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Review Article

APPROACHES FOR TRANSDERMAL DRUG DELIVERY SYSTEM:A REVIEW

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ABSTRACT

As the oral route of drug delivery system shows number of side effects such as gastric irritation, fluctuation in drug level in plasma, hepatic first pass metabolism.The Transdermal drug delivery system (TDDS) provides the effective way to deliver the drug directly in systemic circulation and hence increase in therapeutic effect of the drug. Topical administration of therapeutic agents offers many advantages over conventional oral and other routes of drug delivery.Transdermal administration of drugs is an another way of administration that can significantly deliver the larger molecules in potent quantities that overcome the problem with the oral administration such as poor bioavailability due to first pass metabolism and gastric irritation.To improve the effectiveness of the transdermal drug delivery system, number of approaches are emerged,which will increase the absorption of the drug in systemic circulaton and reduction in dosing frequency.This review article describes the number of approaches for transdermal drug delivery system.

KEY WORDS: *Bioavailability, Dosing frequency, Hepatic first pass metabolism, Transdermal drug Delivery system.*

INTRODUCTION:

Transdermal drug delivery (TDD) is the delivery of the drugs through the skin to elicit a systemic effect. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. This aspect makes it different from topical formulations, where the drug is expected to display only local activity[1] The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981.[2]

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives, and eliminates pulsed entry into systemic circulation which often causes undesirable side effects.[3]

The transdermal Delivery system includes all drug candidates that administer topically,intended to facilitate the drug absorption into the systemic circulation.The continuous delivery of the drug through the skin to the blood circulation can be achieved by this system.[4]

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ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM:[2,5,6,7]

Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half life and low therapeutic effect.

- Reduction of dosing frequency an enhancement of patient compliance.
- Avoidance of first pass metabolism of drugs.
- Reduced plasma concentration levels of drugs, with decreased side effects.
- Transdermal delivery can increase the therapeutic value of many drugs via avoiding specific problems associated with the drug. E.g. GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
- Flexibility of terminating the drug administration by simply removing the patch from the skin.
- Improved patient compliance and comfort via non-invasive, painless and simple application.
- Provides utilization of drugs with short biological half lives, narrow therapeutic window.
- Improving physiological and pharmacological response.
- The drug input can be terminated at any point of time by removing transdermal patch.

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM:[2,5,6]

- Possibility that a local irritation at the site of Application. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.
- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin.
- Cannot administer drugs that require high blood levels.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient.
- The barrier functions of the skin changes from one site to another on the same person, from person to person and with age.
- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

SKIN AS A SITE OF DRUG INFUSION:[7]

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis (Fig 1).

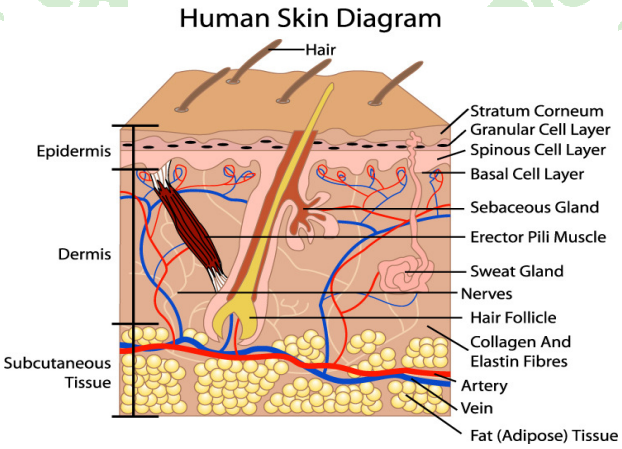

Fig1: Structure of Skin

Microscopically, the epidermis further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendage route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules can, thus, be considered as, a process of passive diffusion through the intact stratum corneum in the inter follicular region.

So, for the sake of mechanistic analysis of transdermal drug infusion (Fig 2), the various skin tissue layers can be represented by a simplistic multilayer model as shown in Fig 2. In the case that the skin serves as the point of administration for systemically active drugs, the drug applied topically will be absorbed, first into the systemic circulation and then transported to target tissues.

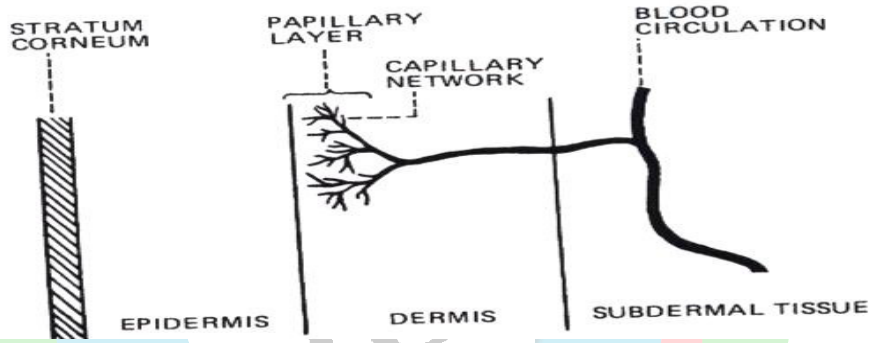

Fig 2: Simplified model of the human skin for mechanistic analysis of skin permeation[1].

BASIC COMPONENT OF TRANSDERMAL DRUG DELIVERY[1,2,6,7,8]

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner and other excipients like plasticizers and solvents

Polymer matrix:

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Polymer is an integral and foremost important component of transdermal drug delivery systems. Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device. Polymer matrix can be prepared by dispersion of 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 and PSAs.

Additionally they should provide consistent and effective delivery of a drug throughout the product"s intended shelf life and should be of safe status. Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on

ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber.

The polymers utilized for TDDS can be 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, Polyisobutylene, Silicon Rubber, Nitrile, Acrylonitrile, Neoprene, Butylrubber *etc*.

Synthetic Polymers: e.g. Polyvinyl Alcohol, Polyvinylchloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate *etc*.

DRUG:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing.

PERMEATION ENHANCER:

The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion).

The fatty acid enhancers increase the fluidity of the lipid portion of the Stratum Corneum. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. Enhancers can increase the drug diffusivity in the Stratum Corneum (SC) by dissolving the skin lipids or by denaturing skin proteins.

The flux J. of drug across the skin can be write as:

$J = D\, dc/dx$

J = The Flux
D = diffusion coefficient
C = Concentration of the diffusing species.
X = Spatial coordinate

The penetration enhancer should be pharmacologically inert, non toxic, non allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogeneous materials.

PRESSURE SENSETIVE ADHESIVE:

Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue.

It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin. It should adhere to the skin aggressively. The three major classes of polymers evaluated for potential medical applications in TDDS include:

- Polyisobutylene type pressure sensitive adhesives
- Acrylic type pressure sensitive adhesives
- Silicone type pressure sensitive adhesives

BAKING LAMINATE:

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer.
The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester film.

RELEASE LINER:

Liner Protects the patch during storage. The liner is removed prior to use.
However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water.

Typically, release liner is composed of a 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. Other materials used for TDDS release liner include polyester foil and metallized laminates.

NOVEL APPROACHES FOR THE TRANSDERMAL DRUG DELIVERY SYSTEM:

structure based enhancement technique:

Microneedles:

These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane.The systems consists of a drug reservoir and a some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug.[9]
These microneedles are of length of 50-110 micrometre will penetrate SC and epidermis to deliver drug.[10]

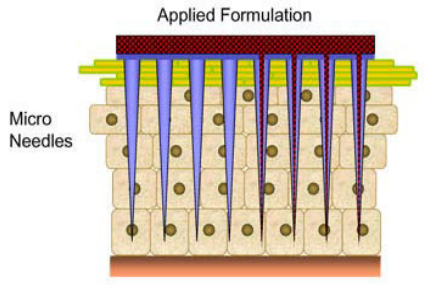

Fig 3: Microneedle

There are number of delivery approaches that have been employed to use the microneedles for TDDS. These includes-
Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.
Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.
Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
Hollow microneedles- Involves injecting the drug through the needle with a hollow bore.

2-Metered-Dose Transdermal Spray (Mdts)[9]

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution .
The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:

- It improve delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture

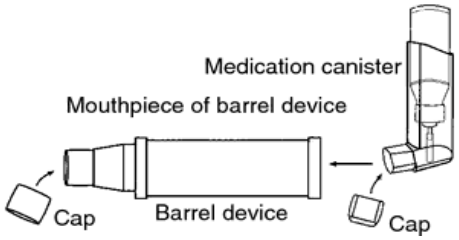

Fig.4: Metered dose Transdermal spray

Electrically based enhancement technique:

***Iontophoresis*:**

Iontophoretic drug delivery is now an accepted method of drug therapy which is gaining wide popularity especially in the area of pain relief. The drug is administered through an electrode (active) which has the same charge as the drug. The oppositely charged electrode (return) is placed some distance away at a neutral site, the size and distance of the 2 electrodes would also affect the transport of ions.[12]

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.[11]

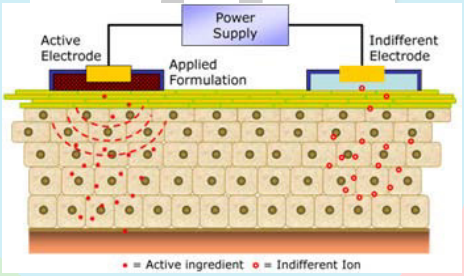

Fig. 5: Mechanism of Iontophoresis

Parameters that effect design of a ionophoretic skin delivery system include electrode type, current intensity, pH of system. 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-perturbation (for both charged and uncharged).[13]

SONOPHORESIS:

In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.[5]

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance

transdermal transport of various drugs including macromolecules.[11]

It uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability.[14]

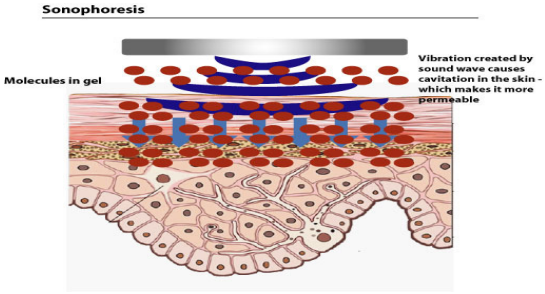

Fig. 6: Mechanism of sonophoresis

ELECTROPORATION:

Electroporation

It involves the application of high voltage pulses to the skin that has been suggested to induce the formation of transient pores. High voltages (100 V) and short treatment durations (milliseconds) are most frequently employed. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and olio nucleotides) including biopharmaceuticals with molecular weights greater that 7Kda.[10]

The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.[9]

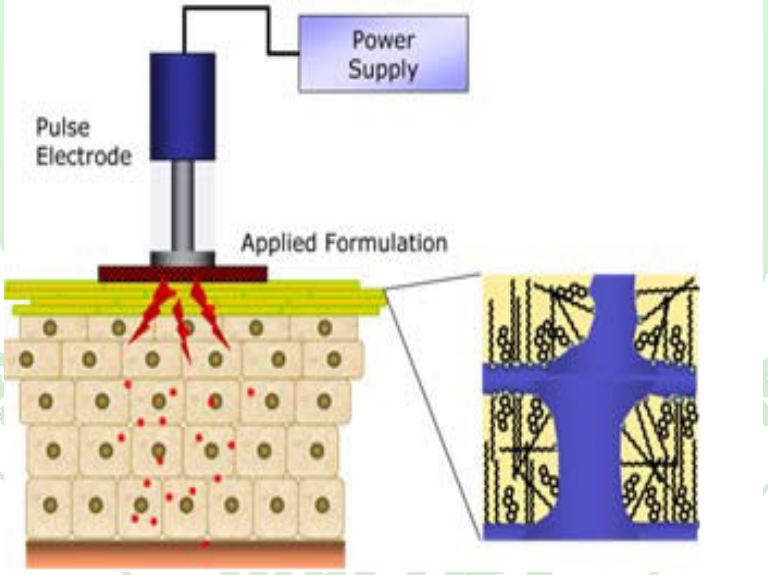

Fig. 7: Electroporation

VELOCITY BASED ENHANCMENT TECHNIQUE:

NEEDLESS INJECTION:

Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source.The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration.This method avoids issues of safety and pain.[15]

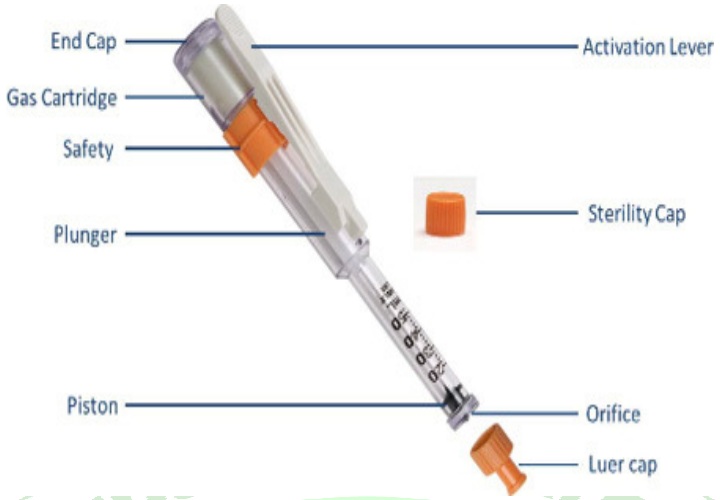

Fig. 8: Needless injection

Powderject Device:

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600–900 m/s. [9]

OTHER ENHANCEMENT TECHNIQUES:

***MAGNETOPHORESIS*:**

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.[5]

It involves application of magnetic field that acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability.[10]

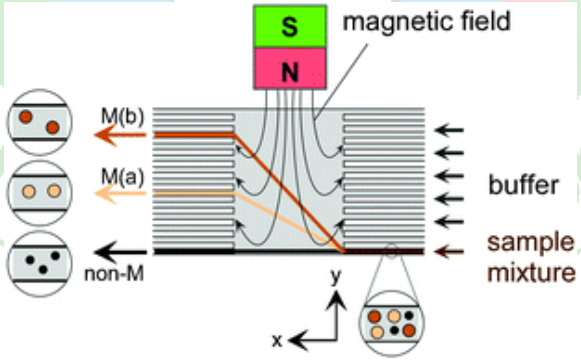

Fig. 9: Magnetophoresis

Controlled Heat Aided Drug Delivery (CHADD) System-

It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists a small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tend to form heat of limited intensity and duration.[9]

Laser Radiation

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the

epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.[9]

VARIOUS METHODS OF PREPARATION OF TRANSVERSAL PATCHES:

Circular Teflon mould method: (16)

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-Nbutylphthalate is added as a plasticizer into drug polymer solution. The total contents are stirred for 12 h and poured into circular teflon mould.

The moulds are placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects.

EVAC membrane" method: (16)

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5%*w/w* sodium hydroxide solution. The drug (in gel form) is placed on a sheet of 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 leak proof device.

By using free film method: (16)

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% *w/w* is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% *w/w* of polymer weight.

Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish.The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

Asymmetric TPX membrane method: (5)

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

NEW CARRIER USED FOR TRANSDERMAL DRUG DELIVERY:

Nanocarriers have demonstrated increased drug absorption, penetration, half-life, bioavailability, stability, etc. Nanocarriers are so small to be detected by immune system and they can deliver the drug in the target organ using lower drug doses in order to reduce side effects.[17]

Nanoparticles

Nanoparticles are smaller than 1,000 nm. Nowadays, it is possible to insert many types of materials such as drugs, proteins, peptides, DNA, etc. into the nanoparticles.

They are constructed from materials designed to resist pH, temperature, enzymatic attack, or other problems.Nanoparticles can be classified

as nanospheres or nanocapsules. Nanospheres are solid-core structures and nanocapsules are hollow-core structures.

Nanoparticles can be composed of polymers, lipids, polysaccharides and proteins.[17]

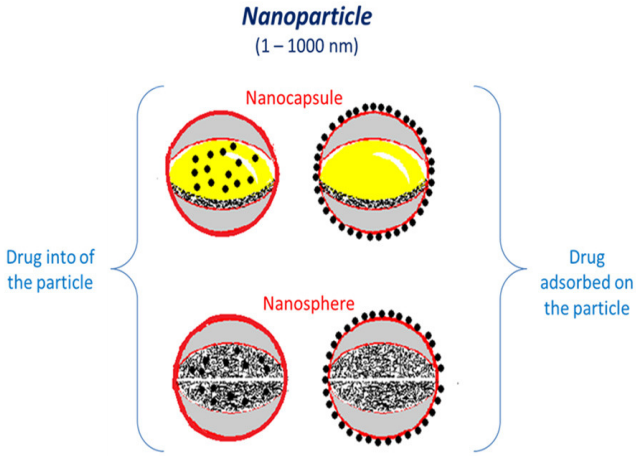

Fig. 10: Nanoparticles

LIPOSOMES:

Liposomes are hollow lipid bilayer structures that can transport hydrophilic drugs inside the core and hydrophobic drugs between the bilayer.They are structures made of cholesterol and phospholipids.They have different properties depending on the excipients included and the process of their elaboration.[17]

Liposomes can be surface-charged as neutral, negative or positive, depending on the functional groups and pH medium. Liposomes can encapsulate both lipophilic and hydrophilic drugs in a stable manner, depending on the polymer added to the surface . There are small unilamellar vesicles (25 to100nm),medium-sized unilamellar vesicles (100 nm and 500nm), large unilamellar vesicles, giant unilamellar vesicles, oligolamellar vesicles, large multilamellar vesicles and multivesicular vesicles (500 nm to microns).The thickness of the membrane measures approximately 5 to 6nm.[17]

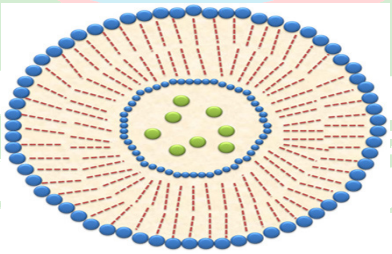

Figure11: liposomes

Nanoemulsions

Nanoemulsions are isotropic dispersed systems of two non miscible liquids, normally consisting of an oily system dispersed in an aqueous system (o/w nanoemulsion), or an aqueous system dispersed in an oily system but forming droplets or other oily phases of nanometric sizes (100 nm).They can be stable (methastable) for long times due to the extremely small sizes and the use of adequate surfactants.[17]

Nanoemulsions can use hydrophobic and hydrophilic drugs because it is possible to make both w/o or o/w nanoemulsions. They are non-toxic and non-irritant systems and they can be used for skin or mucous

membranes, parenteral and non parenteral administration in general and they have been used in the cosmetic field.[17]

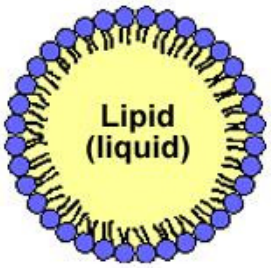

Figure 1. Nanoemulsion: Lipid monolayer enclosing a liquid lipid core.

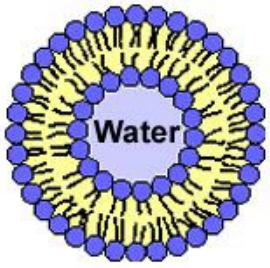

Figure 2. Liposome: Lipid bilayer enclosing an aqueous core.

CONCLUSION:

Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. One of the major advantages of transdermal drug delivery is the steady delivery of drug, resulting in consistent drug levels. Another advantage is the convenience of weekly or bi-weekly application resulting in improved patient co mpliance. The TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising delivery system. The transdermal drug delivery system is the effective way of administration of the drug to the targeted area. Due to recent advances in technology and the ability to apply the drug to the site of action without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. This review article provides the usefull information about transdermal drug delivery system and different approaches for enhancing the absorption of drug through the skin.

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