

# Preliminary Study of $\text{Fe}_x\text{Co}_y\text{Pd}_{100-x-y}$ Nanoparticles as Candidates for Magnetically-Triggered Drug Release

Gregory M. Poole, David E. Nikles, Ph.D.

Department of Metallurgical Engineering, University of Alabama, Tuscaloosa, AL 35487, USA

## Introduction

Cancer is one of the leading causes of death in the world, along with heart disease and other ailments. But while the US mortality rates for pulmonary and cardiovascular diseases have been reduced in the last fifty years, the rate for cancer remains hardly unchanged [1, 2]. This has spurred efforts to find suitable treatments for cancer involving surgical, radiation, or pharmaceutical means. Even so, the forms of chemotherapy in existence today require that drugs are dispersed throughout the body to attack rapidly multiplying tissue, meaning that some healthy tissue is destroyed in the process [10]. In addition, many of the modern procedures are very invasive, and could lead to further damage to the surrounding healthy tissue [4, 7]. Therefore, a novel method is desired to concentrate the administration of the drug exclusively to the tumor and is also minimally invasive, leading to the concept of magnetically triggered drug delivery. In this procedure, polymeric micelles containing anti-cancer drugs and magnetic nanoparticles (MNPs) are injected into the body and locate the tumor using a targeting moiety. A magnetic field is then applied to heat the particles and the nearby micelle, allowing the drug to be released via diffusion [10].

Thus it has become of interest to develop magnetic materials that deliver the maximum amount of power to its surroundings. In order to efficiently perform magnetically triggered drug release, the specific loss power (SLP) must be maximized [3]. This is given by Eq. 1,

$$P = \frac{(mH)^2}{2k_bTV\tau} \quad (1)$$

where  $H$  is applied field ( $H \approx H_0$ ),  $V$  is the volume of the particle, and  $\tau$  is the magnetic relaxation time [5]. A lower relaxation time is advantageous since it would increase the overall SLP. The effective relaxation time

has two components—Brownian and Neel—and the contribution of each is defined by the expression,

$$\tau_{eff} = \frac{\tau_N \tau_B}{(\tau_N + \tau_B)} \quad (2)$$

where,

$$\tau_B = \frac{4\pi r^3 \eta}{k_b T} \quad (3)$$

and,

$$\tau_N = \tau_0 \exp(\sigma), \quad \sigma = K_u V / k_b T \quad (4)$$

For Neel relaxation (4),  $\sigma$  is the ratio of magnetic anisotropy energy to thermal energy, where  $K_u$  is the magnetocrystalline anisotropy of the particle and  $\tau_0$  the damping time equal to  $\sim 10^{-9}$  s. Since the particle is immobilized via the surrounding micelle, Brownian relaxation is very low ( $\sim 10^{-9}$ - $10^{-6}$  s). From (2) it is apparent that a higher  $\tau_N$  is desired since it would make  $\tau_{eff} \approx \tau_B$  [8]. Therefore it is of great interest to maximize the Neel relaxation time in (4) by finding materials with a high  $\sigma$  value. This makes ferromagnetic nanoparticles for data recording and iron oxides such as  $\text{Fe}_3\text{O}_4$  very interesting candidates for producing very high values of SLP. This has led to our interest to study FePd as a possible MNP candidate based on the work of Chen and Nikles [11]. It is hypothesized that partially substituting Co for Fe in the FePd lattice may lead to larger  $\sigma$  values. The synthesis of FeCoPd using a wet chemical reduction method and its subsequent characterization using Scanning Electron Microscopy (SEM), Alternating Gradient Magnetometry (AGM), and X-ray Diffraction (XRD) is reported.

## Experimental

The experiment was performed using a three-neck roundbottom flask under inert N<sub>2</sub> atmosphere. The individual necks contained a condenser, rubber septum, and thermometer. All chemicals were purchased from Sigma Aldrich.

The experimental procedure of MNP synthesis was performed accordingly with a target composition of Fe<sub>33</sub>Co<sub>33</sub>Pd<sub>34</sub>. Co(acac)<sub>2</sub> (0.45 mmol), Pd(acac)<sub>2</sub> (0.45 mmol), 1,2-hexadecanediol (0.5 mmol), and triethylene glycol (50 mL) were placed in the flask along with a magnetic PTFE stir bar. The solution was heated to 80°C and held for five minutes. Oleyl amine (0.5 mL) and oleic acid (0.5 mL) were then added. Heating resumed until 100°C, where a five minute hold period was observed, after which Fe(CO)<sub>5</sub> (0.45 mmol) was added. The conditions were maintained for ten minutes to allow for the thermal decomposition of the pentacarbonyl. A color change from orange to black also occurred during this period, indicating the nucleation of the particles. The temperature was increased to 200°C and maintained for 5 minutes while Superhydride (1 mL of 1.0M in THF) was added. After an additional 10 minute hold, the solution was heated to reflux for one hour, and subsequently cooled. This synthetic route was repeated to verify the results of the first synthesis.

To isolate the particles from solution, 100mL of EtOH was added and the resulting mixture was centrifuged at 4000 rpm for 10 minutes to precipitate the particles. The dark supernatant was discarded and the resulting product was redispersed in EtOH. A 4:1 ratio of EtOH to hexane was added and the solution was centrifuged again to continue removing any remaining solvent and excess surfactant from the particles. This was repeated until a clear supernatant was observed. The final product was redispersed in either EtOH or H<sub>2</sub>O and stored for future use

Since the ferromagnetic L1<sub>0</sub> phase of FePd occurs at elevated temperatures, it was expected that FeCoPd would require annealing to achieve optimal magnetic properties. To test this temperature dependence, samples were placed on Si wafers and annealed in a tube furnace at temperatures of 350°C and 500°C for 3 hrs under an Ar/H<sub>2</sub> atmosphere to prevent particle oxidation.

## Results and Discussion

### Composition

To determine the composition of the MNPs, Electron Dispersive X-ray Spectroscopy (EDS) was performed using a Phillips XL-30 scanning electron microscope. To reduce error, a minimum of 10 measurements were taken. The results of the analysis for each synthesis are found in Table 1. Note that all of the composition of the second synthesis is very close to the target composition.

**Table 1:** Composition of Nanoparticles Produced by the two syntheses

Synthesis	Fe	Co	Pd
1	39.3 ± 1.1	28.0 ± 1.0	32.4 ± 1.1
2	33.4 ± 1.7	31.8 ± 1.6	34.8 ± 0.9

### Crystallography

XRD was performed on both the as prepared and annealed samples in order to gain information on the structure of the as made nanoparticles, and to detect possible phase changes and grain growth as a direct result of annealing. Measurements were taken between 20-60° 2θ. Figure S1 is a plot of all of scans for Fe<sub>39</sub>Co<sub>28</sub>Pd<sub>33</sub> for both annealed and as made samples. For the as made sample, only one peak (FeCoPd <111>) is observed at approximately 41°, and the <200> peak is apparent in the 350°C sample at 47° 2θ. Note the evolution of the peaks as the annealing temperature is increased. The peaks at 45°, 46°, and 53° correspond to the FeCo <110>, Pd <200>, and FePd <201> peaks. This indicates that the particles phase separate to form nanostructures with varying compositions when annealed. Further evidence is given by the presence of multiple lattice parameter values within the XRD spectra. The values of 2.80 and 3.94 Å are consistent with the values for FeCo and Pd, while the 3.92 and 3.77 Å corresponds to FePd and FeCoPd. Thus it appears that annealing is detrimental to drug delivery due to a lack of homogeneous magnetic properties in the composite.

Grain sizes were also calculated using the Scherrer equation. Growth was observed in the annealed samples, as the calculated grain size increased significantly from ~2nm for as made to 15nm for the sample annealed at 350°C and 19nm for the 500°C specimen. Similar results also occurred for the Fe<sub>33</sub>Co<sub>32</sub>Pd<sub>35</sub> particles as well. The as made

particles had a 3nm grain size and phase separated when annealed at 350°C.

### Magnetic Properties

Magnetic properties were determined using AGM. Since determining the energy ratio was the goal of the experiment, DC demagnetization remnance studies were done on each sample. In the experiment, a field of 12000 Oe was applied for one second. Varying reverse fields were applied for time intervals of 1, 2, 5, 10, 20, and 30 s. The process was repeated until the magnetization reached zero, and the corresponding applied field value ( $H_{cr}$ ) was noted. These values were plotted with respect to time. Figure S2 shows an example plot for  $Fe_{33}Co_{32}Pd_{35}$  as prepared. The plot was fitted to (5), where  $f_0$  is the attempt frequency and is assumed to be  $10^9$ /sec [11]. Values of  $H_0$  and  $\sigma$  are reported in Table 2.

$$H_{cr}(t) = H_0 \left\{ 1 - \left[ \sigma^{-1} \ln \left( \frac{f_0 t}{\ln(2)} \right) \right]^{(2/3)} \right\} \quad (5)$$

Using the values of  $\sigma$  for as made particles, a value for  $K_u$  was calculated. Using the grain size for the as made particles to calculate the switching volume,  $K_u \sim 2 \cdot 10^7$  ergs/cc. This value very close to the value given by Weller et al. for FePd nanoparticles, and double that of the  $Fe_3O_4$  nanospheres synthesized by Hyeon [6, 12]. Observe that annealing the particles does increase the energy ratio. Even so, the annealed particles cannot be used due to the phase separation, leading to an inability to control the magnetic properties of the particles.

**Table 2:** Magnetic properties of the FeCoPd Nanoparticles as produced and after heat treatments.

Composition	Treatment	$H_0$ (Oe)	$\sigma$
$Fe_{39}Co_{28}Pd_{33}$	AP	730	47
	350°C – 3h	1050	260
	500°C – 3h	1348	260
$Fe_{33}Co_{32}Pd_{35}$	AP	510	41
	350°C – 3h	625	110

### Conclusions

The synthesis of  $Fe_xCo_yPd_{100-x-y}$  nanoparticles has been reported as a possible candidate MNP for drug delivery. All particles had a  $\sigma_{min} > 40$  and the as made

particles had a  $K_u$  of  $2 \cdot 10^7$  ergs/cc, which leads to longer Neel relaxation times that are desired in drug delivery apparatuses. In addition, the size goal was achieved, as the average grain size was near 2 nm as prepared and continued to remain below 20nm after annealing at 500°C. Still, the XRD studies found that equimolar FeCoPd particles phase separate when annealed. Annealed particles, therefore, cannot be used at the moment due to existing inhomogeneities in the composition, structure, and magnetic properties.

### Future Work

The experiments reported were done for only one target composition. Later experiments will determine values of  $\sigma$  and  $H_0$  for other compositions of FeCoPd. In addition, more work will be necessary to prevent the phase separation of FeCoPd in order to allow for use of annealed particles with higher energy ratios ( $\sigma > 100$ ). Determining the phase separation start temperature will provide a significant advantage, as annealing below it will result in homogeneous properties.

### References

- [1] 1950 Mortality Data-CDC/NCHS, NVSS, Mortality Revised.
- [2] 2004 Mortality Data: US Mortality Public Use Data Tape, 2004, NCHS, Centers for Disease Control and Prevention, 2006.
- [3] Andrä W, d'Ambly CG, Hergt R, Hilger I, Kaiser WA, Richter U, & Schmidt H. (1998). Physical limits of hyperthermia using fine magnetite particles. IEEE Trans. Magn. 34:3745-3754.
- [4] Andrä W, Hergt R, Hiergeist R, Hilger I, Kaiser WA, Kießling A, Linss W, Romanus E, Roskos M, Weber P, & Weitschies W. (2004). Magnetic nanoparticles for selective heating of magnetically labelled cells in culture: preliminary investigation. Nanotechnology. 15:1027-1032.
- [5] Bahadur D, & Giri J. (2003). Biomaterials and magnetism. Sadhana (Eng. Trans.). 28:639-656.
- [6] Best ME, Doerner MF, Folks L, Lee W, Moser A, Schwikert M, Thiele J, Toney MF, & Weller D. (2000).

High  $K_u$  materials approach to 100 Gbits/in<sup>2</sup>. IEEE Trans. Magn. 36:10-15.

- [7] Chang S, Davis RL, Diederich CJ, Gutin PH, Lamb SA, Lamborn KR, Larson DA, Malec MK, McDermott MW, Phillips TL, Prados MD, Sneed PK, Spry L, Stauffer PR, Voss B, Wara WM, & Weaver KA. (1998). Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost  $\pm$  hyperthermia for glioblastoma multiforme. Int. J. Rad. Oncology Biol. Phys. 40:287-295.
- [8] Charles SW, Fannin PC, Mac Oireachtaigh C, & Odenbach S. (2006). Investigation of possible hysteresis effects arising from frequency and field-dependent complex susceptibility effects of magnetic fluids. J. Magn. Magn. Mat. 302:1-6.
- [9] Chen M, & Nikles DE. (2002). Synthesis, self-assembly, and magnetic properties of Fe<sub>x</sub>Co<sub>y</sub>Pt<sub>100-x-y</sub> nanoparticles. Nano Lett. 2:211-214.
- [10] Connolly J, Dobson J, Jones SK, & Pankhurst QA (2003). Applications of magnetic nanoparticles in biomedicine. J. Phys. D: Appl. Phys, 36:R167-R181.
- [11] Harrell JW. (2001). Orientation Dependence of the Dynamic Coercivity of Stoner-Wholfarth Particles. IEEE Trans. Magn. 37:533-537.
- [12] Hyeon T. (2003). Chemical synthesis of magnetite nanoparticles. Chem. Commun. 923-934.

*Gregory Poole is a junior majoring in Metallurgical Engineering from Brookwood, AL. He is currently researching nanoparticles for hyperthermia therapy in Dr. David Nikles's Group. He is a Presidential Scholar and SGA Senator for The College of Engineering.*