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Review Article

A review on current scenario of transdermal drug delivery system

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ABSTRACT

Transdermal delivery system offers an alternative route for administering drugs that by passes the gut and may be a more convenient, safer and non-invasive mean for delivery of drugs especially in case of long-term use. The main objective of the present review was to describe the different categories of drugs used for the preparation of transdermal patches, methods and their applications. Transdermal patch or Adhesive patch used to deliver a drug in controlled release manner through the skin over a period of time. Mainly transdermal patches can be prepared for the different category of drugs such as Analgesics and antipyretics, anti-diuretics, anti-diabetics, anti-asthmatics, antihypertensive, Local Anesthetics and antibiotics. Types of Transdermal patches which include Matrix type, Membrane type, Reservoir type, Microreservoir type. This review article also emphasize most of the technologies involved in better permeation through skin into an effective drug delivery system. Finally concluded that the present review gives the full description about transdermal drug delivery system to maintain the drug levels in blood stream in controlled manner.

Keywords: Transdermal patches; matrix diffusion system; anti-asthmatic drugs; permeation enhancers; Iontophoresis; Electroporation and ultrasound.

INTRODUCTION

Controlled Release dosage forms provides continuous release of active ingredients at a predetermined rate and for a predetermined time. Majorly these formulations are designed for oral administration, however recently such devices have been introduced for Transdermal application. The main objective for the development of this system is to furnish extended duration of action and thus assure patient compliance.

Transdermal drug delivery systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drugs, through the skin, at a controlled rate to the systemic circulation (Jain NK, 2007). Transdermal patches provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding firstpass metabolism. Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application or to have an effect after distribution through the circulatory system (J.Ashok kumar et al., 2010). Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy (Irene Hong et al., 2010).

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Basic Components of TDDS

1. Polymer matrix / Drug reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device (Jain NK, 2007)

Examples:

Natural polymers: Cellulose derivatives, zein, shellac, proteins.

Synthetic Elastomers: Poly butadiene, Polysiloxane, silicone rubber.

Synthetic polymers: Polyvinyl alcohol, polyamide, polyurea

2. Drug

Drug is in direct contact with release liner. For the successful development of transdermal drug delivery, the drug should posses some properties. (Jain NK, 2007).

Physicochemical properties

1. Molecular weight of drug should be less than 1000 daltons.
2. Drug should have affinity for both lipophilic and hydrophilic phases.
3. Drug should have low melting point.

Biological properties

1. Drug should be potent with a daily dose of few mg/ day.
2. Half life of the drug should be short.

3. Drugs which degrade in the G.I Tract are suitable for transdermal drug delivery.
4. Drug should not induce irritation. Examples: Nicotine, Methotrexate and Estrogen.

3. Permeation enhancers

These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. (Jain NK, 2007).

Solvents – Increase penetration by swelling the polar pathway. Examples: Methanol, Ethanol.

Surfactants - Enhance polar pathway transport especially hydrophilic drugs. Examples: Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

Bile salts: sodium taurocholate, sodium deoxycholate.

4. Pressure sensitive adhesive (PSA)

Serves to adhere the patch to the skin for systemic delivery of drug. (Jain NK, 2007). Examples: Acrylates, Polyisobutylene, Silicones.

5. Backing laminate

Protect patch from outer environment (J.Ashok kumar et al., 2010). Examples: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.

6. Release liner

Protects the patch during storage (J.Ashok kumar et al., 2010). Examples: polyester film.

Advantages of Transdermal Drug Delivery System (TDDS)

- Avoidance of 'first-pass' metabolism of drugs.
- Reduced plasma concentration levels of drugs, with decreased side effects.
- Reduction of fluctuations in plasma levels of drugs.
- Utilization of drug candidates with short half-life and low therapeutic index.
- Easy elimination of drug delivery in case of toxicity.
- Reduction of dosing frequency an enhancement of patient compliance (Snigdha bharadwaj et al., 2011)

Limitations

- Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting cannot given by this route due to their low solubility both in water and fat (Snigdha bharadwaj et al., 2011).

APPROACHES FOR DEVELOPMENT OF TRANSDERMAL PATCH

1. Polymer Membrane Permeation controlled system

In this, the drug reservoir is sandwiched between a drug impermeable backing laminate and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an viscous liquid medium e.g. silicon fluid. The rate controlling membrane can be micro porous or nonporous polymeric membrane.

This technology has also been applied to the development of transdermal drug delivery Systems for the rate controlled percutaneous absorption of prostaglandin derivatives (Chein Y.W., 2007, Kamal saroha, 2011).

Marketed systems

- Transderm-Nitro system for once a day.
- Transderm-Scop system- 3 days medication.
- Catapres- TTS – for weekly treatment

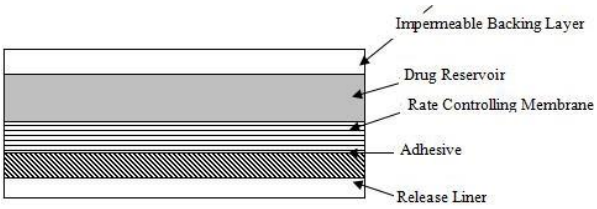

Figure 1: Polymer Membrane Permeation controlled system

2. Adhesive diffusion controlled system

In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non-medicated rate controlling adhesive polymer of constant thickness are applied. 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 (Chein Y.W., 2007, Kamal saroha, 2011).

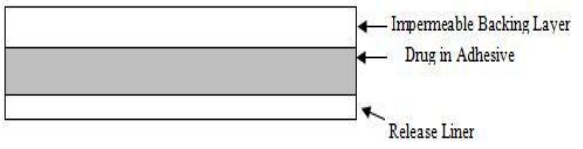

Figure 2: Adhesive diffusion controlled system

Marketed devices

- Climara
- Nicotrol
- Deponit

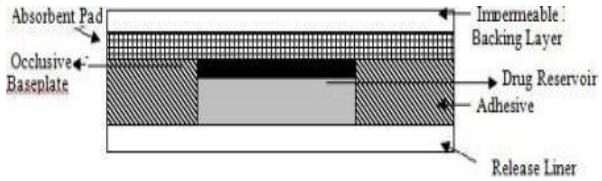

Figure 3: Polymer matrix diffusion controlled system

3. Polymer matrix diffusion controlled system

In this drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and medicated polymer is then molded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc, the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc (Chein Y.W., 2007, Kamal saroha, 2011).

Marketed System

- Nitro-Dur
- Minitran
- Nitro glycerine

4. Microreservoir system

This system is combination of reservoir and matrix dispersion type. In this the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogenously in lipophilic polymer, by high shear mechanical force to form unleachable microscopic spheres of drug reservoir (Chein Y.W., 2007, Kamal saroha, 2011).

Marketed system

- Nitrodisc

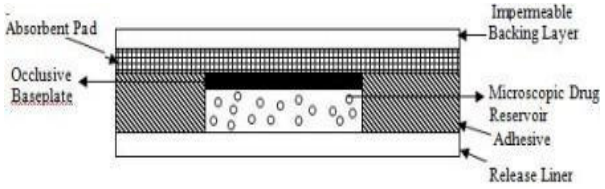

Figure 4: Microreservoir system

EVALUATION OF TRANSDERMAL PATCHES

Evaluation studies are more important in order to ensure their desired performance and reproducibility under the specified environmental condition.

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

Physicochemical Evaluation

Thickness: The thickness of transdermal film is determined by travelingc microscope, dial gauge, screw gauge or micrometer at different points of the film (Kamal saroha, 2011, Aggarwal G, 2009).

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight (Kamal saroha, 2011, Aggarwal G, 2009).

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution (Kamal saroha, 2011, Aggarwal G, 2009).

Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test (Kamal saroha, 2011, Aggarwal G, 2009).

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula (Kamal saroha, 2011, Aggarwal G, 2009).

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \text{ X } 100$$

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below (Kamal saroha, 2011, Aggarwal G, 2009).

$$\%\text{Moisture uptake} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \text{X } 100$$

Flatness: For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness (Kamal saroha, 2011, Aggarwal G, 2009).

$$\% \text{ Constriction} = \frac{I_1 - I_2}{I_1} \text{X } 100$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

Folding Endurance: Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value (Kamal saroha, 2011, Aggarwal G, 2009).

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted (Kamal saroha, 2011, Aggarwal G, 2009).

The tensile strength can be calculated using the following equation.

$$\text{Tensile strength} = F/a.b\ (1+L/l)$$

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point.

Water vapor transmission studies (WVT): weigh one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch (Kamal saroha, 2011, Aggarwal G, 2009).

$$WVT = W/ST$$

W is the increase in weight in 24 h; S is area of film exposed (cm^2); T is exposure time.

Microscopic studies*:* Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope (Kamal saroha, 2011, Aggarwal G, 2009).

Thumb tack test: It is a qualitative test applied for tack property determination of adhesive. The force required to remove thumb from adhesive is a measure of tack (Kamal saroha, 2011, Aggarwal G, 2009).

Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive which is expressed in inch (Kamal saroha, 2011, Aggarwal G, 2009).

Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min which is expressed in ounces or grams per inch width (Kamal saroha, 2011, Aggarwal G, 2009).

Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack and it is expressed in grams (Kamal saroha, 2011, Aggarwal G, 2009).

In vitro release studies

There are various methods available for determination of drug release rate of TDDS (Aggarwal G, 2009).

- The Paddle over Disc
- The Cylinder modified USP Basket
- The reciprocating disc
- Diffusion Cells

Franz Diffusion Cell and its modification Keshary-Chien Cell

In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid *i.e.,* buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically.

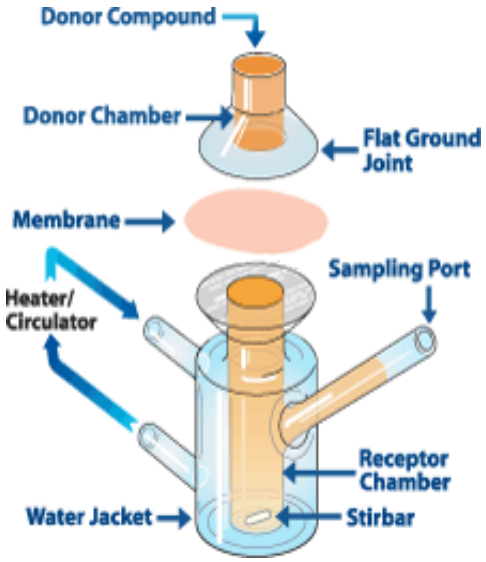

Figure 5: Biochambered donor- receptor compartment model

In vitro permeation studies

It is carried out on wistar rats by using diffusion cell. The isolated rat skin piece is to be mounted between

the compartments of the diffusion cell, with the epidermis facing upward in to the donor compartment. Samples are removed from the receptor compartment at regular intervals and an equal volume of fresh medium is to be replaced samples are to be filtered and can be analysed spectrophotometrically or HPLC (Singh J, et al., 1993).

Skin irritation studies: This testing can be performed on healthy rabbits and the formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is classified in to 5 grades on the basis of the severity of skin injury (Aarti n et al., 1995).

Stability studies: The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations.The TDDS samples are stored at 40±0.5^{o}c and 75±5%RH for 6 months.The samples are withdrawn at 0, 30, 60, 90 and 180 days and analysed for drug content (Singh J, et al., 1993).

MECHANISM OF DRUG PERMEATION

The outer layer of skin named stratum cornea, acts as a physical barrier to those substance that come in contact with the skin membrane. Stratum cornea consists of phospholipids, cholesterol, sulphate, neutral lipids, protein (about 40%) which is mainly keratin.In Transdermal drug delievery system the components like liners, adherents, drug reservoirs, drug release membrane etc. play a vital role in the release of the drug via skin.By diffusion process, the drug enters in the blood stream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow (Main Pankaj et al., 2011).

CURRENTLY AVAILABLE TRANSDERMAL PATCHES

Hormone Patches

There are 5 brand (Alora, Climara, Estraderm, Menostar, and Vivelle-dot) and 1 generic (Mylan) transdermal patches containing estradiol.In addition, 3 patches that contain estrogen in combination with progesterone (Climara-Pro, CombiPatch, and OrthoEvra, Ortho-McNeil [estradiestradiol and levonorgestrel, estradiol andnorethindrone acetate, and norelgestromin and ethinyl estradiol, respectively]) are currently on the market. There is one brand of testosterone available in this dosage form (Androderm) (Irene Hong et al., 2010)

Nicotine Patches

Nicotine replacement therapy is available in 2 brand transdermal patches (Habitrol, NicoDerm) (Irene Hong et al., 2010).

Nitroglycerin Patches

Various brand and generic formulations of transdermal nitroglycerin patches are available. Brand products include Minitran, Graceway, and Nitro-Dur (Irene Hong et al., 2010).

Analgesic Patches

There are 5 brand name transdermal patches available for treatment of pain: diclofenac (Flector,), fentanyl (Duragesic, IONSYS), lidocaine (Lidoderm), and lidocaine/tetracaine (Synera) (Irene Hong et al., 2010).

Miscellaneous

Clonidine, an alpha-2 agonist indicated for treatment of hypertension, is available in a transdermal delivery system known as Catapres TTS.

Rivastigmine is manufactured as a transdermal patch under the trade name Exelon.It is approved for use in the treatment of mild to moderate dementia associated with Alzheimer's or Parkinson's disease.

Selegiline, available in the transdermal formEmSam (Mylan), is indicated for the treatment of major depressive disorder.

Oxybutynin, available transdermally under the trade name Oxytrol (Watson), is used to treat overactivebladder.

Methylphenidate is available transdermally as DaytranaIts indication is the treatment of attention deficit hyperactivity disorder (ADHD) (Irene Hong et al., 2010).

CURRENT ASPECTS IN TRANSDERMAL SYSTEM

Optimizing the passage of medicine through skin is of high importance to modern therapy.Penetration enhancement can be done by Transfollicular release; using vesicles such as

Liposomes, Niosomes, Transfersomes, Ethosomes and active means electrical methods such as Iontophoresis, Electroporation, Sonophoresis, Microneedles (Cristina Dinu Pirvu et al., 2010).

Electrically-Based Enhancement Techniques

Iontophoretic delivery

Iontophoresis refers to the delivery of drugs across the skin by means of an electric field. By having two electrodes placed on the skin, drugs at the electrodes will start to migrate through the skin once a voltage is supplied to the electrodes.

Three main physical mechanisms are involved

- Electrophoresis: Charged species are driven from the electrodes as a result of the electric field.
- Flow of current increases the permeability of the skin.

Table 1: Research on transdermal patches of model drugs

S.No.	Drug	Category	Polymers	Method
1.	Tolterodine (Vinay Pandit et al, 2009)	Antimuscarinic agent	Ethylcellulose, Carbopol, HPMC	Solvent casting method
2.	Glipizide (Srinivas Mutalik et al., 2006)	Anti diabetic agent	EC, PVP, Eudragit	Mercury substrate method
3.	Nicorandil (V G Jamakandi et.al, 2009)	Antianginal agent	HPMC, PEG	Solvent casting method
4.	Lornoxicam (K. Kavitha et al., 2011)	NSAID	HPMC, EC, PEG	Solvent evaporation method
5.	Atenelol and metaprolol (S S Agrawal et al., 2007)	Anti hypertensive agent	HPMC, PVP, Ethyl cellulose	Circular Teflon method
6.	Chlorpheneramine maleate (Vlassios Andronis et al., 1995)	Antihistamine	PVP, Cellulose acetate, Ethyl cellulose	EVAC membrane method
7.	Diltiazem (P. Rama rao., 1999)	Antihpertensive agent	Ethyl cellulose, PVP	Mercury substrate method
8.	Celecoxib (S Jayaprakash et al., 1997)	NSAID	HPMC, Methyl cellulose, PVP	Mecury substrate method
9.	Carvedilol (Yuveraj singh tanwar et al., 2010)	Antihypertensive agent	Methyl cellulose, HPMC, Eudragit	Solvent evaporation method
10.	Glibenclamide (S Sridevi et al., 2000)	Antidiabetic agent	Polymethyl methacrylate, Ethyl cellulose	Mecury substrate method
11.	Haloperidol (R Sadashivaiah et al., 2008)	Anti psychotic agent	Ethyl cellulose, PVP	Solvent evaporation
12.	Ketoprofen (Barhate et al., 2009)	NSAID	Eudragit, HPMC	Mercury substrate method
13.	Proponalol (Krishna Murthy., 2008)	Antihypertensive agent	EC, Eudragit, cellulose acetate	Film method
14.	Tramadolol hydrochloride (Anil J Shinde., 2008)	NSAID	HPMC, Eudragit	Film casting method
15.	Diclofenac (Jadhav R.T et al., 2009)	NSAID	PVA, PVP, EC	Solvent evaporation
16.	Metaprolol tartarate (Meenakshi Bharkatiya et al., 2009)	Antihypertensive agent	Eudragit	Mercury surface method
17.	Meloxicam(Manish kumar et al., 2010)	Antihypertensive agent	PEG	Solvent casting method
18.	Rolipram (Jonathan Hadgraft et al., 1990)	Antidepressant agent	Isopropyl myristate	Free film method
19.	Ketotifen fumerate (A. Shivaraj et al., 2010)	Antiasthmatic agent	HPMC, EC, Eudragit	Solvent casting method
20.	Indapamide (G S Sanap et al., 2008)	Antihypertensive agent	HPMC, EC	Solvent casting method

- Electroosmosis: The established potential difference between the electrodes give rise to an electroosmotic flow (Niclas Roxhed., 2010).

Marketed system

GlucoWatch, a wrist-worn device.

Sonophoresis

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

- Ultrasound is used to treat patients with local Muscoskeletol inflammation using topically applied steroids.
- More recently, ultrasound was explored for chemical activation of drugs for treatment of cancers (sonodynamic therapy).
- Further, ultrasound energy was reported to enhance effects of thrombolytic agents such as urokinase (Ashok k.Tiwary et al., 2007).

Marketed system

Sono Prep- for Lidocaine administration.

Electroporation delivery

A biologically active agent can be introduced into cells by injecting it and applying an electric field to that region. This causes electroporation prior to, simultaneously and/or subsequently to injection of agent. In the first technique, one of the injector was donor electrode and the other injector was the return or counter electrode. The second technique comprised of injectors serving the purpose of donor electrodes. The first technique utilized one injector for applying an electric field to the surface and the other injector was in contact with the tissue and provided electric current in conjunction with one or more electrodes.

Electro-poration can be associated with iontophoresis in order to increase permeability to peptides (vasopressin, calcitonin, LHRH hormone) (Cristina Dinu Pirvu et al., 2010).

Microneedles technology

Microneedle, a new type of delivery method where arrays of miniaturized needles are used to penetrate the skin layer. Since the needles are short, they do not reach the nerve-rich regions of the lower parts of the skin. A gel filled compartment fitted with micro needles was found to be capable of opening the skin permeation pathways up to a depth of 150 µ when applied with pressure. It further included a rate control mechanism to regulate rate and extent of drug delivery and an adhesive thus, immobilizing the microneedles during its insertion into the skin. The microneedles had a blunt, flat tip and a length sufficient to penetrate the stratum corneum without piercing the stratum corneum**.**The needles dissolve within minutes, releasing the trapped cargo at the intended delivery site (Niclas Roxhed., 2010).

Vesicular carriers

Liposomes

These are colloidal particles formed as concentric biomolecular layers that are capable of encapsulating drugs. Their delivery mechanism is reported to be associated with accumulation of the liposomes and associated drug in the stratum corneum and upper skin layers, with minimal drug penetrating to the deeper tissues and systemic circulation. It is interesting that the most effective liposomes are reported to be those composed of lipids similar to stratum corneum lipids, which are most likely to enter stratum corneum lipid lamellae and fuse with endogenous lipids (P.K.Gaur et al., 2009).

Proniosomes

Proniosomes are crystalline compact Niosomal hybrid which is prepared by dissolving surfactant in small amount of suitable solvent and least amount of aqueous phase.This compact form can be converted to niosomes upon hydration. These Proniosomes serves as a promising carrier for Transdermal delivery (Pradnya Chavan et al., 2012).

Transfersomes

These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant (such as sodium cholate) and 3-10% ethanol.The surfactant molecules act as "edge activators", conferring ultradeformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome (P.K.Gaur et al., 2009).

Ethosomes

These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation. It is proposed that alcohol fluidizes the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate (P.K.Gaur et al., 2009).

CONCLUSION

Finally concluded that Transdermal Therapeutic System has been designed to provide controlled continuous delivery of drugs via skin to the systemic circulation which bypasses the first pass metabolism. 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 But day to day increament in the invention of new devices and new drugs that can be administered via this system, the use of TDDS is increasing rapidly in the present time. TDDS have wide variety of research for the effective treatment of so many diseases.

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