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SYNTHESIS AND BIOMEDICAL PROPERTIES OF POLY-[(ETHYLENE-VINYL ALCOHOL)-*g*-ACRYLAMIDE]

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ABSTRACT

This paper deals with the graft copolymerization of acrylamide (AM) onto ethylene-vinyl alcohol copolymer (EVAL) film initiated by cerium(IV) ion. It was found that both the chemical and diffusion factors had influences on the graft reaction. The reaction was initiated on the surface and then penetrated inward as the grafting percentage was increased. The permeability of urea through the grafted EVAL film was improved compared to that of the original film as was the blood compatibility.

INTRODUCTION

EVAL, which is a hydrolyzed copolymer of ethylene and vinyl acetate, has been reported to be crystallizable [1]. These reports also indicated the hydrophilicity of the VAL sequences and the hydrophobicity of the E sequences. Its hydrophilicity is varied by changing the hydrolytic conditions or the molar ratio of ethylene to vinyl alcohol, while its crystallinity is controlled by annealing conditions [2, 3]. The characteristics of the EVAL film produced are dependent on molecular weight [4], microstructure, and the molding conditions.

Thus, EVAL could be designed for use as a hemodialysis membrane whose permeability, mechanical properties, blood compatibility, stability, etc. could be regulated by the microphase-separated structure composed of both the hydrophilic/hydrophobic and the crystalline/amorphous domains [5]. The literature has reported that the characteristics of EVAL are best when it contains 30-45 mol% ethylene units [6].

An EVAL/AM graft polymer has not yet been reported in the literature. These and other considerations have prompted us to investigate in some detail the synthesis of EVAL-polyacrylamide graft polymer (EVAL-*g*-AM) and its biomedical properties. Acrylamide was chosen because of its good blood compatibility.

EXPERIMENTAL

Materials

Two types of EVAL film with VAL/E mole ratios of 67/33 (thickness 30 μm) and 55/45 (thickness 60 μm), respectively (from Kori Company, Japan), were used. AM (chemically pure) was recrystallized from anhydrous alcohol and benzene prior to use. Analytically pure $Ce(NH_4)_2(NO_3)_6$ (CAN) and nitric acid were used as received.

Graft Copolymerization

A 1.0 *M* aqueous solution of AM (30 mL) and 20 mg EVAL film with 67 mol% VAL were placed in a flask. The solution was flushed with nitrogen for about 20 min, and then 0.037 *M* CAN in 1 *N* nitric acid solution was added. The graft copolymerization was carried out at 40°C for the desired period of time. The grafted film was washed with distilled water until its weight no longer changed, and then it was dried at 40°C.

TABLE 1. Elemental Analysis

Sample	C, %	H, %	N, %	*G*, %
EVAL	63.81	11.55	0	0
EVAL-*g*-AM	56.66	10.11	6.14	45.3

From the weight increase, the percent grafting (G) was calculated by

$$G = \frac{W - W_0}{W_0} \times 100, \tag{1}$$

where W_0 and W indicate the weight of the EVAL film and the grafted EVAL film, respectively. The calculated value of G agreed with that obtained by elemental analysis (cf. Table 1).

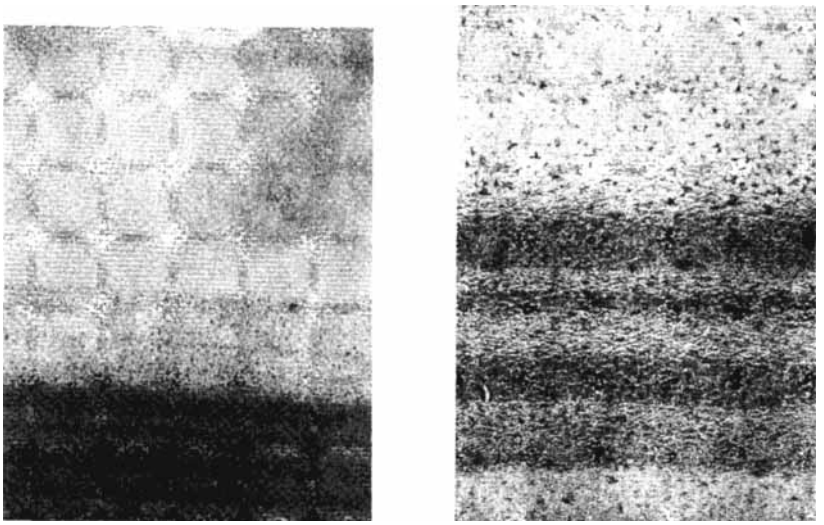
Evidence of Grafting

A. The FT-IR-ATR spectrum of the grafted EVAL film determined with Nicolet-5DX showed the characteristic peaks attributed to $-NH_2$, $\gtrsim C{=}O$, and $-C-N$ at 1614.1, 1655.1, and 1417.2 cm^{-1}, respectively, while there were no such peaks in the spectrum of the ungrafted EVAL film.

B. The grafted EVAL film specimen was stained with a saturated aqueous palladium chloride solution. The morphology of the cross section of the stained film (embedded in epoxy resin and then microtomed) was observed with a Philips EM-400ST transmission electron microscope. The micrographs showed that the surface of the specimen was extensively stained, which indicated that the grafted layer starts from the surface, as shown in Fig. 1.

Measurement of the Apparent Diffusion Coefficient D_a of AM

The uptake of aqueous AM solution by the grafted EVAL film is considered as a diffusion process, and it is assumed 1) that the concentration of the AM solution in which the film is suspended remains constant as diffusion proceeds, and 2) that the concentration of AM at each surface immediately attains its equilibrium value for the AM solution concentration and remains constant afterward. If the apparent diffusion coefficient D_a is taken to be constant, it is related to the initial slope (I_a) of a sorption experiment by the expression [7, 8]



(a) (b)

FIG. 1. TEM micrographs of EVAL-*g*-AM (*G* 37%) film. (a) Cross-section of the grafted film (1450X). (b) Cross-section near the surface of the same film.

$$D_a = \frac{\pi}{16} I_a^2 \tag{2}$$

where I_a can be obtained from the curve of $W(t)/W(\infty)$ vs $t^{1/2}/L$ by the regression method, where $W(t)$ is the weight of the film at time t and eventually approaches a limiting value, denoted by $W(\infty)$, and L is the thickness of the film.

The grafted EVAL film was immersed in a 1.0 *M* aqueous AM solution and taken out at given intervals. As soon as the surface of the film was blotted with a filter paper, the final weight $W(\infty)$ of the film was determined. Then, D_a could be calculated from the results of the sorption experiment.

Determination of the Contact Angle against Water

The dry EVAL-*g*-AM film was put on the sample plate of a ERM-422 goniometer. A drop of water was placed on the surface of the film with a microsyringe.

The angle between the water drop and the surface, which is the contact angle against water, was measured at 28°C.

Water Absorption

The grafted film was immersed in distilled water at 28°C for 24 h. Then the surface was blotted with a filter paper, and the film specimen was quickly weighed. From the difference in weight, the water absorption was calculated.

Evaluation of Permeability of Urea through the Film

A diffusion device, which consisted of two cells, one with 25 mL distilled water and the other with 200 mL of 0.1 *M* aqueous solution of urea, was immersed in a water bath, as shown in Fig. 2. After 8 h the difference in urea concentration between both cells (ΔC) was determined by nitrogen analysis

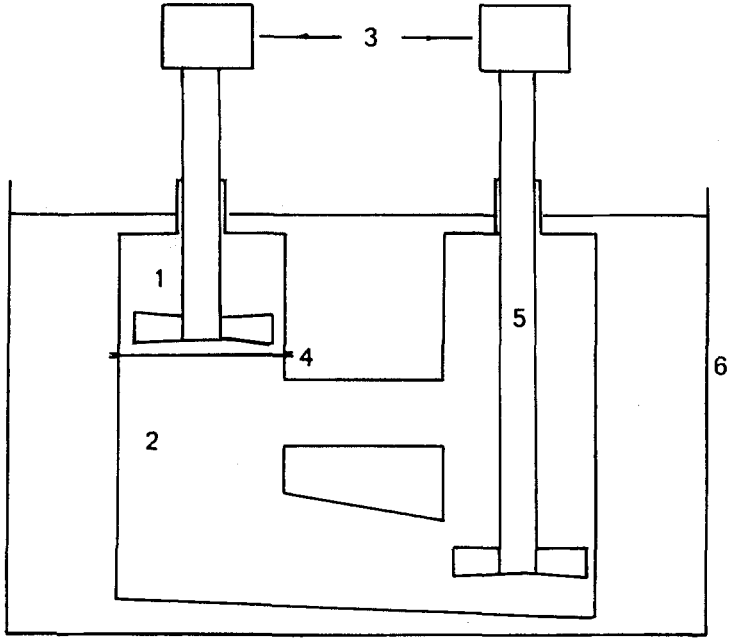


FIG. 2. The permeation apparatus. (1) Cell for distilled water. (2) Cell for aqueous urea solution. (3) Electronic stirrer. (4) EVAL-*g*-AM film. (5) Stirring bar. (6) Water bath.

of the solution. The permeability of urea through the film (thickness L) can be calculated by

$$P = QL/\Delta C, \tag{3}$$

where P is the permeability coefficient and Q is the rate of permeation of urea through the film.

Adhesion Behavior of Blood Platelets

Glass beads (100 mesh) were immersed in a 0.5% (wt/vol) dimethylsulfoxide solution of EVAL-*g*-AM and then were dried at 40°C. The coated beads were packed into a column which was sterilized with ethylene oxide. The blood of a healthy dog was injected through the column with the syringe of a measuring pump (5003 Model) at 1 mL/min. The blood was sampled for counting the platelet number.

RESULTS AND DISCUSSION

Graft Copolymerization of AM onto EVAL Film

EVAL is crystallizable over the entire range of its composition, producing isomorphous crystallites containing ethylene and vinyl alcohol units [9], and is of microphase-separated structure having hydrophilic domains of 300-500 Å [10]. If the graft copolymerization of AM onto EVAL occurs only in the VAL domain, the reaction is not homogeneous. A TEM micrograph of EVAL-*g*-AM revealed heterogeneity on the domain level (Fig. 3).

According to the above concept, grafting AM onto EVAL by the ceric ion method can be explained by assuming the diffusion and permeation of AM and Ce^{4+} into VAL domains on the surface. Then, a complex between ceric ion and polyhydric alcohol forms in the following manner:

$$\text{EVAL} + Ce^{4+} \underset{}{\overset{k_1}{\rightleftharpoons}} \text{Complex I} \xrightarrow{k_d} \text{EVAL}^{\cdot} + Ce^{3+} + H^{+} \tag{4}$$

$$\text{AM} + Ce^{4+} \underset{}{\overset{k_1'}{\rightleftharpoons}} \text{Complex II} \xrightarrow{k_d'} \text{AM}^{\cdot} + Ce^{3+} + H^{+} \tag{5}$$

Complex I decomposes to generate a free radical which provides an active site for the grafting of AM (Eq. 4), while AM can complex with Ce^{4+}, and that leads to the formation of polyacrylamide (Eq. 5) [11].

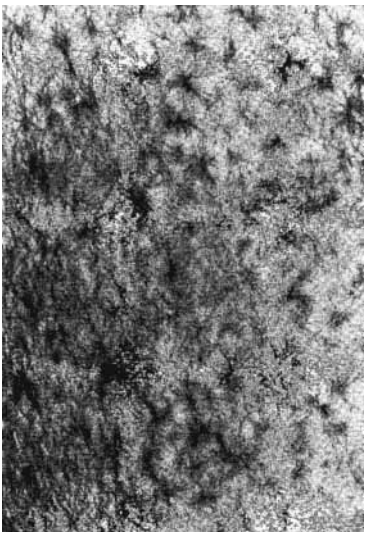


FIG. 3. TEM view of EVAL-*g*-AM (*G* 37%) film (11 000X).

The thickness of the grafted layer increases as the grafting develops inward. The composition, structure, and characteristics, especially the diffusion and permeability coefficients of the matrix, changed progressively, leading to a change in the kinetics of AM grafting onto the matrix and an increase in percent grafting (Fig. 4). It appears that the rate of grafting increases as the reaction proceeds. Moreover, water absorption of the grafted EVAL film increased with the extent of grafting (Fig. 5). The water molecules that have diffused into the matrix can break the polymer/polymer hydrogen bond, causing the matrix to relax and swell [5]. The transfer of AM and Ce^{4+} into the matrix continues, because the water molecules within the matrix network increase the free volume [12].

However, D_a of AM through the matrix film was very small (cf. Fig. 6). The diffusion of AM is limited by the EVAL crystallites, according to the model advanced by Michaels et al. [13, 14]. The effective diffusion coefficient D_{im}' can be defined as

$$D_{im}' = \psi D_{im}/\beta, \tag{6}$$

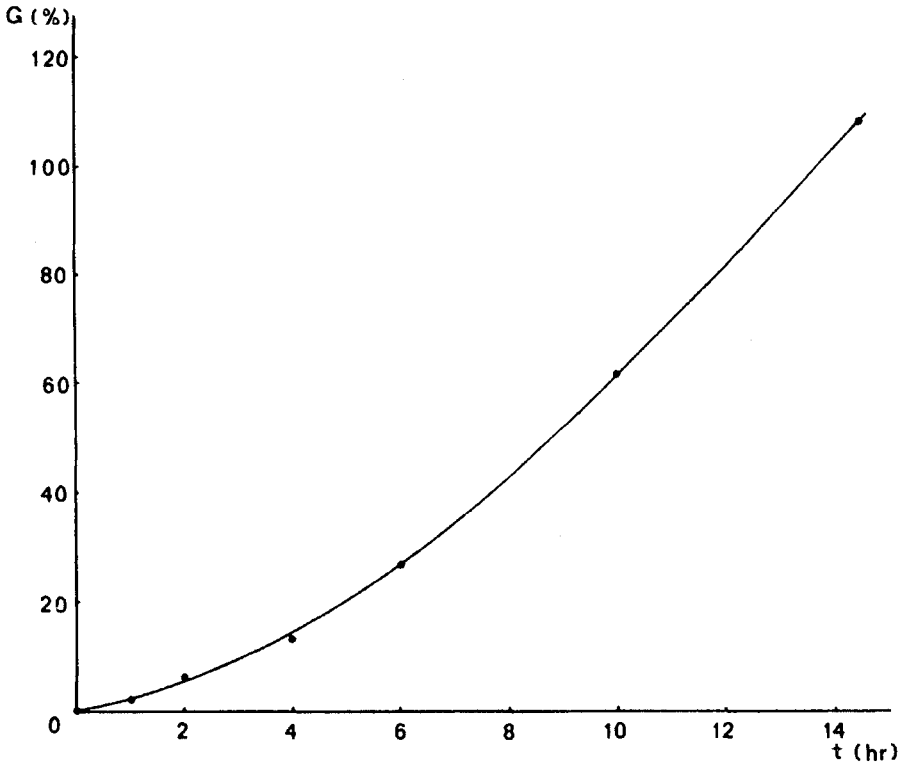


FIG. 4. Dependence of extent of grafting on reaction time. Conditions: AM, 1.0 mol/L, 35°C; CAN, 37 mol/L; 1 N HNO_3.

where D_{im} is the diffusion coefficient in the amorphous rubbery polymer, ψ is the "detour ratio" which accounts for reduction in solute mobility due to the tortuosity of the diffusion paths between crystallites, and β is an "immobilization factor" that accounts for physical crosslinking due to the cryatallites. In addition to the effects of crystallites of EVAL shown in Eq. (6), the EVAL (T_g 53°C) matrix was in the glassy state under some experimental condition. Figure 6 shows how D_a rises with the extent of grafting.

The main factor that caused the extent of grafting to increase with temperature (Fig. 7) was the glass-to-rubber transition of EVAL in the experimental temperature range.

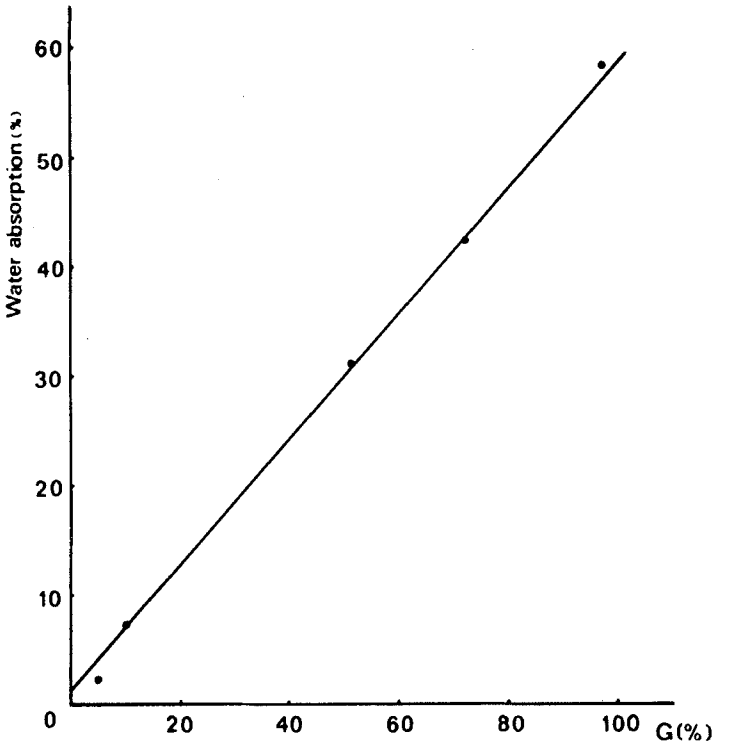


FIG. 5. Water absorption as a function of extent of grafting.

Effects of other reaction parameters, such as concentrations of monomer, CAN, and nitric acid, on the extent of grafting are listed in Table 2. These are analogous to the known behavior of redox graft copolymerization initiated by Ce^{4+} [15].

Permeability of EVAL-*g*-AM Film

Table 3 shows that the permeability coefficient of urea through EVAL-*g*-AM film, *P*, is greater than that of EVAL film by one to two orders of magnitude. Furthermore, *P* increases with the extent of grafting. These findings can be correlated with the grafting of the water-soluble polymer PAM, which influences the surface, domain structure, and crystalline structure of the grafted EVAL.

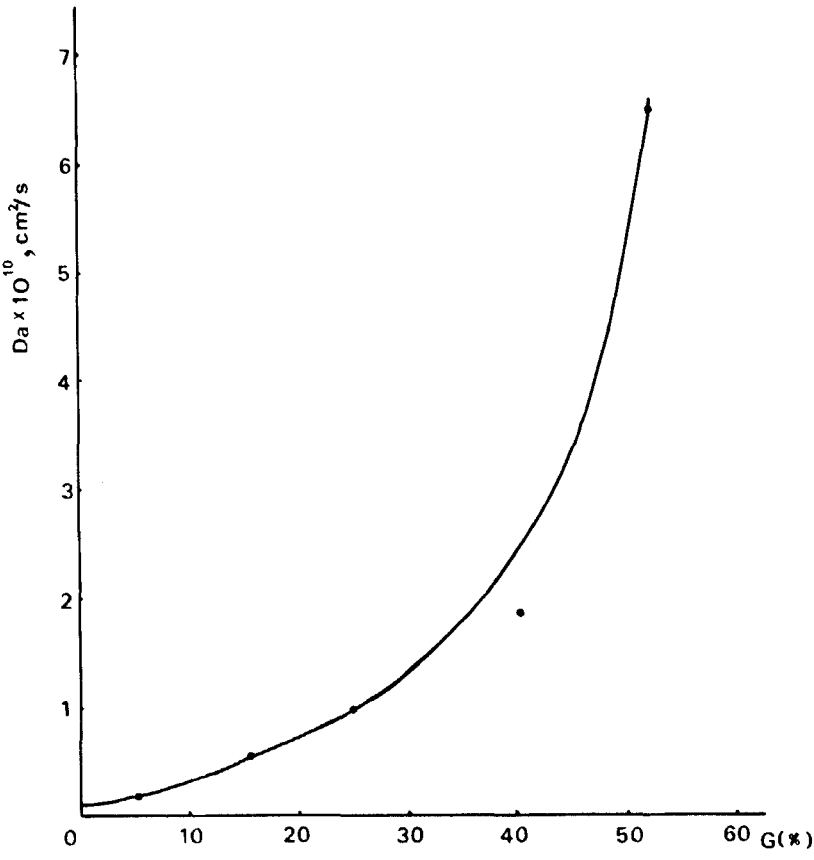


FIG. 6. Apparent diffusion coefficient as a function of extent of grafting.

The grafted EVAL film should possess a normal solid surface in air but a diffuse interface in contact with an aqueous urea solution. This diffuse interface may contain a large amount of water and a very small number of water-soluble PAM chains which are covalently bound to the EVAL substrate. Therefore, the "diffuse layer" proposed by Ikada [16] could promote distribution of urea onto the surface of the grafted EVAL.

In general, a solute only transfers through amorphous regions [13, 14]. Our results show that the crystallinity of EVAL-*g*-AM is less than that of

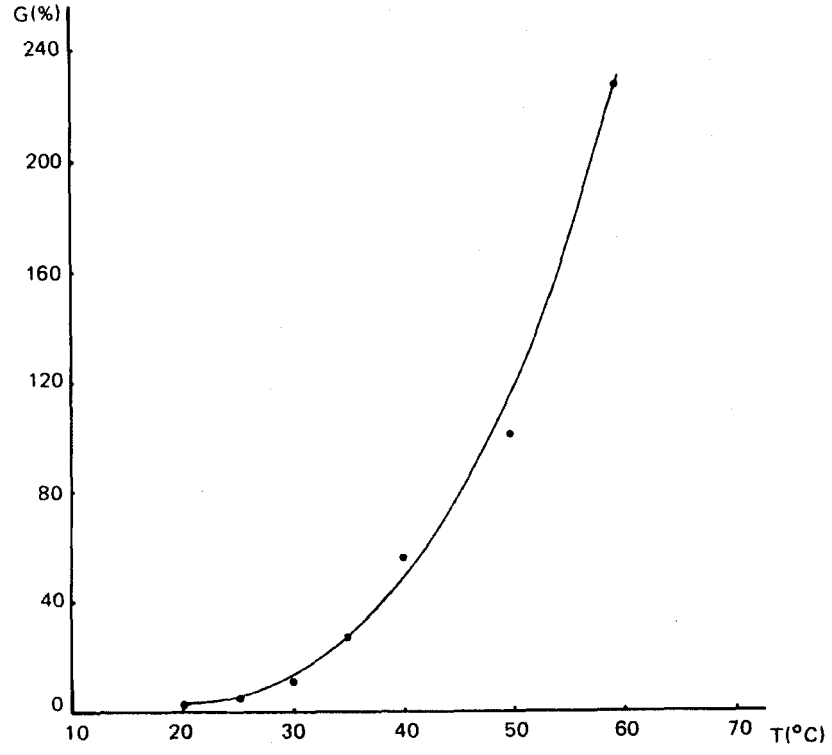


FIG. 7. Percent grafting versus reaction temperature. Conditions: AM, 1.0 mol/L, 20-60°C; CAN, 37 mol/L; 1 *N* HNO_3; 6 h.

EVAL [17], so that the former displays faster diffusion of urea according to Eq. (6).

EVAL-*g*-AM has hydrophilic domains composed of both VAL and PAM, in contrast to EVAL where they are only composed of VAL. As predicted in the light of the increased water absorption of the grafted EVAL (cf. Fig. 5), this led to faster diffusion of urea.

The Antithrombogenicity of EVAL-*g*-AM

The antithrombogenicity of EVAL-*g*-AM was superior to that of EVAL and improved with increasing grafting (Fig. 8). This was presumed to be due

TABLE 2. Effects of Concentrations of Monomer, CAN, and Nitric Acid on Extent of Grafting (40°C, 6 h)

No.	[AM], mol/L	[CAN], mmol/L	[HNO_3], N	G, %
1	0.1	37	1	2.04
2	0.3	37	1	5.16
3	0.5	37	1	12.87
4	0.7	37	1	25.00
5	1.0	37	1	56.25
6	1.5	37	1	97.96
7	1	3.6	1	10.00
8	1	9.1	1	26.50
9	1	18.2	1	40.00
10	1	27.4	1	51.49
11	1	54.7	1	67.37
12	1	91.2	1	71.88
13	1	219	1	58.60
14	0.5	37	0.01	2.00
15	0.5	37	0.03	5.05
16	0.5	37	0.3	13.99
17	0.5	37	0.7	13.30
18	0.5	37	1.0	12.87
19	0.5	37	2.0	10.31

TABLE 3. Permeability Coefficient of Urea through EVAL-*g*-AM Film

G, %	0	37.5	75.3
P, cm^2/s	5×10^{-9}	1×10^{-7}	6×10^{-7}

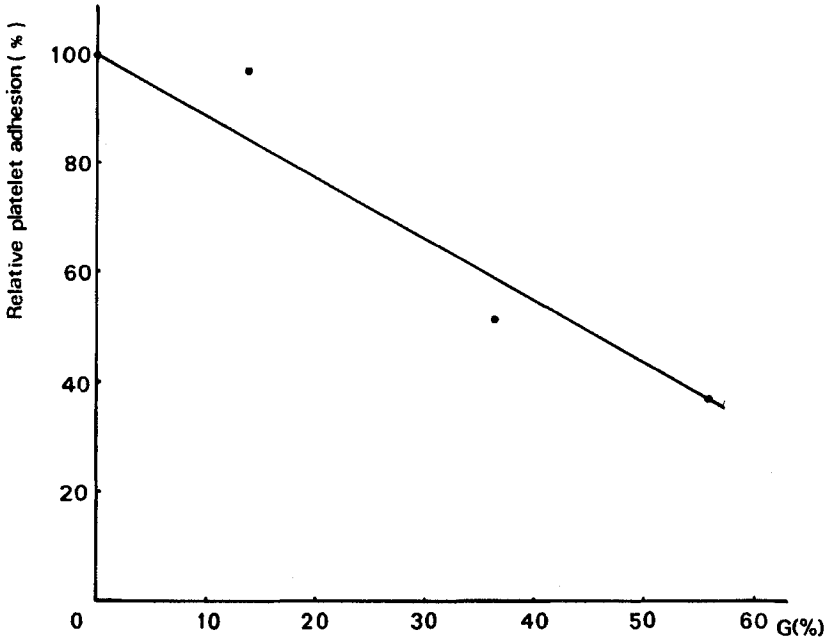


FIG. 8. Relationship between platelet adhesion and extent of grafting.

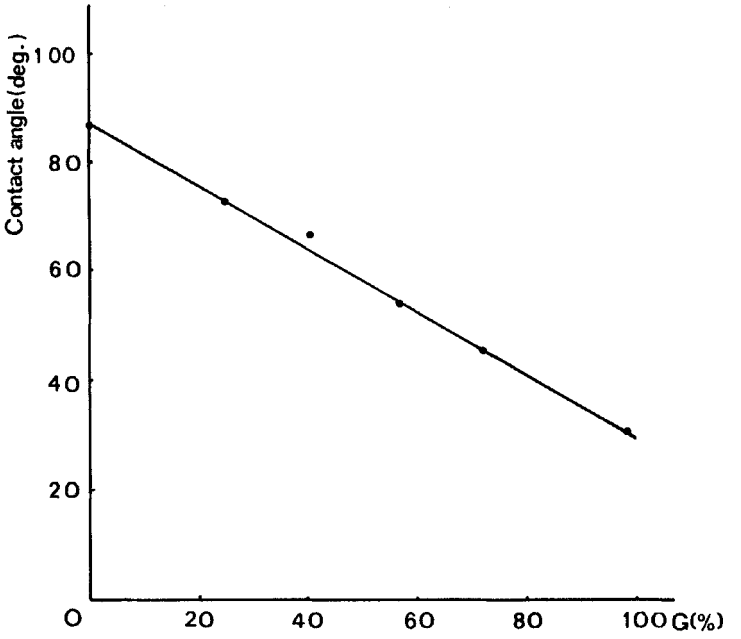


FIG. 9. Dependence of contact angle against water on extent of grafting.

to the formation of the diffuse layer, which retards protein and platelet adhesion on the grafted surface in the aqueous phase. The formation of the diffuse layer leads to a decreased contact angle of the grafted film against water (Fig. 9), and suppresses the adhesion of blood platelets as well [18].

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