development of transdermal therapeutic system[25,26]

- **Membrane permeation-controlled system**

In this system the drug reservoir is completely embedded during a compartment shaped between a drug-impermeable backing laminate and a rate dominant chemical compound membrane the drug molecules area unit allowable to unharness across the speed dominant membrane just by diffusion method through the pores. within the reservoir compartments the drug solids area unit spread homogenously during a solid chemical compound matrix (e.g. polyisobutylene) suspended within the unleachable viscous liquid medium (e.g. atomic number 14 fluid) to create a gel-like suspension, or dissolved during a releasable solvent (e.g. alkyl group alcohol) to create a gel like in answer. the speed dominant membrane, is either a microporous or non-porous chemical compound membrane e.g. ethylene–vinyl acetate polymer, having specific drug porosity. On the highest surface of the chemical compound membrane a skinny layer of drug compatible adhesive chemical compound, e.g., polymer adhesives, is applied, to supply intimate contact of the transdermal system with the skin surface. the discharge rate from this transdermal system is tailored by variable the chemical compound composition, thickness of the speed dominant membrane, porosity constant and adhesive. samples of this method area unit TransdermScop (Scopolamine- three days protection) of nausea and TransdermNitro (Nitroglycerine-for once each day) medication of angina.

- **Matrix diffusion-controlled system**:

In this approach, the drug reservoirs area unit ready by homogeneously dispersing drug particles in an exceedingly hydrophilic or lipotropic chemical compound matrix or combination of each. The resultant medicated chemical compound is then wrought into a medicated disc with an outlined extent and controlled thickness. The dispersion of drug particles in chemical compound matrix are often accomplished by either homogenously commixture the finely ground drug particles with a liquid chemical compound or an extremely viscous base chemical compound followed by cross linking of the chemical compound chains or homogenously mixing drug solids with a rubbery chemical compound at Associate in Nursing elevated temperature and/or underneath vacuum. The chemical compound disc that contains drug reservoir is fastened onto Associate in Nursing occlusive base plate in an exceedingly compartment fancied from a drug-impermeable backing. The adhesive chemical compound is then unfold to create a strip of rim on the medicated disc. This matrix kind of stratum system is best example by the vasodilated emotional stratum therapeutic system. The advantage of matrix dispersion kind stratum system is that the absence of the dose selling since the chemical compound cannot rupture.

- **Adhesive dispersion type system**

The system consists of drug-impermeable backing membrane, the drug reservoir that is ready by directly dispersing the drug in Associate in Nursing adhesive compound then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to make a skinny drug reservoir layer. On the highest of this, a layer of rate-controlling adhesive polymer(non-medicated) of constant thickness is unfold to provide Associate in Nursing adhesive diffusion-controlled drug delivery system with detachable unharness liner that in a perfect state of affairs is removed and also the patch is applied to the skin for a needed amount of your time. Illustration of sort this kind of system is exampled by development and selling of transdermaltherapeutic system of heart disease and Valsartan as Hypertension type one selective blocker for someday medication.

- **Microreservoir type controlled system**

This system is essentially hybrid of reservoir and matrix-dispersion kind of drug delivery system. during this approach, drug reservoir is made by suspending the drug during a solution of liquid compound then dispersing the drug suspension homogeneously in a oleophilic compound e.g. silicone polymer elastomers by high energy dispersion technique by shear mechanical force to make thousands of unapproachable, and microscopic spheres of drug reservoirs. This technology has been utilized within the development of Nitro disc. unleash of a drug from a small reservoir-type system will follow either a partition-control or a matrix diffusion-control relying upon the relative magnitude of solubility of the drug within the liquid compartment and within the compound matrix. Example: Nitrodisc system for angina.

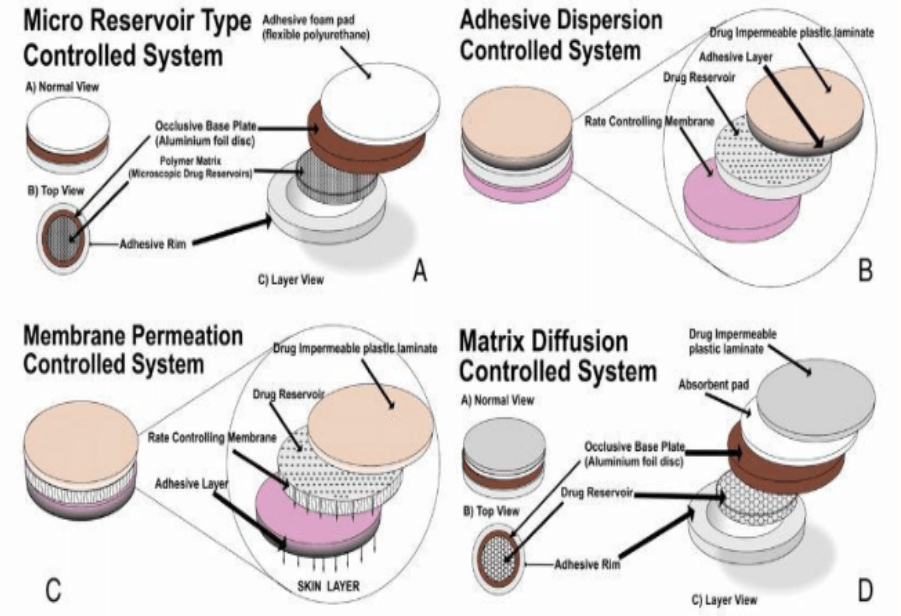

Fig. 4: (A) Showing the presence of microscopic spheres of drug reservoir, (B) Development of adhesive dispersion controlled therapeutic system, (C) Diagrammatic representation of membrane permeation-controlled system, (D) Representation of matrix type transdermal system.

Applications of transdermal patches

- Patch containing alkaloid, that releases alkaloid in controlled manner to assist with stop of tobacco smoking.
- Medication like antihypertensive and non-steroidal anti-inflammatory drug medication are obtainable within the type of transdermal patches.

- Vasodilator patches area unit utilized in the treatment of angina.
- Transdermic agent for the eye deficit upset disorder (ADHD).
- Patch of the selegiline (MAO inhibitor) became the primary transdermic delivery agent for major affective disorder and hydrophobic active substance into promising deliverable drugs. TDDS a realistic practical application as the next generation of drug delivery system and due to large advantages of it, many new researches are going on in the present day to incorporate newer drugs via the system.

Advance Development in TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules.

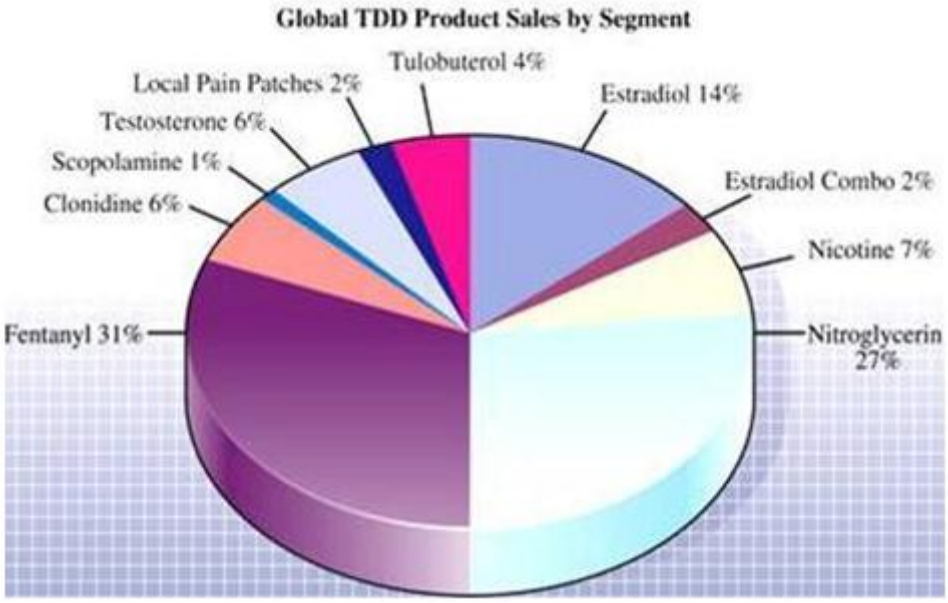

Fig. 5: Advance Development in TDDS.

These so-called "active" transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoretic, has been investigated as a means to increase drug flux across the skin.

Evaluation of transdermal drug delivery system

Evaluation studies are more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage form and can be classified into following types: A) Physicochemical evaluation A. In vitro evaluation B. In vivo evaluation

A. Physicochemical Evaluation:

- Thickness of the patch
- Uniformity of weight
- Drug content
- Content uniformity
- Determination of surface pH
- Moisture content
- Moisture uptake
- Water vapor permeability (WVP) evaluation
- Flatness
- Folding Endurance
- Adhesive properties:

a) Shear adhesion test
b) Peel adhesion test

- Tack properties

a) Thumb tack test
b) Rolling ball tack test
a) c)Quick-stick (peel tack) test
c) Probe tack test

B. In vitro release studies

- Paddle over disc apparatus (USP apparatus 5)
- Cylinder apparatus (USP apparatus 6)
- The reciprocating disc (USP apparatus 7)

In vitro permeation studies

In vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed by spectrophotometry or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

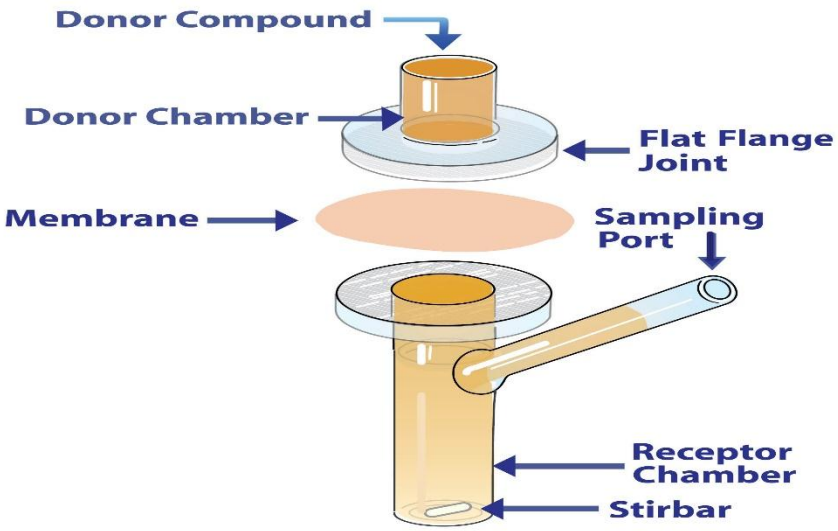

Fig. 6: Franz diffusion cell.

In vivo studies

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models and human volunteers. a) Animal models b) Human models.

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