

# PATENT SPECIFICATION

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(21) Application No. 46414/77 (22) Filed 8 Nov. 1977 (19)  
(31) Convention Application Nos. 2 651 441 (32) Filed 11 Nov. 1976  
2 727 535 18 June 1977 in



(33) Fed. Rep. of Germany (DE)  
(44) Complete Specification published 30 Jan. 1980  
(51) INT. CL.<sup>3</sup> A61K 47/00 C07G 11/00  
(52) Index at acceptance

A5B 170 180 190 20X 20Y 216 21Y 275 27Y 327 832  
835 839 B J L  
C3H A1 K1

## (54) ANTIBIOTIC-CONTAINING COMPOSITION

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, of 250, Frankfurter Strasse, 61 Darmstadt, Federal Republic of Germany, a Joint-Stock Company organised under the laws of the Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with an antibiotic-containing composition and with the use thereof as a surgical synthetic resin material.

It is known that antibiotics, especially gentamycin, are slowly liberated from synthetic resins based on polymethacrylates and/or polyacrylates. A sharp initial drop in concentration, due to the liberation of the antibiotic from the outermost layers of the synthetic resin, is followed by an almost constant rate of liberation which, however, decreases slowly over a long period of time. These antibiotic-containing synthetic resins have hitherto been used as bone cements for fixing endoprostheses, for example total hip endoprostheses, or in the case of changing infected endoprostheses. For combating infection and for prophylaxis, the antibiotic is added before complete polymerisation of the synthetic resin. Furthermore, it is known that synthetic resin particles in the form of a granulate or of small spheroids with a particle diameter of 1 to 20 mm. are especially suitable as carrier materials for antibiotics for this purpose.

Furthermore, it is known from German Patent Specification No. 2,511,122 that an antibiotic can be liberated from bone cement in comparatively high concentration when the bone cement additionally contains sodium chloride, potassium chloride, sodium bromide and/or potassium bromide.

However, the use of these additional materials can cause problems since they have a cell-damaging effect and, therefore, are not to be used in surgery.

In addition, it has been shown that the liberation of the antibiotic from the synthetic resin particles does not take place in an optimum manner and can vary from one batch to another. Furthermore, in the case of some production processes for such synthetic resin particles, sometimes temperatures can be reached in which some of the antibiotic can be decomposed, this amount then no longer being available for therapeutic purposes.

It is an object of the present invention to provide an antibiotic-containing composition of synthetic resin particles from which the antibiotic can be liberated in an optimum manner without a danger of damage due to added materials.

According to the present invention, this object is achieved when the antibiotic-containing synthetic resin particles additionally contain at least one amino acid.

Thus, according to the present invention, there is provided an antibiotic-containing composition comprising synthetic resin particles based on polymethacrylates and/or polyacrylates and containing at least one antibiotic, together with at least one amino acid.

The present invention also provides a process for the improved liberation of antibiotics from antibiotic-containing synthetic resin particles based on polymethacrylates and/or polyacrylates, wherein 0.3 to 5% by weight of at least one amino acid, referred to the synthetic resin, is added to the synthetic resin.

When using the composition for the production of bone cements, especially for endoprostheses, as well as of implantable formed bodies, it is advantageous to start from a pearl polymer of synthetic resin particles with particle diameters of < 30  $\mu$ . This pearl polymer can also be used for the production of synthetic resin particles with a particle diameter of 1 to 20 mm.; if desired, the individual particles can be connected together, at least in part, with the help of filaments or wires.

Surprisingly, the liberation of the antibiotic from the antibiotic-containing synthetic resin particles is substantially improved in the presence of amino acids, i.e. independently of the particular batch, a continuous slowly decreasing liberation of the antibiotic taking place over a comparatively long period of time. Even a low concentration of these physiologically compatible amino acids has this effect, and, in contradistinction to the added materials known from the prior art, a cell-damaging action does not occur. Furthermore, we have, surprisingly, found that the stability of the bone cement is practically unimpaired by the addition of amino acids. Insofar as the composition according to the present invention is produced in the form of particles, which preferably have diameters of 1 to 20 mm., for example by injection moulding, the working temperatures which are thereby necessary can be considerably reduced so that, having regard to the antibiotic, a desirably gentle working up is possible.

As addition to the antibiotic-containing composition according to the present invention, there can, in principle, be used all naturally-occurring and physiologically compatible amino acids. Especially good results are achieved with amino acids which have a water-solubility of about 1 g./100 ml. It is preferred to use aliphatic mono-aminomonocarboxylic acids containing up to 5 carbon atoms, for example, glycine, alanine, threonine, valine, serine, hydroxyproline, and proline. Of these amino acids, glycine and alanine are preferred and glycine is especially preferred. The composition according to the present invention can contain one amino acid or a mixture of several amino acids.

The amount of amino acid or acids to be added can be varied within a wide range the content depending, at least in part, upon the solubility of the amino acid or acids employed. In general, an addition of 0.3 to 5% by weight of amino acid or acids, referred to the polymer, is preferred and in the case of, for example, glycine, an addition of about 1% by weight has proved to be especially advantageous.

The composition according to the present invention preferably contains essentially a copolymer of methyl methacrylate and methyl acrylate. As antibiotic, the composition preferably contains gentamycin. According to an especially advantageous embodiment of the present invention, the individual particles are connected together, at least partially, by the help of filaments or wires.

The composition according to the present invention are especially suitable for the prevention of infection in heavily contaminated and extensive wounds in soft tissues

or in damaged tissues in cases of compound bone fractures such as frequently occur as a result of accidents, with the object of temporarily filling a potentially infected wound with contaminated skin closure. It is thus possible to apply antibiotics locally in depot form, i.e. directly to the infected or endangered places. In addition, the application can be broken off as desired and can also be repeated in any desired manner. In the case of comparatively large wounds, it is especially simple to introduce particles which are connected together since then all the particles can be readily removed again, for example by pulling on one end of the filament.

A further important field of use is in bone surgery, especially in the treatment of post-traumatic osteomyelitis. The composition is suitable for filling osteomyelitic cavities. Surprisingly, connective tissue grows into the interstices between the synthetic resin particles. Thus, in spite of infection, the material is incorporated as in an aseptic medium. The composition can also be used for the provision of an aseptic transplant site for a possible subsequent introduction of spongiosa from the patient's own body. The composition can also be used for the open filling of osteomyelitic cavities when a primary skin closure is not possible. The uppermost layer of the particles can be subsequently removed and the underlying particles are already substantially enveloped by connective tissue so that a skin transplant is possible.

The composition according to the present invention can, in particular, also be used for anchoring joint endoprostheses, for the firm bonding of bones, for cementing in implants and similar surgical procedures. However, it can also be used in the form of implantable formed bodies, complete hardening taking place inside or outside the body.

Synthetic materials for surgical purposes based on polymethacrylates and/or polyacrylates are, in principle, known. Thus, for example, a bone cement is known which, in a standard packing, comprises two packs, each containing about 40 g. of powder, and 2 ampoules, each containing 20 ml. of liquid. The powder is a fine pearl polymer (particle diameter  $<30\mu$ ) of a methyl methacrylate-methyl acrylate copolymer. As catalyst, there is added to the powder about 0.5 dibenzoyl peroxide. For identification of the material, traces of chlorophyll can be polymerised in during the production thereof. As X-ray contrast agent, the powder can also contain, for example, zirconium dioxide. The associated liquid consists of monomeric methyl methacrylate to which is added about 0.7% dimethyl-p-toluidine as accelerator, as well as traces of hydroquinone as stabiliser. As a

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rule, this liquid is also coloured with traces of chlorophyll for identification purposes. The powder, which is packed into polyethylene packs, can be sterilised with ethylene oxide. The liquid can be sterilised by filtration and filled into glass ampoules.

Upon mixing together 2 parts by weight of powder with 1 part by weight of liquid, the dibenzoyl peroxide reacts with the dimethyl-*p*-toluidine in the liquid, radical polymerisation thereby being initiated. The mixture is so adjusted that it can be used after only about 1 minute in the form of a paste. This paste remains kneadable for about 4 minutes and then begins to harden, with the evolution of heat. After 6 minutes, the polymerisation is substantially complete. During the elastic phase, the paste is, when used as bone cement or bone putty, brought together with the parts to be connected and, as a rule, there hardens out. However, the forming and the hardening can also take place outside of the body, the formed parts then being introduced into the body during or after hardening.

The synthetic resin which can be used for the present invention can, however, also be available in already completely polymerised form. It is preferably employed in the form of a pearl polymer for the production of the composition according to the present invention.

The particle diameter is preferably from 1 to 20 mm. and more preferably from 7 to 10 mm. The granulate or the material in the form of spheroids can be produced not only directly before the operation but can also be obtained in finished form. Of course, care must always be taken to ensure sterility. According to a special embodiment of the present invention, the particles are connected together with filaments or wires. This can take place, for example, in such a manner that the material, while it is still in a formable state, is strung like pearls on to a filament or wire or a filament or wire is passed into the material. The filament used can be any desired surgical stitching material or can also be a high alloy steel wire, such as is used in bone surgery. A composition according to the present invention in this form has the advantage that it is simple to handle during an operation and, in the case of a reoperation, can readily be removed again. An initially only temporary filling in the case of first aid is also possible in this manner. The wires used are also X-ray contrastable. In this way, for example, a possibly desired removal of the particles from enveloping connective tissue is made simpler; the temporary introduction of the composition according to the present invention into a marrow cavity is also possible, for example,

after removal of a bone pin because of marrow cavity phlegmons.

For the production of the composition according to the present invention, at least one antibiotic and at least one amino acid is incorporated into the synthetic resin. This can take place by introducing both components into the synthetic resin before complete hardening or by intensively mixing an already polymerised product, for example, a pearl polymer, which possibly contains one of the components, with the or the still missing components and subsequently carrying out the desired forming. In principle, all antibiotics can be used which are not damaged at the temperatures which occur during polymerisation or sintering and which are liberated from the synthetic resin in the desired manner.

Furthermore, the antibiotics should be chemically stable towards the synthetic resin employed. Their spectrum of activity is to include gram-positive and gram-negative micro-organisms or preferably both groups of micro-organisms. If possible, the micro-organisms should have a retarded resistance development with regard to the antibiotics employed. From the large number of antibiotics which can be used, there may be mentioned, by way of example, erythromycin, lincomycin, clindamycin, novobiocin, vancomycin, fusidic acid, rifamycin, polymyxins, neomycin, kanamycin, tobramycin and, in particular, gentamycin. Penicillins and cephalosporins can also be used. Because of their broad antibacterial spectrum and their heat stability, the aminoglycoside antibiotics are especially preferred.

Gentamycin, for example, is an aminoglycoside antibiotic which acts preponderantly bactericidally against gram-positive but especially against gram-negative micro-organisms. However, all these micro-organisms can sustain a chronic osteomyelitis so that this antibiotic has already been used in the case of osteomyelitis, with utilisation of its local and systemic action. According to the present invention, by the addition of proved liberation of gentamycin particularly, amino acids, there is achieved an improved liberation of gentamycin particularly, from synthetic resins based upon polymethacrylates and/or polyacrylates. The very good water-solubility of this antibiotic acts, especially in the presence of an amino acid, such as glycine, apparently very favourably on the diffusion from the synthetic resin. After an initial drop of concentration, the good diffusability permits an almost constant rate of liberation which decreases only slowly over an extraordinarily long period of time. In this manner, sufficient protection is ensured even after several months. This is a great advantage in

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comparison with the previously used treatment in which the liberated amount of antibiotic varies more or less greatly. Furthermore, due to the nature of the added material, tissue cell damage is avoided.

Neither the procedure of polymerisation or sintering nor the physical properties of the synthetic resin material are to influence unfavourably the effectiveness of the antibiotic.

The composition according to the present invention also possesses the advantage that the synthetic resin is completely hardened before introduction into the body. Thus, there no longer occurs in the bone tissue the evolution of heat upon complete polymerisation which means that the operation can be carried out under milder conditions. In the case of extracorporeally hardened synthetic resins, the danger can be reduced that, during the operation, residual monomers are liberated so that a potential risk with regard to the heart-circulatory system does not arise.

The amount of antibiotic to be added can be varied within wide limits and depends essentially upon the activity of the antibiotic. In general, the amount of antibiotic added is 0.2 to 15% by weight, referred to the polymer. In the case of gentamycin, for example, additions of from 1 to 4% by weight, calculated as gentamycin base, have proved to be especially useful. The other antibiotics are preferably also used in amounts of adequate antimicrobial activity.

To the available commercial packs with not yet fully polymerised synthetic resin, there can be added, for example, 0.5 to 1 g. gentamycin for about 60 g. polymer (40 g. powder and 20 ml. liquid). However, other antibiotic additions or mixtures of antibiotics can also be selected. Thus, for example, a substantially higher addition can be made when a comparatively small cavity is to be filled but, nevertheless, a particularly effective dose of the antibiotic is to be introduced. In the case of a change of the cause of infection or of resistance to the incorporated antibiotic, the composition according to the present invention can easily be removed and possibly replaced by another one containing one or more different antibiotics.

The composition according to the present invention is preferably used for the prevention of infection on boundary surfaces between bone cement and bone or endoprosthesis and tissue, in wounds in soft tissues or in compound fractures, as well as for the treatment of chronic osteomyelitis. When carrying out the operation, the powdered pearl polymer, which contains the antibiotic and the amino acid, is mixed with the monomer-containing liquid. The

plastic paste obtained is introduced into the body and formed in the desired manner. A formed body can also be produced from the one cement which can then be implanted into the body. A further possibility is carefully to fill the wound cavity with the composition according to the invention or to introduce the spheroids present on filaments or wires. Due to the dimensioning of the particles, an optimum filling of the cavities is possible. The composition according to the present invention has proved to be outstandingly useful in numerous operations.

When used for the treatment of osteomyelitis, a very rapid overcoming of the putrescent secretion is observed. Open cavities filled with the composition according to the present invention appear to be completely free of irritation, and shown no inflammatory phenomena. As an expression of the freedom from infection, the particles are slowly enveloped by connective tissue. Furthermore, the position of the particles can be very easily monitored since the synthetic particles can be clearly recognized on an X-ray picture.

The following Examples are given for the purpose of illustrating the present invention:—

#### EXAMPLE 1.

40 g. of a sterile, fine pearl polymer (particle diameter  $<30\mu$ ), consisting of a copolymer of methyl methacrylate and methyl acrylate, which additionally contain 0.5% dibenzoyl peroxide, traces of chlorophyll and 15% zirconium dioxide as X-ray contrast agent, are well mixed with 0.5 g. gentamycin sulphate and 0.4 g. glycine. The powder obtained is then mixed with 20 ml. of a liquid which consists of monomeric methyl methacrylate with an addition of about 0.7% dimethyl *p*-toluidine and about 0.006% hydroquinone. From the paste obtained after thorough mixing up, there are formed spheroids with a diameter of about 7 mm. After about 6 minutes, the particles are hardened. A sterilisation, for example by gassing with ethylene oxide, can, if desired, follow. The spheroids can then be used for the prevention of infection in wounds in soft tissue or zones of destruction in the case of compound fractures or also for filling osteomyelitis cavities.

#### EXAMPLE 2.

In a manner analogous to that described in Example 1, spheroids are formed with a diameter of about 7 to 10 mm. To 60 g. of polymer there are added 1 g. gentamycin sulphate and 0.6 g. glycine. Before complete hardening, the particles obtained are strung, at a distance apart of about 2 mm., like pearls on a filament (surgical high-

alloy steel) with a diameter of about 0.1 mm. The spheroids are then allowed to harden in this state. In the case of use, the "string of pearls" can be cut off in any desired length.

#### EXAMPLE 3.

40 g. of a sterile fine pearl polymer (particle diameter  $<30\mu$ ), consisting of a copolymer of methyl methacrylate and methyl acrylate, which contains about 15% zirconium dioxide as X-ray contrast agent, are well mixed with 0.5 g. gentamycin sulphate and 0.4 glycine. The powder obtained is sintered in an appropriate apparatus and formed into appropriate shapes (preferably by injection moulding). The incorporation of filaments or wires can hereby take place at the same time. If desired, sterilisation, for example by gassing with ethylene oxide, can follow. The spheroids can then be used for the prevention of infection in wounds in soft tissues or zones of destruction in the case of compound fractures also for filling osteomyelitic cavities.

#### EXAMPLE 4.

In a manner analogous to that described in Example 1, a paste is produced from the given components. This paste is employed in conventional manner as a bone cement for fixing endoprostheses in hip joint operations.

#### WHAT WE CLAIM IS:—

1. An antibiotic-containing composition comprising synthetic resin particles based upon polymethacrylates and/or polyacrylates and containing at least one antibiotic, together with at least one amino acid.

2. A composition according to claim 1, wherein the amino acid is glycine, alanine, threonine, valine, serine, hydroxy-proline and/or proline.

3. A composition according to claim 1 or 2, wherein the content of amino acid is from 0.3 to 5% by weight, referred to the polymers.

4. A composition according to claim 3, wherein, when the amino acid is glycine, the content thereof is about 1% by weight, referred to the polymers.

5. A composition according to any of the preceding claims, wherein the antibiotic is gentamycin.

6. A composition according to any of the preceding claims, wherein the particles have a diameter of from 1 to 20 mm.

7. A composition according to claim 6, wherein the particles have a diameter of from 7 to 10 mm.

8. A composition according to any of the preceding claims, wherein the individual particles are connected together at least partially with the help of filaments or wires.

9. An antibiotic-containing composition according to claim 1, substantially as hereinbefore described and exemplified.

10. Process for the improved liberation of antibiotics from antibiotic-containing synthetic resin particles based on polymethacrylates and/or polyacrylates, wherein 0.3 to 5% by weight of at least one amino acid, referred to the synthetic resin, is added to the synthetic resin.

11. Process according to claim 10 for the improved liberation of antibiotics from antibiotic-containing synthetic resin particles, substantially as hereinbefore described and exemplified.

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### EXAMPLE 3.

40 g. of a sterile fine pearl polymer (particle diameter  $<30\mu$ ), consisting of a copolymer of methyl methacrylate and methyl acrylate, which contains about 15% zirconium dioxide as X-ray contrast agent, are well mixed with 0.5 g. gentamycin sulphate and 0.4 glycine. The powder obtained is sintered in an appropriate apparatus and formed into appropriate shapes (preferably by injection moulding). The incorporation of filaments or wires can hereby take place at the same time. If desired, sterilisation, for example by gassing with ethylene oxide, can follow. The spheroids can then be used for the prevention of infection in wounds in soft tissues or zones of destruction in the case of compound fractures also for filling osteomyelitic cavities.

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3. A composition according to claim 1 or 2, wherein the content of amino acid is from 0.3 to 5% by weight, referred to the polymers.

4. A composition according to claim 3, wherein, when the amino acid is glycine, the content thereof is about 1% by weight, referred to the polymers.

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