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Ethosomes: The Novel Drug Delivery Carriers

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Review Article

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Abstract: Effective Delivery of bioactive molecules across the human skin has always been a challenge for formulation scientists because of the presence of the most impervious layer of skin, i.e. Stratum corneum. Various approaches have been used to circumvent that layer of skin; one of the easiest and non-invasive methods of them is the use of vesicular systems. Since a long time, various kinds of lipid vesicles have been used for efficient delivery of drugs. Conventional liposomes have been used for delivery of the drug across skin for a long time, but they lack the ability to penetrate the intercellular channels of skin and are unstable. Therefore, to overcome these kinds of difficulties associated with lipid-based vesicles, ethanol-based vesicles were formulated by scientists and they have been used in the effective delivery of the drug across skin since then. Ethosomes are colloidal non-invasive vesicular carriers with a very high ethanolic content, with the high ethanolic content they enable the drugs to reach deep into the skin layers into the systemic circulation. In the current review, an attempt has been made to understand the nature better, preparation, evaluation parameters along with applications, problems and future prospects of these novel ethanol containing vesicles.
Keywords: Ethosomes, Transethosomes, Elasticity.

INTRODUCTION

Topical route of drug delivery is preferred the route of drug delivery to treat dermatological disorders more effectively. Transdermal route offer number of advantages over other routes of drug delivery like avoidance of the first-pass metabolism by the liver, improved patient compliance reduced dosing frequency, ease of use and controlled release of drugs.

However, to administer any drug through topical use one has to circumvent the very first and effective barrier to the human body that is the skin. The most impervious layer of the human skin limiting the transdermal delivery of drugs is the Stratum corneum, which is made up of insoluble bundled keratins surrounded by a cell envelope. Various kinds of approaches have been used since time long to overcome the barrier properties of skin including physical means like iontophoresis, sonophoresis, microneedles. But the physical methods are relatively complicated in use and are invasive technique, therefore offer little patient compliance, chemical means like the use of permeation enhancers is also used to promote transdermal flow, but this approach is also limited by the skin irritation caused by solvents used. One of the strategies for enhancing topical bioavailability of drugs is vesicular systems such as liposomes, transferosomes, niosomes. Among these vesicular systems, ethosomes are essential vesicles first described in the year 1996 by *Touitou et al*. [1]. "Ethosomes are modified and smart liposomes with very high alcohol content". They are non-invasive delivery carriers which are primarily designed for the efficient delivery of drugs with different physicochemical properties into the deeper skin layer/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents, permit controlling the release rate of drug over an elongated time, keeping the drug shielded from the immune response or other elimination systems and thus be able to deliver just the right amount of drug and keep that concentration constant for more extended periods of time. Ethosomes are the slight modification of well-established drug carrier liposomes containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. The size range of ethosomes may vary from tens of nanometers (nm) to microns (μ) ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux.

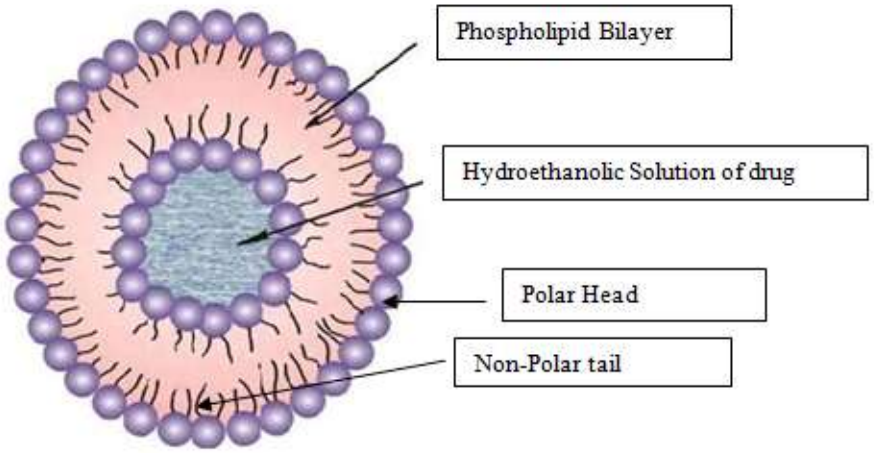

Fig-1: Structure of Ethosomes

Advantages of Ethosomal Drug Delivery

- Ethosomes can be used for efficient delivery of large drug molecules such as lipids, proteins etc.
- Ethosomes can be used as a delivery carrier for both hydrophilic as well as lipophilic drugs.
- Ethosomal drug delivery is passive and non-invasive, as they are formed of non-toxic raw materials.
- Increased permeation of drug through the skin for transdermal drug delivery.
- The ethosomes containing drug can be readily dispersed in gel or cream hence producing high patient compliance.
- It is a simple method for drug delivery in comparison to other complicated methods.

Limitations of the ethosomal system

- Ethosomal drug delivery system can be used only for patent drugs they cannot be used for drugs that require higher blood levels, those requiring a daily dose of 10mg or less.
- Ethosomal administration is not a means to obtain rapid bolus type drug input. Instead, it is usually designed to offer slow, sustained drug delivery.
- For a drug to be delivered through ethosomes, it should have enough solubility in aqueous as well as the lipophilic environment.
- The molecular size of the drug must be just that it should be absorbed percutaneously.
- Skin irritation or dermatitis because of excipients and enhancers of drug delivery systems.
- In case if shell locking is ineffective, then the ethosomes may coalescence and fall apart on transfer into the water.

Types of Ethosomes

On the basis of their chemical composition ethosomes can be classified into three main distinct class:

Classical Ethosomes

They are slight modifications of the conventional liposomes first prepared by Touitou *et al.* composed of Phospholipids and a relatively high concentration of ethanol (up to 45%). The ethosomes has been found to be superior to liposomes in possessing smaller size, more negative zeta potential, higher entrapment efficiency, better transdermal flux and higher stability.

Binary ethosomes

They were first described by *Zhou et al.* [2]. They are just simple ethosomes the only difference between them and classical ethosomes is the type of alcohol, in classical ethosomes ethanol is the only alcohol used but in binary ethosomes alcohol used are propylene glycol(PG) and isopropyl alcohol(IPA). *Zhou et al.* observed that entrapment efficiency of sophoridine, matrine, sophocarpine, and lehmanine extracted from *Sophora alopecuroides* increased to a significant extent when PG was incorporated into the ethosomal system with a ratio of ethanol to PG of 1:1 (total alcohol up to 45%)

Transethosomes

Transethosomes are a new generation of vesicular ethosomal systems first described by *Song et al.* [3] in 2012 for efficient delivery of the drug across skin as they combine the advantages of classical ethosomes and deformable liposomes (transferosomes). They are ethosomes with an edge activator (surfactant) including tweens and span these activators. Therefore, in these systems the alcohol and edge activators act together to increase the vesicular malleability and lipid perturbation[4]. Transethosomes has been proved to be better than other vesicular carriers in many studies. *Garg et al.* [5]compared the transethosomes of piroxicam with the liposomes, ethosomes and transferosomes and it was found that the optimized transethosomal formulation possessed highest entrapment, elasticity, improved stability and highest

drug permeation as compared to other vesicular gel formulations.

COMPOSITION OF ETHOSOMES

CLASS	EXAMPLE	USE
PHOSPHOLIPID	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmitoyl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
ALCOHOL	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane as a penetration enhancer
POLYGLYCOL	Propylene glycol Transcutol RTM	As a skin permeation enhancer
CHOLESTEROL	Cholesterol	For providing stability to the vesicle membrane
SURFACTANTS	Spans and Tweens	As an edge activator, which makes the vesicle boundary more flexible
DYE	Rhodamine-123 Rhodamine red Fluorescence Isothiocyanate (FITC) 6- Carboxy fluorescence	For characterization study
VEHICLE	Carbopol Đ934	As a gel former

ADVANTAGES OF HIGH ETHANOL CONTENT

Ethosomes contain a very high concentration of ethanol (20-50%) which is an established permeation enhancer. However, due to disruption effect of ethanol on lipid bilayers, it was once thought that vesicles could not coexist with the high concentration of ethanol. Touitou[2] discovered and investigated vesicular lipid systems embodying ethanol in relatively high concentration and named them ethosomes. The main difference between liposomes and ethosomes exists in their composition. The synergistic effect of the combination of the relatively high concentration of ethanol (20- 50%) in vesicular form in ethosomes was proposed to be the main reason for their better skin permeation ability. The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer organization. Therefore, when integrated into a vesicle membrane, it could give an ability to the vesicles to penetrate the SC. Furthermore, due to high ethanol concentration, the ethosomal lipid membrane was packed less tightly than conventional vesicles but possessed equivalent stability. Thus allowing it a softer and malleable structure giving more freedom and stability to its membrane, which could squeeze through small openings created in the disturbed SC lipids? In addition, the vesicular nature of ethosomal formulations could be modified by varying the ratio of components and chemical structure of the phospholipids. The high concentration of ethanol imparts high entrapment efficiency. In terms of stability, the liposomes tends to fuse and grow into bigger vesicles due to the absence of electrostatic repulsion on neutral lipoomes and this fusion and breakage cause drug leakage but in case of ethosomes ethanol causes a modification of net charge of the system and confers it some degree of steric stabilization leading to an increased stability against agglomeration that may lead to a decrease in mean vesicle size.

MECHANISM OF DRUG PENETRATION

The main advantage of ethosomes over liposomes is the increased permeation of the drug. *Dayan and Touitou*[6] prepared trihexyphenidyl loaded ethosomes and evaluated them for transdermal permeation in mice skin using CLSM technique, and it was found that the ethosomes show much higher transdermal flux 87 and 4.5 times compared to conventional liposomes and hydroethanolic solution respectively. Although, the mechanism of the drug absorption from ethosomes is not precise. It has been thought that the drug absorption occurs in given two phases:

- Ethanol effect
- Ethosomes effect
- Ethanol effect: Ethanol serves as a penetration enhancer through the skin. The mechanism of this effect is well known. Ethanol penetrates into intercellular lipids and raises the fluidity of cell membrane lipids and reduces the density of lipid multilayer of the cell membrane.
- Ethosomes effect: Enhanced cell membrane lipid fluidity induced by the ethanol of ethosomes results improved skin permeability. So, the ethosomes permeates very smoothly inside the deep skin layers, where it got fused with skin lipids and delivers the drugs into the deep layer of skin.

METHODS OF PREPARATION OF ETHOSOMES

Ethosomes can be prepared by either of the very simple and convenient methods;

- Cold method

- Hot method
- Ethanol injection method
- Mechanical Dispersion method
- Transmembrane pH-Gradient method
- Reverse phase evaporation method

Cold Method: This is the most common method employed for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a closed vessel at room temperature by vigorous stirring with the use of a mixer. Propylene glycol or another polyol is added during stirring. This mixture is heated to 30℃ in a water bath. The water heated to 30℃ in a separate vessel is added to the mixture in a fine stream with constant stirring in a covered vessel. The vesicle size of the ethosomal formulation can be reduced to the desired extent using sonication or extrusion method. Finally, the formulation is stored under refrigeration.

Hot Method

This method was first used by Touitou [7] in 1996 in this method phospholipid is dispersed in water by heating it in a water bath at 40℃ until a colloidal solution is obtained. In a separate vessel, ethanol and propylene glycol are mixed and heated to 40℃. Once both mixtures reach 40℃, the organic phase is added to the aqueous phase. The drug is dissolved in ethanol or water based on its hydrophilic/ hydrophobic properties. The vesicle size of the ethosomal formulation can be modified to the desired extent using probe sonication or extrusion method.

Ethanol Injection-sonication method

This method is a slight alteration of the process described by *Touitou et al.*. In this method, lipids are dissolved in ethanol in a glass bottle, and the drug was independently dissolved in water and is filled in a syringe. The syringe is hermetically attached to the flask, and the aqueous phase was added to the organic phase in a fine stream with constant stirring.

Mechanical dispersion method

In this method, the lipid is dissolved in a mixture of chloroform: ethanol (3:1) in round bottom flask. The organic solvents are extracted using rotary vacuum evaporator above the lipid transition temperature to form a thin lipid film on the wall of the flask. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight followed by hydration with different concentration of the hydroethanolic solution of the drug by rotation at the corresponding temperature.

Transmembrane pH-Gradient method

In all the methods of preparation of ethosomes discussed above, the drug is passively loaded into the ethosomal system by adding in either the aqueous or organic phase. In the transmembrane pH-gradient method the drug is actively loaded, depending on the pH-gradient difference between the acidic interior of the internal phase and the basic exterior of the external phase of the ethosomal system. This method was first applied for the preparation of the liposomes [8, 9] then it was used by Zhou *et al*. 44 and Fan *et al*. 55 for preparation of ethosomal system of total alkaloid extracts of S. alopecuroides and tetrandrine, respectively. Before preparation of ethosomal using this method, some factors need to be taken into consideration, such as physicochemical properties of the drug to be incorporated, the pH of the internal and external phases, and the temperature and duration of the incubation period. This method involves three stages: Preparation of the blank ethosomal system, active loading of the drug, and incubation (final stage). In the first stage, ethosomal suspension is prepared by any of the above-mentioned methods, but the aqueous phase or hydration process uses and acidic buffer (usually citrate buffer pH 3). In the second stage, the drug is actively loaded in empty ethosomal suspension followed by continuous stirring. To make the external phase alkaline and to establish the pH gradient between the acidic internal (pH 3) and basic external phases of the ethosomal system, an alkali. Usually, a sodium hydroxide solution of 0.5M is added to make the external pH 7.4. In the final step, the ethosomal system is incubated at a specified time and temperature to give a chance for the unionized drug to actively pass the bilayer of the ethosomal vesicles and get entrapped.

Reverse phase evaporation method

This is the least used method and especially used to produce large unilamellar vesicles. The organic is prepared by dissolving the phospholipid in diethyl ether and then mixing it with the aqueous phase at a ratio of 3:1 v/v in an ultrasonic bath at 0℃ for 5 minutes to form water in oil emulsion. The organic solvent is removed under reduced pressure to produce a gel, which turns into colloidal dispersion upon vigorous mechanical agitation.

METHOD OF CHARACTERIZATIONS OF ETHOSOMAL FORMULATION

Vesicle shape

Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). Visualization by electron microscopy reveals an ethosomal formulation exhibited vesicular structure 300-400 nm in diameter. The vesicles seem to be malleable as evident by their imperfect round shape.

Vesicle size and Zeta potential

Dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS) can be utilized to determine Particle size and zeta potential.

Drug entrapment

The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique. The ability of ethosomes to efficiently entrap both lipophilic and hydrophilic drugs can be explained by the high degree of lamellarity and the presence of ethosomes in the vesicles.

Entrapment efficiency= DE/DT*100

Where, DE-amount of the drug in ethosomal sediment
DT-Theoretical amount of drug used to prepare the formulation (Equal to amount of drug in supernatant liquid and in the sediment)

Transition Temperature

Differential Scanning Calorimetry can be utilized to determine the transition temperature of the vesicular lipid systems. It can also be used for detection of ethanol-skin phospholipid interaction, a characteristic attributed to fluidizing effect of ethanol on the phospholipid bilayers [10].

Drug content

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high-performance liquid chromatographic method.

Surface tension measurement

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

Stability studies

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM. *Dubey et al.*[11] performed stability study of methotrexate loaded ethosomes at different temperatures, and they found that lowest drug leakage at refrigerated conditions. Various stability studies have been conducted by various researchers and has shown promising results. *Ainbinder et al*. [12] prepared the transethosomal gel of 5-fluorouracil for skin cancer treatment, and it was found that gel was stable for 2 months under accelerated conditions and up to 11 months at room temperature.

Skin permeation studies

The ability of the ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy (CLSM)[13]. Chourasia *et al.* [14] performed CLSM study of ketoprofen loaded ethosomes for transdermal delivery using Rhodamine 123 as a fluorescent probe. Results showed that ethosomes could penetrate up to a depth of 40µ. *In vitro/in vivo* skin permeation studies of

S.no	Parameter	Importance	Method
1.	Size and shape	Determine skin penetration	Scanning electron microscopy, Transition electron microscopy, DLS
2.	Zeta potential	Stability of vesicles	Zeta sizer
3.	Entrapment efficiency	Suitability of method	Ultracentrifugation
4.	Drug content	Important in deciding the amount of vesicle preparation to be used	UV, HPLC
5.	Stability studies	To determine the shelf life of vesicle formulation	SEM, TEM, HPLC
6.	Invitro dissolution	Determine the drug release rate from vesicle	Franz diffusion cell
7.	Skin permeation	Determines the rate of drug transport through skin	Confocal laser scanning microscopy

Therapeutics application of ethosomes

Ethosomes are mainly used as a replacement of liposomes. Primarily the transdermal route of drug delivery is opted. Ethosomes can be employed for the transdermal delivery of hydrophilic and impermeable drugs through the skin. Several drugs have been used with ethosomal carrier.

Pilosebaceous targeting

Maiden *et al*. 2004, prepared and evaluated the potential of ethosomes for delivering highly lipid soluble drug minoxidil. Minoxidil is a lipid-soluble drug used topically on the scalp for the treatment of baldness by pilosebaceous delivery. However, the classical topical formulation has very poor skin permeation and retention properties. It was discovered that the quantity of minoxidil accumulated into nude mice skin after application of ethosomal formulation was 2.0, 7.0, and 5.0 times higher than the ethanolic phospholipid dispersion, hydroethanolic solution and hydroethanolic solution of drug respectively. These results showed the probability of using ethosomes for pilosebaceous targeting of minoxidil to achieve better clinical efficacy.

Transcellular Delivery

Touitou *et al*.[15] in their study demonstrated better intracellular uptake of bacitracin, DNA and erythromycin using CLSM and FACS techniques in different cell lines. Better cellular uptake of anti-HIV drug zidovudine and lamivudine in MT-2 cell line from ethosomes as compared to the marketed formulation recommended ethosomes to be an attractive clinical choice for anti-HIV therapy. *Jain et al.* prepared lamivudine loaded ethosomes for transdermal delivery and evaluated them for cellular uptake study. It was observed that prepared ethanolic formulation showed 25 times more transdermal flux in rat skin compared to plain drug solution. Intercellular uptake of ethosomes was 5 times more in T-lymphoid cell line (MT-2) compared to free drug solution[16].

Delivery of problematic drug molecules

Oral delivery of large biogenic molecules such as peptides or proteins and insulin is difficult because they are completely degraded in the GIT tract hence transdermal delivery is a better alternative. But the conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has poor permeation. Formulating these above molecules into ethosomes significantly increase permeation and therapeutic efficacy. Dkeidek and Touitou studied the effect of ethosomal insulin delivery in lowering blood glucose level *in vivo* in normal and diabetic SDI rats. In that study, a hilltop patch containing insulin-loaded ethosomes was applied on the abdominal area of an overnight fated rat. The result showed that insulin delivered through this patch significantly reduce the blood glucose level (up to 60%) in both normal and diabetic rats[17].

Transdermal Delivery of Hormones

Oral administration of hormones is correlated with problems like high first-pass metabolism, low oral bioavailability and several dose-dependent side effects. *Touitou et al.*,[18] compared the skin permeation potential of testosterone ethosomes across rabbit pinna skin, with the marketed transdermal patch of testosterone (Testoderm® patch, Alza Corporation, California). It was found that the skin permeation of testosterone from the ethosomal formulation was nearly 30 times higher as compared to marketed transdermal patch. The AUC and C_{max} were also observed to be improved in the ethosomal system as compared to Testoderm®.

Delivery of Anti-Arthritis Drug

Topical delivery of the anti-arthritis drug is a better option for its site-specific delivery and overcomes the problem associated with conventional oral therapy. *Lodzki et al.* [19] prepared cannabidiol loaded ethosomal system for the treatment of rheumatoid arthritis. The result of skin deposition study of the prepared formulation showed significant accumulation of cannabidiol(CBD) in the skin and underlying muscle after application to the abdomen of mice. A plasma concentration study showed that steady-state level was reached in 24 hours, which was maintained through 72 hours. A significant increase in biological anti-inflammatory activity of ethosomal formulation was observed.

Delivery of Antibiotics

Topical delivery of antibiotics is a better choice for increasing the therapeutic efficacy of these agents. Conventional oral therapy causes several allergic reactions along with several side effects. Ethosomes can circumvent the problems associated with conventional external preparations like low permeability to deep skin layers and subdermal tissues. Ethosomes penetrate rapidly through the epidermis and bring a significant number of drugs into the deeper layer of skin and suppress infection at their root. With this goal in mind, *Godin and Touitou*[20] prepared bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery. The results of this study revealed that the ethosomal formulation of antibiotic could be highly efficient and would overcome the problems associated with conventional therapy.

Cosmeceutical Applications of Ethosomes

Ethosomes has been successfully used in the cosmetic formulations for a number of advantages they offered like increased stability, decreased skin irritation from the irritating cosmetic chemicals, transdermal permeation enhancement, especially in the elastic forms. However, the composition and sizes of the vesicles are the main factors to be considered to obtain these advantages of the elastic vesicles for cosmeceuticals applications. Ethosomal creams containing *curcuma longa* extract has also been prepared and evaluated for their photoprotective and antiwrinkle properties. In both the studies C. longa extract loaded ethosomal creams showed promising results when applied on human volunteers as either a photoprotective[21] and antiwrinkle[22] agent. Lipoduction is a new cellulite cream using ethosomal technology developed by U.S based company, Osmotics Inc., which penetrates the lipid carriers and deliver ingredients directly into fat cells. Ingredients in lipoduction improved the cellulite appearance by up to 80% in less than 60 days. *Yeh et al*. developed a hair dye of transethosomes, and it was found to be more effective in delivering and enhancing the absorption of black tea extracts to the hair surface than the hydroethanolic solution of the same extract[23].

Other applications of ethosomal systems

Apart from their transdermal drug delivery potential ethosomal system has also been reported for other routes of drug administration such as oral and vaginal. *Chang et al.* studied the ability of liposomes and ethosomes to enhance the oral bioavailability and tissue distribution of silymarin in an *in-vivo* study.

Results showed that both of the vesicular system was able to improve the bioavailability, but better results were gained from liposomes. But for tissue distribution, it was found that silymarin loaded ethosomes had higher accumulation in the lung. The author suggested that the ethosomes may have the potential to be used as a lung-targeting drug carrier for the treatment of lung disease [24].

Marketed preparations using ethosomal technology

Sr. No.	Name of Product	Uses	Manufacturer
1.	Decorin Cream	Anti-aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines.	Genome Cosmetics
2.	Nanominox	First Minoxidil containing product, which uses ethiosomes. Contains 4%Minoxidil, well- known hair growth promoter that must be metabolized by sulfation to the active compound.	Sinere, Germany
3.	Skin Genuity	Powerful cellulite buster, reduces orange pee	Nottingham, UK
4.	Supravir cream	For the treatment of herpes virus	Trima, Israel

Examples of ethosomes as drug carriers

Drug	Application of ethosomal system
NSAIDS (Diclofenac)	Selective delivery of drug to the desired side for prolong period of time
Acyclovir	Increase skin permeation Improved in biological activity two to three times Improved in Pharmacodynamic profile
Insulin	A significant decrease in blood glucose level Provide control release
Methotrexate	
Trihexyphenidyl Hydrochloride	Improved transdermal flux Provide controlled release Improved patient compliance Biologically active at dose several times lower than the currently used formulation
Bacitracin	Improved dermal deposition Improved intracellular delivery Increased bioavailability Improved transdermal flux Improved in biological activity two to three times
Zidovudine	improved in biological activity two to three times Improved in Pharmacodynamic profile

CONCLUSION

It can easily be concluded that ethosomes as a drug delivery carrier promise a better future for transdermal delivery of problematic drugs. Ethosomes improves the transepidermal absorption of drugs to a significant extent. Ethosomes shows a near zero order release in invitro release studies. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Continuous research in ethosomal technology has led to the introduction of a new generation of the ethosomal system called transethosomes which are the updated version of classical ethosomes in terms of vesicle properties and skin permeation abilities. Transethosomes provides flexibility to the formulator to alter the properties of the ethosomal system as required by altering the edge activators or penetration enhancers. The ability of the ethosomal system to be incorporated in a different type of vehicles such as creams, gels and patches represents an important step to get better skin permeation and therapeutic results.

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