Review Article

Transdermal Drug Delivery System :A Novel Alternative For Drug Delivery

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ABSTRACT

Orally administered pharmaceuticals now account for 74% of all prescriptions, however studies have shown that oral medications are often less effective due to first pass metabolism and not stable drug blood level etc.. Transdermal drug delivery system (TDDS) was developed to enhance such qualities. Every 2.2 years, the FDA grants approval for a new transdermal medication delivery system, fueling a multibillion dollar industry. An extensive evaluation of the technology, business, and products has been warranted since the FDA initially authorized the first transdermal medicine patch around 40 years ago. Transdermal medication delivery systems on demand are made possible by patches, a special kind of patch. The transdermal medication delivery system's adhesive plays a key role in the product's safety, effectiveness, and quality. Compared to more traditional delivery modalities, such as oral or invasive injection, topical therapy provides several benefits. Limiting hepatic first-pass metabolism, improving therapeutic efficacy, and maintaining a constant plasma level are all benefits of transdermal drug administration. Types of transdermal patches, production techniques, mechanism of action, kinetics, clinical concerns, and their physicochemical methods of assessment are all covered in this article.

- **Keywords:** Topical drug delivery system (TDDS), Transdermal patches, Permeation enhancers, Polymer Matrix.

INTRODUCTION

In recent years, transdermal drug delivery systems (TDDS) have received a lot of attention. Many medications have been developed that can be injected into the bloodstream straight via the skin. In 1979, the Food and Drug Administration (FDA) granted FDA approval for the first transdermal patch. An anti-motion sickness patch was used to apply to the skin. The FDA authorized four nicotine patches between the end of 1991 and the beginning of 1992 after the pharmaceutical firms began developing a nicotine patch to assist smokers stop smoking in the mid-1980s[(1)] Controlled drug release and painless administration are the key benefits of this approach. A Transdermal patch clings to the skin and delivers the medicine to the skin. When using a Transdermal Patch, there are various components that play an important part in the delivery of the medication through the skin, such as liners, adherents, and drug reservoirs. Transdermal patches are available in a variety of forms and may be applied in a variety of ways. To take advantage of its many benefits, it has become one of the most-researched areas in the pharmaceutical industry The benefits and drawbacks of the transdermal patch, as well as the ways of applying, the care that must be taken when applying, the kinds and applications of transdermal patch, and new patents and market items, have been reviewed here. Evidence of percutaneous medication absorption may be detected in blood levels of the drug and its metabolites, as well as in the patient's clinical reaction to the pharmacological treatment.

First-generation Transdermal delivery systems Clinical usage of tiny, lipophilic, low-dose medicines has continued to rise steadily over the last several years.

Second-generation delivery systems.There are additionally therapeutic solutions that have been developed employing chemical enhancers, noncavitational ultrasound, and iontophoresis. The capability to regulate delivery rates in real time gives further usefulness.

Third-generation delivery systems Microneedles, thermal ablation, microderm abrasion, electroporation, and cavitational ultrasound are used to target the stratum corneum's barrier layer. Insulin, parathyroid hormone, and influenza vaccine are among the macromolecules and vaccines now being tested using microneedles and thermal ablation. When second and third generation transdermal

R PEER REVIEW

delivery augmentation technologies are used, their influence on medicine will soar.

There has been a rise in interest in Transdermal over the last several years due to a number of factors, including new clinical data from technology firms and pharmaceutical companies looking for new ways to prolong patents on their products[(2).]

Drug candidates suitable for TDDS[(3-4)]

In order for a medicine to be effective, its molecular weight must not exceed 500 Daltons.

As long as a drug's water partition coefficient is between 1 and 4, it's OK.

• A low dose of less than 10 mg/day is recommended.

Transdermal permeation is based on a simple principle. Passive diffusion is the underlying principle behind transdermal absorption and absorption via the skin. Only a millimetre of skin tissue separates skin from its capillary network, making it the most intense and easily accessible organ in the body. A number of steps are involved in the release of a therapeutic drug from a skin-applied formulation and its transit into the body's circulation.

1) The rate of drug diffusion from the drug to the rate-controlling membrane is regulated.

2) The dissolution of the formulation and the release of it from it.

3. Accumulation and penetration through a viable epidermis by the stratum corneum.

4) The dermal papillary layer's capillary network takes the medication into the dermis.

5) It has a direct effect on the organ in question.

6) The stratum corneum, the outermost layer of the skin.

7) Through the stratum corneum, lipidic intercellular diffusion is the most common route.

BASIC COMPONENETS OF TRANSDERMAL DRUG DELIVERY SYSTEMS[(5-7)]:

The Transdermal device consists of various components. (Fig:1)

- polymer matrix

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- drug
- permeation enhancers
- other excipients are examples of polymer matrix components.

Polymer Matrix:

The medicine is released from the device under the control of the polymer. A polymer must meet the following requirements before it may be utilised in a Transdermal system. Table 1 : Polymers that might be beneficial in Transdermal devices include;

Natural Polymers:	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives, Zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch.	Polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, Nitrile, Acrylonitrile, Butylrubber, Styrenebutadiene, Neoprene etc.	Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyvinylpyrrolidone, Polymethyl methacrylate, Epoxy, Polyurea, etc.

Drug:

When constructing a Transdermal medication delivery system, the medicine must be carefully selected. Transdermal delivery requires a medication with the following characteristics.•The medicine must have a molecular weight of less than about 1000 Daltons.•Both lipophilic and hydrophilic phases are required for the drug's affinity.

• The medication should have a low melting point.

•

•In order for the medicine to be effective, a daily dosage of a few milligrammes should be sufficient.

•There should be a short half-life (t1/2) for a medicine.

•An allergic or irritative reaction to the medicine must not occur.

• Drugs that degrade in the gastrointestinal system or are inactivated by the hepatic first-pass effect are good candidates for transdermal administration..

UNDER PEER REVIEW

•Under the near zero-order release profile of Transdermal delivery, tolerance to the medication must not develop.

•Transdermal delivery may also be used for drugs that must be taken for a lengthy period of time or that have detrimental effects on non-target tissues.

Permeation Enhancers:

Skin permeability enhancers, also known as permeation promoters, are non-therapeutic substances that may help drug delivery systems reach the skin.[1] A formula for the rate at which medications move over the skin may be expressed as:

If you look at the formula for the diffusion coefficient (D), you can see that it is dependent on the diffusing molecule's size, shape, and flexibility, as well as membrane resistance.

This equation provides a simple framework for understanding how to increase the flow in a system with a variety of boundary conditions and membrane characteristics. Diffusion coefficients are connected to penetration size and shape, as well as energy necessary to create a hole for diffusion, since the concentration gradient is thermodynamic. Thus, enhancing membrane fluidity comes down to the following considerations:

•Furthermore, thermodynamics (lattice energies, distribution coefficients).

•Dimensions of the molecule, including size and form.

One or more of the layers of the skin may be affected by penetration enhancers in order for skin penetration to be boosted. Many substances have been tested for their capacity to improve the permeability of the stratum corneum. These may be neatly grouped into the following categories:

Solvents: The penetration of these chemicals may be increased by one.

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1) Swelling of the skin's polar channels. 2). Lipids are dissolved in water.

Some examples are methanol and ethanol, which are water alcohols; alkyl methyl

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sulfoxides, such as dimethyl sulfoxide and alkyl homologous methyl sulfoxide; pyrrolidones-2-pyrrolidone; laurocapram (Azone); and various solvents, such as propylene glycol, glycerol, silicone fluids, and isopropylpalmitate etc.

Surfactants:

Hydrophilic medicines, in particular, might benefit from these molecules' enhanced polar route trafficking. Head group and hydrocarbon chain length determine the surfactant's capacity to change penetration. Because they are skin irritants, a balance must be struck between increasing penetration and causing irritation. To enter and interact aggressively with the skin, anionic surfactants may be used Large changes may be induced once these surfactants permeate the skin. To far, cationic surfactants have not been extensively explored as skin permeation enhancers, despite their claimed irritancy. Nonionic surfactants have long been regarded as the least irritating of the three main groups of surfactants and have been extensively investigated.

Commonly used surfactants include the following:

Anionic Surfactants: Soybean oil, Dioctyl sulphate, and Decodecyl methylsulphoxide are some of the common ingredients.

Nonionic Surfactants: Pluronic F127, Pluronic F68, etc.

Bile Salts: Deoxycholate, taurocholate, and tauroglycocholate are all sodium salts..

Miscellaneous Chemicals: In addition to anticholinergic drugs, they include N, N, N-dimethyl-m toluamide, calcium thioglycolate, and urea, a hydrating agent. There have lately been several reports of putative permeability enhancers, however the existing evidence on their usefulness is limited. Soyabeancasein and eucalyptol are among the other ingredients.

Other Ingredients:

Adhesives: Transdermal devices have traditionally been attached to the skin via a pressure-sensitive adhesive. Adhesive that is pressure sensitive may be applied to the front or rear of a device, and it can be extended around the item.

UNDER PEER REVIEW

The following requirements should be met by both adhesive systems.

To avoid irritating or sensitising skin or disrupting natural skin flora, it should not be used

During the dosage period, it

- should stick firmly to the skin and not be moved by activities such as bathing, exercising, etc.
- Should be easy to remove.
- Shouldn't leave a sticky residue on the skin that can't be removed.
- Should have great macroscopic and microscopic touch with the skin

Backing Membrane: In addition to providing a strong binding to the drug reservoir, backing membranes also prevent medication from escaping through the dosage form's top, allow for printing, and are easy to clean. When applied to the skin, it acts as an impermeable barrier and shields the product, such as metallic lamination, plastic backing with absorbent pad and occlusive base plate (aluminium foil) etc.

Release Liner: Drug migration into the adhesive layer is prevented by release liner during storage. Rather than being a component of the medicine's dosage form, it is considered to be part of the principal packing material for the drug. There are two layers to the release liner: a non-occlusive (paper fabric) or an occlusive (polyethylene, polyvinylchloride) base, and a silicon or Teflon release coating layer. Polyester foil and metalized laminate are also utilised as TDDS release liner materials.

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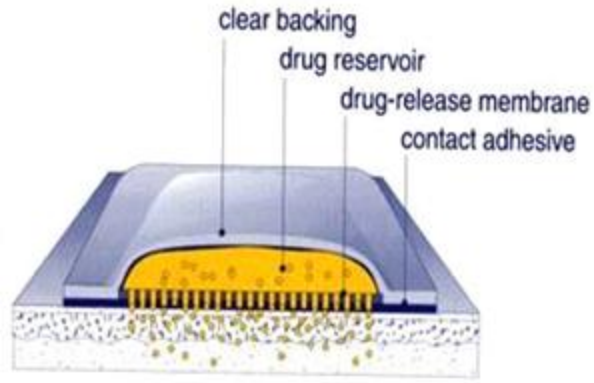

Fig-1 showing main components of transdermal patches [5-7]

TYPES OF TRANSDERMAL PATCHES: [8-12]

a) Single layer drug inadhesive:

The medication is included in the sticky layer of this kind. As well as serving as a bonding agent between the other layers, the adhesive layer is also responsible for the drug's absorption through the skin. A temporary liner and a backing protect the adhesive layer..

b) Multi -layer drug inadhesive:

However, this kind has two layers instead of only one, one of which has a quick-acting medication release and one that has a more gradual release. The medication is released from the sticky layer. Also included is a temporary liner and a permanent backer for this patch.

c) Vapour patch:

While adhering several layers together, the adhesive layer also functions as a vapour releaser in this patch. New to the market, the vapour patches are utilised for releasing essential oils in decongestant applications. There are a variety of alternative vapour patches on the market that may be used to enhance the quality of one's sleep and lessen one's cigarette smoking situations..

d) Reservoir system:

An impermeable backing layer is sandwiched between a rate-controlling membrane and a drug

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reservoir. For example, a micropore or nonporerate-controlling membrane is required for the medication to enter and exit the body. It is possible for the drug to be spread in a solid polymer matrix in the drug reservoir compartment. As an exterior polymeric membrane that is compatible with drug, a hypoallergenic adhesive polymer may be applied..

e) Matrix system:

i. Drug-in-adhesive system:

Medicated adhesive polymers are distributed over an impermeable backing layer by solvent casting or melting (in the case of hot-melt adhesives), forming a drug reservoir of this sort. The reservoir is protected by a layer of unmediated sticky polymer on top of it..

ii. Matrix-dispersion system:

Hydrophilic or lipophilic polymer matrixes spread the medication uniformly. An occlusive base plate holds the drug-containing polymer disc in place, while a drug-impermeable backing layer serves as a barrier. While a medication reservoir's front surface is coated with a thin adhesive strip that runs around its circle, it's not applied there..

f) Micro reservoir system:

This sort of drug delivery system combines a reservoir with a matrix-dispersion mechanism to deliver the medication to the patient. By initially spreading the drug solution homogeneously throughout the lipophilic polymer, we create thousands of inaccessible, tiny drug reservoirs that are unable to access. Using cross-linking agents, this thermodynamically unstable dispersion is instantly stabilised by promptly cross-linking the polymer.

ADVANTAGES AND DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY [13]

Compared to more conventional methods, transdermal medication delivery systems provide a number of major benefits.:

- In addition to reducing the frequency of dose, the longer duration of effect reduces the need for frequent administration.

UNDER PEER REVIEW

•Increased absorption into the body

•Plasma levels will be more consistent.

•There are fewer adverse effects and a better therapeutic outcome since plasma levels are kept stable until the end of the dosage interval, allowing for more flexibility in drug administration.

•The patch may be removed from the skin without affecting the medicine's efficacy or safety.

Some of the greatest *disadvantages* to Transdermal drug delivery are:

There is a possibility of a local irritant at the application location. * The medicine, the adhesive, or any excipients in the patch formulation might produce erythema, irritation, and local edoema. After a certain dosing duration, patches are applied.

The transdermal system can only handle a small amount of medications.

PROPERTIES THAT INFLUENCE TRANSDERMAL DELIVERY[14]

(1) the drug's dissolution from the vehicle,

(2) the skin barrier's breach,

(3) the pharmacological response's activation.

DESIGN OF TRANSDERMAL DELIVERY SYSTEM:

The drug is dissolved or disseminated in an inert polymer matrix that serves as a support and platform for drug release in any transdermal delivery device. The patch system has two fundamental designs that determine the features of medication release and patch behaviour:

1) Matrix or Monolithic: The medication binds to the inert polymer matrix and regulates its release from the device via the inert matrix**.**

2) **Reservoir or Membrane**: Drug release is not controlled by the polymer matrix. For the rate limiting barrier, the drug matrix and sticky layer are separated by a rate-controlling membrane in between**.**

MECHANISM OF ACTION OF TRANSDERMAL PATCH[14-15]

There are a variety of ways to apply the transdermal patch and get the active ingredient into the circulatory system via the skin..

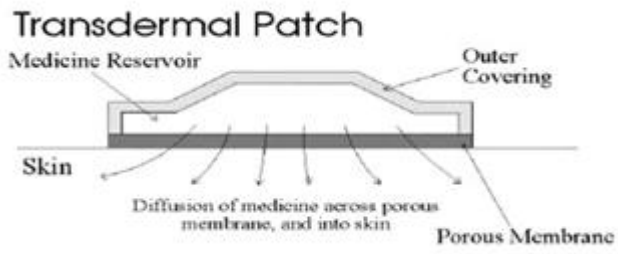

Fig-2. showing application of transdermal patch

1. ***Iontophoresis***

The electrode put in contact with the formulation is used in iontophoresis to provide a few milliamperes of current to a few square centimetres of skin, facilitating medication administration over the barrier. Pilocarpine administration is mostly used to generate sweating as a diagnostic test for cystic fibrosis. Rapid onset of anaesthesia may be achieved via iontophoretic administration of lidocaine.

2. ***Electroporation***

Short, high-voltage electrical pulses are applied to the skin during electroporation. The skin's permeability for drug diffusion is raised by four orders of magnitude after electroporation. The top layer is thought to create transitory aqueous holes as a result of the electric impulses, which allow for drug delivery. Electrodes placed close together in the nerve-free cytoplasm may be used to provide

painless electrical pulses..

3. Application by ultrasound

Transdermal transport of a wide range of medicines, including macromolecules, has beendemonstrated to be improved by the use of ultrasound, especially low frequency ultrasound. Sonophoresis is another name for this procedure. Low-frequency sonophoresis was used by Katz et al. to distribute EMLA cream topically.

4. Use of microscopic projection

In order to make transdermal medication delivery easier, researchers developed patches containing tiny projections known as microneedles. Needles varying in length from 10 to 100 nm are placed in a grid-like pattern. Because of their minuscule punctures, these arrays may transfer macromolecules into the skin without causing any discomfort to the patient. On the microneedles, the medicine is coated so that it may be absorbed quickly and easily. They are used in the creation of tetanus and influenza cutaneous vaccinations.

Transdermal patches may also be applied by thermal portion, magnetophoresis, and photomechanical waves, amongst other ways. There is still a lot of work to be done before these approaches can be put into practise.

VARIOUS METHODS FOR PREPARATION TDDS®[16-20)]

a. Asymmetric TPX membrane method:

Using a polyester sheet (type 1009, 3m) with a concave diameter of 1cm as the backing membrane, a prototype patch may be produced. Poly(4-methyl-1-pentene)-asymmetric membrane (TPX) covers the concave membrane, which is then sealed with an adhesive.

Asymmetric TPX membrane preparatio:

Dry/wet inversion is used to create them. To create a polymer solution, TPX is dissolved in cyclohexane with nonsolvent additives at 60°C. Using a gardener's knife, the polymer solution is cast onto a glass plate at 40°C for 24 hours. A casting film is then dissolved at 50°C for 30 seconds before

being dissolved in a coagulation bath [the temperature is maintained at 25°C]. Membrane removal and drying may begin after 10 minutes of immersion [in an oven at 50°C for 12 hours].

b. Circular teflonmould method:

Polymer solutions in organic solvents are employed in a variety of ways. In half the amount of the same organic solvent, a certain amount of medication dissolves. The remaining half of the organic solvent is used to dissolve the enhancers, which are then added in various quantities. A plasticizer, di-N-butylphthalate, is added to the drug polymer solution to make it more flexible. After 12 hours of stirring, the whole mixture should be placed into a circular teflonmould. In a laminar flow hood model with an air speed of 0.5 m/s, the moulds should be positioned on a flat surface and covered with an inverted funnel to manage solvent vaporization. It takes 24 hours for the solvent to evaporate. Storage at 250.5°C for another 24 hours in desiccators with silica gel will remove ageing effects on the dry films before assessment. Evaluation of the type films is due within a week after their preparation.

c. Mercury substrate method:

Polymer solution and plasticizer are used to dissolve the medication. Solution A is agitated for 10-15 minutes to generate a homogeneous dispersion and poured onto a levelled mercury surface, topped with an inverted funnel to regulate the evaporation of solvents from the solution..

d. By using "IPM membranes"method:

Carbomer 940 polymer is added to a combination of water and propylene glycol and swirled for 12 hours in a magnetic stirrer in this process. Triethanolamine is to be used to neutralize and thicken the dispersion. Solubility in aqueous solution may be improved by using buffer pH 7.4 to form solution gels. For incorporation into IP membrane, gel is generated.

e. By using "EVAC membranes" method:

Polyethylene (PE) and ethylene vinyl acetate copolymer (EVAC) membranes may be employed as rate control membranes to construct the target transdermal treatment system.

Propylene glycol is used to make gel if the medication is insoluble in water. After the medication has

UNDER PEER REVIEW

been dissolved in propylene glycol, a neutralising solution containing 5% w/w sodium hydroxide will be added to the mixture. The gel-based medication is applied on a backing layer that covers the desired area. In order to create a leak-proof device, a rate-controlling membrane will be put over the gel and the borders will be sealed with heat.

f. Aluminum backed adhesive film method:

If the loading dosage is larger than 10 mg, the transdermal drug delivery method may create unstable matrices. Adhesive film supported by aluminum is a good option.

Using chloroform as a solvent is preferable since it is soluble in a wide range of medications and adhesives. Chloroform is used to dissolve the medicine, and then adhesive material is added and dissolved in the drug solution. Custom-madealuminum formers are coated with aluminum foil and the ends are sealed with cork blocks.

g. Preparation of TDDS by using PR liposomes

The carrier approach, using a film deposition process, is used to create the PR liposomes. It is possible to optimise the dosage by using a 0.1:2.0 ratio of the earlier reference medicine to lecithin in the formulation. In a 100 ml round bottom flask, 5mg of mannitol powder is added and the flask is swirled at 80-90 rpm for 30 minutes at 60-70°c to dry the mannitol at vacuum. After drying, the water bath is brought to a temperature of 20-30°C. 0.5ml of the organic solution is added to the round bottomed flask at 37°C, followed by the addition of further 0.5ml of the solution once the first aliquot has dried completely. Proliposomes loaded with drugs are put in a desiccator overnight and then sieved through a 100 mesh screen after the flask holding them has been linked to a lyophilizer. In order to properly characterise the powder, it must first be placed in a glass container and kept frozen.

h. Using a free filmmaking technique:

Casting on a mercury surface produces a cellulose acetate free film. Chloroform is to be used to make a 2 percent w/w polymer solution. Plasticizers are to be added at a 40% w/w polymer weight concentration. A glass ring placed over the mercury surface of a glass petri dish was filled with 5 cc of polymer solution. Placing an inverted funnel over the petri dish allows you to regulate the pace at

UNDER PEER REVIEW

which the solvent evaporates. After the solvent has completely evaporated, the film creation may be seen by looking at the mercury surface. A desiccator will be used to keep the dried film between two sheets of wax paper until it is needed. Changing the volume of the polymer solution may provide films of varying thickness.

KINETICS OF TRANSDERMAL PERMEATION[21-23]

Skin permeation kinetics are crucial for the effective development of transdermal therapeutic devices. Permeation through the skin is accomplished by following these steps:

1.The stratum corneum adsorbs the substance.

2. Drug penetration through the epidermis that is still alive.

3.The dermal papillary layer's capillary network takes up the medication.

4.Only if the medication has particular physiochemical qualities can this penetration occur.

5.Rate of skin penetration is determined by this formula.

$$\frac{dQ}{dt} = Ps\,(Cd - Cr) \quad \ldots \quad \ldots\ldots\ldots (1)$$

Skin penetrant concentrations may be found in two places: the receptor compartment (the human body) and the door compartment (the skin). The skin's total permeability to a penetrant is given by the coefficient Ps. According to the formula, the permeability coefficient is ***:***

$$P_s = \frac{D_{ss}K_s}{\text{----------}}$$

h_s

which is the partition coefficient for the transdermal therapeutic system or solution medium partitioning of the penetrant molecule on to the stratum corneum, Dss is an apparent diffusivity for a steady state diffusion of the penetrant molecule through a thickness of skin tissues, and hs is the total thickness of skin tissues. Under certain situations, the permeability coefficient Ps for a skin penetrant may be assumed to be the same. For a constant rate of drug penetration, Cd > Cr, i.e., the stratum corneum Cd concentration constantly and considerably exceeds the Cr concentration in the body, may be achieved from equation (1). The equation changes.

$$\frac{dQ}{dt} = P_s C_d$$

Skin penetration occurs at a consistent pace as long as the concentration of cadmium stays constant. Drug release from the device should occur at a rate Rr that is either constant or larger than the skin uptake Ra i.e. Rr >> Ra to maintain Cd.

Cd is maintained at a level equal to or larger than the equilibrium solubility of the medication in the stratum corneum Cs, i.e. Cd >> Cs, since Rr is greater than Ra. As a result, a maximum rate of skin penetration may be calculated using the following formula:

In other words, (dQ/dt)m = PsCs

The maximum rate of skin permeation is determined by the skin permeability coefficient PS and the equilibrium solubility in the stratum corneum CS, as shown in the equation above. As a result, stratum corneum seems to be a limiting factor in skin penetration.

TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS:

Many methods have been developed to modulate the rate of medication release and skin

UNDER PEER

permeability. There are four primary approaches to these technologies.[5,24] \Poly mermembrane \spermeation-controlled TDDSystems:

Metal laminate and rate-controlling polymeric membranes are used to protect the drug reservoir in this device. There is a rate-controlling polymeric membrane that restricts the release of medication molecules. As a rate-controlling membrane, it might be a microporous or nonporous polymeric membrane that has drug permeability. Applying a tiny layer of pressure-sensitive adhesive polymer (e.g. silicone) to the polymeric membrane's exterior surface provides a close interface between TDD systems and the skin. Transderm-Nitro system, Transderm-Scop system, Transderm-Catapres TTS system, Estraderm system, and Duragesic system are shown in Figure 3 Ex

TDD Systems Using Polymer Matrix Diffusion Control

Medicated discs are created by dispersing drug particles in a hydrophilic or lipophilic polymer matrix, and the resulting polymer is moulded into a specific surface area and a regulated thickness. An occlusive base plate with a drug-impermeable plastic backing holds the polymer disc holding the drug reservoir. This disc is then attached onto the base plate for final assembly. Adhesive polymer is placed to the patch's periphery to generate an adhesive rim that surrounds the medication disc in this method (Figure 4). Examples include Nitro-Dur and NTS systems..

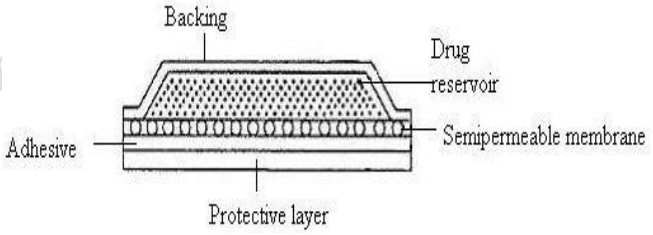

Figure 3: Transderm-Nitro system

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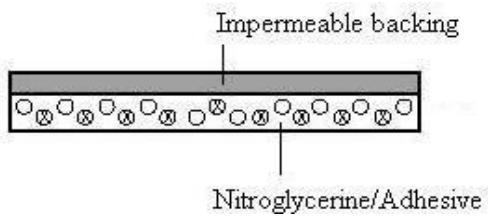

Figure 4: Nitro-Dur Transdermal System

In order to avoid the non-zero order drug release profiles, a polymer matrix drug dispersion-type TDD system may be adjusted to have the drug loading level altered in an incremental way, generating a gradient of drug reservoir along the diffusional channel through the multilaminate adhesive layer. (Figure 5). Deponitsystem, for example.

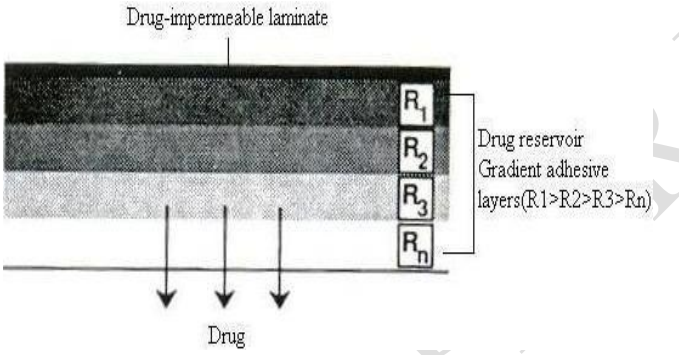

Figure 5: Drug Reservoir Gradient-Controlled TDDS

TDD Systems with Micro reservoir Dissolution Control:

As a hybrid of reservoir and matrix dispersion distribution methods, this sort of delivery system may be used. “First the drug solids are suspended in an aqueous solution of water-miscible drug solubilizer, e.g., polyethylene glycol, and then homogeneously dispersed in a lipophilic polymer by high shear mechanical force”[35], resulting in thousands of unbleachable microscopic drug reservoirs that are essentially impenetrable to water. It is promptly stabilised by instantly cross-linking the polymer chain in situ, which yields a medicated polymer disc with constant surface area and a defined thickness (Figure 6).

Nitrodisc is one example of this.

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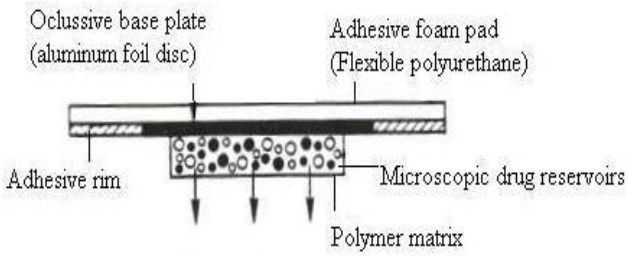

Figure 6: Micro reservoir Dissolution-Controlled TDDS

GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDS:

The following broad recommendations should be given to the patient. In order for the skin to return to its normal permeability and avoid irritation, it is necessary to rotate the location of application[(15)].

Clean, dry skin that isn't greasy or irritated is ideal for using TDDS. It should also be free of hair and not inflamed or damaged. Drug penetration may be accelerated if the skin is wet or damp.

Patch adhesion might be hindered by oily skin. Using a depilatory chemical or wet shaving may remove stratum corneum, which can alter the rate and degree of drug permeability. If hair is present, it should be properly clipped, not wet shaved.

Use of skin lotions should be avoided at the application site since they may modify the drug's partition coefficient by affecting the skin's moisture content.

The integrity of the system is jeopardised if the patient tampers with the TDDS in any way.

Removing the protective backing should be done with extreme caution so as not to scratch the skin. For about 10 seconds, the TDDS should be pushed firmly on the skin spot with the heel of the hand.

There should be no chance of the TDDS being rubbed off by clothes or movement when it is positioned in the right location. When taking a shower, bathing, or swimming, be sure to have TDDS on.

A TDDS should be worn for the specified term, then removed and replaced with a new system according to the manufacturer's recommendations.

After using a TDDS, the patient or caregiver should wash their hands thoroughly. It is important that the patient not wipe their eyes or lips when working with the device.

UNDER PEER REVIEW

The patient should seek reevaluation if a TDDS causes sensitivity or intolerance, or if excessive skin irritation occurs.

To prevent it from being reused, a used TDDS should be folded in half with the adhesive layer together. Dispose of the used patch in a way that is safe for children and pets.

A transdermal patch may be used. Skin irritation may be avoided by using a new application location each day. Suggested rotation is:

Upper right arm, upper right chest, upper right back

On Day 4: – Upper left breast – Upper left arm – Day 1.

PATCHES APPLIED TO THE TRANSDERMAL SURFACE:

When the patient is unable to take oral medicine (dysphagia) and requests an alternate form of drug administration, a transdermal patch is the best option.

Where dependable administration might help with pain management. Analgesic self-medication may be helpful for those unable to do so because of cognitive impairment or other reasons.

Transdermal patches are not used in the following situations:

When using a transdermal patch, avoid doing so because:

(1) Acute discomfort necessitates a treatment.

Rapid dosing is needed in this situation.

For patients requiring a dosage of less than 30 mg/24 hours, this product is appropriate[33,34].

THE ANALYSIS CHARACTERISTICS FOR EVALUATION

1. Research on interactions: [18 -19]

In the majority of pharmacological dosage forms, excipients are essential components. Excipient compatibility is a major determinant in the stability of a formulation, among other things. For a stable product, the excipients must be compatible with the medicine. This means that any potential physical or

UNDER PEER REVIEW

chemical contact must be detected, since this might influence the medication's bioavailability and stability. Compatibility studies are critical when formulating novel excipients that have never been utilised in prior formulations containing the active ingredient. Comparing physicochemical properties is a frequent method of conducting interaction studies in the fields of thermal analysis, FT-IR, UV, and chromatography.

Examples of this include melting endotherms, distinctive wave numbers (e.g. absorption maxima), and assay

2. The patch is 20 mm thick.

With a digital micrometre, several spots of the drug filled patch are measured and the average thickness and standard deviation are calculated to check that the patch is properly produced.

3. Weigh tuniformity[20]

Before testing, the produced patches must be dried at 60°C for four hours. The patch is to be divided into sections and weighed using a digital balance. The individual weights are used to compute the average and standard deviation.

4. Folding endurance[20]:

It is necessary to fold a strip of material until it breaks by cutting it evenly and folding it again in the same spot. How many times a piece of film could be folded without breaking was determined by its folding endurance rating.

5. Moisture content as a percentage[20]:

Each film is should be weighed and stored in a desiccator containing fused calcium chloride for 24 hours at room temperature. Once the films have rested for 24 hours, they should be weighed again and the

UNDER PEER REVIEW

moisture content determined using the procedure below.

[Initial weight-Final weight/Final weight]x100 = Percentage moisture content.

6.Amount of moisture absorbed: [20]

At room temperature for 24 hours, the films have to be stored in a desiccator containing potassium chloride in order to maintain a humidity level of 84%. After 24 hours, the films must be reweighed and the percentage of moisture absorption determined using the formula below.

[Final weight-Initial weight/Initial weight]x100 = Percentage moisture absorption.

7.Evaluation of the water vapour permeability (WVP)

Using the foam dressing approach, the air-forced oven may be substituted with a natural air-circulation oven to measure water vapour permeability. The WVP may be calculated using the formula below.

WVP=W/A

in terms of gm/m2 every 24 hours,

W is the quantity of vapour penetrated through the patch stated in gm/24hrs, and A is the surface area of the exposure samples expressed in m2.

8. Drug content[21]:

The patch is to be dissolved in a precise volume of a suitable solvent. Then, the solution is filtered through a filter media and the medication is analysed using the appropriate procedure (UV or HPLC technique). The average of three separate samples is shown by each value.

UNDER PEER REVIEW

(1). The dose unit test[22]:

Using a precise volumetric flask, a precisely weighed part of the patch needs to be chopped into tiny pieces, dissolved in an appropriate solvent, and sonicated for the total extraction of the medication from the patch. As the soltion cooled, the supernatant was diluted with a suitable solvent in order to achieve the appropriate concentration. Drug content per piece will be estimated after filtering through a 0.2 micron membrane filter and using an appropriate analytical method (UV or HPLC).

(2). Polariscope examination[22]:

The polariscope will be used to study the drug crystals in the patch during this test. To determine whether the patch contains crystalline or amorphous forms of the drug, a particular section of the piece must be placed on an object slide and the drug crystals seen a shear adhesion test:

The purpose of this test is to determine the adhesive polymer's cohesive strength. The molecular weight, degree of crosslinking, polymer composition, kind, and quantity of tackifier used may all have an effect. One side of the stainless-steel plate is covered with an adhesive coated tape, which is pulled in the opposite direction of the plate by a certain weight attached to the tape. The time it takes to remove the tape from the plate is used to gauge its shear adhesion strength. The higher the shear strength, the longer it takes to remove.

1. **Peel Adhesiontest**[22]:

An adhesive coating's peel adhesion is measured by the force needed to remove it from a test substrate in this test. The molecular weight of the adhesive polymer, as well as the kind and quantity of additives, affect the peel adhesion qualities of the glue. At a 180o angle, a single piece of tape is attached to a stainless-steel plate or a backing membrane of choice, and the force necessary to remove the tape is measured.

2.Thumb tack test: ([22])

The tackiness of an adhesive may be determined using this method. The tackiness of the glue may be determined simply by pressing the thumb on it.

3. Test of flatness: [23]

UNDER PEER REVIEW

Each film is to be sliced into three longitudinal strips, one from the centre, one from the left side, and one from the right side, at separate locations. By measuring the percent constriction of each strip, we were able to determine the amount of variation in length due to non-uniformity in flatness. 0 percent constriction is equal to 100% flatness.

4.Percent Elongation Break test: [24]

Using the formula below, the percentage elongation break may be computed by noting the length shortly before the break point.

Length-to-width ratio = L1-L2 x 100

L2

L1 is the ultimate length of each strip and L2 is the beginning length of each strip.

5.. Tack test with a rolling ball: [25]

Softness of a polymer linked to speech is measured by this method. When a 7/16-inch diameter stainless steel ball is released on an inclined track, it rolls down and comes into touch with horizontal, upward-facing adhesive on the other side of the platform. To measure tack, the distance the ball moves on the adhesive is indicated in inches.

6. Peel-tack test:

A speed of 12 inches per minute was used to extract the tape off the substrate at a temperature of 90oC. It is measured and recorded as tack value, which is given in ounces or grammes per inch width, depending on the adhesive and the substrate.

7. Probe Tacktest®[25)]

In this test, the glue is brought into contact with the tip of a clean probe that has a specific surface roughness. The probe is broken when it is removed mechanically. Tack is the force needed to draw the probe away from the adhesive at a constant pace, and it is measured in grammes.

UNDER PEER REVIEW

Splendidness: Weighed 3.14 cm2 patches were placed in 10ml of double-distilled water in a petri plate for absorption. The weight gain of the patch was monitored at predetermined intervals until it reached a constant value30.

The formula was used to determine the extent of swelling (S).

wt – W0 /W0 – 100 = s (percentage)

S is the percentage of swell. In this example, Wt indicates the patch's current weight, whereas Wo represents the weight of the patch at the beginning.

8.Studies of medication efficacy in a laboratory setting:

Patches may be tested for their release of the medicament using the paddle-over-disc technique (USP instrument V). Weigh, cut, and adhere dry films of defined thickness to the glass plate using an adhesive. Dissolution media (pH 7.4) was added to the glass plate and the equipment was brought to room temperature (32°C 0.5°C) before the glass plate was incubated. Once the paddle was at a distance of 2.5 centimeters from the glass plate, the motor was adjusted to 50 revolutions per minute. Samples (5-mL aliquots) may be extracted and examined by UV spectrophotometer or HPLC at suitable intervals up to 24 hours. A mean value may be derived by doing the experiment three times.

9.Studies on skin permeability in the laboratory[18])

The diffusion cell may be used to conduct an in vitro permeation research. Male Wistar rats weighing between 200 and 250 grammes have abdomen skin that is fully thickened. The dermal side of the skin was 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 was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant before starting the experiment. A thermostatically controlled heater was used to keep the cell's temperature at 32+ 0.5°C. The epidermis of the isolated rat skin piece should face upward into the donor compartment of

UNDER PEER REVIEW

the diffusion cell compartment. At regular intervals, a predetermined amount of fresh medium needs to be withdrawn from the receptor compartment and replaced with fresh media. For spectrophotometric or HPLC analysis, samples are to be passed through a filtering media. Stable-state values of drug permeation in mg cm-2 vs. time in hours were used to calculate flux, which was derived by dividing flux by the initial drug load and plotting it against time (mgcm-2).

10. Skin Irritation Research⊗[22)].

Healthy rabbits may be used for skin irritation and sensitization tests (average weight 1.2 to 1.5 kg). It is necessary to clean the rabbit's dorsal surface (50cm2), then shave it clean and clean it with rectified spirit before applying the representative formulations to the cleansed area. After 24 hours, the patch should be removed, and the skin should be examined and graded into five categories based on the degree of skin damage

11. Stabilitystudies⊗[18)]

For six months, the TDDS samples should be stored at 400.5°C and 755 percent RH in accordance with the ICH recommendations. At 0, 30, 60, 90, and 180 days, samples were taken and analysed appropriately for drug content.

LIMITATIONS IN THE SELECTION OF TDDDS:

The Physico-Chemical characteristics of the medicine must be desired before it may be delivered this way.

Not suited for medications requiring high plasma concentrations.

Drugs that cause skin irritation and contact dermatitis should not be used.

High-molecular-weight medications should not be taken here.

Drugs that undergo metabolic while passing through the skin are not suited for this method.

Because the skin is such an effective barrier to drug penetration, the Transdermal method cannot be used for many medications. Only a little amount may be given.

UNDER PEER REVIEW

CONCLUSION:

It's possible because of recent developments in technology and assimilation of medication to the site of action without rupturing the skin barrier.

The transdermal route is rapidly gaining popularity as a medication delivery method. It claims to be able to administer a broad range of pharmaceuticals without the need of needles in the future by using TDDS. Topical Transdermal medication delivery has evolved over time to include the determination of appropriate drug candidates and the development of passive and active technologies that have improved delivery, accuracy in drug dosage, and the ability to address individual requirements. Finding medications with adequate potency that can permeate the skin with an acceptable transdermal technology is a priority in the future development of transdermal patches and related delivery modalities. Meeting clinical needs, which cannot be adequately supplied in a cost-effective way through alternative delivery systems, is a major concern. The information presented here reveals that TDDS have significant potentials, since they may be used to build potentially deliverable pharmaceuticals from both hydrophobic and hydrophilic active substances. Polymer and biological interaction processes must be studied in more detail in order to improve this medication delivery technology. TDDS is a viable option for the next generation of drug delivery systems.

DISCLAIMER:

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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UNDER PEER REVIEW

UNDER PEER REVIEW