

**COMPOSITE POLYMERIC MATERIAL FOR  
BIOLOGICAL AND MEDICAL APPLICATIONS  
AND THE METHOD FOR ITS PREPARATION**

The invention relates to a composite polymeric material for biological and medical applications and to the method for preparation thereof.

The known method for manufacturing of substitutes of organs and tissues was based on composite materials, where one component was a three dimensionally cross-linked synthetic hydrophilic polymer of 2-hydroxyethyl methacrylate or a monomethacrylic ester of higher homologous glycols, and the other component was collagen. The above mentioned procedure consisted in the preparation of gel with opened pores of the size larger than 100  $\mu\text{m}$  (micrometers) and in filling these pores, at least in part, with collagen in the course of polymerization or on completion of polymerization. The resulting composite material consisted of the insoluble spatial network of gel with the average pore size 100-400  $\mu\text{m}$  and of collagen filling in the communicating pores and was modified in the way to attain a controlled resorption of the material after implantation into organism. Some biological properties of this composite material were published in M. Chvapil et al., *J. Biomed. Mater. Res.* 3, 315 (1969).

A disadvantage of this procedure is the final shape of product, which was obtained in the form of bulky blocks or similar spatial figures, e.g. a thick-walled tube. The shape of product can be modified only by difficult machining, as a rule in the frozen state when the material exhibits the necessary rigidity. In addition, the structure of this composite material is macroscopically rough, which fact leads in practice to a non-homogeneous intergrowing by tissues and to imperfect function of implanted prosthesis, e.g. to leakage of prostheses of tubular organs caused by an excessive porosity of their walls. The preparation of thin foils or coatings, e.g. on a textile base, is virtually impossible according to the above mentioned method. These difficulties, following from the used technological procedure, did not allow in particular application of these attractive materials in a larger practical scale beyond the frame of experiments with animals.

The above disadvantages are overcome by a composite polymeric material according to the invention, which consists of 1-99 wt. % of a hydrophilic polymer or copolymer based on methacrylic or acrylate, 1-99 wt. % of fibrillar collagen, 0-2.5 wt. % of a crosslinking agent (related to solids of both polymeric components), and, if it is desired, also of biologically active compounds and auxiliary materials, as plasticizers and fillers, and is prepared by dispersing the fibrillar collagen in a solution or in a highly swollen dispersion of the synthetic hydrophilic polymer or copolymer in a lyotropic agent and by the subsequent removal of the lyotropic agent.

The method for manufacturing of the composite material according to the invention consists in dispersing of fibrillar collagen in a solution or a highly swollen dispersion of the synthetic hydrophilic polymer or copolymer in a lyotropic agent, selected from the group comprising carboxylic acids diluted with water, strongly acidified aqueous mixtures of ethanol and methanol (pH 2-3), high-concentrated aqueous solutions of lyotropic salts, and high-concentrated aqueous solutions of urea or guanidinium chloride, under stirring

at temperature below 37° C., and in the following removal of the solvent from the viscous dispersion at temperature not exceeding 37° C., thus forming a matrix of the synthetic polymer or copolymer penetrated by fibrillar collagen, or vice versa.

Another characteristic feature of the invention is, that a crosslinking agent, selected from the group comprising trimethylolurea, formaldehyde, acetaldehyde, glutaraldehyde, starch dialdehyde, glyoxal, and chromic salts, is added in the amount of 2.5 wt. % at utmost, related to the total amount of the synthetic polymer or copolymer and collagen, either during the preparation of dispersion or after removal of the lyotropic agent, and, if it is desired, also a biologically active component, filler, plasticizer, and the like, are added during the preparation of dispersion or after removal of the lyotropic agent.

The method according to the invention is characterized by

- (a) a separate preparation of the synthetic hydrophilic polymer or copolymer based on methacrylate or acrylate.
- (b) dispersing the fibrillar collagen in a solution or a highly swollen dispersion of the synthetic polymer or copolymer mentioned sub a, using the solvent which has a high solvation effect on both polymeric components present and enables their mutual miscibility in the dispersed or dissolved form,
- (c) removal of the above mentioned solvent from the viscous dispersion mentioned sub b with formation of a matrix of the synthetic polymer or copolymer penetrated by fibrillar collagen, or vice versa,
- (d) the respective application of known crosslinking agents, which cause an intermolecular crosslinking of both polymeric components of the composition, while the said cross-linking agent may be added to the system either during preparation of the dispersion, as mentioned sub b, or first after removal of the solvent, as mentioned sub c,
- (e) the respective application of additives and/or auxiliary compounds, e.g. drugs or other biologically active compounds, plasticizers, fillers, or other additives, which can be added to the system in any of the mentioned steps,
- (f) the respective application of a suitable support or reinforcement, on which the viscous dispersion, mentioned sub b, can be applied by known methods and then the solvent can be removed as stated sub c,
- (g) the respective radiation sterilization of the final product encased in a suitable packing.

The described method overcomes the aforesaid shortcomings, substantially broadens the region of possible applications of the material, and renders some new qualitatively different morphologic and biologic properties to the material. Using the method according to the invention, a broad assortment of materials may be prepared for various biologic and medical purposes, while all these materials are marked by the more intimate contact of both participating polymeric components leading to a microscopically fine structure and to suitable biologic properties. All these new polymeric composite materials are also subjects of the invention. The preparation of the aforesaid polymers and copolymers, based on esters of methacrylic or acrylic acid, is sufficiently described in earlier patents, in particular in U.S. Pat. Nos. 3,575,946, 3,988,305, 4,076,921 and in Canadian Pat. No. 906 149. Suitable hydrophilic polymers according to the invention are, for example, po-