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Review Article

Role of Ethosomes in Treating Acne Vulgaris: A Review

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ABSTRACT

Nanovesicular carriers called ethosomes are used for dermal delivery. Nanovesicular drug deliveries provide thorough insights into the most up-to-date and complete discussion about the preparation of drugs. Sebaceous glands, hair follicles, and the pilosebaceous unit are all impacted by the chronic inflammatory disorder known as acne vulgaris. It is among the most prevalent dermatological problems in the globe. Water, ethanol in quite high concentrations (up to 50%), and phospholipids are the main components of ethosomes. Due to the presence of ethanol, ethosomes are referred to as "soft vesicles" with fluid bilayers. The vesicle form and content make them able to carry more molecules with a variety of physicochemical qualities to the skin's deep layers. Ethosomal systems have been the subject of intensive study ever since they were initially proposed for a variety of purposes. In addition to the face, the back and chest can also be affected by acne, which can manifest as non-inflammatory lesions, combustible sores, or a mix of these two types. Ethosomes improve the drug's penetration of the skin *via* transdermal and dermal distribution. A wide range of medications, including peptides and protein compounds, may be delivered *via* ethosomes. This review is about the ethosomes used for the treatment of acne vulgaris.

Keywords: Ethosomes, Dermal delivery, Soft vesicles, Skin problem, Acne vulgaris

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INTRODUCTION

Drugs can be delivered by ethosomes, a non-invasive drug delivery mechanism, deep into the skin. Even though they are technically challenging, ethosomal systems stand out because they are easy to set up, secure, and effective-a combination that can greatly improve their usage. They are soft, sticky vesicles made to enhance the administration of drugs. Because of their special structure, ethosomes may transfer cationic drugs like testosterone and minoxidil, as well as extremely lipophilic compounds like trihexyphenidyl and propranolol, through the skin (Natsheh H, *et al*., 2019). Later, the ethosomal technique was created to enable the delivery of chemicals into cultivated cells and microbes. Future research and the creation of cutting-edge, more potent treatments are presented with both potential and problems due to the greater dispersion of bioactive substances across epidermal and cellular membranes *via* an ethosomal carrier (Tuchayi SM, *et al*., 2015; Touitou E and Godin B, 2006).

LITERATURE REVIEW

Ethosomes

Ethosomes are vesicular carriers with a high concentration of alcohols made of hydro alcoholic or hydro alcoholic/glycolic phospholipids; any of these substances may be present in ethosomes (or other glycols). With this type of formulation, high amounts of active compounds may be administered through the skin, according to Michaels AS, *et al*., 1975. Alcohol substitutes include water and alcohol. The ratio of polyol to water affects the administration of medications. Common dosage of phospholipon 90 (pl-90) ranges from 0.5% to 10% body weight. Cholesterol was added to the mixture at concentrations ranging from 0.1% to 1% in order to improve Ethosome stability. Commonly used compounds include glycols like propylene glycol and transcutol as well as alcohols like ethanol and isopropyl alcohol. There are times when non-ionic surfactants are used with phospholipids in these formulations. You can employ cationic lipids like cetrimide, cocoamide, and others. The alcohol content of the finished product might be between 20% and 50%.

Acne vulgaris

Contrary to common opinion, it is a condition with persistent inflammation, affecting the sebaceous gland and hair follicle. It is a frequent dermatological disorder worldwide. Processes causing acne formation include hormone microenvironment dysregulation, neuropeptide interaction, follicular hyper keratinization, inflammation induction, and innate and adaptive immune system malfunction. Hyper seborrhea (increased production of sebum) and changes in the fatty acid composition of sebum are related to disruptions in sebaceous gland function. Acne grading is accomplished by the use of lesion counts and photographic techniques. Acne therapy aims to improve the look of both non-inflammatory and inflammatory acne lesions, avoid or limit undesirable side effects, and reduce scarring. Because of the likelihood of antibiotic resistance or severe side effects, pharmacological therapy is not always desirable. Nonpharmacological treatments have the potential to replace conventional therapy. Multiple systems are used to assess the severity of acne. However, it is commonly assumed that mild and moderate acne only has primary lesions, whereas severe acne has open lesions. The severity of acne and scarring caused by *P. acnes* have all been linked to inflammatory factors, bacterial growth metabolites such as allergens, toxins, or porphyrins, and enzymes (Keri JE and Rosenblatt AE, 2008). Acne also has a significant psychological impact on individuals who suffer from it. The retinoid isotretinoin, antibiotics, and oral contraceptives are currently available alternatives for treating systemic acne. All of these are advised for treating severe acne, acne that has shown resistance to previous therapies, and nodulocystic, scarring acne. Even though there are many treatment choices for acne and it is a common condition, the pharmaceutical industry is continuously doing research because there is no known cure. Treatments often used aim to reduce the frequency of inflammatory lesions, block comedone formation, restrict *Propionibacterium acnes* growth, or reduce sebaceous gland size and secretory activity. Due to concerns about the negative effects of orthodox pharmaceuticals, acne sufferers commonly seek complementary and alternative treatments (Rahaman SM, *et al*., 2016; Sutaria AH, *et al*., 2022; Cappel M, *et al*., 2005) (*Table 1*).

Ethosome preparation techniques

As explained further below, ethosomal formulations can be made either hot or cold. Both procedures are simple, do not require complicated equipment, and are easily scaled up to industrial levels (Touitou E, 1998).

Cold method: Drugs and other lipid molecules are dissolved in ethanol at room temperature in a closed jar using a mixer and fast agitation. In a water bath, this mixture is heated to 300 degrees. The mixture is then agitated for 5 minutes in an enclosed vessel with water that has been heated to 300°C in a different vessel. By probing sonication or extrusion, the ethosomal formulation's vesicle size can be reduced to the proper degree. The mixture is then refrigerated for storage (Touitou E, *et al*., 2000) *(Figure 1)*.

Hot method: When phospholipid is heated in a water bath at 400°C, a colloidal solution forms, and this technique disperses it in water. When both mixtures reach a temperature of 400°C, the organic phase is injected into the aqueous phase. Propylene glycol and ethanol are mixed and heated to 400°C in a separate tank. Whether a medication is hydrophilic or hydrophobic is determined based on whether it dissolves in water or ethanol. The ethosomal formulation's vesicle size can be appropriately decreased by probing, sonication, or extrusion (Elsayed MM, *et al*., 2007) (*Figure 2*).

A technique of dispersion employing a rotating vacuum evaporator: In this method the aqueous component i.e. hydro-ethanolic mixture, drug is used and for the organic component i.e. Phospholipid, cholesterol, chloroform, methanol is used in aqueous to organic order of addition at a working temperature heating over the lipid transition temperature with the purpose of forming films at the proper pace, temperature and duration (Patel A, *et al*., 2013; Keerthi A, *et al*., 2013; Bhasin V, *et al*., 2011) *(Figure 3 and Table 2)*.

Table 1: Acne vulgaris classification

Severe acne	Clinical features	Comedones	Papules	Nodule	Cyst
Mild	Comedonal acne and papulopustular acne	The most common lesion (20) are comedones	Small and less in number (<10)	None	None
Moderate	Papulopustular acne and nodular acne	10-40	10-40	0-10	None
Severe	Nodulocystic acne and conglobate acne	40-100 and fused	>40	>10	None

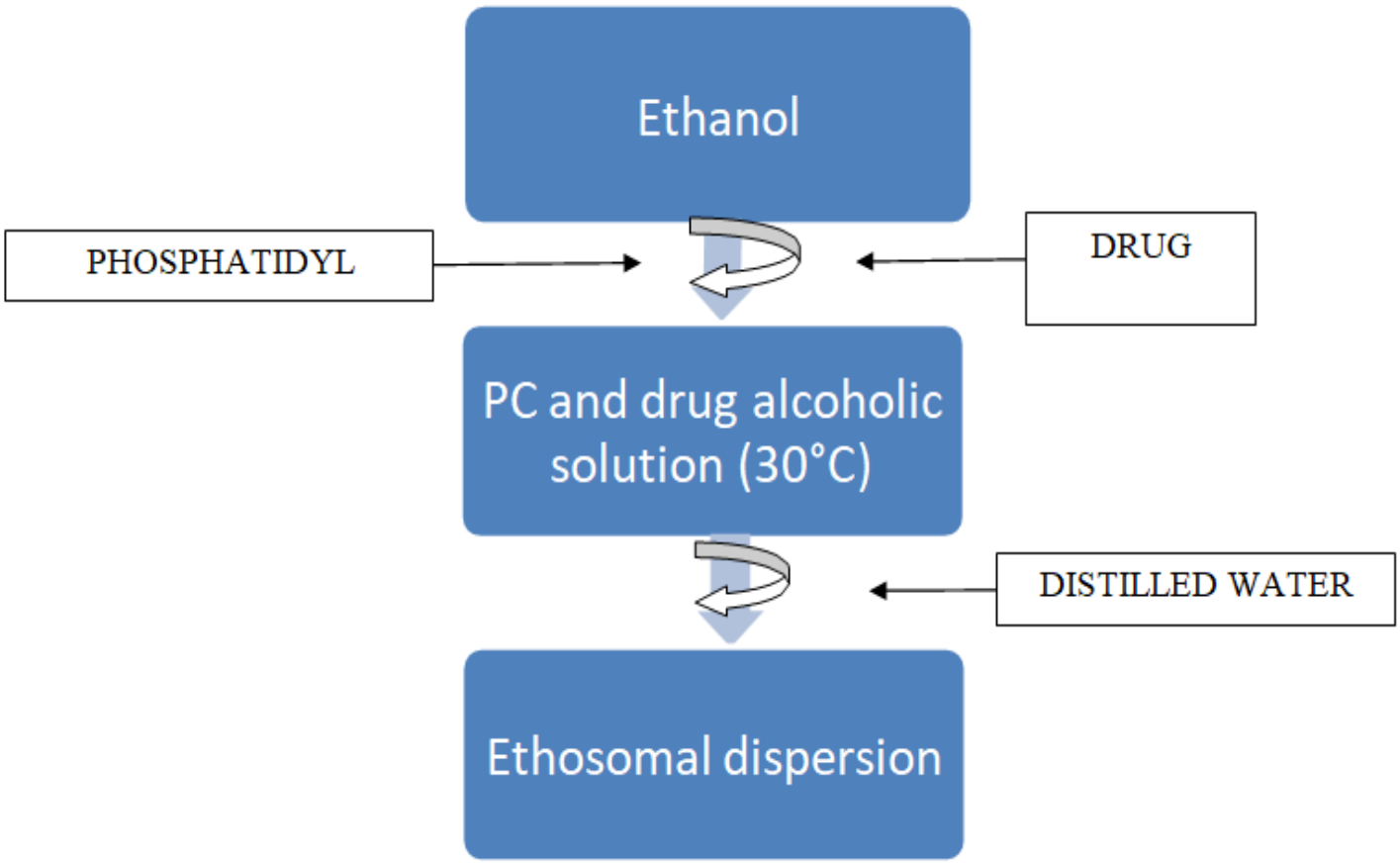

Figure 1: Cold method of ethosomes preparation

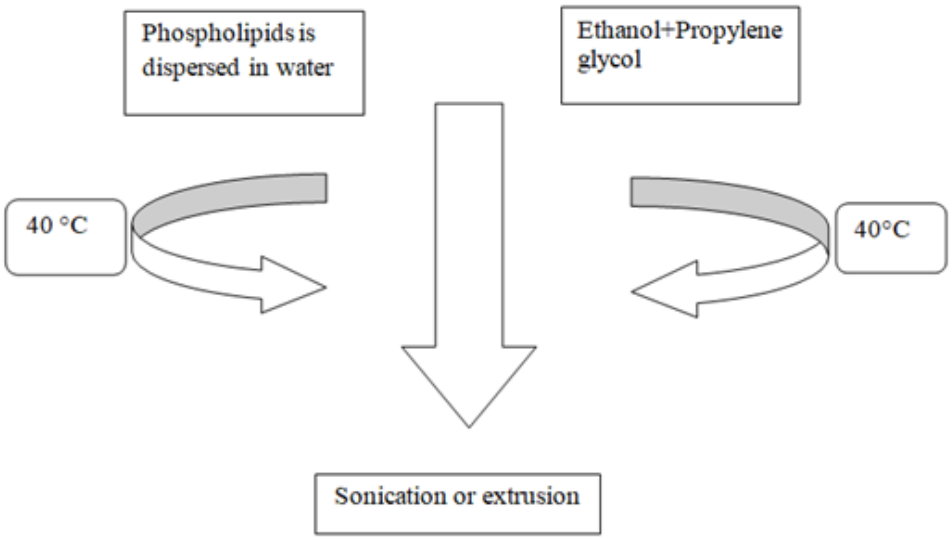

Figure 2: Hot method of ethosomes preparation

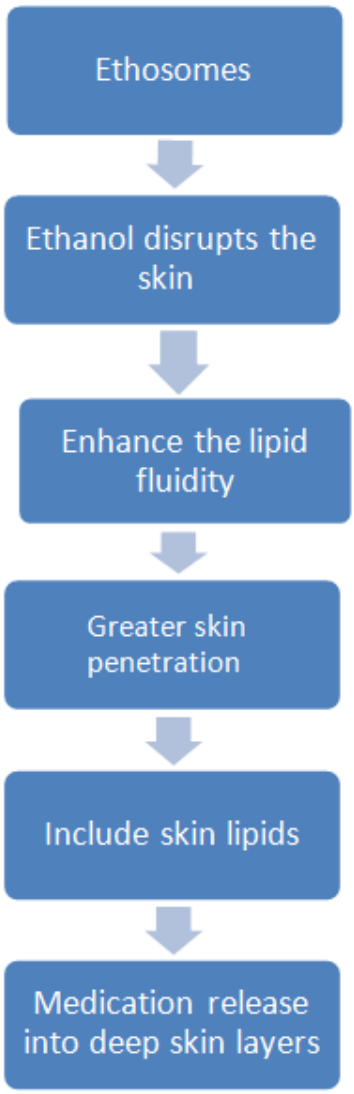

Figure 3: Mechanism of ethosomes medication delivery

Table 2: Application of different drugs and their uses

Drug	Formulation	Application and uses	References
Tetracycline	Capsules, tablets (oral)	Tetracycline is occasionally used for mild inflammatory acne that is very difficult to cure. Tetracycline is used to treat moderate to severe acne.	Paolino D, *et al.*, 2005
Erythromycin	Capsules, suspensions, tablets (oral)	Local drug administration, ease of drug action cessation, and unpleasant effects restrict medication usage. It helps to control the acne	Zhao YZ, *et al.*, 2013
Metroidnazole	Metro gel, cream and lotion (topical)	For mild acne vulgaris, metroidnazole is an efficient, secure, and well- tolerated topical drug.	Paolino D, *et al.*, 2005
Clindamycin	Clindagel, clindamax, lotion (topical)	Clindamycin is used to cover the can under control.	Paolino D, *et al.*, 2005
Doxycycline	Capsules, tablets (oral)	It has a long history of safety and effective on treating acne in patients	Paolino D, *et al.*, 2005
Minocycline	Capsules, tablets (oral)	It is an oral antibiotic used for the acne vulgaris	Zhao YZ, *et al.*, 2013
Benzoyl peroxide	Liquid wash (topical)	It has been an important component for the topical for acne vulgaris	Paolino D, *et al.*, 2005
Tretinoin	Cream (topical)	It has been used as a comedolytic agent to treat mild- moderate acne vulgaris	Zhao YZ, *et al.*, 2013
Tazarotene	Gel (topical)	This medicine works to help clear acne on the face partly by keeping the skin pores clear.	Paolino D, *et al.*, 2005
Salicylic acid	Bar, cream, wash, pads	Salicylic acid has been demonstrated in comparison tests to be more effective than benzoyl peroxide at reducing the overall number of acne lesions.	Paolino D, *et al.*, 2005
Retinoid	Oral	Local drug administration, ease of drug action cessation, and unpleasant effects restrict medication usage. It helps to control the acne	Zhao YZ, *et al.*, 2013
Ketoconazole+Aloe vera	Shampoo (topical)	The topical medication mupirocin is used to treat traumatic skin lesions that have secondary bacterial infections. Impetigo is treated with mupirocin topical ointment.	Zhao YZ, *et al.*, 2013
Nadifloxacin	Lotion	It is used to treat the bacterial infection. Mainly for the treatment of the acne and the infection on the skin	Paolino D, *et al.*, 2005
Mupirocin	Cream	For mild acne vulgaris, this combination is a safe, effective, and well-tolerated topical drug.	Zhao YZ, *et al.*, 2013
Isotretinoin	Tablet	To treat severe, disfiguring nodular acne, isotretinoin is utilized. It should only be taken if other antibiotics or acne medications have been tried and failed to clear up acne.	Paolino D, *et al.*, 2005
Hydroxyzoin	Capsule	Adults and children both use hydroxyzine to treat itching brought on by allergic skin responses.	Paolino D, *et al.*, 2005
Prednisolone	Tablet	Prednisolone is a drug used to treat a variety of medical conditions, such as allergies, blood disorders, skin conditions, and to avoid organ rejection following organ transplantation.	Zhao YZ, *et al.*, 2013
Mometazone	Cream	Skin irritation, swelling, and itching can be treated with mometazone topical therapies. They can aid in treating various eczema conditions.	Zhao YZ, *et al.*, 2013
Mometazone+terbinafine	Cream	Skin irritation, swelling, and itching can be treated with mometazone topical therapies. They can aid in treating various eczema conditions.	Paolino D, *et al.*, 2005
Hydroxyquinone	Cream	Hydroquinone cream is the standard depigmentation or skin lightening agent.	Zhao YZ, *et al.*, 2013

Importance of ethosomes

The use of ethosomes is mainly to treat the dermal disorders. It is becoming more important to focus on the absorption of medication to deep layers of the skin. Ethosomes are the innovative carrier capable of breaching the skin barrier, may provide a remedy for successfully delivering drugs into the deep layers. Ethosomes are low toxic so it hardly has any side effects on the skin. Ethosomes are platforms for the delivery of large and diverse groups of drugs (peptides, protein molecules) (Paolino D, *et al*., 2005; Zhao YZ, *et al*., 2013). It increases the permeation of the drug through the transdermal skin and dermal delivery, therefore ethosomes treats the acne vulgaris by enhancing the permeation. It improves the skin delivery of various drugs. Many patients' populations of different ages are in need of new and advanced therapies for severe and persistent skin disease caused by bacteria and viruses and more effective therapies for disorders associated with the pilosebaceous structure (Esposito E, *et al*., 2004).

Advantages (Saraf S, *et al*., 2011)

- Biodegradable
- Low toxicity
- Easy to prepare
- Softness, malleability
- Targeted drug delivery
- Permeation enhancer
- Low risk profile
- High patient compliances
- High market attractiveness
- Platform for the large and diverse group of drugs
- Improved drug delivery
- High skin retention

Characterization

The characterization of ethosomes is done by seven types of tests, which are as follows (Allen L and Ansel HC, 2013; Jain S, *et al*., 2003; Touitou E, *et al*., 2000):

- **Shape of the particle:** Scanning electron microscopy and transmission electron microscopy are used to determine the shape of the particle. These are the microscopes that employ an electron particle beam to see a specimen and provide a greatly magnified picture.
- **Analysis of the particle size:** To analyze the particle size, optical microscopy is used. It is also known as a light microscope because it employs visible light to magnify pictures of tiny samples through one or more lenses.
- **Drug content:** For this test, High Performance Liquid Chromatography (HPLC) is used. It is a method that uses high pressure to force materials down a chromatographic column in order to separate out the components that comprise the sample.
- **Effectiveness of drug trapping:** In this test, the technique used is ultracentrifugation which entails separation based on centrifugal force generated by the fast rotation.
- ***In vitro* drug release research:** In this test, the technique used is Franz diffusion which often applied to remove human or animal skin.
- ***In vitro* skin permeation research:** In this test, the technique used is Franz diffusion.
- **Transition temperature:** In this test, the technique used is differential scanning calorimetry, which is a useful analytical technique for identifying the physical properties and thermal transitions of polymeric materials.

Diagnosis, management and prevention of acne

Diagnosis: Areas of the body, including the face, chest, and back, that have a lot of pilosebaceous glands are most frequently affected by acne. The initial acne lesion is a microcomedone, a tiny entity that cannot be seen with the unaided eye. First to appear during the course of acne are non- inflammatory lesions like closed (whiteheads) and open (blackheads) comedones, then inflammatory lesions such as papules and pustules (5 mm in diameter), and deep pustules or nodules (Zouboulis CC, *et al*., 2014). Based on severity, kind of lesion and age of development, acne is clinically identified and classified. According to a patient's predominate lesions, acne is classified as mild, moderate, or severe. Acne can be comedonal, papulopustular, nodular, nodulocystic, or globular (acne conglobate). A rare, severe variant of acne vulgaris known as acne conglobate is characterized by clumped comedones, nodules, abscesses, and leaky sinus tracts. Adult males are frequently affected by this kind, which takes a while to develop. The age at which acne first appears can also be determined, including neonatal (4 weeks) (Antoniou C, *et al*., 2009) *(Figure 4)*.

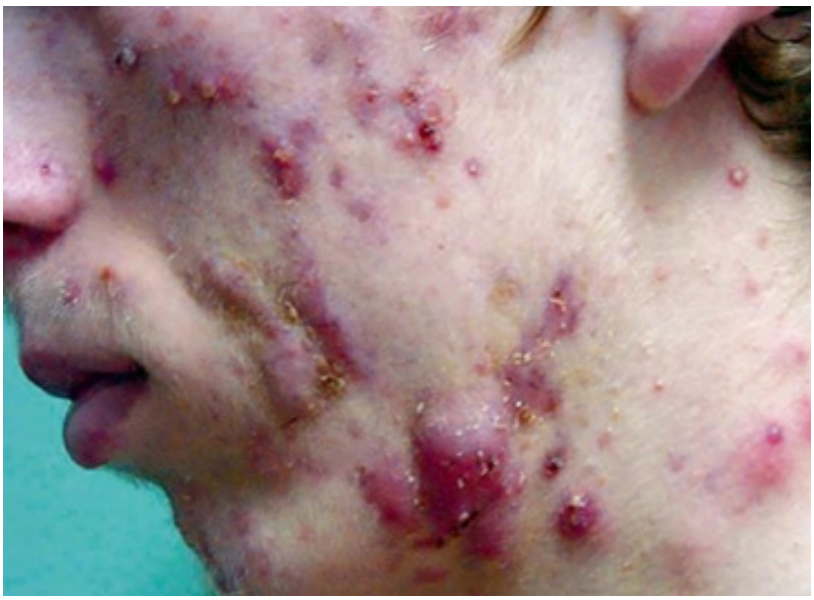

Figure 4: Acne conglobate

Prevention: Acne prevention depends on effectively managing risk factors that may be changed and contribute to its occurrence, such as fundamental systemic disorders and lifestyle choices. Congenital adrenal hyperplasia is an example of a systemic condition for which acne may be the cutaneous manifestation. In these situations, acne can be prevented from developing or worsening by immediately and effectively treating the underlying condition (Zouboulis CC, 2014; Chen W, *et al*., 2011). A multitude of lifestyle choices, such as food, weight, and smoking, can have an influence on acne (Melnik BC, *et al*., 2013). On the other hand, the effectiveness of lifestyle therapies for acne remains a hotly contested topic, with epidemiological research presenting inconsistent outcomes and well-planned trials failing to provide results supported by the available data. An amplified risk of acne growth was shown to be predominantly associated with increasing intake of milk (particularly skim milk), but not with increased consumption of cheese or chocolate, according to a case-control study of dietary patterns in n adults (Chandran SC, *et al*., 2011).

There haven't been many randomized controlled trials to assess the efficacy of dietary acne treatments. A low-glycemic-load diet was associated with a larger reduction in the overall number of acne lesions when compared to a conventional high-glycemic-load diet.

Management: Treatment alternatives exist, and a wide variety of mixture solutions have been created, providing people with a wide range of treatment options. There is a scarcity of robust data to back up many of the recommendations in the acne action guidelines due to a lack of large, carefully planned, randomized controlled studies to evaluate and compare the efficacy of acne treatment alternatives. As a consequence, current suggestions are founded on professional judgment. Additionally, the majority of the material on treatment for systemic disease-related acne is based on case studies.

The common ideas that serve as the basis for these principles are as follows: Since acne is no longer seen as a normal part of life, it needs to be treated quickly and thoroughly to prevent its negative psychological and physical implications. The natural history of acne is still being studied longitudinally, with an emphasis on the value of early intervention in preventing chronic illness (Gollnick H, *et al*., 2003; Strauss JS, *et al*., 2007; Nast A, *et al*., 2012; Dréno B, *et al*., 2004).

DISCUSSION

Ethosomes have opened up a new frontier in transdermal medication delivery. Improved medication release control *in vivo* will be made possible by greater study in this area, which will help doctors deliver more effective treatments. With a focus on skin delivery of proteins and other macromolecules, it provides strong prospects for non-invasive administration of small, medium, and large therapeutic molecules. As well as transcutaneous immunization, the fundamental drawback of transdermal medication administration is how poorly most substances penetrate human skin. The top layer of the skin, or stratum corneum, serves as the primary barrier (Mistry A, *et al*., 2005). There have been a number of methods claiming to increase penetration through the skin. Vesicular systems like ethosomes and liposomes are used in one method, poor yield, not are economical. A tendency for oxidative deterioration, natural phospholipids' purity, and formulations might be pricey. Creating an analytical approach for medication distribution is challenging. Variable distribution processes with kinetics (Laïb S and Routh AF, 2008).

CONCLUSION

Acne is a skin condition that occurs when your hair follicles become plugged with oil and dead skin cells. It causes whiteheads, blackheads or pimples. Acne is most common among teenagers, though it affects people of all ages. Effective acne treatments are available, but acne can be persistent. Ethosomes have the potential to considerably overcome the epidermal barrier, the primary limiting factor of transdermal drug delivery methods. Ethosomes stand out for their simplicity in production, safety, and effectiveness. They may also be altered to boost the skin permeability of active medications. Ethosomes have opened up new avenues for vesicular research for transdermal drug delivery. It has the potential to cure the acne vesicular.

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