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A Review on: Transdermal Patches of Herbal Drugs for Arthritis

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ABSTRACT

The point of the current investigation was to foster an original Transdermal patch containing homegrown concentrates for the treatment of Arthritis. Now day natural medications are more utilized, they are protected on account of having a less incidental effect or minimal expense. Transdermal medication conveyance frameworks are topically directed medicaments. Transdermal patches are drug arrangements of differing sizes, containing, at least one dynamic fixing, planned to be applied to the whole skin to convey the dynamic fixing to the fundamental course in the wake of going through the skin boundaries, and it stays away from first-pass impact. A benefit of a transdermal drug delivery course over different kinds of prescription conveyance is that the fix gives a controlled arrival of the medicine into the patient, for the most part through either a permeable film covering a repository of drug or through body heat softening slender layers of drug installed in the cement.

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INTRODUCTION

ARTHRITIS. Arthritis is the extending and delicacy of somewhere around one of your joints. The essential impacts of joint agony are joint torture and immovability, which regularly fall apart with age. The most notable kinds of joint agony are osteoarthritis and rheumatoid arthritis. Osteoarthritis causes tendon — the hard, precarious tissue that covers the terminations of bones where they structure a joint — to isolate. Rheumatoid joint torment is a disease wherein the protected system advance the joints, beginning with the covering of joints. Uric acid crystals, which structure when there's an increase in uric acid in your blood, can cause gout. Contaminations or hidden sicknesses, like psoriasis or lupus, can cause different kinds of arthritis. Treatments fluctuate contingent upon the sort of joint pain. The principle objectives of joint pain medicines are to decrease side effects and work on personal satisfaction.

Types-Ankylosing spondylitis, Gout, Juvenile idiopathic arthritis, Osteoarthritis, Psoriatic arthritis, Reactive arthritis, Rheumatoid arthritis, Septic arthritis, Thumb arthritis.

Symptoms-

Pain, Stiffness, Swelling, Redness, Decreased range of motion

Causes- The two main types of arthritis — osteoarthritis and rheumatoid arthritis — damage joints in different ways.

Osteoarthritis-

The most recognized kind of joint inflammation, osteoarthritis includes mileage harm to your joint's ligament — the hard, smooth covering on the ending of bones where they structure a joint. Ligament pads the ending of the bones and permits almost frictionless joint movement, yet enough harm can bring about bone-crushing straightforwardly on bone, which causes torment and limited development. This mileage can happen over numerous years, or it very well may be hurried by a joint physical issue or disease.

Osteoarthritis additionally influences the whole joint. It causes changes during the bones and crumbling of the connective tissues that append muscle to bone and hold the joint together. It likewise irritates the joint covering.

Rheumatoid arthritis-

In rheumatoid joint pain, the body's safe framework assaults the coating of the joint container, an intense film that encases every one of the joint parts. This covering (synovial film) becomes excited and enlarged. The illness interaction can ultimately obliterate ligament and bone inside the joint.

Risk factors-Risk factors for arthritis include:

- **Family history.** A few sorts of joint pain run in families, so you might be bound to foster joint inflammation if your folks or kin have the issue. Your qualities can make you more helpless to ecological components that might trigger joint pain.
- **Age.** The risk of many types of arthritis — including osteoarthritis, rheumatoid arthritis, and gout — increases with age.
- **Your sex.** Women are more likely than men to develop rheumatoid arthritis, while most of the people who have gout, another type of arthritis, are men.
- **Previous joint injury.** People who have injured a joint, perhaps while playing a sport, are more likely to eventually develop arthritis in that joint.
- **Obesity.** Carrying excess pounds puts stress on joints, particularly your knees, hips, and spine. People with obesity have a higher risk of developing arthritis.

Complications-Severe arthritis, particularly if it affects your hands or arms, can make it difficult for you to do daily tasks. Arthritis of weight-bearing joints can keep you from walking comfortably or sitting up straight. In some cases, joints may become twisted and deformed.

TRANSDERMAL PATCH (TDDS)

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Transdermal drug delivery system (TDDS patch) are self-contained discrete dosage forms that, when applied to the intact skin, are designed to deliver the drug through the skin at a controlled rate of systemic circulation. For transdermal products, the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. The transdermal route of administration is

recognized as one of the potential routes for the local and systemic delivery of drugs. Currently, transdermal drug delivery (TDD) is one of the most promising methods for drug application. An essential prerequisite for the development of TDDS is that the drug must be capable of passing through the skin at a sufficiently high rate to achieve therapeutic plasma concentrations.

Advantage

1. Topical patches are a painless, non-invasive way to deliver substances directly into the body.

2. Topical patches are a better way to deliver substances that are broken down by the stomach acids, not well absorbed from the gut, or extensively degraded by the liver.

3. Topical patches over a controlled, steady delivery of medication over long periods.

4. Topical patches have fewer side effects than oral medications or supplements.

5. Topical patches are easier to use and remember.

6. Topical patches over an alternative for people who cannot, or prefer not to take medications or supplements orally.

7. Topical patches are cost-effective.

8. People prefer topical patches.

Disadvantage

1. The drug that requires high blood levels cannot be administered and may even cause irritation or sensitization of the skin.

2. The adhesives may not adhere well to all types of skin and may be uncomfortable to wear.

3. High cost of the product is also a major drawback for the wide acceptance of these products.

4. Physical movement and perfuse sweating can lead to detachment of the patch.

5. Either the drug, adhesive, or any other excipients of the patch formulation can cause erythema, itching, and local edema.

6. Hydrophilic drugs with potent therapeutic action diffuse slowly as the skin favors the permeation of lipophilic drugs.

Limitation

1. TDDS cannot deliver ionic drugs.

2. TDDS cannot achieve high drug levels in blood/plasma.

3. It cannot develop for drugs of large molecular size.

4. TDDS cannot deliver drugs in a pulsatile fashion.

5. TDDS cannot develop if the drug or formulation irritates the skin.

SKIN AND DRUG PENETRATION

For understanding the concept of TDDS, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access into the body via skin.

Anatomically, the skin can be divided into two layers:

Epidermis and Dermisor corium.

The skin is one of the most extensive organs of the human body covering an area of about $2m^2$ in an average human adult. This multilayered organ receives approximately one-third of all blood circulating through the body. Epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in the migration of cells from the basal layer towards the skin surface (Flynn,1985). Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum. Together, these other layers constitute the viable epidermis. The dermis is the foundation of firm connective tissue upon which the epidermis is laid and is of mesoderm origin. The dermis or corium consists of a dense felt work of connective tissue in which bundles of collagenous fibers predominate, mingled with a certain proportion of elastic tissue in superficial levels. The dermis contains fine plexuses of blood vessels, lymphatics and nerves, hair follicles, sweat glands, and sebaceous glands (Gros and Clark,1980).

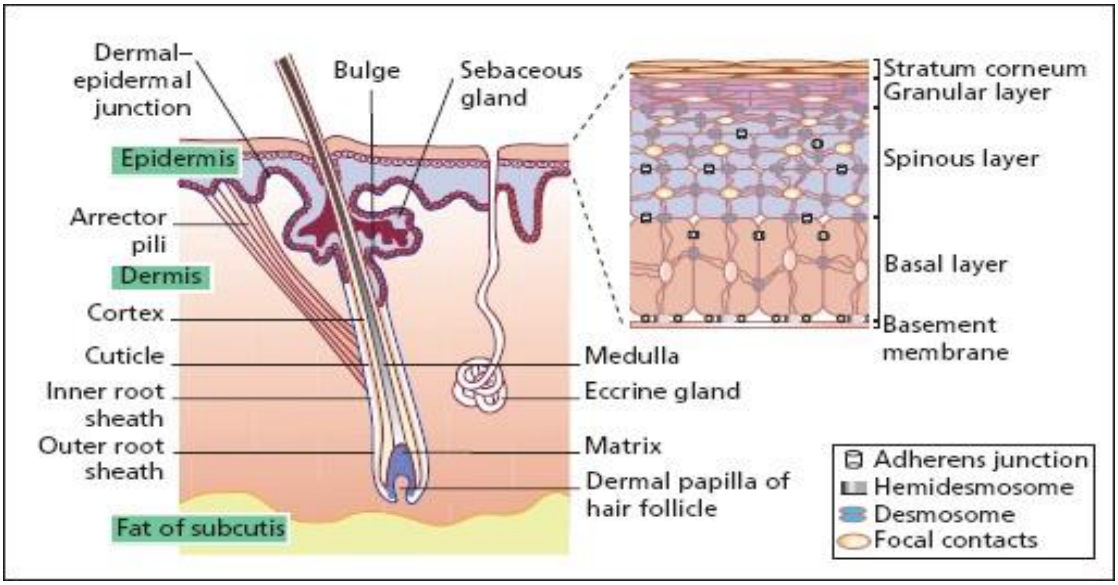


Figure No. 1: Schematic diagram of different layers of skin.

Drug penetration pathways:

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin the appendages (shunt routes); through the intercellular the other layers of the epidermis the stratum lucilipid domains; or by a transcellular route. A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

The appendgeal route:

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by several factors. The surface area occupied by hair follicles and sweat ducts is small (typically 0.1% of skins surface area) therefore limiting the area available for the direct contact of the applied drug formulation.

Transcellular route:

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

Intercellular route:

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons. Recalling the 'bricks and mortar model of the stratum corneum, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which in contrast to the relatively direct path of the transcellular route. The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

FACTORS INFLUENCING TRANSDERMAL DRUG:

Effective transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and vehicles. So, the factors affecting can be divided into classes as biological factors and physicochemical factors.

Biological factors:

Skin condition:

Acids and alkalis, many solvents like chloroform-methanol damage the skin cells and promote penetration. The diseased state of the patient alters the skin conditions. The intact skin is a better barrier but the above-mentioned conditions affect penetration.

Skin age:

Young skin is more permeable than older. Children are more sensitive to skin absorption of toxins. Thus, skin age son of the factors affecting penetration of drug in TDDS.

Blood supply:

Changes in peripheral circulation can affect transdermal absorption.

Regional skin site:

The thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significant penetration.

Skin metabolism:

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

Species differences:

The skin thickness, density of appendages, and keratinization of skin vary from species to species, so affects the penetration.

Physicochemical factors:

Skin hydration:

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So the use of humectants is done in transdermal delivery.

Temperature and pH:

The permeation of the drug increases tenfold with temperature variation. The diffusion coefficient decreases as the temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drugs determines the drug concentration in the skin. Thus, temperature and pH are important factors affecting drug penetration.

Diffusion coefficient:

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

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.

Partition coefficient:

The optimal K, partition coefficient 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.

Molecular size and shape:

Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known.

TYPES OF TRANSDERMAL PATCHES:

Single layer drug in adhesive:

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and this type of layer is responsible for releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

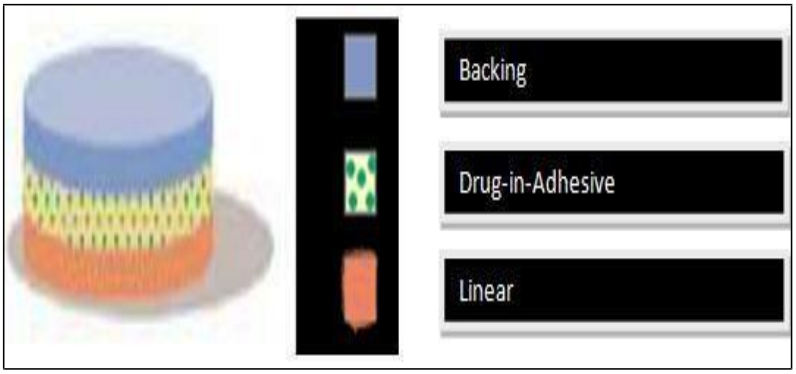


Figure No. 2: Single-layer drug-in-adhesive.

The multi-layer drug in adhesive:

This type is also similar to the single-layer but it contains an immediate drug release layer which is different from another layer which will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the release of the drug. This patch also has a temporary liner layer and a permanent backing.

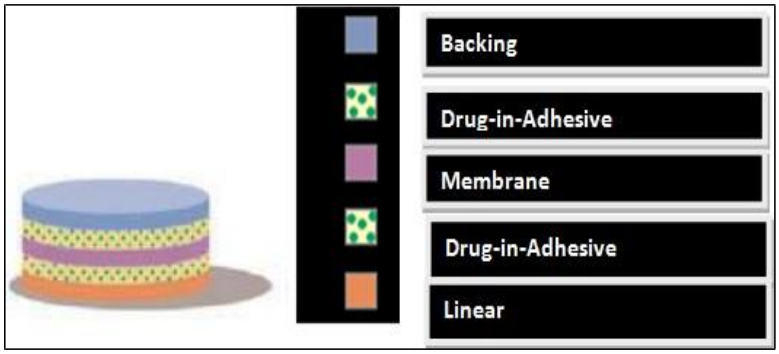


Figure No. 3: Multilayer drug-in-adhesive.

Vapour patch:

In this type of patch, the role of the adhesive layer not only serves to adhere the various layers together but also serves the market, commonly used for releasing essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduce cigarette smoking conditions.

Reservoir system:

In this system, the drug reservoir is embedded between the two layers; an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as an outer surface polymeric membrane that is compatible with the drug.

Matrix system:

Drug-in-adhesive system:

In this type, the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purposes.

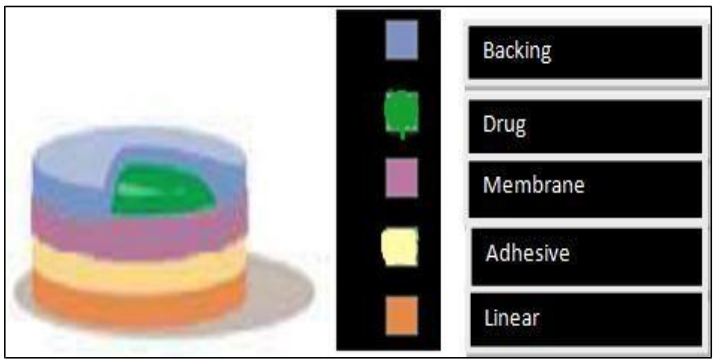


Figure No. 4: Drug reservoir-in-adhesive.

Matrix-dispersion system

In this type, the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug-containing polymer disk 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 with the circumference to form a strip of the adhesive rim.

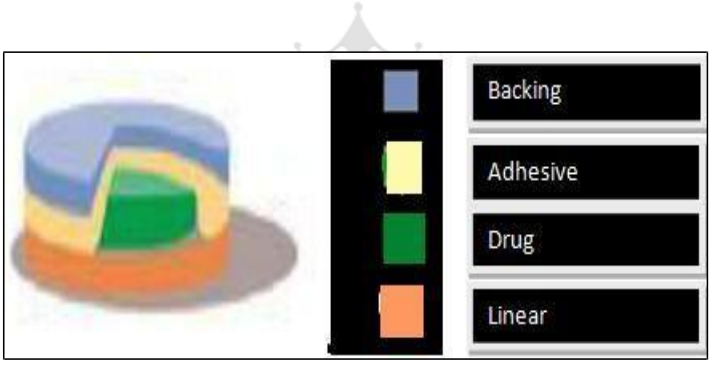


Figure No. 5: Drugmatrix-in-adhesive.

Microreservoir Controlled TDDS:

This drug delivery system is a combination of the reservoir and matrix-dispersion systems. The drugreservoirisformedbyfirstsuspendingthedruginanaqueoussolutionofwater-soluble polymer and then disperses the solution homogeneously in a lipophilic polymer to form thousands of unreachable, 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 center and surrounded by an adhesiverim.

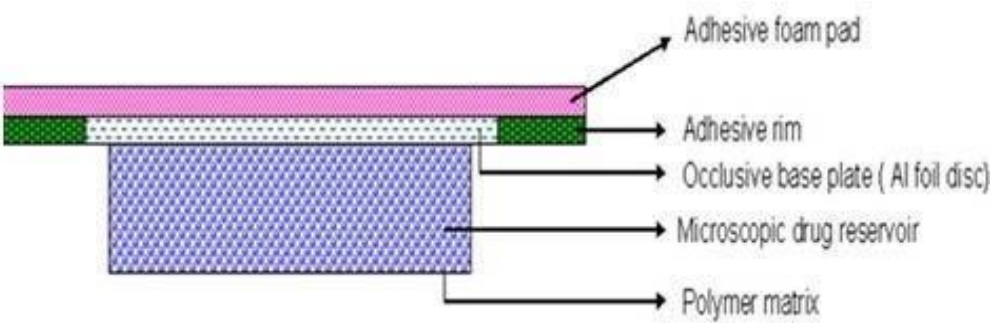


Figure No. 6: Microreservoir controlled TDDS

Mechanism of Action of Transdermal Patch:

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system skin occur through various methods.

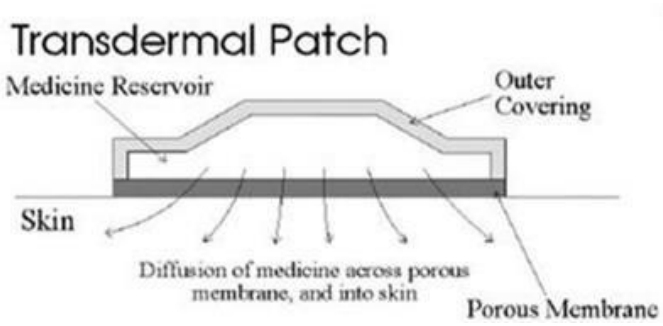


Figure No. 7: Transdermal drug delivery system

Iontophoresis

The basic principle of iontophoresis is that a small electric current is applied to the skin. Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Examples of drugs pilocarpine.

Electroporation

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, thepermeabilityoftheskinfordiffusionofdrugsisincreasedby4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be

administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

Application by ultrasound

Application of ultrasound, particularly low-frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz *et al*. reported on the use of low-frequency sonophoresis for topical delivery of EML Acream.

Use of microscopic projection

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. They are used in development of cutaneous vaccines for tetanus and influenza.

Basic Components of T.D.D. S

a. Polymer Matrix: the Polymer controls the release of the drug from the device.

b. Natural Polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch, etc.

c. Synthetic Polymers: Polyvinyl alcohol, Polyvinylchloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, etc.

d. **Drug** For successfully developing a transdermal drug delivery system, the drug should be chosen with great care.

The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

1. Thedrugshouldhaveamolecularweightlessthanapproximately1000 Daltons.

2. The drug should have an affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not is conducive to successful drug delivery via the skin.

3. The drug should have a low melting point. Along with these properties, the drug should be potent, having a short half-life and be non-irritating.

A. Permeation Enhancers

These are compounds that promote skin permeability by altering the skin as a barrier to the flux of the desired penetrant. These may conveniently be classified under the following main headings:

a. Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids.

Examples

Water alcohols – methanol and ethanol; Alkyl methyl sulfoxides: dimethyl Sulfoxide, alkyl homologs: methyl sulfoxide dimethyl acetamide, Pyrrolidones: 2 pyrrolidones, Natural permeation enhancer Eugenol.

b. Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar headgroup and the hydrocarbon chain length.

- Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate
- Nonionic Surfactants: e.g. PluronicF127, PluronicF68, etc.
- Bile Salts:e.g.Sodiummstaurocholate,SodiumDeoxycholate,Sodiumtauroglycocholate.

B. Other excipients

a. Adhesives

The fastening of all transdermal devices to the skin has so far been done by using a pressure-sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally.

- Should adhere to the skin aggressively, should be easily removed.

- Should not leave unwashable Residue on the skin.
- Should not irritate or sensitize the skin.
- Physical and chemical compatibility with the drug, excipients, and enhancers of the device of which it is apart.
- Permeation of drugs should not be affected.

b. Release liner

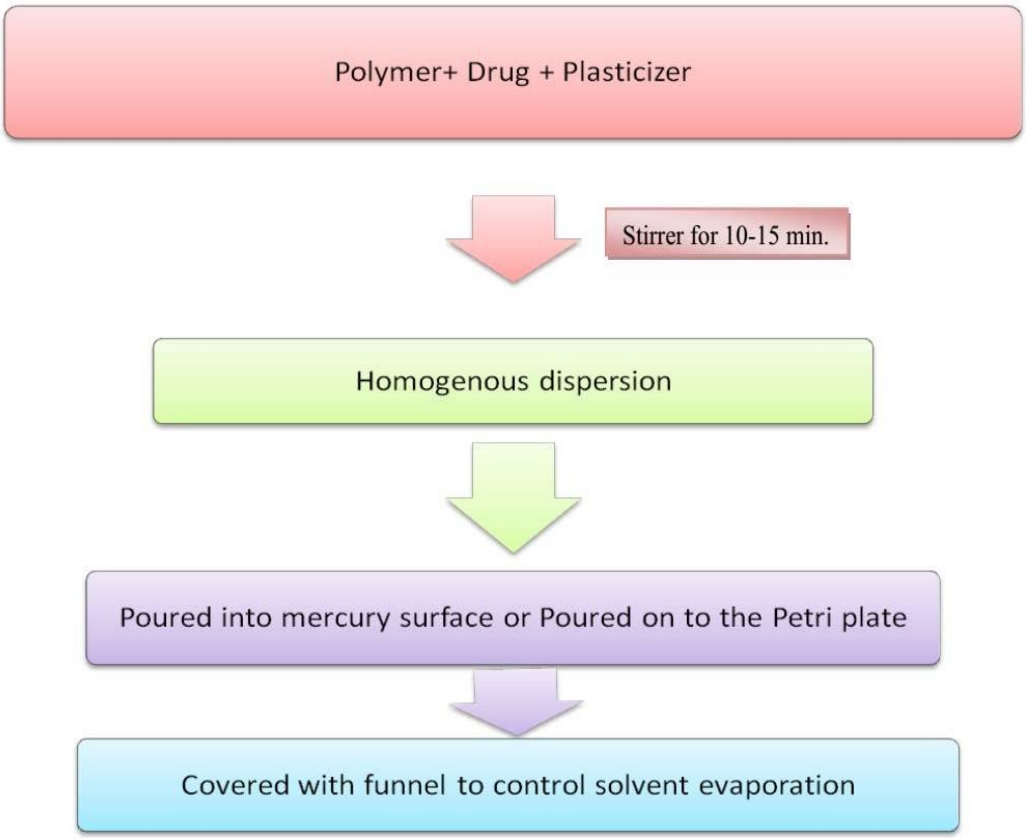
During storage, the release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form for delivering the drug. A release coating layer made up of silicon, Teflon, polyester foil, and metalized laminate.

c. Backing membrane

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent the drug from leaving the dosage form through the top, and accept printing. It is an impermeable substance that protects the product during use on the skin,e.g.metallicplasticlaminate,plasticbackingwithabsorbentpadandocclusivebaseplate(aluminum foil),adhesive foam pad(flexible polyurethane) with occlusive base plate (aluminum foil disc) etc.

Method of Preparing Transdermal Patches:

The method of preparation of TDDS was summarized by modifying the earlier reported methods. The patches were prepared by solvent casting method. The polymer (for example PVP/HPMC) was taken in a beaker with a minimum quantity of the solvent. Then 2/3rd of the solvent was mixed with the other polymers (for example PVA) and was added firstly with stirring at lower rpm and later at a higher speed. The plasticizer was added and homogeneously mixed and the drug was included with enduring agitation and the volume was made the up. The films were cast onto a suitably designed and fabricated glass mold and then dried in the oven at 40 ^{o}C. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place.



HERBAL DRUG LIST USED FOR ARTHRITIS

S.n.	Common name	Botanical name	Chem.. constituents	Uses
1	Ginger	Zingiber officinale	Gingirol, shogaol, zingibrene, zingiron, curcumin	Anti-inflammatory, Pain relieving effect
2	Turmeric	Curcuma longa	Turmeron, alpha-turmerone, beta-turmirone	Anti-inflammatory, Reduce pain, Increase blood circulation
3	Camphor oil	Cinnamomum camphora	Camphor, Cineol, Eugenol, Limonene, safrol	Cal blood flow as a counter-irritant, Analgesic, Antiseptic, Anti-inflammatory, Anti-infective
4	Peppermint	Mentha piperita	Menthol	Relieves muscle and bone pain
5	Eucalyptu	Eucalyptus	1,8-cineole, -pinene,-myrcene,-	Anti-inflammatory,

	s oil	globulus	Terpinene	Analgesic, improve circulation
6	Wintergreen oil	Gaultheria procumbens	Methyl salicylate, alpha-pinene, myrcene, limonene	Analgesic, Induces relaxation
7	Aloe vera	Aloe barbadensis	Vitamins, enzymes, Minerals, Hormones	Anti-inflammatory
8	Clove oil	Syzygiumaromaticum	Eungenol, Acetyleugenol, Vanillin, Tannins	Anti-inflammatoruy
9	Indian borage	Trichodesma indicum	Hexacosane, oleic,linoleic, palmitic and srearic acid	Thermogenic, emmolient, anti-inflammatory
10	Salai guggul	Boswellia serrata	Boswellic acid, Acetyle-beta-boswellic acid	Anti-inflammatory
11	Neem	Azadirachta indica	Betasitosterol, Azadiractin, Myrecetin, Nimbiol, Quercetin	Pain- relieving, anti-inflammatory
12	Katuvira	Capsicum annum	Capsoicin	Reduce swelling, Osteoarthritis, Rheumatoid arthritis
13	Veld grape	Cissus quadrangularis	Methyl gallate, myricetin, geniotein, daidzein	Analgesic, Anti-inflammatory
14	Herbasiegesbeckiae	Sigesbeckia orietalis L	Sesquiterpenoids, diterpenoids, Flavonoids	Anti-inflammatory, antitumor, antiallergis, antithrombotic
15	Madar	Calotropis gigantea	Nicotine, caffeine, quinine	Swelling, Redness, arthritis

CONCLUSION

This review article concluded that an older drug by formulating the min new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increase absorption, delivering to the target site, etc. The patented innovations in the transdermal drug delivery arena aim at these goals. However, the

ultimate test that an innovative technique should pass relates to its successful performance in-vivo. Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. The potential role in the controlled release is being globally exploited by scientists with a high rate of attainment. Due to the large advantages of the TDDS, many new researches are going on in the present day to incorporate newer herbal drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers, and solvents, which play a vital role in the release of the drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, membrane matrix hybrid, micro reservoir type, and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. After preparation of transdermal patches, they are evaluated for physicochemical studies, *in vitro* permeation studies, skin irritation studies, animal studies, human studies, and stability studies.

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