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Review Article

Development, Recent Inventions and Evaluation Techniques of Transdermal Drug Delivery System - A Review

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Abstract

Patch-based transdermal drug delivery offers a convenient way to administer drugs without the drawbacks of standard hypodermic injections relating to issues such as patient acceptability and injection safety. However, conventional transdermal drug delivery is limited to therapeutics where the drug can diffuse across the skin barrier. By using miniaturized needles, a pathway into the human body can be established which allow transport of macromolecular drugs such as insulin or vaccines. The human skin is a readily accessible surface for drug delivery. Skin of an average adult body covers a surface of approximately 2 m 2 and receives about one-third of the blood circulating through the body. Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body. The potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The present article development, recent inventions and evaluation techniques of transdermal drug delivery System.

1. INTRODUCTION

1.1 Development of Transdermal Drug Delivery System (TDDS)

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy. Designing and development of transdermal patches can be described as state of the art. The development of TDDS is multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy[1].

1.2 Transdermal Permeation

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration[2]. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows[3-4]:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

2. BASIC COMPONENTS OF TDDS

2.1 Polymer matrix / Drug reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status[5].

Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber[6]. Similarly Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethylcellulose for isosorbidedinitrate matrix[7-9]. The polymers utilized for TDDS can be classified as[2-3]:

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- **Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*[10].
- **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 cross linked polyethylene glycol[11], eudragits[12], ethyl cellulose, polyvinylpyrrolidone[13] and hydroxypropylmethylcellulose[14] are used as matrix formers for TDDS. Other polymers like EVA[15], silicon rubber and polyurethane[16] are used as rate controlling membrane.

2.2 Drug

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery[17-18]. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day)[19]. Table 1 enlists the currently available drugs for transdermal delivery. In addition drugs like rivastigmine for alzheimer's and parkinson dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

Table 1: Currently available medications for transdermal delivery

Approval year	Drug/Product name	Indication	Marketing company
1979	Scopolamine / Transderm-Scop	Motion sickness	Novartis Consumer Health (Parsippany, NJ, USA)
1981	Nitroglycerin / Transderm-Nitro	Angina pectoris	Novartis (East Hannover, NJ, USA)
1984	Clonidine / Catapres-TTS	Hypertension	Boehringer Ingelheim (Ridgefield, CT, USA)
1986	Estradiol / Estraderm	Menopausal symptoms	Novartis
1990	Fentanyl / Duragesic	Chronic pain	Janssen Pharmaceutica (Titusville, NJ, USA)
1991	Nicotine/Nicoderm, Habitrol, ProStep	Smoking cessation	GlaxoSmithKline (Philadelphia), Novartis Consumer Health, Elan (Gainesville, GA, USA)
1993	Testosterone / Testoderm	Testosterone deficiency	Alza (Mountain View, CA, USA)
1995	Lidocaine with epinephrine (iontophoresis) / Iontocaine	Local dermal analgesia	Iomed (Salt Lake City, UT, USA)
1998	Estradiol with norethidrone / Combipatch	Menopausal symptoms	Novartis
1999	Lidocaine / Lidoderm	Post-herpetic neuralgia pain	Endo Pharmaceuticals (Chadds Ford, PA, USA)
2001	Ethinyl estradiol with norelgestromin / Ortho Evra	Contraception	Ortho-McNeil Pharmaceutical (Raritan, NJ, USA)
2003	Estradiol with levonorgestrel / Climara Pro	Menopausal symptoms	Bayer Healthcare Pharmaceuticals (Wayne, NJ, USA)
2003	Oxybutynin / Oxytrol	Overactive bladder	Watson Pharma (Corona, CA, USA)
2004	Lidocaine (ultrasound) / SonoPrep	Local dermal anesthesia	Echo Therapeutics (Franklin, MA, USA)
2005	Lidocaine with tetracaine / Synera	Local dermal analgesia	Endo Pharmaceuticals
2006	Fentanyl HCl (iontophoresis) / Ionsys	Acute postoperative pain	Alza
2006	Methylphenidate / Daytrana	Attention deficit hyperactivity disorder	Shire (Wayne, PA, USA)
2006	Selegiline / Emsam	Major depressive disorder	Bristol-Myers Squibb (Princeton, NJ, USA)
2007	Rotigotine / Neupro	Parkinson's disease	Schwarz Pharma (Mequon, WI, USA)
2007	Rivastigmine / Exelon	Dementia	Novartis

[a]This list includes transdermal patches and delivery systems approved by the US Food and Drug Administration. Only the first approved product for a given drug or drug combination administered by a given delivery method is shown. Topical creams, ointments, gels and sprays are not included.

2.3 Permeation Enhancers:

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate[20]. Penetration enhancers interact with structural components of stratum corneum *i.e.,* proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability[21]. Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, combination of chemicals, which can act as penetration enhancers. Some of the permeation enhancers have been enlisted in Table 2.

2.4 Pressure sensitive adhesives:

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

Table 2: Permeation enhancers used for TDDS

Category	Example	Reference
Solvents	Methanol	22
	Ethanol	23
	Dimethyl sulfoxide	24
	Propylene glycol	25
	2- Pyrrolidone	26
	Isopropyl myristate	27
	Laurocapram (Azone)	28
Anionic surfactants	Sodium lauryl sulfate	29
Nonionic surfactants	Sorbitanmonolaurate	30
	Pluronic	31
Essential oils	Cardamom oil	32
	Caraway oil, Lemon oil	33
	Menthol	34
	d-limonene	35
	Linoleic acid	36

residue[37-38]. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs[39]. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physicochemically and biologically compatible and should not alter drug release[40].

2.5 Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient 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 occlusivity 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[41-42]. Examples of some backing materials are vinyl, polyethylene and polyester films.

2.6 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 skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*e.g.* paper fabric) or occlusive (*e.g.* polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates[38, 43].

2.7 Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir[14,44]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch[45-46].

3. PREPARATION OF DIFFERENT TYPES OF TRANSDERMAL PATCHES

Schematic diagram of manufacturing of drug in adhesive system of TDDS is shown in fig.1.Several system designs have been used in development and fabrication of TDDSs. The systems that have been introduced in market can be classified into following types [43-47].

3.1 Matrix Type Transdermal Patch(s)

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film[48-49]. Some examples of matrix patches prepared by solvent evaporation method mentioned in literature are given in Table 3. Commonly used polymers for matrix are cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxyl propylmethyl cellulose.

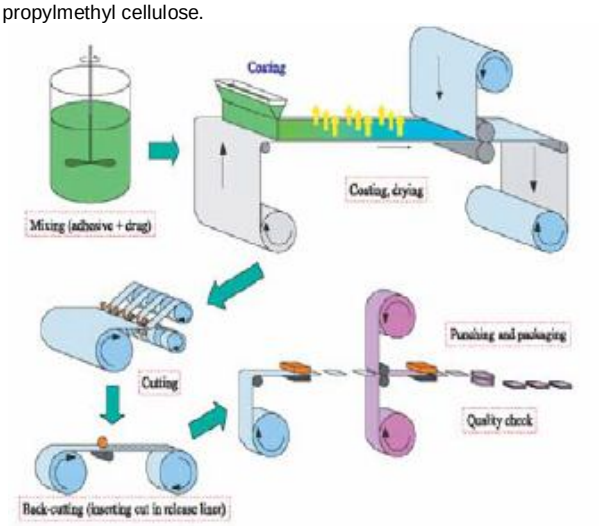

Fig. 1: Schematic diagram of manufacturing of drug in adhesive system of TDDS

Table 3: Examples of matrix patches prepared by solvent evaporation method reported in literature

Drug	Polymer	Solvent	Permeation enhancer	Plasticizer	Reference
Theophylline and salbutamol	PEG 400	Water	-	-	51
Salbutamol sulfate	Eudragit RL100	Isopropanol: water 6:4	Dimethyl sulfoxide, Isopropyl myristate, Tween80, Sodium lauryl sulfate with propylene glycol	-	24
Carvedilol	Ethylcellulose: Polyvinyl pyrrolidone and Eudragit RL100: Eudragit RS100	Chloroform	-	Di-n-butyl phthalate	13
Glibenclamide	Ethylcellulose : polyvinyl pyrrolidone	Chloroform	-	-	52
Naproxan	Eudragit RS100	Dichloromethane	PEG	Span 80	44
Nitrendipine	Eudragit RL100: HPMC and Eudragit RS100: HPMC	Dichloromethane Methanol	Carvone	Propylene glycol	14
Haloperidol	Eudragit NE 30D	Polyvinyl alcohol	-	-	53
Lorazepam	Eudragit RL PM	2- Propanol	Benzalkonium chloride, sodium lauryl sulfate	-	48

The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature[50]. The matrix system is exemplified by the development of Nitro-Dur®. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to

the skin and no interference of adhesive. Design of matrix type patch is shown in Figure 2.

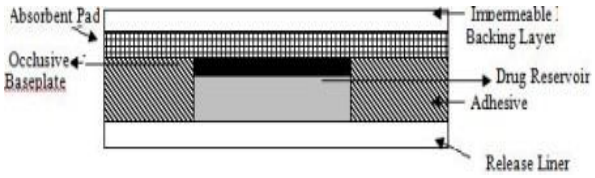

Fig. 2 Design of matrix type transdermal patch

3.2 Reservoir Type Transdermal Patch(s)

The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium (e.g. silicon fluids) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (e.g. ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate[54].

The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness of membrane. Hence, the choice of membrane material is dependent on the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per unit area of the device can be controlled. Mostly EVA, ethyl cellulose, silicon rubber and polyurethanes are used to prepare rate controlling membranes[1,55-57]. EVA is used most frequently to prepare rate controlling membrane in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting vinyl acetate content of polymer. Polyurethane membranes are suitable especially for hydrophobic polar compounds having low permeability through hydrophobic polymers such as silicon rubber or EVA membrane[58] as shown in figure 3.

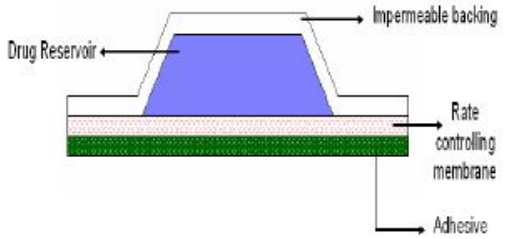

Fig. 3: Reservoir Type Transdermal Patch

3.3 Membrane Matrix Hybrid Type Patch(s)

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate[43] as shown in fig. 3. Examples of marketed preparations are Catapress® and Transderm Scop®.

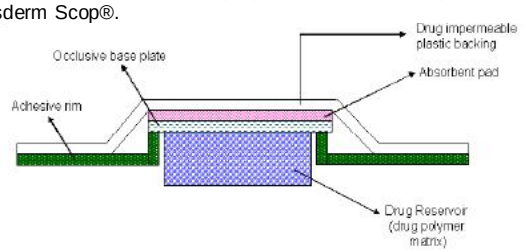

Fig. 4: Membrane matrix hybrid type patch

3.4 Micro-reservoir Type Transdermal Patch(s)

The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unleachable microscopic drug reservoirs (micro reservoirs). The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc ofs a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane[61-62]. This system is exemplified by development of Nitrodisc®. Micro reservoir type transdermal system is shown in Figure 5.

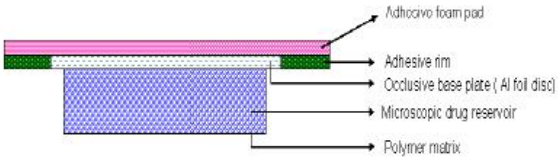

Fig. 5: Micro reservoir type transdermal patch

3.5 Drug in Adhesive Type Transdermal Patch(s)

The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane as shown in figure 5.

Some examples of suitable pressure sensitive adhesives are polysiloxanes, polyacrylates and polyisobutylene. These pressure sensitive adhesives are hydrophobic in nature and are prepared as solutions of polymer dissolved in organic solvents. Hence, this type of system is preferred for hydrophobic drugs as it is to be incorporated into organic solvent based hydrophobic adhesive[63].

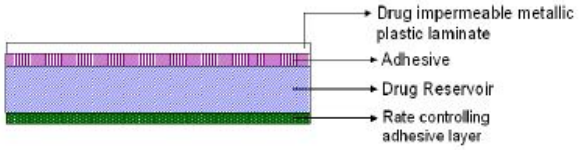

Fig. 6: Drug in adhesive type transdermal patch

4. PREVIOUS TECHNIQUES AND RECENT INNOVATIONS FOR ENHANCING TRANSDERMAL DRUG DELIVERY SYSTEM TDDS

4.1 Structure-Based Enhancement Techniques

4.1.1. Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation [64] . An adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the "stickyness" of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied again and again. Several pharmaceuticals usually combined with substances, like alcohol, within the patch to improve their penetration via skin in order to improve absorption.

Components of Transdermal Patches:

1. Liner - Protects the patch during storage. The liner should be removed before its use.

2. Drug-Drug solution is in direct contact with release liner.

3. Adhesive- It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g. - Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).

4. Membrane- It controls the release of the drug from the reservoir and multi-layer patches.
5. Backing- The film protects the patch from the outer environment [65-66].

4.1.2. Microfabricated Microneedles
These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the memberane. The systems consists of a drug reservoir and some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug.
Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.
Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.
- Biodegradable microneedles: Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- Hollow microneedles*:* Involves injecting the drug through the needle with a hollow bore [67].

4.1.3. Macroflux
These are devices having an area of around 8cm as well as 300 micro projections per cm2 with the length of individual micro projection less than 200Ï¼m. Three types of Macroflux have been designed. They include, Dry-Coated Macroflux system-this is used for short period delivery that consists micro projection array coated with medicament that adhered to a elastic polymer adhesive backing.

4.1.4. Metered-Dose Transdermal Spray (MDTS)
It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution . The use of MDTS reaches the sustained level and better permeation of the drug via skin. The MDTS has the following potential advantages:
- Improves delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture

4.2 Electrically-Based Enhancement Techniques

4.2.1 Iontophoresis
It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anesthesia [68-69].

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

4.2.3. Photomechanical Waves
Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

4.2.4. Electroporation
It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea [70-72].

4.2.5. Electro-Osmosis
To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

4.3 Velocity Based Enhancement Techniques

4.3.1. Needle-Free Injections
- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

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

4.4 Other Enhancement Techniques

4.4.1. Transfersomes
This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

4.4.2. Medicated Tattoos
Medical Tattoos is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

4.4.3. Skin Abrasion
This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules are generally known as Microscissuining.

4.4.4. Controlled Heat Aided Drug Delivery (CHADD) System
It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

4.4.5. Laser Radiation
This involves the exposure of the skin to the laser beam that results in the ablation of the stratum cornea without damaging the epidermis which remains in contact with it. Removal of the stratum cornea by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

4.4.6 Magnetophoresis
The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength [73].

5. EVALUATION PARAMETERS
The various evaluation parameters of TDDS are discussed below[74-79].

5.1 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 play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

5.2 Thickness of the Patch
The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

5. 3 Weight Uniformity
The prepared patches are to be 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.

5.4 Folding Endurance
A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5.5 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. Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

5.6 Percentage Moisture Uptake
Films are weighed and kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs, the films are reweighed and the percentage moisture uptake is determined from the below mentioned formula.
Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100.

5.7 Water vapour permeability (WVP) evaluation
Water vapour permeability is usually determined with foam dressing method. The air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula:
WVP=W/A where, WVP is expressed in gm/m2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m^2.

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

5.9 Uniformity of Dosage Unit Test
An accurately weighed portion of the patch is cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution is allowed to settle for about an hour, and the supernatant is suitably diluted to give the desired concentration with suitable solvent. The solution is filtered using 0.2m membrane filter and analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece is calculated.

5.10 Polariscope Examination
This test is performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is kept on the object slide and observed for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

5.11 Shear Adhesion Test
This test is performed for the measurement of the cohesive strength of an adhesive polymer which is 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 it 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 take for removal, greater is the shear strength.

5.12 Peel Adhesion Test
In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at an 1800 angle. No residue on the substrate indicates 'adhesive failure' which is desirable for transdermal devices. Remnants on the substrate indicate 'cohesive failure' signifying a deficit of cohesive strength in the coating.

5.13 Thumb Tack Test
This test is for tack property determination of adhesives. The thumb is simply pressed on the adhesive and the relative tack property is detected.

5.14 Flatness Test
Three longitudinal strips are cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

5.15 Percentage Elongation Break Test
The percentage elongation break is determined by noting the length just before the reak point, the percentage elongation can be determined from the below mentioned formula.
Elongation percentage = L1-L2 ×100 L2 .Where, L1is the final length of each strip and L2 is the initial length of each strip.

5.16 Rolling Ball Tack Test
This test measures the softness of a polymer. 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.

5.17 Quick Stick (Peel-tack) Test
In this test, the tape is pulled away from the substrate at 90ºC 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.

5.18 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.

5.19 In vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was 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.

5.20 In Vitro Skin Permeation Studies

In vitro permeation study is carried out by using diffusion cell on full thickness abdominal skin of male Wistar rats of weights 200 to 250g. Hair from the abdominal region is removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is replaced. Samples are 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 cm2) vs. time in hours and permeability coefficients is deduced by dividing the flux by the initial drug load (mg cm2).

5.21 Skin Irritation study

Skin irritation and sensitization testing is performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is cleaned and the hairs are removed from the clean dorsal surface by shaving and cleaning the surface by using rectified spirit and the representative formulations is applied over the skin. The patch is removed after 24 hr and the skin is observed and classified into 5 grades on the basis of the severity of skin injury.

5.22 Stability studies

Stability studies are conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0,30,60,90 and180 days. Drug content is analyzed.

6. CONCLUSION

These review work conclude that, older drugs by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. The patented innovations in transdermal drug delivery arena aim at these goals. However, the ultimate test that an innovative technique should pass relates to its successful performance in vivo.

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