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A review on herbal transdermal patch for arthritis

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Abstract
In conventional medicine system the oral route is highly taken but does not give effective or desired effect because of systemic circulation, the first pass metabolism taken more time to get bioavailable or give therapeutic effect. So Transdermal drug delivery has made an important contribution to medical practice. It is a medicated patch that delivers a specific amount of medication through the skin into the blood stream. An advantage of a transdermal drug delivery route over other types of medication delivery is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.
These Formulation consist herbal drugs, now days herbal drugs are more used they are safe because of having less side effects or low cost. And people trust herbal drug more than allopathy. The active drugs which are used to formulate herbal transdermal patches for arthritis are Ginger, Turmeric, Lavender, Katuvera, clove oil, wintergreen, Camphor, Menthol, aloe Vera, turpentine. These herbal drugs are very effective in arthritis and they are potent to formulate transdermal dosage form. Formulated transdermal drug delivery system using different polymeric grades of hydroxyl propyl methyl cellulose and with plastsizer propylene glycol. The Transdermal patches prepared are of matrix diffusion controlled systems. Solvent casting Technique was used to prepare the transdermal patches.

Keywords: Transdermal patches, conventional medicine system, herbal drugs

Introduction
"A transdermal 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. Often this promotes healing to an injured area of the body."
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 the systemic circulation [10].

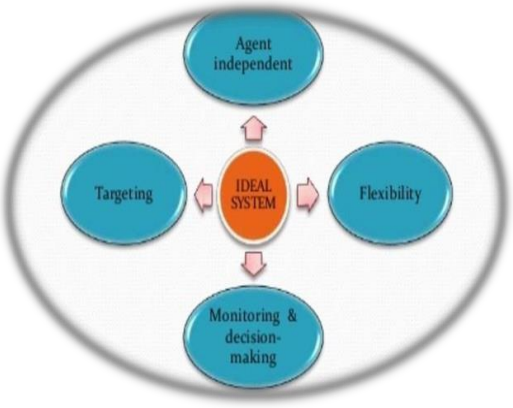

Fig 1: Ideal system of Transdrmal drug delivery system

Transdermal patch provides constant blood levels, avoids first Pass metabolism, increased patient compliance, and avoids dose dumping. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis. Formulation on skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibits local effects in the skin [8].
Currently, transdermal drug delivery (TDD) is one of the most promising methods for drug application. Increasing number of drugs is being added to the list of therapeutic agents that can be delivered to systemic circulation via skin. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication systemically for treating illnesses. Transdermal drug delivery system (TDDS) allows delivery of contained drug into the systemic circulation via permeation through skin layers at a controlled rate. An essential prerequisite for the development of TDDS is that the drug must be capable of passing through skin at a sufficiently high rate to achieve therapeutic plasma concentrations.

However, the outermost layer of skin, stratum corneum (SC), forms a major barrier to most exogenous substances including drugs [9].

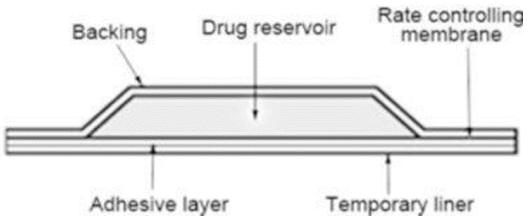

Fig 2: Transdermal Patch

Skin

There are two important layers in skin: Dermis and Epidermis. The outermost layer, the epidermis is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery. Its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, it can enter the blood stream. A process known as passive diffusion, which occurs too slowly for practical use, is the only means to transfer normal drugs be both water-soluble and lipid soluble.

Structure of skin

Skin is a complex biological structure constituting many layers and is the only organ in the body that is most accessible. The skin functions are to safeguard the major internal parts of the body from the external effects, regulation of temperature, sensation and water balance. A normal adult human body skin covers around two square meters surface area and gets about one-third of the blood circulating in the body. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial, and physical influences. The protective properties are provided by the outermost layer of the skin, the epidermis. Although its thickness measure on average only 0.1 mm (from 0.02 mm on the face up to 5 mm on the soles of the feet) it is specially structured to fulfill this challenging task. Out of the five layers of the epidermis, it is mainly the upper most layers (horny layer; stratum corneum) which form the permeability barrier. The stratum corneum consists of horny skin cells (corneocyte) which are connected via desmosomes (protein-rich appendages of the cell

Membrane). The corneocyte are embedded in a lipid matrix [12, 14].

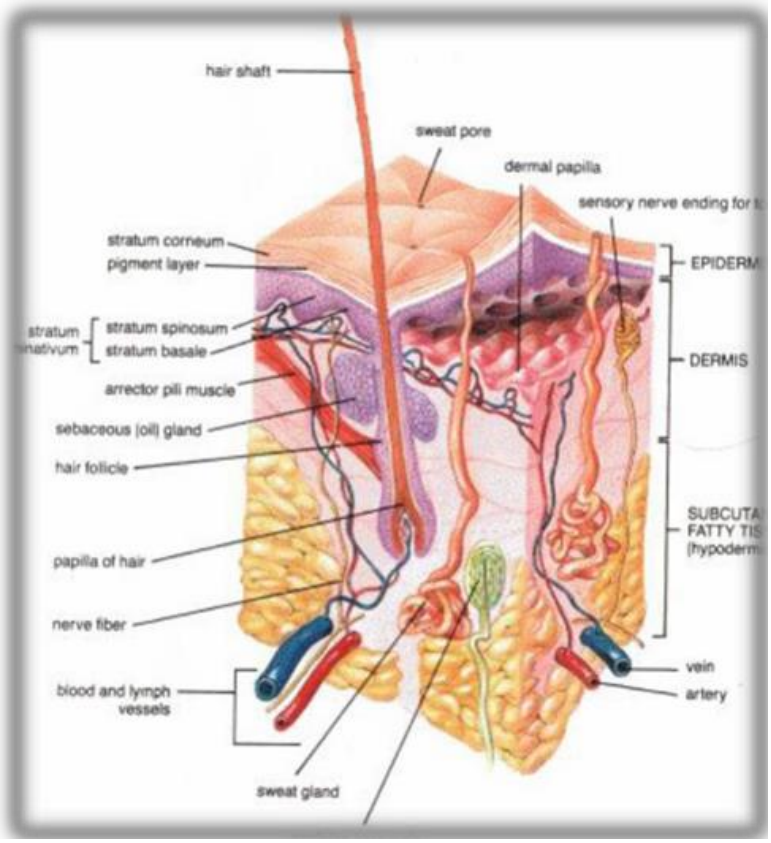

Fig 3: Transverse section of skin

Epidermis

Horney layer (Stratum corneum) viable epidermis

Dermis Hypodermis

Epidermal enzyme systems

Routes of penetration

Illustrates the possible pathway for a penetrate to cross the skin barrier. Accordingly, a molecule may use two diffusion alrouts to penetrate normal intact human skin: the appendageal

route and the transepidermal route. The appendageal route comprises transport via the sweet glands and the hair follicles with their associated sebaceous glands. The routes circumvent penetration through the stratum corneum and are therefore known as shunt routes. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1 % of the total skin area. The appendageal route seems to be most important for ions and large polar molecules which hardly permeation the stratum corneum [28].

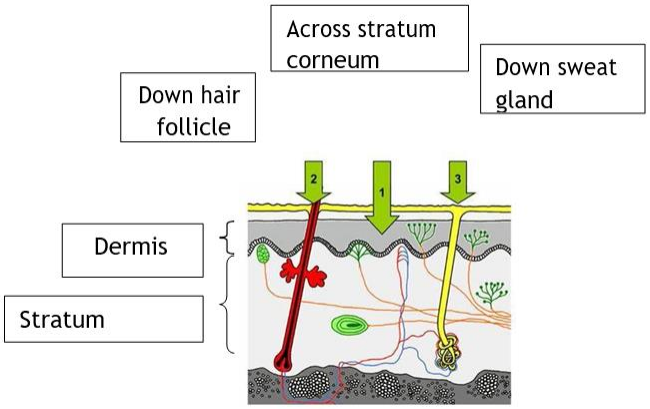

Fig 4: Routes of Penetration

Transdermal drug delivery system designs

TDD can be achieved via active or passive systems depending on whether external energy is used to assist the transport of the drug through the skin. The active systems use heat, electric current (iontophoresis), sound waves (sonophoresis), or transient high-voltage electrical pulses (electroporation) to enhance the delivery of drugs into the systemic circulation. In passive TDDS, the drug diffuses through the skin into the systemic circulation by passive means. In general, chemical permeation enhancers (pharmaceutical excipients) are required for passive delivery to achieve the required delivery of the drug from a patch of a reasonable size (that is, a surface area of ≤ 40 cm) [2].

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 via skin occur through various methods.

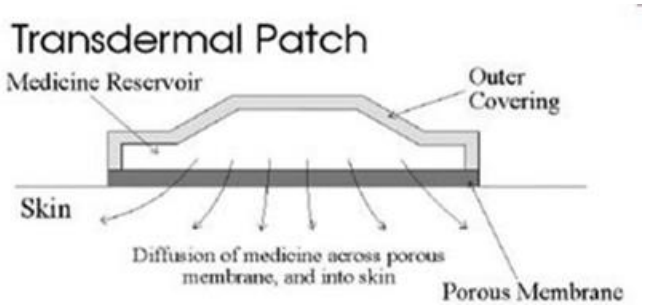

Fig 5: Mechanism of action of Transdermal patch

A. 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.

B. Electroporation

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 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 [13].

C. 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 EMLA cream.

D. 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 [15].

Approaches used in the development of transdermal drug delivery systems

Four different approaches have been utilized to obtain transdermal drug delivery systems.

Membrane Permeation – Controlled Systems

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-

impermeable metallic laminate and a rate controlling membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate-controlling membrane. A thin layer of drug compatible, adhesive polymer like silicone or Polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and skin surface.

Examples: Nitroglycerin-releasing transdermal system (Transdermal-Nitro/Ciba, USA) for once a day medication in angina pectoris. (16)

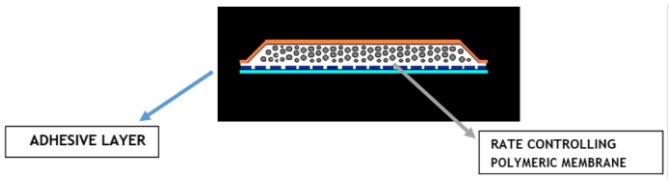

Fig 6: Cross-Section of Membrane Moderated Systems

Matrix Diffusion-Controlled Systems

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vaccum. The advantage of this type of system is the absence of dose dumping since polymer cannot rupture.

Example: Nitroglycerin-releasing transdermal therapeutic system (Nitro-dur and Nitro-Dur II / Key Pharmaceuticals, USA) [24].

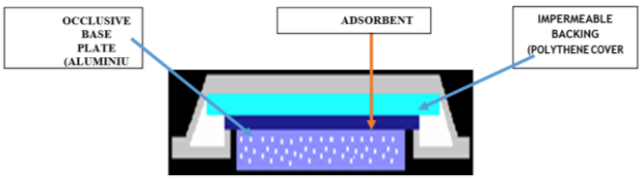

Fig 7: Transdermal therapeutic system

a) Adhesive Dispersion-Type Systems

b) Microreservoir Type or Microsealed Dissolution Controlled System

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, Polyvinyl chloride, 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 [5]

1. The drug should have a molecular weight less than approximately 1000 Daltons.
2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
3. The drug should have low melting point. Along with these properties the drug should be potent, having short half-life and be non-irritating.

A. Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a 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 pyrrolidone, 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 head group and the hydrocarbon chain length.

- Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate
- Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
- Bile Salts: e.g. Sodium ms taurocholate, Sodium Deoxycholate, Sodium tauroglycocholate [29].

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 an 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 a part.
- Permeation of drug should not be affected [30].

b. Release liner

During storage 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 dosage form for delivering the drug. A release coating layer made up of silicon, teflon, polyester foil and metallized laminate [1].

c. Backing membrane

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin, e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc [22].

Types of T.D.D.S

a. Single-layer Drug-in-Adhesive

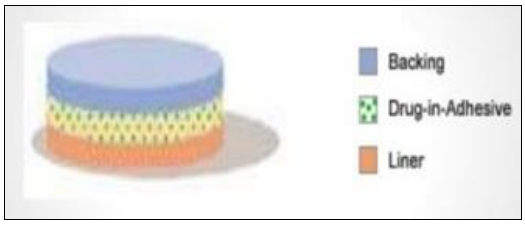

Fig 8: Single- layerd rug-in-adhesive

Multi-layer Drug-in-Adhesive

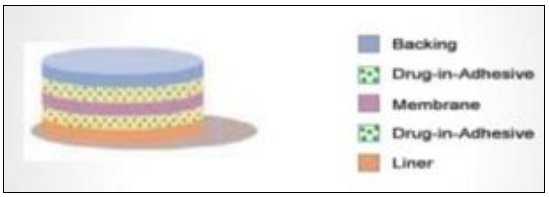

Fig 9: Multi-layer drug in adhesive

Drug Reservoir-in-Adhesive

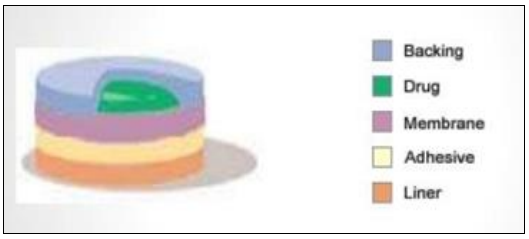

Fig 10: Drug-reservoir-in-adhesive

Drug Matrix-in-Adhesives

Fig 11: Drug-matrix-in-adhesive

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix [26, 27]

History

The first transdermal systems were simply pieces of plastic dipped into a drug that was dissolved in alcohol. The plastic had an adhesive around the edges. Although revolutionary in their day, they created a significant number of skin reactions, more often than not fell off, and had a number of other limitations. These problems gave a lasting negative impression of the whole sector [31].

Advantages

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity and drug interactions with food, drink and other orally administered drugs.
- They can substitute for oral administration of medication when that route is unsuitable, as in case of vomiting and diarrhea.
- They can be used for drugs with narrow therapeutic window [21].

Disadvantages of TDDS

- The drug should have some desirable physico-chemical properties for permeation through stratum corneum and if the dose required for therapeutic values is more than 20mg/day the transdermal delivery will be difficult to formulate, if not impossible.
- Under various environmental conditions, adhesions of the system to different skin types, sometimes result in technical difficulties [11].

Uses

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.
- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.
- The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand name Catapres-TTS [25].

Herbal Remedies for Arthritis

Plant profiles [3, 7]

Fig 12: Ginger

a. Ginger

Ginger is a well-known spice and flavoring agent which has also been used in traditional medicine in many countries.

Plant profile

Kingdom-Plantae Clade-Angiosperms Clade-Monocots Clade-Commelinids Order-Zingiberales Family-Zingiberaceae Genus- Zingiber Species- Z.officinale

Biological name: Zingiber officinale Origin: south-east Asia, India

Morphology

a. Rhizome: The rhizome (underground stem) is brown with a corky (light brown substance) outer layer and pale yellow scented (distinctive, pleasant smell) center.

b. Shoot: The above ground shoot is erect with linear leaves that are arranged ultimately on the stem. The shoot originates from multiple bases and wrap around one another.

c. Flower: Flowering head are produced on shorter stem and the plant produced cone shaped, pale yellow flowers.

Chemical constituents: gingerol, shogaol, zingiberene, zingerone, paradol, arachidonic acid, curcumin

Ginger oil used in arthritis: It has an anti-inflammatory properties and pain reliving effects.

b. Turmeric Kingdom - Plantae Class - angiosperm

Clade: Monocots

Clade: Commelinids Order: Zingiberales Family: Zingiberaceae Genus: Curcuma Species: *c.longa*

Biological name: curcuma longa

Origin: In moist climate such as India (native to the Indian subcontinents), china, South Africa.

Morphology: plants ca. 1m tall. Rhizomes many branched, orange or bright yellow, cylindric, aromatic; roots tuberous at tip.

Chemical constituents: curcuma longa L, turmerone (33.2%), alpha-turmerone (23.5%), beta-turmerone (22.2%).

Turmeric oil: Turmeric oil used in arthritis: turmeric contains curcumin, an active anti-inflammatory compound. Turmeric oil can be used to reduce Inflammation, pain and increases blood circulation.

Fig 13: Turmeric oil

c. Camphor oil

It is found in wood of the camphor laurel (Cinnamomum camphora). It also occurs in some other related trees in the laurel family, notably Ocotea usambarensis. It can also be synthetically produced from oil of turpentine. It is also used in medicinal purposes. Camphor is readily absorbed through the skin and produces a feeling of cooling. Camphor tree is native to China, India, Mongolia, Japan and Taiwan and a variety of this fragrant evergreen tree is grown in Southern United States; Especially in Florida.

Fig 14: Camphor oil

Morphology: Camphor is a white, crystalline substance with a strong odor and pungent taste.

Chemical constituents: The leaf of Cinnamomum camphora contains camphor, as the main component along with cineol, linalool, Eugenol, limonene, safrole, αpinene, βpinene, βmyrecene, αhumulene.

Camphor used in arthritis: camphor is used topically to increase local blood flow and as a "counterirritant", which reduces pain and swelling by causing irritation. Analgesic, antiseptic anti-inflammatory, anti-infective, rubefacient.

d. Menthol

Menthol is an organic compound made synthetically obtained from peppermint or other mint oils.

Menthol having the ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin which is responsible for the well-known cooling sensation Provokes When inhaled, eaten, or applied to the skin.

Morphology: it is a crystaline substance, clear or white in color, which is solid at room temperature and meltes slightly above.

Fig 15: Menthol

Chemical constituents: 5-methyl-2 (prpopan-2-yl) cyclohexan-1-ol

Menthol used in arthritis

It relieves muscles and bone pain.

Menthol is a topical analgesic, it is used as a non-opioid pain reliever since ancient times.

e. Eucalyptus Oil Kingdom - Plantae

Class - Angiosperms

Family - Myrtaceae

Genus - Eucalypteae Species - E. globulus

Botanical name: Eucalyptus globulus

Common name: Nilgiri oil
Morphology: Eucalyptus is an evergreen, tall tree, or shrub, it is native to Australia and Tasmania, nowadays it has extensively spread to other countries.
Chemical constituents: Rich in the oxide (1, 8-cineole and-pinene, -Myrcene, 1, 8-Cineole, -Terpinene.
Eucalyptus Oil Used in arthritis: Eucalyptus oil has a number of anti-inflammatory and analgesic properties. The oil may also improve circulation. And apply topically diluted oil or gel reduces inflammation.

f. Clove oil
Kingdom - Plantae Clade - Angiosperms Family – Myrtaceae Genus - Syzygium Species- S. aromaticum
Botanical name: Syzygium aromaticum
Chemical constituents: Eungenol 72-90% responsible for clove aroma, acetyl Eugenol, beta-caryophyllene and vanillin, crategolic acid, tannins such as bicornin, methyl salicylate.
Morphology: plump is heavy, about 16-20mm long, Crown consist of calyx, corolla, stamen and style.
Clove oil used in arthritis: clove is used as anti-inflammatory in arthritis.

Fig 16: Clove oil

g. Wintegreen oil [17, 20]
Wintergreen, any of several evergreen, aromatic plants of the heath family (Ericaceae). Oil of wintergreen, derived from the leaves of *Gaultheria procumbens*, is a volatile oil used as a flavoring for candies and chewing gum and in the treatment of muscular aches and pain. Genus is pyrola and commonly called shinleaf, native to the North Temperate Zone.
Chemical constituents: Methyl salicylate, (98%), alpha – pinene, Myrcene, delta-3-carene, limonene, and delta-cadinene.

Wintergreen used in arthritis
Wintergreen used as a analgesic or a pain relief, Induces relaxation.

Fig 17: Wintegreen oil

h. Aloe Vera Aloe Vera is a succulent plant species of the genus Aloe. An evergreen perennial, it originates from the Arabian Peninsula but grows wild in tropical climate Around the world and is cultivated for agriculture and medicinal uses.

The species is also used for decorative purposes and grows successfully indoors as a potted plant.
Kingdom: Plantae Clade: angiosperms Clade: Monocots Family: Asphodelaceae Genus: Aloe

Aloe Vera gel used in arthritis: Anti- Inflammatory
Benefits of herbal drug (ginger, turmeric, cellulose) versus the present drug.
As per the WHO reports, about three-quarters of the world's population currently use herbs and other forms of traditional medicines to treat their disease. Herbal products are of natural origine. People believe it as a safe medicine. It is easily available from local market and cost effective too. Herbal medicines are in high demand both in the developed and developing countries due to its biological activities, higher safety margins and lesser costs. Again safety and efficacy of herbal formulation is a cause of concern. Some incidence has been reported, which clearly indicates the doubt on safety and efficacy of herbal products. Many countries like US, UK, New-Zeland have banned few herbal medicines exported from India due to presence of high amount of heavy metals in it.

- Ayurvedic medicines are relatively cheaper as they are mostly produced from different types of readily available plants and herbs. –
- Ayurvedic medicines consists of natural herbs and extracts of fruits, vegetables, spices, etc., which helps in curing diseases without any side effects.

- Ayurvedic medicines deal with permanently healing the person and effectively treating the disease. Ayurvedic literature emphasizes the use of heavy metals in their formulation due to their particular biological properties for curing disease. Ayurveda has described specific physiochemical processes like sublimation, heating etc. to detoxify the metals and to avoid its toxicity. The American medical research community has sounded a heavy metal warning against Ayurvedic cures. Herbal products from the Indian system of medicine sold in the US contain dangerous levels of lead, mercury & arsenic [23].

The main advantages include

Natural Healing Continued Benefits Better Immunity

Table 1: Comparative study of Allopathic drug and Herbal drugs

S.No	Allopathic drugs	Side effects	Herbal drugs	Side effects
1.	Methotrexate	Nausea, vomiting, temporary hair loss, mouth sores, diarrhea, abdominal pain, bone pain.	Ginger	Less side effects
2.	Hydroxychloroquinine	Nausea, vomiting, Uncontrollable itching, retinal damage, epigastria pain.	Turmeric	Nausea and vomiting, stomach upset.
3.	Sulfasalazine	Neutropenia, thrombocytopenia	Wintergreen	Skin irritation
4.	Etanercept	Pain, redness, itching, chest infection.	Katuvera	less side effects
5.	Infliximab	Fever chills, urticaria, bronchospasm.	Menthol	Skin irritation
6.	Anakinra	Chest infections	Eucalyptus oil	Burning, stomach pain, muscles weakness
7.	Leflunomide	Diarrhea, headache, loss of hairs, leucopenia	Castor oil	Skin irritation

Main drawback of allopathic system of medication are its huge side effects, high cost of drugs as well as treatment, lack of curative treatment for chronic diseases and reoccurrence of disease after stoppage of medication. People are losing their faith towards allopathic medicines and going towards the use of traditional medicines due to its holistic approach towards diseases [32].

Conclusion

My project Herbal Transdermal patches for Arthritis gives information regarding the transdermal drug delivery systems and herbal remedies for Arthritis. 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 controlled release is being globally exploited by the scientists with high rate of attainment. Due to 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 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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