

Developments in the biomedical evaluation of silicone rubber

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Passive prosthetic devices, for example artificial heart valves, can be manufactured from elastomeric materials such as silicone rubber. This paper describes how optimum properties for a medical grade heat-vulcanizing silicone rubber can be best achieved. The paper will also describe how the properties of these materials are affected by the different cleaning and sterilization procedures which may be used. The *in vivo* response of this silicone rubber to subcutaneous implantation in guinea pigs has been investigated for periods of up to ten months. Scanning electron microscopy of the surfaces of these elastomers has been performed. As a result, it has been possible to perform detailed examinations of the topological features of the surfaces prior to and after implantation.

1. Introduction

As a consequence of expanding surgical capabilities and developments in biomedical materials research, the implantation of prosthetic devices is now common place [1]. Many prosthetic devices, such as artificial heart valves and finger joints, are made either fully or partly from silicone rubbers. These elastomers have many desirable attributes such as high flexibility, good resistance to body fluids and non-toxicity. Their thrombo-resistant properties are superior to most other elastomers and although not ideal, coating techniques (e.g. hydrogels, heparin) now being developed may considerably improve the thromboresistant properties of these materials [2, 3].

However, there have been many reports that gradual deterioration of the elastomers can occur, leading to the failure of prostheses such as artificial heart valves [4-8], finger joints [9, 10] and intramedullary implants [11]. It is known that implanted silicone rubbers absorb lipids from the biological environment [12] and it has been suggested that prostheses failure may have been due to the uptake of these lipids [8]. Increases in the weight of silicone rubber heart valve poppets used in Starr-Edwards prostheses have been reported to be as high as 16%. This caused

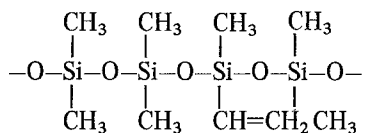
substantial swelling of the silicone rubber with the poppets becoming immobile in the retaining struts.

These high levels of lipid absorption have not been encountered in artificial finger joints made from silicone rubber [10]. Nonetheless; mechanical failure of the implants resulted in about a third of the cases investigated. No correlation could be observed between the incidence of failure and the amount of lipid absorption as had been suggested for the heart valve poppets. It was also found that implants failed in as little as five months, which is contrary to results obtained by Leininger [13] and Swanson and Le Beau [14]. Their reports showed that no substantial changes in the tensile properties of silicone rubber occurred when implanted subcutaneously for periods of up to two years. Hence, while some failures of prostheses can be attributed to the absorption of lipids the majority of failures can not yet be explained. Since the mechanisms of silicone rubber response to the physiological environment have not been adequately investigated, it is difficult to determine the possible causes of premature failure of the prostheses. For example, manufacturing procedures vary and are often not described. Thus, considering the extensive use of silicone rubber for biomedical applications, there

have been surprisingly few reports on the response of this material to manufacturing, cleaning and sterilization procedures employed. This project aims to establish a methodology for assessment of the properties of silicone rubber from the manufacturing stage to the implantation stage. The subsequent response of the elastomer can then be judged on a framework of knowledge rather than a basis of ignorance.

2. Materials and methods

The elastomers most extensively used for bio-medical applications are medical grade silicone rubbers. The silicone rubber investigated is MDX4/4515 (previously known as Silastic 372) and is manufactured by Dow Corning Limited. This elastomer is of the heat-vulcanizing type consisting of methyl and vinyl monomers which are copolymerized to give polymer chains of the type;



These polymer chains have molecular weights of up to 500 000. The methyl component makes up the bulk of the volume of the material (approximately 80%) and a small amount of the vinyl material is present to improve the efficiency of the cross-linking process. The catalyst, which is activated at temperatures in excess of 60°C, links the polymer chains together to give the elastomer its three-dimensional network structure. Silica flour filler, which makes up the rest of the volume of the material (approximately 15%), is a necessary additive since the elastomer would otherwise have insufficient strength for any practical purpose. Circular sheets of medical grade silicone rubber were produced by compression moulding for five minutes at 100°C at a pressure of 2000 kPa. Samples were post-cured in a circulating air oven under various conditions of temperature and time. The weight loss and amount of extractable polymer were determined for each curing condition by methods described elsewhere [15]. The suggested method of cleaning silicone rubbers is by boiling in a solution of distilled water and soap, but Nyilas *et al.* [16] have shown that this results in the absorption of stearic acid. For this reason a different approach was adopted, the silicone rubber being cleaned in a solution of chloroform-ethyl acetate (2:1) for a period of 48 h. The

solvent was removed by placing the specimens in a dessicator under vacuum for a period of 24 h, following which they were stored in a clean air environment for seven days. The silicone rubber was sterilized in a high pressure steam autoclave at the following recommended conditions [17];

- (1) 3 min at 134°C; 30 p.s.i.
- (2) 10 min at 126°C; 20 p.s.i.
- (3) 20 min at 121°C; 15 p.s.i.

3. Measurement of physical properties

The problems associated with a suitable choice of parameters have been discussed elsewhere [15] and preliminary results have shown that reproducible and accurate measurements of the tensile strength, extensibility and cross-linking density of the silicone rubber can be made. A likely cause of mechanical failure of a prostheses such as an artificial leaflet heart valve is by tearing of the thin leaflets. Thus, a measure of the tear strength of silicone rubber would be a useful additional parameter to the ones already mentioned. Usually the tear strength of elastomeric materials is measured for specimens made to specific standards set by the BS or ASTM. But since limitations are imposed on the size and shape of specimens for implantation, strips of the elastomer approximately 1.0 mm thick, 5.0 mm wide and 50 mm long were used. A 1 mm long slit was cut in the samples with a razor blade. The resistance to tearing is then defined as the force per unit unstrained cross-sectional area, necessary to cause catastrophic failure of the specimen and is described as the notched fracture stress. Tests were carried out on an Instron tester at a cross-head speed of 20 cm min⁻¹ with the gauge length set at 2 cm, giving a strain rate of 1000% min⁻¹.

4. Optimization of properties of medical grade silicone rubber

The measurement of loss of weight with curing for medical grade silicone rubber yielded the curves shown on Fig. 1. These results show that the weight loss is strongly dependent on the curing conditions and if we wish to ensure the complete removal of catalyst reaction products, the curing process should be carried out for a considerable length of time. This also ensures that a minimum of uncross-linked polymer, which may subsequently leach out, is left in the polymer (Fig. 2). These results also show that curing at 200°C as opposed to 150°C increases the weight loss and

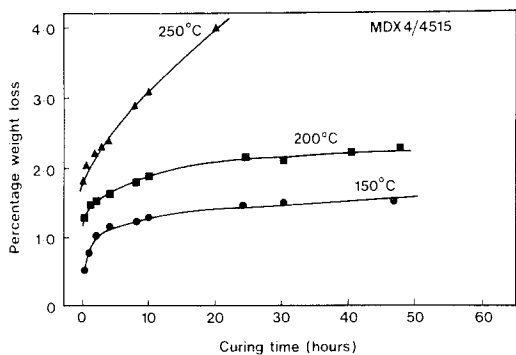


Figure 1 Weight loss of medical grade silicone rubber when cured at various temperatures.

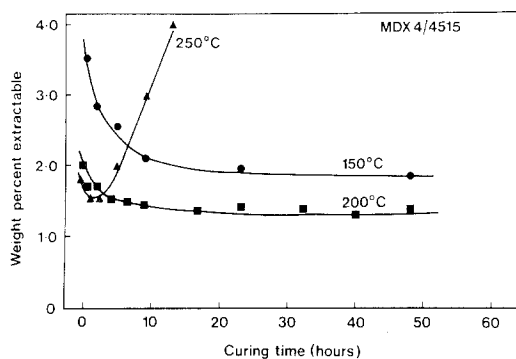


Figure 2 Extractable weight from medical grade silicone rubber after curing at different temperatures.

reduces the amount of extractable polymer. The former may be a result of more efficient removal of reaction products, while the latter may be due to an improved cross-linking process yielding less uncross-linked polymer. Curing at a temperature of 250°C should be avoided since this leads to thermal degradation, causing a continuous increase in weight loss and amount of extractable polymer. This is due to breakdown of the polymer structure by the process of chain scission. This is clearly shown in the results for the tensile strength of the elastomer. As can be seen from Fig. 3, curing at either 150°C or 200°C caused no changes in the ultimate tensile strength, while curing at 250°C caused a gradual decrease in the ultimate tensile strength so that after 20h the elastomer retained only 48% of its initial strength. This behaviour is also observed for the extensibility as shown in Fig. 4. Measurement of the notched fracture stress (cf. Fig. 5) resulted in similar behaviour, with curing at 250°C causing a drastic reduction in this property of the elastomer.

The above results show that curing at neither 150°C nor 200°C had an effect on any of the

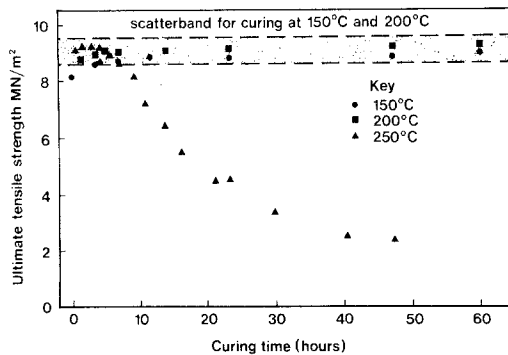


Figure 3 Variation in the ultimate tensile strength of MDX 4/4515 with curing conditions. Standard deviation is approximately 3% in all cases.

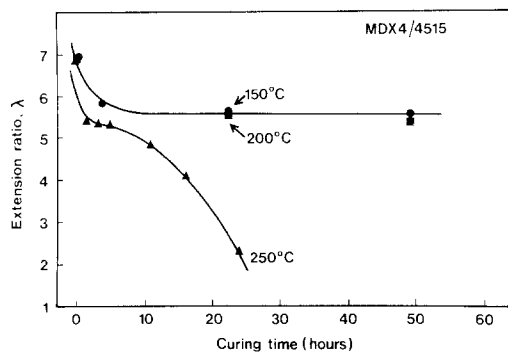


Figure 4 The effect of curing time and temperature on the extension ratio of MDX 4/4515.

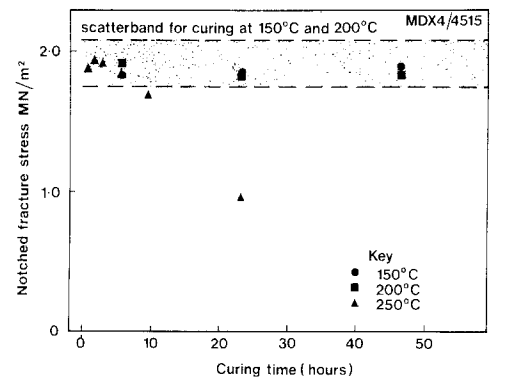


Figure 5 Notched fracture stress as a function of curing conditions.

properties measured, while curing at 250°C caused a gradual deterioration in properties. Hence, the optimum curing conditions for medical grade silicone rubber is suggested to be a 40h cure at 200°C. This will ensure the complete removal of catalyst reaction products, minimize the amount of uncross-linked polymer remaining in the elastomer and produce the best mechanical properties possible.

TABLE I The properties of medical grade silicone rubber after sterilization

Property	20 min at 121° C 15 p.s.i.	10 min at 126° C 20 p.s.i.	3 min at 134° C 30 p.s.i.
Tensile strength (MN m ⁻²)	9.3	9.4	9.1
Standard deviation	0.2	0.2	0.3
Spread	8.8–9.6	8.9–9.6	8.8–9.4
Extensibility (%)	440	450	440
Standard deviation	20	20	10
Spread	410–460	420–470	430–450
Cross-linking density (g mol ⁻¹)	4470	4390	4530
Standard deviation	60	80	50
Spread	4360–4590	4300–4480	4460–4610
Notched fracture stress (MN m ⁻²)	1.93	1.85	1.88
Standard deviation	0.10	0.07	0.08
Spread	1.70–2.06	1.71–1.99	1.73–1.98

TABLE II The effects of various treatments on the properties of medical grade silicone rubber (MDX 4/4515) cured for 48 h at 200° C

Property	Standard	Control	Extracted ^a	Sterilized ^b	Extracted and sterilized
Tensile strength (MN m ⁻²)	9.1	9.1	9.2	9.2	9.2
Standard deviation	0.2	0.2	0.1	0.2	0.2
Spread	8.9–9.4	8.9–9.4	9.0–9.3	9.0–9.5	8.9–9.5
Extensibility (%)	440	440	450	440	440
Standard deviation	20	20	30	10	20
Spread	430–460	420–460	410–480	430–460	410–460
Cross-linking density (g mol ⁻¹)	4560	4490	4450	4480	4420
Standard deviation	70	80	100	120	80
Spread	4420–4680	4390–4570	4300–4550	4200–4670	4340–4580
Notched fracture stress (MN m ⁻²)	1.83	1.85	1.82	1.88	1.87
Standard deviation	0.04	0.08	0.06	0.10	0.09
Spread	1.73–1.92	1.70–1.98	1.74–1.98	1.75–2.01	1.73–1.98

^aChloroform–ethyl acetate for 48 h.

^bSteam autoclave, 3 min at 134° C, 30 p.s.i.

5. The effects of cleaning and sterilizing

As mentioned previously, sterilization was carried out in a steam autoclave at various recommended conditions to determine the effects any of these treatments may have on the silicone rubber. The results for such tests are shown in Table I.

It can be seen that none of the sterilization procedures adopted had a significant effect on the properties investigated. Hence, any of these sterilization procedures can be employed without causing deterioration in the properties of the rubber. The effects of cleaning in a solution of chloroform–ethyl acetate for 48 h and subsequent sterilization by steam autoclaving for three minutes at 134° C and 30 p.s.i. were also investigated. The results for these experiments (cf. Table II) show that none of the treatments had any effect on the properties of the elastomer.

This procedure of preparing specimens of the silicone rubber for implantation can thus be adopted without fear of degradation. It has the advantage that all possible catalyst reaction products and uncross-linked polymer will have been removed from the elastomer and these will not therefore interfere with subsequent *in vivo* response of the elastomer.

6. *In vivo* studies

Twenty silicone rubber samples, 50 mm × 20 mm × 1 mm were implanted in six-month old, female guinea pigs, these implants being prepared by the methods recommended above. The lower back and flank of both sides of the spinal column were shaved and cleaned with tincture of Hibitane. The guinea pigs were anaesthetized with ether and a 2 cm long incision was made parallel to the spinal

TABLE III The physical properties of medical grade silicone rubber as a function of implantation time

Number of days implanted	Tensile strength (MN m ⁻²)	Extensibility (%)	Cross-linking density (g mol ⁻¹)	Notched fracture stress (MN m ⁻²)
Control	9.2 ± 0.2	440 ± 20	4420 ± 80	1.87 ± 0.09
18	9.1 ± 0.4	440 ± 30	4460 ± 30	—
36	9.1 ± 0.2	430 ± 20	—	—
50	9.1 ± 0.2	420 ± 10	4570 ± 70	1.91 ± 0.11
100	9.0 ± 0.3	420 ± 10	4550 ± 100	2.09 ± 0.17
200	9.1 ± 0.3	410 ± 10	4370 ± 200	1.85 ± 0.07
300	8.3 ± 1.0	340 ± 30	3540 ± 60	1.96 ± 0.04

column. The subcutaneous tissue was bluntly dissected producing a subcutaneous pocket large enough to hold the implant. After pre-determined times implants were removed and immediately cleaned and weighed. The physical properties were subsequently determined over a period of two days. Parallel *in vitro* studies were carried out on an identically prepared set of samples of silicone rubber immersed in Ringer solution containing known lipids for a period of nine months. Upon removal the samples were cleaned, weighed and their physical properties measured.

7. Results of implantation studies

The results for the measurement of mechanical properties after implantation are summarized in Table III. They show no observable changes in any of the properties after periods of implantation of up to 100 days, although there is a slight reduction in the extensibility of the elastomer.

For silicone rubber implanted for 200 days a reduction in extensibility of 7% was found. Since none of the other properties showed any significant changes, it can only be concluded that for medical grade silicone rubber implanted for periods of up to 200 days there was no significant alteration in properties. After implantation for 300 days, however, there was a substantial reduction in properties, tensile strength, extensibility and cross-linking density being reduced by 20%, 23% and 20% respectively. In contrast the notched fracture stress remained unaltered even after 300 days.

Measurements of weight change and amount of extractable material were carried out on the implanted samples of silicone rubber. The lipid absorption was determined from the quantity of material extracted, assuming that the extractable material consisted solely of absorbed lipids and residual low molecular weight polymer. Preliminary tests had shown that after initial extraction a second extraction procedure would

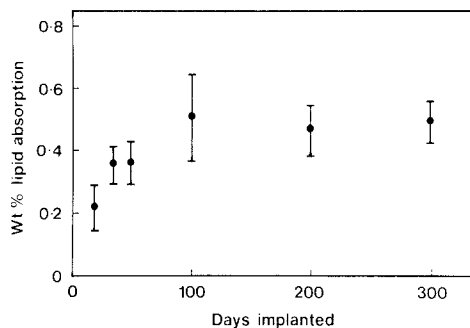


Figure 6 Weight per cent lipid absorption as a function of time implanted.

remove only a further 0.040 ± 0.002 wt% of polymer. The results for the wt% lipid absorption are shown in Fig. 6. Although the standard deviation is large, it can be seen that the lipid absorption stabilizes to a value of approximately 0.5 wt% after 100 days of implantation. This result is in good agreement with results obtained by Swanson and Le Beau [14] who reported a value of lipid absorption for silicone rubber of 0.57 wt%.

Investigation of the surfaces of implanted specimens revealed the presence of a deposit on samples implanted for 200 days or more. These deposits were quite pronounced on specimens implanted for 300 days, as shown in Fig. 7. X-ray microanalysis showed that this deposit contained calcium and phosphorous, the former being more abundant. Unfortunately, the amount of deposit available was insufficient for further analysis and the exact structure could not be ascertained. Removal of the deposit by immersion in ethylene diamine tetra acetic acid revealed a badly pitted surface on the rubber where the deposit had previously been. Fig. 8 clearly shows the badly eroded surface of the silicone rubber which had resulted from the deposit.

There were no changes in the properties of samples immersed in Ringer solution containing lipids, except for a weight increase of 0.62%

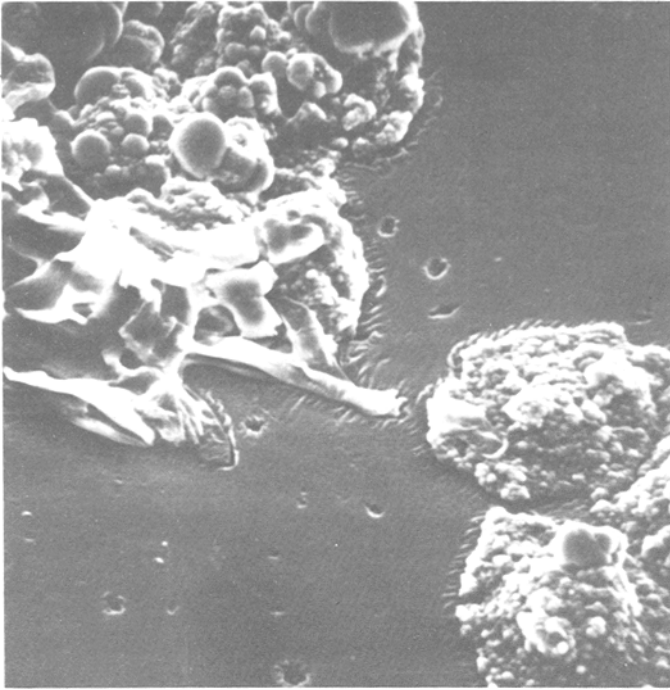


Figure 7 Stereoscan micrograph of the surface of a silicone rubber implanted for 300 days (X 1780).

due to absorption of lipids. Neither were any surface deposits observed.

8. Discussion

Subcutaneous implantation of samples of silicone rubber in ginuea pigs has been shown to cause a gradual deterioration in the properties of the

elastomer. This was most pronounced for rubber implanted for 300 days, the tensile strength, extensibility and cross-linking density being reduced by 10%, 23% and 20% respectively. On the other hand, no change in the notched fracture stress was observed, even after 300 days of implantation. Preliminary experiments after various preparative

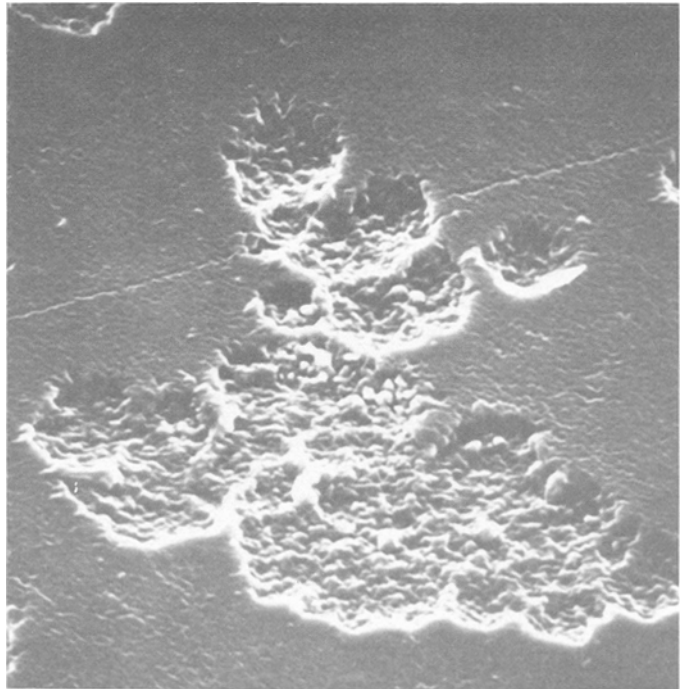


Figure 8 Stereoscan of the surface of silicone rubber after removal of the deposit (X 3900).

methods have shown that these had no deleterious effects on the rubber, so that all observed changes in properties must have been caused by the interaction between the material and the biological environment. The reduction in properties was considerably higher than reported by Swanson and Le Beau [14] who measured a reduction of 8% in the tensile strength and 15% in the extensibility after two years of subcutaneous implantation in beagle dogs, and by Leininger [13] who reported an insignificant change in tensile strength and extensibility after 17 months implantation in mongrel dogs. All samples increased in weight during the implantation period and this was attributed to lipid absorption. The amount of lipid absorption rose over the first 100 days of implantation to 0.5% and thereafter remained constant to at least 300 days of implantation. Similarly silicone rubber immersed in the lipid solution showed stabilization of lipid absorption at 0.6%. Although lipid absorption *in vivo* reached equilibrium after 100 days of implantation, no changes in physical properties occurred until 300 days after implantation. In comparison the *in vitro* specimens of silicone rubber which contained a similar amount of lipids after immersion for nine months as the 300 days implant, showed no change in properties. These results suggest that a small amount of absorbed lipid is unlikely to have caused the observed changes in the properties of the silicone rubber.

Although it is generally known that a certain amount of calcification occurs around scar tissue, it is surprising that the presence of a strongly adhering deposit on the surface of implanted silicone rubbers, containing large quantities of calcium and phosphorous, has not previously been reported. It may be that its presence has not been noticed because generally the surfaces of the silicone rubber implants have not been smooth enough to make these deposits visible to the naked eye, whereas the transparency of the implants used in this laboratory made for easy recognition of the deposit. Other possibilities are either that this calcification process is peculiar to guinea pigs or that it is more pronounced in guinea pigs. Since the authors have not implanted silicone rubber in other species of animals, it is not possible to say conclusively that the calcification process will always occur. Neither is it known whether this deposition becomes progressively worse the longer the implantation time. This is an important point since it would have major implications for many

prosthetic applications such as, for example, in plastic surgery. It is interesting to note that the deposit on the surface of the silicone rubber became very pronounced after 300 days of implantation and this coincided with the drastic reductions in properties. SEM studies of surfaces of the implanted material revealed that a gradual attack of the elastomer took place resulting in deep pits beneath the deposits. Both the tensile strength and extensibility of the rubber are highly sensitive to the presence of surface flaws [15] and we suppose that the reduction in properties may be a consequence of this pitting.

The presence of a deposit on the surface would also affect the measurement of cross-linking density because it would make a contribution to the stiffness. It is significant that no change in the notched fracture stress could be observed. The measurement of this property involves the creation of new surfaces by artificially introducing a notch. This property of the elastomer is therefore independent of the presence or absence of naturally occurring surface flaws, and this result reinforces the suggestion that the reduction in properties was caused neither by molecular changes in the silicone rubber nor by the absorption of lipids, but by surface damage.

9. Conclusions

It has been shown that silicone rubber must be cured under strictly controlled conditions for the elastomer to achieve optimum properties. Residual catalyst reaction products and uncross-linked polymer can easily be removed without causing detrimental changes in the properties. Subcutaneous implantation in guinea pigs resulted in degradation of the rubber, probably as a result of the adsorption of a calcific surface deposit not previously observed which causes a substantial alteration in the surface character. It is not as yet understood what form this degradation process takes and further investigations are being undertaken to determine its cause and effects.

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