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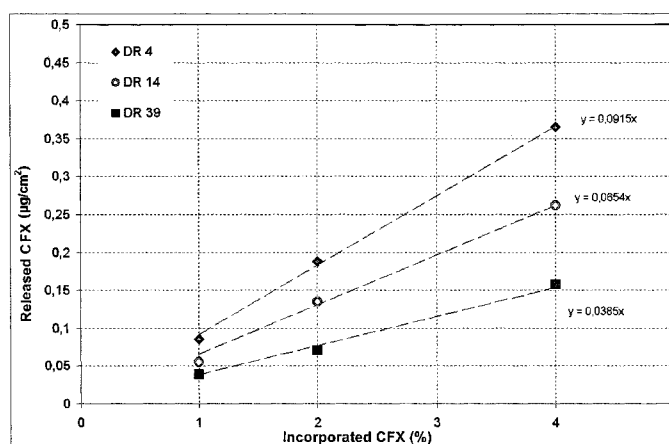


Figure 9

(57) Abstract: Object of the present invention is a method and the related production technology for the manufacturing of multifunctional suture threads with antimicrobial and/or antibiotic and/or cicatrizing properties that can be modulated as a function of the manufacturing conditions. The threads can display single properties or multiple properties among those described above. In particular, it was build up a technology that consider the melt incorporation of an antimicrobial and/or antibiotic and/or cicatrizing agent during the preparation of the suture threads. The spinning process is inline with the extrusion and by modulating the amount of agent, the drawing conditions (isothermal and non-isothermal), it is possible to regulate the final diameter, the mechanical resistance and the release of the necessary amount of agent over the space (i.e. locally in the proximity of the filament) and over the time (i.e. regulating the duration of the antimicrobial and/or antibiotic and/or cicatrizing activity) according to a precise linear function.

MULTIFUNCTIONAL SUTURE THREADS WITH CONTROLLED RELEASE OF ANTIMICROBIAL, ANTIBIOTIC, CICATRIZING AGENTS

The present invention refers to the field of medical-surgical devices and in particular it refers to a method for producing suture threads with multifunctional properties (antimicrobial and/or antibiotic and/or cicatrizing); the preparation method is based on the melt incorporation of the antimicrobial and/or antibiotic and/or cicatrizing agent and allows the modulation of the release of the amount of the antimicrobic and/or antibiotic and/or cicatrizing component as a function of the preparation conditions.

STATE OF THE ART

Sutures are identified on several criteria that essentially regard the need to remove them, their structure and their composition.

Based on the structure of the thread, the sutures can be woven/threaded or made of a single filament. Based on the composition, the suture thread can be natural or synthetic. Depending on their destiny once in contact with a living organism, the threads can be divided into two main categories: absorbable and non-absorbable.

The typical materials used for producing non-absorbable threads are silk and linen – as far as natural materials are concerned – while nylon, polyester, polypropylene, polytetrafluoroethylene, polyvynilidene fluoride as synthetic materials.

Polydioxanone, polyglycolic acid, polylactic acid, polycaprolactone and binary or ternary copolymers of the latter three polymers are the main polymeric materials used to produce absorbable suture threads. Moreover, in some cases, polycaprolactone is used as coating to increase some properties like, for instance, the slippage.

Including an alien material into the organism always causes an immunitary reaction more or less intense. After the contact, the suture thread is covered by fluids highly rich in proteins like fibrinogen and fibronectin that create the ideal environment for bacterial proliferation. Once the suture is contaminated, the immunitary system activates local disinfection systems, typically driven by

granulocytes, that can be ineffective and cause inflammatory reactions that can be more or less severe.

There is therefore the exigency to reinforce the organism defenses in order to eradicate the bacterial colony. This can be achieved either by assuming drugs, like the antibiotics, that are able to slow down or even stop the microbial proliferation,

Other important exigency that suture threads must satisfy is wound healing. The suture thread keeps in contact the tissue edges that must reconstitute a continuum in the shortest possible time. From this point of view, it is particularly useful the presence of appropriate cicatrizing agents.

In both cases above described it is necessary to be able to modulate the release of the additives included in the thread so to grant that the right amount of active component is released in the desired time interval.

The preparation of threads with antimicrobial properties and/or antibiotic and /or cicatrizing is still object of study. The main difficulty is to find a good compromise between the effectiveness of the thread and its cost, aspect that must not to be neglected. In fact if, from one hand, the use of antimicrobial and/or antibiotic and /or cicatrizing threads could reduce or eliminate the expenses for drugs to be assumed during the post-surgical period, on the other side the production costs must be as low as possible.

Providing specific properties to the suture thread can be carried out by different methods and can modify, or less, the polymer structure. In both cases, it must be verified that the introduction of the antimicrobial and/or antibiotic and /or cicatrizing agent does not significantly modify the mechanical properties of the material.

The additive must therefore be compatible with the polymer and keep its antiseptic properties for the whole period between the production of the thread and its use.

Another aspect that must not be underestimated is, as already highlighted, the release rate of the agent. The ideal condition is that wherein the most of the antimicrobial and/or antibiotic and /or cicatrizing agent is released during the most delicate phase (i.e. within the first 10 days after the use of the thread), which is when the wound is most likely affected by bacterial contamination and the cicatrized tissue is not yet formed. It can be therefore understood that it is very

difficult to find a couple polymer- antimicrobial properties and/or antibiotic and /or cicatrizing agent that is able to satisfy all the requested characteristics.

The methods currently used for producing threads with antimicrobial properties are essentially three: coating, grafting and melt incorporation.

5 The coating method consists in the physical coating of a material, the substrate, by immersing it in a fluid (usually a solution) containing the compound that is desired onto the surface. In this way, the substrate will be covered by a thin film of the agent, with a thickness that depends on several factors such as the viscosity of the solution, the extraction rate, the surface tension and the gravity acceleration.

10 More in detail, the process occur in four passages:

- immersion: the substrate is immersed in the solution at a practically constant speed avoiding sudden movements;

- permanence in contact with the solution:

- extraction: the higher is the speed adopted to extract the substrate from the solution, the thickest will be the film;

- Drying and evaporation of the solvent

15 In the scientific literature there are reported several cases of preparing modified thread by coating, i.e. by immersing it in a solution containing the active compound.

20 The grafting method consists in the introduction of particular chemical moieties onto the polymer surface in order to provide the material with properties initially non possessed. It is usually realized by introducing the polymer in a solution under appropriate temperature and pH conditions to promote the grafting of desired functional groups. The grafting extent can be easily controlled by changing the operating variables.

25 As the polymer structure is partly modified, it must be assured that its mechanical characteristics are not compromised.

The melt incorporation method consists in adding the active compound during an extrusion operation. The polymer, under the form of powder or pellets, is pre-mixed at the solid state with the agent that is preferably under the form of powder.

30 The physical mixture is then fed to the extruder hopper and extruded under a certain temperature profile and screw speed, variable and depending on the

polymer used. The material is finally fed, in a separate step, to a spinning unit thus producing the antimicrobial threads.

Although all the three methods are object of studies, the most diffused is the coating method that is also the one used to produce the antimicrobial suture threads commercially available.

The patent GB 2 410 028 describes an antimicrobial monofilament used as testing device for diabetes neuropathies. This monofilament is rigid. In particular, this monofilament is not single-use and therefore it is necessary to provide it with antimicrobial and/or antifungine properties in order to avoid contamination between different patients. Its use is then generalized affirming that it could be used for other application like toothbrushes, hair brushes and suture threads. the polymers indicated for the fabrication of that monofilament are PBT, PET and nylon while the only example reported of antimicrobial agent is Duraban™. It must be pointed out that in the patent it is not reported the preparation method unless a very vague and generic mention to the incorporation of the antimicrobial agent in during a melt extrusion, but without any evidence on the real production of the material or of the suture thread.

In WO 0128601 it is described the preparation of suture threads with antimicrobial properties. They are realized by preparing a coating to be applied onto the external surface or by the incorporation of an antimicrobial agent. Although the patent is extremely detailed, there is no explanation on what the authors mean with "incorporation" and on how it is pursued. The antimicrobial agents used are water soluble glasses that release Ag, Cu or Zn.

The patent EP 1157708 A2 describes the preparation of surgical devices like suture threads with antimicrobial properties realized by melt incorporation (extrusion). In particular, the thread is not realized in a single passage but the material obtained by extrusion is used to feed a second extruder to produce the final item (for instance a suture thread). Moreover, it is not reported the possibility to modulate the mechanical resistance and/or the release of the incorporated compound by changing processing or post-processing variables.

The patent WO86/02561 reports a method for preparing plastic objects containing chlorhexidine by melt incorporation in hydrophobic polymers like polyethylene or

polypropylene. Also in this case there is no mention on the possibility to modulate the quantity released by changing the processing parameters of extrusion, spinning and drawing stages.

Aim of the present invention is to provide a simplified and economically advantageous method to prepare suture threads with controlled release of antimicrobial properties and/or antibiotic and /or cicatrizing agents.

SUMMARY OF THE INVENTION

The present invention solve the above reported problems by providing a method for the manufacturing of multifunctional suture threads with controlled release of antimicrobial and/or antibiotic and /or cicatrizing agents. This method comprising the melt incorporation of one or more of said agents and said melt incorporation followed by an in-line spinning downstream of the extruder by drawing under predetermined drawing conditions so as to impart a controlled release of each incorporated agent according to the following function:

$$Q=(aDR+b)c$$

where:

Q is the amount of agent released per surface unit;

a and b are unique constants which depend on a polymer/agent pair

c is the weight concentration of the agent incorporated in the polymer;

DR is the drawing ratio:

$$DR = D_0^2/D_f^2,$$

where D_0 is the diameter of the extruder nozzle and D_f the final fiber diameter.

The antimicrobial and/or antibiotic and /or cicatrizing agents are incorporated in the melt polymers chosen among those usually adopted for the preparation of suture threads, both absorbable and non-absorbable.

The combinations polymer/agents are identified on the basis of the possible processing temperature; in particular, the maximum temperature of the thermal profile of the extruder must be at least 10 °C above the melting temperature of the polymer and at least 10 °C below its degradation temperature. Moreover, the maximum temperature must be at least 5 °C lower than the melting temperature of the agent to be incorporated or than its decomposition temperature, if lower.

In the present invention, the additives are the above described antimicrobial properties and/or antibiotic and /or cicatrizing agents.

Depending on the drawing conditions, it is possible to modulate the final diameter of the fibers, the mechanical resistance and, above all, the release of the
5 necessary substance, over the space (i.e. locally, in the proximity of the filament) and over the time (i.e. regulating the duration of the antimicrobial and/or antibiotic and /or cicatrizing action).

Said material is appropriate for the preparation or coating of medical-surgical devices. In particular, it is appropriate for preparing surgical suture threads with
10 antimicrobial properties.

The present invention regards therefore suture threads, characterized by the melt incorporation of an antimicrobial and/or antibiotic and /or cicatrizing agent in a biocompatible polymer, chosen among those known for the fabrication of suture threads.

15 Further object of the present invention is a suture thread obtained with the method according to the invention, said thread having antimicrobial properties and/or antibiotic and /or cicatrizing properties with controlled release that can be modulated in the space and in the time based on the drawing conditions adopted during their manufacturing.

20 From a comparison with those above described methods, the present method introduces a wide range of improvements and advantages both on the methodic and on the final product. Among all, the most important advantage is the simplicity of preparation of the final product. In fact, by a single operation it is possible to provide the thread with the properties above described. On the contrary, in the
25 case of coating or grafting it is necessary to act with several post-spinning operations to provide the thread with the above mentioned properties. The reduction of the number of operations has an evident advantage not only for time saving but also avoid the use of other products or solvents different from the polymeric matrix and the antimicrobial agent. This has obvious positive
30 implications from an environmental and economic point of view but also as far as the safety of the thread is concerned. In fact, the use of solvents, necessary for the two other methods has, as a direct consequence, the need to dispose them.

Moreover, during the use of the thread, it could be a release, of course undesired, of residual solvents present in the filament.

The incorporation of the antimicrobial and/or antibiotic and /or cicatrizing agent, beyond providing the thread with specific properties, can also act as reinforcement with an increase of the mechanical properties. This result was unexpected considering the difficulty in finding a polymer-antimicrobial agent couple that satisfies all the characteristics requested for biomedical applications.

Moreover, the incorporation of the antimicrobial agent, rather than having it only onto the surface, allows a higher control of its release by modulating parameters such as:

- the concentration of the antimicrobial introduced
- the processing variables (e.g. the drawing speed)
- the cold drawing of the threads.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 – shows a scheme of the preparation method according the present invention by using an extruder with a primary input and several secondary inputs.

Figure 1a – shows, for the suture threads in PCL/CHX prepared with the method according to the invention, the results regarding the release of the antimicrobial agent as a function of the incorporated concentration and of the drawing conditions.

Figure 2 – SEM micrographs of PCL/CHX suture threads prepared according to the method of the invention

Figure 3 – shows the results of the antibacterial activity of PCL/CHX suture threads prepared according to the method of the invention; the activity is determined with an agar diffusion test against a Gram positive bacterial strain.

Figure 4 – graphically shows the linear law $Q_{CHX} = m_{PCL/CHX} \cdot C_{CHX}$ for the couple PLC/CHX.

Figure 5 – graphically shows how the constants a and b were determined for the system PCL/CHX.

Figure 6 – shows, for PP/CFX suture threads prepared according to the method of the invention, regarding the release of antimicrobial agent by changing the incorporated concentration and the drawing conditions.

Figure 7 – SEM micrographs of PP/CFX suture threads prepared according to the method of the invention

Figure 8 – shows the results of antimicrobial activity of PP/CFX suture threads prepared according to the method of the invention; the activity is determined with an agar diffusion test against a Gram positive bacterial strain.

Figure 9 – graphically shows the results of antibacterial activity of PP/CFX suture threads prepared according to the method of the invention; the activity is determined with an agar diffusion test against a Gram positive bacterial strain.

Figure 10 – graphically shows how the constants a and b were determined for the system PP/CHX.

DETAILED DESCRIPTION OF THE INVENTION

The amount of released agent strongly depends on the concentration of such compound on the surface of the device. This surface concentration can be controlled and modulated both by changing the initial amount of agent incorporated and, above all, by changing the drawing ratio adopted during the production of the fibers. In fact, the surface concentration can be varied and controlled by changing the extension of the lateral surface on which the agent is distributed. This surface ($S = \pi D_f L_f$), where D_f is the fiber diameter and L_f its length) depends on the drawing ratio applied, according to a well-defined law. In particular, in order to obtain such law it is worth reminding the definition of draw ratio: $DR = A_0/A_f$, where A_0 is the section of the extruder nozzle and A_f is the final section of the thread. With appropriate simplification, the draw ratio can be rewritten as a function of the diameters according to the following equation:

$DR = D_0^2/D_f^2$, where D_0 is the diameter of the extruder nozzle and D_f the final diameter of the thread.

Therefore, by changing the draw ratio, it is possible to modulate the surface concentration of the additive and, consequently, to modulate and control the quantity released.

The antimicrobial and/or antibiotic and/or cicatrizing effect directly depends on the quantity of agent released and this quantity can be controlled, as already said, by changing the concentration of additive incorporated and by changing the draw ratio.

- 5 This concept can be mathematically expressed by two functions that bind the quantity of released additive to the concentration and to the draw ratio. In particular, the amount of agent released per surface unit (Q) is bound to the weight concentration of the incorporated agent, c , by the law $Q=mc$ where m is a parameter depending on the draw ratio applied according to:

- 10 $m=aDR + b$ where a and b are constants depending on the specific couple polymer/additive and DR the draw ratio.

By this preparation method – generalizable to all the couples polymer/additive – it is therefore possible to affirm that, once determined the parameters a and b , it is possible to prepare threads with the full control of the quantity of additive released.

- 15 According to the present invention antimicrobial or antibiotic agents refer to antibiotics, lantibiotics, bacteriostatics, bactericides and antiseptics that are small organic molecules either natural or synthetic and approved for the use as medicaments or for medical-surgical use. According to the present invention, metallic ions of silver, copper or zinc and their soluble components are excluded.

- 20 Similarly, organosilanes like 3-(trimethoxysilyl)propyldimethyloctadecyl ammonium chloride are not included.

As healing agents according to the present invention refer to agents able to accelerate the healing up of wounds, ulcers and burns, removing the residues of the inflammatory process and recovering the integrity of the cutaneous structures.

- 25 Such compounds, natural or synthetic, must be approved for the use as medicaments or for medical-surgical use.

The polymers that can be used are those normally adopted for the production of suture threads, both absorbable and non-absorbable, and previously listed above: polyamides (nylons), polyesters, polypropylene, polytetrafluoroethylene, polydioxanone, polyglycolic acid, polylactic acid, polycaprolactone, binary or
30 ternary copolymers of the last three together with their blends.

Choosing the antimicrobial and/or antibiotic and/or cicatrizing agent is mainly correlated to the application which it is addressed for but also to the kind of pathogenic agent that must be contrasted or to the localization of the wound that must be healed. Moreover, the agent must be able to resist, remaining unaltered,
5 to the temperature achieved during its melt incorporation.

As regards to biomedical application and in particular for suture threads, the choice of the agents described above is drastically reduced as the compound must not be toxic or having harmful side effects for the organism. Moreover, related to the protecting action against bacterial attack, the agent must present activity
10 against microorganisms that usually infect a wound such as: *Escherichia Coli*, *Staphylococcus Epidermidis* and *Staphylococcus Aureus*. Last but not least, it must also be compatible with the material that forms the thread. As a mere example, in the class of antimicrobial/antibiotics can be preferred, not being the only, chlorhexidine, neomicine, nalidixic acid, nisin and ciprofloxacin.

15 As a mere example, in the class of cicatrizing agents can be preferred, not being the only, ialuronic acid, *Triticum Vulgaris*, collagene and catalase.

The additive (antimicrobial and/or antibiotic and/or cicatrizing) can be both under the form of powder and of liquid. It can be fed together with the polymer or by one of the secondary hoppers, places at a well-defined distance from the main hopper.

20 In order to include in a way and appropriate measure, the agent in the polymer already molten (fed to the extruder by the main hopper) and to regulate the residence time inside the extruder of the agent and therefore the final properties of the device (Figure 1).

The blend is extruded adopting a thermal profile (generally in the range 70 °C –
25 300 °C) and at a speed (function of the amount of material to be produced and of the residence time) generally in the range 20 sec – 10 min, appropriated for processing the polymeric materials that forms the thread. The polymer/additive couples are identified based on the possible processing temperatures. In particular, the maximum temperature of the thermal profile of the extruder must be
30 at least 10 °C above the melting temperature of the polymer and at least 10 °C below its degradation temperature. Moreover, the maximum temperature must be

at least 5 °C lower than the melting temperature of the agent to be incorporated or than its decomposition temperature, if lower.

At the exit of the extruder, an in-line spinning system allows the direct preparation of the threads that are drawn under isothermal or non-isothermal conditions thus modulating, by changing the drawing conditions, the final diameter, the mechanical resistance but, above all, the release of the necessary amount of additive both in the space (i.e. locally in the proximity of the filament) and in the time (i.e. by regulating the duration of the antimicrobial and/or antibiotic and/or cicatrizing action).

- 10 The antimicrobial action of the thread occurs by migration and consequent release of the active agent. It is therefore possible to modulate the duration of the release, also by appropriately choosing the concentration of antimicrobial agent to be incorporated as well as by modifying in an appropriate manner the structure of the polymeric matrix.
- 15 The present invention can be better understood by the description of two examples reported below.

EXPERIMENTAL SECTION

EXAMPLE 1

- 20 The method described was applied, to provide an example, for the preparation of suture threads made of polycaprolactone (PCL) added with and antimicrobial agent, chlorhexidine diacetate (CHX)
- Both the CHX and the PCL are two commercial samples supplied by Sigma Aldrich.
- 25 The polymer, under the form of pellets, was fed to the main hopper of co-rotating twin-screw extruder while the antimicrobial agent was fed to the extruder by a secondary hopper. The blend was then extruded adopting a thermal profile of 40-50-70-100 °C through a cylindrical nozzle with a diameter of 1 mm. At the exit of the extruder, the thread was cooled down and contextually drawn using a drawing
- 30 unit, until the final desired diameter was achieved. Three draw ratio were applied: DR=11, DR=25 and DR=44 that correspond to fibers with diameters respectively

of 300 μm , 200 μm and 150 μm . The initial concentration of chlorhexidine was 1%, 2% and 4%.

The antibacterial activity of the threads was investigated by agar diffusion tests. The inhibition was studied against of two Gram positive (*M. Luteus* and *B. Subtilis*) and a Gram negative (*E. Coli*) by the evaluation of the inhibition halo around the fibers. Moreover, test for measuring the inhibition of bacterial growth were carried out in a liquid culture.

The release of CHX from the fibers in distilled water was evaluated by UV-vis spectrophotometry using a Shimadzu spectrophotometer.

The different concentration used and, above all, the different draw ratios, allowed modulating the release of the compound incorporated both in terms of quantity and in terms of duration as highlighted in Figure 1a.

The SEM micrographs of Figures 2 a-b confirm that the quantity of CHX released strongly depends on the concentration of such compound on the device surface. In particular, the thread drawn at DR=11 (Figure 2a) present on its surface a higher amount of CHX with respect to that with DR=44 (Figure 2b).

The antibacterial activity of the threads prepared is strictly correlated to the release of the incorporated compound and therefore, by modulating this release, it was also possible to modulate the antibacterial action of the threads as shown in Figure 3 where there are reported, as an example, the inhibition tests against a Gram positive (*M. Luteus*) of both the groups of threads produced.

It is evident that all the threads containing chlorhexidine show a clear inhibition halo. On the contrary, the thread made of pure polymer does not show any antibacterial activity. It is also evident that the inhibition halo is reduced for the case of threads produced with a higher draw ratio. A similar result was obtained also for test again Gram negative. The antibacterial activity of the threads prepared was also evaluated by inhibition test in liquid culture. Also these tests confirmed the clear antibacterial activity of the threads containing chlorhexidine.

The antimicrobial activity directly depends on the amount of antimicrobial released and this quantity can be controlled, as already said, both by changing the concentration of incorporated CHX and by changing the draw ratio. In fact, the comments made for the general case still hold for the specific example reported. In

particular, the quantity of CHX released per surface unit (Q_{CHX}) follows a linear law: $Q_{CHX} = m_{PCL/CHX} \cdot c_{CHX}$ where c_{CHX} is the weight concentration of chlorhexidine incorporated and $m_{PCL/CHX}$ has a value depending on the draw ratio applied as shown in Figure 4. $m_{PCL/CHX}$ can be calculated by: $m_{PCL/CHX} = a_{PCL/CHX} DR + b_{PCL/CHX}$,
5 where a and b are constants that for the system PCL/CHX are equal to - 0,037 and 2,3123 respectively (Figure 5).

EXAMPLE 2:

The method was also applied for the preparation of suture threads of
10 polypropylene (PP) in which the compound added was an antibiotic agent, ciprofloxacin (CFX).

The CFX and the PP used in the example are two commercial sample respectively supplied by Sigma Aldrich and Basell. The polymer under the form of pellets was fed to the main hopper of a co-rotating twin-screw extruder while the antibiotic
15 agent, under the form of powder, was fed by a secondary hopper. The blend was extruded at a thermal profile of 130-180-200 °C through a cylindrical die with a diameter of 1 mm. At the exit of the extruder, the thread was cooled down and contextually drawn using a drawing unit, until the final desired diameter was achieved. Three draw ratios were applied: DR=4, DR=14 and DR=39 that
20 correspond to fibers with diameters respectively 500 µm, 270 µm and 160 µm. The initial concentration of ciprofloxacin was 1%, 2% and 4%.

The antibacterial activity of the threads was investigated by agar diffusion tests. The inhibition was studied against of two Gram positive (M. Luteus and B. Subtilis) and a Gram negative (E. Coli) by the evaluation of the inhibition halo around the
25 fibers. Moreover, test for measuring the inhibition of bacterial growth were carried out in a liquid culture.

The release of CFX from the fibers in distilled water was evaluated by UV-vis spectrophotometry using a Shimadzu spectrophotometer.

The different concentration used and, above all, the different draw ratios, allowed
30 modulating the release of the compound incorporated both in terms of quantity and in terms of duration as highlighted in Figure 6.

The SEM micrographs of Figures 7 a-b confirm that the amount of CFX released strongly depend on the concentration of this compound on the device surface. In particular, the thread drawn at DR=4 (Figure 7a) presents on its surface a larger quantity of CFX if compared with that drawn at DR=39 (Figure 7b)

- 5 The antibacterial activity of the threads prepared is strictly correlated to the release of the incorporated compound and therefore, by modulating this release, it was also possible to modulate the antibacterial action of the threads as reported in Figure 8 where there are reported, as an example, the inhibition tests against a Gram positive (*M. Luteus*) of both the groups of threads produced.
- 10 It is evident that all the threads containing ciprofloxacin show a clear inhibition halo. On the contrary, the thread made of pure polymer does not show any antibacterial activity. It is also evident that the inhibition halo is reduced for the case of threads produced with a higher draw ratio. A similar result was obtained also for test again Gram negative. The antibacterial activity of the threads
- 15 prepared was also evaluated by inhibition test in liquid culture. Also these tests confirmed the clear antibacterial activity of the threads containing ciprofloxacin. The antimicrobial activity directly depends on the amount of antimicrobial released and this quantity can be controlled, as already said, both by changing the concentration of incorporated CFX and by changing the draw ratio. In fact, the
- 20 comments made for the general case still hold for the specific example reported. In particular, the quantity of CFX released per square unit (Q_{CHX}) follows a linear law: $Q_{CHX} = m_{PCL/CHX} \cdot c_{CHX}$ where c_{CHX} is the weight concentration of ciprofloxacin incorporated and $m_{PCL/CHX}$ has a value depending on the draw ratio applied as shown in Figure 9. $m_{PCL/CHX}$ can be calculated by: $m_{PCL/CHX} = a_{PCL/CHX} DR + b_{PCL/CHX}$,
- 25 where a and b are constants that for the system PCL/CHX are equal to - 0,0014 and 0,0923 respectively (Figure 10).

CLAIMS

1. A method for manufacturing multifunctional suture threads with controlled release of antimicrobial and/or antibiotic and/or healing agents, said method comprising the melt incorporation of one or more of said agents and said melt incorporation followed by an in-line spinning downstream of the extruder by drawing under predetermined drawing conditions so as to impart a controlled release of each incorporated agent according to the following function:

$$Q=(aDR+b)c$$

where:

- 10 Q is the amount of agent released per surface unit;
a and b are unique constants which depend on a polymer/agent pair;
c is the weight concentration of the agent incorporated in the polymer;

DR is the drawing ratio: $DR = D_0^2/D_f^2$,

where D_0 is the diameter of the extruder nozzle and D_f is the final fiber diameter;

- 15 the antibiotic and/or healing and/or antimicrobial agents are melt incorporated into polymers selected from those normally used for manufacturing suture threads, both absorbable and non absorbable;
the polymer/agent combinations are determined according to the possible processing temperatures; in particular, the maximum temperature of the extruder thermal profile must be at least 10 °C above the polymer melting temperature and
20 at least 10 °C below the degradation temperature thereof; additionally, such a temperature must be at least 5 °C lower than the melting temperature of the agent to be incorporated or than its decomposition temperature, if lower.

2. A method according to claim 1, wherein the agents are selected from
25 antimicrobials such as chlorhexidine, neomycin or nalidixic acid, antibiotics such as ciprofloxacin and healing substances such as Triticum vulgaris or hyaluronic acid, collagen, catalysis.

3. A method according to any one of claims 1-2, wherein the polymer is selected from nylon, polyester, polypropylene, polytetrafluoroethylene, polyvinylidene fluoride, polydioxanone, polyglycolic acid, polylactic acid, polycaprolactone and binary or ternary copolymers of these last three polymers.
30

4. A method according to claims 2 and 3, wherein the agent is selected from

chlorhexidine and ciprofloxacin, and the polymer is selected from polypropylene and polycaprolactone.

5. Multifunctional suture threads with controlled release of antimicrobial and/or antibiotic and/or healing agents, obtainable from the process according to any one of claims 1-4, wherein the controlled release of each incorporated agent is according to the following function:

$$Q=(aDR+b)c$$

where:

Q is the amount of agent released per surface unit;

- 10 where a and b are unique constants which depend on the polymer/additive pair;
c is the weight concentration of the agent incorporated in the polymer;

DR is the drawing ratio: $DR = D_0^2/D_f^2$,

where D_0 is the diameter of the extruder nozzle and D_f is the final fiber diameter;

- wherein the antibiotic and/or healing and/or antimicrobial agents are molten-state
15 incorporated into polymers selected from those normally used for manufacturing suture threads, both absorbable and non absorbable.

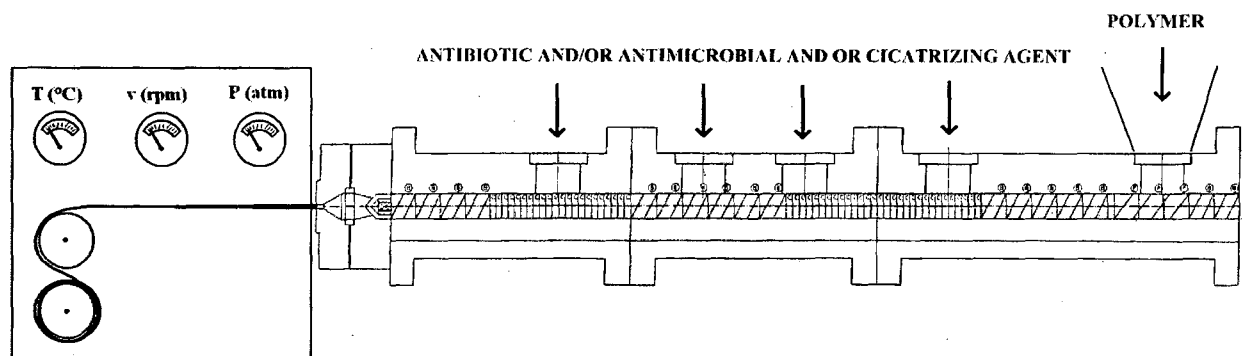


Figure 1

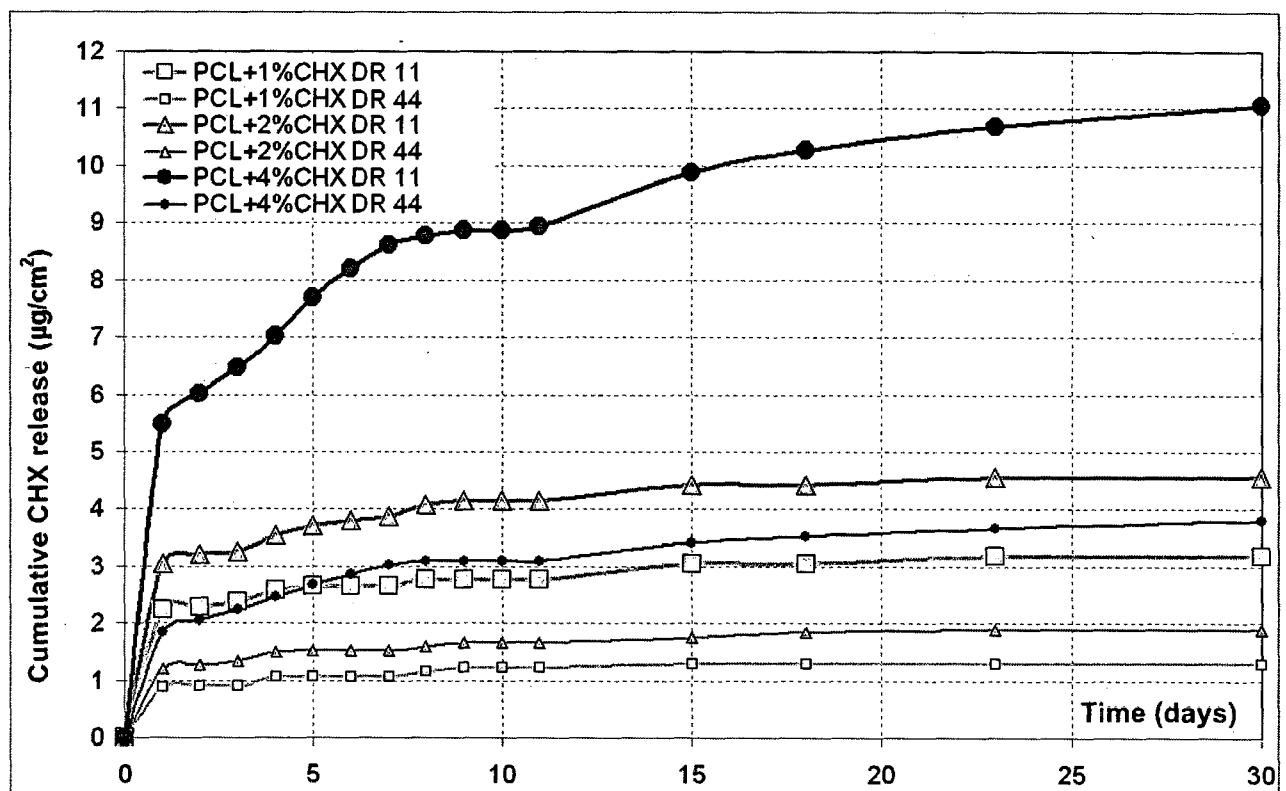


Figure 1a

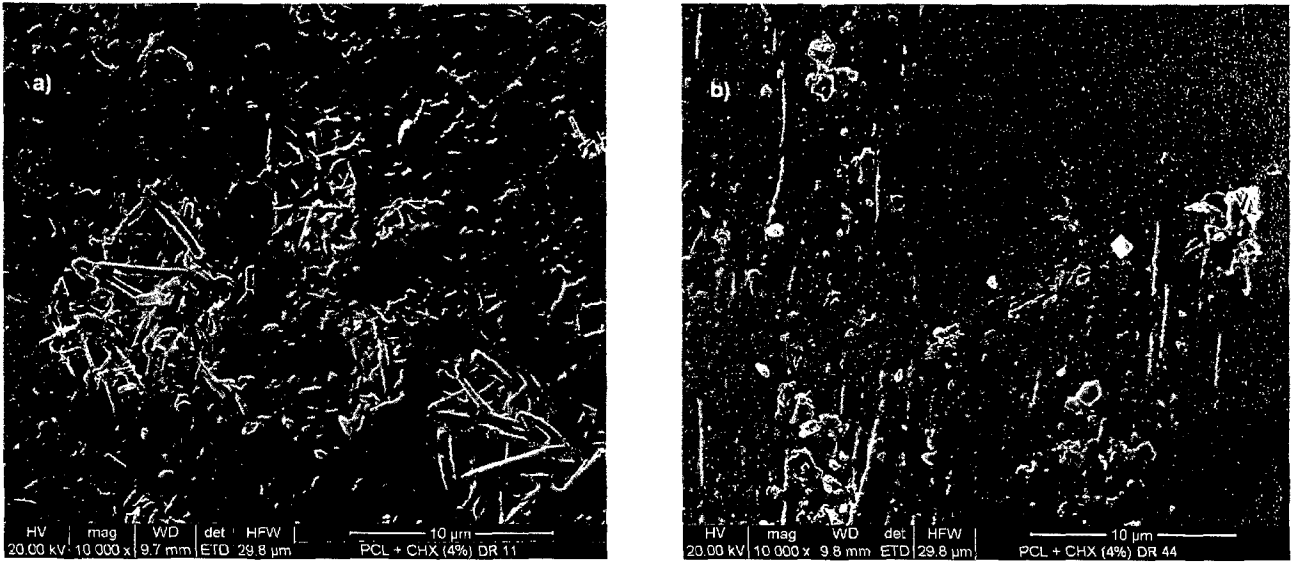


Figure 2

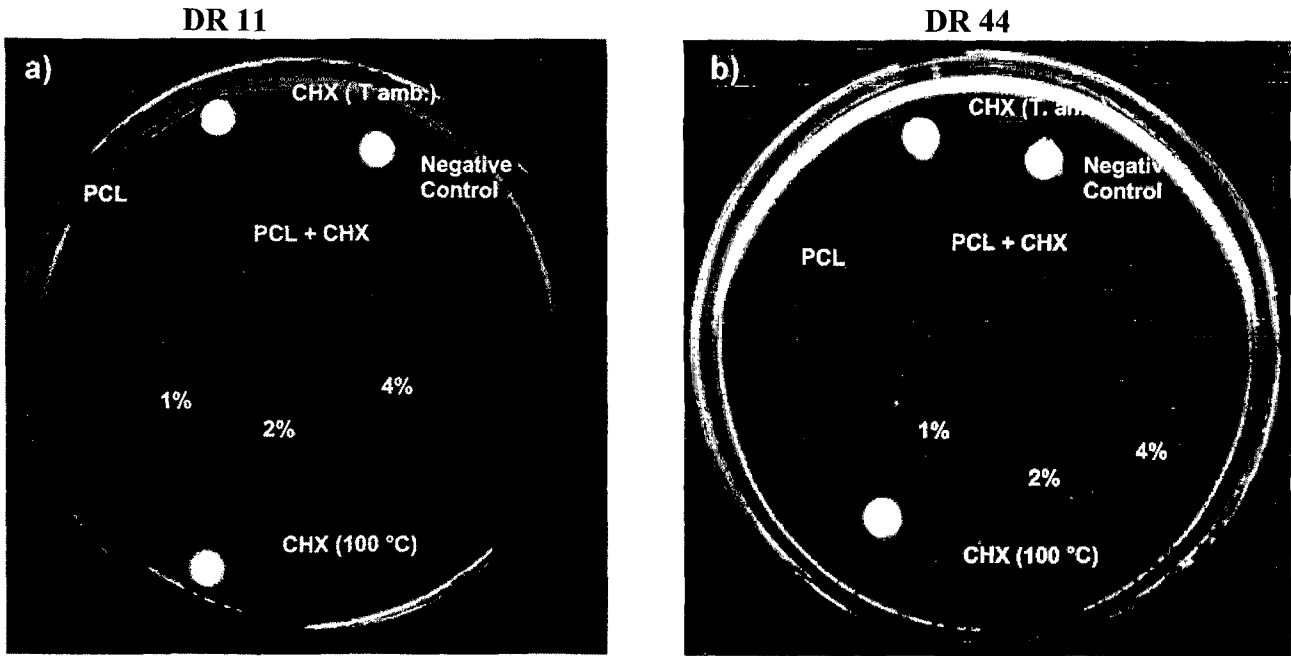


Figure 3

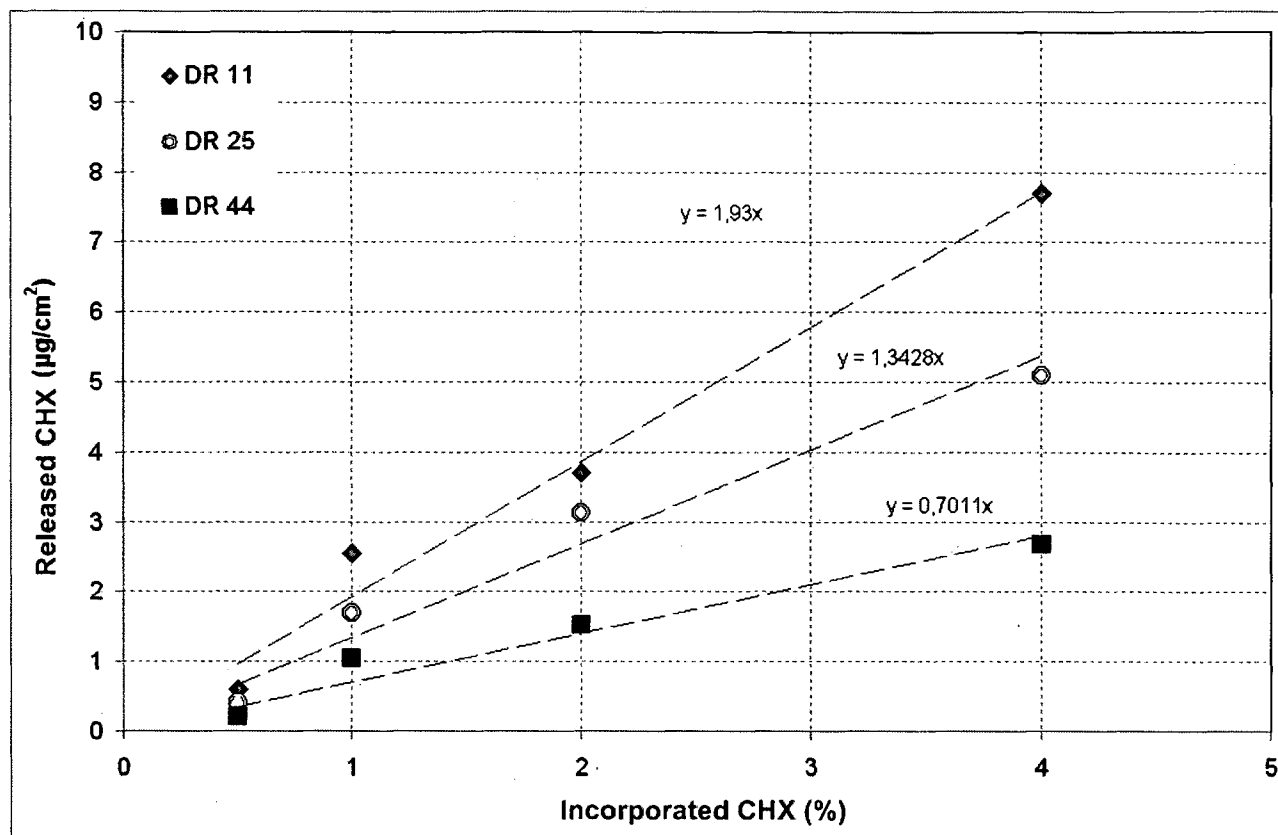


Figure 4

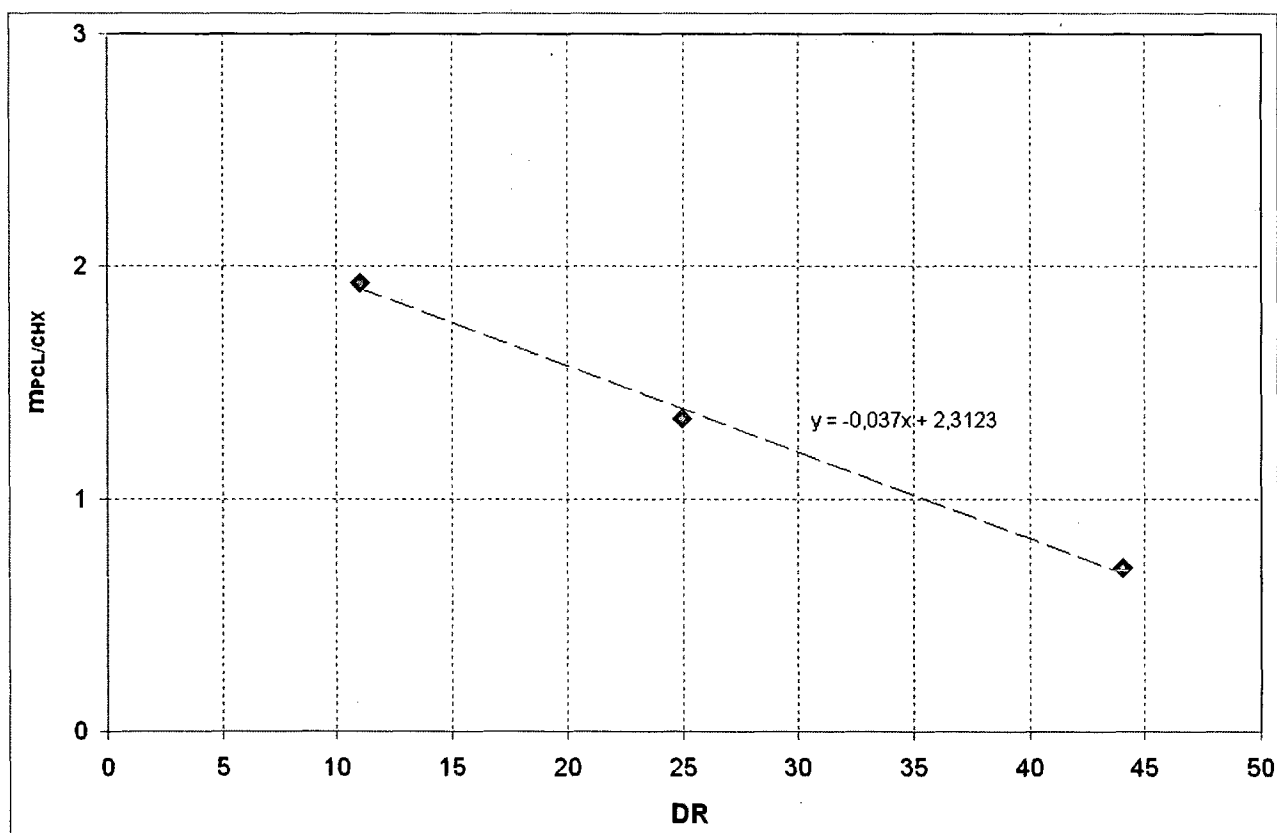


Figure 5

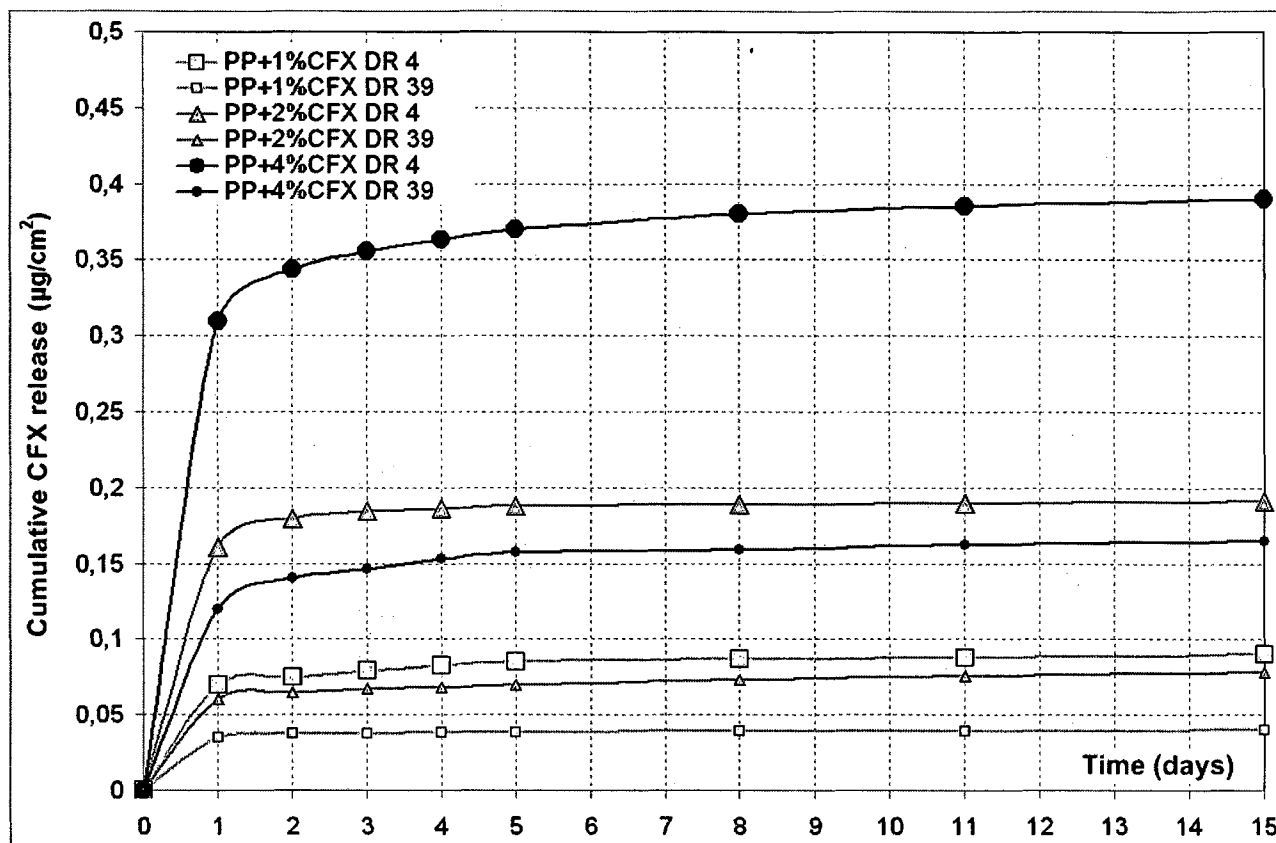


Figure 6

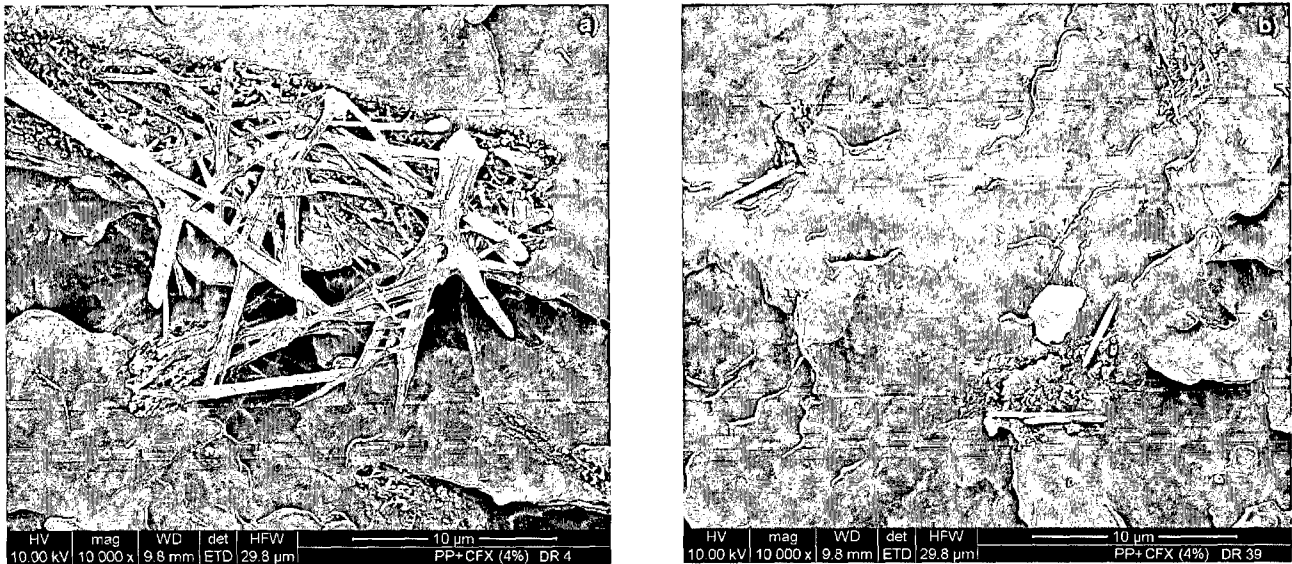


Figure 7

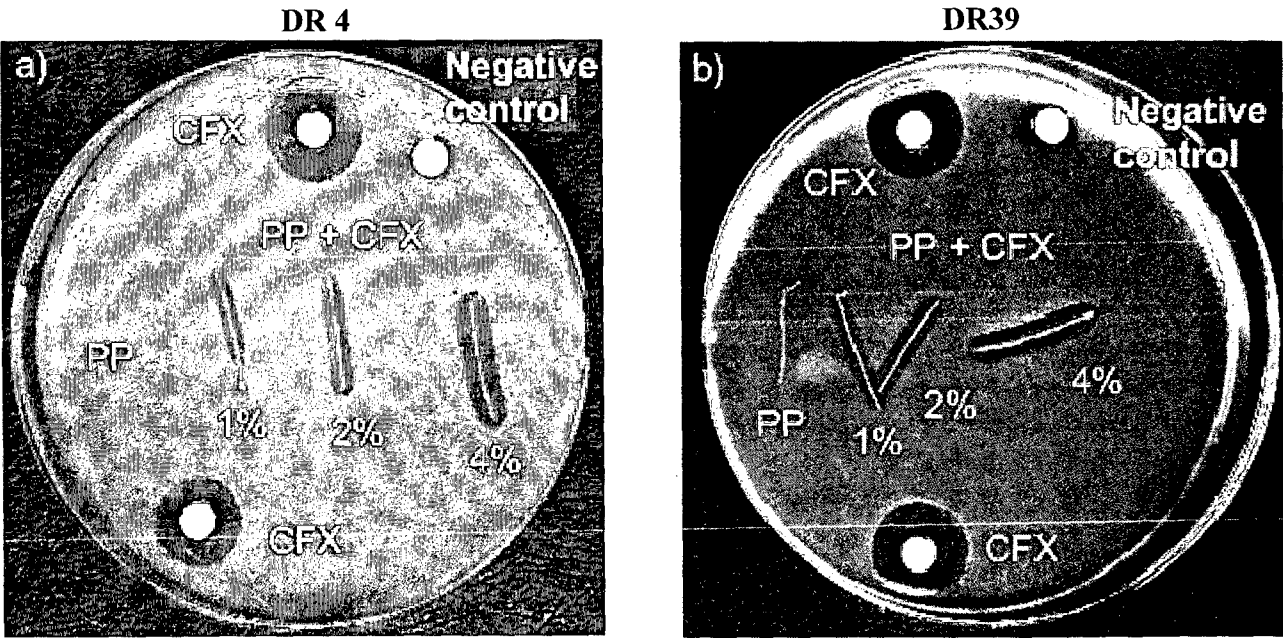


Figure 8

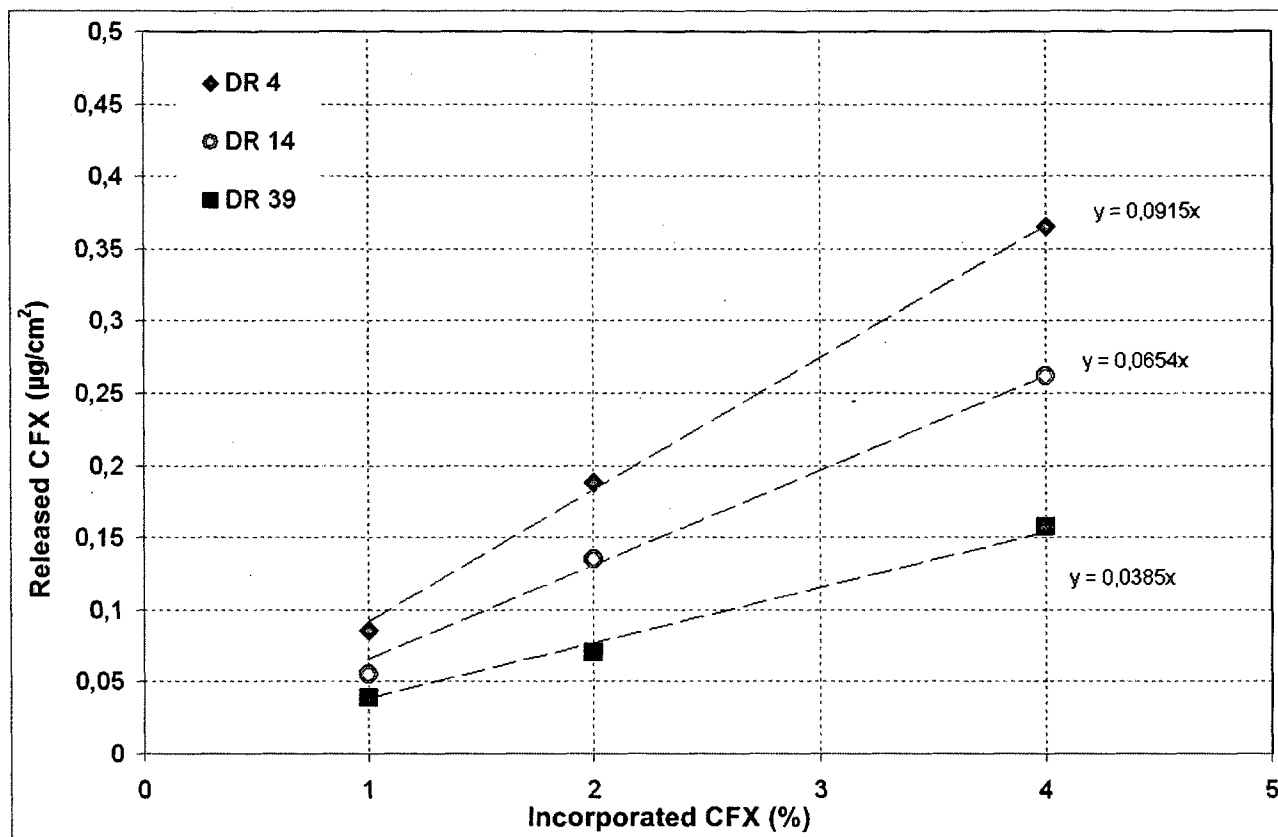


Figure 9

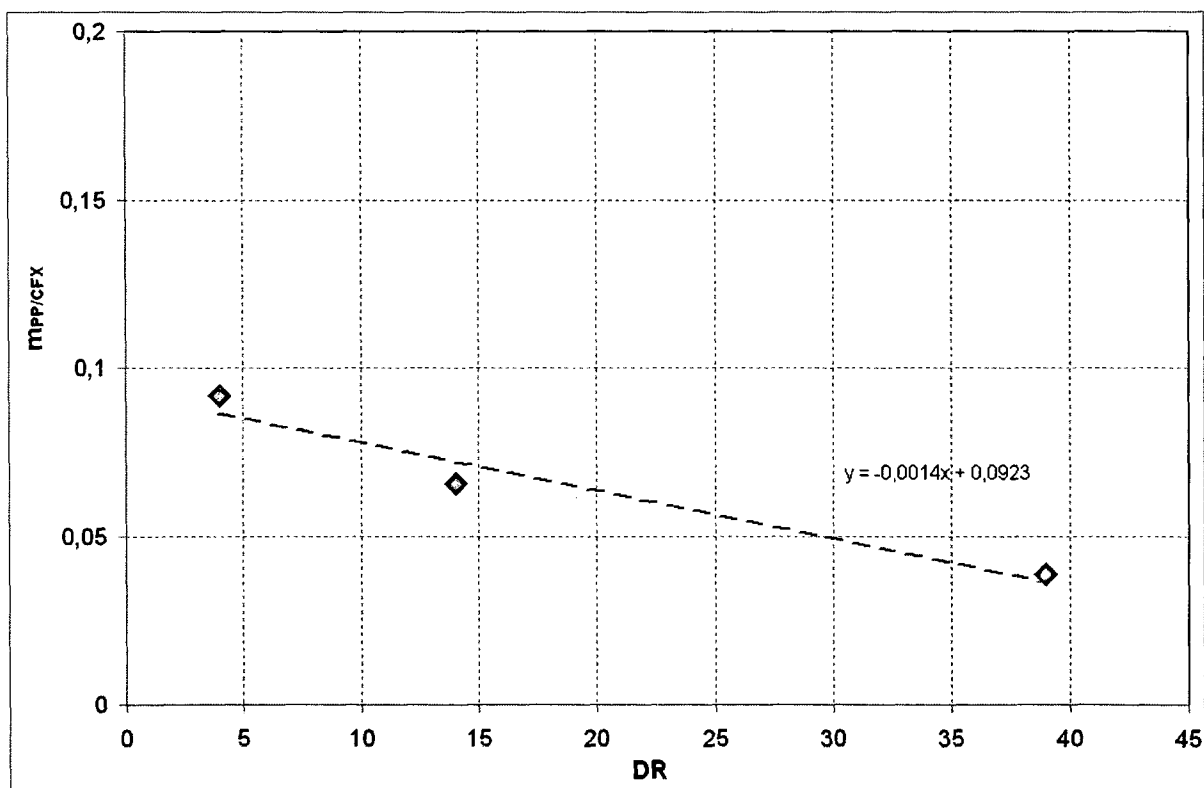


Figure 10

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2013/051594

A. CLASSIFICATION OF SUBJECT MATTER
 INV. D01D5/12 D01F1/10 A61L17/00
 ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

D01D D01F A61L

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, WPI Data

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Y	examples 1,2 claims 1-11 page 14, lines 8-16 page 12, lines 24-27 page 22, lines 10-21 page 6, line 36 - page 7, line 10 page 10, lines 13-22 page 13, lines 11-16 page 15, line 26 - page 19, line 3 -----	1-4
X	EP 1 607 109 A1 (BIORETEC OY [FI]) 21 December 2005 (2005-12-21)	5
A	paragraphs [0037] - [0061] claims 26-28 ----- -/-	1-4



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

30 July 2013

Date of mailing of the international search report

16/08/2013

Name and mailing address of the ISA/

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International application No

PCT/IB2013/051594

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	figures 2A, 2B page 13, lines 7-26 page 18, line 9 - page 19, line 19 page 23, line 21 - page 26, line 22 page 28, line 14 - page 29, line 11 page 30, line 13 - page 33, line 29 page 37, line 25 - page 38, line 11 -----	1-4
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A	paragraphs [0039] - [0047] claims 1-3,7-10 -----	1-4
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Information on patent family members

International application No

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