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A REVIEW - TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system is introduced to overcome the difficulties of oral route of administration of drug. It is important to prevent the problem of Presystemic metabolism and give systemic activity. It is a Targeted drug delivery system in which drug is mainly act at the site of infection. It is important drug delivery system to maintain the plasma steady state level of drug material. The 76% of drug can administered in oral route of administration it cannot give desired therapeutic activity, in case of drug under Transdermal drug delivery system it can give systemic activity in prolonged period of time and maintain its Therapeutic activity. Transdermal drug delivery system is act as micro emulsion, Transdermal patches, Niosomes, Ethosome and liposomal drug delivery system is act as Novel approach of carrier mediated drug delivery system. The present review describes Structure of skin, components, Approach and Evaluation of Transdermal Drug Delivery System.

KEYWORDS

Targeted drug delivery system, Controlled drug delivery system, Transdermal patches, Permeation enhancers, Ethosome and Matrix system.

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INTRODUCTON

The system to deliver a drug or the drug deliver to the system of body to produced therapeutic activity is known as drug delivery system[1]. Drug delivery system is mainly divided in two types, first is Conventional drug delivery system and second is Targeted drug delivery system[2]. The conventional drug delivery system contains Tablet, Capsule dosage form of medicament having limited rate of Absorption and decreases the Bioavailability of drug[3]. But Targeted

drug delivery system having drug can act as Targeted site of infection, it can include Transdermal drug delivery system in which rate of drug Absorption is increases, the rate of drug absorption is increases ultimately Bioavailability of drug is increases[4]. In Transdermal drug delivery system in which the drug Preparation or medicament is applied on the external surface of skin and Mucus membrane[5]. It is Novel drug delivery system or Targeted drug delivery system having important application to prevent the problem related Presystemic metabolism or systemic circulation[6]. In this type of drug delivery system can produces both type of effect local as well as systemic effect[7]. It is important to prevent the GI toxicity, Gastric irritation and GI Mucosal damages[8]. Transdermal drug delivery system is important to maintain the health of skin and prevent the infection of skin or mucus membrane, It can includes in Transdermal Medicament such as Ointment, creams, gels, Micro emulsions, Transdermal patches is important to prevent the infection of skin and maintain the appropriate health of skin[9].

Structure of Skin

Skin is major route of administration of transdermal product or preparations. Skin is transdermal organ having all transdermal products is applied on skin and give local as well as systemic activity[10]. The alternative name of skin is Integumentary system having a largest organ of body, about 16% of total adult body weight. It can required 1.5 to 2m^2 in area. It is protective organ of body and it can compose by two parts cutaneous membrane and accessory structures[11]. The important application of skin is protection; skin is important organ to protect the skin from U.V. light and other environmental pollutant. It also important to maintain pressure of body and regulation of body temperature[12]. Skin is applicable for production of vitamin D[13]. It is excretory organ of body is important to removal of waste material from body[14].

Skin is made by three layers, Epidermis, Dermis, Hypodermis or Subcutaneous layer

Epidermis

Epidermis is an outermost layer of skin it is made by stratified epithelium and proliferating basal differentiated suprabasal keratinocytes[15]. It is important to forms a protective barrier over the surface of body and it is responsible for keeping water in the body and preventing Pathogens from entering[16]. Epidermis is important application to regulate the body temperature. Epidermises also contain Merkel cells, melanocytes and Langerhans cells[17].

Epidermis can divided into following subtypes they as follows

1. Stratum corneum
2. Stratum lucidum
3. Stratum granulosum
4. Stratum spinosum
5. Stratum basale
6. Stratum Germinativum

Stratum corneum (Horny Layer)

Stratum corneum is ahorny layer and tightly packed scale-like cells[18].

Stratum lucidum

Stratum lucidum is a clear layer and it is a small, transparent cells[19].

Stratum granulosum

Stratum granulosum is a granular layer of cells that look like distinct granules like shape. These are the cells dying; in a horny zone[20].

Stratum spinosum (Prickly layer)

Stratum spinosum is a prickle cell layer and the cells undergo mitosis below, the cells are pushed upward direction into the basal layer[21].

Stratum mucosum (basal layer)

It is also called stratum germinativum, but it refers to lowest row of cells to make up basal layer in basal zone of living stratum[22].

Stratum Germinativum (Growing Layer)

Stratum Germinativum composed of single layer of cells and the lowest layer of cells are Composed by living stratum or basal layer and the cell undergoes mitosis, to replace older cells that are shed. 28 days for formation of pigment of granules produced here (melanocytes) is responsible for skin Colour[23].

The epidermal cell is represented by (Figure No.1) for better Understanding of classification or layers of epidermal cell as shown in (Figure No.1)[24].

Dermis

Dermis is second most important layer of skin is made of collagen and elastin or protein fibers and it can

provide strength and flexibility of skin. Dermis is Located between epidermis and subcutaneous layer. Dermis is a Network of nerves, blood and lymph vessels provide nutrition. Dermis is strongly or tightly connected to the epidermis through the basement membrane. Dermis can mainly divide into two types one is papillary layer and second is reticular layer. Papillary layer is consisting of areolar tissue as well as smaller capillaries, lymphatic and sensory neurons and reticular layer is consisting of dense irregular tissue and collagen or elastin fibers[25].

Hypodermis

It is also known as subcutaneous layer, is made by adipose and connective tissue. Hypodermis is a Fatty layer is located bottom side of skin is important function is Protective cushion for the outer skin[26]. For better understanding of Epidermis, Dermis, Hypodermis is shown in (Figure No.2)[27].

BASIC COMPONENTS OF TRANSDERMAL SYSTEM

Polymer matrix

The drug

Permeation enhancer

Other excipients

Polymer matrix

The polymer matrix is important type of component for preparation designing of transdermal drug product and formulation. Polymer selection of transdermal drug delivery system is important to maintain the stability of system. The polymer should be stable Stable in nature and they are non-reactive with the original drug moiety. It should be physicochemical stable, chemically innert, easily available and economical or inexpensive product. It should be maintaining their thermodynamic stability. They are mechanically stable and maintain their constant release property[28].

The different types of polymer are used for transdermal drug delivery system, the polymers used in transdermal drug delivery system is classify according to source of polymers they as follows[29]

Natural polymer

This are the polymers which are obtain in natural origin is known as Natural polymer. For Example- gelatin and cellulose derivative, various types of gums, and natural rubber polymers.

Synthetic Polymer

The polymer is prepared by laboratories and pharmaceutical industries. Example-Polybutadiene, silicon rubber, nylon.

Semi synthetic Polymer

The polymer which are obtain for both natural as well as synthetic origin known as semi synthetic polymer. Example - Cellulose nitrate and cellulose acetate.

Patterned for polymer used in Transdermal Drug Delivery system[30]

Rate controlling membrane

It is important to control the release rate of polymer contain in drug material and they are dispread in inert polymer matrix. The powder of polymer is mixed with drug material by using physical method and they are molded into the desired patterned or shape with appropriate thickness and surface area.

Adhesive

This are the chemically innert material having a maximum stability. It is important to maintain the contact of drug in transdermal drug delivery system. The drug material is dispersed in solution and suspension from. The quantity of drug material is penetrate or diffuses in skin is mainly depend on its holding capacity.

Release liners

It is important application to maintain the properties and characteristics of transdermal patch. It is important to give covering of patch for maintaining their stability in storage condition. The liner is removed before the used of patch over the surface of skin. The polyethylene and polyvinylchloride material is important for preparation of release liners.

Backing laminate

The baking laminate is important for polymer matrix system for preparation of transdermal product. It should be chemically innert and flexible system. It is having an ability to low the water vapour transmission rate is important to promote the skin hydration and maintain the permeability of skin. Examples - Polyethylene and polyester.

The drug

The drug is important component for preparation of transdermal drug product or material having appropriate physicochemical and pharmacokinetic properties[31]. The transdermal patches or transdermal drug delivery system of drug which undergoes first pass metabolism is responsible for the narrow therapeutic window. Ultimately the drug having a shorter half-life and it can cause the non-suitability or non-compliancy to that frequent dosing. E.g. DMSO[32].

Permeations Enhancer

It is third most important approach of component for preparation of transdermal drug delivery system. There are three main pathways for penetration of drug material through skin they are Polar, Non polar and Polar and Non polar. The polar pathways are responsible for protein conformation changes and swelling of the solvent material. The Non polar pathways are responsible for the altering the rigidity of lipid structure of molecule and the crystalline material of compound. The fatty acid is responsible for increasing the fluidity of lipid portion of Stratum Corneum layer of skin. Some other types of enhancers are act as both pathways polar and non-polar pathways is responsible for altering the penetration of multilaminate pathway. The permeation enhancer is increases the drug diffusivity of Stratum Corneum by denaturation of the skin protein. The Enhancers having a significant application for design and development of the drug product. The dermatological drug product for the systemic and controlled drug delivery system such as Transdermal drug delivery system is depends on the penetration of drug through the skin can produced desired therapeutic activity[33].

The drug penetration enhancer is mainly categorized in two pathways, they as follows

Chemical Enhancers

It is one of the most important penetration enhancer to penetrate the drug with skin. The chemical enhancer is important for the penetration of topically as well as Trans dermally applied drugs[34]. They are act as Accelerants of promoters to enhanced chemical penetration. The chemical Enhancer is mainly responsible for the increases the permeability of drug product through the skin. It is important for increasing the thermodynamic stability of drug material when it acts as functioning of cosolvents. It is important to increasing the partition coefficient of drug material and promotes the release of drug from the vehicles of the skin. It is important to promote the drug diffusion and increases the penetration of drug product[35].

Physical Enhancers

It is second most important penetration approach for penetration of drug product through the skin and maintain the permeability of drug material. The iontophoresis and ultra sound methods are used for enhancement of percutaneous penetration and absorption[36].

Other Excipients

Excipients are the chemically innert substances added along with drug, they are phytochemicals stable metabolically innert material and it should not react with original drug product. It is thermodynamically stable material[37]. Excipients are the Maintain its prolong stability in extended period of time. It can include in Additives, bonding agent, Disintegrants, membrane penetrant. The examples of transdermal drug delivery system is includes in Solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane. They are used to prepare drug Reservoir and matrix system and having a high penetration ability of drug to the skin. It is important to provide plasticity to the transdermal patch or drug delivery system[38].

APPROACHES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Membrane permeation - Controlled System

Adhesive Dispersion type system

Matrix Diffusion - Controlled System

Microreserviour type or Micro sealed Controlled System

Membrane permeation - Controlled System

The membrane permeation controlled system is important for determination of capacity of drug material or preparation to penetrate the surface of skin and mucus membrane. The drug material is mainly dissolved in solid matrix of polymer system and they are suspended to the Viscous Liquid medium. The material was allowed to Encapsulate in a shallow

compartment and drug material is impermeable to metallic plastic laminate. The system is important to control the rate of Polymeric membrane system. The release of drug molecule is only penetrate through the rate controlling polymeric membrane system. The micro porous or non-porous polymeric membrane having a rate limiting membrane system is responsible for known drug permeability property. The thin or transparent layer drug molecule is compatible with hypoallergenic adhesive polymer system, this type of system is important to maintain the appropriate contact between drug delivery system with the surface of skin. The polymer composition, permeability of system, Thickness of rate limiting membrane System and quantity of adhesives are changing is responsible for determination of rate of release of drug from Transdermal drug delivery System[39].

The intrinsic rate of drug release from the drug delivery system is given by,

DQ/dT= CR/1/Pm+1/Pa

Where,

CR= Drug concentration in the reservoir compartment.

Pa= Permeability co-efficient of the adhesive layer.

Pm= Permeability co-efficient of rate controlling membrane.

The Cross Section view of Membrane permeation - controlled system is shown in (Figure No.3).

Adhesive Dispersion type system

It is similar to the membrane controlled system or simple from of membrane controlled system. The drug material is directly dispersing on the adhesive polymeric system is important to formulate the drug reservoir system. The thin drug reservoir system is formed by spreading medicated adhesive material in flat sheet of drug impermeable metallic plastic plates. The top layer of the reservoir system having a non-medicated rate controlling adhesive polymeric system is maintain the constant thickness. Drug molecule in adhesive patch system must be signal layer or multiple layer. The multi-layer system is different criteria as compared to the signal phase system. The signal layer system is adding another layer of the drug adhesive mixture having two separate membranes System. It is important type of system is improved the patient acceptance and compliances Due To Their Easy Application on The Surface of Skin. It is important for acceptance of the cosmetic drug delivery system having a good adhesion property[40].

The simple Diagrammatic view for the better understanding the concept of adhesive dispersion system is shown in (Figure No.4)

Matrix Diffusion - Controlled System

The drug material is dispersed in insoluble from of matrix contain in rigid and non swellable hydrophobic material. The Material used in formation of rigid matrix they are insoluble plastic materials, such as PVC and fatty materials like stearic and beeswax. The plastic material of the drug is react with the solution of the polyvinyl chloride is act as an organic solvent and they are granulated with waxy matrix from of material is prepared by the dispersion of drug material molten fat and they followed by congealing. The granules of the material undergoes compression to from tablets are swellable matrix system are popular for the sustained activity for the highly water soluble drug materials. The material such as naturally, semi synthetically and synthetically occurring drug material. The gums are granulated by come into contact with the solvent material. The release of drug is depends on the dehydration of hydrogels involves simultaneous absorption of water and drug material having diffusion mechanism of controlled swelling. The gum material are swells and they are diffuses or transported[41].

The diagrammatic representation of Matrix diffusion - controlled system is shown in (Figure No.5)

Microreserviour type or Micro sealed Controlled System

It is most important type of approach in Transdermal drug delivery system. In this Microreserviour system is a combination of Reservoir and matrix drug delivery system. The drug reservoir system is formed by suspending the solids of drug in aqueous solution of the water soluble nature of polymeric system. The suspension of drug material is dispersed in homogeneously with lipophilic nature of polymer with the help of high energy dispersion technique of Unreachable microspheres of reservoir. The dispersion of drug material homogeneously and maintain their thermodynamic stability by immediately cross linking the polymeric chains. The insitu procedure of

medicated polymeric disk can maintain the constant surface area and fixed thickness and the example is a Nitro disks[42].

The rate of drug release is given by[42],

$$\frac{dQ}{dt} = \frac{D_P D_d m K_p}{D_P h_d + D_d h_p m K_p} nSp \frac{D_l S_l (1-n)}{h_l} (1/K_l + 1/K_m)$$

Where,

m = a/b

a - Ratio of drug conc. in the bulk of medium over drug solubility in the same medium.

b - Ratio of drug conc. at the outer edge of polymer coating & drug solubility in the same.

n - Ratio of drug conc. at the inner edge of inter facial barrier over drug solubility in the

Polymer matrix.

Dl, Dp, Dd - drug diffusivity in liquid layer surrounding drug particles, polymer coating membrane surrounding polymer matrix and hydrodynamic diffusional layer surrounding polymer coating with thickness of hl, hp, hd.

Kl, Km, KP - partition coefficient for inter facial partitioning of drug from liquid to Polymer matrix, from polymer matrix to polymer coating membrane and then to the skin.

SL and Sp - solubilities of drug in liquid compartment and polymer matrix.

The diagrammatic representation of Microreserviour type of system is shown in (Figure No.6)

ADVANTAGES

It can give local and systemic activity and it can prevent problem related to the first pass metabolism, it is directly absorbed in systemic circulation and give systemic activity[43].

It is nontoxic, non-irritant, physicochemically stable system of medicament and having optimum viscosity for easy application on skin[44].

It can prevent problem associated to the GI tract infection and GI instabilities[45].

It can easy to apply the skin and maintain the health of skin[46].

It is important to provide Steady plasma level and shows rapid or systemic activity[47].

DISADVANTAGES

Some Time local irritation may be develop at site of application of skin or the surface of skin[48].

The excessive quantity of drug in patch during application can causes Erythema, itching and skin injury[49].

The optimum quantity of lipophilic drug material is allow to penetrate or delivered through the skin[50].

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Drug content determination

Drug content is important for determination of percent content of drug product. The accurate quantity of drug material is weighed and added into the 100 ml of suitable solvent. The mixture of solvent is shacked continuously for 24 h in shaker incubator. The complete mixture of drug containing solution is sonicated and filtered. The solution mixture is analysed by spectrophotometry by preparing a specific dilutions[51].

Moisture Content

It is important for determination of moisture contamination of drug product and formulation. The formulation are come into content with external environment drug product to decreases there stability and decomposition is arises. The percent content of moisture is calculated by using following formula[52],

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

Stability studies

Stability is important for determination of appropriate properties and characteristics of drug product and formulation. Stability is direct function to that activity. The thin film of drug material is placed in USP type 1 amber coloured vials. Vials are the completely closed and sealed and vials are placed in stability chamber at 40˚c temperature. The atmospheric humidity (RH) is 65% for the next three months. At particular time period films are withdrawn and evaluated the drug

material for determination of their physical properties and drug content[53].

Water vapour permeability

The glass vials having 5 ml capacity and they are washed thoroughly. After the vials are dried in to oven. The 1 gm of calcium chloride is taken from the vials and fixed the film of polymer with the help of adhesive tape. The vials are stored in humidity chamber at 85% for 24 hrs. The vials are removed from humidity chamber from 3, 6, 12, 18, min. of interval and the weight gain is determined[54].

Skin irritation test

It is important type of study for determination of irritation of skin. It is important for determination of skin sensitivity and irritancy. In this type of test is mainly conducted in healthy rabbits. The formulation of drug product is applied on the surface of the skin of rabbit. The transdermal patch is applied on the surface of rabbit skin. After 24 hrs. The patch is removed and observed the surface of skin for determination of injury of skin[55].

APPLICATION

Transdermal drug delivery system is important to prevent problem associated to first pass metabolism or Presystemic metabolism and give local and systemic activity[56]. Transdermal gel is important application to prevent the irritation of skin[57]. Ethosome in Transdermal drug delivery systemis a Novel Approach is used for increases the rate of drug absorption and penetration of skin to give maximum bioavailability[58]. Transdermal drug delivery system is important for micro emulsion, Nanoemulsion, Liposomal approach for prevention of skin infection[59]. Transdermal drug delivery systems is an important application for the Transdermal patches and Transferosomes novel carrier approach for prevention of injury of skin and maintain the health of skin[60].

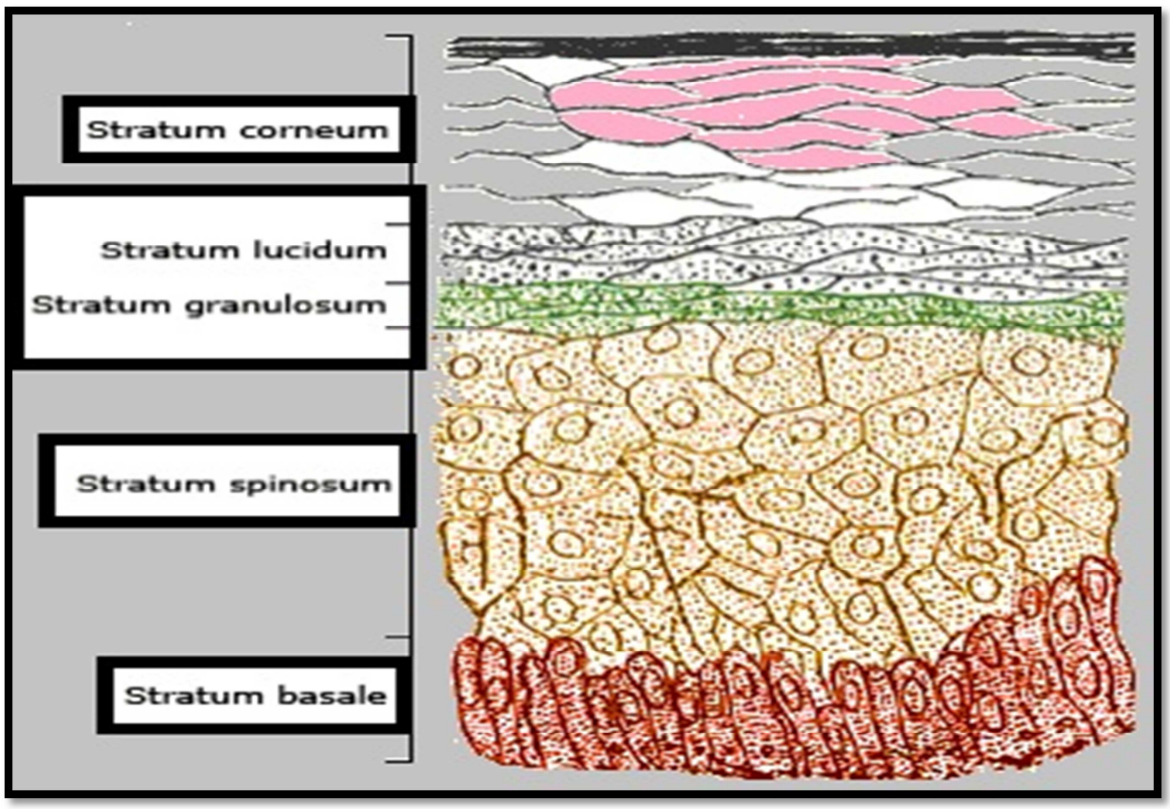

Figure No.1: Diagrammatic view of Epidermis

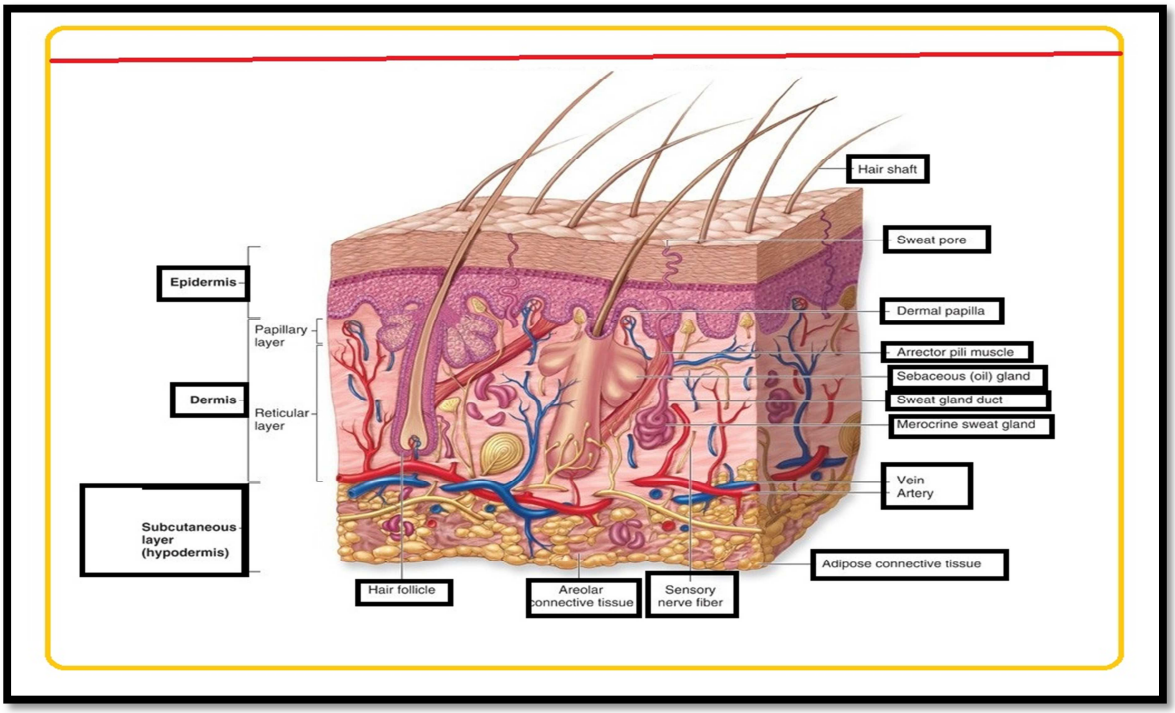

Figure No.2: Anatomy of skin

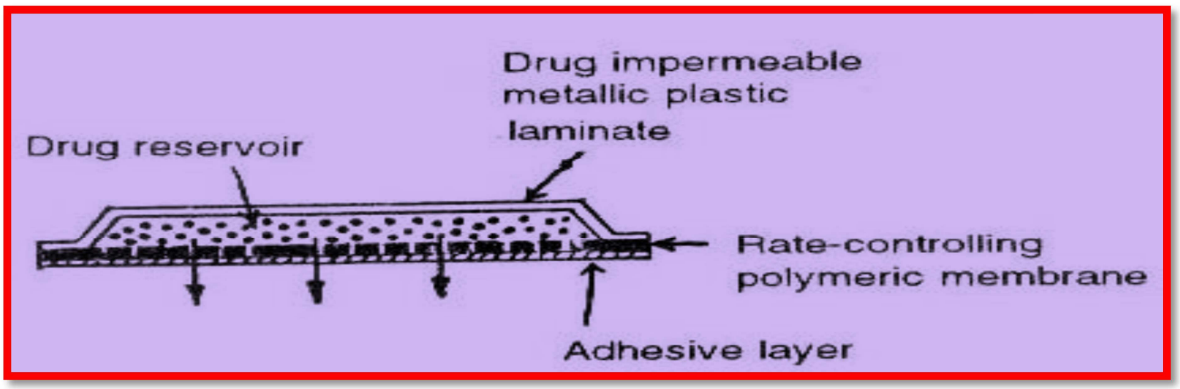

Figure No.3: Membrane permeation - controlled system

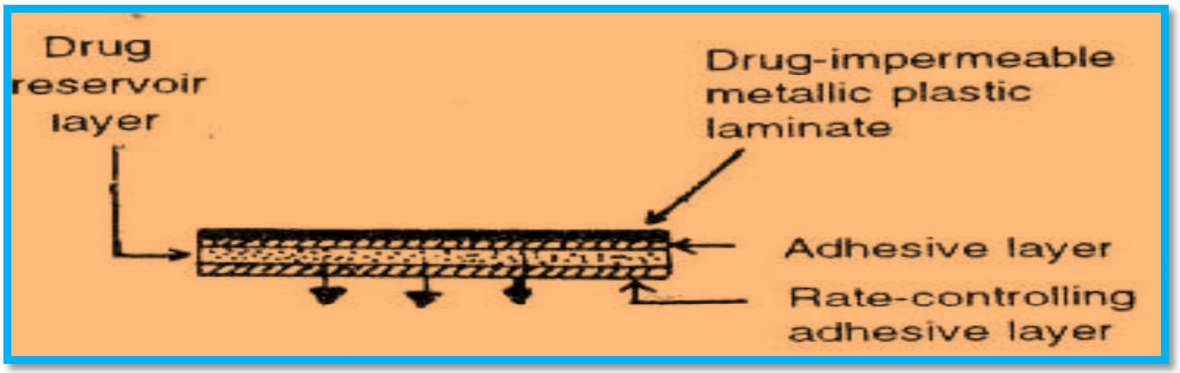

Figure No.4: Adhesive dispersion system

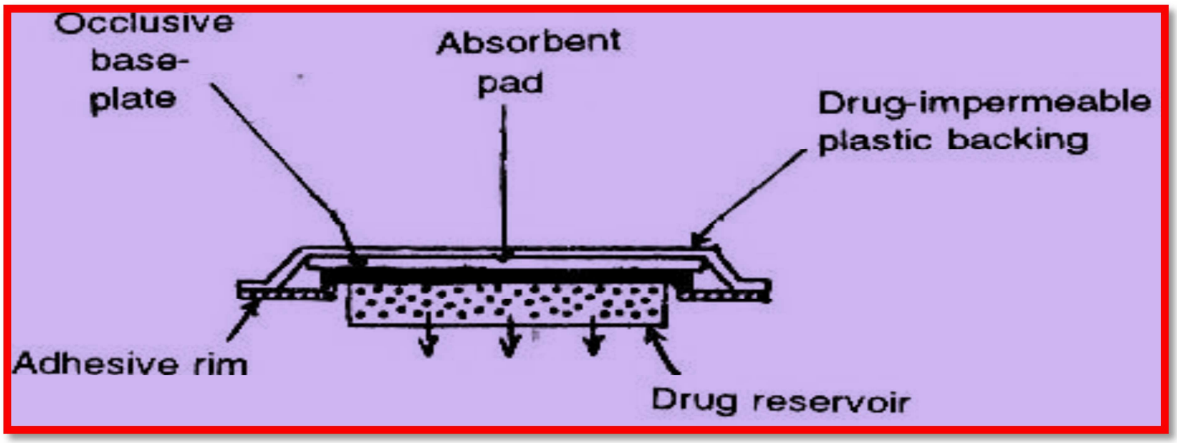

Figure No.5: Matrix diffusion - controlled system

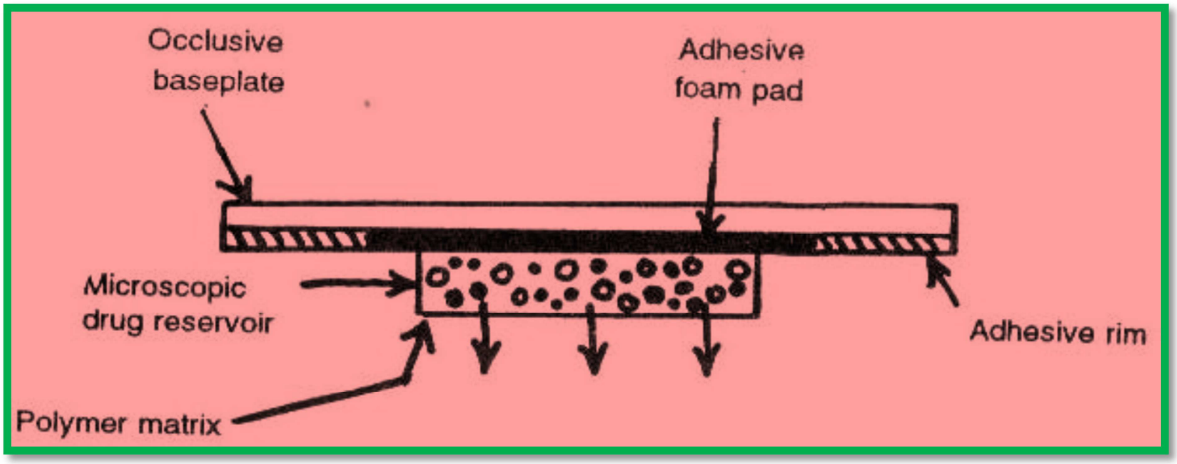

Figure No.6: Micro reservoir type of system

CONCLUSION

The Transdermal drug delivery system is a targeted and controlled drug delivery system in which drug or formulation of drug is mainly act as targeted site of infection. In transdermal drug delivery system some important approaches to prevent the infection of skin and maintain the health of skin, the approaches such as Membrane permeation Controlled System, Adhesive Dispersion type system, Matrix Diffusion Controlled System, Micro reservoir type of System, Membrane permeation Controlled System. Transdermal drug delivery system is act as a Micro emulsion, Nanoemulsion, Liposomal delivery, Ethosome, Niosomes, Transdermal Patches and Transferosomes containing Novel Carrier Drug Delivery system is used to prevent the infection of skin. The new Research and Discoveries for this Transdermal drug delivery system for incorporation of newer drugs or medicaments. The Present article to give Valuable information regarding skin, structure of skin, components, approaches and Evaluation of Transdermal drug delivery system.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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