The invention concerns the manufacture of an antibiotic coating of elements with interconnecting microcavities, elements thus coated as well as their use. In a preferred embodiment, a homogenous solution of gentamicin pentakis dodecyl sulfate, of gentamicin tetrakis dodecyl sulfate, of gentamicin pentakis dodecyl sulfonate or of gentamicin tetrakis dodecyl sulfonate which contains methanol and/or ethanol and/or N,N-dimethyl formamide and/or dimethyl sulfoxide as a solvent is introduced into the microcavities of non-metallic elements with interconnecting microcavities which are built up of collagen or gelatine or polyesters or tricalcium phosphate or hydroxyl apatite through dipping, spraying and dipping, and following evaporation or vaporization of the organic solvent, a layer of gentamicin pentakis dodecyl sulfate, gentamicin tetrakis dodecyl sulfate, gentamicin pentakis dodecyl sulfonate or gentamicin tetrakis dodecyl sulfonate is formed on the surface of the microcavities.
ABSTRACT

The invention concerns the manufacture of an antibiotic coating of elements with interconnecting microcavities, elements thus coated as well as their use. In a preferred embodiment, a homogenous solution of gentamicin pentakis dodecyl sulfate, of gentamicin tetrakis dodecyl sulfate, of gentamicin pentakis dodecyl sulfonate or of gentamicin tetrakis dodecyl sulfonate which contains methanol and/or ethanol and/or N,N-dimethyl formamide and/or dimethyl sulfoxide as a solvent is introduced into the microcavities of non-metallic elements with interconnecting microcavities which are built up of collagen or gelatine or polyesters or tricalcium phosphate or hydroxyl apatite through dipping, spraying and dripping, and following evaporation or vaporization of the organic solvent, a layer of gentamicin pentakis dodecyl sulfate, gentamicin tetrakis dodecyl sulfate, gentamicin pentakis dodecyl sulfonate or gentamicin tetrakis dodecyl sulfonate is formed on the surface of the microcavities.
Process for Antibiotic Coating of Elements with Interconnecting Microcavities, Elements thus Coated as well as their Usage

The present invention concerns a process for antibiotic coating of elements with interconnecting microcavities, substances so coated as well as their usage.

These antibiotic provided substances with interconnecting microcavities should find use as implants in human and veterinary medicine for the treatment of bone defects and, if need be, for the treatment of soft tissue damage. Here a continuous antibiotic release from antibiotic coating situated on the internal surface of the interconnecting microcavities over a time period of several days is sought so that a microbial infection in the region of the bone defect and/or soft part defect to be treated can be effectively prevented or combated.

Bone defects occur relatively frequently in human and veterinary medicine and are in particular caused by bone fistulae, comminuted fractures and tumors. In case of open comminuted fractures and, frequently, additional infections of the bone tissue are observed. The treatment of bone defects can take place by replenishment with suitable implants. In recent years, porous implants, which have an osteo-conductive action on account of their chemical composition and their porosity, have especially been found to be of interest and favor for growing of the surrounding bone tissue. The treatment of bone defects is always problematic when an addition microbial infections of the bone tissue are present. Infections of the bone tissue can be combated by systemic or local applications of suitable antibiotics. The systemic use of antibiotics is a problematic owing to the occasionally not inconsiderable toxicity of the antibiotics. The local application directly in or on the infected tissue, in contrast, offers the advantage that high local antibiotic concentrations can be achieved while avoiding harmful antibiotic concentrations in the rest of the body. Through these high local antibiotic concentrations at the site of the bacterial infection, an almost complete killing off of the microorganisms is possible, so that the bacterial infections are treated very effectively. It is especially advantageous if an effective antibiotic concentration is maintained at the site of the bacterial infection over a period of several days to weeks so that the antibiotic
can penetrate into the infected tissue as deeply as possible, and in this way, hardly accessible germs are also eliminated. Soft tissue damage with bacterial infections can likewise frequently be found in human and veterinary medicine. Local antibiotic treatment for treatment of these infections is therefore also of interest.

Previously, lightly water-soluble salts of aminoglycoside antibiotics found relatively little notice in the manufacture of depot preparations and antibiotically active implants. A series of lightly soluble salts is known. Thus, with gentamicin, the preparation of lightly soluble salts based on higher fatty acids and aryl alkyl carboxylic acids was publicized. (G. M. Luedemann, M. J. Weinstein: Gentamicin and method of production. July 16, 1962, US 3,091,572). Example of this are gentamicin salts of lauric acid, stearic acid, palmitic acid, oleic acid, phenyl butyric acid, and naphthalene-1-carboxylic acid. The synthesis of dodecyl sulfate of gentamicin in diluted or diluted-methanol solution has been described by Jurado Soler et al. (A. Jurado Soler, J. A. Ortiz Hernandez, C. Ciuro Bertran: New Gentamicin Derivatives; Method of Manufacture of the Same and Antibiotically Active Composition Containing Them. September 30, 1974, DE 24 46 640). These salts, nonetheless, prove in many ways to be disadvantageous because they represent waxy, hydrophobic substances which prevent a galenic use. Jurado Soler et al. found that gentamicin pentakis dodecyl sulfate is soluble in solvents such as methanol, ethanol and dimethyl sulfoxide. They used gentamicin pentakis dodecyl sulfate for producing injection preparations, salves and creams. Further possible uses of gentamicin pentakis dodecyl sulfate were not considered. Fatty acid salts and aliphatic sulfates of gentamicin and etamycin were synthesized from the free base or from their salts in water at 50 to 80° C (H. Voege, P. Stadler, H. J. Zeiler, S. Samaan, K. G. Metzger: Barely Soluble Salts of Aminoglycosides as Well as Formulations Containing These With Delayed Active Ingredient Release, December 28, 1982, DE 32 48 328). These antibiotic fatty acid salts should be suitable as injection substances. Barely soluble aminoglycoside flavonoid phosphates (H. Wahlig, E. Dingeldein, R. Kirchlechner, D. Orth, W. Rogalski: Flavonoid phosphate salts of aminoglycoside antibiotics. October 13, 1986, US 4,617,293) represent a more recent development. Salts of the phosphoric acid
monoester of derivatives of hydroxy flavanes, hydroxy flavenes, hydroxy flavones and hydroxy flavylum are described. Derivatives of flavanones and flavones are especially preferred in this connection. These barely soluble salts are supposed to find use as depot preparations. Thus, for example, these salts are introduced into collagen fleece (H. Wahlig, E. Dingeldein, D. Braun: Medicinally useful, fleece made of collagen resorbable in the body. September 22, 1981, US 4,291,013).

The creation of simple antibiotic(s) deposits in the pore systems of porous elements by steeping porous elements with diluted antibiotics solutions is a general state of knowledge (R. Reiner, W. Kiißing, H. Dörning, K. Köster, H. Heide: Implantable Pharmaceutical Deposit. February 20, 1978, DE 2807132). Here a retarded active ingredient release of the easily water soluble antibiotics can be attained by adsorption and/or diffusion processes, which depends upon the material used, the pore volume and porosity. In addition, it is also possible to dissolve lightly water soluble antibiotics salts in suitable organic solvents and to steep the molded elements with these solutions. In this way, active ingredient deposits arise in the molded substances which manifest a retarded active ingredient release. An example of this is the method described by Cimbollel and Nies on the solution of a lightly water-soluble gentamicin salt and its use for coating (M. Cimbollel, B. Nies: Solvent For Lightly Soluble Gentamicin Salt. May 4, 1994, US 5,679,646). This gentamicin salt was synthesized on the basis of 3-p-methoxy benzylidene-6-hydroxy-4'-methoxy flavanone-6-phosphate. A very interesting process is described by Kurtz where lightly water soluble antibiotics salts which are built up of gentamicin or polymycin and penicillin or cephalosporin are dissolved in an organic solvent, and substrates not specified in greater detail are steeped with these solutions (L. D. Kurtz: Water-insoluble biocidal antibiotics salts. November 13, 1973, DE 23 01 633). The penicillin or cephalosporin radicals form the anionic components of the salts and the aminoglycoside radicals the cationic components.

In summary, it can be stated that up until now, no methods were known with which antibiotic components could applied on the surface of interconnecting microcavities which consist of lightly water-soluble gentamicin salts which contain an anionic radical from the alkyl sulfates and/or alkyl sulfonates group. The layer-forming
properties of lightly water-soluble antibiotics salts on the basis of organic sulfates and sulfonates has found no notice until now.

Underlying the present invention is the objective of developing improved elements with antibiotic coating as well as a simple, cost efficient manufacturing process for antibiotic coating of elements with interconnecting microcavities. These antibiotically outfitted substances with interconnecting microcavities should find use as implants for the treatment of bone and soft tissue damage in human and veterinary medicine. With this method, while dispensing with polymer binding agents, antibiotic coatings should be created simply so that they will make possible an antibiotics release over a period of several days. The antibiotic coating should adhere well to the inner surface of bodies with interconnecting microcavities, and may not occlude the interconnecting microcavities.

The objective is accomplished by the characteristics of the independent claims. Advantageous configurations are indicated in the dependent claims.

Underlying the invention is the surprising finding that antibiotic coatings with retarding active ingredient release in the microcavities of elements with interconnecting microcavities are especially formed by introducing into the microcavities a solution of gentamicin pentakis dodecyl sulfate or gentamicin pentakis dodecyl sulfonate in a suitable organic solvent (for example, from the alcohols group) by suitable measures such as steeping, spraying or dripping, and by a layer of gentamicin pentakis dodecyl sulfate or gentamicin pentakis dodecyl sulfonate remaining behind on the surface of the microcavities after removing the organic solvent (such as by evaporation or vaporization). The microcavities can be constructed as pores.

The substances can be of organic or inorganic nature or also be composites of inorganic and organic material. They are, for example, made of collagen, gelatin, polyesters, titanium, titanium alloys, high-grade steel, calcium carbonate, calcium sulfate, tri-calcium phosphate or hydroxyapatite. By metallic elements with interconnecting microcavities are in particular understood such that have microcavities on their surface which are connected with one another and metallic elements the surface of which are so roughed by sand blasting that they have open cavities
connected with one another, are also attributed to them. It is evident that the solvents used are as homogenous as possible. Above all, it is understood that the used lower alcohols as well as N,N-dimethyl formamide (DMF) or dimethyl sulfoxide (DMSO). Methanol or ethanol are preferred solvents.

Gentamicin pentakis dodecyl sulfate, gentamicin tetrakis dodecyl sulfate, gentamicin tetrakis dodecyl sulfonate and also gentamicin pentakis dodecyl sulfonate are non-crystalline, waxy substances which manifest a certain course in connection with the evaporation or vaporization of the organic solvent, and thereby are deposited as a layer on surfaces. Surprisingly, they adhere well to glass, ceramic or plastic surfaces.

Surprisingly, clindamycin dodecyl sulfate, clindamycin dodecyl sulfonate, lincosamine dodecyl sulfate, lincosamine dodecyl sulfonate can be dissolved in methanol, ethanol, dimethyl sulfoxide and N,N-dimethyl formamide. These substances can thus be added to gentamicin solutions without any problems. Adding tetracyclline dodecyl sulfate or tetracyclline dodecyl sulfonate to the solutions is also possible. One can also use the dodecyl sulfates or the dodecyl sulfonates of chlorotetracycline, oxytetracycline, demethyl chlorotetracycline, methacycline, doxycycline, rolitetracycline and monocycline instead of tetracyclline dodecyl sulfate. Ciprofloxacin dodecyl benzyl sulfonate can also be added. Correspondingly, coatings containing the gentamicin components and at least one of the mentioned additional antibiotics components rise to the surfaces of the microcavities. The manufacture of antibiotic coatings only with the dodecyl sulfates, dodecyl sulfonates and dodecyl benzyl sulfonates of the antibiotics enumerated without a gentamicin-containing antibiotic component is also within the context of this invention.

Surprisingly, other antibiotics can be mechanically fixed in place in layers of gentamicin pentakis dodecyl sulfate or gentamicin tetrakis dodecyl sulfate and gentamicin pentakis dodecyl sulfonate or gentamicin tetrakis dodecyl sulfonate by inclusion or overlaying. Therefore, it is possible for first an diluted solution which contains at least one slightly water-soluble antibiotic component from the aminoglycoside antibiotics, tetracycline antibiotics, lincosamide antibiotics and the 4-quinolone antibiotics group, and subsequently after evaporation and/or vaporization of
the water, for a solution which consists of gentamicin pentakis dodecyl sulfate and/or gentamicin tetrakis dodecyl sulfate and/or gentamicin pentakis dodecyl sulfonate and/or gentamicin tetrakis dodecyl sulfonate and the solvent methanol or ethanol or dimethyl sulfoxide or N,N-dimethyl formamide to be introduced by dipping or spraying or dripping. In the end, the result is a double layer. With use in implants, the second antibiotic is first released when the gentamicin layer is at least partially dissolved. In this structural form of the invention, gentamicin sulfate, clindamycin hydrochloride, clindamycin dihydrogen phosphate, lincosamine hydrochloride, kanamycin sulfate, amikacin sulfate, tobramycin sulfate, tetracycline hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride, demethyl chlortetracycline hydrochloride, methacycline hydrochloride, doxycycline hydrochloride, rolitetracycline hydrochloride, minocycline hydrochloride and/or ciprofloxacin hydrochloride and/or moxifloxacin hydrochloride are preferably used as slightly water-soluble antibiotic components.

The invention also concerns a process for the antibiotic coating of substances with interconnecting microcavities in which a solution containing one or more substances from the ciprofloxacin dodecyl benzyl sulfonate and/or moxifloxacin dodecyl sulfate and/or moxifloxacin dodecyl benzyl sulfonate and/or moxifloxacin dodecyl sulfonate and/or the dodecyl sulfates group and/or dodecyl sulfonates of clindamycin, tetracycline, lincosamine, chlortetracycline, oxytetracycline, demethyl chlortetracycline, methacycline, doxycycline, rolitetracycline and minocycline is introduced into the microcavities, and following evaporation or vaporization of the solvent, a layer of these substances arises on the surface of the microcavities.

Furthermore, it is in accordance with this invention that preferably fleece, felt fabric, hosiery and knit fabrics from polyester, collagen and gelatin are coated.

The respective dodecyl sulfate or sulfonate is preferably used in a concentration from 0.1 to 20.0 percent by mass in relation to the solvent.

It is also in accordance with the invention that preferably porous molded substances of polyesters, calcium carbonate, calcium sulfate, tricalcium phosphate, hydroxyapatite and resorbable glass are preferably coated.

It is within the meaning of the invention that the antibiologically coated substances
with interconnecting microcavities are used as implants.

The following examples explain the invention without restricting it.

Examples

The invention should be explained by Examples 1 and 2 below.

Square, resorbable phosphate glasses with dimensions of 20 x 20 x 10 mm are used for Examples 1 and 2 as elements with interconnecting microcavities. They had an overall porosity of 65 percent by volume.

Preparation of Examples 1 and 2

Gentamicin pentakis dodecyl sulfate was used for the examples, the manufacture of which took place in accordance with the method of Jurado Soler et al. (A. Jurado Soler, J. A. Ortiz Hernandez, C. Ciurop Bertran: New Gentamicin Derivatives: Process For Manufacturing the Same And Those Containing Antibiotically Active Composition. September 30, 1974, DE 24 46 640). 135 mg or 270 mg of gentamicin pentakis dodecyl sulfate were dissolved in 1 g of methanol. The previously prepared methanol solution was dripped into the pores in each case of a square-shaped phosphate glass. The sample substances soaked up the solution and were subsequently dried at room temperature until mass constancy.

Tab. 1: Compositions of solutions used as well as weighing out of uncoated and coated sample substances from Examples 1 and 2

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>135 mg GPDS 1000 mg methanol</td>
<td>3949</td>
<td>4087</td>
<td>130</td>
</tr>
</tbody>
</table>
GPDS: Gentamicin pentakis dodecyl sulfate

Antibiotics release of the sample elements from Examples 1 and 2:

The molded elements produced in examples 1 and 2 were added in each case to 20 ml of physiological saline and stored at 37°C over a period of 28 days. Sampling took place after 1, 2, 3, 6, 9, 13, 15, 21 and 28 days of storage time. After each sampling, the releasing medium was completely replaced by fresh medium. Antibiotics determination was conducted with an agar diffusion test using *Bacillus subtilis* ATCC 6633 as a test germ. The results are presented in Tab. 2.

Tab. 2: Results of the microbial determination of gentamicin release of the coated sample elements of Examples 1 and 2 as a function of storage time of the sample elements in physiological saline at 37°C.

Gentamicin release (cumulative, as gentamicin sulfate AK=628)

[mg]

<table>
<thead>
<tr>
<th>Release time [d]</th>
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<tr>
<td>1</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>2</td>
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CLAIMS

1. An element with interconnecting microcavities, characterized in that a layer is formed on the surface of the microcavities which has gentamicin dodecyl sulfate with 1 to 5 dodecyl sulfate groups per gentamicin molecule or gentamicin dodecyl sulfonate with 1 to 5 dodecyl sulfonate groups per gentamicin molecule.

2. The element of claim 1, characterized in that the layer has one or more components selected from gentamicin pentakis dodecyl sulfate and gentamicin tetrakis dodecyl sulfate or one or more components selected from gentamicin pentakis dodecyl sulfonate and gentamicin tetrakis dodecyl sulfonate.

3. An element with interconnecting microcavities, characterized in that a layer is formed on the surface of the microcavities which has one or more of substances selected from:
   
ciprofloxacin dodecyl benzyl sulfonate;
clindamycin dodecyl sulfate;
tetracycline dodecyl sulfate;
lincomycin dodecyl sulfate;
chlorotetracycline dodecyl sulfate;
oxytetracycline dodecyl sulfate;
demethyl chlorotetracycline dodecyl sulfate;
methacycline dodecyl sulfate;
doxycycline dodecyl sulfate;
rolitetracycline dodecyl sulfate;
minocycline dodecyl sulfate;
clindamycin dodecyl sulfonate;
tetracycline dodecyl sulfonate;
lincosamine dodecyl sulfonate;
chlortetracycline dodecyl sulfonate;
oxetetracycline dodecyl sulfonate;
demethyl chlortetracycline dodecyl sulfonate;
methacycline dodecyl sulfonate;
doxycycline dodecyl sulfonate;
rolitetracycline dodecyl sulfonate; and
minocycline dodecyl sulfonate.

4. The element of claim 1 or 3, characterized in that it is consists of collagen, gelatin, polyester, calcium carbonate, calcium sulfate, tricalcium phosphate or hydroxyl apatite.

5. The element according to claim 1 or 3, characterized in that it is designed as fleece, felt, hosiery or knit fabrics, each of which consists of polyester, collagen or gelatins.

6. The element of claim 1 or 3, characterized in that it is designed as a porous molded element of polyester, calcium carbonate, calcium sulfate, tricalcium phosphate, hydroxyl apatite or resorbable glass.

7. The element according to claim 1 or 3, characterized in that it is made of titanium, titanium alloys or high grade steel.

8. The element according to claim 1 or 3, characterized in that the microcavities are constructed as pores.
9. The element with interconnecting microcavities of one of claims 1 to 8 wherein the element is a medical implant.

10. A process for antibiotic coating of the element with interconnecting microcavities according to any one of claims 1 to 9 comprising the steps of:
    a) introducing a solution containing a solvent and gentamicin dodecyl sulfate with 1 to 5 dodecyl sulfate groups per gentamicin molecule and/or gentamicin dodecyl sulfonate with 1 to 5 dodecyl sulfonate groups per gentamicin molecule into the microcavities; and
    b) vaporizing or evaporating the solvent whereby a layer which comprises the gentamicin-dodecyl sulfate and/or gentamicin dodecyl sulfonate rises to the surface of the element.

11. The process of claim 11, characterized in that gentamicin pentakis dodecyl sulfate or gentamicin tetrakis dodecyl sulfate and/or gentamicin pentakis dodecyl sulfonate or gentamicin tetrakis dodecyl sulfonate is used.

12. The process of claim 10 or 11, characterized in that at least one organic solvent is used as the solvent.

13. The process according to claim 12, characterized in that the at least one organic solvent is selected from methanol, ethanol, N,N-dimethyl formamide and dimethyl sulfoxide.

14. The process of any one of the claims 11 to 13, characterized in that the step of introducing the solution comprises dipping, spraying or dripping the solution.
15. The process of any one of claims 11 to 14, characterized in that the element is consists of collagen, gelatin, polyester, calcium carbonate, calcium sulfate, tricalcium phosphate or hydroxyl apatite.

16. The process according to one of the claims 11 to 15, characterized in that the solution further contains one or more of substances selected from:
   - ciprofloxacin dodecyl benzyl sulfonate;
   - clindamycin dodecyl sulfate;
   - tetracycline dodecyl sulfate;
   - lincomicine dodecyl sulfate;
   - chlortetracycline dodecyl sulfate;
   - oxytetracycline dodecyl sulfate;
   - demethyl chlortetracycline dodecyl sulfate;
   - methacycline dodecyl sulfate;
   - doxycycline dodecyl sulfate;
   - rolitetracycline dodecyl sulfate;
   - minocycline dodecyl sulfate;
   - clindamycin dodecyl sulfonate;
   - tetracycline dodecyl sulfonate;
   - lincomicine dodecyl sulfonate;
   - chlortetracycline dodecyl sulfonate;
   - oxytetracycline dodecyl sulfonate;
   - demethyl chlortetracycline dodecyl sulfonate;
   - methacycline dodecyl sulfonate;
   - doxycycline dodecyl sulfonate;
   - rolitetracycline dodecyl sulfonate; and
   - minocycline dodecyl sulfonate.
17. A process for antibiotic coating of an element with interconnecting microcavities comprising the steps of:
   a) introducing to the element a diluted first solution which contains water and at least one antibiotic component which is slightly soluble in water selected from the group consisting of aminoglycoside antibiotics, tetracycline antibiotics, lincosamide antibiotics and 4-quinolone antibiotics into the interconnecting microcavities;
   b) vaporizing or evaporating the water;
   c) introducing to the element a second solution which comprises gentamicin dodecyl sulfate and/or gentamicin dodecyl sulfonate in a solvent comprising one or more components selected from methanol, ethanol, N,N-dimethyl formamide and dimethyl sulfoxide by dipping, spraying or dripping; and
   d) vaporizing or evaporating the solvent whereby a layer which comprises the gentamicin-dodecyl sulfate and/or gentamicin dodecyl sulfonate forms on the surface of the element.

18. The process of claim 17 wherein the gentamicin dodecyl sulfate and/or gentamicin dodecyl sulfonate is one or more compounds selected from the group consisting of gentamicin pentakis dodecyl sulfate, gentamicin tetrakis dodecyl sulfate, gentamicin pentakis dodecyl sulfonate and gentamicin tetrakis dodecyl sulfonate.

19. The process according to claim 17 or 18 wherein the at least one antibiotic component is one or more compounds selected from the group gentamicin sulfate, clindamycin hydrochloride, clindamycin dihydrogen phosphate, lincosamine hydrochloride, kanamycin sulfate, amikacin sulfate, tobramycin sulfate, tetracycline hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride,
dimethyl chlortetracycline hydrochloride, methacycline hydrochloride, doxycycline hydrochloride, rolitetracycline hydrochloride, minocycline hydrochloride, ciprofloxacin hydrochloride and moxifloxacin hydrochloride.

20. The process according to any one of the claims 11 to 19, characterized in that 0.1 to 20.0 percent by mass of dodecyl sulfate or sulfonate in relation to the solvent are introduced.

21. The process according to one of claims 11 to 20, characterized in that the element is a fleece, felt, hosiery or knit fabric, each of which consists of polyester, collagen or gelatins.

22. Process according to any one of the claims 11 to 20, characterized in that the element comprises a porous molded element of polyester, calcium carbonate, calcium sulfate, tricalcium phosphate, hydroxyl apatite or resorbable glass.

23. The process according to any one of the claims 11 to 20, characterized in that the element is a metallic molded element of titanium, titanium alloys or high-grade steel.

24. The process of any of claims 11 to 16 wherein the solution further contains one or more compounds selected from moxifloxacin dodecyl sulfate, moxifloxacin dodecyl benzyl sulfonate and moxifloxacin dodecyl sulfonate.

25. The process of any of claims 17 to 23 wherein the second solution further contains one or more compounds selected from moxifloxacin dodecyl sulfate, moxifloxacin dodecyl benzyl sulfonate and moxifloxacin dodecyl sulfonate.
26. The process according to one of the claims 11 to 23, characterized in that the microcavities are designed as pores.