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Review Article

A NOVEL TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Trasdermal drug delivery system is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. This review article is written to provide a coverage commentary of the recent advancements in TDD enhancement techniques. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. The present review article explores the overall study on transdermal drug delivery system (TDDS) which leads to novel drug delivery system (NDDS).

Key words: Transdermal, skin penetration, bioavailability, Permeation enhancers.

INTRODUCTION:

Transdermal drug delivery systems (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation[1-3]. TDDS in comparison to conventional pharmaceutical dosage forms, offer many advantages, such as reduced side effects, improved patient compliance, elimination of first-pass metabolism, and sustained drug delivery[4-6]. Cardiovascular diseases account for a large proportion of all deaths and disability worldwide. At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient[7].

PERMEATION ENHANCERS:

Three pathways are suggested for drug penetration through the skin: polar, non-polar, and polar/non-polar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the Stratum Corneum. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. Enhancers can increase the drug diffusivity in the Stratum Corneum (SC) by dissolving the skin lipids or by denaturing skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. The success of dermatological drug products that are intended for systemic drug delivery, such as the transdermal, depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve its desired therapeutic effect. The methods employed for modifying the barrier properties of the SC to enhance the drug penetration (and absorption) through the skin can be categorized as (1) Chemical and (2) physical methods of enhancement[8].

CHEMICAL ENHANCERS

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers. Chemical enhancers act by

1. Increasing the drug permeability through the skin by causing reversible damage to the SC.
2. Increasing (and optimizing) thermodynamic activity of the drug when functioning as co solvent.
3. Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin.
4. Conditioning the SC to promote drug diffusion.
5. Promoting penetration and establish drug reservoir in the SC.

PHYSICAL ENHANCERS

The iontophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents[9].

ROUTES FOR DRUG PENETRATION THROUGH SKIN –

There are two major routes named as Macro (Fig. 1) and Micro(Fig. 2) routes.

FACTORS AFFCETING DRUG PENETRATION

The physicochemical nature of the drug particularly size, solubility and partition coefficient

1.The timescale of observation

2.The site and condition of the skin

3.The formulation

4.How vehicle components temporarily change the properties of the stratum corneum

CLASSIFICATION OF TDDS

1. Matrix System: Drug in Adhesive System (Adhesive Diffusion Controlled TDDS) (fig.3)

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer. The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery system.

Deponit® (Nitroglycerine) for once a day medication of angina pectoris

2. Matrix System: Matrix Dispersion System (Matrix Diffusion Controlled System)[10, 11, 12] (Fig. 4)

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix.

This drug containing polymer disk then is fixed onto 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 the circumference to form a strip of adhesive rim.

Nitro Dur® (Nitroglycerine) used for once a day medication of angina pectoris[10-12]

3. Reservoir System (Membrane Moderated TDDS): (Fig. 5)

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 microporous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied. The rate of drug release from this type of transdermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate controlling membrane.

TransdermScop® (Scopolamine) for 3 days protection of motion sickness and TransdermNitro® (Nitroglycerine) for once a day medication of angina pectoris[10-12].

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ. A transdermal system therapeutic system thus formed as a medicated disc positioned at the centre and surrounded by an adhesive rim. Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.

TYPES OF TRANSDERMAL PATCHES

Four Major Transdermal Systems

1. Single Layer Drug In Adhesive

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film9. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The intrinsic rate of drug release from this type of drug delivery system is defined by

$$dQ/dT = \frac{Cr}{1/Pm + 1/Pa}$$

Where,

Cr is the drug concentration in the reservoir compartment and Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane, Pm is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. Pm and Pa, respectively, are defined as follows.

$$Pm = \frac{K_{m/r}.Dm}{hm}$$

$$Pa = \frac{K_{a/m}.Da}{ha}$$

where Km/r and Ka/m are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and hm and ha are the thicknesses of the rate controlling membrane and adhesive layer, respectively[13].

2. Multilayer Drug In Adhesive

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

The rate of drug release in this system is defined by:

$$dQ/dt = \frac{K_{a/r}.Da}{ha} Cr$$

Where

Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

3.Drug Resrvoir In Adhesive

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

The rate of drug release from this drug reservoir gradient controlled system is given by:

$$dQ/dt = \frac{K_{a/r}.Da}{ha\ (t)} A\ (ha)$$

In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time ha (t). To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusion path A (ha).

4. Drug Matrix In Adhesive

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. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix, Where A is the initial drug loading dose dispersed in the polymer matrix and Cp and Dp are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, Cp is essentially equal to CR, where CR is the drug concentration in the reservoir compartment.

BASIC COMPONENT OF TDDS:

1. Polymer matrix / Drug reservoir.
2. Selection of drug
3. Permeation enhancers.
4. Pressure sensitive adhesive (PSA).
5. Backing laminates.
6. Release liner
7. Other excipients like plasticizers and solvent

1. **POLYMER MATRIX/DRUG RESERVOIR SYSTEM**

Polymers are the heart of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide effective released of a drug throughout the device with safe status.

THE POLYMER USED FOR TDDS CAN BE CLASSIFIED AS:

Natural Polymer: e.g. cellulose derivatives, zein, gelatine, shellac, waxes, gums, natural rubber and chitosan *etc*.

Synthetic Elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*.

Synthetic Polymer: e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*. The polymer like polyethylene glycol, eudragits , ethylcellulose, polyvinylpyrrolidone and hydroxy-propylmethylcellulose are used as matrix type TDDS. The polymers like EVA , silicon rubber and polyurethane are used as rate controlling TDDS[14-19].

2. **SELECTION OF DRUGS:** The selection of drug for TDDS is based on physicochemical properties of drug. Transdermal drug delivery system is much suitable for drug having [20, 21.]

1. Extensive first pass metabolism.
2. Narrow therapeutic window.
3. Short half-life which causes non-compliance due to frequent dosing.
4. Dose should be less (mg/day) [22].
5. Low molecular weight (less than 500 Daltons).
6. Adequate solubility in oil and water (log P in the range of 1-3).
7. Low melting point (less than 200°C).

3. **PERMEATION ENHANCERS:**

These compounds are useful to increase permeability of stratum corneum by interacting with structural components of stratum corneum *i.e.,* proteins or lipids to attain higher therapeutic levels of the drug [23]. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability [24]. Some example are Dimethyl sulfoxide, Propylene glycol,2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic, Cardamom oil, Caraway oil, Lemon oil, Menthol, dlimonene, Linoleic acid [25].

4. PRESSURE SENSITIVE ADHESIVE:

The pressure-sensitive adhesive (PSA) affixes the transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure,

be aggressively and permanently tachy and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue . Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability.

PSAs used in commercially available transdermal systems include polyacrylate, polyisobutylene and polysiloxane [28]. Polyacrylates are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices. Polyisobutylenes (PIBs), in contrast, are characterized by a low solvent capacity for drugs. PIBs are often used in membrane-controlled systems where the initial burst of drug released from the adhesive layer should be limited. PIB-based adhesives are mixtures of high and low molecular weight polymers, which provide cohesion and tackiness, respectively. By adjusting the composition of the PIB formulation, cold flow and adhesiveness can be customized for each system.

Silicone, adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups. Hot Melt Pressure Sensitive Adhesives (HMPSA), HMPSA melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flowless state. They are thermoplastic in nature.

5. BACKING LAMINATE:

Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear, pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate [29].

are Ethylene vinyl acetate copolymers, Paraffin waxes, Low density polypropylene, Styrene-butadiene copolymers, and Ethylene-ethacrylate copolymers. Uncompounded HMPSA are Polyesters, Polyamides and Polyurethanes.

Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate.

6. RELEASE LINERS:

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug.

However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements

regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*e.g.* paper fabric) or occlusive (*e.g.* polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon.

Other materials used for TDDS release liner include polyester foil and metalised laminates [30].

7. OTHER EXCIPIENTS:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutyl pthalate, triethyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch [31].

ADVANTAGES[31]

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failure frequently associated with intermittent dosing can also be avoided.
2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
3. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.
4. The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.
5. At times the maintenance desired. Application and removal of transdemal patche produce the optimal effect of pharmacological effect.
6. Self-administration is possible with these systems.
7. Drug input can be terminated at any point of time by removing transdermal patch.

DISADVANTAGES[31]

1. Drug dose is large.
2. Drug has larger molecular size (makes absorption difficult; should be ideally be below 800-1000daltons)
3. Drug is sensitising and irritating.
4. Drug is metabolised in skin.
5. Drug undergoes protein binding in skin.
6. Drug is highly lipophilic or hydrophilic (should be moderately soluble in both oil and water)

APPLICATIONS OF TRANSDERMAL PATCHES

1. The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
2. Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).
3. Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).
4. Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
5. The anti-hypertensive drug Clonidine is available in transdermal patch form.
6. Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
7. Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

THE FUTURE SCOPE OF TRANSDERMAL PATCHES

1. An insulin patch
2. Sufentanil patch for chronic cancer pain
3. Varenicline patch for smoking cessation
4. Estrogen and testosterone patches for post-menopausal women
5. Selegiline patch for depression in the elderly and cocaine addiction
6. Clonidine transdermal for the treatment of delerium in trauma patients
7. Dexamethasone iontophoretic delivery for the treatment of tennis elbow
8. An iontophoretic sumatriptan patch for migraine treatment, and
9. Transdermal glyceryl trinitrate for acute stroke therapy, to name a few

CONCLUSION

Transdermal drug delivery system is useful for topical and local action of the drug. The drug which shows hepatic first pass effect and unstable in GI conditions, are suitable candidate for TDDS. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration and many new researches are going on in the present day to incorporate newer drugs via the system. The properties of the drug, the characteristics of the transdermal device, selection of in-vivo model and the status of patient's skin are all important for safe and effective drug delivery. The transdermal drug delivery system could be one day one of the best novel drug delivery system.

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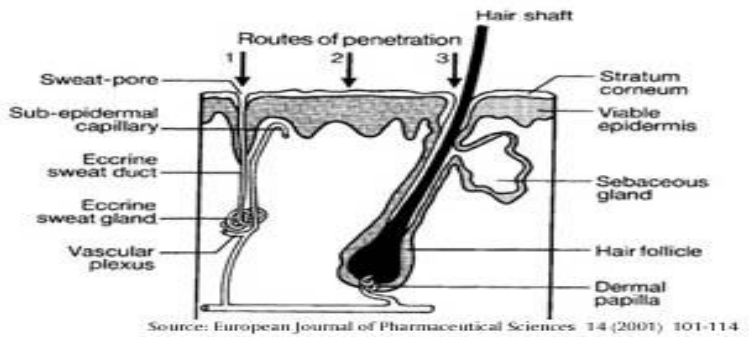

FIGURE 1: DRUG PERMEATION THROUGH THE SKIN

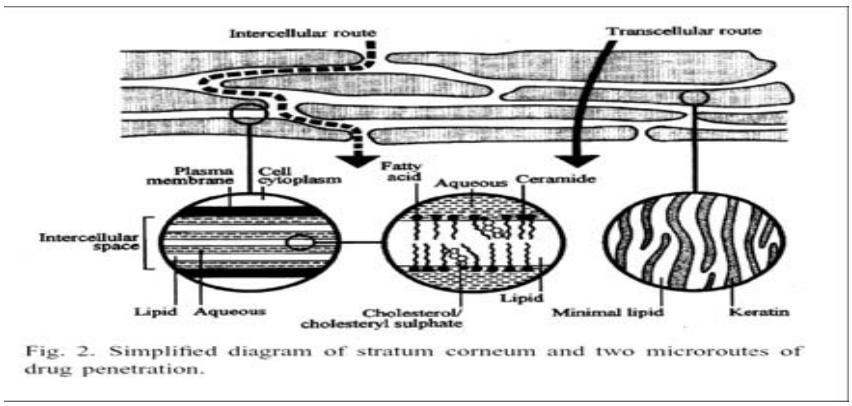

FIGURE 2: MECHANISAM OF SKIN PERMEATION

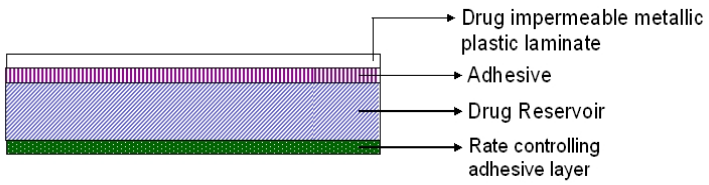

FIGURE 3: DRUG IN ADHESIVE TYPE OF PATCH

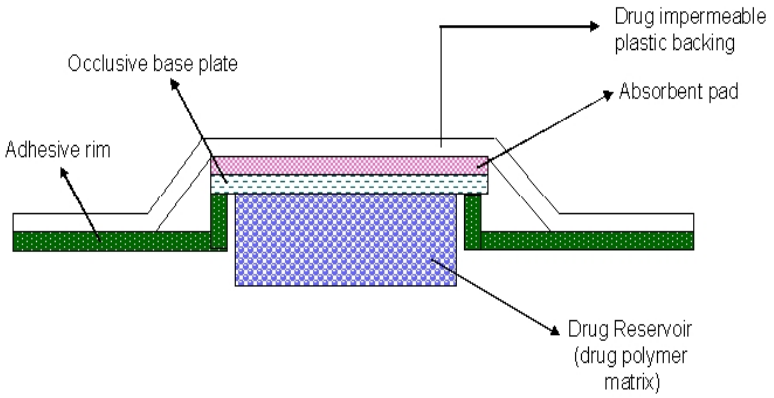

FIGURE 4: MATRIX DISPERSION SYSTEM

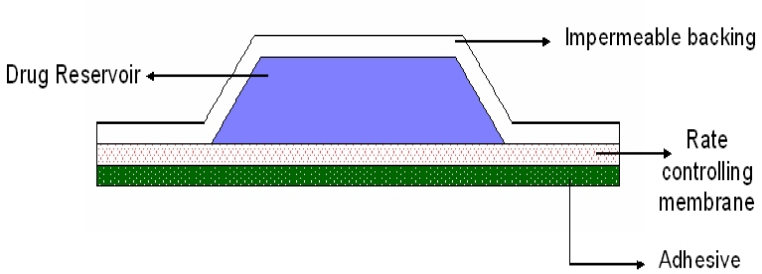

FIGURE 5: RESERVOIR TRANSDERMAL PATCH

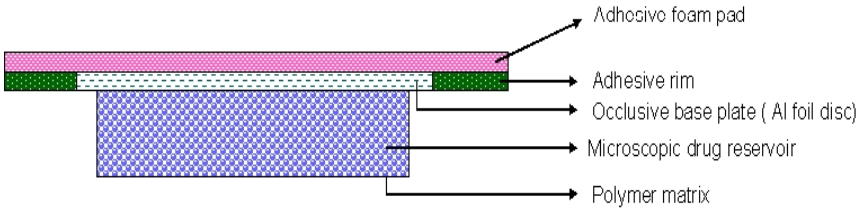

FIGURE 6: MICRORESERVOIR SYSTEM

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