VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ

BRNO UNIVERSITY OF TECHNOLOGY

FAKULTA CHEMICKÁ
ÚSTAV CHEMIE MATERIÁLŮ

FACULTY OF CHEMISTRY
INSTITUTE OF MATERIALS SCIENCE

INVESTIGATION OF THE FLOW CHARACTERISTICS OF BONE CEMENTS DURING CEMENTATION.

DIPLOMOVÁ PRÁCE
MASTER'S THESIS

AUTOR PRÁCE — Bc. MIROSLAV ZEZULA
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ANALÝZA TOKOVÝCH VLASTNOSTÍ KOSTNÍCH CEMENTŮ BĚHEM TVRDNUTÍ.

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MASTER'S THESIS

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BRNO 2010

Vysoké učení technické v Brně
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Zadání diplomové práce

Číslo diplomové práce:	**FCH-DIP0437/2009**	Akademický rok:	**2009/2010**
Ústav:	Ústav chemie materiálů		
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Studijní program:	Chemie, technologie a vlastnosti materiálů (N2820)		
Studijní obor:	Chemie, technologie a vlastnosti materiálů (2808T016)		
Vedoucí práce	**prof. RNDr. Josef Jančář, CSc.**		
Konzultanti:			

Název diplomové práce:

Analýza tokových vlastností kostních cementů během tvrdnutí.

Zadání diplomové práce:

Cílem práce je porovnání viskozity cementů pomocí různých metod za účelem najít vhodnou cestu pro kontrolu pracovního času kostních cementů v chirurgii, případně získat lepší vtlačení a penetraci cementu do kosti během tvrdnutí.

Termín odevzdání diplomové práce: 14.5.2010

Diplomová práce se odevzdává ve třech exemplářích na sekretariát ústavu a v elektronické formě vedoucímu diplomové práce. Toto zadání je přílohou diplomové práce.

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ABSTRAKT

V dnešní době se chirurgové zajímají o vliv viskozity kostních cementů na jejich penetraci do kosti při úplné kostní náhradě. Penetrace cementu závisí na jeho viskozitě, času vsunutí protézy, době tvrdnutí, atd. Viskozita je určena chemickým složením, teplotou a poměrem monomeru a prášku. V této práci bude porovnávána viskozita a penetrace vysoko- a nízko-viskózních cementů. Viskozita bude měřena dvěma modely. V prvním modelu je hrot s konstantní rychlostí vtlačován do cementu. V druhém modelu je cement vytlačován z kapiláry konst. rychlostí.

ABSTRACT

Nowadays, surgeons concern of the effect of viscosity of cement on cement penetration in the total joint replacement. Cement penetration depend on cement viscosity, prosthesis insertion time, cement curing time etc. The viscosity of bone cements is determined by the chemical composition, the temperature and the powder to monomer ratio. In this study will compaired viscosity and penetration into the bone of high and low viscosity cements. Viscosity will measured by two models. In first model the rod is insered in the cement with constant speed. In second model the cement is injected out from a syringe with constant speed

KLÍČOVÁ SLOVA

Kostní cement, polymethylmethakrylát (PMMA), viskozita, tokové vlastnosti.

KEYWORDS

Bone cement, polymethylmethacrylate (PMMA), viscosity, flow characteristics.

ZEZULA, M. *Analýza tokových vlastností kostních cementů během tvrdnutí*. Brno: Vysoké učení technické v Brně, Fakulta chemická, 2010. 55 s. Vedoucí diplomové práce prof. RNDr. Josef Jančář, CSc.

DECLARATION

I declare that the diploma thesis has been worked out by myself and that all the quotations from the used literary sources are accurate and complete. The content of the diploma thesis is the property of the Faculty of Chemistry of Brno University of Technology and all commercial uses are allowed only if approved by both the supervisor and the dean of the Faculty of Chemistry, BUT.

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student's signature .

Acknowledgments

First of all I would like to thank my supervisor prof. RNDr. Josef Jančář, CSc for his good education in the polymer field and patience with my visits. Next I would like to thank Jian-Sheng Wang MD. Ph. D. from Lund University Hospital and Patric Jannasch Ph. D. from Lund University.

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1 INTRODUCTION

The goal of this project is to stud the physical properties of bone cements, and especially viscosity changes during cement use in total hip replacement. Viscosity strongly influences the penetration of bone cements into the bone structure in order to achieve adequate mechanical interlock into the cellular bone structure. Penetration is important in order to gain good load transfer between the prosthesis and bone. Penetration depends on viscosity, cement curing time, time of the prosthesis insertion into the bone cement, pressurization of bone cement and bone bed cleaning. Some of these properties are possibly influenced by the operating process and the cements handling.

There has been a few different bone cements based on different composition, but nowadays the most prefered and used bone cements are based on polymethylmethacrylate – PMMA. PMMA was first used in dentistry. From the middle of 20th century it was started to be used in orthopaedic surgery. The properties of bone cements based on PMMA were the subject of this study. The bone cements which are used today are most often divided into two categories: low-viscosity and high-viscosity cements. In this study, the tested bone cements are designated as low-, medium- and high-viscosity cements. This signification is important information for surgeons, because different categories require different handling of bone cement.

The properties of bone cements are tested by standardised methods, which are however mainly aimed on physical properties. The properties of bone cements are very similar to properties of PMMA, which is the main component. Therefore the methods which are used in this work are concentrated on the behaviour of the cements during the operating process and the changing of viscosity.

One of the factors which influence the viscosity of the cements and which can be easily controlled is temperature. At room temperature the setting time of the bone cements is approximately eight minutes after mixing liquid with powder. Pre-chilling of bone cements is possible to gain a decrease of viscosity and thereby increase of the setting time of bone cement. All measurements done in this project were made at room temperature.

2 THEORY

Nowadays, acrylic bone cements are widely used in orthopaedic surgery for the vast majority of total joint replacements. Bone cement attach the prosthesis to the bone and is cured in situ.[1,2] The primary function of the bone cement is to stabilize the prosthesis. Bone cements fill the gap between the prosthesis and the surrounding bone, and transfer mechanical load from the prosthesis to the bone. Another function is grouting or filling the defects and gaps.[2,3]

Viscosity has a huge influence on the cement's penetration, which ensures a good mechanical interlock between the prosthesis and the bone. The viscosity is changing during the polymerization process, which takes approximately 10 – 15 min. Only a few minutes during this period the cements are usable. The surgeons must inject the cement into the bone bed, pressurize, insert the prosthesis and stabilize it in the cement.[2] Bone cement penetration and the level of interdigitation are functions of the pressurization and the flowability of the bone cement.[4] The viscosity of the cements is determined mainly by the chemical composition.

2.1 Categorization of Bone cements by composition

2.1.1 Colophony, pumice powder, and plaster

If as a bone cements is considered as a compound which fill the cavity in a bone, or function as a material which keeps and stabilizes a prosthesis in a bone, then the first historical application of bone cements dates back more than 100 years. In the end of the 19^{th} century (1890) Dr. Gluck used the bone cement for stabilization of the ivory ball-and-socket joints, which were especially useful in the treatment of diseases of the hip joint, composed of colophony, pumice powder, and plaster. He stated that the cement filled the cavity well between prosthesis and bone, and that the tolerance of this hip joint appeared to be enormous.[5]

2.1.2 Polymethylmethacrylate cements

Polymethylmethacrylate – PMMA was known from the beginning of the 20^{th} century. During the Second World War PMMA was used as bone cement. Commercial bone cements are based on two component systems, a powder and a liquid. The powder contains pre-polymerized PMMA, initiator, antibiotics, contrast and colour agent. The liquid mainly contains MMA, initiator and colour agent. Today PMMA bone cements are the most used bone cements because of their good mechanical properties and tolerance in the body. Bone cement were originally only solid-polymerized materials based on methyl methacrylate whereas for some years the term has been used for materials which were useful for healing bones.[6]

2.1.3 Calcium Phosphate cement

These compounds have better and easier adaptation. They are biocompatible, bioactive and have a good bioresorption. The other advantage of the material is the lack of an exothermic reaction and the absence of necrosis of surrounding tissue. This advantage designates them as a drug and protein delivery system to tissue sensitive on a heat.[7] However, they are mechanically weaker than PMMA bone cements and they are not suitable to be used in prosthesis fixation.

2.1.4 Biodegradable Polyurethane networks

PMMA bone cements have very good mechanical properties. Nevertheless, if the cemented implant becomes loose, is necessary removed them, because they are not biodegradable. Polyurethane networks – (PUR) have been synthesized to be fully integrated with the host tissue and are degradable to non-cytotoxic products. PUR networks undergo controlled biodegradation, and support the attachment and proliferation of new cells. PUR networks have comparable mechanical properties with PMMA, Young's modulus and the compressive yield strength. This properties make PUR networks potentially useful as biodegradable bone cements.[8]

2.2 Categorization of Bone cements by viscosity

Viscosity is defined as the resistance of a fluid to shear deformation. Viscosity is one of the main properties which characterizes the handling and the time axis of using of bone cements.[4,6] In clinical practice acrylic bone cements are divided into three categories: low-, medium- and high-viscosity bone cements. The main indicator for this categorization is the range of values of the apparent viscosity of the cement dough during its curing. In technical practice bone cements are predominately divided only into two categories: low- and high-viscous.[1]

2.2.1 High viscosity cements

Bone cements exhibit a high initial viscosity after mixing. They lose very quickly the stickiness and consequently they have very short waiting phase before the cements can be used. The increase of viscosity during the working phase is almost negligible and the change comes at the end of the phase, when the viscosity starts to increase slowly. Generally the working phase is especially long. High viscosity cements were originally developed for manual application. High initial viscosity allows easy manual handling by rolling and kneading. High-viscosity bone cements can also be used with a syringe system, when cooling is recommended. Cooling in the range 15 – 18 °C achieves a lower viscosity sufficient for syringe application.[6]

2.2.2 Medium viscosity cements

The group of bone cements which is disignated as medium-viscosity exhibit low viscosity during the mixing phase, which is comparable to low-viscosity cements. Indeed, in very short time after mixing their viscosity increase to values which corresponds to a high-viscosity cement. During the working phase the cement behaves like high-viscosity cements.[6]

2.2.3 Low viscosity cements

During the mixing phase bone cements behaves like a liquid. Low-viscosity bone cements have a long waiting phase where it has low viscosity. Cements are typically sticky for three minutes or longer. During the working phase, when propagation is in progress, the chemical reaction creates heat and the viscosity of cements increases rapidly. Polymerization proceed roughly at the same time in all types of cements, which means that the working phase for low viscosity cements is shorter than for the others types. Low-viscosity bone cements were developed later than high- and medium-viscosity cements. Their advantages are mainly important in the handling with syringe and long thin nozzles for retrograde cement injection.[6]

2.3 PMMA Bone Cement

Polymethylmethacrylate (PMMA) became known in 1902 by the chemist Otto Röhm as "Plexiglass", a glass-like hard material.[5] PMMA has been used for many purposes, for the construction for swimming pools, malls and restaurants, tinted sunscreens, in lighting as luminous diffusers, in automotives for instrument panels and lenses, in aviation for windows and canopies.[9] In 1936 the Kulzer company introduced the production of PMMA. The mixture of ground PMMA powder, a liquid monomer and benzoyl peroxide was heated to 100 °C. Autopolymerization of MMA, which produces PMMA bone cements at room temperature, were discovered in 1943, when a co-initiator, tertiary aromatic amines, was added.[5]

2.3.1 History of PMMA Bone Cement

The first introduction of PMMA for medical applications was in 1937 when it was used in dentistry.[3] Partial dentures, orthodontic retainers, artificial teeth, denture repair, and an all-dental restorative were produced from PMMA cement. In 1938 PMMA self-curing cement was subsequently used for bone repairing and filling of other skeletal defects in monkeys. In 1951 cement was being used to repair defects in the skull of a human.[5] On the advice of Dr. S. Smith (a dentist) Dr. J. Charley used and first succeeded with the use of PMMA cement for total hip replacement prosthesis in the femur.

Dr. Charley called the material "bone cement on acrylic basis".[5] Later, the Hospital for Joint Disease in New York used PMMA cement as a means for fixation in total hip arthroplasties. In the next years, the application of bone cement in orthopedic surgery was expanded into the others orthopedics sectors. The variety of applications for PMMA in medicine and dentistry illustrate the importance and utility of PMMA cements as a biomaterial.[3,10]

2.3.2 Composition of PMMA Bone Cement

Commercial bone cements are based on two component systems, a powder and a liquid.[3] The usually used ratio is of the powder and liquid is 2:1 (2 g of powder/ 1 ml of liquid).[11] Bone cements are prepared by mixing the powder and liquid in a closed mixing system directly in the operating room. The mixing system functions as a delivering system. The cement is delivered to the implant site prior to introduction of the prosthesis. The content of the components in a powder and liquid in a package of bone cements is listed in the tables below.

Table 2.3.2.1.: Content of components in a powder in package of bone cements [12]

Powder in a packet (40 g)				
Cement	Osteopal	Refobacin BC R	Refobacin Plus BC	Simplex P
PMMA	33,4 g	33,6 g	38,3 g	6,0 g
MMA /Styren copolymer				29,5 g
Benzoyl peroxide	0,6 g	0,3 g	0,4 g	0,5 g
Gentamicin sulphate		0,8 g	0,9 g	
Zirconium dioxide	6,0 g	6,1 g	5,3 g	
Barium Sulphate				4,0 g
Chlorophyll VIII	-----			

Table 2.3.2.2.: Content of components in a liquid in package of bone cements.[12]

Monomer in an ampoule (20 ml)				
Cement	Osteopal	Refobacin BC R	Refobacin Plus BC	Simplex P
methyl methacrylate	18,4 ml	18,4 ml	18,4 ml	19,5 ml
N,N-dimethyl-p-rluidine	0,4 ml	0,4 ml	0,4 ml	0,5 ml
Hydroquinone	-----	-----	-----	1,5 mg
Chlorophyll VIII	-----	-----	-----	

At the tables before, mark (-----) points present of component without description of amount.

The reduction of the P/L ratio (1,86) leads to higher temperatures and contents of residual monomer, whereas the setting times is shorter. Mechanical properties are similar to conventional P/L ratios.[11] Antibiotics (e.g. Gentamicin) are added to reduce the range of infections of the cemented replacements.[13] The Chlorophyll addition serves as an optical marking of the bone cement at the site of the operation, especially during re-operation.[12]

2.3.3 Polymerization

As mentioned before, bone cements are a self-curing polymer, consisting of a powder polymer and a liquid. After mixing the powder with the liquid, polymerization occurs by a free radical reaction, which takes approximately 10 – 15 minutes.[2]

Nevertheless, if only the polymer powder and the monomer liquid are mixed, the result would be unsatisfactory. Radicals are required to initiate the polymerization process.[14]

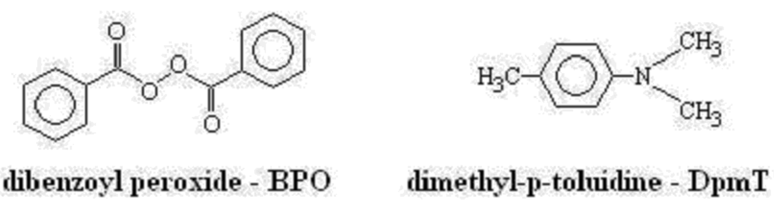

Fig. 2.3.3.1.: Initiators used in initiation at room temperature.[14]

At the room temperature the dimethyl-p-toluidine (DmpT) decomposes the benzoyl peroxide (BPO) in an oxidation/ reduction process by electron transfer. Then it produces a benzoyl radical and anion. From the DmpT a radical cation is produced. As the polymerization process starts, these radicals bind to the C - C double bond in MMA. MMA radicals evoke chain formation by adding themselves to another one MMA. Generally, radical polymerization of MMA does not achieve a 100% conversion.[14]

During the process, the cement changes from a viscous liquid to a hard, elastic solid. Initiation and polymer chain formation is seen below in figures 2.3.3.1 - 3.

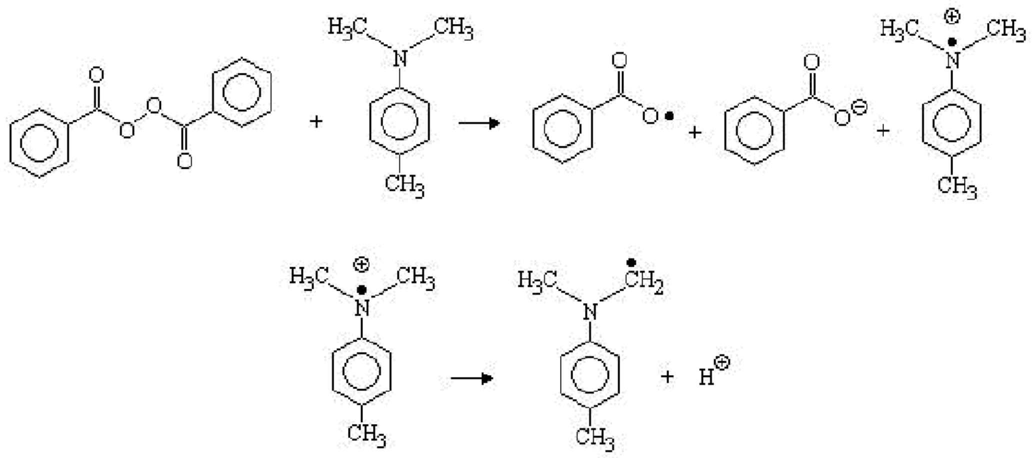

Figure 2.3.3.2.: Decomposition of BPO by DmpT.[14]

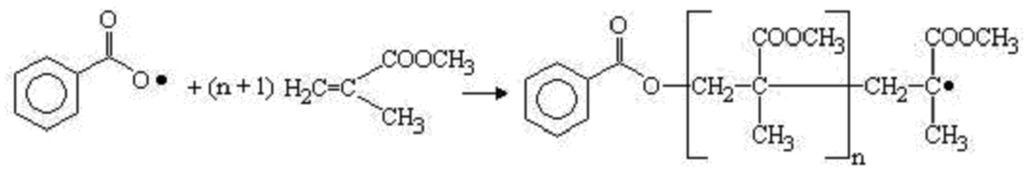

Figure 2.3.3.3.: Formation of chains (radical polymerization) in PMMA bone cements.[14]

2.3.4 Mixing system

Mixing cement that is mixed and delivered under the vacuum can significantly lower the porosity. Furthermore, the use of vacuum could affect antibiotic elution rates. The bulk porosity of the cement is a strongly linearly correlated with the amount of antibiotic.[15] A total of eight different nozzles are available for application with mixing system in different areas.

2.3.4.1 Optivac

The system was originally introduced in 1984. High and low viscosity bone cements of high or low volume can be mixed with the Optivac. Mixing and collection is done under vacuum and procedure a consistently high-quality homogenous cement with low porosity. After powder and liquid loading, the system is closed to assure a safe working environment.[16] The Optivac mixing system is shown in figure 2.3.4.

2.3.4.2 Optipac

Optipac is an improvement of the Optivac mixing system. Optipac is a closed vacuum mixing system, where all ingredients are prepacked. This mixing system minimizes exposure and contact with monomer fumes, which reduces the risk of allergic reactions. Optipac mixing system is shown in figure 2.3.4.

Figure 2.3.4.: Optivac (left) and Optipac (right) mixing system.

2.3.5 Handling with PMMA Bone cement

Many factors influence the handling of bone cements, including: temperature, mixing methods, humidity, amount of monomer, sizes of powder (particles), etc. As mentioned before, the viscosity during the polymerization process change from low-viscous mass, which gets more and more viscous, until finally the dough hardens completely into a solid.

2.3.5.1 Mixing phase

First step in the preparation of bone cements is the mixing of the components. In the initial period, inside the mixing cylinder, the wetting of the powder by the liquid is the main process. Applying vacuum decreases the number of pores and increases the mechanical strength. The mixing system ensures a homogeneous mixing of the cement.[14]

2.3.5.2 Waiting phase

During the waiting phase, swelling of the polymer is largely responsible for the rise in viscosity.[17] Polymerization continues, polymer chains grow and the polymer concentration increases. Initial liquid changes to a sticky dough. Operators, nurse or surgeon, must wait until the dough looses its stickiness, which indicates the end of the waiting phase.[14]

2.3.5.3 Working phase

When the cement is not sticky any more, it is ready to be injected into the bone. After filling the gap with cement, pressurization of cement is required for a good penetration.

The next step is the insertion of prosthesis into the cement. From physical view the increase of viscosity is caused by chain propagation, which reduces mobility and generates heat. For a successful replacement it is necessary to have a clear bone bed, good pressurization and penetration.[14]

2.3.5.4 Hardening phase

In the last phase, chain growth is finished which means that the cement becomes harder until it is almost completely cured. During this process it is necessary to keep the prosthesis in position. Hardening of cement is influenced by the cement temperature, the operating room temperature as well as the body temperature.[14]

The time schedule for the application of non-prechilled Refobacin BC in Optipac is shown below in figure 2.3.5. The time schedule for the other bone cements are given in appendix.

In figure 2.3.5. the area which is hatched shows the temperature range of the measurements (21 ± 1 °C). In table 2.3.5. the handling times are collected for each bone cement at 21 °C. In the case of Simplex P, the graph of handling from the manufacturer shows only the doughing time and the setting time.

Table 2.3.5.: Time schedule for handling with bone cements at 21 °C.[12]

Cement brand	Mixing phase (minute)		Waiting phase (minute)		Working phase (minute)		Hardening phase (minute)	
	Start	End	Start	End	Start	End	Start	End
Osteopal	0	0,5	0,5	3,5	3,5	6,0	6,0	9,0
Refobacin BC R	0	0,5	0,5	1,5	1,5	4,5	4,5	9,5
Refobacin BC Plus	0	0,5	0,5	1,5	1,5	4,5	4,5	9,5
Simplex P	0	---	---	3,0	3,0	---	---	10

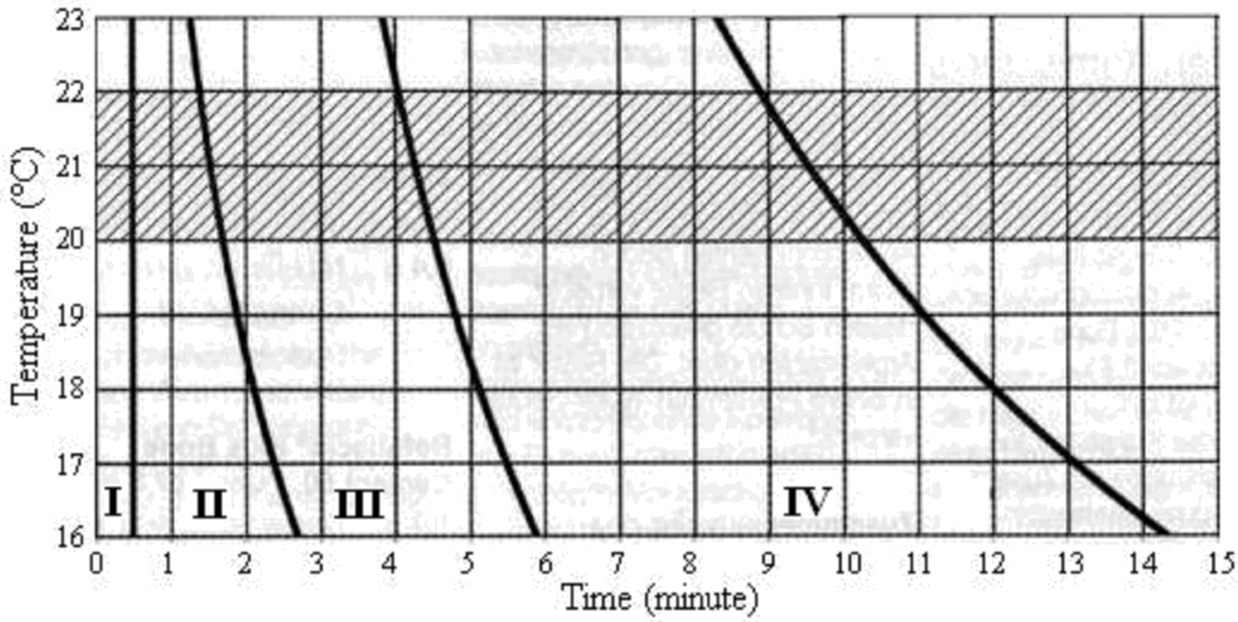

Figure 2.3.5.: Time schedule for the application of non-prechilled Refobacin BC in Optipac. I - Mixing phase, II - Waiting phase, III - Working phase, IV - Hardening phase.[12]

2.3.6 Properties of PMMA Bone Cement

Because PMMA is the main component of bone cements, bone cements will resamble its properties. Polymers are viscoelastic materials and combine the characteristics of elastic and viscous behaviour, or in other words they exhibit elements of Hookean elastic solid and pure viscous flow. The mechanical properties of solid polymers show a marked sensitivity to time and temperature compared with traditional materials like metals and ceramics. Application of stresses of relatively long duration may cause some flow and irrecoverable (permanent) deformation, while a rapid shearing will induce elastic response in some polymeric fluids.[2,3]

The stress - strain properties of polymers are extremely time rate dependent. Under a constant load, the deformations of polymeric materials increase with time (creep). When a polymer is subjected to a constant deformation, the stress required to maintain this deformation decreases with increasing time (stress relaxation).[9]

A comprehensive review of numerous investigations of bone cements properties has been published by Krause and Mathis (from 1974 - 1987) and Lewis (from 1987 - 1997).[18] Influence on the longevity of the prosthesis in the replacement is strongly dependent on the characteristics of the cement. The mechanical failure of the cement was identified as a main cause in the aseptic loosening of the prosthesis in total joint replacements.[1]

2.3.6.1 Mechanical and physical properties

In the beginning cement is a suspension of polymer beads in the monomer fluid with dominant viscous properties. During the polymerization the elastic and viscous properties, which store and dissipate energy, respectively, have changed. Finally, a solid material with elastic properties remains.[6] As the bone cements are based on PMMA they show a viscoelastic behaviour after hardening.[2]

PMMA belong to the group of the acrylic resins, which varies from soft, sticky semi-solids to hard, brittle solids. These characteristics depend upon the monomer constitution and the polymerization. The acrylic resins have excellent optical properties and weather characteristics. They are a relatively strong plastic with tensile strengths in range from 34 to about 76 MPa for short-term service. Long-term service provokes crazing or surface cracking.[19] PMMA has a moderate Tg of 105 °C and maximum service temperature of about 93 °C. The combination of stiffness, density, and moderate toughness makes PMMA very useful.[9]

The rate of increase of the viscosity rises at higher temperatures. Increase of the temperature from 19 - 25 °C cause shortening of the time which the viscosity reached to same value with a factor two.[17] Setting time shows a complex relationship at ambient temperature, because the doughing time is substantially independent of the DmpT or BPO concentrations. This indicates that the sensitivity of the setting time with the temperature depends more on the swelling and dissolution, than on the polymerization.[20]

The addition of antibiotics and contrast agents has adverse effects on the mechanical properties. Both these substances are incorporated into the matrix, but are not homogeneously distributed. However, the concentration of the antibiotics added to bone cements by manufacturers vary from 1,25 to 2,5 wt %. This small amount has negligible effect on the mechanical properties. In the case of $BaSO_4$ and ZrO_2 particles can cause problems with the acetabular cup because they are hard abrasive particles. Less effect on the mechanical properties of the cement is shown by ZrO_2, which is a lot less soluble than $BaSO_4$. [16,21,22]

2.3.6.2 Health and medical properties

PMMA has a very good stability in the body environment. The biological disadvantages of PMMA cement have been shown through numerous studies. Some of these disadvantages were resolved.

As previously mentioned the polymerization of MMA does not reach complete conversion. This means that in the hardened material there remains a certain amount of residual monomer. One of the reasons for this is that diffusion becomes the controlling mechanism during the curing of the cement. As the viscosity increase at higher conversion, the mobility of the monomer greatly decreases. Unreacted MMA monomer, which is somewhat toxic, is released from the cement into the surrounding tissue and causes irritation and impairment of bone and tissue. In the hardened cement the monomer acts as a plasticizer. The amount of monomer in the polymerized cement is in the range from 2 to 6 %. Due to a slow continuous polymerization, this range decreases to 0,5 % within 2 - 3 weeks, approximately. In materials tested after 0,5; 3 and 8 years, the content of monomer was always 0,5 % or less. It was discovered that the monomer is either quickly exhaled or metabolized in the Krebs' cycle. MMA in the bone cement cannot cause prosthesis loosening or respiration and circulation reactions.[14,23]

During the polymerization process heat is produced. The temperature which the cement reaches at the interface is between 60 and 90 °C in vitro and 40 and 50 °C in vivo. The temperature depends on the thickness of the bone cement. Lundskog in his study concluded that the exothermic polymerization had no influence of bone generation.[5] A similar conclusion was made Rhinelander et al., who noted a maximum temperature of 55 °C at the bone cement interface. Moritz and Henriques found that temperatures of 70 °C killed the cells immediately. At 55 °C, cells were destroyed after 30 s., and at 45 °C the cells had to be exposed for more than 5 hours to be affected.[24]

Inorganic contrast agents, such as ZrO_2 and $BaSO_4$, influence the biological behaviour of the cement. Particles of both agents have been shown to enhance macrophage and osteoclast differentiation, which may contribute to bone resorption.[22]

Osteolysis is one of the major problems that restrictive the survival of the total hip replacement. Several mechanisms may lead to osteolysis. The generally accepted explanation for osteolysis involves wear particles. The osteolysis process is provoked at the metal - bone or cement – bone interface of the prosthesis. The flow of joint fluid occurs along a pressure gradient, following the path of least resistance. With increasing flow, particles accumulate locally and as the concentration of particles rises, the process of osteolysis is initiated. As the body tries to clean up these wear particles, it activates an auto-immune reaction, which causes resorption of living bone tissue. This may require a revision and replacement of the prosthesis.[25] There are two problems with blood circulation. First, if the viscosity of the bone cement is too low (lower than bleeding pressure), the blood flows into the cement and create a "lamination" in the bone structure, which can weaken the cement-bone interface and starting crack formation. The second problem is that a low viscosity cement can penetrate into the blood circulation, harden there, and thus clog up.

Even if the operation of total hip joint replacement is done in the sterile environment of operating room and the bone cements are delivered from a sterile package, there still exists a small risk of infection. To prevent these cases or the necessities of reoperation, antibiotic loaded bone cements are used in primary total joint replacements.

In cases of reoperation it is commonly used loaded bone cement with double amount of antibiotics. The plain cement is infected in 2,2 % of the cases and with the gentamicin cement in 1,3 % of the cases in operations.[13] In chronic cases of infections, the prosthesis is removed to allow healing of the implantation site, and then either reimplanted at the same time or after typically 4–8 weeks. In extreme cases, the infected prosthesis result in amputations or death.[1]

2.3.6.3 Modification of PMMA Bone cement

PMMA cement is neither biodegradable nor colonizable by bone tissue.[5] Among the alternatives to modify bone cements to improve the characteristics of the bone cements and achieve better bioactive behaviour, the most useful is the addition of particles. Particles might give better static mechanical properties, but not necessarily better fatigue life, and they may act as crack propagators.

The main reason for the addition of particles is to increase the adhesion to bone and improve the stress distribution between the prosthesis and the bone. Unfortunately, these additives change the physical properties of cement such as for example the viscosity and thus also the penetration of the cement. However, this disadvantage is balanced by the chemical bond at the bone and stimulation of the proliferation and new bone formation.

A system of biodegradable cement combined with bioactive fillers could induce new bone growth, not only at the interface cement-bone but also in the volume removed. A suitable material for this objective is starch, which has been studied for a biomedical applications such as scaffolds for tissue engineering, drug delivery systems, bone replacement and regeneration.[26]

Materials that achieve chemical bonds to bone are glass-ionomer cement, bioactive PMMA cement, modified with alkoxysilane compounds, or sintered hydroxyapatite and glass–ceramic powders. In the glass-ionomer cement the promotion of growth of the bone is attributed to fluoride ions released from the material. PMMA cement with alkoxysilane compounds forms Si–OH groups that provide apatite-forming ability. Aluminium ions have a negative effect, which accelerates Ca^{2+} release from bone. As a solution of this problem, PMMA cements are modified with water-soluble calcium salts that release Ca^{2+} ions from cement. On the other hand, low concentrations of Al stimulate the proliferation and new bone formation. However, almost all these materials have lower mechanical properties such as a tensile strength and fracture toughness.[27,28,29]

An interesting number of modifications are found in the literature. On the laboratory scale, modifications with bioactive and biodegradable fillers such as oligomer fillers, based on an amino acid of trans-4-hydroxy-L-proline are evaluated.[30]

2.4 Methods to determinate properties of PMMA Bone Cement

For characterization of polymer properties are mainly used thermal and mechanical methods. The determination of properties is in accordance with international standards, such as ASTM F451 or ISO 5833.[31] The results of these measurements provide useful data. However surgeons can have difficulties to understand what they mean.

2.4.1 Rheology

One of the most useful rotational rheometer consists of parallel disks that are rotating in a cylindrical cavity. The geometry of parallel disks is showed in figure 2.4.1. The shear rate depends on the radial distance from the axis of rotation and on the gap h, that is: $\gamma(r) = r \cdot \Omega / h$.

For Newtonian fluids, the torque can be expressed as a function of viscosity, that is: $\eta = 2 \cdot T \cdot h / (\pi \cdot \Omega \cdot R^4)$.[32]

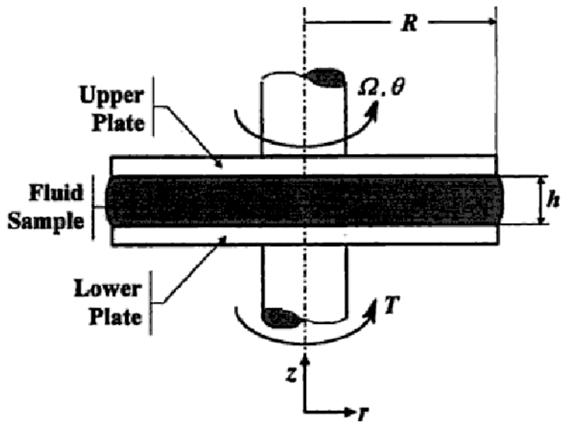

Figure 2.4.1. Parallel disks rheometer geometry.[32]

Properties such as the doughing time, the setting time, the flow rate, the temperature profiles of cements during curing, and the viscosity are usually determined by rheology. Measurements can be done at a variety of temperatures.[2,31]

One major drawback of using of rheology is that the principle treats it as viscous material. This approximation is valid in the early stage after mixing, but later the cement becomes mainly an elastic solid. Between the two stages, the cement responds as a viscoelastic material. Nevertheless it is useful to characterise the cement as a viscoelastic material by using, the oscillatory method of rheology.[17]

2.4.2 Differential Scanning Calorimetry - DSC

DSC is a technique for determining the quantity of heat that is either absorbed or released by a substance undergoing a physical or a chemical change. Such a change alters the internal energy of the substance. At constant pressure the internal energy is known as enthalpy. DSC is the most popular and versatile of the thermal analysis technique.

For practical applications the most interesting endothermic processes are melting, evaporation and glass transition or exothermic processes as crystallization, progressive curing and decomposition.[33] DSC allows the study of the polymerization reaction under different curing conditions and determinate the degree of conversion.[34,35]

The basic difficulty with the measurements at an early stage of the cement is that the cement needs to be put in the DSC right after mixing. As the polymerization starts at once, the initial part of the curve reflects perturbations and is therefore less reliable.[36]

2.4.3 Dynamic Mechanical Analysis - DMA

DMA can characterize a viscoelastic material by means of the storage moduli - G’, loss moduli - G”, phase angle - tan δ, and complex viscosity (η*), against time in dynamic oscillation mode.[37] Testing of mechanical properties is carried out in many different modes. Also these tests, as the compression test, the fracture toughness, the three-point bending test, are described in the international standards. The tests are used frequently for the determination of flexural strength, Young's modulus and modulus of elasticity.[27]

2.4.4 Dynamic Mechanical Thermal Analysis - DMTA

DMTA is a thermal analytical method. It is based on the analysis of the signal from the deformed material under particular conditions. Conditions such as temperature, vibrations frequency and amplitude are variable. DMTA is used to investigate the dynamic viscoelastic relaxation characteristics and the time–temperature superposition.[38,39]

2.4.5 Optical methods

The simplest optical method for determination of the porosity formation on the surfaces is used the visual examination by the naked eye. For high resolution results optical microscope or electron microscope are used. Scanning Electron Microscope (SEM) is used for observation of the morphology, the bone-cement fracture surfaces, the microstructures of the different formulations and dispersion. By laser diffraction, particle sizes are analysed of the PMMA beads. The size of the pores is measured on X-ray films by an optical microscope.[30,37,40,41,42]

2.4.6 Residual monomer

The content of the residual monomer is determined in the hardened cement. For this purpose proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, DSC and gel permeation chromatography are used. In DSC, the sample is heated after isothermal polymerization. If an appropriate column is used in the GC, the chromatograms show a peak which is clearly identified by comparison with MMA retention times of the pure sample.[34,35,37]

2.4.7 Other methods

More and more methods are used to determinate the properties of bone cements. New methods are developed for specific reasons, for example to measure drug diffusion rates, laser granulometry for the particle size distribution, etc.[34,43]

3 EXPERIMENTAL PART

3.1 Materials and methods

3.1.1 Bone cements

The following bone cements were used:

High viscosity BC:	Refobacin Bone Cement R
	Refobacin Plus Bone Cement
Medium viscosity BC:	Simplex P cement
Low viscosity BC:	Osteopal Low viscosity

All materials were stored at room temperature for 24 ± 1 h. For each case, one batch was used for one test. Tests were done in triplicate for each of the cements.

Batches of Refobacin Bone Cement and Refobacin Plus Bone Cement were prepacked in the Optipac vacuum mixing system (Biomet).

3.1.2 Equipment

Rheometer AR 2000 TA Instruments, Instron MTS machine 8511 load frame with MTS TestStar II controller; 250 N load cell; 20 Nm torque cell, B-D Plastipak syringes (1, 5 and 10 ml), measurement device (metal rod, metal rod with plate), vacuum pump, optigun.

3.1.3 Bone cement mixing system

In the study two mixing systems were involved. One was Optipac (Biomet) that was prepacked with Refobacin BC R or Refobacin Plus BC. The other one was Optivac (Biomet) for Simplex P and Osteopal cements. Both systems have the same diameter of the cylinder with the same mixing and collection technique.

3.1.4 Bone cement mixing

Into mixing system the liquid was first put in and then the powder was added. Only in the case of mixing of Simplex P bone cement the procedure was done in the opposite order with regard to the very fine powder. The bone cement was mixed under 30 seconds under vacuum. After mixing the cement was injected into a syringe or a special device for different studies. In the test, the start time was recorded when the monomer came in contact with the powder. Preparation of samples was done at 1 min.

The mixing of bone cements was done in the closed mixing system and in a fume hood. For every handling with bone cements powder free latex gloves and glasses were used. After handling, the bone cement was kept in the hood until it was completely cured.

3.2 Evaluation of bone cement viscosity

For the investigation of the flow characteristics of the bone cements, rheometer measurements, flowability, ejection from syringe, insertion of rod and rotating rod tests were employed. A scheme of flowability, ejection from syringe, the insertion of rod and the rotating rod procedures is shown below in figure 3.2.

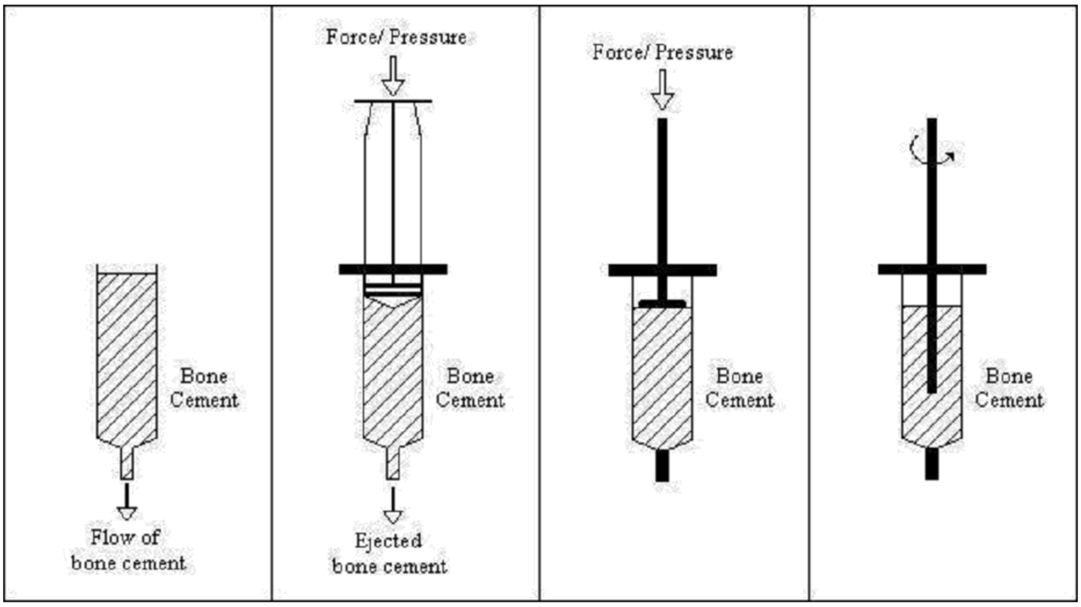

Figure 3.2.: Scheme of the measurement procedures - flowability, ejection from syringe, insertion of rod and rotating rod, respectively.

3.2.1 Rheometer measurement

The viscosity was studied by using a rheometer (AR 2000 TA Instruments) in a dynamical mode as a function of time with a parallel plate configuration immediately after mixing. The measurement setting was frequency 1 Hz, oscillating stress 10 Pa and constant gap 1000 μm. The mixed cement was delivered to the rheometer plate by using the Optipac/ Optivac system. The amount of the bone cement covered the whole plate once the distance between the parallel plates was adjusted. Excess amount of the bone cement was wiped off from the edge before the measurement started. Very important was the prevention of "bridges" between the plates. The gap between the plates was defined before the analysis so that the amount of sample was the same for all measurements.

A value of viscosity equal 10 000 Pa · s was choosen with reference to curves viscosity and phase angle vs time. A minimal decrease of the phase angle meant start of the working phase. Interval in which the bone cements achieved this point was between 9 000 – 11 000 Pa · s.

3.2.2 Flowability test

The bone cement was injected into the 1 ml syringe by a 5 ml syringe (as a delivery system, fig 3.1.6.). The cement was filled into three syringes (1 ml). Then the syringe (1 ml) with the bone cement was placed vertically into a holder. The cement was allowed to flow without any pressure and without a plunger. The bone cement, which flowed through the syringe, was collected in a pan. The observation was stopped when the cement stopped dropping.

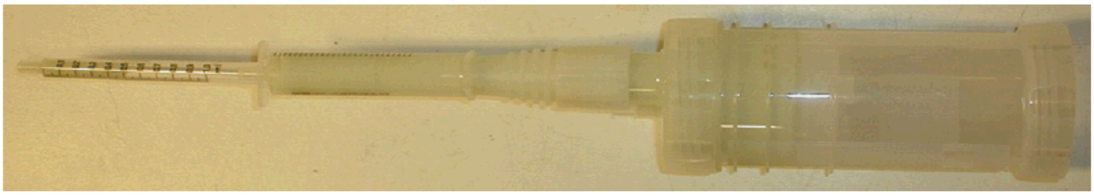

Figure 3.1.6.: Setup for filling 1 ml syringe from the mixing system.

3.2.3 Ejection from syringe test

After mixing, the cement was injected into a 10 ml syringe. The syringe was closed with a plunger and placed in a custom made device. The device was placed in an Instron 8511 load frame with MTS TestStar II controller. The measuring head was attached to the plunger and was displaced by constant speed at 0,1 mm/ second for 8 minutes. The cement was ejected out from the syringe (Fig 3.1.7.). The test started around 2 minutes after the starting powder/monomer mixing. The force of the ejection was recorded. Before the cement loading test, an empty syringe with plunger was tested to measure the friction.

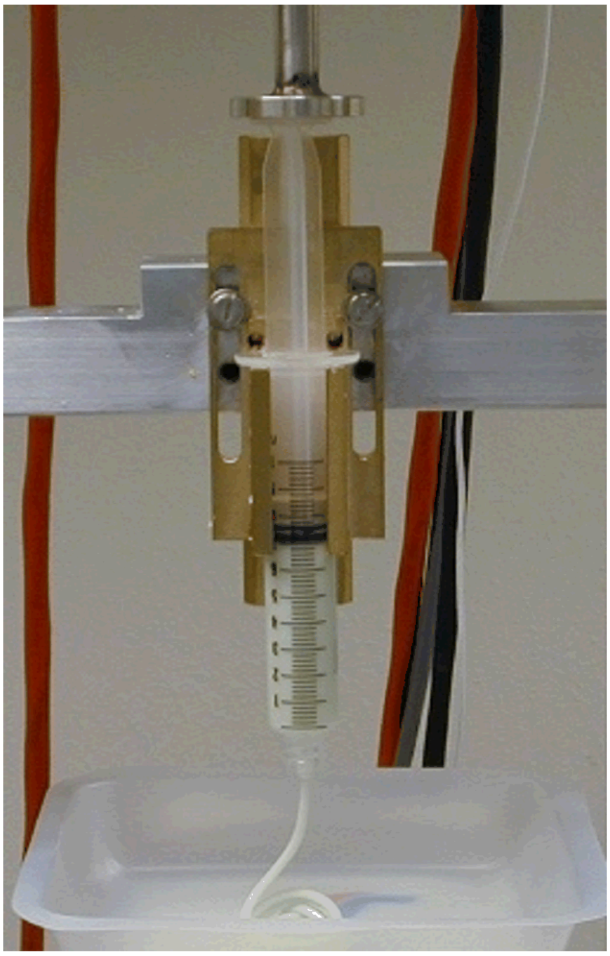

Figure 3.1.7.: Experimental setup for the ejection from syringe.

3.2.4 Insertion of rod with plate test

After mixing, the bone cement was injected into a 1 ml syringe. The syringe was fixed in a custom made device. The device was placed in the Instron/MTS machine equipped with a 250 N load cell. A metal rod (1,4 mm Ø, 100 mm length) with a plate (4 mm Ø) was attached to the surface of the bone cement in the syringe. The plate was inserted into the cement at a constant speed of 0,1 mm/ second for 8 minutes (Fig 3.1.8.). The test started around 2 minutes after monomer was mixed with the powder. The force of the insertion was recorded.

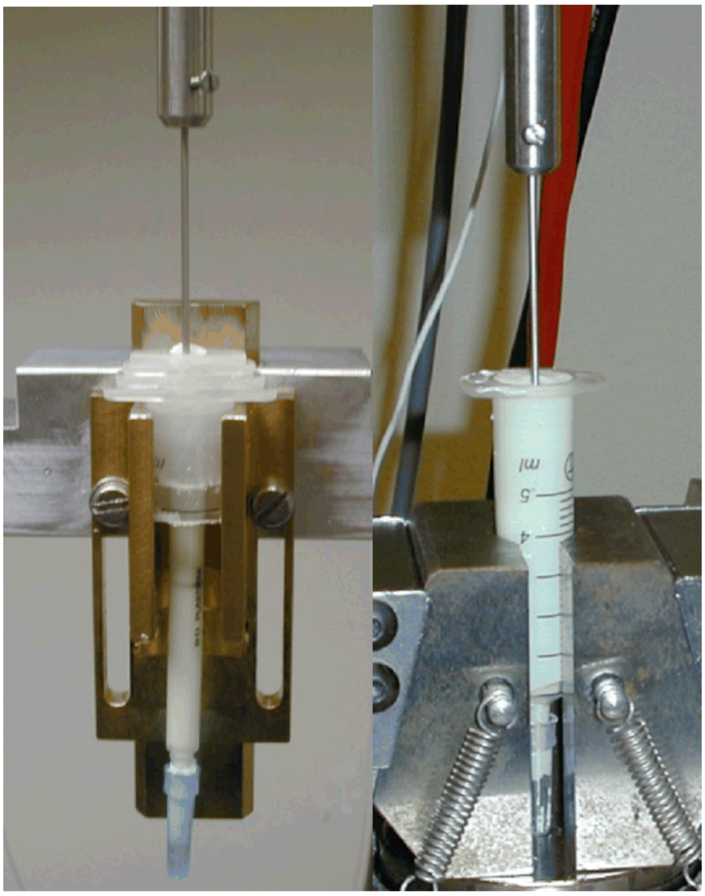

Figure 3.1.8.: Experimental setup with cement for the insertion of rod with plate and rotating rod

3.2.5 Rotating rod test

After mixing, the bone cement was injected into a 5 ml syringe. A metal rod (1,4 mm Ø, 100 mm length) was inserted into the bone cement (50 mm deep). The rod was fixed in the Instron MTS machine equipped with a 20 Nm torque cell. The rod was oscillated in the cement at 90° and at a constant speed of 90°/ 3 seconds. The force of oscillating was recorded.

4 RESULTS

4.1 Rheometer measurement

For the measurements of each bone cement, the individual curves for the specific bone cements are very similar and they achieve the same values. The viscosity on the y-axis is given on a log scale.

4.1.1.1 Osteopal

The osteopal viscosity curve of sample 2 started increase from 1,8 Pa · s. The curve of sample 1, which started 10 seconds later, increased from a value of 3,5 Pa · s and followed the previous curve. Measurement of sample 3 started increased after second minute from value 40 Pa · s. All three curves increased rapidly during 3 minutes. They intersected at 6 000 Pa · s, approximately. Then their growth rate decreased. For the next two minutes the values increased a little. From the 5th to the 8,5 minute, almost a flat curve was observed. After this interval the slope of the curves increased rapidly. In figure 4.1.1.1. the viscosity curves of all three samples of Osteopal are shown.

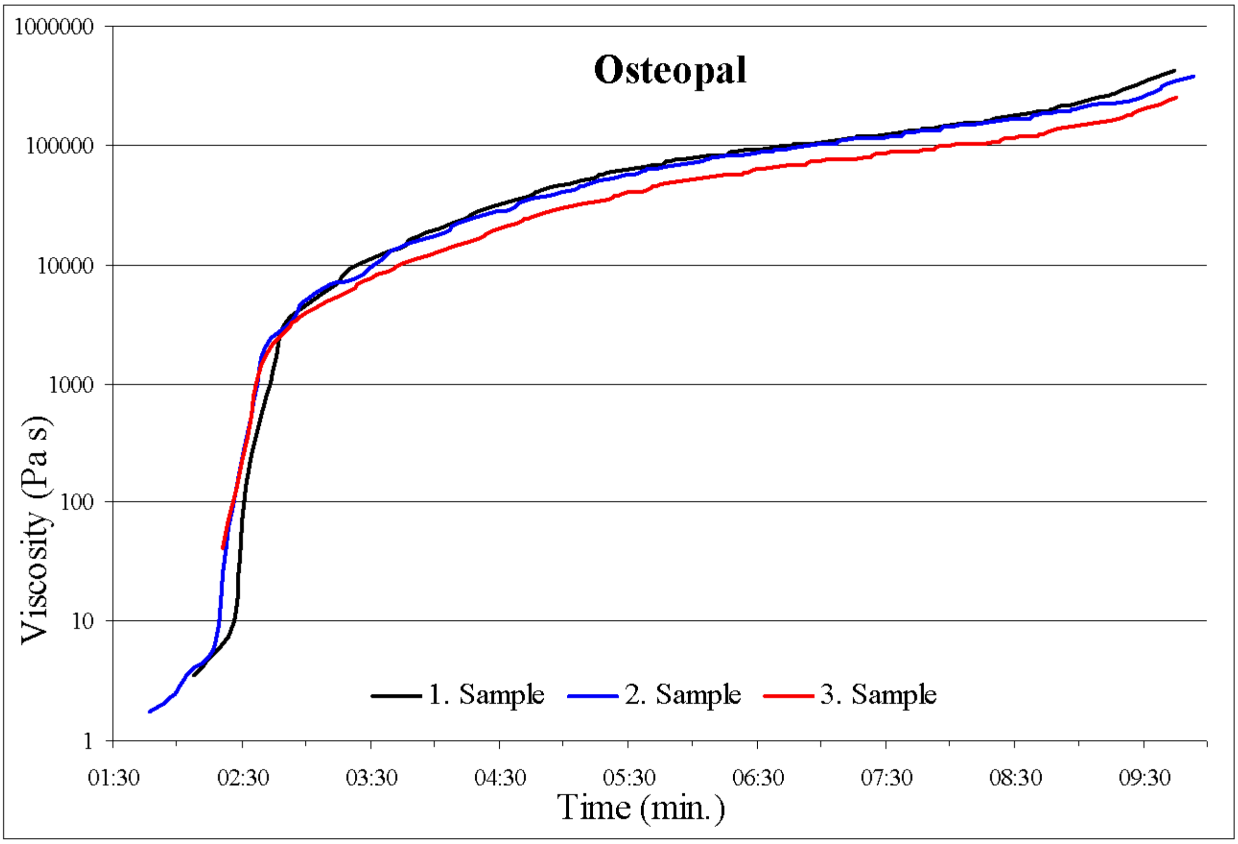

Figure 4.1.1.1.: Viscosity curves of Osteopal

4.1.1.2 *Refobacin BC R*

The initial value of the curve of sample 1 was 3 000 Pa · s after 2 minute then the curve increased to 10 000 Pa · s at 3,5 minute. The curves of sample 2 and 3 had a very similar behaviour and they crossed value at 3 000 Pa · s and 10 000 Pa · s after 3,6 minute and 4 minutes, respectively. Then the slopes of the curves increased linearly up to 8 minutes. At this time, the curve of sample 1 and the curves of samples 2, 3 reached values of 60 000 Pa · s and 50 000 Pa · s, respectively. Then the viscosity strated increase rapidly. In figure 4.1.1.2. the viscosity curves of all three samples of Refobacin BC R are shown.

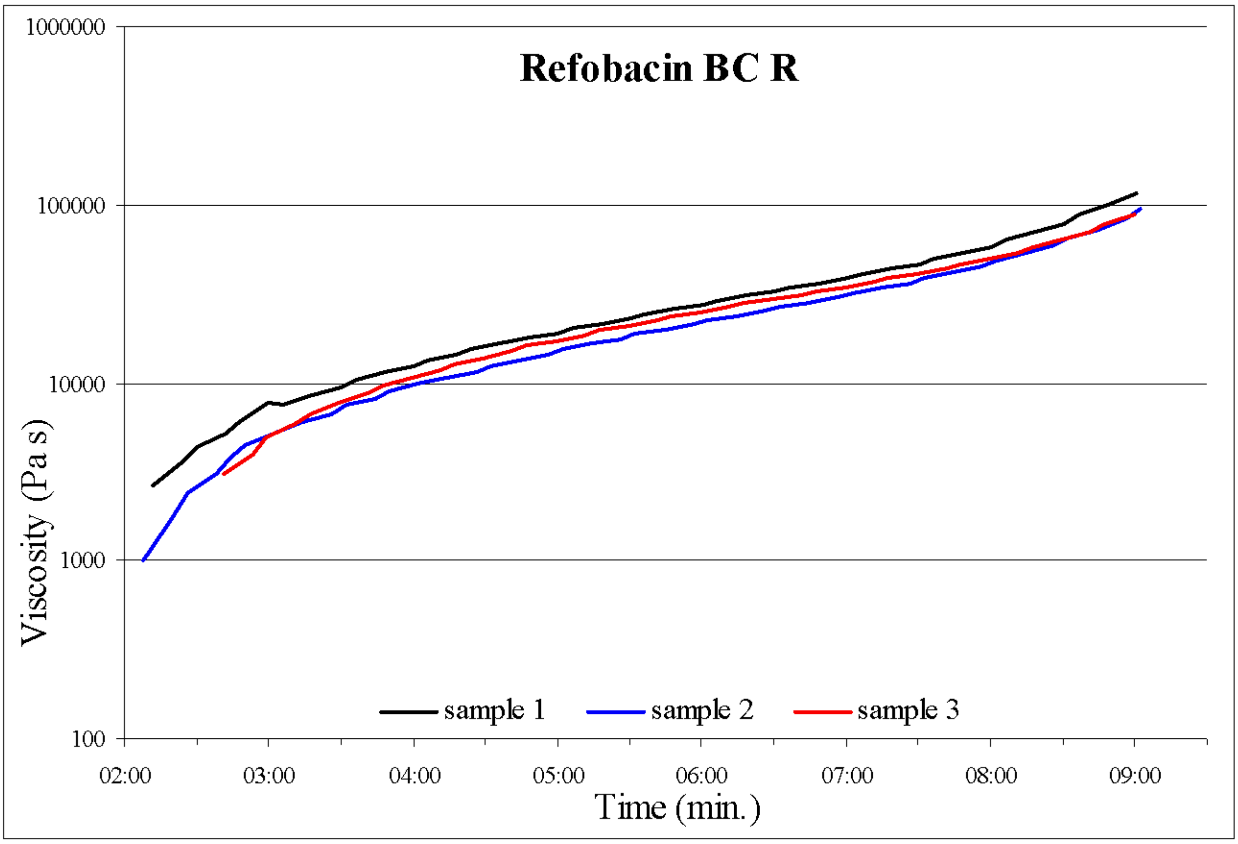

Figure 4.1.1.2.: Viscosity curves of Refobacin BC R.

4.1.1.3 Refobacin Plus BC

The increase of the viscosity Refobacin Plus BC curves was not very steep from the beginning. The start value of sample 1, 2 and 3 was around 5 000 Pa · s at 2; 2,4 and 2,5 minutes, respectively. At the value 10 000 Pa · s the time difference between curves was same. After 5 minutes all curves grew slightly and in interval from 5 to 8 minutes, the curves looked nearly flat. In the next interval from 8 to 9,5 minutes the curves of samples 1, 2 and 3 increased to values of 1 100, 1 200 and 700 kPa · s. After this interval, the curve of sample 2 started to flat out. In figure 4.1.1.3. the viscosity curves of all three samples of Refobacin Plus BC are shown.

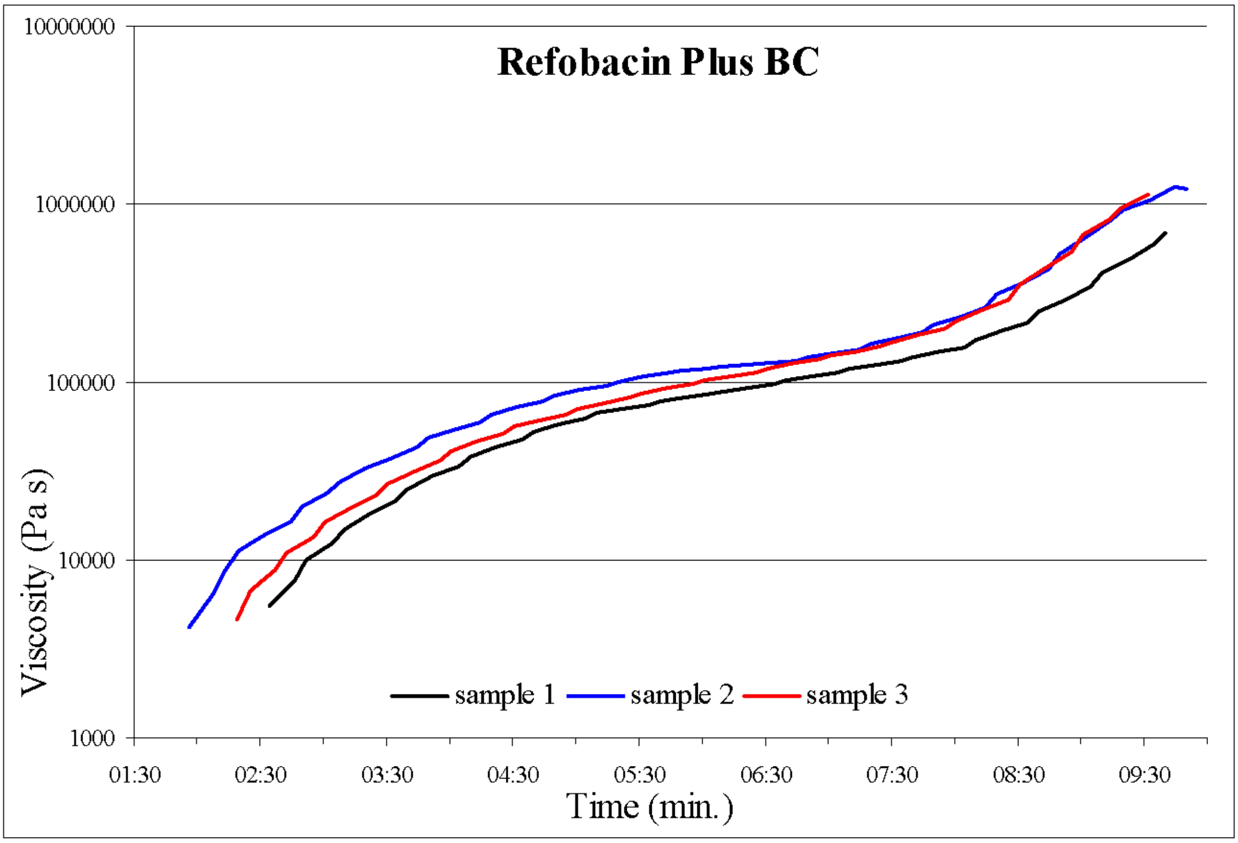

Figure 4.1.1.3.: Viscosity curves of Refobacin Plus BC

4.1.1.4 Simplex P

The curves of samples 1 and 2, 3 increased from startting values of 6 500 Pa · s and 20 000 Pa · s, 8 000 Pa · s at 2 and 2,5 minutes, respectively. At 4 minutes all three curves increased with high slope and achieved a value of 60 000 Pa · s. After they achieved this value the slope decreased and for next 2 minutes forther slowly decreased. From 6 minutes to the end of the measurement, from 100 kPa · s to 210 kPa · s, approximately, the curves were flat without any change. In figure 4.1.1.4. viscosity curves of all three samples of Simplex P are shown.

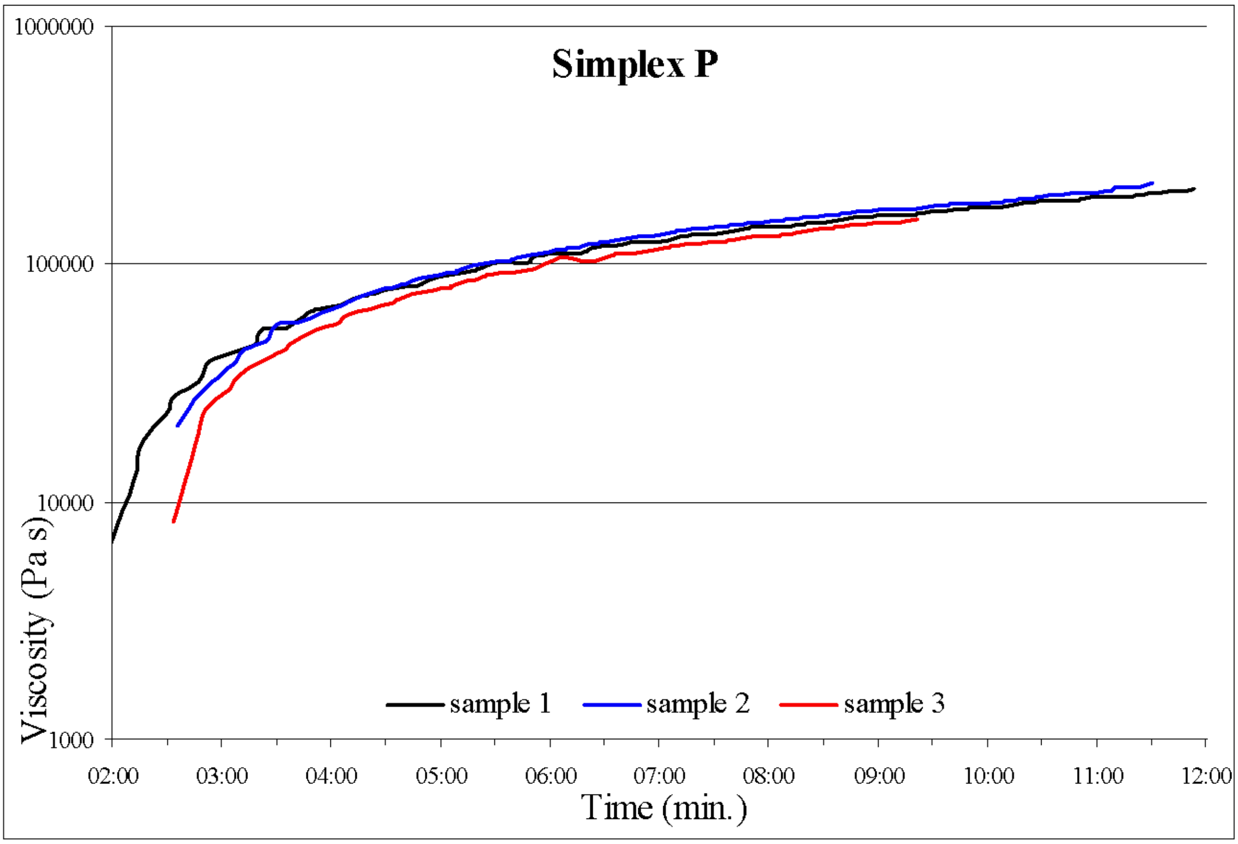

Figure 4.1.1.4.: Viscosity curves of Simplex P

4.1.1.5 *Mean values of the 4 bone cements*

From figure 4.1.1.5.1. the cement viscosity was different for the four cements. After 2 minutes the viscosity curve of Osteopal showed the lowest value of about 17 Pa · s, followed by Refobacin BC R at 1 820 Pa · s, Refobacin Plus BC at 5 611 Pa · s and Simplex P at 6 644 Pa · s, which are low-, high-, high- and medium-viscosity cement, respectively. After 3 minutes the viscosity of Osteopal was higher than Refobacin BC R and it increased a constantly until the end. The viscosity of the Refobacin BC R cement was the lowest until 9,5 minutes, when the viscosity started to grow rapidly. The viscosity curve of Refobacin Plus BC increased from the beginning to 4,5 minutes, then followed flat plateu and after 8 minutes started to grow rapidly. At the end of the measurement of Refobacin Plus BC it was possible to observe a flat plateu with constant value. The viscosity of Simplex P was the highest from beginning until 6 minutes and then kept a constant value.

In figure 4.1.1.5.2. curves of mean values are shifted to cross at parallel value (viscosity 10 000 Pa · s). All bone cements show similar shape of the curves. The behaviour of the bone cements before the value of 10 000 Pa · s was different. The curves of Osteopal, Refobacin Plus BC and Simplexu P in the interval from 10 000 to 100 000 Pa · s had similar trends of polymerization. The viscosity curves increased slowly in this interval, the curves looked nearly flat. The curve of Refobacin BC R increased slowly already after mixing and achieved value of 100 000 Pa · s 2 minutes later than the other cements. Osteopalu, Refobacinu Plus BC and Simplexu P cements started cure between 8 and 8,5 minutes. The curves of the samples of Simplex P did not show a rapid increase as the other viscosity curves. During the testing of the methodology and the measurement a few samples completely cured between plates.

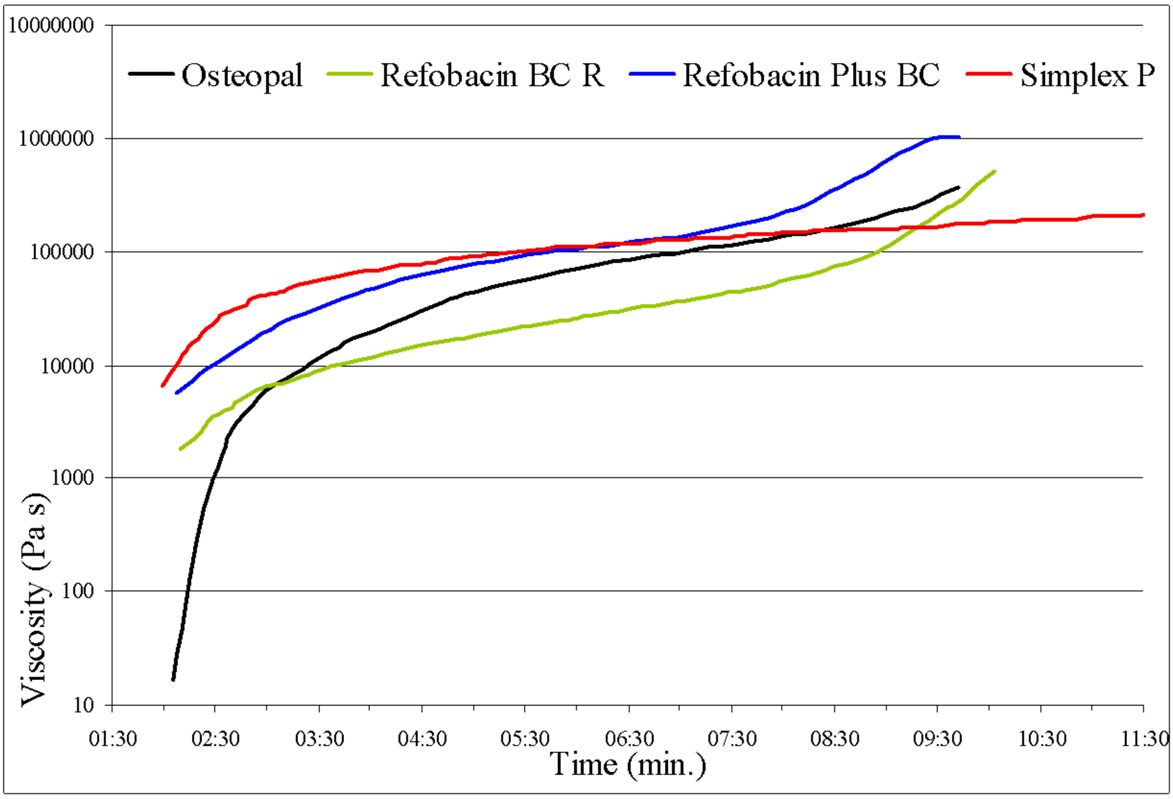

Figure 4.1.1.5.1.: Viscosity curves of all the bone cements (mean values)

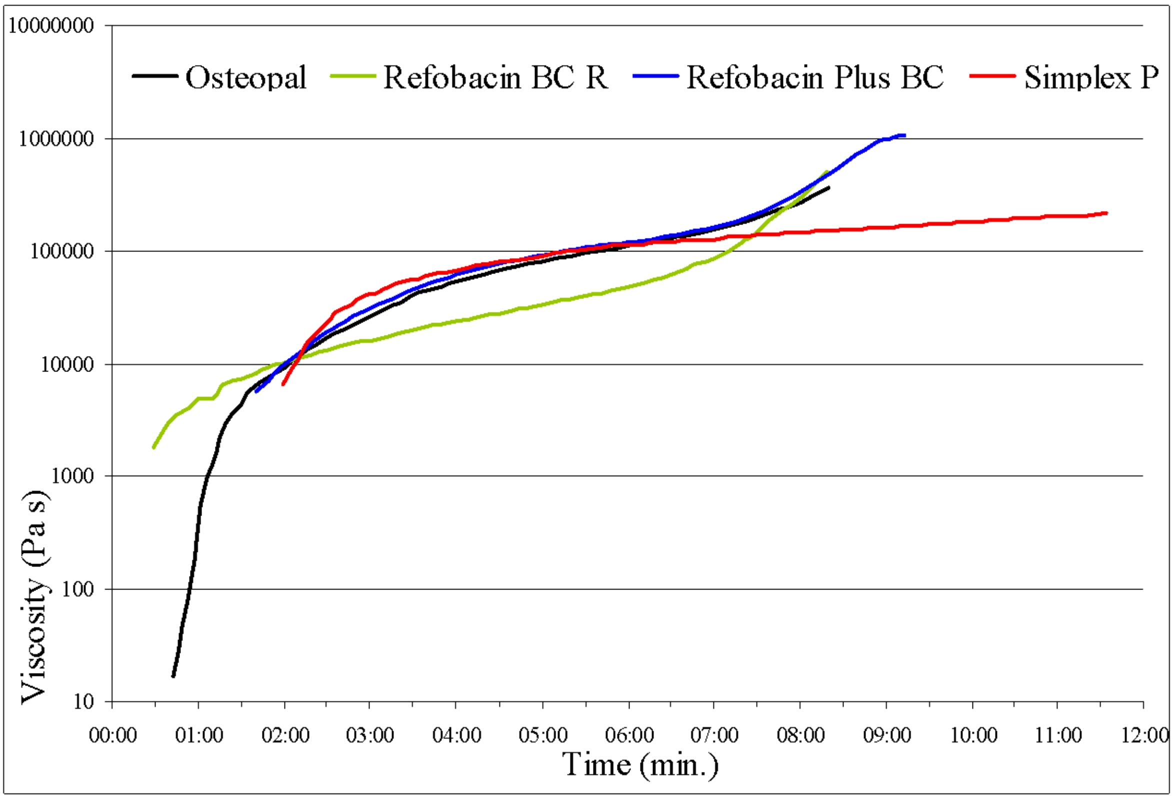

Figure 4.1.1.5.2.: Viscosity curves of all the bone cements (mean values, shifted to 10 000 Pa · s)

4.2 Flowability

The low viscosity bone cement Osteopal flowed for three minutes from the syringe after filling at 90, 105 and 120 ± 5 seconds from beginning. The data from measurement are in table 4.2. After 10 minutes the bone cement was still soft but not sticky.

Medium viscosity bone cement, Simplex P, flowed a little from beginning, produced a droplet, but did not flow from the syringe. After 10 minutes the bone cement was still soft but not sticky.

After injection into a 1 ml syringe high viscosity bone cements Refobacin Plus and Refobacin BC did not flow. They did not flow even from the 5 ml syringe.

Table 4.2.: Flowability of bone cement Osteopal.

Syringe number	Time of filling (second)	Mass (g)		
		Empty pan	Pan with sample	sample
1.	90	0,5	1,0	0,5
2.	105	0,5	0,8	0,3
3.	120	0,7	0,9	0,2

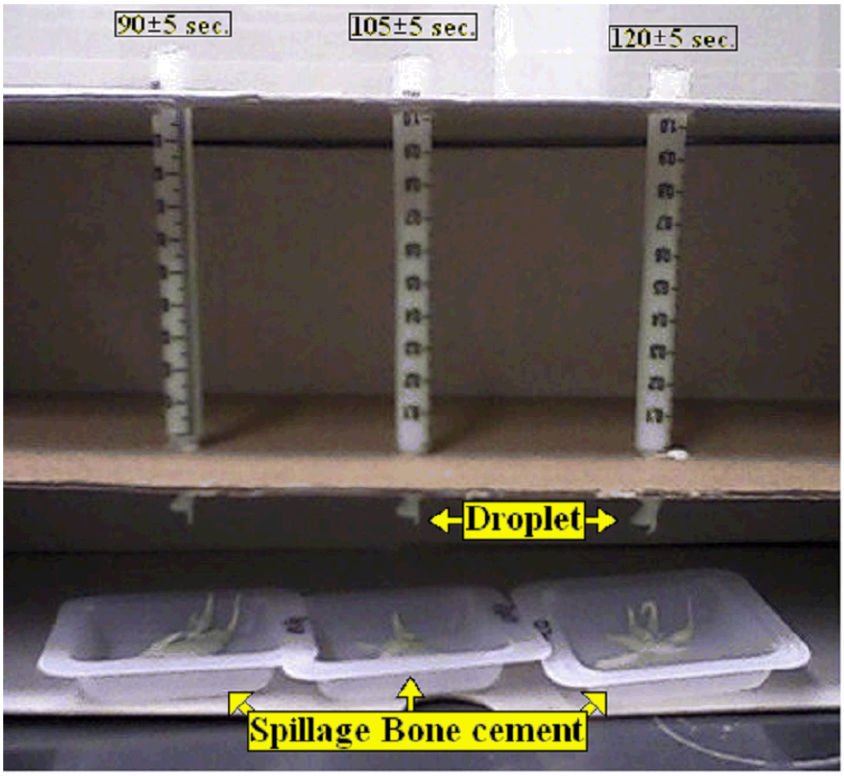

Figure 4.2.: Experimental setup of Flowability - Osteopal Bone cement.

4.3 Ejection from syringe

Before testing the samples of bone cements, an empty syringe was tested for methodology. The data obtained from these tests showed friction between the plunger and the wall of the syringe. This friction was insignificant. Measurement of three samples is shown in figure 4.3.

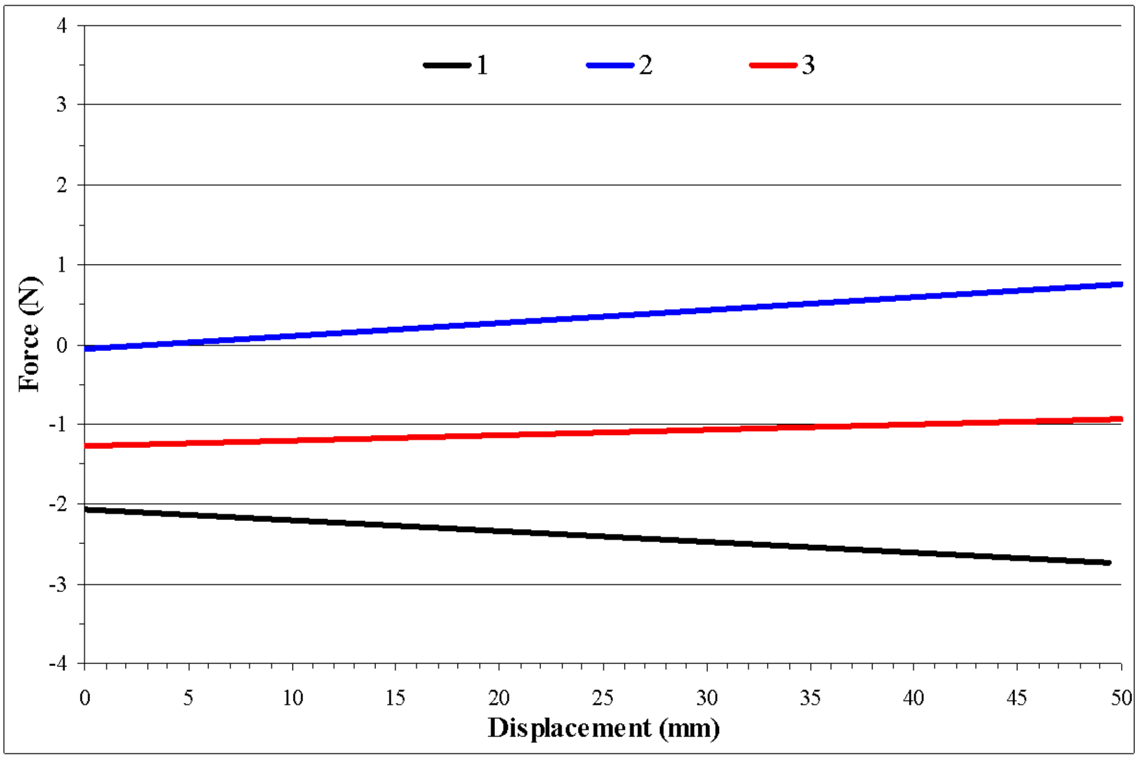

Figure 4.3.: Ejection from the syringe - tests with an empty syringe

4.3.1.1 Osteopal

All three curves of Osteopal had very similar shapes. At the beginning samples 2 and 3 achieved value of 25 N, and sample 1 a value of 20 N. The process of their sequent increase occured with a very small slope until they reached 40 N after 7 minutes, approximately. After this the slope started to increase. After 9 minutes the next increase of the slope began. In the end of the measurement, the curves of samples 1, 2 and 3 achieved values of 115 N, 125 N and 110 N, respectively. On the curves of samples 1 and 3 jumps after 11 and 10 minutes were observed, respectively. In figure 4.3.1.1. the curves of Osteopal are shown.

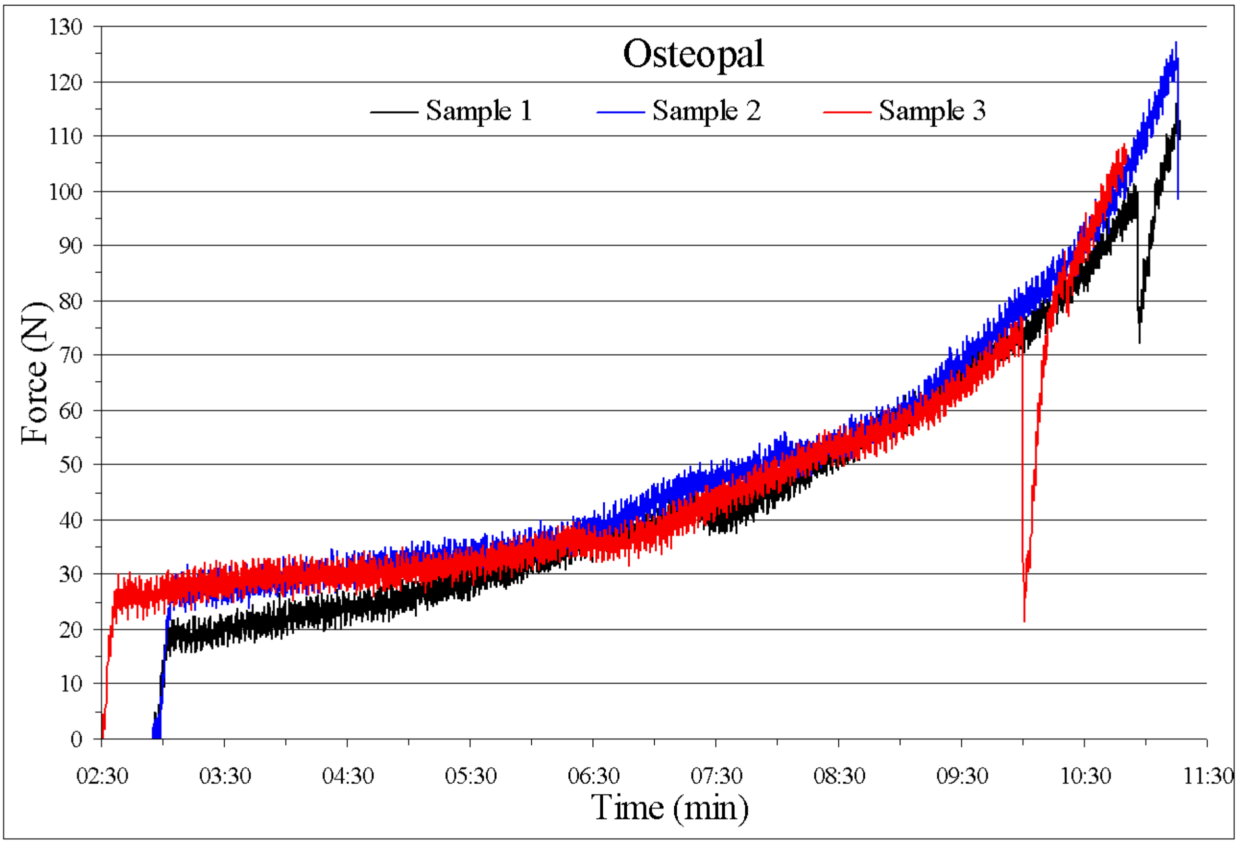

Figure 4.3.1.1.: Ejection from syringe - Osteopal curves

4.3.1.2 Refobacin BC R

All curves showed almost an identical profile. At the beginning they achieved the value of 25 N. During the next 4 minutes they increased with same slope. After this period they achieved a value of 90 N, approximately. Then the slope of the curves started increase rapidly. At the end of the measurement the curves of samples 1, 2 and 3 achieved values of 245 N, 248 N and 245 N, respectively. The time interval which was between curves at the beginning of the measurement was observed also at the end of the measurement. In figure 4.3.1.2. the curves of Refobacin BC R are shown.

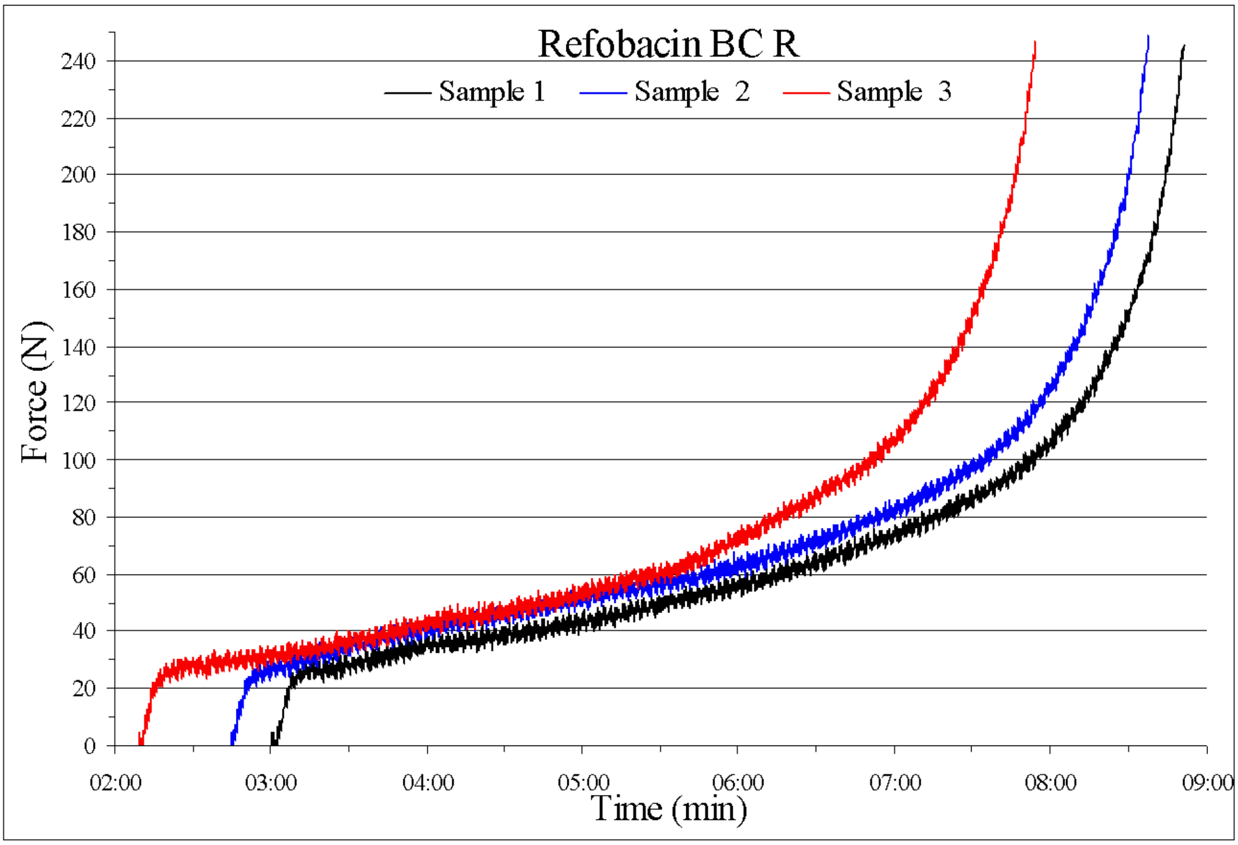

Figure 4.3.1.2.: Ejection from the syringe - Refobacin BC R curves

4.3.1.3 Refobacin Plus BC

Two curves of Refobacin Plus BC, samples 2 and 3, had a very similar profile. At the beginning they increased up to 20 N. Then they increased for 2 minutes until they achieved value of 50 N after 5,5 minutes. After this value the slope of the curves increase a little and the curves continued to grow for two minutes. The measurement of sample 1 started at 3,75 minutes from the beginning and the curve of this sample achieved and followed the values of the other curves after 15 seconds. After 7,5 minutes came a rapid increase. All curves at the end of the measurement showed a value of 245 N. In figure 4.3.1.3. the curves of Refobacin Plus BC are shown.

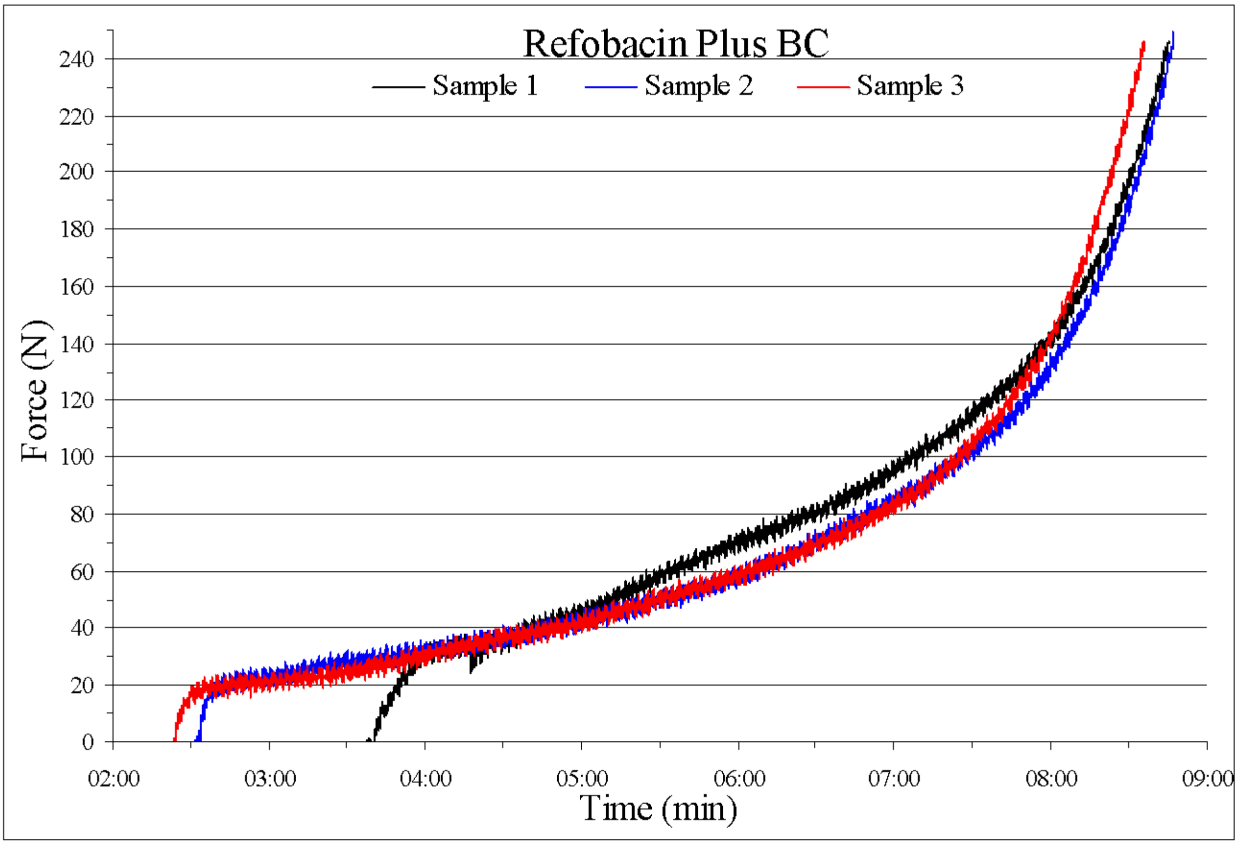

Figure 4.3.1.3.: Ejection from the syringe - Refobacin Plus BC curves

4.3.1.4 Simplex P

All three curves of samples of Simplex increased at the beginning of the measurement to values of 10 N. Only the curve of sample 2 had a little smaller slope than the other two curves. After 7 minutes the curves of samples 1, 2 and 3 reached the values of 65 N, 70 N and 90 N, respectively. All three curves achieved 247 N at the end of the measurement with similar time differences as at the beginning. In all three curves a large jump was seen at the same moment (7,75 minutes). In the curve of sample 1, a small jump was observed also at 7,25 minutes yet. In figure 4.3.1.2. the curves of Simplex P are shown.

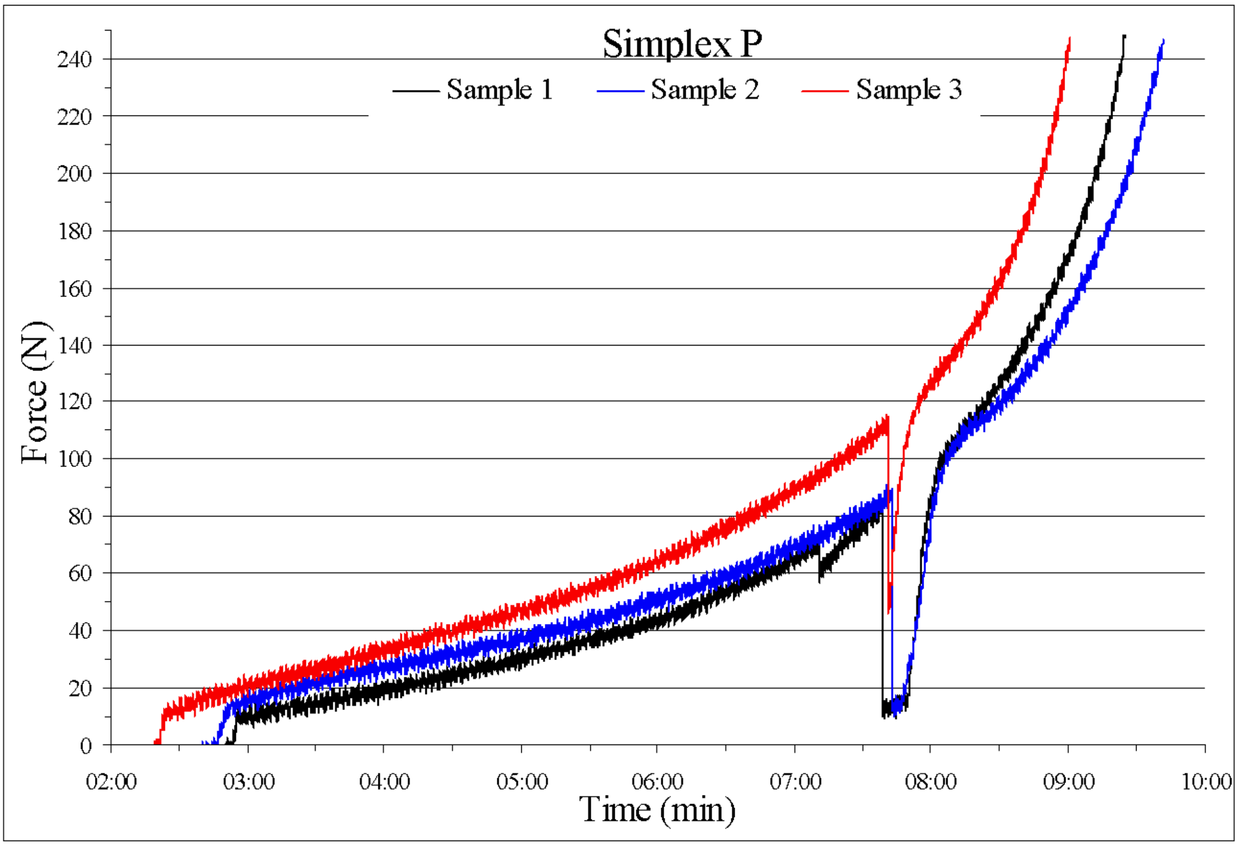

Figure 4.3.1.4.: Ejection from the syringe - Simplex P curves

4.3.1.5 Graph of mean values of 4 bone cements

A graph was created from the mean values of the three samples (Fig. 4.3.1.5). In the graph, the value for each 10 second interval from 2 to 3 minute and every 30 seconds for the rest of measurement are shown.

Starting behaviour was very similar for all bone cements. All curves were more or less stable into 3rd minute. The curve of Osteopal increased from the beginning from 25 N to 40 N in 7 minutes with small slope. The curve started to grow rapidly after 9 minutes, when reached 60 N. The curves of the other bone cements, Refobacin BC R, Refobacin Plus BC and Simplex P, started in values of 30 N, 20 N and 13 N, respectively. These curves started to grow more after 3 minutes. In the interval between 5,5 and 7 minutes curves of these bone cements were very close one to each other, and reached to 60 N after 6 minutes and 100 N after 7,5 minutes, approximately. After 7 minutes curves started to grow rapidly. The curves of Refobacin BC R and Refobacin Plus BC kept same trend. In the end of measurement Osteopals curve achieved 100 N after 11 minutes. The curves of Refobacin BC R and Refobacin Plus BC achieved 200 N after 8,5 minutes and the curve of Simplex P achieved 226 N after 9 minutes.

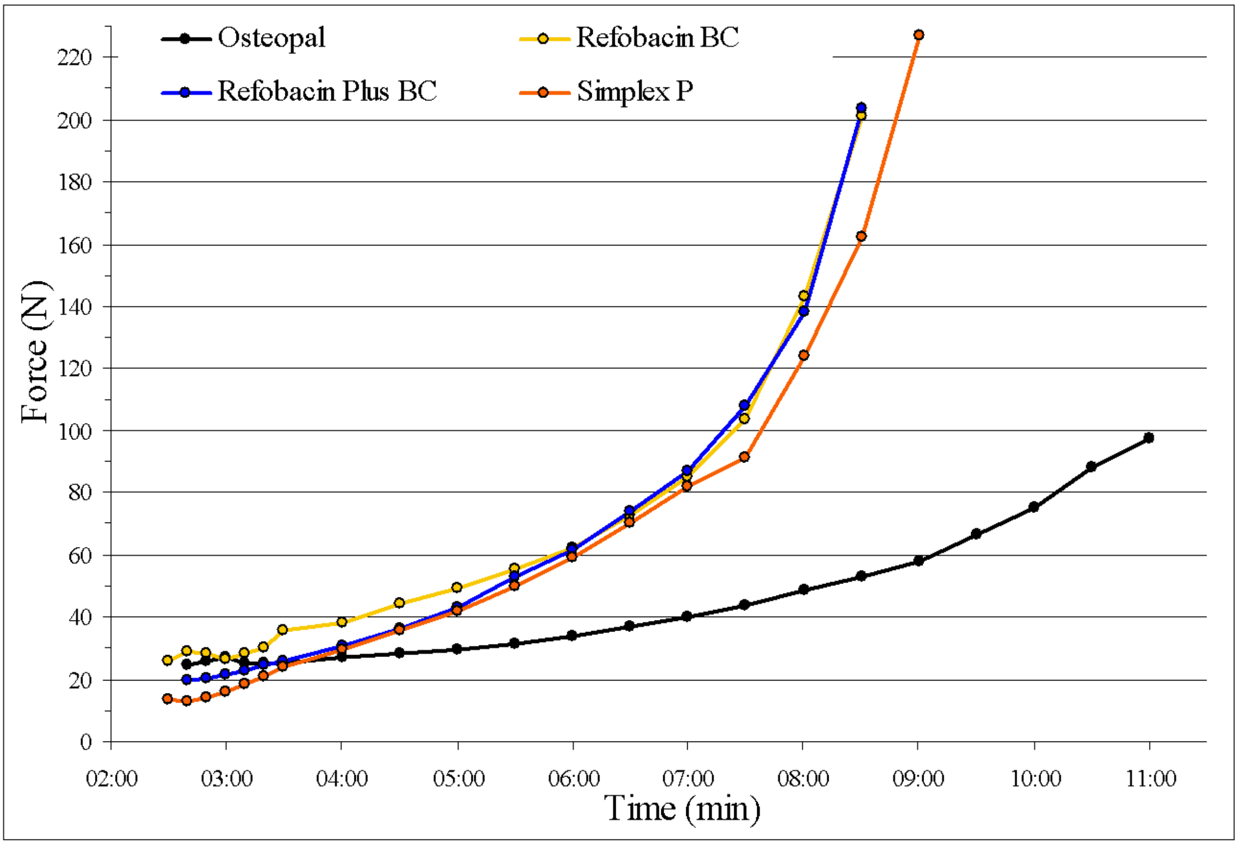

Figure 4.3.1.5.: Ejection from the syringe - Graph of mean values of all bone cements

When comparing the curves of all the bone cements the main difference between the force necessary for ejection the bone cement from the syringe was between the low-viscosity bone cement, Osteopal, and the rest of bone cements, Refobacin BC R, Refobacin Plus BC and Simplex P.

The ejection force was different. When we consider the force of 30 N the Osteopal cement showed the longest time about 5 minutes, and Refobacin BC R showed the shortest time about 2,5 minutes (Table 4.3.1.5.) of all 4 brand cements.

Table 4.3.1.5.: Ejection from the syringe - Time of achieving 30 N in the different bone cements.

Cement brand	Starting value	Starting time	Time of achiving 30 N	Difference
Osteopal	25 N	$2:^{40}$ minute	$5:^{00}$ minute	140 seconds
Refobacin BC	30 N	$2:^{30}$ minute	$2:^{30}$ minute	0 seconds
Refobacin BC Plus	20 N	$2:^{40}$ minute	$4:^{00}$ minute	80 seconds
Simplex P	13 N	$2:^{30}$ minute	$4:^{00}$ minute	90 seconds

4.4 Insertion of rod with plate

Before testing bone cements an empty syringe was tested for methodology. The data obtained from these tests showed friction between the disk and the wall of the syringe (Fig 4.4.). This friction was insignificant. A jump was observed in water test was caused by touch of hand on rod.

In all the graphs of the bone cements an x axis with range from 2 to 6 minutes was chosen, which is related to clinical use – after this period the cements are beyond.

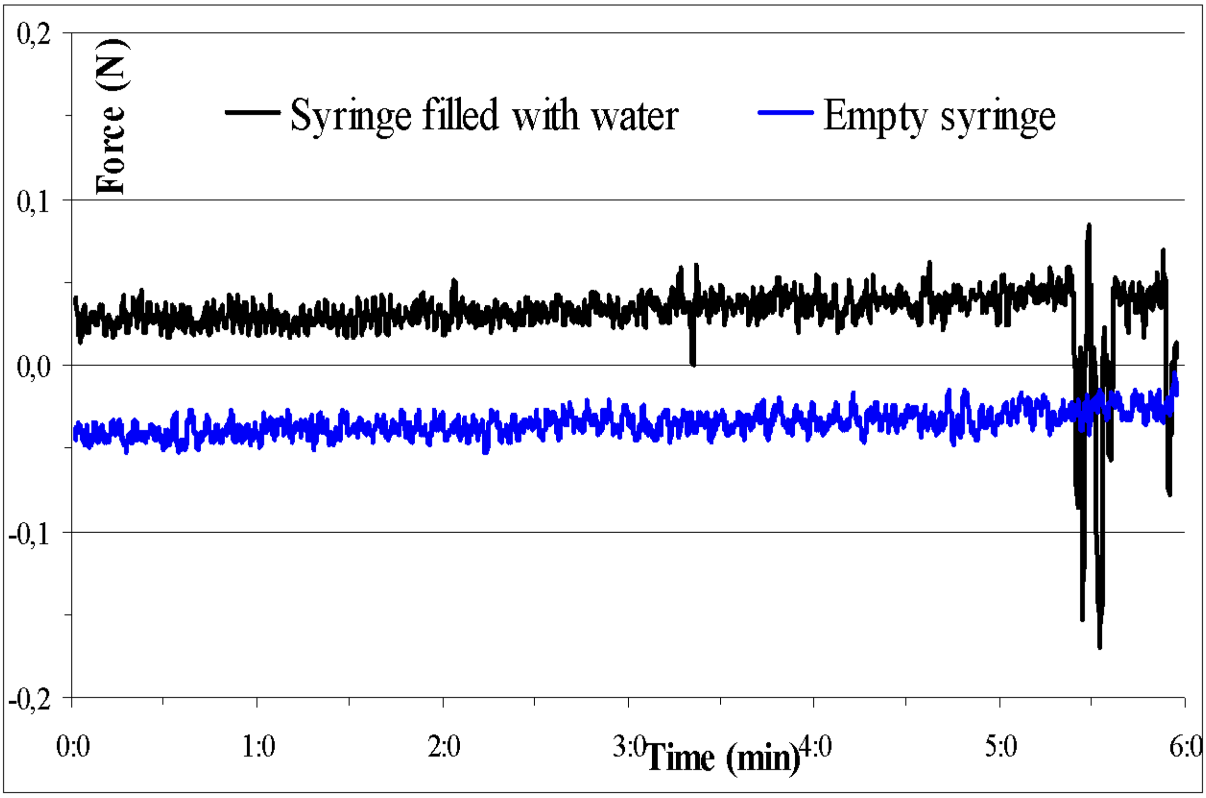

Figure 4.4.: Insertion of the rod with plate – empty syringe tests

4.4.1.1 *Osteopal*

During the first measurement of the Osteopals samples, the curves were very different. The curve of sample 3 showed a very strange behaviour, when after four minutes the curve started to increase rapidly to 55 N, then deceased to 16 N and continued to increase. The curves of samples 1 and 2 increased from the beginning with small slope. These curves achieved value of 0,5 N after 4,25 and 4,75 minutes, respectively. When the curves of samples 1 and 2 achieved 0,5 N then they started increase rapidly, sample 1 increased more steeply. After 6 minutes they achieved 4 and 2 N, respectively. Because the curve of sample 1 showed small variations and the curve of sample 3 had a strange behaviour, three more measurements were done. One of the new measurements, sample 5, showed again a rapid increase to 18 N and then decrease to 5 N. The curves of sample 4 and 6 were almost identical. They increased slowly, and during the measurement achieved 0,5 N after 6 minutes. The graph of the measurements is shown in figure 4.4.1.1.

The curves of the Osteopal samples 3 and 5 were eliminated from results. The graph of all the measurements of the Osteopal cement is shown in the appendix.

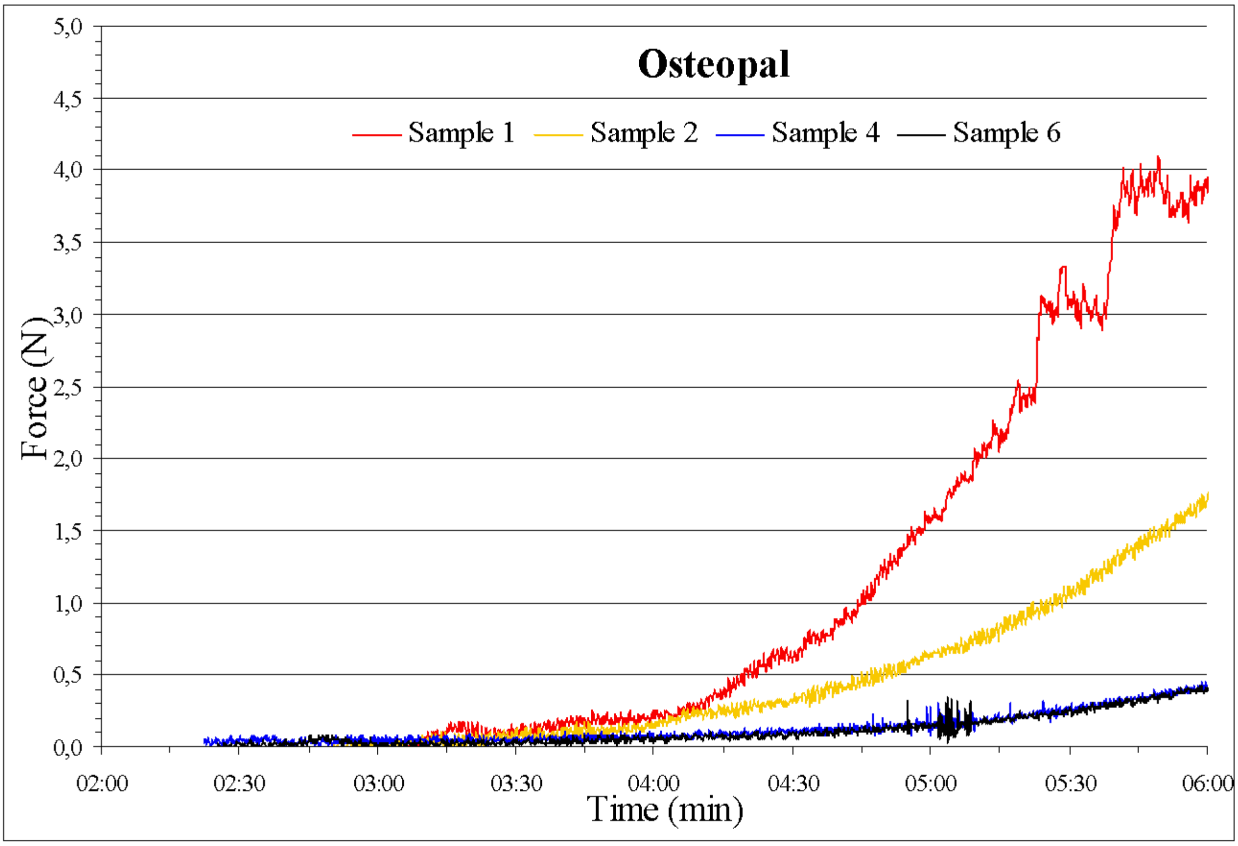

Figure 4.4.1.1.: Insertion of the rod with plate - Osteopal curves (6 minutes)

4.4.1.2 Refobacin BC R

The curves of all three samples of Refobacin BC achieved very similar values during the first 6 minutes (fig 4.4.1.2.). At the beginning of the insertion of the rod into the syringe with Refobacin BC R a small peak was observed on each curve. All the curves of Refobacin BC R had the same behaviour and trends during measurement. In the first 4 minutes there was step of all curves of 0,1 N/ 15 - 20 seconds. All the curves achieved the value of 0,5 N after 3,5 minutes from the beginning. After 4 minutes the curves increased progressively. They achieved a value of 2 N after 6 minutes.

The graph of all the measurements of Refobacin BC cement is shown in the appendix.

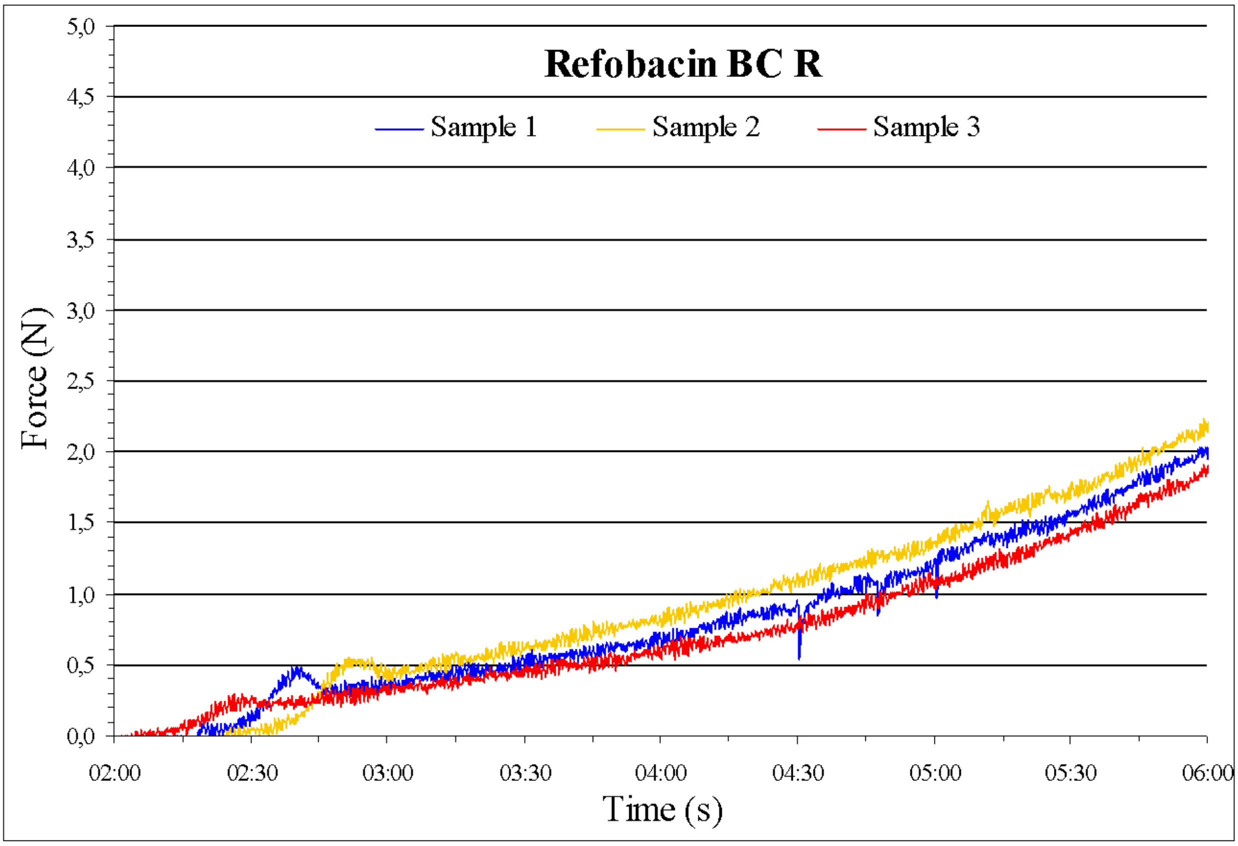

Figure 4.4.1.2.: Insertion of the rod with plate - Refobacin BC R curves (6 minutes)

4.4.1.3 Refobacin Plus BC

The curve of Refobacin Plus BC sample 2 showed a very fast increase to 72 N. The curve of sample 2 was thus excluded from the results. The curve of sample 3 was during the measurement influenced by the reclosing of syringe. For these reasons three additionally measurements were done. On all curves a small peak appeared at the beginning of the measurements. The curves of samples 1, 3, 5 and 6 were very close together. All these curves crossed a value of 0,5 N after 3,5 minutes. After 4,5 minutes the curves of samples 1, 3, 5 and 6 increased with increasing slope and achieved a value of 2 N after 5,5 minutes; 5,3 minutes; 5,6 minutes and 5,5 minutes, respectively. The maximum value of these curves was 2,5 N after 6 minutes, approximately. The curve of sample 4 crossed the value of 0,5 N after 4 minutes. The increase of the other was steady after 4,5 minutes. At the end of the measurements the curve of sample 4 reached the value 1,5 N. The graph of the samples is shown in figure 4.4.1.3. The graph of all the measurements of Refobacin Plus BC cement is shown in the appendix.

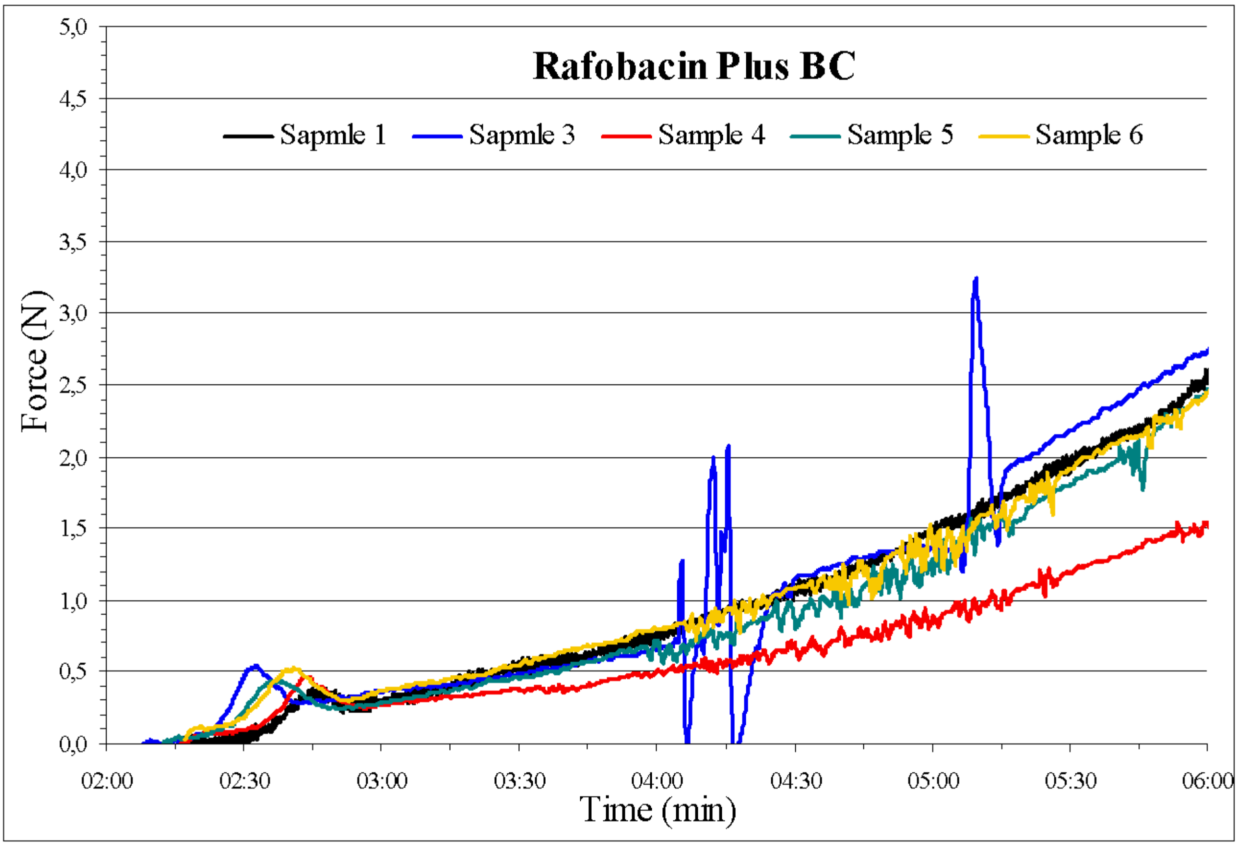

Figure 4.4.1.3.: Insertion of the rod with plate - Refobacin Plus BC curves (6 minutes)

4.4.1.4 Simplex P

The two curves of samples 1 and 3 had almost an identical behaviour from the start of measurement. From the beginning to the 3rd minute these curves had noteless increase. After 3 minutes all the curves started to increase more and they achieved a value of 0,5 N after 3,5 minutes and 2 N after 5,25 minutes, approximately. From 4,25 minutes small difference was observed between the curve of sample 2 and the other two. After 4,75 minutes, the curves increased progressively. The difference between the curves of sample 2 and the other two was after 6 minutes equal to 1 N. Figure 4.4.1.4. shows the measurement of the Simplex P samples. The graph of all the measurements of Simplex P cement is sown in the appendix.

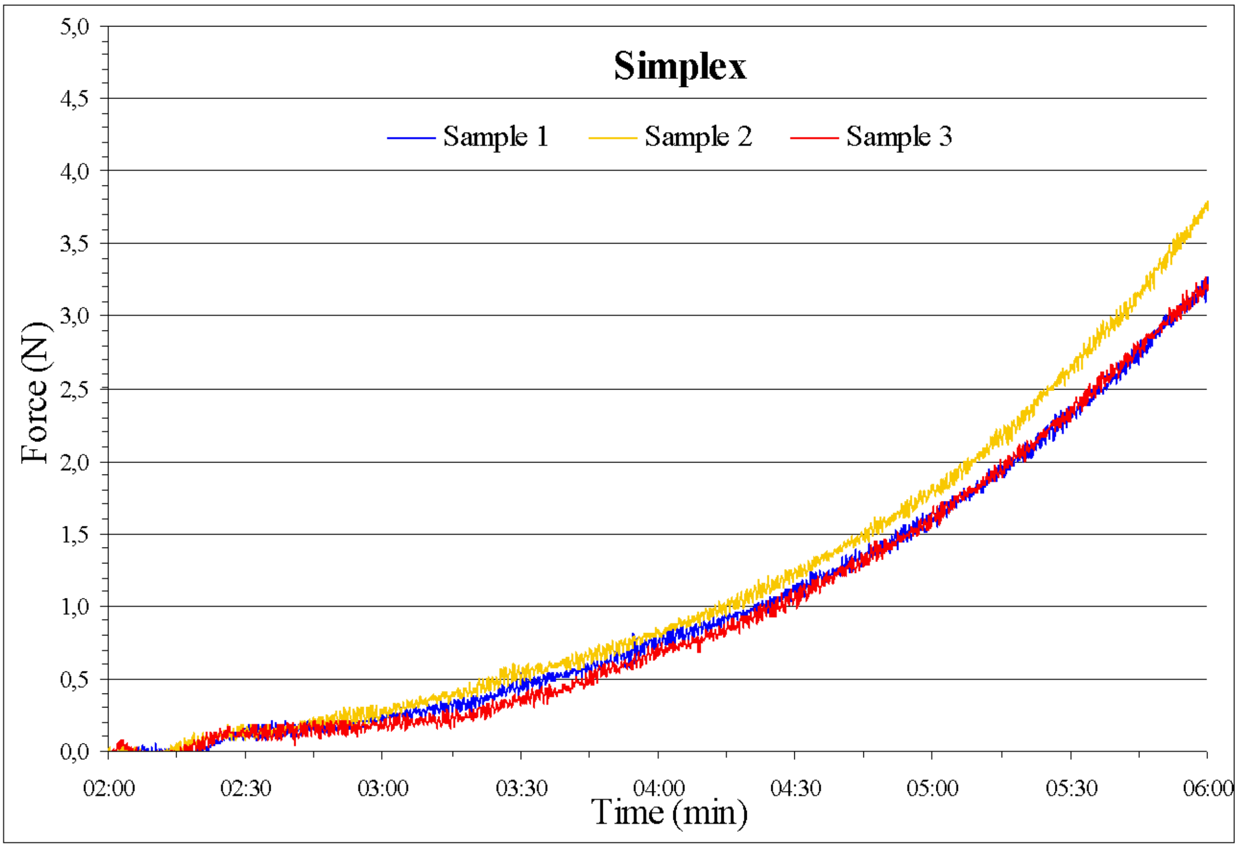

Figure 4.4.1.4.: Insertion of the rod with plate - Simplex P curves (6 minutes)

4.4.1.5 Graph of mean values of 4 bone cements

For comparison of four bone cements, a graph was created from the mean values of the three samples (Fig. 4.4.1.5). In the graph, the value for each 10 second interval from 2 to 3 minute and every 30 seconds for the rest of measurement are shown.

The starting value of the curve of Osteopal was almost 0 N. Refobacin BC R and Refobacin Plus BC curves increased to 0,2 N and 0,3 N respectively at the start. The curve of Simplex P increased to 0,1 N. Osteopal's curve increased from the beginning to 4th minute with a very small slope to only 0,19 N. The curve of the others cements, Refobacin BC R, Refobacin Plus BC and Simplex P, increased slightly to the 4th minute and then increased progressively. Osteopal, Refobacin BC R, Refobacin Plus BC and Simplex P curves achieved a value of 0,5 N after 4,75; 3,5; 3,5 and 3,75 minutes and a value of 2 N after 6,25; 6,15; 5,5 and 5,3 minutes, respectively.

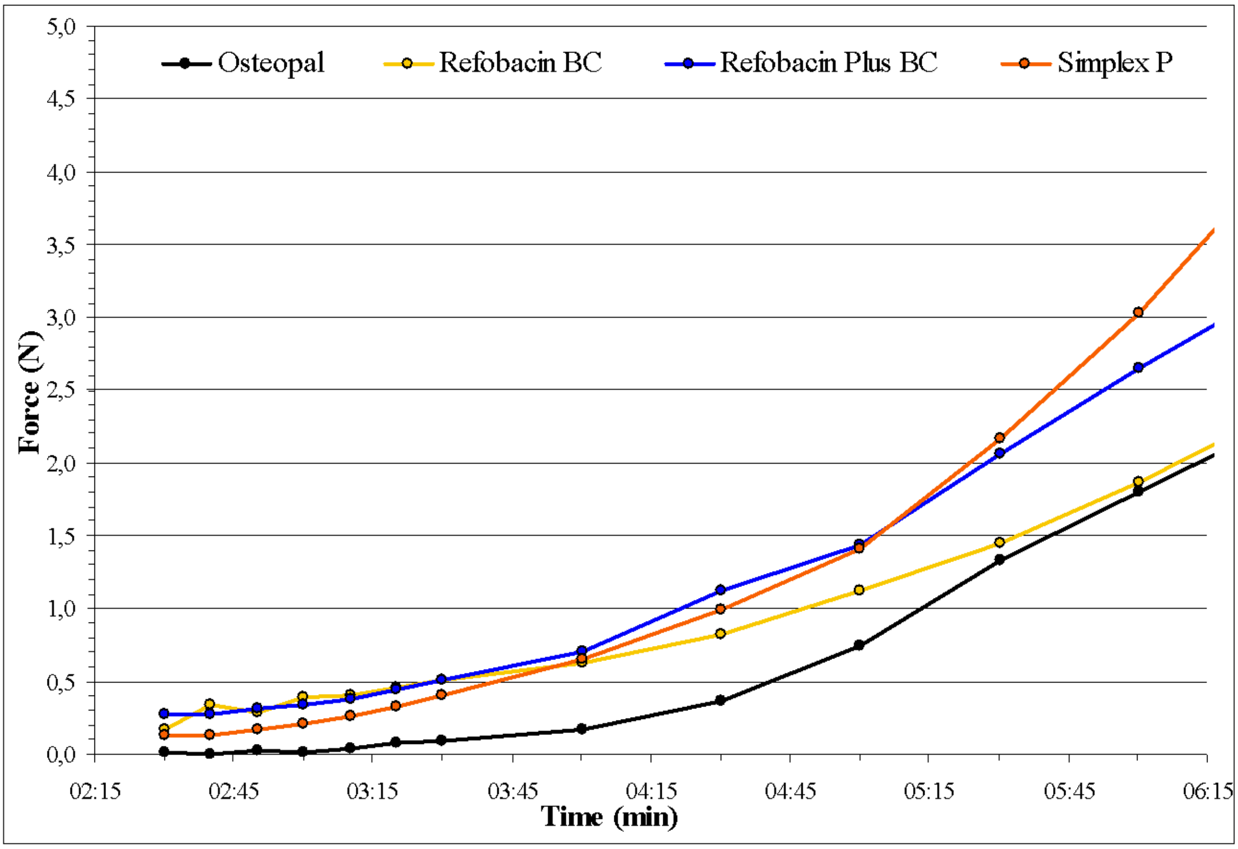

Figure 4.4.1.5.: Insertion of the rod with plate – Graph of mean values of all bone cements

According to the instruction for the use of Refobacin BC cement the working time is from 1,5 to 4,5 minutes after the powder is mixed with the liquid at 21 °C. Prosthesis insertion should wait until the cement reach a certain viscosity to be able to press the cement to the bone bed.

If the force of the insertion rod is between 0,5 to 1,0 N the time varies in the different cements. It showed that the Osteopal cement needed 4,6 minutes to reach 0,5 N and after 35 seconds reached 1,0 N. Refobacin BC needed 3,5 minutes to reach 0,5 N and after 80 seconds reached 1,0 N.

Table 4.4.1.5.: Insertion of rod with plate

Cement brand	Time of achieving 0,5 N	Time of achieving 1 N	Difference
Osteopal	4:^{45} minute	5:^{15} minute	35 seconds
Refobacin BC	3:^{30} minute	4:^{50} minute	80 seconds
Refobacin Plus BC	3:^{30} minute	4:^{20} minute	50 seconds
Simplex P	3:^{45} minute	4:^{30} minute	50 seconds

4.5 Rotating rod

The curves of all the measurements for all the bone cements looked the same. All the curves had a little slope to 6 minutes. After 6 minutes the curves increased slope rapidly. The obtained data for the Osteopal samples are shown in Figure 4.5.

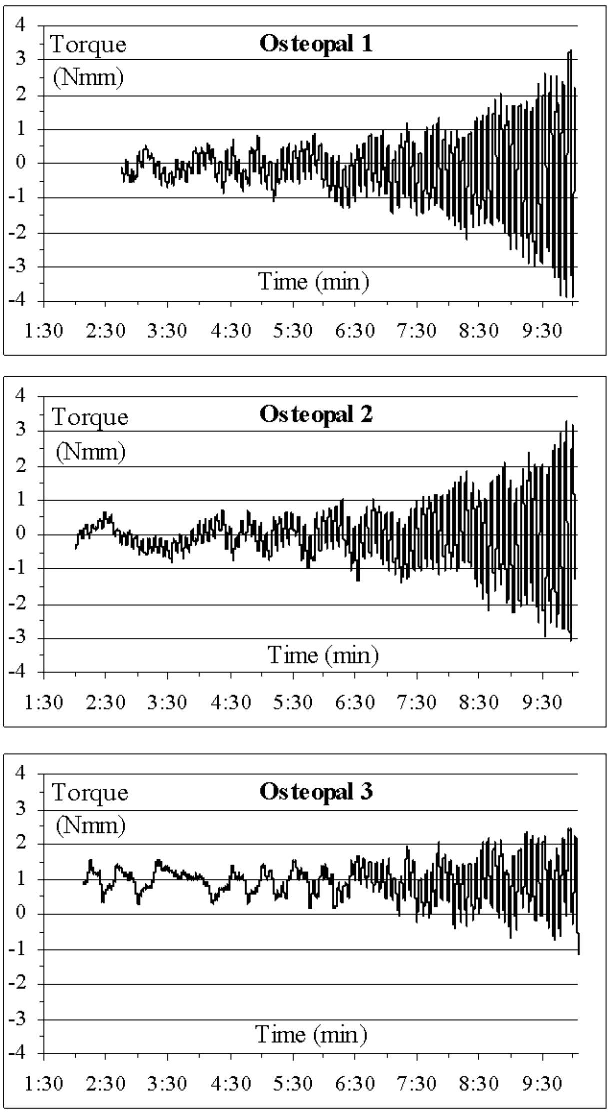

Figure 4.5.: Rotating rod - Torque – Osteopal

5 DISCUSSION

Standard methods which are used for the determination of the properties of bone cement are commonly based on applying a constant force. By this principle, the methods used in this study were created to imitate the cementation procedure during operations and consequently monitored the force needed in order to monitor the viscosity changes which are necessary to manipulate the bone cement.

5.1 Mixing

The subjective impression from the mixing of the bone cement was that the viscosity behaviour responded to the marking of the bone cements, where low-viscosity cement was like a liquid almost during whole mixing period. The opposite experience were with the high-viscosity cements, which transformed to dough very early after mixing of the powder with the liquid.

5.2 Rheometer measurement

Due to the fact that rheology is the standard method, the viscosity behaviour of the bone cements were observed by the rheometer to obtain a detailed view of the behaviour of the cement. One of the important features of the rheometer measurements was the determination of the changes of the phase angle, which correspond to changes in the handling of the bone cement. A viscosity value (10 000 Pa · s) was chosen due to the rapid decrease of the slope of the phase angle and the viscosity curve vs. time.

The viscosity curve of Refobacin Plus BC showed a typical S shape. Refobnacin BC R showed the lowest values of viscosity in all the measurements, compared to other three cements. Against this, Simplex P showed after 5,75 minutes a higher values than the other cements. The Osteopal cement exhibited values which were comparable with the high viscosouc cements during the working and the hadrening phase, provided all curves were shifted to a certain value of viscosity. An example of a graph with the viscosity and phase angle vs. time for Osteopal is shown in the appendix. The behaviour of the cement was compared on the basis of the rheometer results and the other methods.

5.3 Flowability test

The purpose for this test was to investigate how the cement viscosity behaved after mixing, and if it would flow out from a syringe without pressure. Most surgeons will wait until the cement is in a dough condition before injecting of the cement to the bone bed. It is termed a “waiting period”. The test showed that the low viscosity bone cement, Osteopal, flowed from the syringe and the Optivac cylinder.

The time of the test correspond to the waiting time of the cement. The high and medium viscosity cements, Refobacin BC R, Refobacin Plus BC and Simplex P, did not flow out from the syringe. These cements need to be pushed out by force.

5.4 Ejection from syringe test

This method was used to investigate how much force was necessary to eject cement from the syringe. The data provide information that surgeon should carefully control the cement injection time to the bone bed with the different cements.

Changes in force with time responded to the expected behaviour of cements viscosity during measurement. Osteopal kept low values and Refobacin cements had high values. The ejection force of Simplex P cement was different. The force at the beginning of the measurement showed the lowest value but during the measurement the behaviour of this cement was very similar to the high-viscous cements. If we compare the initial force for all 4 brand cements (Table 4.3.1.5.) according to instruction sheets, Osteopal cement showed a relatively high ejection force (about 25 N) at the beginning if compared with the high and medium viscosity cements, Refobacin BC R (30 N), Refobacin Plus BC (20 N) and Simplex P (less 20 N), respectively. The behaviour of the Simplex P and Osteopal cements was similar regarding the force in their waiting phase. When the cements reached the end of waiting phase, the force of ejection started to increase with a small slope. This behaviour was observed for all 4 brand cements. The end of the working phase for Refobacin cements was after 4,5 minutes and the curves achieved values around 40 N. In next phase, the cement became harder and it was assumed that the force grew rapidly. Against this hypothesis, the curve of the Refobacin cements kept a small slope up to 6 minutes and then the slope of the curve increased. The curve of the Osteopal and Simplex P cements started to increase after the end of the working phase. The force which Osteopal achieved at the end of the working phase was only 35 N. It may also show that the viscosity change was proper for the cementation during the period. This viscosity change may be correlated with the ejection force during the period. If the Osteopal cement is injected into the bone marrow cavity at same time as Refobacin BC R or Refobacin Plus BC, the cement may remain under low viscosity conditions during the cementation according to Figure 4.3.1.5.

In some cases, peaks in the curves during the measurement could be due to bubbles of air in the syringe.

5.5 Insertion of rod test

A similar method was used by Klaus-Dieter Kuhn to simply and quickly characterise the curing process of bone cements. The description of the method is given in reference [44]. The method can also imitate the force used for insertion of a prosthesis to the filled bone bed. During the first 6 minutes the bone cements are usually important for the cementation according to the instruction sheets of the manufactures. For this reason the graphs were cut after this time.

The small peak observed at the beginning of the measurements is probably due to the insertion of the rod through the wall of the syringe, which has shape as frustum. This peak was observed in the case of the Osteopal and Refobacin Plus BC measurements. In the waiting phase Osteopal had almost zero values. During the working phase the Osteopal curve increased to the end value 1,8 N. The curves of Refobacin BC R, Refobacin Plus BC and Simplex P showed similar processes and they achieved at the end of working phase (after 4,5 minutes) values of 0,8 N; 1 N and 1,2 N, respectively. The results showed an opposite trend when compared with the ejection from the syringe test. The values of all cements were largely increased after 5 minutes.

When comparing the data from Table 4.4.1.5. between Osteopal and Refobacin BC R, the results provide information that Refobacin BC R allows early prosthesis insertion and also gives longer time for handling the insertion of prosthesis as compared to the Osteopal cement.

5.6 Rotating rod test

Unfortunately these tests did not show any relevant data, which were useful. The reason could be that a rod with a too small diameter, which did not achieve a high enough adhesion.

5.7 Evaluating/ comparing of tests

In order to compare the bone cement viscosity behaviour a Figure 5.7 was made. Two evaluations are summarised in the graph, i.e. the rheometer measurement and the ejection test. The flowability test gives basic information about the beginning of the viscosity behaviour and only shows that the Ostopal cement has a significantly lower viscosity than the other 3 cements. Therefore, it is not included in the graph. The data obtained from the rotating rod test were not relevant for this study. Data from the insertion of the rod test show maximum values of less than 8 N. Due to the scale it is difficult to place it in the same graph for comparison. For these reasons they are not included in Figure 5.7.

If tests were evaluated together, results for the Osteopal bone cement showed that during the waiting time forces for the injection and insertion were almost stable. When the time achieved the working phase, all three curves of the viscosity, the force of ejection and the force of insertion increased with a small slope. Growth of the viscosity was observed at the end of the hardening phase. The data confirmed the handling with the bone cement recommended by the manufacture. Value of the viscosity increased to 7x times higher value during the working time. This fact could made the application time of the cement relatively short. Even if the viscosity of the Osteopal cement wass higher than for Refobacin BC R, the other values were still lower than for the other bone cements.

An interesting phenomenon was found between the rheometer measurement and ejection from the syringe test. That was the viscosity of the Osteopal was higher than Refobacin BC R cement in the rheometer measurement, but was lower than Refobacin BC R in the ejection force. The other view of phenomenon was that viscosity of Refobacin BC R was lower than the other bone cements. Composition of the Refobacin BC R powder was between the composition of Osteopal and Refobacin Plus BC. Composition of the liquid was same for these three cements. The reason of this phenomenon is unknown. Further study need to be considered.

The Refobacin BC R viscosity increased during the working phase. The ejection force and the insertion force were stable during the working phase and then they grew rapidly after 6 and 7 minutes, respectively. Increase of the viscosity was observed at the end of the hardening phase.

Refobacin Plus BC exhibited a high values, which were assumed for the high-viscosity cement. During the working phase viscosity increased with same trend as forces. The behaviour of Refobacin Plus BC in the working phase was similar as in the case of Refobacin BC R.

The viscosity and forces of Simplex P cement were stable in a slight low condition before the end of the waiting phase. When reaching to the working phase, the viscosity achieved values similar to the high viscosity cement (Refobacin BC R and Refobacin Plus BC).

Simplex P cement as only one did not show any change in the viscosity at the end of the measurement. Working with this cements even provided experience that it cured after 9 minutes, which was early in the recommendation by the manufacturer.

Characterization and understanding of the flow properties of the bone cements can benefit total hip replacements.

In general if the cement viscosity is too low, or too high, it will be difficult to inject the cement into the bone bed and to achieved good interlock to the cellular bone or to insert the prosthesis into the cement mass. If low-viscosity cement is injected into the bone at the time of high-viscosity cement, the cement may remain in a low viscosity condition, where it would not be able to balance the blood pressure of the bone marrow cavity. Therefore, the blood could easily enter into the low viscosity bone cement and cause lamination in the bone cement.

Knowing the viscosity behaviour will be helpful for using the bone cement during the operation.

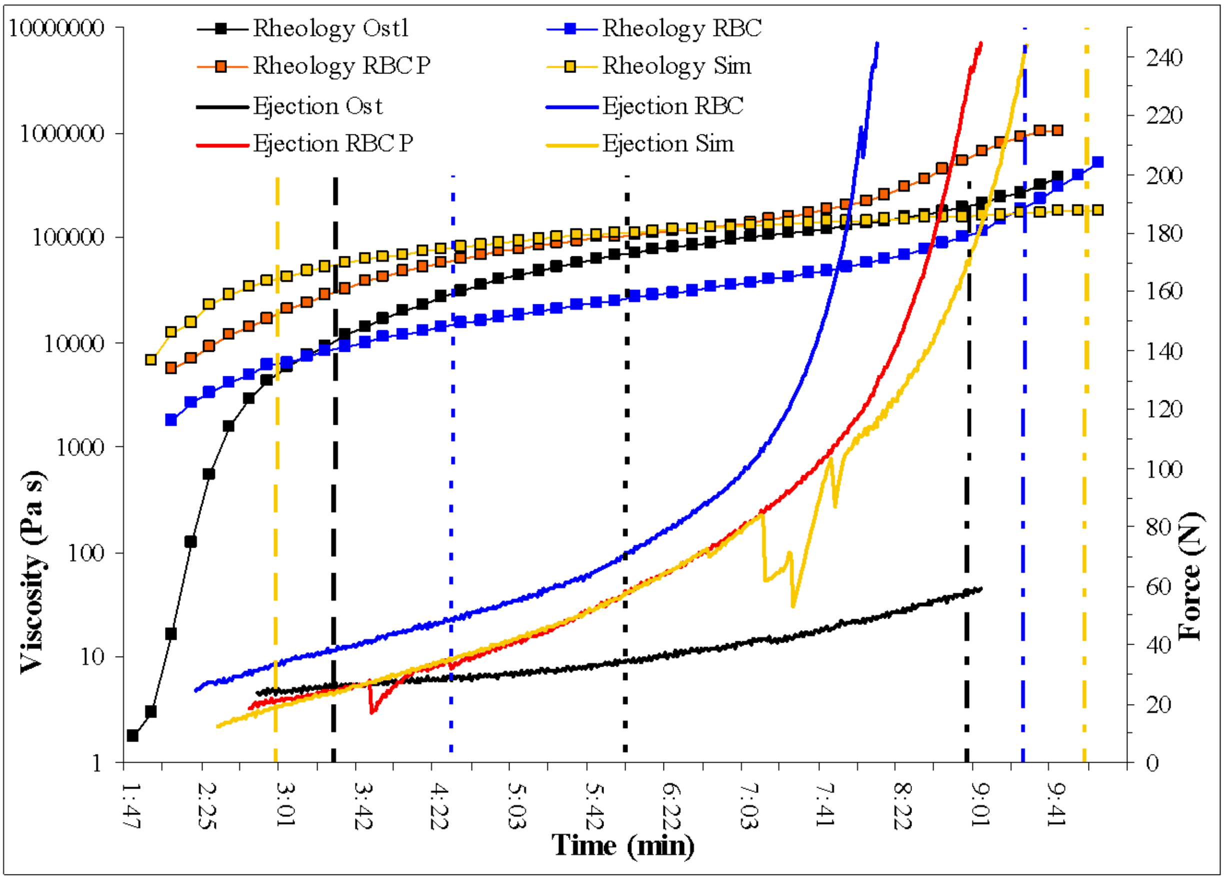

Figure 5.7.: Evaluation of bone cements in rheometer measurements and ejection from the syringe.

In the graph: the colour of curves belong to the colours of cements,
– – – end of waiting phase; · · · end of working phase; – · – end of hardening phase.
The rheometer curves use the viscosity axis, ejection curves use the viscosity axis.

6 CONCLUSIONS

The project should provide answer to the following questions:

What polymerization time is suitable for clinical procedures with the different types of BC?

What combination of polymerization time and ejection force is proper for clinic use?

The best time for injection, pressurization and prosthesis insertion is at the moment when the viscosity raises to a plateu curve and the ejection and insertion forces are stable or increase slowly. Osteopal cement shows this behaviour after 3,5 minutes. Injection time for the high-viscosity cements, Refobacin BC R and Refobacin Plus BC, reached after 2,5 minutes. Unfortunately, the measurement before 2 minutes was not possible. The Simplex P cement has a stable behaviour after 3 minutes. All these times correspond to the working phase of each bone cement.

The data provide information that high-viscosity bone cement, Refobacin BC R and Refobacin Plus BC can be injected directly after mixing. Simplex P cement can be injected after 2,5 minutes. In the case of Osteopal cement, it is necessary to wait until cement achieved a high enough viscosity at the end of waiting phase.

The viscosity measurement by rheology is a standard method, which provides a detailed view of the bone cement behaviour. However, it shows an opposite behavior compared to the other methods. The ejection and insertion tests reveal a clear viscosity change in the polymerization period. The flowability test only indicates that a low viscosity cement in an early period could be tested. The rotation test does not give useful information about the viscosity change.

An interesting difference between the rheometer measurements and the ejection from syringe test of Osteopal and Refobacin BC R cement was found. Further studies need to be done.

Comparing the viscosity curves of all the bone cements suggests that their handling during mixing and waiting phase does not have any influence on their behaviour during the working phase.

Marking the bone cements as low-, medium- and high-viscosity is valid in the mixing phase. The most readily mixed bone cement was Osteopal. If the measured data are compared for all the 4 bone cements, then times which are recommended in the instruction sheets correspond to the measured behaviour of respective the bone cement.

The data provided information that surgeons should control the cement injection time to the bone bed with the different cements.

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8 APPENDIX

A. 1. Symbols

Methylmethacrylate - MMA	BC - Bone Cement
Polymethylmethacrylate - PMMA	N - Newton, unit of Force
Benzyl peroxide - BPO	Pa - Pascal, unit of pressure
N,N-dimethyl-p- toludiene - DmpT	mm - milimeter, unit of distance
Zirconium dioxide - ZrO_2	s - second, units of time
Barium Sulphate - $BaSO_4$	min - minute, units of time

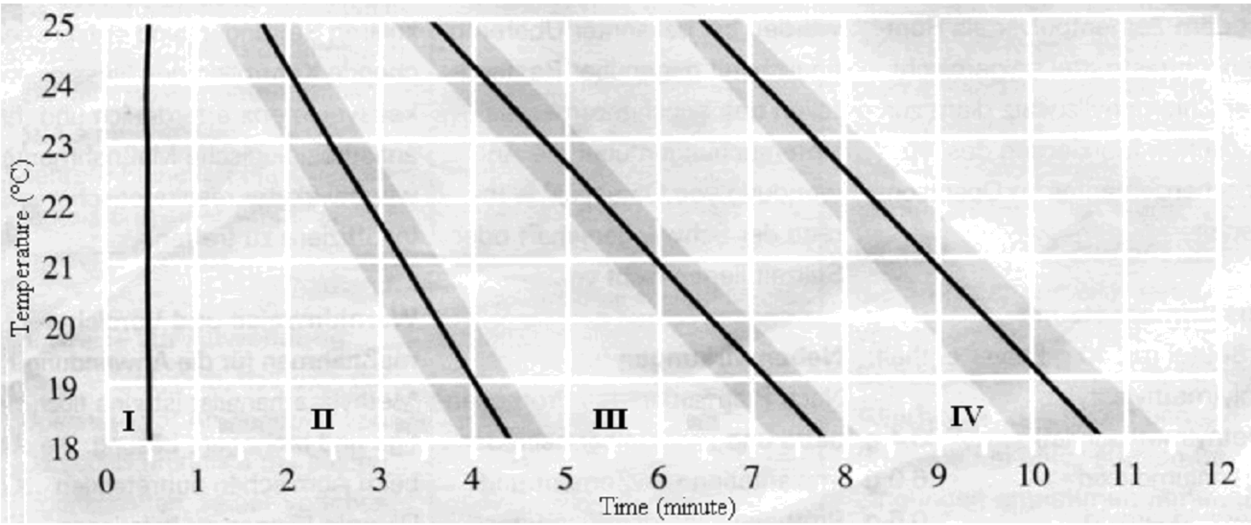
A. 2. Number of batches

Bone cement	Batch number
Refobacin BC R	Ref/ LOT n.: 4710500394/ 916 AB/ 816 BA
	Ref/ LOT n.: 4711500396/ 905 CA
Refobacin Plus BC	Ref/ LOT n.: 4720502083/ 904 AA/ 834 AB/ 929 BA
Simplex P	Ref/ LOT n.: 61910001/ CIO 151/ GFD 065
Osteopal Low viscosity	Ref/ LOT n.: 3805540011/ 9898/ 9799
	Ref/ LOT n.: 4711500396/ 905 CA

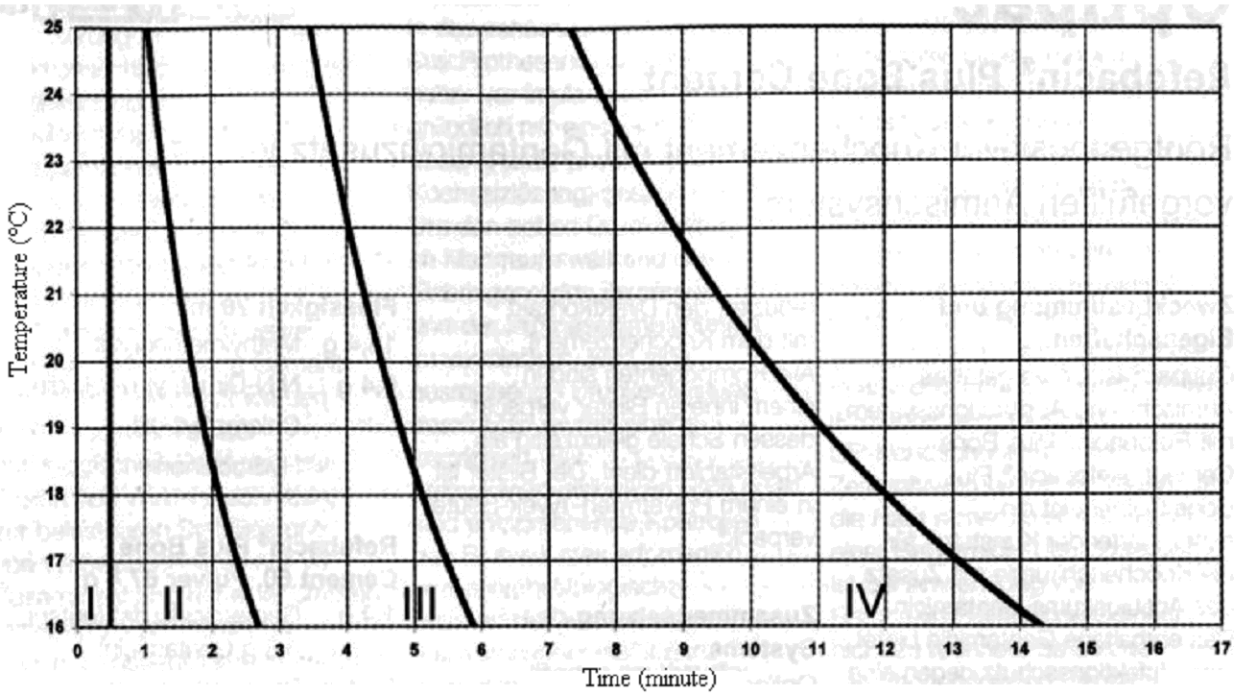
A. 3. Risk assessment

Substance	CAS number	Risk sentence	Save sentence
MMA	[80 - 62 - 6]	11 - 37/ 38 - 43	24 - 37 - 46
ZrO_2	[1314 - 23 - 4]	36/ 37/ 38	26 -36
Benzyl peroxide	[94 - 36 - 0]	1 - 8 - 36 - 43	17 - 26 - 36/ 37
N,N-dimethyl-p- toludiene	[99 - 97 - 8]	23/ 24/ 25 - 33 - 52/ 53	28 - 36/ 37 - 45 - 61

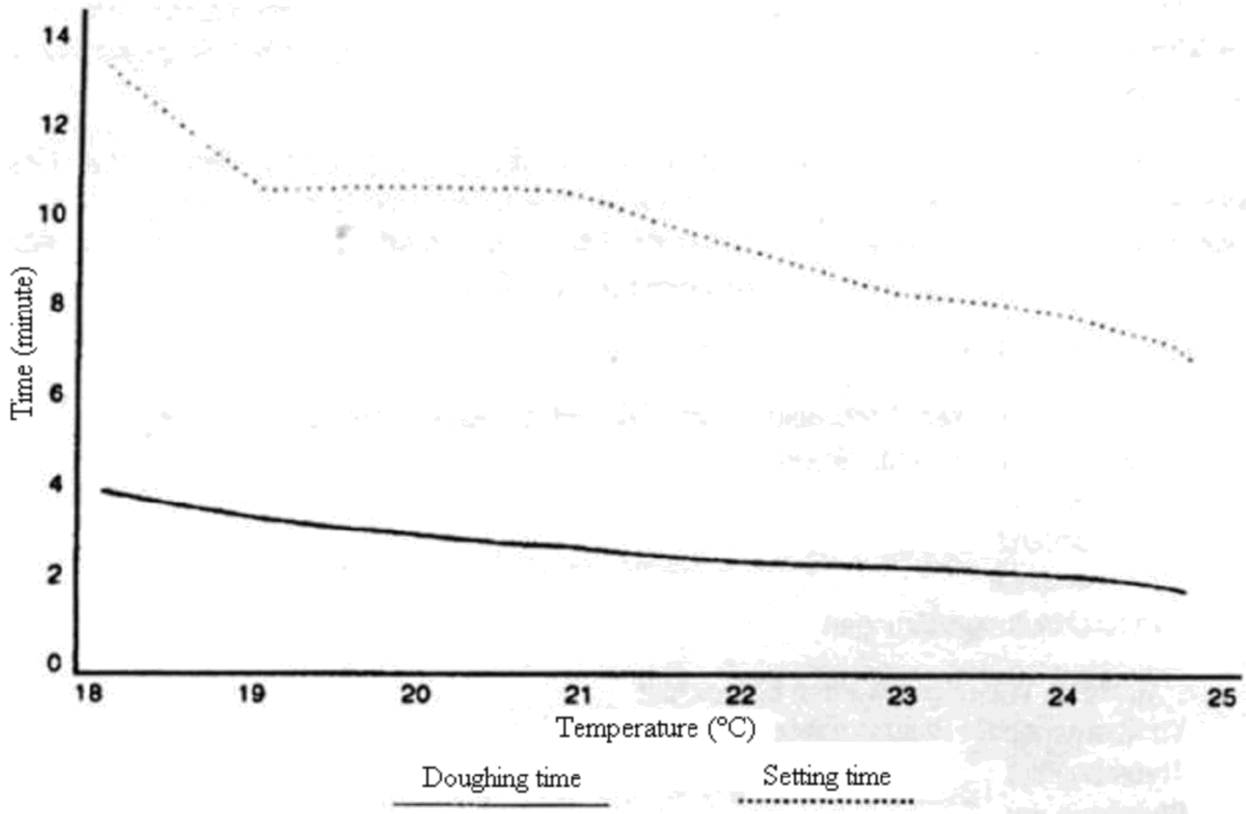
A. 4. Time schedule for application of non-prechilled bone cements



Time schedule for application of non-prechilled Osteopal.

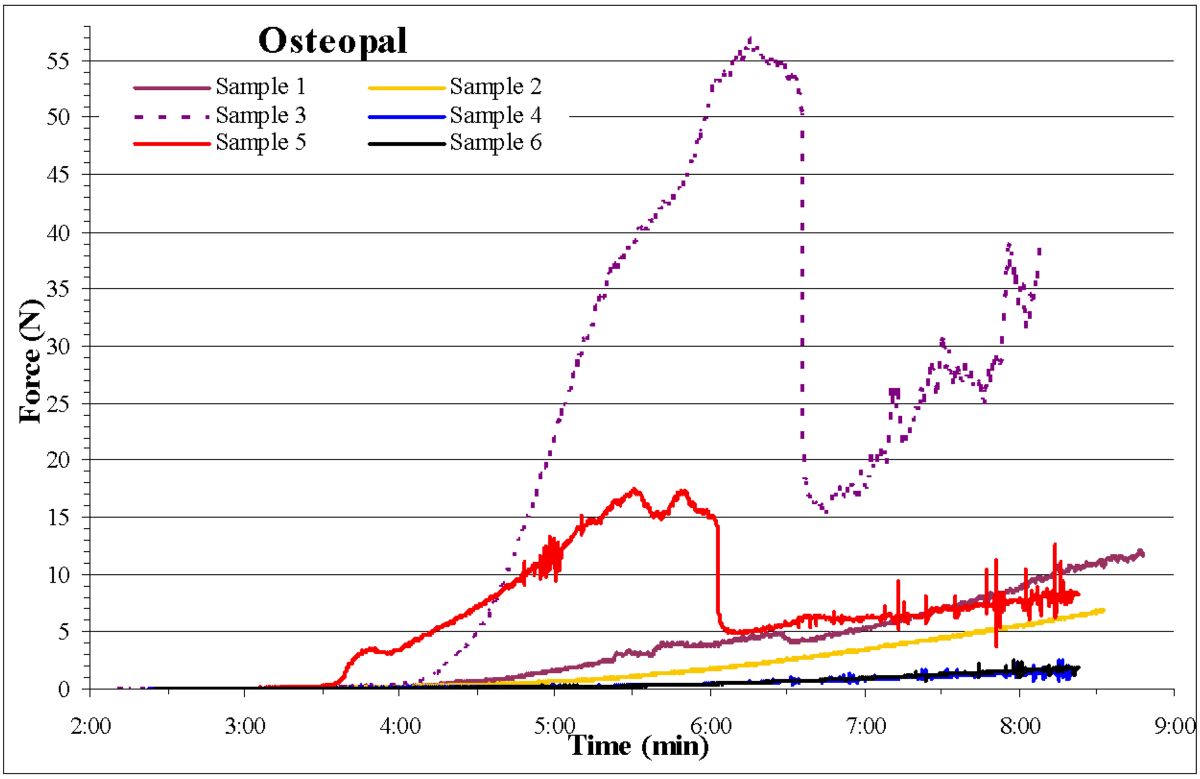


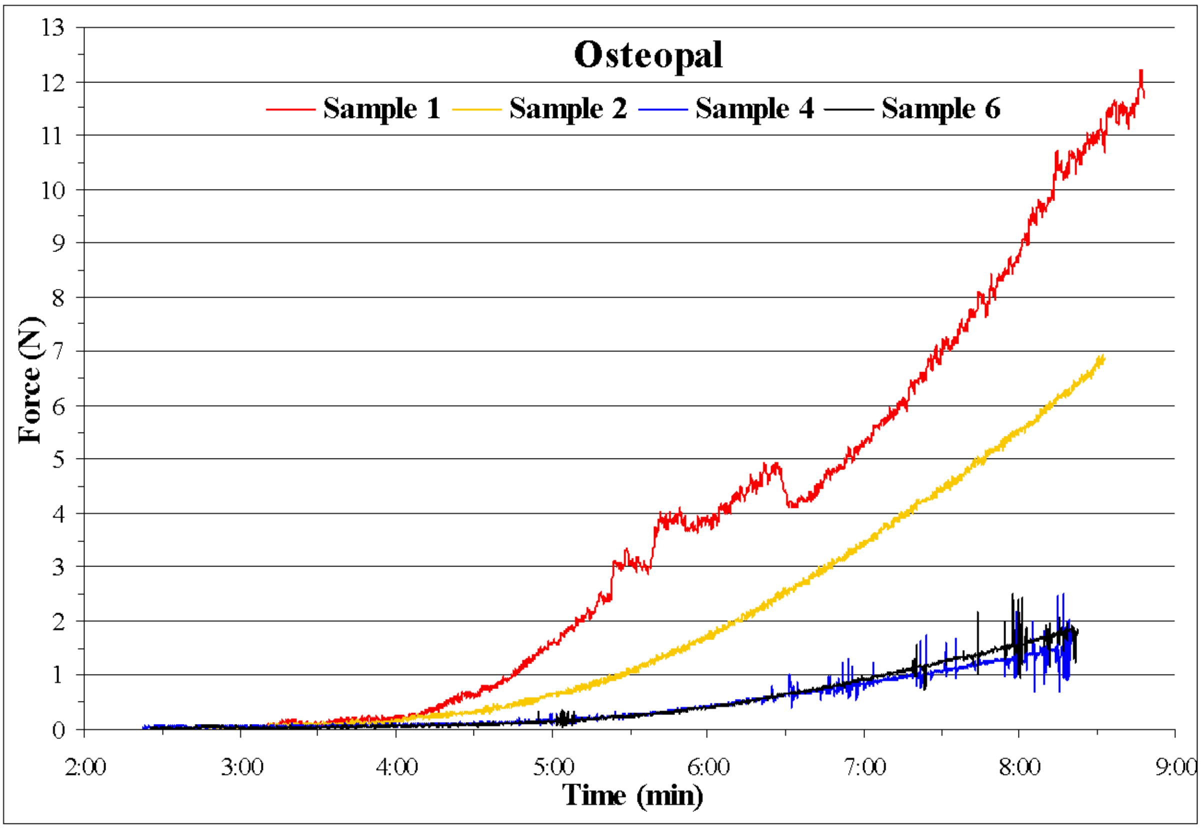
Time schedule for application of non-prechilled Refobacin BC and Refobacin Plus BC.



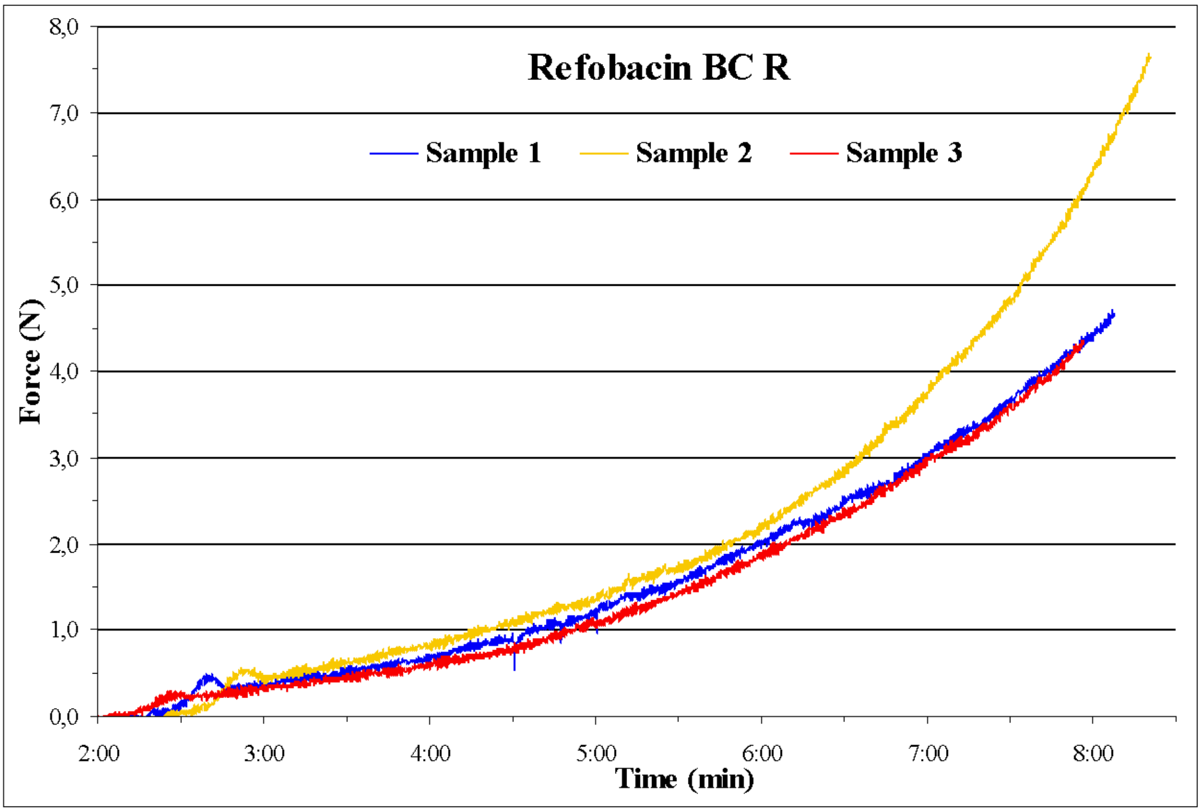
Time schedule for application of non-prechilled Simplex P.

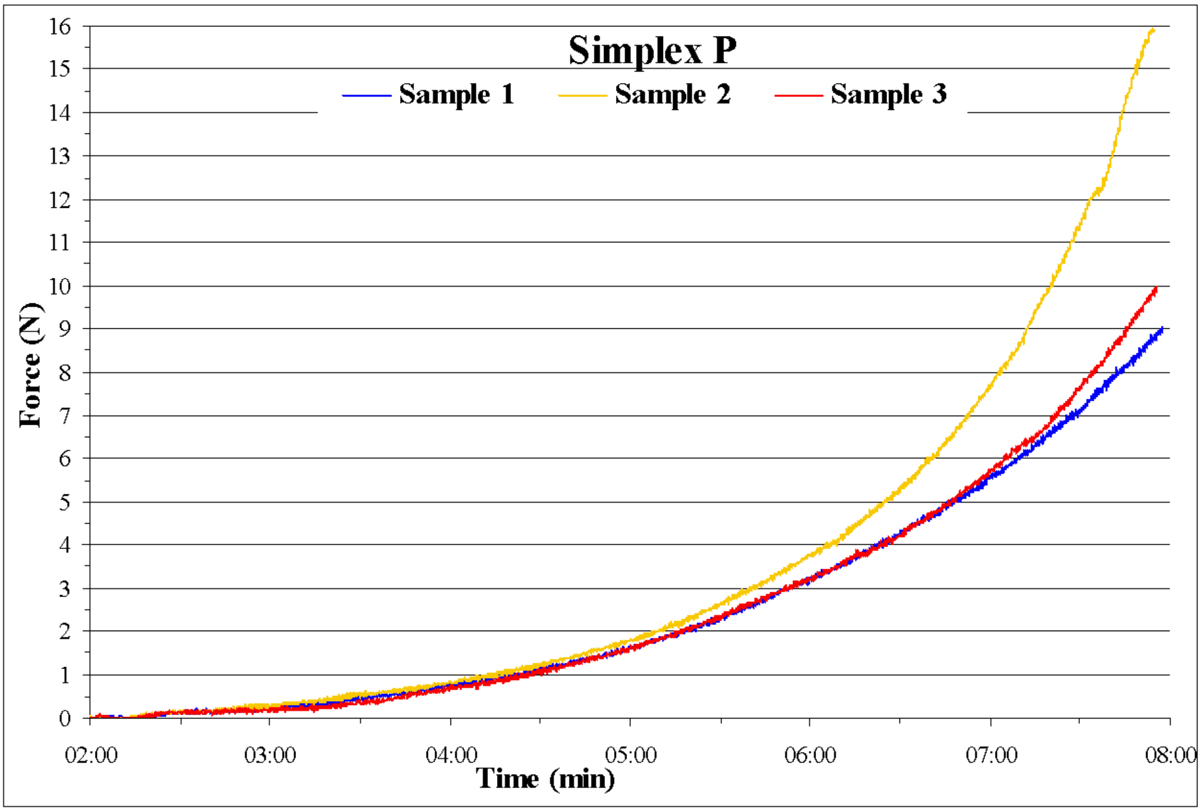
A. 5. Insertion of rod – whole measurement



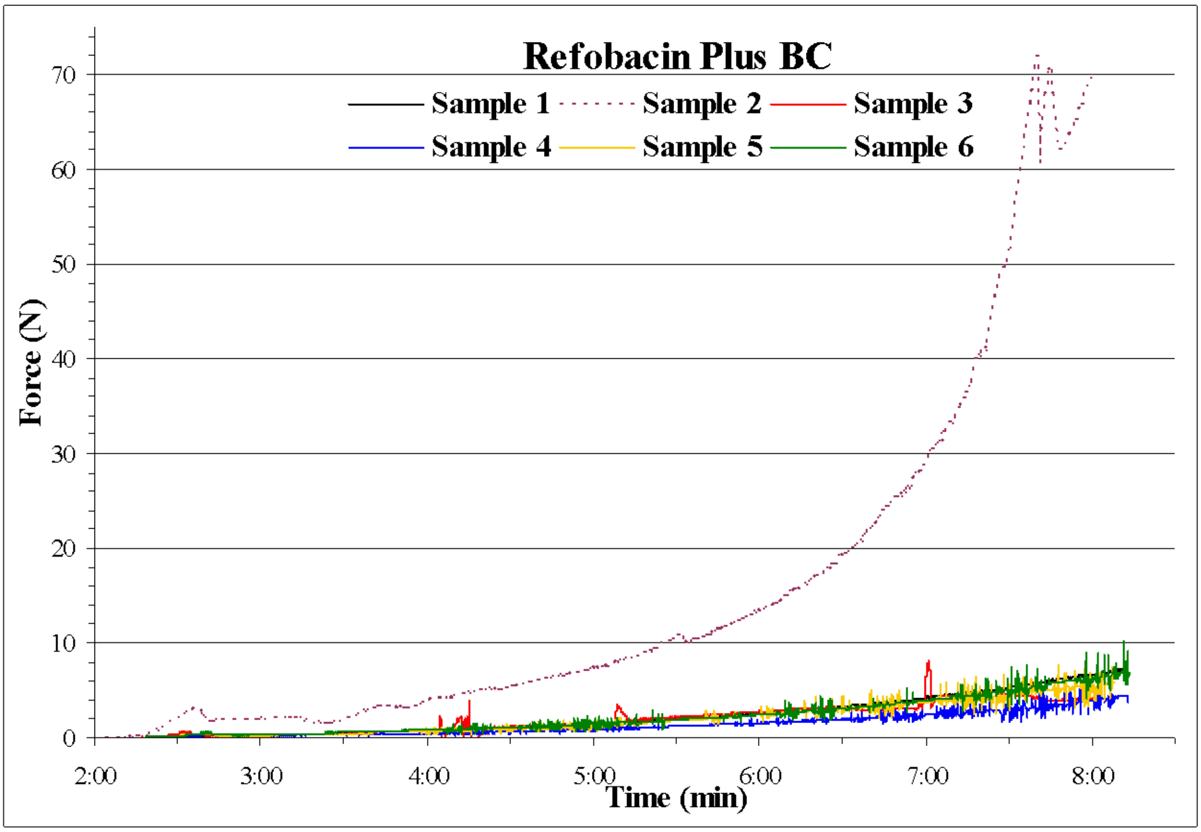


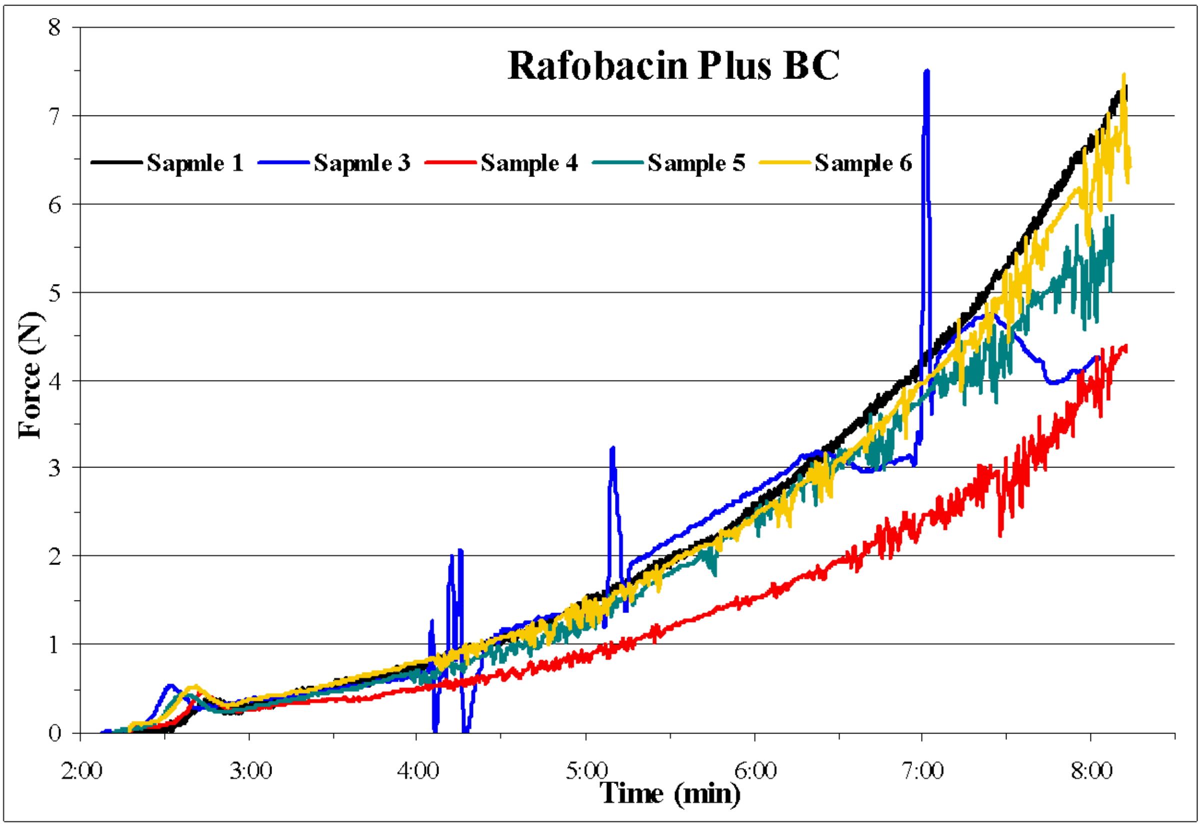
Insertion of rod – whole measurement: Osteopal cement.



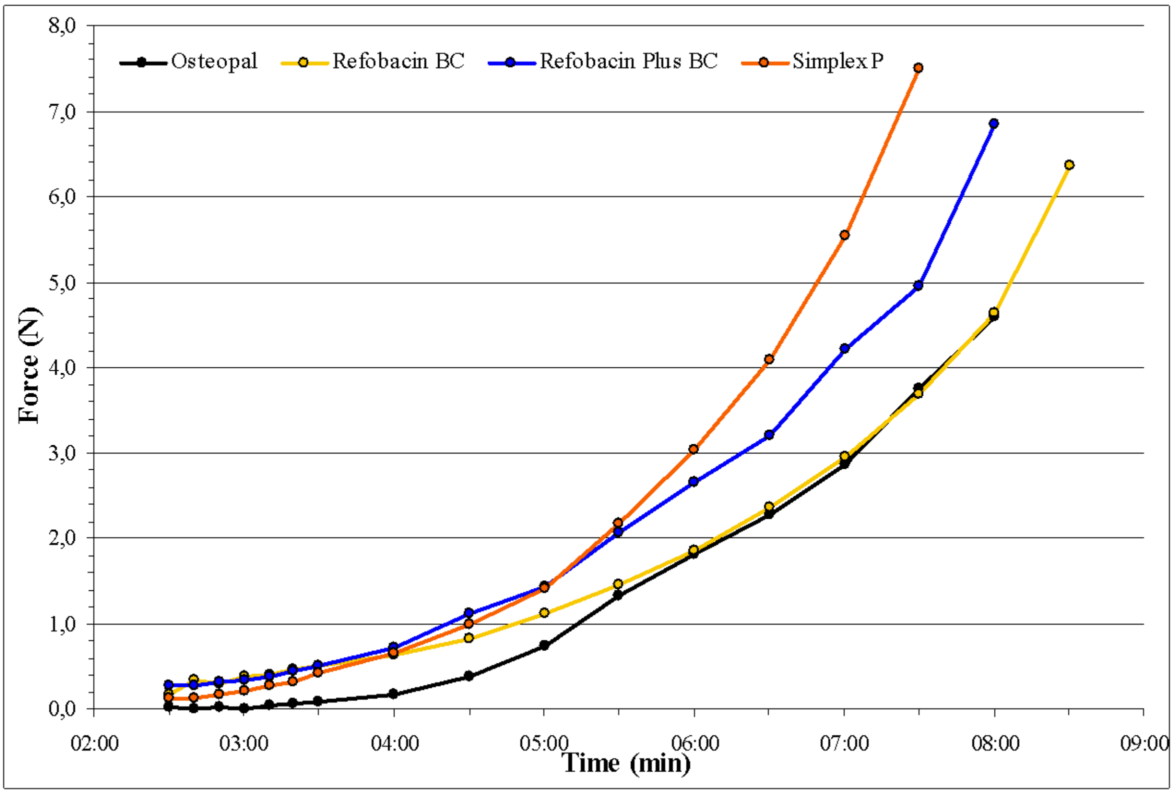


Insertion of rod – whole measurement: Refobacin BC R cement and Simplex P cement.



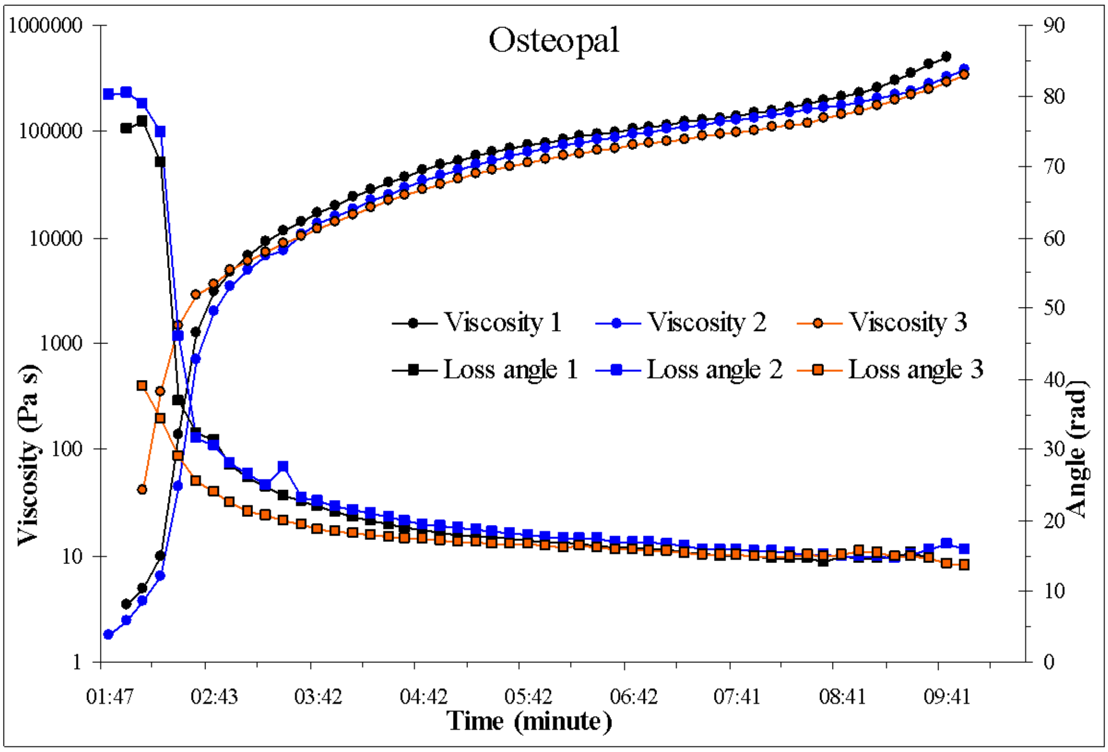


Insertion of rod – whole measurement: Refobacin Plus BC cement.



Insertion of rod – whole measurement: Mean values of 4 bone cements.

A. 6. Rheometer measurement of viscosity and phase angle vs. time.



Rheometer measurement of Osteopal bone cement – viscosity and phase angle vs. time.