표적지향 약물전달을 위한 계면중합법에 의한 Magnetic Poly(ethyl-2-cyanoacrylate) Nanoparticles의 제조

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Preparation of Magnetic Poly(ethyl-2-cyanoacrylate) Nanoparticles containing Anticancer Drug by Interfacial Polymerization for Targeting

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Introduction

The main problems currently associated with systemic drug administration are : even biodistribution of pharmaceuticals throughout the body; the lack of drug specific affinity toward a pathological site; the necessity of a large total dose of a drug to achieve high local concentration; non-specific toxicity and other adverse side-effects due to high drug doses. Drug targeting, i.e. predominant drug accumulation in the target zone independently on the method and route of drug administration, may resolve many of these problems[1].

An interesting example of targeting drug delivery by external physical force is the magnetic drug targeting. For this purpose, the drug is immobilized on a particulate carrier possessing ferromagnetic properties. Magnetic drug targeting should be safe and effective, i.e. with the least amount of magnetic particles a maximum concentration of drug should be easily administered and transported to the site of choice under the action of external magnetic field. This, in turn, would reduce the side-effects of the drug because its levels in the general circulation are lowered[2].

In this study, magnetic poly(ethyl-2-cyanoacrylate) nanocapsules were prepared by interfacial polymerization for targeting. At this point, magnetic material was used magnetite(Fe_3O_4) with quite low toxicity (LD_{50} in rats : 400mg/kg) and well tolerance in the human body[3]. Also, biodegradable polymer was used poly(ethyl-2-cyanoacrylate) (PECA) with fast degradation rate, biodegradability, high biocompatibility, drug compatibility, and permeability. This would have the role of transporting the drug and releaseing it during its biodegradation. And this is a member of the polyalkylcyanoacrylates(PACA) family, which is considered of high interest because of the strong reactivity of the corresponding monomers, able to polymerize easily in various media including water[4].

Theory

Particles can be classified with two kinds by the form of small solids in paticles; spheres in which the small solids are dispersed throughout the particles, capsules in which the small

solids are confined to a central cavity surrounded by a membrane.

Magnetic PECA nanoparticles of the sphere form can be prepared by emulsion polymerization. During the preparation procedure, the drug may be dissolved and magnetite may be dispersed in the polymerization medium either before the addition of the monomer(incorporation method) or after completion of the polymerization process(adsorption method). In this way, the drug is entrapped in the biodegradable core of the nanospheres and/or adsorbed onto their surface[5].

The other form(capsules) can be obtained by interfacial polymerization of the cyanoacrylic monomers at the surface of the oil droplets dispersed on the aqueous phase. A drug can be encapsulated in the internal cavity of the polymerized membrane during the formation of the system provided that its oil-water partition coefficient is in favor of the oily phase. To obtained nanocapsules, a dynamic process must be created which brings the monomer to the oil-water interface. this transfers performed by the diffusion of a cosolvent from the organic phase to the aqueous phase. this cosolvent must be a solvent for the monomer and for the oil on one hand and miscible with the aqueous phase on the other hand[6].

The difference between nanospheres and nanocapsules lies not only in the morphology, body architecture and in drug disposition within the colloidal system but also release behaviour. theoretically, high-quality nanocapsules systems achieve a constant rate drug release(zero-order release), whereas a first-order drug release is typically observed in nanospheres[5].

The mechanism of PECA polymerization is an anionic process. This is interest because it is more rapid and easier to handle, thus suitable for biomedical applications furthermore, even very weak base, such as OH^- ion deriving from water dissociation, are capable to initiate the reaction. Propagation of the polymerization occurs after formation of carbanions that are ables to react with another monomer molecule leading to the formation of living polymer chains. Termination is due to the presence of a cation that leads to the end of the polymerization. Water is able to terminate the polymerization through the conjugate acid H_3O^+. Anionic polymerization leaves a polymer which consists an 'onium salt'[4].

Experiments

The magnetic PECA nanoparticles were prepared by interfacial polymerization method. A lipophilic phase, composed of 0.5ml Miglyol 812N, Rhodamine B, 0.0325g magnetite and 0.13ml monomer (ethyl-2-cyanoacrylate), was dissolved in 25ml organic solvent (acetone). This solution was slowly added to 50ml aqueous phase (pH 6-7) containing 10% w/v of a nonionic surfactant (Pluronic F-68). Polymerization occurred at the oil/water interface of the Miglyol 812N droplets. This system was kept under mechanical stirring (1000rpm) in order to achieve a fine emulsion and to polymerize the monomer around the oil droplets. The immediate polymerization achieved the formation of a nanocapsule colloidal suspension. This system was left at room temperature under continuous stirring until completion of polymerization process (3h). The colloidal suspension was then concentrated under vacuum, allowing the organic solvent to evaporate off. The final volume of nanocapsule suspension (12.5ml) was filtered through a sintered glass filter (9-15㎛). Free magnetite and surfactant were eliminated by repeated cycles of centrifugation at 15000rpm for 60min. The PECA magnetic nanoparticles were dried at 35℃ in a vacuum oven and stored in desicator.

The morphology, size, chemical structural properties of particles and magnetic property were

carried out by epi-fluorescence microscopy, dynamic light scattering(DLS), and IR spectroscopy, respectively.

Results & Discussions

Fig. 1. shows that the morphology of magnetic PECA nanoparticles by epi-fluorescence microscopy. According to figure, The formed particles were spherical shape and moderately homogenous size distribution. Dynamic light scattering(DLS) was used to determine the size of prepared magnetic PECA nanoparticles(Fig. 2.). The size and polydispersity of formed particles is 293.2nm and 0.084, respectively.

Fig. 3. shows magnetic property of magnetic PECA nanoparticles by epi-fluorescence microscopy. The particles did't move without magnetic field(a) but they move to magnet under magnetic field(b).

Fig 4. shows the infrared spectra of the three types of particles which is magnetite, PECA and magnetic PECA nanoparticles. IR spectra of iron oxides exhibit strong bands in the low-frequency region(1000-300cm^{-1}) due to the iron oxide skeleton. In other frequency regions, the spectra of iron oxide have weak bands. Especially magnetite(Fe_3O_4) spectrum exhibits in 570cm^{-1}. The main feature of this figure is the presence of the band of magnetite(570cm^{-1}) in the spectrum of the magnetic PECA nanoparticles.

Magnetic PECA nanoparticles prepared by interfacial polymerization method are monodisperse and their size is less than 300nm. Also, particles have a magnetic susceptibility under external magnetic field.

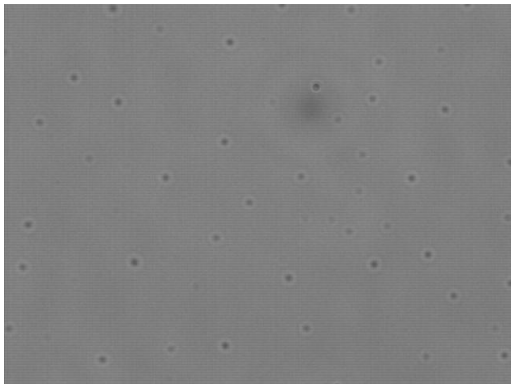
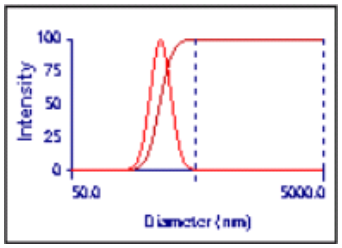


Fig. 1. Morphology of magnetic PECA nanoparticles by epi-fluorescence microscope (x2000)



size	293.2 nm
polydispersity	0.084

Fig. 2. Size and polydispersity of magnetic PECA nanoparticles by dynamic light scattering(DLS)

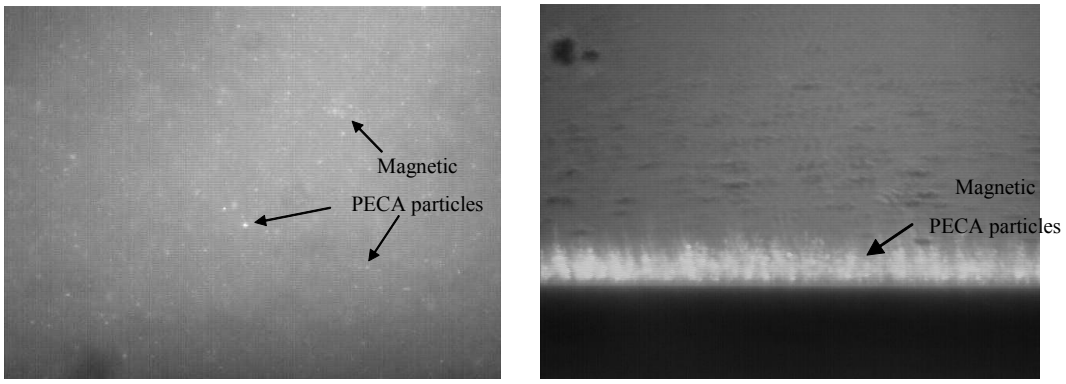


Fig. 3. Magnetic property of magnetic PECA nanoparticles (a)no magnetic field, (b)under magnetic field by epi-fluorescence microscopy.

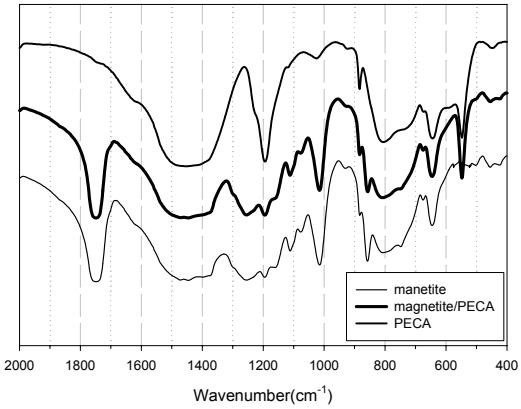


Fig. 4. Chemical structural properties of magnetite, PECA, magnetic PECA nanoparticles by IR spectroscopy.

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