Saletsky, Laser Phys. 2011, 21: 239-244). Denaturation, as a rule, is accompanied by the loss of functional properties of the protein.

Due to all the above mentioned reasons, it is still of interest to achieve new release systems of EGF, easy to standardize, with high homogeneity at the structural level and in its physico-chemical properties, that improve the pharmaceutical and pharmacological properties and/or increase the therapeutic activity of EGF.

Brief description of the invention

The present invention relates to vesicles, as drug delivery system, which comprise EGF, a cationic surfactant and cholesterol or one of its derivatives and have greater therapeutic effectiveness than those previously described.

The present invention also relates to a process for the preparation of said vesicles comprising EGF, a cationic surfactant and cholesterol or derivatives thereof, that includes: a) preparation of an aqueous solution of EGF and a cationic surfactant, b) the dissolution of cholesterol or one of its derivatives in an organic solvent expanded with a CF, c) the synthesis of the vesicles by depressurization of the solution resulting from stage b) on the solution resulting from stage a).

A pharmaceutical composition characterized by comprising vesicles that include EGF, a cationic surfactant and cholesterol, or derivatives thereof, and at least one pharmaceutically acceptable excipient is also an object of the invention. Another object of the invention is the use of said vesicles for the manufacture of medicaments and cosmetics.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating complex wounds of peripheral soft tissues.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating a diabetic foot ulcer.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating a venous ulcer, a decubitus ulcer or a burn.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating adult respiratory distress.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating digestive tract lesions.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating mucositis, ulcerative colitis, duodenal ulcers or distal colitis.

The present invention also relates to the use of vesicles as described herein for the manufacture of a medicament for treating eye lesions.

The pharmaceutical compositions of this ~~invention~~disclosure, which contain EGF vesicles with other components, are useful as drugs to accelerate the healing process of diabetic foot ulcers and other complex wounds, such as: venous ulcers, decubitus ulcers, burns, among others; to repair the anterior chamber structures in damaged eyes, in systemic mucositis and in all the diseases of the gastrointestinal tract that involve the need to regenerate mucosa and submucosa. In particular, it has been found that these vesicles have significantly greater therapeutic effectiveness for healing diabetic foot ulcers and venous ulcers than those described in the prior art.

The invention also relates to a cosmetic product characterized by comprising vesicles of EGF, a cationic surfactant and cholesterol or derivatives thereof.

CLAIMS

VESICLES COMPRISING EPIDERMAL GROWTH FACTOR AND COMPOSITIONS THEREOF

1. Vesicles comprising epidermal growth factor (EGF), a cationic surfactant and cholesterol or derivatives thereof.
2. The vesicles of claim 1, wherein the cationic surfactant is of quaternary ammonium type.
3. The vesicles of claim 2, wherein the cationic surfactant of quaternary ammonium type is a surfactant selected from the group consisting of cetyltrimethylammonium bromide (CTAB), cetrimide and benzalkonium chloride (BKC).
4. The vesicles of claims 1-3, wherein the molar ratio between the cationic surfactant and cholesterol, or derivatives thereof, is in the range of 10 M:1 M to 1 M:5 M, and the molar ratio between EGF and cholesterol, or derivatives thereof, is in the range of 0.5 μM:1 M to 100 μM:1 M.
5. The vesicles of claims 1-4, which are characterized by having unilamellar structure and an approximate mean size between 25 and 500 nm, preferably between 50 and 300 nm.
6. The vesicles of claims 1-5, wherein the EGF is incorporated into the vesicle bilayer.
7. The vesicles of claims 1-6, which are obtained by the compressed fluid (CF) technology.
8. The vesicles of claim 7, wherein the CF technology includes a process comprising:
    a) the preparation of an aqueous solution of EGF and a cationic surfactant,
    b) the dissolution of cholesterol, or derivatives thereof, in an organic solvent expanded with a CF,
    c) the synthesis of the vesicles by depressurization of the solution resulting from stage b) on the solution resulting from stage a).
9. The vesicle of claim 8, wherein the cationic surfactant is of quaternary ammonium type.

10. Process for the preparation of vesicles comprising EGF, a cationic surfactant and cholesterol, or derivatives thereof, characterized by comprising:
    a) the preparation of an aqueous solution of EGF and a cationic surfactant,
    b) the dissolution of cholesterol or derivatives thereof in an organic solvent expanded with a CF,
    c) the synthesis of the vesicles by depressurization of the solution resulting from stage b) on the solution resulting from stage a).
11. The process of claim 10, wherein the cationic surfactant is of quaternary ammonium type.
12. The process of claim 10, wherein the organic solvent of stage b) is a solvent selected from the group consisting of monohydric alcohols, polyhydric alcohols, ketones, ethylene diamine, acetonitrile, ethyl acetate and mixtures thereof.
13. The process of claim 10, wherein the CF is a compound selected among carbon dioxide, ethane, propane, hydrochlorofluorocarbons, and hydrofluorocarbons.
14. The process of claims 10-13, wherein the ratio between the quantity of CF and organic solvent corresponds to an approximate molar fraction of CF of 0.3 to 0.95, preferably 0.5 to 0.8.
15. The process of claims 10-13, wherein the dissolution of cholesterol, or derivatives thereof, in a CF is carried out in a reactor at an approximate pressure of 1 to 30 MPa and an approximate temperature of about 10 to 70 °C, preferably between 10 and 50 °C.
16. The process of claims 10 to 15, wherein the EGF is dissolved in an aqueous solution containing a cationic surfactant with a concentration above its critical micellar concentration.
17. Pharmaceutical composition comprising the vesicles of any of claims 1-9, and at least one pharmaceutically acceptable excipient.
18. The composition of claim 17, which can be administered by systemic, intralesional, mucosal, topical, transdermal, ophthalmic routes or as an inhaled formulation.
19. The use of vesicles of any of claims 1-9 for the manufacture of a medicament.

20. The use of claim 19, wherein the medicament is used to treat complex wounds of peripheral soft tissues.
21. The use of claim 20, wherein the complex wound is a diabetic foot ulcer.
22. The use of claim 20, wherein the complex wound is a venous ulcer, a decubitus ulcer or a burn.
23. The use of claim 19, wherein the medicament is used for the treatment of adult respiratory distress.
24. The use of claim 19, wherein the medicament is used for the treatment of digestive tract lesions.
25. The use of claim 24, wherein the medicament is used for the treatment of mucositis, ulcerative colitis, duodenal ulcers or distal colitis.
26. The use of claim 19, wherein the medicament is used for the treatment of eye lesions.
27. Cosmetic product comprising vesicles of any of claims 1-9, and at least one excipient.
28. The use of the vesicles of any of claims 1-9 for the manufacture of a cosmetic product.
29. The use of claim 28, wherein the cosmetic product is a product to prevent senescence and aging of the skin.

CLAIMS

VESICLES COMPRISING EPIDERMAL GROWTH FACTOR AND COMPOSITIONS THEREOF

1. Vesicles comprising epidermal growth factor (EGF), a cationic surfactant and cholesterol or derivatives thereof.
2. The vesicles of claim 1, wherein the cationic surfactant is of quaternary ammonium type.
3. The vesicles of claim 2, wherein the cationic surfactant of quaternary ammonium type is a surfactant selected from the group consisting of cetyltrimethylammonium bromide (CTAB), cetrimide and benzalkonium chloride (BKC).
4. The vesicles of claims 1-3, wherein the molar ratio between the cationic surfactant and cholesterol, or derivatives thereof, is in the range of 10 M:1 M to 1 M:5 M, and the molar ratio between EGF and cholesterol, or derivatives thereof, is in the range of 0.5 μM:1 M to 100 μM:1 M.
5. The vesicles of claims 1-4, which are characterized by having unilamellar structure and an approximate mean size between 25 and 500 nm, preferably between 50 and 300 nm.
6. The vesicles of claims 1-5, wherein the EGF is incorporated into the vesicle bilayer.
7. The vesicles of claims 1-6, which are obtained by the compressed fluid (CF) technology.
8. The vesicles of claim 7, wherein the CF technology includes a process comprising:
    a) the preparation of an aqueous solution of EGF and a cationic surfactant,
    b) the dissolution of cholesterol, or derivatives thereof, in an organic solvent expanded with a CF,
    c) the synthesis of the vesicles by depressurization of the solution resulting from stage b) on the solution resulting from stage a).
9. The vesicle of claim 8, wherein the cationic surfactant is of quaternary ammonium type.

10. Process for the preparation of vesicles comprising EGF, a cationic surfactant and cholesterol, or derivatives thereof, characterized by comprising:
    a) the preparation of an aqueous solution of EGF and a cationic surfactant,
    b) the dissolution of cholesterol or derivatives thereof in an organic solvent expanded with a CF,
    c) the synthesis of the vesicles by depressurization of the solution resulting from stage b) on the solution resulting from stage a).
11. The process of claim 10, wherein the cationic surfactant is of quaternary ammonium type.
12. The process of claim 10, wherein the organic solvent of stage b) is a solvent selected from the group consisting of monohydric alcohols, polyhydric alcohols, ketones, ethylene diamine, acetonitrile, ethyl acetate and mixtures thereof.
13. The process of claim 10, wherein the CF is a compound selected among carbon dioxide, ethane, propane, hydrochlorofluorocarbons, and hydrofluorocarbons.
14. The process of claims 10-13, wherein the ratio between the quantity of CF and organic solvent corresponds to an approximate molar fraction of CF of 0.3 to 0.95, preferably 0.5 to 0.8.
15. The process of claims 10-13, wherein the dissolution of cholesterol, or derivatives thereof, in a CF is carried out in a reactor at an approximate pressure of 1 to 30 MPa and an approximate temperature of about 10 to 70 °C, preferably between 10 and 50 °C.
16. The process of claims 10 to 15, wherein the EGF is dissolved in an aqueous solution containing a cationic surfactant with a concentration above its critical micellar concentration.
17. Pharmaceutical composition comprising the vesicles of any of claims 1-9, and at least one pharmaceutically acceptable excipient.
18. The composition of claim 17, which can be administered by systemic, intralesional, mucosal, topical, transdermal, ophthalmic routes or as an inhaled formulation.
19. The use of vesicles of any of claims 1-9 for the manufacture of a medicament

for treating complex wounds of peripheral soft tissues.

20. The use of vesicles of any of claims 1-9 for the manufacture of a medicament for treating a diabetic foot ulcer.

21. The use of vesicles of any of claims 1-9 for the manufacture of a medicament for treating a venous ulcer, a decubitus ulcer or a burn.

22. The use of vesicles of any of claims 1-9 for the manufacture of a medicament for treating adult respiratory distress.

23. The use of vesicles of any of claims 1-9 for the manufacture of a medicament for treating digestive tract lesions.

24. The use of vesicles of any of claims 1-9 for the manufacture of a medicament for treating mucositis, ulcerative colitis, duodenal ulcers or distal colitis.

25. The use of vesicles of any of claims 1-9 for the manufacture of a medicament for treating eye lesions.

26. Cosmetic product comprising vesicles of any of claims 1-9, and at least one excipient.

27. The use of the vesicles of any of claims 1-9 for the manufacture of a cosmetic product.

28. The use of claim 27, wherein the cosmetic product is a product to prevent senescence and aging of the skin.