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(54) **Title:** METHOD OF PRODUCTION OF FIBERS AND A DEVICE FOR CARRYING OUT THE METHOD

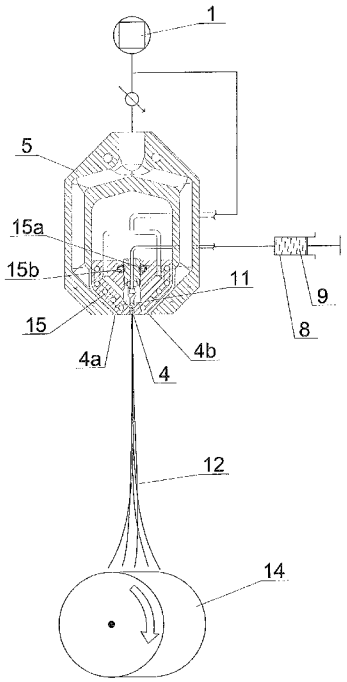

Fig. 3A

(57) **Abstract:** The present invention refers to a method and device for the production of microfibres or nanofibres based on hyaluronic acid and/or a water-soluble metal or non-metal salt thereof or a mixture of salts and/or a derivative of hyaluronic acid by method of dry spinning and/or solution blow spinning, and two-dimensional or three-dimensional fibrous materials from this microfibres and nanofibres. The resulting 2D or 3D materials can be for example in the shape of a layer or cotton wool. Furthermore, the present invention relates to a device for carrying out this method, that contains an extrusion piece containing a pass-through channel, that has an inlet opening for feeding the spinning solution and a dispensing opening for dispensing the spinning solution and furthermore the device contains an air nozzle, the air outlet opening of which is arranged to direct the exiting air into the area surrounding the dispensing opening of the extrusion piece parallel to the axis of the dispensing opening of the extrusion piece.

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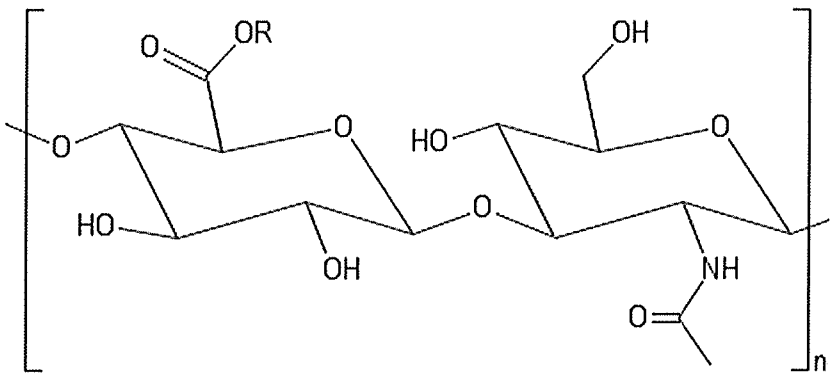
Method of production of fibers and a device for carrying out the method

Technical field

The invention relates to a method and device for production of microfibres or nanofibres based on hyaluronic acid and/or its water-soluble metal or non-metal salt or a mixture of salts and/or its derivative by the method of dry spinning and/or solution blow spinning, and two-dimensional or three-dimensional fibrous materials made of these microfibres or nanofibres. Furthermore, the invention relates to a device for carrying out said method.

State of the art

Hyaluronic acid (HA or hyaluronan) is a linear polysaccharide formed by repeating disaccharide units composed of D-glucuronic acid and N-acetylglucosamine according to the formula I



(I),

where R is H^+ or a metal cation.

Hyaluronan is found in the intercellular spaces of most human tissues, where it influences a number of processes including the maintenance of homeostasis, regeneration and wound healing. Hyaluronan products have a variety of forms, such as injectable solutions and gels, foils or textiles. These products are used in medicine and cosmetics, for example, as medical devices for wound healing, treatment of osteoarthritis, prevention of postoperative adhesions or reduction of wrinkles.

In order to modify the properties of the native hyaluronan, a number of hyaluronan derivatives have been prepared in the past.

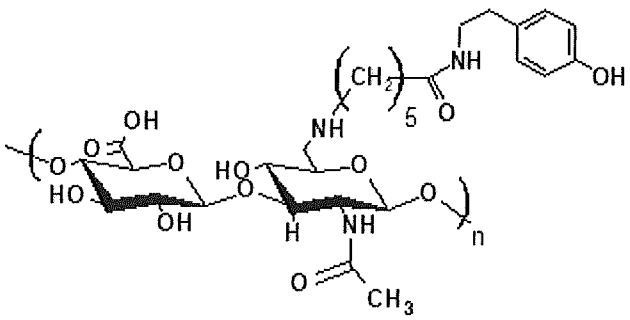
Hyaluronan chloramide is a derivative of hyaluronic acid in which most of the hydrogens of the amide group -NH-CO- are substituted by a chlorine atom to -NCl-CO-. The

production thereof and the properties thereof, which include antimicrobial, antifungal and antiviral activity, are described in the document CZ 308010.

Crosslinkable hyaluronan derivatives are derivatives containing groups enabling the connection of polymer chains by covalent bonds. These include 3-(2-furanyl)acryloyl ester of hyaluronan and tyramine hyaluronan.

Hyaluronan 3-(2-furanyl)acryloyl ester can be crosslinked by UV radiation in the solid phase. The synthesis and electrospinning thereof are described in the document CZ 304977 B6.

Tyramine hyaluronan is the name for various conjugates of hyaluronan with tyramine, which can be used, for example, to prepare crosslinked hydrogels. The synthesis of tyramine hyaluronan according to Formula II is described in the document CZ 303879 B6. Crosslinking of tyramine hyaluronan using riboflavin and UV radiation is described in the publication Donnelly, P. E., Chen, T., Finch, A., Brial, C., Maher, S. A., & Torzilli, P. A. (2017). Photocrosslinked tyramine-substituted hyaluronate hydrogels with tunable mechanical properties improve immediate tissue-hydrogel interfacial strength in articular cartilage. Journal of Biomaterials Science, Polymer Edition, 28(6), 582–600.



(II).

Non-polar derivatives of hyaluronan contain hydrophobic substituents. They can be classified to esters and acylated derivatives. The esters are hyaluronan benzyl ester and hyaluronan ethyl ester, their production is described in document US 5622707.

The acylated derivatives are hyaluronan derivatives in which primarily the primary alcohol of N-acetyl-glucosamine and to a lesser extent the secondary alcohols of glucuronic acid are acylated with fatty acids. The acyl group can be, for example, caproyl (hexanoyl), capryloyl (octanoyl), caprinoyl (decanoyl), lauroyl (dodecanoyl), myristoyl (tetradecanoyl),

palmitoyl (hexadecanoyl), stearoyl (octadecanoyl) and oleoyl (octadec-9-enoyl). Examples of the production of acylated derivatives are given in document WO 2014082611 A1.

In the field of spinning of hyaluronan and derivatives thereof, two types of technologies clearly prevail: electrospinning and wet spinning.

In electrospinning, the polymer solution is drawn into a fibre shape by the action of electrical forces. The production of fibres from an aqueous solution of hyaluronan by electrospinning is very difficult, therefore fibres are usually prepared from a mixture of hyaluronan with other polymers, for example polyethylene glycol or gelatin. Alternatively, pure hyaluronan can be spun by classical electrospinning when dissolved in a mixture of water and dimethylformamide or by the electroblowing method when dissolved in an aqueous solution of HCl at pH = 1.5, which method uses, in addition to the electric field, an air stream that draws and dries the fibre (Lee, K. Y., Jeong, L., Kang, Y. O., Lee, S. J., & Park, W. H. (2009). Electrospinning of polysaccharides for regenerative medicine. Advanced Drug Delivery Reviews, 61(12), 1020–1032).

Hyaluronan fibres prepared by electrospinning are mostly deposited on a collector in the form of a thin non-woven fabric (two-dimensional structure). Document WO 2020/124072 A1 discloses a method of expanding two-dimensional nanofibrous layers into a three-dimensional structure by exposure to gas bubbles. Document CZ 2013-913 A3 describes the spinning conditions under which a bulky layer of nanofibres is directly formed.

One of the drawbacks of the hyaluronan electrospinning technology is its limitation to the production of fibres of small diameters, in most cases less than 1 micrometer. Such fibres are characterized by low stiffness, low strength and a very fast dissolution in an aqueous environment. Furthermore, the solvents used for spinning pure hyaluronan are either unsuitable for use in healthcare due to their toxicity (e.g., dimethylformamide), or cause hyaluronan degradation (e.g., acid hydrolysis in an aqueous HCl solution). In case of using a mixture of hyaluronan with another polymer, the overall properties of the material change.

The principle of wet spinning of a polymer is the extrusion of a polymer solution into a coagulation bath, in which the coagulation (precipitation) of the polymer into a fibre form occurs and the original solvent diffuses bidirectionally from the fibre into the coagulation bath and from the coagulation bath into the fibre. For example, the document US 8753671 B2 discloses the production of an endless fibre (filament) from hyaluronan by wet spinning. The document WO 94/17837 discloses the production of non-woven fabrics from staple fibres

obtained by cutting the hyaluronan ester filament prepared by wet spinning, the cohesion of these fibres is additionally improved by chemical bonding. The document CZ 304651 B6 describes the direct production of staple fibres by hyaluronan spinning in a non-stationary coagulation bath and their subsequent processing into a non-woven fabric with steps including at least filtration and drying of the fibres.

The main disadvantage of the wet spinning technology is the two-way mass transfer during the fibre precipitation, which makes the fibre formation process slower than in other types of spinning. After removing the fibres from the coagulation bath, it is necessary to dry them from the residues of the coagulation bath, often the residues of the low-volatile components of the coagulation bath must be washed out of the fibres first. In case of hyaluronan spinning, acid coagulation baths are most often used, in which acid hydrolysis of hyaluronan chains occurs and hyaluronan salts are converted to an acidic form. Non-woven fabrics from hyaluronan are not prepared directly by wet spinning, but the obtained fibres must be processed into their form in further steps by one of the known procedures, typically wet or dry way of the production of non-woven fabrics.

Due to the aforementioned disadvantages of wet spinning, dry spinning or even better melt spinning is preferred when spinning polymers. The principle of melt spinning is the extrusion of the polymer melt into a cooling gas, where the melt stream solidifies into fibres. Therefore, neither a coagulation bath nor a solvent is present here, and the solid fibre is formed from the liquid state very quickly, since the process is not slowed down by mass transfer. However, hyaluronic acid cannot be melted, because due to the presence of strong intermolecular bonds between its chains, it degrades, when heated, before it starts to melt. The same applies to most of its derivatives.

Only WO 2005/028632 A2 discloses the production of hyaluronan esters in which aliphatic acyls disrupt the intermolecular bonds to such an extent that the hyaluronan derivative becomes meltable. The document WO 2017/039335 A1 discloses the production of hyaluronan fibres using a melt spinning device, where the fibre is formed from hyaluronan comprising 5 to 20% of water at 150 to 200°C and is subsequently cured in mixtures of water and ethanol, so it is not a true melt spinning.

The principle of dry spinning is the extrusion of a polymer solution into a drying gas, in which the solution is dried into fibres. There is a one-way transfer of mass, solvent from the solution to the drying gas, and therefore dry spinning is between the wet spinning and the melt

spinning in terms of difficulty and speed of production. Dry spinning of hyaluronan is not known yet. Snetkov in his comprehensive article (Snetkov, P., Morozkina, S., Uspenskaya, M., & Olekhnovich, R. (2019). Hyaluronan-Based Nanofibers: Fabrication, Characterization and Application. Polymers, 11(12), 2036) reported that dry spinning of hyaluronan is difficult to be carried out due to the solubility of hyaluronan in water and could probably be carried out for hydrophobic hyaluronan derivatives that are soluble in easily evaporable organic solvents.

The document WO 89/10941 A1 refers to a production and processing of crosslinked acidic polysaccharide esters including hyaluronan and as one of the options for spinning thereof mentions the dissolution of the crosslinked polysaccharide in an organic solvent and – if the solvent used does not have a very high boiling point – removal of the solvent by a dry spinning process. In Examples, however, only the wet spinning of cross-linked carboxymethyl cellulose is described.

The document JP 2007-262595 A, which is the closest to dry spinning of hyaluronan, discloses production of an ultrathin filament from crosslinked hyaluronan, which is prepared by extruding a crosslinked gel and its subsequent mechanical stretching and pulling in an oven.

The document WO 2018/235745 A1 describes the production of non-woven fabrics by extruding a heated polymer solution that is captured in an air stream coming from a nozzle that is not in contact with the extrusion nozzle. The invention discourages the arrangement where the air flows around the extrusion nozzle. The air carries the solution to the collector, where it is deposited in the form of partially dried fibres that need to be dried by lyophilization, which in Examples takes 72 hours, which significantly complicates and prolongs the process. In addition, the document mainly focuses on the spinning of gelatin, for which there are all examples, hyaluronan is only mentioned, without any parameters.

Centrifugal solution spinning is based on a principle similar to dry spinning. The principle is the extrusion of the solution by centrifugal force through the openings in the walls of a rotating container, the stream of the extruded solution is then drawn into the form of a fibre by the action of centrifugal force and frictional force caused by air resistance, and the resulting fibres are collected on a circular collector, in the centre of which the rotating container is located. The document US 2013/0312638 A1 discloses a device for centrifugal spinning of polymers, but does not give any examples or specific parameters for hyaluronan. The document CN 110424059 A discloses centrifugal spinning of blends of biopolymers with auxiliary polymers (e.g. polyethylene oxide, polyvinyl alcohol and polyvinylpyrrolidone), but does not

provide any examples or specific parameters for hyaluronan. The document WO 2014/127099 A2 then states that centrifugal spinning in a classical arrangement is not suitable for solutions with slowly evaporating solvents (such as water) and recommends for them a technology called "immersed rotary jet spinning", which differs from the classical centrifugal spinning by bath of the liquid into which the fibres are deposited. So, it is a kind of combination of centrifugal and wet spinning. Even this document only mentions hyaluronan and does not give any examples or parameters. Chantre in his publication describes the use of "immersed rotary jet spinning" technology, directly for spinning hyaluronan (Chantre, C. O., Gonzalez, G. M., Ahn, S., Cera, L., Campbell, P. H., Hoerstrup, S. P., & Parker, K. K. (2019). Porous Biomimetic Hyaluronic Acid and Extracellular Matrix Protein Nanofiber Scaffolds for Accelerated Cutaneous Tissue Repair. ACS Applied Materials & Interfaces, 11(49), 45498–45510).

The document CN 110424059 A recommends the addition of another polymer (e.g., polyethylene glycol or polyvinyl alcohol) for spinning biopolymers by centrifugal spinning, similarly to the case of electrospinning.

A relatively new polymer solution spinning technology first described by Medeiros in 2009 (Medeiros, E. S., Glenn, G. M., Klamczynski, A. P., Orts, W. J., & Mattoso, L. H. C. (2009). Solution blow spinning: A new method to produce micro- and nanofibers from polymer solutions. Journal of Applied Polymer Science, 113(4), 2322–2330) is solution blowing, also called solution blow spinning. The principle thereof is to dose a polymer solution into a stream of high-speed unheated gas through a needle located coaxially in an air nozzle. The publication describes the processing of synthetic polymers dissolved in organic solvents into fibres with diameters from hundreds of nanometers to units of micrometers. In document US 8641960 B1, the same author also mentions spinning of other polymers, e.g. polyethylene oxide, polyvinylpyrrolidone and polyvinyl alcohol, by this technology.

Document IN 201741017782 A discloses a simple device for solution blow spinning and lists hyaluronan derivatives in the list of spinnable materials, but does not specify any specific parameters for them or which derivatives they are.

Summary of the invention

The drawbacks and limitations of the technical solutions mentioned in the state of the art are solved by the invention of the method of the production of fibres, where fibres are based on hyaluronic acid and/or water-soluble metal or non-metal salt thereof or on the basis of water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or on the basis of

hyaluronic acid derivative, where the essence of a method based on the principle of dry spinning and/or solution blow spinning is to prepare a spinning solution comprising hyaluronic acid and/or a metal or non-metal salt thereof or a mixture of salts and/or a hyaluronic acid derivative, which is then spun by extrusion into a drying air stream and the fibres are deposited on a collector in the form of a non-woven fabric. The present invention is advantageous and differs significantly from the state of the art in that it allows simultaneously:

1. to spin hyaluronan with the addition of other polymers acceptable in healthcare and using solvents acceptable in healthcare;

2. to spin hyaluronan without the use of a coagulation bath;

3. to direct the fibres to the collector by a stream of air without applying an electrical voltage

4. to deposit the fibres on a collector directly in the form of both a flat and a bulky non-woven fabric of hyaluronan, which can be removed from the collector as a finished product immediately once the spinning is completed;

5. to dry the fibres on the collector in the order of units of up to tens of seconds, preferably of up to 30 seconds.

The present invention differs from the experts' opinions in that it successfully uses the dry spinning principle to spin hyaluronan and its water-soluble derivatives.

The invention therefore refers to the method of production of fibres based on hyaluronic acid and/or a water-soluble metal or non-metal salt thereof or on the basis of a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or on the basis of a hyaluronic acid derivative by the method of dry spinning and/or solution blow spinning, where a spinning solution of hyaluronic acid and/or a water-soluble metal or non-metal salt thereof or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative is prepared, containing 0.5 to 22% by weight of hyaluronic acid and/or its water-soluble metal or non-metal salt or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative, 0.1 to 13% by weight of spinning-aid polymer, such as polyethylene oxide, polyvinylpyrrolidone, polyvinyl alcohol, or pullulan, 0 to 54% by weight of organic solvent, and 44 to 98% by weight of water, and after the complete dissolution of the polymer, the spinning solution is extruded through at least one opening for dispensing the solution, the opening having the diameter from 80 to 410 μm in the rate from 0.01 to 0.52 mL/min into the drying air stream, thereby obtaining fibres that are carried onto the collector. The water-soluble metal or non-metal salt refers for example to a compound of

alkali metal, for example Na^+, K^+, Li^+, or alkaline earth metals, such as Ca^{2+}, Mg^{2+}, or metals, such as Ag^+, Au^+, Zn^{2+}, Cu^{2+}, or non-metal, for example NH_4^+. The water-soluble mixture of metal and/or non-metal salts of hyaluronic acid can include in addition to monovalent metals or non-metals, bi- or tri-valent metal or non-metal salt. The hyaluronic acid derivative is preferably selected from the group comprising hyaluronan chloramide, hyaluronan 3-(2-furanyl)acryloyl ester, tyramine hyaluronan, hyaluronan benzyl ester, hyaluronan ethyl ester and acylated derivatives of hyaluronan selected from the group comprising capronoyl, capryloyl, caprinoyl, lauroyl, myristoyl, palmitoyl, stearoyl, oleoyl hyaluronan.

The weight average molecular weight of hyaluronic acid and/or the water-soluble metal or non-metal salts thereof and/or the derivative thereof is preferably in the range from 10 kDa to 2.5 MDa.

In a preferred embodiment the organic solvent is selected from the group comprising methanol, tetrahydrofuran, methyl acetate, methyl ethylketone, 1,2-dimethoxyethane, acetonitrile, isopropylalcohol, 1-propanol, ethanol and acetone, preferably isopropylalcohol in the amount from 40 to 45% by weight.

In a preferred embodiment, the spinning-aid polymer is selected from the group comprising polyethylene oxide, polyvinylpyrrolidone, polyvinyl alcohol and pullulan, preferably polyethylene oxide having a viscosity average molecular weight of 0.4 to 1 MDa. The spinning solution is preferably prepared by first dispersing hyaluronic acid and/or a water-soluble metal or non-metal salt thereof or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or a hyaluronic acid derivative and a spinning-aid polymer in an organic solvent, water is added to the resulting dispersion with thorough mixing, or hyaluronic acid and/or a water-soluble metal or non-metal salt thereof, or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or a hyaluronic acid derivative and a spinning-aid polymer are directly dissolved in water. Then the solution is stirred for 1 to 24 hours at temperature 20 to 30°C until the polymer is completely dissolved. The prepared spinning solution is for example filled into a cartridge, which is sealed and connected to compressed air with an overpressure of +5 to +7 bar for 1 to 8 hours in order to dissolve the gas bubbles.

In another preferred embodiment, cooler air flows around the outlet opening for dispensing the solution, which air carries the spinning solution into a stream of warmer drying air. The drying air temperature is preferably 15 to 250°C, more preferably 15 to 190°C, and the absolute humidity of the drying air is preferably 0 to 14 g/m^3, more preferably 0 to 2 g/m^3, and

the drying air flow rate is preferably 1.6 to 315 m/s, more preferably 5 to 260 m/s. Preferably, the drying air can be directed by one or more hollow cylinders.

In another preferred embodiment, the collector is covered with an inert material with a low surface energy, for example with polytetrafluoroethylene or polyethylene, from which the fibres are easily removed, or it is covered with a textile, for example polyester knitted fabric, on which the fibres are deposited and which remains a part of the final product.

Preferably, the fibres have a diameter of 100 nm to 100 μm and form a non-woven fabric on the collector, having an area weight 0.1 to 120 g/m^2.

In another embodiment, the spinning solution comprises, besides the spinning-aid polymer, also hyaluronan 3-(2-furanyl)acryloyl ester, or a mixture of hyaluronic acid or a water-soluble salt thereof and hyaluronan 3-(2-furanyl)acryloyl ester, with the total concentration of the mixture of 1 to 5% by weight and the resulting fibres in the form of a non-woven fabric are subsequently crosslinked by radiation with a wavelength in the range from 280 to 750 nm, preferably 302 nm, for 2 - 60 minutes, wherein the substitution degree of hyaluronan with 3-(2-furanyl)acryloyl is in the range from 0.1 to 20%, and the proportion of hyaluronan 3-(2-furanyl)acryloyl ester in the mixture with the native HA is at least 0.1%, preferably 0.1-75%.

In any of the above-mentioned embodiments, the spinning solution can preferably contain another polymer, such as carboxymethyl cellulose or oxycellulose, and/or a pharmaceutically and/or cosmetically acceptable low molecular weight substance that can be dissolved or dispersed in the solvent mixture used, selected from the group comprising antibacterial agents, e.g., octenidine dihydrochloride or carbethopendecinium bromide, antivirals, e.g., acyclovir, antifungals, e.g., clotrimazole or terbinafine, drugs, e.g., lidocaine hydrochloride, vitamins, e.g., riboflavin, plant extracts, e.g., bisabolol, surfactants, e.g., polysorbate 80, peptides, e.g., antimicrobial peptides, e.g., cathelicidine LL-37, pexiganan MSI-78, WR-12, wound healing promoting peptides, e.g., dalargin, TP-508, biotin-GHK, hormonal peptides, e.g., lysipressin, terlipressin, dyes, e.g., Patent Blue VF.

The method according to the invention is carried out first by preparing a spinning solution of hyaluronic acid and/or a water-soluble metal or non-metal salt or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative containing 0.5 to 22% by weight of hyaluronic acid and/or a metal or non-metal salt thereof or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative, 0.1 to 13% by weight of spinning-aid polymer, 0 to 54% by weight of an organic

solvent and 44 to 98% by weight of water, preferably 1 to 22% by weight of hyaluronic acid and/or a metal or non-metal salt thereof or a mixture of metal and/or non-metal salts of hyaluronic acid and/or a derivative thereof, 0.25 to 3% by weight of spinning-aid polymer, 30 to 45% by weight of 2-propanol and 52 to 68% by weight of water.

The initial hyaluronic acid and/or the water-soluble metal or non-metal salt thereof and/or the derivative thereof has a weight average molecular weight (determined by the method of Size Exclusion Chromatography coupled to Multi-Angle Laser Light Scattering, SEC-MALLS) 10 kDa to 2.5 MDa. The molecular weights used must be adapted to the concentration of the polymer in the spinning solution to achieve its optimal viscosity, for higher molecular weights lower concentrations must be chosen and vice versa. If the viscosity of the spinning solution is too high, there is no effective elongation of the resulting fibre and the extruded solution stream breaks instead.

A spinning-aid polymer means a pharmaceutically acceptable polymer that is more easily spun by the method of dry spinning than hyaluronic acid. An addition of such polymer facilitates the fibre formation process and allows the organic solvent in the spinning solution to be partially or completely replaced by water. In a preferred embodiment, the proportion by weight of the spinning-aid polymer with respect to the total weight of the dry-matter of the spinning solution is less than 50 %, preferably less than 25 %.

If a hyaluronic acid derivative is used, e.g., lauroyl hyaluronan, it is defined in Examples by the content of the bound fatty acid, which indicates the mass proportion of the bound fatty acid in the total derivative weight.

In a preferred embodiment, the proportion by weight of hyaluronic acid and/or salt and/or derivative thereof to the total weight of the dry matter of the spinning solution is equal to or greater than 50 %, preferably equal to or greater than 75 %.

In a preferred embodiment, the spinning solution comprises a solution of a hyaluronic acid derivative, which is hyaluronan chloramide, or a mixture of a hyaluronic acid derivative, which is hyaluronan chloramide, and native hyaluronic acid, wherein the substitution degree of hyaluronan chloramide is in the range from 0.1% to 100%, preferably 50 to 100%.

The procedure for preparing the spinning solution is preferably such that first hyaluronic acid and/or the metal or non-metal salt thereof or the water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative and the spinning-aid polymer are dispersed in an organic solvent, then water is added with thorough mixing, or

optionally, they are dispersed in water directly, and the solution is stirred for 1 to 24 hours at the temperature 20 to 30°C until the polymer is completely dissolved. The spinning solution is then filled into the cartridge of a pneumatic dosing device (working on the principle of extruding the solution from the storage cartridge with compressed air, an example of such a dosing device is the Vieweg DC 1200), the cartridge is sealed and connected to the compressed air with an overpressure of +5 to +7 bar for 1 to 8 hours until the gas bubbles dissolve.

The spinning solution is extruded by an extrusion piece with at least one dispensing opening with an internal diameter of 80 to 410 micrometers, preferably 100 to 210 micrometers. The term extrusion piece in this description preferably refers to a conventional extrusion needle with a blunt end and with 1 to 4 capillaries, which may be straight or bent to allow their better positioning in the air stream, or a conical extrusion needle, the internal diameter of which gradually decreases up to the dispensing opening, thanks to which it can dispense viscous solutions at a lower pressure, or a nozzle containing more than one dispensing opening, preferably more than 10, more preferably more than 50 dispensing openings arranged for example in a row.

The spinning solution is extruded from the dispensing opening with a rate from 0.01 to 0.52 mL/min. At a lower dosing rate, drawing and air-drying of the fibres are both more efficient and the fibres fall onto the collector dried better, but at the same time the spinning solution in the extrusion piece is more heated and especially when the extrusion piece is flown around with air of a higher temperature, there is a risk of drying the solution and clogging the dispensing opening.

The spinning solution is extruded from the dispensing opening into a stream of drying air that flows around the extrusion piece. The stream of drying air draws the extruded spinning solution into a fibre shape, speeds up the evaporation of the solvent from the spinning solution and drifts the resulting fibres onto the collector.

In a preferred embodiment of the invention, the extrusion piece is flown around by a smaller amount of cooler air, which carries the spinning solution into a stream of a larger amount of warmer drying air, wherein this embodiment prevents overheating of the spinning solution already in the extrusion piece.

The temperature of the drying air is 15 to 250°C, preferably 15 to 190°C, the absolute humidity of the drying air is 0 to 14 g/m^3, preferably 0 to 2 g/m^3, the drying air flow rate is 1.6 to 315 m/s, preferably 5 to 260 m/s. The air flow rate at the nozzle outlet depends on the

combination of the nozzle cross-section and the volumetric flow rate. In general, when using a higher drying air flow rate, a lower drying air temperature can be used to effectively dry the fibres and vice versa, because the faster flowing drying air draws the resulting fibre more effectively into a smaller diameter fibre from which the drying air more easily removes solvents. Similarly, the use of a dispensing opening with a smaller internal diameter supports the formation of a fibre with a smaller diameter.

In a preferred embodiment of the invention, the drying air carrying the resulting fibre is directed by one or more hollow cylinders, which prevent the expansion of the drying air stream and its mixing with the surrounding air, thereby reducing its speed and temperature.

The fibres are deposited in the form of a non-woven fabric on a collector with a shape of a cylinder, bars, belt or board. In one preferred embodiment, the collector is in the form of an inverted cone disposed in a cylindrical vessel, wherein the side edges of the cone are formed by bars. The collector is immobile or preferably mobile, such as a cylinder rotating around its axis or a belt rewound from cylinder to cylinder. The surface of the collector is preferably covered with an inert material with a low surface energy, for example with polytetrafluoroethylene or polyethylene, from which the fibres can be easily removed. The collector's distance from the dispensing opening is preferably in the range from 5 cm to 140 cm. In another embodiment of the invention, the collector is covered with a fabric or a film, for example polyester or polyamide fabric or film, which forms one of the layers of the final product, and the prepared fibres are applied directly thereon as another layer.

In a preferred embodiment of the invention the arrangement of the collector is such that the fibres deposited on the collector hang most of their length in the air and can thus dry more effectively. In this embodiment, the collector is formed for example by bars or is covered with a fabric with larger meshes.

In another preferred embodiment of the invention the collector with the shape of a cylinder rotating around its axis can be moved along this axis, so that the fibres gradually fall on its entire surface in a uniformly thick layer.

In another preferred embodiment of the invention the collector is an object on the surface of which a layer of a non-woven fabric is formed and then together with the object it forms the final product. It's for example an implantable medical device (pacemaker, joint...) on the surface of which a bio-compatibilizing or an antimicrobial layer is formed, for example on the

basis of hyaluronan chloramide, or on the basis of hyaluronan, with an addition of octenidine dihydrochloride.

Further, the subject of the invention is a two-dimensional or three-dimensional material made of microfibres or nanofibres prepared in the manner described above. The non-woven fabric of the invention has preferably an area weight from 0.1 to 120 g/m^2 and is made of fibres with a diameter in the range from 100 nm to 100 micrometers. Non-woven fabrics of higher area weights, approx. from 5 g/m^2, can be used as self-supporting two-dimensional materials, non-woven fabrics of lower area weights are not rigid enough to maintain the shape of a flat structure, and after being removed from the collector, they self-fold into a three-dimensional structure similar to cotton wool.

As mentioned above, the amounts of solvents contained in the fibres falling on the collector can be influenced by the parameters selection (in particular, the rate of spinning solution dosing, the diameter of the dispensing opening, the drying air temperature and the drying air flow rate). For obtaining high-quality fibres and the non-woven fabric formed by them, preferably such combination of parameters is selected, that the fibres fall on the collector dry enough (i.e., with such a low residual content of solvents) to retain the shape of the fibre and to complete drying quickly enough (preferably within a few tens of seconds at most) to prevent a layer of gel growing on the collector. If not completely dried fibres fall on each other, they coalesce in the places where they cross each other. In a preferred embodiment of the invention, the fibres fall on the collector dry enough, so their coalescence does not occur. The resulting non-woven fabric is characterized by a lower volumetric mass. In another preferred embodiment of the invention, the fibres fall on the collector dry enough to directly form a three-dimensional, cotton wool-like formation, so it is not necessary to assemble such a formation from thin two-dimensional layers.

Furthermore, the subject of the invention is a device for the production of two-dimensional or three-dimensional materials from microfibres or nanofibres, which includes an extrusion piece containing a pass-through channel, which has an inlet opening for feeding the spinning solution and at least one dispensing opening for dispensing the spinning solution. Furthermore, the device comprises an air nozzle, the main air outlet opening of which is arranged to direct the exiting air to an area surrounding the dispensing opening of the extrusion piece parallel to the axis of the dispensing opening of the extrusion piece, the air nozzle comprising additional outlet openings arranged to direct the additional air flow to the area below the dispensing opening into the air flow from the main air outlet opening at an angle of 30° to

60°, preferably 40° to 50°, more preferably 45°. The device further comprises at least one cooling channel for guiding the coolant liquid through the walls of the air nozzle.

In a preferred embodiment the device contains a source of drying air, air nozzle, device for dosing of the spinning solution, extrusion piece, e.g., a extrusion needle, positioned coaxially with the air nozzle, and a collector which is arranged at a distance from the extrusion piece and the dispensing opening of the extrusion piece is facing the collecting surface of the collector.

The collector may be, for example, in the form of a cylinder, a cylinder formed by bars, an inverted cone formed by bars, or in the form of an implantable medical device.

In a preferred embodiment, the device comprises a heating element for heating the air supplied to the additional outlet openings of the air nozzle.

In another preferred embodiment of the invention, the stream of the drying air carrying the stream of the spinning solution is directed through a defined space, which prevents mixing with the surrounding air, by means of a focusing part arranged between the collector and the dispensing opening of the extrusion piece and containing a pass-through cavity, the axis of which is identical to the axis of the dispensing opening. The main outlet opening of the air nozzle is arranged coaxially with the dispensing opening of the extrusion piece and is preferably annular or circular, wherein the extrusion piece area containing the dispensing opening is arranged in the area of the main outlet opening of the air nozzle, and/or the main outlet opening of the air nozzle is arranged further away from the collector than the dispensing opening.

The prepared two-dimensional and three-dimensional fibrous materials can be used in medicine as covers or fillings for wound treatment, or as envelopes for implantable medical devices.

Description of the drawings

Figure 1 shows an embodiment of a device with a heat gun (not shown) as an air source which does not fall within the scope of the invention.

Figure 2 shows a second embodiment of a device with a compressor as an air source and with an extrusion conical needle coaxially located in the centre of the air nozzle, which does not fall within the scope of the invention.

Figure 3A shows an exemplary embodiment of a device according to the invention with the combination of non-heated and heated air.

Figure 3B shows a detailed section through a three-dimensional model of the exemplary embodiment of the device with the combination of non-heated and heated air.

Figure 3C shows the central part of the air nozzle of the exemplary embodiment of the device in detail, with the combination of non-heated and heated air.

Figure 4 shows another exemplary embodiment of the device according to the invention, based on the principle of solution blow spinning technology.

Figure 5 shows a rotary collector formed by bars.

Figure 6 shows a stationary collector in the shape of an inverted cone, formed by bars.

Fig. 7 shows fibres made of a mixture of sodium hyaluronan and polyethylene oxide prepared according to Example 4.

Figure 8A shows a non-woven fabric made of a mixture of sodium hyaluronan and polyethylene oxide on a polyester knitted fabric backing prepared according to Example 5.

Figure 8B shows the non-woven fabric made of a mixture of sodium hyaluronan and polyethylene oxide on a polyester knitted fabric backing in detail, prepared according to Example 5.

Figure 9 shows fibres made of a mixture of lauroyl hyaluronan and polyethylene oxide prepared according to Example 9.

Figure 10A shows fibres made of a mixture of hyaluronan chloramide and polyethylene oxide prepared according to Example 10.

Figure 10B shows a pacemaker mounted on the collector axis, covered with a non-woven fabric made of a mixture of hyaluronan chloramide and polyethylene oxide prepared according to Example 10.

Figure 11A shows the structure of the nonwoven fabric made of a mixture of 3-(2-furanyl)acryloyl ester of hyaluronan and polyethylene oxide prepared according to Example 11.

Figure 11B shows the structure of crosslinked fibres made of a mixture of 3-(2-furanyl)acryloyl ester of hyaluronan and polyethylene oxide prepared according to Example 11 after 2 weeks in demineralized water.

Figure 12 shows fibres made of a mixture of sodium hyaluronan and polyethylene oxide prepared according to Example 14.

Figure 13 shows fibres made of a mixture of sodium hyaluronan and polyvinylpyrrolidon prepared according to Example 15.

Figure 14 shows fibres made of a mixture of sodium hyaluronan and pullulan prepared according to Example 18.

Figure 15 shows cotton wool made of a mixture of sodium hyaluronan, polyvinylpyrrolidon and octenidine prepared according to Example 24.

Figure 16 shows cotton wool made of a mixture of sodium hyaluronan, polyethylene oxide, tartrazine and Patent Blue VF, prepared according to Example 25.

Figure 17 shows fibres made of a mixture of sodium hyaluronan and polyethylene oxide prepared according to Example 29.

Figure 18 shows fibres made of a mixture of sodium hyaluronan and polyethylene oxide prepared according to Example 30.

Figure 19 shows cotton wool made of a mixture of sodium hyaluronan and polyethylene oxide prepared according to Example 31.

Examples

The device according to the present invention thus comprises an extrusion piece 11 comprising a pass-through channel having an inlet opening for feeding a spinning solution 9 and a dispensing opening 11a for discharging of the spinning solution, and an air nozzle 5, having a main outlet opening 4 for the exit of air which is arranged for directing of the exiting air into the region surrounding the dispensing opening 11a of the extrusion piece 11 in parallel to the axis of the dispensing opening 11a of the extrusion piece 11. Furthermore, the device preferably comprises a collector 14 arranged in a certain distance from the extrusion piece 11, wherein the dispensing opening 11a of the extrusion piece 11 faces the collecting surface of the collector 14.

In a preferred embodiment, the device comprises a focusing part 13 arranged between the collector 14 and the dispensing opening 11a of the extrusion piece 11, said focusing part 13

comprising a pass-through cavity, the axis of which being identical to the axis of the dispensing opening 11a.

The main outlet opening 4 of the air nozzle 5 is preferably annular and arranged coaxially with the dispensing opening 11a of the extrusion piece 11 and/or the main outlet opening 4 of the air nozzle 5 is arranged farther from the collector 14 than the dispensing opening 11a.

The device may comprise a compressor 1 for feeding the air into the air nozzle 5.

In another preferred embodiment, the device also comprises a heating element 2 for heating the air fed into the air nozzle 5.

Fig. 1 shows schematically the first embodiment of the device (outside of the scope of the invention) for the production of two-dimensional or three-dimensional fibre materials from microfibres or nanofibres, wherein the device comprises an extrusion piece 11 in the form of an extrusion needle through which a pass-through channel extends, said pass-through channel comprising a feeding opening and a dispensing opening 11a. The extrusion piece 11 is adapted for a fluid connection with a dosing device 8 on the side of the feeding opening, in this case in the form of a cartouche with a piston 81.

The pass-through channel has a diameter of 80 to 410 micrometres, preferably 100 to 210 micrometres, at least in the region of the dispensing opening 11a.

The device further comprises an air nozzle 5, here in the form of a hot-air pistol. The air nozzle 5 has a main outlet opening 4 which is directed and adapted for directing the hot air stream such that it flows around the extrusion piece 11 in parallel to the direction of the exit of the spun solution from the dispensing opening 11a of the extrusion piece 11. To this end, the air nozzle 5 is arranged so that the axis of its main outlet opening 4 corresponds to the axis of the dispensing opening 11a of the extrusion piece 11.

The device further comprises a collector 14 for depositing the produced fibres, in this case in the form of a rotatably arranged cylinder, wherein the dispensing opening 11a of the extrusion piece 11 faces the depositing surface of the collector 14.

A focusing part 13 having a pass-through cavity is arranged between the collector 14 and the dispensing opening 11a of the extrusion piece 11, wherein the axis of said pass-through cavity corresponds to the axis of the dispensing opening 11a. The pass-through cavity of the focusing part 13 is cylindrical.

By means of the piston 81, a polymer solution 9 is extruded from the dosing device 8 by means of a bent extrusion needle forming an extrusion piece 11 and being arranged coaxially under the main outlet opening 4 of the air nozzle 5. The resulting fibres are led through the focusing part 13 onto the collector 14.

Fig. 2 shows schematically another embodiment of the device (outside of the scope of the invention) for the production of two-dimensional or three-dimensional fibre materials from microfibres or nanofibres which differs from the device of Fig. 1 particularly in that the extrusion piece 11 is partially housed inside the air nozzle 5 and at the same time protrudes from the air nozzle 5 with the part that comprises the dispensing opening 11a. Furthermore, the device of Fig. 2 is supplemented with a compressor 1 which is fluidly interconnected with the air nozzle 5 for feeding an air stream to the air nozzle 5. A heating element 2 for heating the air fed to the air nozzle 5 is arranged in a piping interconnecting the compressor 1 and the air nozzle 5.

The polymer solution 9 is brought from the dosing device 8 to the extrusion piece 11 which comprises a tube 10 followed by an extrusion needle. The air stream generated by the compressor 1 is heated by the heating element 2 and exits the air nozzle 5 through the main outlet opening 4 having a shape of annulus, the dispensing opening 11a of the extrusion piece 11, or extrusion needle, being coaxially arranged therewith. The resulting fibres 12 are led by the focusing cylinder 13 onto the collector 14.

Figs. 3A, 3B, and 3C show schematically an embodiment of the device according to the invention for the production of two-dimensional or three-dimensional fibre materials from microfibres or nanofibres according to the invention with a combination of non-heated and heated air.

The device of Figs. 3A, 3B, and 3C differs from the device of Fig. 2 particularly in that the dispensing opening 11a of the extrusion piece 11 is arranged substantially in the same plane as the main outlet opening 4 of the air nozzle 5 and that additional outlet openings 4a, 4b of additional air nozzle 5 are directed to the region below the dispensing opening 11a of the extrusion piece.

The axes of the additional outlet openings 4a, 4b of the air nozzle 5 intersect the axis of the dispensing opening 11a of the extrusion piece 11 and form an angle of 45° with said axis.

Fig. 3C shows that the air nozzle 5 comprises a cooling channel 15 for a coolant liquid for cooling the air nozzle 5, wherein said cooling channel 15 has an inlet opening 15a adapted for connecting a hose for feeding the coolant liquid and an outlet opening 15b adapted for connecting a hose for discharging the coolant liquid. Between the inlet opening 15a and the outlet opening 15b, the cooling channel 15 passes in a labyrinth-like manner through the material of the wall of the air nozzle 5 for effective cooling of the air nozzle 5.

The dosing device 8 extrudes the polymer solution 9 through a straight extrusion needle forming the extrusion piece 11 arranged coaxially in the main outlet opening 4 of the air nozzle 5, into which the air form the compressor 1 is fed. Said air brings the solution into a flow of warmer (heated) air exiting the outlet openings 4a, 4b. The coolant flows inside the channel 15, which prevents the heat transfer from the heated air to the non-heated air through the body of the nozzle 5. The resulting fibres 12 are led onto the collector 14.

Fig. 4 shows schematically another embodiment of the device for the production of two-dimensional or three-dimensional fibre material according to the invention based on the solution blow spinning technology with a compressor 1 as a source of air and a narrow air nozzle 5 through which the air exits with a high velocity. The diameter of the air nozzle 5 is in the range of 2 to 4 mm, the velocity of the air is in the range of 50 to 350 m/s. The diameter of the needle is in the range of 80 to 210 micrometres. A dosing device 8 extrudes a polymer solution 9 through a bent extrusion needle forming an extrusion piece 11 arranged coaxially in the outlet opening 4 of the air nozzle 5. The resulting fibres 12 are deposited on the collector 14.

Fig. 5 shows an example of the collector 14 in the form of a rotatably arranged cylindrical cage.

Fig. 6 shows an example of the collector 14 in form of a stationary conical cage.

The following examples demonstrate various embodiments of the method according to the invention. The air velocity is primarily indicated in l/min, in some examples it is converted to an approximate air velocity in m/s at the exit of the air nozzle 5.

The terms "hyaluronic acid", "hyaluronan" and "native hyaluronic acid" always refer to hyaluronic acid, the sodium salt thereof and the mixture of the acid and the sodium salt, unless otherwise indicated.

Example 1

2 grams of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 0.67 grams of polyethylene oxide having the viscosity average molecular weight 1 MDa are dispersed in 27.4 mL of 2-propanol. 86.1 mL of water are added to the resulting dispersion with thorough mixing, the solution is stirred until the polymer is completely dissolved for 8 hours at 21°C, resulting in a solution with concentration of 1.81% by weight of sodium hyaluronan and 0.60% by weight of polyethylene oxide. The spinning solution 9 is then filled into the cartridge of the pneumatic dosing device 8, the cartridge is sealed and connected to the compressed air of +6 bar for 6 hours until the gas bubbles dissolve. Subsequently, the spinning solution 9 is spun on the device shown in Fig. 1. The spinning solution 9 is extruded by the extrusion piece 11, which is a bent blunt extrusion needle of length 12.7 mm with an internal diameter of 160 micrometers with the rate of 0.1 mL/min. The extrusion needle is located coaxially under the air nozzle 5, which is formed by point nozzle of the heat gun Wagner FURNO 750 so that the end of the extrusion needle is located 15 mm under the main outlet opening 4 of the air nozzle 5. The air nozzle 5 blows the drying air of the temperature of 140°C and absolute humidity of 6 g/m^3 with the volume flow of 280 L/min, which corresponds to an average air velocity of 17 m/s. The drying air is directed by a cylinder 13 located coaxially with the extrusion needle, this cylinder 13 of the internal diameter 3.7 cm and length 27.5 cm starts at 1 cm below the end of the extrusion needle. The resulting fibers 12 are carried by the air stream to the collector 14 in the shape of a cylinder with a diameter of 15 cm formed by 38 bars of 3 mm thickness (shown in Fig. 5) rotating at the speed of 2 revolutions per minute located 100 cm under the extrusion needle. The surface of the collector 14 is covered with polytetrafluoroethylene foil. The resulting fibers 12 having the diameter of 0.8-5.5 micrometers were obtained from the collector 14 in the form of thin layers that were packed into a bulky 3D structure (cotton wool).

Example 2

2 grams of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 0.67 grams of polyethylene oxide having the viscosity average molecular weight 1 MDa are dispersed in 27.4 mL of 2-propanol. 86.1 mL of water are added to the resulting dispersion with thorough mixing, the solution is stirred until the polymer is completely dissolved for 19 hours at 22°C, resulting in a solution having the concentration 1.81% by weight of sodium hyaluronan

and 0.60% by weight of polyethylene oxide. The spinning solution 9 is then filled into the cartridge of the pneumatic dosing device 8, the cartridge is sealed and connected to the compressed air of +5.5 bar for 5 hours until the gas bubbles dissolve. Subsequently, the spinning solution 9 is spun on the device shown in Fig. 2. The spinning solution 9 is extruded by the extrusion piece 11, which is a blunt extrusion needle of the length of 6.4 mm with an internal diameter of 160 micrometers with the rate of 0.1 mL/min. The extrusion needle is located coaxially in the center of the air nozzle 5, the end of the needle is located 20 mm under the end of the air nozzle 5. The drying air flows from the air nozzle 5 through an annular outlet opening 4 with an internal diameter of 19 mm and external diameter of 25 mm, the temperature of the drying air is 100°C, the absolute humidity is 0.2 g/m^3 and it has the volume flow 400 L/min, which corresponds to the average air velocity of 32 m/s. The resulting fibers 12 are carried by the air stream to the stationary collector 14 (shown in Fig. 6) in the shape of an inverted cone located in a cylindrical container with a height of 12 cm and an internal diameter of 26 cm, the side edges of the cone are formed by 12 bars 34 cm long and 2 mm thick, and the opposite side edges form an angle of 90°. The bottom of the cylindrical container, which is a part of the collector 14, is located 112 cm under the extrusion needle. The surface of the collector 14 is covered with a polytetrafluoroethylene foil. The resulting fibers 12 having the diameter of 0.5-2.2 micrometers on the collector bars form directly a bulky 3D structure (cotton wool).

Example 3

10 grams of sodium hyaluronan having the weight average molecular weight 76 kDa and 2.5 grams of polyethylene oxide having the viscosity average molecular weight 1 MDa are dispersed in 45.4 mL of 2-propanol. 83.2 mL of water are added to the resulting dispersion with thorough mixing, the solution is stirred for 18 hours at 24°C, until the polymer is completely dissolved, resulting in a solution having the concentration 7.62% by weight of sodium hyaluronan and 1.91% by weight of polyethylene oxide. The spinning solution 9 is then filled into the cartridge of the pneumatic dosing device 8, the cartridge is sealed and connected to the compressed air of +5.0 bar for 4 hours until the gas bubbles dissolve. Subsequently, the spinning solution 9 is spun on the device shown in Fig. 3A. The spinning solution 9 is extruded by the extrusion piece 11, which is a blunt extrusion needle of the length of 6.4 mm with an internal diameter of 160 micrometers with the rate of 0.04 mL/min. The extrusion needle is located coaxially in the main outlet opening 4 of the air nozzle 5 with the diameter of 3 mm, the end of the needle is located 1 mm above the underside of the nozzle body 5. The air flows through this

main outlet opening 4, having the temperature of 30°C and absolute humidity of 0.2 g/m^3 with the volume flow of 30 L/min, which corresponds to the average air velocity of 71 m/s. This air carries the stream of the spinning solution 9 to the stream of the heated air having the temperature of 185°C and absolute humidity of 0.2 g/m^3 with the volume flow of 200 L/min coming out simultaneously from two additional openings 4a, 4b of the nozzle 5, forming an angle of 90° with each other and having a rectangular cross-section with sides of 2 and 30 mm and being arranged 20 mm apart from each other. Water with the temperature of 10°C flows through the channel 15 for the cooling liquid having the diameter of 4 mm, with the volume flow of 250 mL/min. The resulting fibers 12 are carried by the air stream to the stationary collector 14 (shown in Fig. 6) in the shape of an inverted cone located in a cylindrical container with the height of 12 cm and an internal diameter of 26 cm, the side edges of the cone being formed by 12 bars 34 cm long and 2 mm thick, and the opposite side edges forming an angle of 90°. The bottom of the cylindrical container, which is part of the collector 14, is located 124 cm under the extrusion needle. The surface of the collector 14 is covered with a polytetrafluoroethylene foil. The resulting fibers 12 having the diameter of 5-20 micrometers on the collector 14 bars form directly a bulky 3D structure (cotton wool).

Example 4

2 grams of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 0.67 grams of polyethylene oxide having the viscosity average molecular weight 1 MDa are dispersed in 70 mL of 2-propanol. 67.2 mL of water are added to the resulting dispersion with thorough mixing, the solution is stirred for 16 hours at 20°C until the polymer is completely dissolved, resulting in the spinning solution 9 having the concentration of 1.60% by weight of sodium hyaluronan and 0.53% by weight of polyethylene oxide. The spinning solution 9 is then filled into the plastic dosing device 8, which is a syringe that is inserted into a syringe pump. Subsequently, the spinning solution 9 is spun on the device shown on the Fig. 4. The spinning solution 9 is extruded by the extrusion piece 11, which is a bent blunt extrusion needle of the length of 12.7 mm having an internal diameter of 160 micrometers with the rate of 0.01 mL/min. The extrusion needle is located coaxially in the air nozzle 5 formed by a polyamide tube of the internal diameter of 4 mm so that the end of the needle exceeds the end of the tube by 1 mm. The air nozzle 5 blows the drying air of the temperature of 29°C and absolute humidity of 0.2 g/m^3 with the volume flow of 15 L/min, which corresponds to the average air velocity of 20 m/s. The resulting fibers 12 are carried by the air stream to the collector 14 in the shape of a

cylinder with a diameter of 7 cm rotating at the speed of 40 revolutions per minute and located at a distance of 30 cm from the extrusion needle. The surface of the collector 14 is covered with a low-density polyethylene foil. The resulting fibers 12 having the diameter of 0.4-10 micrometers were removed from the collector 14 in the form of thin layers that were packed into a 3D structure (cotton wool) (Fig. 7).

Example 5

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 was extruded by a blunt extrusion needle of the internal diameter of 340 micrometers with the rate of 0.4 mL/min. The resulting fibers 12 were carried by the air stream to the collector 14 in the shape of a cylinder with a diameter of 15 cm rotating at the speed of 6 revolutions per minute and located 74 cm under the extrusion needle. The surface of the collector 14 was covered with a polyester non-reinforced knitted fabric Zuzana (manufacturer: SILK & PROGRESS). The resulting non-woven fabric has the area weight of 93 g/m^2 and is formed by fibers 12 of diameter 10-82 micrometers. The nonwoven fabric thus prepared is removed from the collector 14 together with the polyester fabric on which it is deposited, and can be used as such, as the resulting two-layer product, or the nonwoven fabric can be removed from the polyester fabric (Fig. 8A; Fig. 8B).

Example 6

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 3.01% by weight of sodium hyaluronan having the weight average molecular weight 1.15 MDa and 0.60% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 3 grams of sodium hyaluronan, 0.6 grams of polyethylene oxide, 72.0 mL of water and 30.6 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.7-5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 7

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 0.55% by weight of sodium hyaluronan having the weight average molecular weight of 2.05 MDa and 0.55% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 1 gram of sodium hyaluronan, 1 gram of polyethylene oxide, 90.5 mL of water and 115.2 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.6-1.8 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 8

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1,59% by weight of lauroyl hyaluronan having the weight average molecular weight 0.3 MDa and containing 16,4% by weight of bound lauric acid, and 1.59% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 2 grams of lauroyl hyaluronan, 2 grams of polyethylene oxide, 67.2 mL of water and 70.0 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.08 mL/min. The resulting fibers 12 having a diameter of 2-9 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 9

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.60% by weight of lauroyl hyaluronan having the weight average molecular weight 1.06 MDa and containing 6.5% by weight of bound lauric acid, and 0.80% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 2 grams of lauroyl hyaluronan, 1 gram of polyethylene oxide, 67.2 mL of water and 70.0 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 1.5-4 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 9).

Example 10

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 3.57% by weight of hyaluronan chloramide having the weight average molecular weight 0.1 MDa and the substitution degree of 96 %, and 0.51% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 5 grams of hyaluronan chloramide, 0.71 grams of polyethylene oxide, 87.3 mL of water and 59.8 mL of 2-propanol. A Biotronik Actros DR pacemaker mounted on the axis of the collector 14 rotating at the speed of 13.5 revolutions per minute at a depth of 45 cm under the extrusion needle was used as the collector 14. The resulting non-woven fabric covering the pacemaker has the area weight of 42 g/m^2 and is formed by fibers 12 having a diameter of 0.5-2.5 micrometers (Fig. 10A; Fig. 10B).

Example 11

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 3.47% by weight of hyaluronan 3-(2-furanyl)acryloyl ester having the weight average molecular weight 98 kDa and the substitution degree of 12.5 %, and 0.50% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 4 grams of hyaluronan 3-(2-furanyl)acryloyl ester, 0.57 grams of polyethylene oxide, 88.6 mL of water and 28.2 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.06 mL/min. The resulting fibers 12 were carried by the air stream to the collector 14 in the shape of a cylinder with a diameter of 15 cm rotating at the speed of 24 revolutions per minute and located 74 cm under the extrusion needle. The surface of the collector 14 is covered with a polytetrafluoroethylene foil. The resulting non-woven fabric, which can be easily removed from the surface of the collector 14, has an area weight of 7 g/m^2 and is formed by fibers 12 with the diameter of 0.5-2.5 micrometers. The crosslinking of hyaluronan 3-(2-furanyl)acryloyl ester contained in the fabric was carried out in UVP Crosslinker CL-3000 (Analytik Jena), where the textile was exposed to radiation of a wavelength of 302 nm and energy intensity 350 μJ/cm^2 for 60 minutes. To verify the insolubility, the fabric sample was placed in demineralized water at temperature 23°C, after 2 weeks the fibrous structure was preserved (Fig. 11A; Fig. 11B).

Example 12

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.92% by weight of sodium hyaluronan having the weight average molecular weight 2.05 MDa and 0.64% by weight of polyethylene oxide having the viscosity average molecular weight 100 kDa was prepared from 2 grams of sodium hyaluronan, 0.67 grams of polyethylene oxide, 56.0 mL of water and 58.4 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 1-4 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 13

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.39% by weight of sodium hyaluronan having the weight average molecular weight 2.05 MDa and 1.92% by weight of polyethylene oxide having the viscosity average molecular weight 400 kDa was prepared from 2 grams of sodium hyaluronan, 1.6 grams of polyethylene oxide and 80 mL of water. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 1-5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 14

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.34% by weight of sodium hyaluronan having the weight average molecular weight 2.05 MDa and 0.29% by weight of polyethylene oxide having the viscosity average molecular weight 5 MDa was prepared from 2 grams of sodium hyaluronan, 0.25 grams of polyethylene oxide and 83.3 mL of water. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.5-6 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 12).

Example 15

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.35% by weight of sodium hyaluronan having the weight average

molecular weight 2.05 MDa and 3.76% by weight of polyvinyl pyrrolidone having the weight average molecular weight 1.3 MDa was prepared from 2 grams of sodium hyaluronan, 3.2 grams polyvinyl pyrrolidone and 80 mL of water. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.25-6 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 13).

Example 16

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.66% by weight of sodium hyaluronan having the weight average molecular weight 2.05 MDa and 1.78% by weight of polyvinyl pyrrolidone having the weight average molecular weight 1.3 MDa was prepared from 2 grams of sodium hyaluronan, 1.33 grams polyvinyl pyrrolidone, 57.4 mL of water and 18.3 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.5-9 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 17

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.63% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 3.48% by weight of pullulan was prepared from 3 grams of sodium hyaluronan, 3.96 grams of pullulan and 107.1 mL of water. The viscosity of the 10% by weight of pullulan aqueous solution used at 30°C is 141 mPa·s. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 1-4 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 18

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.97% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 1.97% by weight of pullulan was prepared from 2 grams of sodium hyaluronan, 2 grams of pullulan, 83 mL of water and 18.7 mL of 2-propanol. The

viscosity of 10% by weight of pullulan aqueous solution used at 30°C is 141 mPa·s. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.7-3.5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 14).

Example 19

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 4.17% by weight of sodium hyaluronan having the weight average molecular weight 76 kDa and 12.5% by weight pullulan was prepared from 5 grams of sodium hyaluronan, 15 grams of pullulan and 100 mL of water. The viscosity of 10% by weight of pullulan aqueous solution used at 30°C is 141 mPa·s. The resulting fibers 12 having a diameter of 1-5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 20

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.14% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 0.11% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 2 grams of sodium hyaluronan, 0.1 grams of polyethylene oxide, 50.4 mL of water and 52.5 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.16 mL/min. The resulting fibers 12 having a diameter of 0.6-5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 21

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.93% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 1.29% by weight of polyvinyl pyrrolidone having the weight average molecular weight 1.3 MDa was prepared from 1.17 grams of sodium hyaluronan, 0.78 grams of polyvinyl pyrrolidone, 26.4 mL of water and 40.9 mL of ethanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter

of 1-8 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 22

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.55% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa and 0.62% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 0.98 grams of sodium hyaluronan, 0.39 grams of polyethylene oxide, 46.1 mL of water and 19.6 ml of acetone. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.4-4 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 23

The procedure was the same as in Example 1, only with the differences, that the spinning solution 9 containing 1.64% by weight of sodium hyaluronan having the weight average molecular weight 2.05 MDa, 1.64% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa and 0.41% by weight of calcium chloride was prepared from 2 grams of sodium hyaluronan, 2 grams of polyethylene oxide, 0.5 grams of calcium chloride and 117.6 mL of water. The absolute humidity of the drying air was 4 g/m^3 and the drying air was not directed by the cylinder. The collector 14 was located 80 cm under the extrusion needle. The resulting fibers 12 having a diameter of 1-6 micrometers were obtained from the collector 14 in the form of thin layers that were packed into a bulky 3D structure (cotton wool).

Example 24

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 2.66% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa, 1.78% by weight of polyvinyl pyrrolidone having the weight average molecular weight 1.3 MDa and 0.018% by weight of octenidine dihydrochloride was prepared from 3 grams of sodium hyaluronan, 2 grams of polyvinyl pyrrolidone, 0.02 grams of octenidine dihydrochloride, 86.1 mL of water and 27.4 mL of 2-propanol. The spinning solution

9 was extruded with the rate of 0.16 mL/min. The resulting fibers 12 having a diameter of 0.5-10 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 15).

Example 25

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.96% by weight of sodium hyaluronan having the weight average molecular weight 2.12 MDa, 0.65% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa, 0.118% by weight of tartrazine and 0.013% by weight of Patent Blue VF was prepared from 1.5 grams of sodium hyaluronan, 0.5 grams of polyethylene oxide, 90 miligrams of tartrazine, 10 milligrams of Patent Blue VF, 59.6 mL of water and 19.0 mL of 2-propanol. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 0.5-20 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 16).

Example 26

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 5.46% by weight of sodium hyaluronan having the weight average molecular weight 85 kDa, 1.82% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa and 1.82% by weight of carboxymethyl cellulose sodium salt having the weight average molecular weight 700 kDa was prepared from 6 grams of sodium hyaluronan, 2 grams of polyethylene oxide, 2 grams of carboxymethyl cellulose and 100 mL of water. The spinning solution 9 was extruded with the rate of 0.12 mL/min. The resulting fibers 12 having a diameter of 1-5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Basically the same result differing only in the substitution of carboxymethyl cellulose by oxycellulose can be achieved by the same procedure with the only difference, that spinning solution 9 containing 5.46% by weight of sodium hyaluronan having the weight average molecular weight 85 kDa, 1.82% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa and 1.82% by weight of oxycellulose (Okcel Ca-L, Synthesia a.s., Czech Republic) is prepared using 6 grams of sodium hyaluronan, 2 grams of polyethylene oxide, 2 grams oxycellulose and 100 mL of water. The resulting fibers 12 have diameter of 0.4-

1.4 micrometers and are obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 27

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 was extruded by the extrusion piece 11, which is an extrusion needle with the internal diameter of 210 micrometers, with the rate of 0.08 mL/min. The heated air had the temperature of 80°C and its volume flow was 300 L/min, which corresponds to the average air velocity of 42 m/s. The resulting fibers 12 having a diameter of 2-8 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 28

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 was extruded by an extrusion needle with an internal diameter of 210 micrometers, with the rate of 0.08 mL/min. The air having the temperature of 32°C was flowing through the main outlet opening 4 in the center of the air nozzle 5, in which the extrusion piece 11 (extrusion needle) was located coaxially, having the volume flow of 60 L/min, corresponding to the average air velocity was 142 m/s. The heated air had temperature of 231°C and volume flow 150 L/min, so the average air velocity of 21 m/s. The resulting fibers 12 having a diameter of 9-25 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 29

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 was extruded by the extrusion needle having an internal diameter of 210 micrometers, with the rate of 0.08 mL/min. Through the outlet opening 4 in the center of the air nozzle 5, in which the extrusion needle was located coaxially, the air was flowing with the temperature of 29°C and with the volume flow of 40 L/min, corresponding to the average air velocity was 94 m/s. The heated air had temperature of 105°C and volume flow of 400 L/min, corresponding to the average air velocity of 56 m/s. The resulting fibers 12 having a diameter of 1.5-9

micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 17).

Example 30

The procedure was the same as in Example 2, only with the differences, that the spinning solution 9 was extruded by the extrusion piece 11, which was a conical extrusion needle Tecdia ARQUE-S having an internal diameter of 100 micrometers. The resulting fibers 12 having a diameter of 0.5-2.5 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 18).

Example 31

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 was extruded by the extrusion piece 11, which was an extrusion needle with an internal diameter of 410 micrometers, with the rate of 0.2 mL/min. The resulting fibers 12 having a diameter of 20-70 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool) (Fig. 19).

Example 32

The procedure was the same as in Example 2, only with the differences, that the extrusion piece 11 was an extrusion needle, which had 4 capillaries 20 mm long with an internal diameter of 200 micrometers and the blunt ends of the capillaries formed the vertices of a square with a side of 4.5 mm. The spinning solution 9 was extruded with the rate of 0.1 mL/min per one capillary. The resulting fibers 12 having a diameter of 0.3-10 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 33

The procedure was the same as in Example 5, only with the differences, that the spinning solution 9 was extruded by the extrusion needle with an internal diameter of 210 micrometers, with the rate of 0.08 mL/min. The surface of the collector 14 was covered with a low-density polyethylene foil (LDPE). The resulting non-woven fabric, which can be easily removed from

the collector 14 surface, has the area weight of 11 g/m^2 and is made of fibers 12 having a diameter of 5-20 micrometers.

Example 34

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 3.07% by weight of sodium hyaluronan having the weight average molecular weight of 86 kDa and 2.05% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 2.5 grams of sodium hyaluronan, 1.67 grams of polyethylene oxide, 46.4 mL of water and 39.4 mL of 2-propanol. The spinning solution 9 was extruded by an extrusion needle having an internal diameter of 210 micrometers, with the rate of 0.52 mL/min. The resulting fibers 12 having a diameter of 6-60 micrometers were obtained from the collector 14 in the form of a porous non-woven fabric.

Example 35

The procedure was the same as in Example 4, only with the differences, that the spinning solution 9 was extruded with the rate of 0.1 mL/min, with the drying air volume flow of 75 L/min, which corresponds to the average air velocity of 100 m/s, and the distance of the collector 14 from the extrusion needle was 50 cm. The resulting fibers 12 having a diameter of 0.25-5 micrometers were obtained from the collector 14 in the form of thin layers that were packed into a 3D structure (cotton wool).

Example 36

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 1.60% by weight of sodium hyaluronan having the weight average molecular weight 2.15 MDa and 0.53% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 2 grams of sodium hyaluronan, 0.67 grams of polyethylene oxide, 67.2 mL of water and 70 mL of 2-propanol. The air with a temperature of 28°C was flowing through the main outlet opening 4 in the center of air nozzle 5, in which an extrusion needle, i.e., the extrusion piece 11, was located coaxially, with the volume flow of 50 L/min, corresponding to the average air velocity of 118 m/s. No air flowed from the two additional outlet openings 4a, 4b of the nozzle 5. The resulting fibers 12 having a diameter of

0.6-3.2 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Example 37

The procedure was the same as in Example 3, only with the differences, that the spinning solution 9 containing 20.3% by weight of sodium hyaluronan having the weight average molecular weight 30 kDa and 1.63% by weight of polyethylene oxide having the viscosity average molecular weight 1 MDa was prepared from 25 grams of sodium hyaluronan, 2 grams of polyethylene oxide, 72.0 mL of water and 30.6 mL of 2-propanol. The spinning solution 9 was extruded through the extrusion piece 11, which was an extrusion needle having an internal diameter of 340 micrometers, with the rate of 0.36 mL/min. The resulting fibers 12 having a diameter of 41-88 micrometers were obtained from the collector 14 in the form of a bulky 3D structure (cotton wool).

Overview of reference signs in the drawings:

1 compressor
2 heating element
4 main outlet opening of the air nozzle
4a, 4b additional outlet openings of the air nozzle
5 air nozzle
8 dosing device
81 piston
9 spinning solution
10 tube
11 extrusion piece
11a dispensing opening
12 fibers
13 focusing part
14 collector
15 cooling liquid channel
15a inlet opening
15b outlet opening

CLAIMS

1. A method of production of fibers based on hyaluronic acid and/or a water-soluble metal salt thereof and/or a derivative thereof by the method of dry spinning and/or solution blow spinning, **characterized in that** a spinning solution is prepared, containing:

- 0.5 to 22% by weight of hyaluronic acid and/or a water-soluble metal or non-metal salt thereof or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative, where the water-soluble metal or non-metal salt of hyaluronic acid is selected from the group comprising Na^+, K^+, Li^+, Ca^{2+}, Mg^{2+}, Ag^+, Au^+, Zn^{2+}, Cu^{2+}, NH_4^+ salt of hyaluronic acid and the hyaluronic acid derivative is selected from the group comprising hyaluronan chloramide, hyaluronan 3-(2-furanyl)acryloyl ester, hyaluronan tyramine, hyaluronan benzyl ester, hyaluronan ethyl ester and acylated hyaluronan derivatives selected from the group comprising capronoyl, capryloyl, caprinoyl, lauroyl, myristoyl, palmitoyl, stearoyl, oleoyl hyaluronan,
- 0.1 to 13% by weight of spinning-aid polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyvinyl alcohol and pullulan,
- 0 to 54% by weight of organic solvent and
- 44 to 98% by weight of water,

and after complete dissolution of the polymer, the spinning solution is extruded through an extrusion piece having at least one opening having the diameter of 80 to 410 μm with the rate of 0.01 to 0.52 mL/min into a stream of drying air, resulting in fibers that are carried towards the collector.

2. The method of production of fibers according to claim 1, **characterized in that** the spinning solution contains:

- 1 to 22% by weight of hyaluronic acid and/or a water-soluble metal or non-metal salt thereof or a water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or hyaluronic acid derivative,
- 0.25 to 3% by weight of spinning-aid polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyvinyl alcohol and pullulan,

- 30 to 45% by weight of organic solvent, which is isopropyl alcohol, and
- 52 to 68% by weight of water.

3. The method of production of fibers according to any of claims 1 to 2, characterized in that the spinning-aid polymer is polyethylene oxide having the viscosity average molecular weight in the range of 0.4 to 1 MDa.

4. The method of production of fibers according to any of claims 1 to 3, **characterized in that** the spinning solution of hyaluronic acid derivative, which is hyaluronan chloramide, or a mixture of a hyaluronic acid derivative, which is hyaluronan chloramide, and native hyaluronic acid is used, wherein the substitution degree of hyaluronan chloramide is in the range from 0.1% to 100%, preferably 50 to 100%.

5. The method of production of fibers according to any of claims 1 to 4, **characterized in that** the weight average molecular weight of hyaluronic acid and/or the water-soluble metal or non-metal salt thereof and/or the hyaluronic acid derivative is within the range from 10 kDa to 2.5 MDa.

6. The method of production of fibers according to any of claims 1 to 5, **characterized in that** the organic solvent is selected from the group comprising methanol, tetrahydrofuran, methyl acetate, methyl ethyl ketone, 1,2-dimethoxyethane, acetonitrile, isopropyl alcohol, 1-propanol, ethanol and acetone.

7. The method of production of fibers according to any of claims 1 to 6, **characterized in that** the spinning solution is prepared first by dispersing hyaluronic acid and/or the water-soluble metal or non-metal salt or the water-soluble mixture of metal and/or non-metal salts of hyaluronic acid and/or the hyaluronic acid derivative in an organic solvent, water is added to the resulting dispersion with thorough mixing, and then the solution is stirred for 1 to 24 hours at temperature 20 to 30°C until the polymer is completely dissolved.

8. The method of production of fibers according to any of claims 1 to 7, **characterized in that** the prepared spinning solution is filled into a cartridge, which is sealed and connected to the compressed air of +500 to +700 kPa for 1 to 8 hours until the gas bubbles dissolve.

9. The method of production of fibers according to any of claims 1 to 8, **characterized in that** the spinning solution further contains an additional polymer, preferably carboxymethyl cellulose or oxycellulose, and/or a pharmaceutically and/or cosmetically acceptable low molecular weight substance selected from the group comprising antibacterial agents, preferably octenidine dihydrochloride or carbethopendecinium bromide, antivirals, preferably acyclovir, antifungals, preferably clotrimazole or terbinafine, drugs, preferably lidocaine hydrochloride, vitamins, preferably riboflavin, plant extracts, preferably bisabolol, surfactants, preferably polysorbate 80, peptides, preferably antimicrobial peptides, preferably cathelicidine LL-37, pexiganan MSI-78, WR-12, wound healing promoting peptides, preferably dalargin, TP-508, biotin-GHK, hormonal peptides, preferably lysipressin, terlipressin, dyes, preferably Patent Blue VF.

10. The method of production of fibers according to any of claims 1 to 9, **characterized in that** the drying air temperature is in the range from 15 to 250°C, preferably 15 to 190°C, and the absolute humidity of the drying air is in the range from 0 to 14 g/m^3, preferably 0 to 2 g/m^3, and the drying air flow rate is in the range from 1.6 to 315 m/s, preferably 5 to 260 m/s.

11. The method of production of fibers according to any of claims 1 to 10, **characterized in that** the fibers are deposited on a collector, which is covered with an inert material having a low surface energy, preferably with polytetrafluoroethylene or polyethylene, from which the fibers are easily removed, or on a collector, which is covered with a textile, preferably polyester knitted fabric, which remains a part of the final product.

12. The method of production of fibers according to any of claims 1 to 10, **characterized in that** the fibers are deposited on the collector, which is an implantable medical device.

13. The method of production of fibers according to any of claims 1 to 12, **characterized in that** the fibers have a diameter of 100 nm to 100 μm and that they form a non-woven 2D or 3D fabric on the collector, the fabric having an area weight of 0.1 to 120 g/m^2.

14. A device for carrying out the method according to any of claims 1 to 13, **characterized in that** it comprises:

- an extrusion piece (11) containing a pass-through channel, which has an inlet opening for feeding a spinning solution (9) and at least one dispensing opening (11a) for dispensing the spinning solution (9), and
- an air nozzle (5), wherein its main outlet opening (4) for exiting air is arranged to direct the exiting air into the area surrounding the dispensing opening (11a) of the extrusion piece (11) parallel to the axis of the dispensing opening (11a) of the extrusion piece (11), the air nozzle (5) comprising additional outlet openings (4a, 4b) that are arranged to direct the additional air flow to the area under the dispensing opening (11a) into the air flow from the main outlet opening (4) at an angle of 30 to 60°, preferably 40 to 50°, most preferably 45°,
- at least one cooling channel (15) for directing the cooling liquid through the air nozzle (5) walls.

15. The device according to claim 14, **characterized in that** it comprises a collector (14), arranged in a certain distance from the extrusion piece (11), wherein the dispensing opening (11a) of the extrusion piece (11) faces the collection surface of the collector (14).

16. The device according to claim 15, **characterized in that** the collector (14) is in the form of a cylinder, a cylinder formed by bars, an inverted cone formed by bars, or in the form of an implantable medical device.

17. The device according to claim 14 or 15 or 16, **characterized in that** it comprises a focusing part (13) that is arranged between the collector (14) and the dispensing opening (11a) of the extrusion piece (11) and comprises a pass-through cavity, the axis of which is identical to the axis of the dispensing opening (11a).

18. The device according to any of claims 14 to 17, **characterized in that** the main outlet opening (4) of the air nozzle (5) is annular or circular and arranged coaxially with the dispensing opening (11a) of the extrusion piece (11) and/or the main outlet opening (4) of the air nozzle (5) is arranged at a greater distance from the collector (14) than the dispensing opening (11a).

19. The device according to any of claims 14 to 18, **characterized in that** it comprises a compressor (1) for feeding the air to the air nozzle (5).

20. The device according to any of claims 14 to 19, **characterized in that** it comprises a heating element (2) for heating the air fed to the additional outlet openings (4a, 4b) of the air nozzle (5).

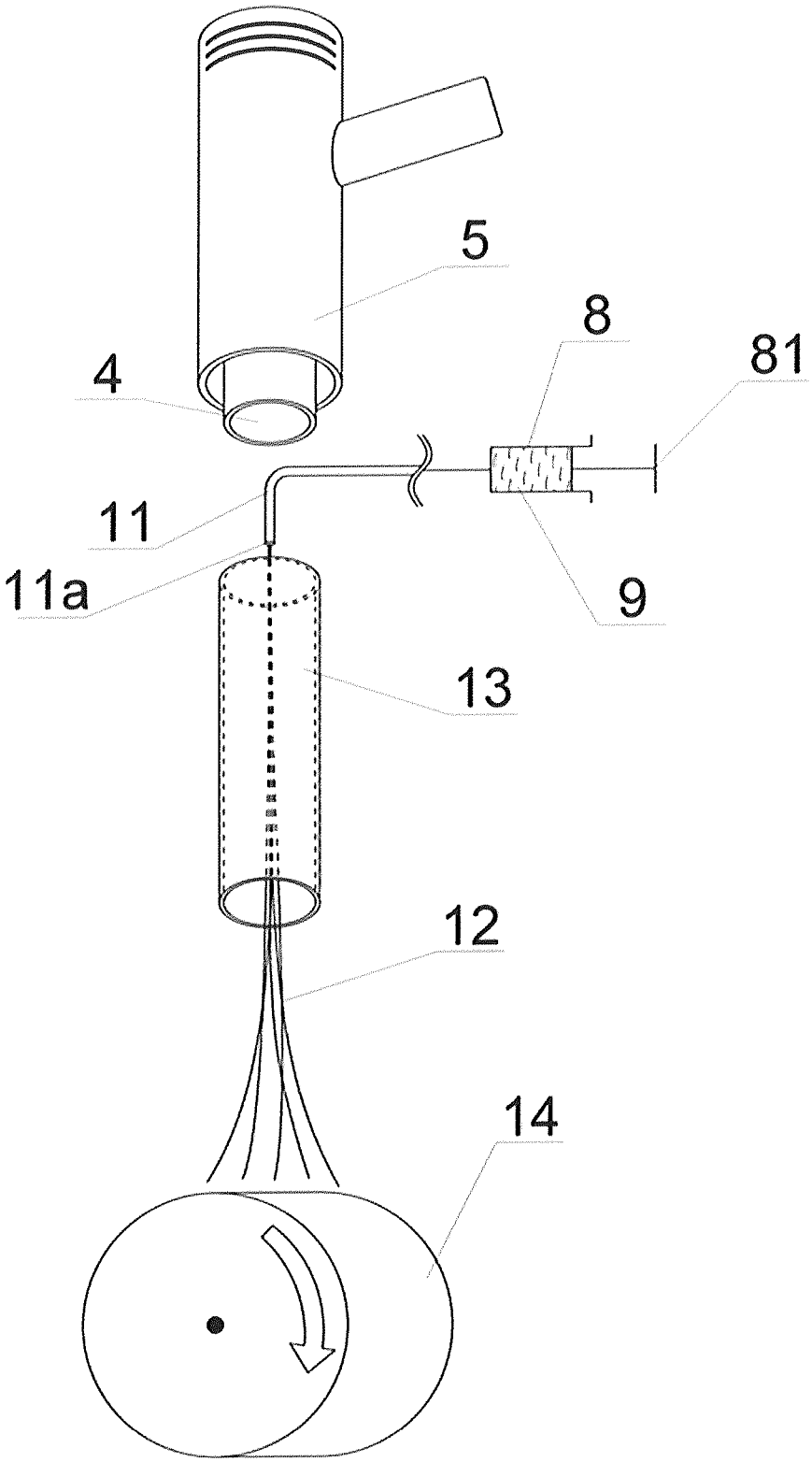


Fig. 1 (not part of the invention)

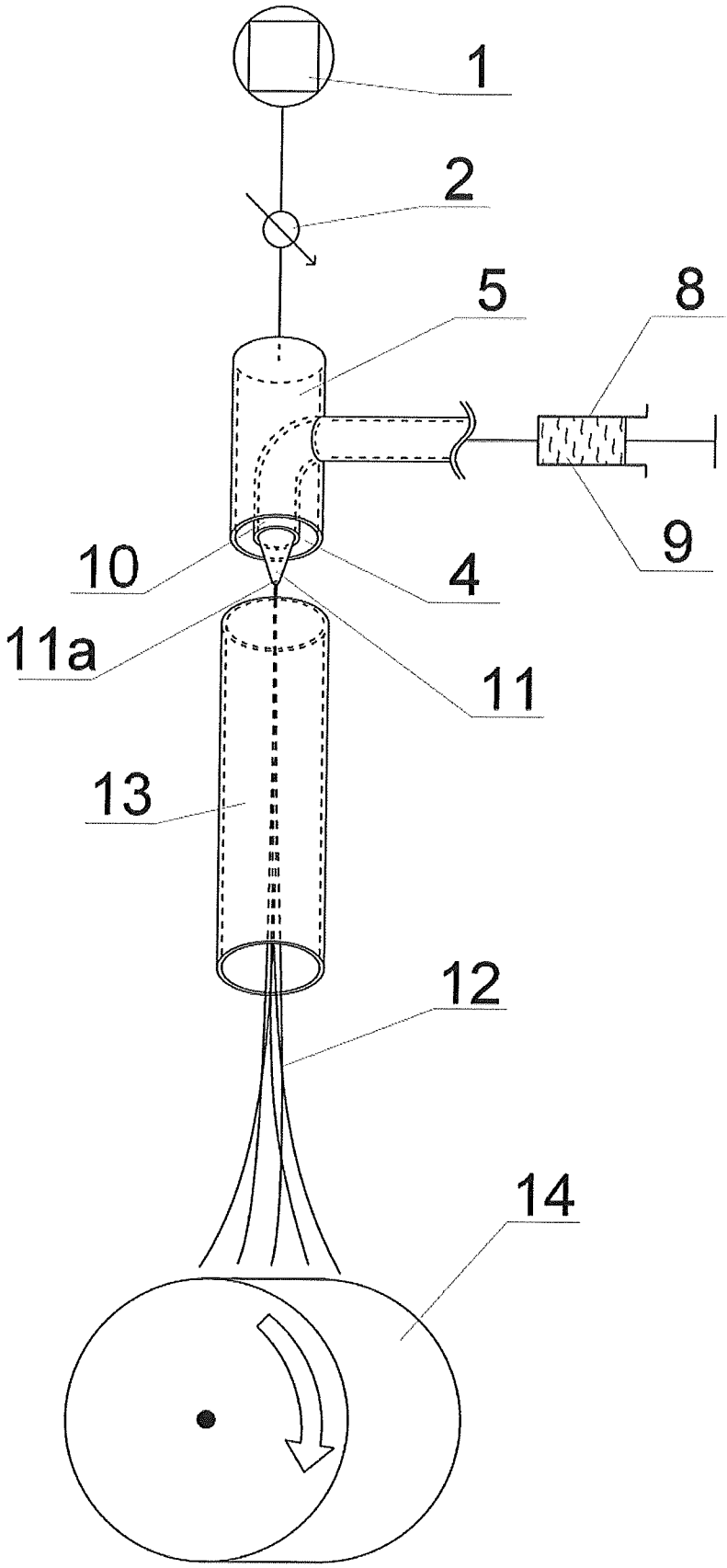


Fig. 2 (not part of the invention)

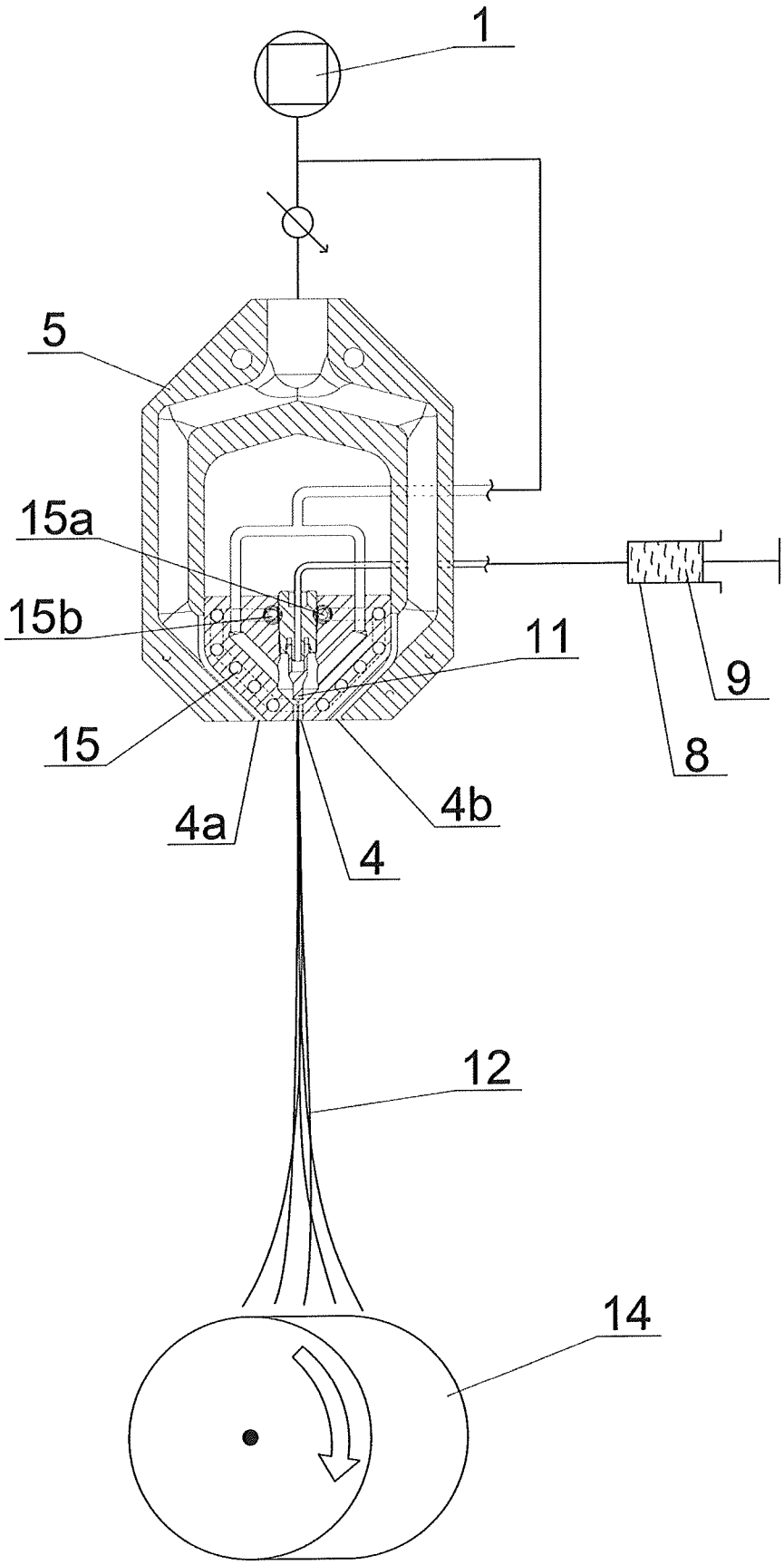


Fig. 3A

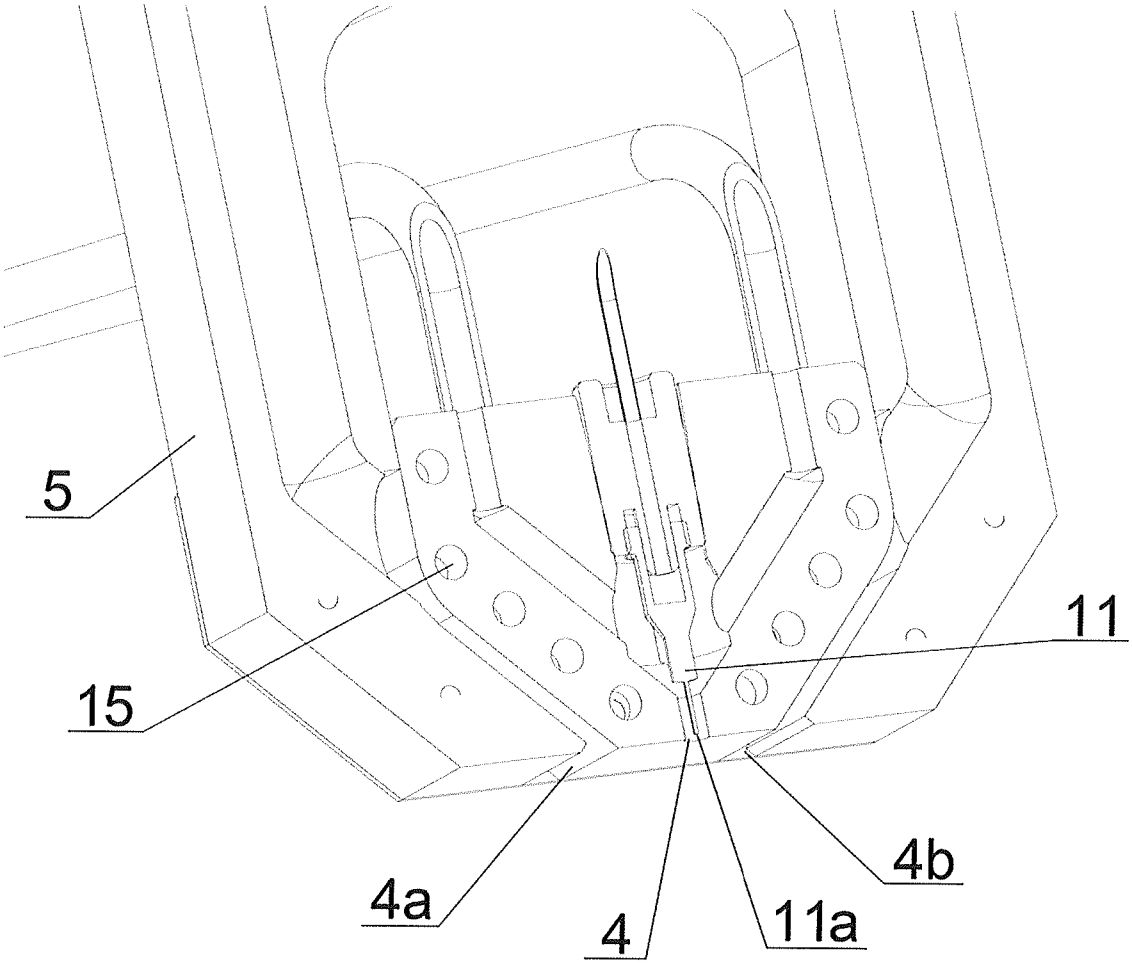


Fig. 3B

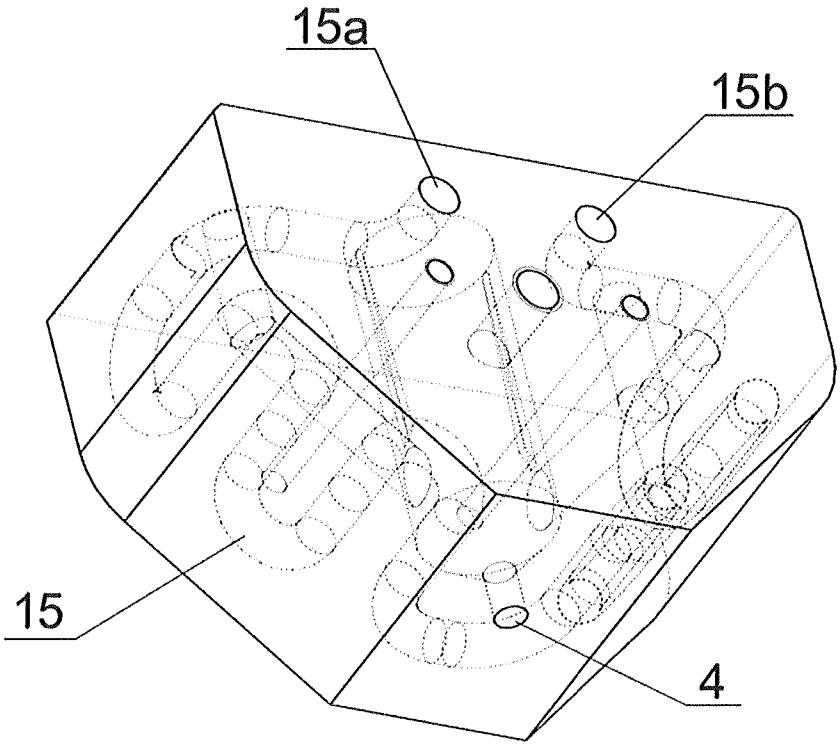


Fig. 3C

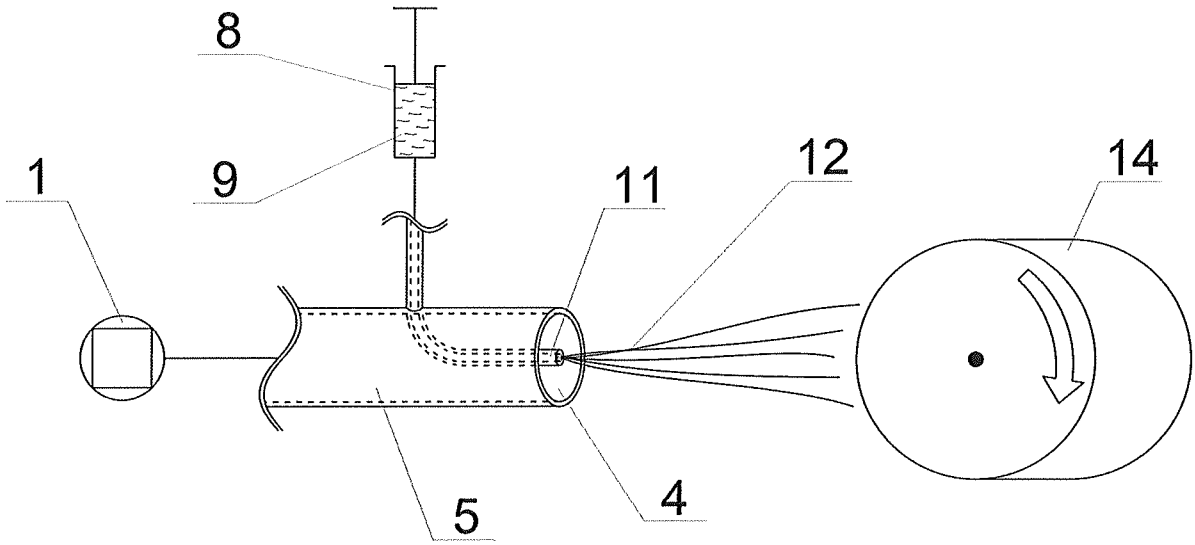


Fig. 4

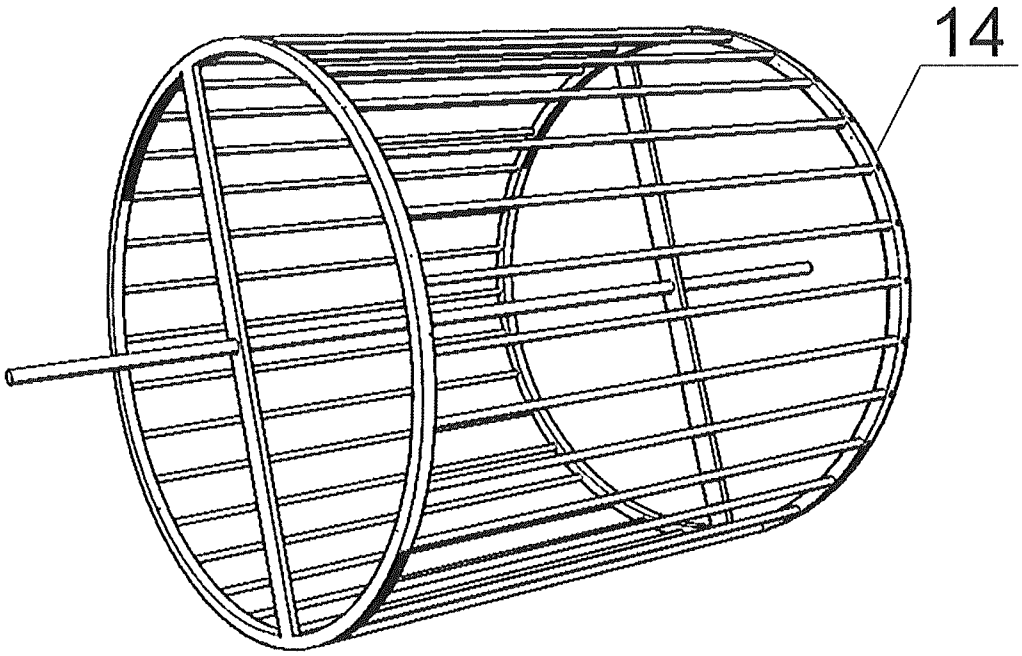


Fig. 5

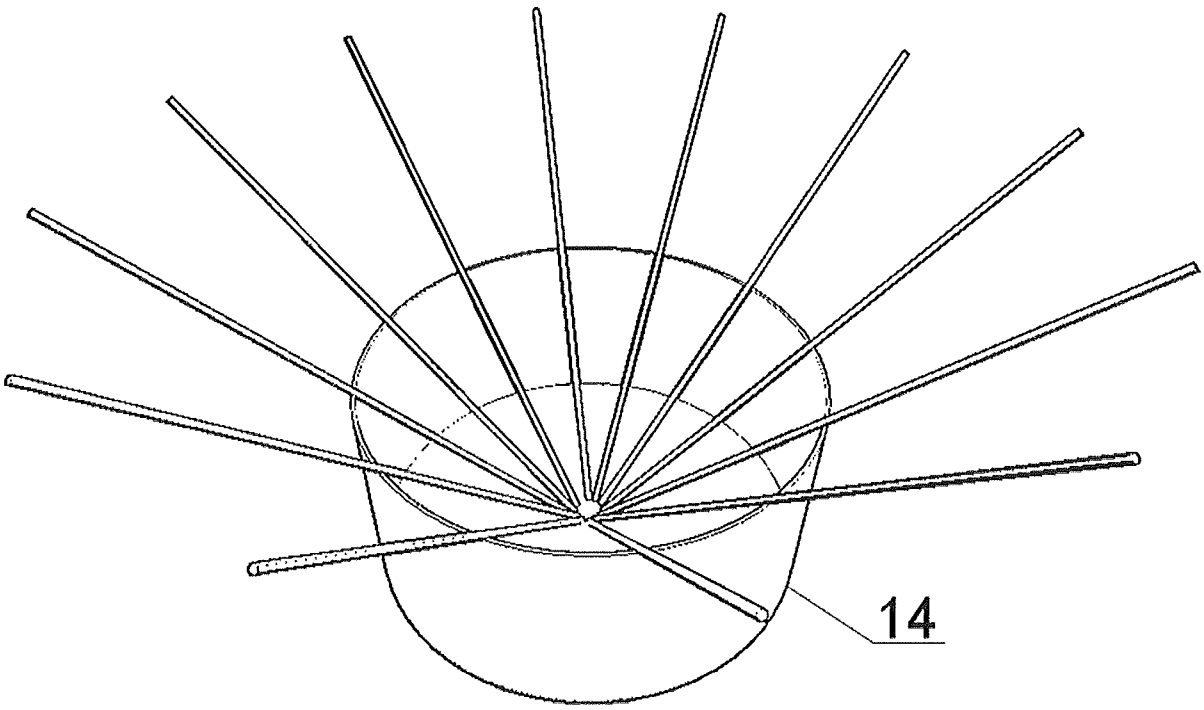


Fig. 6

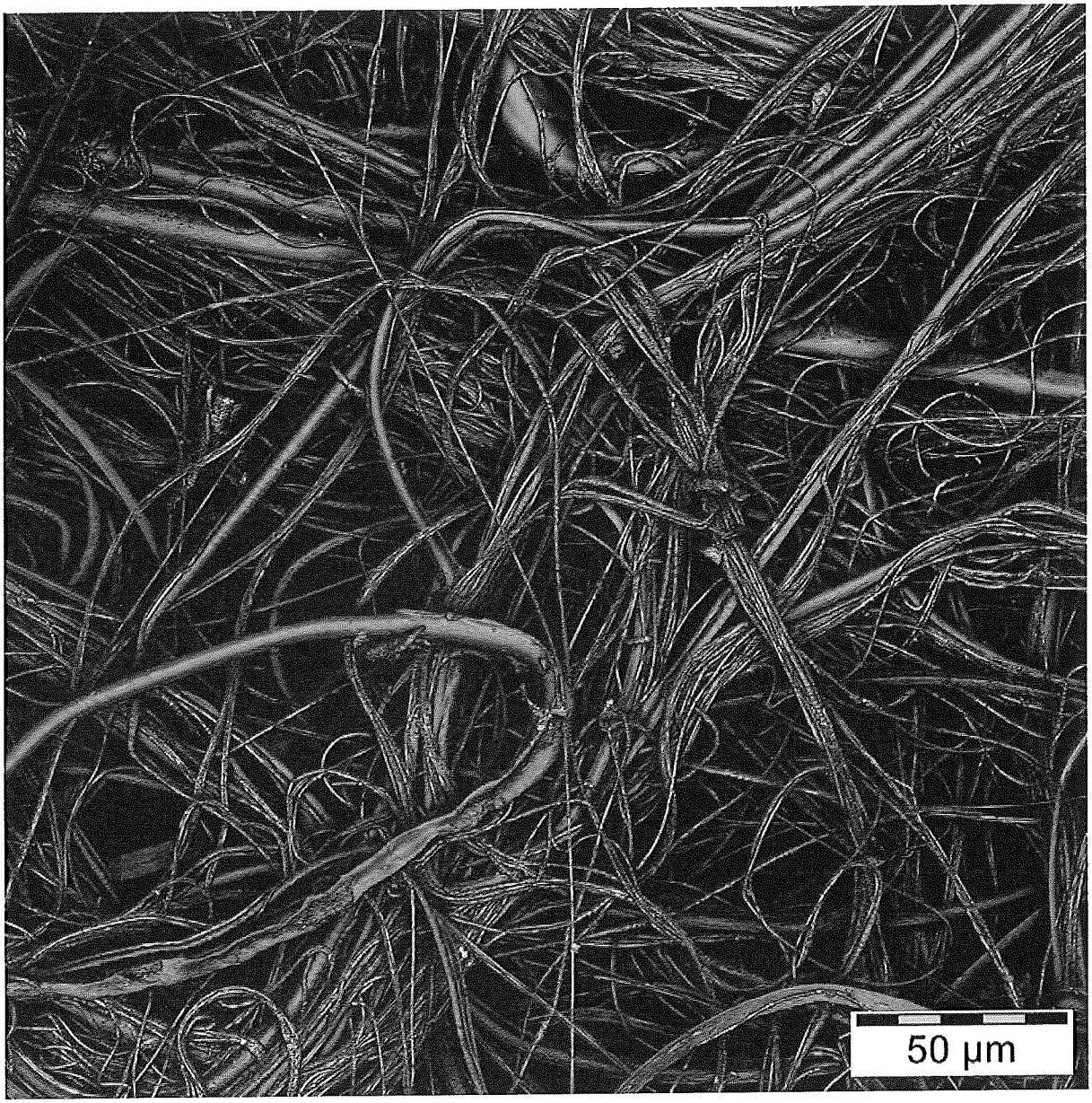


Fig. 7

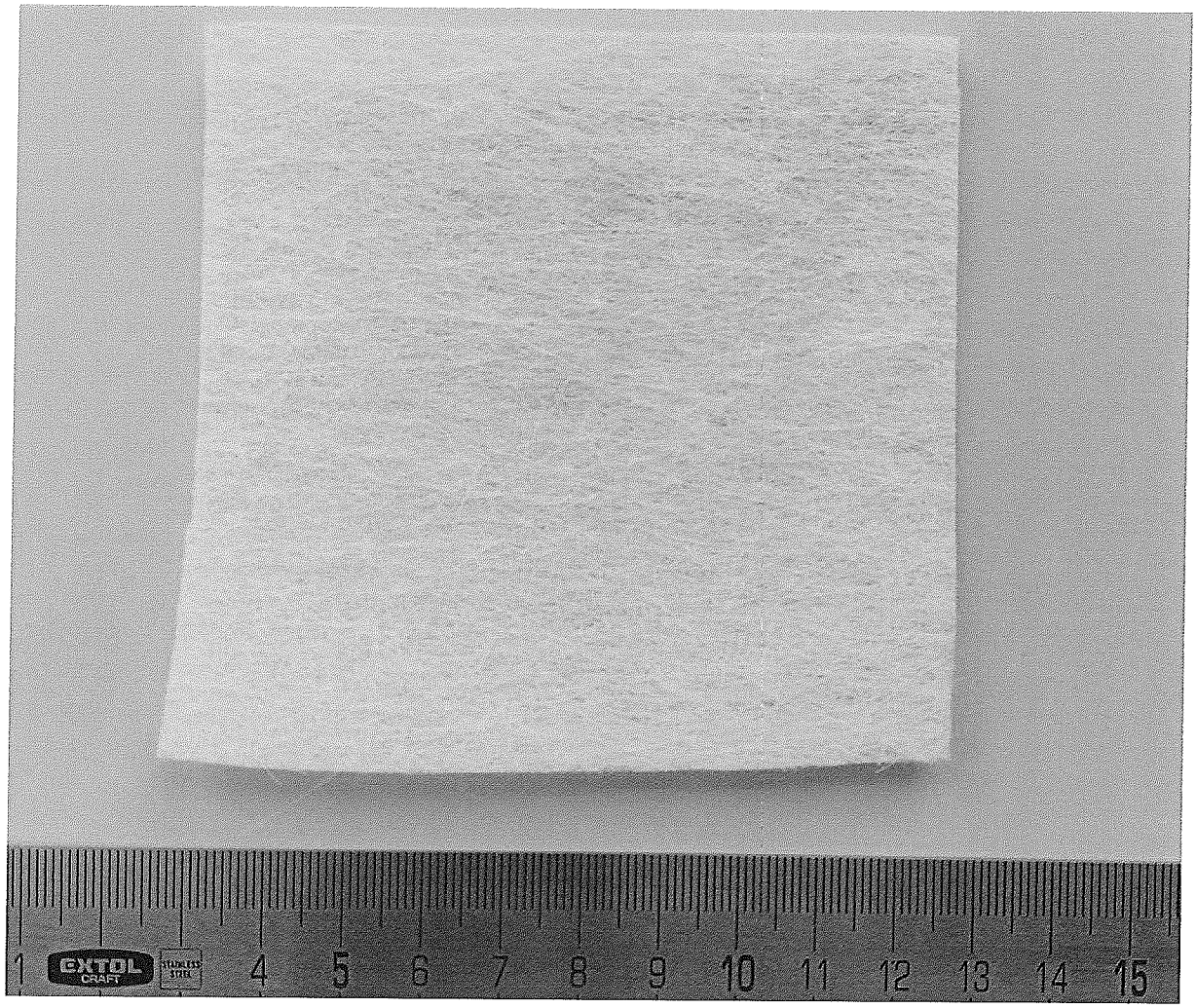


Fig. 8A

Fig. 8B

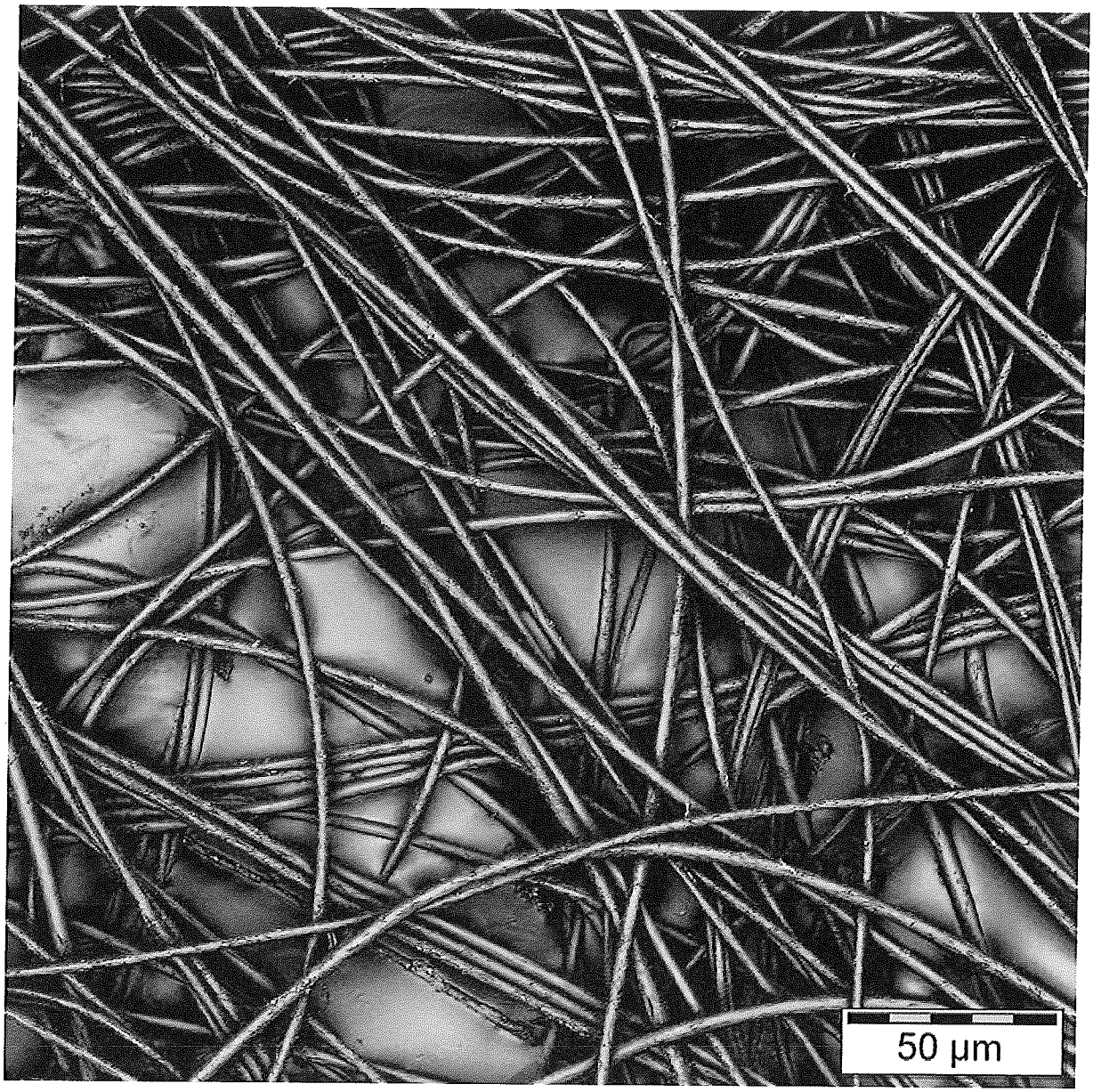


Fig. 9

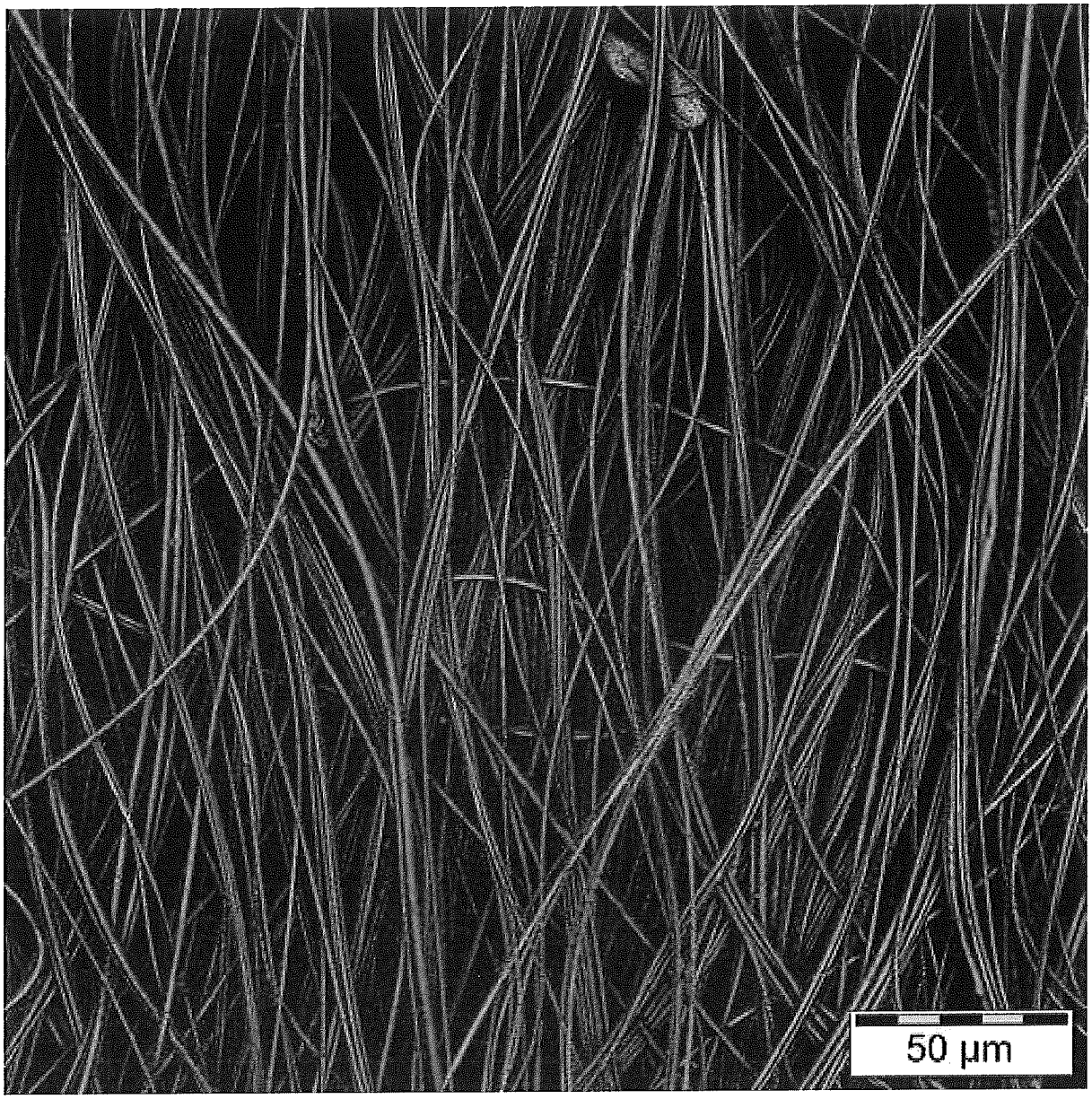


Fig. 10A

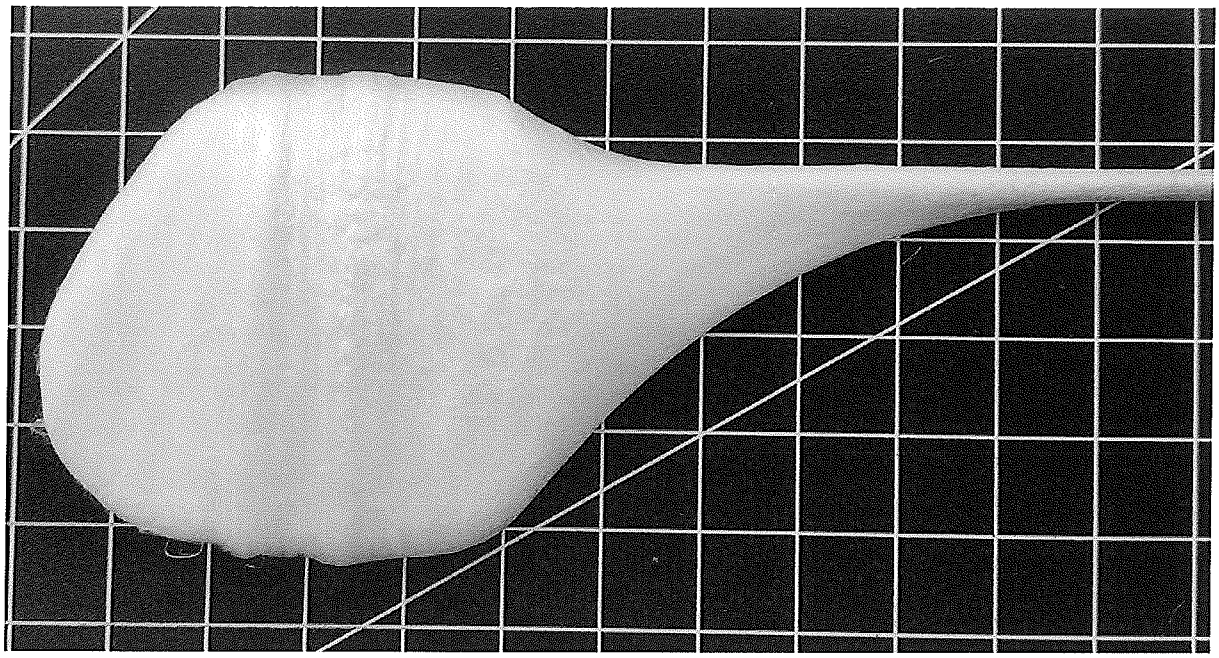


Fig. 10B

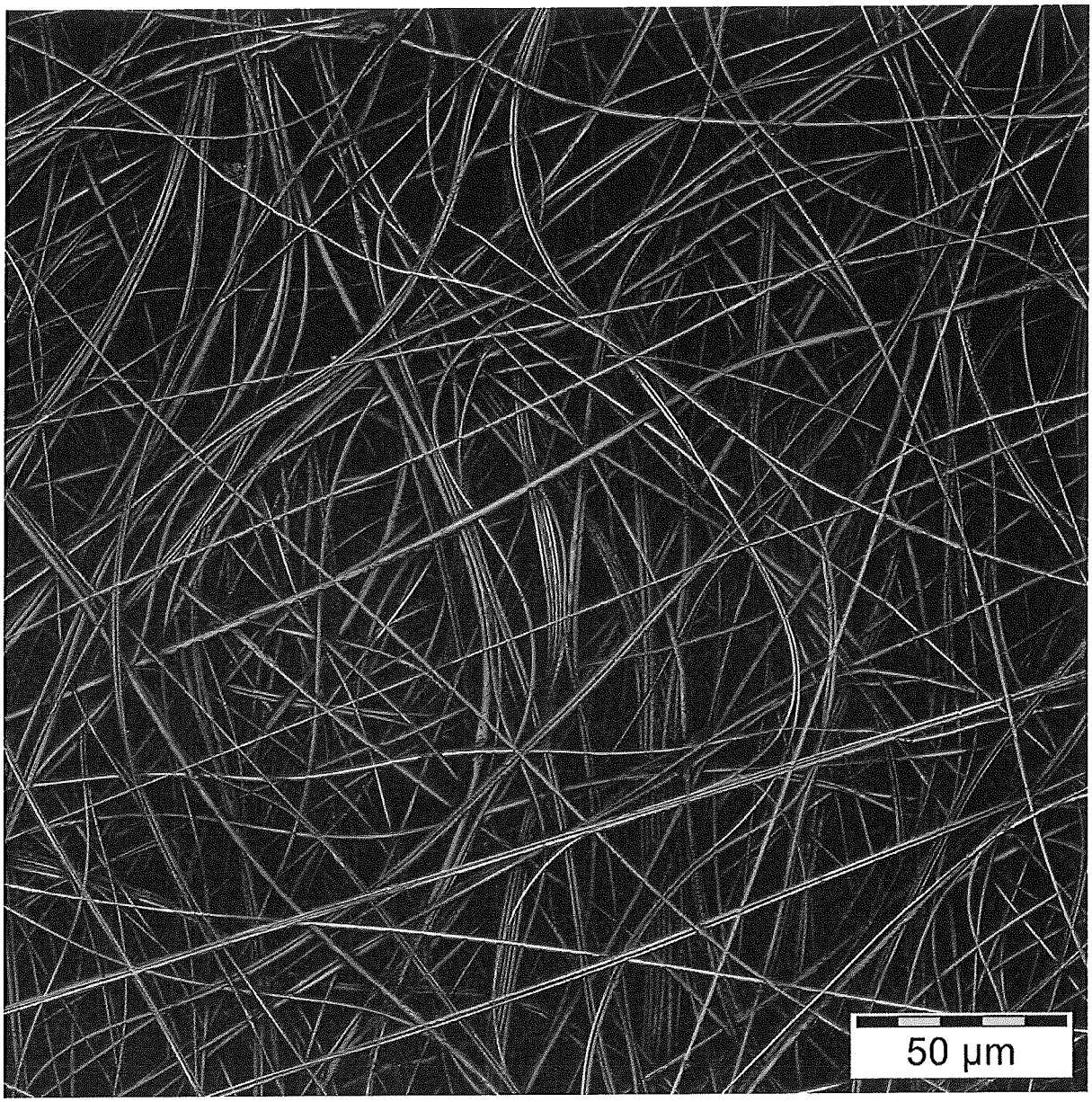


Fig. 11A

Fig. 11B

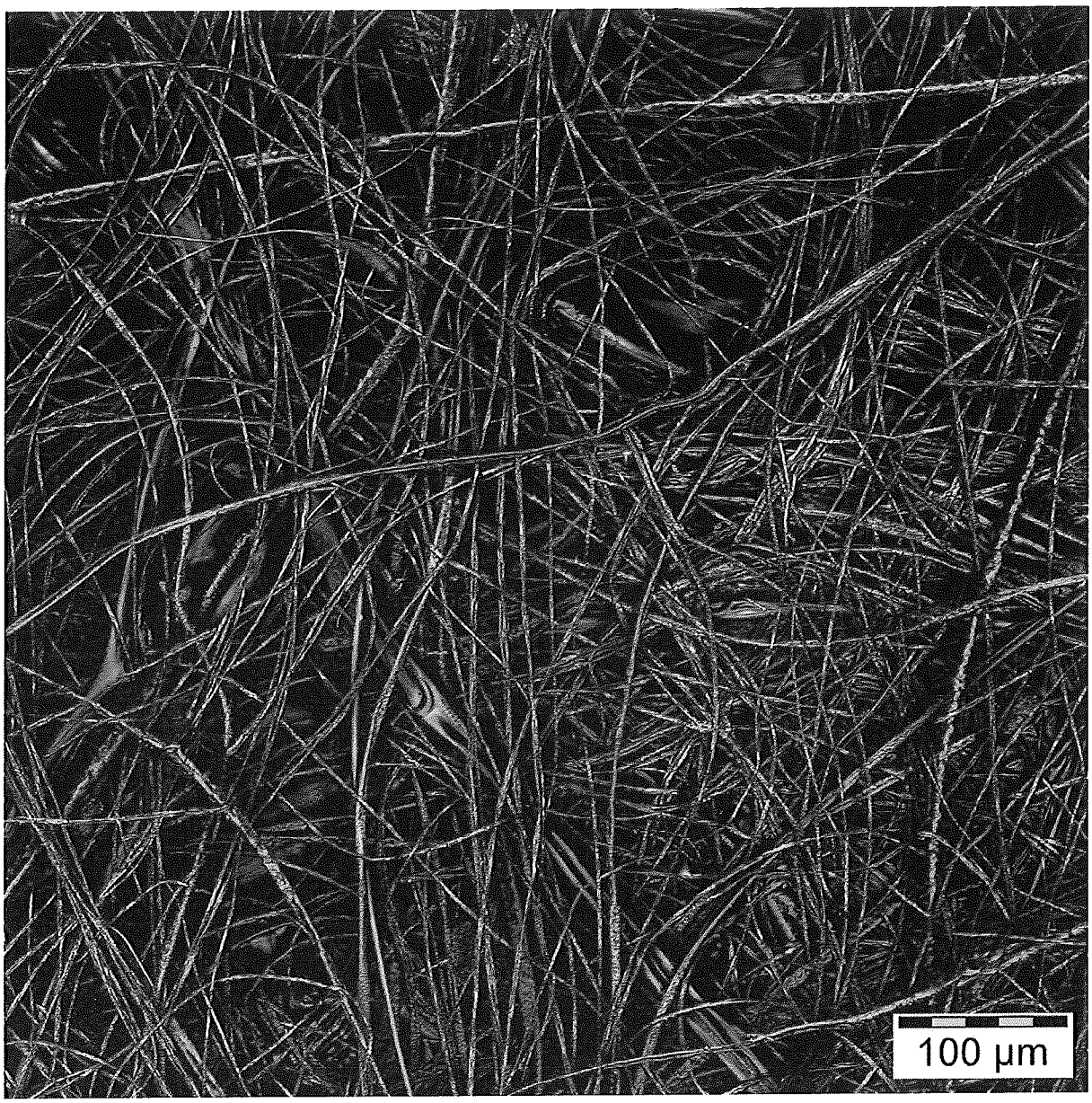


Fig. 12

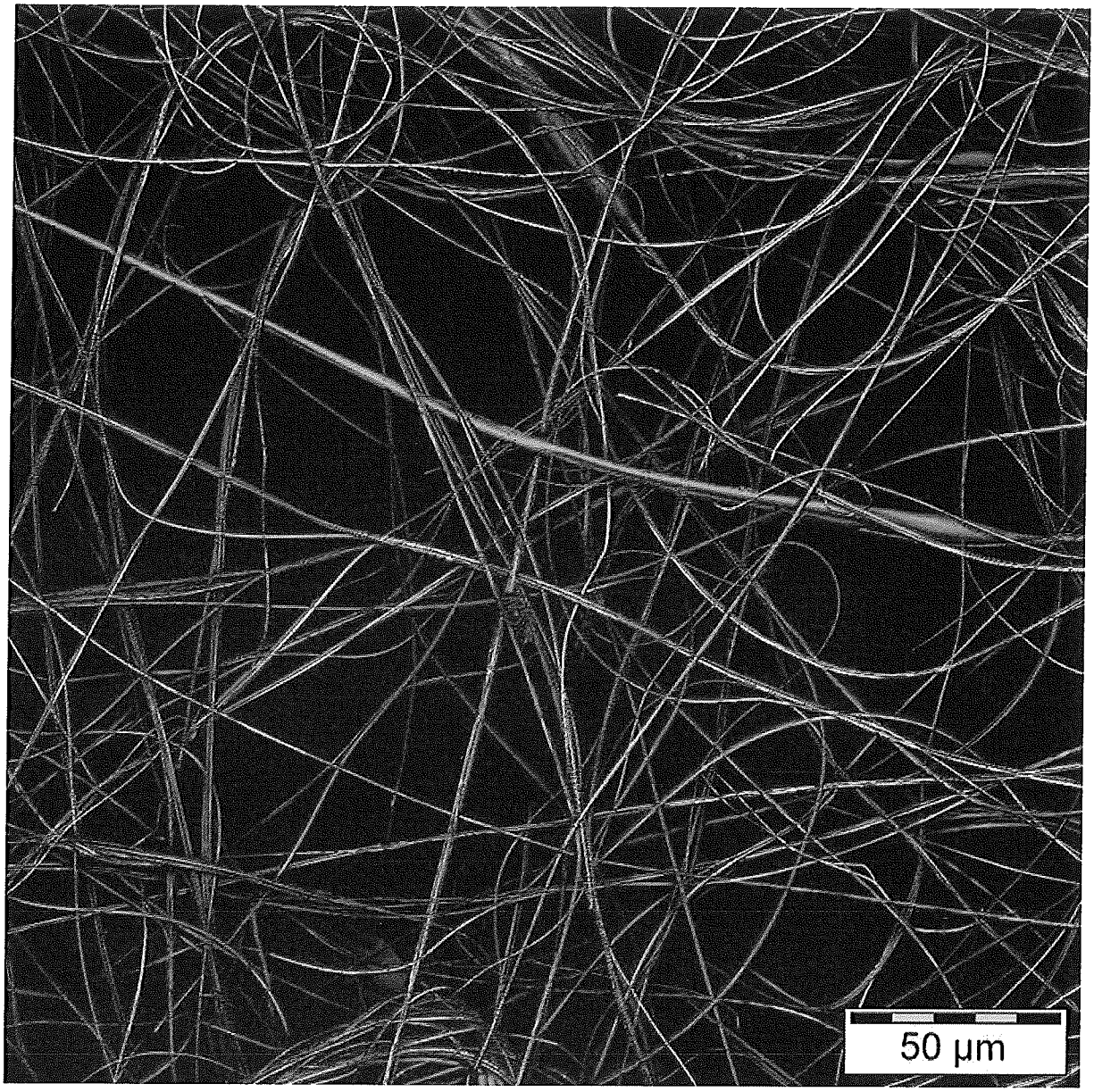


Fig. 13

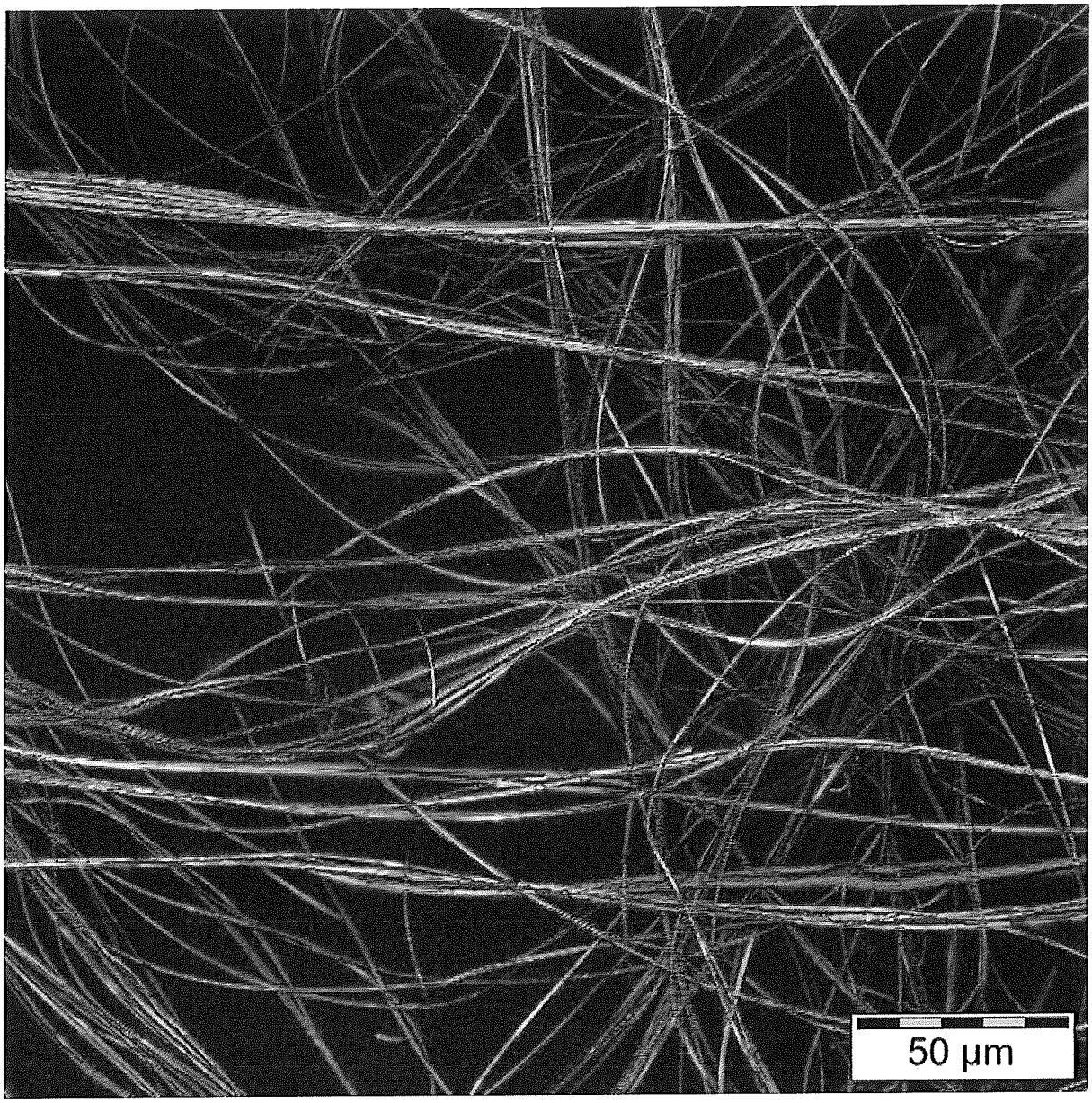


Fig. 14

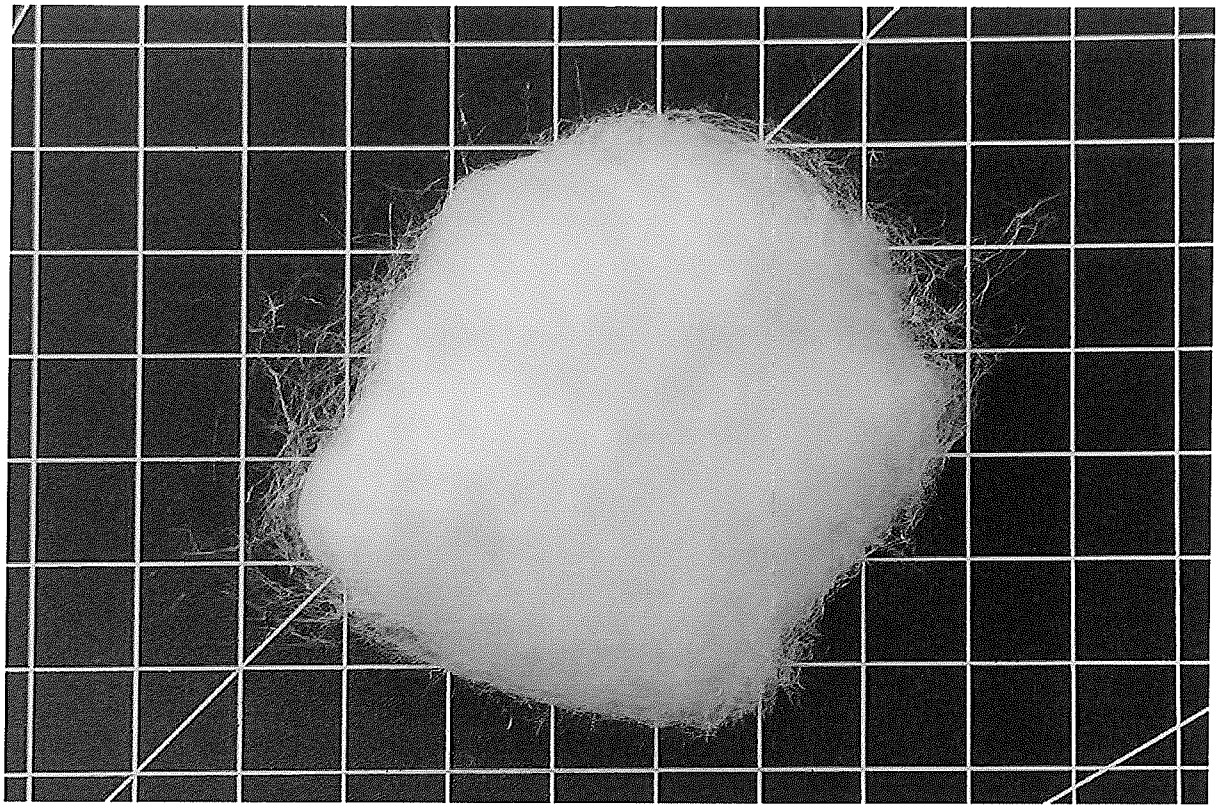


Fig. 15

Fig. 16

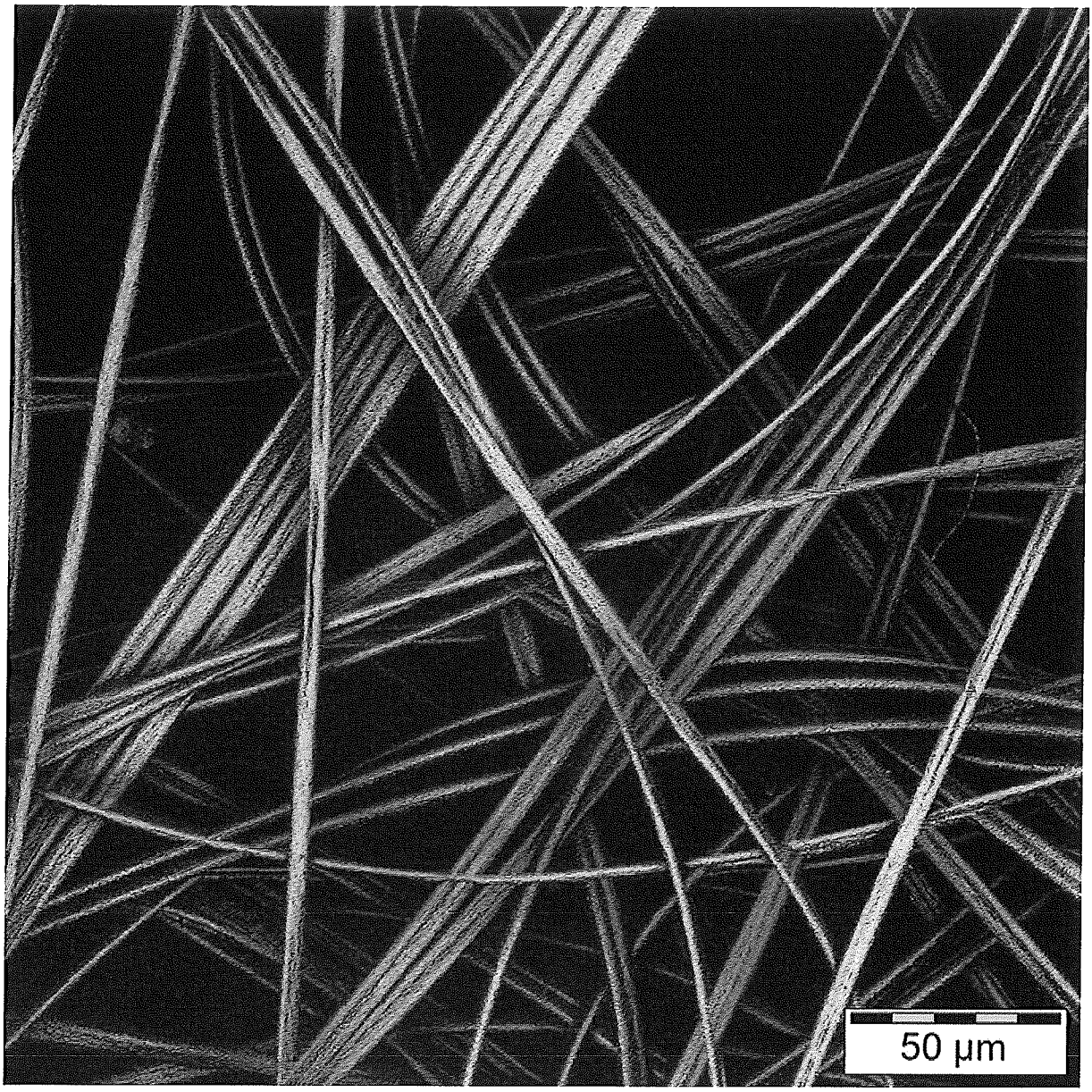


Fig. 17

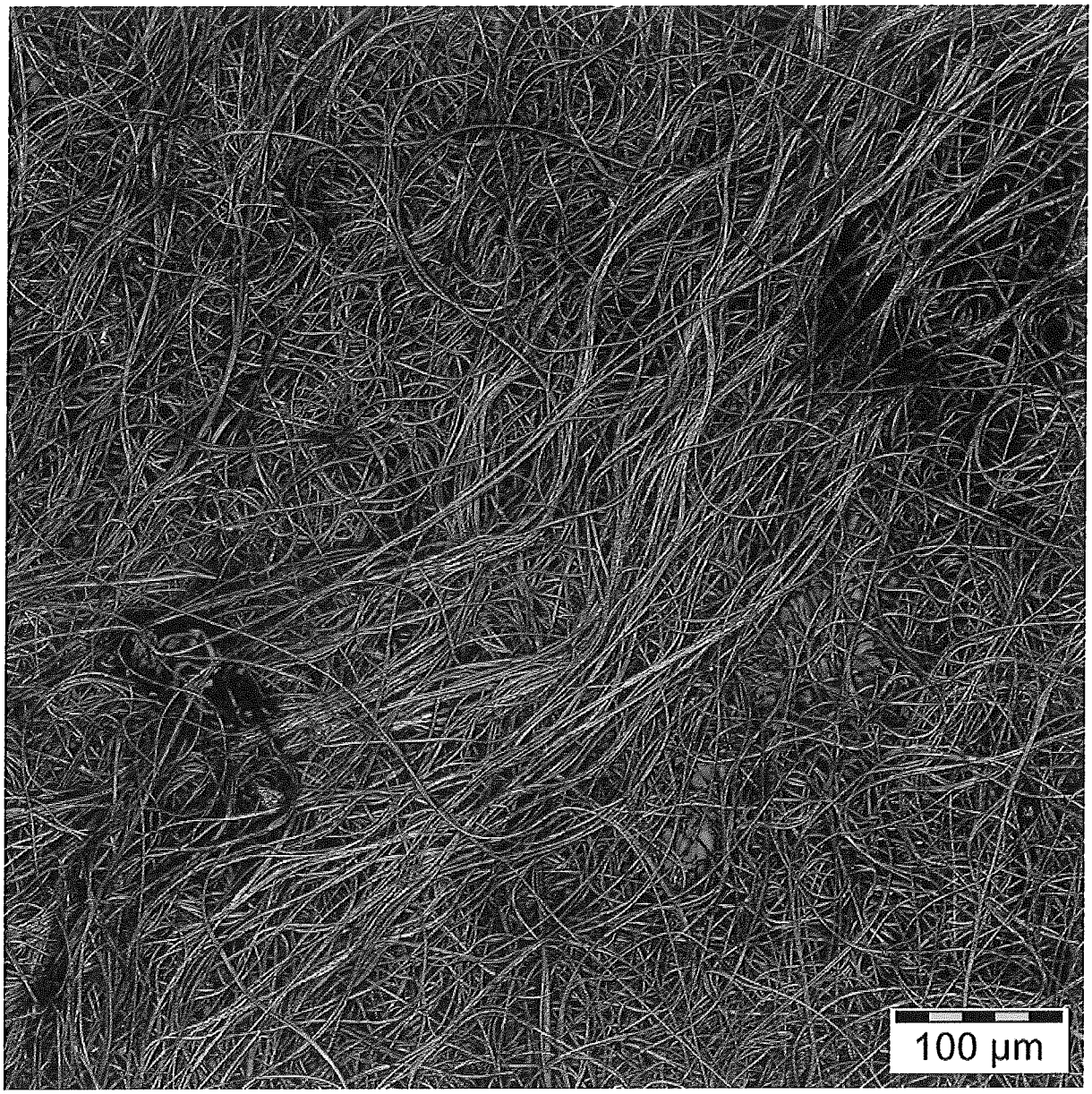


Fig. 18

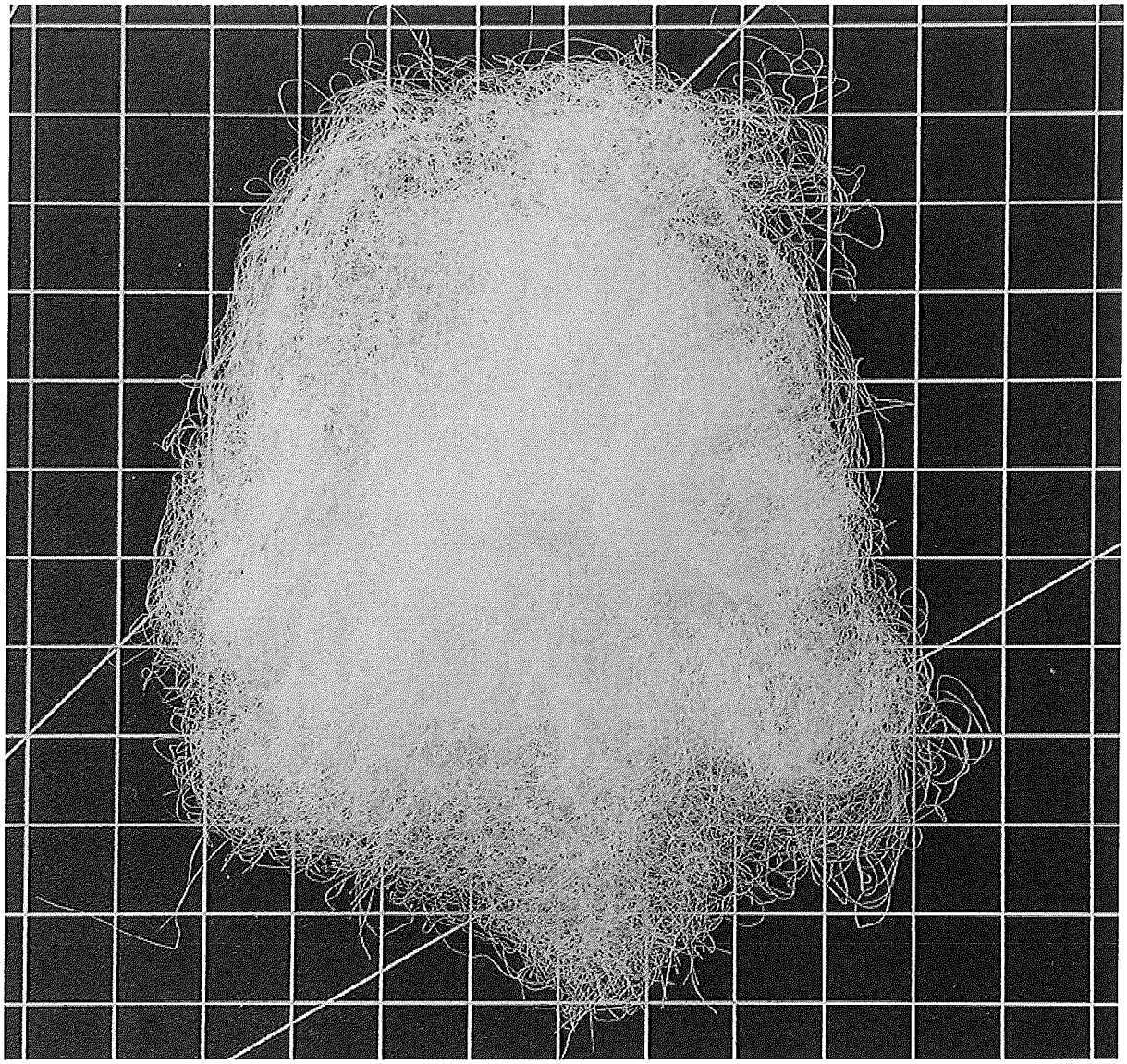


Fig. 19

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2024/050016

A. CLASSIFICATION OF SUBJECT MATTER
INV. D01D1/02 D01D5/04 D01D5/14
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)
D01D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	claims 1,4,16 figures 6,7 paragraph [0069]	1-13
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2024	19/09/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Queste, Sébastien

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 2013/309494 A1 (BURGERT LADISLAV [CZ] ET AL) 21 November 2013 (2013-11-21) claim 1	1-20
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