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Magnet–PNIPA hydrogels for bioengineering applications

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Abstract Temperature-sensitive Poly (*N*-isopropylacrylamide), PNIPA gels were synthesized with micron-sized iron and iron oxide (Fe_3O_4) particles to investigate their viability for hyperthermia applications. Induction heating of the magnetic hydrogels with varying concentration of magnetic powder was conducted at a frequency of 375 kHz for magnetic field strength varying from 1.7 kA/m (21 Oe) to 2.5 kA/m (31.4 Oe). It was observed that the maximum temperature induced in the magnetic hydrogels increased with the concentration of magnetic particles and magnetic field strength. The PNIPA gel underwent a collapse transition at 34 °C. It was found that a 2.5 wt.% Fe_3O_4 in PNIPA composite took 260 s to be heated to 45 °C under a magnetic field strength of 1.7 kA/m, the specific absorption rate (SAR) was found to be 1.83. SAR of iron oxide was found to be higher than the SAR of iron.

Introduction

Hyperthermia is a heat treatment approach in cancer therapy. Cancerous cells are vulnerable at high temperatures, by raising the temperature of the target tissue to between 43 °C and 46 °C, the viability of the cancerous cells is reduced and their sensitivity to chemotherapy and radiation is increased [1]. The vascular and nervous systems are not fully developed in a tumor, the tumor is thus not effectively cooled by blood flow, increasing its susceptibility to temperature, cancer cells are destroyed at about 43 °C, while normal cells can survive at higher temperatures of up to 48 °C, this offers us a window for hyperthermia therapy. It has been suggested that hyperthermia may additionally stimulate activities of the host immune system against growing cancer cells.

Magnetic hyperthermia refers to the introduction of ferromagnetic or superparamagnetic particles into the tumor tissue, followed by the application of an external varying magnetic field. The particles transform the energy of the magnetic field into heat by several mechanisms: eddy current and hysteresis loss and relaxation loss including Brownian and Neel relaxation. The efficiency of the transformation of energy is strongly dependent on the strength and frequency of the magnetic field, the properties of the magnetic particles and the cooling capacity of the blood flow [2, 3]. Superparamagnetic materials have zero remanence and the energy transformation is mainly attributed to Brownian and Neel relaxation losses.

Recently, the use of hydrogel coated magnetic particles has been explored for hyperthermia applications [4]. The polymer networks have properties which make the hydrogels suitable for applications in controlled drug delivery systems, while the magnetic particles, with ferromagnetic or superparamagnetic properties, are used for hyperthermia [5]. Hydrogels have been extensively used in a wide range of biomedical applications including soft contact lenses, coatings for intravascular devices, wound dressings, drug delivery systems and lubricants for surgical gloves because of their biocompatibility and general

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physical resemblance to living human tissue. An important property of some hydrogels is the ability to undergo abrupt changes in volume without dissolving in the immersed medium, ''smart gels'' are able to swell or shrink up to 1000 times in response to small changes in temperature, pH level, electric fields or solvent and ionic composition. The temperature-sensitive poly(*N*-isopropylacrylamide) (PNIPA) hydrogels were found to exhibit volume changes of over 800% when immersed in distilled water or seawater solutions at temperatures ranging from 5 °C to 50 °C. PNIPA hydrogels have a lower critical solution temperature (LCST) of 34 °C; the hydrogels are swollen at temperatures below 34 °C but collapse at 34 °C and above [6].

In a previous investigation, the PVA–iron oxide system was studied for its suitability for hyperthermia applications [4]. It was found that a maximum temperature of 43 °C was obtained at 2.5 wt.% iron oxide concentration. The time taken to reach this temperature was about 5 min for a field amplitude of 1.7 kA/m (21 Oe) and a frequency of 375 kHz. We wished to extend this work by introducing the magnetic particles within a ''smart'' hydrogel rather than PVA; as the magnetic particles get heated by application of an AV magnetic field, they will raise the temperature of the surrounding hydrogel, inducing the collapse transition. If drug molecules are dissolved in the hydrogel, they will be released during this collapse transition, this will create a novel combined triggered drug release and hyperthermia system. Other advantages include the fact that maximum temperature can be controlled by altering the magnetic powder concentration and/or magnetic field strength. The temperature control is obtained without complex and cumbersome manipulation of the alloy composition to alter the Curie temperature of the material. This approach can be extended to in situ gelation, which will make the treatment less invasive for the patient.

The size of the magnetic particles decides the mechanism of heating since the particles can exhibit superparamagnetism in the nm size range. Superparamagnetic particles have been studied earlier and heating (and hence SAR values) attributed to Brownian and Neel relaxation [7]. On the other hand, in the present work iron oxide and iron particle sizes in the range of 3–5 μm have been chosen which will heat up due to eddy current and hysteresis loss mechanisms and are thus expected to yield different values of SAR.

In this paper, we focus on the suitability of this system for hyperthermia applications.

Experimental methods

PNIPA gels were prepared by free radical polymerization. 0.8475 g of *N*-isopropylacrylamide (NIPA) was mixed with 7.5 mg of crosslinker *N*,*N*-methylene(bis)acrylamide (BAAm) and 10 μL of accelerator *N*,*N*,*N*′,*N*′-tetramethylenediamine (TEMED) in 8 mL of distilled water. The mixture was placed in nitrogen environment to remove residual oxygen. Depending on the weight percentage, Fe_3O_4 powder in the size range of 3–5 μm and Fe powder of average size 4.08 μm were added to the solution and mixed homogenously. Finally, 50 μL of initiator ammonium persulfate (APS) was added. The mixture was then let to stand for 2 h for gelation to take place. The gels were subsequently washed thoroughly with water to remove any remaining reactants.

The sample was placed in the solenoid coil for induction testing where an alternating magnetic field ranging from 1.7–2.5 kA/m and frequency of 375 kHz was applied. The temperature rise was recorded as a function of time.

Results and discussion

Temperature vs. time as a function of magnetic field strength *H*

Figure 1a, b show the increase in temperature as a function of heating time for 2 wt.% and 2.5 wt.% Fe_3O_4 in the PNIPA–Fe_3O_4 system, respectively, for various applied magnetic field strengths. Figure 2 shows the temperature increase obtained for 2 wt.% Fe in the PNIPA–Fe system. The maximum temperatures reached by the systems were found to be dependent on the magnetic field strength; higher maximum temperatures were obtained when higher magnetic field strengths were applied.

For a field strength of 2.0 kA/m (1 kA/m = 12.57 Oe), the PNIPA–Fe_3O_4 system reached a maximum temperature of 44 °C and maintained this temperature for more than 2 min. This is suitable for hyperthermia application since the desired temperature to be induced ranges from 43 °C to 46 °C, importantly the temperature stabilized at 44 °C, thus overheating was avoided. Below 42 °C, the temperature is insufficient to heat up the tumor tissue effectively. Above 48 °C, the neighboring tissue would be heated up as well, causing acute necrosis, coagulation or carbonization of tissue [7]. The same magnetic field strengths were applied to PNIPA–Fe systems with up

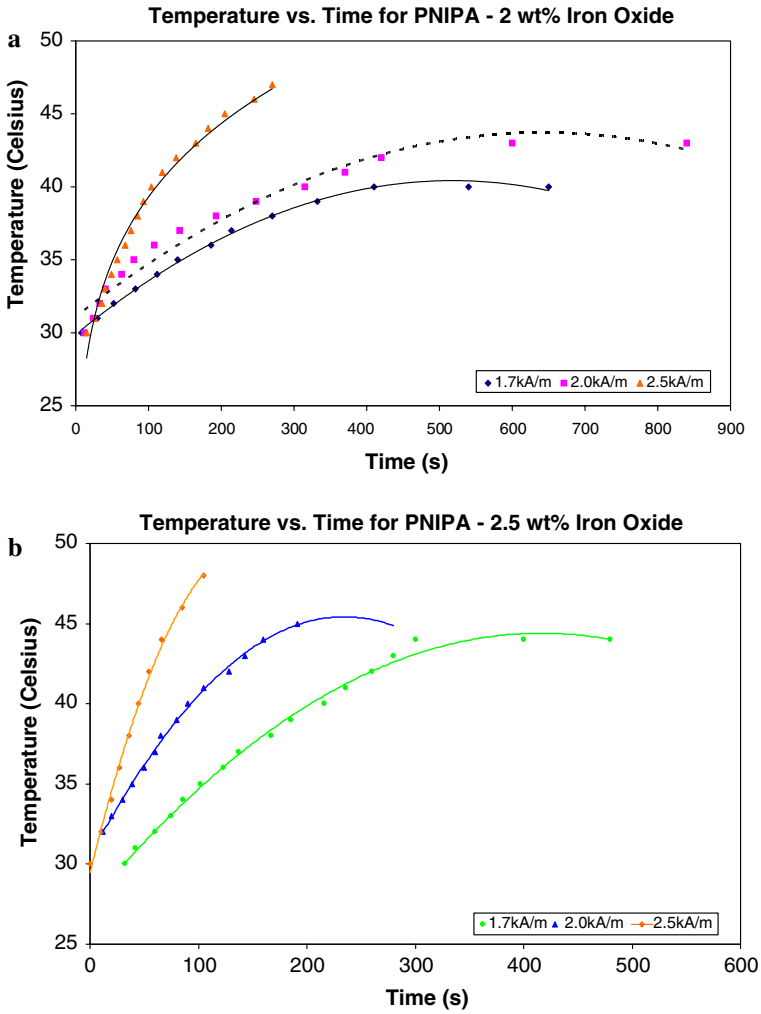

Fig. 1 Temperature vs. time for PNIPA–2 wt.% iron oxide (**a**) and PNIPA-2.5 wt.% iron oxide (**b**)

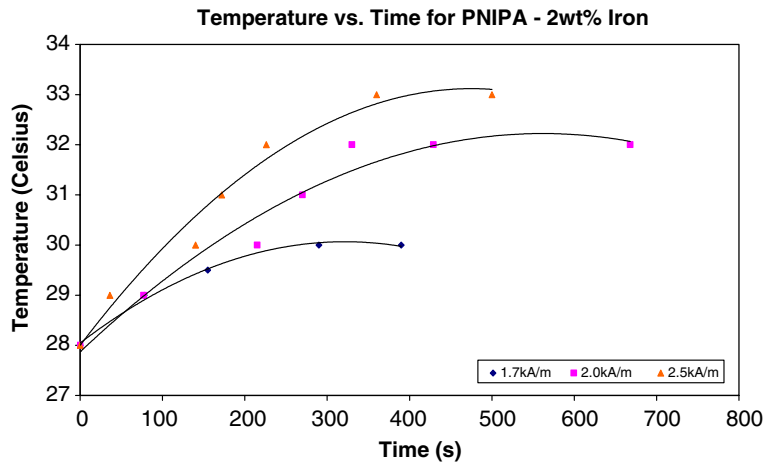

Fig. 2 Temperature vs. time for PNIPA–2 wt.% iron

to 8 wt.% Fe, but the maximum temperatures reached were all under 34 °C, indicating that the PNIPA–Fe system is not effective for hyperthermia application.

Temperature vs. time as a function of magnetic particle concentration

Figures 3 and 4 showed that an increase in the magnetic particle concentration in both the PNIPA–Fe_3O_4 and PNIPA–Fe systems led to an increase in the initial slopes of temperature increase versus heating time ($\Delta T/\Delta t$). This means that the magnetic hydrogels with higher iron oxide or iron concentration were heated up faster than those with lower concentration. The particle size of iron oxide was in the range 3–5 μm, the coercivity *Hc* of iron is about 24 kA/m [8]. The average particle size of iron was 4.08 μm, the *Hc* of iron is substantially lower, 80 A/m [3]. In this range of particle sizes the hysteresis loss is the main mechanisms of energy transformation, the larger coercivity of iron oxide results in a much larger hysteresis loss, hence the heating effect is much greater in iron oxide compared to iron.

The hydrogels collapsed at 34 °C for all magnetic particle concentrations studied under various magnetic field strength, indicating that the magnetic particles did not affect the collapse transition of the polymer network.

Specific absorption rate (SAR)

The SAR is used to describe the energy absorbed by the magnetic particles during RF induction hyperthermia. It is given by the expression $SAR = c\ (\Delta T/\Delta t)$

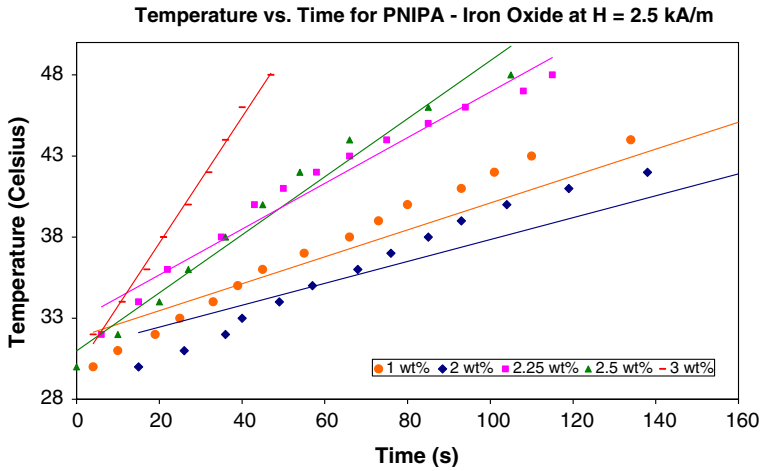

Fig. 3 Temperature vs. time for PNIPA–iron oxide at $H = 2.5$ kA/m

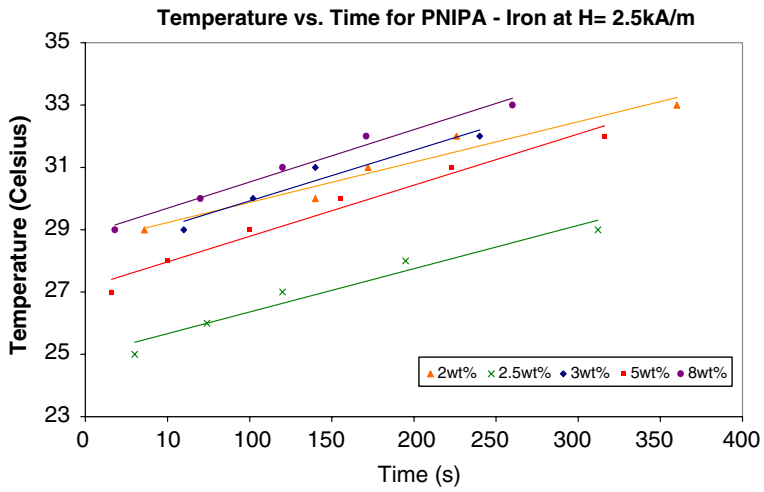

Fig. 4 Temperature vs. time for PNIPA–iron at $H = 2.5$ kA/m

where c is the sample specific heat capacity and $(\Delta T/\Delta t)$ is the initial slope of temperature increase versus heating time. These values are provided in Table 1. Just as Hc is affected by the magnetic particle size, SAR is also dependent on the particle size. Previous research shows that other factors influencing SAR include magnetic field strength, field frequency and magnetic particle concentration.

The calculated SAR for PNIPA–Fe_3O_4 and PNIPA–Fe systems are tabulated in Tables 2 and 3, respectively. The average SAR for each system is tabulated in Table 4. For magnetic field strengths 1.7 kA/m and 2.0 kA/m, the SAR of Fe_3O_4 was not very sensitive to the iron oxide concentration. However, when subjected to magnetic field strength 2.5 kA/m, the SAR varied significantly from 2.7 to 10.6 as the iron oxide concentration was increased (Table 2). The SAR obtained for the PNIPA–Fe system was small, ranging from 0.18 to 0.67. For a constant concentration of magnetic particles, an increase in magnetic field strength led to an increase in SAR (Fig. 5).

Figure 6 shows the comparison between PVA–Fe_3O_4 system and PNIPA–Fe_3O_4 system when subjected to magnetic field strength 2.5 kA/m. For the same wt.% of Fe_3O_4, the slopes $(\Delta T/\Delta t)$ were similar for both the PVA and the PNIPA based systems. However, because the c values differ for PVA and PNIPA, the SAR values were different. With an increase in wt.% of Fe_3O_4, the slope of the curve increased for both systems.

Table 1 Specific heat c of each component in system

Component	Heat capacity (J/g K)
Water	4.118
PNIPA	1.200
PVA	1.670
Fe_3O_4	0.937
Fe	0.440

Table 2 SAR of iron oxide

Wt.% Fe_3O_4	H (kA/m)	dT/dt ($\times 10^{-2}$)	Heat capacity of the system (J/g K)	SAR (W/g of Fe_3O_4)
1	2.0	2.3	3.79	2.34
2	1.7	2.5	3.76	1.08
2	2.0	3.2	3.76	1.34
2	2.5	6.8	3.76	2.66
2.25	2.0	6.1	3.76	2.31
2.5	1.7	5.8	3.75	1.83
2.5	2.5	17.9	3.75	7.41
3	2.5	38.8	3.74	10.62

Table 3 SAR of Iron

Wt.% Fe	H (kA/m)	dT/dt ($\times 10^{-2}$)	Heat capacity of the system (J/g K)	SAR (W/g of Fe)
2	1.7	4.6	3.75	0.20
2	2.0	11.6	3.75	0.46
2	2.5	12.9	3.75	0.55
2.5	2.5	15.7	3.74	0.67
3	1.7	7.1	3.72	0.22
3	2.5	16.3	3.72	0.47
5	2.5	16.4	3.66	0.36
8	2.5	16.8	3.57	0.18

Table 4 Average SAR

System	Block	Magnetic field strength H (kA/m)	Wt.%	SAR (W/g)	Average SAR (W/g)
PNIPA–Fe_3O_4	1	1.7	2	1.08	1.455
			2.5	1.83	
	2	2.0	1	2.34	1.997
			2	1.34	
			2.25	2.31	
PNIPA–Fe	1	1.7	2	0.20	0.210
			3	0.22	
	2	2.5	2	0.55	0.446
			2.5	0.67	
			3	0.47	
			5	0.36	
			8	0.18	

Selection of optimum particle concentration and field strength

A series of tests were performed with different magnetic particle concentrations under various magnetic field strengths. The best combination was found for the PNIPA–Fe_3O_4 system. A loading of 2.5 wt.% Fe_3O_4 in PNIPA–Fe_3O_4 system took 260 s to be heated to 45 °C under a magnetic field strength of 1.7 kA/m, the SAR was found to be 1.8. (In the corresponding PVA–Fe_3O_4 system, a maximum temperature of 43 °C was obtained at 2.5 wt.% iron oxide concentration, the time taken to reach this temperature was about 5 min [9].) Other combinations were unsuitable because the maximum temperatures reached were above 46 °C or the samples had to be heated for more than 10 min in order to reach the maximum temperature, shorter heating time would enable faster hyperthermia treatment and hence less discomfort in the patient. In the PNIPA–Fe system, the maximum temperature ranged from 30 °C to 34 °C with 1 wt.% to 5 wt.% Fe. These

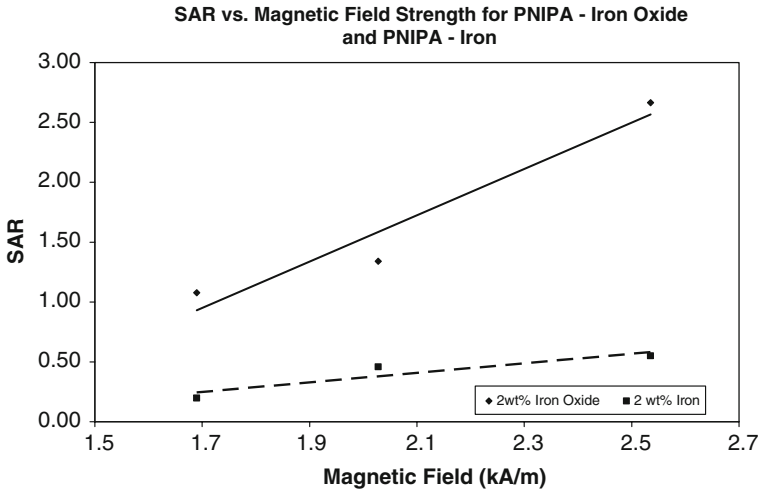

Fig. 5 SAR vs. magnetic field

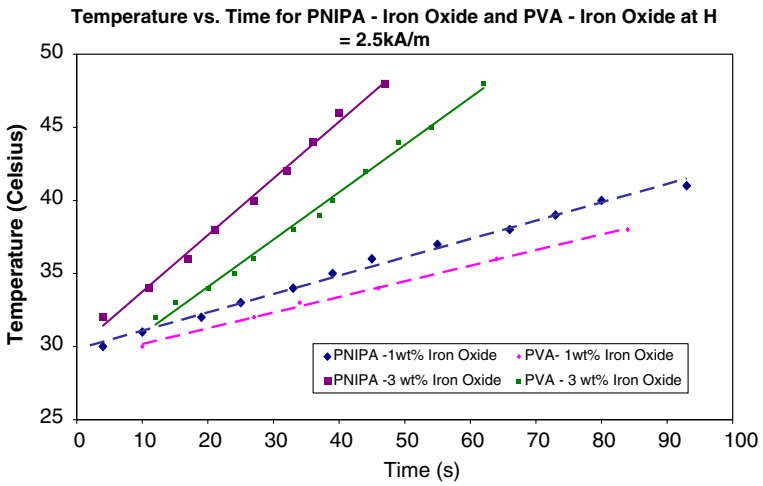

Fig. 6 Temperature vs. time for PNIPA–iron oxide and PVA–iron oxide

temperatures were insufficient to heat up the tumor tissue; therefore, this system was not suitable for hyperthermia applications [10 , 11].

Conclusions

PNIPA hydrogels were prepared with iron oxide and iron powder to study their use in hyperthermia applications. The following results were obtained:

1. It was found that PNIPA–Fe_3O_4 system can be used for hyperthermia but not PNIPA–Fe system because the latter was unable to reach the temperatures required for hyperthermia to be effective.
2. The maximum temperatures reached by the systems increased with an increase in the magnetic field strength and magnetic particles concentration.
3. SAR was found to increase with magnetic field strength, but insensitive to magnetic particles concentration at low magnetic field.
4. An optimum combination of particle concentration and magnetic field strength was found. Maximum temperature of 45 °C was obtained using 2.5 wt.% Fe_3O_4, the time taken was approximately 4 min under field amplitude of 1.7 kA/m and frequency of 375 kHz.

References

1. Shinkai M (2000) J Biosci Bioeng 94(6):606
2. Ma M, Wu Y, Zhou J, Sun Y, Zhang Y, Gu N (2004) J Magn Magn Mat 268:33
3. Jiles D (1991) Introduction to magnetism and magnetic materials. Chapman and Hall, London
4. Lao LL, Ramanujan RV (2004) J Mater Sci Mater Med 15:1061
5. Babincova M, Leszczynska D, Sourivong P, Cicmanec P, Babinee P (2001) J Magn Magn Mat 225:109

6. Kim SJ, Lee CK, Lee YM, Kim SI (2003) J Appl Polym Sci 90:3032
7. Chan DC, Kirpotin DB, Bunn PA Jr (1997) Scientific and clinical applications of magnetic carriers. Plenum Press, New York, p 607
8. Craik DJ, Tebble RS (1965) In: Wohlfarth EP (ed) Selected topics in solid state physics: ferromagnetism and ferromagnetic domains. John Wiley and Sons, New York
9. Park BH, Koo BS, Kim YK, Kim M (2002) Korean J Radiol 2:98
10. Jones SK, Gray BN, Burton MA, Codde JP, Street R (1992) Phys Med Biol 37:293
11. Mitsumori M, Hiraoka M, Shibata T, Okuno Y, Nagata Y, Mishimura Y (1996) Hepatogastroenterology 43:1431