

**METHOD OF PREVENTING ADHESION  
BETWEEN BODY TISSUES, MEANS FOR  
PREVENTING SUCH ADHESION, AND PROCESS  
FOR PRODUCING SAID MEANS**

This invention is concerned with a method of preventing adhesions or accretions of body tissues inter se with the aid of a degradable gel of a crosslinked polysaccharide containing carboxyl groups. The invention also comprises a gel product which is suited to this purpose, and a process for producing that gel product.

In many instances of practical surgery, it is highly desirable to have a simple means and method for preventing direct contact between tissues and for maintaining this contact-inhibiting effect also during a postoperative period the length of which will vary according to the actual type of surgery involved. Examples of such surgical procedures are manifold, spanning over a wide field: E.g. operations performed in abdominal regions where it is important to prevent adhesions of the intestine or the mesentery with concomitant gastrointestinal disorders; operations performed in the urogenital apparatus where it is important to ward off adverse effects on the ureter and bladder, and on the functioning of the oviduct and uterus; and nerve surgery operations where it is important to minimize the development of granulation tissue. When tendons are operated on there is generally a tendency towards adhesion between the tendon and the surrounding sheath or other surrounding tissue during the immobilization period following the operation. Essentially unsuccessful attempts have been made to solve this problem by using various kinds of sutures and by means of passive movements of the tendon during the healing process. In ophthalmological surgery it is often desirable to have degradable implants at one's disposal which are to be applied in the angle of the anterior chamber of the eye for the purpose of preventing synechiae between the cornea and the iris; this applies especially in cases of reconstructions after severe damaging events. Moreover degradable or permanent implants are often desirable means for preventing adhesion in e.g. glaucoma surgery contexts (preventing adhesion in the subconjunctival filtration space) and in strabismus surgery.

Tubular implants may be employed for obtaining an improved flow from the anterior chamber, for thwarting obstruction of the lachrymal duct, and for improving the result of dacryocystorhinostomy.

In one particular type of articular surgery described by Engkvist et al. in *Scand. J. Plast. Reconstr Surg.* 14 (1980), 71-87, silicone plates Silastic  $\frac{1}{2}$  (Dow Corning) are introduced surgically in order to prevent accretions of cartilaginous tissue. After some 12 to 16 weeks, however, it is necessary to again remove the implant surgically. Thus, the techniques presently available necessitate removal of the inserted material after a suitable period of time in all cases where this material has to be of a rigid type for the sake of securing a high degree of mechanical stability. In other cases, where mechanical stability is not a major factor, it has been customary to use non-crosslinked dextran or hyaluronic acid. But even if a substance of such high viscosity as hyaluronic acid is used for application to contact surfaces the protection period thus obtained is too short to be satisfactory.

What is needed is therefore a product which is applicable in a suitable form for preventing adhesions and

accretions between tissues and which optionally is to have the property of being degradable after a desired period of time.

We have now found that a gel of a crosslinked carboxyl-containing polysaccharide is exceedingly suitable for being used as a degradable implant.

The present invention is thus concerned with a novel degradable gel consisting of a polysaccharide which contains carboxyl groups—such as for example carboxymethyl starch, carboxymethyl dextran, carboxymethyl cellulose and glucosaminoglycans such as e.g. heparin, heparan sulfate, chondroitin sulfate and hyaluronic acid—and which has been crosslinked with a di- or polyfunctional epoxide. Examples of such epoxides are 1, 4-butanediol diglycidyl ether (BDDE), 1, 2-ethanediol diglycidyl ether (EDDE), 1-(2, 3-epoxypropyl)-2, 3-epoxycyclohexane (Bakelite epoxy resin ERL 4206, Union Carbide), N, N-diglycidyl aniline (Leuktherm X 50, Bayer), and epoxy-substituted pentaerythritol (Shell 162). These crosslinking reagents and other suitable epoxy compounds are well known to persons skilled in the art. The same applies to the choice of polysaccharides available which either contain carboxyl groups from the outset or may be derivatized so as to then contain such groups. The crosslinking has been carried out in an acidic medium, in the presence of an acidic catalyst. A great number of substances have been found to act as catalysts in the crosslinking reaction. Examples of such substances are inorganic acids such as e.g. sulfuric acid, nitric acid, hydrochloric acid and phosphoric acid; furthermore organic mono- and polycarboxylic acids, e.g. lower aliphatic acids such as for instance formic acid, acetic acid, propionic acid, lactic acid, trichloroacetic acid, succinic acid, and aromatic mono- or polyfunctional carboxylic acids or sulfonic acids, e.g. benzoic, salicylic and paratoluenesulfonic acids. The term "polycarboxylic acids" comprises all acids having more than one carboxyl group. It is possible to replace the free acids employed by their hydrogen salts in those cases where such salts can be formed.

The present invention also relates to a process for producing a degradable gel by means of reacting a carboxyl-containing polysaccharide with a bi- or polyfunctional epoxide at a pH of from 2 to 5, preferably from 2.5 to 4.5, in the presence of an acidic catalyst of the aforesaid type.

In a preferred embodiment of the invention the carboxyl-containing polysaccharide is hyaluronic acid or a salt thereof such as the sodium salt. Hyaluronic acid exists in a wide range of forms of different molecular weights depending on its source and on the purification methods employed. Products within the range of 20,000 to 5,000,000, in particular 500,000 to 3,000,000, are suitable for producing gels according to this invention. In cases where the molecular weight exceeds  $10^6$  the concentrations of such hyaluronic acids in the reaction mixture may suitably be 5 to 10% by weight. Considerably higher concentrations have to be employed for achieving gel formation with low molecular polysaccharide starting materials. Similarly, the amount of crosslinking agent may be varied within a very broad range, from about 10 to about 500% by weight of the hyaluronic acid, depending on the particular properties desired in the gel. The reaction may advantageously be performed at an elevated temperature of 30° to 80° C., although temperatures of 30°-50° C. are preferred for minimizing the risk of acid hydrolysis. As regards the