ORIGINAL

FORM-2

THE PATENTS ACT, 1970
&
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COMPLETE SPECIFICATION

ETHOSOME COMPOSITIONS OF CURCUMIN FOR TRANSDERMAL DELIVERY

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The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed

FIELD OF THE INVENTION

The invention relates to ethosome compositions for transdermal drug delivery. It specifically relates to transdermal drug delivery compositions in the form of ethosomes of curcumin. More specifically, it relates to transdermal drug delivery ethosome compositions of curcumin in the form of gel and process for preparation of ethosomes and their gel forms.

BACKGROUND OF THE INVENTION

One of the major advances in vesicle research was the finding that some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin. Transdermal delivery is important because it is a noninvasive procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with parenteral drug administration can be avoided. It is the most preferred route for systemic delivery of drugs to several diseases. Hence, transdermal dosage forms enjoy being the most patient compliant mode of drug delivery. The principle of transdermal drug delivery system is that they could provide sustained drug delivery (and hence constant drug concentrations in plasma), over a prolonged period of time. The perceived advantages for transdermal drug delivery include:

1. Avoids vagaries associated with gastro-intestinal absorption due to pH, enzymatic activity, drug-food interactions etc.
2. Substitute oral administration when the route is unsuitable as in case of vomiting, diarrhoea, etc.
3. Avoid hepatic "first pass" effect.
4. Avoid the risk & inconveniences of parenteral therapy.
5. Reduces daily dosing, thus improving patient compliance.
6. Extends, the activity of drugs having short plasma half-life through the reservoir of drug present in the therapeutic delivery system and its controlled release characteristics.
7. Rapid termination of drug effect by removal of drug application from the surface of the skin.
8. Rapid identification of the medication in emergencies, eg. Non-responsible, unconscious or comatose patient.
9. Enhance therapeutic efficacy, reduce side effects due to optimization of the blood concentration – time profile and elimination of pure entry of drugs into systemic circulation.

10. Provide predictable activity over extended duration of time & ability to approximate zero-order kinetics.
11. Improved control of the concentration of drug with small therapeutic indices.
12. Minimize inter and intra-patient variation.
13. Provide suitability for self – administration.

Difficulty of permeation through human skin: In addition to physical barrier, human skin functions as a chemical barrier. The outer most layer of skin, the stratum corneum is an excellent barrier to all chemicals including drugs. If a drug requirement is more than 10 mg. per day, the transdermal delivery will be difficult. Only relatively potent drugs can be given through this route.

Skin irritation: Skin irritation or contact dermatitis due to excipients and enhancers of the drug delivery system used for increasing percutaneous absorption.

Clinical need: It has to be examined carefully before developing a transdermal product.

Most of transdermal preparations are meant to be applied to the skin. So, basic knowledge of skin and its physiology function and biochemistry is very important. The skin is the heaviest single organ of the body, combines with the mucosal lining of the respiratory, digestive and urogenital tracts to from a capsule, which separates the internal body structures from the external environment. The pH of the skin varies from 4 to 5.6. Sweat and fatty acids secreted from sebum influence the pH of the skin surface. It is suggested that acidity of the skin helps in limiting or preventing the growth of pathogens and other organisms.

"Ethosomes are soft malleable vesicles composed mainly of phospholipid, ethanol (relatively high concentration) and water. These soft vesicles represents novel vesicular carrier for enhance delivery to / through skin. The size of ethosome vesicles can be modulated from tens of microns to nanometres." Typically, ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), unsaturated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Such a composition enables delivery of high concentration of active ingredients through skin. In comparison to other transdermal & dermal delivery systems the advantages of ethosomes are:

1. Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.

2. Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).
3. Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use.
4. Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature.
5. High patient compliance- The Ethosomal drug is administrated in semisolid form (gel or cream), producing high patient compliance by is high. In contrast, Iontophoresis and Phonophoresis are relatively complicated to use which will affect patient compliance.
6. High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.
7. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
8. Various application in Pharmaceutical, Veterinary, Cosmetic field.

Ethosomes can be used for many purposes in drug delivery. Ethosomes are mainly used as replacement of liposomes. Mainly the transdermal route of drug delivery is preferred. Ethosomes can be used for the transdermal delivery of hydrophilic and impermeable drugs through the skin.

Curcumin (CUR), a constituent of *Curcuma longa* (Family-*Zingiberaceae*), chemically known as diferuloylmethane. It is used in cancer; inflammatory disease, arthritis, oxidative disease, diabetes, multiple sclerosis, Alzheimer disease, HIV, septic shock, cardiovascular disease, lung fibrosis, liver disease, kidney disease, and angiogenic disease can be cured by curcumin. Some of the novel formulations developed using curcumin include liposomes, solid lipid nanoparticles, transdermal film, microspheres, nanoemulsion, etc. Following oral administration (up to 8 g per day), it is poorly absorbed, and only the traces of compound appear in blood. It undergoes extensive first-pass metabolism, and hence is a suitable candidate for ethosomal gel formulation.

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high