

standing overnight at 50° C. The gel that had formed by then was washed with water.

2 (b) 400 mg of carboxymethyl cellulose (Fluka CMC sodium salt) was dissolved in 3 ml of water, whereafter the reaction was carried out as in Example 2 (a) but with 200 μ l of BDDE and 200 μ l of glacial acetic acid. An opalescent elastic gel was obtained.

2 (c) 800 mg of chondroitin sulfate (sodium salt, Sigma) was dissolved in 2 ml of water, whereafter the reaction was carried out as in Example 2 (a) but with 200 μ l of BDDE and 100 μ l of glacial acetic acid. A gel of firm consistency was obtained.

3. Preparation of an alkali-catalyzed gel of crosslinked hyaluronic acid

2.5 g of sodium hyaluronate having a molecular weight of 3×10^6 was dissolved in 18.75 ml of 0.5% NaOH, with stirring, until a clear homogeneous solution was obtained. 0.94 ml of BDDE was added, and after thorough mixing the solution was introduced into a container in which a gel of desired shape was formed during 2 hours at 50° C. Before being used the gel was washed carefully and sterilized in an autoclave.

This is an example of the more stable type of gels of crosslinked carboxy-containing polysaccharide the preparation of which is described in detail in SE 8403090-7.

4. Degradation of a hyaluronate gel in vivo (rat)

A gel produced in the same manner as in Example 1 was shredded into small pieces. These were weighed and inserted into small Plexiglas® chambers which were then covered with nylon net and implanted subcutaneously in rats. After suitable periods of time the gel pieces were removed, weighed and analyzed with respect to their hyaluronate contents, with the results^(a) as set forth below. The hyaluronate content was determined in accordance with three mutually independent methods: The orcinol method (Mejbaum W., *Physiol. Chem.* 258 (1939), 117), the hyaluronidase method (Dische Z., *J. Biol. Chem.* 167 (1947), 189), and the carbazole method (Jourdan G.W. et al., *Anal. Biochem.* 96 (1979), 474). The results obtained with these three methods were in good agreement inter se, and for this reason only those obtained with the carbazole method are set forth below.

Time, hours	Weight before implantation, mg	Weight after implantation, mg	Amount of hyaluronate remaining in gel, % of original
0	133	—	100
0	131	—	100
24	144	206 ^(b)	—
24	141	215 ^(b)	106
32	133	245 ^(b)	—
32	128	259 ^(b)	89

^(a)double samples were analyzed

^(b)the samples had taken up water, resulting in a softer jelly consistency

5. Prevention of peritoneal adhesions with hyaluronate gel film

Forty-eight Wistar male rats (250–300 g each) were used. Of these were three animals excluded because they did not survive the operation (one animal in the test group) or died from peritonitis during the first post-operative day (two animals in the control group).

Anaesthesia was accomplished with a 10% solution of etorfine and acepromazine (Immobilon®), Pharmacia A/S) i.m. and postoperative reversal was achieved with a 10% solution of diprenorfine (Reui-

von®, Pharmacia A/S). Coeliotomy was performed through a 4-cm median incision. One cm to the right of the midline 1×3 cm of peritoneum and underlying muscle was excised. The peritoneal defect was then closed with seven atraumatic 3/0 single silk sutures. At this point of the procedure the animals were randomly allocated to a test group or a control group.

In the test group a hyaluronate gel film prepared according to examples 1a or 3 with the dimensions 2×2 cm was introduced between the exposed tissue surfaces.

On the seventh day all rats were sacrificed by ether exposure and the abdomen was opened through a left-sided curved incision. The sutured 3 cm long peritoneal defect to the right of the midline was visualized and the part of the defect occupied by adhesions was measured in mm. The abdomen was then examined for pathological conditions other than adhesions.

In the test group, that is the hyaluronate gel film treated group, no adhesions were found.

In the control group adhesions involving the greater omentum, and in eight animals the small intestine as well, were present in all animals. The median length of attachment being 27 mm.

No pathological conditions other than adhesions, i.e. bowel obstruction, peritonitis, abscesses or fluid in the abdomen, were found.

6. Prevention of post-operative adhesions between tendon and tendon sheath

Six rabbits were used divided into a test group and a control group with three animals in each. In each animal two tendons in the fore paw were divided and the hyaluronate gel film, prepared according to examples 1b or 3, was folded around the tendon after that it had been rejoined with sutures. The tendon sheath was partly sealed. After four weeks, the animals were sacrificed and the operated tendons were inspected.

In the control group, most of the operated tendons presented adhesions to the surrounding tendon sheath. In the test group, however, the adhesions were very rare and of small size.

We claim:

1. A gel of sodium hyaluronate or hyaluronic acid cross-linked with a di- or polyfunctional epoxide at a pH within the range of from 2 to 5.

2. A process for preparing a gel consisting of a cross-linked carboxyl-containing polysaccharide selected from the group consisting of carboxymethyl dextran, carboxymethyl starch, carboxymethyl cellulose and glucosaminoglycans formed by reacting the polysaccharide at a pH of from 2 to 5 with a bi- or polyfunctional epoxide in the presence of an acid.

3. A process according to claim 2 wherein said pH is in the range of 2.5 to 4.5.

4. The process according to claim 2 in which said acid is selected from the group consisting of inorganic acids, organic acids and hydrogen salts thereof.

5. A process according to claim 2 in which said acid is selected from the group consisting of hydrochloric, sulfuric, nitric or phosphoric acid, or a hydrogen salt thereof.

6. A process according to claim 2 in which said acid is selected from among (a) lower aliphatic mono- or polycarboxylic acids or (b) aromatic mono- or polycarboxylic acids and sulfonic acids, or (c) hydrogen salts of acids belonging to group (a) or (b).

7. A process according to claim 2 in which said acid is selected from the group consisting of formic, acetic,