

Formulation and Evaluation of Herbal Ethosomal Cream of *Passiflora foetida* Linn. for the Treatment of Psoriasis

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ABSTRACT

Psoriasis is an autoimmune condition with the most significant and far-reaching consequences for humans. In order to cure psoriasis, an herbal ethosomal cream was developed, and one of the plants that went into its production was the *Passiflora foetida* Linn. plant. A large number of distinct phytochemical identification tests were carried out with the use of a broad range of reagents. The ability of an antioxidant to reduce free radicals, as measured by 2,2-diphenyl-1-picrylhydrazyl (DPPH), is one way that its effectiveness may be shown. Coconut oil, olive oil, and vitamin E oil are the three essential oils combined to make the final product. All of these oils bring its own unique set of medicinal benefits to the table. The liquid chromatography-mass spectrometry (LC-MS) analysis carried out on the herbal extract revealed the presence of phytoconstituents inside the sample. The overall quality of the cream that was produced was evaluated. The LC-MS approach was used to dissect the anti-inflammatory and psoriasis-fighting components included in herbal remedies. An attempt to treat psoriasis using herbal medicine was made using the ethosomes of the *P. foetida* Linn. plant.

Keywords: *Passiflora foetida* Linn., Psoriasis, Ethosomes.

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INTRODUCTION

Both ethosomes and liposomes, which are two more types of drug transporters, operate in an entirely distinct manner. Because ethosomal drug carriers can penetrate the skin more deeply than liposomal drug carriers can, they can be used as an alternative to liposomal drug carriers. This makes it possible to use ethosomal drug carriers. There is a possibility that the increased amounts of phospholipids and ethanol seen in ethosomal drug carriers are responsible for the better medicine penetration into the deeper epidermal layers. Penetration enhancers, such as sonophoresis, iontophoresis, and other procedures, are used to increase the amount of medicine that is absorbed by the skin. These penetration enhancers may be based on chemical or physical principles.^{1,2}

Ethosomes

Ethosomes are a particular kind of vesicle that are capable of transporting drugs in a way that is both adaptable and unobtrusive. It is possible for therapeutic drugs to have their ethosomes encased, despite the fact that their hydrophilicity, lipophilicity, or amphiphilicity may vary. The ethosome will increase the flow of particles via the transdermal layer of the skin, and these particles, whose sizes range from tens of nanometers to microns, will penetrate the skin more rapidly.

Because of this, ethosomes are a fascinating and cutting-edge method of administering medication, which has become more significant over the course of the last several years. Ethosomes are only one illustration of how the use of ethosomes has contributed to developing more effective strategies for administering medicinal medications (Figure 1). Another kind of vesicular carrier is safe penetration enhancers and other vesicular carriers.^{3,4}

Properties of Ethosomes

Effect of high alcohol concentration

In order for ethanol, which acts as a penetration enhancer, to get through the lipid bilayer, the ethosomal lipid layer of the membrane first has to be fluidized, and then the outer layer needs to be smoothed. After that, one will finally be able to access the lipid bilayer. When the percentage of ethanol increased from 20 to 50%, there was a corresponding increase in the amount of medication absorbed *via* the skin. Because of the smaller packing of the molecules in these vesicles compared to more traditional vesicles, neither the solubility nor the stability of the molecules is impacted in any way. Consequently, the ratio of the amounts of ethosomal's components, of which phospholipids make up the bulk, may be altered to produce a variety of different formulations.^{5,6} The ethosome vesicles

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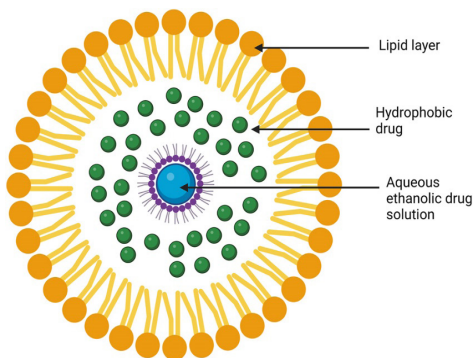


Figure 1: Structure of ethosome vesicle

swell up when there is a lower concentration of ethanol in the body than is typical. We were successful in locating the most probable entrance point for the illegal chemical and its corresponding location. The impact of ethanol, which raises the fluidity of lipids and lowers the concentration of lipid multilayers or bilayers, is the primary mechanism that contributes to the occurrence of this phenomenon. This action is only feasible under conditions in which ethanol is unable to pass through lipid membranes. Second, because of the inter-lipid penetration that ethosomes offer, it is now possible for medications to enter the body through paths that had not previously been investigated. Ethosomes have the capability of transporting medications to the deeper membrane layers of the skin as a result of their malleability and their capacity to mix with the lipids that are found in the skin. In order for a medication to be absorbed into the body, it must first enter the body by one of the two principal entry points.⁷

Ethanol effect

In most cases, ethanol is superior to other solvents in terms of its ability to enter the skin. There are often well-established mechanisms that, when combined, allow for greater medication penetration through the skin. This may be achieved in a number of ways. Once it has entered the cell, ethanol can cause changes to the lipid bilayer that makes up the membranes. As a direct consequence of factor,⁸ ethosomal preparations have the highest levels of ethanol.

Ethosome effect

Ethanol has the effect of making cell membranes more fluid, which in turn increases the permeability of the skin. This shows that ethosomes can quickly enter deeper skin layers, where they may interact with the lipids of the skin to speed up the absorption of herbal drugs.⁹

Medicinal Potential of *Passiflora foetida*

Hysteria, giddiness, liver issues, diarrhea, tumors, neurological illnesses, anxiety, sleep difficulties, skin infections, and asthma are just some of the ailments that have historically been treated with the stinking passion flower (Figure 2), also known as *P. foetida*. These are only some of the conditions that people have attributed to being cured by using this plant. *P. foetida* has been linked to a broad variety of therapeutic benefits, some



Figure 2: *P. foetida* plant

Table 1: Mineral content of the fruits of *P. foetida*

Minerals	Total minerals (%)
Manganese	0.05
Copper	0.04
Iron	0.15
Zinc	0.17
Phosphorus	14.44
Sodium	1.68
Magnesium	6.71
Potassium	75.70
Calcium	1.06

of which include protection against cancer, inflammation, and diabetes. *P. foetida* has also been shown to aid with digestion. Flavonoids, polysaccharides, pyrones, and cyanohydrins are the primary components of this plant's primary metabolites. Other components include cyanohydrins. The chemical extraction method used various plant components, such as the leaves, stems, seeds, and fruits of the plant in addition to the resins. The stems of *P. foetida* contain a significant amount of the biopolymer cellulose.¹⁰ Due to the plant's high nutritional value, the *P. foetida*'s leaves and fruits are used to manufacture nutrient-rich powders, herbal drinks, and tablets. These products may be found in health food stores. In order to determine the total quantity of vitexin present, a high-performance thin-layer chromatography (HPTLC) experiment was carried out. These substances have an effect on living organisms that may be broadly classified into a wide variety of categories and subcategories. The plant known as *P. foetida* is becoming more well-known for its potential therapeutic effects for humans. Antibacterial, anti-inflammatory, hepatoprotective, antiepileptic, analgesic, ulcer-fighting, antioxidant, hyperglycemic, cytotoxic, anti-diarrheal, cardioprotective, anti-dyslipidemia, anti-osteoporotic, and hypersensitive effects were some of the things we investigated regarding the extracts. As a result of the ABTS test, it was determined that the IC₅₀ value for the ethyl acetate extract was 25.18 g/mL,¹¹ and this was the conclusion drawn from the experiment. This provides evidence that the extract contains a significant amount of antioxidants.

Mineral composition

The fruit of the *P. foetida* plant has a much higher concentration of both phosphorus and potassium¹² with reference to the mineral composition reported in Table 1.

MATERIALS AND METHODS

The specimen of the *P. foetida* plant was obtained from the botanical garden. The plant was investigated and proven to be authentic. The process of rigorously crushing the dried plant and making a total of forty passes through a sieve was required before it could be stored in an airtight container.¹³

Preparation of Extracts

It is possible to manufacture complete MePF by maceration. In order to extract the oil from the dried leaves of *P. foetida*, we started with 500 g of dried leaves, then added 1.5 L of methanol and evaporated the mixture using a rotary evaporator. A temperature of 4°C was maintained on the complete methanol extract while it was waiting to be analyzed.^{14,15}

Qualitative analysis of phytochemicals

Analyses are carried out to assess the phytochemical potential of an unprocessed herbal extract. A battery of tests was used to identify the presence of fifteen different chemical compounds, including alkaloids, flavonoids, tannins, sugars, glycosides, saponins, triterpenoids, amino acids, and proteins. These chemical substances were found to be present.

LC-MS studies

The LC-MS technique was used to analyze the herbal extract in order to determine its constituent parts. The sections that follow provide further information on the different sorts of study tools.

- *Specifications*

In the LC system that will be using an Acquity Uplc Beh C18 1.7 m column, we were given the opportunity to choose the solvent that would be used. Option A is a solution consisting of formic acid that has been diluted into water to a concentration of 0.1%. B: The procedures in the synthesis of acetonitrile that are performed multiple times: Structure of Ionization: The ES⁺ carries a charge in the positive direction. According to the specifications, the injection volume should be 2 liters, the column should be 25 cm long and 2.5 mm in diameter, and the mass range should be between 50 and 1500 grams. The number 1.40.2532 refers to the software's version number.

Development of Ethosomes Containing Drugs

Here we used cold method for the preparation of ethosomes.

Preparation of Herbal Ethosomal Cream

The production of an oil-in-water (O/W) emulsion cream has a viscosity between liquid and solid. Celsius to dissolve the stearic acid and other oil-soluble compounds such as cocoa butter, cetyl alcohol, coconut oil, olive oil, and vitamin E oil, the oil phase of part A was heated to 75°C. Other oil-soluble substances included. This process was carried out using a double boiler. In order to dissolve the preservatives, the aqueous phase of part B was heated to a temperature of 75°C.

The preservatives were triethanolamine, propylene glycol, and neem ethanol extract. Before the aqueous phase was added,^{16,17} the oil phase was heated; then, when the aqueous phase was added, the combination was constantly stirred. Numerous times, the same activities were carried out. The ingredients that go into the cream are outlined in Table 2.

Evaluation of Creams

Type of emulsion under dye test

When blended with color cream, the gorgeous red dye produces a new color with significant dimensionality. A drop of cream was placed on a microscopic slide, and the slide was then covered with a cover slip before being seen under a microscope. After this, the slide was examined. O/W cream is normally colorless, however, upon closer inspection, it could be able to identify red globules scattered throughout the cream, which otherwise has no discernible hue. When seen in the hue red¹⁸, the distributed globules of W/O cream, on the other hand, appear absolutely colorless.

Appearance

The color, pearlescence, and roughness of the cream were the criteria that were used to evaluate it.

Homogeneity

Visual and physical comparisons were performed on the compositions to ensure that they were all of the same standard.

pH of the cream

In order for the pH meter to function properly, it has to be calibrated with the use of a reference buffer solution. The pH of the solution that was produced by dissolving half a gram of cream in 50 mL of sterile water was measured after the solution was created.

Viscosity

In order to determine the level of viscosity possessed by the formulation, spindle number 7 of the Brookfield Viscometer was rotated at a rate of 100 revolutions per minute.

Biological Evaluation of Topical formulations

In-vitro study for skin permeability

The evaluations were carried out on each and every animal in compliance with the protocols established by the IAEC.

Table 2: Composition of herbal cream preparation

Ingredients	Quantity
<i>P. foetida</i> Linn. loaded ethosomes (mg)	500
Cocoa butter (g)	3
Stearic acid (%)	3
Cetyl alcohol (%)	2
Coconut oil (mL)	2
Olive oil (mL)	1
Vit E oil (mL)	1
Methyl paraben (%)	1
TEA (mL)	0.5

The *in-vitro* skin permeation experiment utilized albino male Wistar rats weighing between 150 and 200 grams apiece as test animals. The rats were chosen for this experiment because of their resistant skin. Before moving on to further approaches, the dorsal hairs of rats were first shaved off using a hair removal lotion as a preparatory step. For the purpose of cleaning the connective tissues and subcutaneous fat of the skin¹⁹, physiologic salt solution (PSS) and distilled water were used. Following the sterilization process, the skin was placed in a refrigerator, covered with aluminum foil, and stored at a temperature of 4°C until the experiment began. The depth of the skin was measured using a digital micrometer, and the result was 2.6 mm with an error range of 0.2 mm. Following that, the temperature of the skin was brought up to its typical level in a Franz diffusion cell. The receptor area contains 10 milliliters of phosphate buffer solution that has a pH of 7.4; this solution acts as a barrier at the base of the donor zone, which is only partially permeable. A magnetic stirrer continuously agitated the liquid at 200 revolutions per minute to keep the temperature at 37°C (plus or minus one degree). After collecting precise measurements, one gram of ethosomal cream containing *P. foetida* Linn. was administered to the donor compartment of the skin. In order to keep the sink environment stable for a period of 0.24 hours, aliquots of samples with a volume of one mL each were removed from the receptor region at regular intervals of one, two, three, four, and so on hours and replaced

with new medium. This process was repeated 24 times. After the materials had been gathered, they were passed over a membrane with holes of 0.45 micrometers in size so that they could be percolated. The results of the tests that were carried out at 299 nm were compared to a blank with the assistance of a UV/visible spectrophotometer. After multiple cycles of the technique had been completed for each formulation²⁰, a graph was constructed to depict the cumulative drug release over time. Three separate measurements were taken of each ethosomal preparation, and the results were reported.

RESULTS AND DISCUSSION

Qualitative Analysis of Phytochemicals

The methodologies employed to identify which chemicals were present in each extract are outlined in Table 3, which can be seen here. Alkaloids, flavonoids, tannins, sugars, glycosides, saponins, and triterpenoids were some of the active components that were found in the plant extract. Other active components were triterpenoids.

LC-MS studies

The base peak ionization (BPI) chromatogram of the methanolic extract of *P. foetida* Linn showed that the component with a molecular weight of 540.601 g/mol retained 1.62 seconds. This information was gleaned from the analysis of the chromatogram. It's possible that the RT's mass spectrum as shown in Figures 3 and 4. ART value of 3.16 and a molecular

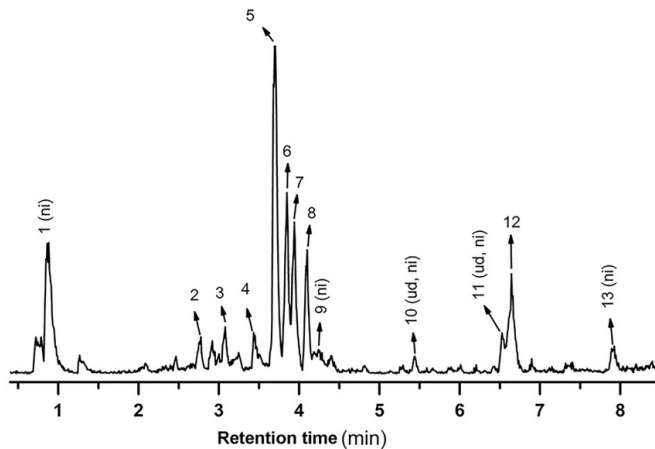


Figure 3: Base peak ionization (BPI) chromatogram of *P. foetida* Linn.

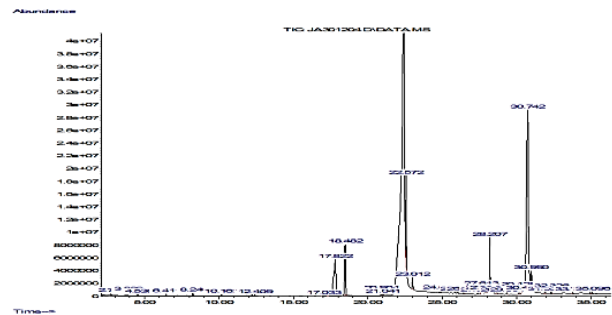


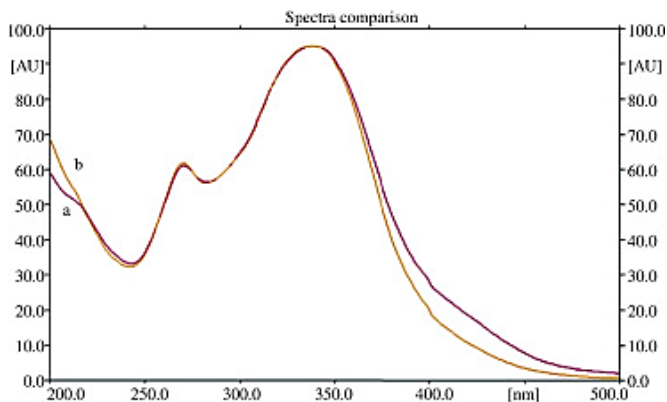
Figure 4: Mass spectrum of methanolic extract of *P. foetida* Linn.

Table 3: Phytochemicals present in methanolic extracts of *P. foetida* Linn.

S No	Constituents	Test	Observation	Results
1	Alkaloids	Mayer's test	Formation of creamy precipitate.	Positive
2	Flavanoids	Lead acetate test	Formation of yellow precipitate	Positive
3	Carbohydrates	Molish's test	Formation of violet ring at the junction.	Positive
4	Triterpenoids and steroids	Salwonski test	If lower layer turns red indicates the presence of steroids. The golden yellow layer at bottom indicates the presence of triterpenoids	Positive
5	Deoxy sugars	Killer kiliani's test	Formation of blue color in the acetic acid layer	Positive
6	Glycosides	Legal's test	Formation of pink to blood red color	Positive
7	Reducing sugars	Benedict's test	Solution appears green or yellow or red depending on the amount of reducing sugar present in the test solution	Positive
8	Amino acids	Ninhydrin test	Formation of blue color	Negative

Table 4: Composition of *P. foetida* Linn loaded ethosomes

Composition	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
Ethanollic <i>P. foetida</i> Linn extract (mg)	100	100	100	100	100	100	100	100	100
Soya lecithin (mg)	200	200	200	300	300	300	400	400	400
Ethanollic neem extract (%)	30	35	40	30	35	40	30	35	40
Propylene glycol (ml)	1	1	1	1	1	1	1	1	1
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

**Figure 5:** Spectrum of *P. foetida* Linn.

weight of 720.721 g/mol are both associated with it. *P. foetida* Linn. is the name that botanists use to refer to this plant. The spectrum is shown in Figure 5, which may be found here.

Development of Ethosomes Containing Drugs

After performing the procedure of placing the medication and the soy lecithin in a water bath heated to 30°C, we next added the ethanollic extract of *P. foetida* Linn. and the propylene glycol. In order to finish out the solution, very little distilled water was utilized at a very slow flow rate. An airtight container was used to store the magnetic stirrer that was manufactured by Remi equipment in Mumbai. This particular stirrer turned at a rate of 700 revolutions per minute while it was being used. The probe sonicator was used to sonicate the solution thrice for 10 minutes, with a five-minute break between each cycle. The solution was then thoroughly mixed. This step was carried out after maintaining the solution at a temperature of 4°C. The composition of ethosomes is reported in Table 4.

Preparation of Herbal Ethosomal Cream

At a concentration of 0.75% by weight, Carbopol 934 K and distilled water were mixed together using a magnetic stirrer for one hour. The final concentration was 0.75%. As a direct result of this, the polymer grew in size. Following this step, the mixture was vigorously mixed while 20 mL of an ethosomal solution containing *P. foetida* Linn. was added. This was done while continuously swirling the constituents together. It seemed to take an eon to acquire the consistency of an ethosomal gel, which required constant whirling in a container at 700 revolutions per minute at a temperature of 30°C. After bringing the pH of the liquid to a neutral state, 7.4 milliliters of triethanol amine were added to it while it was being

stirred, and the mixture was allowed to continue to be stirred. Glycerine is included in the mixture because it is a humectant, which increases the efficiency with which the skin absorbs the medicine. Using the aforementioned procedures, nine distinct ethosomal formulations with varying concentrations were produced, and after their creation, these formulations were evaluated using a predetermined set of criteria.

Evaluation of Creams

The cream was evaluated for following parameters as mentioned in Table 5.

Dye test

It confirmed that the formulation prepared was an o/w type of emulsion cream.

Appearance

There is no change in the color of cream.

Homogeneity

By visual appearance and by touch, it is confirmed that the formulation is homogenous.

pH of the cream

The formulation had shown pH nearer to the skin, i.e., 6.4.

Viscosity

The viscosity of cream was 649 cps which indicates that the cream is easily spreadable by small amounts of shear.

Biological Evaluation of Ethosomal Cream Formulations

In-vitro study for skin permeability

The application of each mixture to the healthy skin of wistar albino rats allowed us to assess the features of the release. The amount of *P. foetida* Linn. secreted into a certain habitat is directly influenced by the levels of ethanol and lipids present in that environment. The slope of the straight line that graphed the total amount of medicine absorbed over time per unit area of rat skin served as the basis for the calculation used to determine the diffusion rate of the medication, which was then reported

Table 5: Evaluation parameters of formulated cream

Parameters	Results
Dye test	o/w type emulsion
Appearance	No change
Homogeneity	Homogenous
pH	6.4
Viscosity (cps)	649

as a percentage. In order to attain this goal, the slope of the line was figured out. The following is the total dose that is administered over the course of a single day for each of the nine different formulations (PF1-PF9): 64.98 0.63, 71.39 0.45, 59.47 0.02, 75.08 0.65, 83.45 2.51, 60.57 0.61, 55.49 0.07, 49.60 0.85, and 45.27. Formulation PF5 had the highest level of successful drug entrapment, which therefore resulted in the highest level of successful drug release (83.45, 2.51 in comparison to the other formulations). No other formulations came close to the total amount of medication that the PF9 formulation gave (45.27, 0.92). Because of the lipid bilayer's ability to govern drug diffusion, the initial release of the medication may be rather quick, and its efficacy may be maintained for an extended period of time. There is a possibility that the lipid bilayer is the fundamental cause of this phenomena. Because PF5 formulations include just a trace amount of fat, it is possible to quickly dispense medicine with these products. Because of this, the amount of ethanol and lipids present in a formulation significantly impacts how rapidly the medicine is released from it. After taking into account all that was important, it was found that the present formulation of PF5 operates fairly well when administered to different kinds of animals.

DISCUSSION

In order to produce herbal ethosomal gel, the active component was infused into an ethanolic extract of *P. foetida* Linn. Under laboratory conditions that were carefully controlled, it was discovered that the primary component of the extract, a flavonoid, has antifungal characteristics. The 2-phenylbenzopyrane is a heterocyclic structure that consists of two benzene rings coupled to a pyran ring. This substance is also referred to as the flavan nucleus on occasion. There is a possibility that phytoplankton contains substantial levels of flavonoids. Although these compounds exhibit a wide variety of biological and pharmacological effects, one of which is antifungal activity, this is not the only role they serve. Testing was done both *in-vitro* and *in-vivo* on the generated construct to see whether or not it was effective and suitable for therapeutic application. The findings of research that looked at particle size and PDI also showed that the quantities of soya lectin and ethanolic neem extract substantially influenced the size of the vesicles. This information was found in the results of the study. Significant changes occur in the particle size and the PDI dispersion when the content of soy lecithin or ethanolic neem extract is increased to more than 200 mg or 35%, respectively.^{21,22} Changing the proportion of lipids to ethanol or ethanol to lipids in the ethosome may have a major effect on the physiological processes that take place in the cell. It is essential to remember that the capacity of medications to permeate the skin is inversely proportional to the amount of ethanol present in them, and that the skin will only allow particles smaller than a particular size to do so. To assume that PF5 may have a topical use is a valid assumption on our part. Suppose the suspension has a high anionic charge or a high cationic charge (a high value with a negative or positive sign). In that case, the particles will be attracted to one another and will resist agglomeration. This

is how the zeta potential function works. Because there is not enough force between the particles in a suspension with a low zeta, the particles in the suspension have a tendency to cluster together, and this tendency exists regardless of whether the potential is positive or negative. As a consequence of this, the ethosome will achieve a higher level of stability as a result of an increase in its surface charge. Because it has the highest zeta potential, the PF5 formulation is the one that is least likely to undergo any changes. As a direct consequence of this, PF5-formed particles have a lower propensity to adhere to one another. Experiments with the zeta potential have shown that the size of the vesicle influences the charge. The technique known as transmission electron microscopy (TEM) was used to investigate ethosomes, and the results demonstrated that these particles had a spherical shape and a smooth, drug-free surface. Images obtained using an AFM give more information regarding the shape, behavior, and swelling dynamics of a formulation in comparison to those obtained using a TEM. This is because AFM photos have a heightened sensitivity to detect even the most minute of details. In order to elaborate on the shape of the structure, it is helpful to have images that demonstrate that the dimensions of the ethosome (its height, area, and diameter) are within the anticipated bounds of size. The height of an ethosome is 1.067 nm, the surface area of an ethosome is 548.813 nm squared, and the diameter of an ethosome is 26.434 nm.^{23,24}

CONCLUSION

The lipid layer of the skin is able to effectively convey the herbal ethosomes that the *P. foetida* plant generates to other parts of the body. The herbal ethosomes of *P. foetida* contain a high quantity of ethanol, which both preserves the skin's permeability and makes it easier for medications to be absorbed into lipid vesicles. This results in an increase in the bioavailability of the medicine. According to this experiment's results, the vesicle's ideal size may be determined, which results in higher entrapment efficacy and better penetration. The medication discharge will continue as normal because the temperature is now 4°C and the humidity is between 60 and 5%. The ethanol and lipids included in the formulation have a direct bearing on the efficacy of the ethosomal vesicle approach for the delivery of drugs. As a treatment for fungal infections, ethosomes are exploited as a delivery system for the antifungal medication luliconazole. This is accomplished in a way that is both regulated and continuous. Companies developing new formulations and wanting to present them to the market could find this improved process beneficial.

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