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# Magnetite-poly(lactic-co-glycolic acid) hybrid particles: Preparation and viscoelastic properties

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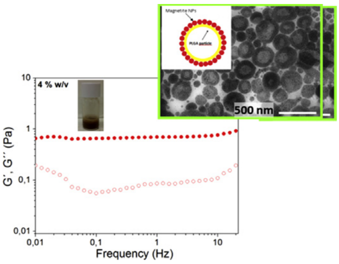
## HIGHLIGHTS

- Magnetite-PLGA particles have been synthesized by emulsion–evaporation method.
- Magnetite is incorporated on the surface of PLGA particles.
- Magnetite nanoparticles stabilize the O/W emulsion and yields smaller hybrid PLGA particles.
- Aqueous dispersions of magnetite-PLGA particles rheologically behave as weak networks.

## GRAPHICAL ABSTRACT



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## ABSTRACT

Magnetite-poly(lactic-co-glycolic acid) (PLGA) hybrid particles were prepared by an emulsion–evaporation method (O/W single emulsion) in which magnetite nanoparticles were dispersed in the aqueous phase. The morphology of the resulting samples was determined through scanning electron microscopy (SEM and FESEM) which revealed the formation of core–shell particles because of the incorporation of magnetite nanoparticles on the surface of PLGA particles. Magnetite-PLGA hybrid particles present a much lower particle size than blank PLGA particles prepared under the same experimental conditions due to the effect of stabilization of the magnetite nanoparticles during the formation of the O/W emulsion. The main focus of the paper is the determination of the viscoelastic properties of aqueous dispersions of magnetite-PLGA hybrid materials as a means to elucidate the influence of the presence of magnetite nanoparticles on the rheological behaviour of the dispersions. Results have shown that aqueous dispersions of pristine PLGA particles and magnetite-PLGA particles present a very weak gel structure and that the presence of magnetite nanoparticles does not result in the increase of the elastic modulus of their aqueous dispersions.

## 1. Introduction

The incorporation of inorganic nanoparticles in polymer particles allows the preparation of polymer-inorganic hybrid particles that can be tailored to present different physical properties and functionalities. These include self-assembly of particle chains [1], ionic fluid flow [2], enhanced mechanical properties in nanocomposites [3], magnetic [4] or optical properties [5]. In particular, extensive studies have been carried out on the preparation of polymer particles with embedded iron oxide nanoparticles, mainly magnetite and maghemite whose magnetic properties can be employed for the development of biomedical applications [6,7]. In this context, poly(lactic-co-glycolic acid) (PLGA), a copolymer of lactic and glycolid acid, offer advantages such as their biocompatibility and biodegradability to nontoxic metabolites as well as their approval by the US Food and Drug Administration (FDA) for human therapeutic uses [8–10]. The combination of the biodegradability of PLGA particles with the superparamagnetic properties of

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magnetite nanoparticles yields materials that can be employed for dual magnetically responsive drug delivery and diagnostic applications [11–13]. The preparation of magnetite-PLGA particles is commonly accomplished by a solvent extraction method in which an emulsion is prepared by adding an organic solution containing PLGA to an aqueous phase containing dispersed magnetite nanoparticles and a surfactant [14,15]. The extraction of the organic solvent can be achieved by simple evaporation [16] of by employing supercritical fluid extraction [17].

In spite of the vast information found in literature about the preparation and characterization of PLGA particles and magnetite-PLGA particles mainly regarding their use in biomedical applications, to the best of our knowledge, the viscoelastic properties of aqueous dispersions of PLGA particles have not been reported before. Oscillatory dynamic rheological measurements allow to determine changes in the structural organization of polymer particles in dispersion that cannot be detected by particle size analysis, as for example, long term physical stability [18]. In addition, the determination of viscoelastic properties yields information on the presence of interactions among particles and the elastic properties of the dispersion [19]. This information is relevant for the design of biomedical applications of aqueous dispersions of polymer particles [20]. Aqueous dispersions of polymer-inorganic hybrid particles might give rise to different viscoelastic properties than those corresponding to dispersions of blank polymer particles. For example, the incorporation of magnetite nanoparticles in microparticles of poly(acrylamide-acrylic acid) increases the interactions between them and this leads to the increase of the elastic modulus of the resulting aqueous dispersions [21]. Similar results have been obtained in the study of magnetite chitosan nanoparticles by means of oscillatory rheological measurements [7].

In this paper, a conventional emulsion–evaporation method (O/W single emulsion) was employed to prepare magnetite-PLGA hybrid particles. The organic phase concentration was varied in order to determine its influence on particle size, particle size distribution and final magnetite loading. Finally, we focused on the determination of the viscoelastic properties of aqueous dispersions of PLGA particles in order to elucidate the influence of the incorporation of magnetite nanoparticles on the rheological response of these materials.

## 2. Experimental

### 2.1. Materials

RESOMER® RG 504 poly(D,L-lactide-co-glycolide) 50:50 was purchased from Boehringer-Ingelheim, inherent viscosity 0.45–0.60 dl/g (0.1% (g/mL) in chloroform, 25 °C), and $M_w$: 38,000–54,000. Polyvinyl alcohol 89+% hydrolyzed (PVA) $M_w$: 31,000–50,000, magnetite nanoparticles (NPFe) dispersed at 10% (g/mL) in water were purchased from NANOGAP subnmparticles. Deionized water was purified by using a Milli-Q Plus purification system (Millipore Corp.). Chloroform and acetone were purchased from Carlo Erba Reactifs.

### 2.2. Preparation of PLGA particles by emulsion–evaporation method

PLGA particles and magnetite-PLGA hybrid particles were prepared by an O/W single emulsion with subsequent solvent evaporation as previously reported [16]. Briefly, 5 mL of the organic solution of PLGA in chloroform was slowly added to 50 mL of the aqueous phase with the surfactant, PVA, under mechanical stirring provided with an Ultraturrax. The agitation rate was set at 10,000 rpm. The emulsion was maintained under magnetic stirring at room temperature during 48 h to remove the organic solvent from droplets. The concentration of PVA in the aqueous phase was fixed at 1% (w/v) and two different concentrations of PLGA in the organic phase, 0.2% (w/v) and 2% (w/v), were employed. Particles were collected by centrifugation (Heraeus-Megafuge 1.0) and washed twice with distilled water to eliminate the excess of surfactant solution. Finally, washed particles were freeze-dried and stored at room temperature. Samples were denoted as 0.2PLGA and 2PLGA were numbers refer to the concentration of the PLGA in the organic phase.

For the preparation of magnetite-PLGA hybrid particles, 0.025 g of magnetite nanoparticles were added to the aqueous phase containing PVA at a 1% (w/v) which represents a concentration of magnetite nanoparticles of 0.05% (w/v). Samples were denoted as 0.2PLGA_NPFe and 2PLGA_NPFe were the numbers refer the concentration of PLGA in the organic phase.

### 2.3. Characterization

#### 2.3.1. Morphology

The morphology of the PLGA particles was studied with a Scanning Electron Microscope (SEM, XL30 Philips). For visualization of PLGA particles with magnetite nanoparticles, a Field Emission Scanning Electron Microscope (FESEM Hitachi model SU8000) operating at 25–30 kV with TE detector (FESEM-TE) was employed. Each sample was dispersed in distilled water at 0.1 mg/mL and a drop of the sample was deposited onto a cover glass was dried overnight at room temperature and gold coated in a Sputter Coater (Au–Pd) – Polaron SC7640. The cover glass was kept at room temperature during 24 h to dry the sample by evaporation of the water. Subsequently, the dried sample was coated with an ultrathin coating of gold deposited on the sample by high-vacuum metallization.

The mean diameter size and the polydispersity of the particles were obtained from the analysis of SEM and FESEM images using Image J software. The polydispersity of particles was determined as the coefficient of variance, CV. CV (%) = $(\sigma/D) \times 100$ where $\sigma$ is the standard deviation of the particles size and $D$ is the mean diameter of particles.

#### 2.3.2. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was carried out on a TA-TGA Q500 analyzer under nitrogen atmosphere at flow of 60 mL/min, using platinum pans where approximately 5 mg of each sample was deposited. The samples were heated from 20 °C to 800 °C at 10 °C/min.

#### 2.3.3. Rheological characterization

Rheological studies were performed using the AR-G2 TA Instruments stress controlled oscillatory rheometer. Freeze-dried PLGA and PLGA_NPFe particles were dispersed in distilled water at a fixed concentration of 0.5, 2 and 4% (w/v). The geometry used was 60 mm acrylic parallel plate. The gap employed for the rheological measurements was maintained at 60 μm. Two types of experiments were carried out: strain sweep tests ranging from 0.01 and 1000% strain at 0.5 Hz frequency to detect the linear viscoelastic regime and frequency sweeps between 0.01 and 10 Hz at $\gamma$ (%) within the linear viscoelastic regime. All experiments were performed at $T = 20\,^{\circ}\mathrm{C}$. Each measurement was performed three times on different samples from the same synthesis to ensure reproducibility.

## 3. Results and discussion

### 3.1. Particle size and particle size distribution

The effect of the concentration of PLGA in the organic phase and the incorporation of magnetite nanoparticles on the size and