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SEPARATION OF NONREACTED ACRYLAMIDE FROM POLYACRYLAMIDE GEL FOR ENDOPROTHESING

Modest GERTSIUK[1*)], Yuriy SAMCHENKO[2)]

[1)] Institute of Geochemistry of an Environment of National Academy of Science of Ukraine and Ministry for Extraordinary Situations of Ukraine,
e-mail: chrtgsoc@gmail.com
[2)] F.D. Ovcharenko Institute of Biocolloidal Chemistry,
e-mail: yu1sam@yahoo.com

ABSTRACT

The separation of toxic acrylic monomers (mainly acrylamide) from some polymeric hydrogels of medical application was studied. It was found that "clean hydrogel" can be obtained after 4-6 days of washing with nonpyrogenic water. The quantity of monomeric acrylamide remained in the samples was controlled by a liquid chromatography method.

Keywords: Hydrogels, Acrylamide, Acrylic monomers, Liquid chromatography Endoprothesis,

INTRODUCTION

Hydrogels are insoluble, cross-linked, polymers swollen in aqueous media [1]. They exibit high biocompatibility because of their high hydrophilicity (some hydrogels can absorb more than 10 kg of water per 1 g of a dry polymer). Owing to this property, the hydrogels are widely used in medicine, e.g. for manufacturing soft contact lenses [2] and transdermal therapeuthic systems with prolonged release of pharmaceuticals [3], as well as for producing wound and burn dressings [4]. The hydrogels made of acrylic monomers also are used (*i*) for soil structurization and sewages treatment, (*ii*) in cosmetic and textile industry, and (*iii*) in laboratory practice (e.g. electrophoretic separations) [5]. However, the main application of acrylamide and other hydrogels in medicine is plastic and

* Corresponding author

reconstructive surgery. In the last years, various hydrogels, mostly those injectable, were used for augmentation of breast [6], lips [7] and other soft tissues of the human body. Moreover, applications such as shaping and asymmetry correction of facial soft tissues or a long-term correction of natural and acquired skin depressions were reported in the corresponding literature [8]. The main advantage of the non-operative injection method is minimum trauma of tissues with a significant cosmetic effect. It is necessary, however, to take into consideration the fact that although acrylic polymers are harmless to the human body, the respective monomers are very toxic, i.e. LD_{50} for acrylic acid is 2.59 g/kg, for acrylamide 170 mg/kg, and for acrylonitrile this value is 93 mg/kg [9]. According to the classification of the International Agency of Cancer Research, the acrylic monomers belong to the second category of danger, i.e. they are substances with possible carcinogenic activity. On the other hand, it is well known that some quantity of unreacted monomers always remains in a polymer and contaminates a hydrogel. Therefore, the problem of effective acrylic hydrogels cleaning after synthesis is still very important.

EXPERIMENTAL

All reagents were purchased from Sigma (for molecular biology) and used without additional purification. The hydrogel was prepared by free radical polymerization of acrylamide at room temperature in an aqueous medium. The reaction was carried out in the presence of a red-ox intitiators system (ammonium persulfate – tetramethylethylenediamine) and a cross-linking agent – N,N'-methylene-bis-acrylamide. The concentration of acrylamide was varied from 2 to 7 %. The concentration of the components of the red-ox system was 0.1 % and the concentration of the cross-linking agent was 0.5 %.

In order to separate nonreacted acrylamide from polyacrylamide after the synthesis, the hydrogel samples were washed with nonpyrogenic water at 45 ^{o}C. Water was changed once per day, and the ratio between mass of gel and mass of water was always 1:4. Then, hydrogels were sterilized and the content of monomers was determined.

The influence of washing duration on the maintenance of remaining acryl-amide was investigated by the HPLC method. For this purpose, 50 cm^3 of the mixture of methanol and distilled water (1:4) was added to the hinge-plate of 5 g of polyacrylamide and shaked for over 4 h. For the analysis, 20 μL of the mixture were then injected into a chromatograph. The determination of nonreacted acrylamide was carried out with a Waters liquid chromatograph equipped with a column with Nucleosil C18 (25×4 mm). As the eluent, a mixture of methanol and water in the 1:9 ratio was used. A flow-rate of the eluent was 1 mL/min and the column temperature was 20 ^{o}C. Retention time of the monomeric acrylamide peak was 2.35 min. The measurements were carried out at λ=205 nm, and the concentrations of acrylamide were determined using the respective graduated graph. For this

purpose, the standard working solutions of acrylamide in the methanol-water solutions were prepared from the initial standard solution of 200 μkg/mL concentration. The range of the measured concentrations was 0.1-50 μkg/mL The concentration of the monomer in the polymeric material (C) was calculated with the following formula:

$$C = C_{\text{exp}} V / a \text{ , μkg/mL,}$$

where C_{exp}, V and a denote the experimentally found concentration in the extract, the mass of polymer and extract mixture (g), and the hinge-plate of gel taken for the analysis (g), respectively. The method provides the determination of the acrylamide monomer content in the products of polymerization within the range 0.001-0.1 % with RSD lower than 15%.

RESULTS AND DISCUSSION

A highly biocompatible, colorless, transparent gel containing 2-7% of the polymer and more than 90 % of nonpyrogenic water was synthesized from cross-linked polyacrylamide. The results of toxicological and clinical investigations indicate that this gel is nontoxic, stable and nonresorbable. Moreover, this hydrogel is suitable for injection into soft tissues in order to correct contours, remove facial defects, and enlarge mammary glands. Injections of the gel can be performed under local anesthesia.

As it was demonstrated by the HPLC method, immediately after finishing the process of polymerization, the content of the nonrected monomer is very high, i.e. ca. 2000 mkg/g. The washing procedure presented in this paper, when applied for over 4 days, results in very low concentrations of the nonreacted admixtures, i.e. 1-10 μkg/g. A further increase in washing time does not result in a substantial influence on the cleanness of the polymeric product (Fig.1).

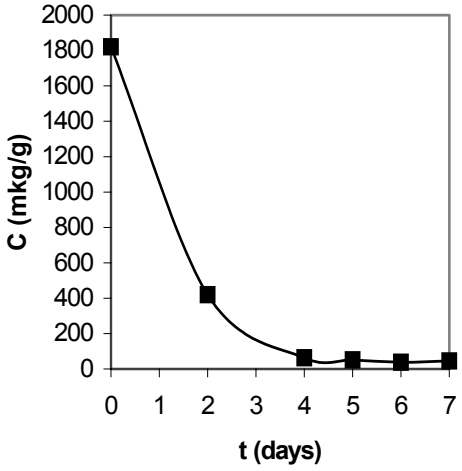

Fig.1. Time dependence of acrylamide content in polyacrylamide gel during washing according to the HPLC method.

It is not expected that this peak characterizes dimmers or other oligomers of acrylamide.

CONCLUSION

The results presented in this paper indicate that the extraction of impurities from polyacrylamide gel with water is the effective method for lowering the content of the nonreacted monomer. Minimum 4 days washing is recommended in order to achieve a practically full removal of the toxic monomer from the product for medical applications.

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