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Synthesis of Flexible Heparinized Polysilicone Using Radiation Grafting

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ABSTRACT

Polysilicone tubing retained 79 to 93% of its original flexibility after radiation grafting with 2-chloroethylacrylate (CEA), quaternization with pyridine, and heparinization. The amount of CEA grafted was linear with time following an induction period. Sample flexibility was studied as a function of CEA add-on, pyridine add-on, and heparin add-on. Grafted CEA was found to increase the flexibility of the tubing, thus tending to offset the stiffening effects of the quaternization and heparinization reactions. Tensile moduli and compression load measurements were compared for heparinized and untreated tubing.

INTRODUCTION

A number of investigators have shown that polymers containing chemically bound heparin exhibit thromboresistance (resistance to clotting) when in contact with blood. A recent review [1] lists 18 techniques for heparinizing polymers by combining with heparin or coating with heparin compositions, and presents the results of thromboresistance testing compiled by the investigators of each technique. Information on the physical properties of the heparinized

product was not obtained in most of the studies. The objective of the present research is to reverse the usual approach by first studying the effect of heparinization on the physical properties of the product before spending time and effort on the evaluation of its thromboresistance.

Research results recently reported in this Journal [2] demonstrated that polysilicone tubes can be rendered thromboresistant by radiation grafting with chloromethylstyrene (CMS), followed by quaternization with pyridine, then reaction with sodium heparin. However, it was found that the heparinized polysilicone tubing produced by that technique was stiffer than the unheparinized control tubing, a finding that would rule out the use of the heparinized tubing in catheters and other applications requiring flexibility. A simple flexometer has been designed to measure the flexibility of the sample tubes, and enables data to be obtained concerning the successive effects of grafting, quaternization, and heparinization on sample flexibility. Use of the flexometer has shown that a minor amount of CMS grafted on a silicone tube produces a major decrease in flexibility.

The radiation grafting of silicone tubes with other monomers was studied next, in the hope of finding one which could replace CMS in the grafting reaction without causing the tubes to stiffen. The most promising graft copolymers were obtained with 2-chloroethylacrylate (CEA), which was found to impart increased flexibility to the substrate silicone tubes. This result is not surprising in view of the known high flexibility of polyacrylates [3], and the fact that copolymers often exhibit an approximate average of the properties of the homopolymers of their component monomers [4].

EXPERIMENTAL

The present technique of grafting monomers on polysilicone tubes is essentially the same as that described in the previous reports [2, 5]. The polymer sample to be grafted is sealed with monomer or monomer solution in a Pyrex tube, which is then positioned precisely in the cobalt-60 source. An exposure dose rate at the sample location of 200 R/h was measured using ferrous sulfate dosimetry [6].

The CEA or CMS monomer from Polysciences, Inc. was washed three times with cold 5% aqueous sodium hydroxide, then three times with distilled water, dried over anhydrous calcium sulfate, distilled at reduced pressure, and stored over anhydrous calcium sulfate at refrigerator temperature. For grafting with CMS, the polysilicone sample was immersed in pure CMS in its sealed capsule. For grafting with CEA, the CEA was diluted with a solution of dioxane/benzene in the sealed reaction capsule, which caused a slowing of the grafting reaction and reduced the amount of homopolymerization exterior to the sample.

Prior to each grafting run, the portion of monomer or monomer solution containing the sample was deoxygenated by freeze-thaw cycling in a vacuum system. The reaction capsule containing monomer and polymer was then frozen in a Dry-Ice trap, sealed from the vacuum line with a hand torch, and placed in the ^{60}Co source in the precisely selected position. The polysilicone samples for grafting were cut from Stock No. 6411-43, Cole-Parmer Instrument Co. Each sample was 4.0 cm long, 0.065 in. i.d., and 0.194 in. o.d. The specific sample size and shape were chosen so that selected heparinized samples could be tested later for thromboresistance as described previously [2].

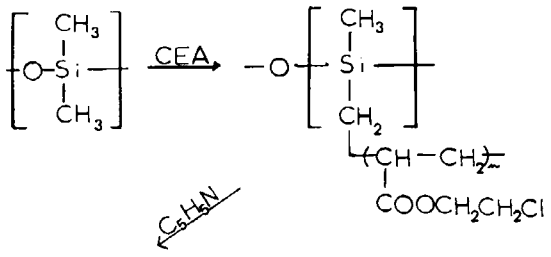
After each grafting run the grafted sample was stirred in warm benzene for 48 h to remove any CEA or CMS homopolymer formed within the sample. All grafting runs were made at the temperature of the irradiation room, 23 ± 1°C. Percent grafting was computed from original sample weight (P_0) before grafting, and the weight after drying to constant weight following grafting (P_g) by use of the equation,

$$\% \text{ Grafting} = \frac{P_g - P_0}{P_0} \times 100 \qquad (1)$$

The grafting procedure resulted in the attachment of CMS or CEA chains to the molecules of the polysilicone sample. The quaternization and heparinization of the CMS-grafted samples have been discussed in previous reports [2, 5]. In carrying out the quaternization of the CEA-grafted samples, each sample was immersed in a small quantity of pyridine contained in a Pyrex tube 20 cm long and 7 mm i.d. which was connected to a vacuum line while freezing the pyridine end of the tube in a Dry-Ice trap. The air was pumped from the sample tube and it was sealed from the vacuum line with a hand torch. The sealed tube containing sample plus pyridine was then placed in a constant temperature bath at 80°C for the required time.

The technique of heparinization was similar. Sodium heparin (Calbiochem-Behring) prepared from porcine intestinal mucosa was used. The sample plus a 5.0% solution of sodium heparin in a 40/60 volume ratio of dioxane/water was sealed in a tube and held at 80°C for the required time. It had been shown earlier that the dioxane/water solvent dissolves the sodium heparin and produces adequate penetration into the solid polysilicone sample [2]. The grafting, quaternization, and heparinization reactions can be indicated as shown on the following page. A literature survey revealed that this is the first use of CEA grafting in this way for the heparinization of polymers [1].

The nonstandard test for sample flexibility was performed with the apparatus shown in Fig. 1. The sample tube to be tested was supported at points A and B separated by 3.0 cm. A weight of 50 g was brought to bear upon the center of the sample as shown. The deflection of the sample in millimeters at its midpoint was read on the scale. The



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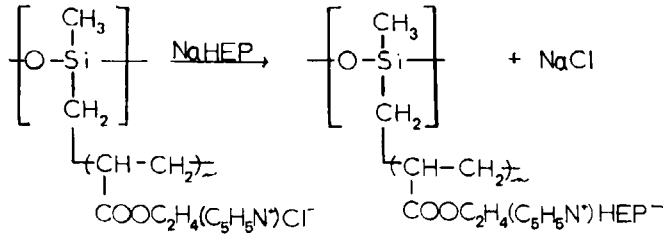

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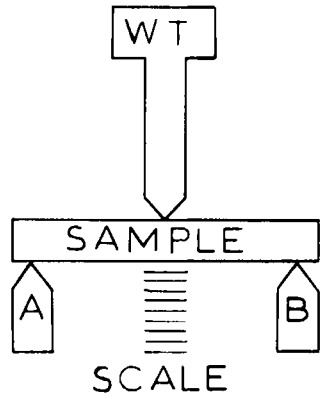

FIG. 1. Flexometer used for measuring deflection of 4.0 cm sample tubes under a constant weight.

original deflection was taken as 100%, and later measurements after reaction with CEA, pyridine, or heparin were reported as percent of the original deflection. Each reported deflection represents the average of 10 measurements. The original deflection in each case was in the range of 5 to 6 mm, with slight variations from sample to sample due to nonuniformity in the extrusion of the polysilicone tube from which the samples were cut.

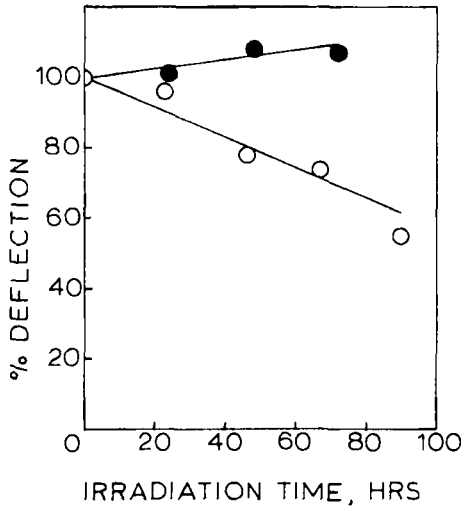

FIG. 2. Deflection versus time for samples irradiated in a vacuum (•), and for samples irradiated (grafted) in CMS (○). Exposure dose rate of 200 R/h.

Comparative tensile modulus and compression load tests were also made on heparinized and unheparinized (control) samples. The tensile moduli were run on an Instron Universal Testing Instrument Model 1130 in the usual way, employing a crosshead speed of 1 in/min. The compression load measurements were carried out on an Instron Tester Model TTB. In these measurements the sample tube was placed in a horizontal position between flat platens, and the load in pounds was recorded that was found necessary to crush the tube and reduce the original diameter by 0.07 or 0.12 in.

RESULTS

The effect on flexibility of radiation alone was studied first, and was found to be very slight for the present small cobalt-60 source. Figure 2 shows sample deflection as a function of time for samples irradiated in evacuated capsules containing no monomer. It can be seen that an irradiation of 72 h increased the deflection by about 9%. All runs were made with the sample placed horizontally at precisely the same spot inside the cobalt source.

In contrast, a 72-h irradiation of the sample immersed in CMS produced a corresponding deflection drop to about 69% of the original value (Fig. 2). A study of deflection versus CMS add-on showed deflection retentions of 74 and 55% at CMS add-ons of 3.5 and 7.8%,

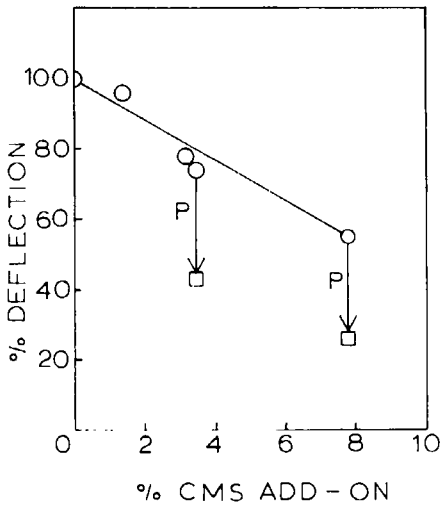

FIG. 3. Percent deflection versus percent CMS add-on. Effect shown of 2.8% pyridine add-on at 3.5% CMS, and 5.4% pyridine add-on at 7.8% CMS.

respectively (Fig. 3). Quaternization at 3.5% CMS produced a pyridine add-on of 2.8% and a further drop to 43% of the original deflection (Fig. 3). The stiffness of the CMS-grafted samples is not surprising in view of the well-known stiff, brittle properties of the polymers of styrene and its derivatives.

The above results led the writer to drop CMS as a feasible monomer for use in heparinizing polysilicone (and other polymers). The bulk of the present research deals with 2-chloroethylacrylate (CEA) as the grafting monomer. In all runs with CEA the monomer was diluted with a dioxane/benzene solvent combination to slow the grafting reaction and allow better control of CEA add-on (typical grafting formulations shown in Table 1). The amount of CEA add-on was an approximately linear function of grafting time (Fig. 4). As the figure shows, an induction period of about 9 h of irradiation had to elapse before any grafting took place.

Measurement of the percent deflection of CEA-grafted samples demonstrated an approximately linear increase in deflection with percent CEA add-on (Fig. 5). The points show some scatter, but not an undue amount for physical property measurements. The target range for CEA add-on in the present work was about 5 to 7%, which was consistent with the concept of keeping the add-on to the minimum value which would just offset the stiffening effect of added pyridine and heparin.

In the quaternization reaction the rate of pyridine addition was influenced by the percent CEA add-on (Fig. 6). For Sample 93

TABLE 1. CEA Grafting Runs and Formulations

Hours	% CEA	CEA/dioxane/benzene
17.3	5.6	40/40/20
20.9	7.4	30/46/24
21.3	7.2	40/35/25
23.2	10.4	40/25/35
24.0	9.8	50/25/25
28.0	10.6	30/46/24
41.3	21.7	40/35/25
44.2	21.4	50/25/25

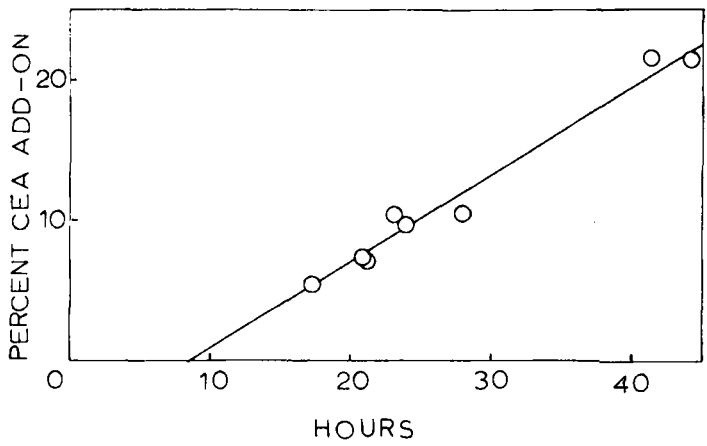

FIG. 4. Room temperature grafting showing percent CEA add-on versus time. Exposure dose rate of 200 R/h.

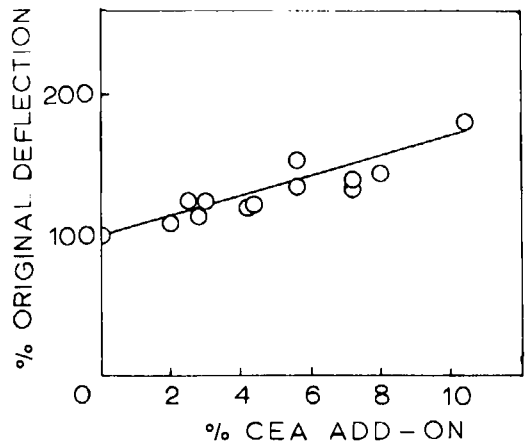

FIG. 5. Percent deflection versus percent CEA add-on.

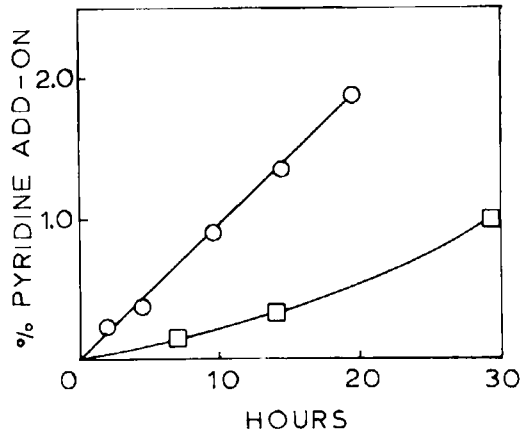

FIG. 6. Percent pyridine add-on versus time at 80°C for 5.6% CEA add-on (□) and 10.4% CEA add-on (○).

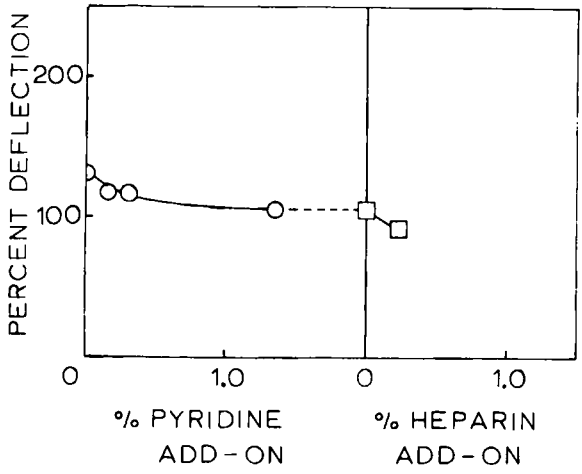

FIG. 7. Percent deflection versus percent pyridine and heparin add-on for sample having 7.2% CEA add-on.

(10.4% CEA) the pyridine add-on versus time gave an essentially linear plot. At lower concentrations of CEA the addition of pyridine started slowly and then accelerated as time passed, as shown for the sample having only 5.6% CEA add-on. The latter behavior probably indicates slow pyridine penetration of the sample at the start, which accelerates as the extent of quaternization increases.

The addition of pyridine markedly decreases the flexibility of the samples (Figs. 7, 8, and 9). The drop in deflection is rapid for the first 0.1 to 0.3% pyridine add-on, and more gradual thereafter. The dotted line in Figs. 7 and 8 has no physical meaning, and serves only to connect the point of the last pyridine add-on with the point where the heparin add-on commences. The intention was the addition of about 1% pyridine but not much more. At less than about 1% pyridine add-on the subsequent reaction with heparin takes place extremely slowly or not at all (probably due to poor heparin penetration into the sample). Greater than 1% pyridine add-on produces an undesirable and unnecessary stiffening of the sample. In Fig. 9, Sample 93 (10.4% CEA) had such a large deflection (180%) that even the add-on of 1.88% pyridine did not reduce the deflection below the original 100%.

The heparin addition was carried out with the sample immersed in a 5% solution of sodium heparin in dioxane/water at 80°C. The target was a heparin add-on of 0.2 to 0.5%, an amount believed adequate to impart thromboresistance based on earlier work with CMS-grafted polysilicone [2]. Heparin add-on plotted against time is shown in Fig. 10 for a sample having a CEA add-on of 8.0% and a pyridine add-on of 1.18%.

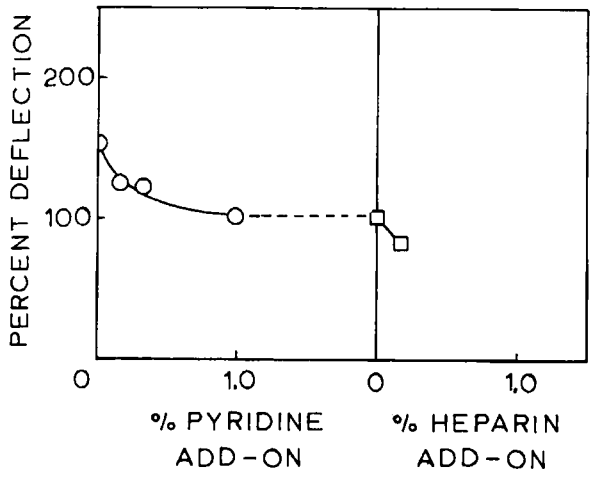

FIG. 8. Percent deflection versus percent pyridine and heparin add-on for sample having 5.6% CEA add-on.

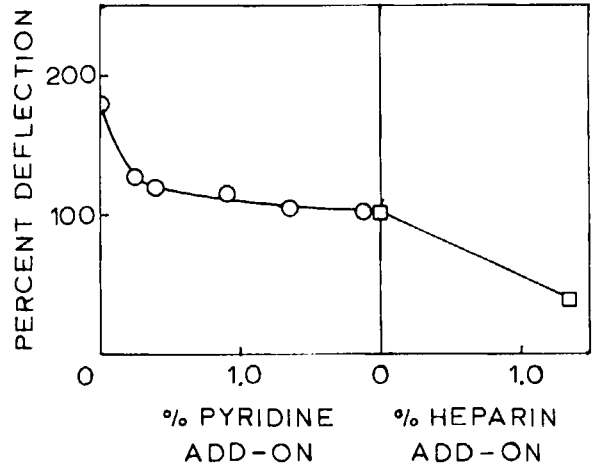

FIG. 9. Percent deflection versus percent pyridine and heparin add-on for sample having 10.4% CEA add-on.

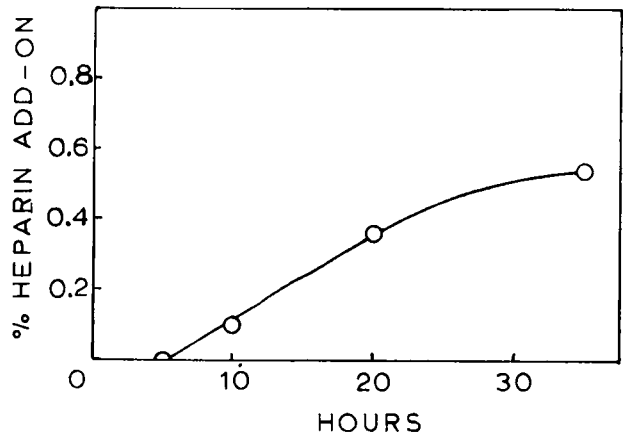

FIG. 10. Percent heparin add-on versus time at 80°C for sample having 8.0% CEA add-on and 1.18% pyridine add-on.

Enough data have been obtained on other samples to show that the heparin addition rate increases with pyridine content. Figure 10 shows the typical induction period observed in the heparinization reaction, which was apparently due to the delay in penetration of the sample by the dissolved heparin.

The effect of heparinization on sample flexibility is indicated in Figs. 7, 8, and 9. The add-on of 0.1 to 0.2% heparin reduced the measured deflection of the sample by 10 to 20% from the value that remained following quaternization (Figs. 7 and 8). Add-on of 1.4% heparin reduced the deflection by approximately 60% (Fig. 9). The stiffening effect of the heparin may be due to the orientation of negative centers on the heparin chains adjacent to the positive N^+ centers of the quaternized chains, with the attraction between the positive and negative centers amounting to a sort of electrostatic bonding. Rembaum [7-9] has referred to such electrostatic heparin linkages as "pseudo-cross-links," and has studied their effect on the physical properties of heparinized polymers. Theoretical aspects of the bonding of high molecular weight ions to polymers of opposite charge have been discussed by Strauss [10], Reichenberg [11], and Fettes [12].

Physical property measurements on polysilicone samples heparinized by the present technique are summarized in Table 2. The table compares the properties of five individual heparinized samples with those of untreated (control) samples. The properties shown for the control represent the averages for 10 individual samples. The CEA add-ons for the heparinized samples ranged from 5.6 to 7.6%, the pyridine add-ons from 0.99 to 1.93%, and the heparin add-ons

TABLE 2. Effect of Heparinization on Physical Properties

	Sample 96	Sample 97	Sample 119	Sample 123	Sample 125	Control sample
% CEA add-on	7.2	5.6	7.6	7.4	6.4	0.0
% Pyridine add-on	1.35	0.99	1.93	1.19	1.20	0.0
% Heparin add-on	0.22	0.16	0.24	0.28	0.27	0.0
% Original deflection	93	83	92	89	79	100
Tensile modulus, psi	740	800	890	680	550	295
Compression load, lb at 0.07 in.	10.6	9.2	12.4	10.0	9.6	6.6
Compression load, lb at 0.12 in.	19.6	20.4	22.4	17.6	16.6	10.9

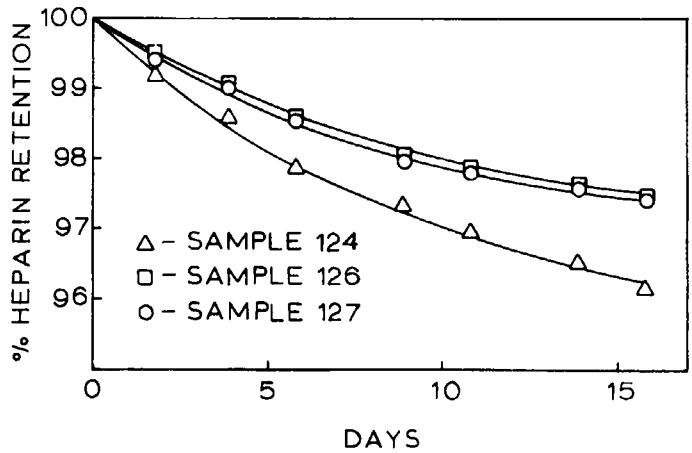

FIG. 11. Percent of heparin content retention versus soaking time in phosphate-buffered saline for samples shown in Table 3.

TABLE 3. Composition of Samples Used in Elution Tests

	% CEA add-on	% Pyridine add-on	% Heparin add-on
Sample 124	5.5	1.63	0.33
Sample 126	8.3	2.32	0.54
Sample 127	7.0	1.94	0.55

from 0.16 to 0.28%. The effect of the heparinization (including CEA and pyridine add-on) was to reduce the deflection (flexibility) to 79-93% of the original value, increase the tensile modulus by a factor of 1.9 to 3.0, and increase the compression load at 0.12 in. compression by a factor of 1.5 to 2.1. Both heparinized and control samples sprang back to the original size and shape following stretching or compression. After heparinization the samples tended to absorb water vapor from the air, and it was necessary to dry them in a desiccator before testing in order to obtain consistent results.

The rate of extraction of heparin from the heparinized 4.0 cm tubes was determined by soaking them at room temperature in phosphate-buffered saline (0.05 M sodium phosphate, 0.15 M sodium chloride, pH 7.4) and measuring the heparin content of the PBS periodically. Each sample was enclosed in a small capped bottle containing 4.0 mL of the PBS, which just covered the sample. The heparin assay was carried out by a modification of a technique described by Sefton [35]. Samples (0.5 mL) of the wash liquid were analyzed by adding 3.7 mL toluidine blue solution (17.5 mg/L distilled water) and measuring the change in absorbance at 500 nm. The heparin content was found by comparing the change in absorbance to a standard curve, prepared with known amounts of the same heparin in PBS. The detection limit of the assay was estimated to be < 2 ppm (w/w) heparin. The wash liquid was changed at the time of each analysis. The percent heparin remaining in each silicone sample was determined by a mass balance. Percent heparin retention versus time in days is plotted for three samples in Fig. 11. The starting composition of these samples is shown in Table 3.

DISCUSSION

The work reported here is part of a broad research study on the heparinization of several commercial plastics in an attempt to prepare thromboresistant and blood-compatible biomaterials. The objective is the development of biomaterials that are useful in blood contact applications within the human body and in external devices such as heart-lung and kidney machines. While the present work emphasizes

suitable physical properties of the product, an ideal polymeric biomaterial should also not interfere with the normal clotting mechanism, not induce inflammatory reactions, not be carcinogenic, not be toxic, retain necessary properties during sterilization, and retain necessary properties during aging in the biological environment [13].

Polysilicones can be adapted to satisfy a variety of mechanical, electrical, gas-transmission, and optical criteria. In tissue replacement applications the effectiveness of a polysilicone is evaluated mainly in terms of its pliability and its ability to elicit a low physiological response. The data in Table 2 do indicate some loss in pliability of polysilicone samples following CEA grafting and heparinization, but the tests used were very sensitive. In terms of manual handling and examination, the heparinized tubes exhibited pliability quite similar to that of the control (unheparinized) tubes. The flexibility retention was certainly superior to that of earlier samples that were grafted with chloromethylstyrene, quaternized, and heparinized [2].

The radiation grafting technique used in the present research almost always results in monomer grafting within the polymeric substrate rather than on its surface [14]. The subsequent reactions with pyridine and heparin also take place within the substrate, meaning that diffusion and penetration of the reactants play an important role in determining the extent and location of the several reactions. If the monomer is slow in diffusing into the polymer for any reason, the grafting may take place only in a thin layer near the surface. Theoretical equations have been derived showing the effect of reactant diffusion on reaction kinetics within a solid phase [15, 16]. In the present case, CEA grafting may be more concentrated in certain regions of the substrate than in others, depending mainly on the distance from the surface (penetration distance). The amount of pyridine reacting in a certain region will depend on the local concentration of grafted CEA, and the amount of heparin reacting in a region will be limited by the amount of pyridine add-on in that locality. Hence the physical properties of the product will depend not only on the add-on of each reactant, but also in a complicated way on the locus of the several reactions.

Many investigators have employed ionic bonding to attach heparin to polymers [2, 7, 17-22], while others have used covalent bonding of the heparin [23-28]. Researchers appear to agree that ionically bound heparin is more readily eluted by blood than covalently bound heparin [1]. Some investigators have theorized that gradual leaching of heparin from a heparinized polymer is necessary to produce thromboresistance, and have postulated required rates of leaching [29-31]. Doubt was cast on the need for heparin leaching by Goosen and Sefton [27], who observed thromboresistance in heparinized styrene/butadiene/styrene copolymers from which heparin could not be leached by 3 M saline. Furthermore, Merrill [23] showed that a thromboresistant hydrogel of PVA/glutaraldehyde/heparin retained a significant amount of heparin after infinite washing with

3 M saline. Thromboresistance without heparin elution has also been reported for heparinized polymethyl acrylate [32] and heparin-methyl methacrylate graft copolymers [33].

Hence the accumulated evidence suggests that heparin chemically bound to a polymer can, like heparin in solution [34], be effective in preventing thrombogenesis by accelerating the inactivation of thrombin through the formation of thrombin-antithrombin III inactive complex at the polymeric surface. If this is so, it remains important to investigate the rate of heparin leaching from the point of view of the potential decrease in thromboresistance caused by heparin loss. It is probable that the continuous elution of heparin from a heparinized polymer would reduce its term of usefulness in a blood contact application.

While it is true that ionically bound heparin generally leaches more rapidly than covalently bound heparin, a distinction must be made between heparin ionically bound to the substrate surface and that ionically bound to the interior layers of the substrate following radiation grafting as in the present technique. In the present case the heparin will be lost most readily from the surface layer, and then diffuse more slowly from the progressively deeper layers of the substrate. Such a decrease in heparin loss rate with time is clearly shown in Fig. 11 for all three samples. However, from an inspection of Fig. 11 it is impossible to know whether the curves will level out at a constant percentage of heparin retention or continue to drop at a gradually decreasing rate over a very long period of time. The extraction experiments of Fig. 11 were extended to a total of 142 d, at which point 92.84, 96.09, and 95.78% of the original heparin content was retained by Samples 124, 126, and 127, respectively.

The underlying assumption of the present research is that it is more feasible to modify an existing commercial polymer by adding on a minor amount of heparin than it is to synthesize an entirely new polymer or copolymer which contains heparin as an integral component. The latter approach has two major disadvantages: 1) It would be unreasonable to expect heparin to behave as an ideal polymeric component for imparting flexibility, stability, tensile strength, and all the other properties that have enabled the survival of the existing commercial polymers. 2) Even if a molding or extrusion resin could be developed which contains chemically-bound heparin, the poor thermal stability of the heparin would probably cause the resin to degrade during the high temperature molding or extrusion operation necessary to fabricate the finished article (not to mention the detrimental effect of the high temperature on the activity of the heparin).

On the other hand, the radiation grafting of existing commercial plastics has substantial advantages. By methods similar to those described in this report, a minor amount of heparin can be chemically bound to a commercial polymer with no major changes in the latter's physical or chemical properties—properties which are unique enough to have assured its competitive survival thus far. Furthermore,

the grafting can be done on an article which has already been fabricated in its final form, and which remains essentially unchanged in size and shape during the grafting and heparinization process. Radiation grafting is similar to surface coating in that it can be applied to a fabricated article, but different from a surface coating in that it can never be peeled or abraded from the surface. A final advantage of radiation grafting is its generality of application: the gamma rays employed are so highly energetic that a wide variety of monomers can be grafted onto almost any commercial polymer.

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