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Review Article

Recent Advances in Transdermal Drug Delivery System and its Utilization in Herbal Medicines

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ABSTRACT

Transdermal delivery systems are one type of treatment for a variety of disorders that can be utilized as an alternative to invasive procedures. Pharmaceutical preparations are incorporated into transdermal delivery systems, which can release the medication in a regulated manner. When compared to the oral mode of administration, it provides higher bioavailability and eliminates the disadvantage of first pass metabolism. Herbal medicine has played an important role in recent decades due to its strength and few adverse effects. Herbal medicines loaded with transdermal delivery techniques are becoming increasingly popular. The current advancements in transdermal delivery systems provide a significant advantage in treating illness. Natural substances contain complex components that combine with other compounds to produce therapeutic effects. The improved and upgraded transdermal delivery system contributes to reducing the problem and simplifying the transport of the medicament to the skin. The current review aims to analyse the various types of transdermal systems, their advancement and the effectiveness of herbal-based treatments.

Keywords: First pass metabolism, Herbal medicines, Transdermal.

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INTRODUCTION

Transdermal delivery system is an extremely effective medication delivery method with numerous advantages, when compared to oral or parenteral methods. Avoiding 1st pass metabolism, preserving a constant level of active medicine in the blood, enhancing patient compliance and lowering side effects are some benefits.[1]

It has been suggested that a liquid concoction rich in ochre, found at the Blombos Cave in South Africa, was used for skin decoration and protection about 100,000 years ago.[2]

The earliest known form of transdermal patches (Emplastra transcutanea) dates to Ancient China (around 2000 BC), when medicated plasters (emplastra) were applied topically to treat local ailments. Many herbal medicine ingredients were often placed onto an adhesive natural gum rubber foundation and attached to a backing support composed of cloth or paper in these early plasters.[3]

Transderm-Scop, the first Transdermal Drug Delivery (TDD) device, was developed in 1980 to cure motion sickness. Scopolamine was the medicine utilized in this device. The transdermal device is powered by a membrane-moderated mechanism. The membrane in this technology is made of a microporous polypropylene sheet. The drug reservoir is created by dissolving the medication in a blend of mineral oil and poly isobutylene. The period of this study release is three days.[4]

Herbal plants were initially used to produce transdermal medicine delivery systems, which later led to the development of patch technology. This generation of formulations requires lipophilicity, a low molecular weight and low dosage effectiveness. These formulations include ointments, creams, sprays, gels and patches. Due to these reasons, the number of medications that can be absorbed through the skin is restricted. Lipophilic medications, for instance, can slowly pass through the stratum corneum and enter the capillary bed.[5]

Phytotherapeutics are delivered as medicinal products via various routes of administration. A scientific approach is essential to ensure the components are distributed in a sustained manner, thereby enhancing patient compliance and minimizing the need for repeated administration. Though incorporating and delivering an herbal novel way of administering medicine is a challenging task, it also boosts bioavailability while decreasing

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administration frequency and toxicity. Currently, research is focusing on enhanced and unique drug delivery systems that are integrated with herbal-based medicine to provide effective and safer treatment for diverse ailments.

The goal of the review is encompass the various types of novel transdermal delivery systems and its utilisation in herbal based medicine.

IONTOPHORESIS

The fundamental principle that like charges repel one another forms the basis of the iontophoretic approach. To deliver a positively Charged Drug (DC) via iontophoresis, the drug is solubilized in the electrolyte that encircles the anode, the electrode exhibiting similar polarity. An electromotive force is exerted to repel the drug, enabling it to traverse the stratum corneum towards the cathode, situated in a separate region of the body.[6]

Iontophoresis's effectiveness is contingent upon the drug's polarity, valency and mobility, the type of electrical cycle being applied and the drug's composition.[7]

Iontophoresis combined with traditional Chinese herbal medicine improves blood circulation and accelerates the formation of bony callus, offering a novel treatment method for bone fracture healing.[8]

A 50-year-old man with knee osteoarthritis was treated with a new iontophoretic herbal gel (that includes *Symphytum officinale*) and exercise therapy, which had a substantial impact on his pain, function, sleep quality and gait patterns.[9]

SONOPHORESIS

Sonophoresis, often called phonophoresis, is the general term for the application of ultrasound to deliver therapeutic substances via the skin. For almost 40 years, High frequency sonophoresis was still in operation and researchers investigated frequencies as high as 16 MHz. The amplitude and frequency of ultrasonic waves are the 2 most important properties of sonophoresis. The movement of the ultrasonic horn during each half cycle determines the amplitude of the ultrasound wave. The number of times the transducer tip is shifted per second of application time is correlated with the ultrasonic wave's frequency.[7,10]

The medication is utilized in conjunction with a specific coupler, such as a gel or cream, which transmits ultrasonic waves to the skin. This process disrupts the skin's layers and creates an aqueous channel through which the drug can be administered. Typically, pathways generated by the application of ultrasonic waves with frequencies between 20 kHz and 16 MHz are employed for drug delivery.[7,10]

ELECTROPORATION

High-voltage pulses applied to the skin can transfer different chemicals through and into the skin by increasing its permeability. It has been demonstrated that electroporation increases transdermal medication delivery.[11]

This technique involves the application of high-voltage electric pulses, varying from 5 to 500V, for brief exposure durations (approximately milliseconds) to the skin. This process results in the creation of small pores within the stratum corneum, enhancing permeability and facilitating drug diffusion. To ensure safe and painless drug delivery, electric pulses are administered through electrodes that are placed near one another.[7]

The use of electroporative pulses with niosomes entrapping *Annona squamosa* improved transdermal distribution. The proposed approach would aid in the removal of toxic pollutants and oxidants from the body using topical medication enhancers administered directly to the skin.[12]

MAGNETOPHORESIS

The magnetophoretic drug permeation "flux enhancement factor" rises in proportion to the magnetic field strength. Modulating the stratum corneum's permeability improves transdermal medication penetration.[13]

LASER THERAPY

Photomechanical waves that are compressible, unipolar and broadband are known as lasers. Photomechanical waves, in contrast to ultrasound, are characterized solely by positive pressure and do not possess the negative pressure component that is associated with cavitation effects in ultrasound. Various lasers, including erbium-doped yttrium aluminium garnet, Q-switched ruby and carbon dioxide lasers, have been employed to enhance the permeability of the skin to medications through mechanisms such as ablation or disruption of the lipid bilayer.[13]

MICROWAVE THERAPY

Phototherapy is still ineffective in treating tissue infections due to low light penetration depth and laser-induced nonspecific heat diffusion. Microwave thermal therapy is favourable due to its high heating rate and strong tissue penetration. Furthermore, transdermal administration of drugs aids in the treatment of tissue infections.[14]

MICRONEEDLE

The medication is administered via the topical route utilizing a diffusion mechanism. During the administration of microneedle medication, the skin experiences a brief disturbance. A microneedle device is designed by organizing numerous microneedles into arrays on a small patch, allowing for the delivery of an adequate

quantity of medication to elicit the intended therapeutic effect. This device penetrates the stratum corneum, effectively bypassing the barrier layer. The medication is promptly deposited in the epidermis or upper dermis, subsequently entering systemic circulation and producing a therapeutic response upon reaching the target site.[15]

Hyaluronic acid is a linear glycosaminoglycan made up of N-acetyl-d-glucosamine and d-glucuronic acid, which is found naturally within the extracellular matrix of human connective tissue. For medicinal and cosmetic applications, it is obtained through microbial fermentation processes involving *Streptococcus zooepidemicus* and *Corynebacterium glutamicum*. This compound is utilized in various drug delivery systems, such as nanoemulsion hydrogels, microemulsions, nanostructured carriers and microneedles.[16]

THERMAL ABLATION OR THERMOPHORESIS

Thermal ablation represents a fascinating method for enhancing permeability within the stratum corneum of the skin while safeguarding the underlying living tissues. This research utilized finite element modelling, which indicated that the skin's surface should be subjected to heating for only a microsecond to prevent significant temperature elevations in the living cells and nerve endings located in the deeper layers of tissue.[17] The process of thermal ablation of the stratum corneum necessitates achieving temperatures above 100°C, which results in the heating and vaporization of keratin.[7]

VESICLES

The utilization of vesicles in transdermal drug delivery is primarily attributed to their function as carriers that transport encapsulated drug molecules through the skin, in addition to serving as penetration enhancers owing to their unique composition. The emergence of elastic vesicles, including transferosomes, ethosomes, cubosomes and phytosomes, has renewed interest in the development of transdermal delivery systems.[18]

LIPOSOMES

Liposomes are drug delivery vesicles composed of self-assembled phospholipids, which can create either a single bilayer (uni-lamellar) or multiple concentric bilayers (multilamellar) that encapsulate a central aqueous space. Their dimensions vary from 30 nm to the micrometer range, with the thickness of the phospholipid bilayer measuring between 4 and 5 nm.[19] Liposomes are considered an effective drug delivery method due to their structural plasticity, biocompatibility, biodegradability, non-toxicity and non-immunogenicity.[20]

TRANSFEROSOMES

Transferosomes represent a promising vehicle for drug delivery in transdermal applications, as they have the capability to transport larger quantities of active substances to the deeper layers of the skin. The structure of a transferosome primarily consists of amphipathic substances, which are the key components that form the lipid bilayer of the vesicle. These amphipathic substances include phospholipids such as soy phosphatidyl choline, dipalmitoyl phosphatidyl choline, distearoyl phosphatidyl choline and egg lecithin. Among these, lecithin and soy phosphatidylcholine are the most utilized natural and synthetic lipid components in the formulation of transferosomes.[21]

Resveratrol transdermal distribution is a desirable option when compared to other methods of administration because it avoids gastrointestinal issues and first-pass metabolism. The low permeability of Resveratrol transdermal administration, on the other hand, poses a therapeutic challenge. In addition, Resveratrol has a low solubility (0.03 g/L) and poor water stability due to photoisomerization, which lowers its activity.[22]

Resveratrol loaded into a transfersome using a unique carrier. Phosphatidylcholine and non-ionic edge activators combine to form a transfersome. Its ultrade formability allows medications to penetrate the skin and increases the flexibility of the lipid bimolecular membrane of transfersomes.[23]

ETHOSOMES

Ethosomes are soft, flexible lipid vesicles made up of phospholipids, ethanol (or isopropyl alcohol) in high concentrations (20-45%) and water. The ethosomal system contains phospholipids, ethanol and water. Phospholipids have many chemical structures, including phosphatidyl choline, hydrogenated phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol and phosphatidyl inositol.[24]

Anti-inflammatory activity has been investigated by developed an ethosomes of *Sesbania grandiflora* seeds, which may deliver the medication to the targeted site more efficiently than marketed gel preparations and also solve the issues associated with oral administration of the medicine.[25]

NANOEMULSION

A nanoemulsion is a clear and stable mixture of 2 non-miscible liquids, such as oil and water, which is stabilized by surfactants. The droplet sizes in oil-in-water and water-in-oil emulsions typically range from 50 to 1000 nm. Alternative names for emulsion include small emulsion, sub-micron emulsion and ultrafine emulsion.[26]

The nanoemulsion was 160% more efficient than the usual cream, which contained 0.13% extract. The nanoemulsion demonstrated appropriate qualities as a carrier for the topical application of

Rapnea ferruginea extract, as well as a technique for increasing topical anti-inflammatory efficacy.[27]

MICROEMULSION

Microemulsions have the potential to improve drug delivery by incorporating hydrophilic pharmaceuticals into a thermodynamically stable and clear oil-in-water emulsion. This integration can lead to enhanced solubility and permeability of the drug, ultimately resulting in increased bioavailability and therapeutic effectiveness.[28]

Triptolide is a purified chemical derived from the shrub like the vine *Tripterygium wilfordii* Hook. F (*Celastraceae*), which is used in traditional Chinese medicine. It has a wide range of biological effects, including anti-inflammatory, immunosuppressive, antifertility and antineoplastic activity. However, its therapeutic application is limited due to its low water solubility and hazardous effects. To overcome these effects micro emulsion was prepared.[29]

CONCLUSION

The article focuses on various types of transdermal medication delivery systems, as well as the natural substances that were used when combined with them. The herbal transdermal delivery drug system outperforms conventional transdermal systems in terms of bioavailability, rate of release, onset of action, mode of therapy and therapeutic action. Many herbal medicine compounds have begun to draw consumer attention and response because of their innovative delivery strategy. Various published articles and clinical data proved the efficacy of herbal medicine delivery. However, systemic mechanisms are considered effective to have a deeper understanding of the prepared innovative drug delivery systems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BC: Before Christ; **TDD:** Transdermal Drug Delivery; **DC:** Direct current; **MHz:** Megahertz; **kHz:** Kilohertz; **Q:** Quality factor; **°C:** Degree Celsius; **g/L:** Gram per Litre.

SUMMARY

Recent advances in transdermal drug delivery systems have revolutionized the way drugs, including herbal medicines, are administered. Transdermal drug delivery system offers several advantages over traditional methods such as oral or injectable routes, including enhanced bioavailability, controlled release and bypassing first-pass metabolism. This has opened new possibilities for delivering herbal medicines in a more effective and non-invasive manner. Recent innovations in transdermal drug delivery technologies, including microneedles, liposomes and nanocarriers, have improved the penetration of active compounds from herbal medicines through the skin. These systems not only provide a sustained release of the herbal actives but also reduce the risk of side effects and enhance therapeutic outcomes.

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