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Ethosomes:A Novel Vesicular Carrier System For Therapeutic Applications

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Abstract:- Ethosomes Are Innovative Novel Vesicular System That Have Appeared In Fields Of Pharmaceutical Technology In Which Drugs Are Entrapped To Increase The Therapeutic Efficacy Of Drugs.Ethosomes Are Composed Of Phospholipid, Alcohol, Polyglycol And Water. Ethanol Increases The Penetration Rate Of The Skin And Delivers The Drug Into The Deeper Layers Of Skin. Ethosomes Is Widely Used Instead Of Liposomes Due To Its Improved Drug Delivery, Penetration Rateetc.Ethosomes Are Soft, Malleable Vesicles, And Can Be Used For Topical As Well As Systemic Administration. Ethosomes Carrier Have Many Opportunities In The Research And Development Of Therapies. The Main Purpose Of This Review Article Is To Provide Full Information On Ethosomes.

Keywords: *Ethanol,Ethosomes, Skin Penetration, Topical/Transdermal Delivery, Transition Temperature*

I. INTRODUCTION

Apart From This Numbers Of Novel Drug Delivery Systems Have Been Reported For Various Routes Ofadministration, To Achieve Local And Systemic Drug Delivery In Controlled Manner, Whereas Lipidicvesicular Drug Delivery Systems Such As Liposomes, Niosomes, Transfersoms And Pharmacosomes Were Also Developed For Topical/Transdermal Administration Of Drug Molecules[1, 3]. Recently An Innovative Flexible Vesicular System, Ethosomes Has Been Developed For Topical/ Transdermal Delivery Of A Drug. This System Has Wonderful Property To Permeate Intact Through The Human Skin Due To Its High Elasticity Properties, Which Has An Immense Consequence For Design Of Carrier System To Be Applied Topically Both For Local And Systemic Delivery Of Hydrophilic And Lipophilic Drugs[3,4].

One Of The Major Advances In Vesicle Research Was The Finding That Some Modified Vesicles Possessed Properties That Allowed Them To Successfully Deliver Drugs In Deeper Layers Of Skin. Transdermal Delivery Is Important Because It Is A Noninvasive Procedure For Drug Delivery. Further, Problem Of Drug Degradation By Digestive Enzymes After Oral Administration And Discomfort Associated With Parenteral Drug Administration Can Be Avoided. It Is The Most Preferred Route For Systemic Delivery Of Drugs To Pediatric, Geriatric And Patients Having Dysphasia. To Overcome The Stratum Corneum Barrier, Various Mechanisms Have Been Investigated, Including Useof Chemical Or Physical Enhancers Such As Iontophoresis, Sonophoresis, Etc. Liposomes, Niosomes,Transferosomes And Ethosomes Also Have The Potential Of Overcoming The Skin Barrier And Have Beenreported To Enhance Permeability Of Drug Through The Stratum Corneum Barrier[2].

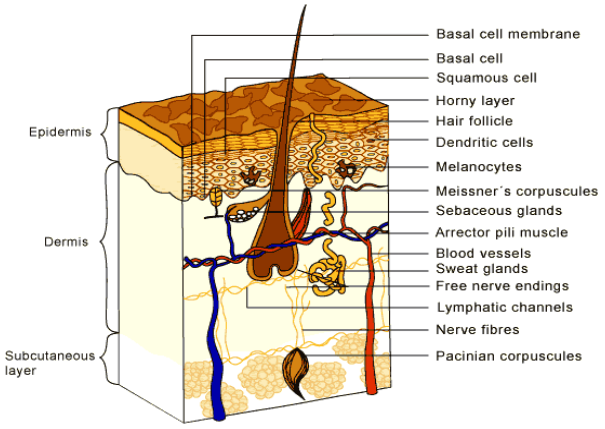

Figure 1: Structure Of Skin

II. ETHOSOMES

Ethosomes Are Non-Invasive Delivery Carriers That Enable Drugs To Reach The Deep Skin Layers And/Or The Systemic Circulation. These Are Soft, Malleable Vesicles Tailored For Enhanced Delivery Of Active Agents[15]. The Size Range Of Ethosomes May Vary From Tens Of Nanometers To Microns (M)[6,7]. Drug Can Be Entrapped In Ethosomes Which Have Various Physicochemical Characteristics *I.E.* Hydrophilic, Lipophilic, Or Amphiphilic [8,27].

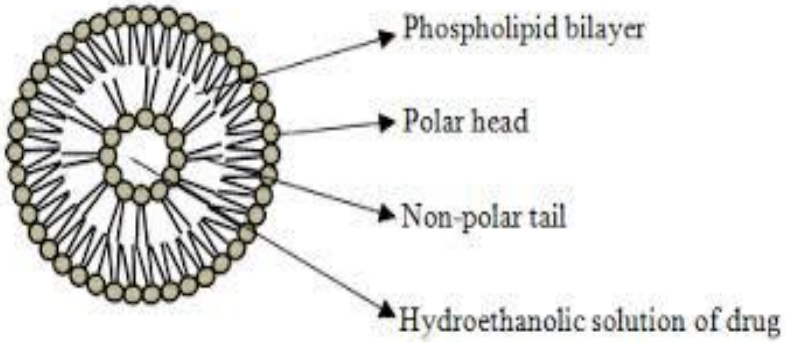

Figure 2: Structure Of Ethosomes

Lipophilic Drugs Can Pass Throughthe Skin But The Drugs Which Are Hydrophilic In Nature Can't Pass Through. Water Soluble Drugs Either Show Very Less Or No Permeation. To Improve The Permeation Of Drugs Through The Skin Various Mechanisms Have Been Investigated, Including Use Of Chemical Or Physical Enhancers, Such As Iontophoresis, Sonophoresis, Etc. Liposomes, Niosomes, Transferosomes And Ethosomes Also Have Been Reported To Enhance Permeability Of Drug Through The Stratum Corneum Barrier. Permeation Enhancers Increase The Permeability Of The Skin, So That The Drugs Can Cross Through The Skin Easily. Unlike Classic Liposomes,[6,13,14] That Are Known Mainly To Deliver Drugs To The Outer Layers Of Skin, Ethosomes Can Enhance Permeation Through The Stratum Corneum Barrier[6,9-11].

III. COMPOSITIONOFETHOSOMES

They Are Composed Mainly Of Phospholipids,(Phosphatidylcholine, Phosphatidylserine, Phosphatitidic Acid), High Concentration Of Ethanol And Water. The High Concentration Of Ethanol Makes The Ethosomes Unique, As Ethanol Is Known For Its Disturbance Of Skin Lipid Bilayer Organization Therefore, When Integrated Into A Vesicle Membrane, It Gives That Vesicle The Ability To Penetrate The Stratum Corneum. Also, Because Of Their High Ethanol Concentration, The Lipid Membrane Is Packed Less Tightly Than Conventional Vesicles But Has Equivalent Stability, Allowing A More Malleable Structure And Improves Drug Distribution Ability In Stratum Corneum Lipids[15].

Table No.1: Composition Of Ethosomes[5,15]

S.No	Materials	Examples	Uses
1	Phospholipid	Soya Phosphatidyl Choline Egg Phosphatidyl Choline Dipalmitylphosphatidyl Choline Distearylphosphatidyl Choline	Vesicles Forming Component
2	Polyglycol	Propylene Glycol Transcutol Rtm	As A Skin Penetration Enhancer
3	Alcohol	Ethanol Isopropyl Alcohol	For Providing The Softness For Vesicle Membrane As A Penetration Enhancer
4	Cholesterol	Cholesterol	For Providing The Stability To Vesicle Membrane
5	Dye	Rhodamine-123 Rhodamine Red Fluorescenisothiocynate (Fitc) 6- Carboxy Fluorescence	Rhodamine-123 Rhodamine Red Fluorescenisothiocynate (Fitc) 6- Carboxy Fluorescence
6	Vehicle	Carbopol 934	As A Gel Former

IV. METHOD OF PREPARATION

1. Cold Method

This Is The Most Common And Widely Used Method For The Ethosomal Preparation. Phospholipid, Drugand Other Lipid Materials Were Dissolved In Ethanol In A Covered Vessel At Room Temperature With Vigorous Stirring. The Mixture Was Heated At 30^0c In A Water Bath. Water Was Heated Up-To 30^0c In A Separate Vessel And Was Added To The Mixture And Then Stirred For 5 Min. The Vesicle Size Of Ethosomal Formulation Was Decreased To Desire Extent Using Sonication. Finally, The Formulation Was Properly Stored.

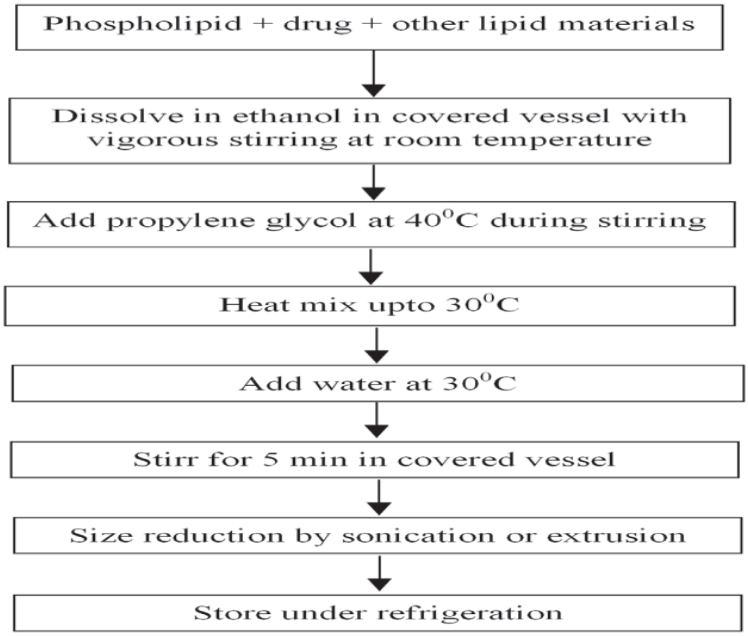

Figure 3: Cold Method For The Preparation Of Ethosomes

V. HOT METHOD

According To This Method, Phospholipid Was Dispersed In Water By Heating In A Water Bath At 40^0cuntil A Colloidal Solution Is Obtained. Ethanol, Propylene Glycol And Drug Was Mixed In A Separatevessel And Heated Up-To 40^0c. Organic Phase Was Added To Aqueous Phase And Stirred For 5 Min. Thevesicle Size Of Ethosomal Formulation Was Decreased To Desire Extent Using Sonication. Finally, Theformulation Was Properly Stored[15,16].

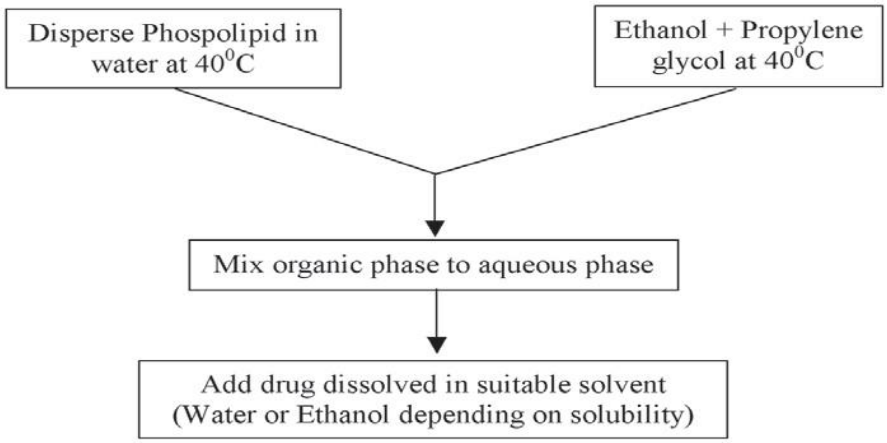

Figure 4: Hot Method For The Preparation Of Ethosomes

Mechanismof Penetration

The Main Advantage Of Ethosomes Over Liposomes Is The Increased Permeation Of The Drug. The Mechanism Of The Drug Absorption From Ethosomes Is Not Clear. The Drug Absorption Probably Occurs In Following Two Phases:

1. Ethanol Effect
2. Ethosomes Effect

1. Ethanol Effect:

Ethanol Acts As A Penetration Enhancer Through The Skin. The Mechanism Of Its Penetration Enhancingeffect Is Well Known. Ethanol Penetrates Into Intercellular Lipids And Increases The Fluidity Of Cellmembrane Lipids And Decrease The Density Of Lipid Multilayer Of Cell Membrane.

2. Ethosome Effect:

Increased Cell Membrane Lipid Fluidity Caused By The Ethanol Of Ethosomes Results Increased Skinpermeability. So The Ethosomes Permeates Very Easily Inside The Deep Skin Layers, Where It Gotfused With Skin Lipids And Releases The Drugs Into Deep Layer Of Skin [12,17].

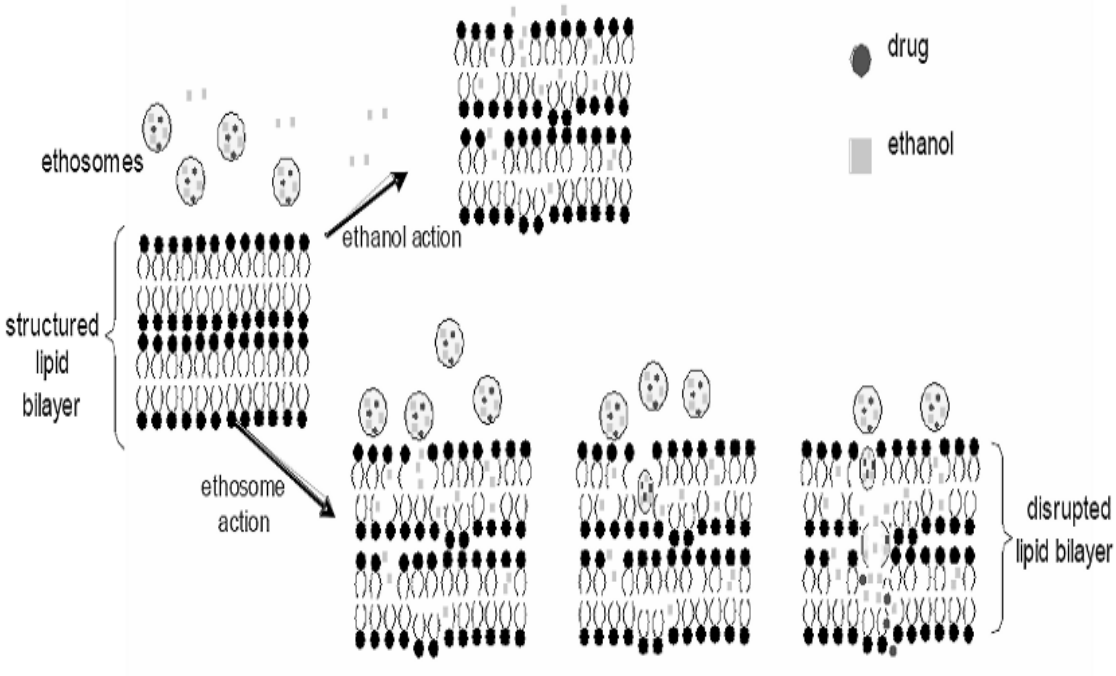

Figure 5: Drug Penetration Through Ethosomes

VI. ADVANTAGEOF HIGH ALCOHOL CONTENT

Ethanol Is An Established Efficient Permeation Enhancer And Is Present In Quite High Concentration (20-50%) In Ethosomes. However, Due To The Inter-Digitation Effect Of Ethanol On Lipid Bilayers, It Was Commonly Believed That Vesicles Could Not Coexist With High Concentration Of Ethanol. Touitou Discovered And Investigated Lipid Vesicular Systems Embodying Ethanol In Relatively High Concentration And Named Them Ethosomes. The Basic Difference Between Liposomes And Ethosomes Lies In Their Composition. The Synergistic Effect Of Combination Of Relatively High Concentration Of Ethanol (20-50%) In Vesicular Form In Ethosomes Was Suggested To Be The Main Reason For Their Better Skin Permeation Ability. The High Concentration Of Ethanol (20-50%) In Ethosomal Formulation Could Disturb Theskin 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. This Allowed 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 Versatility Of Ethosomes For Systemic Delivery Is Evident From The Reports Of

Enhanced Delivery Of Quite A Few Drugs Like Acyclovir, Minoxidil, Triphexyphenidyl,Testosterone, Cannabidol And Zidovudine [24, 28].

Advantagesofethosomal Drug Delivery

1. Delivery Of Large Molecules (Peptides, Protein Molecules) Is Possible.
2. It Contains Non-Toxic Raw Material In Formulation.
3. Enhanced Permeation Of Drug Through Skin For Transdermal Drug Delivery.
4. Ethosomal Drug Delivery System Can Be Applied Widely In Pharmaceutical, Veterinary, Cosmetic Fields.
5. High Patient Compliance: The Ethosomal Drug Is Administrated In Semisolid Form (Gel Or Cream) Hence Producing High Patient Compliance.
6. Simple Method For Drug Delivery In Comparison To Iontophoresis And Phonophoresis And Othercomplicated Methods
7. The Ethosomal System Is Passive, Non-Invasive And Is Available For Immediate Commercialization [12,17].

Disadvantagesofethosomes[15,20,21]

1.Drugs That Require High Blood Levels Cannot Be Administered – Limited Only To Potent Molecules,Those Requiring A Daily Dose Of 10mg Or Less.
2. Ethosomal Administration Is Not A Means To Achieve Rapid Bolus Type Drug Input, Rather It Is Usually Designed To Offer Slow, Sustained Drug Delivery.
3.Adequate Solubility Of The Drug In Both Lipophilic And Aqueous Environments To Reach Dermalmicrocirculation And Gain Access To The Systemic Circulation.
4. The Molecular Size Of The Drug Should Be Reasonable That It Should Be Absorbed Percutaneously.
5. Adhesive May Not Adhere Well To All Types Of Skin. Uncomfortable To Wear.
6. May Not Be Economical. Poor Yield.
7. Skin Irritation Or Dermatitis Due To Excipients And Enhancers Of Drug Delivery Systems.
8. In Case If Shell Locking Is Ineffective Then The Ethosomes May Coalescence And Fall Apart On Transfer Into Water.
9. Loss Of Product During Transfer From Organic To Water Media.
10. The Main Advantage Of Ethosomes Over Liposomes Is The Increased Permeation Of Thedrug.

Limitations Ofethosomes[2]

1. Poor Yield [22].
2. In Case If Shell Locking Is Ineffective Then The Ethosomes May Coalescence And Fall Apart On Transfer Into Water.
3. Loss Of Product During Transfer Form Organic To Water Media [23].

Table 2: List Of Various Drug Molecules Used In Ethosomal Drug Delivery[6,18,19]

Drug	Applications	Advantages
Acyclovir	Treatment Of Herpetic Infection	Improved Drug Delivery
Zidovudine	Treatment Of Aids	Improved Transdermal Flux
Trihexypenidylhcl	Treatment Of Parkinsonian Syndrome	Increased Drug Entrapment Efficiency, Reduced Side Effect &Constant Systemic Levels
Erythromycin	Efficient Healing Of S. Aureus - Induced Deep Dermal Infections	Improved Drug Penetration And Systemic Effect
Insulin	Treatment Of Diabetes	Improved Therapeutic Efficacy Of Drug
Testosterone	Treatment Of Male Hypogonodism	Enhance Skin Permeation
Cannabidol	Prevents Inflammation And Edema	Significant Accumulation Of The Drug In The Skin
Minodixil	Hair Growth Promotion Effect	Higher Skin Retention
Bacitracin	Treatment Of Dermal Infections	Reduced Drug Toxicity
Salbutamol	Anti-Asthmatic Bronchodilator	Enhanced Drug Delivery Through Skin Withethosomes
Cyclosporine	Treatment Of Inflammatory Skin Disease	Git Degradation, Poor Oral Absorption And Bioavailability

VII. CHARACTERIZATION OF ETHOSOMES[24]

Vesicle Shape [6]

Transmission Electron Microscopy (Tem) And Scanningelectronic Microscopy (Sem) Are Used To Characterize Thesurface Morphology Of The Ethosomal Vesicles. Prior To Analysis, Mount The Ethosomes Onto Double Sided Tape Thathas Previously Been Secured On Copper Stubs And Coatedwith Platinum, Then Analyzed At Different Magnifications.

Vesicle Size And Zeta Potential

Dynamic Light Scattering (Dls) Using A Computerizedinspection System And Photon Correlation Spectroscopy (Pcs)Are The Two Methods Used In Assessing The Particle Size Andzeta Potential Of Prepared Ethosomes.

Entrapment Efficiency [25]

Ultracentrifugation Is The Widely Used Technique To Measurethe Entrapment Efficiency Of Ethosomes. The Vesicles Areseparated In A High Speed Cooling Centrifuge At 20,000 Rpmfor 90 Minutes In The Temperature Maintained At 4°C.Separate The Sediment And Supernatant Liquids Determine Theamount Of Drug In The Sediment By Lysing The Vesicles Usingmethanol. From This, Determine The Entrapment Efficiency Bythe Following Equation,

Entrapment Efficiency = De⁄Dt X 100 Where,

De - Amount Of Drug In The Ethosomal Sediment

Dt - Theoretical Amount Of Drug Used To Prepare Theformulation (Equal To Amount Of Drug In Supernatant Liquidand In The Sediment)

Penetration And Permeation Studies [26]

Confocal Laser Scanning Microscopy (Clsm) Method Is Used To Determine The Depth Of Penetration From Ethosomes. The Ethosomes Shows Significantly Higher Skin Deposition Possibly Due To Combined Effect Of Ethanol And Phospholipid Thus Providing A Mode For Dermal And Transdermal Delivery.

Transition Temperature [25]

The Transition Temperature (T) Of Vesicular Lipids Is Measured In Duplicate By Dsc In An Aluminum Pan At A Heating Rate Of 10°C Per Min, Under A Constant Nitrogen Stream

Surface Tension Measurement [6]

Du Nouy Ring Tensiometer Is Used. Ring Method Is Used To Know The Surface Tension Activity Of Drug In Aqueous Solution.

Vesicle Stability [6]

The Ability Of Ethosomal Preparations To Retain The Drug (I.E.,Drug-Retentive Behavior) Can Be Checked By Keeping The Preparations At Different Temperatures, I.E., 25 ± 2°C (Room Temperature, Rt), 37 ± 2°C And 45 ± 2°C For Different Periods Of Time (1, 20, 40, 60, 80 And 120 Days). The Ethosomal Preparations Were Kept In Sealed Vials (10 Ml Capacity) After Flushing With Nitro-Gen. The Stability Ofethosomes Was Also Determined Quantitatively By Monitoring Size And Morphology Of The Vesicles Using Dls And Tem.

Drug Content [25]

Drug Can Be Quantified By A Modified High Performance Liquid Chromatographic Method.

Table 3: Characterization Of Ethosomes[6]

Sl. No.	Parameter	Importance	Method
1	Size And Shape	Determine Skin Penetration	Sem, Tem, Dls
2	Zeta Potential	Stability Of Vesicles	Zeta Meter
3	Entrapment Efficiency	Suitability Of Method	Ultracentrifugation
4	Drug Content	Important In Deciding The Amount Of Vesicle Preparationto 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 Rate Of Drug Transport Through Skin	Clsm

Therapeutic Applicationofethosomes[6, 28-38]

Ethosomes Can Be Used For Many Purposes In Drug Delivery.Ethosomes Are Mainly Used As Replacement Of Liposomes. Mainly The Transdermal Route Of Drug Delivery Is Preferred. Ethosomes Can Be Used For The Transdermal Delivery Of Hydrophilic And Impermeable Drugs Through The Skin. Various Drugs Have Been Used With Ethosomal Carrier (Table 2).

Marketed Productsofethosomes

In 2000, The Ethosomes Technology Began Tocommercialize. There Are Only Two Companies Which Developed Ethosome Products [27, 39](Table 4).

Table 4. Marketed Products Based On Ethosomal Drug Delivery System

Name Of Product	**Uses**	**Manufacturer**
Cellutight Ef	Topical Cellulite Cream, Contains A Powerful Combination Of Ingredients To Increase Metabolism And Break Down Fat	Hampden Health, Usa
Decorin Cream	Anti-Aging Cream, Treating, Repairing, And Delaying The Visible Aging Signs Of The Skin Including Wrinkle Lines, Sagging, Age Spots, Loss Of Elasticity, And Hyperpigmentation	Genome Cosmetics, Pennsylvania, Us
Nanominox	First Minoxidil Containing Product, Which Uses Ethosomes. Contains 4% Minoxidil, Well-Known Hair Growth Promoter That Must Be Metabolized By Sulfation To The Active Compound.	Sinere, Germany
Noicellex	Topical Anti-Cellulite Cream	Novel Therapeutic Technologies,Israel
Skin Genuity	Powerful Cellulite Buster, Reduces Orange Peel	Physonics, Nottingham, Uk
Supravir Cream	For The Treatment Of Herpes Virus, Formulation Of Acyclovir Drug Has A Long Shelf Life With No Stability Problems, Stable For At Least Three Years, At 25°C. Skinpermeation Experiments Showed That The Cream Retained Its Initial Penetration Enhancing Propertieseven After Three Years	Trima, Israel

VIII. CONCLUSION

Ethosome Are Superior By Offering Safety, Efficacy, Long Term Stability, Simplified Industrial Manufacture As Well As Better Patient Compliance. Thus, It Can Be A Logical Conclusion That Ethosomes Can Become A Promising Drug Carrier In Future For Not Only Topical Treatment Of Local And Systemic Disorders, But Also For The Cosmetic And Pharmaceutical Fields.

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