Review Article

Transdermal Drug Delivery System: An Overview

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ABSTRACT
The conventional oral dosage forms have some drawbacks like poor bioavailability, first pass effect, frequent dosing which may be inconvenient to patients. The transdermal drug delivery system is one of the novel drug delivery system which overcome the problems arises from conventional dosage forms. A transdermal patch is an adhesive patch that has a coating of drug, the patch is placed on the skin to deliver particular amount of drug into the systemic circulation over a period of time. This review gives valuable information about the TDDS like its advantages, disadvantages, types of TDDS, different methods for formulation of transdermal patches, different evaluation of transdermal patches. Skin permeation enhancement techniques have been developed to improve the bioavailability the number of transdermal patches is formulated from past few decades. This painless drug delivery system is slowly gaining and will be one of the important drug deliveries in future.

Keywords: TDDS, bioavailability, first pass effect, systemic circulation, skin permeation.

INTRODUCTION

The Transdermal Drug Delivery System otherwise known as Transdermal patch which delivers a specific amount (dose) of the drug into the blood stream via skin, when they are directly applied on the intact skin. Now a days the oral route of administration is most commonly used to deliver the drugs in humans, but in this route the drawback such as drug degradation, first pass metabolism can occur. It may reduce the bio-availability of the active moiety in blood. The novel drug delivery systems were developed to rectify the difficulties in the oral drug delivery system. The TDDS is one of the novel drug delivery system here the drug will be deliver through the skin in the form of transdermal patch. Transdermal drug delivery system (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, at a controlled rate to systemic circulation. TDDS is one of the potential routes for local and systemic delivery of drug.[1, 2.]

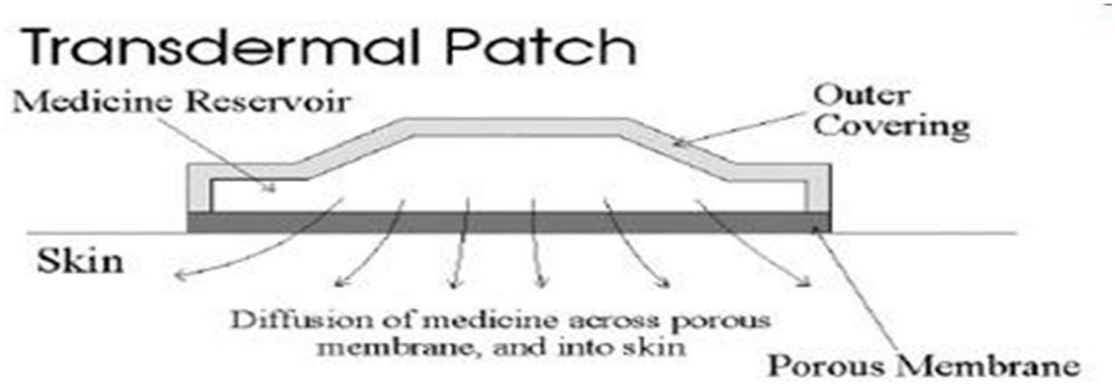

Fig. 1: Model for Transdermal Patch

Ideal Requirements of Transdermal Patches[3]

- The shelf life of the patches up to 2 years.
- The patch should be in small size (i.e. < 40cm2)
- Should provide convenient dose frequency (i.e. once a day or once a week)
- Cosmetically acceptable (i.e. clear, white colour).

Advantages Of TDDS Over The Conventional Dosage Forms: [1, 4, 5]

- ✓ In TDDS we can able to deliver the drug in to the blood stream with required quantity (dose) to produce therapeutic efficacy.
- ✓ Steady permeation of drug across the skin will maintain the drug level in serum, often a goal of therapy.
- ✓ It is one of alternative drug delivery system for patients who can't able to tolerate oral dosage forms.
- ✓ We can able to administer the drug in unconscious patients by using the TDDS.
- ✓ Drugs that irritate the GIT, produces nausea, vomiting and other GIT disturbances can be used in TDDS which is avoid the direct effects of the drug on stomach & intestine.
- ✓ Most convenient to use.
- ✓ Sustained drug delivery is possible.
- ✓ First pass metabolism has been estimated in TDDS
- ✓ The frequency of administration is minimized.
- ✓ The drug input can be terminated at any point of time by removing transdermal patch.
- ✓ Self administration is possible.
- ✓ TDDS are non-invasive which avoids many problems in parenteral therapy.
- ✓ It is one of the painless parenteral application drugs.
- ✓ Bioavailability can be improved.
- ✓ The drugs with short half life and narrow therapeutic index are the best candidates for TDDS.

Disadvantages of TDDS: [6, 7, 8.]

- o Some drugs penetrate into the skin slowly which may affect the efficacy of the treatment. Example: hydrophilic drugs.
- o The components in the TDDS formulation may produce skin irritation, local oedema & erythema.
- o Damage to a transdermal patch may cause the poor control on the release rate.
- o The barrier function of the skin changes from one site to another on the same person from person to person and with age.
- o Adhere of patches on the skin is very difficult.
- o It is not suitable for drugs with higher doses.
- o It is not suitable for the substance having higher molecular weight.
- o Drugs are metabolised by the skin and undergoes protein binding in skin are not suitable in TDDS formulation.

Properties that Influence Transdermal Delivery: [9, 10]

- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response.

Conditions in which the Transdermal Patches are not used: [11]

- o The transdermal patch is not suitable when, treatment of acute pain.
- o Where rapid dose irritation is required.
- o Where the required dose is equal to or less than 30 mg/24 hours.

Limitations [11]

- The ionic drugs are not suitable in TDDS formulation.
- TDDS can't achieve high levels in blood plasma.
- TDDS can't able to formulate with drugs having high molecular size.
- Pulsatile Delivery System is not possible.
- Drugs having direct dermatological effects are can't able to formulate as transdermal patch.

The above limitation may be rectified by using novel approaches like ionophoresis, electroporation & ultrasound etc.

Care taken while applying Transdermal Patch[5, 12]

- ❖ The part of the skin where the patch is to be applied should be properly cleaned.
- ❖ The patch should not be cut, because it destroys the drug delivery.
- ❖ The old patch should be removed before applying new patch.
- ❖ Don't touch the adhesive layer before application by hand itself or by other things it may produce changes in release rate & bioavailability.
- ❖ Then the patch is placed accurately to the site of application.

Basic components of TDDS

- Polymer matrix/drug reservoir
- Drug
- Permeation enhancer
- Adhesive
- Backing film
- Liner
- Plasticizer

Polymer matrix/Drug Reservoir[13, 14, 15]

- o It is the very important component in TDDS and control the release of drug from patch.
- o The polymers used in TDDS should be stable.
- o They should not produce any toxic effect either alone (or) with other excipients in TDDS formulation.
- o They shouldn't expensive one and it should be easily manufactured.
- o They should have good stability and more compatibility with drugs and other components of system.
- o The cross linked poly ethylene glycol, eudragit, ethyl cellulose, poly vinyl pyrolidine and hydroxyl propyl methyl cellulose are used as matrix formers in TDDS.
- o The polymers like EVA, poly urethane and silicone rubber are used as rate controlling membrane.

Table 1: List of Polymers Used In TDDS

Polymers used in TDDS		
Natural polymers	**Synthetic elastomer**	**Synthetic polymer**
• Cellulose derivative • Gelatin • Shellac • Starch • Waxes • Gums • Natural rubber • Chitosan etc.	• Poly butadiene • Hydrin rubber • Poly iso butylenes • Silicon rubber • Nitrile • Acronitryle • Neoprene • Butyl rubber etc.	• PVA • Poly vinyl chloride • Polyethylene • PVP • Poly acrylate etc.

Drug[16, 17]

The selection of drug is based on its properties like physiochemical as well as biological properties.

- ✓ Drug should have higher first pass metabolism.
- ✓ Drugs having narrow therapeutic window.
- ✓ Drugs with short half life.
- ✓ Drugs with frequent dosing.
- ✓ Low molecular weight moieties (<1000 Dalton)
- ✓ Drugs with low dose (mg/day).
- ✓ Low melting point substances (<200ºC)
- ✓ Drugs having affinity with both lipophilic and hydrophilic phases.
- ✓ Drugs without any dermatological effect are suitable for formulation as transdermal patch.

Permeation Enhancers

These are the substances which are reversibly changes the structure of stratum cornium and increase the permeation of drug from skin to blood stream. They are two types

1) **Chemical enhancers [accelerants, absorption promoters (or) permeation enhancers][18, 19]**

They act by

- Increasing drug permeability by reversible damage to stratum cornium.
- To consider the stratum cornium
- To increase partition coefficient of drug.

Table 2: List of Chemical Enhancers Used In TDDS

Chemical Enhancers	Examples
Solvents	➢ Water ➢ Methanol ➢ Ethanol ➢ Propylene Glycol ➢ Di-Methyl Acetamide
Terpenes	➢ Menthol ➢ Cardamom Oil ➢ Cinnamon Oil ➢ 18-Cineol ➢ Carvone
Pyrolidine	➢ N-Methyl 2-Pyrolidine ➢ Axone
Sulfoxides	➢ DMS ➢ Didecyl Sulfoxides
Fatty Acids & Esters	➢ Oleic Acid ➢ Linoleic Acid ➢ Lauric Acid ➢ Capric Acid
Surfactants	Anionic ➢ SLS ➢ Decodecyl Methyl Sulfomide ➢ Non-Ionic: ➢ Pluronic F127 ➢ Pluronic F68 ➢ Bile Salts: ➢ Sodium Taurocholate ➢ Sodium Deoxy Cholatte
Amides	➢ Dimethyl Acetamide ➢ Dimethyl Formamide
Miscellaneous	➢ Phosphor Lipids ➢ Amino Acid Derivatives ➢ Enzymes ➢ Urea

2) **Physical Enhancers[18]**

The following physical techniques have been used for enhancing the permeability of drug through skin.

- o Ionotophoresis
- o Electrophoresis
- o Sonophoresis
- o By using micro needles
- o Magnetophoresis
- o By using laser radiation

The combination of chemical enhancer and the magnetophoresis having greater enhancing power which is recently detected in lidocaine hydrochloride patch.

Adhesive[20]

- It is used to affix the patch on the skin.
- It should be adhere on the skin with light pressure applied by finger.
- It should be easily removed from the skin surface without leaving any residue.
- It should not produce any irritation.
- It should have excellent contact with the skin.

- Should compatible with other components in formulation.
- It should be allow permeating the drug freely from the patch

E.g. polyacrylates, poly iso butylenes, silicone derivatives.

Backing Laminate[21,22]

- ❖ It is used to protect the patch from outer environment.
- ❖ They must be chemically resistant.
- ❖ They won't allow to permeation of components in the patches.
- ❖ They have optimal elasticity, flexibility and tensile strength.
- ❖ It should have low water vapour transition rate.
- ❖ If a drug incorporated into a liquid (or) gel in the formulation, the backing material should be heat stable to allow fluid tight packing of drug reservoir (form-fill seal process). E.g. vinyl, poly ethylene and poly ester film

Liner[22]

It is used to protect the patch during the storage.

- ✓ It is removed during application of patch on skin.
- ✓ It should be chemically inert.
- ✓ It consists of two layers, one is base layer and other is release coating layer.
- ✓ The base layer may be occlusive (E.g. poly ethylene, poly vinyl chloride).
- ✓ The release coat layer made up of silicon (or) Teflon.
- ✓ The polyester foil and metallized laminate are also used as release liner.

Plasticizer[23]

- o They are used to provide plasticity to transdermal patch.
- o This also chemically inert and compatible will all other ingredients in the formulation. E.g. PEG, PG, tri-ethyl citrate, di-butyl phthalate.
- o Some of the plasticizer also act as a permeation enhancer E.g. propylene glycol

Types of Transdermal Patches

1) Single Layer Drug In Adhesive[1]

In these patches the adhesive layer holds the drug. In this system the adhesive layer not only used affix the patch on the skin, but also responsible for drug release. The temporary liner and the backing laminate are surround the adhesive layer.

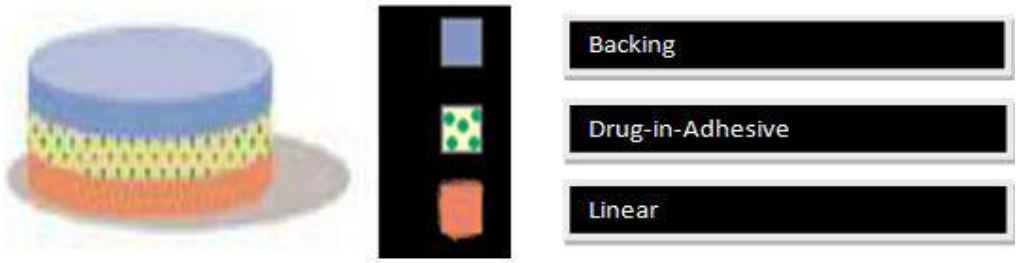

Fig. 2: Single-Layer Drug-In-Adhesive

2) Multi Layer Drug In Adhesive:[24]

The multi layer drug in adhesive type of patches is also similar to that of the single layer, but it contains two layers,

a) Immediate drug release layer
b) Controlled drug release layer

In this system also the adhesive layer is responsible for drug release. The patch also has a temporary liner and a backing laminate on its surrounding.

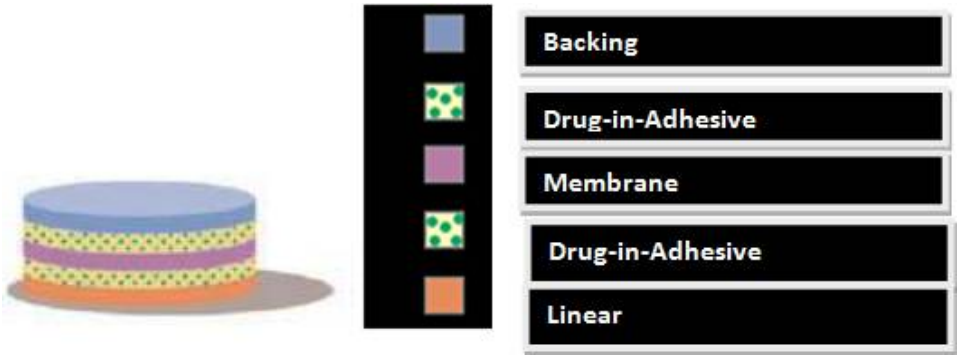

Fig. 3: Multi-Layer Drug-In-Adhesive

3) Vapour Patch[25]

In the vapour patches the adhesive layer not only used to affix the patch on the skin but also to release the vapour. The vapour patches are new types of transdermal patches on the market. The vapour patches release the essential oils for up to 6 hours, which is mainly used in cases of decongestion primarily. Other vapour patches for various purposes like reduce the quantity of cigarettes smoking and improve the quality of sleep are also available in market.

4) Reservoir System[24, 25]

Unlike single layer and multilayer drug in adhesive types of patches, the reservoir transdermal drug delivery system has a separate drug layer. In this reservoir layer (or) compartment the drug can be present in the form of solution, suspension, gel (or) dispersed in a solid polymer matrix. The reservoir compartment is lie between the backing laminate and the rate controlling membrane which follows zero order. The outer surface of the polymeric membrane can be coated with the hypoallergenic adhesive polymer which is compatible with the active moiety and other components in the formulation.

Fig. 4: Reservoir Transdermal Patch Construction

5) Matrix System[25]

a) Drug In Adhesive System

The drug is dispersed in the adhesive polymer to forms the drug reservoir. By using solvent casting (or) melting (incase of hot melt adhesives) the medicated adhesive polymer is spreads over on the backing laminate. After the formulation the un medicated adhesive polymer layers are applied in the top of the reservoir to protect the patch and provide great adhering power to skin.

Fig. 5: Drug-In-Adhesive Matrix System

b) Matrix Dispersion System

The drug is dispersed in hydrophilic (or) lipophilic polymer to produce a homogenous mixture. This is poured on the glass plates which are fabricated with the backing layer. Instead of applying the adhesive on the face of the reservoir, it is speeded along with the circumference to form a strip of adhesive rim.

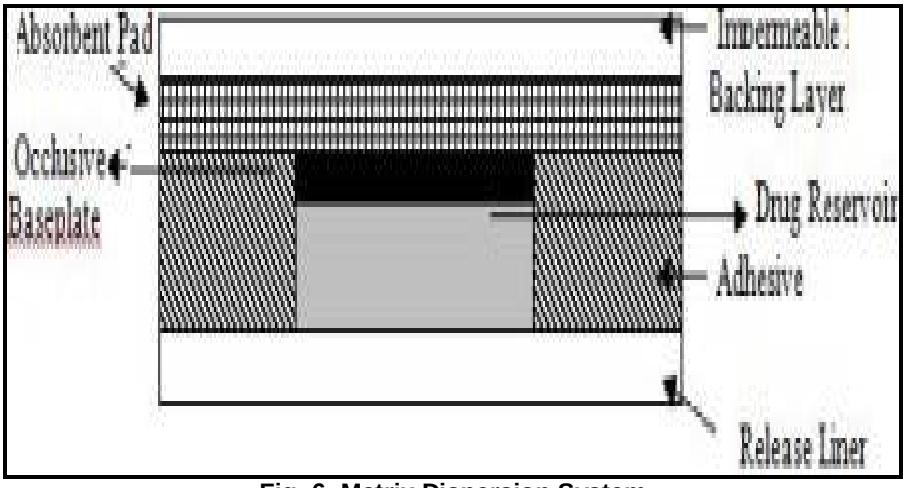

Fig. 6: Matrix Dispersion System

6) Micro Reservoir System[25, 26]

The micro reservoir system is the combination of the reservoir and matrix-dispersion type. The drug is first suspended in hydrophilic polymer solution to produce drug reservoir and disperse this solution homogeneously in a lipophilic polymer. They produce thousands of unreachable, microscopic spheres of drug reservoirs. These are thermodynamically unstable one. So this dispersion is stabilised quickly by the help of cross linking agents (cross linking polymers insitu by using cross linking agents).

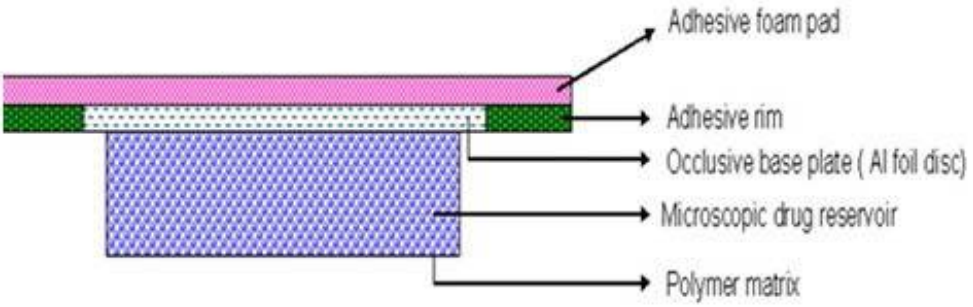

Fig. 7: Micro Reservoir System

Methods for Formulation of TDDS

1) Asymmetric TPX Membrane Method[26]

Step1

This membrane fabricated by using dry (or) wet inversion process. The required quality of TPX is taken and it is dissolved in a mixture of solvents and non-solvent additives. The temperature is maintained at 60ºC. The polymer solution will form which is kept aside for 24 hours at 40ºC. Then the polymer solution is cast on glass plate and the thickness is maintained by using gardener knife. After the casting, the film is evaporated for 30 seconds at 50ºC. Then the glass plates are immersed in coagulation bath in the temperature maintained at 25ºC. After 10 minutes the membrane is removed and it is dried on oven at 50ºC for 12 hours.

Step2

The drug is dispersed into the heat sealable polyesters film (1009, 3m) with a concave of 4cm diameter is used a backing laminate.

Step3

Then it is covered by a TPX [poly (4-methyl-1-pentene)] asymmetric membrane, finally it is sealed by using adhesive.

2) Circular Teflon Mould Method[26]

The polymer solution is prepared by simple dissolving the polymers in organic solvents. Calculated amount of drug is dispersed (or) dissolved in the half the volume of same organic solvents which is used to prepare polymer solution. The other half of the organic solvents holds the enhancer. Then the polymer solution, drug solution and the enhancer mixture are added together and the Di-N-butylpthalate is added to thtis mixture as a plastisizer. The above mixture is stirred for 12 hours and it is poured in to circular Teflon mould which placed on a levelled surface and covers the funnel in invert position over the mould to control the vaporisation of solvent in laminar flow (hood model). The air speed is maintained at 0.5 m/s For 24 hours. Then the dry films are stored for another 24 hours in desiccators contain silica gel at 25$\pm$ 0.5ºC. This type of film are evaluated which in one week of their formulation.

3) Mercury Substrate Method[27, 28]

In this method the drug is simply dissolved in polymer solution which is also contains plasticizer and other components. Then the solution mixture is stirred for 10-15 minutes which forms a homogenous dispersion and poured into a levelled mercury surface. The rate of evaporation is controlled by placing a funnel in an invert position over the surface.

4) By using “IPM membrane” method[29, 30]

The drug is dispersed in a mixture of solvents such as water and propylene glycol which already contains carbomer 940 polymers and stirred for 12 hours by using magnetic stirrer. Then add triethanolamine to above mixture causes the neutralisation and viscous solution (gel) the formed gel will be incorporated on the IPM membrane.

[Note: If the drug is insoluble in water (or) poor soluble in water means we can use buffer pH-7.4 as a solvent]

5) By using “EVAC Membrane” method[31]

It is majorly used to formulate the target transdermal drug delivery system. Other than ethylene vinyl acetate co polymer (EVAC) membrane, the poly ethylene (PE) membrane, 1% carbopal reservoir gel membrane gel membrane are also used for target transdermal drug delivery system. If the drug is water soluble, the water is used as solvent otherwise the propylene glycol is used for the formulation of gel. The drug is dissolved in solvent and carbopol resin is added to above solution which is neutralised by 5% sodium hydroxide solution. Then the gel is placed in the sheet of backing laminate. And finally the rate controlling EVAC membrane is placed over the gel. The leak proof device is obtained by sealing of the patch on its edges by using thermal energy.

6) Aluminium Backed Adhesive Film Method[31, 32]

For the drugs having the dose greater than the 20 mg for its therapeutic action, the aluminium backed adhesive film method is most suitable to formulate these drugs as transdermal patches. Chloroform is a choice of solvent because almost all drugs as well as other components in the TDDS formulation are easily soluble in chloroform. The polymers are dissolved in the chloroform alone (or) mixture of

solvent. Then the drug and other components are to the polymer solution, stirred well. After the casting the solution is poured in a aluminium foil with a proper size and shape and the evaporation rate of solvent is controlled by inverting a funnel over the plates (or) petridish.

7) By Using Free Film Method[32]

The free film of the cellulose acetate is prepared by casting on the mercury surface. 2% w/w polymer solution is prepared by using chloroform. plasticizer is accurately weighed (40%w/w of polymer weight) and added to polymer solution. 5ml of polymer solution placed on mercury sulphate in a glass petridish. After the evaporation of solvent the free film formulation on mercury surface was observed. The dry film is collected and it is stored between the sheets of wax paper in a desiccators. Free films can be developed with different thickness by changing the volume of polymer solution.

Table 3: Currently Approved USFDA Drugs for TDDS

Year	Generic (brand) names	Indication
1979	Scopolamine (Transderm Scop®)	Motion sickness
1984	Clonidine (Catapress TTS®)	Hypertension
1986	Estradiol (Estraderm®)	Menopausal symptoms
1990	Fentanyl (Duragesic®)	Chronic pain
1991	Nicotine (Nicoderm®, Habitrol®, Prostep®)	Smoking cessation
1993	Testosterone (Androderm®)	Testosterone deficiency
1995	*Lidocaine/epinephrine (Iontocaine®)*	Local dermal analgesia
1998	Estradiol/norethindrone (Combipatch®)	Menopausal symptoms
1999	Lidocaine (Lidoderm®)	Post-herpetic neuralgia pain
2001	Ethinyl estradiol/norelgestromin (OrthoEvra®)	Contraception
2003	Estradiol/levonorgestrel (Climara Pro®)	Menopause
2003	Oxybutynin (Oxytrol®)	Overactive bladder
2004	*Lidocaine/ultrasound (SonoPrep®)*	Local dermal anesthesia
2005	Lidocaine/tetracaine (Synera®)	Local dermal analgesia
2006	*Fentanyl/iontophoresis (Ionsys®)*	Acute postoperative pain
2006	Methylphenidate (Daytrana®)	ADHD
2006	Selegiline (Emsam®)	Depression
2007	Rotigotine (Neupro®)	Parkinson's disease
2007	Rivastigmine (Exelon®)	Dementia
2008	Granisetron (Sancuso®)	Chemo-induced emesis
2009	*Oxybutynin (Gelnique®)*	Overactive bladder
2010	Buprenorphine (Butrans®)	Chronic pain

EVALUATION

1) Physical Appearance[33]

All the formulated patches were visually inspected for colour, clarity, opaque, transparency, flexibility & smoothness.

2) Interaction Studies[33, 34]

Not only in TDDS almost all the dosage forms contain the exipients.These excipients must be compatible with the drug to avoid a loss of stabiliaty and reduce in bioavailability. The interaction studies are commonly carried out in thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physiochemical properties of drug excipients.

3) Thickness of Patch[35]

The thickness of patch is measured in a different points of the formulated patches by different points of formulated patches by using digital micrometer/micrometer screw gauge/ travelling microscope/vernier callipers. Determine the average thickness and standard deviation for the same ensure the thickness of the formulated patch.

4) Weight Uniformity[35]

Before done the weight uniformity test the formulated patches were dried at 60^{o}c for 4 hours. A specified area of the patch is to be cut in different parts of patch and it is weighed in digital balance. The average weight and standard deviation values are to be calculated from individual weights.

5) Folding Endurance[35]

A specific area of the patch is cut evenly and folds it repeatedly at the same place till it broke. The number of folding is noted before the breaking of patch. It will give the folding endurance.

6) Percentage Moisture Loss[35]

The formulated patches are weighed individually and kept in a desiccators containing anhydrous calcium chloride at room temperature for 24 hours. After the 24 hours the patches are weighed at a specific time interval until the constant weight is obtained. The percentage moisture loss is calculated by using following formulae

Percentage moisture loss = (Initial wt - final wt)/initial wt) X 100

7) Percentage Moisture Uptake[35]

Formulated patches are weighed individually and kept in a desiccators containing saturated potassium chloride or ammonium chloride. The RH is maintained as 84%. After 24 hours the patches are reweighed at a specific time intervals till the constant weight is attained.

Percentage moisture uptake = (final wt - initial wt)/initial wt) X 100

8) Water Vapour Permeability Evaluation(WVP)[36]

It is determined by natural air circulation over. It can be determined by following formulae;

WVP=W/A

WVP is expressed in g/m^2 per 24 hours.

Where,

W = amount of vapour permeated through the patch (gm/24 hour)

A = surface area of the exposure samples (m^2)

9) Drug Content Analysis[36]

An accurately weighed portion of formulated patches is dissolved in a suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 hours by using shaker incubator. Then the solution is sonicated and it is filtered. Then the filtrate is analysed by using suitable techniques such as UV (or) HPLC etc., with proper dilution.

10) Uniformity Of Dosage Unit[37]

An accurately weighed portion of formulated patches are cut in small pieces which are transferred in to a specific volume in volumetric flask. Dissolve it in a suitable solvent and sonicate for complete extraction of drug from patch and volume make up with solvent. The solution is allowed to settle down for an hour and the supernatant liquid was collected and performs a proper dilution to give desired concentration. It is filtered using 0.2 µm membrane filter and analysed by using suitable analytical techniques like UV, HPLC etc.

11) Percentage Elongation Break Test[39]

It is determined by calculating the length of the patch just before the break point.

Percentage elongation = (Final length-initial length)/initial lengthx100

12) Flatness[38]

A transdermal patch should posses a smooth surface which not constrict with time. It can be studied by flatness test. In this test, one strip is cut from centre and two strips are cutted from right and left sides. The length of each strip is measured. The variation in length is measured by percentage constriction. If the percentage constriction is 0%, it indicates 100% flatness.

% construction = (initial length -final length)/initial length x100

13) Thumb Tack Test[37]

It is one of the qualitative test applied for the determination of tack property of adhesives. Simply the thumb is pressed over the adhesive layer and the relative tack property is determined.

14) Rolling Ball Tack Test[40]

In this evaluation, the distance that stainless steel ball travels along an upward facing adhesive is measured. If the further travelling of ball, it indicates the adhesive is less tacky.

15) Quick Stick (Or) Peel Tack Test[40]

It is used for the measurement of the peel force required to break the bond between the adhesive and the substrate by pulling the tape (adhesive layer) away from substrate (stainless steel plate) at the speed of 12 inch/minute.

16) Probe Tack Test[40]

The measurement of the force which is required to pull the probe away from the adhesive lower at fixed rate.It is expressed in grams.

17) Polariscope Examination[37]

The specific surface area of pieces from the patch is cutted and placed on the objective slide to observe the drugs crystals. It is used to find out the drug whether in crystal form (or) amorphous form in the patch.

18) Shear Adhesion Test[37]

It is used to measure the cohesive strength of the adhesive polymer. Adhesive film is placed over a stainless steel and a specified amount is hung from the tape to affect it pulling in direction parallel to the plate. Shear adhesion strength is measured by calculating the it takes to pull the tape of the plate. If the longer time take for removed, the shear strength is greater.

19) Peel Adhesion Properties[37]

The peel adhesion is known the force required to remove the adhesive film from the substrate. The force required to pull a single coated tape is measured in this test. The coat is must applied to a substrate at 180ºC.

20) In-vitro Drug Release Studies[33]

The paddle over disc method (USP apparatus-V) can be utilised for the assessment of the drug release from the prepared patches. The dry film is cutted with specific size and the shape and it is weighed accurately. Then the piece of cutted patch is affixed in a glass plate by using adhesive. Then the plates are immersed in a 500ml of dissolution medium placed in the cylindrical vessel. The temperature is maintained at 30º $\pm$ 5º C and the paddle was set at a distance of 2.5cm from the glass plate at the bottom. RPM is fixed as 50. The samples are withdrawn at appropriate time intervals up to 24 hours, fresh medium is replaced during each sampling. Then the samples are analysed by UV (or) HPLC to detect the drug release.

21) In-Vitro Drug Permeation Studies[33]

It is done by using Franz diffusion cell. Abdominal skin with full thickness of male wistar rats (200-250 gm weight) is act as a semi permeable membrane. The membrane (abdominal skin) was isolated from rat abdomen and it is cleared properly, the tissues and the blood vessels present over the skin also removed. Then the skin is equilibrated in medium for 1 hour before starting the experiments and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of diffustant. The temperature of the cell was maintained at 32º $\pm$ 5º C using thermostatically controlled heater. The isolated rate spin is mounted between the donor receptor compartments of the cell, with the epidermis facing upward in to the compartment. The specified volume is taken out from the receptor compartment and it is repeated with fresh medium. Then the samples are filtered and analysed by UV (or) HPLC.

22) Skin Irritation Test[37]

Skin permeation and sensitization testing is performed by using healthy rabbits. The formulated patches are applied on the dorsal surface of the skin rabbits. Before affixing the patch the hair is removed from the skin of the rabbits. After 24 hours the skin is to be observed.

23) Stability Studies[33]

It is carried out according to ICH guidelines. The formulated transdermal patches are stored at 40º $\pm$ 0.5º C and 75 $\pm$ 5% RH for six months. The samples were withdrawn at 0,30, 60, 90 and 180 days and it analyse suitably for drug content.

CONCLUSION

Now a days the TDDS becoming a most widely used routes of drug administration directly in to blood stream without any pain and without rupturing skin membrane.This article gives valuable information about the formulation and evaluation of transdermal patches.We can overcome the challenges associated with current popular drug delivery by formulating the drug as transdermal patches.Some advanced techniques are also developed in TDDS, so it might be one of the best novel drug delivery system in future.

BIBLIOGRAPHY

1. Chein YW. Transdermal drug delivery and delivery system. In, novel drug delivery system. Marcel Dekkar, Inc., New York, 1992;50:031-381.
2. Chien YW. Novel drug delivery systems, drugs and the Pharmaceutical sciences. Marcel Dekkar, New York, NY. 1992;50:797.
3. Jalwal P, Jangra A, Dahiya L, Sangwan Y and Saroha R. A Review on Transdermal Patches. The Pharma Research. 2010;3:139- 149.
4. Guy RH. Current status and future prospects of transdermal drug delivery. Pharm Res. 1996; 13:1765-1769.
5. Guy RH, Hadgraft J and Bucks DA. Transdermal drug delivery and cutaneous metabolism. Xonobiotica. 1987;7:325-343.
6. Jain A, Mishra A, Nayak S and Soni V. Transdermal delivery of antihypertensive agents: A tabular update. International Journal of Drug Delivery. 2011;3:1-13.
7. Patel RP and Baria AH. Formulation and evaluation considerations of transdermal drug delivery system. International Journal of Pharmaceutical Research. 2011;3:1-9.
8. Bhargava T, Ramchandani U, Shrivastava SK and Dubey PK. Current trends in NDDS with special reference to NSAIDs. International Journal of Pharmacy and Bio Sciences. 2011;2: 92-114.
9. Brown MB and Jones SA. Hyaluronic acid: a unique topical vehicle for localized drug delivery to the skin. JEDV. 2000;19:308-318.
10. Bernar B and John VA. Pharmacokinetic characterization of Transdermal delivery systems. Jour. Clinical pharmacokinetics, 1994;26(2):21-34.
11. Shah S. Transdermal drug delivery technology revisited: recent advance, pharmainfo.net. 2008:6(5).
12. Chein YW. Transdermal controlled systemic Medication. New York and Basel, Marcel Dekkar Inc. 1987;159-176.
13. Keith AD. Polymer matrix considerations for transdermal devices. Drug Dev Ind Pharm. 1983; 9:605. Bromberg L. Cross linked polyethylene glycol networks as reservoirs for protein delivery. J Apply Poly Sci. 1996;59:459-66.
14. Verma PRP and Iyer SS. Transdermal delivery of propranolol using mixed grades of eudragit: Design and in vitro and in vivo evaluation. Drug Dev Ind Pharm. 2000;26:471-6.
15. Boretos JW, Detmer DE and Donachy JH. Segmented polyurethane: a polyether polymer. J Biomed Mat Res.1971;5:373.
16. Chung SJ. Future drug delivery research in south korea. J Controlled. Release. 1999;62:73-9.
17. Gordon RA and Peterson TA. Four myths about transdermal drug delivery. Drug Delivery Technology. 2003;3:1-7.
18. Williams AC and Barry BW. Penetration enhancers, Advanced drug delivery reviews. 2004; 56:603-18.
19. Karande P, Jain A, Ergun K, Kispersky V and Mitragotri S. Design principles of chemical penetration enhancers for transdermal drug delivery, Proceedings of the national academy of sciences of the United States of America. 2005;102:4688-93..
20. Walters KA. Transdermal drug delivery systems In:Swarbick K., Boylan J.C, eds. Encyclopedia of pharmaceutical technology. New York, Marcel Dekker Inc. 1997;253-293.
21. Godbey KJ. Improving patient comfort with non occlusive transdermal backings. American Association ofPharmaceutical Scientists. 1996;1-2.
22. Foco A, Hadziabdic J and Becic F. Transdermal drug delivery systems. Med Arch. 2004;58: 230-4.
23. Rao PR and Diwan PY. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. Pharm Acta Helv. 1997;72:47-51.
24. Malthiowitz ZE, Chickering DE and Lehr CM. Bioadhesive drug delivery systems; fundamentals, novel approaches and development, Marcel Dekkar, Inc, NewYork, Basel.
25. Aarti N, Louk ARMP, Russel OP and Richard HG. Mechanism of oleic acid induced skin permeation enhancement invivo in humans. Jour control Release 1995;37:299-306.
26. Bagyalakshmi J, Vamsikrishna RP, Manavalan R, Ravi TK and Manna PK. Formulation development and invitro and invivo evaluation of membrane moderated transdermal systems of ampicilline sodium in ethanol: pH 4.7 buffer solvent system AAPS Pharm Sci Tec. 2007;8: Article7.
27. Baker W and Heller J. Material Selection for Transdermal Delivery Systems In Transdermal Drug Delivery: Developmental Issues and Research Initiatives. J Hadgraft and R.H.Guys, Eds. Marcel Dekker, Inc New york 1989;293-311.

28. Al- Khamis K, Davis SS and Hadgraft J. Microviscosity and drug release from topical gel formulations. Pharm Res. 1986;3:214-217.
29. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum. 1980;14:3860-3865
30. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. Int J pharm. 1996;132:71-79. Deo MR, Sant VP, Parekh SR, Khopade AJ and Banakar UV. Proliposome-based Transdermal delivery of levonorgestrel. Jour Biomat Appl. 1997;12:77-88.
31. Yan-yu X, Yun- mei S, Zhi-Peng C and Qi-nerg P. Preparation of silymarin proliposomes; A new way to increase oral bioavailability of silymarin in beagle dogs. Int pharm. 2006;319:162-168.
32. Crawford RR and Esmerian OK. Effect of plasticizers on some physical properties of cellulose acetate phthalate films. J Pharm Sci. 1997;60:312-314.
33. Singh J, Tripathi KT and Sakia TR. Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev Ind Pharm. 1993;19:1623-1628.
34. Wade A and Weller PJ. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association. 1994:362-366.
35. Rhaghuram reddy K, Muttalik S and Reddy S. Once daily sustained- release matrix tablets of nicorandil: formulation and invitro evaluation. AAPS Pharm Sci Tech. 2003;4:4.
36. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm Sci. 2006;68:179-184
37. Aarti N, Louk ARMP, Russsel OP and Richard HG. Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. Jour control Release 1995;37:299-306.
38. Wade A and Weller PJ. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association. 1994;362-366.
39. Lec ST, Yac SH, Kim SW and Berner B. One way membrane for Transdermal drug delivery systems / system optimization. Int J Pharm. 1991;77:231 -237.
40. Vyas SP and Khar RK. Targetted and controlled Drug Delivery Novel carrier system1st Ed., CBS Publishers and distributors, New Delhi. 2002;411-447.