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Transdermal Patch: Recent approaches for the effective treatment of Rheumatoid Arthritis.

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ABSTRACT
Administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the non-invasive nature of drug delivery. Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy marketed Transdermal V (present day marketed as transdermic Scop) to prevent the nausea and vomiting associated with motion sickness. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and interpatient variation.

Keyword: Transdermal Patch, Recent Approaches,Rheumatoid Arthritis.

I. INTRODUCTION

Transdermal drug delivery system (TDDS) also known as "patches" (non-invasive delivery) is dosage form designed to deliver a medication across a patient skin [1,2]. Skin is the largest and most accessible organ of human body with the help of skin layers drug reaches into the blood stream given as sustained release, controlled release, or extended-release formulation. [16].Transdermal delivery systems are specifically designed to obtain systemic blood levels and have been used in the US since the 1950s. The first transdermal system, transdermal SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient from several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug, and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy. [18]

Transdermal permeation or percutaneous absorption can be defined as the passage of a substance, such as a drug, from the outside of the skin through its various layers into the blood stream. [17]

Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. [1]. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and interpatient variation. In addition, because transdermal patches are user-friendly, , convenient painless, and offer multi day dosing, it is generally accepted that they offer improved patient compliance 10.The growth rate for transdermal drug delivery systems is expected to increase 12% annually by 2009.[13].

Advantages of transdermal drug delivery systems[2]

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are.

- Avoidance of gastrointestinal incompatibility.
- Avoidance of first pass metabolism.
- Predictable and extended duration of activity.
- Minimizing undesirable side effects.
- Improving physiological and pharmacological response.
- Avoiding the fluctuation in drug levels.
- Inter and intra patient variations.
- Maintain plasma concentration of potent drugs.

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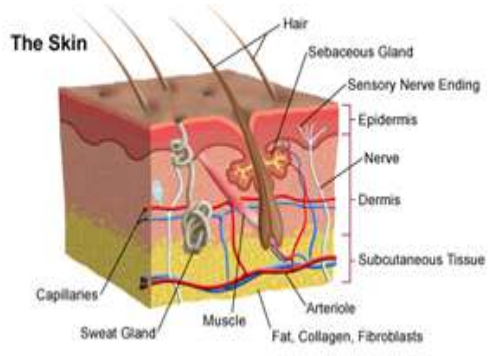
- Termination of therapy is easy at any point of time.
- Greater patient compliance due to elimination of multiple dosing profile.

Limitations of transdermal drug delivery systems [3],[4],[5]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin.
- Cannot administer drugs that require high blood levels.
- Drug of drug formulation may cause irritation or sensitization.
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient.
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

Human skin [6],[7]

The skin plays an important role in the transdermal drug delivery system. The skin of an average adult body covers a surface area of approximately 2 sq. m. and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. The main three layers of skin play an important role in the transdermal drug delivery system.



Anatomy and physiology of skin

Human skin comprises of three distinct but mutually dependent tissues namely: [39],[40]

1. The stratified, a vascular, cellular epidermis;
2. Underlying dermis of connective tissues and;
3. Hypodermis.

The Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and theEpidermis The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis, also called viable epidermis, cover a major area of skin.[39]

Stratum corneum:

This is the outermost layer of skin, also called Horney layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.[39],[40]

Viable epidermis:

This is situated beneath the stratumcorneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basale layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratumcorneum.

The Dermis

Dermis is a 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels, and nerves. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules

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penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation.[39],[40]

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug must penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.[39],[40]

ROUTES OF PENETRATION

The diffusant has two potential entry routes to the blood vasculature through the epidermis itself or diffusion through shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts.[46] Therefore, there are two major routes of penetration.[47]

Trans corneal penetration

Intra cellular penetration

Drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

Transappendegeal penetration

This is also called as the shunt pathway [47]. In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands.[50]

The route through which permeation occurs is largely dependent on physio-chemical characteristics of penetrant, most importunately being the relative ability to partition into each skin phase. The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation. The viable tissue layer and the capillaries are relatively permeable, and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step.

Factors of transdermal Patches

There are various factors which affects the action of transdermal patches. These are given below;

Physicochemical Properties

- Partition coefficient.
- Molecular size
- Solubility/melting point
- Ionization

Physiological & Pathological Conditions of Skin

- Reservoir effect of horny layer.
- Lipid film.
- Skin hydration.
- Skin temperature.
- Regional variation.
- Pathological injuries to the skin.
- Cutaneous self-metabolism.
- Skin barrier properties in the neonate and young infant.
- Skin barrier properties in aged skin .
- Race.
- Body site.
- Penetration enhancers used [46]

Future of Transdermal Drug Delivery System

Future aspects in Drug delivery system include liposomes, Niosomes and micro emulsion. Aim of this development is to improve delivery of drug that has low inherent solubility in most of classical formulation excipients. A wide range of potential drugs for delivery like steroids, antifungal, antibacterial, interferon, methotrexate, local anesthetics are formulated. The market for transdermal patches has been estimated to increase in future and has recently experienced annual growth of at rate of 25%. This figure will increase in future as novel devices emerge and list of marketed transdermal drug increases. Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. [51]

Basicprinciplesoftransdermalpermeation[6]

Transdermal permeation is based on passive diffusion. Before a topically applied drug

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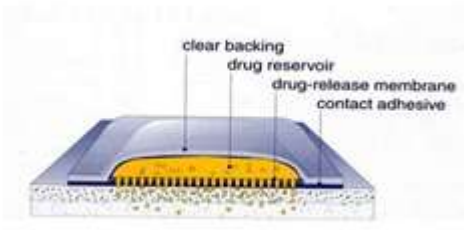
can act either locally or systemically, it must penetrate the stratum corneum – the skin permeation barrier. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep stratum process, which involves.[7] Dissolution with in and release from the formulation.

- Partitioning into the skin's outermost layer, the stratum corneum.
- Diffusion through the SC, principally via a lipidic intercellular pathway.
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake into the papillary dermis and into the microcirculation.

Basic components of transdermal drug delivery systems



Polymer matrix

- Molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug.
- Polymers and its degradation products must be non-toxic.[9],[10]

Drug substance

Selection the of drug for transdermal drug delivery depends upon various factors.

Physicochemical properties [8],[11]

- The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml).
- Substances having a molecular weight of less than 1000 units are suitable.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.
- Hydrogen bonding groups should be less than 2. 2.4.

Biological properties [4]

Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day).

- The drug should have short biological half-life.
- The drug should be non-irritant and non-allergic to human skin.
- The drug should be stable when in contact with the skin.

Penetration enhancers

They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself.[9] The penetration enhancer should be pharmacologically inert, non-toxic, non-allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogenous materials.

Drug reservoir components

It must be compatible with the drug and must allow for drug transport at the desired rate. If an ointment is used, the drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process. It must possess the desired adhesive and cohesive properties to hold the system together. Materials used are: mineral oils, polyisobutylene, and colloidal silica, HPC.

Backing laminate

Backinge primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through top. They must be impermeable to drugs and permeation enhancers. They should a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Type backing membranes are composed of a pigmented layer, an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

Rate controlling membrane

Rate controlling membranes in transdermal devices govern drug release from the dosage form. Membranes made from natural polymeric material such as chitosan show great promise for use as rate controlling membranes. Recently composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been

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evaluated as rate controlling barriers for transdermal application.[12]

Adhesive layer

The fasting of all transdermal devices to the skin using a pressure sensitive adhesive that can be positioned on the face or in the back of device is necessary. It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin. It should adhere to the skin aggressively.

The three major classes of polymers evaluated for potential medical applications in TDDS include:

- Polyisobutylene type pressure sensitive adhesives.
- Acrylic type pressure sensitive adhesives.
- Silicone type pressure sensitive adhesives.

Release liners

The release liner has to be removed before the application of transdermal system, and it prevents the loss of the drug that has migrated into the adhesive layer during storage. It also helps to prevent contamination. It is composed of a base layer, which may be nonocclusive or occlusive, and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metallized laminates.

Patch design and technology [13]

There are two major types of transdermal delivery system products:

- Thin flexible colored or nearly invisible matrix patches.
- Flexible colored or transparent liquid or semisolid filled reservoir patches.

Four major transdermal systems [14]

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 film.

Multi-layer 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 drugs in adhesive layers or the addition of multiple drugs in adhesive layers under a single backing film,

Reservoir

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.

Matrix

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.

Ideal product requirements [15]

- Shelf life up to 2 years.
- Small size patch (i.e., less than 40 cm2).
- Convenient dose frequency (i.e., once a day to once a week).
- Cosmetically acceptable (i.e., clear, white colour).
- Easy removal of the release liner (i.e., for children and elderly patients).
- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma).the following:[19]

Various methods for preparation of TDDS

Circular teflon mould method .[22]

Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccator containing silica gel before evaluation to eliminate aging effects. These types of films are to be evaluated within one week of their preparation. [24] have studied about bioadhesive film containing ketorolac. Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC),

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hydroxypropylmethyl cellulose (HPMC) and Carbopol 934.

Asymmetric TPX membrane method

[23] A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath (maintained the temperature at 25°C). After 10 minutes of immersion, the membrane can be removed, air dried in a circulation oven at 50°C for 12 h [28] have studied that asymmetric poly(4-methyl-1-pentene) (TPX) membranes, fabricated by the dry/wet inversion method, were applied to transdermal delivery of nitroglycerin (NTG), a drug for treating angina pectoris.

Mercury substrate method

The drug is dissolved in polymer solution along with plasticizer. It is followed by stirring for 10- 15 minutes to produce a homogenous dispersion and poured into a levelled mercury surface, covered with inverted funnel to control solvent evaporation. [26],[27] have studied that transdermal matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The polymeric combinations showed good film forming properties and the method of casting on mercury substrate was found to give good films.[28] have studied transdermal patches containing glibenclamide (1.06 % w/v, i.e. 13.5 mg/cm2) were prepared by solvent casting technique employing mercury as substrate to formulate transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method. The formulation containing Eudragit RL 100 with propylene glycol as plasticizer showed complete and prolonged release with 98.02 % at the end of 24 h.

"IPM membranes" method

The drug is dispersed in a mixture of water and propylene glycol containing carbomer-940 polymers and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of tri-ethanolamine. Buffer (pH 7.4) can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM (isopropyl myristate) membrane [29] have studied the drug-in-adhesive transdermal patch and evaluated for the site-specific delivery of anastrozole. Different adhesive matrixes, permeation enhancers and amounts of anastrozole were investigated for promoting the passage of anastrozole through the skin of rat in-vitro.

"**EVAC membranes" method**

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device. [30] have studied the irritation of transdermal devices delivering levonorgestrel and the permeation enhancer ethyl acetate with or without ethanol were evaluated in rabbits. Erythema and oedema were assessed 24, 48 and 72 h and 7 days after application of the 24-h delivery system.

Approaches used in development of transdermal patch

Membrane moderated systems:

The rate controlling membrane can be micro porous or nonporous polymeric membrane e.g., ethylene vinyl acetate co- polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo-allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with skin surface. The membrane moderated transdermal systems are available under the various brand names including Transdermal- Nitro system (once a day provide continuous controlled release of nitro-glycerine for the prevention of angina pectoris due to coronary artery disease), Transdermal- Scop system (3 days

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medication for prevention of nausea and vomiting), and Catapres- TTS (providing continuous systemic delivery of clonidine for 7 days for the treatment of high blood pressure) [20],[31]

Adhesive diffusion-controlled system:

It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non- medicated rate controlling adhesive polymer of constant thickness are applied. Drug - in - adhesive patch may be single layer or multi-layer.

Matrix dispersion system:

The drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix. The medicated polymer is then moulded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc; the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive.

Recent advances in the field of transdermal patches

Recently several therapeutically acts substances are delivered transdermal including large proteins, testosterone, oxybutynin and patches for the relief of pain.

Patch technology for protein delivery

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. Trans Pharma uses its unique printed patch technology for transdermal delivery of proteins .It is postulated that the highly water- soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF- Micro Channels, forming a highly concentrated protein solution in-situ. The delivery of the dissolved molecules is then carried out, via the RF- Micro Channels, into the viable tissues of the skin, diffusing across a steep concentration gradient.[32]

Pain free diabetic monitoring using transdermal patches

The patch (about 1cm2) is made using polymers and thin metallic films. The metallic interconnections and sampling array can be clearly seen. When the seal is compromised, the interstitial fluid, and the biomolecules contained therein, becomes accessible on the skin surface. This painless and bloodless process results in disruption of a 40–50 μm diameter region in the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites.[33]

Testosterone transdermal patch system in young women with spontaneous premature ovarian failure

In premenopausal women, the daily testosterone production is approximately 300 μg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone. The addition of TTP to cyclic E2/MPA therapy in women with sPOF produced mean free testosterone levels that approximate the upper limit of normal.[34]

Transdermal Patch of Oxybutynin used in overactive Bladder (OAB)

The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe under the brand name of Kentera. Oxytrol is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three-to-four-day interval. Oxytrol offers OAB patient's continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with and oral formulation. In most patients these side effects however are not a troublesome[21],[35].

Pain relief

Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch [36] Several others are available in the market. Lidoderm, a lidocaine patch (5%), which is used for post herpetic neuralgia [37] Other exciting advancements in pain control include the E- Trans fentanyl HCl patch.[38] Molecular absorption enhancement technology Absorption enhancers are the compounds that promote the passage of drugs

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through the stratum corneum. Terpene derivatives as well as certain phenols seem to improve transdermal absorption [41],[42] For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it toa therapeutic level [43] Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen.[44] Phloretin, a polyphenol, enhanced the absorption of lignocaine.[45]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken [53]

All this damage to the joints causes deformities and bone erosion, usually very painful for a patient. Common symptoms of RA include morning stiffness of the affected joints for >30 min, fatigue, fever, weight loss, joints that are tender, swollen and warm, and rheumatoid nodules under the skin. The onset of this disease is usually from the age of 35 to 60 years, with remission and exacerbation.

The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight bearing exercise, educating patients about the disease, and rest. Treatments are generally customized to a patient's needs and depend on their overall health. This includes factors such as disease progression, the joints involved, age, overall health, occupation, compliance, and education about the disease. [44]

Pathogenesis

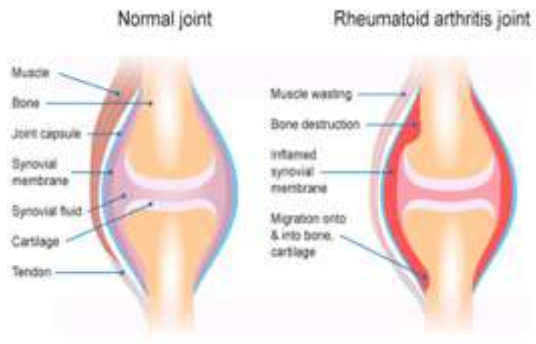
The disease process leading to rheumatoid arthritis begins in the synovium, the membrane that surrounds a joint and creates a protective sac. This sac is filled with lubricating liquid called the synovial fluid. In addition to cushioning joints, this fluid supplies nutrients and oxygen to cartilage. Cartilage is composed primarily of collagen, the structural protein in the body, which forms a mesh to give support and flexibility to joints .In rheumatoid arthritis, an abnormal immune system response produces destructive molecules that cause continuous inflammation of the synovium.

Causes

The exact reasons are unknown. The condition is most likely triggered by a combination of factors including an abnormal autoimmune response, genetic susceptibility, biologic trigger such as a viral infection or hormonal changes. T cells and B-cells are two important components of the immune system that play a role in the inflammation associated with rheumatoid arthritis. These genetic factors do not cause RA, but they may make the disease more severe once it has developed. Infections may stimulate the immune system to prolong RA once the disease has been triggered by some other initial infection. Other potential triggers include Mycoplasma, parvovirus B19, retroviruses, mycobacteria, and Epstein-Barr virus.

Symptoms

Symptoms can include fatigue, loss of energy, lack of appetite, low-grade fever, muscle and joint aches, and stiffness. Muscle and joint stiffness are usually most notable in the morning and after periods of inactivity.The small joints of the feet are also commonly involved, which can lead to painful walking, especially in the morning after arising from bed. Chronic inflammation can cause damage to body tissues, including cartilage and bone. This leads to a loss of cartilage and erosion and weakness of the bones as well as the muscles, resulting in joint deformity, destruction, and loss of functions.[52]



Complications of rheumatoid disease

Since rheumatoid arthritis is a systemic disease, its inflammation can affect organs and areas of the body other than the joints. Inflammation of the glands of the eyes and mouth can cause dryness of these areas and is referred to

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as Sjogren's syndrome. Dryness of the eyes can lead to corneal abrasion. Inflammation of the white parts of the eyes is referred to as scleritis and can be very dangerous to the eye. [54]

Diagnosis

Rheumatoid arthritis can be difficult to diagnose. Many other conditions resemble RA. Its symptoms can develop insidiously. Blood tests and x-rays may show normal results for months after the onset of joint pain. Specific findings or presentation more likely to suggest the diagnosis of rheumatoid arthritis include morning stiffness, involvement of three joints at the same time, involvement of both sides of the body, subcutaneous nodules, positive rheumatoid factor, and changes in x rays.

Blood Tests

Various blood tests may be used to help diagnose RA, determine its severity, and detect complications of the disease. Rheumatoid Factor In RA, antibodies in the blood that collect in the synovium of the joint are known as rheumatoid factor. In about 80% of cases of RA, blood tests reveal rheumatoid factor.

Erythrocyte Sedimentation Rate

An erythrocyte sedimentation rate (ESR or sed rate) measures how fast red blood cells (erythrocytes) fall to the bottom of a fine glass tube that is filled with the patient's blood.

Tests for Anaemia

Anaemia is a common complication. Blood tests determine the amount of red blood cells (haemoglobin and haematocrit) and iron (soluble transferrin receptor and serum ferritin) in the blood.

Rheumatologistsstatus of people with rheumatoid arthritis as follows:

Class I: completely able to perform usual activities of daily living.

Class II: able to perform usual self-care and work activities but limited in activities outside of work (such as playing sports, household chores).

Class III: able to perform usual self-care activities but limited in work and other activities.

Class IV: limited in ability to perform usual self-care, work, and other activities.

Treatment of Rheumatoid Arthritis

"First-line" rheumatoid arthritis medications [55]

Acetylsalicylate, naproxen, ibuprofen and etodolac are examples of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are medications that can reduce tissue inflammation, pain, and swelling. Aspirin in doses higher than those used in treating headaches and fever is an effective anti-inflammatory medication for rheumatoid arthritis.

" Second-line" or "slow-acting" rheumatoid arthritis drugs (disease-modifying antirheumatic drugs or DMARDs)[54]

While "first-line" medications can relieve joint inflammation and pain, they do not necessarily prevent joint destruction or deformity. Sometimes a number of DMARD second-line medications are used together as combination therapy. Sulfasalazine Zulfi dine) is an oral medication traditionally used in the treatment of mild to moderately severe inflammatory bowel diseases, such as ulcerative colitis and Crohn's colitis. Azulfidine is used to treat rheumatoid arthritis in combination with anti-inflammatory medications.

Transdermal patch effective for treatment of rheumatoid arthritis

The aim of this study was to design a compound transdermal patch containing diclofenac (DA) and teriflunomide (TEF) for the treatment of rheumatoid arthritis (RA).

TDD systems have been effective for painless, efficient, non-toxic, and patient-compliant drug delivery. Various NSAID drugs may be incorporated for targeting a variety of skin disorders but all NSAIDs cannot be given by this route because of their physicochemical properties which are essential for the transdermal delivery of drugs. Therefore, the potential of this delivery system needs to be explored in the case of NSAIDs.

- The Transdermal patch of Repaglinide improves the bioavailability of drug and patient compliance.
- Stavudine can permeate through the rat abdominal skin and hence could permeate through the human skin.
- Terpenes (anethole) along with propylene glycol and polyethylene glycol as penetration enhancers could be effective in achieving therapeutic plasma levels for AZT.
- The Transdermal patch of Atenolol provides the delivery of the drug at a controlled rate across intact skin

II. CONCLUSION AND PERSPECTIVE

Improvement in the TDDS is a successful story of the pharmaceutical endeavour. Several transdermal patches are present in the market, which were a valid proof that the transdermal systems were feasible, safe, and effective with maximum patient compliance. Transdermal drug

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delivery of tacrine was developed mainly to overcome first-pass metabolism and to reduce the frequency when compared to oral route of administration. Oral route of administration is having many disadvantages like less bioavailability, high dose is needed or frequent dosing, which may be cost prohibitive and also not convenient to some patients. Using Eudragit polymer, transdermal patches can be prepared by solvent casting method. In general, matrix type of transdermal patches was manufactured using polymers. All these transdermal patches were evaluated for various parameters such as physical appearance, thickness, weight variation, drug content, moisture uptake, moisture content, and swelling studies.

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