Doctoral Thesis

Iron oxide nanoparticles and polymer composites on thereof for magnetic hyperthermia

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A review by Takeshi Kitano

This thesis is concerned with the research works relating with magnetic hyperthermica (HP) for non-surgical tumor treatment under AC magnetic field and is composed with the review of the previous works (Chaper 1) and two chapters. In Chapter 1, research works on various subjects such as 1) nano scale magnetism of nanoparticles, 2) magnetic iron oxides: their strucures, magnetic properties and synsesis 3) hyperthermia: principle, modalities, 4) magnetic hyperthermia (HP): application of magnetic materials, heating mechanism, in-vitro studies and clinical trials of this method and 5) present status of arterial embolization hyperthermia (AEH) etc. were precisely reviewed.

From the analysis of the various research works concerning with magnetic HP technology for cancer, the following items are induced as the most important subjects to study in this field.

1) Design/preparation of magnetic nano-particles which possess effective tumor heating
2) Development of a mediator on the basis of magnetic nanoparticles which can be delivered and retained in the tumor long enough for thermal treatment and provide a homogeneous nanoparticles distribution (polymer composites on thereof with AC magnetic field energy absorption and rheological properties for the application in magnetic HP, particularly for the arterial embolization HP.)

In this study, a bi-functional magnetic composite, combining the embolization ability and high heating efficiency in AC magnetic fields was prepared. The silicone elastomer was used as a matrix of the composite. As a magnetic phase of composite the maghemite nanoparticles with high heating potential developed in this study were used, so various complex properties have to be measured for the assesment/characterization of these materials from various point of view. In Chapter 2, the aim of the measurements, their conditions, analythical methods and so on are shown.

In Chapter 3, the results and discussion on the research subjects of 1) preparation of iron oxide nanoparticles and their characterization and 2) these particles filled silicone composites and theit various properties were shown.

In the section of the preparation of magnetic iron oxide nanoparticles for magnetic hyperthermia(HP), 1)the synsesis conditions effect on structures and heating efficiency in AC magnetic field , especially the influence of the reaction course on morphology and crystalline structure of naoparticles, the influence of the reaction course on the magnetic properties, and the correlatin between magnetro-structural properties and heating efficiency were investigated to make clear the various factors influenced on the structure formation, magnetic properties and heating behavior under AC magnetic field. 2)the influence of synsesis parameters on nucleation and growth of iron oxide nanoparticles in solution, here the infuence of coprcipitation course on the formation of the structure of the materials were investigated. 3) the effect of after-treatment(anneling) on their structure and magnetic properties, here the sample obtained by coprecipitation method which is the mixture of magnetite (72%) and maghemite(28%) (called original sample)was post-treated for pure maghemite by anneling at 300 °C in air for 2 and 6 hours, and various properties such as the change of the structure, magnetization curve and complex magnetic permeability dispersion were investigated. 4) AC field energy absorption in the dispersion of iron oxide nanoparticles in viscous medium, here the effect of interparticle interactions was investigated. Heating curves of original, annealed samples with iron oxide nanoparticle dispersed in viscous Grycerol medium were prepared and measured. Similar heating behavior and no difference in specific loss power (SLP) values were obserbed. This means that the phase composition has minor impact on SLP, and SLP less than 30W/g was explained by the combined effect of interparticle magnetic interactions and the properties of the carier medium.

In the section of nanoparticles based polymer composites for AEH, 1) the effective embolization and 2) conditions for attainment of hyperthermic temperatures were investigated. Various composites with different composition of silicones and additives as the medium were prepared for the measurement of rheological properties which were characterized by time dependent dynamic viscoelastic properties, and effect of the concentration of additives and magnetic filler were measured and discussed. Valcanization (gelation) time of various samples were also measured from this measurement. Heating efficiency of the composites were also measured. It was found that when the viscosity increase of the medium, specific loss power (SLP) values of the composites decrease. It is generally considered that for low viscous medium, Brown relaxation is predominant and Neel elaxation for higher viscous medium. From the experimental results obtained, the newly developed iron oxcide nanoparticle based silicone composites show the excellent properties for the AEH application from the point of view of the magnetic nanoparticles delivery and uniform distribution and retention in tumor .

Through the present research work,many interesting and fruitful results were obtained. It is thought that these newly obtained knowledge/techniques have the high possibility as new materials which will be able to apply for magnetic HP, AEH and other various fields. The contents in this thesis had been prepared for four paper manuscripts and submitted or accepted for publication in the international Journals.
Concerning the thesis, I have some primitive questions or comments as shown below.

Finally, from the above reasons, I think this thesis is able to be accepted as the Doctoral thesis.

Question/comments:

Chapter 1:

1) Critical sizes of SD nanoparticle, D_{cr}^{SD} and D_{cr}^{SPM} are important for characterization of magnetic properties of iron oxide nanoparticles. It is shown in the text that these critical values are calculated by Eqs.(7) and (9). Explain breifly about these equations, especially Eq.(9). I can not imagine how this equation is induced. What is the meaning of measuremant time, t_{meas} ? (P.18-19)

2) In the dry state, magnetite is readily oxidized to maghemite by air, so it was written that the heat treatment of magnetite (oxidation process) under controll is important , and it is cosidered from the literatures that the structure formation seems to be very sensitive to the treating temperature. Why do you select or fix the temperature of 300 C as anneling temperature in this study? (P.24)

3) Explain the mechanism shown in Figure 15 relating with arterial embolization hyperthermia(AEH), which is the main subject of this work. How about the relation Between this figure and flow /delibery of magnetic nanoparticles composite?

Chapter 2:

4) It is considered that the measurement of heat efficiency of iron oxide nanoparticles and their suspensions under AC magnetic field, and also the calculation of specific loss power (SLP) values are important in this research work. It was written that the home-made apparatus was used for the measurements. Do'nt you have any influence factors for the differences of the SLP values of other researchers ? How about the international standerization of this method ?

Chapter 3:

5) When we compare the values of SLP shown in Table 4 from the data of the literatureand those in Table 8, the latter values from this study are very lower than those of the former. How do you think about the main reasons of these clear differences?

6) The concept of domain-wall motion, **dw** and magnetization rotation, **mr** and the cotribution of them to the complex complex magnetic permeability (Fig.42 anf Fig.53) is not clear for me. How do you calculate these values ? Are these included as a parameter in both terms of μ' and μ'' of frequency dispersion formula of permeability equation ?

7) Can you change or control of induction period time (vulcanization or gelation?) widely of magnetic NP filled liquid by selection of different types of elastomer or composition, combination with other component of the medium?

8) Is it possible for modelling/ computer simulation of a serial proscess such as the flow of magnetic nanoparticles filled liquid in artery, uniform distribution, valcanization process, retention in tumor and so on?

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