Modification of Natural Rubber Tubes for Biomaterials I. Radiation-Induced Grafting of *N,N*-Dimethyl Acrylamide onto Natural Rubber Tubes

MIRZAN T. RAZZAK, KASUSHIGE OTSUHATA, *Department of Nuclear Engineering,* YONEHO TABATA, *Nuclear Engineering Research Laboratory, Faculty of Engineering,* F. OHASHI and A. TAKEUCHI, *Department of Veterinary Surgery and Obstetrics, Faculty of Agriculture, University of Tokyo, Bunkyo-ku, Japan*

Synopsis

Radiation-induced simultaneous grafting of *N,N*-dimethyl-acrylamide (DMAA) onto natural rubber (NR) tubes has been studied to improve blood compatibility of the NR tubes. Concerning grafting of DMAA onto NR tubes, it was found that the grafting proceeds effectively in the presence of carbon tetrachloride (CCl_4) as a solvent. The degree of grafting was found to be saturated at about 26 wt%, but a higher degree of grafting can be obtained by either "so called two-step grafting" or "putting a standing time for a while before irradiation." The initial grafting rate was proportional to 0.85 power of dose rate. The apparent activation energy of the graft-copolymerization was 7.42 kcal/mol. Evaluation of blood compatibility of DMAA-grafted NR tubes has been carried out by ex vivo test. According to the results, significant improvement of blood compatibility was obtained for the samples in which degree of grafting is higher than 30 wt%.

INTRODUCTION

Natural rubber (NR) has been used to produce such medical materials as tubings and catheters, as well as silicone rubber (SiR) and polyvinylchloride (PVC).[1] However, blood compatibility of materials made of NR is poor compared with that of materials made of SiR or PVC.

According to our survey, work related to improvement of blood compatibility of NR materials has not been done before, although work for SiR or PVC materials has been done.[2-4] If improvement of blood compatibility of NR medical materials can be accomplished, biomedical applications of NR could be extended greatly. The excellent elasticity and flexibility of NR would be advantageous. Particularly, resistance against splitting of NR is higher than that of SiR. Therefore, in the present article, we have tried to improve blood compatibility of NR tubes which are used as transfusion tubes.

As reported previously, our laboratory has already succeeded in improving blood compatibility of polytetrafluoroethylene (PTFE) or AFLON COP by radiation-induced grafting of DMAA.[5,6] Thus, the same idea has also been applied to improving blood compatibility of NR tubes.

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The present article reports kinetics of radiation-induced graft copolymerization of DMAA onto NR tubes and blood compatibility of DMAA-grafted NR tubes judged by the ex vivo test.

EXPERIMENTAL

Materials

Natural rubber (NR) tube of 1 mm thickness (inner diameter 3.5 mm, outer diameter 5.5 mm) was purchased from Komine Rubber Mfg. Co. Ltd. This tube was cut into pieces of 35 mm length, washed thoroughly with tap water, and subsequently washed with acetone and distilled water in an ultrasonic cleaner for 15 min. The tube was then dried in vacuo at room temperature and weighed. *N,N*-dimethylacrylamide (DMAA) was supplied by Kohjin Co. Ltd., and used as received. The other reagent-grade chemicals were used without further purification.

Graft Copolymerization

The simultaneous irradiation method was used as the grafting technique. A piece of weighed NR tube was immersed into excess monomer with or without

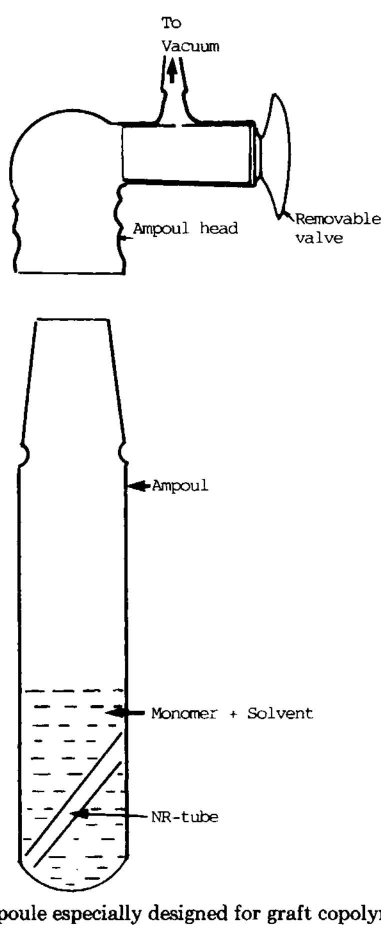

Fig. 1. A glass ampoule especially designed for graft copolymerization experiments.

a solvent in a specially designed glass ampoule as shown in Figure 1. A glass ampoule containing the reactants was connected to a vacuum system and then frozen, degassed under reduced pressure, and thawed. This process of freeze-thaw technique was repeated four times. A valve on the head of the glass ampoule was rotated to seal the ampoule when the vacuum degree of 10^{-4} torr was attained. The glass ampoule was then warmed up to room temperature and irradiated with gamma rays from a Co-60 source at a fixed position.

Following irradiation, the grafted NR tube was removed from the glass ampoule, washed thoroughly with tap water, and soaked overnight in distilled water. It was then boiled in distilled water for 5 h to extract the residual monomers and the homopolymers involved in the tube. The tube was dried under vacuum at room temperature for 24 h, and weighed.

The degree of grafting was determined by the percent increase in weight as follows.

$$\text{Degree of grafting (wt\%)} = (W_g - W_o)/W_o \times 100$$

where W_o and W_g represent the weights of initial and grafted NR tube, respectively.

Blood Compatibility Evaluation

Blood compatibility of grafted NR tubes were evaluated by using an ex vivo test developed by Ikada et al.[7] with slight modifications by us on the manner of observation As Figure 2 shows, NR tubes of 35 mm length were connected to each other by 15 mm polytetrafluoroethylene (PTFE) tube connectors. Using a 19G Teflon sheathed needle, blood from the femoral artery of a mongrel dog was first introduced to Syringe I to discard the blood which contained tissue thromboplastin. Then with Syringe II, blood from the femoral artery was introduced into the grafted NR tubes.

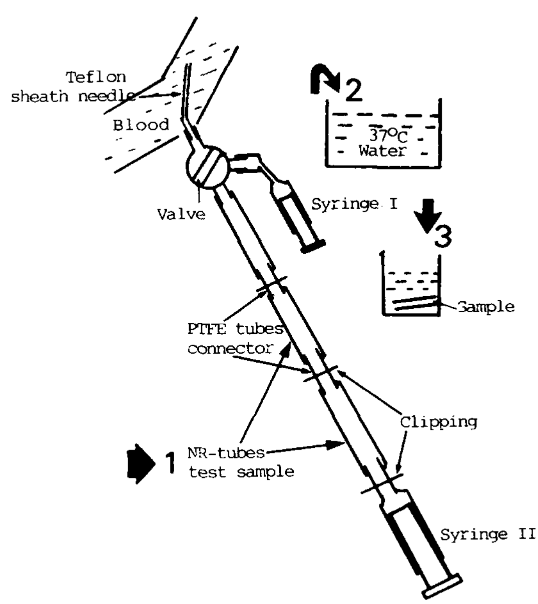

Fig. 2. Experimental arrangement for ex vivo test.

After all the grafted NR tubes were filled with fresh blood, PTFE tube connectors were clipped and all the grafted NR tubes were immersed in a water bath kept at 37°C. After 15 min the grafted NR tubes were removed from the water bath, put into 100 mL of distilled water in a beaker, and stirred gently. They were then removed from the beaker and dried.

Evaluation of blood compatibility of DMAA-grafted NR tubes was based on visual observation of the appearance of NR tubes, That is, it was considered that the decreased amount of blood clotting in the NR tubes means that blood compatibility is improved.

RESULTS AND DISCUSSION

Graft Copolymerization

In a radiation-induced grafting method, it is generally important to have monomer molecules as close as possible with the active centers formed in polymeric substrate during irradiation.

According to Chapiro,[8] a higher grafting ratio could be achieved when monomer has the ability to continuously diffuse into swollen polymeric substrates. Therefore, if the substrate cannot be swollen with monomer for grafting, an appropriate solvent for graft copolymerization is generally necessary to swell substrate in order to get higher grafting yield.

In the grafting system of NR tube and DMAA, NR tube could not be swollen enough with DMAA. Thus, considering the necessity of the sample with higher grafting yield, appropriate solvent for the grafting of DMAA onto NR tube has been sought.

Table I shows the degree of grafting which was obtained in several kinds of solvents. According to Table I, it is clear that the highest grafting yield is obtained in the presence of carbon tetrachloride (CCl_4). In addition, it has also been found that the grafting of DMAA onto NR tubes does not take place without the solvents. Thus, in the present article, CCl_4 was selected as the solvent for graft copolymerization of DMAA onto NR tubes.

Figure 3 shows the effect of monomer concentration on the grafting of DMAA onto NR tubes. A maximum grafting yield is obtained at a monomer concentration around 30 vol% DMAA in CCl_4. This probably indicates that

TABLE I
Effect of Solvent on the Grafting of DMAA onto NR Tubes

No.	Solvent	Total dose (kGy)	Grafting yield (wt%)
1	None	0.08	None
2	Ethylacetate	0.66	None
3	Acetone	0.66	None
4	Benzene	0.66	0.61
5	$CHCl_3$	0.50	2.14
6	CCl_4	0.17	9.45

[a]Grafting conditions: Dose rate 0.33 kGy/h; monomer concentration 30 vol%; DMAA in a solvent; temperature 27°C.

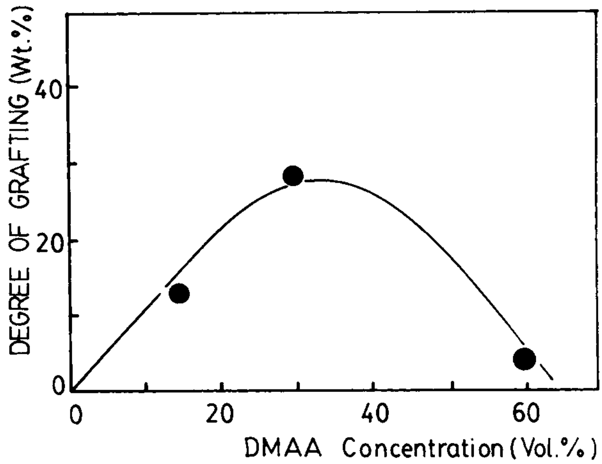

Fig. 3. Effect of monomer concentration on the degree of grafting. Dose rate 1.50 kGy/h. Temperature 27°C.

the highest concentration of DMAA in NR tube could be achieved under the swelling condition at 30 vol% DMAA in CCl_4.

Figure 4 shows effect of temperature on grafting. At a constant temperature, degree of grafting is increased with irradiation time. By Arrhenius plot activation energy was found to be 7.42 kcal/mol as shown in Figure 5. This value suggests that the graft copolymerization proceeds via a free radical mechanism.

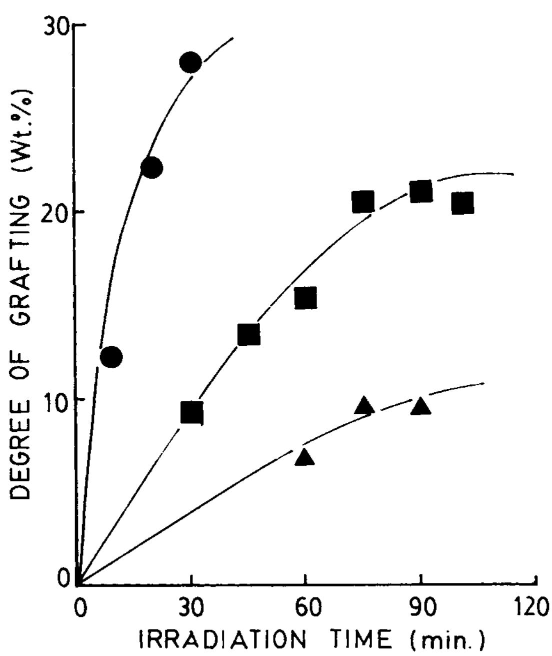

Fig. 4. Effect of dose rate on grafting of DMAA onto NR tubes. Monomer conc. 30 vol% DMAA in CCl_4, temperature 27°C. (●) 1.50 kGy/h, (■) 0.33 kGy/h, (▲) 0.10 kGy/h.

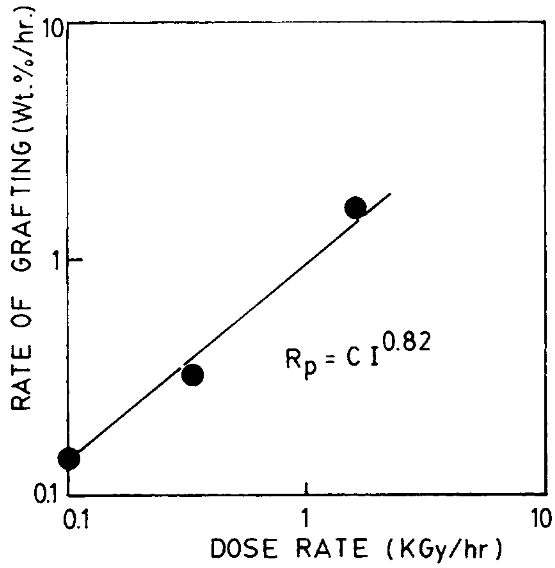

Fig. 5. Logarithmic plots of initial grafting rate (R_p) against dose rate. Grafting conditions are the same as in Fig. 4.

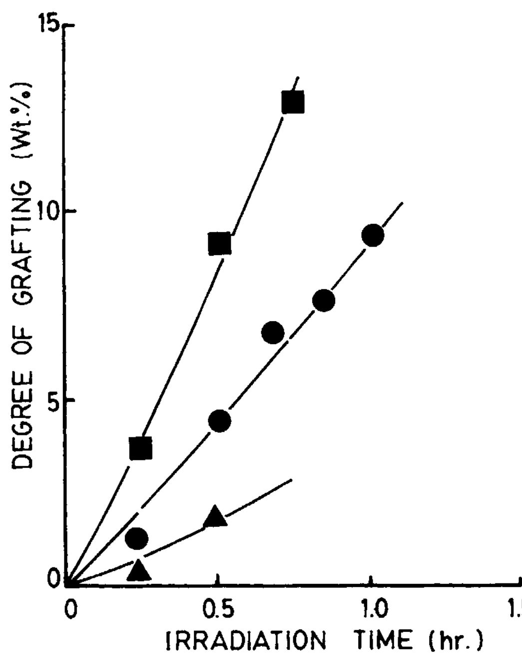

Fig. 6. Effect of temperature on degree of grafting. Dose rate 1.50 kGy/h. Monomer conc. 30 vol% DMAA in CCl_4. (■) 42°C, (●) 27°C, (▲) 0°C.

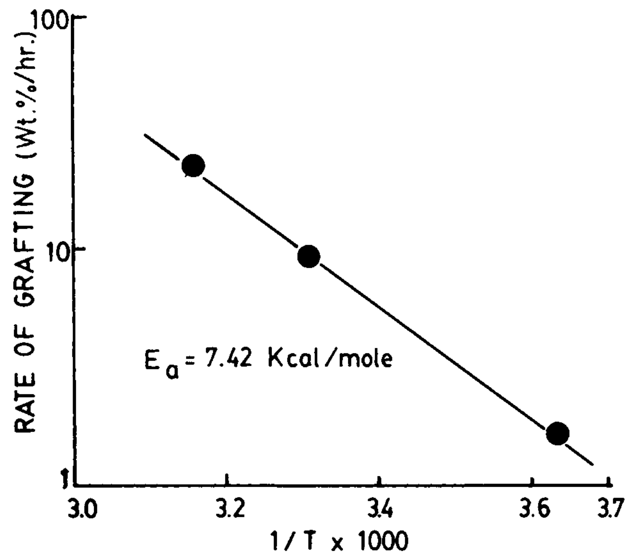

Fig. 7. Arrhenius plot of graft copolymerization of DMAA onto NR tubes. Grafting conditions are the same as in Fig. 6.

Dose rate dependency of the grafting at 27°C is shown in Figure 6. At any condition of dose rate, degree of grafting increases with irradiation time and reaches a saturated level at a certain irradiation time. Figure 7 shows the dependency of initial grafting rate on dose rate. The initial rate of grafting was calculated to be proportional to a 0.82 power of dose rate. This result indicates that both terminations, unimolecular and bimolecular, occurred.

According to Figures 4 and 6, we have found that degree of grafting of DMAA onto NR tube is saturated at about 26 wt%, although different dose, dose rate, and temperature have been examined. According to Chapiro,[9] grafting yield about 30 wt% is required to enhance blood compatibility of silicone rubber (SiR) tubes when *N*-vinylpyrolydone (NVP) is employed as a monomer.

Although a grafting system of DMAA-NR tube differs from NVP-SiR tube, both substrate of NR tube and SiR tube are elastomer. Thus, it is interesting to evaluate DMAA-g-NR tube with about 30 wt% grafting. Therefore, in order to increase the grafting beyond the saturation, so called "two-step grafting" has been tried. This is a very simple method, wherein grafting of DMAA was repeated twice for the same NR tube sample.

Figure 8 shows results of the two-step grafting. All the samples which have already had 18 or 25 wt% grafting yield were employed in the second-stage grafting. As irradiation time is increased, grafting yield is increased, and reaches approximately 30 wt% for the samples whose initial grafting yield is either 18 or 25 wt%. Thus, this modification method is found to be available to enhance grafting yield. Kinetics of two-step grafting will be discussed in the near future.

Other methods to increase degree of grafting beyond saturation include one in which standing time is allowed before irradiation. In this method, after the samples for irradiation were made, they are kept at room temperature for a

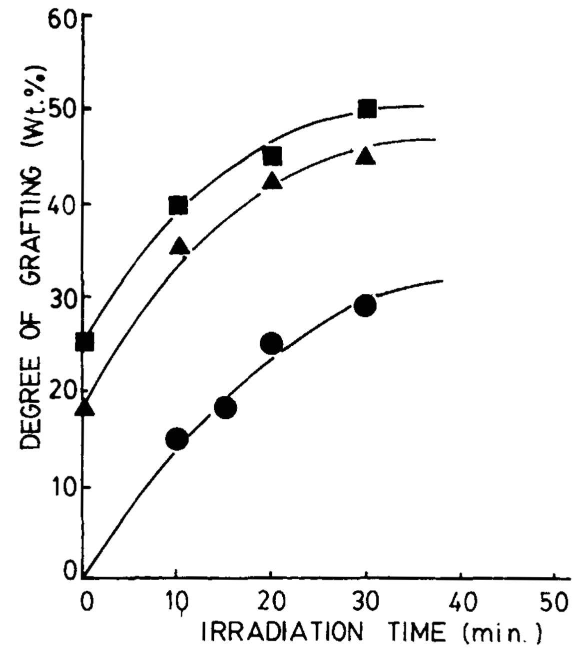

Fig. 8. The degree of grafting against irradiation time of graft copolymerization of DMAA onto NR tubes; (●) one-step grafting; (▲) two-step grafting with initial degree of grafting was 18 wt%; (■) two-step grafting with initial degree of grafting was 25 wt%.

period of several days, before they are irradiated. The relation between standing time and degree of grafting is shown in Figure 9. It is clear by the curve in the figure, that the degree of grafting of 30 wt% is obtainable by allowing a standing time of about 30 h. Therefore, this method is also available to obtain grafting yield of about 30 wt%.

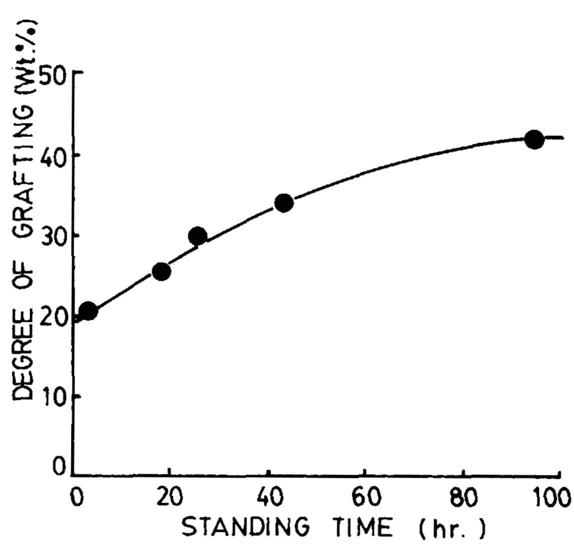

Fig. 9. Effect of standing time on the degree of grafting. Dose rate 1.50 kGy/h. Monomer conc. 30 vol% DMAA in CCl_4. Temperature 27°C.

TABLE II
Typical Results of Ex Vivo Tests

Sample	DMAA vol%	Dose rate (kGy/h)	Total dose (kGy)	% Grafting[a]		Visually
				A	B	
GR3-3	60	0.33	0.22	6.86		clot
GR2-4	30	0.10	0.61	12.40		clot
GR2-5	30	0.10	0.80	12.70		clot
GR1-9	30	0.33	0.53	17.70		clot
GR5-10	30	1.50	2.50	26.24		clot
DGR1-2	30	0.33	0.83		30.63	no clot
DGR2-3	30	0.33	1.00		33.90	no clot
DGR6-9	30	1.50	0.80		43.13	no clot
DGR2-3	30	1.50	3.00		56.30	no clot
DGR6-1	30	1.50	1.00		61.03	no clot
DGR6-2	30	1.50	1.25		79.88	no clot

[a]A is obtained by one-step grafting; B is obtained by two-step grafting (regrafting).

Evaluation of Blood Compatibility

Results of ex vivo test are listed in Table II. Clotting occurs in all samples which contain less than 30 wt% grafting yield. On the other hand, clotting is not found when the grafting yield is higher than 30 wt%. Specifically, there seems to be a boundary at about 30 wt%. The yield of this boundary is almost consistent with that obtained by Chapiro[9] in spite of a different grafting system, namely, NVP-g-SiR tube.

Furthermore, Table II shows that grafting parameters such as initial monomer concentration of DMAA and dose rate do not influence the blood compatibility of grafted NR tubes. Therefore, according to ex vivo test, degree of grafting is the most significant factor to improved blood compatibility of NR tube. In addition to improving blood compatibility of NR tubes by simultaneous grafting of DMAA, modified grafting technique as described before must be employed. By such modified techniques, sample grafting yield of more than 30 wt% is obtained.

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