# Synthesis and characterization of polymer encapsulated Cu–Ni magnetic nanoparticles for hyperthermia applications

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## Abstract

Copper nickel alloy nanoparticles were synthesized by polyol reduction method and by physical melting process. The particles were further coated with a biodegradable polymer, polyethylene glycol. The particles have a curie temperature in the range of 43–46 °C and are designed to be used for hyperthermia applications. Morphology of these encapsulated particles was determined by electron microscopy. The curie temperature for alloy particles and encapsulated particles was also measured.
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## 1. Introduction

The viability of cancer cells is reduced and their sensitivity to chemotherapy and radiation increased when human or animal malignant cells are heated to 41–46 °C [1,2]. Heating of certain tissues in this temperature range preferentially for cancer therapy is called hyperthermia. In magnetic fluid hyperthermia, ferromagnetic particles coated with a biodegradable polymer or molecule are heated by using external alternating magnetic field to produce localized heating in the affected area

[3]. The production of localized heat for tumor treatment has been hindered due to certain factors, such as heterogeneous temperature distribution [4] and the inability of heating smaller visceral masses [4]. In order to achieve better control of local heating effects without damaging normal cells, particles are designed with a desired curie temperature range. In fact localized hyperthermia technique was first proposed by Gilchrist in 1957 [5] and is still an active area of research.

In certain compositions Cu–Ni alloy particles (Cu-30–33%, Ni-66–70%) are known given a curie temperature in the range of 41–46 °C [6]. Lilly et al. first reported Cu–Ni alloy particles for hyperthermia applications [7]. They developed these particles by physical melting process and they found

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good temperature homogeneity throughout a small visceral mass when heated by an array of Cu–Ni thermoseeds. In this paper Cu–Ni particles (synthesized by chemical and physical process) are further encapsulated with a biodegradable polymer which has a melting temperature in the range of 43–46 °C. These encapsulated particles are designed to be used for local heating in the affected area. These encapsulated particles are designed in such a way that when they are heated by an external AC magnetic field, they will melt and release the alloy particles and drugs in them to affect the tumor cells. Cu–Ni particles used here are generated by using polyol reduction method and also by physical melting and further ball milling. The detailed physical method has been described already by the authors [8]. The chemical method has been selected as one of the method to generate the seed particles as it gives the flexibility to synthesize particles in desired composition range and in smaller uniform size. Polyol reduction method has been used to synthesize metallic alloy particles such as, Ag–Pd, Co–Ni, Cu–Pd particles [9–11].

The synthesized particles are characterized by transmission electron microscopy and their curie temperatures ($T_c$) were measured. Seed particles with appropriate size and desired $T_c$ are chosen for further encapsulation. Two processes of encapsulation with polymers have been used here, oil in water inverse emulsion process and emulsion coupled with chemical crosslinking. These particles are further characterized by transmission electron microscopy and magnetic properties of these particles are also measured.

## 2. Materials and methods

Nickel powder (325 mesh, 99%) and copper powder (500 mesh, 99%) was obtained from Alfa Aesar. Nickel acetate tetrahydrate and copper acetate monohydrate and ethylene glycol were obtained from sigma Aldrich and used as obtained. Mineral oil, sodium sesqueoleate and n hexane are also obtained from sigma Aldrich and Zirmel M, a commercial crosslinking agent

has been obtained from Magnesium Electron Corporation, US.

### 2.1. Physical method of synthesis for Cu–Ni alloy particles

The detailed process has been described elsewhere. In brief mixture of copper and nickel powder are heated at 1465 °C (100 °C above the melting temperature of Cu–Ni alloy) for three hours under nitrogen atmosphere. Then the bulk solid alloy was mechanically abraded to produce a powder texture and further ball milled for 3–7 days in acetone.

### 2.2. Chemical method of synthesis for Cu–Ni particles

0.2 M metallic precursor (mixture of metal salts) in ethylene glycol was mixed with 1 M sodium hydroxide and heated at 195 °C. As the temperature rises, a complete precipitation was obtained at 60 °C, where as subsequent nucleation and growth of the metallic particles started at 150–160 °C. Water and volatile products of the reaction were distilled off while the polyol was refluxed. After a few hours the metal alloy particles was quantitatively precipitated from the solution and this portion recovered by centrifugation, washed with ethanol and dried in air at 50 °C. Three different salt compositions (Ni:Cu 30:70, 70:30 and 40:60 by weight) were made.

### 2.3. Encapsulation of Cu–Ni particles by polymer

(a) In the first method polyethylene glycol (PEG, MW = 1540) was dissolved in water and 30% of its weight of Cu–Ni alloy particles added and ultrasonicated to prepare a homogeneous dispersion. The pH of the medium was maintained between 8–10 and a commercial crosslinking agent zirmel M was added dropwise until a precipitate formed. Zirmel M contains zirconium and is used to crosslink molecules containing functional hydroxy groups by H bonding. The precipitate was separated by centrifugation, washed with water and acetone, and dried.

(b) In the second method an oil in water micro-emulsion was made and crosslinked. In the water phase, 250 mg of PEG and 75 mg metallic particles (30% of the weight of the polymer) were dispersed in 1 ml of water and ultrasonicated. In the oil phase 30 ml of n-hexane, 10 ml of mineral oil and 0.05 ml of sodium sesquioleate (an oil soluble surfactant) were mixed. The water and oil phase were then mixed by ultrasonication for 1 min, followed by adding 10 ml of gluteraldehyde to the emulsion and stirring for another 2 h. The crosslinked product was then separated and washed with water and acetone.

## 2.4. Methods of characterization

All Cu–Ni alloy particles and encapsulated particles were further characterized in terms of their morphology and magnetic properties. A JEOL 2010 transmission electron microscope and JEOL 840 scanning electron microscope were used to determine particle morphology. Magnetic properties were measured using an MPMS 5 SQUID magnetometer. Wide angle X-ray diffraction pattern was taken in a Siemens 500 X-ray diffractometer with CuK$\alpha$ ($\lambda = 0.154$ nm) radiation. Melting point of pure polymer and for encapsulated particles was measured using a Perkin Elmer DSC 7 with a 3700 data station.

## 3. Results and discussion

## 3.1. Morphology

Transmission electron micrographs for the chemically synthesized and physically synthesized Cu–Ni alloy particles are shown in Figs. 1 and 2. Physically synthesized particles do not have regular shapes and they have flake like structures with grains and boundaries. Mechanical abrasion and further ball milling are responsible for the rough texture of the particles. The size range of the Cu–Ni physically synthesized particles is 300–400 nm whereas chemically synthesized parti-
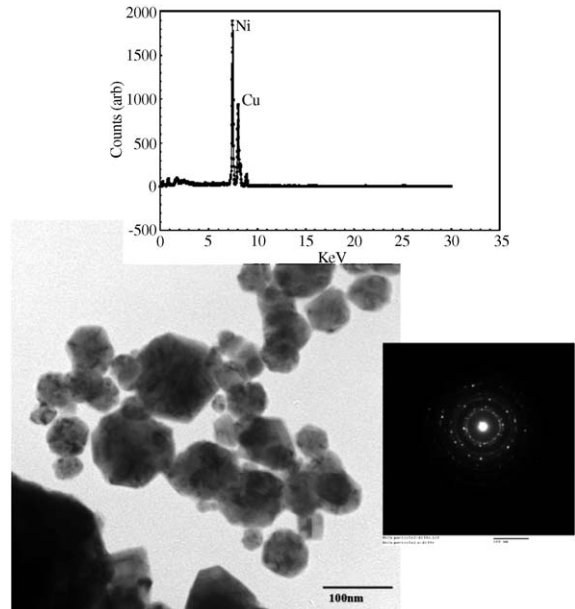


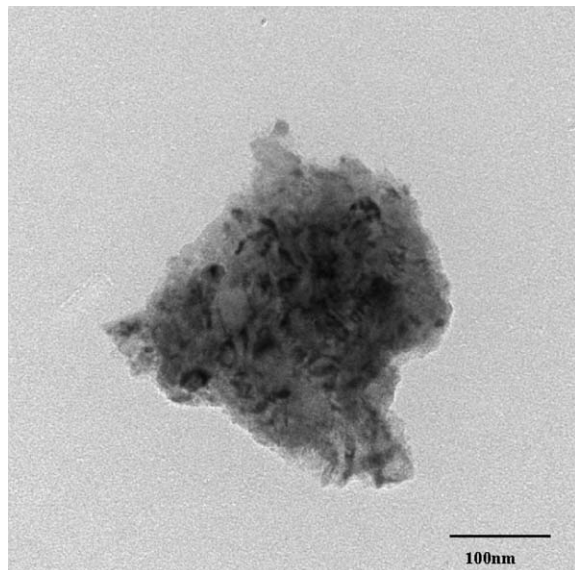Fig. 1. TEM micrograph, EDS and Electron Diffraction pattern for chemically synthesized Cu–Ni particles.



Fig. 2. TEM micrograph for physically synthesized Cu–Ni particles.

cles have more regular shapes and uniform sizes and their average size range is 50–80 nm (Fig. 1). Electron dispersive X-ray spectroscopy (EDS)

showed a composition of nickel and copper as 66% and 33% respectively which is very close to the composition started with and the electron diffraction pattern showed the polycrystalline nature of the particles.

Morphology of the polymer encapsulated particles is shown in Figs. 3 and 4. Fig. 3 shows the particles formed by chemical crosslinking and
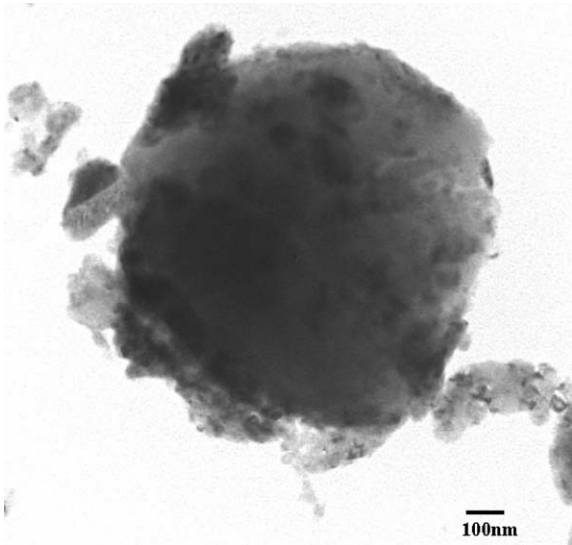


Fig. 5. Scanning Electron Micrograph for PEG encapsulated particles.



Fig. 3. TEM micrograph for polymer encapsulated particles formed by chemical crosslinking.
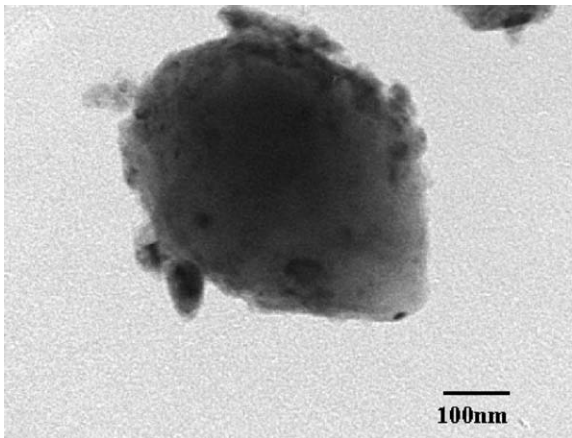


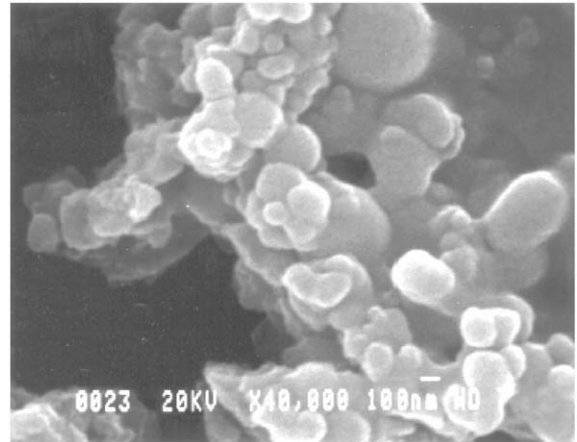Fig. 4. TEM micrograph for the polymer encapsulated particles formed by emulsion and crosslinking.

Fig. 4 shows particles formed by oil in water inverse emulsion and further crosslinking. In both methods some of the particles are formed as composites where Cu–Ni particles attached onto the polymer particles. First process of encapsulation which was simply done by chemical crosslinking has a larger tendency to form composite rather than encapsulated particles, whereas the other method mostly gave encapsulated spherical particles. The sizes of the encapsulated particles is in the range of 200–500 nm depending on the size of the pure alloy particles. Scanning electron micrographs of the encapsulated particles confirmed the particle size (Fig. 5).

### 3.2. Magnetic properties

Curie temperature ($T_c$) for both physically and chemically synthesized particles are measured. Both physically synthesized ballmilled particles (Cu–Ni = 30:70) and the same composition of the chemically synthesized particles showed a $T_c$ of 350 °K. Fig. 6 showed the combined plot for $T_c$ for both physically and chemically synthesized particles and for polymer encapsulated particles. Encapsulated particles showed $T_c$ in the desired range of 320–330 °K which is lower than the original $T_c$ for Cu–Ni alloy.
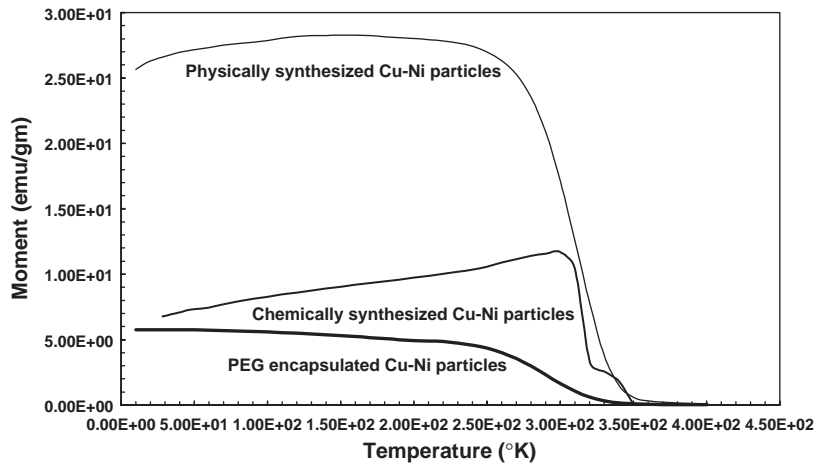
Fig. 6. Temperature vs. moment plot (combined) for metallic alloy and PEG encapsulated particles.
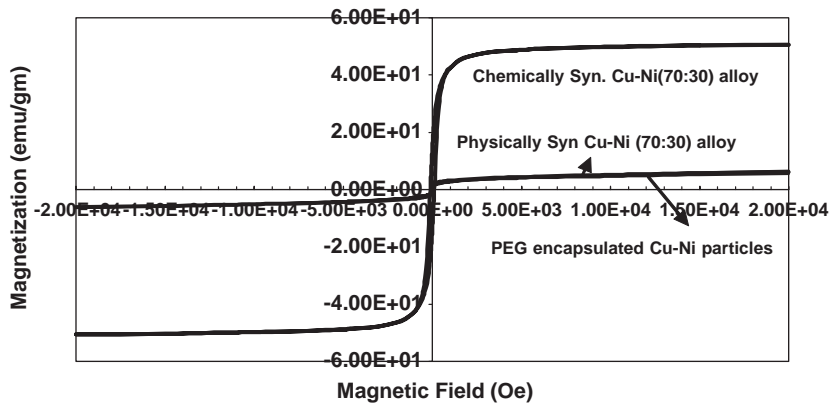
Fig. 7. Applied field vs. magnetization plot (combined) for pure alloy and for the encapsulated particles.

The particle magnetization was measured to optimize the range of external AC magnetic field to be used for their final application in hyperthermia. Fig. 7 shows the combined magnetization plot for pure alloy and polymer encapsulated particles (with physically synthesized alloy). The saturation magnetization is in the range of 6–8 emu/gm where as chemically synthesized alloy for the same composition (Cu:Ni = 30:70) showed a saturation magnetization of 45 emu/gm and the particles also showed superparamagnetic nature [12].

Polymer encapsulated particles showed a depression of melting point compared to the pure polymer as observed in Fig. 8. Melting point has been decreased by about $3°$ in the encapsulated particles ($T_m$, $43.8\,°C$) than that of the pure polymer ($T_m$, $46.8\,°C$). This depression of melting point has ensured the presence of Cu–Ni alloy particles in the pure polymer and it has been confirmed by the wide angle X-ray diffractogram. The WAXS pattern for the pure alloy and for encapsulated particles is shown in Fig. 9. The lattice planes remaining same ($2\Theta = 44.21$ and $55.24$) the diffractogram for encapsulated particles showed more amorphous nature compared to that of the pure alloy indicating the presence of polymer.
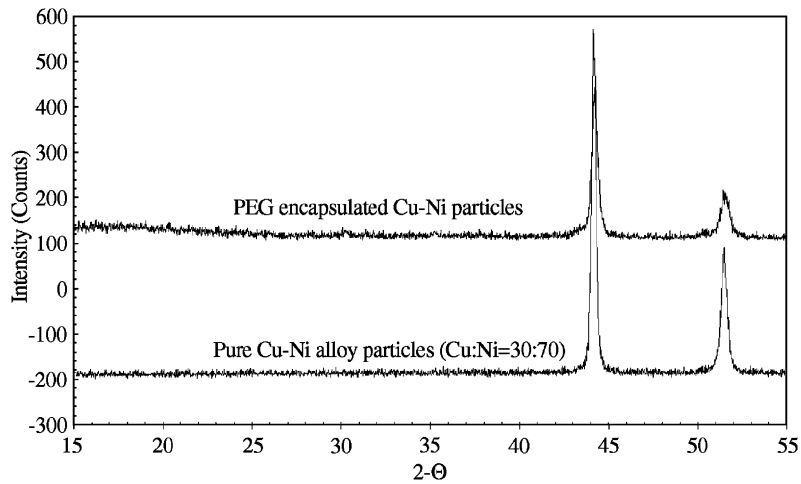
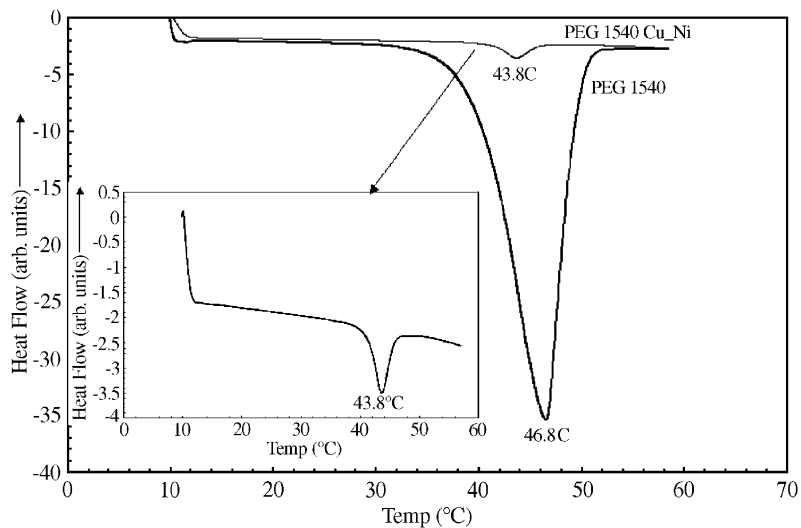Fig. 8. WAXS pattern for Cu–Ni alloy and for PEG encapsulated Cu–Ni particles.



Fig. 9. Temperature vs. heat flow for pure PEG and for PEG encapsulated particles.

## 4. Conclusion

Copper nickel alloy particles with desired composition are synthesized both by physical and chemical procedure. These alloy particles can be encapsulated by a biodegradable polymer by emulsion and chemical crosslinking processes. PEG encapsulated particles (in submicron range) have potential for use in hyperthermia treatment of cancer.

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