TechnoChem
International Journal of TechnoChem Research
ISSN:2395-4248 www.technochemsai.com
Vol.02, No.03, pp 244-256, 2016

A Brief Review on Antihypertensive Drug Delivery through Transdermal Patches

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Abstract: TDDS are topically administration of medicaments through the skin for systemic effects at a predetermined and controlled rate in the form of transdermal patches. Transdermal drug delivery of antihypertensive drugs is able to provide optimum amount of drug to control the disease condition along with minimum side effects. The TDDS avoidance of first pass metabolism and other variables associated with the GI tract, such as Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Oral drug administration is limited by many disadvantages. This review on different antihypertensive drugs showed that, by delivering drug through this route improves bioavailability a well as patient compliance. This can also lead to cost effectiveness of healthcare treatment for the long term management of hypertension. But the main limitation is that, the drug should possess certain specific physicochemical properties which should be suited to permeate through the skin, therefore all antihypertensive drugs cannot be given by this route.
Key words: Anithypertensive drug delivery, Transdermal patches.

INTRODUCTION

HYPERTENSION

Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mm Hg, a criterion that characterizes a group of patients whose risk of hypertension-related cardiovascular disease is high enough to merit medical attention.

Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India.

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.

The possibility of achieving controlled zero order absorption, simple mode of administration and the option of easy withdrawal of dose in case of adverse manifestations make them desirable in antihypertensive therapy.[1,3]

DRAWBACKS OF CONVENTIONAL DOSAGE FORM

Oral drug administration is limited by many disadvantages, some of them are mentioned below:

1. Some of oral preparations undergo a first-pass effect in the liver, requiring larger doses.

2. The rate and extent of absorption can vary greatly depending on the drug, its formulation, presence or absence of food in the stomach, drug interactions, and pH of gastrointestinal fluids.

3. Drug metabolites formed following first-pass through the liver may not be as active or as potent as the parent drug (e.g. butorphanol), thus necessitating the oral dose to be much greater than the parenteral dose required to cause the same clinical effect.

DRUGS USED AS ANTIHYPERTENSIVE PATCHES

Carvedilol:

Carvedilol is a β1 + β2 + α1 adrenoceptor blocker; produces vasodilation due to α1 blockade as as calcium channel blockade, and has antioxidant property. It has been used in hypertension and is the β blocker especially employed as cardioprotective in congestive heart failure (CHF).

Shashikant D. Barhate*et al.*, formulated transdermal patches of carvedilol by using combination of polyvinyl alcohol (PVP) and polyvinyl pyrrolidone (PVP K30) along with glycerin, polyethylene glycol 400 and propylene glycol as a plasticizers.[4,5]

Metoprolol:

It is a prototype of cardio-selective (β1) blockers; is incompletely absorbed (oral bioavailability 35%), has short elimination half life of 2-3 hrs and undergoes extensive first pass metabolism.[4]

MeenakshiBharkatiya*et al.,* prepared transdermal patch of metoprolol tartrate by solvent casting method employing a mercury substrate by using the combinations of EC:PVP and Eudragit RL100:PVP in different proportions.[6]

Atenolol:

Atenolol is relatively a selective β1 blocker having low lipid solubility. It is completely absorbed orally, but first pass metabolism is not significant. It is one of the most commonly used β blockers for hypertension and angina.[4]

P Eswaramma*et al.*, developed matrix type transdermal films of atenolol by optimizing different ratios of cellulose acetate phthalate (CAP) and polyvinyl pyrrolidone (PVP) incorporating 15% w/w dibutyl phthalate as a plasticizer with different concentration of oleic acid and isopropyl myristate as permeation enhancer by the solvent evaporation technique.[7]

Propranolol:

Propranolol is a β blocker which is used in management of hypertension. Due to short biological half-life of 3.9 hrs it necessitates for controlled delivery.[8]

Guru Sharan*et al.*, prepared Propranolol hydrochloride loaded patches using various biocompatible polymers like (EC: PVP) and (Acrycoat L-100: HPMC) by using solvent casting and evaporation technique and checked the effect of various permeation enhancers on formulated patches.[9]

Nicardipine hydrochloride (NC- HCl):

Nicardipine hydrochloride (NC-HCl) a calcium channel blocker for the treatment of chronic stable angina and hypertension. The onset of action is 5-10 min, and duration of action is between 15-30 min. The half life of the drug varies between 2-4 hr and bioavailability ranges 20-40%.

Y S R Krishnaiah*et al*., developed a membrane-moderated transdermal therapeutic system (TTS) of nicardipine hydrochloride using 2%w/w hydroxypropyl cellulose (HPC) gel as a reservoir system containing 4%w/w of limonene as a penetration enhancer.[10]

Clonidine:

Clonidine is a centrally acting antihypertensive drug having plasma half life of 8-12 hrs and peak concentration occurs in 2-4 hrs Clonidine effectively reduces blood pressure in patients with mild-to-moderate hypertension.[11]

Mao Zhenmin*et al*., prepared, a new type of polyacrylates polymer synthesized in lab by UV curing method and studied in membrane controlled drug release systems.[12]

Nicorandil:

Nicorandil belongs to the class of potassium channel activators, which exert their action by arterio-dilating and vasodilating properties and represents a novel type of compound for use in the treatment of angina pectoris.

V G Jamakandi et al., employed solvent casting technique to formulate HPMC patches containing different grades of HPMC polymer (6 cps, 15 cps and K4M) as matrix base, polyethylene glycol as plasticizer.[13]

Amlodipine:

Pharmacokinetically it is the most distinct dihydropyrimidines belonging to the class of calcium channel blockers. It has complete but slow oral absorption: peak after 6-9 hr. Volume of distribution and $t^{1/2}$ are exceptionally long: diurnal fluctuation in blood level is small.[4]

Jiang Yu-xuan*et al.*, prepared drug-in adhesive patches for amlodipine besylate and evaluate its in vitro transdermal permeability. Drug-in adhesive patches of amlodipine besylate were prepared by dissolving amlodipine besylate and different enhancers into the home-made pressure sensitive adhesive.[14]

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Transdermal drug delivery system (TDDS) are defined as self-contained, discrete dosage form which, when applied to the intact skin, deliver the drug(s), through skin at controlled rate to the systemic circulation. To provide continuous drug infusion through an intact skin several transdermal therapeutic systems have been developed for topical application onto the intact skin surface through the skin tissue.[1]FDA approved the first transdermal patch products in 1981.Nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm-Nitro). TDDS can deliver certain medication to systemic circulation in a more convenient and effective way than is possible with conventional dosage form. The potential of skin as a path of drug administration has been amply demonstrated by the acceptability of marketed therapeutic systems. Administration of systemic drugs using a transdermal patch represents a noninvasive route, with improved patient compliance.

Transdermal drug delivery can provide a number of advantages over conventional methods of drug administration, including enhanced efficiency, increased safety, greater convenience and improved patient compliance. By delivering a steady flow of drugs in to bloodstream over an extended period of time, transdermal system can avoid “peak and valley” effect of oral or injectable therapy and can enable more controlled, effective treatment. By avoiding first pass metabolism through the gastrointestinal tract and liver, the therapeutically equivalent dosage for the transdermal delivery of certain compound can be significantly less than the corresponding oral dosage, potentially reducing dosage related side effect.[15]

ADVANTAGES

- The avoidance of first pass metabolism and other variables associated with the GI tract, suchas pH, gastric emptying time.

- Sustained and controlled delivery for a prolonged period of time.
- Reduction in side effects associated with systemic toxicity, i.e. minimization of peaks andtroughs in blood-drug concentration.
- Improved patient acceptance and compliance.
- Self administration is possible with this system.
- Ease of dose termination in the event of any adverse reactions, either systemic or local.
- Convenient and painless administration.
- Ease of use may reduce overall healthcare treatment costs.
- Provides an alternative in circumstances where oral dosing is not possible (in unconscious ornauseated patients).[16]

DISADVANTAGES

- The drug must have some desirable physicochemical properties for penetration through stratum corneum.
- If the drug dosage required for therapeutic value is more than 10mg/day, the transdermal delivery will be very difficult
- Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.[17]

THE SKIN

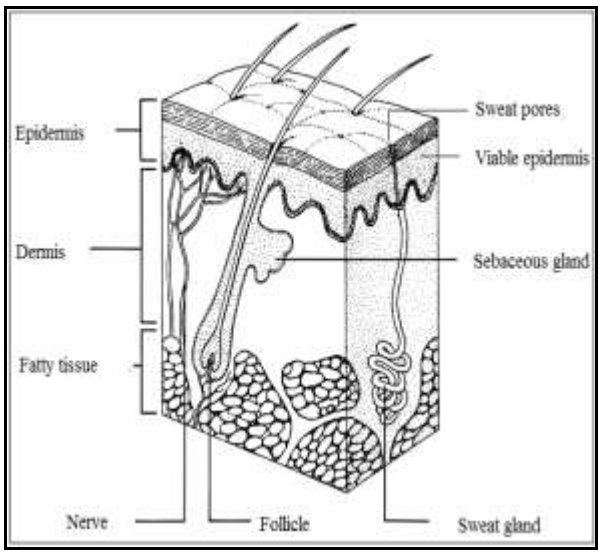

Fig. No.1: Structure of Skin

The skin covers the external surface of the body. It is the largest organ of the body in surface area and weight. In adult, the skin covers an area of about 1.5-2.0 square meters and weighs 4.5-5 kg, about 16% of total

body weight. However, over most of the body it is 1-2mm thick. The average square inch of skin holds 650 sweat glands, 20 blood vessels, 60,000 melanocytes and more than a thousand nerve endings. Structurally, the skin consists of two main parts. The superficial, thinner portion, which is composed of epithelial tissue, is the epidermis. The deeper, thicker connective tissue part is the dermis.[18,20]

The subcutaneous tissue just deep to skin is known as the hypodermis.

FUNCTION OF SKIN

1. **Thermoregulation:**The skin contributes to thermoregulation, the homeostatic regulation of body temperature, in two ways: by liberating sweat at its surface and by adjusting the flow of blood in the dermis.

2. **Protection:** Keratin in the tissue protects underlying tissues from microbes, abrasion, heat, and chemicals. It also protects from physical agents like dehydration, UV light.

3. **Cutaneous sensations:** These include tactile sensation- touch, pressure, vibration, and tickling as well as thermal sensation and pain.

4. **Excretion:** It has small role in the excretion; about 400ml of water evaporates through it daily. It also eliminates nitrogen containing wastes like ammonia, urea and uric acid.

5. **Absorption:** Absorption of lipid soluble material like fat soluble vitamins A, D, E and K certain drugs, steroids, heavy metals, organic solvents, O_2 and CO_2.

6. **Synthesis of vitamin D:** Synthesis of Vitamin D is done by activation of precursor molecule in the skin in presence of UV rays in sunlight.

7. **Blood reservoir:** The dermal vascular supply is extensive and can hold large volumes of blood.[18,20]

DRUG PERMEATION PATHWAY

There are critically three ways in which a drug molecule can cross the stratum corneum:

- Via skin appendages (shunt route)
- Epidermal route
    1) Through intercellular lipid domains
    2) By a transcellular route.[21]

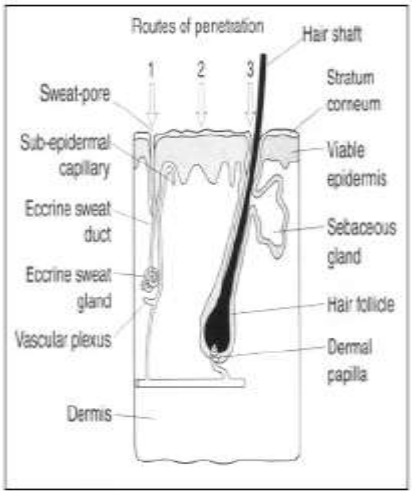

Fig.No.2 : Routes for Drug Permeation

THE APPENDAGEAL ROUTE

The permeation of drug through the skin includes the diffusion the intact epidermis and through the skin appendages (Shown as no.1&3 in fig.2), i.e. hair follicles and sweat glands, which form shunt pathways through the intact epidermis. However, these skin appendages occupy only 0.1% of the total human skin surface and the contribution of this pathway is usually considered to be small.[22]

EPIDERMAL ROUTE (shown as No.2 in fig.No.2)

For drugs, which mainly cross-intact horney layer, two potential micro routes of entry exists, the transcellular (intracellular) and intercellular pathway

1) Transcellular route

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrate keratin, provide an aqueous environment for which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion step.

2) Intercellular route

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons.

i. Recalling the 'bricks and mortar' model of the stratum corneum,theinterdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route

ii. The intercellular domain is a region of altering structured bilayers. Consequently, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small unchanged molecules penetrating the skin.

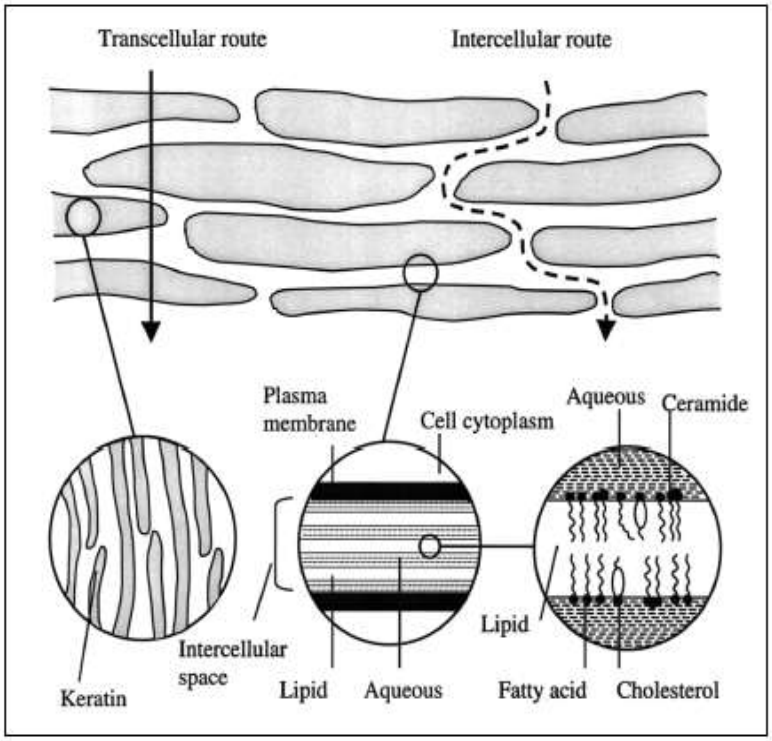

Fig. No.3: Epidermal Routes for Drug Permeation

FACTORS AFFECTING TRANSDERMAL PERMEABILITY

1) Biological Factors:

- **Skin condition**: The intact skin is a tough barrier but many agents like acids and alkalis; many solvents such as chloroform and methanol injure barrier cells thereby promote penetration. Diseased state alters the skin conditions of patient.
- **Skin age**: The skin of young and the elderly is more permeable than adult tissue. Children are also more susceptible to toxic effect of drugs and chemicals; partly because of their greater surface area thus skin age also affects the penetration of drug through TDDS.
- **Blood flow**: The changes in the peripheral circulation could affect transdermal absorption. In clinically hyperaemic skin, any increase in absorption almost always arises because the disease damages the skin barrier.
- **Regional skin sites**: Variations in cutaneous permeability around the body depend on the thickness and nature of the stratum corneum and the density of skin appendages. These factors affect significantly to the penetration.
- **Skin metabolism**: The skin metabolizes steroid hormones, chemical carcinogens and some drugs. Metabolism of skin determines efficacy of drug permeated through the skin.
- **Species differences**: Skins thickness, sweat gland and hair follicle densities and pelt condition affect the routes of penetration and the resistance to permeation.

2) Physicochemical factors:

- **Skin hydration**: In contact with water saturates the skin the tissue swells, softens and wrinkles results increases permeability. Hydration of the stratum corneum is one of the most important factors in increasing the penetration rate, so use of humectant is done in the transdermal therapeutic system.
- **Temperature and pH**: The penetration rate of material through human skin can change tenfold for a large temperature variation, as the diffusion coefficient decreases as the temperature falls. Weak acids and bases dissociate to different degrees, depending on the pH and their pKa or pKb values. Thus, the proportion of unionized drug in the applied phase determines the effective concentration gradient, and this fraction depends on pH. Thus, temperature and pH are factors which affect the penetration of drug.
- **Diffusion coefficient**: Penetration of drug depends upon the diffusion coefficient. For a constant temperature, the diffusion coefficient of a drug in a topical vehicle or in skin depends on the properties of the drug and the diffusion medium and on the interaction between them.
- **Drug concentration**: The flux of solute is proportional to the concentration gradient across the entire barrier phase and concentration gradient will be more if drug concentration saturated across donor site.
- **Partition coefficient**: The optimal K, partition coefficient is required for good skin penetration required a K close to unity. However, drug with low values they are too water soluble to partition well into the horny layer. At higher values the compounds are so lipid soluble that they do not readily pass from the stratum corneum into the water-rich viable tissue.
- **Molecular size and shape**: Absorption is apparently inversely related to molecular weight: small molecules penetrate faster than large ones. However, the specific effect of the size of the penetrating molecule on the flux could only be determined if the effect of size could be separated from the resultant change in solubility characteristics. This is difficult to do, as the role of the partition coefficient is so dominant. Because it is difficult to determine the effect of molecular shape, separated from partition coefficient domination and so nothing is known about this factor in skin permeation.[23]

COMPONENTS OF A TRANSDERMAL PATCH

Transdermal patch may include the following components:

- **Liner** - Protects the patch during storage. The liner is removed prior to use.
- **Drug** - Drug solution in direct contact with release liner
- **Adhesive** - Serves to adhere the components of the patch together along with the skin
- **Membrane** - Controls the release of the drug from the reservoir and multi-layer patches
- **Backing** - Protects the patch from the outer environment.[24]

1) Polymer Matrix:

The polymer controls the release of the drug from the device.

Criteria for polymer to be used in a transdermal system

i. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and get released through it.

ii. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive

iii. The polymer and its degradation product must be non-toxic or non-antagonistic to the host

iv. The mechanical properties of the polymers should not deteriorate excessively when large amounts of agent are incorporated into it.

Useful polymers for transdermal delivery system are:

- Natural: Cellulose derivatives, Gelatin, Gums and their derivatives etc.
- Synthetic polymers: Polyvinyl alcohol, Polyvinyl chloride, Polymethacrylates,
- Synthetic Elastomer:Polybutadiene, Polysiloxane, Silicon rubber etc.

2) Drug:

For successfully developing transdermal drug delivery system selection of drug is most important.

IDEAL PROPERTIES FOR SELECTION OF DRUG

Following are some of the desirable properties of drug for transdermal delivery

1) Physicochemical properties:

- The molecular weight is less than 500 Da.
- Aqueous solubility >1mg/ml
- An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ml).
- Optimum partition coefficient is required for good therapeutic action
- Low melting point of drug is desired. (<200°C)

- The pH of the saturated solution should be in between 5 to 9.
- The potent drug with dose deliverable 10-15 mg/day.

2) Biological properties:

- The drug should be potent with daily dose <10-15 mg/day
- The half ($t_{1/2}$) life of drug should short.
- The drug must nonirritant to skin and not produce allergy.[17,25]

TECHNOLOGIESFORDEVELOPINGTRANSDERMALDRUGDELIVERY SYSTEMS

1) Polymer Membrane Permeation-Controlled TDD Systems:

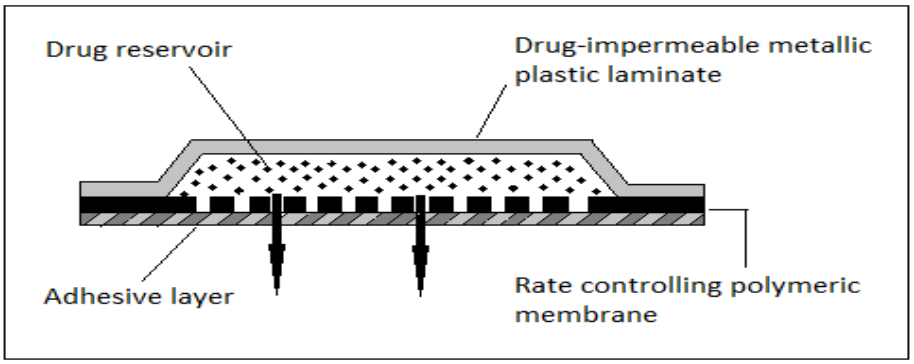

Fig. No.4: Cross-sectional view of polymer membrane permeation-controlled TDD systems

In this type of system the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane allowed to release only through the rate-controlling polymeric membrane. The drug solids are dispersed homogeneously in a solid polymer matrix e.g. polyisobutylene, suspended in anunleachable, viscous liquid medium to form a paste like suspension e.g. silicon fluid, or dissolved in a releasable solvent to form a clear drug solution e.g. alkyl alcohol. The rate controlling membrane can be either a microporous or a nonporous polymeric membrane, e.g. ethylene-vinyl acetate copolymer with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, e.g., silicon adhesive, may be applied to provide intimate contact of the TDD system with the skin surface.

The rate of drug release through TDDS system can be controlled by varying the composition of drug reservoir formulation and the permeability coefficient and thickness of the rate-controlling membrane.

E.g. Several FDA approved system –

1. Transderm-Nitro system for once-a-day medication of angina pectoris,
2. Transderm-Scop system for 3-day protection of motion sickness,
3. Catapres-TTS system for weekly therapy of hypertension,

2) Polymer Matrix Diffusion-Controlled TTD Systems

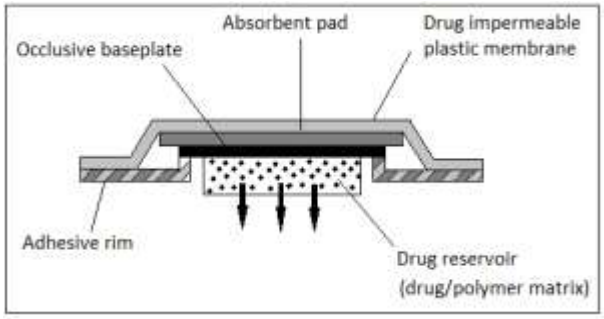

Fig. No.5: Cross-sectional view of polymer matrix diffusion-controlled TDDS

In this type the drug reservoir is formed by homogeneously dispersing the drug solid in a hydrophilic polymer matrix, and the medicated polymer formed is then molded into medicated disks with a defined surface area and controlled thickness. This drug reservoir-containing polymer disks is then mounted on occlusive base plate in a compartment fabricated from drug-impermeable plastic backing. In this system the adhesive polymer is applied along the circumference of the path to form a strip of adhesive rim surrounding the medicated disk.

E.g. Minitran system, Nitro DurII system for angina pectoris.

3) Drug Reservoir Gradient-Controlled TDD System:

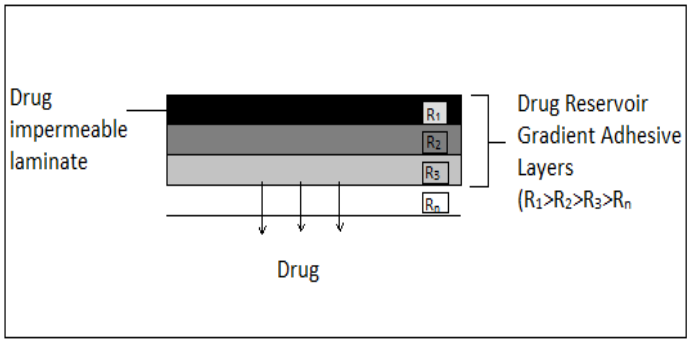

Fig.No.6: Cross-sectional view of a drug reservoir gradient-controlled TDDS

Polymer matrix drug dispersion-type TDD systems can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the m-ltilaminate adhesive layer.

E.g.Nitro-glycerine releasing TTD system, the Deponit system.

4) Microreservoir Dissolution-Controlled TTD Systems

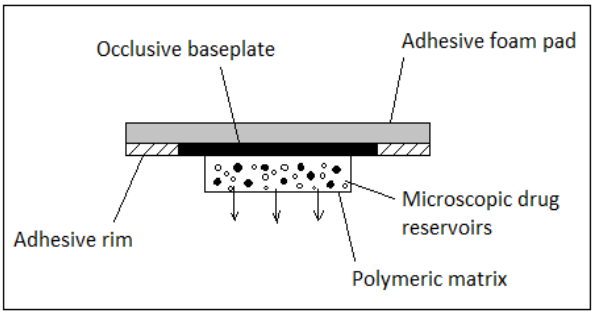

Fig.No.7:Cross-sectional view of a drug micro reservoir dissolution-controlled TDD system.

This type of drug delivery system can be considered a hybrid of the reservoir and matrix dispersion type drug delivery systems. In this approach the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer, e.g. polyethylene glycol and then homogeneously dispersing drug suspension, with controlled aqueous solubility in a lipophilic polymer, using high shear mechanical force to form thousands of unleachable microscopic drug reservoirs.

Thermodynamically unstable dispersion is quickly stabilized by immediately in situ cross linking of the polymer chains to form a medicated polymer disk with constant surface area and fixed thickness.

E.g. Nitrodisc system once a day treatment of angina pectoris.[17,26]

GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDS

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

1. TDDSs should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken or callused. Wet or moist skin can accelerate drug permeation time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved, nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.

2. Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.

3. Cutting should not physically alter TDDS, since this destroys integrity of the system.

4. The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds.

5. A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing or swimming.

6. A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system.

7. The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system.

8. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.

9. Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets.[27]

CONCLUSION:-

1) TDDS are topically administration of medicaments through the skin for systemic effects at a predetermined and controlled rate in the form of transdermal patches.

2) Transdermal drug delivery of antihypertensive drugs is able to provide optimum amount of drug to control the disease condition along with minimum side effects.

3) This review on different antihypertensive drugs showed that, by delivering drug through this route improves bioavailability a well as patient compliance.

4) This can also lead to cost effectiveness of healthcare treatment for the long term management of hypertension. But the main limitation is that, the drug should possess certain specific physicochemical properties which should be suited to permeate through the skin, therefore all antihypertensive drugs cannot be given by this route.

5) Transdermal drug delivery market is growing and there is a prospect of higher growth in this market over the next several years.

6) Transdermal delivery of antihypertensive drugs is expected to have a profound impact on patient care.

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