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A brief Review on Transdermal Patches

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Abstract:

The skin is the largest epithelial surface of the human body. As an external organ, it is vulnerable to over 3,000 potential skin disorders, including injuries, inflammation, infections from microbes and viruses, as well as skin cancer. Transdermal delivery offers a non-invasive method for drug administration through the skin, allowing for the controlled release of medication at a specified rate across the dermis to achieve either localized or systemic effects. This approach may serve as an alternative to oral medications and hypodermic injections.A transdermal patch is a medicated adhesive device applied to the skin, designed to release drugs systematically at a predetermined rate over an extended timeframe to ensure absorption. Its primary advantages include controlled drug release with minimal side effects, enhanced bioavailability, and avoidance of first-pass metabolism, among others. Various physiochemical and biological factors can influence the bioavailability of transdermal medications. Different types of transdermal patches can be created using various methods. The evaluation of transdermal patches involves assessing interaction studies, folding endurance, patch thickness, weight uniformity, drug content, and in vitro studies. This review discusses general aspects such as the advantages, preparation methods for transdermal patches, evaluation processes, and the basic components involved in transdermal drug delivery.

Key Words : Skin- as an external organ, Medicated adhesive patch, Approches of Transdermal patch, Polymer matrix, Methods and Evaluation , Future.

Introduction :

As the body's largest external organ with a significant epithelial surface area, the skin is susceptible to numerous environmental factors, including pathogens and harmful chemicals. Consequently, skin disorders are among the leading contributors to the global disease burden, affecting millions worldwide. Over 3,000 different types of skin conditions, ranging from eczema to skin cancer, have been documented among patients. Effective treatment options for skin diseases involve either systemic delivery (such as oral, sublingual, buccal, subcutaneous, intramuscular, and intravenous routes) or topical drug application (see Figure 1). When medications are taken orally, they are often rapidly metabolized by the liver, leading to diminished bioavailability before reaching their intended target, which necessitates administering a higher oral dose compared to intravenous administration.Dermal and transdermal delivery methods offer an alternative to oral and injectable routes. These methods provide predictable and prolonged drug activity, eliminate gastrointestinal absorption issues, allow for controlled and adjustable dosages, and enhance patient compliance, making them ideal candidates for next-generation drug delivery systems. However, transdermal patches can cause skin irritation, and various external factors

might prevent them from adhering properly. Additionally, not all medications are suited for this delivery method, as the low permeability of the skin can restrict the absorption of certain drugs. Despite these challenges, transdermal drug delivery has significantly advanced medical practice by enabling controlled and minimally invasive drug release for the treatment of skin diseases. To date, a variety of drugs have been successfully delivered using dermal and transdermal adhesive patches, although these patches often face challenges in penetrating the stratum corneum, the skin's outermost layer. To address this issue, microneedles—tiny needles incorporated into patches—have been developed to facilitate drug penetration. However, limitations still exist regarding the types of drugs and their maximum dosages that can be effectively loaded into these patches. To tackle this challenge, innovative polymers have been designed and developed to enhance the advantages of these technological solutions and broaden their applicability in drug delivery across diverse medical fields. [1][2]

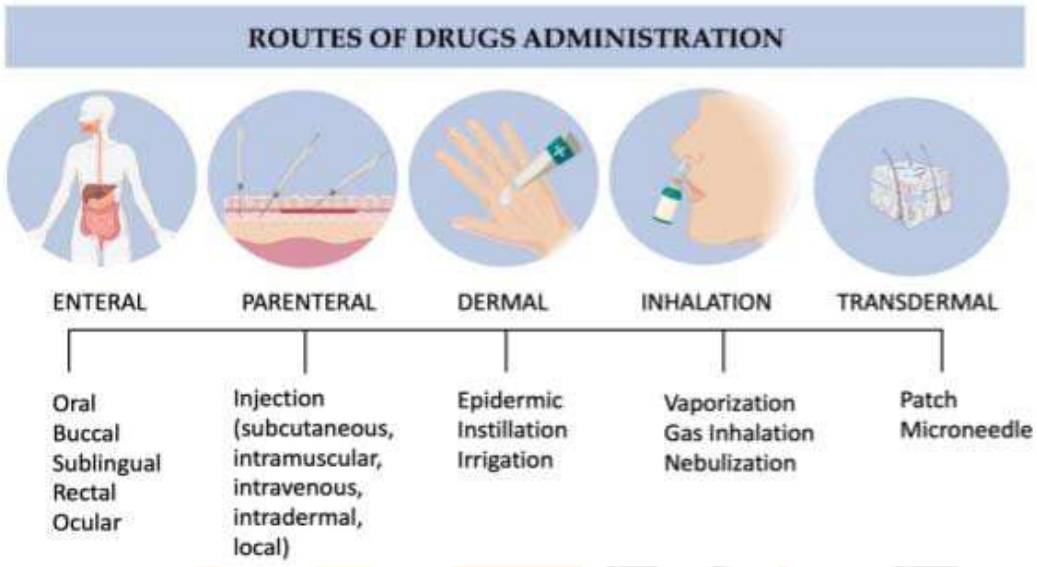

Fig 1. Main drug administration routes.

Transdermal patches have become increasingly popular for cosmetic, topical, and transdermal delivery purposes. These patches are a significant achievement resulting from advancements in skin science, technology, and expertise, developed through a combination of trial and error, clinical observations, and evidence-based research that dates back to ancient human history. This review starts by exploring the origins of topical therapies and follows the evolution of topical delivery methods to modern transdermal patches. It outlines the initial experiments, devices, and drug delivery systems that form the foundation of contemporary transdermal patches and their active ingredients. The discussion then shifts to the advancements in patch designs, their limitations, and the criteria that active ingredients must meet for effective transdermal delivery. Additionally, it addresses the properties and challenges associated with currently available products, including variability, safety concerns, and regulatory factors. The review concludes by looking ahead at the future opportunities for transdermal patches and drug delivery systems. [4]

Anatomy and physiology of skin :

Human skin comprises of three distinct (Keleb et al 2010) but mutually dependent tissues: · The stratified, vascular, cellular called as “epidermis” · Underlying dermis of connective tissues · Hypodermis (Figure 2).

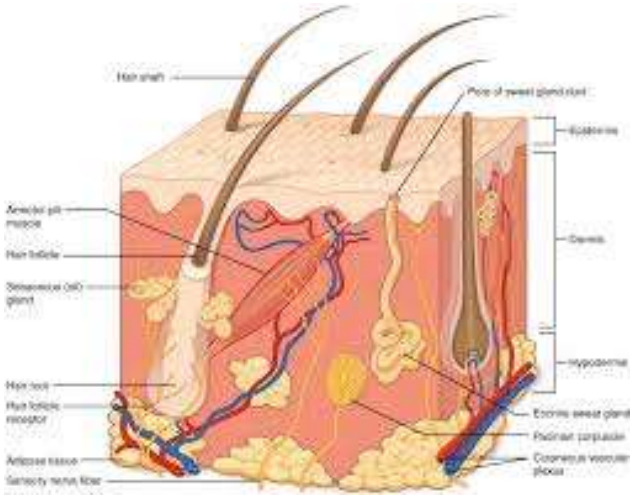

Fig no 2 Anatomy and Physiology of skin

1)Epidermis :-

The epidermis is a multilayered structure that varies in thickness due to differences in cell size and the number of cell layers, measuring around 0.8 mm on the palms and soles, and as thin as 0.06 mm on the eyelids.

Stratum corneum

Known as the outermost layer of skin, the stratum corneum, or horny layer, has an approximate thickness of 10 mm when dry, but can swell to several times that thickness when fully hydrated. This layer comprises 10 to 25 layers of dead, keratinized cells referred to as corneocytes. While it is flexible, it remains relatively impermeable. The stratum corneum serves as the primary barrier against the penetration of drugs. Its structure can be likened to a wall, with keratinized cells acting as protein "bricks" held together by lipid "mortar." These lipids are arranged in multiple bilayers, and there is enough amphiphilic material in the lipid fraction, including polar free fatty acids and cholesterol, to maintain the bilayer configuration.

Viable epidermis

Located beneath the stratum corneum , the viable epidermis exhibits a thickness that ranges from 0.06 mm on the eyelids to 0.8 mm on the palms. As one moves inward, this layer consists of several sub-layers: stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Within the basal layer, cell mitosis continuously renews the epidermis, with this proliferation compensating for the loss of dead horny cells from the skin surface. As the basal layer's newly produced cells migrate outward, they undergo morphological and histochemical changes, leading to keratinization and the formation of the outermost stratum corneum layer.

2)Hypodermis

The hypodermis, also known as subcutaneous fat tissue, serves to support both the dermis and epidermis. This layer acts as a storage area for fat and plays a vital role in temperature regulation, providing nutritional support, and offering mechanical protection. It contains major blood vessels and nerves that supply the skin and may also house sensory organs associated with pressure. In the case of transdermal drug delivery, the substance must penetrate all three skin layers to enter systemic circulation. Conversely, for topical drug delivery, it is sufficient for the drug to penetrate the stratum corneum, after which retention within the skin layers is desirable (Tortora, 1999; Schofield and Rees, 2002; Vyas and Khar, 2012).

3)Dermis :-

The dermis is a layer that measures between 3 to 5 mm in thickness and is formed from a matrix of connective tissue that includes blood vessels, lymphatic vessels, and nerves. The blood supply within the skin plays a crucial role in regulating body temperature and delivers vital nutrients and oxygen while facilitating the removal of toxins and waste. Capillaries

extend to within 0.2 mm of the skin's surface, creating sink conditions that favor the uptake of most molecules that penetrate the skin barrier. Consequently, this blood supply maintains low concentrations of permeating substances in the dermis, leading to a concentration gradient across the epidermis that is essential for transdermal permeation [3]

History:-

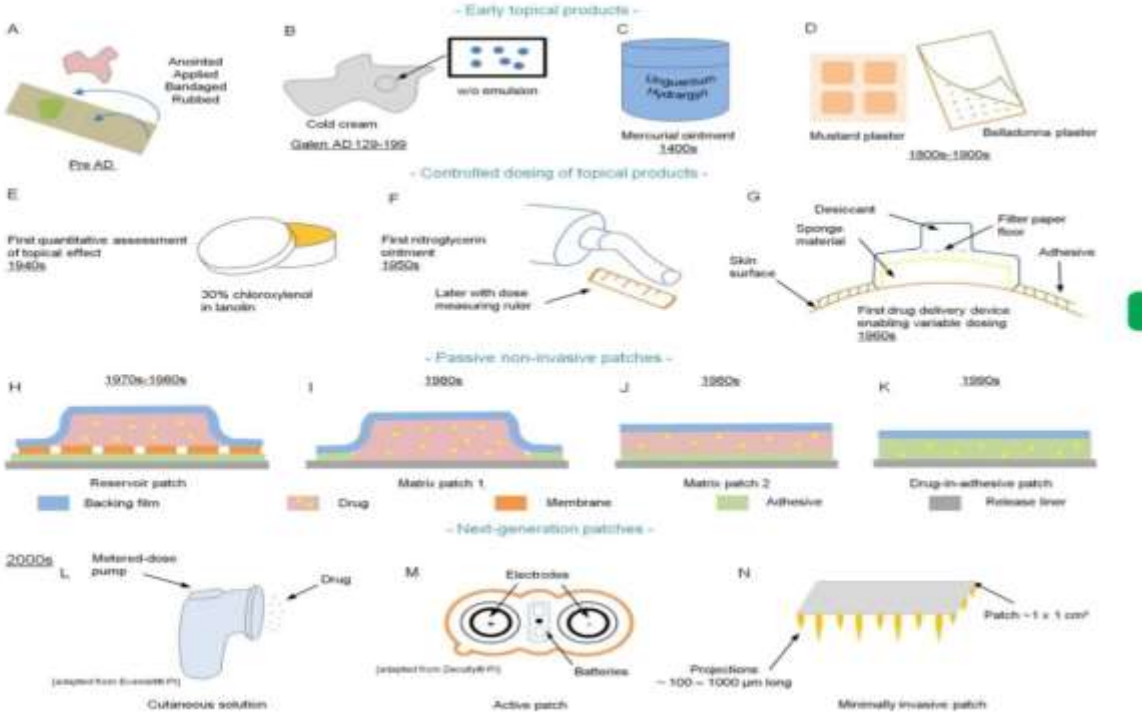

Fig no 3 History

Historical development of patches. Early topical products: (A) products from ancient times; (B) Galen's cold cream; (C) mercurial ointment; (D) mustard and belladonna plasters; controlled dosing of topical products. (E) First quantitative systemic delivery (Zondek's system). (F) Individualized delivery system: nitroglycerin ointment. (G) Topical delivery device (Wurster & Kramer's system). Passive non-invasive patches. (H) First patch system – the reservoir – introduced for scopolamine, nitroglycerin, clonidine and oestradiol. (I, J, K) Other types of patches – matrix and drug-in-adhesive (e.g. fentanyl and nicotine patches). Next-generation patches. (L) Cutaneous solutions (e.g. Patchless Patch®, Evamist®). (M) Active patches (e.g. iontophoresis, Zecuity®). (N) Minimally invasive patches (e.g. microneedles, Nanopatch®) [4]

Merits :

1) It bypasses first-pass metabolism.

2) The duration of action can be both extended and predictable.

3)The use of transdermal drug delivery systems (TDDS) is advisable to address challenges related to drug absorption in the gastrointestinal tract.

4) TDDS can serve as an alternative to oral medications in cases where the oral route is impractical, such as for patients experiencing vomiting or diarrhea.

5) It allows for the maintenance of drug plasma concentrations.

6) As a non-invasive method, TDDS avoids the inconveniences associated with parenteral therapy.

7) It minimizes the likelihood of concentration fluctuations.

8) It can be utilized for drugs that have a short half-life and a limited therapeutic range.

9) Drug therapy can be promptly terminated in the event of poisoning.

10) It decreases the frequency of drug administration, thereby enhancing patient adherence. [5][6][7]

Demerits :-

1)Only relatively potent drugs can be effectively administered via transdermal delivery systems, as skin permeability limits drug entry.

2) Hydrophilic drugs are less suitable than lipophilic drugs due to lower permeability.

3) Drugs with a molecular size greater than 1000 Daltons face challenges with absorption.

4) It is not applicable for drugs that require high doses.

5) The drug molecule needs to be sufficiently potent, as the patch size restricts the quantity that can be delivered.
6) This system may lead to allergic reactions at the application site, including symptoms such as itching, rashes, and local edema [5][6][7]

Factors affecting transdermal bioavailability

Two major factors affect the bioavailability of the drug via transdermal routes:

A)Physicochemical factors

1)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 humectant is done in transdermal delivery.

2)Temperature and pH :

The permeation of drug increase ten folds 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.

3)Diffusion coefficient :

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

4)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.

5)Partition coefficient :

The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

6) Molecular size and shape :

Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

B) Biological factors

1)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.

2)Skin age :

The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.

3)Blood flow:

Changes in peripheral circulation can affect transdermal absorption.

4)Regional skin sites:

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

5)Skin metabolism :

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

Species differences:

The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration[8][9]

APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL PATCH

A.Membrane moderated systems

In this system, the drug reservoir is entirely enclosed within a shallow compartment made from a drug-impermeable metallic-plastic laminate combined with a polymeric membrane that controls the release rate. Within the drug reservoir, the drug can either be dispersed within a solid polymer matrix or suspended in a non-leachable, viscous liquid medium such as silicone fluid. The rate-controlling membrane can either be micro-porous or non-porous, such as an ethylene-vinyl acetate copolymer on the outer layer of the polymeric membrane. To enhance the contact of the transdermal drug delivery system (TDDS) with the skin, a skin-compatible hypoallergenic adhesive polymer may be applied as a top layer.

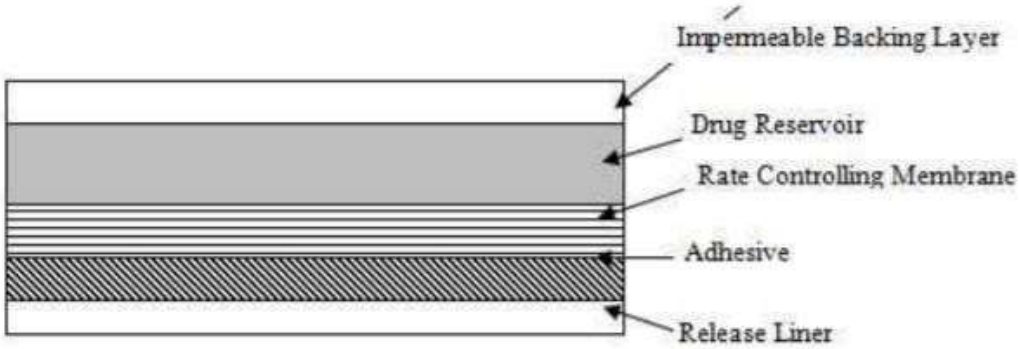

Fig. 1: Design of Membrane moderated transdermal patch

Fig 4 Membrane moderated systems

B. Adhesive diffusion controlled system

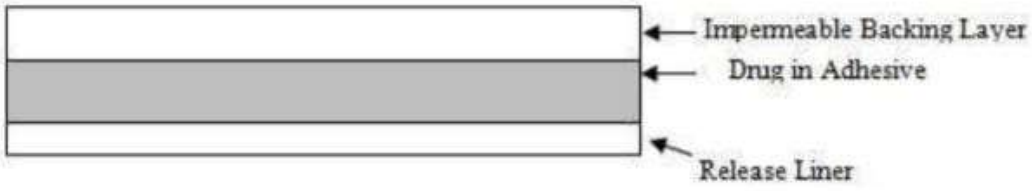

Fig. 2: Design of adhesive diffusion controlled transdermal patch

Fig 5 Adhesive diffusion controlled system

This system represents the most straightforward iteration of membrane-moderated drug delivery systems. In this approach, the drug reservoir is created by directly mixing the drug with an adhesive polymer. This medicated adhesive is then applied to a flat sheet made of drug-impermeable metallic plastic through solvent casting, forming a thin drug reservoir layer. On top of this reservoir layer, layers of non-medicated, rate-controlling adhesive polymer of uniform thickness are added. The drug-in-adhesive configuration can be either a single layer or a multi-layer system. The multi-layer design differs from the single-layer setup by incorporating an additional layer of drug-in-adhesive, which is typically separated by a membrane. The properties of the drug adhesive patch may lead to enhanced patient compliance due to the simplicity of remembering to apply a weekly patch, improved cosmetic appeal, and superior adhesion.

C. Matrix dispersion:

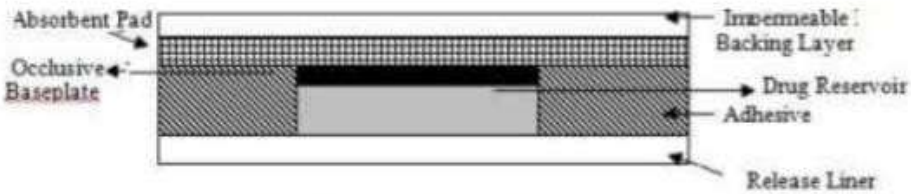

Fig. 3: Design of matrix dispersion transdermal patch

Fig 6 Matrix dispersion of Patch

In this approach, a drug reservoir is created by evenly distributing the drug solids within either a hydrophilic or lipophilic polymer matrix. The medicated polymer is then shaped into a disc with specific dimensions in terms of area and thickness. This disc is attach to an occlusive base plate, and an adhesive polymer is applied around the edges to create an adhesive rim. The matrix patches present several benefits, including the elimination of dose dumping, direct contact of the polymeric matrix with the skin, and reduced interference from adhesive components.

D. Microreservoir system:

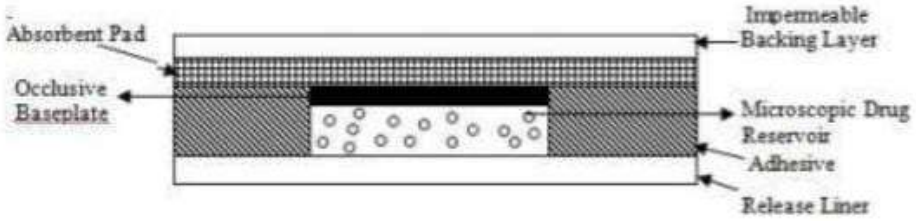

Fig. 4: Design of micro reservoir transversal patch

Fig 7 Microreservoirsystem

This system is regarded as a hybrid of both reservoir and matrix dispersion methods. In this case, the drug reservoir is initially formed by suspending drug solids in an aqueous solution of a water-soluble polymer, followed by the uniform dispersion of the drug suspension within a lipophilic polymer using high shear mechanical force. This process results in the formation of unleachable microscopic spheres of the drug reservoir. The dispersion is quickly stabilized through the cross-linking of polymer chains, resulting in a medicated disc that maintains a consistent surface area and thickness.[10][11]

Components of transdermal pathches :-

1.Polymer Matrix :-

The polymer is responsible for controlling the drug's release from the transdermal patch. To be suitable for this application, a polymer must meet the following criteria:

a) The molecular weight and chemical functionality of the polymer should allow for the efficient diffusion and release of the specific drug.

b) The polymer must exhibit stability.

c) It should be non-toxic.

d) The polymer should be easy to manufacture.

e) It should be cost-effective.

f) Both the polymer and its degradation products must be non-toxic and not antagonistic to the host.

g) The polymer should be capable of incorporating large amounts of the active agent.

Types of polymer: -

a)Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

b)Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

c)Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy

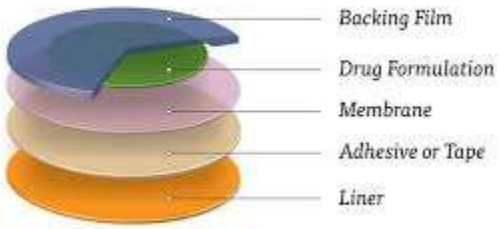

Fig no 8 Componants of Patch

2.Drug: -

The drug solution is in direct contact with the release liner.

Physicochemical Properties:

a) The drug should have a molecular weight of less than 1000 Daltons.

b) It should possess an affinity for both lipophilic and hydrophilic phases.

c) The drug ought to have a low melting point.

3. Permeation Enhancer: -

The flux J. of drug across the skin can be write As

J = D dc/dx

J = the Flux
D = diffusion coefficient
C = Concentration of the diffusing spectes
X = Spatial coordinate

a)Solvent: -
These compounds increase penetration possibly by swelling the polar pathway. e.g.: Water alcohols–Methanol & ethanol, / Dimethyl acetemide Propylene glycol and Glycerol.

b)Surfactants: -
The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.
i) Anionic surfactant:- Sodium lauryl sulphate Diacetyl sulphosuccinate
ii) Nonionic Surfactant:- Pluronic F127, Pluronic F68
iii) Bile Salt: - Sodium taurocholate, Sodium deoxycholate.

c) Miscellaneous Chemicals: -

This category encompasses urea, which serves as a hydrating and keratolytic agent; N,N-dimethyl-m-toluamide; calcium thioglycolate; and anticholinergic agents. Recently identified potential permeation enhancers include eucalyptol, di-omethyl-β-cyclodextrin, and soybean casein; however, data regarding their efficacy remains limited.

d) Enhance the permeation :eg. Urea, calcium thioglycolate.

e)Other excipients: -

a) Adhesives:

Pressure-sensitive adhesives can be placed either on the front or back of the device. Key requirements for these adhesives include:

i) They should not cause irritation.

ii) They must be easily removable.

iii) They should not leave behind any non-washable residue on the skin.

iv) They should establish excellent contact with the skin.

v) They need to be physically and chemically compatible with the drug.

vi) Drug permeation should remain unaffected.

4. Linear: -

The release liner serves to protect the patch during storage and is removed prior to use. It acts as primary packaging that safeguards the patch throughout the application process. The liner may consist of a) non-occlusive materials (e.g., paper fabric) or b) occlusive materials (e.g., polyethylene, polyvinyl chloride) and is typically made of silicone or Teflon. The release liner must be chemically inert and allow permeation of the drug, penetration enhancers, and water

5. Backing: -

This component protects the patch from external environments. It consists of a supportive material that is impermeable to both drugs and permeation enhancers. The backing must be chemically compatible with the drug, enhancer, adhesive, and other excipients. Common materials include vinyl, polyethylene, and polyester films.[13-18]

Types of Transdermal Drug Delivery System

1)Single-layer Drug-in-Adhesive System:

In this patch design, the adhesive layer itself contains the drug. This adhesive not only binds the different layers together and adheres the entire patch to the skin but also plays a crucial role in drug release. The adhesive layer is enclosed by a temporary liner and a backing.

2)Reservoir System:

In this system, the drug reservoir is positioned between the backing layer and a rate-controlling membrane. The drug is released through a microporous membrane that regulates the release rate. The drug can exist as a solution, suspension, gel, or be dispersed within a solid polymer matrix in the reservoir compartment..

3) Matrix System:

This system is of Two type

a) Drug-in-Adhesive System:

This process involves dispersing the drug into an adhesive polymer to create a drug reservoir, which is then applied onto an impervious backing layer either by solvent casting or melting the adhesive (in the case of hot-melt adhesives).

b) Matrix-Dispersion System:

Here, the drug is uniformly dispersed within a hydrophilic or lipophilic polymer matrix. This polymer-drug mixture is attached to an occlusive base plate made from a drug-impermeable backing layer. In this method, the adhesive is applied around the perimeter rather than directly on the surface of the drug reservoir, creating an adhesive rim. [19]

4) Micro-Reservoir System:

This system combines elements of both the reservoir and matrix-dispersion systems. In this design, the drug is suspended in an aqueous solution containing a water-soluble polymer and then evenly dispersed within a lipophilic polymer, resulting in thousands of microscopic spheres that act as drug reservoirs. [20].

Methods of Preparation of TDDS

1)Asymmetric TPX membrane method.
2) Circular Teflon mould method.
3) Mercury substrate method.
4) By using "IPM membranes" method.
4) By using "EVAC membranes" method.
5) By using free film method.

1) Asymmetric TPX Membrane Method:

This technique was introduced by Berner and John in 1994. It involves preparing a prototype patch using a heat-sealable polyester film (type 1009, 3M) as the backing membrane, which has a concave shape with a diameter of 1 cm. The drug is dispersed on the concave membrane, covered with an asymmetric TPX membrane (poly (4-methyl-1-pentene)), and then sealed using an adhesive.

Preparation: The preparation can be achieved through either the dry or wet inversion process. In this method, TPX is dissolved in a solvent mixture (cyclohexane) combined with non-solvent additives at 60°C to create a polymer solution. This solution is maintained at 40°C for 24 hours before being cast onto a glass plate. The casting film is then evaporated at 50°C for 30 seconds, after which the glass plate is immediately immersed in a coagulation bath maintained at 25°C. After 10 minutes of immersion, the membrane is removed and air-dried in a circulating oven at 50°C for 12 hours.

2)Circular Teflon Mould Method:

Discovered by Baker and Heller in 1989, this method involves using a polymer solution that contains various proportions of an organic solvent. The solution is divided into two parts: one part has a calculated amount of drug dissolved, while the other contains enhancers in varying concentrations. These two parts are then blended together. A plasticizer (e.g., Di-n-butyl phthalate) is added to the drug-polymer mixture. The combined contents are stirred for 12 hours, then poured into a circular Teflon mold. The molds are placed on a leveled surface and covered with an inverted funnel to regulate solvent evaporation in a laminar flow hood with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hours, resulting in a dry film that is then stored in a desiccator containing silica gel for an additional 24 hours at 25±0.5°C to mitigate aging effects**.**

3)Mercury Substrate Method:

In this method, the drug and plasticizer are dissolved in the polymeric solution and stirred for 10 to 15 minutes to achieve a homogeneous dispersion, which is then poured onto a leveled mercury surface. An inverted funnel is placed over the mixture to control solvent evaporation**.**

4) By Using "IPM Membranes" Method:

This approach involves dispersing the drug in a mixture of water and polymer (propylene glycol containing Carbomer 940) and stirring for 12 hours with a magnetic stirrer. The dispersion is neutralized and thickened with triethanolamine. If the drug has poor solubility in the aqueous solution, a gel is formed using buffer with a pH of 7.4. The resulting gel is then incorporated into the IPM membrane.

5) By Using "EVAC Membranes" Method:

To prepare a transdermal drug delivery system (TDS), a reservoir gel containing 1% carbopol, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) is utilized as the rate-controlling membrane. If the drug is insoluble in water, propylene glycol is used for gel preparation. The drug is dissolved in propylene glycol, and carbopol resin is added to this solution, then neutralized with a 5% w/w sodium hydroxide solution. The drug (in gel form) is applied to a backing layer covering a specified area, and a rate-controlling membrane is placed over the gel. The edges are heat-sealed to create a leak-proof device.

6)By using Free Film Method:

In this process, a cellulose acetate free film is initially prepared by casting it on a mercury surface. A 2% w/w polymer solution is created using chloroform, with plasticizers added at a concentration of 40% w/w relative to the polymer weight. Five milliliters of this polymer solution are poured into a glass ring situated over the mercury surface within a glass petri dish. The solvent evaporation rate is controlled by using an inverted funnel over the petri dish. Film formation is confirmed by observing the mercury surface after the solvent has completely evaporated. The resulting dry film is separated and stored between sheets of wax paper in a desiccator until required. This method allows for the preparation of free films of varying thicknesses by adjusting the volume of the polymer solution. [21,22].

EVALUATION OF TRANSDERMAL PATCH5

Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their
desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

A]Physicochemical evaluation

B]In vitro evaluation

A.Physicochemical evaluation

1)Thickness:
The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

2) 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.

3)Drug content determination:

An accurately weighed portion of film (about 100mg) is dissolved In
100 mL of suitable solvent in which drug is soluble and then thesolution is shaken continuously for 24h in shake r incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is esti mated spectrophotometrically by appropriate dilution.

4)Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extr eme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it br eak. The number of times the films could be folded at the same place without breaking is folding endurance value

B. In vitro permeation studies

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature usually 32±5°C for skin and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount

of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thikness of skin&temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e., drug permeated per cm 2 per second. [23]

Advance development in TDDS

The development of drug-infused adhesive technologies has emerged as a leading approach for passive transdermal delivery systems. Current formulation research is primarily concentrating on two key areas: adhesives and excipients. Research on adhesives aims to tailor them for enhanced skin adherence throughout the duration of wear, as well as to improve drug stability and solubility, shorten lag time, and boost the delivery rate. Since a universal adhesive that meets the requirements of all drug and formulation chemistries does not exist, personalizing adhesive chemistry enables transdermal formulators to optimize the performance of patch polymers as needed. TDDS is seen as a promising practical application for the future of drug delivery systems. [24, 25]

Future of Transdermal Drug Delivery System

Looking ahead, developments in drug delivery systems are exploring options such as liposomes, niosomes, and microemulsions. These advancements aim to enhance the delivery of drugs with low inherent solubility, which are commonly found in traditional formulation excipients. There is a broad scope for potential drugs to be delivered, including steroids, antifungals, antibacterials, interferon, methotrexate, and local anesthetics. The transdermal patch market is projected to grow significantly, having recently witnessed an annual increase of 25%. This number is expected to rise further with the advent of novel devices and an expanding range of marketed transdermal drugs. The transdermal delivery of analgesics is likely to gain further traction as designs continue to evolve. Research endeavors are underway to enhance both safety and efficacy, addressing practical concerns to improve the user experience of patches while also ensuring more accurate drug delivery with extended durations of action. Further advancements may also include the refinement of transdermal technologies that leverage mechanical energy to enhance drug flux through the skin, either by modifying the skin barrier or by increasing the kinetic energy of the drug molecules. Following the successful development of patches utilizing iontophoresis, various "active" transdermal technologies are being explored for diverse drugs. Innovations include electroporation, which employs short high-voltage electrical pulses to create transient aqueous pores in the skin; sonophoresis, which uses low-frequency ultrasonic energy to disrupt the stratum corneum; thermal energy, which heats the skin to improve permeability and elevate the energy of drug molecules; and magnetophoresis, which investigates magnetic energy to boost drug flux through the skin.Transdermal patches may be an underleveraged method for managing both acute and chronic pain. With improved delivery mechanisms and a broader spectrum of analgesics, we anticipate a rise in the popularity and applicability of this drug delivery modality. In the current landscape, the transdermal route of drug delivery is considered one of the most successful innovative research fields, with approximately 40% of drug delivery candidates undergoing clinical trials related to transdermal or dermal systems. TDDS is designed as a safer and more convenient method for systemic drug delivery through the skin, offering significant advantages such as maintaining stable drug levels

in blood plasma, minimizing side effects, improving bioavailability by bypassing hepatic first-pass metabolism, and enhancing patient compliance with treatment regimens. Recently, the skin has been recognized as a safe and effective route for continuous drug administration into systemic circulation. [26].

Conclusion:-

Transdermal patch technology is a highly effective drug delivery method with numerous advantages over other delivery routes. Patches can avoid the digestive system and bypass the first-pass effect. Metabolism is responsible for providing a continuous supply of drugs over an extended period of time. They are frequently employed to administer medications for a range of conditions, including chronic pain , other medical needs, motion sickness, and hormone replacement therapy. A significant advancement will be the production of total dissolved solids units that transport peptide and protein substances, such as insulin and growth hormon are available for delivery. The transdermal patch is often overlooked as a valuable tool for managing certain conditions of both short-term and long-term pain. With enhanced delivery capabilities and a broader selection of Painkillers, we expect that the use and effectiveness of this method will continue to grow to administer medication to enhance.

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