Polymer Science

Use of porous biodegradable polymer implants in meniscus reconstruction. 1) Preparation of porous biodegradable polyurethanes for the reconstruction of meniscus lesions

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Abstract: Porous biodegradable poly(urethanes) for reconstructing menisci have been prepared using two different combinations of techniques: freeze-drying/salt-leaching and in-situ polymerization/salt-leaching. Using these methods, homogenous porous materials with a controllable and reproducible morphology can be prepared. The materials were made of three different poly(urethanes): a methylenediphenyldiisocyanate-based polyurethane, a lysine diisocyanate-based poly(urethane), and a poly(ε-caprolactone)-based poly(urethane). The compressive stress-strain behavior of the Estane foams was determined. Foams made by the freeze-drying/salt-leaching technique implanted in dogs showed healing and good ingrowth of fibrocartilaginous tissue.

Key words: Porous materials, foams, biodegradable polyurethanes, meniscus reconstruction, freeze-drying, salt leaching.

Introduction

Menisci are very important mobile buffers that distribute the pressure of the upper leg over a larger area of the lower leg and increase the elasticity of the knee joint [1]. Causes leading to damage or injury of the meniscus are multiple, and usually occur when the knee is exposed to excessive demands [2]. Nowadays one of the most frequently performed orthopaedic operations is in the past a total meniscetomy was often performed partial meniscectomy. However, the results of meniscectomy in humans have been disappointing. Follow-up studies [3] show satisfactory results in only 42 % to 68 % of the cases, while Jørgensen et al. [4] found radiographic changes of degeneration in 89 % of the meniscectomy in athletes up to 14.5 years post operatively. Taking these results into account, reconstruction of the meniscus as an alternative has been gaining success.

As early as 1936, it was shown by King [5] that the regenerative response of the meniscus is poor [6]. Healing is limited to lesions in the vascularized peripheral of 10–25 % of the meniscus. Lesions extending to the avascular central part of the meniscus do not heal, probably because they are not exposed to stimulatory factors normally present in blood, such as certain growth factors [7].

To overcome this problem, a connection between the lesion and the synovial lining should be made; this is possible by implanting a porous polymer matrix into an acces channel which has been made between the synovial lining and a longitudinal lesion in the central part of the meniscus [8]. We have shown that repair of meniscus lesions in dogs is possible using a porous biodegradable PU/PLLA matrix. The materials were prepared by dipcoating. Ingrowth of fibrous, fibrocartilaginous tissue, and vessels occurred over a considerable distance starting at the peripheral side of the implants, and signs of repair

could be observed [9]. Due to the positive results of this research, we decided to undertake further studies.

For implantation, the porous materials should fulfill a number of requirements. It has been found that optimum ingrowth of fibrocartilaginous tissue takes place if the pore size is in the range of 200–300 μm [10]. These pores have to be highly interconnected. The tensile strength warrants stability and long-term patency. Compressibility is of great importance, because the nourishment of the cartilage comes from the flow of liquid brought on by compressions and relaxations arising from body movements [11]. Compression movements also seem to stimulate fibroblasts to differentiate into chondrocytes. Porous implants should be compliant, i.e., act as a temporary biodegradable matrix scaffold for ingrowth [12] of fibrocartilaginous tissue into implant and lesion, and leave a healed meniscus. Therefore, the implant should be made of polymers designed to release only non-toxic degradation products. Nothing is known about the required degradation speed.

It is the purpose of this paper to describe different methods of making porous materials that fulfill these requirements. A modified salt-leaching technique combined or not combined with freeze-drying has been used to prepare low-density polymer materials with controllable and reproducible structure and good mechanical properties. Foams are made of three different polymers: a methylenediphenyldiisocyanate-based polyurethane (Estane 5701-F1), a lysine diisocyanate-based polyurethane, and a poly(ε-caprolactone)-based polyurethane. Some of these materials were implanted in dogs.

Experimental

Material and technique

Estane 5701 F1 (Goodrich, Brecksville, Ohio, USA) used for implantation was purified once by precipitation from a 5 % (w/w) polymer solution in dimethylformamide (DMF) into a six-fold volume of ice/water mixture. Dioxane was distilled from sodium. Saccharose and NaCl crystals were sieved to 100–300 μm. NaCl was dried in an oven at 225 °C. Hexamethylenediisocyanate (HDI) was vacuum-distilled before use. Dicumylperoxide (DCP) was recrystallized from methanol. Poly(ε-caprolactone)diol [(PCLdiol) M.W. = 1250] and Poly(e-caprolactone)triol [(PCLtriol) molecular weight MW = 900 (Aldrich Chemical)] were azeotropically dried with benzene.

Poly(ε-caprolactone) diol (MN = 1160; Janssen Chemical, Belgium) was dried under vacuum before use; 1,4-butadiol (Merck) was dried by distillation. The procedure for synthesizing ethyl 2,6-diisocyanatohexanoate (EDI) has been described in a previous publication [13]. EDI was vacuum distilled prior to use.

The materials were freeze-dried in a freeze-drying apparatus connected to a vacuum pump at 0.05 mBar.

PLLA fibers were prepared by a dry-spinning and subsequent hot-drawing of the filaments method.

Compressive stress-strain curves were determined using an Instron (4301) tensile tester (cross-head speed 2 mm per min^{-1}, specimen height about 9 mm, 100 N load cell).

Lysine diisocyanate-based poly(urethane) (LDI-PU): Synthesis

First, 1.0 equivalent poly(ε-caprolactone diol, 2.1 equivalent ethyl 2,6-diisocyanatohexanoate, and 1.0 equivalent 1.4-butanediol were mixed together and degassed at 90 °C. Polymerizations were carried out under nitrogen atmosphere at 90–100 °C for 3 h, using 0.05–0.1 wt. % stannous octoate (Sigma Chemicals, USA) as a catalyst. The resulting polymer was dissolved in DMF, precipitated into a tenfold excess of water, and subsequently dried under vacuum, yielding 95–97 %.

Foam preparation

The foams were made using two different methods: a combination of freeze-drying/salt-leaching techniques and a combination of in-situ polymerization/salt-leaching techniques.

Freeze-drying/salt-leaching

The polymer or prepolymer was dissolved in a solvent. Non-solvent was added to encourage phase separation. An amount of water-soluble crystalline materials of variable particle size (NaCl and saccharose) was added. The mixture was poured into a mould and frozen at −15 °C. Afterwards, the mould was placed in a freeze-drying apparatus connected to a vacuum pump. The co-solvent was removed under reduced pressure (0.05 millibar). Due to endothermic evaporation of the co-solvent and high melting point of the solution, the samples remained frozen so that active cooling was not necessary. Saccharose and NaCl crystals were removed by washing the polymer/crystal mixture with water. Foams were made of three different polymers: Estane, LDI-PU, and a poly (ε-caprolactone)-based poly(urethane) (PCL-PU).

Estane foams: Estane was dissolved in 1,4-dioxane. Water and c-hexane were added as non-solvents. The polymer solution was mixed with saccharose crystals (100–300 μm). Density of the foams was changed by varying the concentration of saccharose crystals.

Crosslinked LDI-PU foams: The polymer was dissolved in 1,4-dioxane. c-Hexane was added as a non-solvent. The polymer solution was mixed with DCP and NaCl crystals (100–300 μm). After freeze-drying, the foam was crosslinked under nitrogen atmosphere for 3/4 h at 150 °C. Afterwards, the crosslinked porous polymer was extracted with chloroform (gel = 90 %).

PCL-PU foam: PCLdiol, PCLtriol, and HDI were dissolved in 1,4-dioxane and mixed with NaCl crystals (50 wt. % 50–90 μm and 50 wt. % 250–300 μm). c-hexane was added as a non-solvent. As a catalyst, 0.1 wt. % stannous octoate was added. After freeze-drying, the mixture was cured under nitrogen atmosphere at 60 °C for 48 h and at 120 °C for 5 h using 0.1 wt. % stannous octoate as catalyst. Afterwards, the foam was extracted with chloroform.

In-situ polymerization/salt-leaching

The prepolymers used were diluted with solvent, to encourage the homogeneity of the prepolymers with the crystals, and were removed by evaporation before curing. The polymer/crystal mixture was washed with water to remove the crystals.

PCL-PU foam: PCLdiol, PCLtriol, and HDI were dissolved in dichloromethane (37 wt. % solution) and mixed with NaCl crystals (50 wt. % 50–90 μm and 50 wt. % 250–300 μm). As a catalyst, 0.1 wt. % stannous octoate was added. Dichloromethane was removed by evaporation at 40 °C. The mixture was cured under nitrogen atmosphere at 60 °C for 48 h and at 120 °C for 5 h using 0.1 wt. % stannous octoate as a catalyst.

Compressibility

Load-compression curves were obtained for a series of Estane foams varying in density φ = 0.174 to 0.288 g/cm [3]. All data presented were obtained at room temperature and at a strain rate of 2 mm/min. Young's modulus and the modulus at 20 % compression of the foams were determined.

Characterizations

An Ubbelohe viscometer (type Oa) was used for determining intrinsic viscosities of LDI-PU in chloroform at 25 °C. Thermal analysis was performed with a Perkin Elmer DSC-7 (scan-speed 10 °C/min.). Characterizations of pore structure in the materials was performed using an ISI-DS scanning electron microscope.

Implant preparation

Estane foams used for implantation were prepared as described above. They were divided into two groups with different microporous structure due to different composition of the cosolvent: 1,4-dioxane/trioxane and 1,4-dioxane/c-hexane/water. Of the implants, made by freeze-drying an Estane solution in 1,4-dioxane/trioxane, 50 % were reinforced with PLLA fibers.

Implantation technique

Foams used for implanation were made of Estane 5701-F1. A series of foams with different microporous structure were implanted. Large T-shaped lesions, occupying 30 % of the meniscus, were made in the mid-portion of the lateral menisci. Prostheses were sutured into place using 3.0 Dexon or mersilene sutures. After operation, the dogs were allowed to walk as soon as possible. The follow-up period varied from 9–56 weeks, and the menisci were studied both morphologically and histologically. Detailed information about the implantation technique has been described in a paper to be published [14].

Results and discussion

We have shown that flexible porous polymer materials can be used for reconstructing meniscus lesions [8]. For the ingrowth of fibrocartilaginous tissue in lesions and implant, the pores of the implant ought to be in the range of 200–300 μm and highly interconnected [10]. In the past, a dipcoating procedure was used [8, 15] and the resulting materials had a laminated structure. In these materials, larger pores were dispersed in a denser matrix with pore sizes up to about 60 μm [16]. Materials induced showed complete repair and ingrowth of fibrocartilaginous tissue and vessels [8]. The micro-porous matrix provides an excellent scaffold for capillary ingrowth. Although dipcoating is a suitable method, the resulting layered structure was inhomogenous, thus, a more controllable and reproducible technique would be preferable.

Several other methods for producing flexible foams with an open-pore structure can be divided into two groups. The first group utilizes blowing-agents [17]. In order to stabilize the structure and to control the pore size, additives (surface-tension depressants) have to be added. The second group utilizes phase separation [18]. During cooling, polymerization of a polymer/prepolymer solution, or adding non-solvent to a polymer solution, phase separation can take place. Removing the solvent results in a porous structure. When the phase-separated system is stable due to crystallization of the polymer out of the polymer-rich phase (eutectic-crystallization) [19] or due to the high Tg of the polymer-rich phase [20], the solvent can be removed by evaporation with no shrinkage of the porous structure. Otherwise, the solvent has to be removed by sublimation (freeze-drying). The system is frozen and the polymer is not able to relax during solvent removal. To prevent the porous structure from shrinking and to avoid the need for adding toxic components, the freeze-drying technique was chosen to prepare the porous materials.

Freeze-drying process

Freeze-drying of a polymer solution is a process in which the solvent is removed by sublimation from the frozen material so that it leaves a porous structure. The experimental process can be described as follows [21]: first, the polymer is dissolved into a solvent system. The solution is then cooled until the solvent is frozen. Next the solvent is sublimated under vacuum resulting in a porous polymer structure.

The density of the resulting porous polymer is determined by concentrating the polymer in solution. The morphology of the foam is determined by phase separation. Phase separation can be divided into

liquid-liquid phase separation (which may occur prior to freezing of the solvent) and liquid-solid phase separation (which occurs when the solvent freezes). Adding a non-solvent to the solution may induce liquid-liquid phase separation [22].

The morphology may be predicted from a phase diagram [20]. At low concentrations, the polymer-rich phase is dispersed in a dilute matrix. At high polymer concentrations, the situation is inverted. During cooling, the solution moves from a homogenous solution to a domain in which phase separation occurs. Phase separation takes place until the solvent is frozen. The final morphology is determined by whether liquid-liquid phase separation occurs before freezing or whether liquid-solid phase separation occurs.

Aubert et al. [22] showed that if liquid-liquid phase separation occurs, the solution becomes cloudy before freezing and the resulting foam is isotropic and has small cell sizes (e.g., 10 μm). If only liquid-solid phase separation occurs, then the resulting foam is anisotropic with a morphology depending on the crystal shape of the solvent.

The pore sizes can be regulated by the polymer concentration and the quench rate. An increase in the quench rate may increase the nucleation rate or lead to spinodal decomposition. It decreases the time for phase separation and results in smaller pores. Foams made by the freeze-drying technique have controllable and reproducible porous structure.

The systems used in this paper are poly(urethanes) dissolved in a mixture of 1,4-dioxane and water and/or c-hexane.

Foam morphology

Figure 1 shows a scanning electron micrograph of a freeze-dried foam made from a 20 wt. % polyesterurethane (Estane 5701-F1) solution in 1,4-dioxane/water (84/14 w/w). The solution was frozen at –15°C. The structure is basically isotropic with pore sizes of <50 μm. It is due to a combination of liquid-liquid phase separation and liquid-solid phase separation. This agrees with the observation that the solution becomes cloudy before freezing.

Figure 2 shows a detailed scanning electron micrograph of the same foam. The pores are interconnected. The interconnected pores reach sizes in the range of 50 μm and are too small to fulfill the requirement for ingrowth of fibrocartilaginous tissue. The pore size can be controlled by varying the polymer concentration and the quenching rate. Although the pore sizes can be increased to about 200 μm by lowering the polymer concentration and/or the quenching rate, such foams do not have sufficient strength for surgical applications.

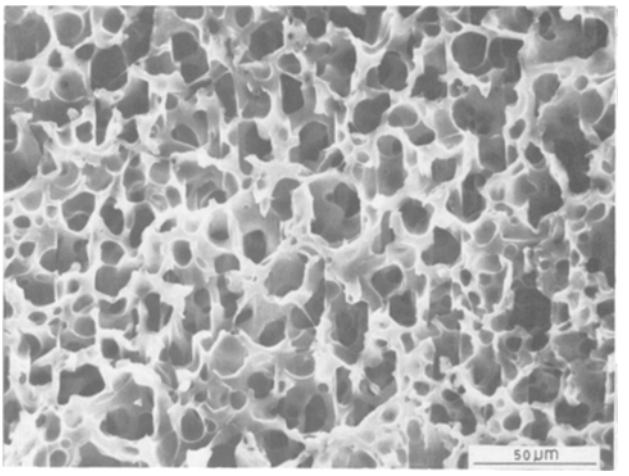

Fig. 1. Scanning electron micrograph of a foam made by freeze-drying a 20 wt. % PU solution in 1,4-dioxane/water (84/14 w/w)

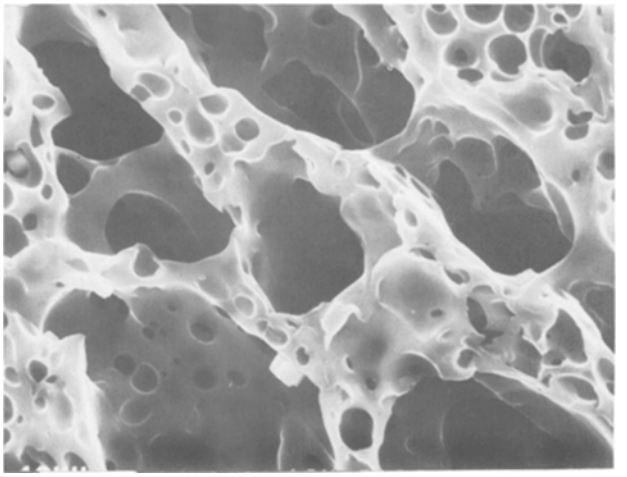

Fig. 2. Detailed scanning electron micrograph of the foam presented in Fig. 1

To overcome this problem, a modified combination of freeze-drying and salt-leaching was used. The polymer solution was mixed with saccharose crystals (100–300 μm). After freeze-drying this mixture, the saccharose crystals were washed out in water, leaving the macroporous structure.

Figure 3 shows a scanning electron micrograph of a freeze-dried foam made from a 20 wt. % PU (Estane

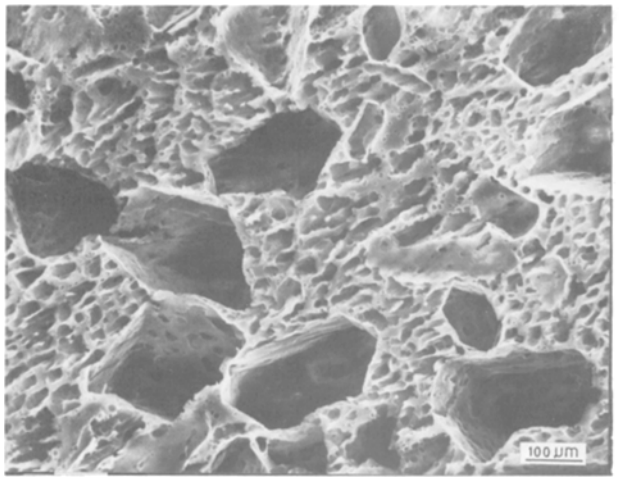

Fig. 3. Scanning electron micrograph of a foam made by freeze-drying a 20 wt. % PU solution in 1,4-dioxane/c-hexane (79/21 w/w) mixed with saccharose crystals (100–300 µm)

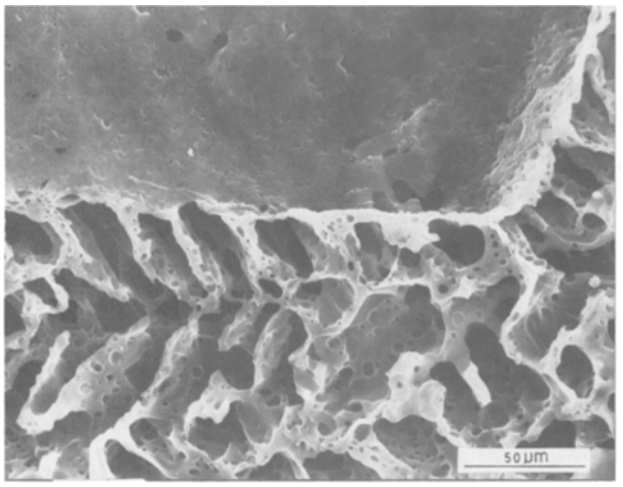

Fig. 4. Detailed scanning electron micrograph of the foam presented in Fig. 3

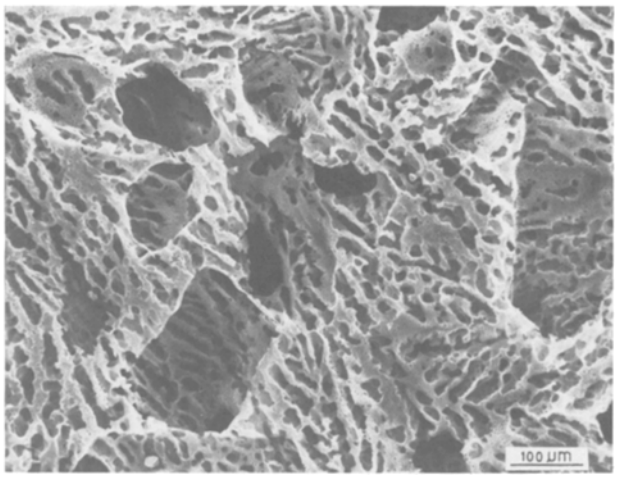

Fig. 5. Scanning electron micrograph of a foam made by freeze-drying a 20 wt. % PU solution in 1,4-dioxane/c-hexane/water (78/18/4 w/w/w)

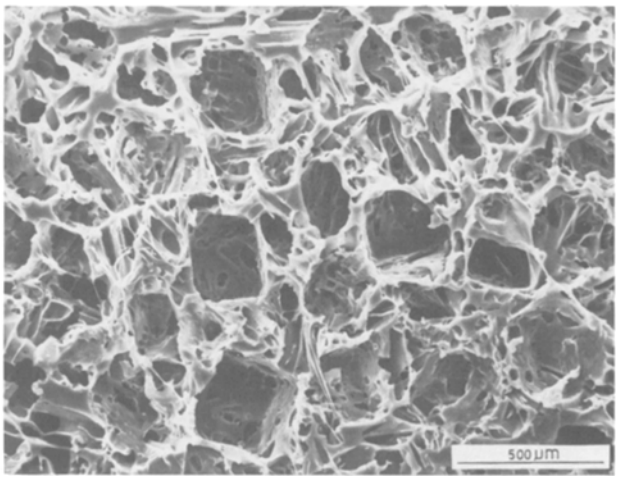

Fig. 6. Scanning electron micrograph of a foam made by freeze-drying a 20 wt. % solution in 1,4-dioxane/trioxane (50/50 w/w) mixed with saccharose crystals (100–300 µm)

5701-F1) solution in 1,4-dioxane/c-hexane (79/21 w/w) mixed with saccharose crystals (100–300 µm). The weight ratio of the polymer solution to the saccharose crystals was 1:1. The structure contains large pores (100–300 µm) and small channel-like pores with diameters of <50 µm. The large pores are due to the dissolution of the saccharose crystals and are connected with the small pores, which arise from the freeze-drying process.

Figure 4 shows a detailed scanning electron micrograph of the foam. Each large pore contains a skin so that the pores are not as well interconnected as they should be to fulfill the requirement of interconnectivity. Better interconnected structure was obtained by adding some water to the PU-co-solvent-sugar mixture. The sugar crystals partially dissolved in the water, resulting in a better connection between large and small pores.

Figure 5 shows a scanning electron micrograph of a freeze-dried foam made from a 20 wt. % PU (Estane 5701-F1) solution in 1,4-dioxane/c-hexane/water (78/18/4 w/w/w) mixed with sugar crystals (100–300 µm). Weight ratio of the polymer solution to the saccharose crystals was 46/54. The large pores are

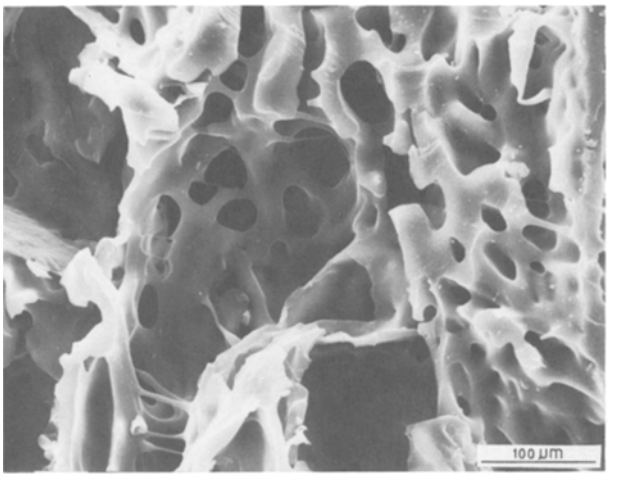

Fig. 7. Scanning electron micrograph of a foam crosslinked with dicumylperoxide, made by freeze-drying a 20 wt. % lysine diisocyanate-based PU solution in 1,4-dioxane/c-hexane (90/10 w/w) mixed with NaCl crystals (100–300 µm)

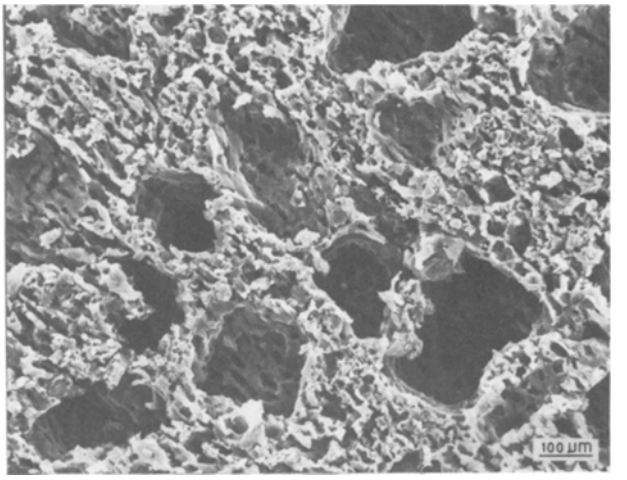

Fig. 8. Scanning electron micrograph of a crosslinked foam made by a 37 wt. % poly(ε-caprolactone)diol, poly(ε-caprolactone)triol, and hexamethylene-diisocyanate solution in 1,4-dioxane mixed with NaCl crystals (50 wt. % 50–90 µm and 50 wt. % 250–300 µm)

very open and contain no skin. This structure, with its heavily interconnected large and small pores, fulfills the requirements for ingrowth of fibrocartilaginous tissue and is suitable for surgical applications.

The morphology can be altered by changing the solvent. Figure 6 shows a scanning electron micrograph of a freeze-dried foam made from a 20 wt % PU (Estane) solution in 1,4-dioxane/trioxane (50/50 w/w) mixed with NaCl crystals (100–300 µm). Weight ratio of the polymer solution to the salt crystals was 54:46. The microstructure contains needle-like pores due to the crystallization of the trioxane. Liquid-liquid phase separation did not occur before freezing. The microporous structure is not as porous as the microporous structure obtained by using 1,4-dioxane/c-hexane/water as co-solvent, described previously. The freeze-drying/saltcasting process is applicable for any polymer for which appropriate solvents are available.

Estane is a methylenediphenyldiisocyanate (MDI)-based poly(urethane), which is converted into the toxic, mutagenic, carcinogenic diamine 4,4-dimethylenedianiline (MDA) after degradation [23]. This problem can be overcome by using aliphatic diisocyanate-like hexamethylene diisocyanate (HDI). Bruin et al. [13] used L-lysine-based diisocyanate for the synthesis of biodegradable PU.

Figure 7 shows a scanning electron micrograph of a freeze-dried foam made from a 25 wt. % LDI-PU (with an intrinsic viscosity of $[\eta] = [1.7]$) in dioxane/c-hexane (90/10 w/w) mixed with NaCl crystals (100–300 µm). Before freeze-drying, the polymer was mixed with 10 % DCP. After freeze-drying, the foam was crosslinked for 3/4 h at 150 °C. Crosslinking of the polymer was necessary, because the melting point of the polymer is 40 °C due to the caprolactone fragments, so that structure looses its integrity after implantation. Part of the microstructure was lost due to melting of the polymer before crosslinking. Pores are highly interconnected and the foam releases non-toxic components when it degrades.

Another method of producing porous materials of polyurethanes is to polymerize in-situ the components in the presence of salt crystals. Before the polymerization, the solvent either can be removed by freeze-drying or by evaporation.

Figure 8 shows a scanning electron micrograph of a freeze-dried foam made from a 37 wt. % solution of 6 equivalent PCLdiol, 2 equivalent PCLtriol, and 9 equivalent HDI in dioxane mixed with NaCl crystals (50 wt. % 50–90 µm and 50 wt. % 250–300 µm). Salt crystals with small diameters were added to increase the viscosity of the prepolymer solution/salt mixture so that crystals restrained from sagging. The weight-ratio monomer/solution was 3:7. After freeze drying, the components were cured and the salt crystals were removed. The microstructure is not lost during the polymerization. Macropores are highly

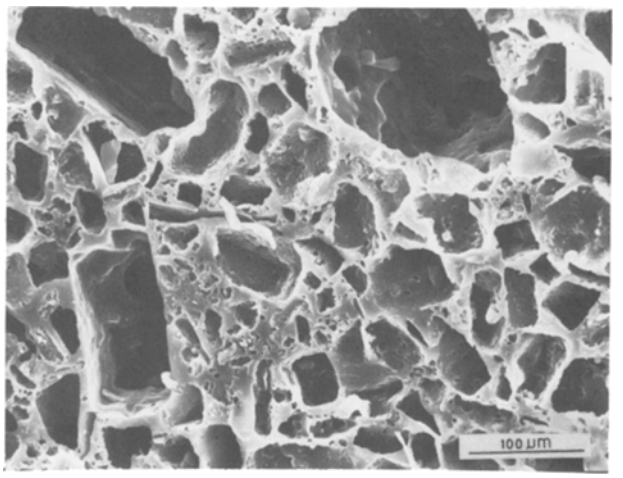

Fig. 9. Scanning electron micrograph of a foam made of a 37 wt. % poly (ε-caprolactone)diol, poly(ε-caprolactone)triol, and hexamethylenediisocyanate solution in dichloromethane mixed with NaCl crystals. The solvent evaporized before polymerization

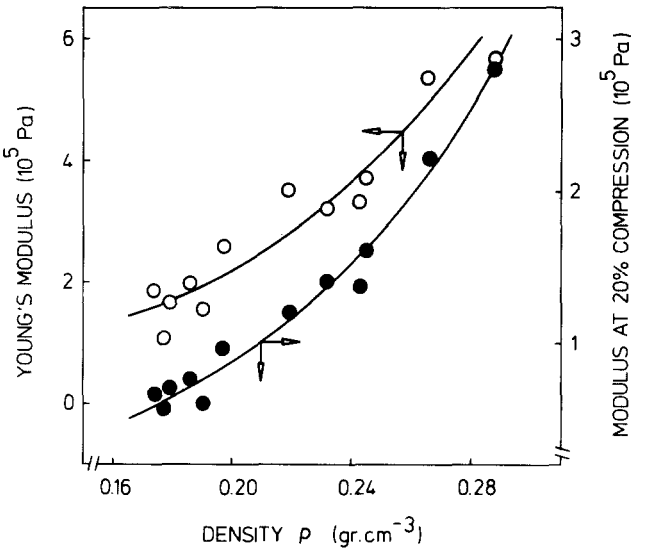

Fig. 10. Relationship between modulus and density: (○) Young's modulus, (●) modulus at 20 % compression

interconnected with the micropores (<10 µm). During cooling, liquid-liquid phase separation took place because the macrostructure is predominently isotropic. This system can be used for any polymer in which the components are soluble in a suitable solvent. The components can easily be changed.

Figure 9 shows a scanning electron micrograph of a foam made from 37 wt. % solution of 6 equivalent PCLdiol, 2 equivalent PCLtriol, and 9 equivalent HDI in dichloromethane. The solvent evaporated before polymerization so that structure is due only to the salt crystals. In this structure, the pores are less interconnected than in the previous structures, where a freeze-drying step was added. Increasing the salt concentration increases the porosity, but decreases the strength of the foam drastically. Using this method and increasing the salt concentration, a highly interconnected structure is obtained so that crystals touch each other. However, these foams are not suitable for surgical applications.

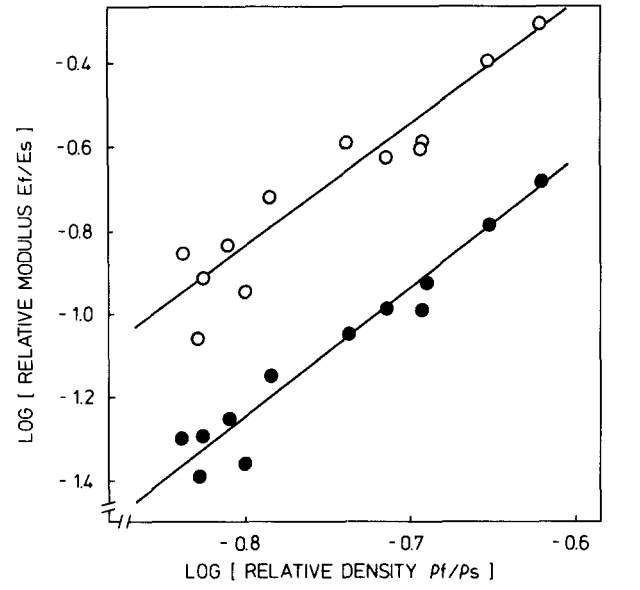

Fig. 11. Relationship between the relative modulus $\frac{E_f}{E_s}$ and the relative density $\frac{\rho_f}{\rho_s}$: (○) Young's modulus, (●) modulus at 20 % compression

Compressibility

Because compressibility is of great importance for performing the implant, the compressive stress-strain behavior was determined. The compressive stress-strain curve for a flexible foam exhibited linear elasticity at low stresses. It is followed by a long collapse plateau, due to the buckling of the walls between the pores, which is truncated by a regime of densification in which the stress rises steeply [24].

For a series of Estane foams of different densities, the compression moduli Young's modulus and the modulus at 20 % compression) were obtained. The modulus-density relationship is plotted in Fig. 10.

Doherty et al. [25] have shown that the change in physical properties of the density of urethane foams can be expressed as a straight line on log-log plots. The logarithm of the relative density, $\frac{\rho_f}{\rho_\sigma}$, is plotted against the logarithm of the relative modulus, $\frac{E_f}{E_s}$, in Fig. 11, and fall on a linear curve with slopes for Young's modulus and the modulus at 20 % compression of 2.8 and 3.0, respectively. E_f and E_s are Young's modulus (or modulus at 20 % compression) of foamed and solid materials, respectively, and pf and ps are the respective densities.

Theoretically, the relative Young's modulus for a foam is given [26] by:

$$\frac{E_f}{E_s} = \left(\frac{\rho_f}{\rho_s}\right)^2. \quad (1)$$

This formula is based on the assumption that the structure remains the same, when density is changed. Because of the great importance of the macropores in implants, the density of Estane foams is varied by changing the saccharose crystal concentration. Thus, the macropore concentration increases with decreasing density. In this case, it is obvious that the modulus becomes more dependent on the density.

Implantation

Results of the PU-PLLA and PU implants were comparable, but there were considerable differences between the PU implants. The macroporous structure was similar in all the PU implants. The microporous structure was obtained using 1,4-dioxane/trioxane and 1,4-dioxane/c-hexane/water as cosolvents, respectively. The latter and more porous structure showed better results [10].

These implants showed a relatively quick ingrowth. Fibrocartilaginous tissue turned out to be formed 15 weeks after implantation starting from the peripheral side of the meniscus. After 33 weeks, about 50 % of the polymer was degraded and 100 % of the pores were filled with active chondroblasts and fibrocartilaginous matrix. This is the highest percentage fibrocartilaginous tissue ever seen in implants.

Figure 12 shows a detail of an implant 33 weeks after implantation, including PU matrix (colored white). The pores are totaly filled with cartilaginous tissue (colored dark), in which the active chondrocytes making this tissue are dispersed.

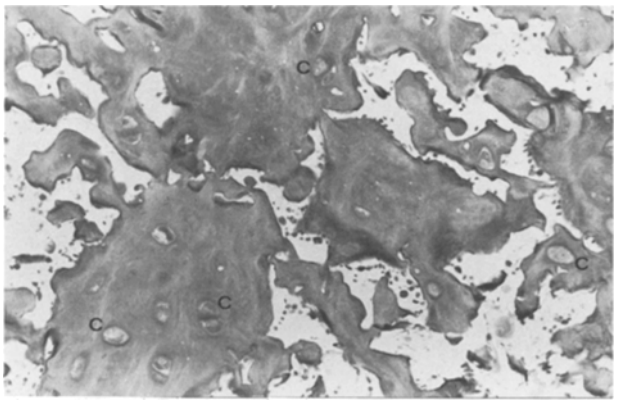

Fig. 12. Detail of an implant 33 weeks after implantation, including PU matrix (colored white) filled with fibrocartilaginous tissue (colored dark) in which the chondrocytes are dispersed (C)

Conclusions

Salt casting in combination with freeze drying is a very good method for preparing reproducible porous polymer materials suitable for surgical application. The freeze-drying step is of great importance in order to accomplish highly interconnected porous polymer materials with good mechanical properties.

Using a combination of in-situ polymerization and freeze-drying techniques enables us to prepare porous networks in which the components could easily be varied for preparation.

Implants with a macroporous structure (100–300 μm) highly interconnected with a microporous structure (<50 μm) showed excellent ingrowth of fibrocartilaginous tissue. Porosity seems to affect tissue's speed of ingrowth into the implant.

References

1. Ghosh P, Taylor TKF (1987) Clinical Orthopeadics and Related Research 224:52–63
2. Ricklin P, Ruttiman A, Del Buono MS (1971) Meniscus Lesions. Georg Thieme Verlag, Stuttgart, pp 7–9
3. Veth RPH (1978) "On the results of meniscetomy of the knee", Thesis, University of Groningen, The Netherlands
4. Jørgensen U, Sonne-Holm S, Lauridsen F, Rosenklint A (1987) J of Bone and Joint Surgery 69–B1(1):80–83
5. King D (1936) J Bone Joint Surg 18–A:333
6. Chadially FN, Wedge JH, van Lalende JMA (1986) J Bone Joint Surg 68–B:106
7. Webber JR, Harris HG, Hough Jr AJ (1985) J Orthop Res 3:36
8. Leenslag JW, Pennings AJ, Veth RPH, Nielsen HKL, Jansen HWB (1984) Macromol Chem Rapid Commun 5:815–821
9. Leenslag JW (1987) Poly(L-lactide) and its biomedical applications. Thesis University of Groningen, The Netherlands
10. Elema HA, de Groot JH, Nijenhuis AJ, Pennings AJ, Veth RPH, Jansen HWB (part 2, this journal)

11. Caplan AI (1984) Sci Am 4:82
12. Leenslag JW, Kroes MT, Pennings AJ, van der Lei B (1988) New Polymeric Materials 1:111
13. Bruin P, Veenstra GJ, Nijenhuis AJ, Pennings AJ (1988) Makromol Chem Rapid Commun 9:589
14. Klompmaker J, Veth RPH, Jansen HWB, Nijenhuis AJ, de Groot JH, Pennings AJ (accepted in Biomaterials)
15. Gogolewski S, Pennings AJ (1982) Makromol Chem Rapid Commun 3:839
16. Leenslag JW, Nijenhuis AJ, Pennings AJ, Veth RPH, Nielsen HKL, Jansen HWB (1986). Proceedings of the Noordwijkerhout, The Netherlands, pp 10/1–10/9
17. Saunders JH, Frisch KC (1964) Polyurethanes chemistry and technology, part 2. Interscience, New York, pp 4–7
18. Frisch KC, Saunders JH (1972) Plastic foams. Marcel Dekker, New York, pp 60–64
19. Smith P (1976) Thesis University of Groningen, The Netherlands
20. Hikmet RM, Callister S, Keller A (1988) Polymer 29:1378
21. Coudeville A, Eyharts P, Perinne JP, Rey L, Rouillard R (1981) J Vac Sci Technol 3:18
22. Aubert JH, Clough RL (1985) Polymer 26:2047
23. Szycher M, Porier VL, Dempsey DJ (1983) J Elastomers Plast 15:81
24. Rusch KC (1967) J Appl Polym Sci 13:2297
25. Doherty DJ, Hurd R, Lester GR (1962) Chem and Ind 30:1340
26. Gibson LJ, Ashby MF (1988) Cellular Solids, structure and properties. Pergamon Press, New York, pp 122–153

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