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Ethosomes: A Novel Vesicular Carrier for Topical Delivery of Drug

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ABSTRACT

Skin is the largest organ of body; it serves as route of drug administration for systemic effects. Ethosomes are mainly used to deliver a drug through transdermal route. They are lipid vesicular carriers composed of phospholipid, ethanol and water. Ethosomes are simple to prepare and easy to use. They are flexible, malleable vesicles designed to improve active agent delivery. Such nanoparticles are specifically developed for the efficient delivery of therapeutic agents in deep skin layers and through the skin with various physicochemical properties. In this article reviews various aspects of ethosomes including their advantages, disadvantages, ethosomal types, Mechanism of penetration, Method of preparation, evaluation and application of ethosomes, marketed formulations of ethosomes.

INTRODUCTION: [1,2]

The skin is the largest and most easily accessible organ of the body; it serves as a potential route of drug administration for systemic effects. The skin is an external multilayered organ that functions as a protective tissue and as a permeability barrier, preventing penetration of foreign molecules from the exterior environment. Represents the most resistant barrier to drug penetration through the skin, which restricts drug bioavailability in transdermal form.

Transdermal drug delivery system (TDDS) showed promising result in comparison to oral drug delivery system as it eliminates gastrointestinal interferences and first pass metabolism of the drug but the main drawback of TDDS is it encounters the barrier properties of the stratum corneum i.e. only the lipophilic drugs having molecular weight < 500 Dacan pass through it.

TDDS have been developed in order to enhance the driving force of drug diffusion or increase the permeability of the skin. These approaches include the use of penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles. 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 non-invasive procedure for drug delivery.

ETHOSOMES: [3,4,5]

Ethosomes (lipid vesicular carriers) were developed as novel lipid carriers, composed of phospholipids, ethanol, and water. These vesicular systems can be defined as the second generation of liposomes, characterized by greater malleability, stability and ability to trap hydrophilic and hydrophobic molecules. They possess attractive properties in terms of cost-effectiveness and ease of application.

Alcohol induces a mechanism in which it interacts with the polar region of the lipid molecules, resulting in a reduction of the melting point of the corneal layer lipids Ethanol is known as an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Its inclusion in liposomes to form ethosomes has already been investigated.

Ethosomes are mainly used for the delivery of drugs through transdermal route. The transdermal delivery is one of the most important routes of drug administration. The main factor which limits the application of transdermal route for drug delivery is the permeation of drugs through the skin. Human skin has selective permeability for drugs. Lipophilic drugs can pass through the skin but the drugs which are hydrophilic in nature can't pass through.

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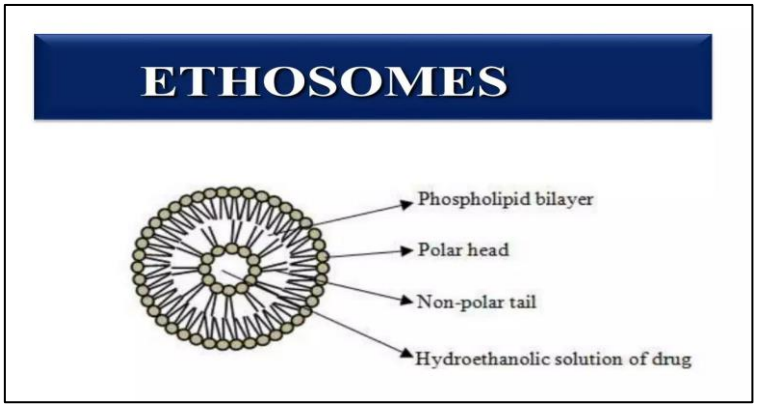

Water soluble drugs either show very less or no permeation. To improve the permeation of drugs through the skin various mechanisms have been investigated, including use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum barrier. Permeation enhancers increase the permeability of the skin, Transdermal drug delivery uses the skin as an alternative route for the delivery of systemically acting drugs.

This has the advantage that high concentrations of drugs can be localized at the site of action, reducing the systemic drug levels and therefore also reducing the systemic side effects. Transdermal delivery route includes several advantages compared with oral route. This route has advantages of avoidance of first pass metabolism, predictable and extended duration of activity, minimizing under able side effects, utility of short half- life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter and intra patient valuations, and most importantly, it provides patient compliance.

ETHOSOME COMPOSITION- I: [6]

Additives	Uses	Examples
Phospholipids	Vesicle forming component	Soya phosphatidyl Choline egg phosphatidylcholine Dipalmityl phosphatidyl choline, distearyl phosphatidyl choline
polyglycol	Skin penetration enhancer	Propylene glycol transcutol
Cholesterol	Stabilizer	Cholesterol
Alcohol	For providing the softness for vesicle membrane as a penetration enhancer	Ethanol isopropyl alcohol
Vehicle	As a gel former	Carbopol 934
Dye	For characterization study	6-carboxy fluorescence, rhodamine 123, rhodamine red, fluorescence

TYPES OF ETHOSOMAL SYSTEMS: [1,2]

1. Classical ethosomes:

Classical ethosomes are a modification of classical liposomes and are composed of phospholipids, a high concentration of ethanol up to 45% w/w, and water. Classical ethosomes were reported to be superior over classical liposomes for transdermal drug delivery because they were smaller and had negative ζ-potential and higher entrapment efficiency. Moreover, classical ethosomes showed better skin permeation and stability profiles compared to classical liposomes.

Binary ethosomes were developed by adding another type of alcohol to the classical ethosomes. The most commonly used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).

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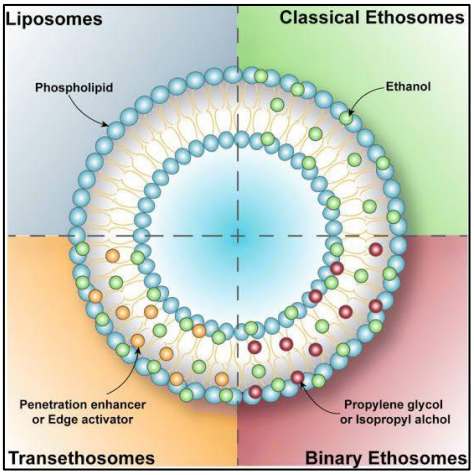

2. Transethosomes:

This ethosomal system contains the basic components of classical ethosomes and an additional compound, such as a penetration enhancer or an edge activator (surfactant) in their formula. These novel vesicles were developed in an attempt to combine the advantages of classical ethosomes and deformable liposomes (transferosomes') in one formula to produce Transethosomes.

3. Binary ethosomes:

Binary ethosomes were introduced by Zhou et al. We were created essentially by adding a different form of alcohol to the classical ethosomes. Propylene glycol and isopropyl alcohol are the most widely used ethosomes in binary alcohol.

ADVANTAGES: [1]

- Ethosome enhance permeation of drugs through skin for dermal, transdermal and intracellular delivery.
- Deliver various molecules with different physicochemical properties, hydrophilic and lipophilic molecules, peptides, proteins and other macromolecules.
- The components of the ethosomes are generally recognized as safe (GRAS), non-toxic and approved for pharmaceutical and cosmetic use.
- Low risk profile Ethosome structure has no large- scale drug development risk as the Ethosome feature toxicology profiles are well established in the scientific literature.
- The ethosomal system is passive and non-invasive, and is suitable for immediate marketing.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Biotechnology, Veterinary, Cosmetic & Nutraceutical fields.
- High patient compliance: The ethosomal drug is delivered in a semi-solid form (gel or cream) with high patient compliance ensuing.
- Simple method for drug delivery in comparison to Iontophoresis and sonophoresis and other complicated methods.
- Ease of industrial scale-up: Relatively simple to manufacture with no complicated technical investments required for production of ethosomes. Multiliter amounts can be conveniently prepared for ethosomal formulation.
- Ethosomes enhance permeation of drugs across/through the skin in an efficient manner, thereby enabling the drug to reach the desired site in the skin or to the blood.
- Higher entrapment efficiencies of drugs when compared to liposomes can be observed.
- Excellent stability over long periods can be observed.

- Alcohol in the ethosomes acts as natural preservative, and hence there is no necessity to add any other preservative.
- The cost of manufacturing ethosomes is very cheap.
- The transport of drugs across the skin is not concentration dependent.

DISADVANTAGES: [7]

- Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery.
- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
- Adhesive may not adhere well to all types of skin.
- May not be economical.
- Poor yield.
- Skin irritation or dermatitis due to 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 water.

LIMITATIONS: [8]

- Poor yield.
- In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
- Loss of product during transfer from organic to water media.

MECHANISM OF DRUG PENETRATION: [13]

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

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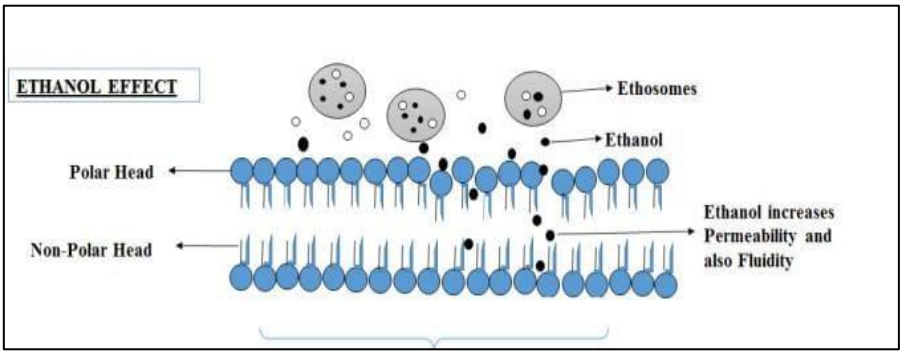
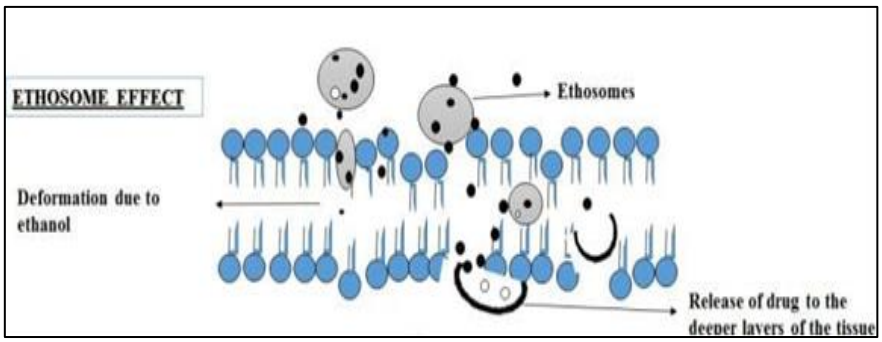
1. Ethanol effect:

Ethanol act as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intracellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.



2. Ethosomes effect:

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability.so the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.



METHODS OF PREPARATION: [12]

Ethosomes can be prepared and formulated by four methods. All methods are sound simple and convenient because no need of complex processes or sophisticated instruments.

1. Cold method:

This is the most common method utilized for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or another polyol is added during stirring. This mixture is heated to 300C in a water bath. The water heated to 300C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication 32 or extrusion 33 method. Finally, the formulation is stored under refrigeration.

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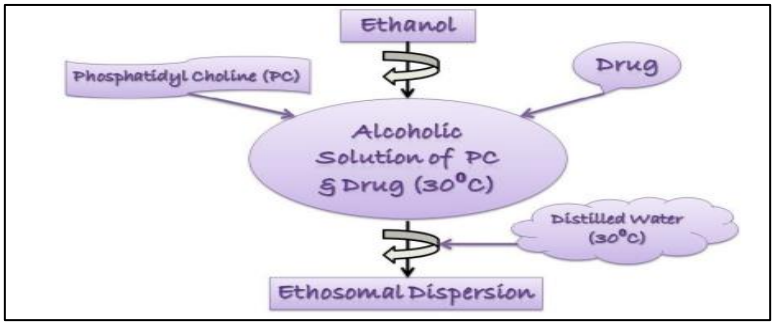
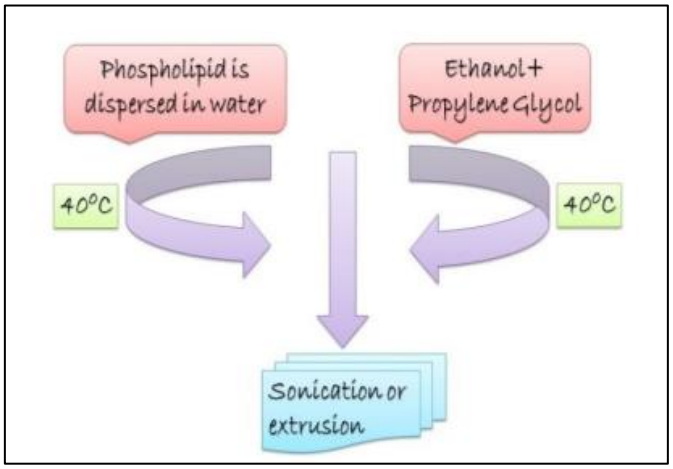


2. Hot method:

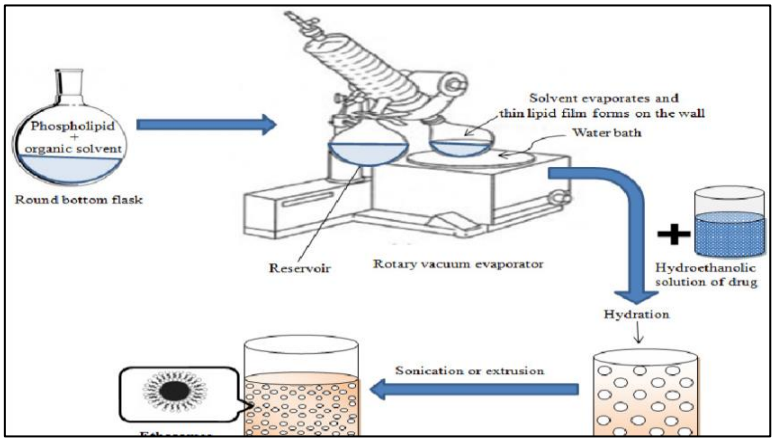
In this method phospholipid is dispersed in water by heating in a water bath at 400C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400C. Once both mixtures reach 400C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/hydrophobic properties.

The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.



3. Classical method:

Phospholipid and drug are dissolved in ethanol and heated to 30°C in a water bath. Double distilled water is added in a fine stream to the lipid mixture, with constant stirring at 700rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles 36.



4. Mechanical dispersion:

Soya phosphotidylcholine is dissolved in a mixture of chloroform: methanol in round bottom flask (RBF). The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form a thin lipid film on wall of the RBF. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the RBF at suitable temperature 36.

EVALUATION TESTS:[8]

1. Filter Membrane-Vesicle Interaction Study by Scanning Electron Microscopy:

Vesicle suspension (0.2 mL) was applied to filter membrane having a pore size of 50 nm and placed in diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in contact with PBS (phosphate buffer saline solution), (pH 6.5). The filters were removed after 1 hour and prepared for SEM studies by fixation at 4°C in Karnovsky's fixative overnight followed by dehydration with graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% vol/vol in water). Finally, filters were coated with gold and examined in SEM (Leica, Bensheim, Germany).

2. Skin Permeation Studies:

The hair of test animals (rats) was carefully trimmed short (<2 mm) with a pair of scissors, and the abdominal skin was separated from the underlying connective tissue with a scalpel. The excised skin was placed on aluminium foil, and the dermal side of the skin was gently teased off for any adhering fat and/or subcutaneous tissue. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm2 and 10 mL, respectively. The temperature was maintained at 32°C ± 1°C. The receptor compartment contained PBS (10 mL of pH 6.5). Excised skin was mounted between the donor and receptor compartment. Ethosomal formulation (1.0ml) was applied to the epidermal surface of the skin. Samples(0.5ml) were withdrawn to through the sampling port of the diffusion cell at 1-, 2-, 4-, 8-, 12-, 16-, 20-, & 24 hr time intervals & 24 hr time intervals & analysed by high performance liquid chromatography (HPLC) assay.

3. Stability Study:

Stability of the vesicles was determined by storing the vesicles at 4°C ± 0.5°C. Vesicle size, zeta potential, and entrapment efficiency of the vesicles was measured after 180 days using the method described earlier.

4. Vesicle-Skin Interaction Study by TEM and SEM:

From animals, ultrathin sections were cut (Ultracut, Vienna, Austria), collected on formvar-coated grids and examined under transmission electron microscope. For SEM analysis, the sections of skin after dehydration were mounted on stubs using an adhesive tape and were coated with gold palladium alloy using a fine coat ion sputter coater. The sections were examined under scanning electron microscope.

5. Vesicle-Skin Interaction Study by Fluorescence Microscopy:

Fluorescence microscopy was carried according to the protocol used for TEM and SEM study. Paraffin blocks are used, were made, 5-µm thick sections were cut using microtome (Erma optical works, Tokyo, Japan) and examined under a fluorescence micro cytotoxicity Assay MT-2 cells (T-lymphoid cell lines) were propagated in Dulbecco's modified Eagle medium (HIMEDIA, Mumbai, India) containing 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin and 2 mmol/L L-glutamine at 37°C under a 5% CO2 atmosphere. Cytotoxicity was expressed as the cytotoxic dose 50 (CD50) that induced a 50% reduction of absorbance at 540 nm.

6. Drug Uptake Studies:

The uptake of drug into MT-2 cells (1×106 cells/mL) was performed in 24-well plates (Corning Inc) in which 100 µL RPMI medium was added. Cells were incubated with 100 µL of the drug solution in PBS (pH 7.4), ethosomal formulation, or marketed formulation, and then drug uptake was determined by analyzing the drug content by HPLC assay.

7. HPLC Assay:

The amount of drug permeated in the receptor compartment during in vitro skin permeation experiments and in MT-2 cell was determined by HPLC assay using methanol: distilled-water: acetonitrile (70:20:10 vol/vol). mixture as mobile phase delivered at 1 mL/min by LC 10-AT VP pump (Shimadzu, Kyoto, Japan). A twenty - microliter injection was eluted in C-18 column (4.6×150 mm, Luna, 54, Shimadzu) at room temperature. The column eluent was monitored at 271 nm using SPDM10A VP diode array UV detector. The coefficient of variance (CV) for standard curve ranged from 1.0% to 2.3%, and the squared correlation coefficient was 0.9968.

8. Statistical Analysis:

Statistical significance of all the data generated was tested by employing ANOVA followed by studentized range test. A confidence limit of P <05 was fixed for interpretation of the results prism (GraphPad, Version 2.01, and San Diego, CA).

APPLICATIONS OF ETHOSOMES: [13,17,21]

1. Acne Treatment:

Ethosomal vesicles containing 2%w/w lecithin and 30%w/w ethanol were found to have shown the best entrapment percentage (99.21%). It was concluded that the ethosomal vesicles and enhancers increased the skin permeation and depot formation of drug in the skin.

2. Anti-Inflammatory:

Optimized ethosomes showed superior skin targeting both in vitro and in vivo. They also reported the reduction of cyclooxygenase 2 level in mouse skin inflammation inducted by ultraviolet B (UVB) light and represent a promising therapeutic approach for the treatment of UVB induced skin inflammation.

3. Anti Arthritis Drug Delivery:

Cannabidol (CBD) is a recently developed drug candidate for treating rheumatoid arthritis. CBD ethosomal formulation for transdermal delivery has been prepared by Lodzki et al. Results show considerably increase its skin penetration and hence its activity.

4. Bronchial Asthma, Chronic Bronchitis, and Emphysema:

The transdermal delivery of salbutamol sulfate (SS), from ethosomes and classic liposomes containing various cholesterol and dicetylphosphate concentrations. The entrapment efficiency percentage was significantly increased by increasing concentrations of ethanol, cholesterol and dicetylphosphate.

In vitro permeation studies of the prepared gels containing the selected vesicles showed that ethosomal systems were much more efficient at delivering SS into mice skin (in terms of quantity and depth) than were liposomes or aqueous or hydroalcoholic solutions.

5. Fungal Infections:

As a vesicular carrier system, ethosomes was found to have incredible capability of improving transdermal permeation of Ketoconazole. Ethosomes offers advantages of rapid onset and maximum release of drug with reduction of side effects. Furthermore, ethosomes do not damage the architecture of skin and so, drug is transported into the systemic circulation across undamaged skin. Ethosomal fluconazole gel formulation offers better remission from the disease and reduces the duration of therapy in treatment of candidiasis patients.

6. Anti-Parkinsonism Agent:

THP is a M1 muscarinic receptors antagonist and used in the treatment of Parkinson disease. The results showed better skin permeation potential of ethosomal-THP formulation and its use for better management of Parkinson disease.

7. For Menopausal Syndromes:

An interesting recent finding is that buspirone HCl (BH), an anxiolytic drug, could affect hot flashes, the most common menopausal syndrome in women. The pharmacodynamic effects of the transdermal ethosomal BH system in the treatment of menopausal syndromes were investigated in both hot flashes and anxiety animal models.

8. Analgesic and Antipyretic:

The analgesic effect of ethosomal ibuprofen gel was compared to oral treatment by tail flick test in mice. A statistically significant higher effect was obtained for the ethosomal ibuprofen system 120 and 360 min after administration.

MARKETED PRODUCTS OF ETHOSOMES: [12]

Marketed Product	Uses	Manufacturer
Decorin cream	Antiaging cream treating, repairing the visible aging signs of the skin including wrinkles lines, sagging, age, spots, loss of elasticity and hyper pigmentation.	Genome Cosmetics, Pennsylvania, US
Supravir cream	For the treatment of herpes virus.	Trima, Israel
Noicellex	Topical anti-cellulite cream.	Novel therapeutic technologies, Israel
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
Cellutight EF	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and breakdown fat.	Hampden Health, USA
Skin Genuity	Powerful cellulite buster reduces orange peel.	Physonics Nottingham, UK
Body Shape	Gell executive solidification cellulite education, stretching the skin flexible and based on a technology called ethosomes.	Maccabi CARE

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Conflict of Interest Statement: All authors have nothing else to disclose.