IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2023 Vol.:27, Issue:2

A Review on Transdermal Drug Delivery of Antihypertensive Drugs

IJPPR
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HUMAN

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Submitted: 23 April 2023
Accepted: 29 April 2023
Published: 30 May 2023

Keywords: Transdermal drug delivery, Skin, Antihypertensive drug

ABSTRACT

Transdermal drug delivery system was presented to overcome the difficulties of drug delivery especially oral route. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. it provides a controlled release of medication into the patient usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layer of medication embedded in adhesive. The main disadvantage of transdermal drug delivery system is skin irritation in some individuals. Various transdermal patches are used for treatment of various disease. In that series antihypertensive patches are mostly used because of patient acceptance. Antihypertensive patch with the established dosage form reduced the occurrence of hospitalization and diagnostic costs. This study focuses on introduction, principles, components and method of preparation of transdermal patches of antihypertensive drugs.

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INTRODUCTION

During the past few years interest in the development of novel drug delivery systems for existing drug molecules has been renewed. Transdermal drug delivery system is a novel drug technology which is lying under the category of controlled drug delivery system. The word transdermal has been derived from the combination of two words that is trans and dermal. The trans means across or passage through and the dermal means skin. Skin is the largest organ in the body which covers approximately $2m^2$ and which receives the one third of blood circulation. The main objectives of the transdermal drug delivery system are to deliver the drugs into systemic circulation through the skin without loss. The development of transdermal drug delivery system not only improve the drug efficacy, safety and also which improves the patient compliance and therapeutic benefits. In this method has been introduced to overcome the difficulties in the other route of administration. The main advantage of this system is minimizing the side effects and avoidance of first pass metabolism and controlled rate of drug release. Due to this advantage the action of drug is prolonged and the half life and the efficacy of drug is also increased. It is the self-contained discrete dosage form which is also known as "patches". The transdermal patch containing high dose of one or more active ingredient and other drug content which is retained on the skin for prolonged period of time and produce the action. The action is produced through diffusion process where the drug molecules were diffused through the systemic circulation from the skin. The patches are available in different sizes and shapes. The size and shapes are based on the formulation approaches of patches [1].

Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mmHg, a criterion that characterizes a group of patient's whole risk of hypertension – related cardiovascular disease is high enough to merit medical attention. Antihypertensive are the class of drugs that are used to treat hypertension. Antihypertensive therapy seeks to prevent the complications of stroke and myocardial infraction. The various class of drugs used in the treatment of hypertension such as ACE inhibitors (captopril, enalapril), ARBs(losartan), Calcium channel blockers (amlodipine, nifedipine), Diuretic (amiloride, furosemide), Beta blockers (atenolol, propranolol) and other drugs are clonidine, hydralazine etc. These drugs are mainly administered through the oral route, due to the several disadvantages it can be given through the transdermal drug delivery system. Antihypertensive patch with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs.

These advantages prepared the target consumers to accept antihypertensive patches as a costlier alternative to the conventional therapy [2].

ANATOMY OF SKIN

The skin is the largest organ in the body which covers approximately about $2m^2$ in the body surface. Which receives about one third of blood circulation. It acts as the barrier in the chemical and microorganism. It acts as the first line barrier in some disease-causing organism [3].

IDEAL CHARACTERS OF SKIN [2]

- It acts the covering in the internal body parts.
- It regulates the body temperature.
- It protects the skin from the UV rays.
- In transdermal drug delivery skin act as the passage way of drug reach from outer environment to inner environment.

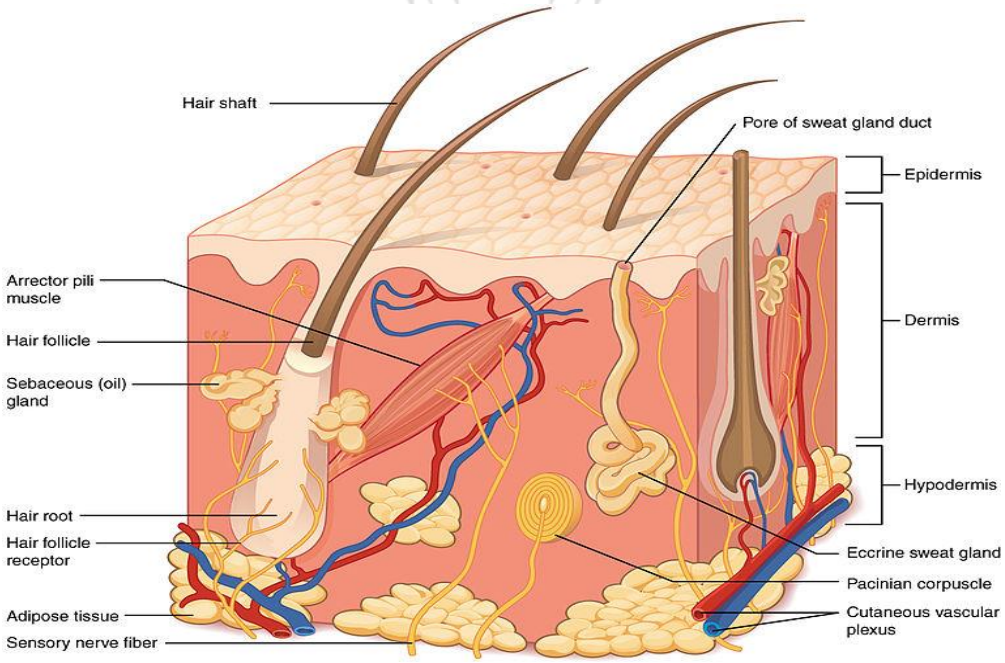

Figure.1: Schematic representation of skin

The structure of the skin can be categorized into three different layers;

- Epidermis

- Dermis
- Hypodermis

EPIDERMIS

It is the outermost layer of the skin, which covers the most of the body part. It is the continually self-renewing, stratified squamous epithelium. It is made up of several layers:

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum Basale

Stratum corneum is the outermost layer of the skin, it is also called horny layer. The barrier nature of the horny layer depends critically on its consistent; 75-80% proteins and 5-15% lipids. It is approximately 10mm thick when dry when it is swells to several times thickness fully hydrated. The architecture of horny layer is made by the keratinized cell functions as protein "bricks "embedded in lipid mortar. The lipid is arranged in multiple layers.

Going inward it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and stratum basal. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensate the loss of dead horny cells from the skin surface. As the cell produced by the basale layer move outward, they itself alter the morphologically and histochemical, undergoing keratinized to form the outer most layer of stratum corneum [4].

DERMIS

Dermis is the second layer of the skin, it's just beneath the epidermis. It provides physiological support for the epidermis. It is approximately 3 to 5 mm thick layer and is composed of a matrix of connective tissues which contain blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin. It provides a minimal barrier to the delivery

of most polar drugs, although the dermal barrier may be significant when delivery highly lipophilic molecules [4].

HYPODERMIS

The hypodermis is also called as subcutaneous fat tissue, which supports dermis and epidermis. It serves as the fat storage area. This layer helps to regulate body temperature and provide mechanical support, it carries principal blood vessels and nerves to skin and may contain sensory pressure organs. It also provides supply of high energy molecules.

The transdermal drug delivery system drug is to penetrate through these three layers and reaches the systemic circulation and produce the pharmacological action [1].

ACCESSORY ORGANS OF THE SKIN

Hair and hair follicles, secretory ducts, sweet glands (sebaceous, eccrine and apocrine) and nails are the principle accessory organ of the skin. On an average 40-70 hair follicles and 200 – 250 sweat ducts /cm^2 present in healthy human body. Sweat glands are capable of secreting amino acids, proteins and antibodies. These accessory organs are helpful in the efficient transport of drug molecules [3].

BASIC PRINCIPLES OF TRANSDERMAL PERMEATION

Transdermal permeation is based on passive diffusion process. The drug must penetrate the stratum corneum. In the initial transient diffusion stage drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium through the intact stratum corneum becomes primary pathway for transdermal permeation [2].

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves;

- Dissolution with in and release from the formulation.
- Partitioning in the skin's outermost layer, the stratum corneum.
- Uptake of drug by capillary network in the dermal papillary layer.
- Effect on the target organ [4].

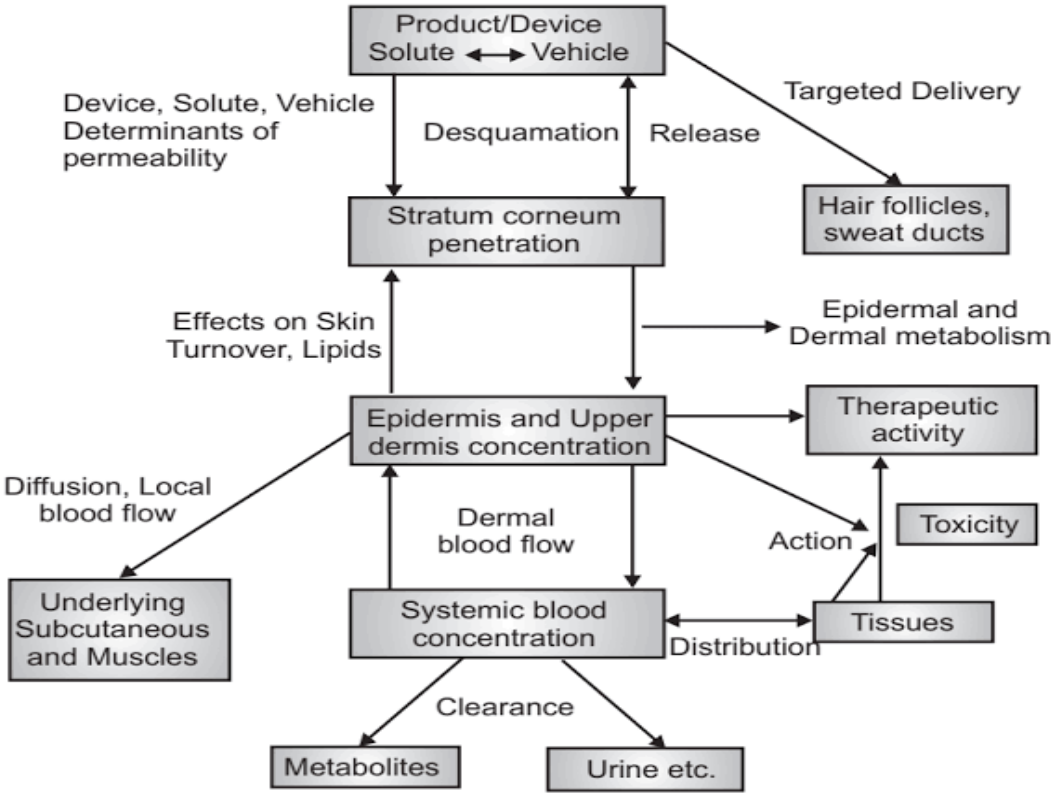

Figure.2: Schematic representation of drug permeation

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM [5]

- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- Predictable and extended duration of activity.
- Improving physiological and pharmacological action.
- Avoiding the over dosage.
- Controlled and predetermined drug release.
- Maintain plasma concentration of potent drugs.
- Termination of therapy at any time.
- Greater patient compliance due to elimination of multiple dosing profile.
- Ability to deliver drug more selectively to a specific site.
- Provide suitability for self-administration.

- Enhance therapeutic efficacy.
- It is cost effective.

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM [5]

- In some individual's patches cause irritation and allergy reactions.
- The adhesive may not adhere well to all types of skin and may leads to drug loss in that particular area.
- Physical movement and sweating leads to detachment of patch.
- It cannot achieve high drugs level in blood.
- It cannot deliver drugs in a pulsatile fashion.
- It cannot deliver ionic drugs.

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM

The effective transdermal drug delivery can be formulated by considering three factors such as Drug, Skin, and the vehicles. So, the factors affecting can be divided in to classes as biological factors, physicochemical factors and environmental factors.

1. BIOLOGICAL FACTORS

- SKIN CONDITION

Acids and alkalis, many solvents like chloroform methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above-mentioned conditions affect penetration [6].

- SKIN AGE

The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS [7].

- BLOODSUPPLY

The changes in the peripheral circulation can affect transdermal absorption [1].

- REGIONAL SKIN SITE

Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significantly penetration [6].

- SKIN METABOLISM

Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So, skin metabolism determines efficacy of drug permeated through the skin [7].

- SPECIES DIFFERENCES

The skin thickness, density of appendages, and keratinization of skin vary species to species, so affects the penetration [5].

2. PHYSIOCHEMICAL FACTORS

- SKIN HYDRATION

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So, use of humectants is done in transdermal delivery [7].

- TEMPERATURE AND pH

The permeation of drug increases tenfold with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration [5].

- DRUG CONCENTRATION

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier [7].

- PARTITION COEFFICIENT:

Water and lipid soluble drugs favorably absorbed through the skin. Intercellular route is applicable for drugs with intermediate partition coefficient (logK 1 to 3) and having high lipophilicity. The transcellular route probably predominates for more hydrophilic molecules (logK< 1) [5].

- MOLECULAR SIZE AND SHAPES

Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known. The normally selected candidates of transdermal delivery tend to lie between the molecular range of 100-500 Dalton [6].

3. ENVIRONMENTAL FACTORS

- SUN LIGHT

Due to sunlight the walls of blood vessels become thinner leading to bruising with only minor trauma in sun exposed areas [7].

- COLD SEASON

Cold season often result in itchy, dry skin. Skin responds by increasing oil production to compensate for the weathers drying effects. A good moisturizer will help ease symptoms of dry skin [7].

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. DRUG

The transdermal drug delivery system is limited to the potent drugs as drugs with daily dose between 5mg to 10 mg are ideal condition for this route. The drug candidate should have a low molecular weight that is less than 600 Dalton and intermediate lipophilicity (log P = 1-3) as it provides good solubility and penetration properties [8]. The drug should have a low melting point as it correlates with good solubility which is predicted by the ideal solubility theory. The melting point should be less than 200°C and pH of saturated solution of the drug should be between 5 to 9. Half-life of the drug should be less than 10 hours. The drug must be non-allergenic to the skin [9].

2. POLYMER

Polymers are used to strengthen the foundation of transdermal drug delivery system. Polymer used should be inert and should not react with the active ingredient or other excipients. It should be stable and must not decompose on storage. The chemical functionality and molecular weight of the polymer should allow diffusion of drug at desired rate. The selected polymer should be biocompatible with skin and should not be toxic [10].

3. VEHICLE

The factor considered in the selection of vehicle for transdermal drug delivery system is the stability of the vehicle. It should not chemically react with the drug or alter its nature. It must be non-toxic or antagonistic to the host skin [9].

4. PERMEATION ENCHANCER

Penetration enhancers are also known as accelerants, sorption promoter or permeation enhancer. The barrier function is essential for the protective role of stratum corneum but at the same time it may hinder the transdermal delivery of drug through it. As the major route of drug is through the intracellular channels, the lipid section is a viable determinant in the first step of absorption. Penetration enhancers can temporarily diminish the barrier function of skin and to enhance the drug delivery. Penetration enhancers such as dimethyl sulphoxide (DMSO), alcohols and fatty acids are most commonly used in the preparations [9].

THE IDEAL PROPERTIES OF PENETRATION ENHANCERS

- It should not be toxic, irritant or allergenic to the skin.
- The activity of the penetration enhancer should be predictable and reproducible.
- It should be inert and should not possess any pharmacological property. Its effect should be unidirectional i.e., they should only allow the drug to pass in while preventing the loss of endogenous material from the skin.
- It should not interact with the drug or other excipients in the system. Penetration enhancers should be compatible with a wide range of excipients and drugs [10].

5. PLASTICIZER

Plasticizers are used for the improvement of film formation, to prevent cracking, improve flexibility and to enhance appearance of the patch. Plasticizer can also control the release rate of drug from the transdermal drug delivery system; depending on the plasticizer type and concentration. They also decrease the glass transition temperature of polymer thereby increasing diffusivity of polymer. It has been reported that the plasticizer such as glycerin, sorbitol and PEG can change release rate of the therapeutic components contained in the formula of transdermal drug delivery system [10].

6. BACKING LAMINATE

The backing layer serves to hold the system together. It protects the patch from external environment. It is often chosen for flexibility, appearance, need of occlusion and impermeability to permeation enhancers and drug [9].

7. RELEASE LINER

The release liner is covered by a protective liner that is removed before the application of patch to the skin. It protects the patch during storage [10].

8. ADHESIVE

Adhesive is used to stick the components of patch to the skin. The adhesive should not be toxic, irritant or allergenic to the skin. It should have good adhesive properties on all type of skins i.e., oily, normal, wrinkled, wet or hairy. It should provide good resistance against water and humidity. The adhesive should be easy to remove without causing damage to the skin [10].

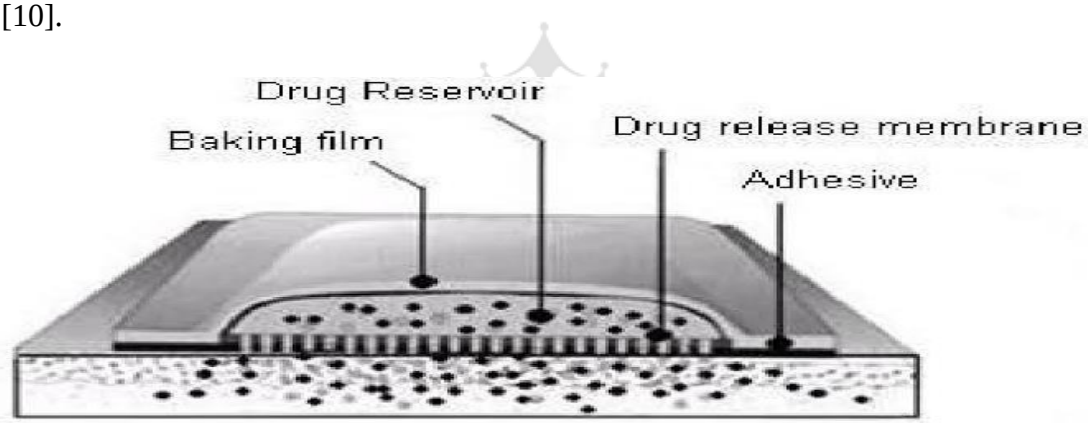

Figure.3: Schematic representation of components of transdermal drug delivery system

TYPES OF TRANSDERRMAL PATCHES

1. THE DRUG IN TDDS ADHESIVE

In the system the drug is dispersed in the adhesive layer of the pond. The layer of adhesive not only works in the attach the patch with skin, but also works in the regulate the rate of drug delivery. The adhesive layer is the surrounded by a liner. There are two types,

- SINGLE-LAYER ADHESIVE

In this type adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layer together and this type of layer is responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing [11].

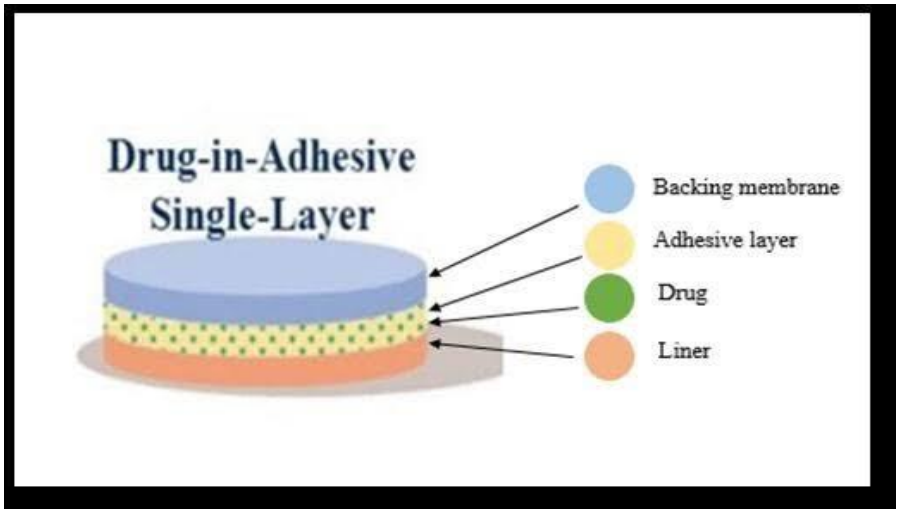

Figure.4: schematic representation of single layer adhesive.

- MULTI-LAYER DRUG IN ADHESIVE

This type is always similar to the single layer but it contains an immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. This patch also has a temporary liner layer and a permanent backing [11].

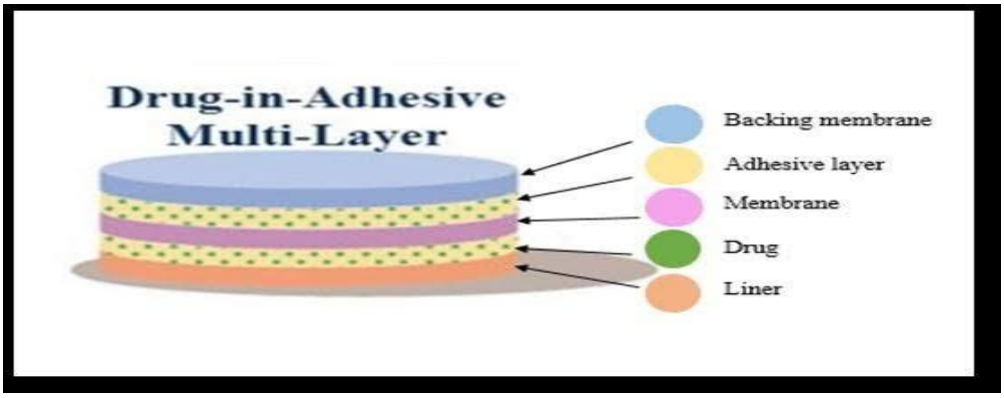

Figure.5: schematic representation of multilayer adhesive.

2. VAPOUR PATCH

In this type of patch, the role of adhesive layer not only serves to adhere the various layers together but also to release vapour, the vapour patches are new on the market. Commonly it is used for releasing of essential oils for up to 6 hours [11].

3. RESERVOIR SYSTEM

In this system, drug reservoir can be placed between the backing layer and rate controlling membrane. Drug may be in the form of suspension, gel or solution. These drugs are dispersed on the solid polymeric matrix [10].

4. MATRIX SYSTEM

The matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension, which is in direct contact with the release liner [8].

5. DRUG IN ADHESIVE SYSTEM

The drug reservoir is formed by the dispersion of drug to an adhesive polymer, then it spread on the medicated adhesive polymer[8].

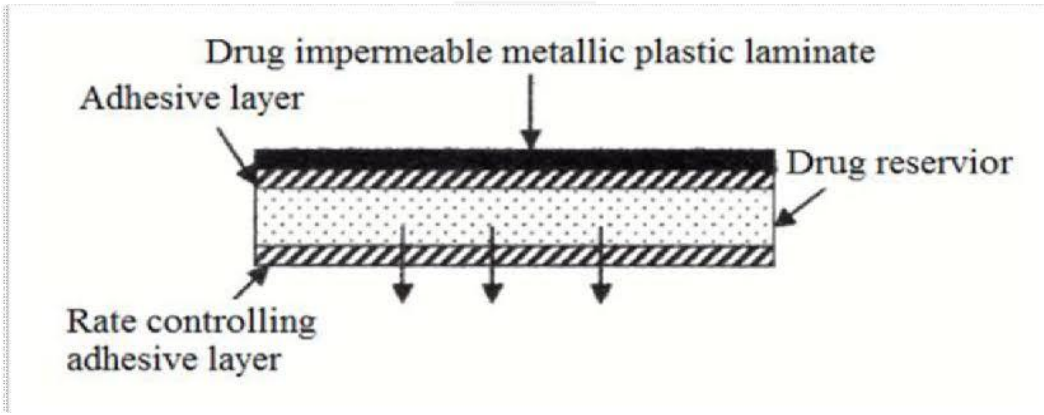

Figure.6: schematic representation of drug in adhesive system.

6. MATRIX DISPERSION SYSTEM

The drugs are homogeneously dispersed in the lipophilic or hydrophilic polymer matrix. The drugs having polymer is fitted on a particular 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 [11].

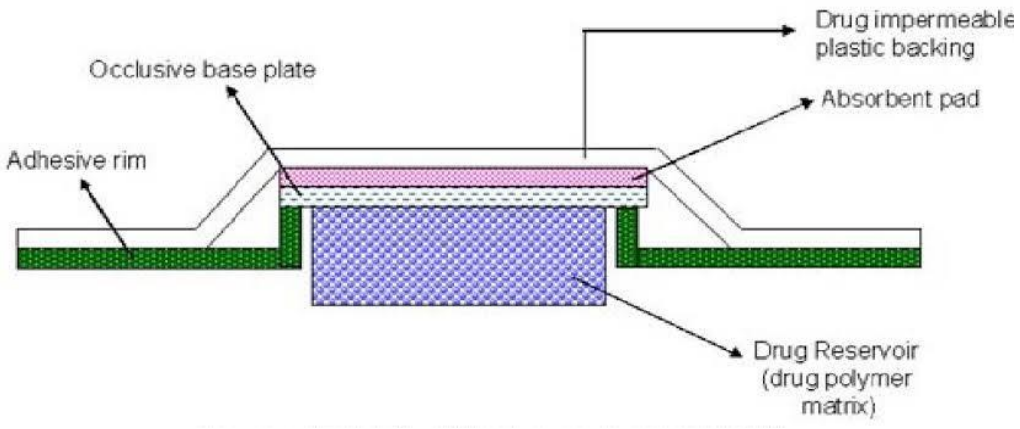

Figure.7: schematic representation of matrix dispersion system

7. MICRO RESERVOIR SYSTEM

This system refers to the combination of reservoir and matrix dispersion systems. The drug is suspended in an aqueous solution of water-soluble polymer and then dispersing the solution homogenously in a lipophilic polymer to form thousands of unleachable microscopic spheres of drug reservoirs [10].

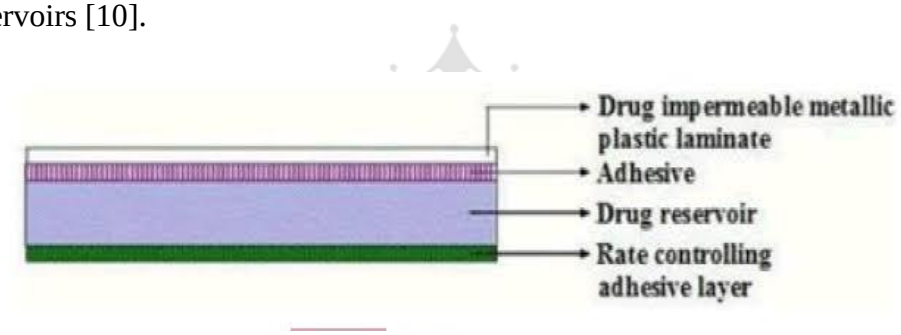

Figure.8: schematic representation of reservoir system

FORMULATION OF TRANSDERRMAL PATCHES:

1. MERCURY SUBSTRATE METHOD

The patches were prepared by the solvent casting method. The polymer likes PVP and HPMC was taken in a beaker mixed with the other polymers and was added firstly with stirring at lower rpm and later at a high speed. The plasticizer was added and homogenously mixed and the drug was added and make up the volume and it is poured into the glass ring which is placed over the mercury surface in a glass Petri dish. The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at 40 ^{o}c. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place [12].

2. CIRCULAR TEFLON MOULD METHOD

Polymeric solutions in various ratios is used as an organic solvent. Then that solution is divided into two equal half's. In one half is added to the calculated amount of drug and is dissolved and the other half is mixed with the enhancers in different concentrations are dissolved. The next step is the mixed the both halfs together, and the plasticizer is added into the drug polymer solution. These mixtures are stirred for 12 hrs and then it is poured into the circular Teflon mould. The moulds are to be placed in the leveled surface and covered with inverted funnel to control solvent vaporization. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24hrs at 25 ±0.5^{o}c in a desiccator[13].

3. BY USING IPM MEMBRANES METHOD

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscus by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane [13].

4. BY USING EVAC MEMBRANES METHOD

In order to prepare the target transdermal therapeutic system, 1% Carbopol reservoir gel, polyethylene, ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate-controlled membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; Carbopol resin will be added to the above solution and neutralized by using 5%w/w sodium hydroxide solution. The drug is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device [12].

5. ALUMINIUM BACKED ADHESIVE FILM METHOD

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10mg. Aluminum backed adhesive film method is the one of the suitable methods. In this method of preparation chloroform is choice of solvent because of the important advantages that is most of the drugs as well as adhesives are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution

and dissolved. A custom-made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks [13].

EVALUATION OF TRANSDERRMAL DRUG DELIVERY SYSTEM

Evaluation is a process that critically examines the dosage form. It examines the whether the product contain the correct dosage form, other physical properties of the product and also compare the dosage form against the standard product [14].

1. FOLDING ENDURANCE

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value [13].

2. FLATNESS TEST

For flatness determination, the three patches should be selected. 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 % flatness. It can be determined by the equation that is given below;

$$\textbf{Percentage constriction} = \frac{I_1 - I_2}{L_1} \times 100$$

Where,

I_1= Initial length of each strip

I_2 = Final length of each strip

3. THUMB TACK TEST

It is a qualitative test applied for determination of tack property of adhesive. The relative tack property is detected by simply pressing on the adhesive with the thumb [14].

4. PEEL ADHESION TEST

In this test the force is required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additive

used determine the peel adhesion properties. A single tape is applied to a stainless-steel plate or a backing membrane. The force required to remove the tape is measured [12].

5. POLARISCOPIC EXAMINATION

A specific surface area of the piece is to be kept on the polariscope slide and observe for the drugs crystals to distinguish whether the drug is present in crystalline form or amorphous form in the patch [13].

6. ROLLING BALL TEST

This test involves the measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further ball travel [14].

7. 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 [13].

8. DRUG CONTENT TEST

A specified area of the patch is to be dissolved in a suitable solvent of specific volume. Then the solution is filtered through a filter medium and analyses the drug content by suitable method such as UV or HPLC. Then takes the average of three different samples[12].

CURRENTLY APPROVED TDDS[13]

YEAR	GENERIC (BRAND) NAMES	INDICATION
1984	Clonidine (catapress TTS)	Hypertension.
1990	Fentanyl (Duragesic)	Chronic pain.
1999	Lidocaine (Lidoderm)	Post-herpetic neuralgia pain.
2005	Lidocaine/tetracaine(synera)	Local dermal analgesia.
2007	Rivastigmine (Exelon)	Dementia.
2010	Buprenorphine (butrans)	Chronic pain.

CONCLUSION

The future development of transdermal therapeutic system is multifaceted. Improvement in the presently available devices to provide optimum blood levels, availability of better skin permeability enhancer and extensive use of redesigned drug molecules. The market for transdermal device has been estimated to increase in future and has recently experienced in annual growth rate of 25%. Magnetic energy, magnetophoretic has been investigated as a means to increase drug flux across the skin. In recent times, skin considered as a safest port for drug administration, to provide continues drug release into systemic circulation. During the past few years various drugs can be formulated in the TDDS [15].

The mostly available antihypertensive drug is clonidine which is highly active in transdermal patches, so it is more convenient in patients. Nowadays clonidine patches are the most available in the market. The other antihypertensive drugs such as carvedilol and metoprolol are also available in TDDS form. The all the antihypertensive drugs are cannot be formulated and delivered in the transdermal patches system, because of the particular physiochemical properties. In the recent trends various research can be done in the field of transdermal delivery of antihypertensive drugs [13].

In the formulation of enalapril maleate using the piperidine as penetration enhancer, in this study indicates the matrix type of EM patches helps to management of the hypertension for 2 days [15].

The matrix type of transdermal therapeutic system containing carvedilol with different ratios of hydrophobic and hydrophilic polymeric combinations by the solvent evaporation technique. The physiochemical compatibility of the drug and polymers was studied by the IR spectroscopy and DSC. These researches reported the there is no incompatibility in the drug and polymers. The antihypertensive activity of the carvedilol patches is the comparative more availability than the oral administration in the preclinical studies [13].

The transdermal patch of Atenolol for its prolonged and controlled release in the systemic circulation. To achieve desired and controlled release, different combination of the polymers is used. These preparations are evaluated for in vitro release and other animal studies. This study evolved that designed polymeric matrix combination gives the better action compared to the conventional therapy [15].

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