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ISSN: 2349 7025
Journal Homepage: www.prlpublisher.com/pharmacy/pjpps

Panacea Journal of Pharmacy and Pharmaceutical Sciences
ISSN: 2349 7025

Review Article

Review on: Development of Novel Herbal System for Rheumatoid Arthritis

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Article Info

Article history:
Received: 2th April 2014
Received in revised form: 5th April 2014
Accepted: 8th April 2014
Available online: 20th April 2014

Keywords:
Cell mediated immunity, Granuloma, Inflammation, Rheumatoid arthritis, TDDS

Abstract

Rheumatoid arthritis is a major inflammatory disease which is caused due uric acid crystal formation in the joints which causes inflammation. Rheumatoid arthritis is both an extravascular immune complex disease and a disorder of cell mediated immunity leads to chronic inflammation, granuloma formation and joint destruction. Conventional drugs form a major line treatment in management of rheumatoid arthritis includes analgesics, non steroidal anti inflammatory drugs, disease modifying antirheumatic drugs, corticosteroids. Since conventional drug delivery has many problems such as poor drug concentration, undesirable side effects and poor efficiency, which creates a need for development of novel drug delivery systems which could overcome these problems. The present investigation was aimed to formulate transdermal system possessing anti-inflammatory activity which would bypass the first pass metabolism and maintain a steady serum concentration. This experiment is one of the first few attempts to utilize ayurvedic drugs through transdermal drug delivery system for anti rheumatic activity.

Introduction

Transdermal Drug Delivery is one of the most worked upon routes for the delivery of drug in to systemic circulation. The fundamentals of successful formulation are to deliver the active substance at target organ with minimal discomfort and side effects. In this respect, transdermal route excels because of avoidance of hepatic first pass metabolism, typical peak trough plasma profile, ease of administration. However, the improvement of drug permeability through the skin is always a difficult problem, because of barrier function of human skin epithelia to exogenous substances. Therefore, the major challenge in topical administration is to increase the drug penetration into the skin. Moreover, most of the pharmaceutical substances are lipophilic in nature. The clinical efficacy of such drugs is being impeded by their low aqueous solubility resulting in poor absorption and penetration mainly when they are designed for transdermal administration.

One way is to use the skin penetration enhancers and the other way is to develop appropriate vehicles to increase the solubility and the thermodynamic activity of the drug and then to increase the permeation. Transdermal drug delivery takes advantage of the relative accessibility of the skin. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the film and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the

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These authors have no conflict of interest to declare.

retention and metabolism of the drug in the skin. Transdermal drug delivery system (TDDS) can deliver certain medication to systemic circulation in a more convenient and effective way than is not possible with conventional dosage form, this help to eradicate many disease conditions including rheumatoid arthritis due to better patient compliance.

Anatomy of Human Skin

The skin of an average adult body covers a surface area of approximately 2 m^2 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. It is one of the most readily available organs of the body with a thickness of only a few millimeters (2.97 ± 0.28 mm). The skin

- ✓ Separates the underlying blood circulation network from the outside environment.
- ✓ Serves as a barrier against physical, chemical and microbiological attacks.
- ✓ Acts as a thermostat in maintaining body temperature.
- ✓ Plays role in the regulation of blood pressure.
- ✓ Protects against the penetration of UV rays.

As skin is major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. It is quite worthwhile to highlight some important characteristic of skin. The diffusion resistance of the skin is greatly dependent on its anatomy and ultra structure. Figure 1 shows the stratified organization of the skin. The composite structure of the skin is indicated by three distinct layers: the epidermis, dermis and subcutaneous fat layer.

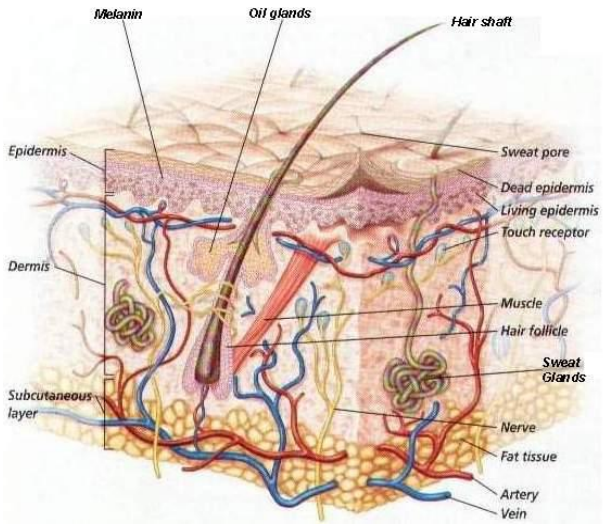

Figure 1. Stratified organization of the skin.

For the purpose of transdermal drug delivery, we can examine the structure and function of human skin categorized into following four main layers:

Subcutaneous Fat Layer: The subcutaneous fat layer or hypodermis, bridges between the overlying dermis and the underlying body constituents. In most areas of the body this layer is relatively thick, typically in the order of several millimetres. This layer of adipose tissue principally serves to insulate the body and to provide mechanical protection against physical shock. The subcutaneous fatty layer can also provide a readily available supply of high-energy molecules, whilst the principal blood vessels and nerves are carried to the skin in this layer.

Dermis: The dermis has numerous structures embedded within it: blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands (eccrine and apocrine). Thus provides physiological support for the epidermis. The dermis (or corium) is typically 3–5 mm thick and is the major component of human skin. It is composed of a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility, embedded in a mucopolysaccharide gel. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

Epidermis: The epidermis is approximately 100 μm thick in man and may be further classified into a number of layers. The stratum germinativum is the basal layer of the epidermis. Above the basal layer are the stratum spinosum, the stratum granulosum, the stratum lucidum and finally, the stratum corneum.

Stratum Corneum: The stratum corneum or the horny layer is the rate limiting barrier that restricts the inward and outward movement of chemical substances consists of flattened keratin-filled cells (e.g., corneocytes). Upon reaching the stratum corneum, these cells are cornified and flatten. The corneocytes are then sloughed off the skin at a rate of about one cell layer per day, a process called desquamation. The man source of resistance to penetration and permeation through the skin is the stratum corneum. Stratum corneum is approximately 15-20 μm thick over much of the human body and corneocytes are composed of cytoplasmic protein matrices comprising keratin embedded in the extracellular lipid. In the simplest sense, therefore, the skin may be represented as a bilaminated membrane; and to reach the dermal vasculature (and

rapid systemic distribution), a penetrating molecule must traverse both, the lipophillic environment of the stratum corneum and the aqueous environment of the underlying viable epidermis and upper dermis.

Transdermal Patch

Transdermal patch is a device for delivering the therapeutic substances through the skin for systemic effect at predetermined and controlled rate; comprising of backing membrane, drug incorporated into matrix, release liner and with/without rate controlling membrane.

The components of transdermal patch include:

- ✓ Polymer matrix or matrices.
- ✓ The drug (active pharmaceutical ingredient).
- ✓ Permeation enhancers.
- ✓ Pressure sensitive adhesives.
- ✓ Backing membrane & release liner.
- ✓ Microporous or semipermeable membrane.

Basic Principles of Transdermal Permeation: Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum, the skin permeation barrier. Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway). In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact stratum corneum becomes the primary pathway for transdermal permeation (Figure 2).

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves:

- ✓ Dissolution within and release from the formulation.
- ✓ Partitioning into the skin's outermost layer, the stratum corneum.
- ✓ Diffusion through the stratum corneum, principally *via* a lipidic intercellular pathway (the rate-limiting step for most compounds).
- ✓ Partitioning from the stratum corneum 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.

Routes of Transdermal Drug Penetration: There are two main pathways by which drugs can cross the skin and reach the systemic circulation (Figure 3). Major route of drug permeation is through skin.

Transcellular Pathway: The more direct route is known as the transcellular pathway. By this route, drugs cross the skin by directly passing through both the lipids membranes and the cytoplasm of the dead keratinocytes that constitute the stratum corneum. Although this is the path of shortest distance, the drugs encounter significant resistance to permeation. This is because the drugs must cross the lipophilic membrane of each cell, then the hydrophilic cellular contents containing keratin, and then the lipids bilayer of the cell one more time.

Intercellular Pathway: The more common pathway through the skin is *via* the intercellular or paracellular route. Drugs crossing the skin by this route must pass through the small spaces between the cells of the skin, making the route more tortuous. Although the thickness of the stratum corneum is only about 20 μm, the actual diffusional path of most molecules crossing the skin is on the order of 400 μm. The 20-fold increase in the actual path of permeating molecules greatly reduces the rate of drug penetration.

Follicular Route: A less important pathway of drug penetration is the follicular route. Hair follicles penetrate through the stratum corneum, allowing more direct access to the dermal Microcirculation. However, hair follicles occupy only 1/1,000 of the entire skin surface area. Consequently, very little drug actually crosses the skin *via* the follicular route.

Release Pattern of Drug from Transdermal System: The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process (Figure 4) which involves:

- ✓ Dissolution within and release from the formulation.
- ✓ Partitioning into the skin's outermost layer, the stratum corneum.
- ✓ Diffusion through the stratum corneum, principally *via* a lipidic intercellular pathway.
- ✓ Partitioning from the stratum corneum into the aqueous viable epidermis.
- ✓ Diffusion through the viable epidermis and into the upper dermis.
- ✓ Uptake into the local capillary network and eventually the systemic circulation.

Drug Profile

Curcumin, is the active constitute of *Curcuma longa* commonly known as the turmeric (haldi in hindi). It belongs to the *Zingiberaceae* family. It is widely used as a medicinal plant all over the India. Nowadays the use of medicinal plant is increasing in therapeutics because it has very less or no side effects, it is also very easily available and cheap as compared to synthetic drugs. It has several activities such as antiinflammatory, antidiabetic, antibacterial, antiseptic, blood purifier. It is cost effective, due to easy availability and has higher safety margin.

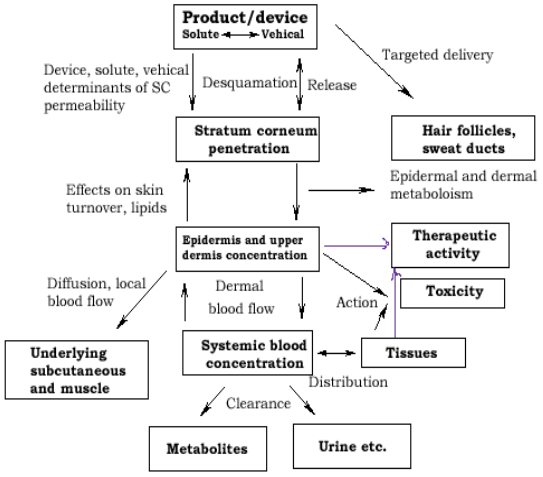

Figure 2. Schematic illustration of percutaneous permeation.

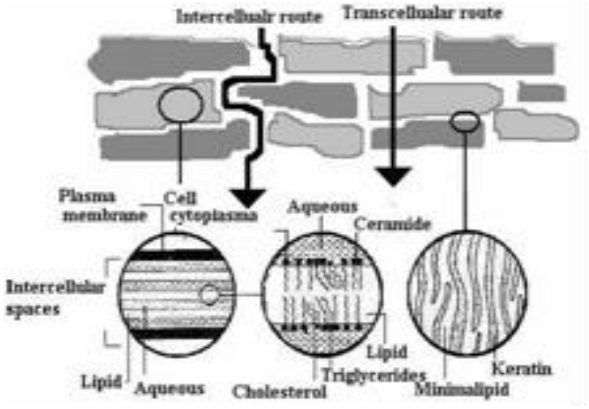

Figure 3. Route of drug permeation through skin.

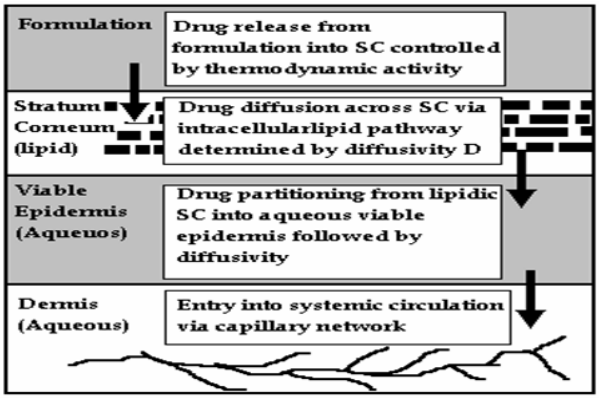

Figure 4. Release pattern of transdermal drug release.

As per literature survey and folkloric history, curcumin possesses antiinflammatory action. Previous pharmokinetic studies of curcumin have reported the low absorption from GIT and it's rapid metabolism, hence it was thought worthwhile to formulate a transdermal system of curcumin.

Mechanism of Action: Its antiinflammatory action may be due to its inhibitory effect on arachidonic acid metabolism *via* the lipoxygenase and cyclooxygnase pathways (Figure 5).

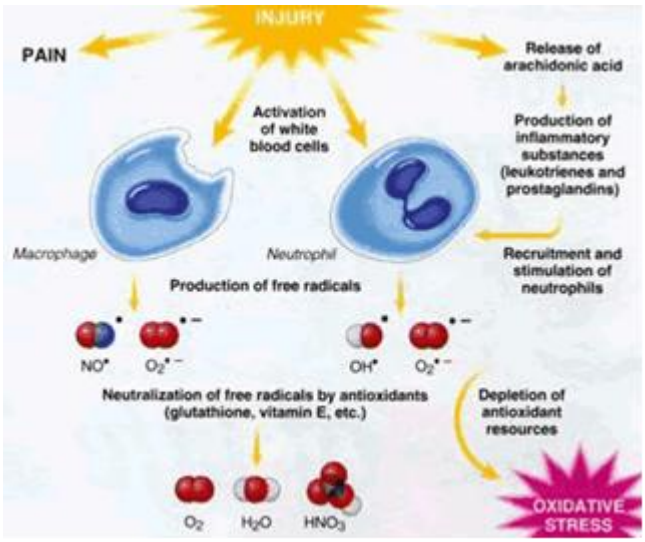

Figure 5. Mechanism of action of curcumin.

Conclusion

Plants play a vital role in treatment of various ailments of human being and herbal formulations are increasing patient compliance as they are devoid of typical side effects unlike allopathic medicines. Rheumatoid arthritis has affected mankind since ages and one of the commonest inflammatory conditions in developing countries. Nowadays scientists have focus on developing a novel drug delivery system for RA using herbal medicines. Novel systems of herbal drugs not only reduce the repeated administration to overcome non-compliance but also help to increase the therapeutic value by reducing toxicity and increasing bioavailability.

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