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Review Article

POTENTIAL PHYTOTHERAPEUTIC AGENTS IN DESIGN OF ETHOSOMES: A REVIEW

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ABSTRACT
Transdermal drug delivery is one of the efficient methods in novel drug delivery system. Skin is a major target as well as a principle barrier for transdermal drug delivery. The major disadvantage of this system is low diffusion rate of drug(s) across stratum corneum. Ethosomes are modified lipid carriers that enables drug to reach deep into the systemic delivery system. Ethosomes are soft, malleable vesicles embodying alcohol in relatively higher concentration and efficient in delivering drug across the skin. The present review is an attempt to overview the applications of ethosomal formulations and various herbal options (plants or their active therapeutic principles) that may be explored further in the form of ethosomes for treating various types of skin ailments v.i.z. itching , eczema , leucoderma , scabies and other skin diseases.
KEYWORDS: Drug delivery, ethosomes, herbals, lipid vesicles, plants.

INTRODUCTION

Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol or isopropyl alcohol) in relatively high concentration in water.[1] Ethosomes were reported to improve the skin delivery of various drugs.[2] Ethosomes have also been prepared by adding penetration enhancers such as propylene glycol and showed enhanced penetration efficacy.[3] The presence of edge-activator agents (i.e. ethanol and sodium cholate) in the lipid bilayers noticeably improves carrier penetration through the stratum corneum, allowing an efficacious local and systemic delivery of both hydrophobic and hydrophilic compounds.[4] Ethosomes have been proved to be a good delivery carrier in transdermal field and its enhancement effect has been widely recognised.[5] In ethosomal composition, various additives used are phospholipids, polyglycol, alcohol, cholesterol, dye and vehicle.[1] Different additives used and their application in the formulation of ethosomes are mentioned in Table 1.[6] The arrangement of different layers and drug molecule (s) in an ethosome are represented in Figure 1.

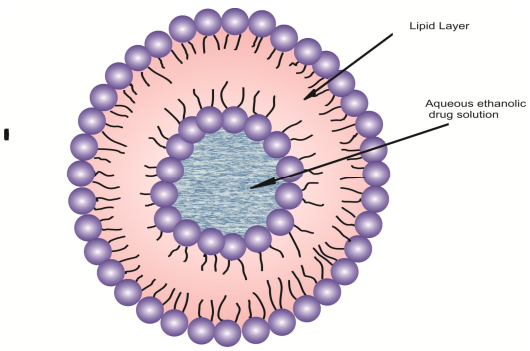

Figure 1.Ethosome

Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies. Ethosomal drug delivery system has been applied to many drugs some of which are mentioned below:

1. The transdermal delivery of salbutamol sulfate, a hydrophilic drug being used as a bronchodilator, was studied in the form of ethosomal and classic liposomal formulations and compared. Both the systems were characterized for their shape, particle size, entrapment efficiency, percentage yield, image analysis using optical or transmission electron microscopy and laser diffraction studies. The presence of ethanol in the aqueous compartment of ethosomal vesicles favored the encapsulation of salbutamol sulfate and enhanced its permeation via skin of newly born mice because of synergistic effects of ethanol, vesicles and skin lipids. Ethosomal systems of salbutamol sulfate was capable of delivering higher amount of salbutamol sulfate at a controlled release rate through mice skin than classic liposomes of salbutamol sulfate.[2]
2. In a research study, two vesicular colloidal carriers, ethosomes and transfersomes of linoleic acid were proposed for the topical delivery. Dynamic light scattering was used for the physicochemical characterization of these vesicles and mean size, size distribution and zeta potential were also evaluated. The stability of formulation was also evaluated using turbiscan lab expert based on the analysis of sample transmittance and photon back scattering. Ethosomes and transfersomes of linoleic acid were prepared using phospholipon 100 G, ethanol and sodium cholate. The percutaneous permeation experiments of linoleic acid-loaded ethosomes and transfersomes through human stratum corneum epidermidis membranes showed that both carriers were accumulated in the skin membrane model as a function of their lipid composition. It was concluded that both vesicular carriers have good potential for the topical treatment of hyperpigmentation related disorders.[4]
3. In another research study, a novel transdermal drug delivery system that facilitated skin permeation of finasteride was designed using finasteride encapsulated in novel lipid-based vesicular carriers in the form of ethosomes. The finasteride transdermal flux from ethosomal formulation (1.34±0.11 μg/cm^2/h) was 7.4, 3.2 and 2.6 times higher than that of finasteride from aqueous solution, conventional liposomes and hydro ethanolic solution respectively ($p<0.01$). Furthermore, ethosomes produced a significant ($p<0.01$) finasteride accumulation

in the skin, especially in deeper layers, for instance, in dermis it reached to 18.2±1.8 μg/cm^2. The study demonstrated that ethosomes are promising vesicular carriers for enhancing percutaneous absorption of finasteride.[5]

4. Miconazole incorporated different novel carriers such as liposomes and ethosomes were prepared and compared for their *in vitro* skin permeation studies using skin model. *In vitro* skin permeation studies results proved that the steady state fluxes of miconazole was higher in case of ethosomal suspension incorporated ointment as compared to liposomal ointment.[7]
5. A novel ethosomal carrier containing trihexyphenidyl HCl was investigated against its classic liposomal formulation. Ethosomes of trihexyphenidyl HCl was reported to show a higher entrapment capacity and a greater ability to deliver entrapped fluorescent probe to deeper layers of skin. The flux of trihexyphenidyl HCl through nude mouse skin from trihexyphenidyl HCl ethosomes (0.21 mg/cm^2 h) was 87, 51 and 4.5 times higher than from liposomes, phosphate buffer and hydroethanolic solution respectively ($p<0.01$). The quantity of trihexyphenidyl HCl, remained in the skin at the end of 18 h experiment, was statistically significantly greater from the ethosomal system than from liposomes or a control hydroethanolic solution. Results indicated that the ethosomal trihexyphenidyl HCl system may be a promising candidate for transdermal delivery of trihexyphenidyl HCl.[8]
6. The effects of pH and ethanol content on mycophenolic acid solubility were evaluated to find out the suitable dispersion medium for ethosome preparations. The solubility profiles of mycophenolic acid were investigated as a function of pH and ethanol content. In addition, the effects of formulation composition on the physical appearance, entrapment efficiency, zeta potential, particle size and size distribution were also investigated. The mycophenolic acid ethosomal formulation gave vesicular size of 371 ± 8 nm, zeta potential of -46 ± 5 mV and the entrapment efficiency of 56 ± 1%.[9]
7. Tacrolimus-loaded ethosomes were prepared and assessed for dermal delivery against tacrolimus liposomes. Both the delivery systems were characterized for particle size, polydispersity index, and entrapment efficiency. Physical stability was found to be good for tacrolimus-loaded ethosomes under 4°C storage conditions. Results demonstrated that the tacrolimus ethosomal system might be a promising candidate for dermal delivery of tacrolimus in case of atopic dermatitis.[10]

Transfersomes are another mode of transdermal drug delivery system and consist of phospholipids and an edge activator, which destabilizes lipid bilayers of the vesicles and increases their deformability. On the other hand, ethosomes as additional novel lipid carriers are composed of ethanol, phospholipid and water. Ethosomes has been reported to improve skin delivery of various drugs. Ethanol is known as an efficient permeation enhancer and believed to act by affecting the intercellular region of the stratum corneum.[2]

THERAPEUTIC APPLICATIONS OF ETHOSOMES

Since composition and components of ethosomes are safe, they have various applications in pharmaceutical, veterinary and cosmetics field.

1. Pilosebaceous targeting: Pilosebaceous units have been used for localised therapy, particularly for the treatment of follicle related disorders such as acne or alopecia. Ethosomal formulation of minoxidil, a lipid soluble drug has been used for the treatment of baldness. The drug was accumulated into nude mice skin two to seven fold higher and proved as a useful tool for pilosebaceous targetting and better clinical efficacy.[1]
2. Transdermal delivery: As stratum corneum provides a greater resistance to penetration of drugs, the ethosomal formulation enhances the permeability of drugs through stratum corneum e.g. ethosomes of ascorbic acid. [3]
3. Delivery of antifungal drugs: Deep aerated fungal infections are difficult to treat with conventional topical formulation, while ethosomal formulation of miconazole nitrate are found to be effective and showed better skin penetration.
4. Delivery of antiarthritic drugs: Topical delivery of anti arthritic drugs in the form of ethosomal formulations has overcome the problems associated with conventional oral therapies being used in the treatment of arthritis. e.g. cannabidiol.[11]
5. Delivery of antiparkinsonism drugs: Recently, ethosomal formulation of trihexyphenidyl HCl has been used for better management of parkinsonism.[8]

Some of the applications of ethosomal formulations are enlisted below in Table 2.

Table 1.Different Additives Employed In Formulation of Ethosomes [6]

SN	Class	Example	Uses
1.	Phospholipid	Soya phosphatidylcholine, Egg phosphatidyl choline, Dipalmitylphosphatidyl choline, Distearylphosphatidyl choline	Vesicles forming component
2.	Polyglycol	Propylene glycol, Transcutol RTM	As a skin penetration enhancer
3.	Alcohol	Ethanol, Isopropyl alcohol	For providing the softness for vesicle membrane, as a penetration enhancer
4.	Cholesterol	Cholesterol	For providing the stability to vesicle membrane
5.	Dye	Rhodamine-123, Rhodamine red, FluoresceneIsothiocynate (FITC) 6- Carboxy fluorescence	For characterization only
6.	Vehicle	Carbopol 934	As a gel former

Table 2: **Application of ethosomes as a drug carrier**[1]

S. No.	Drug	Application (s)
1.	Antiviral agents (Zidovudine, Lamivudine and Stavudne)	Prolonged drug action, reduced drug toxicity, Control release for prolonged period of time, improved biological anti-inflammatory activity sustained effect
2.	Trihexyphenidyl hydrochloride	Higher entrapment capacity, improved tansdermal flux
3.	Antibiotics (Erythromycin, Cannabidol)	Complete inhibition of infection, prolonged drug action, improved skin deposition and biological activity
4.	Pilosebaceous targeting (Minoxidil)	High penetration into deep layers of the skin
5.	NSAIDS (Diclofenac)	Selective and prolong delivery of drug to desired side
6.	Acyclovir	Increased skin permeation and biological activity
7.	Topical Photodynamic Therapy (PDT) (5- aminolevulinic acid)	Greater penetration ability than that of liposomes
8.	Insulin	Significant decrease in blood glucose level
9.	Ammonium glycrrhizinate	Improved biological anti-inflammatory activity, sustained effect
10.	Salbutamol sulphate	Controlled release rate, enhanced skin permeation
11	Propranolol	Better skin permeation
12.	Testosterone	Significantly higher permeation into the skin increased systemic delivery
13.	Bacitracin	Reduced drug toxicity

Some plants/ herbal options, that may be explored further to ratify as a novel herbal drug delivery in the shape of ethosomes are enlisted in Table 3.

Table 3. List of the some traditional plants containing active principle (s) present against skin inflammation and may be explored in future in the form of ethosomal herbal formulation are: [12]

[12]

S. No	Plant Name	Family	Part Used	Uses
1	*Hiptage benghalensis*	Malvaceae	leaves	Skin diseases
2	*Abelmoschus moschatus medic*	Malvaceae	Seeds	Leucoderma, itching
3	*Abutilon indicum sweet*	Malvaceae	Whole plant (dried)	Antiinflammatory
4	*Kydia calcina*	Malvaceae	Leaves	Skin diseases
5	*Sida rhombifolia*	Malvaceae	Leaves	Skin diseases
6	*Thespesia lampas*	Malvaceae	Floral parts	Scabies, psoriasis, Eczema
7	*Thespesia populnea*	Malvaceae	Leaves, flower, Fruit	Skin diseases
8	*Memecylon umberratum*	Melastomataceae	Leaves	Antiinflammatory
9	*Azadirachta indica*	Meliaceae	Bark	Skin diseases
10	*Meliaazedarach*	Meliaceae	Flower	Skin diseases
11	*Toona ciliate*	Meliaceae	Bark	Itching
12	*Tinospora sinensis*	Meliaceae	Stem	Skin ailment
13	*Glinus lotoides*	Molluginaceae	Crushed plant	Itching
14	*Broussonetia papyrifera*	Moraceae	Bark	Eczema
15	*Ficus arnotiaana*	Moraceae	Leaves & Bark	Skin diseases
16	*Ficus lacor buch-ham*	Moraceae	Whole plant (dried)	Inflammation
17	*Ficus racemosa*	Moraceae	Infusion of leaf	Skin diseases
18	*Ficus religiosa*	Moraceae	Infusion of bark	Scabies
19	*Moringa olifera*	Moringaceae	Infusion of root	Inflammation
20	*Embelia tsjeriam-cottam*	Myrsinaceae	Fruit	Skin diseases
21	*Ecualyptus globulus*	Myrtaceae	Leaves	Skin diseases
22	*Boerhavia diffusa*	Nyctaginaceae	Leaves	Inflammation
23	*Mirabilis jalapa*	Nyctaginaceae	Leaves	Itching
24	*Jasminum multifiorum*	Oleaceae	Flower	Inflammation
25	*Nyctanthes arbos-Tristis*	Oleaceae	Leaves	Skin diseases
26	*Vanda tesserata*	Orchidaceae	Leaves	Swelling
27	*Averrhoa carambola*	Oxalidaceae	Whole plant (dried)	Scabies
28	*Pandanus fanicularis*	Pandanaceae	Leaves	Scabies
29	*Argemone mexicana*	Papaveraceae	Seedoil	Skin diseases
30	*Martynia annua*	Pedaliaceae	Fruit	Inflammations
31	*Sesamum orientale*	Pedaliaceae	Seed oil	Skin Complaints
32	*Piper longum*	Piperaceae	Roots & fruit	Leucoderma
33	*Piper nigrum*	Piperaceae	Leaves	Skin diseases
34	*Plumbago zeylanica*	Plumbaginaceae	Root	Skin diseases

35	*Bambusa bambos*	Poeaceae	Stem	Leucoderma
36	*Bambusa vulgaris*	Poeaceae	Leaves	Skin diseases
37	*Cymbopogon martini*	Poaceae	Leaves	Skin diseases
38	*Ventilago madeasptana*	Rhamnaceae	Bark	Itching
39	*Garclenia resinifera*	Rubiaceae	Leaves	Skin diseases
40	*Haldina cordifolia*	Rubiaceae	Bark	Skin diseases
41	*Hymenodictyon orixense*	Rubiaceae	Bark	Skin diseases
42	*Tarenna aslatica*	Rubiaceae	Leaves	Skin diseases
43	*Andrographis paniculata*	Acanthaceae	Leaves	Vitiligo
44	*Barleria cristata L.*	Acanthaceae	Leaves	Itching, other skin diseases
45	*Barleria priontis L.*	Acanthaceae	Bark	Itching, Scabies
46	*Achyranthes aspera*	Amaranthaceae	Leaves	Healing of Cracked skin on the feet
47	*Aerva lanata*	Amaranthaceae	Bark	Skin affections
48	*Amaranthus spinosus*	Amaranthaceae	Stem	Eczema
49	*Curculigo orchioides*	Amaryllidaceae	Leaves	Leucoderma
50	*Buchanania lanzan*	Anacardiaceae	Leaves	Itching
51	*Lannea coromandelica*	Anacardiaceae	Leaves	Skin diseases, Impetigo
52	*Semecarpus anacardium*	Anacardiaceae	Whole plant (dried)	Eczema
53	*Artabotrys hexapetalus*	Annonaceae	Leaves	Itching
54	*Canaga odorata*	Annonaceae	Fruit	Itching
55	*Nerium indicum*	Apocynaceae	Leaves	Skin diseases
56	*Plumeria accuminata*	Apocynaceae	Leaves	Itching
57	*Rauvolfia tetraphylla*	Apocynaceae	Root	Chronic Skin disease
58	*Tabernaemontana divaricata*	Apocynaceae	Leaves	Skin diseases
59	*Wrightia arborea*	Apocynaceae	Whole plant (dried)	Skin diseases
60	*Wrightia tinctoria*	Apocynaceae	Leaves	Skin diseases
61	*Acorus calamus*	Araceae	Root	Eczema
62	*Areca catechu*	Arecaceae	Whole plant (dried)	Skin diseases
63	*Aristolochia bracteolate*	Aristolochiaceae	Leaves	Eczema
64	*Calotropis gigantea*	Asclepiadaceae	Root	Ringworm
65	*Acanthospermum hispidum*	Astecaceae	Leaves	Skin ailment
66	*Centratherum anthelminticum*	Asteraceae	Root	Leucoderma
67	*Eclipta prostrate*	Asteraceae	Leaves	Skin diseases
68	*Helianthus annus*	Asteraceae	Leaves	Itching, Skin diseases
69	*Sphaeranthues indicus*	Asteraceae	Leaves	Eczema
70	*Vernonia cinerea*	Asteraceae	Leaves	Ringworm, Eczema
71	*Oroxylum indicum*	Bignoniaceae	Leaves	Skin diseases
72	*Spathodea campanulata*	Bignoniaceae	Leaves	Skin diseases
73	*Bixaorellana*	Bixaceae	Whole plant (dried)	Skin diseases
74	*Trichodesma indicum*	Boraginaceae	Leaves	Skin diseases
75	*Trichodesma zeylanicum*	Boraginaceae	Leaves	Leucoderma
76	*Lepidium sativum*	Brassicaceae	Leaves	Skin diseases
77	*Boswellia serrata*	Burseraceae	Leaves	Skin diseases
78	*Canarium strictum*	Burseraceae	Leaves	Psoriasis
79	*Cadaba fruticosa*	Capparidaceae	Leaves	Eczema
80	*Capparis sepiaria*	Capparidaceae	Stem	Eczema, Psoriasis
81	*Capparis spinsoa*	Capparidaceae	Root	Pruritis
82	*Carica papaya*	Caricaceae	Whole plant (dried)	Ringworm, Psoriasis
83	*Cassineglauca*	Celastraceae	Leaves	Eczema, Skin diseases
84	*Gloriosa superba*	Colchicaceae	Leaves	Itching
85	*Anogeissus iatifolia*	Combretaceae	Leaves	Skin diseases
86	*Quisqualis indica*	Combretaceae	Whole plant (dried)	Skin diseases
87	*Terminalia chebula*	Combretaceae	Whole plant (dried)	Skin diseases
88	*Cuscuta reflexa*	Convolvulaceae	Leaves	Dermititis
89	*Merremia gangetica*	Convolvulaceae	Leaves	Leucoderma
90	*Bauhinia racemosa*	Fabaceae	Leaves	Skin diseases
91	*Bauhiniavariegate*	Fabaceae	Leaves	Leucoderma
92	*Caesalpinia bonduc*	Fabaceae	Root	Skin diseases
93	*Cassia absus*	Fabaceae	Leaves	Ringworm
94	*Cassia auriculata*	Fabaceae	Leaves	Skin diseases
95	*Cassia fistula*	Fabaceae	Leaves	Eczema
96	*Cassia occidentalis*	Fabaceae	Leaves	Eczema
97	*Anisomeles indica*	Lamlaceae	Leaves	Itching
98	*Hyptis suavedens*	Lamiaceae	Leaves	Skin diseases
99	*Urginea indica*	Liliaceae	Leaves	Scabies
100	*Ammannia baccifera*	Lythraceae	Leaves	Ringworm

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY [1, 13]

In comparison to other transdermal & dermal delivery system, ethosomes have several advantages as follows:

1. Ethosomes have enhanced permeation of drug through skin for transdermal drug delivery.
2. The ethosomal drug can administrated in semisolid form (gel or cream) hence produce high patient compliance. The ethosomal system is passive, non-invasive and is available for immediate commercialization.
3. In contrary to deformation of liposomes, ethosome improves skin delivery of drugs both under occlusive and non-occlusive conditions.
4. Ethosomes have better stability and solubility as compared to conventional vesicles.
5. Ethosomes are relatively smaller in size as compared to conventional vesicles.

CONCLUSION

For transdermal delivery of drugs, stratum corneum is the main barrier layer for penetration of any drug. Preface to ethosomes has initiated a new area in vesicular research. Ethosomes has shown promising results and great potential for delivery of various agents, better control over drug release, non – invasive delivery of small, medium and large sized drug molecules etc. Ethosomal formulations may be one of the promising tool for dermal/transdermal drug delivery of various phytochemicals/ biologically active molecules besides synthetic agents.

REFERENCES

1. Nikalje A, Tiwari S. Ethosomes : a novel tool for transdermal drug delivery. Ind J Pharm Sci 2012;2(1):1-20.
2. Bendas E R, Tadros M I. Enhanced transdermal delivery of salbutamol sulfate via ethosomes . AAPS Pharm Sci Tech 2007;8(4):1-8.
3. Verma P. Transdermal penetration efficacy of ethosomal systems with and without permeation enhancer : a comparative study . Int J Pharm Sci Res 2011;2(9):2472-2474.
4. Celia C, Cilurzo F, Trapasso E, Cosco D , Fresta M, Paolino D. Ethosomes and transfersomes containing linoleic acid: physicochemical and technological features of topical drug delivery carriers for the potential treatment of melasma disorders. Biomed Microdevices 2012;14:119–130.
5. Rao Y, Zheng F, Zhang X,Gao J Liang W. *In vitro* percutaneous permeation and skin accumulation of finasteride using vesicular ethosomal carriers. AAPS Pharm Sci Tech 2008;9930:860-865.
6. Samala U, Pannala S. Ethosomes, a novel transdermal drug delivery systems: a review. Drug Invent Today. 2011;4(12):4628-4630.
7. Singh A, Rathore P ,Shukla M, Nayak S. Comparative studies on skin permeation of micanozole using different novel carrier. Int J Pharm Sci Res 2010;(9):61-66.
8. Dayan N, Touitou E. Carriers for skin delivery of triexphenidyl HCl: ethosome vs lipsomes. Biomaterials 2000;21:1879-1885.
9. Limsuwana T , Amnuaikita T. Development of ethosomes containing mycophenolic acid. Procedia Chem 2012;4: 328-335.
10. Li G, Fan C, Li X, Fan Y, Wang X, Li M et al. Preparation and *in vitro* evaluation of tacrolimus-loaded ethosomes. The Sci World J. doi:10.100/2012/874053.
11. Kumar P, Radhika PR, Kumar S. Ethosomes: a priority in transdermal drug delivery. Int J Pharm Sci Res 2010;1:111-121.
12. Parrotta JA. Healing plants of peninsular India. 1st ed. Singapore: MRM graphics Ltd. 2001.
13. Rasheed S H, Girhepunje K, Kumar V V , Priyanka G B , Vani P S , Gajavalli S R. Ethosomes: a novel tool for transdermal drug delivery. World J Pharm Res 2012;1(2):59-71.

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