Development of Polydimethylsiloxane Microparticles for Biomedical NMR

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***Abstract*—Nuclear magnetic resonance spectroscopy is a technique for identifying molecular structures, compositions etc. and is widely used in many life science research fields. The purpose of this project is to synthesize PDMS microparticles with a magnetic susceptibility matching water, which makes them applicable for use in NMR of biological samples. The microparticles are intended to be used as a chromatographic medium for NMR while avoiding line broadening. The vast majority of the project was conducted at the Biomedical Center, Department of Clinical Sciences, at Lund University. The microparticles were synthesized using a needle-based microfluidics set-up. Susceptibility matching was attempted with a composite of PDMS and an additive of metallic powder. Calculations for additive mass fraction were conducted to guide the susceptibility matching. The calculations helped guide our choice for the composition of the microparticles. Line-width of NMR spectra were used as an indicator of magnetic susceptibility matching. The synthesised microparticles provided a nearly two-fold decrease in line-width compared to the original polymer. This result indicated that the suggested additive could indeed be used for adjustment of magnetic susceptibility of PDMS. Further steps were identified to achieve a more precise matching.**

I. Introduction

WE ARE INTRODUCING the development of a product viable for application in the research field of nuclear magnetic resonance spectroscopy. The interdisciplinary nature of this project prompt us to provide necessary background information from each of the intersecting fields. We hope it is an appropriate foundation for understanding the complex subject matter of this project.

A. Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopy is an advanced scientific technique for characterizing the molecular structure of compounds and sample compositions. A powerful magnetic field applied over a sample aligns nuclear spins of the sample constituents. The parameter describing magnetic susceptibility, which is denoted χ, indicates a material's response to the external magnetic field. The magnetic properties of all appliances and involved materials will affect the signal and the quality of the NMR spectra. Researchers within the field are continuously combating the issue of overlapping signals, essentially poor sample resolution, which deteriorates the quality of the spectra [3]. Various techniques are applied to improve the separation of signals, either physical filtering from high-molecular weight proteins or digital filtering.

We used the NMR spectra presented below, in *figure* 1, as a reference for our measurements. The sample is a solution of malic acid in heavy water. The spectra below has one distinct peak at 2500Hz corresponding to the heavy water, D_2O. Three smaller peaks that correspond to the malic acid can be seen along the spectra. In an NMR spectra the x-axis is the relative frequency of the signal and the y-axis the amplitude of the signal.

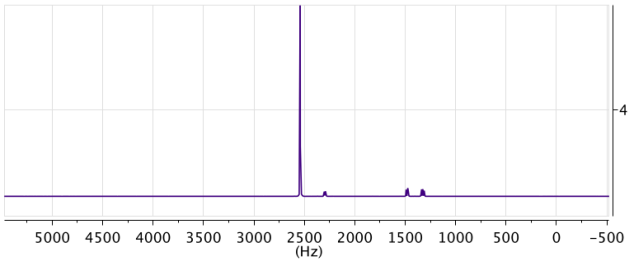

Fig. 1: NMR spectra of malic acid dissolved in heavy water with a big peak corresponding to D_2O and three small peaks corresponding to malic acid.

In NMR spectroscopy the resolution is important. The resolution is often determined by measuring the full peak width of water at half-height (see *figure* 2) [14]. The width is a good measure of the resolution of the NMR, as the width of peaks are related to the homogeneity of the external magnetic field. A wide peak indicates that the magnetic field has been greatly distorted, while a narrow peak follows from less deformation in the magnetic field.

B. Polymers

Polymers are present in many aspects of life. Both natural and synthetic polymers are used in biology, chemistry, medicine and related innovation. Polymers consist of long chains of identical and repeating chemical structures, and synthetic polymers are in layman's terms referred to as plastics [9]. Polymeric components are usually not used inside an NMR sample. Introducing such a material will inevitably distort the homogeneity of the magnetic field, and the resolution of the spectra. Modifying the magnetic susceptibility of a polymer could help combat this problem. Polymethylmethacrylate, polydimethylsiloxane

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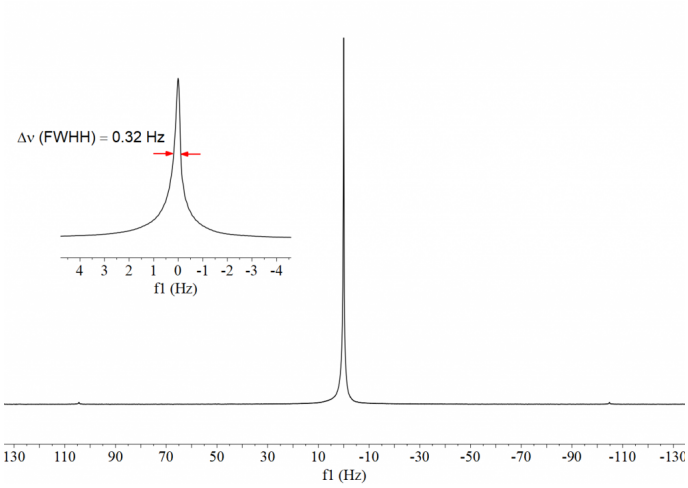

Fig. 2: An illustration of an evaluation of line-width resolution being done on a spectra. The resolution being measured to be 0.32Hz [14].

(PDMS), polyurethane, and polypropylene are all synthetic, bio-compatible, polymer materials that are used for biomedical appliances [1] [5]. Polymers vary in durability, chemical reactivity, biodegradability and other material properties. Polymer curing can be done by mixing monomer components that can form a polymer chain [4].

C. PDMS

We believe Polydimethylsiloxane (PDMS), is an excellent choice for this project. The PDMS elastomer cures in a process called crosslinking. The crosslinking of PDMS is an oxidative addition reaction between its two components, the base and the curing agent. *Figure* 3 is a schematic representation of the polymerization process of PDMS [13].

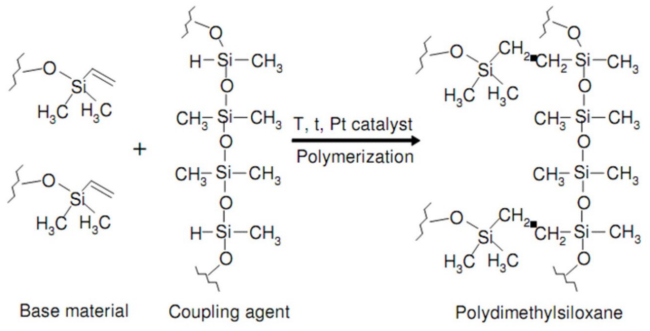

Fig. 3: Crosslinking reaction of base and curing agent [13]

D. Microparticles

Microparticles (MPs) are used in several areas of biomedical research and new potential applications are being discovered rapidly. The International Union of Pure and Applied Chemistry affirms that a microparticle should be recognized by its size, which is limited between 1×10^{-7} and 1×10^{-4} m [8]. This project targets synthetically manufactured polymeric particles only slightly outside the range, and we believe the term microparticle is still adequate. Similar particles have previously been used for drug-delivery, as bulking agents and as soft tissue fillers [4] [5]. By varying the composition of the polymer used to synthesize the MPs new application areas can be developed. Previous work in our lab has motivated us to investigate if MPs could be beneficially applied to NMR spectroscopy. There are several commercially available synthetic polymer based microparticles, varying in size, composition, quality, shape, etc. However, the intended application of our MPs put extraordinary requirements on the magnetic susceptibility, and there is not yet any product available on the market with the desired properties. The polymeric composition of the microparticles will affect their applicability. Beyond the primarily intended application of the microparticles, synthetic polymeric compounds are prosperous materials for state-of-the-art biomedical research. For instance, the microparticles could also be used as soft tissue prosthetic matter or drug-delivery carriers.

E. Problem

In very recent years, a new technique called “chromatographic NMR” has evolved for separation of signals in NMR spectra in organic solvents, based on using a solid-phase chromatographic medium (silica gel) directly in the NMR tube. To avoid the line broadening of the NMR signals caused by the differences in magnetic susceptibility of the chromatographic medium and the original sample solvent, the solvent is modified by adding co-solvents with complimentary magnetic properties, providing a magnetic analogue to the solid phase and the liquid sample. Such an approach, however, is not yet possible for biological samples (e.g. biofluids). Any modification of the aqueous solvent will interfere with the metabolites and their molecular interactions [6]. Since currently available chromatographic media are not suitable for biological samples, we aim to synthesize biocompatible polymeric microparticles with a matched magnetic susceptibility to that of various biological samples (blood serum, cerebrospinal fluid and other biofluids, cell extracts, cell suspensions, etc). The approach we will try is production of microparticles from synthetic polymers using magnetically complementary additives. Since the overall magnetic susceptibility of such a mixture is a weighted sum of its components, we should be able to compose a material that will make the microparticles “magnetically invisible”, when mixed with the biological sample. We hypothesize that we can produce susceptibility matched PDMS microparticles for NMR. We believe the microparticles will allow for chromatographic peak separation of NMR signals, directly in the NMR tube and without deterioration of the spectrum quality.

F. ”Agenda”

This paper presents research work focused on the synthesis, analysis and evaluation of ”magnetically invisible” PDMS microparticles for NMR application. In the method and

materials section we first describe materials, then the experimental set-up, theory and calculations, and finally the laboratory experimentation. In the results section we describe properties and provide microscopy pictures of the MPs. An NMR analysis is presented as the basis for evaluation of MPs. In the discussion section we review our choice of material and list possible sources of error. We describe the innovative value of the MPs and consider the ethics and sustainability of the project.

II. Method and materials

A. Materials

All microparticle synthesis in this project uses Sylgard 184 Polydimethylsiloxane (Dow Corning Corporation, MI, US). The high viscosities of PDMS precursors, being one of the many benefits of the material, also raises some difficulties for microparticle production, as droplets can sometimes adhere to one another. We use the surfactant polyvinyl alcohol (PVA) to combat adhesive droplets. Literature research supports the choice to manufacture the microparticles in PDMS. It is chemically inert and malleable, resistant to high temperatures as well as light degradation [5]. Furthermore, it is hydrophobic and non-toxic [2]. PDMS microparticles can be fabricated using suspension polymerization technique. The major benefits of this technique is the straightforward methodology and the large quantity the of product. We will use a metal powder additive to adjust the magnetic susceptibility of the MPs. The additive was ordered from US Research Nanomaterials, Inc. [12]. It is a dispersion of 99.9% pure metal powder. The metal makes up 20wt% in a silicone oil dispersion. However, we have intentionally chosen not to disclose the additive material due to the innovative value of the project. Supplied by Sigma-Aldrich, we used Malic acid, $C_4H_6O_5$, heavy water, D_2O, and acetone, $(CH_3)_2CO$, for the washing and analyzing procedures.

B. Needle-based microfluidics set-up

The rig was put together using a metal scaffold. It held in place a Harvard Apparatus syringe pump that provides a continuous flow of the liquid PDMS through a needle. A beaker filled with a solution of water and surface-active agent PVA, was placed on a heated magnetic stirring machine. It was put in place to collect the liquid PDMS as it exits from the needle. The solution ensures that the droplets maintain a spheroid shape and that they do not lump together. By simultaneously stirring and heating the solution, the drops are agitated at the tip of the needle, and are pulled off, into the solution to be cured. To reliably produce microparticles of the desired size we made several production trails.

C. Set-up and microparticle production trials

We decided upon the needle-based suspension polymerization based on previous work showing promising results of monodisperse microparticle production [2] [7]. We have replicated a previously successful laboratory set-up and evaluated the accuracy and efficiency of the set-up. By a sequence of tests we could determine the optimal: (1) flow rate of the PDMS, (2) rotations per minute of the magnetic stirring, (3) and needle gauge, in order to require feasible microparticles. The final set-up of the rig is showed in *figure* 4. The parameters explored are later illustrated in *figure 5*.

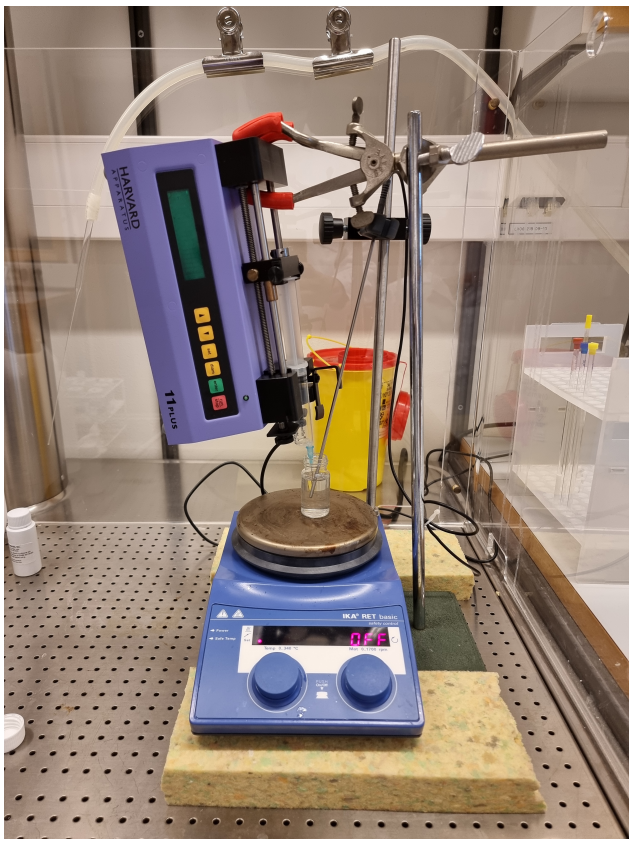

Fig. 4: The rig used when producing the microparticles.

D. Additive to Microparticles

Previous work from Walper et al. mapping magnetic susceptibility of various materials, including some polymers, allow a theoretically grounded hypothesis for the proposed composite [1]. There are several potential additives that can be used in such a composite to correct the magnetic susceptibility of the microparticles. However, the volume fraction undoubtedly limits the list of viable additives, this limitation is explored further on in the calculations. A short list of relevant materials are presented below in table I.

According to Lee et al. [6] the isotropic susceptibility of a composite material can be controlled by embedding a small fraction volume of randomly oriented small particles. Making use of the equation used in the article, the susceptibility of the resulting material can be calculated using:

$$\chi_{Composite} = \chi_{Additive} f + \chi_{PDMS}(1-f) \tag{1}$$

In our search for an additive we focused on those that required only a small volume fraction. We limit the volume fraction to 0.1, equaling 10% of the total volume. As the fraction of additive increases, material properties of the additive will compete against the desired properties of the

TABLE I: The magnetic susceptibility of some relevant materials exported from literature [10] [11].

Substance	Magnetic susceptability, χ (SI, 10^{-6})
Graphite	-213
Bismuth	-166
Gold	-34.7
Silver	-24.1
Diamond	-22
H2O	-9.035
D2O	-8.97
PDMS	-8.10

PDMS. Limiting the volume fraction should prevent unwanted changes in the material properties. The volume fraction can be derived from equation 1 as follows:

$$f = \frac{\chi_{Composite} - \chi_{PDMS}}{\chi_{Additive} - \chi_{PDMS}} \tag{2}$$

Using equation 1 again, the minimal value of susceptibility of the additive can be derived using:

$$\chi_{min} = \frac{\chi_{Composite} - \chi_{PDMS} + f_{max}\chi_{PDMS}}{f_{max}} \tag{3}$$

The additive chosen was a metal powder suspended in silicon oil with a 20wt% of the additive. Some concerns about the additive is considered in the discussion section of this report. Since weighting of the materials is the preferred method of quantifying additives, due to the high viscosity of the dispersion, the volume fraction was converted into a mass fraction. The assumption was made that the density and magnetic susceptibility of silicone oil was close enough to that of PDMS as to not affect the calculated weight of additive to be added.

The mass fraction m_f is defined as follows:

$$\mathrm{m}_f = \frac{\mathrm{m}_a}{\mathrm{m}_a + \mathrm{m}_{PDMS}} \tag{4}$$

With m_a being the mass of the additive and m_{PDMS} being the combined mass of the PDMS and added silicone oil.

The volume fraction V_f is defined as follows:

$$\mathrm{V}_f = \frac{\mathrm{V}_a}{\mathrm{V}_a + \mathrm{V}_{PDMS}} \tag{5}$$

With V_a being the volume of the added additive, and m_{PDMS} the combined volume of the PDMS and added silicone oil. Using the definition of density $\rho = \frac{m}{V}$ and equations 4 and 5, we derive the equation for the mass fraction as a function of the volume fraction and the densities of PDMS and the additive.

$$1 + \frac{\rho_{PDMS}}{\rho_a}\left(\frac{1}{V_f} - 1\right) = \frac{1}{m_f} \tag{6}$$

Having converted the volume fraction into a mass fraction, we made use of equation (4) to derive the mass of the additive dispersion. Taking into consideration the silicon oil, in the dispersion, we substitute m_{PDMS} with $m_{syl} + 4m_a$, with m_{syl} being the mass of PDMS used and the $4m_a$ coming from the mass fraction of the silicone oil. The following equation (7) was used to calculate the mass of the additive:

$$\mathrm{m}_a = \frac{\mathrm{m}_{syl}}{\frac{1}{m_f} - 5} \tag{7}$$

Multiplying the result from 7 by 5 gave us the total amount of the dispersion to be added. The resulting susceptibility of the microparticles was dependent on the amount of the dispersion. In the process of synthesizing the microparticles with additives, the dispersion is added to the elastomer base before mixing with the curing agent. The additive was stirred, manually, before weighing, to get an even dispersion of the powder in the silicone oil. This is done to ensure the correct amount of additive is being extracted when weighing the dispersion.

E. Analyzing, washing and evaluating microparticles

Evaluation of the microparticles was done with NMR spectroscopy. We first had to wash the particles to get rid of any surfactant on the surface that might affect the spectra. We heated up some distilled water to 90°C in a beaker, the temperature at which PVA is best dissolved. The microparticles were then added to this beaker and mixed using a magnetic stirrer. After leaving the water to stand, the microparticles sink to the bottom and any excess water can be poured off. This procedure is repeated. Finally we wash the MPs with room temperature water an additional three times. The microparticles are then transferred to a test tube, extracting as little water as possible. The microparticles are then washed using heavy water. Lastly they are mixed with a solution of malic acid and heavy water, like the one used as a reference for the NMR analysis, *figure* 1. The microparticles are transferred to an NMR tube together with the solution and put in the spectrometer. The resulting spectra is shown in *figure* 8. Ocular observation of the particles and their content was done using an optical microscope, pictures shown in *figure* 7

An additional evaluation of the magnetic susceptibility matching was done by adding small quantities of acetone to the MP sample before analyzing in the NMR. This was done to shift the susceptibility of the solution relative to the MPs, and acetone has a magnetic susceptibility lower than both PDMS and water. The amount of acetone can be used as an indicator if we need to add more or remove some of the metal additive.

III. Results

A. Set-up trials

By individually adjusting (1) the flow rate of the PDMS, (2) rotations per minute of the magnetic stirring, (3) and the needle gauge, we could determine a general pattern of how microparticle size related to these parameters. At this point we were only considering the variation in size and the number of particles produced. A simplified schematic drawing of the general parameter rules is presented in *figure* 5. Our aim was to obtain MPs in the size range of 200-500 µm. The desired size of the particles were obtained smoothly with (1) a flow

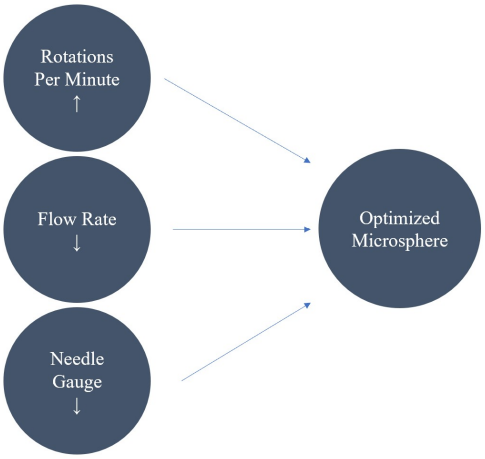

Fig. 5: Illustration of the general parameter rules for optimal microparticle production.

rate of 0.075ml/min,(2) stirring rpm of 1200, and (3) a 23G needle.

Having established a reliable rig we could move on to correcting the magnetic properties of the product. Using equation 2, we plotted a graph of the required volume fraction as a function of the magnetic susceptibility of the additive. This helped guide us when estimating the range of susceptibilities that are viable for the additive. With the lower limit of the susceptibility given by equation 3 as $\chi_{min} = -17.45$. To match magnetic susceptibility of the particles to that of water, we use equation 2. A material with low volume magnetic susceptibility would require a smaller volume fraction, and vice versa. We plot the relation between additive volume fraction as a function of the volume magnetic susceptibility of the additive in *figure* 6. The materials listed in table I correspond to the vertical lines that intersect with the graph. The points of intersection give the volume fraction needed to match the composite to water. The red horizontal line shows the upper limit of the volume fraction, 0.1.

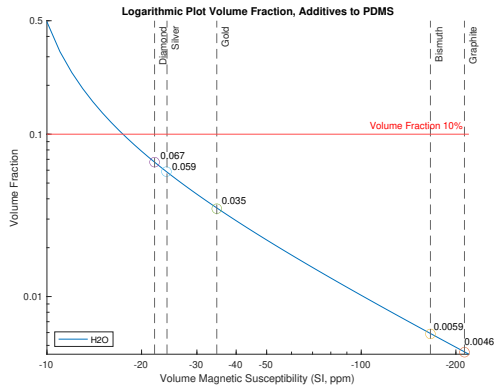

Fig. 6: The volume fraction corresponding to different magnetic susceptibilities with logarithmic scales on the axes.

B. *Final results*

We continued using the settings for synthesis determined as optimal in the trials. Before using the additive, microparticles where obtained varying in size, within the desired range. Observing the particles under an optical microscope, and using the built-in size scale of the microscope, we noticed that the particles with additive are generally smaller than those without. We estimate that particles with additive do not exceed the size of 500 µm, while some of the particles without additive surpass this limit. Additionally, when observing them under the microscope, at 20X magnification, we determined that the particles have a relatively even distribution of the additive as seen in right panel of *figure* 7.

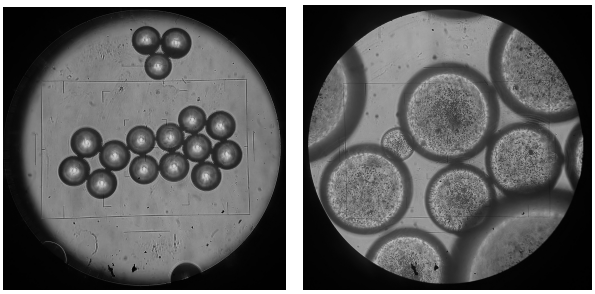

Fig. 7: Left: Commercially available microparticles, d=100 µm. Right: Our produced microparticles with metal additive, at the same magnification.

NMR spectroscopy analysis for evaluation of the susceptibility can be seen below in *figure* 8.

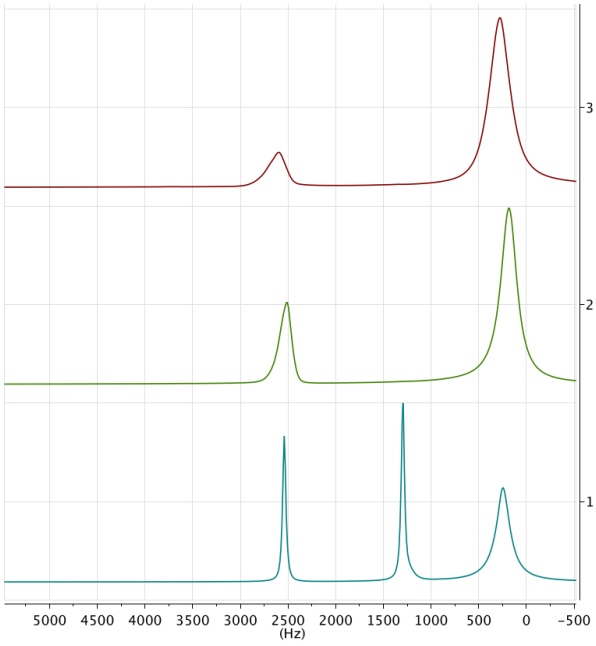

Fig. 8: NMR spectra taken for evaluation of microparticles. 1: Spectra of microparticles with additive with an addition of 180 µL acetone. 2: Spectra of microparticles with additive five days after synthesis. 3: Spectra of microparticles without additive.

Centered in each spectra in *figure* 8, at 2500Hz, is the peak corresponding to water in the sample. The rightmost peak, at 250Hz, corresponds to the PDMS of the microparticles. Spectrum 1 has an additional peak at 1300Hz corresponding to acetone in the sample. The particles without additive, in spectrum 3, has a line-width resolution of 219 Hz. The MPs with additive has a line-width resolution of 162Hz. The line-width measured being that of the water-peak. This result shows that our additive has partially matched the magnetic susceptibility of the MPs. Interestingly, analysis of the same sample carried out five days later, shown in spectra 2, indicates a line-width resolution of 145Hz, which is significantly lower.

The results of the evaluation of the degree of matching done using additions of acetone was compiled in a plot, see *figure* 9. Both the MPs with and without additive behaved similarly. It was observed that there is a decrease in the resolution with the first couple of additions of acetone. Adding 220 µL and more gives an increase in resolution for the MPs with additive. For MPs without additive this point was higher, at around 250 µL. There is clear shift of the points between the two different groups of points. Assuming a linear decrease and increase in resolution, the practically lowest resolution that can be achieved is given at the point where the two graphs of the same color intersect.

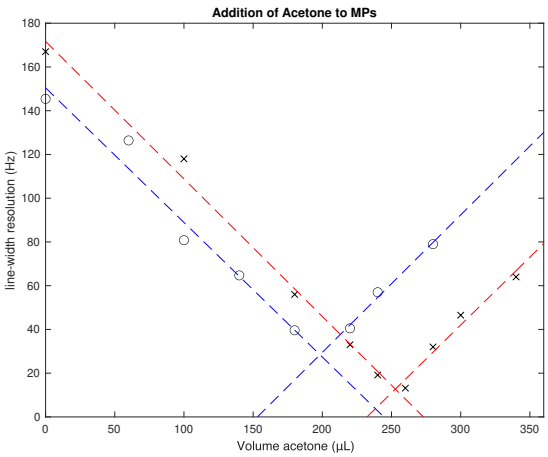

Fig. 9: Plot of the different additions of acetone to both the samples of MPs analyzed. The o-points and blue lines correspond to the addition of acetone to MPs with additive. The x-points and red lines correspond to the addition of acetone to MPs without additive.

IV. Discussion

A. Production

The calculations in equation 2 and *figure* 6 were made to show that choosing an additive with a lower volume magnetic susceptibility will require a lower volume fraction. A benefit of using a low volume fraction, especially using a powder, is the more even distribution of the additive inside the particle. It also contributes to more homogeneous additive distribution between MPs. We do see some distribution irregularities as seen in the right panel of *figure* 7. When producing the MPs we chose to disregard differences in density and magnetic susceptibility between silicone oil and PDMS, arguing that they should be virtually identical. We also assumed that the weight ratio of the additive dispersion was exactly 20 wt% at the time of adding it to the PDMS base. Manually mixing the dispersion might not have been adequate for an even distribution of the powder in the silicone oil, as the provider recommends high-shear mixing for an oil phase dispersion [12]. This method will be used in further work on the project.

B. Final Product and Evaluation

We noted that the final version of MPs were smaller than those without additive. We believe it is due to a change in the viscosity and density of the PDMS mixture when combined with the additive. The synthesized particles still fell into the desired size range. Looking at the resulting spectra it is clear that there is still line broadening due to a mismatch in magnetic susceptibility between water and the microparticles. The decrease in line-width is proof that we have indeed improved the magnetic susceptibility matching. The improvement in resolution between the spectra of the same sample after five days could be explained by diffusion of the additive in the MPs or by continued curing of the PDMS, resulting in a more even sample.

A possible source of error for correct matching is the amount of powder additive in the microparticles. Calculations of the volume fraction of the additive were made with the assumption that the powder was evenly distributed as randomly oriented particles in the dispersion. The additive is seen to be evenly distributed in the microparticles, but there was a small number of microparticles in which the additive was lumped together. These could possibly affect the NMR spectra and filtering those odd microparticles out could resolve this query.

The trials with addition of acetone clearly show that the amount of additive in the MPs is significantly less than what is needed for perfect susceptibility matching. The addition of acetone corresponds to an increase of the additive in the MPs. It can be seen according to the relation in *figure* 9, that the resolution of the MPs with additive can be brought down to about 30Hz and any further addition would lead to an increase in line-width. Interestingly for the line-width of the MPs without additive it seems as it can be brought down even lower. Theoretically, both the linear graphs could be crossing at a lower line-width, 1Hz, as this is the absolute lowest limit of resolution. We interpret this as an indication of some unknown factor limiting the achievable resolution of the susceptibility matching. Importantly, we argue that the line-width discrepancy is too big to be coming from an error in our calculations or when weighing materials. Instead it would indicate a systematic error. A possible explanation is that the magnetic susceptibility of the additive does not match the expected value, which was gathered from a reference table [10].

We wonder if the additive undergoes a chemical change when mixed with the PDMS base and curing agent, or during the curing of the MPs. As the additive is a pure metallic

compound, it could have been oxidized. Looking in the table we can see that magnetic susceptibilities of oxidized metals is significantly different to its pure counterpart and in our case higher [10]. While the metal used is not expected to oxidize at a significant rate at room temperature, the oxidization rate could have been affected in the process of curing the MPs as they are heated up to 80°C. Another possibility is the curing agent speeding up the oxidization of the metal, as the crosslinking of the PDMS is an oxidative reaction, see *figure* 3.

Finally, surface interactions between the additive and the magnetic field of the spectrometer could affect the spectra. A powder has a large surface area compared to a bulk piece of metal. The value of the magnetic susceptibility of the compound that was found in literature, corresponds to chunks of the material being studied and may not be applicable to a powder of the same compound [10].

C. Future work

Examining the points brought up in the discussion section should be the top priority for the future work, before manufacturing new MPs. Adjusting the magnetic susceptibility of polymers can be accomplished with techniques other than the one we have employed. One such method would be doping the MPs by letting them sit in an alkane hydrocarbon solution. Comparing the susceptibility matching of MPs from the two methods would be interesting, and perhaps testing a combination of the two.

D. Innovative Value

Matching of the chromatographic medium to the sample, will enable use of microparticles in NMR analyzes of biological samples and other aqueous solutions. Using our microparticles in the context of NMR will expand the useability of the technique for medical science and biomedical research. We have not disclosed all details of the research in order to preserve the prospective value of the product. Therefore, the innovative value of this project still lies predominately in its promising potential. The results from this project has advanced the innovation toward a developed product.

E. Ethics and sustainability

In recent years plastic materials have been under scrutiny in relation to debris ending up in the oceans. Polymer microparticles, and metallic powders, should be handled with proper laboratory etiquette, ensuring waste material does not end up outside of the recycling domain. United Nation sustainability goals describe appropriate practices regarding chemical waste in Chapter 19 of Agenda 21. They explain that scientific innovation, like our MPs, is essential to meet the social and economic goals of the world community. Chemicals can be used with a high degree of safety when practicing environmentally sound management of ”toxic chemicals” [15]. We have employed best practice during the full course of this project, following the global and on-site sustainability guidelines. The potential future product of this project is intended for laboratory and clinical use. Commercial availability of our MPs raises some ethical concerns since the product will be used in combination with biological fluids and extracts. The MPs would have to be approved by CE/ISO standards for medical products. However, we feel it is premature to examine these ethical concerns in depth.

V. Conclusion

We have been able to synthesize and adjust the magnetic susceptibility of PDMS microparticles by using a metal additive. We present NMR spectras to show how the MPs affect line-broadening in an external magnetic field. We hypothesized that we could produce susceptibility matched MPs using additives. With our obtained data we can confirm that the additive has improved the susceptibility matching of the microparticles and further work is needed to achieve perfect matching.

VI. Afterword

We want to acknowledge project supervisor Vladimir Densiov, who has guided our theoretical work and provided space for our laboratory experiments. Thank you for all the encouragement and your generous mentorship. Author contributions: JD has written the abstract, conclusion, and introduction sections, as well as the: future work, innovative value, ethics and sustainability sections. MAS has written the majority of the results section and the materials and method section. MAS authored the MATLAB scripts for mathematical equations and plots used in the paper. Authoring the discussion section and conducting the practical laboratory work has been carried out by both authors together. NMR spectra have been recorded by the project supervisor.

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