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Subject | Minutes of the WG2 SAR sub-group Meeting of COST Action TD1402 - Multifunctional Nanoparticles for Magnetic Hyperthermia and Indirect Radiation Therapy (RADIOMAG)

Universtity of Zaragoza, Zaragoza (Spain)
9th -10th of February 2017

1. Welcome to participants / Adoption of the agenda

The meeting started at 9:00 AM. Present are Margarida Cruz, Eneko Garaio, Eva Natividad, Daniel Ortega, Olivier Sandre, and Simo Spassov. Excused: Sofia Costa Lima, James Wells, Frank Wiekhorst.

The agenda was adopted, one additional point was added to the Agenda concerning the RADIOMAG web-page todo's.

2. Refresher about the 1st SAR ring test

See presentation Daniel Ortega (Annex 3). Further general points discussed:

- Eva pointed out the concept of thermal relaxation times as possible explanation to the higher data dispersion of the most diluted sample
  - The internal relaxation time accounting for heat losses from NPs to the carrier fluid inside the vial should be much smaller than the relaxation time accounting for the heat flow from vial to the environment in order to have good SAR values.
- While discussing the suitability of SAR and ILP as relevant parameters for characterising heat losses, Daniel mentioned that the CEM_{43} parameter used by clinicians as common metric for the thermal dose, is being questioned now. It was proposed to contact G.C. van Rhoon from The Netherlands who is a Hyperthermia specialist.
- The issue of the vial material was discussed, better not use glass vials as they contain iron. Instead quartz vials would be much better.

3. Presentation of the 2nd SAR ring test: methodology and data collection

The 2nd round basically consisted in repeating the 1st one with some improvements on the protocol, namely:

- Samples 1 and 2 have been re-measured because:
  - (i) the measurement protocol has been modified, and repeating the first ones will ensure that all the measures will be comparable from now on;
  - (ii) some measurers did not follow the protocol - to a variable extent - thus rendering those measurements not comparable with the rest, and
  - (iii) some others were just incomplete.
- Measurement of a sample of non-conductive water.
- Again all SARs were determined with the corrected slope method

- 3 weeks to complete the measurements.
- Time resolution: one temperature measure per second.

4. Analysis of the outcomes from the 2nd SAR ring test

- Unfortunately only 13 out of 22 laboratories participated
- Zero-conductivity water $T(t)$: 8 out of 13 measures see significant temperature increase resulting from heat produced by the coil during AMF application. Very few others showed that the temperature was not fully equilibrated before conducting the experiments; the temperature was slowly decreasing during the water measuremen.
- The preliminary analysis shows that measurements are somewhat less scattered compared to the 1st round (cf. Annex 3).
- Although the 2nd round is not conclusive due to the low number of submitted results, the median absolute deviations for samples 1 and 2 were overlapping between 1st and 2nd rounds in particular for the more concentrated sample 1, yet the spread increased for dilute sample 2

5. Field calibration procedure: current status and future work

This point was postponed and will be treated at the Szeged meeting 6th to 7th of March 2017.

6. Results on nanoparticle suspension stability

Prior the meeting, Olivier Sandre carried out DLS measurements on ring test samples № 1-7 in order to assess the stability of the nanoparticle suspensions, because the samples were made already in autumn 2015. It turned out that sample:

- № 1 - not stable (170 nm, PDI=0.21)
- № 2 - not stable (87 nm, PDI=0.24)
- № 3 - stable (66 nm, PDI=023)
- № 4 - stable (47 nm, PDI=0.21)
- № 5 - not stable (468 nm, PDI=0.21)
- № 6 - stable (55 nm, PDI=0.24)
- № 7 - not stable (129 nm, PDI=0.22)

Along with this, Olivier gave an overview about the determination of NP hydrodynamic grain size and polydispersity index (PDI) by DLS.

7. Discussion of the paper proposition from Uwe Steinhoff

This point was not treated, because the group from the PTB hat to decline their participation at short notice due to force majeure. The frustrated physical meeting may be replaced by an email discussion until a suitable time and place is found or discussed in Szeged.

8. Planning of the 3rd ring test

Despite the low number of results submitted for the 2nd ring test, it was agreed that a 3rd round should be carried out in any case. The SAR protocol and the used AMFs were revised. The following was decided:

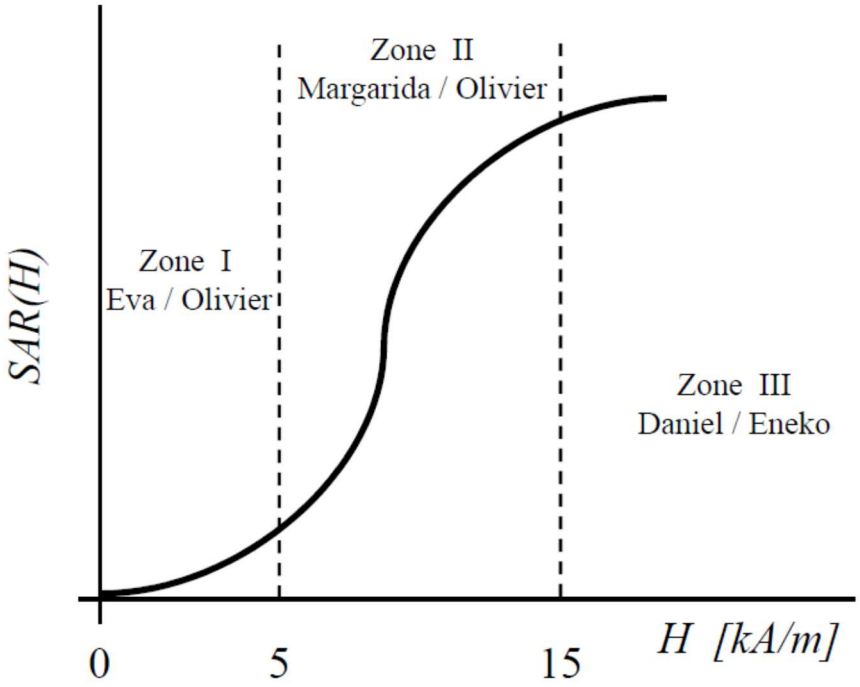
- The zero-conductivity water sample should be measured in any case, for checking the “background” heat uptake of MNP suspensions for different SAR setups.
- The corrected slope method may not be precise at too high temperatures, as $SAR = SAR(T)$ due to the temperature dependence of dynamic magnetic susceptibility,
- therefore the Excel file containing the measurement protocol should contain a warning to abort the experiment in case the temperature reaches > 60 °C in order to
  - avoid the damage of the fibre optic temperature sensor,
  - to keep evaporation as low as possible and
  - to avoid too strong $SAR(T)$ dependence.
- The measurers are asked to provide $T(t)$ curves only, there is no need to recalculate SAR and ILP because individual calculation of these parameters is one of the reasons of the high MADs.

- The SAR will be determined by the analysis team using two different methods: a) a polynomial fit and b) corrected slope method.
- Take better into account the different AMF strengths used by the individual measurers by studying the field dependence of the SAR in order to use it for ILP calculation.
- The 3rd round will be carried out on samples №4, 6 and 8. The latter is a commercial ferrofluid, to be acquired and diluted to achieve a MNP concentration of 20 *mg*/*ml*.
- The 3rd round will take place between mid-March and mid-April, the results to be presented at the Bilbao meeting.
- The excel files containing the protocol will be simplified. There will be one file per sample, containing following sheets:
    - A much simpler, step-by-step, measurement protocol,
    - the Measurement parameters (type of instrument, *H*, *f*, room temperature, storage temperature, …
    - comments for possible issues,
    - data columns time and temperature for 3 measurements per sample and possibly an additional optional column for monitoring the applied field *H*(*t*), and
    - concise information of the coil system (number of turns, diameter, distance between turns, number of layers).
    - The tab containing the average temperature over time graph will be removed from the excel template.
- Objective to be achieved: $MAD_{ILP} \leq 5\%$

It was further discussed that the test samples should be too concentrated, in order to avoid the high temperature range for keeping the evaporation at a minimum. The discussion turned then to the highly concentrated sample № 8

A pre-test will be carried out before mid-March by a smaller team investigating *SAR*(*H*), *cf.* figure below, showing the 3 expected zones of *SAR*(*H*) dependence:

I. the quadratic region within limit of linear response theory (typically $H < 5$ *kA*/*m*),
II. the inflection point when the scaling law exponent gets higher than 2 (typically 3-4), for a field strength *H* exceeding the anisotropy field of either block moments or multi-domain magnetic NPs (H =10-15 *kA*/*m*),
III. the plateau region for high fields ($H > 20$-30 *kA*/*m*) at which the energy dissipated at every hysteresis cycle does not increase anymore (as expected by Stoner-Wohlfarth model of ferromagnetic NPs).



Measurements will be carried out for all 3 samples (№ 4, 6, 8) at 300 *kHz*. For each field zone, *T*(*t*) curves will be acquired at 4 different field values and then interpolated. This allows to better take into account the relation $SAR \sim H^n$, *n* being different in each zone. For ring test rounds 1 and 2, the ILP was determined assuming $n = 2$ for all setups.

9. AOB

The issue of making the webpage more attractive was discussed. Daniel will get in contact with the webmaster for solving small issues:

- Titles of STSMs are not appearing, instead the host institution appears as title
- Update of information together with Sofia Costa Lima
- Ask a login for the back-office for Sofia
- Simo will upload all MC meeting minutes and of the info
- As a login for MC members having access to the restricted area
- How to setup new keywords when submitting a paper to the webpage

10. Closing

WG2 leader Daniel Ortega thanked the participants for their fruitful discussions, the local organiser Eva Natividad for her hospitality and the perfect organisation, and closed the meeting closed around 4 PM.

ToDo- list

Action	Deadline	Responsible
Ask Ferrotec about possible dilution media for ferrofluids № EFH1 (light hydrocarbon)	asap	Eva
As an offer to Ferrotec and order EMG 408, (10 nm cores in water, phi=1.2% vol., thus 60 mg/mL), which are not affecting the NP suspension stability	asap	Simo, partially done, awaiting input from Ferrotec
Order sample vials for 3rd ring-test	asap	Simo
Measure magnetic properties of ring-test samples № 4, 6, 8 and/or EMG408	asap	Simo
Send ring-test sample № 6 to Eva and sample 8 to all measurers	asap	Simo, partially done
DLS measurements of samples 6 and 8	end of February	Olivier
Send e-mail to participating ring test labs announcing 3rd ring test	end of February	Daniel
Carry out the pre-SAR ring-test as discussed	5th of March	Daniel, Eneko, Eva, Margarida, Olivier
Update ring-test protocol excel file as discussed, including appropriate *H* for group I, II and III	12th of March	Daniel
Send the ring test protocol to participating labs	15th of March	Daniel
Dilute the commercial ferrofluid by factor 3 in deionized water and send out samples to all labs participating in the ring test	15th of March	Simo
Send back SAR measurements	16th of April	All participating labs
SAR recalculation corrected slope method	23rd of April	Daniel, Simo
SAR recalculation polynomial fit method	23rd of April	Eneko
Result interpretation 3rd ring test	26th of April	Daniel, Simo
Presentation results 3rd ring test in Bilbao	27 or 28th of April	Daniel, Simo

Abbreviations

AMF	Alternating magnetic field
AOB	Any other business
CEM_{43}	Cumulative equivalent minutes at 43 °C
DLS	Dynamic light scattering
MAD	Median absolute deviation
NP	Nanoparticle
SAR	Specific absorption rate

List of Annexes

Annex A1: Meeting agenda
Annex A2: Signed COST Attendance list
Annex A3: Presentation Daniel