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Research Article

Synthesis and Characterisation of Superparamagnetic Polylactic acid based Polymers

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Abstract

In this article, a novel superparamagnetic polymer is introduced for the use in magnetic particle imaging (MPI). This MPI-sensitive material is synthesized by blending of superparamagnetic iron-oxide nanoparticles (SPIONs) during the last step of the synthesis chain of the chosen polymer, that is in the case discussed here, polylactic acid (PLA). The synthesis products are characterized by magnetic particle spectrometry (MPS) as a utility indicator for MPI, because a strong signal in the harmonics of the signal spectrum is a necessary condition for visibility in MPI. We demonstrate experimentally that the produced compound is MPI-visible. A stable and biocompatible polymer material that gives contrast in MPI opens the door to many medical procedures, for instance, surgical devices may be coated with superparamagnetic PLA and then tracked with magnetic-based navigation instruments. Furthermore, stents and catheters may be coated with PLA, which would allow their navigation inside the vascular system, eliminating today's radiation dose in the catheter lab.

I. Introduction

Magnetic particle imaging (MPI) is an imaging technology [1, 2] that uses superparamagnetic iron-oxide nanoparticles (SPIONs) as tracer material [3, 4]. The SPIONs are excited by a sinusoidally oscillating magnetic field with sufficiently high amplitude that covers the nonlinear part of the particle's magnetization curve. In this way, the forced re-magnetization dynamics of the particles induces an inharmonic oscillating voltage in a receive-coil set. The spectrum of the measured voltage shows the excitation frequency together with harmonics reflecting the nonlinearity of the SPION magnetization.

A magnetic gradient field overlaid to the object of interest allows for spatial coding of the re-magnetization, because only in the narrow vicinity of the gradients zero-crossing, i.e. the field-free point (FFP), the SPIONs are able to re-magnetize. Beyond this area the SPIONs are in saturation and do not significantly contribute to the measured signal.

The principle of this method is quite simple. However, some questions are still open. The focus of this article will be on the tracer material. A standard synthesis method for MPI-optimized SPIONs is not yet established. Furthermore, standard instruments for surgical and catheter interventions are not available for visualization in MPI-based procedures. Therefore, here, a novel superparamagnetic polymer is introduced for the use in magnetic particle imaging (MPI). It will be described in the material and methods sections how a polymer like polylactic acid (PLA) can be manufactured by blending of SPIONs within the synthesis chain. For characterization

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of the MPI-sensitive polymer the material is analyzed by magnetic particle spectrometry (MPS), i.e. an MPI scanner without the gradient field mentioned above.

The field of polymers for different applications is wide. Stents and catheters, for instance, coated with PLA, which would allow the navigation of the instruments inside the vessels, eliminating today's radiation dose in the catheter lab.

Since the artificially synthesized polymers discussed here are intended to be applied in and around the human body, a compulsory property is biocompatibility. This means that the synthesized polymer may not have toxic effects. Fortunately, there is a variety of biocompatible polymers [5, 6].

Polylactic acid fulfills this important demand. And, it can be produced straightforwardly and easily even in chemical laboratories not specialized in polymerization synthesis.

In the application discussed here, PLA has been chosen, because it is already used as medical suture material and as intramedullary bone nails [7], and therefore, biocompatibility of PLA has already been extensively investigated [5]. PLA is also bio-degradable. This ensures that PLA molecules, may be disseminated in the human body by unavoidable mechanical interactions, will be decomposed into water, carbon dioxide, and lactic acid that can be eliminated by the human body [8, 9].

Therefore, PLA seems to be an ideal candidate for instrument coating. Even coating or filling of implants may improve medical examinations. For instance, the position of the implants may be measured without X-ray dose, and on the long term, the coating would be degraded by the human body [10, 11].

II. Material

II.I. Polylactic Acid (PLA)

Polylactic acid is a biodegradable and thermoplastic aliphatic polyester with a simple structure. It is synthesized from lactic acid, which is a chiral molecule. Both enantiomers, i.e. D- and L-lactic acid, are optically active [8]. Lactic acid can be gained by petrochemical synthesis or by bacterial fermentation, e.g. from starch. In the last decades, the latter method is becoming very popular [8], because it is environmentally friendly and resource saving.

To synthesize PLA, two different techniques are available. The products of both show the same chemical structure, but vary in their mechanical elasticity characteristics due to different chain lengths. On the one hand, PLA can be synthesized through direct polycondensation from lactic acid.

Fig. 1 shows, how the polymer is formed through a condensation reaction, where the lactid momomers join together, losing water. E.g. as melting-polymerisation at 190 °C in the presence of $Sn(Oct)_2$ and lauryl alcohol. Since lactic acid is a chiral molecule, PLA can be synthesized from pure L-, pure D-lactic acid, or from a mixture of both [12]. The alternative way is the ring-opening polymerization from lactide. Lactide is synthesized by dimerization of two lactic acid molecules.

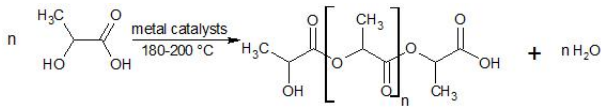

Figure 1: Synthesis of PLA via polycondensation of lactic acid.

In Fig. 2 the polymerization by opening lactide, the dimer of lactic acid, is illustrated [8].

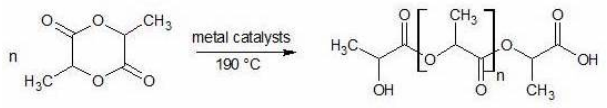

Figure 2: Synthesis of PLA via ROP (ring-opening polymerization of lactide).

Regardless of the particular synthesis route a chemically identical molecule is synthesized. However, the product of the ring-opening polymerization is also called polylactide, while the product of the direct polycondensation is always called polylactic acid [12]. In this work, PLA will be used as an abbreviation for both.

II.II. Properties of PLA

PLA is a semi-crystalline polymer with a glass transition temperature between 55 °C and 59 °C. The melting point is between 174 °C and 184 °C [8]. However, the properties of PLA differ, depending on the particular synthesis route. PLA synthesis through ring-opening polymerization from lactide has a higher molecular weight than PLA gained through direct polycondensation from lactic acid. A higher molecular weight means longer monomer chains in the polymer. However, the ring-opening polymerization is far more complicated than the polycondensation, not at least because a double-screw extruder [12] and nitrogen as inert gas are needed [8]. For the PLA synthesis from lactic acid, on the other hand, tin-II-chloride as catalyst and lactic acid have to be heated for a period of time [12].

PLA with high molecular weight is characterized by a good mechanical strength, a high elastic modulus and thermal plasticity. In addition, PLA can easily be further processed after synthesis. Pure PLA is unstable in a humid environment. It decomposes into lactic acid, carbon dioxide and water. These are all nontoxic components, which can be degraded in the human body [8]. However, the decay of PLA in a humid environment must be kept

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in mind, when PLA is to be stored, as the air humidity can be enough to begin the hydrolysis of the polymer.

Compared to other bio-degradable polymers PLA has a big advantage, low cost of the used material and the synthesis process [5]. Moreover, PLA has been used as biocompatible material for medical devices in the last decades, wherefore its properties are well known [12].

III. Methods

In this section, insights are given into the details of the chosen synthesis and into the characterization methodology of the PLA-SPIONs, potentially used as tracer material in MPI.

III.I. Synthesis of SPIONs

SPIONs were synthesized via alkaline co-precipitation [5]. The SPIONs are built of a magnetite iron oxide core with a dextran coating. After the alkaline co-precipitation the SPIONs were dried at 70 °C.

III.II. Synthesis of PLA

To synthesis PLA 40 mg to 50 mg tin-(II)-chloride ($SnCl_2$ 2 H_2O, 0.2 mmol, Carl Roth) were weighted into a 20 ml beaker and 5 ml lactic acid (0.05 mmol, Carl Roth, 80 %) were added. The reaction mixture was stirred vigorously with a magnetic stirrer for 5 min until the tin-(II)-chloride was completely dissolved. In the next step the mixture was heated until a temperature of approx. 90 °C. Then, the temperature was increased to 110 °C. The heating period was varied between 45 min and 70 min.

The highly viscous material was poured into a silicone mold for cooling and curing for 30 min at least. Thereafter, the cured PLA can be easily removed of the mold.

III.III. Synthesis of PLA with commercial iron oxide nanopowder (IONP)

For the synthesis of SPION-doped PLA, the PLA was performed as described before. However, in the last phase of the heating, IONP (Fe_3O_4, Sigma Aldrich, CAS 1317-61-9) has been blended and intensively stirred using a Rotispeed stirrer trying to obtain a spatially homogeneous particle distribution. However, even after long stirring phases of up to one hour the result shows partially inhomogeneous distributions (Fig. 3). The IONP have a high magnetization $M_s = 218\,\mathrm{Am^2/kg}$ and a saturation magnetization of $83\,\mathrm{Am^2/kg}$ and are characterized by TEM measurements in [13]. In a series of experiments the amount of IONP was increased from 7 mg up to 44 mg to study the effect of different IONP concentrations in the polymer.

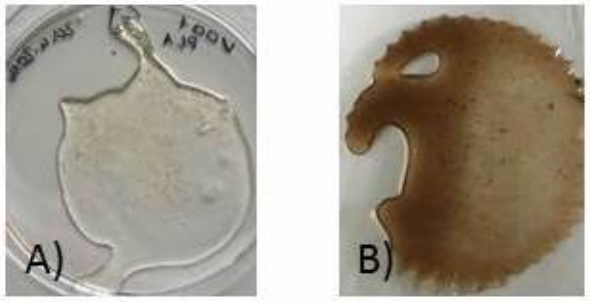

Figure 3: A) Product of the PLA synthesis and B) product of the PLA synthesis with commercial IONP.

III.IV. Synthesis of PLA with SPIONs

For the synthesis of PLA with superparamagnetic nanoparticles three different approaches were tested.

a) To the tin-(II)-chloride and the lactic acid 1 ml liquid SPIONs, i.e. water dispersed particles, were blended. The other parts of the synthesis chain stay unchanged.

b) The synthesis of PLA was carried out the way described in Sec. III.II. However, dried SPIONs were blended and the mixture was heated for an additional time interval of 10 min. In a series of experiments the amount of SPIONS was increased from 8 mg up to 110 mg to study the effect of different SPION concentrations in the polymer.

c) In the third approach, the in water dispersed SPIONs were blended after the mixture had reached 90 °C, after approximately 20 min. The heating period was increased up to 90 min. In a series of experiments the amount of SPIONS was increased from 54 mg up to 300 mg to study the effect of different SPION concentrations in the polymer.

Approach a) and b) showed very stable results in terms of homogeneous distribution of the SPIONs in the polymer. Experiments in approach c) revealed that SPIONs must not be blended too late to the PLA, because otherwise no homogeneous distributions are obtained.

In Fig. 4 the different products with different concentration of SPIONs are shown. The sample in Fig. 4 B) contains a three times higher concentration of iron than the sample in Fig. 4 A). The materials show spatially homogenous SPION distributions within the PLA matrix. However, homogeneity has been determined here just by visual inspection.

III.V. Magnetic Particle Spectroscopy

For the characterization of MPI suitability of SPION-doped PLAs a magnetic particle spectrometer (MPS) was used [3, 4]. The MPS is a development of the University of Lübeck. The following measurement parameters have

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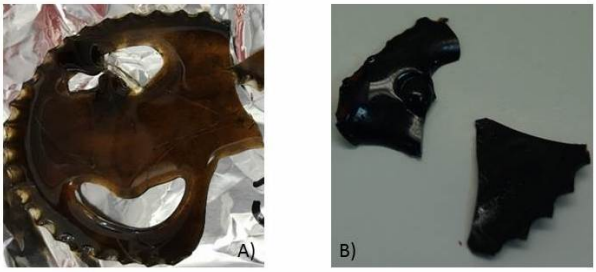

Figure 4: PLA with SPIONs, different concentrations of SPIONs. The concentrations differ by a factor of 3.

been chosen. Maximum field strength: 25 mT, measurement time: 5 s, number of repetitions: 12500, frequency 25 kHz. Each measurement was repeated 3 times. The MPS standard procedure is to put a 10 l sample into the sample holder.

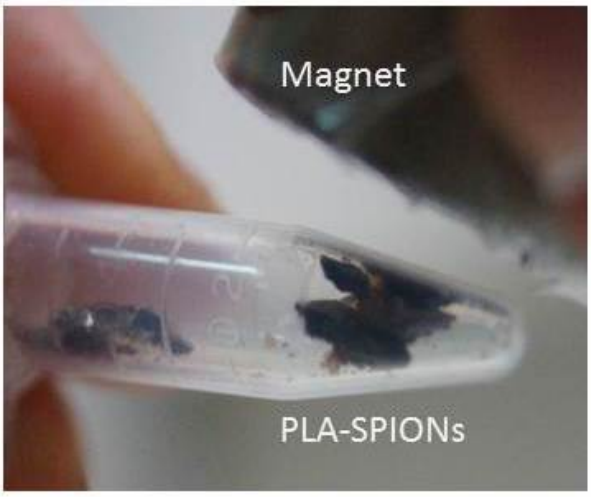

Figure 5: SPION-doped PLA flakes in the MPS sample holder manipulated with a magnet.

IV. Results

IV.I. Coating of tubes with PLA

A potential medical application of superparamagnetic PLA is the coating of catheters or other instruments and devices that need to be visualized in the catheter lab with MPI. First experiments have been carried out to transfer SPION-doped PLA onto the surface of plastic tubes. In this paper we do not refer to results with IONPs due to the inhomogeneous distribution of the particles in the PLA matrix. In Fig. 6 it is shown that a stable coating of PE-tube surfaces with PLA (A) and SPION-doped PLA (B) is feasible.

However, the integration of a large amount of SPIONs into the PLA matrix leads to brittle polymers. Further investigation of the mechanical properties of SPION-doped PLA has not been carried out here.

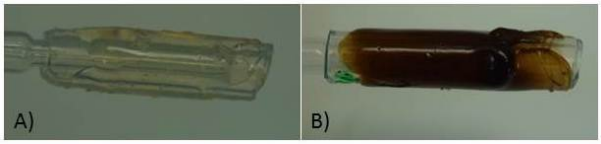

Figure 6: PLA coating for PE-tubes. A) PLA coating and B) SPION-doped PLA coating.

IV.II. MPS measurements

The SPION-doped polymers have been analyzed using MPS in comparison to pure PLA as well as pure SPIONs (dried). In Fig. 7 the results of the different MPS measurements are shown as absolute graphs and, as insert, the graphs normalized to the third harmonics for pure SPIONs and SPION-doped PLA. It can be seen that pure SPIONs and the SPION-doped PLA give significant signals. The raw PLA matrix does not show any relevant harmonics in the MPS measurement.

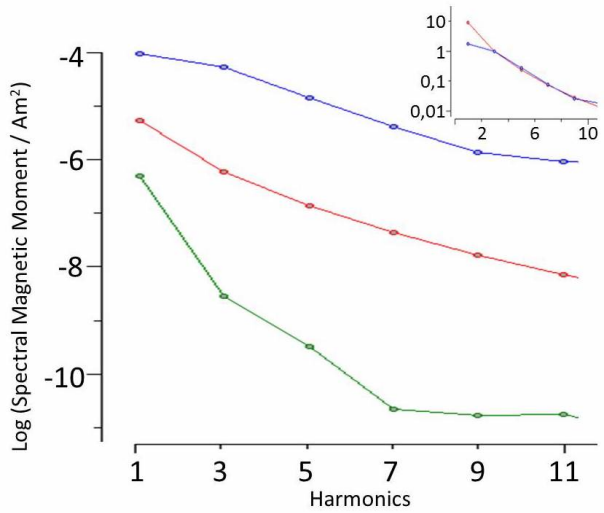

Figure 7: Comparison of MPS measurement of pure SPIONs (blue), pure PLA (green) and the SPION-doped polymer (red). The insert shows the normalized spectra of pure SPIONs and SPION-doped PLA.

The insert in Fig. 7 shows that the embedding of SPIONs into the PLA matrix does not influence the decay characteristic of the SPIONs.

Tab. 1 shows different PLA-SPION combinations, which are synthesized and characterized with MPS. The measurement conditions are given in Sect. III.V.

In general, a higher number of the SPIONs within the PLA matrix leads to a higher MPS signal and mean magnetic moment, respectively. Fig. 8 demonstrates

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Table 1: Different synthesized PLA for MPI.

Polymer	Blended SPIONs	MPS Signal Quality
PLA	-	-
PLA	Fe_3O_4 - Sigma Aldrich	++
PLA	Dried SPIONs	++
PLA	Liquid SPIONs	+

this relation. Dried SPIONs have been integrated into the PLA matrix in experiments with increasing SPION concentration. In Tab. 2 the results of SPIONs with 0.05 Fe mmol/mg are summarized. The dried SPIONs have an iron concentration of 0.05 mmol Fe per mg.

Table 2: PLAs with different dried SPION concentrations.

Polymer	Amount of dried SPIONs / mg	Iron content in mg / 5 ml lactid acid
UzL_105	105	5.25
UzL_150	150	7.5
UzL_196	196	9.8
UzL_300	300	15

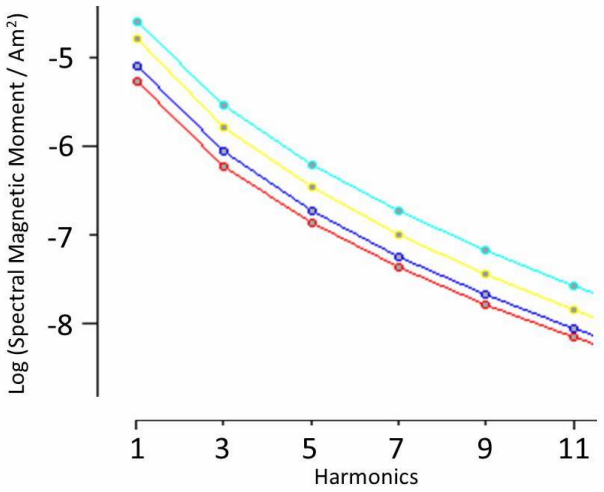

Figure 8: Comparison of MPS measurement of different SPION concentrations in PLA polymer matrices. The color code corresponds to Tab. 2 where concentrations are indicated.

IV.III. MPI measurements

In order to demonstrate the MPI visibility of the SPION-doped PLA, a system matrix has been recorded. For this procedure, a small sample with dimensions 3 mm × 3 mm × 1 mm (see Fig. 9 A) has been positioned sequentially in 13 × 9 × 9 voxels inside the field of view of the commercially available Bruker MPI system (see Fig. 9 B).

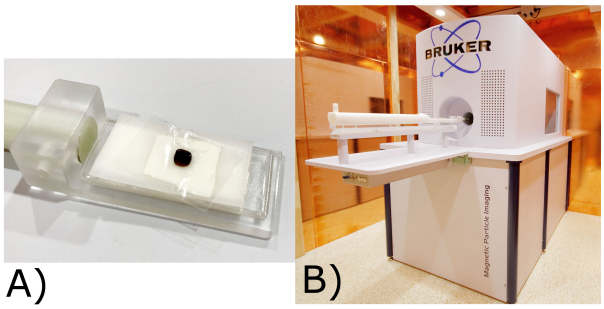

Figure 9: A) The prepared small sample for the acquisition of the MPI system matrix (approximately 3 mm × 3 mm × 1 mm); B) Frontend of the preclinical MPI system.

For each position spectral data have been recorded. For the spatial encoding a gradient strength of 0.625 T/m in x/y-direction and 1.25 T/m in z-direction was applied, and the excitation field was set to an amplitude of 12 mT in all three spatial directions. Fig. 10 depicts the spectral intensities received in x direction on the xy plane through the center of the field of view for four exemplary frequencies (see caption Fig. 10).

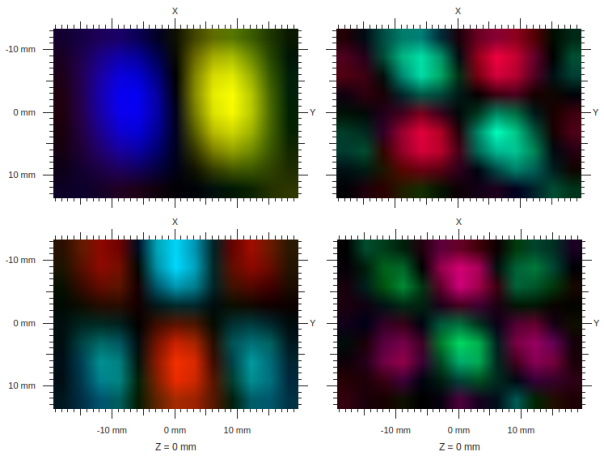

Figure 10: Four exemplary frequency components of the recorded MPI system matrix. upper left: 150.1225 kHz, upper right: 228.2475 kHz, lower left: 200.6740 kHz, lower right: 252.7574 kHz, all received on the x-channel.

The clearly resolved patterns indicate, that the signal from the SPION-doped sample is spatially distinguishable [16]. This means that images can be reconstructed and the material can thus be considered as MPI visible. With the recorded MPI system matrix, the reconstruction of objects made of, or coated with the doped PLA is possible. Fig. 11 shows an MPI image of the small sample that was prepared for the system matrix acquisition displayed in a field of view with dimensions 39 mm × 27 mm.

As Fig. 11 shows, the SPION-doped PLA is clearly visible in MPI.

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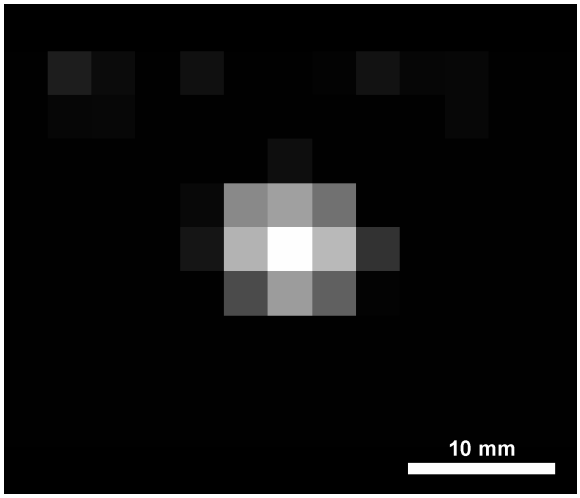

Figure 11: MPI result of a small rectangular piece of SPION-doped PLA compound. The scan was performed with the commercially available Bruker BioSpin MPI system at the University of Lübeck. Neither regularization nor interpolation or thresholding have been applied.

V. Conlusion

PLA, SPION-doped PLA and IONP-doped PLA can be straightforwardly synthesized with comparably low effort. Spectrometric measurements with MPS showed a clear re-magnetization signal, which indicates that the synthesis of SPION-doped polylactic acid was successful and promising in terms of potential MPI applications.

In a next step, MPI measurements have been carried out with this new material to demonstrate that visualization with this imaging technique is possible. The outcome is promising and further optimization will be a subject of future work.

Additionally, possible improvements of the mechanic properties of PLA will be analyzed, because as mentioned above the integration of a large amount of SPIONs into the PLA matrix leads to brittle polymers that should be investigated further, because ideally, PLA coated catheters and stents should be elastic and flexible. On the other hand, the magnetic signal increases with the amount of SPIONs, which will lead to a better signal to noise ratio. A possible solution for this trade-off might be the PLA synthesis through ring-opening polymerization instead of polycondensation, since the product then has longer monomer chains, which will lead to a higher mechanical integrity.

Before the hardening PLA is highly viscos, adhesive and even after the hardening PLA adheres to most surfaces. This makes PLA an ideal candidate for coatings. However, the coated surface should not be sensitive to heat or acid, as the synthesized PLA reaches temperatures up to and over 110 °C and a pH of 4 when transferred to a potential device surface.

Acknowledgements

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References

[1] B. Gleich and J. Weizenecker. Tomographic imaging using the nonlinear response of magnetic particles. *Nature*, 435(7046):1214–1217, 2005. doi:10.1038/nature03808.

[2] T. M. Buzug, G. Bringout, M. Erbe, K. Gräfe, M. Graeser, M. Grüttner, A. Halkola, T. F. Sattel, W. Tenner, H. Wojtczyk, J. Haegele, F. M. Vogt, J. Barkhausen, and K. Lüdtke-Buzug. Magnetic particle imaging: Introduction to imaging and hardware realization. *Z. Med. Phys.*, 22(4):323–334, 2012. doi:10.1016/j.zemedi.2012.07.004.

[3] S. Biederer. *Magnet-Partikel-Spektrometer - Entwicklung eines Spektrometers zur Analyse superparamagnetischer Eisenoxid-Nanopartikel für Magnetic Particle Imaging*. Springer, Berlin/Heidelberg, 2012.

[4] S. Biederer, T. Knopp, T. F. Sattel, K. Lüdtke-Buzug, B. Gleich, J. Weizenecker, J. Borgert, and T. M. Buzug. Magnetization response spectroscopy of superparamagnetic nanoparticles for magnetic particle imaging. *J. Phys. D: Appl. Phys.*, 42(20):205007, 2009. doi:10.1088/0022-3727/42/20/205007.

[5] L. T. Sin, A. R. Rahmat, and W. A. Rahman. *Polylactic Acid: PLA Biopolymer Technology and Applications*. Elsevier, 2012. doi:10.1016/B978-1-4377-4459-0.00009-3.

[6] V. P. Shastri. Non-Degradable Biocompatible Polymers in Medicine: Past, Present and Future. *Curr. Pharm. Biotechnol.*, 4(5):331–337, 2003. doi:10.2174/1389201033489694.

[7] Biokompatibilität synthetisch, bioresorbierbare Polymere – Knochenregenerationsmaterial in drei Konsistenzen. *ZWR Zahnärzteblatt*, 119(5):267, 2010. doi:10.1055/s-0030-1255388.

[8] A. J. R. Lasprilla, G. A. R. Martinez, B. H. Lunelli, J. E. J. Figueroa, A. L. Jardini, and R. M. Filho. Synthesis and Characterization of Poly (Lactic Acid) for Use in Biomedical Field. *Chem. Eng. Trans.*, 24:985–990, 2011. doi:10.3303/CET1124165.

[9] S. Jacobsen. Polylactide - Biologisch abbaubare Kunststoffe aus nachwachsenden Rohstoffen für neue Anwendungen. *Wechselwirkungen, Jahrbuch aus Lehre und Forschung der Universität Stuttgart*, 2000. doi:10.18419/opus-1520.

[10] C. Wischke. *Oberflächenmodifizierte proteinbeladene Mikropartikel für das Targeting dendritischer Zellen*. FU Berlin, 2006.

[11] T. Knopp and T. M. Buzug. *Magnetic Particle Imaging: An Introduction to Imaging Principles and Scanner Instrumentation*. Springer, Berlin/Heidelberg, 2012. doi:10.1007/978-3-642-04199-0.

[12] K. Masutani and Y. Kimura. PLA Synthesis. From the Monomer to the Polymer. In *Poly(lactic acid) Science and Technology: Processing, Properties, Additives and Applications*, pages 1–36. Royal Society of Chemistry, 2014. doi:10.1039/9781782624806-00001.

[13] S. Peng and S. Sun. Chemical Synthesis of Monodisperse Magnetic Nanoparticles. *Material Matters*, 4(1):14, 2009.

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