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Review on drug delivery applications of ethosomes: Current developments and prospects

Mayuri Shitole[1†], Sopan Nangare[2†], Udaykumar Patil[1], Namdeo R. Jadhav[1*]

[1]Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India, [2]Department of Pharmaceutical Chemistry, H. R. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra, India
[†]These authors contributed equally as first authors.

Corresponding Author:
Prof. Namdeo R. Jadhav, Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur - 416 013, Maharashtra, India.
E-mail: nrjadhav18@rediffmail.com

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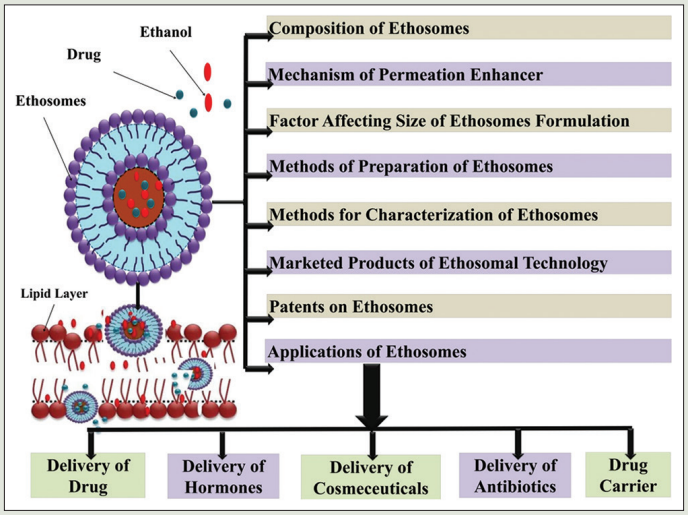
ABSTRACT

Transdermal drug delivery system networks are primarily affected by poor penetration of therapeutically active compounds. The stratum corneum (SC) is the foremost barrier of the skin, which restricts the permeation of the drug molecule. In this context, to date, numerous approaches have been implemented to overcome the SC barrier limitations. Out of this, few advanced approaches including liposomes, niosomes, ethosomes, and transferosomes are majorly used to boost the permeation of drug and cosmetic agents across the SC barrier. Among these vesicles, ethosomes are stand out as the best substitute for topical drug delivery. In a nutshell, ethosomes are the elastic nanosized, stable vesicles that contain phospholipid and high content of ethanol that interacts with the polar head domain of the lipid molecules and decline the SC lipid melting point. Finally, it increases lipid fluidity plus cell membrane permeability. In this segment, this review gives the recent updates of ethosomes based on several pharmaceutical dosage forms such as ethosomal gels, creams, and patches. In addition, updated patents on ethosomes are also discussed in brief. In conclusion, ethosome is an ideal carrier for the delivery of drugs, cosmetic agents, etc., and can be used as a replacement for traditionally used pharmaceutical applications.

Keywords: Carriers, ethosomes, penetration enhancer, skin permeability, transdermal drug delivery

GRAPHICAL ABSTRACT

Drug delivery applications of ethosomes



INTRODUCTION

Skin is the most easily accessible organ of the body, that helps to drug delivery with the therapeutically efficient amount for a prolonged period.[1] The current scenario of drug delivery reveals that around 40% of drugs are commonly used in transdermal drug delivery. For that purpose, ethosome is the most favored carrier. Because it can prevent metabolic effects (first-pass effect) and eliminates deleterious impact. As SC is the challenge to the transdermal and topical drug administering process, the recently developed ethosomal drug delivery system can easily accomplish this goal.[2] As per published literature, an ethanol-containing lipoidal vesicular system (ethosome) was discovered by Touitou in 1996.[3] It is non-invasive, soft, malleable, bilayer vesicles, containing phospholipid, and alcohol (ethanol or isopropyl alcohol). Usually, at the core (center) of the ethosomes, the co-surfactant and drug/s are encapsulated.[4-7] Especially, the size of ethosomes is dependent on the method of preparation and duration of sonication performed. In addition, ethosomes are lipophilic plus hydrophilic in nature that available in different sizes ranges from nanometer (nm) to micrometer (μm).[8] As per literature, ethosomes vesicles containing ethanol impart a negative net charge on the surface of vesicles. Furthermore, it decreases the size at concentrations ranging from 20% to 50%. However, the high content of ethanol can increase the permeability of the skin. Therefore, it boosts drug penetration. Herein, ethanol extracts the skin lipids, and penetrates intracellularly. Furthermore, it increase lipid fluidity and finally this resulted into penetration rate enhancement. Accordingly, the ethosomes can reach the deep skin layer and then fused with skin lipids. Finally, the release of drug in a deep skin layer and systemic circulation are facilitated.[9] Taken as whole, ethosome is an excellent carrier for topical drug delivery applications.

Advantages of Ethosomes

In the shade of merits, ethosomes can avoid the first-pass effect. In addition, ethosomes can overcome the drug absorption complications caused by pH of the gastro-intestine, enzymatic activity. It is more useful for orally unsuitable drug administration purposes. Besides, ethosomes can easily enhance the permeation of the drug through the skin barrier. Regardless of drug molecules, the delivery of different macromolecules including protein and peptide can be achievable using ethosome. Ethosomes can provide the controlled drug delivery and accordingly, it reduces the dosing frequency. Furthermore, the ethosomes centered pharmaceutical applications demonstrate high patient compliance. In a conclusion, the ethosomes relied on a delivery system is passive, non-invasive, and existing for urgent commercialization.[10-12] Therefore, the current review article is an attempt to update the readers about ethosomes. Especially, we have discussed the composition, methods of preparation, process conditions, drug delivery applications, and patients on ethosomes in brief.

Composition of Ethosomes

As we know, ethosome [Figure 1] is a type of phospholipid vesicles that are intended for delivery of drug/s into or across

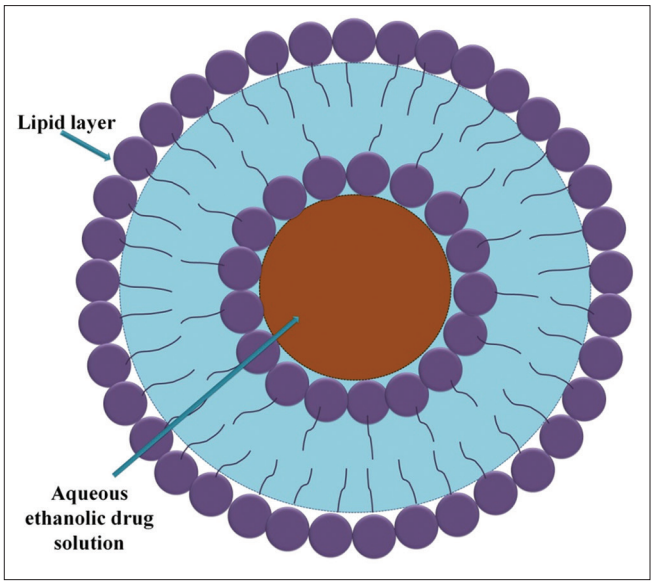


Figure 1: Structure of ethosomes

the skin with a high permeation rate.[9] It is a composition of the appropriate concentration of phospholipids and water as the conventional liposomes. Besides, it encloses a high ratio of ethanol 20–45% v/v.[13] In brief, ethosomes can be developed through dissolving a suitable amount of phospholipid(s) and hydrophobic drug(s) in ethanol and further the slow addition of the aqueous phase is made with constant mixing. Interestingly, as compared to conventional liposomes, ethosomes are a considerably smaller diameter. It may due to the presence of high ethanol content. In ethosomes formulation, ethanol contributes a strong negatively charged surface (i.e., zeta potential) of the vesicle. In addition, it decreases the size of ethosome vesicles.[14] The literature reported that the encapsulation efficiency of lipophilic drugs in ethosomes is higher in comparison to conventional vesicles, especially deformable liposomes. Table 1 enlisted the admirable additives which contribute to the major role in the good ethosomes vesicles.

Mechanism of Permeation Enhancer

The highest therapeutic effect of a drug can be achieved through the incorporation of a permeation enhancer that forms a complex with lipids and increases the SC permeability.[14] These complexes can interact with SC and chemically modifies the functions of SC that lead to rise in permeability rate. In this way, ethanol gives the synergistic mechanism between ethosomes and skin lipids.[17] As a measure of the vesicle softness, the transition temperature of the liquid in the vesicular systems can be defined. Furthermore, both the active and concentration of ethanol can affects the vesicular lipid temperature that influences skin penetration rate.[14] Mechanisms of skin permeation and drug delivery by ethosomes[9,15] are shown in Figure 2.

Critical Consideration in Ethosomes

Regarding ethosomes size, the concentration of ethanol can decreases the size of ethosomes. As per data, the ethosomes with more than 40% ethanol exhibited a smaller size than classical liposomes. An increase in ethanol concentration

Table 1: List of various additives used in ethosomes formulation

Class	Use	Examples
Phospholipid[9,15,16]	Vesicles forming component	Soya phosphatidylcholine, Egg phosphatidylcholine, Dipalmityl phosphatidylcholine, Distearyl phosphatidylcholine
Polyglycol[9,15]	As a skin penetration enhancer	Propylene glycol, Transcutol RTM.
Alcohol[9,15]	As a penetration enhancer, To provide softness to the vesicle membrane	Ethanol, Isopropyl alcohol.
Cholesterol[9,15]	To provide stability to the ethosomes vesicle Membrane	Cholesterol
Dyes[9,15,16]	For characterization study	Rhodamine -123, Rhodamine red, Fluorescence isothiocyanate, 6-carboxy fluorescence.
Vehicle[9,15,16]	As a gel provider	Carbopol 934.

results in a leaky bilayer. It increases the size of ethosome vessels and reduces entrapment efficiency.[18] Besides, the increase in the concentration of ethanol resulted in the solubilization of vesicles. Literature reported that a high concentration of ethanol causes interruption of the organic compound hydrocarbon chain. It gives a reduction in vesicular membrane thickness and vesicular size.[19] Ethanol also affects the surface charge of ethosomes. It resulted in the electrostatic repulsion that avoids the aggregation of the vesicular system. As per the literature, the entrapment efficiency of vessels was found to be linear with an increase in ethanol concentration. More specifically, for formulation purpose, optimized ethanol concentration was found to be in the range of 20–45%v/v.[20,21] On the other hand, the preference and concentration of phospholipids are an important factor in formulating ethosomes. It demonstrates the effect on vesicle size, entrapment efficacy, zeta potential, polydispersibility index (PDI), permeation property, and the stability of ethosome vesicles. As per a study, phospholipid concentration should be in the range of 0.5–5% for ethosomal preparation. It has been noted that, as the concentration of phospholipid increases, the size of ethosome vesicles also increases beyond the range. On the contrary, the phospholipid concentration does not affect entrapment efficiency.[22] Interestingly, the phospholipid is a steroidal rigid molecule, which is commonly incorporated into ethosomes for enhancement of ethosomes stability and drug entrapment efficiency. Furthermore, it decreases vesicular permeability plus the fusion of vesicles

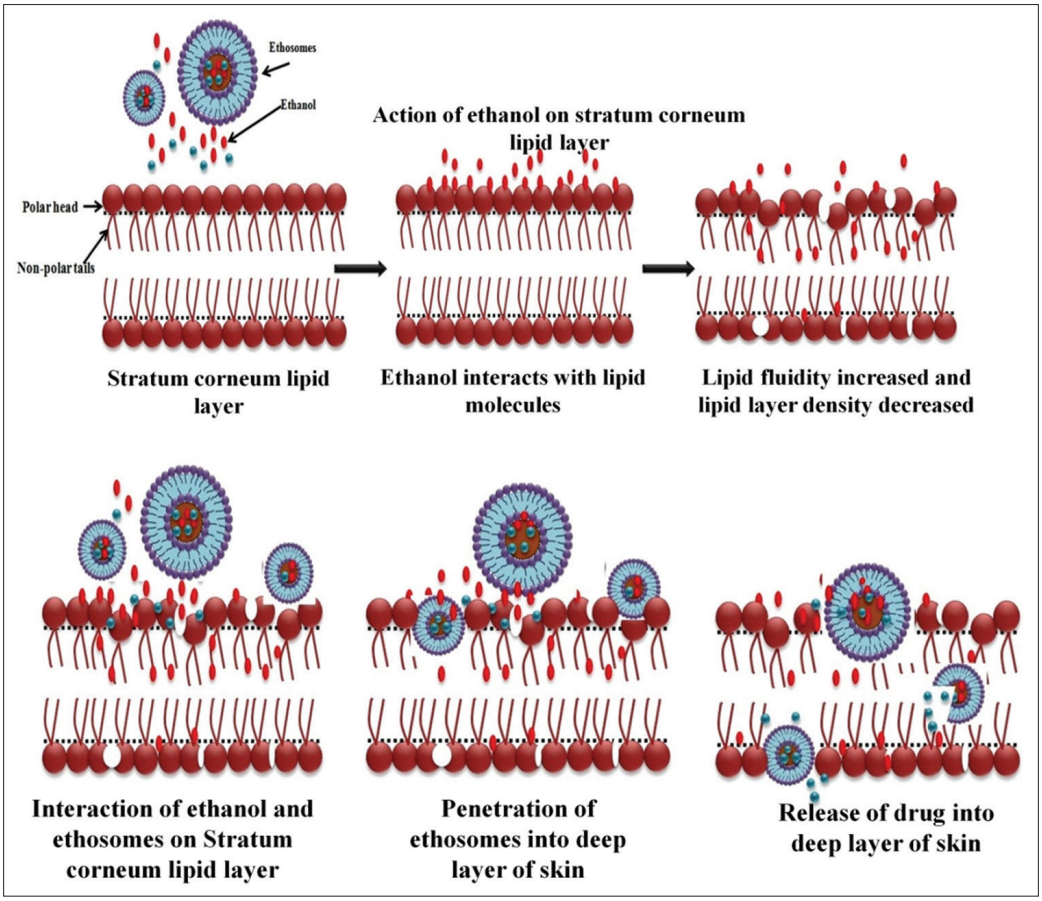


Figure 2: Mechanism of skin permeation and drug delivery by ethosomes

and avoids the leakage of ethosomes. In addition, cholesterol concentration in ethosomes vesicles has been reported up to 70% of total phospholipid concentration.[23,24] Simply, as per published literature the cholesterol concentration in ethosomes should be <3%. It is worthy to mention that, cholesterol increases the size of vessels.[25] In brief, when the cholesterol concentration is within a range of 0–0.15%, the size increases from 136 ± 42 nm to 230 ± 27 nm with no solubilization effect of cholesterol on ethosomes. An increase in the concentration of cholesterol beyond the range makes vesicles such as multilamellar, rigid, and less elastic that is difficult to cross SC of skin.[26] As we know, surfactants reduce surface tension. In addition, it can boost the aptitude of the molecule to develop the structure of micelles, solubilization activity, lowers thermodynamic activity, and increases skin permeation. As per the literature, non-ionic surfactants have been used in ethosomes preparation. It may because of less irritation and non-toxic nature than ionic surfactants[26] At the total ethosomes formulation, 10–50% of a tween has been used for designing of ethosomal formulation. When the combination of tween 80 used in ethosomes preparation, it reduces the vesicular size and improves stability plus increases skin permeability.[26,27] The key role of the tween in the vesicles is the solubilization and prevention of vesicles. In general, the tween 20 with 15% of total phospholipid concentration resulted in smaller vesicular size and more entrapment efficiency as compared to spans 20, 40, and 60.[26] Another factor like oleic acid can affect the vesicular size, zeta-potential, elasticity, and skin permeability properties. The use of 0.5% oleic acid is primarily a penetration enhancer and consequently, it resulted in good SC fluidity.[26] Notably, ethosomes containing polyethylene glycol (PEG) only increase vesicular size, but did not shows any effect on entrapment efficiency, stability, and permeation property.[28] The most frequently used cremophor EL-35 is a non-ionic surfactant concentration from 0.5% w/w-1.5% w/w concentration that can be used for design ethosomes formulation. It reduces the size of vesicles and enhances the solubility of the drug.[26] The numerous types of surfactants and their concentrations are depicted in Table 2.

Methods of Preparation of Ethosomes

Conventionally, ethosomes vesicles can be prepared by using main three methods including a hot method[26,36,37] a cold method,[38] and a dispersion method.[39-41] These methods can produce multilamellar vesicles (MLVs). After this, the obtained MLVs can convert to small lamellar vesicles (SLVs) using the sonication method. In this case, the probe sonicator has mostly been preferred for the size reduction of ethosomes. A method of preparation of ethosomes with processing conditions is depicted in Table 3.

Methods for Characterization of Ethosomes

In general, ethosomes can be characterized by different techniques including vesicle shape, size distribution, zeta potential, dynamic light scattering method, confocal laser scanning microscopy, and *in vitro* drug release study. Herein, the parameters and characterization techniques used in ethosomes are enlisted in Table 4.

APPLICATION OF ETHOSOMES IN DRUG DELIVERY

In the recent two decades, ethosomes have been widely used for transdermal/topical drug delivery applications. Due

Table 2: Surfactant and their concentration

Name of the surfactant	Safe/Allowed concentration range used in ethosomes	Ref.
Anionic surfactants		
Sodium dodecyl sulfate	About 0.1% w/v of the total ethosomes preparation.	[26]
Sodium stearate	Phosphatidylethanolamine: cholesterol: sodium stearate at a molar ratio of 2:1:2.5.	[29]
Sodium taurocholate	About 0.53% of the total ethosomal system.	[26]
Sodium cholate	About 0.66% of the total ethosomal preparation.	[30]
Deoxycholic acid	Phosphatidylcholine: cholesterol: deoxycholic acid at molar ratios of 2:1:1 and 6:2:1.	[26]
Sodium deoxycholate	About 0.8% w/v of the total ethosomes preparation.	[31]
Cationic surfactant		
Hexadecyltrimethylammonium bromide	It should be 1% of the total ethosomes formulation.	[32]
Non-ionic surfactant		
Tween 80	Among 10–50% of total phospholipid concentration.	[24,26]
Tween 60	Up to 50% of the total phospholipid concentration.	[26]
Tween 20	Among 15–50% of total phospholipid concentration.	[26]
N-Decylmethyl sulfoxide	It should be 0.35–1% of total ethosomes preparation.	[33]
Cremophor EL-35	Among 0.5–1.5% of the total preparation.	[17]
Cremophor RH-40	Up to 50% of total formulations.	[17]
PEG 4000	Phosphatidylcholine: cholesterol: polyethylene molar ratios of 2:1:1 and 6:2:1.	[34]
Span 80, 60, 40, 20	Up to 50% of the total phospholipid concentration.	[35]

Table 3: Methods of preparation of ethosomes with processing conditions

Method of preparation	Component		Addition Order	Temperature	Duration and speed
	Organic	Aqueous			
Hot method[26,36,37]	Phospholipid, Drug	Ethanol, PEG Drug, Water	Aqueous to organic	40^{0}C	5 min at 700–1000 rpm
Cold method[38,42]	Drug, ethanol Phospholipid and other lipidic materials	Water	Aqueous to organic	30^{0}C	5 min at 700–1000 rpm
Mechanical dispersion method[39-41]	Phospholipid, cholesterol, Drug, methanol	Drug Hydro-Ethanolic mixture	Aqueous to organic	Heating above Transition temperature for film formation	Suitable speed, temperature, Time

Table 4: Methods for characterization of ethosomes

Parameter	Characterization techniques	References
Vesicle shape (morphology)	Transmission electron microscopy (TEM), and Scanning electron microscopy (SEM)	[16,24,43]
Entrapment efficiency	Mini column centrifugation method, and Fluorescence spectrophotometer	[16,25,44]
Vesicle size and size distribution	Dynamic light scattering method	[16,45,46]
Vesicle skin interaction study	Confocal laser scanning microscopy, Fluorescence microscopy, Transmission electron microscopy, and Eosin-Hematoxylin staining	[47,48]
Phospholipid-ethanol interaction	^{31}NMR Differential scanning calorimeter	[27,49]
Degree of deformability	Extrusion method	[33,50]
Zeta potential analysis	Zeta meter	[16,33]
Turbidity	Nephelometer	[30]
In vitro drug release study	Franz diffusion cell with an artificial or biological membrane, Dialysis bag diffusion	[16,30,44]
Drug deposition study	Franz diffusion cell	[33]
Stability study	Dynamic light scattering method, and Transmission electron microscopy	[16,30,33]

amphiphilic nature of ethosomes, it is frequently used as a popular nano-carrier for drug and protein/peptide delivery, cosmeceuticals applications, etc. The plentiful literature survey suggested that the novel ethosomes have to gain immense importance in advanced drug delivery systems, especially delivery through skin membranes. In this subsection, we have discussed the numerous pharmaceutical applications of ethosomes nanocarrier such as the delivery of the different active agents for the effective management of severe life-threatening diseases and disorders.

Antifungal Agent Delivery

In the lipid carrier system, ethosomes show incredible ability to enhance transdermal permeation. Ethosomes based formulations have been designed to achieve a rapid onset of action, maximum drug release, and fewer side effects. There is no harmful effect to the skin during drug transport to systemic circulation across undamaged skin. Furthermore, it reduces the duration during treatment.[51,52] In 2020, Dave and co-authors investigated the luliconazole-loaded ethosomes and capped them with *Azadirachta indica*. Further, incorporation into carbopol 934 K (gelling agent) resulted in the drug-loaded ethosomal gel. The composition of soya lecithin (300 mg) and ethanol (35%) resulted in good entrapment efficiency (86.56%), nano-sized vesicle (155.30 nm), zeta potential (−42.20 mV), and PDI (0.186 ± 0.07). Besides this, it showed about 83.45 ± 2.51% drug release within 24 h. Due to the synergistic effect of neem and drug, the *in vivo* activity confirmed that the drug-loaded ethosomes were more active and effective against *Candida parapsilosis* in comparison to *Aspergillus niger*. The *in vivo* research confirmed that drug-loaded ethosomes were more active and effective against *Candida parapsilosis* than *Aspergillus niger* due to the synergistic effect from need and drug. Therefore, it can be used as a potential antifungal agent in biomedical applications.[53] The ciclopirox (8% w/v) loaded ethosomes have been developed using soya lecithin (3%) and ethanol (40%) through the cold method. The entrapment efficiency and drug content of ethosomes were found to be 93.61% and 99.7%, respectively. On the other hand, the carbopol based drug-loaded ethosomal gel demonstrates the zero-order release kinetics ($R^{2:}$ 0.959). Hence, ethosomes as a vehicle for antifungal provides more benefits as compared to the other vesicles.[42] Dhurve and co-author developed the fluconazole-loaded ethosomes using soya lecithin (1% w/w) and ethanol (35%w/w) using the cold method. The fluconazole-loaded ethosomes exhibited 73.53% drug entrapment efficiency. Notably, the phospholipid concentration was found to be inversely proportional to the entrapment efficiency. Whereas, the ethanol concentration is directly proportional to the ethosomes entrapment efficiency. Furthermore, the particle size of the fluconazole-loaded ethosomes was found to be 3.89 μm. Interestingly, it has been reported that the size of ethosomes vesicle directly proportional to the soya lecithin concentration and inversely proportional to the ethanol concentration. In conclusion, ethosomes can serve as a potential carrier for the delivery of fluconazole through topical routes.[54] In recent attempts, Jaya

Kumar designed the miconazole nitrate-loaded ethosomes using ethanol, poloxamer 407, and cholesterol through the solvent evaporation method. In brief, ethosomes showed a controlled zero-order drug release (R^2:0.99) with a diffusion mechanism. Besides this, it exhibited significant therapeutic efficacy towards the cutaneous candidiasis caused by *Candida albicans*. Taken as a whole, ethosomes can be integrated as an alternative for miconazole nitrate transdermal drug delivery, which can overcome the limitations of conventional topical administration.[55] With growing interest in ethosomal in drug delivery, Mbah *et al.* have been developed the griseofulvin-loaded ethosomes using phospholipid, ethanol, cholesterol, and PEG through the thin-film method. Herein, differential scanning calorimetry (DSC) study divulged the reversible perturbation of the skin layers based on griseofulvin loaded ethosomes permeation mechanism. The permeation rate can be increased with a high content of ethanol. Besides this, the ethosomes vesicle size can be reduced with continuous increment in the ethanol concentration. In conclusion, the ethosomes would be a suitable alternative for sustained and enhanced permeation of griseofulvin for topical application.[56]

Anti-inflammatory Drug

From its inception, an anti-inflammatory agent such as nonsteroidal anti-inflammatory drugs (NSAIDs) is generally used for the treatment of chronic pain and inflammation. Oral administration of NSAIDs can show gastric ulcer, abdominal pain, and disturbances, and kind of vessel issues. In addition, NSAIDs can fail the quick onset of action owing to the low bioavailability and half-life.[57] As we know, a topical drug delivery system is a better selection for site-specific delivery in the pharmaceutical field. Compare to oral drug delivery, it overcomes the problem in transdermal drug delivery. Ethosomes give a higher permeation rate for topical drug delivery, significantly increase skin permeation, accumulation, and give fast on a set of actions.[58] Regarding this, Barupal *et al.* prepared aceclofenac ethosomes for topical delivery and compared its activity to a marketed gel preparation.[59] Another work has been accomplished the piroxicam loaded ethosomal gel using phospholipid, ethanol, propylene glycol through the cold method. It resulted in excellent *in vitro* drug release compared to the gel containing free drug followed by first-order release kinetics. Therefore, in the future, ethosomes can pave the pathway for the delivery of anti-arthritis drug molecules.[60] Another work reported the piroxicam-loaded ethosomes (transethosomes) using soya lecithin and ethanol.[61] Flurbiprofen is an NSAID that exhibits anti-inflammatory, antipyretic, and analgesic activities. In 2019, Paliwal and co-investigators have been prepared the flurbiprofen-loaded ethosomes for transdermal application. In brief, it has been prepared using phospholipid (200 mg) and ethanol (35%). It showed 95% entrapment efficiency of flurbiprofen. In addition to this, it showed 82.56 ± 2.11 g/cm^2 *in vitro* permeation of flurbiprofen in 24 h. They have claimed that the vesicle size of ethosomes plays a crucial role in the topical administration of drugs. On the other side, ethanol concentration and particle size can affect the skin penetration rate. Besides, the augmentation of ethosomes may occur due to the increase in the zeta potential. Therefore, it offers the alternative carrier for targeted drug delivery of NSAIDs.[62] Similarly, Supraja and co-author developed stable mefenamic acid-loaded ethosomes using a cold method. It gives good entrapment efficiency, nanosize stable vesicles. Furthermore, it showed high drug content spreadability and the sustained release profile for 12 h. In general, it gives a new option for the effective delivery of mefenamic acid.[63] In another pioneering work, the authors have been accomplished the indomethacin loaded ethosomes using soybean phosphatidylcholine, ethanol. Besides, the vesicular size can be increased with an increased ethanol concentration (up to 30%). As well, ethanol was a major effect on the vesicle size reduction in the state of indomethacin solubility enhancement. Moreover, ethosomes volume of core and bilayer membrane has been decreased with the reduction of vesicle size and ultimately resulted in the low entrapment efficiency. Overall, it furnishes a novel replacement for the delivery of indomethacin.[64] In 2018, Ma *et al.* revealed the stable, spherical-shaped paeonol loaded ethosomes using soybean phosphatidylcholine (2.5% w/v) and ethanol (25% v/v). It demonstrates good entrapment efficiency (84.33%), particle size (120.2 nm), and zeta potential (–16.8 mV). Herein, the zeta potential of ethosomes confirmed the formation of stable paeonol loaded ethosomes. Furthermore, the paeonol-ethosomes *in vitro* skin penetration and skin retention study confirmed the high permeation rate (138.58 μg/cm^2) and skin retention (52.60 μg/cm^2). In nutshell, ethosomes could be an exceptional nanocarrier for potential drug delivery application, especially transdermal administration of paeonol.[65] In a recent study, celecoxib (1% w/w) loaded ethosomes have been reported by Chowdary *et al.* Briefly, celecoxib loaded ethosomes provides the nanosized stable vesicles that show good entrapment efficiency and *in vitro* permeation rate. Based on this, ethosomes would be promising substitute for transdermal delivery of celecoxib.[66] In similar line work, Ghanbarzadeh and Arami have been developed the diclofenac sodium loaded ethosomes using phospholipids (100 mg/mL) and ethanol (30 mg/mL). In this study, the ethosomes stable vesicle showed a good permeation rate than the ethanolic phospholipid and hydroethanolic solution. The ethanol offers softness and flexibility to the ethosomal vesicles which resulted in high penetration. As well, the high concentration of ethanol increased the skin permeation rate.[67] In 2016, Mistry and Ravikumar reported the spherical, smooth surface, unilamellar azelaic acid ethosomes using a thin-film hydration method. The developed ethosomes give good vesicle size (4.25 μm) and entrapment efficiency (91.86%). Besides this, the anti-acne activity of azelaic acid-loaded ethosomes was found to be high as compared to the marketed cream. Whereas, the *in-vitro* and *ex vivo* drug release of diclofenac was found to be 89.6% and 94.3%, respectively, within 12 h. Hence, in the future, ethosomes could be an excellent carrier for the topical delivery of azelaic acid.[68]

Anti-viral Drugs

Acyclovir loaded ethosomal gel has been reported for the management of Herpes zoster. It has been prepared using ethanol, phospholipid, and PEG through the cold method. The optimized batch showed about –20.5 mV zeta potential and about 331.69 nm vesicle size. Finally, 1% w/w carbopol 980 showed better *in vitro* acyclovir drug release (82.23%) after 8 h, and release kinetic was found in the zero-order model

($R^{2:}$ 0.989). Therefore, it can be used as a budding vehicle for the delivery of the antiviral agent for an extended time in the case of the affected skin part.[69] Similarly, another group designed the spherical-shaped lamivudine-loaded ethosomes using phospholipid, ethanol, tween 80 through solvent dispersion method for the therapy of acquired immunodeficiency syndrome (AIDS) disease. The designed ethosomes showed good entrapment efficiency in the existence of a composition of phospholipid (3 g) and ethanol (40 mL). Moreover, lamivudine-loaded ethosomes showed 78.49% drug release within 120 min. On the whole, ethosomes can serve as carriers for the antiviral drug (lamivudine) for the effective management of AIDS disease.[70]

Ethosomes in Cosmeceuticals

Various cosmetic preparations contain numerous active ingredients that only help to offer appropriate penetration to the SC layer of the skin. However, due to the resistance of the SC to the transport into the skin, the efficacy of several topically applied formulations is comparatively less. Therefore, it requires modification in the formulation. Accordingly, the appropriate modification in the formulation will lead to the high permeability of the formulation containing a drug. Interestingly, ethosomes can be used as an excellent carrier to supply a wide range of ingredients through topical routes.[71,72] The benefit of ethosomes in cosmeceuticals is increased stability of the cosmetics and decrease skin irritation from the irritating cosmetic chemicals. It also offers transdermal permeation enhancement, mainly in elastic forms. Topical administration of various antioxidants using ethosomes is one of the several approaches to reduce oxidative injury in the skin for cosmetic and cosmeceutical applications.[10,73] In upcoming days, applications of ethosomes in cosmeceuticals would be the new era for pharmaceuticals and cosmetic industries.

Anticancer Drug Delivery

In the world of medical sciences, cancer therapy is still a challenging task. It may due to the inefficiency of the existing clinical approaches used for the treatment and it resulted in the large numbers of death occur each year.[57] Hence, there is an urge to expand a suitable carrier for the delivery of the drug to the targeted area and systemic application. In this context, Cristiano *et al.* have been developed stable sulforaphane-loaded ethosomes and trans-ethosomes using 40% w/v ethanol and 2% w/v phospholipon 90G. Notably, it provides about 227 nm of particle size. The negative zeta potential (–26 mV) of ethosomes indicates the excellent stability of ethosomes. Moreover, the *in vitro* test of percutaneous permeation through human SC and epidermis membranes showed an improvement in the percutaneous sulforaphane permeation. Moreover, increased anticancer activity was observed for sulforaphane-ethosomes relative to pure sulforaphane. It may due to the fusion of ethosomes with the outer cell membranes that allow the cell permeation and active release directly into the cytoplasm.[74] Melanoma is the world's deadliest and life-threatening skin cancer with rising incidence rates. Peram *et al.* have been developed the curcumin loaded ethosomes using phospholipon® 90G and ethanol for the effective management of melanoma. In this, the designed ethosomes enhanced the penetration of curcumin into the deeper skin layer that confirmed by fluorescence microscopy. Besides, the *in vitro* cytotoxicity and cellular uptake have been performed using A375 human melanoma cell lines, which revealed the curcumin-loaded ethosomes improved the cellular uptake as well as cytotoxicity. In addition to this, curcumin-ethosomes exhibited a good antiproliferative effect and it induces cell death in cell lines through apoptosis mechanism. On the whole, this study motivates the delivery of curcumin in dealing with skin cancer.[75] Therefore, it furnishes the pathway as a pristine and alternative nanocarrier for anticancer drug delivery.

Delivery of Analgesic Agent

Nowadays, effective pain management is a challenging task for researchers. It may because of severe side effects of the different analgesic agents. In 2020, Sundar *et al.* developed the tramadol hydrochloride loaded trans-ethosomal gel formulation for effective pain management using phospholipid (Soya lecithin and L-α Phosphatidylcholine from egg yolk) and edge activator (Span 20 and Cremophor EL 35). Herein, the particle size of ethosomes vesicles was in the range of 149.34–278 nm. The ethosomes vesicle size of formulations has been influenced by the polymer concentration. In brief, the concentration was directly proportional to the ethosomes vesicle size. On the other side, a higher concentration of the phospholipids and edge activator produces thick vesicles with high density and thus increases the size. The zeta potential of an optimized batch of ethosomes formulation was found to be –22 mV, it confirmed the stability of ethosomes formulations. In this study, span 20 based ethosomes exhibited a faster drug release (91.91–95.7%) as compared to the cremophor-based ethosomes. Besides, the drug release kinetics exhibited extended drug release (78.96–79.34%) at the end of the 8^{th} h that follows the first-order kinetics ($R^{2:}$ 0.991). Hence, it opens the new door for the topical delivery of tramadol hydrochloride.[76] Yet another work reported the tramadol hydrochloride loaded ethosomes based on the composition of soya lecithin, ethanol, and cholesterol that showed good *in vitro* and *ex vivo* release profile.[77] Therefore, the delivery of analgesic agents using ethosomes is gaining much interest from researchers and in the future, it could be an excellent option to overcome the severe side effects of the analgesic agent.

Delivery of Anti-psoriatic Agent

Psoriasis is a chronically non-infectious skin condition, joint, and/or both with relapsing inflammatory and hyperkeratotic plaque episodes. In such conditions, efficient delivery of the drug is an important factor during formulation design. In this segment, Fathalla and co-authors have been developed the anthralin (0.1%, w/v) loaded ethosomal and liposomal gel for topical delivery in psoriatic patients. The ethosomal particle size and entrapment efficiency were found to be 146–381 and ≥77%, respectively. Moreover, the Psoriasis Area and Severity Index of ethosomes were found to 3.6, which was significantly different from liposomal formulation (3.4). In addition to this, the mean of the Psoriasis Area and Severity Index for ethosomes and liposomes was found to be 81.84% and 68.66%, respectively.[78] Therefore, anthralin-loaded ethosomes could be considered as a potential treatment of psoriasis.

Delivery of Anti-hypertensive Agent

Over the past decades, hypertension incidence has increased dramatically. Moreover, it is the leading cause of death also. For the last couple of decades, the scientific fraternity is working on the various effective carriers for the delivery of anti-hypertensive agents via a different route. In 2019, Dave *et al.* developed the losartan potassium loaded ethosomal polymeric patch for hypertension management. It showed good particle size, zeta potential, and encapsulation efficiency (89.21%). Furthermore, it gives 86.45% release within 24 h. Besides this, the *in vivo* demonstrated the significant management of hypertension as compared to the plain drug. In conclusion, drug-loaded ethosomes can offer a sustained effect in the case of hypertension.[79] Thus, in the future, it can be a suitable carrier for the delivery of the antihypertensive agent that will lead to the effective management of hypertension.

Miscellaneous Applications of Ethosomes

Despite the abovementioned ethosomes applications, other numerous applications are also reported by research scholars. It includes drug delivery of Antiparkinsonian agents and other actives. In this context, cationic trihexyphenidyl hydrochloride is a good action for the adjunctive treatment of all forms of Parkinsonian syndrome. It may be owing to its anti-M1 muscarinic activity. Besides this merits, trihexyphenidyl hydrochloride has a low half-life (3 h) and therefore, it requires multiple dosing to produce the peak blood levels. In 2000, Dayan and Touitou prepared the trihexyphenidyl hydrochloride-loaded ethosomes using 2% soybean phosphatidylcholine and 30% ethanol. Remarkably, it exhibited high entrapment efficiency and efficient delivery of active to the deeper layer of skin. Besides, it showed high skin deposition as compared to the control hydro-ethanolic solution and liposomes up to 18 h. Overall, drug-loaded ethosomes open the new door for transdermal delivery of trihexyphenidyl hydrochloride.[13] In another pioneering work, cannabidiol-loaded ethosomes have been reported by Touitou *et al.* It gives the significant accumulation of cannabidiol in the skin as well as underlying muscle. In addition, the cannabidiol-ethosomes transdermal application in mice showed steady-state levels at about 24 h and lasted at the end of the experiment (72 h). Besides this, it prevents the inflammation and edema in an animal model that was induced using a sub-plantar injection of carrageenan. Due to good skin permeation and accumulation in depots as a level, it can be a new substitute for cannabidiol delivery.[80] As we know, dermatitis is the most common chronic and episodic disease of the skin characterized by severe itching, causes significant disturbances, and has been on the rise. Tacrolimus ointment has been used for the treatment of such diseases with the trade name of Protopic, an immunosuppressant. Unfortunately, it shows less patient compliance. In 2012, Li *et al.* prepared the tacrolimus (0.1% w/v) loaded ethosomes using Lipoid S 100 and ethanol. Briefly, the developed ethosomes exhibited a small vesicle size and good entrapment efficiency as compared to the liposomes. Moreover, it also suggested that the ethosomes contain high skin permeation ability than the marketed formulation (Protopic). Besides, it showed the efficient suppression of allergic reactions. Therefore, ethosomes can be used as a promising substitute for the delivery of tacrolimus to the managing of atopic dermatitis.[81] Sebaceous glands and hair follicles have been identified as potential components in percutaneous drug delivery. Herein, the follicles can release the drugs systemically.[40] In general, lipid-soluble drugs are used for topical treatments. As per published data, ethosomal formulation demonstrates pilosebaceous targeting for better clinical efficacy. In 2004, the minoxidil ethosomal formation was developed and topically used on the scalp for baldness treatment. It overcomes the limitations of previous formulations including penetration rate. Therefore, it opens the new windows for pilosebaceous gland targeting applications.[73,82] Antibiotics can be delivered transdermally for better therapeutic effectiveness compared to oral drug delivery. However, oral delivery of antibiotics may lead to many allergic reactions also lower therapeutic efficacy, and several other severe side effects. In this regard, the ethosomes can avoid these problems by a deeper layer of skin penetration.[83] Godin and co-authors have prepared the erythromycin[83] and bacitracin[84] loaded ethosomal formulation for dermal and intracellular delivery.[85,86] They reported that ethosomes reduce the side effects and demerits associated with systemic administration of the antibiotic. Therefore, antibiotic-loaded ethosomes could be considered as an exceptional carrier that shows efficient antibiotic delivery to the deep skin layer.[84] Interestingly, oral administration of hormones is related to abundant difficulties such as low bioavailability, first-pass digestion, and different dosages side effects.[52] In 2000, Touitou *et al.* developed the hormones loaded and compared the skin penetration of testosterone ethosomes on rabbit pinna skin with an advertised fix of testosterone. It was observed that the ethosomes offer 30% higher skin saturation.[18] Another study reported the melatonin-loaded ethosomes for the prevention of ultraviolet-visible (UV) radiation. It showed good entrapment efficiency and stability (–17 mV). Alongside this, it improved the melatonin permeation with zero-order release kinetics that is more acceptable for topical administration. Thus, in the future, there is a necessitate to subjecting melatonin-loaded ethosomes for clinical applications.[87] A large biogenic molecule such as protein and peptides is difficult to orally deliver because the gastrointestinal tract (GIT) completely degrades these molecules. Hence, transdermal delivery is the best option for problematic drug delivery (difficult to oral route); these drug molecules can formulate ethosomes formulation for enhancing therapeutic activity and reduce the side effect.[82,88] Duloxetine prevents the reuptake of norepinephrine and serotonin in the central nervous system. Duloxetine transdermal films loaded with an optimized drug ethosomes formulation have been reported. It enhanced the skin drug permeability (86.34%) as a compared plain film (22.14%) and extended the drug release that ultimately decreased the dosing frequency. Besides, it showed about 94.7% drug release in 24 h. To sum up, it avoids hepatic first-pass metabolism and it can be considered as an alternative administration route for acid-sensitive drugs.[89] Several studies related to the application of ethosomes as carrier systems are depicted in Table 5.

MARKETED PRODUCTS OF ETHOSOMAL TECHNOLOGY

As per the literature, the ethosomes are gained much attention from researchers and different pharmaceutical industries.

Table 5: Different studies related to the application of ethosomes as a carrier system

Active	Category	Composition	Vesicle size (nm)	PDI	Zeta Potential (mV)	Effects	Ref.
Luliconazole	Antifungal	Soya lecithin (300 mg), Ethanol (35%)	155.30	0.186	–42.20	1. It provides maximum entrapment efficiency. 2. It is more active and effective against fungus.	[53]
Ciclopirox	Antifungal	Soya lecithin (3%), Ethanol (40%)	4010	--	--	1. It shows higher entrapment efficiency. 2. It provides a zero-order release.	[42]
Fluconazole	Antifungal	Soya lecithin (1% w/w) Ethanol (35% w/w)	3890	--	--	1. It improves entrapment efficiency. 2. It provides maximum drug release.	[54]
Miconazole nitrate	Antifungal	Ethanol (10 mL), Poloxamer (100 mg)	--	--	--	1. It enhanced drug delivery and therapeutic efficiency.	[55]
Griseofulvin	Antifungal	Phospholipon® 90H (2 g) , Ethanol (45% v/v)	137.70	0.55	--	1. It showed sustained drug release. 2. It enhanced the skin permeation rate.	[56]
Piroxicam	NSAIDs	Soya phosphatidylcholine (2.20% w/v), Ethanol (36% v/v)	655.369	--	0.341	1. It improved the stability of the formulation. 2. It showed the highest elasticity. 3. It increased the drug permeation rate. 4. It gives prolonged drug release. 5. It showed the highest drug retention.	[61]
Flurbiprofen	NSAIDs	Phospholipid (200 mg), and Ethanol (35%)	162.2	0.341	-48.14	1. It enhanced the drug penetration rate. 2. It showed maximum entrapment efficiency. 3. It improved the stability of the ethosomes formulation.	[62]
Mefenamic acid	NSAIDs	Soya lecithin (1 g), Ethanol (2 mL)	359.7	--	-31.1	1. It showed high entrapment efficiency. 2. It increased drug content spreadability. 3. It showed sustained drug release.	[63]
Indomethacin	NSAIDs	4% w/v 3-*sn*-Phosphatidylcholine cholesterol: deoxycholic acid (6:2:1 M ratio), Ethanol (20% v/v)	55	0.207	−39.06	1. It enhanced the permeation rate.	[64]
Paeonol	Anti-inflammatory	Ethanol (25% v/v) , Soya phosphatidylcholine (2.5%w/v)	120.8	0.14	-17.2	1. It increased the skin permeation rate. 2. It improved skin retention. 3. It increased entrapment efficiency.	[65]
Celecoxib	NSAIDs	Phospholipids (2 w/w%, Isopropyl alcohol (30%)	2930	--	--	1. It improved the *in vitro* drug release. 2. It improved entrapment efficiency.	[66]

(Contd...)

Table 5: *(Continued)*

Active	Category	Composition	Vesicle size (nm)	PDI	Zeta Potential (mV)	Effects	Ref.
Azelaic acid	NSAIDs	Soya phosphatidyl choline (0.85%), Ethanol (22.5 mL)	514.3	0.08	-35.44	1. It showed prolong drug release.	[68]
Diclofenac Sodium	NSAIDs	Phospholipid, cholesterol (100:30 mg/mL)	145-202	0.35	-41.2	1. It shows selective delivery of the drug to the desired side for a prolonged period.	[67]
Acyclovir	Anti-viral	Ethanol (10 mL), Phospholipid (500 mg)	331.69	--	-20.5	1. It increased skin permeation. 2. It improved in biological activity two to three times. 3. It improved the pharmacodynamics profile.	[69]
Lamivudine	Anti-viral	Phospholipid (3 g), Ethanol (40 mL)	--	--	--	1. It increased entrapment efficiency. 2. It showed maximum drug release.	[70]
Sulforaphane	Anti-cancer	Ethanol (40%w/v), Phospholipon 90G (2% w/v).	227	0.01	-26	1. It increased percutaneous permeation. 2. It improved anticancer activity.	[74]
Curcumin	Anti-cancer	Ethanol (40% v/v), Phospholipon 90G (3% w/v).	247	0.19	-9.13	1. It improved skin permeation. 2. It improved cytotoxicity and cellular uptake.	[75]
Tramadol hydrochloride	Analgesic	ethanol 30%, Phospholipid 3%	149–198	--	-22.69	1. It extended the drug release.	[76]
Anthralin	Anti-psoriatic	Ethanol 40% (v/v), Phospholipon 90G 3% (w/v).	201.5	0.4	--	1. It shows a higher permeation rate. 2. It provides effective and safe treatment for psoriatic patients. 3. It gives an excellent ability to sustain drug release.	[78]
Losartan potassium	Anti-hypertensive	Soya lecithin (3%w/w), Ethanol (35%w/w)	112.2	0.45	-59	1. It improved entrapment efficiency. 2. It provides the sustained drug release. 3. It shows increased bioavailability.	[79]
Trihexyphenidyl hydrochloride	Antiparkinsonian Agents	Soybean phosphatidylcholine (2%), Ethanol (30%)	109	--	+7.2	1. It shows improved transdermal flux. 2. It provides controlled release. 3. It improved patient compliance. 4. It provides a several times lower biologically active dose than the currently used formulation.	[13]
Cannabidiol	Rheumatic treatment	Ethanol (40%w/w), Phospholipon 90	300–400	--	--	1. It improved skin deposition. 2. It improved biological activity. 3. It prolonging drug action.	[80]

(Contd...)

Table 5: *(Continued)*

Active	Category	Composition	Vesicle size (nm)	PDI	Zeta Potential (mV)	Effects	Ref.
Tacrolimus	Immunosuppressant	Phosphatidylcholine (17%), Ethanol (30%v/v)	103.7	0.26	--	1. It enhanced the penetration ability. 2. It improved retention in the epidermis. 3. It increased entrapment efficiency.	[81]
Minoxidil	Hair growth stimulator	Phospholipids, Ethanol	--	--	--	1. It improved the skin permeation rate. 2. It increased skin retention of minoxidil.	[73]
Erythromycin	Antibiotic	Phospholipon 90 (2%), Ethanol (30%)	116.6	--	--	1. It improved skin deposition. 2. It improved biological activity. 3. It prolonging drug action.	[83]
Bacitracin	Antibiotic	Phospholipon 90, Ethanol (25%w/w)	114.9	--	--	1. It improved dermal deposition. 2. It improved intracellular delivery. 3. It increased bioavailability.	[84]
Testosterone	Hormone	Soybean phosphatidylcholine (2%), Ethanol (30%)	118-249	---	-4.3	1. It shows high entrapment capacity. 2. It improved transdermal penetration. 3. It improved the bioavailability of the drug.	[18]
Melatonin	Hormone	Soya lecithin (7%w/v), Ethanol (20%)	249	0.201	-17	1. It improved *in vitro* drug permeation. 2. It provides a zero-order release.	[87]
Duloxetine	Antidepressant	Alcohol (5 mL), Phospholipid (10 mg)	161	--	--	1. It extended drug release. 2. It increased drug penetration.	[89]

Based on the literature, we observed that various manufacturers have been developed different creams and other formulations for the effective treatment of various health-related issues. In this subsection, ethosomes technology-based marketed products are enlisted in Table 6.

PATENTS ON ETHOSOMES

Initially, the ethosomes were invented as well as patented by Professor Touitou Elka with her students, at the Hebrew University School of Pharmacy (Department of Pharmaceutics). In 1995 and 1996 Prof. Touitou Elka have filed the first patent on ethosomes entitled as a composition for applying active substances to or through the skin (US 5716638) and compositions for applying active substances to or through the skin (US5540934 A), respectively. In this context, the patient information based on ethosomes is depicted in Table 7.

DISCUSSION

At present, there are various directions in reviewing the applicability of phospholipid vesicles in enhanced drug delivery for dermatology. In the transdermal drug delivery system, the epidermal barrier limiting factor for drug delivery through skin can be overcome by ethosomes. To a significant extent, ethosomes are more beneficial, when compared to transdermal and dermal delivery. Their more penetration ability and stability as compared to liposomes make the ethosomes potential candidates for topical applications. Ethosomes can enable drug penetration in the deep skin layers and finally delivering to the systemic circulation. The high patient compliance of ethosomes in the form of semisolid could hold several applications in pharmaceuticals. The key constituent of ethosomes is ethanol, which modifies the constrict arrangement of cuticle lipid molecules. It enhances lipid fluidity and promotes ethanol-based liposome membrane

Table 6: Marketed products of ethosomal technology

Name of product	Manufacturer	Uses	References
Decorin cream	Genome Cosmetics, Pennsylvania	Anti-aging cream	[90]
Noicellex	Novel Therapeutic Technologies, Israel	Topical anti-cellulite cream.	[8]
Cellutight EF	Hampden Health, USA	Increase metabolism and break down fat.	[91]
Supravir cream	Trima, Israel	Good stability for at least 3 years, at 25°C. Cream retained its initial penetration enhancing properties even after 3 years.	[92]
Noicellex	Novel Therapeutic Technologies, Israel	Topical anti-cellulite cream.	[93]
Skin Genuity	Orange peel Physonics, Nottingham, UK	Powerful cellulite buster reduces.	[94]

Table 7: Patent on ethosomes

Patent No.	Title	Reported Results
CN102144972A	Podophyllotoxin ethosomes and preparation methods thereof.	Increasing curative effect, reducing regress and toxic side effects are fulfilled. The invention also discloses two preparation methods for the podophyllotoxin ethosomes.[95]
CN102133183B	Acyclovir ethosome and preparation method thereof.	Acyclovir ethosomes have high stability along with narrow particle size distribution. Therefore, it can be an excellent alternative carrier for acyclovir delivery.[96]
CN102579323A	Paclitaxel ethosome gel and preparation method thereof.	In this work, the action of stimulation to the skin can be reduced. The admirable percutaneous permeation effect has been found.[97]
CN102813624B	Lidocaine ethosome and preparation method thereof.	It provides the rapid onset of action.[98]
CN102397255B	Progesterone ethosome, and preparation method and application and application thereof.	It can be preferred as a potential alternative for the delivery of progesterone in hormone replacement therapy, functional aplastic bleeding, secondary amenorrhea, premenstrual syndrome, etc.[99]
CN102552147B	Bullatacin ethosome gel and preparation method thereof.	The bullatac in ethosomes gel provided by the invention can reduce irritation to the skin and gives good percutaneous penetration effects.[100]
CN102406605A	Ethosome preparation of male hormone medicaments and its preparation method.	It improves the transdermal transport of male hormones and enhancing their curative effects.[101]
CN103006562B	Daptomycin ethosome preparation.	It provides high entrapment efficiency and excellent transdermal performance. It offers a simple and convenient, low in cost, and good stable product.[102]
CN103893394A	Ethosome gel film coating agent with multiple wound repair effects and preparation method of ethosome gel film coating agent.	The ethosomes entrapped film-coating agent helps to upgrade healing and supplying nutrition of the wound tissue. The ethosomes gel film coating agent is suitable for wound clinical care and treatment.[103]
CN103536700B	Chinese medicinal ethosome herpes gel patch for treating zoster and preparation method thereof.	It is effortless in medication and handy to employ. It showed a good therapeutic effect, quick response, and strong analgesic action. Despite this, there is no adverse reaction[104]
CN103800277A	Leflunomide ethosome composition and its preparation method.	It improves the transdermal rate of leflunomide, can notably decrease the side effects of oral administration of leflunomide and improves curative effects.[105]
US10137079B2	Transdermal composition of treating pain.	It can be used for the treatment of pain. The transdermal ethosomes composition comprises alcohol; phospholipid; water; magnesium salt, and TRPV1 receptor.[106]
US9987234B2	Nanolipidic particle assembly populations	Nanolipidic particles have been synthesized with an average mean diameter of 1–20 nm. Additionally, it can be loaded with the desired passenger molecule.[107]

flexibility and mobility. Therefore, ethosomes can speed up the deformation of the SC and improves its carrying and penetration capability of a drug through disordered SC in the skin. As we know, ethosomes are colloidal dispersions, which exhibits optical properties, ethosomes formulation demonstrated the creaming and cracking during storage with the respective condition.[108] Further, phospholipid content is an important ethosomal formulation component. Unfortunately, it is fully susceptible to the oxidation and hydrolysis process, which severely affects the stability of ethosomes. And because

of this, the leakage of the encapsulated drug from ethosomes can arise. Further, the changes in the average vesicle size of ethosomes due to the aggregation and fusion of vesicles.[6] Recently, the Turbiscan Lab® Expert explored as an optical analyzer. It has been widely utilized for the measurement of optical properties of colloids for long-term stability studies of ethosomes formulation.[109] Thus, it is a new avenue for long stability testing of ethosomes. It is noteworthy that this technique provides plentiful information relating to the kind of destabilization process going on in ethosomal formulation. In addition to this, it also proficient to classify the stability issues of ethosomes based on sedimentation, coalescences, and creaming. Moreover, it is a non-destructive method. During the dosage from the stabilization study, it could be successfully applied for the measurement of the variation of droplet volume friction, mean of vesicle size (in case of coalescence). As a result, this study researcher easily understands the stability of ethosomal formulation.[109] An abundant literature survey revealed that the ethosomal formulations exhibited good stability over 1 year. On contrary, some active compounds-based ethosomes were found to stable for only 1 year. On the other hand, the trans-ethosomal gel of few drugs was found stable for a few months under accelerated storage conditions and months at room temperature. It is noticeable that only few researchers accomplished the stable ethosomes formulations. Whereas, the few ethosomes formulations stability studies have been tested. Out of them, a few studies were carried out for more than 1 year. Therefore, it necessitates performing long-term stability study and evaluation of ethosomal formulation. In the future, there is a huge need to perform preclinical and clinical trials to explore the ethosomes as an ideal carrier for pharmaceutical applications.

CONCLUSION

Ethosome is a non-invasive carrier for the delivery of special drugs with varied physicochemical properties for the skin. It is majorly suitable for local and systemic applications. It is worthy to mention that, ethosomes demonstrate controlled/sustained drug release, good biocompatibility, reduced toxicity, and several advantages in the pharmaceutical field. Notably, simplicity in composition and method preparation of ethosomes make them attractive drug delivery carriers. Especially, the presence of ethanol in vesicles offers several merits as compared to the other lipidic vesicles for topical/transdermal applications. Even, ethosomes can easily incorporate into different types of dosage forms including gels, patches, and creams. Consequently, it can be concluded that, in years to come, ethosomal formulations would find their place in the therapeutic world due to enhanced permeability for better therapeutic activity.

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