표적지향 약물전달을 위한 마그네타이트가 함유된 poly(ethylene glycol - b – ε caprolactone) nanoparticle의 제조

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Preparation of magnetite loaded poly(ethylene glycol-b-ε caprolactone) nanoparticles for targeted drug delivery

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Introduction

Magnetic polymer particles have been used extensively in several biomedical applications, such as magnetic cell separation, enzyme immunoassay, targeted drug delivery and diagnostics, etc. [1] Our goal is the preparation of magnetite-contained biodegradable polymer nanoparticles for tageted drug delivery system. In this study, magnetite-contained poly(ethylene glycol-b-ε caprolactone) nanoparticles were prepared by emulsion method. As a magnetic material, magnetite (Fe_3O_4) was used with low toxicity and well tolerance in the human body. Also, biodegradable polymer was used poly (ε-caprolactone) providing biodegradability, high biocompatibility, drug compatibility, and permeability. The magnetic particles coated with biodegradable polymer can make it possible to direct the particles to the specified location by means of external magnetic fields. [2] This, in turn, would reduce the side-effects of the drug because its level in the general circulation is lowered. The polymer coated around magnetite would play the roles of transporting the drug and releasing it during its biodegradation. Morphology, size as well as magnetite loading efficiency of prepared magnetic particles, were characterized to examine the possible use as a magnetic drug carrier.

Theory

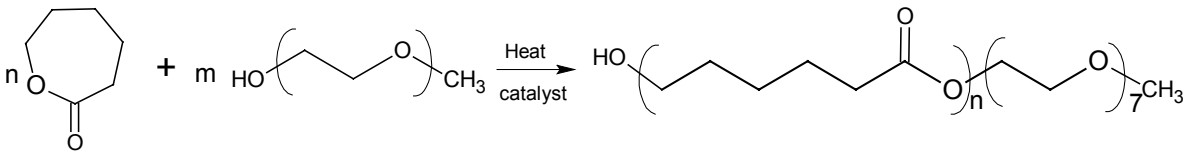
Magnetic nanoparticles that display high saturation magnetization and high magnetic susceptibility are of great interest for medical applications. Nanosized magnetite is particularly desirable because it displays strong ferrimagnetic behavior, and is less sensitive to oxidation than magnetic transition metals such as cobalt, iron, and nickel. For *in-vivo* applications, it is important that well-defined

organic coatings surround the nanomagnetite particles. It is rationalized that this will prevent any aggregation of the nanoparticles *in-vivo*, and may also enable efficient excretion and protection of the body from toxicity. [3]

The development of biodegradable drug-carrying nanoparticles provides a modality to continuously deliver the drug after administration of the particles. This procedure improves the efficiency of the therapeutical treatment by preserving the drug in its active form and by limiting its possible toxic effects.

Poly(ethylene glycol) (PEG)-coated nanoparticles have been developed over the past years since they showed great potential as long circulating systems after intravenous administration together with an ability to bypass natural barriers such as the nasal mucosa. [4] For example, the use of PEGylated copolymers (PEG-R), where R is a hydrophobic block copolymer could provide flexible EG spacers for ligand coupling to interact with its target. The ligand could be covalently linked to the block copolymer containing PEG segments prior to nanoparticle formation by nanodeposition or solvent evaporation. [5]

PEG modified block copolymers are synthesized by several methods, mainly polymerization in the melt, or in a solvent. The presence of a solvent reduces the polydispersity index (PI) compared to the melt. For example, PEGylated ε-caprolactone copolymer preparation showed in Fig. 1.



ε-caprolactone monomethoxy polyethylene glycol Diblock copolymer

Fig. 1 ε-caprolactone and polyethylene glycol copolymerization

Experiments

Nanosized magnetic particles were prepared by co-precipitation method. In detail, starting with initial molar ratio of Fe(III) / Fe(II) was set to 2 in round-bottom flask under nitrogen flow. Then, ammonia solution is added to the mixed solution dropwise for 30 min until pH reached 9 to 10. When reaction was over, product was decanted and washed to remove residues. To prepare oleic acid coated magnetic particle, magnetite was redispersed in water and heated to 80 °C. Then, oleic acid was added and reacted for 30 min with same temperature.

The ring opening polymerization of ε-caprolactone was initiated by the hydroxyl terminus of monomethoxy polyethylene glycol (MPEG), using stannous octanoate as a catalyst. The reaction was carried out under nitrogen flow for 4 h at 110 °C in 10 mL anhydrous toluene. The polymer was

finally precipitated in ether and dried under vacuum.

The magnetite contained polymer nanoparticles were prepared by emulsion polymerization method. Magnetite and polymer were dispersed and dissolved in organic phase and poly vinyl alcohol (PVA) as emulsifier was dissolved in aqueous phase. Then, two phases were mixed and sonicated. After the polymerization completed, the suspension of particles obtained was passed through the filter which has 0.45 ㎛ pore size. Free magnetite and surfactant were removed by repeated cycles of centrifugation. The magnetite contained polymer nanoparticles were dried at 35 °C in a vacuum oven and stored in desicator.

The morphology, size and structural properties of particles were carried out by transmission electron microscopy (TEM), dynamic light scattering (DLS), and IR spectroscopy. Also, the total magnetite concentration of particle was determined by UV spectroscopy.

Results & Discussions

Nanosized magnetic particles were obtained as shown in Fig. 2. The particle size of magnetite was about to 5 ~ 10 nm. Fig. 3 shows the infrared spectra of the three types of materials which are oleic acid, magnetite and oleic acid coated magnetite particles. IR spectra of iron oxides exhibit strong bands in the low-frequency region (1000 ~ 300 cm^{-1}) due to the iron oxide skeleton. Magnetite (Fe_3O_4) spectrum exhibits in 570 cm^{-1}. Noticeable band of oleic acid presence was observed in the spectrum of the oleic acid coated magnetic particles.

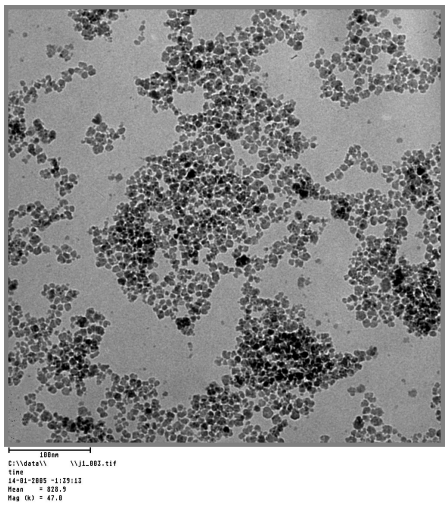


Fig. 2 TEM image of magnetic particle

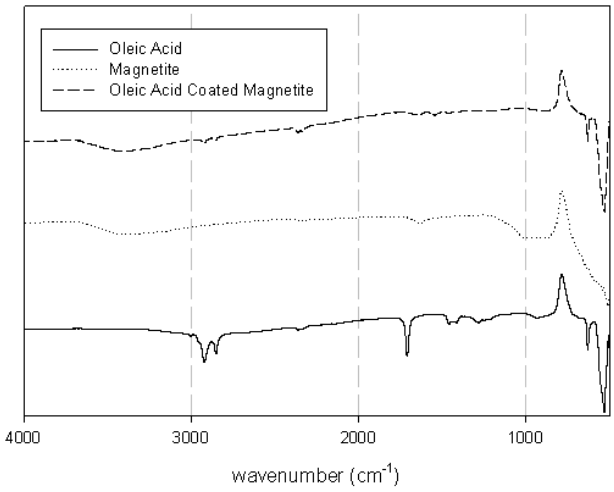


Fig. 3 Structural properties of magnetite, Oleic Acid, Oleic Acid Coated magnetite particles by IR spectroscopy

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