

Pharmacophore

(An International Research Journal)

Available online at <http://www.pharmacophorejournal.com/>

Original Review Article

RECENT APPROACHES OF TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. 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. This article deals with the innovations in the field of TDDS to improve the release rate and other parameters and most suitable to the patient. The number of medications and the ways in which they can be administered have expanded dramatically over the years. One such advance has been the development of transdermal delivery systems. The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successful delivery of the drug molecules to the systemic circulation via this route. Various types of transdermal approaches used to incorporate the active ingredients include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Innovations in technologies continue to occur at a positive rate, making the technology a fertile and vibrant. This article deals with the innovations in the field of TDDS to improve the release rate and other parameters and most suitable to the patient.

Keywords: Transdermal delivery, diffusion, biological half life, permeation enhancer.

INTRODUCTION

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Other advantages of using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored: the possible toxicity or non biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations. Providing control over the drug delivery can be the most important factor at times when traditional oral or injectable drug formulations cannot be used. These include situations requiring the slow release of water-soluble drugs, the fast release of low-solubility drugs, drug delivery to specific sites, drug delivery using nano particulate systems, delivery of two or more agents with the same formulation, and systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that

would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in Figure 1, in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Figure 2, remaining constant, between the desired maximum and minimum, for an extended period of time. Depending on the formulation and the application, this time may be anywhere from 24 hours (ProcardiaXL) to 1 month (Lupron Depot) to 5 years (Norplant).

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled release systems can respond to changes in the biological environment and deliver—or cease to deliver—drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered. While much of this work is still in its early stages, emerging technologies offer possibilities that scientists have only begun to explore.

Controlled-Release Mechanisms

There are three primary mechanisms by which active agents can be released from a delivery system. Diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the polymer matrix—or on a molecular level, by passing between polymer chains. Examples of diffusion-release systems are shown in Figures 1 and 2. In Figure 2, a polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. In the reservoir systems shown in Figures 3a and 3b, the drug delivery rate can remain fairly constant. In this design, a reservoir—whether solid drug, dilute solution, or highly concentrated drug solution within a polymer matrix—is surrounded by a film or membrane of a rate-controlling material. The only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Since this polymer coating is essentially uniform and of a non-changing thickness, the diffusion rate of the active agent can be kept fairly stable throughout the lifetime of the delivery system. The system shown in Figure 3a is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 3b illustrates a transdermal drug delivery system, in which only one side of the device will actually be delivering the drug. Once the active agent has been released into the external environment, one might assume that any structural control over drug delivery has been relinquished. However, this is not always the case. For transdermal drug delivery, the penetration of the drug through the skin constitutes an additional series of diffusional and active transport steps, as shown schematically in Figure 4.2 (A thorough analysis of transdermal drug delivery may be found in a review by Cleary³ or in other sources listed in the bibliography.) For the diffusion-controlled systems described thus far, the drug delivery device is fundamentally stable in the biological environment and does not change its size either through swelling or degradation. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.

Advantage And Disadvantage Of Tdds

Advantages

- i) They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administered drug.
- ii) They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
- iii) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liver when taken orally.
- iv) They are noninvasive, avoiding the inconvenience of parenteral therapy.

- v) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine day.
- vi) The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- vii) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin .

Disadvantages

- i) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- ii) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.
- iii) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
- iv) Long time adhere is difficult.

Structure Of Human Skin

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum. This is the outermost layer of skin also called as horny layer. It is approximately 10 m thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar." The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form. Viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal 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 basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

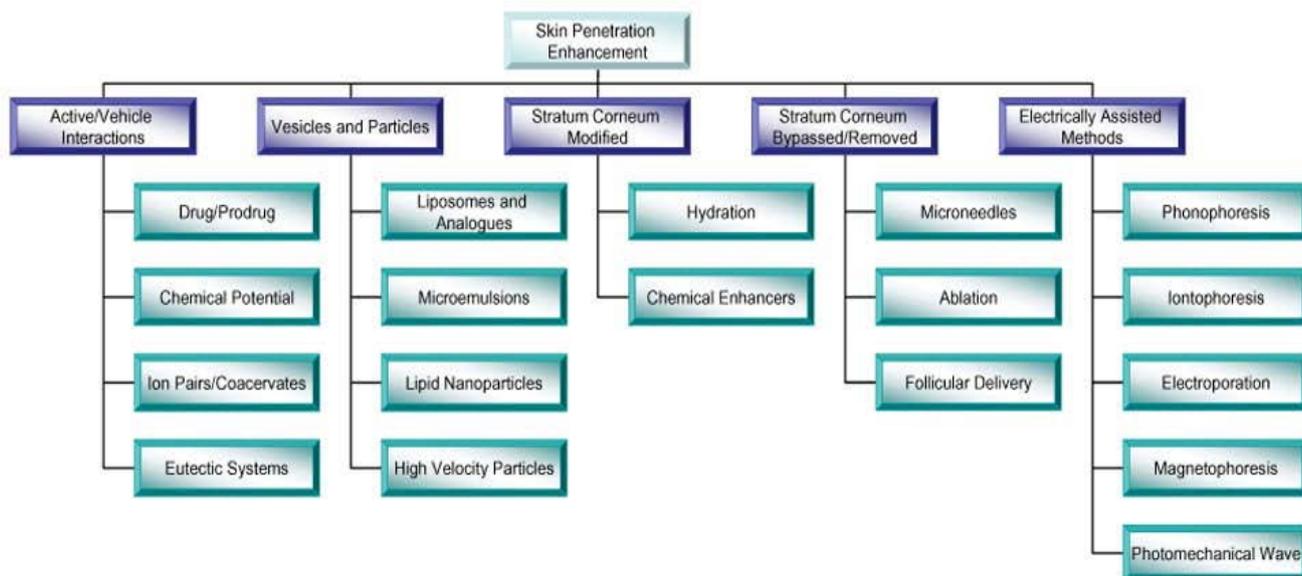
Dermis

Dermis is 3 to 5 mm thick layer and is composed of a matrix of connective tissue, 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 a permeate very low and the resulting concentration difference across the epidermis provides essential concentration gradient for transdermal permeation.

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 mechanically 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 these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

Methods For Enhancing Transdermal Drug Delivery



Drug/prodrug-The prodrug approach has been used to enhance the dermal and transdermal delivery of drugs with unfavourable partition coefficients the prodrug design involves addition of a promoiety to increase partition coefficient and also solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimising solubility in the aqueous epidermis. For example: The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6- acyloxymethyl and 9-dialkylaminomethyl promoieties. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs, like naltrexone nalbuphine buprenorphin alpha-blockerand other drugs .

Eutectic system-A eutectic system is a mixture of chemical compounds or elements that has a single chemical composition that solidifies at a lower temperature than any other composition. According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anesthesia for pain-free venepuncture and other procedures .

Liposomes and vehicles- Liposome are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, unscreening and tanning agents, enzymes, etc. Phosphatidylcholine from soybean or egg yolk is the most common composition although many other potential ingredients have been evaluated . Cholesterol added to the composition tends to stabilize the structure thereby generating more rigid liposomes. The mechanism of enhanced drug uptake into the stratum corneum is unclear. It is possible that the liposomes either penetrate the stratum corneum to some extent then interact with the skin lipids to release their drug or that only their components enter the stratum corneum.

Solid lipid Nanoparticles-Solid lipid nanoparticles (SLN) have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. It is thought their enhanced skin penetration is primarily due to an increase in skin hydration caused by the occlusive film formed on the skin surface.

Iontophoresis-This method involves permeation of a topically applied therapeutic agent by application of low level electric current either directly to skin or indirectly via dosage form. Parameters that effect design of a iontophoretic 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).

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 oligonucleotides) including biopharmaceuticals with molecular weights greater than 7kDA.

Ultrasound (sonophoresis and phonophoresis)- This technique involves the use of ultrasonic energy to enhance the transdermal delivery of solute either simultaneously or via pre-treatment. It uses low frequency ultrasound (55 kHz) for an average duration of 1 second to enhance skin permeability.

Laser radiation and photomechanical waves- Lasers are frequently used for treatment of dermatological conditions like acne and to confer facial rejuvenation. This method involves direct and controlled exposure of a laser to the skin that results in the ablation of the stratum corneum without significantly damaging the underlying epidermis.

Radio frequency- It involves the exposure of skin to high frequency alternating current resulting in formation of heat induced micro channels in the membrane. The rate of drug delivery is controlled by number and depth of micro channels formed by device. Treatment duration takes less than a second.

Magnetophoresis- 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.(fig.6)

Microneedle based devices-The first ever patents for drug delivery for percutaneous administration of drug was based on this method. These microneedles of length 50-110 micrometre will penetrate SC and epidermis to deliver drug.(fig.7)

Skin Abrasion- The abrasion technique involves the direct removal or disruption of the upper layers of the skin. These devices are based on techniques employed by dermatologists for superficial skin resurfacing which are used in the treatment of acne, scars, hyperpigmentation and other skin blemishes.

Needle-less 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, pain and fear

Application of pressure- The application of modest pressure i.e. 25kPa provides a potentially non-invasive and simplest method of skin permeability of molecules such as caffeine.

TYPES OF TRANSDERMAL PATCHES

a) Single layer drug in adhesive

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi-layer drug in adhesive

This type is also similar to the single layer but it contains an immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduce the cigarette smoking conditions.

d) Reservoir system

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be porous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with the drug.

e) Matrix System

i) Drug in adhesive system

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii) Matrix-dispersion system In this type the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir. It is spread along with the circumference to form a strip of adhesive rim.

f) Micro reservoir system

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachably small, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

Factors Affecting Transdermal Bioavailability

Two major factors affect the bioavailability of the drug via transdermal routes:

Physicochemical Factors

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.

Temperature and pH: The permeation of drug increase 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.

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.

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. **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.

Molecular size and shape: Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

Biological Factors Skin Condition

Acids and alkalis, many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

Skin age: The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS.

Blood flow: Changes in peripheral circulation can affect transdermal absorption. Regional skin sites Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration. Skin metabolism Skin metabolizes steroids, hormones, chemical carcinogens and some drugs.

Species differences: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration metabolism determines efficacy of drug permeated through the skin.

Basic Components Of Tdds

1. Polymer matrix / Drug reservoir
2. Drug
3. Permeation enhancers

4. Pressure sensitive adhesive (PSA)
5. Backing laminates
6. Release liner
7. Rate controlling membrane
8. Other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir: Backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high. E.g.- cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate.

Natural polymers: e.g. cellulose derivatives, zein, gelatine, 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. The polymers like polyethylene glycol¹⁷, eudragits¹⁸, ethyl cellulose, polyvinylpyrrolidone¹⁹ and hydroxypropyl methylcellulose²⁰ are used as matrix type TDDS. The polymers like EVA²¹, silicon rubber and polyurethane are used as rate controlling TDDS.

Permeation enhancers: These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings:

A) Solvents -These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl ethyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-pyrrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

B) Surfactants - These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length. Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decylmethyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate. Binary system: These systems apparently open up the heterogeneous multilaminar pathway as well as the continuous pathways. e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

C) Miscellaneous chemicals -These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-β-cyclodextrin and soybean casein.

Pressure Sensitive Adhesives:

The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device. It should not be irritant ii) It should be easily removed. It should not leave an unwashable residue on the skin. It should have excellent contact with the skin. Physical & chemical compatibility with the drug. Permeation of drug should not be effected. Several classes of PSAs are used for skin contact application include acrylics, polyisobutylene and silicone polymers (Grossberg GT *et al* 2010). The functional properties of PSAs such as tackiness, adhesive property, release force, and cohesive strength as well as adhesive formulations having attributes such as enhanced drug flux and skin friendliness. A PSA must be able to perform effectively under a wide range of temperatures, humidity levels, and application frequency (from 24 hrs for some products to one week for others). The effects of mechanical stresses (e.g., stretching) as well as skin irritation and sensitization also must be considered. ²¹ The human studies of various commercially available transdermals are examined and reported to assess the relative performance capabilities of each type of transdermal design. ²⁴ Monolithic TTS was fabricated in PSAs- (a) terpolymer (PSA1) of 2-ethylhexyl acrylate, methyl methacrylate, and acrylic acid, (b) copolymer (PSA2) of 2-ethylhexyl acrylate, methyl

methacrylate, acrylic acid, and vinyl acetate, and (c) Eudragit E100 pressure sensitive adhesive (PSA3). The transport of nicorandil via skin can be achieved by the skin permeation enhancer i.e. N-methyl-2-pyrrolidone (NMP) was investigated at different concentrations (5%) in PSAs .

Backing 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. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. 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 films.

Release Liner: During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to the skin. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form delivering the active principle. However, because the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding the chemical inertness and permeation to the drug, penetration enhancer, and water. In case cross-linking is induced between the adhesive and the release liner, the force required to remove the liner will be unacceptably high.

Other Excipients: Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Various Methods For Preparation Tdds

A. Asymmetric Tpx Membrane Method: 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.

Asymmetric TPX membrane preparation: These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.

b. Circular teflon mould method: Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the Wquantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be 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 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c. Mercury substrate method: In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

d. By using “IPM membranes” method: In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

e. By using “EVAC membranes” method: In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (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 will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. Aluminium backed adhesive film method: Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custommade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

g. Preparation of TDDS by using proliposomes: The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

h. By using free film method: 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. 5 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 petridish. 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. Aluminium backed adhesive film method is a suitable one.

Approaches In The Development Of Transdermal

Therapeutic System: - Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies are as follows:

Adhesive Dispersion Type System: - The system consists of drug-impermeable backing membrane, the drug reservoir which is prepared by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug-impermeable backing to form a thin drug reservoir layer. On top of this, a layer of rate-controlling adhesive polymer (non-medicated) of constant thickness is spread to produce an adhesive diffusion-controlled drug delivery system with detachable release liner which in an ideal situation is removed and the patch is applied to the skin for a required period of time. Illustration of this type of system is exemplified by development and marketing of transdermal therapeutic system of angina pectoris and Valsartan as angiotensin II type 1 selective blocker for one day medication.(fig.8)

MEMBRANE PERMEATION CONTROLLED SYSTEM: - In this system the drug reservoir is totally embedded in a compartment molded between a drug-impermeable backing laminate and a rate controlling polymeric membrane. The drug molecules are permitted to release across the rate controlling membrane simply by diffusion process through the pores. In the reservoir compartments the drug solids are dispersed homogeneously in a solid polymeric matrix (e.g. polyisobutylene) suspended in the unextractable viscous liquid medium (e.g. silicon fluid) to form a gel-like suspension, or dissolved in a releasable solvent (e.g. alkyl alcohol) to form a gel like in solution. The rate controlling membrane, can be either a microporous or non-porous polymeric membrane e.g. ethylene-vinyl acetate copolymer, having specific drug permeability. On the top surface of the polymeric membrane a thin layer of drug compatible adhesive polymer, e.g., silicone adhesives, can be applied, to provide intimate contact of the transdermal system with the skin surface. The release rate from this transdermal system can be tailored by varying the polymer composition, thickness of the rate controlling membrane, permeability coefficient and adhesive. Examples of this system are TransdermScop (Scopolamine- 3 days protection) of motion sickness and TransdermNitro (Nitroglycerine-for once a day) medication of angina pectoris (fig.9)

Matrix Diffusion Controlled System: - In this approach, the drug reservoirs are prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix or combination of both.. The resultant medicated polymer.

is then molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature and/or under vacuum. The polymer disc which contains drug reservoir is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is then spread to form a strip of rim along the medicated disc. This matrix type of transdermal system is best exemplified by the nitroglycerin releasing transdermal therapeutic system. The advantage of matrix dispersion type transdermal system is the absence of the dose dumping since the polymer cannot rupture. (fig.10)

Micro Reservoir Type Controlled System: - This system is basically hybrid of reservoir and matrix dispersion type of drug delivery system. In this approach, drug reservoir is formed by suspending the drug in an aqueous solution of liquid polymer and then dispersing the drug suspension homogeneously in lipophilic polymer e.g. silicone elastomers by high energy dispersion technique by shear mechanical force to form thousands of unreachable and microscopic spheres of drug reservoirs. This technology has been utilized in the development of Nitro disc. Release of a drug from a micro reservoir-type system can follow either a partition-control or a matrix diffusion-control depending upon the relative magnitude of solubility of the drug in the liquid compartment and in the polymer matrix. (fig.11)

Evaluation Of Parameters

Interaction Studies

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characters wave numbers, absorption maxima etc.

1. Thickness of the patch The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film.

2. Weight uniformity The prepared patches are dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

3. Folding endurance A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

4. Percentage Moisture content The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula 2, 13. % Moisture content = $\frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$

5. Content uniformity test 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

6. Moisture Uptake Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below 11, 13. % moisture uptake = $\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$

7. Drug content A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug content with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

8. Shear Adhesion test This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect its pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken for removal, greater is the shear strength.

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

10. Water vapor transmission studies (WVT) For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated. $WVT = \frac{W}{ST}$ W is the increase in weight in 24 h; S is area of film exposed (cm²); T is exposure time.

11. Rolling ball tack test This test measures the softness of a polymer that relates to tack. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

12. Quick Stick (peel-tack) test In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

13. Probe Tack test In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams

14. In vitro drug release studies The paddle over disc method (USP apparatus V) is employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness are to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate is then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32± 0.5°C. The paddle is then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

15. In vitro skin permeation studies

An 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 an 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 spectrophotometrically 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}).

16. Skin Irritation study Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm^2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

17. Stability studies Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at $40\pm 0.5^\circ\text{C}$ and $75\pm 5\%$ RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content .

Applications Of Transdermal Patches

- 1) Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- 2) Nitroglycerine patches are also sometimes prescribed for the treatment of Angina.
- 3) Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflammatory drug are also available in the form of transdermal patches.
- 4) Transdermal form of the MAOI selegiline became the first transdermal delivery agent for an antidepressant.
- 5) Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Transdermal Market

The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The table 1 gives detail information of the different drugs which are administered by this route and the common names by which they are marketed; it also gives the conditions for which the individual system is used. (Table .3)

Future Of Transdermal Drug Delivery System

Future novel formulation approaches and technologies include liposomes, niosomes and micro emulsion. Aim of this strategy is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal devices has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will rise in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low-frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetophoresis, has been investigated as a means to increase drug flux across the skin. The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase. In current scenario, transdermal route of drug delivery system in comparison with oral treatment as the most successful innovative research area in new drug delivery system, with around 40% of the drug delivery candidate products under clinical trails related to transdermal or dermal system. The transdermal drug delivery systems (TDDS) have been designed as an alternative, safest and easy route for systemic drug delivery. The systemic drug administration though skin holds several advantages such as maintenance constant drug level in blood plasma, less number

of side effects, and improvement of bio availability by circumvention of hepatic first pass metabolism and increase patient compliance with respect to drug regime used for treatment. In recent times, skin considered as a safest port for drug administration, to provide continuous drug release into systemic circulation.

CONCLUSION

Transdermal drug delivery systems have been used as safe and effective drug delivery devices since 1981. A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity. This article provides valuable information regarding the transdermal drug delivery systems and its evaluation process in details.

ACKNOWLEDGEMENT

We are thankful to the management of J.K.K.MUNIRAJAH COLLEGE OF PHARMACY, komarapalayam and our principal Dr N. Senthil Kumar for the support and cooperation.

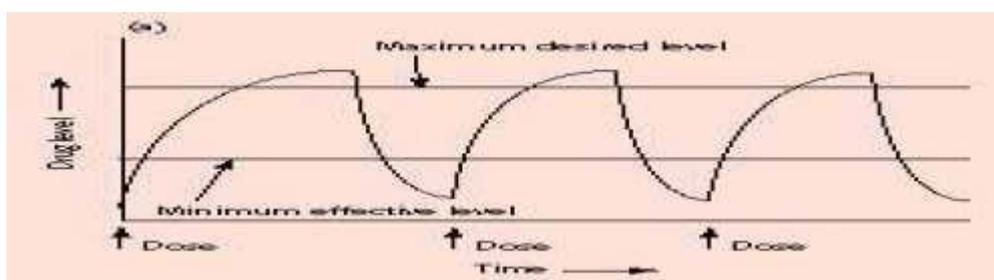


Figure 1. Drug levels in the blood with traditional drug dosing

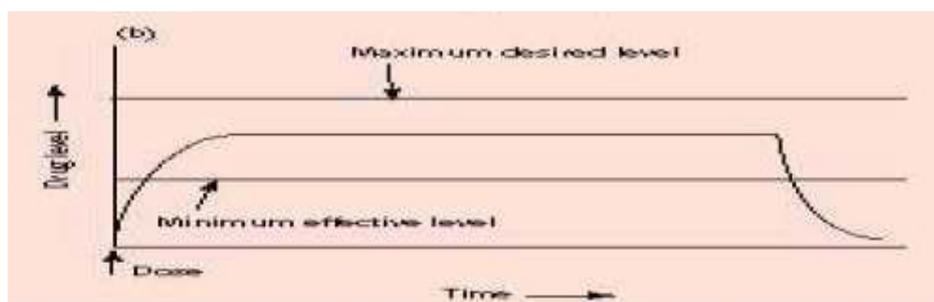


Figure 2. Drug levels in the blood with controlled delivery Dosing

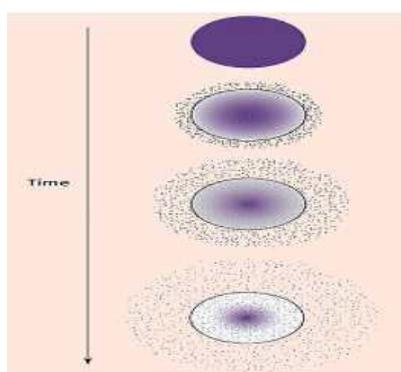


Figure 3. Drug delivery from a typical matrix drug delivery system

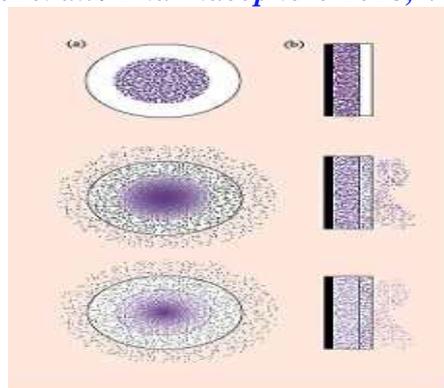


Figure 4. Drug delivery from typical reservoir devices

(a) implantable or oral systems, and
(b) transdermal systems

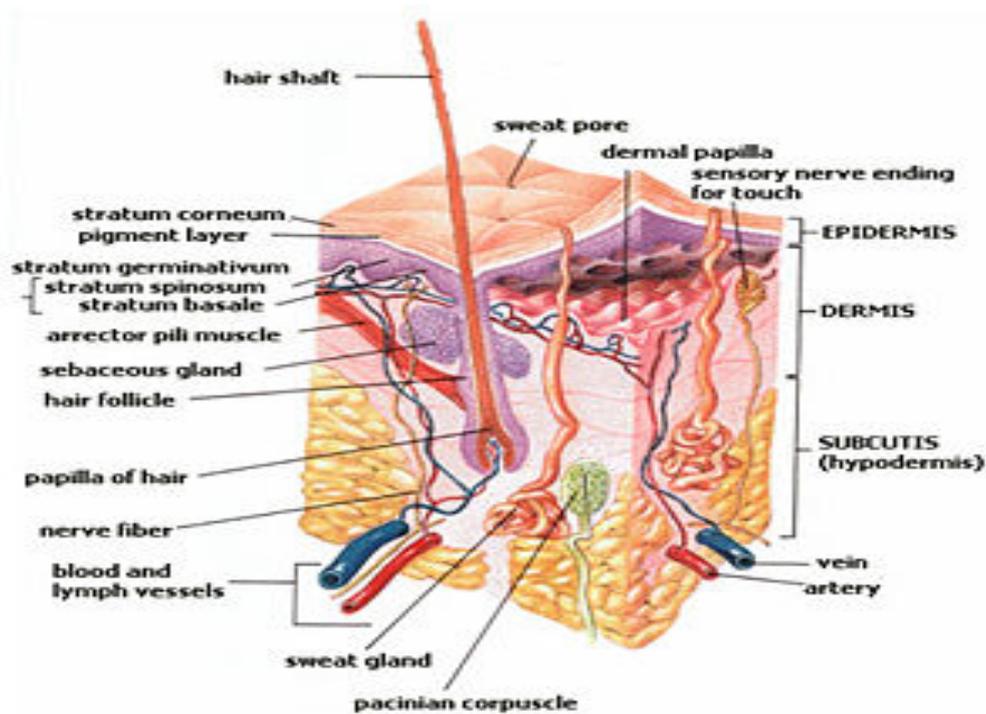


Figure 5. Structure Of Human Skin

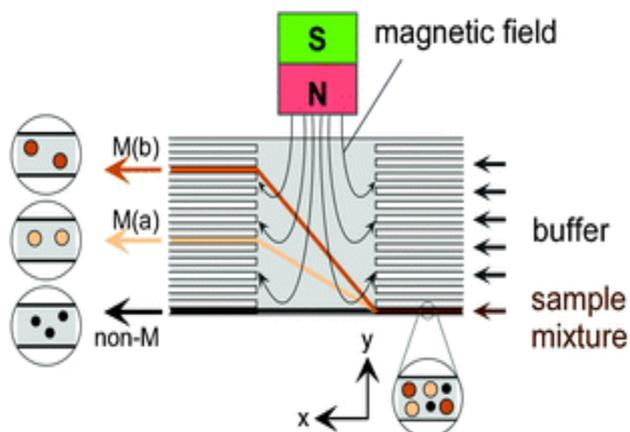


Figure 6: Technique of magnetophoresis

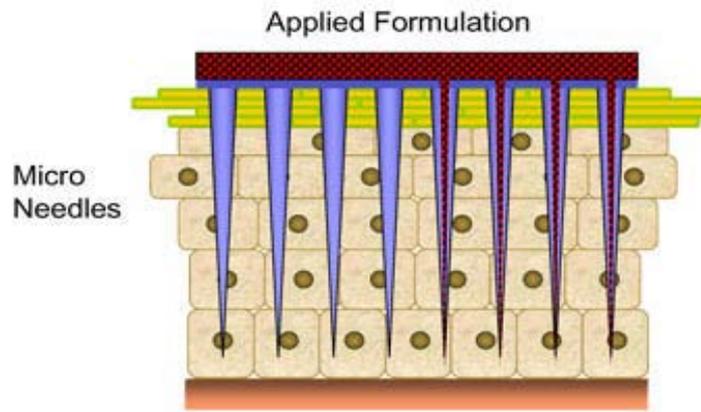


Figure 7: Basic design of micro needle delivery devices

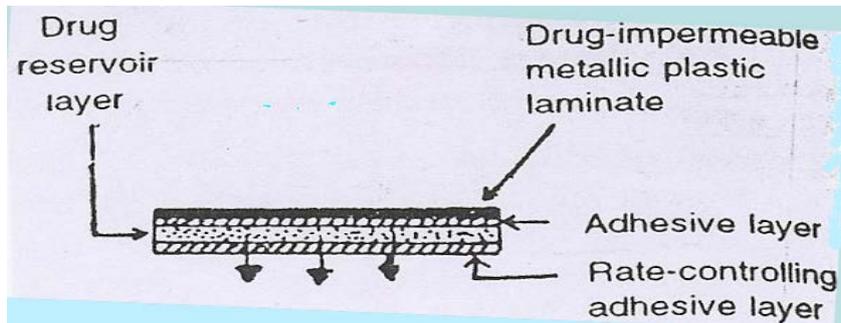


Figure 8: Adhesive Dispersion-Type System

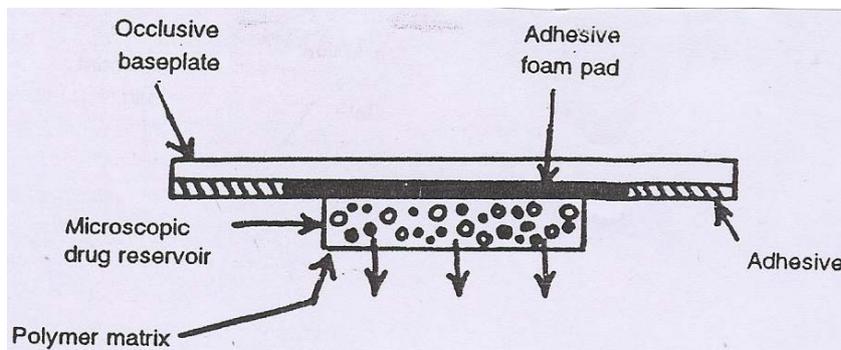


Figure 9: Membrane Permeation Controlled System

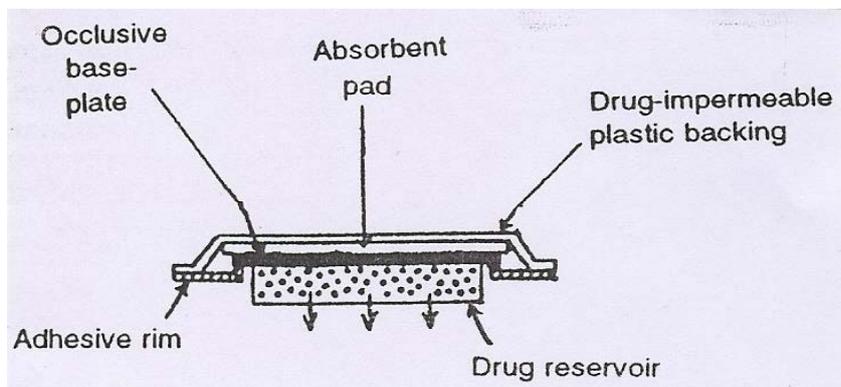


Figure 10: Matrix Diffusion Controlled System

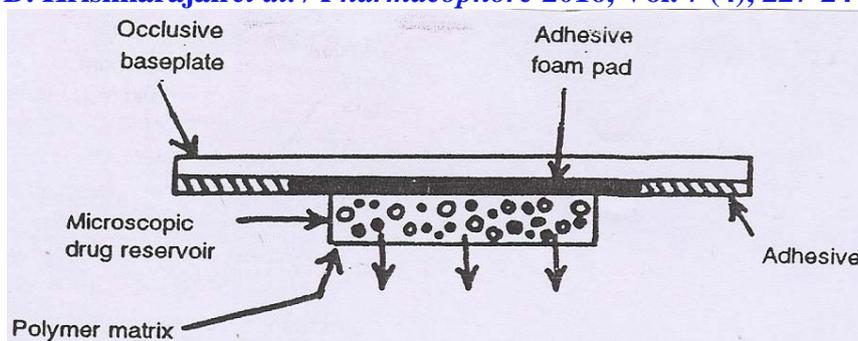


Figure 11: Micro Reservoir Type Controlled System

Table 1: Ideal properties of transdermal drug delivery system

S.No	Properties	Range
1	Shelf life	Should be upto 2.5 years
2	Patch size	Should be less than 40cm ²
3	Dose frequency	Once a daily – once a week
4	Appearance	Should be clear or white color
5	Packaging properties	Should be easily removable of release liner
6	Skin reaction	Should be non-irritating
7	Release properties	Should have consistent pharmacokinetic and pharmacodynamic profiles over time
8	Packaging properties	Should be easily removable of release liner

Table 2: Ideal properties of drug for TDDS

S.No	Parameter	Properties
1	Dose	Should be low
2	Half life in hour	Should be 10 or less
3	Molecular weight	Should be less than 500
4	Partition coefficient	Log P (octanol – water) between 1 and 3
5	Skin permeability	Should be less than 0.5x10 ⁻³ cm/hr
6	Skin reaction	Should be non-irritating
7	Oral bioavailability	Should be low
8	Therapeutic index	Should be low
9	Concentration	Minute
10	Ph of saturated aqueous solubility	5-9
11	Dose deliverable	<10mg/day

Table 3: Marketed Products of Transdermal Drug Delivery System

S.No	Product	Active Drug	Type Of Transdermal Patch	Purpose
1	Estraderm	Estradiol	Membrane	Postmenstrual Syndrome
2	Duragesic	Fentanyl	Reservoir	Pain Relief Patch
3	Transderm-Scop	Scopolamine		Motion Sickness
4	Alora	Estradiol	Matrix	Postmenstrual Syndrome
5	Climara	Estradiol	Matrix	Postmenstrual Syndrome
6	Androderm	Testosterone	Membrane	Hypogonadism In Male
7	Captopress TTS	Clonidine	Membrane	Hypertension
8	Combipatch	Estradiol	Matrix	Postmenstrual Syndrome
9	Esclim	Estradiol	Matrix	Hormone Replacement Therapy
10	Deponit	Nitroglycerine	Drug In Adhesive	Angina Pectoris
11	Fempatch	Estradiol	Matrix	Postmenstrual Syndrome

12	Lidoderm	Lidocaine	Drug In Adhesive	Anesthetic
13	Ortho Evra	Estradiol	Drug In Adhesive	Postmenstrual Syndrome
14	Testoderm TTS	Testosterone	Reservoir	Hypogonadism In Male
15	Habitraol	Nicotine	Drug In Adhesive	Smoking Cessation
16	Prostep	Nicotine	Reservoir	Smoking Cessation
17	Nicotrol	Nicotine	Drug In Adhesive	Smoking Cessation
18	Vivelle	Estradiol	Reservoir	Postmenstrual Syndrome
19	Matrifen	Fentanyl	Reservoir	Pain Relief Patch
20	Nupatch 100	Dioclofenac Diethylamine	Drug In Adhesive	Anti Inflammatory
21	Nicoderm CQ	Nicotine	Drug In Adhesive	Smoking Cessation
22	Vivelle-Dot	Estradiol	Reservoir	Postmenstrual Syndrome
23	Minitran	Nitroglycerine	Drug In Adhesive	Angina Pectoris
24	Tranderm Nitro	Nitroglycerine	Micro Reservoir	Angina Pectoris
25	Nitrodur	Nitroglycerine	Matrix	Angina Pectoris
26	Nitro Disc	Nitroglycerine	Reservoir	Angina Pectoris
27	Oxytroyl	Oxybutynin	Matrix	Overactive Bladder
28	Nuvelle TS	Estradiol	Drug In Adhesive	Hormone Replacement Therapy
29	FEMATRIX	Estrogen	Matrix	Postmenstrual Syndrome
30	CLIMADERM	Estradiol	Matrix	Postmenstrual Syndrome

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Cite This Article: D. Krishnarajan* ,V.Varadharajan , N.Gobi, D. Gowtham , G. Yuva srinivas , P. Vasudevan (2016), “Recent Approaches Of Transdermal Drug Delivery System: A Review”, *Pharmacophore*, Vol. 7 (4), 227-244.

