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Improved materials for blood-contacting applications: blends of sulphonated and non-sulphonated polyurethanes

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Propyl sulphonate groups were grafted on to the urethane nitrogens of Pellethane 2363-80A at three levels: 1.2, 14, and 50%. Blends with an effective level of 1.2 and 14% were made by blending the 14 and 50% sulphonated polyurethanes with the unsubstituted material. Tensile testing was performed on the materials in both their dry and hydrated state. The blend materials exhibited a small improvement in tensile strength over their bulk analogues. Dynamic contact angle and X-ray photoelectron spectroscopy (XPS) showed an enrichment of sulphonate groups at the surface of the blend materials compared to bulk samples of the same overall composition. Canine *ex vivo* shunt experiments revealed fewer platelets adherent and less platelet spreading on the blend materials than on the bulk materials with the same level of sulphonation. This suggests that sulphonated polyurethanes can be developed that have improved blood compatibility while maintaining good physical properties in an aqueous environment.

1. Introduction

Polyurethane block copolymers have gained acceptance in the biomedical field since they were first proposed as biomaterials by Boretos and Pierce in 1967 [1]. They have been suggested for use in blood-contacting applications due to their excellent physical properties and relatively good blood compatibility [2]. Improvement in the blood compatibility of the materials has been sought to allow their use in more demanding blood-contacting situations such as small diameter vascular grafts, blood pumps, and the artificial heart.

One method of improving the blood compatibility of polyurethanes is to incorporate ionic groups on to the polymer backbone. This was motivated by other investigations of the effect of ionic groups on platelet reactivity and coagulation action [3–5]. Cooper and co-workers have found that the blood compatibility of polyurethanes was improved by using a bimolecular nucleophilic substitution reaction to graft propyl sulphonate groups on to the urethane nitrogen of polyurethanes or by using a *N*,*N*-bis(2-hydroxyethyl)-2-aminoethanesulphonic acid (BES) chain extender. Brash *et al.* [6] observed similar behaviour by using a 4,4′-diamino 2,2′ biphenyl-disulphonic acid chain extender. These polymers were highly hydrophilic, had low platelet deposition, but had unusually high fibrinogen deposition levels [7–9]. A specific interaction between fibrinogen and the sulphonate groups was hypothesized to take place [10, 11]. The platelets that did adhere to the surface exhibited minimal spreading.

Although sulphonated polyurethanes dramatically increase the blood compatibility of polyurethanes, they are unsuitable, in their present form, for use as vascular grafts. The sulphonated polyurethanes are highly water-absorptive. At high levels of sulphonation, the polymers become water soluble. At lower levels, while not water soluble, the sulphonated polymers become hydrogels with a large loss of their tensile properties.

In this paper, sulphonated polyurethane blends were made from highly sulphonated polyurethanes and the unsubstituted base polyurethane. It was hypothesized that the SO_3^- groups from the highly sulphonated polymer component would be expressed at the surface of the hydrated polymer, thus giving the blend the excellent blood compatibility of the sulphonated polyurethanes. The bulk of the blend would be composed primarily of the unsubstituted polyurethane, which would maintain the hydrated polymer's good mechanical properties.

2. Materials and methods

2.1. Synthesis

A commercial polyetherurethane (Pell), Pellethane 2363-80A from Dow Chemical Inc. was provided by Medtronic, Inc. The hard segment of Pellethane is composed of methylene diphenylene diisocyanate (MDI) and butane diol (BD), while the soft segment is composed of poly(tetramethyleneoxide) (PTMO). The polyurethane was extracted with toluene for 48 h to

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remove some of the low molecular mass extrusion waxes. The sulphonation reaction has been previously described [8]. The Pell was dissolved in dimethylacetamide (DMAc) and cooled to ~ 0 °C. Sodium hydride was added and allowed to react with the polyurethane to abstract a fraction of the urethane hydrogens from the polymer. Finally, propane sultone was added. A bimolecular nucleophilic substitution reaction took place resulting in a propyl-sulphonate grafted polymer.

Polyurethanes containing three degrees of sulphonation based on the fraction of the urethane nitrogens grafted were synthesized. The levels of substitution were 1.2, 14, and 50% (1.2 Bulk, 14 Bulk, and 50 Bulk, respectively). A polymer with an effective substitution level of 14% was made by blending a 50% sulphonated polymer with unsubstituted Pellethane (14B(50)). Likewise, two polymers with an approximate substitution level of 1.2% were made by blending either a 14 or 50% sulphonated polymer with the unsubstituted Pellethane (1.2B(14) and 1.2B(50)). The nomenclature and levels of sulphonation of the polymers are summarized in Table I.

2.2. Bulk characterization

All samples were sent to Galbraith Laboratories (Knoxville, TN, USA) for elemental analysis to determine the level of propyl sulphonate substitution.

Films ~ 0.2 mm thick were spin-cast from solution. These films were used for water absorption, tensile testing, and dynamic mechanical analysis.

Spin-cast films were weighed and put in distilled water for 24 h to measure their water absorption. The films were reweighed after removing from the water.

Uniaxial tensile testing was performed on an Instron Table Model testing device. Samples were stamped out with an ASTM D1708 tensile die from the spin-cast films. The extension rate was 1.25 cm min^{-1} (0.5 in min^{-1}) (57% min^{-1}). Samples were tested in both their dry and hydrated states. The hydrated samples were immersed in water for at least 24 h before the test. Dry samples were dried under vacuum for at least 24 h before testing. Three separate tensile specimens were used for each material and condition.

Dynamic mechanical analysis was done by using a Rheometrics RSA-II testing device. The temperature range of the tests was from − 150 to 250 °C, or until the sample became too compliant to test. The test frequency was 100 rad s^{-1} (16 Hz).

TABLE I Water absorption and sulphonation levels of the polyurethane blends

Material	Water absorption (%)	Sulphonation (%)
Pell	1.7	0.0
1.2 Bulk	1.9	1.2
1.2B(14)	2.7	1.7
1.2B(50)	1.1	2.4
14 Bulk	36.1	14.4
14B(50)	29.5	14.6
50 Bulk	853.4	50.4

2.3. Surface characterization

Glass cover slides were coated with the polymers. A Cahn surface force analyser was used to perform the dynamic contact angle measurements. Two immersion cycles were done for each slide. Contact angles were based on the average of the data from five separate slides for each material.

The inner lumen of 3 mm i.d. polyethylene tubing was oxidized with a mixture of chromic and sulphuric acid. The oxidized tubing was then filled with 10% solutions of the polymers. The polymer solutions were drained from the tubing after ~ 2 h. The coated tubes were dried under nitrogen at room temperature for seven days and then under vacuum at 50 °C for at least 48 h. The tubing was used for X-ray photoelectron spectroscopy (XPS) analysis and for blood-contacting experiments.

Coated tubing was split in thirds for XPS analysis. XPS spectra were obtained by using a Physical Electronics PHI 5400 spectrometer with a 300 W, 15 kV magnesium anode. The emission angle of the photoelectrons was 45°. The relative atomic percentage of each element at the surface was estimated from peak areas by using the atomic sensitivity factors specific for the PHI 5400.

2.4. Blood compatibility

The blood-contacting properties of the series of polyurethanes were evaluated using the canine *ex vivo* series shunt experiment which has been previously described [7].

Adult mongrel dogs were selected after hematological screening. They were injected with autologous ^{111}In-labelled platelets and ^{125}I-labelled fibrinogen. No anticoagulants were used in the procedure. Each shunt contained three replicates of each material coated on to the inner lumen of polyethylene tubing. The shunts were filled with sterile, degassed phosphate buffered saline (PBS) solution (pH 7.4) and hydrated overnight at 4 °C. Shunts were run for 1, 2, 5, 10, 15, 20, 25, 30, 45, and 60 min of blood contact. Three separate surgeries were performed.

The blood flow was continuously monitored by using an electromagnetic flow probe. The initial flow rate was controlled at 280 ± 20 ml min^{-1}. Blood samples were collected hourly to determine bulk radioactivity, platelet and fibrinogen concentration, hematocrit, blood gas analysis and hematological function tests.

Blood flow was stopped after the appropriate blood-contacting interval and the shunts were flushed with Tyrodes buffer at a flow rate of approximately 60 ml min^{-1}. Immediately following flushing and detachment from the canine, the shunts were fixed with 2% glutaraldehyde. The test sections were subdivided into sections for gamma counting and scanning electron microscopy (SEM).

The SEM tubing sections were serially dehydrated in ethanol–water solutions, dried by using the critical point method, mounted and sputter coated with gold for examination in a Jeol-JSM 35C SEM using an accelerating voltage of 15 kV.

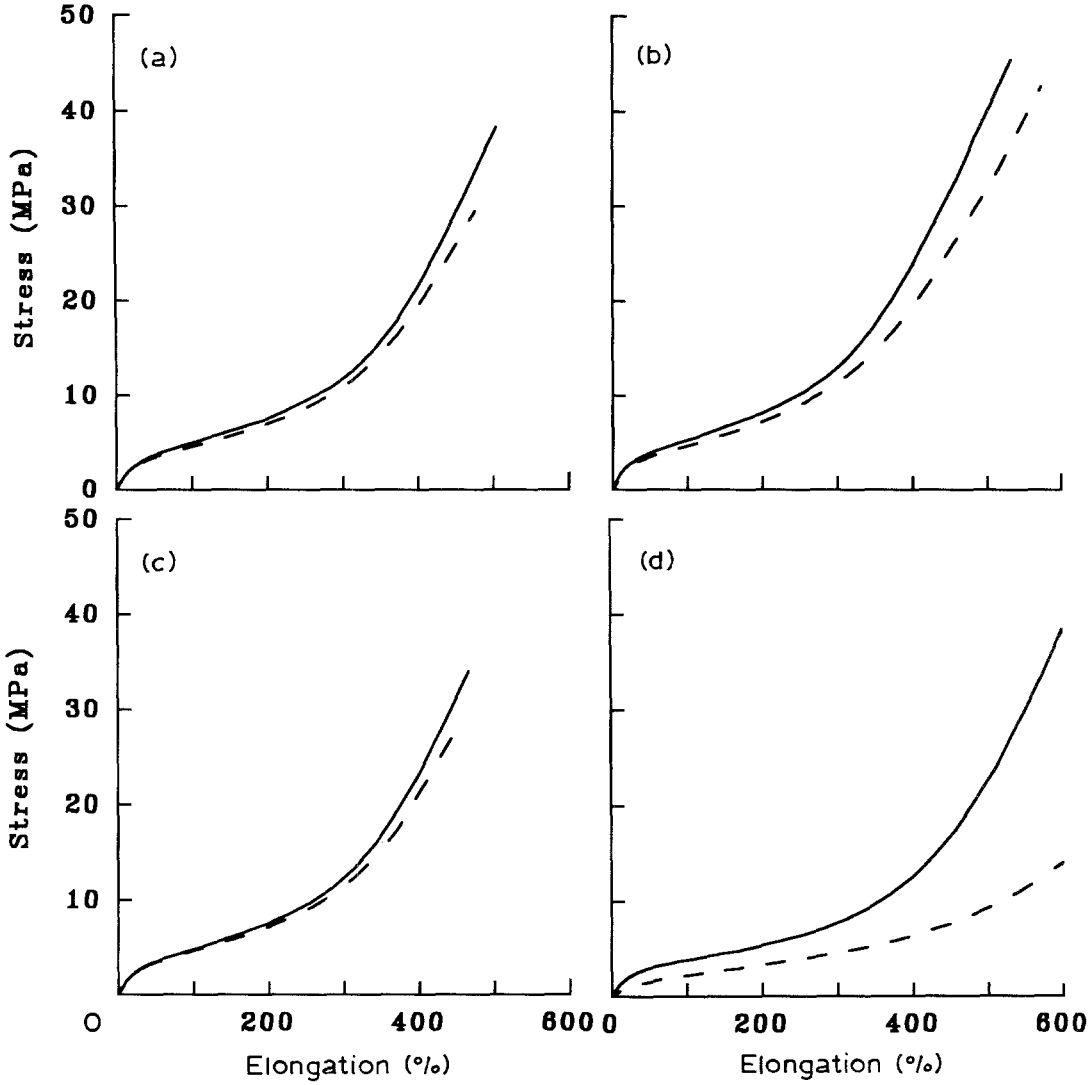


Figure 1 Stress–strain curves for (a) Pell, (b) 1.2 Bulk, (c) 1.2B(14), and (d) 14 Bulk; in the (——) dry and (– –) hydrated states.

TABLE II Tensile testing results: (T) toughness, (σ) ultimate tensile strength, (ε) ultimate elongation, (E) Young's modulus

Material	T_{dry} (J cm^{-3})	T_{hyd} (J cm^{-3})	ΔT (%)	σ_{dry} (MPa)	σ_{hyd} (MPa)	$\Delta\sigma$ (%)	ε_{dry} (%)	ε_{hyd} (%)	$\Delta\varepsilon$ (%)	E_{dry} (MPa)	E_{hyd} (MPa)	ΔE (%)
Pell	66.0	51.4	− 22.1	38.2	29.4	− 23.0	505	477	− 5.5	13.1	14.2	. 8.4
1.2 Bulk	83.4	85.5	2.5	45.4	42.6	− 6.2	531	572	7.7	16.3	11.9	− 27.0
1.2B(14)	44.3	46.3	4.5	34.0	27.8	− 18.2	466	450	− 3.4	11.6	14.2	22.4
1.2B(50)	80.1	66.1	− 17.5	47.3	38.8	− 18.0	503	492	− 2.2	17.9	15.8	− 11.7
14 Bulk	72.8	32.8	− 54.9	39.2	14.1	− 64.0	605	602	− 0.5	11.9	4.8	− 59.7
14B(50)	68.5	39.1	− 42.9	32.8	19.8	− 39.6	530	550	3.8	24.6	8.9	− 63.9
50 Bulk	101.2	1.2	− 98.8	37.3	0.3	− 99.2	621	993	59.9	94.5	0.04	− 99.9

3. Results and discussion

3.1. Bulk characterization

The levels of sulphonation for the polymers and their water absorption values are shown in Table I. The 50% sulphonated bulk polymer absorbed over 8.5 times its weight in water and became very soft. The blends and their bulk counterparts absorbed water in amounts dependent on the overall degree of sulphonation.

Stress–strain curves for Pell, 1.2 Bulk, 1.2B(14), and 14 Bulk of both the dry and hydrated samples are shown in Fig. 1. The results of the tensile tests are summarized in Table II. Toughness, which is defined as the area under the stress–strain curve and has units of energy per unit volume, is shown for the polymers before and after hydration. The ultimate stress, σ_B; ultimate elongation, ε_B; and modulus, E are also shown for the dry and hydrated states. A Student t-test was performed on the data and significant differences are noted below at the 95% confidence level.

Upon hydration, decreases in toughness occurred in the higher (14 and 50%) sulphonated polyurethanes for both the bulk and blend. The ultimate tensile strength showed decreases for all of the polyurethanes except for the 1.2 Bulk and 1.2B(14). The ultimate elongation changed for the 50 Bulk, which showed a large increase after hydration.

When the blends and the corresponding bulk polyurethanes were compared, it was found that the 1.2B(14) had lower mechanical properties in both the

dry and hydrated states than the 1.2 Bulk. The 1.2B (50) had a lower dry value of ε_B than the 1.2 Bulk sample. A comparison of the two 1.2% blends revealed that the 1.2B(14) had lower tensile properties in the dry state than the 1.2B(50). These differences became less and in fact were not statistically significant after hydration.

The 14B(50) sample had a lower ε_B than the 14 Bulk in both the dry and hydrated state although the 14 Bulk ε_B decreased after hydration while the 14B(50) ε_B increased. After hydration, 14B(50) had a greater σ_B than the bulk analogue. This suggests that, upon hydration, the blend does not lose its tensile properties as much as the bulk sulphonated polyurethane.

The 1.2% sulphonated polymers maintained their tensile properties in water better than the 14% sulphonated polymers. This can be attributed to the lower total sulphonate content of the 1.2% polymers.

Dynamic mechanical analysis spectra of Pell, 14B(50), and 50 Bulk are shown in Fig. 2. The results of the dynamic mechanical analysis are summarized in Table III. The T_g is shown as well as the breadth of the T_g transition. The breadth of the T_g transition is defined as the temperature range through which the T_g transition takes place. The Pell has the highest T_g at $-31\,^{\circ}C$. As the sulphonation level increases, the T_g generally decreases, down to $-54.7\,^{\circ}C$ for 50 Bulk. This is caused by an increased driving force for microphase separation due to the sulphonation of the hard segment [8]. As a result, less hard segments are miscible with the hydrophobic polyether soft segment component of the polyurethane, allowing the PTMO to approach more closely the homopolymer value of $-84\,^{\circ}C$ [12]. There is a $5\,^{\circ}C$ difference between the T_g of the 1.2B(50) and the other 1.2% sulphonated polyurethanes. This could be due to a greater degree of phase separation due to the highly sulphonated part of the blend. All of the 1.2% sulphonated polyurethanes and the Pellethane have about the same breadth of their respective T_gs. The 14B(50) sample has a higher T_g than the 14 Bulk as well as a slightly narrower T_g transition region.

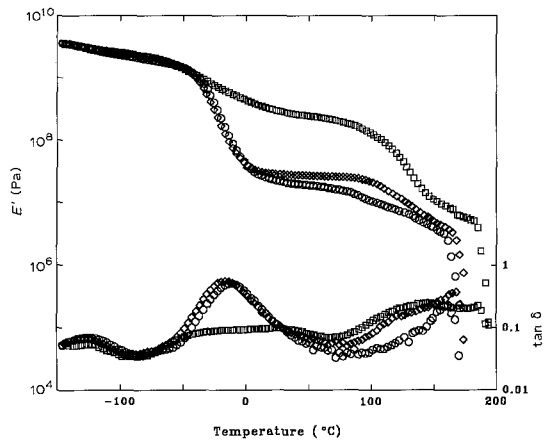


Figure 2 Dynamic mechanical analysis spectra of Pell (○), 14B(50) (◇), and 50 Bulk (□).

3.2. Surface characterization

Fig. 3 shows the results of the dynamic contact angle measurements. Both the advancing and receding contact angles are shown. As the sulphonation level increases, the advancing angle generally increases, while the receding angle decreases. This is in agreement with previous work [13]. The sulphonate groups orient away from the air interface due to their polar nature. Once in the water, the groups rearrange towards the polymer–water interface, resulting in a more hydrophilic surface.

All of the blends had a significantly ($p > 95\%$) lower receding contact angle than their bulk analogues. These receding angles were closer to the values of the sulphonated component that makes up the blend. This suggests that there has been some enrichment of the sulphonated component at the surface of the polymer over that of the bulk polymer.

Table IV shows the elemental concentration ratios of nitrogen to carbon and sulphur to carbon for both the bulk and surface of the polymers. The bulk concentration was determined by elemental analysis and the surface concentration by XPS. The nitrogen/carbon (N/C) ratio shows that there is an enrichment of the soft segment at the surface of the tubing in vacuum for all the materials since nitrogen is found

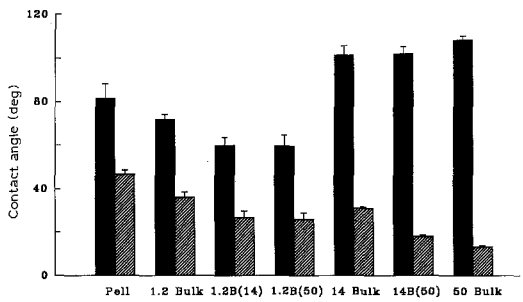


Figure 3 Dynamic contact angle results for sulphonated polyurethanes; (■) advancing angle, (▨) receding angle.

TABLE III Dynamic mechanical analysis results

Material	T_g (°C)	Breadth of T_g (°C)
Pell	− 31.0	39.1
1.2 Bulk	− 34.2	38.5
1.2B(14)	− 34.1	39.2
1.2B(50)	− 39.3	37.7
14 Bulk	− 39.4	45.8
14B(50)	− 34.0	42.3
50 Bulk	− 54.7	74.5

TABLE IV Bulk and surface elemental ratios

Materials	Bulk N/C	Surface N/C	Bulk S/C	Surface S/C
Pell	0.0570	0.0382	0.0000	0.0026
1.2 Bulk	0.0588	0.0326	0.0016	0.0030
1.2B(14)	0.0582	0.0300	0.0023	0.0115
1.2B(50)	0.0543	0.0316	0.0030	0.0043
14 Bulk	0.0592	0.0275	0.0195	0.0071
14B(50)	0.0573	0.0331	0.0191	0.0088
50 Bulk	0.0495	0.0303	0.0571	0.0164

exclusively in the urethane linkages of the hard segment. The sulphur/carbon (S/C) ratio shows an enrichment of the sulphur at the surface for the 1.2% level of sulphonation while there is a surface depletion of the sulphur at the higher levels of sulphonation. The 1.2B(14) material had a very high level of sulphonation at its surface, rivalling that at the surface of the 50 Bulk. The XPS data show that all of the blends had higher levels of sulphur at the surface than their bulk analogues.

3.3. Blood compatibility

Fig. 4 shows the platelet deposition profiles of the unsubstituted Pell and the bulk sulphonated polyurethanes. At low times, the 14 Bulk had approximately an order of magnitude lower level of platelet deposition than the Pell or the 1.2 Bulk. The 50 Bulk was about an order of magnitude below the 14 Bulk. At long times (> 30 min), the 14 Bulk and 50 Bulk had similar levels of platelet deposition, which were about a factor of 10 less than the Pell or 1.2 Bulk.

The fibrinogen deposition profiles, which are shown in Fig. 5, were interesting in that the highly sulphonated polymers did not show dramatically higher fibrinogen deposition than the base Pellethane [7]. The 50 Bulk had much higher fibrinogen deposition than the other materials at short times (< 10 min), but the level of deposition remained fairly constant for the length of the experiment. Pell and 1.2 Bulk had fibrinogen deposition profiles that were very close to each other, while 14 Bulk had the lowest fibrinogen deposition of all the materials after 10 min.

Fig. 6 shows the platelet deposition profiles of the 1.2% sulphonated polyurethanes. There was no apparent improvement in platelet deposition with the 1.2B(50) material compared to the 1.2 Bulk. However, the 1.2B(14) showed very little deposition after 2 min, and at times greater than 30 min, showed an order of magnitude less platelet deposition than the other 1.2% sulphonated polymers.

The fibrinogen deposition profiles for 1.2 Bulk and 1.2B(50) were similar to the data shown in Fig. 5 for the 1.2 Bulk and are not shown. The profile of 1.2B(14) was more erratic, suggesting that some thromboembolization was taking place.

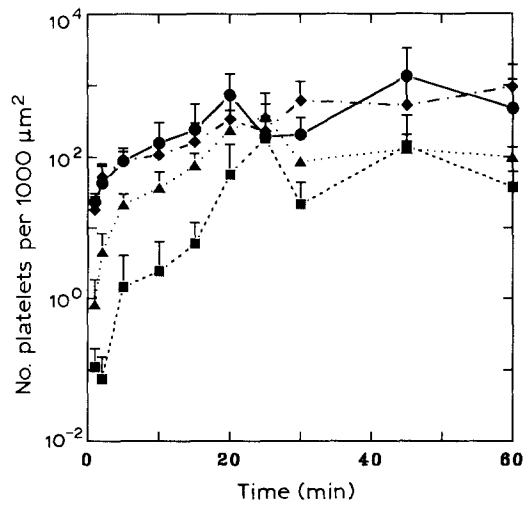


Figure 4 Platelet deposition profiles for Pell (●), 1.2 Bulk (◆), 14 Bulk (▲), and 50 Bulk (■).

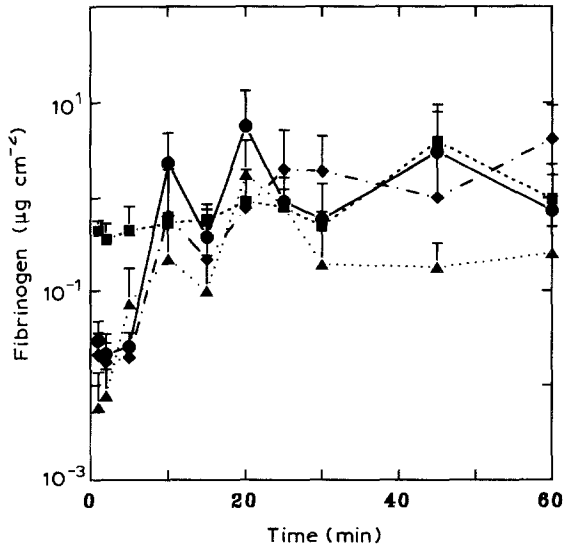


Figure 5 Fibrinogen deposition profiles for Pell (●), 1.2 Bulk (◆), 14 Bulk (▲), and 50 Bulk (■).

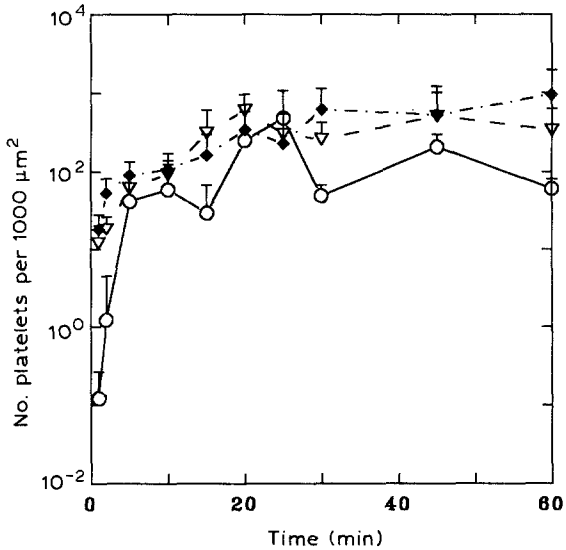


Figure 6 Platelet deposition profiles for 1.2 Bulk (▲), 1.2B(14) (○), and 1.2B(50) (▽).

The platelet deposition profiles for the 14% sulphonated polyurethanes are shown in Fig. 7. There was very little difference between the two materials. The fibrinogen deposition for the 14B(50) material was similar to the data shown in Fig. 5 for the 14 Bulk.

The 1.2B(14) platelet deposition profile was very similar to the 14 Bulk profile. Fig. 8 shows the superposition of the 1.2B(14) and 14 Bulk platelet deposition profiles. This suggests that the 1.2B(14) blend polymer is exhibiting an enrichment of the less thrombogenic 14% sulphonated polyurethane at the surface.

Fig. 9a, b shows scanning electron micrographs of the Pellethane tubing after 5 and 60 min exposure to blood. At 5 min, there were a large number of platelets adherent to the surface, with a large degree of platelet spreading. After 60 min, large numbers of white cells had adhered, platelets were completely spread, and fibrin strands had started to form.

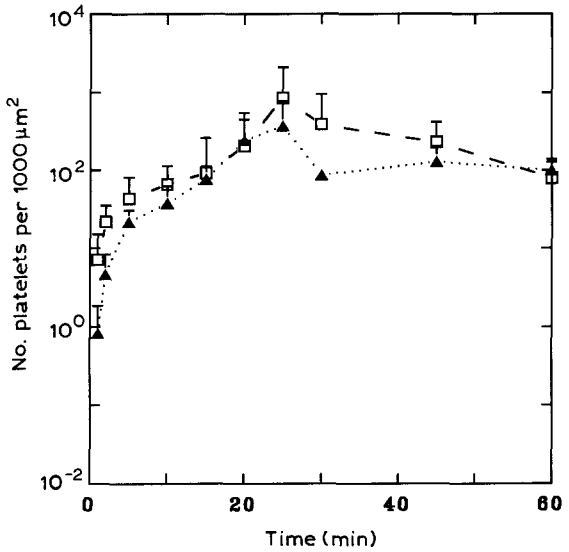


Figure 7 Platelet deposition profiles for 14 Bulk (▲) and 14B(50) (□).

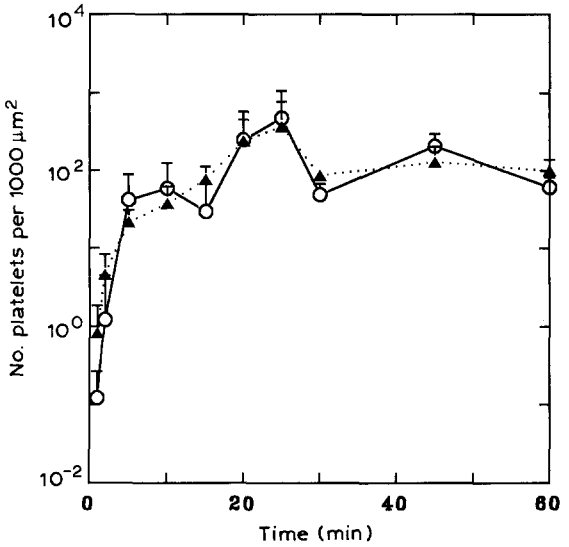


Figure 8 Platelet deposition profiles for 1.2B(14) (○) and 14 Bulk (▲).

SEMs of 1.2 Bulk after 5 and 60 min are shown in Fig. 10a, b. There were many platelets on the surface after 5 min, but they were not as spread as the ones on the Pellethane. After 60 min, the platelets had not completely spread, in marked contrast to the platelets on the Pellethane.

The 1.2B(14) material showed far less platelet deposition than the 1.2 Bulk material as shown in Fig. 11a, b. At 5 min, there were very few platelets on the surface of the material. This low level of platelet deposition remained until after 15 min. By 60 min, the material had slightly fewer platelets on the surface

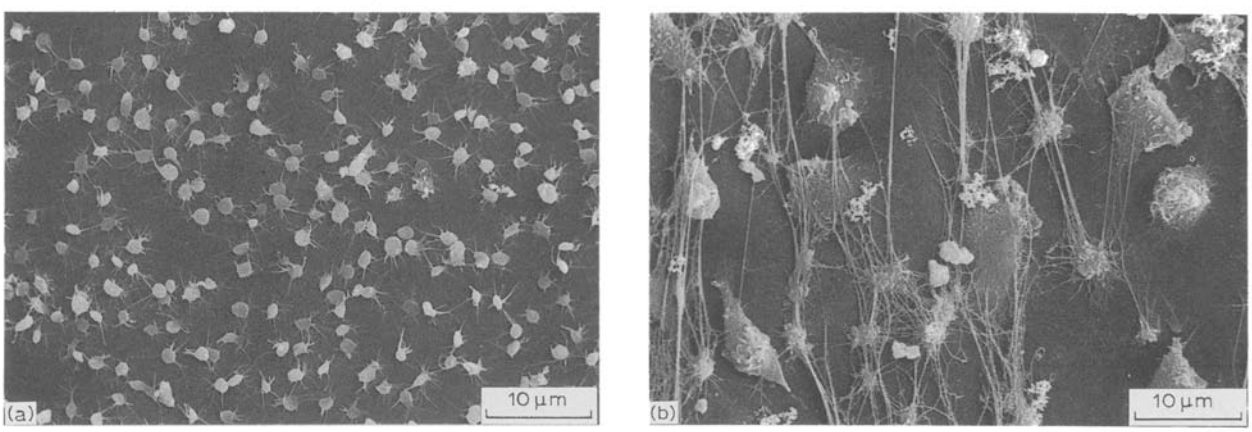


Figure 9 SEM of Pell after (a) 5 min and (b) 60 min.

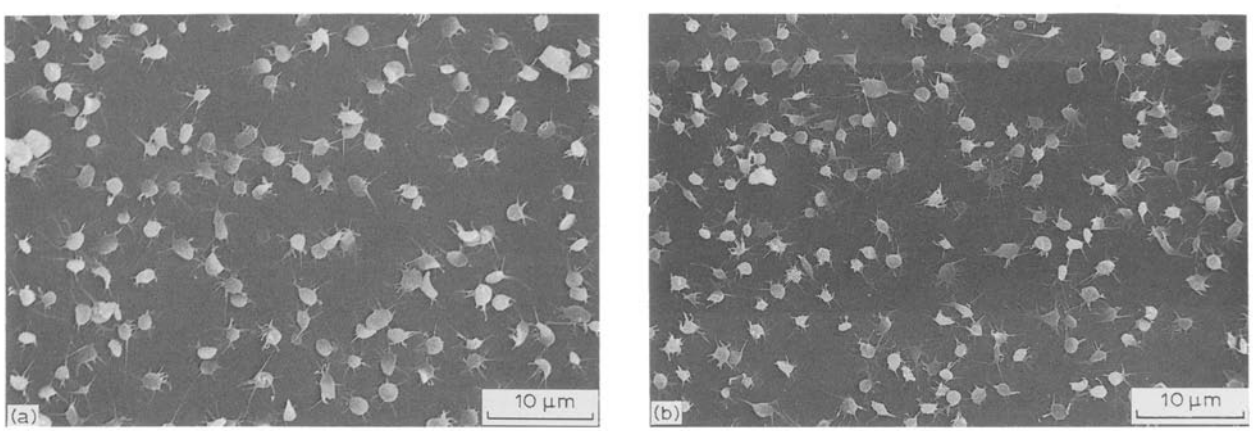


Figure 10 SEM of 1.2 Bulk after (a) 5 min and (b) 60 min.

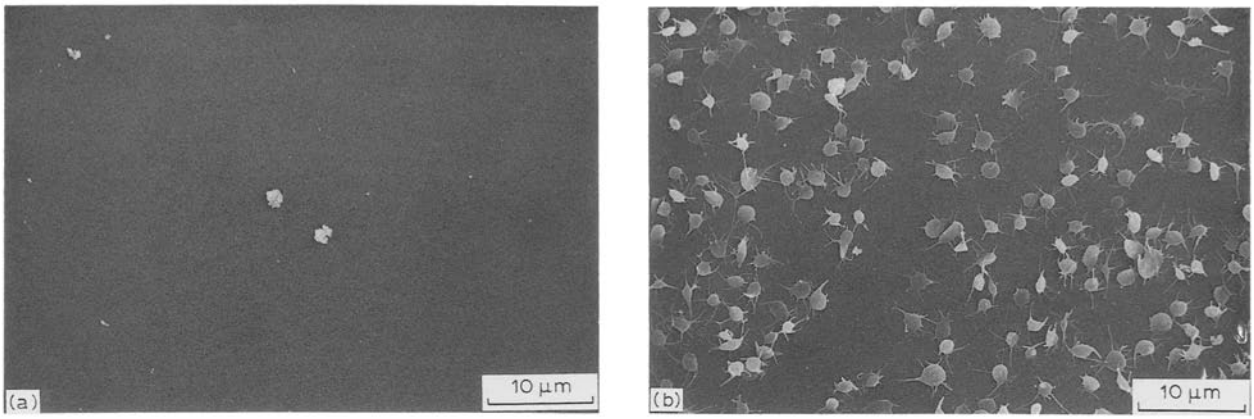


Figure 11 SEM of 1.2B(14) after (a) 5 min and (b) 60 min.

than 1.2 Bulk, and the platelets were also a little less spread.

Fig. 12a, b shows the SEMs for the 1.2B(50) material after 5 and 60 min. The 5 min SEM showed a lower level of platelet deposition than the 1.2 Bulk, but not as low as the 1.2B(14). After 60 min, the level and degree of spreading of the platelets on the 1.2B(50) surface was approximately the same as the 1.2 Bulk.

The SEMs of the platelet deposited on the surface of the 14% materials showed very little difference between them. Fig. 13a, b and Fig. 14a, b show the SEMs of 14 Bulk and 14B(50) at 5 and 60 min, respectively. There did not appear to be any improvement in the number of platelets adhering to the surface of the blend materials. This corresponds to the platelet deposition profiles shown in Fig. 7.

Fig. 15a, b shows the SEMs of the 50 Bulk material. At 5 min, there were very few platelets on the surface. Those that had deposited were very round with only slight pseudopod extension. Also seen in Fig. 15a are large bubbles on the surface of the tubing. These bubbles were places where the polymer coating began

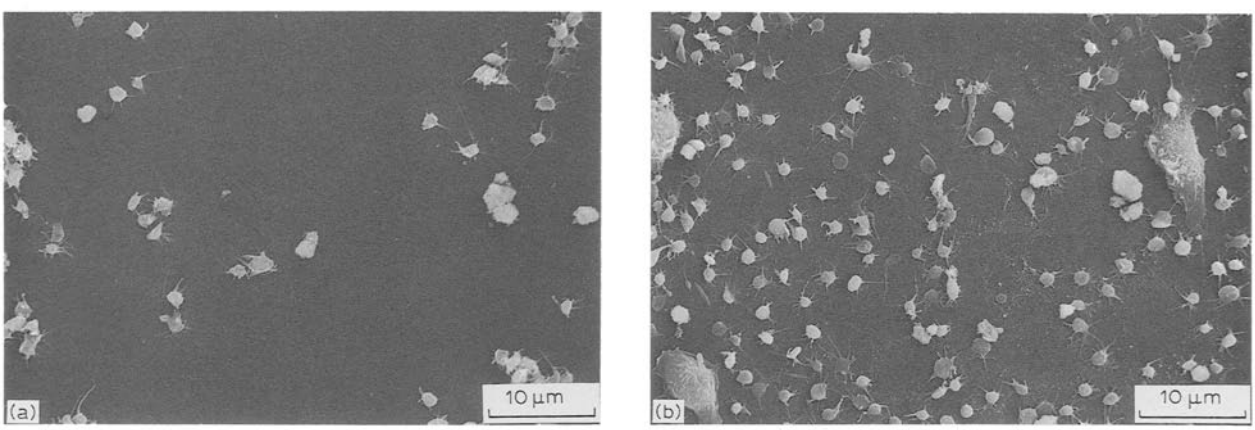


Figure 12 SEM of 1.2B(50) after (a) 5 min and (b) 60 min.

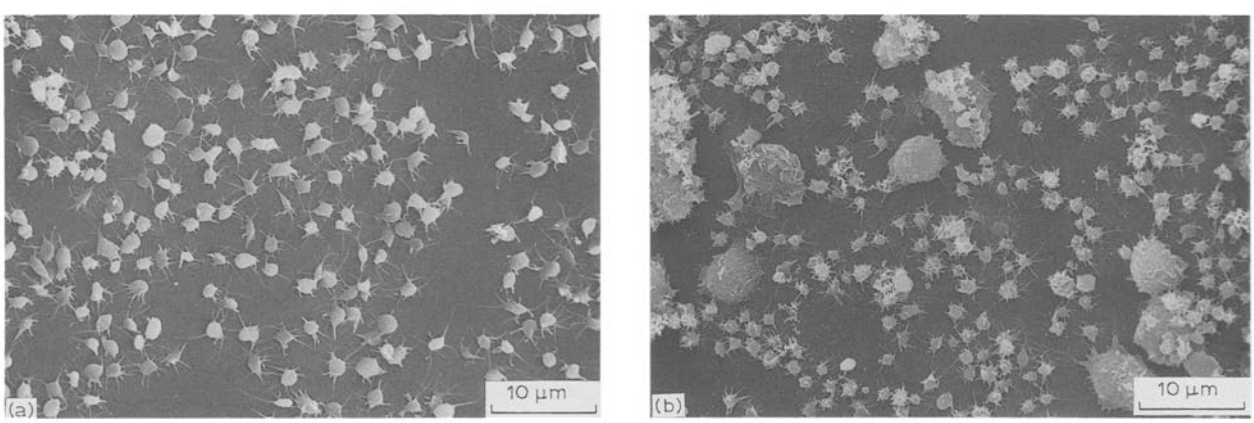
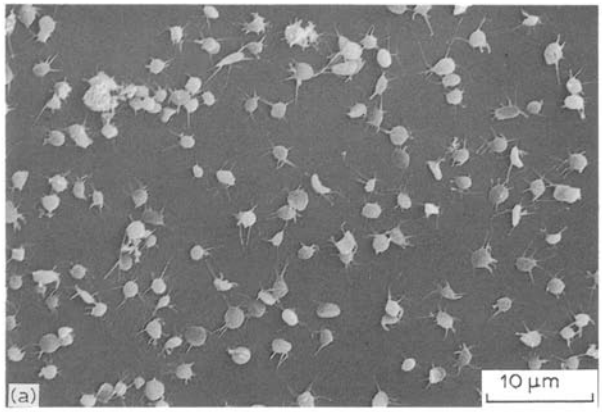


Figure 13 SEM of 14 Bulk after (a) 5 min and (b) 60 min.



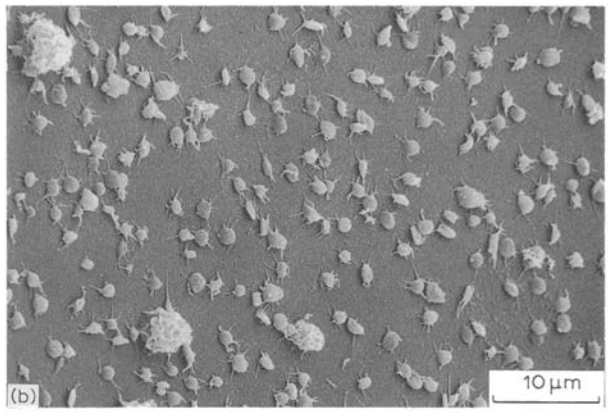
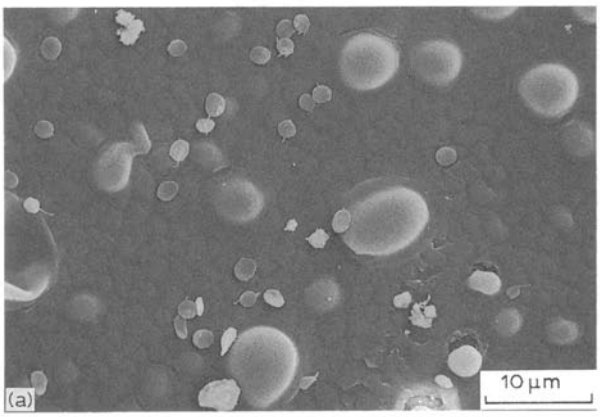


Figure 14 SEM of 14B(50) after (a) 5 min and (b) 60 min.



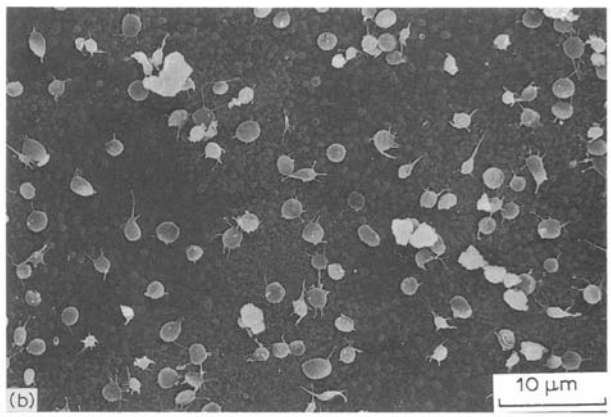


Figure 15 SEM of 50 Bulk after (a) 5 min and (b) 60 min.

to peel off of the oxidized polyethylene tubing due to the swelling of the material in aqueous solution. At 60 min, there were more platelets on the surface, but there was still very little spreading.

The *ex vivo* results demonstrate that there is some enrichment of the sulphonated polyurethanes at the blend surfaces. Not all of the blends showed dramatic improvements in blood compatibility. The 1.2B(50) polymer had very little 50 Bulk polymer blended into it, so that there may not have been enough of the 50 Bulk at the surface of the shunts to influence the deposition profiles greatly. The 1.2B(14) had more of the 14 Bulk blended with it, allowing a more effective enrichment of the tubing surface to take place.

4. Conclusions

Blends of sulphonated and non-sulphonated polyurethanes were made. The blends showed a surface enrichment of the sulphonate group, as evidenced by dynamic contact angle, XPS, as well as by canine *ex vivo* shunt studies. Blended polymers showed little improvement in tensile properties over the bulk analogues when hydrated. However, since there is an enrichment of the sulphonate groups at the surface due to blending, it may be possible to use a lower overall level of sulphonation and maintain the same level of blood compatibility. This lower level of sulphonation would result in better tensile properties in the hydrated state.

Further studies are needed to determine the proper ratio of sulphonated and non-sulphonated materials to achieve both good mechanical properties and blood compatibility. The overall level of sulphonation does not need to be large, but there must be enough of the sulphonated material in the blend so that enrichment at the surface is possible.

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