

A PROCESS FOR THE PREPARATION OF THERAPEUTICALLY
USEFUL, CROSSLINKED DEXTRAN GRAIN POLYMERS AND THERAPEUTICAL
COMPOSITIONS CONTAINING THEM

5 The invention relates to an improved process for
preparing therapeutically useful dextran grain polymers
and the therapeutical compositions containing them.

 According to the process of the invention, the
crosslinked grain polymer is swollen in water at a pH
10 of 1.5 to 5.5, suitably at a pH of 4.0 and after removing
the acidic water, it is treated with a water-miscible
organic solvent, suitably with ethanol.

 After removing the aqueous ethanolic phase, the
thus dehydrated grain polymer is again swollen in ion-
15 free water, washed until free from acid, dried and formu-
lated suitably after sterilizing by irradiation with
gamma-rays into a therapeutically useful form.

 It is known that water-absorbing methods (use
of halved tomato, or plantain leaves for covering wounds)
20 have been used in the popular medicine for healing
succulent, infected, purulent wounds.

 Although these therapeutical methods were based on
experience, their success could be attributed to that
the open wounds were purified from the tissue fluids and
25 necrotized tissue residues, thereby the possibility of

fixation and propagation of microorganisms on the wound surfaces was decreased and, on the other hand, the wounds were protected from the harmful effect of the metabolic products and toxins of the microorganisms;

5 further on, the air supply of the wounds was improved and an appropriate water-absorbing effect was achieved by covering the wounds with the above-mentioned materials of natural origin. When this water-absorbing effect has also been extended to the edematic parts of the wounds,

10 then a better blood supply could be provided in the environment of the wounds, whereby the restoration of the tissues was also made possible.

The composition according to the UK-PS No. 1,454,055 of Pharmacia AB, a Swedish company (known as Debrisan^R

15 in the commerce), completely satisfies the physical and chemical conditions of an optimum wound-healing. In this patent specification, the authors refer to processes reported in their previous patent specifications for preparing the dextran gel representing the active ingredient

20 of the composition (UK-PS Nos. 845,715, 936,039, 974,054 and 1,013,585).

It has been observed in the course of our experiments that the dextran grain polymer (prepared as described in Example 1 of the UK-PS No. 974,054), when crosslinked with

25 epichlorohydrin in an alkaline solution by using polyvinyl acetate as a suspension stabilizing agent, did not possess

in animal experiments the therapeutic effect indicated in the UK-PS No. 1,454,055, though its water regain (water-absorbing capacity) and particle size corresponded to the data given in the last-mentioned patent specification.

- 5 The pharmacological properties of the grain polymers prepared according to the Examples 2, 3, 4 and 5 of the UK-PS No. 974,054 were also investigated but the result expected could not be achieved even by these preparations (As compared to Example 1, said Examples are only
10 different concerning the suspension medium: toluene is used in Example 1, o-dichlorobenzene in Example 2, dichloromethane in Example 3, dibromoethane in Example 4 and 1,2-dichloroethane in Example 5.)

During animal experiments, KAHIB (a Hungarian
15 breed) swines of both sexes with a body-weight of 8 to 12 kg. were used. Burns of 20 mm. in diameter were evoked on both sides of the animals by using the end of a copper rod heated to 170 to 180 °C, under anaesthesia induced by 35 mg./kg. Evipan [sodium 5-(1-cyclohexen-1-yl)-1,5-dimethyl-
20 barbiturate] administered intravenously [according to the method of S. Jacobson et al.: Scand. J. Plast. Reconstr. Surg. 10, 97-101 (1976)]. 'Evipan' is a registered Trade Mark.

Six animals each were used in both the experimental and control groups. The observation period lasted 14 days.

- 25 After injuring the animals, the infected wounds were treated beginning from the 3rd day with the grain polymer

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prepared as described in Example 1 of the UK-PS No. 974,054 (which was reproduced as described in Example 1 of this invention) or with the commercially available Debrisan^R. The wound in one side of the swines was treated with Debrisan^R, whereas the wound in the other side was treated with the grain polymer prepared as described in the UK-PS No. 974,054. The treatment was carried out once a day.

It could be stated in the course of these experiments that, although the tissue fluids were absorbed and the bacteria as well as tissue debris were removed and thus the wound was cleansed by the grain polymer prepared as described in Example 1 of the UK-PS No. 974,054, however, an undesired side-effect appeared which became very obvious on studying the histological samples: the wound and its environment became intensely edematic. Thus, although the wound was cleansed, the blood and oxygen supply were decreased as a consequence of the edema formation, whereby the healing was inhibited.

The use of the Debrisan^R composition resulted in the expected effect: the wounds healed and the formation of an edema was not observed.

On the basis of our above investigations it was concluded that the grain polymer prepared as described in Example 1 of the UK-PS 974,054 may contain materials which have been occluded by the grains in the course of

the manufacturing process whereby, after diffusion of these materials from the grains on the wound surface, an edema development by irritation occurred and the healing was retarded.

5 This hypothesis was supported by microscopic investigation: the particles of the grain polymer prepared according to Example 1 of the UK-PS No. 974,054 were opalescent and opaque.

Surprisingly, it was observed that the contaminating
10 material could be removed from the grains by washing at a pH value of 1 to 5.5 and a following treatment with ethanol. After this treatment, the grains were swollen in water, stirred with water until free from acid, made free from water by using ethanol and dried to give clear,
15 transparent grains (prepared as described in Example 5 of this invention) which gave the same advantageous results in the animal experiments carried out as reported above, as Debrisen^R used as control.

The purified product can be formulated e.g. as wound
20 powder in spreading boxes; as wound plug closed in a filter; or in the form of a paste.

The process of the invention is illustrated in detail by the following non-limiting Examples.

(13)

Example 1

Reproduction of Example 1 of the UK-PS No. 974,054

Dextran with an average molecular weight of 40,000 was moistened with 20% of water and 6N aqueous sodium hydroxide solution was added to this mixture in order to adjust a final concentration of 40% of the solution. The thus-obtained dextran solution weighing 600 g. was poured into a cylindrical reaction bottle which had been fitted with a thermometer and stirrer. The solution of polyvinyl acetate with an average molecular weight of 430,000 in 500 ml. of toluene was portionwise added as a suspension-stabilizing agent, the stirring was started and continued at such a rate that the aqueous phase was dispersed in the toluene phase in the form of little droplets. Then 50 g. of epichlorohydrin were portionwise added while keeping the temperature at 50°C. A gel was formed within 1 hour. After completion of the reaction, the gel grains were filtered out, the suspension-stabilizing agent was washed out by toluene, then the toluene was removed by washing with ethanol. Finally, the product was washed with water until neutral and dried at 110°C. The thus-obtained grains had a particle size of 30 to 100 μ and a water regain of 3.0 g./g. of dry substance.

Example 2

100 g. of dry dextran grain polymer, crosslinked with epichlorohydrin, obtained as described in Example 1, were

swollen for 4 hours in 100 ml. of water, the pH value of which had been adjusted to 4. During the swelling the mixture was continuously and mildly stirred and the pH value was controlled. Thereafter, the acidic liquid was discarded and the swelling was repeated by using 500 ml. of water adjusted to a pH value of 4 by adding hydrochloric acid while the mixture was mildly and continuously stirred for 1 hour. After discarding the acidic water, the swollen grains were stirred with 500 ml. of ethanol for 1 hour, the supernatant was discarded and the treatment with ethanol was repeated in the above manner. The dehydrated grains were swollen by using ion-free water, washed until reaching a pH value of 5.5 and after making the grains water-free with 500 ml. of ethanol, the grain polymer was dried at 80°C. The grain size and water regain of the thus-obtained grains were the same as described in Example 1.

Example 3

100 g. of dry dextran grain polymer crosslinked with epichlorohydrin, obtained as described in Example 1, were swollen for 4 hours in 100 ml. of water, then the pH was adjusted to 1 by adding hydrochloric acid under continuous and mild stirring, whereafter the Example 1 was followed. The water regain and size of the thus-obtained grains were identical to those described in Example 1.

Example 4

100 g. of dry dextran grain polymer crosslinked with

epichlorohydrin, obtained as described in Example 1, .
were swollen for 4 hours in 2000 ml. of water adjusted to
pH 4 by adding hydrochloric acid. During this swelling, the
mixture was continuously stirred and the pH value was
5 controlled. Thereafter, the Example 1 was followed. The
water regain and size of the thus-obtained grains were
identical to those described in Example 1.

Example 5

32 g. of polyvinyl acetate with an average molecular
10 weight of 430,000 were dissolved in 380 ml. of toluene
while stirring at 50 to 55 °C, then cooled to 20 °C. 100 g.
of dextran powder with an average molecular weight of
40,000 were dissolved in 100 ml. of water and the solution
of 24 g. of sodium hydroxide in 27 ml. of water was added.
15 The thus-obtained mixture was stirred, then 42 ml. of
epichlorohydrin and the above-prepared toluene solution of
the polyvinyl acetate were added and the reaction mixture
was stirred at 50 to 55 °C for additional 16 hours. The
thus-formed grain polymer was washed with toluene until it
20 became free from polyvinyl acetate, then washed with
ethanol and water. Thereafter, the grains were stirred for
1 hour in 500 ml. of water adjusted to a pH value of 4 by
adding hydrochloric acid. The washing with acid was repeated
and then the process of Example 1 was followed. The thus-obtained grains
25 had a particle size of 40 to 100 μ and a water regain of
2.8 g./g. of dry substance.

Example 6

The final product obtained as described in Example 1 was classified according to the particle size. 60 g. doses of the grains having a diameter of 100 to 350 μ were
5 filled into boxes and sterilized in unit packages while keeping a value of 20 kg./0.1 m³, by using a Co⁶⁰ irradiation with a dose of 25 kGy.

Example 7

The final product obtained as described in Example 1
10 was classified according to the particle size. The grains having a diameter of 40 to 100 μ were divided to amounts of 1 g. each between two layers of physiologically indifferent filter papers and the paper layers were welded together. The sterilization was carried out as described
15 in Example 6.

Example 8

The final product obtained as described in Example 1 was classified according to the particle size. 6800 g. of the grains having a diameter of 40 to 100 μ each were
20 suspended in a mixture of 2900 g. of polyoxethen-200 and 300 g. of sorboxethen monooleate for 30 minutes, then 10 g. doses of the thus-obtained paste each were placed into bags prepared from aluminium foil laminated with polyethylene, whereupon the chartulas were closed by welding.
25 The sterilization was carried out as described in Example 5.

CLAIMS

1. A process for the preparation of a therapeutically useful crosslinked dextran grain polymer and compositions containing the said polymer, which process comprises swelling the crosslinked grain polymer in water at a pH value of 1.0 to 5.5 while stirring, removing the acidic water and dehydrating by using a water-miscible organic solvent, removing the supernatant while stirring, swelling the dehydrated grain polymer in ion-free water, washing it until acid-free, dehydrating and/or drying it, classifying it according to the particle size and formulating it into a desired form.
2. A process as claimed in claim 1, which comprises carrying out the washing with acid by using acidic water in a 5 to 20-fold volume calculated for the weight of the grain polymer.
3. A process as claimed in claim 1 or claim 2, wherein the pH of the water in the swelling step is 4.0.
4. A process as claimed in any one of claims 1 to 3, wherein the water -miscible organic solvent is ethanol.
5. A process as claimed in any one of claims 1 to 4, wherein the polymer is sterilised with gamma irradiation prior to classifying it.
6. A process as claimed in any one of claims 1 to 5, wherein the polymer is formulated into a powder, a plug or a paste.
7. A process as claimed in any one of claims 1 to 5, which comprises formulating grains having a diameter of 100 to 350 μ obtained by classifying the dried grain polymer into the form of a dusting powder.
8. A process as claimed in any one of claims 1 to 5, which comprises formulating grains having a diameter of 40 to 100 μ obtained by classifying the dried grain polymer into the form of a plug closed between two physiologically acceptable filter papers.



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9. A process as claimed in any one of claims 1 to 5, which comprises formulating grains having a diameter of 40 to 100 μ obtained by classifying the dried grain polymer into the form of a paste suspended in a mixture of polyoxethane and sorboxethene monooleate.

10. A process as claimed in claim 1, substantially as hereinbefore described in any one of Examples 2 to 5.

11. Cross-linked dextran powder obtained by a process as claimed in any one of claims 1, 2 and 9.

12. A therapeutical composition or material for treating wounds comprising cross-linked dextran powder as claimed in claim 11 optionally together with a pharmaceutically acceptable carrier.

13. A composition as claimed in claim 8, substantially as hereinbefore described in any one of Examples 6 to 8.
