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(54) Title: MULTILAYER PATCH FOR POSTOPERATIVE DRUG ADMINISTRATION

(57) Abstract: The present invention relates to the field of drug administration, in particular the field of in situ postoperative drug administration. Among the many options available to fight cancer, tumor ablation can be one of the most effective one, depending on the case and on the cancer type. However, there are some cases wherein the residual tumoral cells left after the ablation can seed the propagation of a new tumor afterward. The invention provides a way to address this problem and relates to a multilayer patch comprising: - A biocompatible carrier layer, - A first polymeric layer comprising a first drug, and - A second polymeric layer comprising a second drug, wherein the first drug is different from the second drug. Particularly, the inventors tested the invention in case of pancreas cancers whence it proved especially useful.



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MULTILAYER PATCH FOR POSTOPERATIVE DRUG ADMINISTRATION

The present invention relates to the field of drug administration, in particular the field of *in situ* postoperative drug administration.

5 Among the many options available to fight cancer, tumor ablation can be one of the most effective one, depending on the case and on the cancer type.

However, there are some cases wherein the residual tumoral cells left after the ablation can seed the propagation of a new tumor afterward. Such issues are especially dramatic in case of pancreas cancers.

10 Being able of treating the aforesaid residual tumoral cells is therefore of utmost importance.

Typically, it is known to apply a sponge impregnated with anti-cancerous drug upon the ablated zone.

15 However, such device can only be used so as to apply drugs for a short amount of time after the operation. It cannot be set up *in situ* and left inside the body so as to apply a continuous release of anti-cancerous drug on the ablated zone.

Furthermore, a given sponge can administrate only one drug, whereas the treatment of a tumor is more efficient when combining the effects of several drugs.

20 Thus, there is a need for a local post-surgery treatment which can be applied *in situ*.

An object of the invention is therefore to provide a biocompatible patch which can be applied and fixed upon a zone to be treated after a surgery, typically an ablated zone, so as to release medications consisting in several drugs, preferably tailored to the tumor which is to be treated with the patch.

25 For this purpose, it is provided a multilayer patch for therapeutic use, comprising:

- A biocompatible carrier layer,

- A first polymeric layer comprising a first drug, and
- A second polymeric layer comprising a second drug, wherein the first drug is different from the second drug.

5 The multilayer patch according to the present invention can be manufactured on demand on a patient per patient basis so as to provide a tailored treatment, opening the way for personalized medicine.

10 The drugs contained on the multilayer patch can diffuse over a few millimeters in the tissues on which the patch is applied and treat the corresponding zone. Using a local treatment allows for high concentration of drugs and corresponding greater efficiency of the treatment. Such high concentrations cannot be used when the drugs are administrated through the general circulation. Indeed, in conventional practices, drug is systematically injected intravenously and then by binding to cytoskeleton, DNA strains, or other drug targets it results in the formation of various defects in DNA molecules, forcing the cell to undergo apoptotic death path.

15 Because of the nonselective treatment of normal and cancer cells, the conventional treatments lead to many secondary effects and force to dose limitation and decrease in efficiency.

20 The multilayer patch according to the present invention allows circumventing this issue.

The multilayer patch is particularly suited for all post-surgery residual tumor treatment consecutive to pelvis surgery and abdomen surgery, particularly in case of liver or pancreas cancer.

25 In order to achieve a given physico-chemical property, depending on the treatment to be applied, at least one layer of the multilayer patch according to the present invention may be tailored by undergoing processes selected from grafting and copolymerization.

The biocompatible carrier layer serves both as a mean for facilitating the acceptance of the patch in the body, as a mean for controlling the release rate of

the drugs – the thicker the carrier layer, the slower the release – and as a mean for controlling the adherence of the patch.

As such, the biocompatible carrier layer is preferably auto-adhesive. It can be provided together with a protection layer which is to be removed before used. If
5 the biocompatible carrier layer is not auto-adhesive, it can be attached to the desired zone with any suitable means such as suture points.

The multilayer patch can be coupled with 3D impression processes with e.g. PLA or other nontoxic mono/polymers so as to better correspond to the shape of the zone to be treated.

10 Preferably, the biocompatible carrier layer is designed so as to be easily distinguished over the other side of the patch. Such distinction can take the form of a printing, of a different color, of a different texture, or any other suitable means.

The biocompatible carrier layer is preferably a medium which is permeable to
15 the drugs and which allows their diffusions there through.

A preferred material for the biocompatible carrier layer is collagen, fibrin or any commercial biocompatible substrates such as Steralloy films (HAPCO), a bi-component commercial elastomer or even biocompatible PU.

. Indeed, collagen membranes are widely used in post-surgery treatments to
20 provide isolation of operated zone, preventing adhesion of internal organs and scar tissue and intended to promote tissue regeneration. Such membranes thus represent an excellent base for drug delivery systems.

The biocompatible carrier layer preferably has a thickness comprised between 1 and 3 mm. The thickness of the biocompatible carrier layer is chosen based on
25 the drugs to be delivered and on the desired release rate of the drug. The aforementioned values are typical thicknesses which correspond to suitable release rates of typical

Each polymeric layer can be a single sort of polymer chosen e.g. from biocompatible polymers such as PEG or PCL. Alternatively, each polymeric
30 layer can be in a mixture of polymers chosen from eg copolymers PCL-PEG.

Each polymeric layer can also comprise non-polymeric material, as long as the layer contains a majority of polymers. The polymeric layer preferably consists only of biodegradable materials. Each layer can also comprise sublayers, each sublayer presenting its own composition. Typically, the drugs contained in the polymeric layers can be sandwiched between two sublayers.

Every polymeric layer can be identical to the others or, alternatively, some layer can be different than the other layers both in terms of thickness and in terms of composition.

The first polymeric layer preferably has a thickness comprised between 100 nm and 1000 nm. The drugs contained in other polymeric layers, e.g. in the second polymeric layer, will diffuse through the first polymeric layer toward the biocompatible carrier layer and the tissues to be treated. Therefore, the thickness of the polymeric layer is to be chosen depending on the drugs contained in the multilayer patch according to the present invention, depending on the desired release rates, the material of the layer and on the thickness of the biocompatible carrier layer. The aforementioned values are preferred values between which the thickness of the layer can be chosen.

The second polymeric layer preferably has a thickness comprised between 70 and 500 nm. In case there are more than two polymeric layers, the drugs contained in other polymeric layers, will diffuse through the first polymeric layer toward the first polymeric layer, the biocompatible carrier layer and the tissues to be treated. Therefore, the thickness of the polymeric layer is to be chosen depending on the drugs contained in the multilayer patch according to the present invention, depending on the desired release rates, the material of the layer and on the thickness of the biocompatible carrier layer and of the first polymeric layer. The aforementioned values are preferred values between which the thickness of the layer can be chosen.

The first drug and/or the second drug preferably comprises an antibody. As a matter of fact, since the multilayer patch allows for personalized treatment, it is especially suited for immunotherapy. The antibody can be chosen depending on the patient and the cancer type. The combination of the multilayer patch

according to the present invention with antibodies or with any kind of immunotherapy is a particularly advantageous embodiment of the present invention.

5 The first drug and/or the second drug is preferably an anti-cancer drug, more preferably an anti-cancer drug selected from personalized medication.

In a preferred embodiment, the first drug and/or the second drug can also comprise a platinum salt or carboplatin. As a matter of fact, platinum salt is particularly suited for treating cancer, especially pancreas cancers.

10 Of course, any other drug or medication suitable for the particular treatment of the patient and compatible with the multilayer patch would be acceptable.

The multilayer patch according to the present invention can further comprise at least one additional polymeric layer comprising at least one additional drug. Said additional layers and drugs can be identical or different than the other polymeric layers and drugs. Some polymeric layers can also comprise no drug
15 e.g. so as to serve only as a retardant for the drugs comprised in a more external layer. A patch with several layers comprising the same drug can have an interest so as to administrate a drug several times or over a longer period of time. Indeed, chemotherapies are efficient only when cells are in a proliferation phase. Therefore, it is important to repeat the treatment, which can be achieved by a
20 patch comprising several layers with the same drugs. There is also an interest in a multilayer patch comprising different drugs, in order to administrate a complex treatment consisting of several drugs or medications.

At least one drug can be trapped between two polymeric layers. Although there are several suitable ways to imprison a drug into a polymeric layer, such as
25 impregnation, trapping a drug between two polymeric layers provides an easy to manufacture, efficient, patch.

The multilayer patch according to the present invention can further comprise a layer of PEG (Polyethylene glycol), preferably a layer of PEG which molecular weight is below 20,000 g/mol PEG can act as a good diffusion retardant if need
30 be, as an external layer, or as a buffer layer.

The multilayer patch according to the present invention can further comprise a layer of PEG (Polyethylene glycol), preferably a less crosslinked layer and with retention of the EG moieties whose molecular weight is less than 1000amu determined by MALDI-ToF. Such layers present cell non-adhesive properties which avoid the adhesion of cells on the external layer of the DDS.

The polymeric layers are preferably made of Diethylene glycol dimethyl ether, PEG, ϵ -caprolactone, poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) and other nontoxic mono/polymers.

The patch according to the present invention is preferably for use in a medicament.

The patch according to the present invention is preferably for use in a method for a treatment of a patient suffering of cancer, preferably solid cancer, more preferably pancreas or liver cancer.

The present invention also relates to a manufacturing process of a multilayer patch according to the present invention comprising the step of depositing a polymeric layer under plasma.

The plasma used in the manufacturing method according to the present invention is preferably cold plasma. By cold plasma, it is meant that the gas temperature is very low, e.g. ambient temperature whereas the electron temperature is very high. It is sometimes referred to as non-equilibrium plasma. In such plasmas reactive species are created which will fragment the monomer to create radicals which recombine to give polymer layers in the gas phase or on the surface. Such plasmas include low pressure inductively coupled plasma (ICP) reactor, and atmospheric pressure plasma. ...

Another object of the present invention is a multilayer patch for therapeutic use according to the present invention comprising a treatment to treat a pathology of a patient, said multilayer patch being applied on a tumor or an ablated area resulting from an operation of the patient so as to ablate at least part of a tumor.

Preferably, said pathology of a patient is a tumor which has been previously analyzed, and the treatment to treat said pathology has been selected so as to treat this specific tumor through

Another object of the present invention is a method of treatment comprising the steps of:

- providing a multilayer patch according to the present invention wherein said multilayer patch comprises a treatment having previously been customized to treat a pathology of a patient;
- operating said patient so as to ablate at least part of a tumor, thereby generating an ablated area;
- applying said multilayer patch on said ablated area.

The invention can be better understood at the reading of the detailed examples below, which constitute non-limitative embodiments of the present invention and at the examining of the annexed drawing, on which:

- figure 1a is a schematic representation of a Low pressure inductively coupled plasma (ICP) reactor;
- figure 1b is a schematic representation of Polymers formation from Polycaprolactone PCL and Polyethylen glycol PEG via plasma radio pulses;
- figure 2 is a SEM image of multilayer barrier film; and
- figure 3 is a series of SEM images of multilayer patches according to the present invention.

An exemplary embodiment of a multilayer patch according to the present invention has been realized in the form of multilayer polymer layers with thicknesses ranging from a few nm to a few hundreds of nm.. These multi-layers were loaded with drug, in case of this exemplary embodiment, carboplatin, and ported on collagen biodegradable membranes. The drug-loaded films were implanted in vivo in BALB/C mice model having already developed colon cancer. Scanning Electron Microscopy SEM-FEG, Energy-dispersive X-ray spectroscopy, histology and cell

death detection were applied on produced tumors and implanted films to check their efficiency.

The multilayer patches according to the present invention were prepared as follows. Diethylene glycol dimethyl ether (diglyme, 134.17 g/Mol, C₆H₁₄O₃, Sigma-Aldrich) and ϵ -caprolactone were used as the precursor materials and delivered into a low pressure inductively coupled plasma (ICP) reactor schematically illustrated in Figure 1a, through bubbling in argon gas. Operating pressure was set at 50 Pascals (375 mTorr) and controlled through adjusting argon gas flow rate and gate valve of turbomolecular pump. Power supply was controlled and programmed to deposit sequence of layers with varying density and thicknesses, so as to allow automating multi-step deposition procedures to deposit composite films with different deposition parameters and fabricate films with alternating or gradually changing density, chemical composition and mechanical properties.

Two polymers were used to deposit these layers, Polycaprolactone (PCL) and Polyethylen glycol (PEG) (Figure 1b). Carboplatin, oxaloplatin drugs, Iron beads and M2yn were used to make films with mono- or multi-layers: 300 μ g of carbopaltin and, cis-Platin? oxaloplatin, X μ l of Iron beats and 30 μ l of M2yn were deposited for drug loaded film respectively.

Collagen films without drug, which were considered as control films, and carboplatin loaded films were incubated in the culture medium for different amounts of time: 4h, 24h, 72h, 120h, 168h at 37°C, with 5% CO₂ and over 80% humidity.

The films and the media were then submitted to Energy-dispersive X-ray spectroscopy and ICP-MS (Inductively Coupled Plasma Mass Spectrometry, Elan DRCe, Perkin Elmer®) so as to measure carboplatin liberation.

The obtained DDS(Drug Delivery System) films have a thickness comprised between 10 and 2000 nanometer.

The obtained layers were deposited on 100 μ m of collagen as illustrated on Figure 31, 300 μ g of carboplatin per square centimeter were deposited over a first

plasma polymerized layer, i.e. a first polymeric layer, which allowed isolating the drug from reaching the collagen substrate and thus acted as a barrier film layer. Another barrier film layer was deposited to encapsulate the drug inside the two layers. Figure 3c is a scanning electronic microscopy(SEM-FEG) image of carboplatin deposited over the barrier film. Fig 3d 3c is a scanning electronical microscopy image of the obtained sandwich structure.

Figures 3e and 3f show similar structures with, respectively, oxaloplatin and M2yn (a natural extract) instead of carboplatin.

Figures 3g and 3h represent multilayers structures. On Figure 3h, three layers can be identified. One of these layers contains oxaloplatin whilst another one contains carboplatin.

Figure 3i shows a multilayer structure according to the invention wherein a protection layer has been deposited on its most external part: a nano barrier film deposition of 290 nm has been highlighted.

About 10^5 of colon cancer cell line CT26 were injected to the inguinal lymph node of 24 BALB/C mice. After two to three weeks, once the tumor reached a 0.3 to 0.5 mm size, either a control or a drug loaded multilayer patch was implanted.

After developing the tumor, mice were anesthetized with 2% isoflurane. Skin was opened around 2cm where the tumor is developed. The implants of collagen (1 x 0.5 cm) were deposited on the tumor and skin closed via stitching.

After 10 days of implantation, mice were anesthetized again for collecting the samples. The sizes of the tumors were measured so as to assess the efficiency of the treatment. Tumors and films were recuperated after marketing the contact side of the tumor with the film. Each tumor was divided into three parts, one for histological analysis, one for immunofluorescence study and one for checking the presence of carboplatin in the tumor after film implantation.

The tumors which had been applied a control patch showed a +3.78 increase in size whereas the tumors which had been applied a drug loaded multilayer patch

only showed a +1.9 increase in size, thus effectively proving the technical advantage of the multilayer patch according to the present invention.

It is understood that the described embodiments are not restrictive and that
5 it is possible to make improvements to the invention without leaving the framework thereof.

Thus, we can for example provide protocols of treatment according other pathology such as immunotherapy (ex: psoriasis) or anti-hypertrophic scars drugs (ex: keloid scar) as well as for local cancer (ex: melanoma, skin cancer).,without
10 departing from the scope of the present invention.

Unless otherwise specified, the word “or” is equivalent to “and/or”. Similarly, the word 'one' is equivalent to 'at least one' unless the contrary is specified. Unless otherwise specified, all percentages are weight percentages.

CLAIMS

1. Multilayer patch comprising:

- A biocompatible carrier layer,
- A first polymeric layer comprising a first drug, and
- 5 - A second polymeric layer comprising a second drug, wherein the first drug is different from the second drug

2. Multilayer patch according to claim 1, wherein the biocompatible carrier layer has a thickness comprised between 1 and 3 mm.

10 3. Multilayer patch according to any of the preceding claims, wherein the first polymeric layer has a thickness comprised between 100 and 1000 nm

4. Multilayer patch according to any of the preceding claims, wherein the second polymeric layer has a thickness comprised between 75 and 1000 nm.

5. Multilayer patch according to any of the preceding claims, wherein the first drug and/or the second drug comprises an antibody.

15 6. Multilayer patch according to any of the preceding claims, wherein the first drug and/or the second drug comprises a platinum salt.

7. Multilayer patch according to any of the preceding claims, further comprising at least one additional polymeric layer comprising at least one additional drug.

20 8. Multilayer patch according to any of the preceding claims, wherein at least one drug is trapped between two polymeric layers.

9. Multilayer patch according to any of the preceding claims, further comprising a layer of PEG, preferably a layer of PEG which molecular weight is below 20,000 g/mol.

25 10. Multilayer patch according to any of the preceding claims, wherein the polymeric layers are made of Diethylene glycol dimethyl ether, PEG, ϵ -caprolactone, poly (lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) and other nontoxic mono/polymers.

11. Multilayer patch according to any of the preceding claims, wherein the biocompatible carrier layer comprises collagen.

12. Multilayer patch according to any of the preceding claims, for use in a method for a treatment of a patient suffering of cancer, preferably solid cancer,
5 more preferably pancreas or liver cancer.

13. Manufacturing process of a multilayer patch comprising the step of depositing a polymeric layer under plasma.

14. Manufacturing process according to the preceding claim, wherein the plasma is cold plasma.

10 15. Multilayer patch for therapeutic use comprising a treatment to treat a pathology of a patient, said multilayer patch being applied on a tumor or an ablated area resulting from an operation of the patient so as to ablate at least part of a tumor.

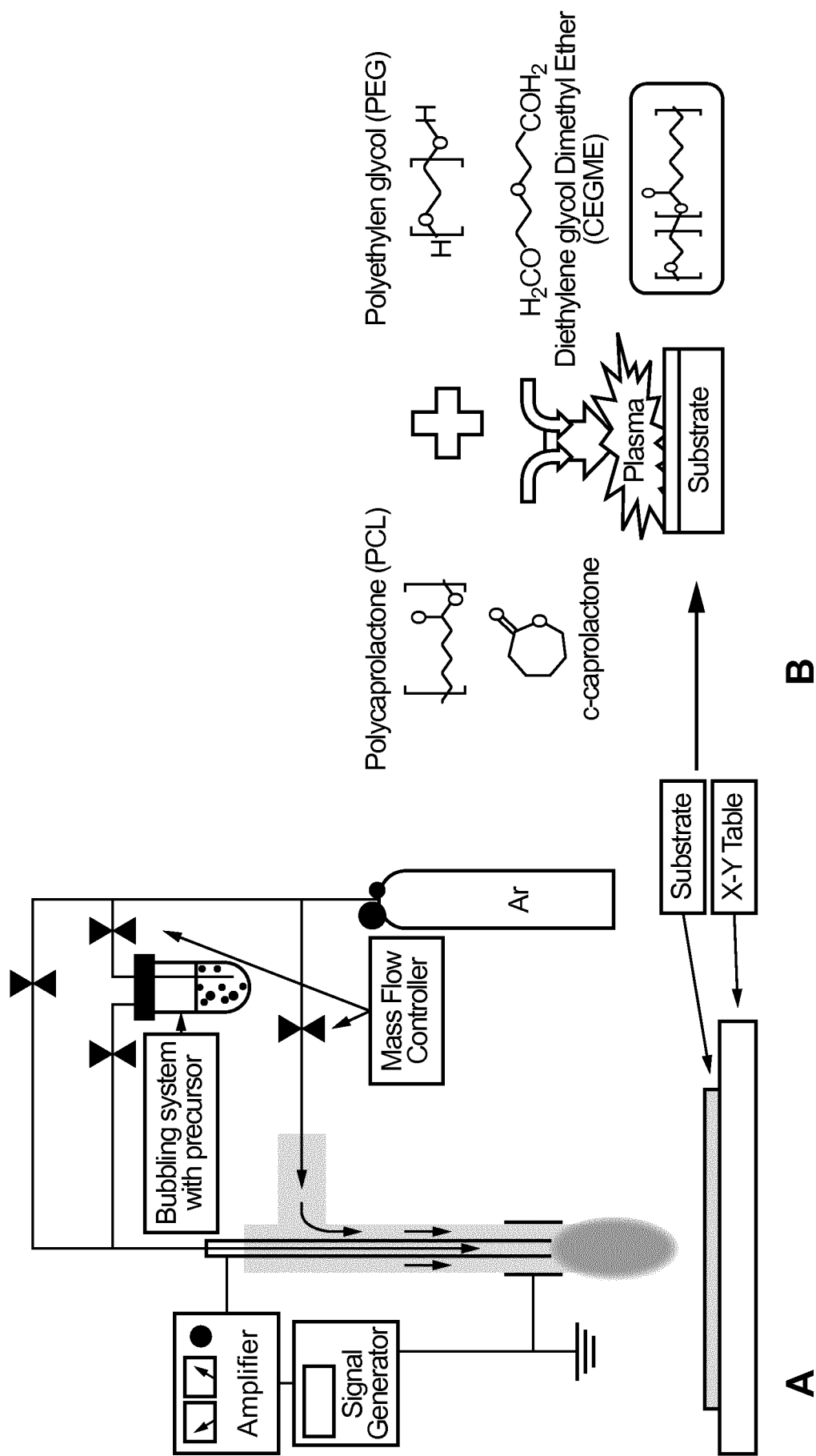
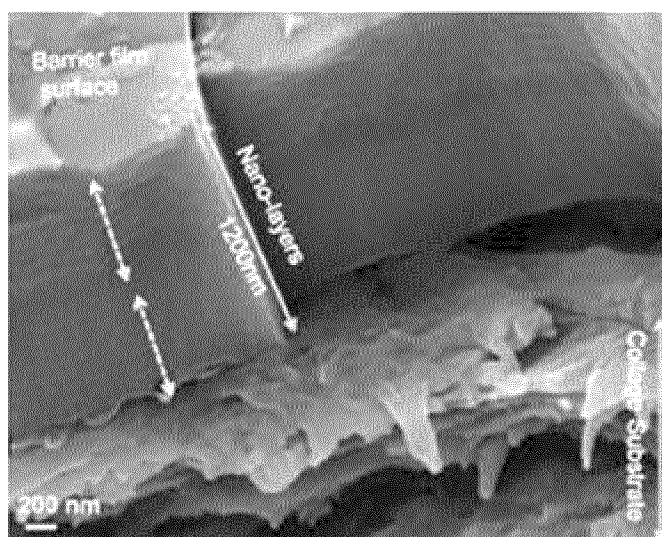


FIG. 1

**FIG. 2**

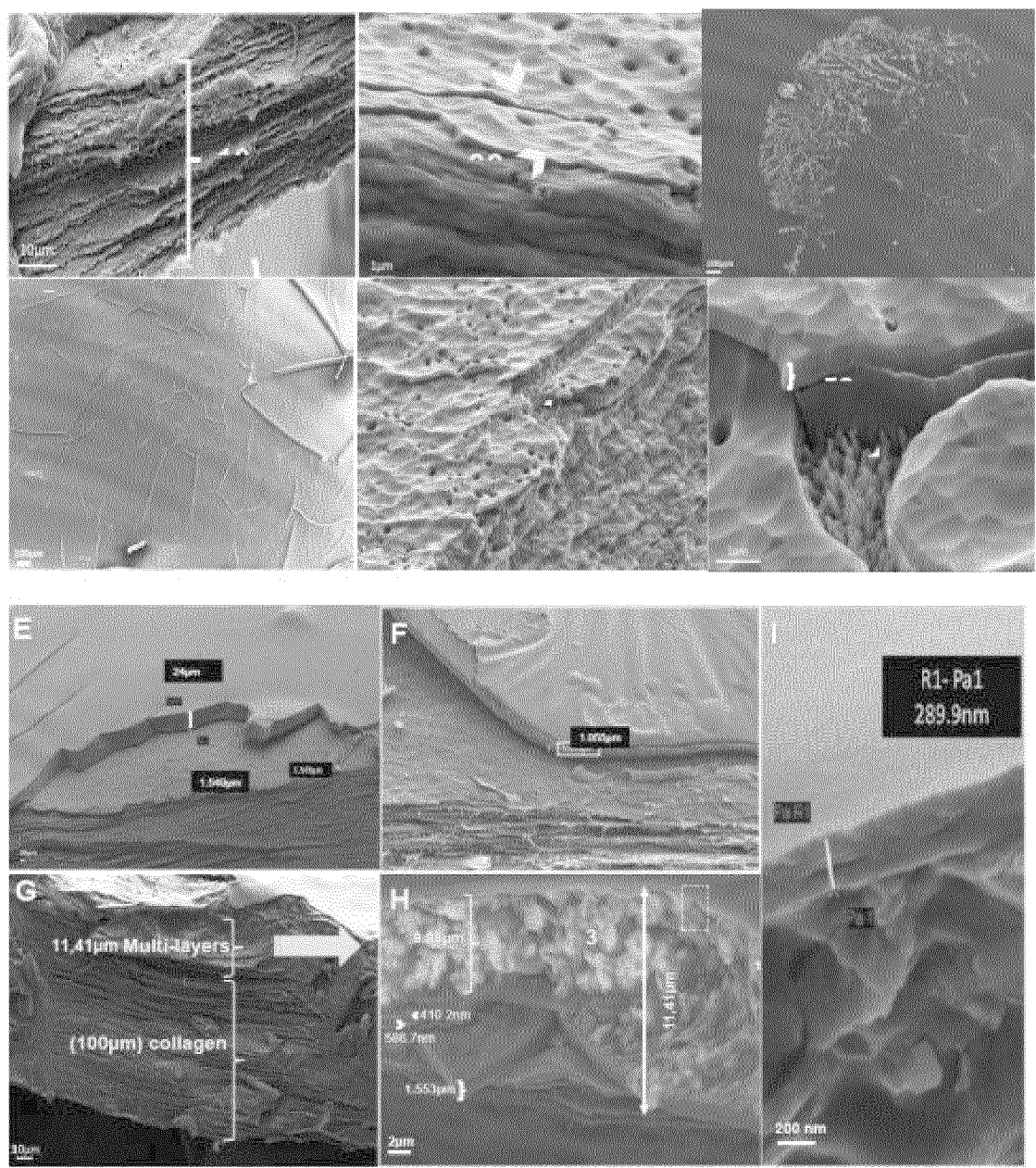


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/066972

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/70 A61K38/00 A61K31/555 A61K33/24 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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19/08/2019

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Authorized officer

Sindel, Ulrike

INTERNATIONAL SEARCH REPORT

International application No
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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