General introduction

Meniscus

Menisci are wedge-shaped semilunar disks of fibrocartilage interposed between the condyles of the femur and tibia. Although in the past menisci were seen as functionless remains of leg muscle, nowadays it is realized that menisci are essential components in the complex biomechanics of the knee joint.

Menisci are composed of several different materials. 60-70% of the dry weight of a human meniscus consist of collagen fibers, mainly collagen type I, although other types have also been identified (type II, III, V, VI) [1]. A distinction has to be made concerning the inner and outer part of the meniscus. Histologically, the inner 30% of the meniscus resembles hyaline cartilage (a specific type of cartilage that is found in the airways and on the articular surfaces of bones) more closely, whereas the outer 70% is more fibrous in appearance [2]. The major collagen type of this inner rim is...
type II collagen whereas the peripheral part of the meniscus is almost completely composed of type I collagen.

Histologically, the fibrocartilagenous tissue of the meniscus within the collagen fiber network contains cells that resemble fibroblasts as seen via light microscopy. Besides collagen the extracellular matrix consists of proteoglycans (1% dry weight), noncollagenous proteins (8-13% dry weight) and water (70-75%) [3,4]. The proteoglycans (PG), which are aggregated by hyaluronic acid, consist of a protein core with many glycosaminoglycans [4,5].

The meniscus is only partially vascularized. The vascular supply to the menisci arises from the medial, lateral, and middle genicular arteries. Arnoczky and Warren have found that this arteriolar network nourishes the peripheral 20-30% of the meniscus [4,6]. Beginning with the fetal meniscus the vascular network extends to the most central zones and recedes to the periphery with aging. The central third of each meniscus in adults is avascular and receives nourishment by diffusion of synovial fluid into its superior and inferior surfaces.

**Meniscal structure and function**

The collagen fibers are organized within layers: a superficial, a surface and a middle layer [7-10]. In the middle layer collagen fibers are oriented circumferentially, parallel to the periphery of the meniscus. They appear to be continuous with those of the anterior and posterior ligamentous horns that anchor the menisci to the bone. This is combined with a few radial fibers preventing splitting of the collagen fibers [28]. The middle layer is covered by fine collagen fibrils which are meshlike woven. A thin, compactly woven surface layer of irregular aligned collagen fibers then covers this.

In (fibro) cartilage, collagen fibres are responsible for the tensile strength. They are the dominant features of the extracellular matrix of the meniscus [7] and compose 75% of the dry weight [11]. Both bovine and human meniscal tissue revealed the vast majority of collagen type I which is typical for tissue resisting tear forces. Type II collagen, which is the major type in articular cartilage, is only present in minor amounts [12-14]. Especially these circumferentially oriented fibers play an important role in load distribution. The wedge-shaped form of the meniscus causes a radial externally directed force, which is developing stress along the circumferentially arranged collagen fiber bundles. In this way the force is transferred towards the meniscal horns [15]. Due to this orientation large differences in mechanical properties in circumferential and radial direction are found. The Young’s modulus and tensile strength of bovine menisci have been found to be 140-200MPa and 30MPa, respectively [16].

The deforming capacity of the meniscus tissue is also beneficial in protecting the bearing surfaces. Due to deformation of the meniscus during load, the surface contact area increases which decreases the pressure. Furthermore the joint lubrication minimizes wear by preventing direct surface-to-surface contact [7].
Meniscectomy, cartilage degeneration and meniscal lesion repair

Clinical and animal studies have shown that preservation of the meniscus improves stability and distributes weight bearing forces in the knee, thereby reducing degenerating contact stresses across the articular cartilage surfaces [17-22]. Several studies have documented the negative effect of meniscectomy on knee biomechanics. Especially, the 30 to 50% increase of knee contact pressure plays an important role [23-25]. This role, as it results in an increase of the stress concentration in the contact area. Partial meniscectomy leads to less severe degenerative changes, with the degree of change directly related to the amount of meniscus removed [26,27]. Repair of the meniscus is generally only possible for lesions in the vascular peripheral 10-30% part of the meniscus [28-30], although several methods based on improving the vascularity of the defect by stimulating ingrowth of vascular tissue have also been successful in inducing repair of these lesions [31-35]. Moreover, various bioabsorbable implants were developed which permit all-inside arthroscopic repairs of well vascularized lesions in the vascular periphery [30]. Nowadays, for lesions in the avascular central part of the meniscus partial meniscectomy is the golden standard. With the development of arthroscopical surgery this procedure is even more commonly utilized.

Meniscal replacement

The main goal of meniscal substitution is re-establishment of a normal joint load distribution in order to prevent cartilage degeneration, which is common after meniscectomy. Only a substitute which closely matches normal meniscal tissue properties can re-establish meniscal functions. Several different possibilities have been mentioned in literature.

Autograft/autologous tissue

Autograft/autologous tissue is one option. Immunologic factors and disease transmission are avoided by the use of autograft tissue. Several people tried different methods and types of autografts, they all found that initially some protection of the articular cartilage was found [36-39]. Nevertheless, the different autografts were all more prone to degeneration during the implantation period. Individual shaping of the meniscus, relevant in meniscal replacements, also seemed to be a problem in case of an autograft.

The meniscal allograft as homologous scaffold is already commonly used [1,23,40-47]. Initially an allograft was considered as replacement for the native meniscus when it was excised. However it was found that recipient cells replaced all of the donor meniscal cells within several weeks and after 6 to 8 months host cells seem to replace the donor population [22,48,49]. It should be mentioned that up until now there is no proof that allografts can prevent degeneration of the hyaline cartilage [50].

Permanent synthetic

A synthetic permanent implant is also an option that has been tried. Toyonaga et al. introduced a Teflon-net substitute meniscus with which the formation of
fibrocartilaginous cells and matrix was observed [51], but this yielded foreign body responses and massive particle debris and reactive synovitis as a result of the prosthesis wear [52-54]. A polyester-carbon fiber prosthesis had a cartilage protecting effect and was encapsulated by fibrous tissue but the expected tissue invasion into the prosthesis was not observed [55].

Collagen
Collagen fiber scaffolds may be a logical scaffold material considering that collagen is the main component of the meniscus [56]. In a canine study Stone et al. introduced meniscal regeneration after implantation with collagen type I scaffolds [57-59]. After 12 months the scaffold regenerated tissue resembled the normal native meniscus. In later clinical studies biopsies were taken 12 months after surgery, which showed invasion and replacement of the collagen implant by fibrochondrocyte-like cells producing a new meniscus-like matrix [58,60,61]. Complete meniscal replacement by a collagen scaffold was not described.

Degradable synthetic
Besides degradable scaffolds based on natural materials, scaffolds from synthetic resorbable materials open up a much wider spectrum of properties. Several authors described the desired properties of scaffolds in order to induce regeneration of the meniscal tissue [52,62-64]. Both Arnoczky and Stone agree that the scaffold should provide a matrix framework for restoration of vascular, cell and matrix elements of the tissue [63,64]. Klompmaker described the importance of the porosity, pore size and compression modulus of the scaffold for the ingrowth of tissue and differentiation into neo-fibrocartilage [62]. An adequate fit of the scaffold may even improve knee stability and, consequently, initially protect the articular cartilage from damage [59,63]. In case of a degrading scaffold, the process of degradation should be in optimal relation with the tissue restoration [59,63,65].

Several materials have been suggested in literature. Poly(glycolic acid) is described by several research groups as scaffold for meniscal cell ingrowth [66,67]. In all presented studies, after in vitro seeding of meniscal cells, new fibrocartilage developed and after subcutaneous implantation, in vitro cultured meniscal cells on meniscus shaped scaffolds could form a cell-polymer construct [67]. After implantation in the knee, this resulted in new meniscal tissue [66]. Polyesterurethane/poly(L-lactide) mixtures reinforced with fibers of carbon [68,69] have also been used as meniscal scaffold. By reinforcing a polymer with fibers, the structure of fibrocartilage was imitated. In the grafts, larger pores of 200-250µm were dispersed in a more dense matrix with pores sizes up to about 60µm. Not only ingrowth of connective tissue and blood vessels was observed but also areas of fibrocartilage were found. It is surmised that under the right circumstances, the ingrown fibrous tissue transforms into fibrocartilaginous tissue [70,71]. It is likely that properties of implant influence the transformation into fibrocartilaginous tissue. However, the carbon fibers lead to the development of synovitus because of the release of small carbon particles in the knee joint. PLLA fibers were used as an
alternative, but PLLA fibers seemed to retard the degradation process and the ingrowth of fibrocartilagenous tissue [72,73].

Several polyurethanes have also been used to obtain foams via the combination of freeze drying and salt leaching or via in situ polymerization and salt leaching. The freeze dried foams showed healing and good ingrowth of tissue [74-77]. Based on these materials Klompmaker described the relevance of the appropriate pore-size for the rapid ingrowth of fibrocartilagenous tissue [77]. A pore-size between 150 and 500µm provided the best ingrowth of mesenchymal tissue and the least inflammatory response. It was found that these foams could show stress hysteresis which made the implant fail. In contrast to this, crosslinked foams did not show this, but lacked resistance against tear which had to be circumvented by a complex suturing technique [78].

Alternative foams were made of high molecular weight 50/50 L-lactide/ε-caprolactone copolymers. With these materials it was found that a sufficiently high compression modulus is needed for ingrowth while at the same time it was found that this polymer degraded too quickly to enable fibrocartilage formation [79].

Scaffolds based on of polyurethane urea’s combined slow degradability and high mechanical properties, although it was found later that these materials lacked reproducibility and did not yield suitable interconnected pores to enable the ingrowth of tissue [80,81].

**Polyurethanes**

Polyurethanes form a versatile class of polymers, which are used in a broad range of applications like foams, coatings, fibers and biomedical materials [82-85]. The first interest in isocyanate chemistry goes back to the 1880’s, but the pioneering work in the field of polyurethanes as was done by Otto Bayer since 1937 [86,87]. He described the polyaddition of diisocyanates and diols (Figure 1-2). The group of polyurethanes comprises all polymers that contain urethane, urea or other isocyanate-derived groups, even if they are only a minor part of the total structure.

![Figure 1-2. Reaction of an isocyanate and a hydroxyl group yielding a urethane.](image)

There are a few major groups of polyurethanes. Covalently crosslinked polyurethanes are thermosets and are, besides other applications, used as both rigid and flexible foams depending on their chemical composition. Another very important group are the segmented polyurethanes, the category of polyurethanes that show a phase-separated structure and possess (thermoplastic) elastomeric properties and are used in a wide variety of applications [88]. One of the most well known commercial materials of this category is Lycra, a material produced by Du Pont.
Polyurethane chemistry

The generally used reactants for segmented polyurethanes are a diisocyanate, a polyl and an extender. Segmented polyurethanes can be considered as multiblock copolymers, consisting of a hard and a soft block (segment). The hard segment originates from the diisocyanate and chain extender, whereas the soft segment usually is the polyl. Commonly used diisocyanates are diphenylmethane-4-4’-diisocyanate (MDI), toluenediisocyanate (TDI) and hydrogenated MDI [89]. One of the main reasons of their use is the low volatility, although the fact that they yield materials with excellent properties is of course even more important. These diisocyanates are also used for biomedical polyurethanes even though it is known that the corresponding polyurethanes are able to release toxic and carcinogenic aromatic diamines originating from the aromatic diisocyanate based groups in the polymer upon degradation [90,91]. Polyurethanes based on 1,4-butanediisocyanate (BDI) can be a good non-toxic alternative, since upon degradation they are expected to yield 1,4-butanediamine, putrescine, a non-toxic polyamine that is essential for cell growth and differentiation [92]. Although the starting material for the diisocyanate is 1,4-butanediamine which is industrially readily available, there are only a few examples of the use of its corresponding isocyanate (1,4-butanediisocyanate) in polyurethane synthesis. This is mainly caused by the volatile nature of this compound.

A special group of isocyanates is the group of acylisocyanates (or also called carbonyl isocyanates), that form an acylurethane after reaction with an alcohol (Figure 1-3).

\[
\begin{align*}
\text{R} & - \text{C} & - \text{NCO} & + & \text{R'} & - \text{OH} & \rightarrow & \text{R} & - \text{C} & - \text{N} & - \text{C} & - \text{O} & - \text{R'}
\end{align*}
\]

**Figure 1-3. Reaction of an acylisocyanate and a hydroxyl group yielding an acylurethane.**

These acylisocyanates are much more reactive and decrease reaction times compared to regular isocyanates. Very important might be that the formed acylurethane groups are not expected to degrade into aromatic amines. This might open up a complete new class of polyurethanes, which will not release toxic compounds upon degradation. An extensive review of acylisocyanates and its reactions has been published although there is no description of polymerizations based on acylisocyanates in this book even though some polymerizations have been tried [93]. Polycondensation using acyldiisocyanates has been reported by Takeshio Endo et. al. They showed that it is possible to prepare poly(n-acylurethane)s, poly(N,N-diacylurea)s, and poly(N-acrylamide)s using acyldiisocyanates and diols, diamides and dicarboxylic acids, respectively [94-96]. The polyacrylurethanes were prepared using propane diols and aroyl diisocyanates. Even though only very briefly, they also mentioned the polycondensation of PTMO with isophthaloyl diisocyanate forming the corresponding polyacrylurethane. Nothing has been mentioned on the synthesis of polyesteracrylurethanes which might be very interesting as biomaterial.
The other major compound of polyurethanes is the polyol. Commonly used polyols are polysiloxanes, polyethers like poly(tetramethyleneoxide), polyester like poly(\(\varepsilon\)-caprolactone) and hydrocarbon based polyols like polybutadiene. Polyesters together with polysiloxanes are of interest for biomedical applications. The former gives polyurethanes degradable and resorbable properties while the latter has good bacterial and protein repellant properties. Depending on the preferred properties the molecular mass varies between 800 and 4000g/mol.

Common chain extenders are compounds like 1,4-butanediol, 1,4-butanediamine, 1,6-hexanediol. The choice of chain extenders has a major influence on the final properties of the resulting polymer. Diamines often result in hard segments with higher degree of hydrogen bonding and accompanying properties. Aromatic extenders produce stiffer polyurethanes compared to aliphatic extenders. It is also known that the number of carbon atoms in the extender has a major influence on the structure of the hard segment and influences properties like the degree of phase separation and melting points [97-99].

Polyurethanes are often prepared in a one- or two-pot procedure. In the first procedure all reactants are mixed and the resulting polymer is a random distribution of monomer and polyol units. If more control is desired over monomer and polyol distribution along the polymer chain the two-step process is preferred. For this procedure the polyol is first reacted with an excess of the diisocyanate to form a so called prepolymer, which is subsequently reacted with the chain extender and results in the formation of the high molecular weight polyurethane. When a diamine is used as chain extender the polyurethane also contains urea groups.

The generally used synthetic procedures to prepare polyurethanes have the intrinsic disadvantage that it leads to a distribution in the hard block lengths [100]. In addition to this the prepolymer that are generally used are polydisperse. Both facts result in a quite inhomogeneous chemical composition of the copolymer. The dispersities in hard and soft block length directly influence the material properties of the polymers. The phase separation within these block copolymers is incomplete. One part of the hard blocks, in particular the shorter ones, are dissolved in the soft phase causing an increase in the glass transition temperature which is undesired for the low temperature flexibility of the material. The polydispersity of the hard block is manifested in a broad melting range and a rubber plateau of the E-modulus that is dependent on temperature.
Phase separation

When multifunctional reagents are used, highly crosslinked polymer networks are formed. Generally the hard and soft segments have a positive heat of mixing and are therefore incompatible and will try to phase separate. However, the topology of the polyurethane chains restricts the segregation leading to microdomain formation. This domain formation is a very important property of this class of materials. Most theories on block copolymer microphase separation and the thermodynamics behind the process consider 4 factors: the Flory-Huggins solubility parameter $\chi$, the degree of polymerization, conformational and steric constraints and the weight fraction of the components [101]. For example, longer block length leads to higher degrees of phase separation and more ordered hard segment domains. Of course the morphology of these systems plays an important role in determining the final properties of a product. For polyurethanes several factors influence the morphology. Factors like crystallization, interphase mixing, hydrogen bonding in both segments and dependence on thermal history all influence the final morphology of a system. A wide variety of literature has been dedicated to this [102].

Side reactions

The major reaction for the synthesis of polyurethanes is the reaction between a diisocyanate, chain extender and polyol which is supposed to give a linear polymer. It is also generally known that this type of polymerization is very sensitive to relative small changes in conditions which can greatly affect the final product. Several other reactions can occur during the synthesis of polyurethanes [103]. The major side reactions are dimerization, trimerization, carbodiimide, biuret and allophanate formation as depicted in Figure 1-5 [97,99,104,105].
Depending on the group next to the isocyanate, these reactions can occur under a wide variety of circumstances. An example of the influence of the neighboring group is that aromatic diisocyanates are easily dimerized at low temperatures, especially in the presence of acidic or basic catalysts, while aliphatic diisocyanates appear to form dimers only in low yields although both of them can form trimers [97,106]. It is also found that these side reactions can already occur at room temperature and are strongly influenced by the catalyst and type of solvent used [107-109]. Carbodiimide formation only occurs at high temperatures and is stable above 200°C and is generally considered as not very important. The formation of allophanates and biurets can occur under a wide variety of circumstances, especially at temperatures of 120-150°C the reaction has a significant contribution. At temperatures lower than 80°C, the rate of the reaction between isocyanates and urea groups (biuret reaction) is approximately 20 times lower than the reaction between isocyanates and alcohol functionalities [110]. Under these conditions, the allophanate reaction is negligible, although one should not forget that several types of compounds also catalyze the reaction. All these side reactions change the initial stoichiometry of the extension and thereby limit the final molecular weight and yield branched or even crosslinked polymers [111]. The catalysts and solvents that are used for polymerization of polyurethanes or even catalysts or metal based impurities that are used or present during the synthesis...
of the reactants (and which are not removed afterwards) do not only catalyze the chain extension, but will also catalyze these side reactions. This makes it very important to use high purity reactants in order to obtain high molecular weight linear polyurethanes with known (amounts of) catalysts.

**Mechanical properties**

The superior mechanical properties of polyurethanes are a result of microphase separation of the hard and soft domains. The hard segment acts as filler and multifunctional crosslink and is very important for the mechanical properties of the material. Below the soft segment $T_g$, polyurethanes are rigid. Above the hard segment $T_g$ or melting temperature, the materials behave as amorphous, non-crosslinked liquids. Between these two transition temperatures, the materials behave as typical thermoplastic elastomers with strength and modulus decreasing as temperature increases.

In general, the behavior of these materials depends on the size and concentration of the hard segment domains, the strength of the hard segment aggregation, the ability of the segments to orient in the direction of stress and the ability of the soft segment to crystallize under strain [112]. The length of the soft segments also has a strong influence on the mechanical properties. Short soft segments ($M_n=800-1500$g/mol) generally lead to rigid, high modulus materials while long soft segments ($2000-5000$g/mol) yield elastic materials which may show strain induced crystallization of the soft segments. For further reading there are several reviews about mechanical properties of polyurethanes [98,99,101,113].

**Polymeric scaffold formation**

In order to (re)generate tissue, (degradable) scaffolds are used in most cases. The idea of the scaffold is that it supports the ingrowth of tissue and facilitates vascularization and cell nutrition. In case of degradable scaffolds the material should retain its function until the tissue is able to function without the scaffold. At this moment the scaffold should degrade and finally be resorbed.

There are a few generally used guidelines for scaffolds, but one of the most important ones is the porosity of the polymer scaffold. A high surface area favors cell attachment and growth, whereas a large pore volume is required to accommodate and subsequently deliver a cell mass sufficient for tissue repair. Besides this, a high interconnectivity will enable easy diffusion of nutrients and waste products to and from the implant to enable cell growth and vascularization. The surface-area/volume ratio of a porous material depends on the density of the material and average diameter of the pores. Nevertheless, the diameter of the cells that are supposed to infiltrate the scaffold determine the minimum pore size and minimum interconnectivity, which thus varies from one cell type to another. Depending on the envisioned applications, the pore size must be carefully controlled [77,114-116].
The mechanical strength of a polymer scaffold has to be considered also in the reconstruction of load bearing tissue such as bone and cartilage. This can be a limiting factor for the porosity of the scaffold. With increasing porosity the mechanical properties will decrease, so an optimal balance between porosity and mechanical properties is needed.

A wide variety of methods have been tried to obtain a porous polymeric structure. There are two major groups: one is based on methods using solvents while the other is based on melt processing.

Examples include particulate leaching, freeze drying, 3D-printing, fiber spinning, aggregation of polymer micro particles and foaming with blowing gasses. All these methods yield foams with different properties, depending on the method. The scaffold can have a high/low porosity, high/low interconnectivity, varying mechanical properties and limitation in sizes and shapes.

**Fiber meshes**

These consist of individual fibers either woven or knitted into three-dimensional patterns of variable pore size. PGA and PLA have been used a lot for this method [73,117,118]. Large surface area is an advantage, but these structures often lack structural stability.

![Figure 1-6. PLGA knitted mesh. Picture taken from [117] and reproduced with permission from Wiley-VCH Verlag GmbH, Weinheim.](image)

**Phase separation of polymer solutions**

Methods to produce porous materials via phase separation of polymer solutions can be divided into two groups: immersion precipitation and freeze drying techniques.

**Immersion precipitation**

Porous membranes have been designed for a variety of industrial applications such as filtration, reverse osmosis and gas separation [119]. Membrane formation is based on immersing a polymer solution into a non-solvent bath in order to induce phase separation. Although different types of phase separation can occur, liquid-liquid demixing seems to be essentially responsible for the structure formation. The major disadvantage of this method is that only relatively thin structures can be produced.
Freeze drying
Freeze drying of polymer solutions is being explored as an original method to prepare highly porous 3D polymer scaffolds [74,120,121]. The basic principle relies upon thermally induced phase separation, which occurs when the temperature of a homogeneous polymer solution is decreased. Once the phase-separated system is stabilized, the solvent phase is removed by sublimation leaving behind the polymer as a foam. The foam morphology is of course controlled by any phase transition that occurs during the cooling step (i.e. L-L or S-S). The obtained structures are very porous although it is difficult to control the pore size and interconnectivity, which are also generally relatively small.

Particulate leaching
This method consists of dispersing calibrated (in)organic particles in a polymer solution. This dispersion is processed either by casting or freeze drying in order to produce a porous structure. The porosity basically results from the selective extraction of the particles from the polymer composite, although phase separation of the polymer solution can also contribute to the porous structure [72,74,122-124].

Rapid prototyping techniques
These methods are relative new methods of fabricating porous structures. Compared to traditional methods, it is possible with these to make a predefined or controlled microstructure as well as macrostructure. There are several different methods: membrane lamination, adhesion bonding, laser sintering, photo polymerization and droplet deposition [125]. A major advantage of these systems is that the smallest feature can be very small although the current machines do not offer these small structures yet.

Aggregation of polymer microparticles
Porous structures have been prepared via the aggregation of microparticles. The porosity is created by the interstices between the aggregated microspheres and it is directly related to the microsphere diameter. The aggregation can be made permanent by chemical crosslinking or local fusion by heat [79]. Good mechanical properties can be obtained via this method, although porosity and pore size are rather limited.

Foaming with blowing gasses
A method that has also been used is foaming based on gases that are separately added to the polymer (solution) or are formed during the in-situ polymerization [126] [127]. The method is similar to the foaming methods used industrially [113]. In principle this method can be very suitable although industrially a wide variety of additives are used which are unsuitable for scaffold preparation due to biocompatibility problems. Moreover, because of physical reasons these blown foams tend to have a closed cell structure which also make them less suitable.
Aim and structure of the thesis

The aim of this study is to make a (bio)degradable scaffold that can be used as meniscus reconstruction material. The goal of the scaffold is to support the body in regenerating a new meniscus while at the same time the scaffold degrades and dissolves so that finally a meniscus will only consist of natural material.

Chapter 2 describes the synthesis of a polyurethane based on endcapping poly(ε-caprolactone) of variable molecular weight with 1,4-butanediisocyanate and subsequent extension with 1,4-butanediol yielding a polyurethane with a uniform hard segment. The complete polymerization was performed in absence of solvent and catalysts. In the same chapter the thermal and mechanical properties are described.

Chapter 3 describes the influence of soft segment polydispersity on the thermal and mechanical properties of polyurethanes made as described in the previous chapter. Since chain extension in absence of catalysts is relatively slow a more reactive isocyanate is also used. Chapter 4 shows that terephthaloyl diisocyanate was found to be much more reactive compared to regular isocyanates and yielded, in combination with poly(ε-caprolactone) and in absence of catalysts, within 4 minutes a polyurethane in a microextruder.

Chapter 5 describes a method to obtain porous structures of a commercially available polyurethane Estane. This method is comparable with the method described by De Groot et al. although in this case a higher interconnectivity was achieved since a higher degree of liquid-liquid phase separation was obtained.

Chapter 6 described here uses thermally induced phase separation in combination with salt leaching to obtain foams. Compared to Chapter 5 this method makes use of a better solvent, which is also considered to be non-toxic. With this method it was found to be possible to obtain highly interconnected porous foams in combination with suitable mechanical properties. The influence of several variables like non-solvent concentration, salt size and hard segment content were evaluated.

In chapter 7 phase transitions of the polyurethanes mentioned in chapter 3 in DMSO/water mixtures are described. This system combines several phase transitions like liquid-liquid phase separation and hard segment crystallization. The influence of polymer and water concentration and hard segment content on these transitions were investigated.

The next chapter, chapter 8, describes the in vitro degradation of the polymers and foams described in chapter 3 and 7. The influence of hard segment content on the rate of degradation was evaluated.

During the foam making NaCl crystals were used and a minor amount could not be removed. Chapter 9 describes the influence of these on the degradation behaviour.

Chapter 10 describes the results that were found from the biological evaluation of two scaffolds that had been implanted in beagles. The results showed that the foam was completely infiltrated with tissue, which after some time had a meniscus like appearance.
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