Béla Pukánszky Jr.
Ph.D. Thesis

Segmented Polyurethane Elastomers for Endovascular Surgery: Kinetics, Properties, Application
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Contents

Chapter 1
Introduction
1.1 Embolization 8
1.2 Contrasting 11
1.3 Polyurethane synthesis and properties 13
   1.3.1 Composition 13
   1.3.2 The chemistry of polyurethanes 14
   1.3.3 Kinetics of polyurethane synthesis 18
   1.3.4 Structure 22
   1.3.5 Properties, requirements 23
1.4 Scope 25
1.5 References 27

Chapter 2
Polymerization kinetics of three-component segmented linear polyurethane elastomers
2.1. Introduction 31
2.2. Experimental 32
2.3. Results and Discussion 33
   2.3.1. Primary Results 33
   2.3.2. Quantitative evaluation, modeling 35
   2.3.3. Kinetic parameters, composition dependence 39
2.4. Conclusions 43
2.5. References 44

Chapter 3
Effect of molecular and phase structure on the properties of polyurethane elastomers
3.1. Introduction 45
3.2. Experimental 45
3.3. Results and Discussion 46
   3.3.1. Molecular weight 46
   3.3.2. Mechanical properties 47
   3.3.3. Relaxation, mobility 49
   3.3.4. Phase structure 52
   3.3.5. Discussion 53
3.4. Conclusions 54
3.5. References 54
# Contents

<table>
<thead>
<tr>
<th>Chapter 4</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase separation in segmented polyurethane elastomers – effect of specific interactions</td>
<td></td>
</tr>
<tr>
<td>4.1. Introduction</td>
<td>57</td>
</tr>
<tr>
<td>4.2. Experimental</td>
<td>57</td>
</tr>
<tr>
<td>4.3. Results and Discussion</td>
<td>58</td>
</tr>
<tr>
<td>4.3.1. Molecular structure</td>
<td>58</td>
</tr>
<tr>
<td>4.3.2. Phase structure, mobility</td>
<td>60</td>
</tr>
<tr>
<td>4.3.3. Structure-property correlations, interactions</td>
<td>62</td>
</tr>
<tr>
<td>4.4. Conclusions</td>
<td>65</td>
</tr>
<tr>
<td>4.5. References</td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 5</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation and characterization of barium sulfate particles as contrast materials for surgery</td>
<td></td>
</tr>
<tr>
<td>5.1. Introduction</td>
<td>69</td>
</tr>
<tr>
<td>5.2. Experimental</td>
<td>70</td>
</tr>
<tr>
<td>5.3. Results and Discussion</td>
<td>71</td>
</tr>
<tr>
<td>5.3.1. Particle size and shape</td>
<td>71</td>
</tr>
<tr>
<td>5.3.2. Particle size distribution</td>
<td>73</td>
</tr>
<tr>
<td>5.3.3. Sedimentation, suspension stability</td>
<td>75</td>
</tr>
<tr>
<td>5.4. Conclusions</td>
<td>79</td>
</tr>
<tr>
<td>5.5. References</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 6</th>
<th>83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast materials for endovascular surgery – efficiency and characterization</td>
<td></td>
</tr>
<tr>
<td>6.1. Introduction</td>
<td>83</td>
</tr>
<tr>
<td>6.2. Background</td>
<td>83</td>
</tr>
<tr>
<td>6.2.1. Contrast efficiency</td>
<td>83</td>
</tr>
<tr>
<td>6.2.2. Suspension stability</td>
<td>85</td>
</tr>
<tr>
<td>6.3. Experimental</td>
<td>86</td>
</tr>
<tr>
<td>6.4. Results and Discussion</td>
<td>87</td>
</tr>
<tr>
<td>6.4.1. Particle size and shape</td>
<td>87</td>
</tr>
<tr>
<td>6.4.2. Particle size distribution</td>
<td>89</td>
</tr>
<tr>
<td>6.4.3. Sedimentation, suspension stability</td>
<td>92</td>
</tr>
<tr>
<td>6.5. Conclusions</td>
<td>96</td>
</tr>
<tr>
<td>6.6. References</td>
<td>96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 7</th>
<th>98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>List of symbols</td>
<td>102</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>104</td>
</tr>
<tr>
<td>List of Publications</td>
<td>105</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

Arteriovenous diseases are extremely dangerous and threaten a considerable part of the population. A large number of premature deaths are caused by such diseases, and both their detection and treatment is often extremely difficult. These problems usually originate from the formation of aneurysms or arteriovenous malformations (vein tumors) in the blood vessels. The walls of the vessels become weak at certain places and the burst of the veins may result in bleeding. Such malformations can form everywhere in the body, but they are extremely dangerous in the brain. 50% of the patients who have a bleeding (stroke) do not survive, and even in the case of a successful treatment there is a high chance of permanent brain damage. The early way to prevent bleeding in these cases was open surgery, which was extremely dangerous and showed high mortality rate. Aneurism and artero-venous malformations are treated more and more frequently by endovascular techniques. These methods, in which the treatment takes place directly in the blood vessel, show better results than micro-neurosurgical methods. Micro balloons and spirals are frequently applied, but liquid embolizing agents are the newest materials used for the treatment. These are less invasive than earlier methods and result in very high recovery ratios.

Although polymer based embolizing agents are available already on the open market, but they have numerous drawbacks, which hinder the more extensive spread of this approach. Intensive research is going on in the field as a consequence, and the improvement of existing solutions as well as finding completely new materials or approaches are equally interesting for the medical community. Medical doctors from the University of Pécs approached the Laboratory of Plastics and Rubber Technology to join their effort in finding a polymer with optimum properties for endovascular surgery. They did considerable research already and found that a certain polyurethane polymer performs much better than the commercial embolizing preparation based on an ethylene-vinyl alcohol copolymer. The polymer, which is a commercial product, is produced expressively for medical applications, but not for endovascular surgery. As a consequence, its properties are not optimal for the purpose, its characterization is insufficient, the production technology is not known, thus it cannot be certified as the component of a registered product for embolization. The discussions between the Laboratory and the doctors lead to a few preliminary experiments and finally to a large project financed by the National Bureau for Research and Development (NKTH). Although the project is stalled at the moment because of difficulties created by the industrial partner, the research continues nevertheless.
Introduction

The first steps of the research were extremely difficult. At first even finding the common language with the medical doctors created some problems. Based on the scant information available, we tried to identify the chemical composition and structure of the polymer, characterized it as thoroughly as possible, explored various reaction routes and preparation technologies, developed methods for characterization, etc. During this preliminary stage we found that besides producing an appropriate polymer, we must pay attention also to the entire preparation, to the solution used for embolization. As it turned out, we had to look into contrasting methods and the factors affecting the stability of the suspension prepared with the selected contrast material. Commercial contrast agents often separated from the suspension by sedimentation. Quite a few of these problems were completely new to us and we often failed to find the right solutions, wandered off the main path towards reaching our goal, sometimes even got completely stuck. In spite of the difficulties we learned the trade, made some progress and got closer and closer to our goal. This PhD thesis is one of the first products of this large project and it reports some of the results obtained up to now. The thesis might not seem to be completely coherent and the chapters focus on apparently different problems, but all of them represent a very important step toward the final goal. The components and the composition of the polyurethanes studied cover a wide range and we investigated various questions from polymerization kinetics, through structure-property correlations, to the problematic of contrasting. We hope that the work done and the compilation of the results in this thesis give a further boost to the project resulting in even better scientific results and a material, which finds widespread use in surgery.

1.1. Embolization

The medical problem which is in the focus of our research is not widely known among chemists, thus needs a more detailed introduction. Aneurysms and arteriovenous malformations (AVM) are the main target of embolization procedures. An aneurysm is a localized, blood-filled dilation (balloon-like bulge) of a blood vessel (Fig 1.1). Aneurysms can be as small as 10 mm in diameter, but larger size ones with 4-5 cm are also common. Aneurysms are caused by the weakening of the vessel wall. Aneurysms most commonly occur in arteries at the base of the brain and in the aorta (the main artery coming out of the heart), a so-called aortic aneurysm. The bulge in a blood vessel can burst and lead to death at any time. The larger an aneurysm becomes, the more likely it is to burst. Arteriovenous malformation is a congenital disorder of the connections between veins and arteries in the vascular system. AVM is not generally thought to be an inherited disorder [1-3].
During the discussion of these medical problems and their treatments we focus our attention on the brain. Although aneurysms pose a huge threat to life wherever they occur, treatment of brain aneurysms is the largest challenge mainly because of the diameter of blood vessels there. Aneurysms and similar problems described above can be treated using several techniques. In general we can distinguish two major directions. The method used for treatment initially was open surgery. In the case of a brain aneurysm the skull of the patient was cut open as the first step of the procedure and during the usually lengthy operation the surgeon saw the weakened part of the blood vessel. Although the mortality rate was quite high, the nature of this medical problem and the lack of treatment options made it necessary to carry out such operations [4-5]. The second, more recent method of treatment includes a number of similar techniques. These can be called endovascular embolization techniques. Endovascular surgery is a form of minimally invasive surgery that was designed to access many regions of the body via major blood vessels [6-9]. Embolization is the process where the defect in the blood vessel is repaired by filling the bulge, thus excluding the weak part of the wall of the vein from the blood flow. These techniques involve the introduction of a catheter percutaneously or through the skin, into a large blood vessel. Typically the blood vessel chosen is the femoral artery or vein found near the groin. A major blood vessel is necessary due to the large diameter of the catheter used.

Endovascular techniques were originally designed for diagnostic purposes. Access to the femoral artery for example, is required for angiographic procedures. The catheter is injected with a radio-opaque dye that can be seen on live X-ray. As the dye passes through the blood vessels, characteristic images are seen by experienced viewers and can assist in the diagnosis of diseases such as aneurysms (see contrasting techniques in section 1.2). In recent years, however, the development of intravascular balloons, stents and coils have allowed for new therapies as alternatives to traditional surgeries [10-13]. Stents and coils are composed of fine wires such as platinum, which can be inserted through a thin catheter and expanded into a predetermined shape once they are guided into place. Once the stents are in place blood will begin clotting between the wires excluding the week part from the blood flow (Fig. 1.2). An alternative to platinum wires is the application of balloons. These are inserted in the same manner as coils through a catheter, and once inside the aneurysm they are inflated to fill the bulge.

![Fig. 1.2 Treatment of aneurysm, with platinum coils](image)
The most recent treatment is based on the use of polymers [14,15]. These polymers are dissolved, mostly in DMSO. They are then injected through a catheter in the same manner as coils or balloons. Once the solution reaches the aneurysm it fills the bulge either through a chemical reaction or precipitation (Fig. 1.3).

Several polymer systems exist which have been considered for such application. One of such materials is N-butyl-cianoacrilate. However, this polymer has never been commercialized due to several problems occurring during embolization. Adhesion to the catheter and to the wall of the blood vessels was one of the largest drawbacks of this polymer. The material can also enter the bloodstream causing heart attack. However, even if these problems could be resolved, its precipitation behavior would exclude N-butyl-cianoacrilate from such applications, small aneurysms can not be completely embolized with it. Another polymer must be mentioned as well. Research on poly(ethylene-vinyl alcohol) copolymers showed considerable results. A commercial product with the trade name Onyx is already on the market, although the properties are far from optimal. Problems related to the application of Onyx include the requirement of a large amount of DMSO, which can prolong operations considerably. Due to the toxicity of this solvent, regulation allows the introduction of maximum 0.1 ml/min DMSO to the human body. The high viscosity of such poly(ethylene-vinyl alcohol) solutions also poses a problem, since it increases the time of the embolization, a thick catheter is required and the larger pressure developing in the catheter is also harmful. The shape of the precipitate does not follow the wall of the aneurysm during treatment and full embolization can not be achieved in one step prolonging the operation even further.

Polyurethanes are also considered for such application. PUR elastomers have been present in the medical field for several years now. A variety of devices can be prepared from these materials applied both inside and outside the human body. These can range from gloves to catheters, implants and coatings. This polymer is preferred for implants as good mechanical properties are coupled with good bio- and haemocompatibility. One of the results of good biocompatibility is that tissue can naturally grow on the surface of polyurethane.
The solvent currently used for embolization is DMSO. Because of its toxicity, it would be beneficial to decrease its amount or replace the entire solvent system. DMSO is often replaced by ethanol in medical practice and also in endovascular surgery. However, the solubility of the polymer is usually quite poor generally and usually requires the formation of specific interactions between the characteristic groups of the polymer and the solvent. Clearly the composition of the solvent mixture modifies the solubility of the polymer. Solubility depends very much on the molecular structure of the polymer, which can be controlled through the proper selection of the components, composition and polymerization conditions.

1.2. Contrasting

Research in endovascular embolization must not consider only the polymer applied, but the entire embolization preparatum used for treatment. Preparatums usually consist of the polymer, a solvent or solvent mixture, and a contrast agent. Radiocontrast agents (also simply contrast agents or contrast materials) are compounds used to improve the visibility of internal bodily structures in an X-ray image (Fig. 1.4). Contrast agents are also used in MRI (Magnetic Resonance Imaging). The degree of contrast and the suitability of a material for surgical purposes depend on the electron density of the material and on the stability of the suspension, which on the other hand, is determined by the particle size and density of the contrast agent and the viscosity of the dispersion [16-19].

There are two basic types of contrast agents used in X-ray examinations. One is based on metals or metal salts like barium sulfate, which is an insoluble white powder. Several other contrast materials are also used in medical practice like, gold and tantalum.

Colloidal gold is used in various applications in medicine, biology and materials science [20,21]. Colloidal gold in water is intensely red-colored, and can be made with tightly-controlled particle sizes up to a few tens of nanometers by the reduction of gold chloride. The technique of immunogold labeling, for example, exploits the ability of the gold particles to adsorb protein molecules onto their surfaces [22-24].

Colloidal silver is a liquid suspension of microscopic particles of silver. Its broader commercial definition includes products that contain various concentrations of silver colloids, ionic silver compounds or silver proteins in purified water. Long-term intake of silver products may result in a condition known as argyria, one symptom of which is a blue or gray discoloration of the skin [25].
Tantalum is also suitable as a radiocontrast material due to the fact that it resists attack by body fluids and is nonirritating. Tantalum is widely used in making surgical instruments and implants [26-28]. For example, porous tantalum coatings are used in the construction of orthopedic implants due to the ability of tantalum to form a direct bond to hard tissue. Tantalum is also suitable as a radiocontrast material due to the fact that it resists attack by body fluids and is nonirritating. Tantalum is widely used in making surgical instruments and implants. For example, porous tantalum coatings are used in the construction of orthopedic implants due to its ability to form a direct bond to hard tissue.

Barium sulfate is mixed with water and some additional ingredients to make the contrast agent. It is mostly used in the digestive tract [29,30]; it is usually swallowed. After the examination, it leaves the body. It is administered, orally, as a suspension of fine particles in an aqueous solution. Although barium is a heavy metal, and its water-soluble compounds are often highly toxic, the extremely low solubility of barium sulfate protects the patient from absorbing harmful amounts of the metal. Due to the relatively high atomic number (Z = 56) of barium, its compounds absorb X-rays more strongly than compounds derived from lighter atoms.

The other type of contrast agent is based on iodine. This may be bound either in an organic (non-ionic) compound or an ionic compound. Ionic agents were developed first and are still in widespread use depending on the examination they are required for. Ionic agents have a poorer side effect profile. Organic compounds have fewer side effects as they do not dissociate into component molecules [31-34]. Many of the side effects are due to the hyperosmolar solution being injected. Many different molecules used currently. Some examples of organic iodine molecules are iohexol, iodoxanol, ioversol. Iodine based contrast media are water soluble and harmless to the body. Modern iodinated contrast agents can be used almost anywhere in the body. They are used intravenously the most often, but for various purposes they can also be used intraarterially, intrathecally (the spine) and intraabdominally, meaning just about any body cavity or potential space. An older type of contrast agent, Thorotrast was based on thorium dioxide, but this was abandoned since it turned out to be carcinogenic.

Currently iodine based radiocontrast materials are used for the examination of aneurysms, and tantalum based is used during treatment. However there are problems with the currently applied tantalum material. Although it has all the relevant approvals it does not always behaves optimally during treatment. The largest problem is that tantalum might sediment in the catheter clogging it. The phenomenon is very dangerous as high pressures are required to push the plug through, even if it is possible at all.

The degree of contrast and the suitability of a material for surgical purposes depend on its electron density [35-37] and on the stability of the suspension, which on the other hand, is determined by the characteristics of the particles and the dispersion medium [38,39]. The contrast materials available in the open market
Chapter 1

come in various particle sizes. The stability of the suspension prepared with them is very often not sufficient; the particles frequently separate from the dispersion by sedimentation. Separation of the contrast material in the body is very dangerous, since the operation cannot be safely completed; the contrast material may block the arteries and cause damage [40,41]. The proper adjustment of the factors determining contrast efficiency and suspension characteristics may result in more efficient contrast materials than those available presently.

1.3. Polyurethane synthesis and properties

The structure and properties of the polyurethane used must be thoroughly considered and controlled for the application in question. Structure and properties are influenced by many factors including the type of components, composition and the conditions of preparation. In this section we discuss questions related to the synthesis and properties of linear polyurethane elastomers.

1.3.1. Composition

In general three types of components are used for the synthesis of polyurethanes: an isocyanate, a polyol and a chain extender [42,43]. Isocyanates with two or more functional groups are required for the formation of polyurethane polymers. Volume wise, aromatic isocyanates account for the vast majority of global diisocyanate production. Aliphatic and cycloaliphatic isocyanates are also important components for polyurethane materials, but in much smaller volumes for several reasons. First, the aromatically linked isocyanate group is much more reactive than the aliphatic one. Second, aromatic isocyanates are more economical to use; aliphatic isocyanates are used only if special properties are required for the final product, e.g. light stable coatings and elastomers can only be obtained from aliphatic isocyanates. Even within the same class of isocyanates, significant differences exists in the reactivity of the functional groups due to sterical hindrance. In the case of 2,4-toluene diisocyanate, the isocyanate group in the para position to the methyl group is much more reactive than the one located in the ortho position. The two most important aromatic isocyanates used are toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI). TDI consists of a mixture of the 2,4- and 2,6-diisocyanatotoluene isomers. Diphenylmethane diisocyanate (MDI) has three isomers, 4,4'-MDI, 2,4'-MDI, and 2,2'-MDI, and can be polymerized to provide oligomers with functionality of three and higher. The 4,4' isomer is most widely used, and is also known as pure MDI. MDI can be acquired in the form of the monomer molecule or as polymer MDI.

Polyols can be classified the most easily as polyether or polyester polyols. They can be further divided according to their end use to flexible or rigid polyols depending on their chain structure and their molecular weight. Flexible polyols have molecular weights from 2,000 to 10,000, while rigid polyols have molecular weights from 250 to 700. Polyols with molecular weights from 700 to 2,000 are used to add stiffness or flexibility to base systems, as well as to increase solubility of low molecular weight glycols in high molecular weight polyols [42,43].
Chain extenders, where the average functionality is 2, and cross linkers, where the average functionality is 3 or larger, are low molecular weight hydroxyl and amine terminated compounds that play an important role in the determination of polymer morphology of polyurethane fibers, elastomers, adhesives, and certain microcellular foams. The choice of chain extender also determines flexural properties as well as heat, and chemical resistance. The most important chain extenders are ethylene glycol, 1,4-butanediol (BD), 1,6-hexanediol, cyclohexane dimethanol and hydroquinone bis(2-hydroxyethyl) ether.

In addition, additives such as catalysts, surfactants, blowing agents, cross linkers, flame retardants, light stabilizers, and fillers are also used to control and modify the reaction process as well as the performance characteristics of the polymer.

In our research we used three component polyurethanes based on (MDI) a bifunctional polyol and a chain extender (BD). Such materials are widely used as a coatings for medical instruments mainly due to their good biocompatibility. Composition was changed in different ways during the research. We synthesized polymers with different type of polyols, with various molecular weights and different compositions. However we found that polyester polyols are the most suitable for our purpose. We also changed the ratio of the isocyanate (NCO) and hydroxyl (OH) functional groups as well as that of the polyol and the BD chain extender. No catalysts were used in our research. These are mainly required to increase reaction rate, thus increasing the output during synthesis. As mentioned earlier, the size of aneurysms are relatively small, the amount of the polymer required is measured in grams. The omission of catalyst is also supported by the requirement that no contaminants should be present in materials intended for use inside the human body.

Another aspect must be also considered, in the determination of the composition of PU elastomers. One of the primary requirements for this material is solubility. As mentioned before, linear polymers are prepared if only bifunctional compounds are used for synthesis. However, even in the case of linear elastomers, solubility and the stability of solutions can change in a wide composition range. The molecular weight of the polymer changes drastically with the stoichiometric ratio of the functional groups. The size of the molecules influences solubility at some extent. However, depending on the polarity and the type of the end groups even large molecular weight polymers can be dissolved in DMSO. While polyurethanes based on polyether polyl might not dissolve even at lower molecular weight, we found that in the case of polyurethanes prepared from polyester polyls can be dissolved more or less independently of their size.

1.3.2. The chemistry of polyurethane

Polyurethanes can be synthesized in solution or in melt. During our work we favored melt reactions over solution polymerization. Although homogeneity is better in the latter case, the long reaction time necessary because of the lack of
catalysts compared to reactions done in melt under the same conditions makes solution polymerization less favorable. The reaction carried out in solution also requires a solvent removal step after preparation which is not necessary in the case of melt polymerization. The reaction can be carried out in different processing instruments. The internal mixer offers several advantages. It provides quite good homogeneity and the reaction can be monitored easily through the measurement of temperature and torque.

Polyurethane synthesis is a polyaddition reaction, with the consequence that the degree of polymerization is very sensitive to the stoichiometric ratio of the two components. The chemical characteristics of the isocyanate groups are extremely important. These groups are very reactive, especially with nucleophile agents. The reactivity of the NCO group is determined by the electrophile characteristic of the central carbon atom of the cumulated bond \[42,43\]. The electron structure of the group can be described with the following mesomer structures:

\[
\begin{align*}
R\equiv N\equiv C\equiv O & \quad \leftrightarrow \\
R\equiv N\equiv C\equiv O & \quad \leftrightarrow \\
R\equiv N\equiv C\equiv O & \quad \leftrightarrow \\
R\equiv N\equiv C\equiv O & \quad \leftrightarrow
\end{align*}
\]

(Scheme 1.1)

The fourth mesomer structure forms only in the case of aromatic isocyanates, where the aromatic ring can stabilize the negative charge of the nitrogen atom (Scheme 1.1). The formation of this mesomer explains the higher reactivity of aromatic isocyanates compared to aliphatic compounds.

Reaction rate is fastest with the primary aliphatic alcohols; secondary alcohols react considerably slower. Isocyanates can react with phenols as well, but the reaction product is not stable, decomposes. Reaction with phenols gained importance in the preparation of masked isocyanates. The reaction of the isocyanate is strongly exothermic in every case. The heat of reaction is 84 kJ/mol for aromatic isocyanates and primary alcohols \[42\] (Scheme 1.2). The reaction of water with isocyanates is also extremely important (Scheme 1.3). The carbamic acid reaction product is not stable, it dissociates immediately to amine and carbon dioxide (Scheme 1.4.). Amines react even faster with isocyanates yielding carbamid derivatives (Scheme 1.5).

\[
R_1\equiv N\equiv C\equiv O + R_2\equiv OH \rightarrow R_1\equiv NH\equiv C\equiv O\equiv H_2
\]

(Scheme 1.2)

\[
R\equiv N\equiv C\equiv O + H_2O \rightarrow R\equiv NH\equiv C\equiv OH
\]

(Scheme 1.3)
The products of these primary reactions still contain active hydrogen atoms, which can further react with isocyanates forming alphanates from urethanes (Scheme 1.6) or biuret from carbamide (Scheme 1.7).

Isocyanates can also react with themselves. Aromatic isocyanates dimerize in the presence of basic catalysts (Scheme 1.8). Dimerization of MDI can occur even at room temperature. Since this reaction is reversible, it has no influence on polyurethane synthesis:

The reaction of isocyanates with themselves may yield carbo-diimides, however this reaction occurs only at high temperatures without catalysis (Scheme 1.9).
During the reaction of the isocyanate and alcohol electron is transferred between the carbon atom of the electrophile isocyanate and the nucleophile oxygen atom of the hydroxyl group, resulting in an intermediate complex, which then leads to the final urethane product. The literature on the structure of the complex is not unified, alcohol-alcohol, alcohol-urethane, isocyanate-alcohol and isocyanate-urethane complexes have been assumed [42-44] (Scheme 1.10-1.13). The primary complexes continue to react and give more stable cyclic complexes, which form urethanes in a separate step (Schemes 1.14 and 1.15).
The structure of the intermediate cyclic complex is independent of the initial complex, which can be based on either alcohol or isocyanate. The reaction can be catalyzed by Lewis bases and acids. Lewis acids polarize the isocyanate, while Lewis bases have the same effect on alcohols.

1.3.3. Kinetics of polyurethane synthesis

Numerous methods exist for the characterization of the kinetics of polyurethane synthesis. In order to be able to compare different models and results, it is convenient to use a unified description method. The differential description is frequently used in literature [45-49]. Kinetic equations can be described in other ways as well; however this approach offers several advantages. If the two components are present in equimolar ratio in the reaction mixture, the use of conversion instead of concentration can significantly simplify kinetic equations. In this case we define conversion as $\alpha = 1 - [RNCO]/[RNCO]_0$, where $[RNCO]_0$ is the initial and $[RNCO]$ is the actual concentration of the isocyanate. Using this approach the general form of most kinetic equations can be given as:

$$\frac{d\alpha}{dt} = k(T)f(\alpha)$$

(1.1)

where $d\alpha/dt$ is the rate of conversion, $k(T)$ is a temperature dependent, while $f(\alpha)$ is a conversion dependent term. $k(T)$ is usually described by the Arrhenius equation:

$$k = A \exp\left(-\frac{E_a}{RT}\right)$$

(1.2)
where $T$ is temperature, $R$ is the universal gas constant, $E_a$ is the activation energy of the reaction and $A$ is the pre-exponential factor.

Limited number of models is available for the description of the reaction kinetics of polyurethanes. The simplest is the $n$-th order model, which can be used in those cases when the initial, maximum reaction rate decreases continuously with time. Here $n$ is the total reaction order, which is the sum of $a$ and $b$, the reaction orders related to components $A$ and $B$. If $[R’OH]$ is the actual concentration of the alcohol component the kinetic equation can be written as:

$$v = -\frac{d[RNCO]}{dt} = -\frac{d[R’OH]}{dt} = k[RNCO]^a[R’OH]^b$$  \hspace{1cm} (1.3)

In the case of an equimolar composition:

$$\frac{d\alpha}{dt} = k(1 - \alpha)^n$$  \hspace{1cm} (1.4)

Different values are given in the literature for reaction order. In solution, or in the case of mono-functional compounds, several researchers use $n = 2$, while in melt reactions $n = 1$ is proposed. Others claim that the alcohol catalyzes urethane synthesis, thus $n = 3$ is the proper value [42,51].

If the measured reaction rates do not decrease continuously as a function of time, we must assume that reaction products influence the further course of polymerization, have catalytic effect on it. In such cases the autocatalytic model can be applied reasonably well. This model describes chemical processes in which the initial zero reaction rate increases as the reaction progresses. Several researchers found, that the urethane formed during polymerization has such catalytic effect. In this case reaction rate is given as:

$$v = -\frac{d[RNCO]}{dt} = -\frac{d[R’OH]}{dt} = k[RNCO]^a[R’OH]^b[RNCOOR]^m$$  \hspace{1cm} (1.5)

where $m$ is the order of the autocatalytic reaction. In the case of equimolar composition:

$$\frac{d\alpha}{dt} = k\alpha^m(1 - \alpha)^n$$  \hspace{1cm} (1.6)

Eq. 1.5 indicates that in the autocatalytic model the initial reaction rate is 0, which means that in itself cannot be used to describe real systems. As a consequence, this approach is usually combined with the $n$-th order model. The result is known in literature as the Kamal-Sourour equation (Eq. 1.6) [48,49].
where $k_1$ is the rate constant of the $n$–th order, while $k_2$ that of the autocatalytic reaction. This combined model can describe real systems quite well with the appropriate choice of the parameters $n$ and $m$. However, contradictions can be found in the literature concerning the proper choice for the value of $n$ and $m$. Sato [45,46] claims that the best values are $n = 2, m = 1$, while others suggest that the values are smaller for both parameters, or that the most accurate results can be obtained when $n + m = 2$.

Although the Kamal-Sourour model describes most two-component polymerization reactions quite well if reaction orders are selected arbitrarily as non-integer numbers, the physical meaning of these constants is questionable. The equation developed by Sato [45,46,57] offers a more rigorous approach by considering polyurethane synthesis as the combination of an alcohol (Schemes 1.16 and 1.17) and a urethane catalyzed (Schemes 1.18 and 1.19) process:

$\frac{d\alpha}{dt} = (k_1 + k_2\alpha^n)(1 - \alpha)^m$ \hspace{1cm} (1.7)

The assumed structure of complexes 1 and 2 is given in Schemes 1.12 and 1.13. The kinetic equations describing these chemical processes are shown by Eq. 1.8 for the alcohol catalyzed, and Eq. 1.9 for the urethane catalyzed process:

$RNCO + R'OH \xrightleftharpoons{k_{1}/k_{2}} \text{complex1}$

(Scheme 1.16)

$\text{complex1} + R'OH \xrightarrow{k_3} RNHCOOR' + R'OH$

(Scheme 1.17)

$RNCO + RNHCOOR' \xrightleftharpoons{k'_{1}/k'_{2}} \text{complex2}$

(Scheme 1.18)

$\text{complex2} + R'OH \xrightarrow{k_3'} RNHCOOR' + RNHCOOR'$

(Scheme 1.19)

The assumed structure of complexes 1 and 2 is given in Schemes 1.12 and 1.13. The kinetic equations describing these chemical processes are shown by Eq. 1.8 for the alcohol catalyzed, and Eq. 1.9 for the urethane catalyzed process:

$v = -\frac{d[RNCO]}{dt} = \frac{k_1k_3[RNCO][R'OHI]^2}{k_2 + k_3[R'OHI]}$ \hspace{1cm} (1.8)
For aromatic isocyanates the values of \( k_2 \) and \( k_2' \) are several magnitudes larger than \( k_3 \) and \( k_3' \), the equation can be rewritten in the following form (Eq. 1.10,1.11):

\[
v = -\frac{d[RNCO]}{dt} = \frac{k_1 k_3}{k_2} [RNCO][R'OH] [RNHCOOR']
\] (1.10)

\[
v = -\frac{d[RNCO]}{dt} = \frac{k_1' k_3'}{k_2'} [RNCO][R'OH] [RNHCOOR']
\] (1.11)

These equations can be simplified if we define \( K_1 = k_1 k_3 / k_2 \) and \( K_2 = k_1' k_3' / k_2' \) (Eq. 1.12,1.13):

\[
v = -\frac{d[RNCO]}{dt} = K_1 [RNCO][R'OH]^2
\] (1.12)

\[
v = -\frac{d[RNCO]}{dt} = K_2 [RNCO][R'OH][RNHCOOR']
\] (1.13)

Sato did extend his equation to account for cases when a catalyst is used but this has no relevance for non-catalyzed systems. Based on the definition of conversion (Eq. 1.15):

\[
v = -\frac{d[RNCO]}{dt} = K_1 [RNCO][R'OH]^2 + K_2 [RNCO][R'OH][RNHCOOR']
\] (1.14)

\[
\frac{d\alpha}{dt} = (K_1' + K_2' \alpha)(1 - \alpha)^2
\] (1.15)

where \( K_1' = K_1 A_0^2 \) and \( K_2' = (K_2 - K_1) A_0^2 \) if \( A_0 = [NCO]_0 = [OH]_0 \). The relation described in Eq. 1.15 is especially important and advantageous because contrary to Eq. 1.14, it allows us to compare reactions with different initial concentrations. However, during its application we must consider that the model described by Eq. 1.15 was developed by Sato [45,46] for reactions carried out in solution, so it does not take into consideration diffusion control.

Diffusion control must be considered in melt polymerization for several reasons [42,51,58]. In such reactions, apart from the initial phase, the actual reaction rate is usually slower in the entire conversion scale than expected from chemical considerations. Additionally, the reaction does not proceed to 100 % conversion. Considering these aspects, the equation must be modified for melt reactions (Eq. 1.16):
where \( f_c(\alpha) \) expresses the chemical term of conversion dependence, while \( f_d(\alpha) \) is the diffusion term. According to Fournier the function describing the effect of diffusion can be written as [42,58] (Eq. 1.17):

\[
f_d(\alpha) = 2 \left( 1 + \exp \left( \frac{\alpha - \alpha_f}{b} \right) \right)^{-1} - 1
\]

where \( \alpha_f \) is final conversion, while \( b \) is an empirical parameter which is related to the width of the glass transition temperature range. Complementing any kinetic model with the Fournier equation provides more accurate results, since diffusion can have a rather large impact on the polymerization reaction.

The measurement of reaction kinetics is difficult for bulk polymerization. Titration can be used for soluble components and relatively slow reactions [45,46,58,59]. Regular sampling provides information on the progress of the reaction; however continuous measurement is not possible with this technique. FTIR spectroscopy can be much faster and can monitor all chemical changes simultaneously [49,57,61,62]. Thermal methods can be used as well. One of the most frequently used techniques to follow reaction kinetics is differential scanning calorimetry (DSC) [43,63-67]. However, DSC is less useful if the reaction is very fast, or for foams. The measurement of adiabatic temperature rise is also used for the characterization of polyurethane kinetics [67-69], and it is especially effective for RIM formulations.

1.3.4. Structure

Almost independently of the type of PU, these polymers possess segmented structure (Fig. 1.5). The soft segments, which are formed from high molecular weight polyols, are mobile and are normally present as coils, while the hard segments, which are formed from the isocyanate and the chain extender, are stiff and immobile. Because the hard segments are covalently coupled to the soft segments, they act as cross-links, and inhibit the plastic flow of the polymer chains thus creating elastomeric resiliency. Upon mechanical deformation, parts of the soft segments are stressed by uncoiling, and the hard segments align in the stress direction. This reorientation of the hard segments and the consequent powerful hydrogen bonding results in high tensile strength, elongation, and tear resistance. [70,71] Hydrogen bonds and van der Waals interactions develop between the polymer chains. The segmented structure of the polyurethane chains leads to phase separation, which occurs because the mainly non-polar, low melting soft segments are incompatible with the polar, high melting hard segments. An increase in the chain length of the polyol results in an increased flexibility of the polymer chain
resulting in a more elastomer like behavior. Polyurethanes containing short chain length polyols are stiffer materials with larger strength [72]. However, the size, structure and properties of the actual hard and soft segments may vary in a wide range depending on the exact composition of the polymer chain. The separation of the two phases depends on the interaction between the polymer chains and the developing phase structure determines mechanical properties. The soft and hard segments can organize into micro crystallites or fibrils. The formation of the crystalline phase is related to the ordered structure of the polyurethane chains.

It is generally accepted that changes in thermal history result in different microphase structures. With increasing temperature amorphous hard segments dissolve in the soft phase. This process is very fast above the melting temperature of the crystallites of the hard segment, and the melt becomes homogeneous. During cooling from the melt phase separation starts again. Since the mobility of the polymer chains decreases with decreasing temperature, phase separation is hindered. Depending on cooling and post annealing conditions, different domain sizes and crystalline morphologies as well as varying degrees of phase separation are possible. The hard segment micro domains show a more or less ordered state which can be analyzed by wide-angle X-ray scattering (WAXS) and differential scanning calorimetry. The multiple melting behavior of MDI-diol-based polyurethanes observed in DSC traces shows two endothermic transitions at about 170 °C and from 190 to 230 °C. The lower transition is considered to be caused by the disordering of hard segment crystallites with relatively short-range order, while the endothermic peaks at higher temperatures are related to hard segment crystallites with long-range order. The existence and relative amount of different hard segment morphologies strongly depend on preparation conditions, on thermal history, on the degree of phase separation and on overall thermoplastic polyurethane (TPU) morphology. The processing-structure-property relationship is very complex as a consequence. [73-76]

1.3.5. Properties, requirements

An additional challenge is presented by working closely together with the surgeons responsible for such treatments. They are effectively using these materials for treatment, thus they have an intimate knowledge about the required behavior of these polymers. However, most of the time this knowledge is based on years of experience, and not on the deep understanding of materials science. In order to be able to prepare the polymer, with the best combination of properties, the detailed
requirements of the surgeons had to be translated to the appropriate chemical, physico-chemical and physical characteristics. The requirements of surgeons are translated into the language of the material scientist in Table 1.1.

**Table 1.1 Correspondence of surgical aspects and material properties**

<table>
<thead>
<tr>
<th>Surgical aspect</th>
<th>Material property</th>
</tr>
</thead>
<tbody>
<tr>
<td>time of solution</td>
<td>polarity, interaction</td>
</tr>
<tr>
<td>shape of the precipitated polymer</td>
<td>surface tension</td>
</tr>
<tr>
<td>diffusion rate of solvent</td>
<td>diffusion coefficient</td>
</tr>
<tr>
<td>dilutability with alcohol</td>
<td>miscibility, interaction</td>
</tr>
<tr>
<td>porosity</td>
<td>diffusion rate</td>
</tr>
<tr>
<td>stiffness</td>
<td>Young’s modulus</td>
</tr>
<tr>
<td>repeated dissolution and precipitation</td>
<td>linear molecular structure</td>
</tr>
<tr>
<td>expansion during precipitation</td>
<td>solubility, polarity</td>
</tr>
<tr>
<td>flow through a catheter</td>
<td>molecular weight, viscosity</td>
</tr>
<tr>
<td>solution stability</td>
<td>polarity, interaction</td>
</tr>
</tbody>
</table>

As the table shows interactions and the polarity of the polymer plays a crucial role in the determination of properties important for the medical application in question. Mechanical properties however play a somewhat lesser role than solubility, viscosity, etc. The large number of different aspects and parameters also increase the problems related to the development of an appropriate material. Polyurethane based on a polyether polyol might have better mechanical properties for such applications, but inferior solubility than a polymer prepared from polyester polyol. Changes in one parameter, like the choice of the polyol used, will influence several characteristics important for the application, i.e. a wide range of properties have to be controlled simultaneously.

We pointed out on several occasions that besides the properties of the polyurethane, also the characteristics of the entire embolizing preparatum must be considered during development. The requirements for the embolization system are listed below. Low viscosity is very important (the procedure is carried out in a 0.1 mm thick catheter), other requirements include rapid filling of large aneurysms, quick precipitation, but not in the catheter, during precipitation it should take on the shape of the aneurysm, the material should be flexible, the preparatum must be able to be withdrawn into the catheter for a short period of time, no washing with DMSO should be required, stability against a turbulent blood stream should be exhibited, the catheter need to be easily removed from precipitate and no sticking to wall of blood vessels must occur. A closer scrutiny clearly shows that requirements can be
fulfilled by the appropriate choice of the polymer. On the other hand, a number of properties are influenced by the contrast material and the solvent as well. The viscosity of the solution, for example depends on the choice of all three components.

1.4. Scope

As we described in previous sections, both the chemistry and the structure-property correlations of segmented polyurethanes are extremely complicated. As a consequence many questions are still open in spite of many decades of research and industrial application. Our task, the preparation of a polymer with optimum properties for endovascular surgery is further complicated by the stringent conditions and complex requirements of the application. As mentioned in the introductory part, the apparently diverse issues discussed in this thesis are connected by the same goal and drive the project towards its conclusion. Instead of randomly selecting interesting scientific problems, we had to carry out experiments oriented by the application and by the needs of our partners. In spite of the prominent role of practical questions in our research, we always drove for deeper understanding of the problems investigated in the hope that we can find correlations of general validity, which can help us in the further course of the project. Accordingly, this thesis addresses questions which have not been investigated up to now, or have not been answered satisfactorily yet. Most, but not all, of these issues are in line with our competence, but the entire thesis represents the opening of a new area for the Laboratory by focusing attention onto the medical application of polymers and within this huge area more specifically onto the sensitive question of polymers used for endovascular surgery.

As described in the background section of the thesis, polyurethane chemistry is rather complex and the kinetics of polymerization cannot be described with very simple models. Moreover, most of the existing models were developed for and verified on two-component isocyanate/diol mixtures. However, in industrial practice three-component isocyanate/polyol/chain extender mixtures are used in order to be able to adjust polymer properties more flexibly and accurately. Additionally, contrary to industrial practice, we could not and did not used catalyst during polymerization in order to avoid any possible health hazard. Under such conditions the study of polymerization kinetics was extremely important for us in order to obtain information about the time dependence of polymerization, the effect of composition on it and about any factor, which might influence structure and properties. Accordingly, in Chapter 3 we report the results of a polymerization kinetic study carried out on three-component mixtures based on a polyester polyol. The segmented polyurethane elastomers in question were prepared from MDI, butandiol and a polyester polyol with the molecular weight of 2000. The ratio of the polyol and the chain extender varied from 0 to 1. Reaction kinetics of urethane polymerization was followed with isothermal DSC measurements at different temperatures. We developed an evaluation protocol for the processing of the primary data and fitted various existing models to the results in order to find the most suitable one for the description of our rather complex system. Subsequently we
analyzed the kinetic parameters obtained and tried to draw conclusions of general validity for further research. The results strongly confirmed our preliminary assumptions about the complexity of the chemistry and pointed out several important facts, which might be used for further polymerization experiments.

Kinetic experiments called our attention to the fact that in polymerization reactions carried out without catalyst at least two kinds of self catalysis occurs and one or more side reactions may also take place. Polymers with various structures may form in these reactions depending on reaction conditions and composition. Molecules with varying chain structure may enter into a number of interactions with each other that can lead to the formation of polymers with different phase structure. The detailed knowledge of structure-property correlations is one of the key issues for designing polymers for the intended application. Because of their importance we discuss structure-property correlations of polyether polyurethanes in the next two chapters. In Chapter 4 we describe the preparation and study of linear polyurethanes with various stoichiometry from 4,4’-methylenebis(phenyl isocyanate), 1,4-butanediol and poly(tetrahydrofuran). The reaction was carried out in the melt and we changed the relative ratio of NCO and OH functionalities in this series of experiments. The molecular weight of the polymers was estimated from the equilibrium torque measured during the reaction, mechanical properties were characterized by tensile testing and DMA measurements, while phase separation by the determination of transparency. Properties depended differently on composition, which seemed to be rather contradictory at the first glance. Molecular weight decreased drastically with changing stoichiometry as expected, but the composition dependence of ultimate tensile properties were asymmetric, and tensile modulus changed in the opposite direction than the rest of the properties. A hypothesis was developed to explain the apparently contradictory results. Further experiments were carried out to verify the hypothesis later, the results of which are reported in Chapter 5. Molecular weight was determined also by GPC in order to verify conclusions drawn from changes in equilibrium torque, relaxation transitions were characterized also by DSC, and interactions by the measurement of equilibrium solvent uptake as well as by the calculation of Flory-Huggins interaction parameters. The results completely confirmed our hypothesis and proved that the specific interactions drive phase separation and phase structure determines completely some of the properties of the polymer. However, besides phase structure other properties depend also on molecular weight, i.e. a combination of molecular and phase structure determines them. These relationships must be closely regarded in further research and development work.

In the final part of the study we focused our attention on a completely different question, which, however, is extremely important for the application in question. We mentioned earlier that the embolization solution must be made visible with the help of a contrast material. Several elements and compounds can be used as contrasting agents and a few are available also in the open market. However, these materials are not characterized very well, their contrasting efficiency is not known and the stability of their suspensions is not determined at all. Our partners faced the situation quite frequently that a contrast material purchased for the preparation of
embolizing solutions separated very fast as a result of sedimentation. In Chapter 6 we describe the results of experiments carried out on some contrast materials. In order to extend the selection of potential contrasting agents we prepared barium sulfate particles by precipitation. With the modification of the preparation technology, a large number of barium sulfate samples were prepared in a range of particle sizes and shapes. The size of the particles was characterized by two methods, dynamic laser light scattering and scanning electron microscopy. Two commercial samples were used as reference materials. The particles prepared by us showed definite advantages compared to samples available from commercial sources. One of the most important characteristics of embolizing solutions is their stability. One can see the obvious and very dangerous consequences of fast sedimentation of the contrasting agent during surgery within the catheter or in the arteries. Since we did not find an appropriate method for the determination of sedimentation rate and suspension stability, we developed our own technique. The method is described in detail in this chapter and the results show that sedimentation stability changes quite drastically from one sample to the other, indeed. In Chapter 7, which is closely related to the previous one, the study was extended also to contrasting agents others than barium sulfate. Tantalum and silver particles of various sizes and shapes were acquired from commercial sources and characterized with the same techniques developed in the previous part of the work. The results further corroborated our conclusions that very few of the commercial contrasting agents are suitable for the purpose of endovascular surgery.

In the final chapter of the thesis, in Chapter 8, we briefly summarize the main results obtained during the work, but refrain from their detailed discussion, because the most important conclusions were drawn and reported at the end of each chapter. This chapter is basically restricted to the listing of the major thesis points of the work. The large number of experimental results obtained in the research supplied useful information and led to several conclusions, which can be used during further research and development related to the preparation of a segmented linear polyurethane elastomers applied for endovascular surgery. Nevertheless, quite a few questions remained open in the various parts of the study, their explanation needs further experiments. Research continues in this project at the Laboratory and we hope to proceed successfully further along the way indicated by this thesis.

1.5. References

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Chapter 2

Polymerization kinetics of three-component segmented linear polyurethane elastomers

2.1. Introduction

The large versatility of polyurethanes are the result of the flexibility of urethane chemistry as described in Chapter 1 [1-13]. The right selection of component type, composition and reaction parameters allows the design and modification of properties. The proper characterization and control of the polymerization reactions of polyurethanes are rather difficult [1-4, 13-29]. Although the main reaction of the isocyanate with a diol seems to be rather simple, it proved to be much more complicated in reality. Usually a catalyst is added to control reaction rate, but metal containing catalysts or amines cannot be used in polymers intended for medical applications. Non-catalyzed reactions are relatively slow and self catalysis also occurs, both the diol and the urethane formed influence reaction kinetics [13, 14]. It is not very surprising that simple kinetic models cannot describe the time dependence of polymerization properly even for two-component isocyanate/diol mixtures [15, 16]. Additionally, at the slow reaction rates, side reactions may also proceed with comparable rates and modify reaction kinetics, structure and the properties of the polymer. Moreover, in industrial practice usually three components are used, besides the oligomeric diol and the isocyanate, a short chain diol or chain extender, is also added to the reaction mixture. The addition of the diol further increases the flexibility of the chemistry and offers another possibility to modify properties, but also complicates reaction kinetics [6]. Very few papers are available in the open literature, which present kinetic data about the polymerization kinetics of three-component polyurethane elastomers.

The goal of this part our research was to prepare a segmented polyurethane elastomer for a specific medical application, for the endovascular treatment of aneurisms and arteriovenous malformations. We can adjust the properties of the polymer to the requirements of the application only if we completely control its synthesis. In order to obtain information about the factors influencing the polymerization reactions and the properties of the products, kinetic measurements were carried out as a function of composition in three-component systems. The stoichiometric ratio of the hydroxyl groups of the polyol and the chain extender, respectively, was changed from 0 to 1. We tried to analyze our experimental results with various kinetic models and to select the most appropriate one for the quantitative description of the polymerization process.
2.2. Experimental

Polyurethanes were prepared from 4,4'-methylenebis (phenyl isocyanate) (MDI), 1,4-butanediol chain extender (BD) and a polyester polyol with the molecular weight of 2000 and average functionality of 2. MDI and the chain extender were purchased from Aldrich. The polyol and butanediol were dried under vacuum at 50 °C for 12 hours before the experiment. The commercially available polyol Lupraphen 8101 was supplied by Elastogran Kemipur Kft. The NCO/OH functional group ratio was kept constant at 1.0 in all experiments, while the ratio of the polyol and the chain extender was varied in this study. In our work, we define POH/OH as the ratio of hydroxyl groups from the polyol and the total number of OH groups present in the mixture. Preliminary studies showed that the reaction between the three components starts at room temperature even without any catalysts. Proper sample preparation procedure was essential to achieve reliable and accurate results [27,28,29]. The MDI was ground before use to a fine powder. A reaction mixture of 10 cm³ volume was prepared initially. The polyol and butanediol were homogenized then the MDI powder was added to the mixture. After 10 seconds intensive mixing the mixture was cooled to -70 °C. Samples of 10 mg weight were introduced into the DSC cell at -100 °C.

Differential scanning calorimetry (DSC) was carried out using a Perkin Elmer Diamond DSC at 80, 90, 100, 110 and 120 °C under constant helium flow. 200 °C/min heating rate was used to reach the starting point of the measurement. Additionally temperature scans were carried out with heating rates of 20 °C/min and 200 °C/min between -100 °C and 200 °C for every composition. We had to convert the primary results obtained by DSC in order to determine the relevant kinetic parameters. First the registered heat flow vs. time curves were transformed to conversion rate vs. conversion traces. Conversion was defined as the ratio of the overall reaction heat and the heat released up to the given time. Overall reaction heat was determined by integrating the heat flow-temperature trace, while its partial differential at any given time gave the heat released up to that point. To acquire accurate results, the reaction heat had to be corrected, since heat was released even before reaching the isotherm temperature of the measurement and reactions did not always proceed to 100 % conversion. The heat released until the temperature of isotherm measurement was determined from the scan made at 200 °C/min heating rate, while the residual heat for not reaching 100 % conversion was derived from the scan done at 20 °C/min rate. After these corrections, conversion rates were plotted against conversion for each composition.

Additional corrections were necessary to achieve an accurate fitting to the model used. The converted curves consist of discreet points. However these points are distributed unevenly along the conversion scale, they appear more frequently at large conversions. These results in different weighting of the data at low and high conversions and the model fail to describe the examined system as a consequence. The bias was corrected by generating functions with equidistant distribution of values for fitting and further evaluation.
2.3. Results and Discussion

We must call attention here to the fact again that while compositions with POH/OH ratios of 0 and 1 are two-component systems, most examined mixtures contained three constituents. Only limited information is available about the kinetics of such polymerization in the open literature. The results are discussed in several sections. First we present the primary results obtained by DSC, then we analyze the adequacy of various models for the quantitative description of our results. Finally we discuss the composition dependence of the kinetic parameters derived from the model.

2.3.1. Primary results

Primary results obtained by direct measurement at three different temperatures are presented in Fig. 2.1 for the two-component MDI/butanediol mixture. The reaction is very fast, it is completed within 2 minutes at higher temperatures, which justifies the procedure to account for reaction heat developing before reaching the temperature of isothermal measurement. The catalytic effect of the urethane group is shown clearly by the shape of the correlations, by the maximum appearing in the traces. Lack of autocatalysis would result in continuously decreasing reaction heat as the functional groups are consumed during the reaction. Reaction rate increases with increasing temperature, as expected.

![Primary DSC traces recorded on the sample with the POH/OH ratio of 0 at 80°C (——), 100°C (·······) and 120 °C (--------).](image)

Fig. 2.1 Primary DSC traces recorded on the sample with the POH/OH ratio of 0 at 80°C (——), 100°C (·······) and 120 °C (--------).
A very interesting feature of the traces is the appearance of a shoulder at longer reaction times, indicated by arrows. Although the shoulder is not very pronounced, but it can be undoubtedly observed on all traces measured at small polyol contents. The only plausible explanation for the phenomenon was the assumption of a side reaction, probably the formation of allophanates. The large concentration of functional groups at small polyol content as well as fast reaction rates initiate allophanate formation. At such compositions the concentration of both end-groups and urethane groups is larger due to the short chains of the chain extender. The short distances among functional groups and their high concentration increase the possibility of the reaction of an isocyanate with a urethane group. Later we will observe that this reaction is initiated at relatively high conversions, which confirms the role of the urethane group. On the other hand, allophanate formation must be confirmed by other measurements, which are under way at the moment.

\[ \text{Fig. 2.2 Kinetics of urethane polymerization recorded by DSC at the POH/OH ratio of 0.5 at 80°C, 100°C and 120°C.} \]

The shape of the heat flow vs. time traces differs considerably at intermediate POH/OH compositions (Fig. 2.2). Reaction rate decreases considerably with increasing polyol content shown both by the heat flow values and the time scale of the figure. The decrease of reaction rate may result from the different reactivity of the two diols, but we find it more probable that it is caused by the changing concentration of functional groups as a result of the larger molecular weight of the polyol. A further difference compared to Fig. 2.1 is the disappearance of both the maximum and the shoulder observed at high butanediol content. Urethane catalysis
is almost completely absent, which is difficult to explain. The disappearance of the shoulder assigned to allophanate formation may be explained by decreasing reaction rates and smaller concentration of functional groups.

The kinetics of urethane polymerization is presented in Fig. 2.3 for the two-component MDI/polyol mixture. Reaction rate decreased further as expected. Urethane catalysis is very pronounced again, which further complicates the interpretation of the results. The absence of this effect at intermediate POH/OH ratios is very difficult to explain, indeed. The side reaction indicated by the appearance of a shoulder at high butanediol content is completely absent here too, which supports our assumption that side reactions occur mainly at high concentrations of the functional groups.

![Graph showing isotherm polymerization of the MDI/polyol reaction mixture.](image)

**Fig. 2.3** Isotherm polymerization of the MDI/polyol reaction mixture \((\text{POH/OH} = 1)\) in the DSC cell at 80 (---), 100 (-----) and 120 °C (------).

2.3.2. Quantitative evaluation, modeling

We hope to obtain further information from the quantitative evaluation of the results, which can be carried out much more easily if we convert the results into conversion rate vs. conversion correlations. As the first step, we carried out the detailed study of existing models. Fig. 2.4 presents an example comparing the fitting of three models, the \(n\)-th order, the Kamal-Sourour and the Sato-Fournier models to kinetic data obtained at \(\text{POH/OH} = 0.8\) and 110 °C. In view of the results of Figs. 2.1-2.3, the \(n\)-th order model could not be considered seriously, because it does not take into account urethane catalysis at all, although it has a pronounced effect on
polymerization at certain composition ranges. The very poor fit of this model in Fig. 2.4 clearly confirms these conclusions. The Kamal-Sourour model offers a more reasonable fit. However, the non-integer order parameters do not have physical meaning and the model does not consider diffusion control, which is important in melt reactions. As a consequence, we decided to use the Sato-Fournier model for further evaluation, which considers both hydroxyl (see first term of Eq. 1.14) and urethane catalysis (second term of Eq. 1.14), and through the introduction of the Fournier equation accounts also for diffusion control.

![Fig. 2.4 Fitting of various models to the isothermal polymerization kinetic data obtained on at POH/OH = 0.8 and 110 °C; (——) n-th order (k = 0.06, n = 1.25), (⋯⋯⋯⋯⋯) Kamal-Sourour (K’1 = 0.048, K’2 = 0.173, n = 2.40, m = 0.94), (-----) Sato-Fournier (K’1 = 0.052, K’2 = 0.123, αf = 0.8, b = 0.064).](image)

The converted results are presented in Fig. 2.5 for the two-component MDI/butanediol mixture. The qualitative conclusions drawn from the scrutiny of primary DSC results on reaction rate and on the shape of the curves are confirmed by the figure, but additional information can be also gained from this representation. The figure emphasizes strongly the fact that at low POH/OH ratios the polymerization proceeds with a considerable rate already before reaching the isotherm temperature of the measurement. The effect is less pronounced at lower temperatures, where reaction rate is slower. Although the phenomenon is related to the measurement technique rather than reaction kinetics, it can not be neglected during the interpretation of our results. It is also important to note that mainly at lower temperatures the reaction stops before reaching 100 % conversion, the reaction freezes. This can be possibly related to the changing T_g of the hard
segments, which increases with conversion. The freezing of polymerization appears mostly in the butadiene containing two-component system and in reaction mixtures containing large amounts of the chain extender. The $T_g$ of the hard segments is high for these polymers leading to the observed effect, which obviously validates the use of the Fournier correction in the model used and in the fitting procedure. The final observation related to Fig. 2.5 concerns the side reaction mentioned earlier. It appears very pronouncedly in the figure, especially at higher temperatures. Large conversion, high temperature, high concentration of functional groups and short chains favor the initiation of this reaction.

Fig. 2.6 shows the conversion rate vs. conversion traces for the three-component reaction mixture containing equal amounts of the two diols (POH/OH = 0.5). The slower rate, the lack of side reaction and especially the absence of urethane catalysis can be observed very clearly in the figure. The last phenomenon is especially surprising, because as Fig. 2.7 shows, urethane catalysis is quite pronounced again at even smaller butanediol content. Accordingly, the disappearance of the peak, i.e. lack of urethane catalysis, cannot result from concentration effects, but it must be initiated by some other factor. A possible explanation might be the changing interaction and miscibility of the hard and soft segments with composition, and the consequent modification of phase structure. In a related study [30] we observed considerable differences in phase structure and properties of polyether polyurethane elastomers due to the interaction of end-groups.

**Fig. 2.5** Modeling of the polymerization kinetics of the two-component MDI/butanediol reaction mixture (POH/OH = 0) with the Sato-Fournier model. Symbols are measured values; the solid line is the fitted model. Polymerization temperatures: (□) 80, (○) 90, (△) 100, (▽) 110 and (◇) 120 °C.
Fig. 2.6 Converted reaction rate vs. conversion traces for the sample with POH/OH = 0.5. Symbols are the same as in Fig. 2.5.

Fig. 2.7 Fitting the Sato-Fournier model to the kinetic data obtained during the polymerization of the MDI/polyol reaction mixture (POH/OH = 1). Symbols are the same as in Fig. 2.5.
The POH/OH ratio was kept constant in those experiments and the NCO/OH ratio was modified resulting mainly in the change of molecular weight. Modification of the polyol/diol ratio must have a much more pronounced effect on phase separation and morphology. Although this hypothesis is pure speculation based on earlier experience obtained on a different system, we do not have a more plausible explanation for the phenomenon at the moment. Further experiments are under way to verify it or to find the real one. The slow reaction rate and the lack of side reaction are visible also in Fig. 2.7 and confirm observations made earlier.

Comparison of Figs. 2.5-2.7 calls attention also to the fact that the quality of fitting improves as the polyol content of the mixture increases, irrespectively of the presence or absence of urethane catalysis. The very high reaction rates at large butadiene content result in technical problems, on the one hand, and the observed side reaction is not considered by the model, on the other hand. Other, complementary techniques must be used to overcome the first difficulty, while the side reaction must be correctly identified and accommodated into the model to obtain a better fit.

2.3.3. Kinetic parameters, composition dependence

By fitting the Sato model to the measured data we determined various kinetic parameters characterizing urethane polymerization. The determination of the temperature dependence of the rate constants $K_1$ and $K_2$ allows us to calculate the activation energy of the reactions, while the evaluation of the $K'_1$ and $K'_2$ parameters offer information about the relative weight of the two mechanisms, -OH and urethane catalysis, respectively. However, at this point we must emphasize that these two rate constants are not independent of concentration.

Parameter $K'_1$ characterizing the -OH catalyzed reaction is plotted against the POH/OH ratio in Fig. 2.8. Reaction rate decreases gradually with increasing polyol content. The decrease might result from the different reactivity of the two diols, or from changing concentration due to the different molecular weights of the diols. At lower temperatures we see a somewhat different picture. At 80 °C reaction rate is slower than expected for samples with low polyol contents. The deviation from the expected tendency is probably caused by the immiscibility of BD and MDI in this composition range. Separation of the components can be seen already during the preparation of the samples. A very good homogeneity is achieved by grinding at low temperature and by the thorough mixing of the components, but at low reaction temperatures the rate of polymerization is slow and sufficient time is available making phase separation possible. Miscibility is better and the reaction is faster at larger polyol contents and higher temperatures, thus phase separation does not occur under these conditions.
Fig. 2.8 Composition dependence of the apparent rate constant $K'_1$ at three different temperatures: (□) 80, (○) 100 and (△) 120 °C.

Fig. 2.9 Effect of the POH/OH ratio on the apparent rate constant of $K'_2$ at (□) 80 and (△) 120 °C. Values measured at other temperatures fall between the two sets shown.
Fig. 2.10 Arrhenius plot of rate constants (○) $K_1$ for the -OH and (□) $K_2$ for the urethane catalyzed reaction at the POH/OH ratio of 0.

Fig. 2.11 Arrhenius plot for the (○) $K_1$ and (□) $K_2$ rate constants at POH/OH = 1.
The composition dependence of the $K'_2$ parameter related to the urethane catalyzed reaction is very interesting (Fig. 2.9). It reflects very clearly the changes observed qualitatively in Figs. 2.1-2.3 and 2.5-2.7. Urethane catalysis is very strong at small polyol content, which seems to be obvious in view of the higher concentration of functional groups in a unit volume. The largest value (4.2 at POH/OH = 0) at 120 °C was omitted from the figure in order to be able to extend the scale. Although the results at large butanediol content must be regarded with some caution because of the difficulties in fitting, the tendency is clear and valid for all temperatures. A strong minimum is observed in the value of $K'_2$ at the POH/OH ratio of around 0.3. The negative values indicate that the $-\text{OH}$ catalyzed reaction dominates polymerization in this composition range (see definition $K'_2 = (K_2 - K_1)A_0$). The weight of the two reactions changes considerably at larger polyol content. The strange correlation was explained earlier with changing interactions, miscibility and phase structure, but it must be verified with further experiments.

![Fig. 2.12] Composition dependence of the activation energies (○) $E_1$ for the $-\text{OH}$ and (□) $E_2$ for the urethane catalyzed reaction; the solid line represents $E_a$ value given by Macosko [6].

The temperature dependence of the $K_1$ and $K_2$ rate constants was described with the Arrhenius equation. The Arrhenius plot is presented in Fig. 2.10 for the two-component MDI/butanediol reaction mixture. The two rate constants are more or less similar in magnitude, indicating that the two reactions proceed with approximately the same rate. However, the scatter of the points is considerable and
the correlations should be treated with care because of difficulties in evaluation discussed before (early, fast reaction; phase separation; side reaction). The fit is much better at larger polyol contents as the correlation presented for the two-component MDI/polyol reaction shows in Fig. 2.11. The considerably larger $K_2$ values indicate that the urethane catalyzed process dominates polymerization at higher polyol concentrations.

The activation energy of the two reactions was determined from the Arrhenius plots. The values obtained are plotted against composition in Fig. 2.12. The scatter of the points is very large due to the difficulties discussed before, but a clear tendency definitely cannot be seen as a function of composition. Both values cover the same range and generally agree quite well with the activation energy of 55 kJ/mol given by Macosco [6]. The independence of activation energy from composition indicates that the reactivity of the -OH group with the isocyanate is the same in both diol compounds. This clearly proves that changing reaction rates result from concentration effects and not from the dissimilar reactivity of the two diols.

2.4. Conclusions

The kinetic study carried out on three-component segmented polyurethane elastomers clearly proved that melt polymerization is very complicated and it is affected by many factors. The results of the kinetic experiments could be analyzed relatively well by the Sato-Fournier model, while the simple n-th order and the Kamal-Sourour models failed in the studied system. Modeling clearly proved that the relative weight of hydroxyl and urethane catalyzed reactions changes with composition, with the polyol/butanediol ratio. The lack of urethane catalysis in certain composition range was explained by the effect of changing interactions, miscibility and phase structure, but the assumption must be proved with further experiments. Phase separation and changing $T_g$ hindered reaching complete conversion at high butanediol contents, which justified the use of a term taking into account diffusion control. The analysis also showed that a side reaction, probably allophanate formation, also occurs at high butanediol content, which is not accounted for by the model used. The analysis of rate constants and activation energies proved that changing reaction rates result from concentration effects and not from the dissimilar reactivity of the diol components. The experimental and fitting procedure developed takes into consideration most of the factors affecting urethane polymerization and yield valuable information about the complex system studied. Kinetic analysis must be and will be supplemented with the study of molecular and phase structure as well as polymer properties.
2.5. References


Chapter 3

Effect of molecular and phase structure on the properties of polyurethane elastomers

3.1. Introduction

Polyurethanes (PU) are very versatile materials used in a large variety of application areas [1-2]. As detailed in Chapter 1, the choice of components and composition determine the structure developing, thus the properties of the polymer [3-20]. Molecular weight and molecular architecture have the same importance like in all other polymers. However, the distribution of structural elements and the end groups formed may result in strongly differing properties even at the same composition [21-23]. The extent of phase separation, the size of the structural units and their properties may have strong effect on the final properties of the polymer [24-27]. The various factors, i.e. molecular characteristics, interactions and phase structure influence each property of the polymer in a different way [28-30], thus the knowledge of these relationships is essential to achieve the desired combination of properties.

During our research we synthesized a wide range of polymers with various compositions, structure and properties. In one series of experiments we prepared polyurethanes with varying stoichiometric ratio of the isocyanate and hydroxyl groups to change the molecular weight of the polymer. However, the modification of composition changed also interactions and phase structure. In this chapter we report the effect of various factors on the properties of the segmented polyurethanes prepared.

3.2. Experimental

The polyurethanes were prepared from 4,4’-methylenebis(phenyl isocyanate) (MDI), 1,4-butanediol chain extender (BD) and poly(tetrahydrofuran) polyether polyol with a molecular weight of 1000 (PTHF). All three ingredients were purchased from Aldrich and used as received. The –OH functional group ratio of polyol/diol was kept constant at 0.4 in all experiments. In this study the variable was the ratio of the isocyanate and hydroxyl groups (NCO/OH), which changed between 0.940 and 1.150. Polymerization was carried out by melt reaction in an internal mixer (Brabender W 50 EH) at 150 °C, 50 rpm for 30 min. The polymer was compression molded into 1 mm plates at 200 °C and 5 min for characterization using a Fontijne SRA 100 machine.

A wide range of techniques were used for the detailed characterization of the samples including Fourier transform infrared spectroscopy (FTIR), wide angle X-ray diffraction (XRD), differential scanning calorimetry (DSC), dynamic mechanical analysis (DMA), gel permeation chromatography (GPC), mechanical testing and the determination of light transmission. In the first part of this report
only a part of the results will be presented, we give the details only of the most relevant techniques here. The torque and temperature of mixing was recorded during polymerization, which give information about the kinetics of polymerization and the molecular weight of the final product. DMA spectra were recorded on samples with 20 x 10 x 1 mm dimensions between -120 and 200 °C at 2 °C/min heating rate in N₂ atmosphere in tensile mode using a Perkin Elmer Pyris Diamond DMA apparatus. The mechanical properties of the samples were characterized by tensile testing on dog bone type specimens with 50 x 10 x 1 mm dimensions at 100 mm/min cross-head speed using an Instron 5566 apparatus. Tensile strength and elongation-at-break were derived from recorded force vs. elongation traces, while Young’s modulus was determined from the initial, linear section of the traces. The transparency of the samples was measured by a Spekol UV-VIS apparatus at 500 nm wavelength.

3.3. Results and Discussion

The various aspects of the structure and properties of the polyurethanes prepared are discussed in separate sections. Molecular weight, mechanical properties and phase structure are presented first, followed by the discussion of structure-property correlations.

3.3.1. Molecular weight

According to the rules of stepwise polymerization, the molecular weight of the polymer decreases with the changing stoichiometric ratio of the two functional groups. Molecular weight decreases drastically with increasing deviation from equimolar stoichiometry. The torque of the polymer melt in the internal mixer is proportional to viscosity, which on the other hand depends on molecular weight. Accordingly, torque is a good indicator of changes in molecular weight if all other conditions are the same. The torque measured at the end of the reaction is plotted against the NCO/OH ratio in Fig. 3.1. The expected correlation is obtained, molecular weight decreases drastically with changing stoichiometry. The maximum of the correlation is not at equimolar ratio of the two components probably because of side reactions, some impurities or the effect of moisture which cannot be avoided in spite of all efforts done.

We must call the attention here to a few important facts. The polymer flows freely and the sample could be compression molded into plates even at large isocyanate/hydroxyl ratios indicating that considerable cross-linking did not take place. The determination of possible cross-linking was difficult by any other means since the solubility of the samples is rather poor in all common solvents. We found it also important that the correlation is almost completely symmetrical, viscosity is only slightly higher on the side of isocyanate excess than at large OH content. The slight difference might result from the different effect of chain ends and the stronger interaction of the urethane moieties. In further consideration we assume that the polymer consists of mainly linear chains.
3.3.2. Mechanical properties

The tensile strength of the samples is plotted against the stoichiometric ratio of the components in Fig. 3.2, while the corresponding elongation-at-break values in Fig. 3.3. The two correlations are very similar to each other, but unlike the torque vs. NCO/OH correlation they are highly asymmetric. Increasing length of the molecules makes possible the formation of multiple entanglements and strongly increases tensile strength and the ultimate deformation of the samples. This effect is clearly demonstrated in the left hand side of the correlations, where excess number of –OH groups were added to the reaction mixture. On the isocyanate side larger strengths and elongations were measured, which cannot result from cross-linking or longer chains, because viscosity changed symmetrically with changing stoichiometry. The asymmetry of the correlation is probably caused by the stronger interactions prevailing on the right hand side of the correlation; both the urethane and the amine end groups formed may enter into stronger interactions with each other than the free –OH end groups. These results clearly indicate that interactions have a stronger influence on properties in the solid than in the melt state.
**Fig. 3.2** Dependence of the tensile strength of segmented polyurethanes on the NCO/OH ratio of the reaction mixture.

**Fig. 3.3** Changes in the elongation-at-break values of segmented polyurethanes as a function of the relative number of functional groups.
Fig. 3.4 Tensile modulus of polyurethanes plotted against the stoichiometric ratio of the functional groups.

The composition dependence of stiffness is presented in Fig. 3.4. The correlation differs very strongly from those shown previously (see Figs. 3.1-3.3). Stiffness decreases almost linearly with increasing NCO/OH ratio until a minimum, which more or less corresponds to the maximum observed in Figs. 3.1-3.3, and then increases also linearly with further increase in isocyanate content. The figure clearly shows that modulus does not depend on molecular weight practically at all, but on some other factor, which also changes with composition. Based on the results presented up to now, a trivial explanation cannot be given for the correlation.

3.3.3. Relaxation, mobility

DMA is a powerful tool for the characterization of the molecular structure of polymers; it reveals the number of relaxing units and offers some information also about their size and mobility. A typical DMA spectrum is presented in Fig. 3.5. Three relaxation transitions of various intensities can be observed on the traces of storage and loss modulus as well as on the temperature dependence of loss tangent. The first appears at around -75 °C with a relatively low intensity. The exact identification of the relaxing species is relatively difficult; it might belong to the aliphatic units of the polytetrahydrofuran segments. The second transition detected at around -13 °C is obviously the relaxation transition of the soft segments of the PU chains. The intensity of this transition is considerable and dominates the spectrum. The third, weak transition appears at higher temperature, at around 75 °C indicating the movement of larger, less mobile structural units. We may assume that this
transition belongs to the movement of the hard segments. The small intensity of this transition can be explained by the stiffness of these segments, which does not change much during the transition from the glassy to the rubbery state.

![DMA spectrum of a polyurethane sample with the NCO/OH ratio of 1.045.](image)

**Fig. 3.5** DMA spectrum of a polyurethane sample with the NCO/OH ratio of 1.045. 

(-----) storage modulus, $E'$, (......) loss modulus, $E''$, (—) loss tangent, $\tan \delta$.

Changing composition and sequence distribution as well as changing interactions modify the mobility of the structural units and influence transition temperatures. The composition dependence of the transition temperature of the soft and hard segments is presented in Fig. 3.6. The $T_g$ of the soft segments increases relatively steeply with increasing isocyanate content, the total increase of $T_g$ is about 15 °C, which is considerable, then slightly decreases after reaching a maximum ($\Delta T_g \approx 4$ °C). The continuous decrease of mobility can be explained with the effect of the increasing amount of isocyanate groups which hinder the movement of the soft segments. The composition dependence of the $T_g$ of the hard segments is more or less similar with the difference, that it increases at a slower rate at low NCO/OH ratio and much sharper at around the equimolar ratio of the two components followed by a slower increase again at large NCO/OH ratios. The strong increase of slope observed in the range of equimolar stoichiometry suggests that besides the interaction of individual groups, also phase structure might influence the behavior of the chains and the properties of the polymer. Unfortunately, the correlations presented in Fig. 3.6 do not explain the decrease of modulus presented in Fig. 3.4. The mobility of both soft and hard segments decreases continuously, which should result in the continuous increase of polymer stiffness as well. Further information and considerations are need for the reliable explanation of the contradiction.
Fig. 3.6 Effect of composition on the temperature dependence of the glass transition temperature of the soft and hard segments of PU; (O) soft segments, ( ) hard segments.

Fig. 3.7 Changes in the relaxation intensity of the soft segments with composition; NCO/OH ratio: a) 0.965, b) 1.045, c) 1.125.
Transition temperatures indicate the mobility of the relaxing units, while the intensity of the transition depends on the number of relaxing units. The loss tangent of three samples is compared to each other in Fig. 3.7. The three samples were prepared with different NCO/OH ratios. It is obvious from the figure that the intensity of the transition of the soft segment is significantly larger at the NCO/OH ratio of 1.045 than in the two other cases. Besides larger intensity, the width of the relaxation peak also becomes larger in these two latter cases indicating more hindrance and a wider distribution of relaxing moieties. Although it is rather difficult to explain that the intensity of the relaxation increases when the mobility of the units decreases as the increasing $T_g$ indicates, this larger intensity might explain the minimum observed in the stiffness of the samples. A larger amount of soft segments will definitely result in smaller modulus.

### 3.3.4. Phase structure

![Graph showing transmittance vs. NCO/OH ratio](image)

**Fig. 3.8** Changes in transparency indicating the extent of phase separation with changing composition.

Segmented polyurethanes are known to undergo phase separation during their polymerization, which result in the formation of soft and hard segments [20-30]. The relative amount of the two phases as well as their characteristics determines the properties of the polymer. A relatively simple way to study phase separation is the measurement of the transparency of the polymer. Completely homogeneous polymers produce transparent samples, while phase separation leads to a loss of light transmission. The degree of transparency depends on the extent of phase separation.

52
Effect of molecular and phase structure

and on the size of the phases. The transparency of the various samples is presented in Fig. 3.8. A maximum appears in light transmission around the equimolar ratio of the functional groups. Obviously the surplus of either functional groups results in a larger extent of phase separation and a stiffer material. The relatively small extent of phase separation observed at around equimolar stoichiometry results in a larger amount of flexible chains which on the other hand leads to a decrease of stiffness. Obviously modulus is determined mainly by the phase separated morphology of the polymer.

3.3.5. Discussion

The results presented above indicate that different factors influence each property of segmented polyurethanes. Viscosity and the related torque are determined mainly by the molecular weight of the polymer. Mechanical properties are influenced by molecular weight as well, but interactions also play a role in their determination. The stiffness of the samples, i.e. modulus is mainly determined by phase separation, by the heterogeneous structure of the polymer.

The extent of phase separation and the properties of the phases formed are determined by competitive interactions acting among various groups. The results of DMA experiments indicated that the mobility of both the soft and the hard segments decrease with increasing isocyanate content. The change in the slope of glass transition temperature of both phases as well as the changing amount of relaxing soft segments indicate that phase separation plays a considerable role in the determination of properties. Apparently the dominating interaction, the properties and the size of the phases change with composition.

At small isocyanate content we have short chains and a large number of chain-end –OH groups which strongly interact with each other through the formation of hydrogen bridges. These interactions lead to phase separation, as well as to the decreased mobility and smaller number of relaxing soft segments. With increasing isocyanate content, the chains become longer and the number of –OH groups decreases leading to an increase in the number of relaxing soft segments, but with a decreased mobility due to the larger number of isocyanate groups, which decrease the mobility of the connecting soft segments. Less phase separation and increasing number of mobile soft segments lead to increased transparency and decreased stiffness.

A further increase in the NCO/OH ratio results in the association of the urethane groups and the dominating role of the hard segments. This interaction seems to be stronger than that of the –OH groups, shown by the larger strength and elongation-at-break of the polymers formed. At very high isocyanate content also the amine end groups forming seem to enter into interaction and influence phase separation and properties. The smaller molecular weight achieved at these extreme compositions also play a role in the determination of phase structure and the characteristics of the polymer. The strong interaction of the hard segments excludes soft segments, which leads to the decrease of the $T_g$ of these latter in this
composition range. The combined effect of molecular weight, interaction and phase separation determine properties, but the influence of these factors is different for each property. The proper consideration of these relations explains the apparent contradictions observed.

3.4. Conclusions

Changes in the NCO/OH ratio of the segmented polyurethanes prepared in this study led to the expected changes in molecular weight. Other properties, however, did not depend only on molecular weight, and composition dependence showed apparent contradictions. Both strength and elongation-at-break increased with increasing isocyanate content up to the equimolar ratio of the two functional groups, but decreased only slightly at larger NCO/OH ratios, i.e. the correlations were asymmetric. On the other hand, modulus assumed minimum value in the same composition range. The analysis of various interactions developing in the polymer showed that phase separation plays an important role in the determination of properties. The interaction of chain end –OH groups dominates at small NCO/OH ratio, while the interaction of hard segments at large isocyanate content. The extent of phase separation is the smallest and the number of mobile soft segments the largest at around the equimolar ratio of the two functional groups. While viscosity depends only on molecular weight, strength and deformability are strongly influenced also by interactions, which on the other hand drive phase separation and determine stiffness completely. Taking into account these considerations makes possible the design of polymers with targeted properties.

3.5. References

Effect of molecular and phase structure

Chapter 4

Phase separation in segmented polyurethane elastomers – effect of specific interactions

4.1. Introduction

In the next stage of the research we carried out additional experiments to confirm the hypothesis presented in Chapter 3. As described, several properties, like tensile ultimate deformation and stiffness strength do not depend only on molecular weight but also on other factors, and their composition dependence shows apparent contradictions. This can be the result of differences in the sequence distribution of structural elements and in the type and number of end-groups formed [1-27]. Polyurethanes contain several highly polar groups which enter into various interactions with each other. Specific interactions usually lead to phase separation as described in Chapter 1, to the formation of soft and hard phases. The morphology developing during production, the miscibility of the phases, the size of the dispersed particles and their characteristics affect strongly the final properties of the polymer [28-32]. The various factors, i.e. molecular characteristics, interactions and phase structure influence each property of the polymer in a different way [33,22], thus the knowledge of these relationships is essential to achieve the desired performance. The tentative explanation offered in Chapter 3 for the apparent contradictions observed included that interactions and changing phase structure with composition. In this part of our work we present new results, analyze this in detail together with previously obtained information and point out the important role of specific interactions in structure formation.

4.2. Experimental

Sample preparation was described in Chapter 3; the same samples were used also in this part of the study. As mentioned above, the samples were further characterized with new techniques. Molecular weight was determined by gel permeation chromatography (GPC). Measurements were done in tetrahydrofuran (THF) using a Waters 201 chromatograph with 5 UltraStyragel columns. Polystyrene samples of narrow molecular weight were used for calibration. Specific interactions were estimated by the measurement of solvent adsorption. Ethanol and n-octane were used as solvents and Flory-Huggins interaction parameters were calculated from the equilibrium solvent uptake [39]. The transitions of the various phases of the polymers were studied also by differential scanning calorimetry (DSC). Two heating and a cooling runs were carried out on 10 mg samples with a rate of 20 °C/min. Dynamic mechanical analysis (DMA) and tensile testing were carried out as described in Chapter 3. The structure of the samples was characterized also by XRD using a Phillips PW 1830/PW 1050 equipment with CuKα radiation at 40 kV and 35 mA in reflection mode.
4.3. Results and Discussion

The various aspects of the structure and properties of the polyurethanes prepared are discussed in separate sections. Molecular and phase structure, as well as mechanical properties are presented first, followed by the discussion of structure-property correlations and the role of specific interactions.

4.3.1. Molecular structure

The modification of the stoichiometric ratio of –NCO and –OH functional groups resulted in the expected changes in the molecular weight of the polymer. The dependence of the number average molecular weight measured by GPC in THF on composition is plotted in Fig. 1. The composition dependence of $M_n$ is almost completely symmetric as dictated by the rules of step-wise polymerization; molecular weight sharply decreases as the stoichiometric ratio deviates from equimolarity. The scatter of the points is surprisingly small on the side of hydroxyl excess, but deviations occur from the general tendency when larger amounts of isocyanate were added to the reaction mixture. These deviations might result from side reactions or partial cross-linking of the polymer. We had difficulties to dissolve the samples in THF, but also in practically all other common solvents including DMSO, which is routinely used in endovascular surgery.
Because of these difficulties in sample preparation, we had serious doubts about complete solubility and could not exclude the possibility of cross-linking either, as mentioned above. A further way to obtain information about the molecular weight of our samples was the evaluation of torque measured during the reaction. Torque is proportional to melt viscosity, which on the other hand depends on molecular weight. Plotting equilibrium torque against composition (see Fig. 3.1) resulted in a correlation very similar to that presented in Fig. 4.1. To check the reliability of the measurements even further, we plotted the two quantities, i.e. equilibrium torque and number average molecular weight, against each other in Fig. 4.2. We obtained a very close correlation, especially if we consider the significant standard deviation of both measurements. The non-linear character of the correlation is the result of changing temperature during the reaction in the mixer. At larger molecular weights the frictional heat was considerable; the increase of temperature exceeded 30 °C in a few cases. Nevertheless, the similarity of the results obtained by two different methods indicate that considerable cross-linking did not take place during polymerization and in subsequent evaluation we assume that the polymer consists of mainly linear chains, just as before.

![Fig. 4.2](image.png)

*Fig. 4.2* Correlation between the equilibrium torque of the melt at the end of the polymerization reaction and the number average molecular weight.

Three-component polyurethanes organize into hard and soft segments consisting of the isocyanate and the chain extender, on the one hand, and of the PTHF chains, on the other. The sequence distribution of these segments may change also with composition and influence phase separation, the formation of hard and soft phases. A further factor of molecular structure, which might influence properties, is
Chapter 4

the type and number of end groups. Hydroxyl end-groups form at diol excess, while we assume the formation of amine end-groups at large isocyanate content. The number of the respective end-groups increases with decreasing molecular weight. The interaction of these end-groups with each other and with the other functional groups of the molecule may considerably influence phase separation and properties, as it was described in our hypothesis presented in Chapter 3.

4.3.2. Phase structure, mobility

Relaxation methods offer valuable information about the size, number and mobility of various structural units in a polymer chain. Small, flexible entities have relaxation transition at low temperatures, while large and stiff segments have high glass transition. Relaxation spectra reflect phase structure as well, random copolymers and miscible blends possess a single glass transition temperature, while block copolymers containing immiscible blocks exhibit two glass transitions. A typical dynamic mechanical spectrum, which exhibits three relaxation transitions, was already presented in Fig. 3.5. DMA spectra indicate phase separation and varying phase structure with changing composition.

Further information can be obtained about phase structure from the analysis of DSC traces. A typical set of results is presented in Fig. 4.3. The low temperature transition of the aliphatic segments of the PTHF chain could not be determined by this technique, but the transition of the soft and hard segments can be detected in the traces. Their position is different from that observed in the DMA spectrum due to the considerable differences in heating rate. The transition of the hard segment is extremely weak since the heat capacity change of the stiff molecules upon glass transition is very small. An additional transition can be detected at higher temperatures resulting from the melting of the hard phase. The melting and crystallization peaks observed indicate some order or crystallinity in this phase. The initial study of WAXS patterns proved that some regularity can be detected in the hard phase indeed, but it is very small and does not change much with composition.

Both DMA and DSC measurements prove that phase separation occurs, which is not very surprising, but the results indicate also changes in the properties of these phases with composition. Since the relative ratio of hard and soft segments is not modified much, these changes need further study and explanation. The glass transition temperature of the two phases was shown on Fig. 3.6. The \( T_g \) of the soft segments cover a range of 15 °C, while that of the hard phase changes more than 30 °C. Both increases with increasing NCO/OH ratio and the changes at around equimolar stoichiometry indicate considerable modification of the phase structure in this range. The glass transition temperature of the soft segment increases with increasing number of isocyanate groups up to a certain composition, then decreases slightly with further change of stoichiometry. The \( T_g \) of the hard segment increases continuously, but with different slopes at the various sections of the composition range. Molecular weight, but even more the changing number of end-groups must modify the mutual miscibility of the phases, as well as their size and structure.
The phase structure of blends and block copolymers is reflected well by the transparency of samples prepared from them. Homogeneous, miscible samples are transparent, while two-phase morphology results in a considerably decrease of light transmission. The transparency of our polymers has already been shown as a function of composition in Fig. 3.8. Strong differences among the various samples and a maximum in transparency can be observed at around equimolar stoichiometry indicating considerable modification of phase structure. Since the correlation is very similar to that obtained for molecular weight (see Fig. 4.1), we might assume that larger molecular weight hinders phase separation and results in better transparency.
at a NCO/OH ratio around 1. However, this explanation is contradicted by the result shown in Fig. 4.4, since better miscibility of the hard and soft segments should decrease the number of relaxing segments, but exactly the opposite happens.

![Graph of Intensity of transition vs NCO/OH ratio](image)

**Fig. 4.4** Dependence of the relaxation intensity (height of loss tangent) of the soft segments on composition.

### 4.3.3. Structure-property correlations, interactions

The considerations presented above clearly prove that changes in molecular weight with stoichiometry alone do not offer a plausible explanation for all the results and observations. Molecular weight and viscosity (torque) are unambiguously determined by stoichiometry, their dependence on composition follows the rules of step-wise polymerization. The rest of the properties are influenced by other factors as well. The asymmetric shape of the dependence of tensile strength and ultimate elongation on composition indicates that the stronger interaction of chain-end amine groups also play a role. The increase in the number of soft segments at around equimolar stoichiometry and the strange composition dependence of tensile modulus are even more difficult to explain. They are definitely not determined by molecular weight, but some other factors.

Since interactions seem to play an important role in phase separation and in the determination of properties, we tried to estimate them by the measurement of equilibrium solvent uptake carried out with n-octane and ethanol. The first solvent enters only into dispersion interactions with the polymer, while ethanol may also
form strong hydrogen bonds with it. The strength of interaction can be characterized by the Flory-Huggins interaction parameter [8-13]. Interaction parameters determined with n-octane are presented in Fig. 4.5. The values are positive, i.e. miscibility of this solvent with the polyurethane is limited. However, the correlation shows that n-octane enters into much stronger interactions with polymers prepared with excess isocyanate than with those having hydroxyl end-groups, since $\chi$ decreases from approximately 1.7 to 1.35 as NCO/OH ratio increases. A very similar correlation was obtained with ethanol, but the values were negative ranging from around -0.3 to -0.7 indicating specific interactions, probably the formation of hydrogen bridges, between the solvent and the polymer.

![Fig. 4.5 Composition dependence of the Flory-Huggins interaction parameter ($\chi_{\text{CS}}$) determined from solvent absorption with n-octane indicating changes in the strength of interaction.](image)

The role of interactions is demonstrated well by Fig. 4.6, in which the strength of the polymer was plotted against the Flory-Huggins interaction parameter measured with ethanol. The figure strongly corroborates our previous hypothesis that the larger strength and elongation values are the consequence of stronger interactions. At small $\chi$ values the effect of interaction dominates, while at large values, i.e. when interactions are weaker, the molecular weight of the polymer determines strength. The explanation might seem farfetched, but we must call attention here to the fact that the first two points at the left hand side of the figure was measured on very small molecular weight polymers compared to those in the right hand side of the figure. Accordingly molecular weight plays a much smaller role than interactions at smaller $\chi$ values.
**Fig. 4.6** Effect of molecular weight and interaction on the tensile strength of segmented polyurethane elastomers.

The measurement of solvent uptake and the considerations presented above may explain the unexpected and very strange dependence of stiffness on composition and confirms our hypothesis (see Chapter 3). At high diol content, short chains form with –OH end-groups. The number of these groups is considerable because of the small molecular weight of the polymer. The end-groups associate, form a separate phase, hinder the mobility of the soft segment, lead to inferior light transmittance and relatively large stiffness. With increasing NCO/OH ratio the number of –OH groups decreases, and increasing isocyanate content results in increased $T_g$ and decreased mobility of the soft segment. However, phase separation also decreases, the number of flexible chains increases and stiffness decreases at the same time. At high isocyanate content stiffness increases again, the hard phase and the interactions of the amine end-groups dominate properties in this composition range. This explanation is supported also by the changes in the $T_g$ of the soft segments (Fig. 3.6). These latter are excluded from the hard phase since hard segments interact mainly with each other, and the mobility of the segments increases. On the other hand, their number decreases because of changing composition (see Fig. 4.5).

Fig. 3.4 indicates the symmetrical change of stiffness with composition and we might even assume the development of similar structure and properties for the two phases, which does not seem to be logical. Plotting stiffness against transparency reveals that the structure and properties of the phases must differ...
Nanophase separation in polyurethanes: effect of interactions

considerably (Fig. 4.7). Two very close correlations are obtained which run parallel to each other. The close relationships prove that mainly interactions and phase structure controls the stiffness of the samples, but also show that the structure and properties of phases differ considerably from each other.

![Fig. 4.7 Correlation of phase structure (light transmittance) and the properties of the phases (tensile modulus) in segmented polyurethanes. (○) samples prepared with diol excess, (□) isocyanate excess.](image)

4.4. Conclusions

The molecular weight and viscosity of segmented polyurethane elastomers prepared at various stoichiometry of the isocyanate and the diol components change according to the rules of step-wise polymerization. Other properties, however, are not determined only by molecular weight, but also by specific interactions. Each property is influenced by these factors in a different way. The two types of end-groups associate with each other and influence phase separation. The strength of interaction determines properties at large isocyanate content, while molecular weight is the decisive factor at excess diol. The structure and properties of the phases forming at the two ends of the stoichiometric range differ considerably from each other. The proper adjustment of composition and interaction offers a way to control polyurethane structure and properties.
4.5. References

Chapter 5

Preparation and characterization of barium sulfate particles as contrast materials for surgery

5.1. Introduction

During the introduction we explained, that several contrast materials are used in current medical practice [1-19]. The degree of contrast and the suitability of a material for surgical purposes depend on its electron density [20-22] and on the stability of the suspension. Gold, tantalum and barium sulfate (BaSO₄) are added the most frequently to improve contrast in the body during endovascular surgery [20, 23-25]. Gold is extremely expensive, while a larger amount of BaSO₄ is needed in order to achieve the necessary contrast. Barium sulfate suspension in water is the universal contrast medium used also for the examination of the upper gastrointestinal tract [26]. However, a simple barium sulfate/water mixture has several undesirable properties including the tendency to sediment as explained earlier. Flocculation and sedimentation of suspended solids in a liquid phase are one of the most central problems in colloid science. A number of studies have been devoted to the understanding of the stability of colloidal suspensions and especially on aggregation [28-32] or settling phenomena [33] from a fundamental point of view. Information on particle size, packing density and the mechanism of settling for both flocculated and deflocculated systems have been discussed by several authors [34-36]. Different approaches have been proposed to describe the settling process; some of them extend the hydrodynamic calculations developed for macroscopic particles to flocculated suspensions. The stability of the suspension is determined by particle size and density, and by the viscosity of the dispersion [37,38]. The contrast materials available in the open market come in various particle sizes. The stability of the suspension prepared with them is very often not sufficient; the particles frequently separate from the dispersion by sedimentation. Separation of the contrast material in the body is very dangerous, since the treatment cannot be safely completed; the contrast material may block the arteries and cause damage [39-41]. The proper adjustment of the above mentioned factors, i.e. electron density, particle characteristics, solution viscosity and density, may result in more efficient contrast materials than those available presently.

The goal of our research in this area was to explore the possibility of finding efficient and economically viable materials for contrasting purposes. We also wanted to investigate the effect of the main factors on contrast and dispersion stability. Since gold and tantalum are very expensive and BaSO₄ is also used in medical practice, we decided to prepare such particles under different conditions and to characterize them with various methods. In this report we discuss the effect of reaction conditions on particle characteristics and on the stability of suspensions.
5.2. Experimental

Barium sulfate (BaSO_4) particles were prepared from solution by mixing barium chloride (99.0 %, Spektrum 3D, Hungary) and sodium sulfate (99.5 %, Reanal, Hungary). The reagents were used as received. The reaction was carried out under various conditions; we changed the concentration of the solutions, reaction temperature, the order and way of mixing. The solution of the reactants was either put into dropping funnels or into the collection beaker in which the reaction took place. The conditions of the reactions are summarized in Table 4.1. Ethanol (96 %, Spektrum 3D, Hungary) was added to the suspension in order to prevent aging either at the beginning (before) or at the end (after) of the reaction (see last column of Table 1). Always 50 ml was used from both reactants and the suspension was stabilized with 100 ml ethanol. Altogether 9 samples were prepared and characterized in this study.

Table 5.1 The conditions of the preparation of BaSO_4 particles for contrasting purposes

<table>
<thead>
<tr>
<th>Sample</th>
<th>T (°C)</th>
<th>c_{\text{sol}} \text{a)} (mol/dm^3)</th>
<th>Beaker \text{b)}</th>
<th>Funnel 1 \text{b)}</th>
<th>Funnel 2 \text{b)}</th>
<th>EtOH \text{c)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>30</td>
<td>1.00</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>after</td>
</tr>
<tr>
<td>B2</td>
<td>30</td>
<td>1.00</td>
<td>BaCl_2</td>
<td>–</td>
<td>Na_2SO_4</td>
<td>after</td>
</tr>
<tr>
<td>B3</td>
<td>30</td>
<td>1.00</td>
<td>Na_2SO_4</td>
<td>BaCl_2</td>
<td>–</td>
<td>after</td>
</tr>
<tr>
<td>B4</td>
<td>30</td>
<td>1.00</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>–</td>
</tr>
<tr>
<td>B5</td>
<td>30</td>
<td>0.10</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>after</td>
</tr>
<tr>
<td>B6</td>
<td>30</td>
<td>0.01</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>after</td>
</tr>
<tr>
<td>B7</td>
<td>50</td>
<td>1.00</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>after</td>
</tr>
<tr>
<td>B8</td>
<td>10</td>
<td>1.00</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>after</td>
</tr>
<tr>
<td>B9</td>
<td>30</td>
<td>1.00</td>
<td>–</td>
<td>BaCl_2</td>
<td>Na_2SO_4</td>
<td>before</td>
</tr>
</tbody>
</table>

\text{a)} concentration of the BaCl_2 and Na_2SO_4 solutions
\text{b)} content of the beaker and the funnels before the reaction
\text{c)} conditions of the addition of ethanol

Since we found that the dried particles cannot be resuspended again for further study, we used solvent exchange to transfer the particles from water to other suspension liquids. The solid particles were separated in a centrifuge, water was removed from the upper phase and it was exchanged to the required solvent. Separation in the centrifuge did not change the morphology of the particles in any visible way and they could be easily resuspended after separation. The particles were suspended in the new solvent by vigorous stirring and then separated again. Solvent exchange was repeated three times in order to achieve perfect exchange of the
solvent. Even a superficial visual inspection indicated significant differences among the prepared particles; the sample prepared without ethanol could be resuspended much easier than the others. Commercial barium sulfate particles were used as reference contrast materials; one is offered specifically for medical purposes (BR1), while the other, a general purpose sample, was purchased from Aldrich (BR2).

The size of the particles was determined by scanning electron microscopy (SEM) and laser light scattering (LLS). 1 g material was suspended in 100 ml ethanol for SEM. One droplet was placed on a sample holder, the solvent was evaporated and the particles were coated with gold. Micrographs were taken with a JEOL JSM-6380 apparatus. Dynamic laser light scattering measurements were done using a Brookhaven BI 9000 apparatus at 90° scattering angle in ethanol and DMSO, the solvents used in endovascular surgery. The concentration of the suspension was 0.1 g/100 ml and the suspension was treated with ultrasound for 10 min before the measurement. The sedimentation of the particles was studied by recording the movement of the sedimentation front. The initial rate of sedimentation and the sedimentation volume were used for their characterization. 1 g material was suspended in 10 ml solvent in a closed graduated cylinder and the suspension was shaken vigorously for 5 min before the measurement. The movement of the sedimentation front was followed by a camera, visualized with the Vision GS software, recorded by Bulent’s Screen Recorder and evaluated by the BSR Movie Lab software. Sedimentation was studied in water, ethanol and DMSO.

5.3. Results and Discussion

The results of the measurements are presented in three sections. First we describe the size and shape of the particles and the effect of reaction conditions on them. Then we discuss the results of the light scattering measurements and finally the stability of the suspensions, which is extremely important from the medical point of view.

5.3.1. Particle size and shape

The particle size and shape of the contrast material strongly influences the stability of the suspensions. As mentioned before, different reaction conditions resulted in various particle sizes and shapes. A few examples are shown in Fig. 5.1. The reference samples (BR1, BR2) are also included for comparison. The size and shape of both the particles and the aggregates differ significantly from each other. Sample B3 deviates considerably from the other particles prepared; it has a plate-like geometry (Fig. 5.1a), while all the others possess more or less spherical shape (see Fig. 5.1b). The main difference here was the drop-wise addition of BaCl₂ into Na₂SO₄, while in all other experiments the two solutions were introduced to the collecting vessel simultaneously or sodium sulfate was added to barium chloride. The large size and plate-like shape of the particles must influence sedimentation rate
and the stability of the suspension. The primary particles of the medical grade BaSO₄ (BR1) are also spherical, just like those of the commercial product purchased from Aldrich (BR2) (Figs. 5.1c and 5.1d, respectively). Most of the products form large aggregates consisting of smaller primary particles (see Fig. 5.1b and d).

![Fig. 5.1 Size and shape of selected BaSO₄ samples; a) B3, b) B6, c) medical grade (BR1), d) general purpose (BR2).](image)

The characteristic size of the primary particles, as well as their shape was determined by SEM and the results are listed in Table 5.2. Aggregates were not considered in this evaluation. As mentioned above, most of the particles have spherical shape. The size of the primary particles is always below 1 micron, but they form aggregates of different sizes. The estimation of aggregate size is very difficult from the micrographs, although they determine the sedimentation characteristics and stability of the dispersions. Since simple visual inspection and semi-quantitative characterization of the particles do not give any information about the behavior of the suspensions, further characterization was carried out by methods which offer information about the behavior of the samples in bulk.
Table 5.2 *Particle size and shape of the prepared BaSO₄ particles determined by various methods*

<table>
<thead>
<tr>
<th>Sample</th>
<th>Shape</th>
<th>Particle size (μm)</th>
<th>SEM</th>
<th>Light scattering measured in EtOH</th>
<th>DMSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR1</td>
<td>sphere</td>
<td>0.7</td>
<td>1.49 ± 0.19</td>
<td>1.12 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>BR2</td>
<td>sphere</td>
<td>0.5</td>
<td>1.15 ± 0.17</td>
<td>1.71 ± 0.86</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>sphere</td>
<td>0.1</td>
<td>–</td>
<td>1.97 ± 1.56</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>sphere</td>
<td>0.1</td>
<td>–</td>
<td>0.43 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>plate</td>
<td>10.0</td>
<td>0.74 ± 0.42</td>
<td>1.06 ± 0.45</td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>sphere</td>
<td>0.2</td>
<td>0.45 ± 0.05</td>
<td>0.35 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>B5</td>
<td>sphere</td>
<td>0.3</td>
<td>0.61 ± 0.14</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>B6</td>
<td>ellipsoid</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>B7</td>
<td>sphere</td>
<td>0.2</td>
<td>–</td>
<td>0.75 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>B8</td>
<td>sphere</td>
<td>0.1</td>
<td>–</td>
<td>0.42 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>B9</td>
<td>sphere</td>
<td>0.2</td>
<td>–</td>
<td>0.19 ± 0.07</td>
<td></td>
</tr>
</tbody>
</table>

5.3.2. Particle size distribution

The size distribution of the particles was determined by laser light scattering in DMSO and ethanol. The measurements could not be carried out in all cases, either because the size of the particles was outside the range of the equipment (4 μm) or because the particles and/or aggregates sedimented too fast. This latter happened especially frequently in ethanol, since both the viscosity and the density of this solvent are small compared to our other solvent, DMSO. A typical particle size distribution is presented in Fig. 5.2. The continuous line was created by fitting a Gaussian function to the experimental data. The distribution range is relatively wide from 50 to 650 nm. On the other hand, the average particle size is still rather small especially if we compare it to that of commercial fillers or to the reference BaSO₄ obtained from Aldrich (BR2). Most of the particles produced by us had a similar particle size distribution, although average particle sizes varied.
Fig. 5.2  Particle size distribution of sample B8 determined by laser light scattering in DMSO.

Fig. 5.3  Bimodal size distribution of the commercial BaSO₄ sample (BR2) obtained from Aldrich. Laser light scattering in DMSO.
Two of the samples showed bimodal particle size distribution. One of them was the general purpose commercial reference sample purchased from Aldrich (BR2), while the other was sample B1. The particle size distribution of the former is presented in Fig. 5.3. The distribution shows two distinct peaks with maximums at around 400 and 1250 nm. The bimodal size distribution is clearly disadvantageous for our purpose, because the suspension separates very easily with the fast sedimentation of the larger particles. The bimodality of sample B1 was not as strong as that of the commercial sample mentioned above (BR2), but it could be definitely observed. The reason for the development of such a distribution is unclear; it must be determined again by the reaction conditions, which should be analyzed for a more exact explanation.

Average particle size and its standard deviation are collected in Table 5.2. Only two samples could not be characterized in DMSO, but the size of more than half of the samples could not be determined in ethanol. Average particle sizes cover approximately one decade from 0.19 μm for sample 9 to 1.97 μm for the commercial reference sample. The width of the distribution also varies, but it seems to depend on the actual value of particle size. These results indicate that at least some of the particles will form stable suspensions and can be applied as contrast material in endovascular surgery.

It is also worth to compare the results obtained by the two different methods, i.e. SEM analysis and laser light scattering. The general tendency between the quantities determined by the two techniques compares well, but the exact values are quite different and considerable contradictions can be also observed occasionally. Large sizes were determined for both reference samples (BR1, BR2), as well as for Sample B3 by both methods. On the other hand, the size of the B1 particles proved to be very large in the light scattering measurement, while the SEM study yielded a much smaller value. This apparent contradiction can be easily explained by the fact that primary particles were determined by SEM, while light scattering cannot differentiate between these and the aggregates. Finally we must mention here that much smaller aggregates formed in DMSO than in ethanol. The observation was later confirmed by the sedimentation experiments described below. The different aggregation tendency of the samples must be related to dissimilar surface characteristics and interactions, but we did not investigate them in this study.

5.3.3. Sedimentation, suspension stability

As a first approximation the sedimentation rate of spherical particles $v_s$ can be predicted by Stokes’ law:

$$v_s = \frac{d^2 g (\rho_p - \rho_s)}{18 \eta}$$

(5.1)
where $d$ is the diameter of the particles, $g$ gravitational acceleration, $\rho_p$ and $\rho_l$ are the density of the contrast material and the solvent, respectively, and $\eta$ is the dynamic viscosity of the medium. Equation 5.1 clearly shows that the main factors determining sedimentation are the size of the particles, the density difference between the particles and the liquid, and the viscosity of the medium. Particle size has an especially dominating effect on sedimentation rate since it appears on the square in the equation. In the case of small particles, the solvate layer adsorbed onto the surface of the particles also influences particle size and must be taken into consideration. The results and their analysis presented above clearly show that the size of our particles cover a wide range thus we may expect considerable differences in the stability of the suspensions.

![Figure 5.4](image-url)

**Fig. 5.4** Rate of sedimentation of samples B3 and B8 in ethanol. Symbols: (□) B3, (◯) B8.

Sedimentation experiments were carried out in water, ethanol and DMSO. Occasionally we could not measure the sedimentation characteristics of the samples because a homogeneous suspension could not be prepared or because sedimentation was excessively fast (samples BR1, B5 and B6). We present two typical sedimentation curves in Fig. 5.4, which show the progress of the sedimentation front as a function of time. The SEM micrograph taken from sample B3 (see Fig. 5.1a) clearly showed the plate-like particle geometry and large size of this sample. The sedimentation curve agrees well with these observations, the rate of sedimentation is relatively fast, the particles rapidly fall to the bottom of the vessel. Both microscopy and light scattering experiments indicated that the particle size of sample B8 is much smaller. The particle characteristics of this sample can be observed quite well in Fig.
5.5. We see that the primary size of the particles is relatively small and they form small aggregates. This aggregate formation appears in the light scattering experiments as a relatively large size, i.e. $0.42 \pm 0.24 \mu m$ compared to the value determined by SEM. In spite of some aggregation, the size of B8 particles is much smaller than that of the B3 sample thus its sedimentation proceeds significantly slower.

![Image](image-url)

**Fig. 5.5** Particle characteristics and aggregation tendency of sample B8.

Initial sedimentation rates were determined in the three media for all samples and they are presented in Table 5.3. The relative order of the samples is more or less the same in the three solvents. Apart from the commercial BaSO$_4$ sample purchased from Aldrich (BR2), only the B3 sample sediments faster than the others. The larger viscosity and density of DMSO is clearly seen in the values of the table; in most cases sedimentation is significantly slower in this solvent than in the other two. DMSO differs from the other two solvents in other respects as well. On several occasions, independently of the propagation of the sedimentation front, a sediment consisting of larger particles appeared in the vessel used for the experiments. This sediment could not be suspended any more in the same way as at the beginning of the experiments. These samples are indicated with an asterisk in Table 5.3. The phenomenon might be caused by some aging process, by the transformation of the material, aggregation, or recrystallization. We did not carry out further experiments to find an unambiguous and exact explanation for the process. Nevertheless, we must draw the conclusion that BaSO$_4$ particles cannot be stored infinitely in DMSO, i.e. the embolization suspension must be freshly prepared if BaSO$_4$ is used for contrasting or some other solution must be found for the stabilization of the suspension. Such an approach might be the application of a mixture of DMSO and ethanol, which is frequently used in endovascular surgery anyway in order to decrease the level of toxic DMSO load on the patient [42-44].
Table 5.3 Sedimentation rate of the studied BaSO₄ particles in various media

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sedimentation rate (mm/h) in</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water</td>
<td>EtOH</td>
<td>DMSO</td>
<td></td>
</tr>
<tr>
<td>BR2</td>
<td>390</td>
<td>360</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>3</td>
<td>6</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>5</td>
<td>15</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>10</td>
<td>60</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>2</td>
<td>4</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>B7</td>
<td>4</td>
<td>15</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>B8</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B9</td>
<td>4</td>
<td>10</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

a) Reliable data could not be obtained for samples BR1, B5 and B6, since sedimentation was too fast.

Fig. 5.6 Demonstration of the aging of BaSO₄ particles occurring in DMSO by the comparison of particle sizes calculated from sedimentation rates determined in ethanol and DMSO, respectively.
In other cases just the opposite phenomenon was observed. Instead of the formation of sediment with increased particle size, the sedimentation front proceeded much slower than expected. The slower rate could not be justified by the difference in density and viscosity compared to ethanol or water. This phenomenon indicated the partial decomposition of the aggregates formed during the production of the samples. The observed phenomena prove again that preparation conditions strongly influence the final characteristics of the samples, including particle characteristics and stability. Moreover, in certain media BaSO_4 particles may undergo further transformation, which changes their behaviour.

The particle size of the samples can be indirectly determined also from the initial rate of sedimentation using Stokes’ law (see Equation 5.1). All parameters necessary are known and the average particle size can be calculated. This calculation was carried out and we compare particle sizes derived from results obtained in ethanol and DMSO in order to study the aging phenomena further. The results are presented in Fig. 5.6 for those samples which could be studied by this technique, i.e. by sedimentation, at all. The commercial BR2 sample was omitted from the correlation, since the much larger value obtained for it would have dominated the correlation pushing the rest of the values closely together. Although the number of points is rather small, a general tendency can be established in the figure. The large difference in the absolute values must be assigned to the inadequacy of the model used (Stokes’ law), since it is supposed to take into account changes in the density and viscosity of the solvents used. The deviation from the general tendency must be related to the aging phenomena mentioned above, which occur in DMSO. Samples falling above the tendency consist of larger, while those below it contain smaller particles than in ethanol indicating aggregation or disaggregation, respectively. These results further support our observations about the aging of BaSO_4 particles in DMSO, which might considerably influence the stability of the suspension. Moreover, the deviations from the general tendency call the attention to the fact that the results of all measurements must be treated with the utmost care, since some of them can be biased by various factors.

The results presented here unambiguously prove that commercial contrasting agents, like the medical reference sample used in this study (BR1), are not always optimal and the stability of the suspensions prepared from them might be poor. On the other hand, by the selection of the reaction conditions properly, barium sulfate particles can be prepared with proper shape and particle size, which completely fulfill the strict requirements of medical application and yield a suspension with appropriate stability. The contrasting efficiency of the samples, their effect on the viscosity of the embolizing fluid and the concentration necessary for surgical application requires further study and optimization.

5.4. Conclusions

In this stage of the study barium sulfate particles were prepared under various conditions to explore their potential application as contrast materials in endovascular surgery. The results showed that the particle characteristics of the
samples depend very much on reaction conditions. Particles were obtained in spherical and plate-like shape and in a variety of sizes. Primary particles of nanometer size formed aggregates in most cases. Some of the samples had bimodal particle size distribution. Particle characteristics determined from SEM micrographs, by laser light scattering measurements and calculated from sedimentation experiments often differed from each other. The discrepancy could be explained by the different behavior of various fractions and by the dissimilar sensitivity of the measurements to them. Some of the samples showed various aging phenomena in DMSO leading either to the formation of larger particles or to the break down of aggregates. The experiments also proved that the appropriate selection of preparation conditions results in particles yielding stable suspensions, which can be used in the intended application.

5.5. References

Preparation and characterization of barium sulfate for contrasting


Chapter 6

Contrast materials for endovascular surgery – efficiency and characterization

6.1. Introduction

We have seen in Chapter 5 that a wide variety of contrast agents can be used in embolizing formulations, but still much room is available for improvement [1-39]. The stability of the suspension is determined by the characteristics of the particles and the dispersion medium [40,41] as defined by Stokes’ law. While in the pervious chapter we focused our work on different BaSO₄ samples, other contrast agents were also examined in a latter stage of the work. Similarly to barium sulfate, other contrast materials available in the open market come in various particle shapes and sizes. Particulate contrast materials like tantalum and silver, show the same problems discussed in the pervious chapter, the stability of the suspension prepared with them is very often not sufficient [42,43]. The proper adjustment of the factors determining contrast efficiency and suspension characteristics may result in more efficient contrast materials than those available presently.

Just as before, the goal of the study was to explore the possibility of finding efficient and economically viable materials for contrasting purposes. In this part of our work we characterized various commercial particulate contrast materials and compared them to the barium sulfate samples prepared in our laboratory [44]. We focused our attention on the characterization of the particles and on the stability of the dispersions, since this latter is the basic condition of practical application. The selected contrast materials included silver and tantalum.

6.2. Background

As mentioned earlier, two main factors determine the suitability of a material as contrast agent, its capacity to absorb X-ray and the behavior of the suspension. In medical practice more attention is paid to the first, but practical problems may arise from the instability of the suspension. Since besides BaSO₄, we compare the efficiency of other materials, first we give a summary on the factors determining contrast efficiency and then discuss the characteristics of the suspensions briefly.

6.2.1. Contrast efficiency

Various materials have different X-ray absorption capacity. Only those materials can be used as contrast agents, which absorb significantly more X-ray radiation than the tissues of the human body. The physical interaction of the material
with $\gamma$ rays is well defined \cite{45}. The intensity of $\gamma$ ray radiation passing through a layer decreases exponentially with distance

$$I(x) = I_0 e^{-\mu x} \quad (6.1)$$

where $I_0$ and $I$ are the intensities of the incident and exiting rays and $x$ is the thickness of the layer. The linear absorption coefficient $\mu$ consists of three components

$$\mu = \tau + \sigma + \kappa \quad (6.2)$$

where $\tau$ is the photoelectric, $\sigma$ the Compton, and $\kappa$ the pair forming term. In the range of the energy ($E$) used and at the atomic numbers ($Z$) occurring usually, the last two terms can be neglected and $\mu$ can be expressed as

$$\mu \approx \tau \sim \frac{Z^5}{E^{7/2}} \quad (6.3)$$

Eq. 6.3 can be used only for elements. For compounds $\mu$ can be calculated from the absorption coefficients of its components in the following way

$$\mu = \rho \sum \frac{\mu_i}{\rho_i} w_i \quad (6.4)$$

where $\mu_i$ and $\rho_i$ are the absorption coefficient and density of the components, $w_i$ their weight fraction and $\rho$ is the density of the compound.

Eq. 6.3 clearly shows that the atomic number of the material has the largest effect on its X-ray absorption. The soft tissues of the body consist of compounds built from elements with small atomic numbers (C, H, N, O); their X-ray absorption is small. Bones also contain considerable amount of elements with medium atomic numbers (Ca, P), thus they give sharper X-ray images. Since embolizing solutions also consist of light elements, they cannot be easily distinguished from the surrounding environment in the body and contrast materials must be used in surgery. The density and atomic number of the elements and compounds most often used for contrasting purposes are listed in Table 6.1. We can see that gold and tantalum has the highest X-ray absorption efficiency, while silver and iodine are much less efficient. The effective atomic number of barium sulfate is less than third than that of gold or tantalum, which means that much larger amounts of this material must be used for contrasting to achieve the same effect. The use of larger amount, however, raises the question of aggregation, sedimentation and the viscosity of the dispersion.
Table 6.1  Factors determining the contrast efficiency of various elements and compounds

<table>
<thead>
<tr>
<th>Material</th>
<th>Abbreviation</th>
<th>Character</th>
<th>Density (g/cm³)</th>
<th>Atomic No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium</td>
<td>Ba</td>
<td>element</td>
<td>3.5</td>
<td>56</td>
</tr>
<tr>
<td>Barium sulfate</td>
<td>BaSO₄</td>
<td>compound</td>
<td>4.5</td>
<td>21ᵃ</td>
</tr>
<tr>
<td>Tantalum</td>
<td>Ta</td>
<td>element</td>
<td>16.6</td>
<td>73</td>
</tr>
<tr>
<td>Silver</td>
<td>Ag</td>
<td>element</td>
<td>10.5</td>
<td>47</td>
</tr>
<tr>
<td>Ioversolᵇᶜ</td>
<td>I</td>
<td>compound</td>
<td>1.4</td>
<td>39ᵃ</td>
</tr>
<tr>
<td>Goldᶜ</td>
<td>Au</td>
<td>element</td>
<td>19.3</td>
<td>79</td>
</tr>
</tbody>
</table>

ᵃ) Zeff is given for BaSO₄ and iodine
ᵇ) commercial non ionic radiocontrast material
ᶜ) Gold and iodine was not used in this study.

6.2.2. Suspension stability

Under the stability of a suspension we understand the homogeneous distribution of the dispersed particles in the medium. The most frequent form of inhomogeneity is the development of a concentration gradient because of sedimentation. The tendency for sedimentation depends on several factors, one of the most important being the size of the particles. Particles dispersed in a medium may interact with each other and particle-particle interactions lead to aggregation. Aggregated particles behave like large entities and sediment faster. The tendency for aggregation depends on the relative magnitude of adhesion and separation forces, which also depend mainly on particle size. With decreasing particle size the tendency for aggregation increases, and below a certain size becomes dominating.

As a first approximation the sedimentation rate ($v_s$) of relative large hydrophilic particles can be described by Stokes’ equation shown in Equation 5.1. If the particles strongly interact with the solvent, they are solvated and a liquid film will cover them increasing their effective diameter. Changing diameter and the presence of the film modify the sedimentation characteristics of the particles. Further factors influencing sedimentation are the possible aggregation of the particles, the back-stream caused by sedimentation, and the increase of viscosity at large particle content. The quantitative prediction of sedimentation is further complicated in the case of anisotropic particle geometry. Since the exact description of the sedimentation rate of real suspensions is extremely difficult, we use Eq. 5.1 for the evaluation of the sedimentation characteristics of our materials; even the rough approximation is sufficient for our purposes, for the comparison of the behavior of various samples.
Information published in the open literature is insufficient for the selection of proper contrasting agents. Medical papers usually do not contain any reference to the factors determining contrast efficiency and the behavior of the suspension. They might mention the contrast material used, but rarely discuss behavior or performance. Questions are also open related to the physical-chemistry of concentrated suspension. The lack of sufficient information and the open questions initiated a closer look into these questions and a more detailed study of possible contrast materials.

6.3. Experimental

We investigated solid materials not dissolving in water or in any embolizing solution. Mostly commercial products were used; some of them are medical grade materials, while others are offered for general purposes. Although we acquired commercial barium sulfate samples, we also prepared various particles in order to extend the range of sizes and shapes. The details and characteristics of these particles were reported in Chapter 5. We include only two of the samples into this section for comparison. The identification and source of the particles used in this comparative study are listed in Table 6.2.

The size of the particles was determined by scanning electron microscopy and laser light scattering as described in Chapter 5. Since we did not find a proper method or equipment, which could have been used in a sufficiently broad range of sedimentation rates, we developed our own technique for the characterization of the suspensions. The method developed was also described in the pervious chapter.

Table 6.2 Identification of the various contrast materials used in the study

<table>
<thead>
<tr>
<th>Sample</th>
<th>Abbreviation</th>
<th>Origin</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium sulfate 1</td>
<td>Ba1</td>
<td>Hungaropharma</td>
<td>medical grade</td>
</tr>
<tr>
<td>Barium sulfate 2</td>
<td>Ba2</td>
<td>Sigma Aldrich</td>
<td>general purpose</td>
</tr>
<tr>
<td>Barium sulfate 3</td>
<td>Ba3</td>
<td>lab. product</td>
<td>experimental product</td>
</tr>
<tr>
<td>Barium sulfate 4</td>
<td>Ba4</td>
<td>lab. product</td>
<td>experimental product</td>
</tr>
<tr>
<td>Tantalum 1</td>
<td>Ta1</td>
<td>Medlines Kft.</td>
<td>medical grade</td>
</tr>
<tr>
<td>Tantalum 2</td>
<td>Ta2</td>
<td>Merck</td>
<td>medical grade</td>
</tr>
<tr>
<td>Tantalum 3</td>
<td>Ta3</td>
<td>Sigma Aldrich</td>
<td>nano sized</td>
</tr>
<tr>
<td>Silver 1</td>
<td>Ag1</td>
<td>Sigma Aldrich</td>
<td>micron sized</td>
</tr>
<tr>
<td>Silver 2</td>
<td>Ag2</td>
<td>Sigma Aldrich</td>
<td>nano sized, active</td>
</tr>
<tr>
<td>Silver 3</td>
<td>Ag3</td>
<td>Sigma Aldrich</td>
<td>nano sized, coated</td>
</tr>
</tbody>
</table>
6.4. Results and Discussion

The presentation and evaluation of the results follows the same path as in the previous chapter. First, we describe the size and shape of the particles, and then we present the results of the light scattering measurements. Finally, we discuss the stability of the suspensions, which is extremely important from the medical point of view.

6.4.1. Particle size and shape

As shown earlier, the particle size and shape of the contrast material strongly influence the stability of the suspensions. It is impossible to present all the samples studied; we show only a few characteristic micrographs in order to demonstrate the wide variety of shapes and forms available. Micrographs taken from selected samples are presented in Fig. 6.1. Figs. 6.1a and 6.1b compare one of the medical grade tantalums to the nano-material obtained from Aldrich.

![Fig. 6.1 Size and shape of the particles of selected samples used as potential contrast materials in medical practice; a) Ta1, b) Ta3, c) Ag1, d) Ag3.](image)

The different characteristics of the two samples are clear for the first sight. Ta1 consists of very large particles (see scale) with elongated shape and a porous surface. Porosity might not be advantageous for contrasting purposes, but large particle size definitely is not (see Eq. 5.1). Sample Ta3 contains much smaller particles, but also a few larger ones. The presence of large particles is also not very
convenient; they easily separate from the suspension causing damage during treatment. The appearance of the silver particles differs considerably from each other, as well as their size. The primary particles of the nano-silver are very small, but they form large aggregates (Figs. 6.1c and d). The micron-sized silver consists of larger particles which form loose associations. The extent of aggregation and the size of aggregates may considerably influence the stability of the suspension and sedimentation rate. Barium sulfate samples prepared by us show an even larger variety of sizes and shapes as demonstrated by Figs. 5.1a and 6.1e. Sample Ba3 consists of relatively large particles with plate-like geometry (Fig. 5.1a), while the primary particles of sample Ba4 are very small, similarly to the nano-sized silver, but they form larger, rather dense aggregates (Fig. 5.1b). The micrographs prove that both commercial materials and our own samples cover a very wide range of shapes and sizes. SEM micrographs offer only a qualitative picture about the samples and do not give any information about the behavior of the suspensions prepared from them.

Table 6.3 Particle size and shape of the prepared BaSO₄ particles determined by various methods

<table>
<thead>
<tr>
<th>Sample</th>
<th>Shape</th>
<th>Particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SEM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ba1</td>
<td>sphere</td>
<td>0.7</td>
</tr>
<tr>
<td>Ba2a</td>
<td>sphere</td>
<td>0.5</td>
</tr>
<tr>
<td>Ba3</td>
<td>plate</td>
<td>10.0</td>
</tr>
<tr>
<td>Ba4</td>
<td>sphere</td>
<td>0.2</td>
</tr>
<tr>
<td>Ta1</td>
<td>elongated</td>
<td>40.0</td>
</tr>
<tr>
<td>Ta2</td>
<td>sphere</td>
<td>5.0</td>
</tr>
<tr>
<td>Ta3</td>
<td>sphere</td>
<td>2.5</td>
</tr>
<tr>
<td>Ag1a</td>
<td>sphere</td>
<td>0.1</td>
</tr>
<tr>
<td>Ag2</td>
<td>sphere</td>
<td>0.2</td>
</tr>
<tr>
<td>Ag3</td>
<td>sphere</td>
<td>1.0</td>
</tr>
</tbody>
</table>

a) bimodal particle size distribution

The characteristic size of the particles and their shape were determined by SEM and the results are listed in Table 6.3. The size listed in the table under the heading of SEM refers to primary particles, aggregates were not considered in this
Contrast materials for endovascular surgery

evaluation. As mentioned above, most of the particles have spherical shape. In accordance with the qualitative evaluation the size of the primary particles covers a wide range from 0.1 to 40 micron, but small particles form aggregates of different sizes. The estimation of aggregate size is very difficult from the micrographs, although they determine the sedimentation characteristics and stability of the dispersions. Since simple visual inspection and semi-quantitative characterization of the particles do not give any information about the behavior of the suspensions, further characterization was carried out by methods which offer more information about the behavior of the samples in bulk.

6.4.2. Particle size distribution

The size distribution of the particles was determined by laser light scattering in dimethyl sulfoxide and ethanol. The measurements could not be carried out in all cases, either because the size of the particles was outside the range of the equipment (4 μm) or because the particles and/or aggregates sedimented too fast (Ta1, Ag1). The particle size distribution of the large medical grade particles (Ta1) is shown in Fig. 6.2. The particles are large and the distribution range is relatively wide from about 300 to 4000 nm.

![Particle size distribution of the tantalum contrast material used for medical purposes (Ta1) determined in DMSO by laser light scattering.](image)

The size distribution of the nano-sized sample is presented in Fig. 6.3. In order to help comparison, the same scale is used as in Fig. 6.2. The drastic difference between the size and size distribution of the two samples is striking. The size
distribution of this latter sample (Ta3) is plotted also in an extended scale for better visibility and it is presented in the inset of Fig. 6.3. The distribution ranges from 30 to 300 nm in this case. The widely differing sizes of the various samples must result in completely different sedimentation behavior and dispersion stability.

Two of the samples showed bimodal particle size distribution. They are indicated with asterix in Table 6.3. One of them is the micron sized silver powder, while the other is Ta2. The particle size distribution of two silver samples, i.e. Ag1 and Ag2, is compared to each other in Fig. 6.4. The different ranges of the two distributions and the bimodal character of the Ag1 sample are clearly seen in the figure. Two distinct peaks with maximums at around 550 and 4100 nm appear on the distribution of sample Ag1. A bimodal size distribution is clearly disadvantageous for our purpose, because the suspension separates very easily with the fast sedimentation of the larger particles. The bimodality of sample Ta2 was not as strong as that of sample Ag1, but it could be definitely observed.

![Fig. 6.3 Particle size distribution of the nano-sized tantalum obtained from Sigma Aldrich determined by laser light scattering in DMSO. The scale is the same as in Fig. 6.2 for comparison; the insert shows the same distribution in extended scale for better visibility.](image)

Average particle size and its standard deviation are collected in Table 6.3. Two samples could not be characterized for reasons mentioned above. Average particle sizes cover a wide range from 0.18 \( \mu \)m for sample Ag3 to 4.11 \( \mu \)m for one of the medical grade tantalum reference samples. The width of the distribution also varies, but it seems to depend on the actual value of the particle size. These results
Contrast materials for endovascular surgery

indicate that we can expect very different suspension behaviors from the samples; some of the particles may form stable suspension and might be applied as contrast materials in endovascular surgery, while others will sediment very fast.

**Fig. 6.4** Comparison of the particle size distribution of two of the silver powders \((O)\) \(\text{Ag1}\), \((\Box)\) \(\text{Ag2}\). Laser light scattering in ethanol.

It is also worth to compare at least qualitatively the results obtained by the two different methods, i.e. SEM analysis and laser light scattering. Some agreement can observed between the quantities determined by the two techniques, but the exact values are quite different and considerable contradictions can be also observed occasionally. Although different, but large sizes were determined for sample Ta1 by both methods, while very different values were obtained for the Ag1 powder. One of the largest sizes was determined by light scattering for this sample, while SEM pictures revealed extremely small primary particles. These apparent contradictions have several reasons. One of them is that primary particles were determined by SEM, while light scattering cannot differentiate between these and the aggregates. We must take into account the detection limit of the LLS equipment as well, the upper limit of detection is \(4 \mu\)m, i.e. larger particles cannot be detected by it. Moreover, the fast sedimentation of very large particles and aggregates further complicates determination, since these settle to the bottom of the vessel very fast and do not appear in the particle size distribution determined in the suspension. Obviously, additional information is needed for the complete characterization of the suspensions, which might be supplied by sedimentation experiments.
6.4.3. Sedimentation, suspension stability

As mentioned in the experimental section, we developed our own technique for the characterization of the sedimentation behavior of the suspensions prepared from the samples studied in this project. The method and the different behavior of the suspensions are demonstrated by Fig. 6.5 showing a snapshot taken from sedimenting suspensions at an arbitrarily selected moment. All five suspensions were prepared from various barium sulfate particles. The behavior, i.e. rate of sedimentation of the five suspensions obviously differs considerably from each other.

![Figure 6.5](image)

**Fig. 6.5** Determination of the sedimentation characteristics of various BaSO₄ particles prepared in our lab.

Just as in the previous stage of the research, occasionally we could not measure the sedimentation characteristics of certain samples because a homogeneous suspension could not be prepared from them or because sedimentation was excessively fast (see sample Ba1). We present two typical sedimentation curves in Fig. 6.6, which show the progress of the sedimentation front as a function of time. The SEM micrograph taken from sample Ta1 (Fig. 6.1a) clearly showed the elongated particle geometry and very large size of this sample. The sedimentation curve agrees well with these observations, the rate of sedimentation is extremely fast, the particles rapidly fall to the bottom of the vessel. Both microscopy and light scattering experiments indicated that the particle size of sample Ta3 is much smaller (see Fig. 6.1b). The considerably smaller size of this sample leads to much slower sedimentation as shown by the figure. This smaller rate indicates that stable suspension might be prepared from this sample, and it might be safely used for medical purposes including endovascular surgery. However, we must call attention
here to the fact that sample Ta3 contained also some large particles. Neither laser light scattering nor the sedimentation curve presented in Fig. 6.6 reflects the behavior of these particles and their segregation may cause damage during surgery.

![Sedimentation curve](image_url)

**Fig. 6.6** Sedimentation of tantalum particles with time in DMSO: (○) medical grade tantalum (Ta1), (□) nano-sized tantalum (Ta3).

Initial sedimentation rates were determined in the three media for all samples and they are presented in Table 6.4. The sedimentation of the silver particles could not be determined in water, since they aggregated and dropped to the bottom very fast. The relative order of the samples is more or less the same in the three solvents, although deviations might be also observed, occasionally. The formation and effect of a possible solvate layer also depend on the characteristics of the solvents. Very large differences exist in the sedimentation rates of the samples. Large particles (Ta1, Ba2, Ag2) sediment very fast, while nano-sized particles extremely slowly. The comparison of the sedimentation rates measured in the three solvent shows also the effect of the character, but especially the influence of the viscosity of the solvent. We can see this effect very well if we compare the results obtained for sample Ta3. The larger density and viscosity of DMSO increase the stability of the suspensions. On the other hand, further study is needed to explain the order of sedimentation rates obtained for sample Ta1 which is completely the opposite what we would expect.
Table 6.4 Sedimentation rate of the studied contrast materials in various media

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sedimentation rate (mm/h) in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water</td>
</tr>
<tr>
<td>Ba1</td>
<td>–</td>
</tr>
<tr>
<td>Ba2</td>
<td>390</td>
</tr>
<tr>
<td>Ba3</td>
<td>10</td>
</tr>
<tr>
<td>Ba4</td>
<td>2</td>
</tr>
<tr>
<td>Ta1</td>
<td>180</td>
</tr>
<tr>
<td>Ta2</td>
<td>210</td>
</tr>
<tr>
<td>Ta3</td>
<td>180</td>
</tr>
<tr>
<td>Ag1</td>
<td>–</td>
</tr>
<tr>
<td>Ag2</td>
<td>–</td>
</tr>
<tr>
<td>Ag3</td>
<td>–</td>
</tr>
</tbody>
</table>

As mentioned in Chapter 5, behavior of BaSO₄ samples in DMSO further complicates the interpretation of the results. Aging processes were observed in several suspensions. Increased sedimentation rate might have been caused by the transformation of the material, aggregation, or recrystallization, while the decreased rate indicated the partial decomposition of the aggregates formed during the production of the samples. We did not carry out further experiments to find an unambiguous and exact explanation for these phenomena. Nevertheless, we drew the conclusion that BaSO₄ particles cannot be stored infinitely in DMSO, i.e. the embolization suspension must be freshly prepared if BaSO₄ is used for contrast or some other solution must be found for the stabilization of the suspension. Such an approach might be the use of a mixture of DMSO and ethanol, which is frequently used anyway in endovascular surgery in order to decrease the level of toxic DMSO load on the patient [47-49].

The particle size of the samples can be indirectly determined also from the initial rate of sedimentation using Stokes’ law (see Eq. 5.1). This calculation was carried out and we compare particle sizes derived from results obtained in DMSO to those determined by laser light scattering in the same solvent. Naturally only those results are presented in Fig. 6.7, which could be determined by these techniques, i.e. sedimentation and LLS, respectively (see Table 6.4). The large difference in the absolute values must be caused by the inadequacy of the model used (Stokes’ law), but also by the limitations of the various methods. Two points strongly deviate from the general tendency, the particle size of samples Ag2 and Ta2 derived from
sedimentation experiments, are much larger than the corresponding values obtained by laser light scattering. The difference can be explained by the fact that large particles fall outside the detection limit of the LLS equipment, and by the fast sedimentation of large particles, which prevents the determination of sizes by this method at all. Such deviations from the general tendency call the attention to the fact that the results of all measurements must be treated with the utmost care, since some of them can be biased by various factors. Moreover, particle size determination alone done by any method does not give information about the sedimentation behavior and the stability of the suspension.

![Graph showing particle size comparison](image)

**Fig. 6.7** Comparison of particle sizes determined by laser light scattering and derived from sedimentation experiments.

The results presented here unambiguously prove that commercial contrasting agents are not always optimal and the stability of the suspensions prepared from them might be poor. On the other hand, samples are available either commercially or can be prepared with proper shape and particle size, which completely fulfill the strict requirements of medical application and yield suspensions with appropriate stability. The contrasting efficiency of the samples, their effect on the viscosity of the embolizing fluid and the concentration necessary for surgical application requires further study and optimization.
6.4. Conclusions

The efficiency of solid particles used as contrast materials in endovascular surgery depends on their X-ray absorption capacity and on the stability of the suspension prepared from them. X-ray absorption is determined mainly by the real or effective atomic number of the element or compound used. Gold and tantalum have the strongest X-ray absorption among the materials used in practice. The stability of the suspension prepared from the contrast materials is equally important. The sedimentation rate of particles depends on their size, but also on the density difference between the particles and the solvent, and the viscosity of the medium. The particle characteristics and sedimentation behavior of the contrast materials studied covered a very wide range. Particle characteristics determined by various methods often differed from each other. The discrepancy was caused by the dissimilar behavior of various fractions and by the different sensitivity of the measurements to them. The experiments proved that commercial contrast materials are not always ideal for the intended application and the appropriate selection of the contrast material yield stable suspensions, which safely can be used in endovascular surgery.

6.5. References

Contrast materials for endovascular surgery

Summary

In recent years we obtained several indications that the interest of both the public and the scientific community turned much more towards bio-related materials and the medical application of polymers than before. Projects related to natural polymers were initiated by some companies, thus we carry out research on natural fibers, wood flour filled polymers and plasticized starch. We launched smaller or larger projects on the mechanical testing of tissues and knee joints, on the regeneration of bones or on the application of polyurethane for brain surgery. This last project was initiated upon the request of medical doctors, who actually use these materials in practice. The first, rather simple goal of the research was to reproduce the polymer applied presently and prepare one with similar or the same properties. However, new and more ambitious goals were defined as the research progressed and the project expanded. Besides producing tailor made polymers for the treatment of specific diseases, we hoped to generate both scientifically and practically relevant knowledge and solutions, which might be used in further research and development. This thesis is dedicated to the investigation of specific questions related to the preparation and use of segmented linear polyurethane elastomers for endovascular surgery. We focused attention on the kinetics of polymerization, on the characterization of structure and on structure-property correlations, i.e. on questions which traditionally constitute the strengths of the Laboratory. Although we summarized the most important results of the research at the end of each chapter, we briefly repeat them here to give a concise overview of our achievements. At the end of this chapter we compile the most important new findings of this work in a few thesis points.

The kinetic study carried out on three-component segmented polyurethane elastomers confirmed the assumption that melt polymerization is very complicated and it is affected by many factors. The results of the kinetic experiments could be analyzed relatively well by the Sato-Fournier model, while the simple n-th order and the Kamal-Sourour models failed in the studied system. Modeling proved that the relative weight of hydroxyl and urethane catalyzed reactions changes with composition. The lack of urethane catalysis in certain composition range was explained by the effect of changing morphology, but the assumption must be proved with further experiments. Phase separation and changing T_g hindered reaching complete conversion at high butanediol contents, which justified the use of a term taking into account diffusion control. The analysis also showed that a side reaction, probably allophanate formation, also occurs at high butanediol content, which is not accounted for by the model used. The analysis of rate constants and activation energies proved that changing reaction rates result from concentration effects and not from the dissimilar reactivity of the diol components. The experimental and fitting procedure developed takes into consideration most of the factors affecting urethane polymerization and yield valuable information about the complex system studied.
In the next stage of the research results showed that changes in the NCO/OH ratio of segmented polyurethanes led to the expected changes in molecular weight. Other properties, however, did not depend only on molecular weight, and composition dependence showed apparent contradictions. Both strength and elongation-at-break increased with increasing isocyanate content up to the equimolar ratio of the two functional groups, but decreased only slightly at larger NCO/OH ratios, i.e. the correlations were asymmetric. On the other hand, modulus assumed a minimum value in the same composition range. By the analysis of various interactions developing in the polymer we developed a hypothesis which claims that phase separation plays an important role in the determination of properties. The interaction of chain-end –OH groups dominates at small NCO/OH ratio, while the interaction of hard segments at large isocyanate content. The extent of phase separation is the smallest and the number of mobile soft segments the largest at around the equimolar ratio of the two functional groups. While viscosity depends only on molecular weight, strength and deformability are strongly influenced also by interactions, which on the other hand drive phase separation and completely determine stiffness. Further experiments carried out to check the hypothesis completely confirmed its validity. We found that the strength of interaction determines properties at large isocyanate content, while molecular weight is the decisive factor at excess diol. The structure and properties of the phases forming at the two ends of the stoichiometric range differ considerably from each other.

In the last part of the research barium sulfate particles were prepared under various conditions to explore their potential application as contrast materials in endovascular surgery. The results showed that the particle characteristics of the samples depend very much on reaction conditions. Particles were obtained in spherical and plate-like shape and in a variety of sizes. Primary particles of nanometer size formed aggregates in most cases. Some of the samples had bimodal particle size distribution. Particle characteristics determined from SEM micrographs, by laser light scattering measurements and calculated from sedimentation experiments often differed from each other. The discrepancy could be explained by the different behavior of various fractions and by the dissimilar sensitivity of the measurements to them. Some of the samples showed various aging phenomena in DMSO leading either to the formation of larger particles or to the break down of aggregates. The experiments also proved that the appropriate selection of reaction conditions yield particles, which can be used for the preparation of stable suspensions. In the further course of the study we showed that the efficiency of solid particles used as contrast materials in endovascular surgery depends on their X-ray absorption capacity and on the stability of the suspension prepared from them. X-ray absorption is determined mainly by the real or effective atomic number of the element or compound used. The stability of the suspension prepared from the contrast materials is equally important. The sedimentation rate of particles depends on their size, on the density difference between the particles and the solvent, and on the viscosity of the medium. The particle characteristics and sedimentation behavior of the contrast materials studied covered a very wide range. The experiments proved that commercial contrast materials are not always ideal for the intended application and the appropriate selection of the contrast material yield stable suspensions, which safely can be used in endovascular surgery.
The most important conclusions of this thesis can be briefly summarized in the following points:

1. In a detailed kinetic study carried out on a three-component polyester polyurethane we proved that simple $n$-th order kinetics cannot describe the complicated mechanism of the polymerization. Hydroxyl and urethane catalysis takes place simultaneously and the actual weight of the two mechanisms changes with composition, with the ratio of the two diol components.

2. With the kinetic analysis of urethane polymerization we detected a side reaction in reaction mixtures containing large amounts of the butanediol chain extender. We assumed that this side reaction is the formation of allophanates caused by the large concentration of functional groups, the short chains of butanediol and by fast urethane catalyzed reactions. This latter assumption is proved by the fact that the relative intensity of the side reaction increases with temperature.

3. We developed a data processing and evaluation technique which facilitated considerably the testing of existing kinetic models. We showed that the only approach, which can be reasonably used for the analysis of our reaction system, is the Sato-Fournier model. The kinetic parameters derived from the model proved that the reactivity of the two diols used is similar and the large differences observed in reaction rates are caused mainly by concentration effects.

4. We established by the detailed study of structure-property correlations in polyether polyurethane elastomers that the two main factors determining properties are molecular weight and interactions. Different properties depend dissimilarly on the two factors; some are determined only by molecular weight, while interactions dominate for others. The strength of specific interactions are also important, molecular weight determines ultimate tensile properties at large –OH excess, while interactions are more important at larger isocyanate content.

5. We also pointed out that phase separation is driven by specific interactions in the studied polyether polyurethanes. However, besides the interaction of the urethane groups, the respective end-groups also interact with each other leading to a larger degree of phase separation and self-association within the phases. The properties of the phases differ considerably from each other as a consequence.

6. We prepared barium sulfate particles as potential contrast materials for endovascular surgery. We found that preparation conditions considerable change the shape and size of the particles. We observed that various aging phenomena may occur in DMSO suspensions of barium sulfate particles, they might dissociate or form larger aggregates considerably influencing their application as contrast materials.

7. We developed our own technique for the determination of the stability of contrasting suspensions. We could characterize most contrasting agents quite well with the method through the determination of sedimentation rate and sedimentation volume.
8. We proved that commercial contrast materials are delivered in a very wide range of particle sizes and shapes and the majority cannot be used as contrast agent in endovascular surgery, since the stability of the suspension prepared from them is insufficient. The separation of the components by sedimentation may cause serious damage during surgery.
List of symbols

Abbreviations

A  pre-exponential factor
AVM  arteriovenous malformations
BD  1,4-butanediol chain extender
DMA  dynamic mechanical analysis
DMSO  dimethyl sulfoxide
DSC  differential scanning calorimetry
EtOH  ethanol
FTIR  Fourier transform infrared spectroscopy
GPC  gel permeation chromatography
LLS  laser light scattering
MDI  4,4’-methylenebis(phenyl isocyanate)
MRI  magnetic resonance imaging
NCO  isocyanate functional group
NCO/OH  isocyanate-hydroxyl group ratio
OH  hydroxyl functional group
POH/OH  ratio of hydroxyl groups from the polyol and the total number of
OH groups present in the mixture
PTHF  poly(tetrahydrofuran)
PUR  polyurethane
TDI  toluene diisocyanate
TPU  thermoplastic polyurethane
RIM  reaction injection molding
SEM  scanning electron microscopy
XRD  X-ray diffraction
WAXS  wide-angle X-ray scattering

Variables

d  diameter of the particles
$E_a$  activation energy
$g$  gravitational acceleration
$I_0$  intensity of incident ray
$I$  intensity of exiting ray
$k,k',K$  rate constant
$P_n$  degree of polymerization
$T$  temperature
$R$  universal gas constant
$q$  ratio of the two components in step-growth polymerization
$v$  reaction speed
$v_s$  sedimentation rate
$Z$  atomic number
$\alpha$  conversion
List of symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\eta$</td>
<td>dynamic viscosity</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>pair production forming term of absorption coefficient</td>
</tr>
<tr>
<td>$\mu$</td>
<td>linear absorption coefficient</td>
</tr>
<tr>
<td>$\mu_i$</td>
<td>absorption coefficient</td>
</tr>
<tr>
<td>$\rho_p$</td>
<td>density of contrast material</td>
</tr>
<tr>
<td>$\rho_s$</td>
<td>density of the and the solvent</td>
</tr>
<tr>
<td>$\rho_i$</td>
<td>density</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Compton term of absorption coefficient</td>
</tr>
<tr>
<td>$\tau$</td>
<td>photoelectric term of absorption coefficient</td>
</tr>
<tr>
<td>$w_i$</td>
<td>weight fraction</td>
</tr>
<tr>
<td>$x$</td>
<td>thickness of the solvate layer</td>
</tr>
</tbody>
</table>
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List of Publications

The thesis is based on the following papers


Other Publications


**Conference presentations**


