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Improved Polymeric Contrast Agents for Roentgenologic Examination of the Gastrointestinal Tract

I. Preliminary Report on the Chemistry of the Polymers

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ABSTRACT

Improved water-soluble iodine-containing polymers intended as contrast substances for use in the roentgenologic examination of the gastrointestinal tract have been synthesized. These polymers have a high solubility in water even at relatively low pH values, and, therefore, do not precipitate in the stomach.

INTRODUCTION

In an earlier publication in *Investigative Radiology* we reported on polymeric water-soluble iodine-containing contrast agents intended for use in roentgenologic examination of the gastrointestinal tract (1). In contrast to the iodine-containing contrast agents used at present, these polymeric contrast substances retain their solubility in water even at relatively low pH values and therefore do not precipitate in the stomach. The molecular weight and molecular dimensions are considerably larger than for the monomeric contrast substances used at present for this purpose. Aqueous contrast solutions of the polymers are less hypertonic than solutions of the currently available contrast substances at comparable iodine concentrations. The diffusion coefficients of the polymers are lower than the diffusion coefficients of the monomeric contrast agents. The advantages of water-soluble polymeric contrast agents of this type in certain instances in the roentgenologic examination of the gastrointestinal tract were briefly presented in our earlier paper (1).

In this report, improved polymeric contrast substances for this purpose are described. The synthesis method has been modified. Compared with our earlier polymers the improved polymers have an even higher solubility in water at low pH values. The average molecular weights M_w and the molecular weight distributions have been changed slightly.

Preparation of water-soluble polymeric contrast substances for examination of the gastrointestinal tract

The structure of the polymers reported in our previous paper (1) is presented in the schematic Fig. 1*a*. In this figure –A– denotes iodine-substituted benzene derivatives (preferably 2, 4, 6-triiodobenzoic acid derivatives) and –B– denotes intermediate hydroxyl-bearing aliphatic bridges. The group –A– had for example the structure given in Fig. 1*b* or in 1*c*. For contrast agents for oral use, the bridge –B– between the iodine-containing aromatic groups contained several

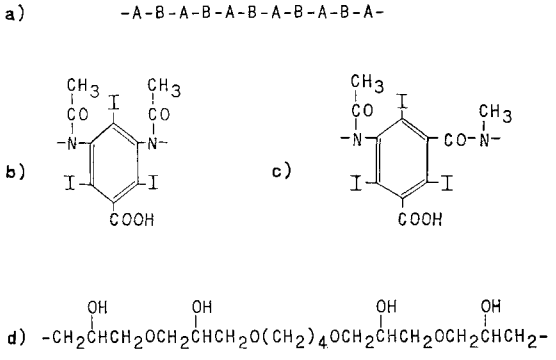

Fig. 1. (a) Basic structure of the polymeric contrast substances. –A– indicates iodine-substituted benzene derivatives, mainly 2,4,6-triiodobenzoic acid derivatives. –B– indicates hydroxyl-bearing aliphatic bridges. *(b)* Example of group –A– (*c*) Example of group –A– (*d*) Example of the hydroxyl-bearing aliphatic bridge –B–. In the substance 730 E, described in this report, group –A– was represented by the example given in (*c*). The bridge –B– in this substance was of the type shown in (*d*), but the hydroxyl groups were partly replaced by glycerol ether groups.

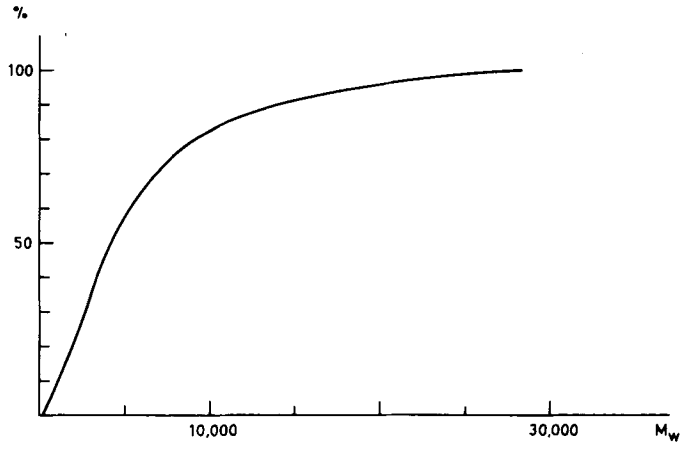

Fig. 2. Integral molecular weight distribution curve. Substance 730 E.

hydroxyl groups so that the contrast polymer would be readily soluble in water, even at low pH values. Thus, the bridge –B– was preferably of the type shown in Fig. 1*d*.

In order to further increase the solubility at low pH values, additional hydroxyl groups have now been introduced into the molecules by treating the polymers with glycidol in an alkaline aqueous solution. In this reaction the hydroxyl groups of the bridge –B– are partly replaced by glycerol ether groups. Substitution at the ends of the molecules can also occur. Thus, as a result of the reaction with glycidol the number of hydroxyl groups in the polymeric contrast molecules is increased.

As an example, the synthesis of substance 730 E is described below. The group –A– in substance 730 E has the formula given in Fig. 1*c*. The bridge –B– in this substance is principally of the type shown in 1*d*, but the hydroxyl-groups have been partly replaced by glycerol ether groups.

Synthesis of substance 730 E

245.6 grams of 5-acetylamino-2,4,6-triiodo-*N*-methyl-isophtalic acid monoamide were suspended in 140 ml of 4 N aqueous NaOH. At 30°C, 51.2 ml of glycidol were slowly added dropwise during 5 hours with continuous stirring. The reaction mixture was allowed to stand for an additional 1 hour at 30°C and then for 16 hours at about 20°C, after which 10 ml of 5 N aqueous NaOH was added. Then 70 ml of 1,4-butanedioldiglycide ether were added dropwise, with continuous stirring, during 5 hours, at 30°C, The reaction mixture was allowed to stand for another 1 hour at 30°C and then for 18 hours at about 20°C. Thereafter, 100 ml of water was added and the mixture was stirred during 2 hours at 30°C. Then 20 ml of glycidol were added dropwise, with continuous stirring, during 2 hours, at 30°C. The reaction mixture was allowed to stand for 2 hours at 30°C and then for 23 hours at about 20°C. With stirring, 6 N aqueous HCl was added dropwise to adjust the pH to 1.6. The solution was kept at this pH for 2 hours. No precipitate was obtained. The solution was neutralized with 4 N aqueous NaOH to pH 7.0. 400 ml of water was added and then 2500 ml of acetone in order to precipitate the polymer. After one day, the supernatant was separated from the syrup-like lower phase containing the sodium salt of the polymeric polyacid formed in the reaction. 200 ml of water was added to the lower phase and then 1000 ml of acetone. After one day, the supernatant was separated from the lower phase whereafter 3 more reprecipitations with acetone were carried out in the same manner. The precipitate was dried at 50°C in a vacuum. The substance obtained was designated 730 E and was used for the animal experiments described in part II of this report. The yield was 292 grams. The product contained 0.8% NaCl. The iodine content of the sodium salt of the polymeric contrast substance obtained was 35.7%. The weight average molecular weight ($\bar{M}_w$), determined by light scattering, was about 5000. Fig. 2 shows the smoothed out integral molelcular weight distribution curve of substance 730 E determined by Dr Granath by gel chromatography on a mixture of Sephadex

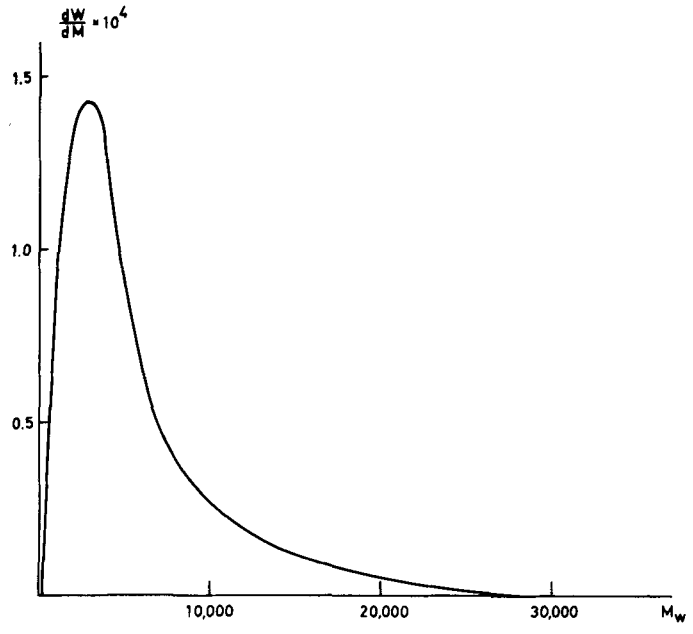

Fig. 3. Differential molecular weight distribution curve. Substance 730 E.

G 50 Fine and Sephadex G 75 Fine. The concentration of the contrast substance in the eluted fractions was estimated from the absorbance at 242 nm. Fig. 3 shows the differential molecular weight distribution curve obtained by graphical derivation of the integral distribution curve shown in Fig. 2. (The method has earlier been used for the determination of molecular-weight distribution curves for other polymers and has been described by Granath & Kvist (2) and Arturson & Granath (3.)

DISCUSSION

The new polymeric contrast substances, for example substance 730 E, have improved solubility properties in water at low pH values. A relatively low average molecular weight was chosen for these polymers in these introductory tests. Thus, the average degree of polymerization is low but can be increased. The molecular weight distribution was such that the upper limit lay well below the limit of permeability of the renal glomeruli. Thus, should the contrast agent escape from the gastrointestinal tract, e.g., into the abdominal cavity through a perforation in the intestinal wall, it would be easily excreted in the urine. If a higher average degree of polymerization is chosen molecules with a size above the renal threshold can be removed by fractionation methods.

As these improved polymeric contrast substances have the desired chemical and physical-chemical properties, tests in animals have been started. In part II of this report, preliminary studies of substance 730 E in animals are described.

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