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TRANSDERMAL DRUG DELIVERY: A NOVEL APPROACH TO DRUG DELIVERY

Neetu Bishnoi[1]*, Praveen Tahilani[2] and Dr. Jitendra Banweer[3]

[1]M. Pharm Scholar, Sagar Institute of Research Technology & Science – Pharmacy.
[2]Associate Professor, Sagar Institute of Research Technology & Science – Pharmacy.
[3]Director, Sagar Institute of Research Technology & Science – Pharmacy.

***Corresponding Author: Neetu Bishnoi**
M. Pharm Scholar, Sagar Institute of Research Technology & Science – Pharmacy.

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ABSTRACT
The skin has attracted much attention as an alternative route for administering systemically active drugs. The potential advantages associated with transdermal drug delivery are well documented. Transdermal therapeutic system are defined as self contained, discrete dosage forms which, when applied to the intact skin, delivery the drug through the skin, at controlled rate to the systemic circulation. Thus, it is anticipated that transdermal drug delivery system (TDDS) can be designed to maintain suitable plasma drug level for therapeutic efficacy by using skin as the port of entry of drugs. The goal of pharmaceutical research is to find drugs with desirable therapeutic and low risk of undesirable side effects. Recent research and development efforts have been channelized into the development of drug delivery system for controlled drug administration through various routes (or parts) of administration, for example, the skin, to maximize the bioavailability, to optimize the therapeutic efficacy, and/or minimize the side effects of the drug.

KEYWORDS: Transdermal Drug Delivery System, Novel drug Delivery System, Skin, Bioavailability.

INTRODUCTION
Transdermal drug delivery system has been accepted as potential non-invasive route of drug administration, with advantages of prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy. Non-steroidal anti nflamatory drugs (NSAID) represent the most commonly used medications for the treatment of pain and inflammation, but numerous well- described side effects can limit their use. Therefore transdermal delivery of NSAID has advantages of avoiding hepatic first pass effect, gastric irritation and delivering the drug for extended period of time at a sustained level. On various NSAID by formulated and delivered as transdermal patches to decrease the side effects associated with the oral delivery.[1]

The skin has attracted much attention as an alternative route for administering systemically active drugs. The potential advantages associated with transdermal drug delivery are well documented. Transdermal therapeutic system are defined as self contained, discrete dosage forms which, when applied to the intact skin, delivery the drug through the skin, at controlled rate to the systemic circulation. Thus, it is anticipated that transdermal drug delivery system (TDDS) can be designed to maintain suitable plasma drug level for therapeutic efficacy by using skin as the port of entry of drugs.

The goal of pharmaceutical research is to find drugs with desirable therapeutic and low risk of undesirable side effects. Recent research and development efforts have been channelized into the development of drug delivery system for controlled drug administration through various routes (or parts) of administration, for example, the skin, to maximize the bioavailability, to optimize the therapeutic efficacy, and/or minimize the side effects of the drug.

The advantages of delivering drugs across the skin for systemic therapy are well documented. Some of the skin main advantages of transdermal drug delivery system are to delivery infusion of drug over extended period of time to increase the therapeutic drug of many drug by avoiding specific problems association with the drug e.g. GI irritation, low absorption, decomposition, due to hepatic, “first pass” effect, formation of metabolites that cause side effect, short half-life necessitating frequent dosing etc.

Application and removal of transdermal patch produce the optimal sequence of pharmacological effects. The drug input can be terminated at any point of time by removing transdermal patch because self administration is possible with this system.

USFDA approved the first transdermal patch in 1981. This patch delivered scopolamine, a drug which suppresses nausea and vomiting in motion sickness treatment of chronic disease such as asthma, rheumatoid arthritis by transdermal routr of drug administration might prove to have several advantages over the other routes of administration over the last two decades, more than 35 transdermal products have been approved. This rapid increase in market value has led to transdermal drug delivery becoming one of the fastest growing sectors within pharmaceutical industry. The skin is one of the most extensive and readily accessible organs of the human body.

It covers an area of about 3 cm^2 and at any point in time is in contact with about one third of all blood circulating through the body.[2]

NDDS (Novel Drug Delivery System)

NDDS are the method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio-conjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side- effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.

Controlled and Novel Drug Delivery which was only a dream or at bests a possibility is now a reality. During the last decade and half pharmaceutical and other scientists have carried out extensive and intensive investigations in this field of drug research. Among drug carriers one can name soluble polymers, micro particles made of insoluble or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release Passive and Active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.[1]

Fig. 1: Types of Drug Delivery.

Any drug delivery system may be defined as a system comprising of

- Drug formulation.
- Medical device or dosage form/technology to carry the drug inside the body.
- Mechanism for the release.

Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dose requirement, lower effectiveness, toxicity and adverse side effects. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession.

These systems can be characterized as controlled drug release systems and targeted drug delivery systems.

The therapeutic benefits of these new systems include

- Increased efficacy of the drug.
- Site specific delivery.
- Decreased toxicity/side effects.
- Increased convenience.
- Viable treatments for previously incurable diseases.
- Potential for prophylactic applications.
- Better patient compliance.

❖ Advantages of NDDS

- Decreased dosing frequency.
- Reduced rate of rise of drug concentration in blood.
- Sustained and consistent blood level within the therapeutic window.
- Enhanced bioavailability.
- To achieve a targeted drug release.
- Reduced side effects.
- Improved patient compliance.[2]

❖ Types of NDDS

There are number of novel drug delivery systems are available. They are

a. Hydrogels
b. Colloidal drug carrier systems
- Micelles
- Microspheres
- Liposomes and neosomes
- Nanoparticles

c. Mucoadhesives
d. Transdermal drug delivery
e. Ocular drug delivery
f. Nasal drug delievery

a. Hydrogels

Hydrogels are three dimensional hydrophilic polymeric networks capable of absorbing large amount of water or biological fluids. These networks are composed of homopolymers or copolymers and are insoluble because of the presence of chemical or physical crosslinks like entanglements or crystallites. The hydrogels exhibit thermodynamic compatibility with water which allows them to swell in aqueous medium. They are used to control the drug release in reservoir based controlled release system or as carriers in swellable and swelling control release devices.

b. Colloidal drug carrier systems

Colloidal drug carrier systems like micellar solutions, vesicle and liquid crystal dispersions, microspheres, nanoparticles, consisting of small particles, ranging from 10nm to 400nm diameter. They show great promise as drug delivery systems. When developing these formulations the aim is to obtain systems with optimized drug loading and release properties, long shelf life and low toxicity.

- **Micelles-** Micelles formed by the self assemble of amphiphilc block copolymers in aqueous solutions. The size ranges from 5 to 50 nm. They will provide grate interest in drug delivery applications. The drugs can be physically entrapped in the core of block co polymer micelle and transported at concentration that can exceed their intrinsic water solubility.

- **Microspheres-** Microspheres are the delivery systems that contain a matrix of the polymer in which the drug in micron size is uniformly dispersed. Microcapsules are those where the drug is coated with the polymer. The microcapsules and microspheres prolong drug release where as microspheres are used for drug targeting.

- **Liposomes and niosomes-** Liposomes are a form of vesicles that consists of many or one phospholipid bi layer the polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphillic and lipophilic molecules are solubilised with in the phospholipid bi layer according to their affinity towards phospholipids. Presence of non ionic surfactant instead of phospholipids in the formation of bilayers results in the formation of neosomes.

- **Nanoparticles-** The size ranges from 10 to 1000nm. They can absorb and encapsulate a drug thus protecting it from chemical and enzymatic degradation. The nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane. Nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers will be formed from both biodegradable and non

biodegradable polymers. They will provide massive advantages regarding drug targeting, delivery, and release.

c. Mucoadhesive systems

Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and mucin molecules. They can adhere to the gastric mucosa or the buccal mucosa. This concept has altered the possibility that these polymers can be used to overcome physiological barriers in long term drug delivery. This mucoadhesive drug delivery system gives more effective and safe treatment not only for topical disorders but also for systemic problems.

d. Transdermal drug delivery

Transdermal drug delivery is the administration of drugs across the skin. If the skin is the site of action then high concentration of drugs can be localized at the skin, which results in reducing the systemic drug levels and also reducing the systemic side effects. It is an alternative route for the delivery of systemically acting drugs. This route have several advantages when compared with oral drug administration. It bypasses the lever there by the dose is reduced and the side effects are minimized.

e. Ocular drug delivery

Ocular drug delivery is the one of the most challenging drug delivery system. This field has improved significantly over the past 20 years. The improvements have largely focused on maintaining the drug in eyes for an extended period of time un like conventional eye drops.

f. Nasal drug delivery

The nasal route appears to be an alternative to parenterals for administrating drugs intended for systemic effects9. The nasal route provides rich vascularity high permeable structure for absorption. It avoids hepatic first pass metabolism. Proteins such as insulin are reported to have fast and sustained action when administered through the nasal route.[3] TDDS is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe.[4]

The positive features of delivery drugs across the skin to achieve systemic effects are

- Avoidance of first pass metabolism.
- Avoidance of gastro intestinal incompatibility.
- Predictable and extended duration of activity.
- Improving physiological and pharmacological response.
- Termination of therapy is easy at any point of time.
- Greater patient compliance due to elimination of multiple dosing profile.
- Provide suitability for self administration.
- Enhance therapeutic efficacy.

Sonophoresis is a process that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages by ultrasonic energy. Sonophoresis is a localized, non-invasive, convenient and rapid method of delivering low molecular weight drugs as well as macromolecules into the skin. Mechanistically, sonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and mechanical alterations within the skin tissue. Ultrasound at various frequencies in the range of 20 kHz–16 MHz with intensities of up to $3W/cm^2$ has been used for sonophoresis.

Ultrasound parameters such as treatment duration, intensity, and frequency are all known to affect percutaneous absorption, with the latter being the most important. Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules making up topical agents. The ultrasound probably enhances drug transport by cavitation, micro-streaming, and heating. Ultrasound mediated transdermal delivery of key compounds was first reported in 1954 by Fellinger and Schmid through successful treatment of digital polyarthritis using hydrocortisone ointment in combination with ultrasound. Sonophoresis is widely used in hospitals to deliver drugs through the skin. Pharmacists compound the drugs by mixing them with a coupling agent (gel, cream, ointment) that transfers ultrasonic energy from the ultrasound transducer to the skin. Thus, Application of ultrasound to the skin increases its permeability (sonophoresis) and enables the delivery of various substances into and through the the skin. Sonophoresis is also used in Physical Therapy. Reverse ultrasound technology may also be used for the extraction of interstitial fluid samples for analysis. So, In addition to its effects in delivering compounds into the skin, sonophoresis is being investigated as a way of drawing compounds such as glucose out of the skin.[5]

Table 1: Examples of Patents for Transdermal Drug Delivery.

S.No	Patent No.	Assignee Inventors	Filed On	Title
1.	US20110190716[30]	Easter Brook; Timothy J.et el.	June 2,2009	Transdermal Drug Device
2.	US20110182949[31]	Tang; Jiashang	May 29,2009	Stablished TDDS
3.	US20100222751[32]	Pharmapatch Llc San Diego, Ca	September 22,2009	TDDS
4.	US20100143448[33]	Koninklijke Philips, Electronics N.V., Eindhoven, NL	September 26,2007	Multiple Nozle TDDS

Table 2: Some Commercially Available Marketed Transdermal Systems.[6]

S.No.	Product Name	Chemical	Developer/ Marketer	Indication
1.	Alora	Estrodiol	Theratech /proctor and ganble	Postmenopausal syndrome
2.	Catapres-tts	Clonidine	Alza/boehinger ingelheim	Hypertension
3.	Deponit	Ntg	Schwarz-pharma	Angina pectoris
4.	Minitran	Ntg	3m Pharmaceuticals	Angina pectoris
5.	Transdermscop	Scopolamine	Alza/novartis	Motion sickness

Transdermal Drug Delivery System

Introduction- In recent years it has been shown that the skin is a useful route for drug delivery to the systemiccirculation. Transdermal drug delivery system includes all topically administered drug formulations intended to deliver the active ingredients into the circulation. They provide controlled continuous delivery of drugs through the skin to the systemic circulation. The drug is mainly delivered through the skin with the aid of transdermal patch. A Transdermal patch is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. A drug is applied in a relatively high dose to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration in 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.[7-9]

Table 3: Ideal Properties of Drug for Tdds.

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

Table 4: Ideal Properties of Transdermal Drug Delivery System.[10-11]

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

- Factors That Influence Transdermal Drug Delivery-
- Biological factors include-
  - Skin condition.
  - Skin age.
  - Blood flow.
  - Regional skin sites.
  - Skin metabolism.

- Species differences.

➢ Physiological factors include-
- Skin hydration.
- Temperature and pH.
- Diffusion coefficient.
- Drug concentration.
- Partition coefficient.
- Molecular size and shape.

➢ Basic Components Of Tdds-
- The drug.
- Polymer matrix.
- Permeation enhancers.
- Adhesive.
- Backing layer.[12-20]

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal delivery system iscurrently available for treatment of various diseases such as cardiovascular diseases, Parkinson's disease, Alzheimer's disease, depression, anxiety and attention deficit hyperactivity disorder (ADHD), skin cancer, female sexual dysfunction, post-menopausal bone loss and urinary incontinence.[21] Transdermal route offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal routes provides constant blood levels, avoids first pass metabolism, increased patient compliance, and avoids dose dumping. The choice of drugs delivered transdermally, clinical needs, and drug pharmacokinetics are some of the important consideration in the development of transdermal drug delivery. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis.[22] Polymers are used in delivery systems in various ways, including as matrix formers (such as cross linked polyethylene glycol, acrylic acid matrices, ethyl cellulose and polyvinylpyrrolidone, hydroxypropyl methylcellulose, organogels), rate controlling membranes (such as sillicon rubber, polyurethane, polyisobutylene, polyacrylates, silicones), pressure sensitive adhesives (ethylene vinyl acetate copolymers, paraffin waxes, polyamides, styrene butadiene copolymers), backing layer (polyethylene, polyvinyl chloride, ethylene vinyl acetate, polypropylene, polyurethane, polyethylene terephthalate), release liner.[23-30]

Transdermal Patche

Transdermal patch generally refers to topical application delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Transdermal Patch offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal patch provides constant blood levels, avoids first pass metabolism, increased patient compliance, and avoids dose dumping.[31-32] The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis. Formulation on skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibits local effects in the skin. Transdermal drug delivery can closely mimics the slow intravenous infusion without its potential hazards and also offer another most important advantage in allowing the patient to terminate the drug therapy by simply removing the patch at desired time if toxicity develops.[33]

➢ **Evaluation and Characterization**
- **Thickness of Patch**- The thickness of each patch was measured by using screw gauge at five different positions of the patch and the average was calculated.[34]
- **Weight Uniformity-** Patches sizes of 2cm radius (4cm diameter) was cut. The weights of five patches were taken and the weight variation was calculated.[35]
- **Folding Endurance**- A patch of 2cm radius (4cm diameter) was cut evenly and repeatedly folded at the same place till it brakes. The numbers of times the film was folded at the same place without breaking give the value of the folding endurance.[36-37]
- **Percentage Moisture Content-** The prepared films were weighed individually and kept in a desiccators containing fuse calcium chloride at room temperature for 24h. After 24h, the films were reweighed and determined the percentage moisture content from the mentioned formula.[38-39]
- **Percentage Moisture Uptake-** The weighed films were kept in desiccators at room temperature for 24h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24h, the films were reweighed and determined the percentage moisture uptake from the below mentioned formula.[40-41]
- **Drug Content-** A specified area of patch was dissolved in a phosphate buffer solution. The content was stirred to dissolve the film. The content was transferred to a volumetric flask. The absorbance of the solution was measured at wavelength 284nm and determines the drug content.[42]

➢ **Types of Transdermal Patches**
- **Single Layer Drug In Adhesive**

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

- **Multi -layer drug in adhesive**

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

- **Vapour patch**

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

- **Reservoir system**

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

- **Matrix system**

a) Drug-in-adhesive system

This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

b) Matrix-dispersion system

The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

- **Microreservoir system**

The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Microreservoir system is a combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.[43]

➢ **Components of transdermal patch**

The basic components of transdermal patch consists of polymer matrix / Drug reservoir, active ingredient (drug), permeation enhancers, pressure sensitive adhesive (PSA), backing laminates, release liner, and other excipients like plasticizers and solvents.

a) Polymer matrix

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion cohesion balance, physicochemical properties, compatibility and stability with other components of the system as well as with skin. The polymers utilized for TDDS can be classified as natural polymers includes cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc, synthetic elastomers includes polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc, synthetic polymers includes polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

b) Drug

The most important criteria for TDDS are that the drug should possess the right physicochemical and pharmacokinetic properties. 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. For example, 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.

c) Permeation enhancers

To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug permeation enhancers interact with structural components of stratum corneum i.e., proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for trans-epidermal and trans-follicular permeation. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water soluble drugs.

d) Pressure sensitive adhesive (PSA)

A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. These include polyacrylates, polyisobutylene and silicon based adhesives. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device (as in reservoir system) or in the back of the device and extending peripherally (as in case of matrix system).

e) Backing laminate

The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipients compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or permeation enhancer through the layer. They should have a low moisture vapour transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are aluminium vapour coated layer, plastic film (polyethylene, polyvinyl chloride, polyester) and heat seal layer.

f) Release liner

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene and polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

g) Other excipients

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

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