

## Regular Article

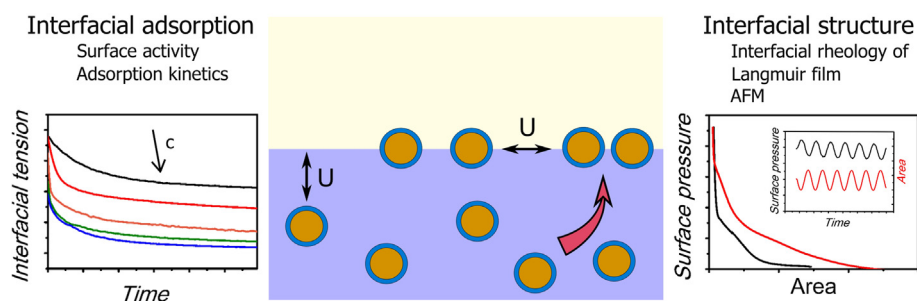
## Interaction of poly(lactic-co-glycolic acid) nanoparticles at fluid interfaces



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## GRAPHICAL ABSTRACT



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## ABSTRACT

**Hypothesis:** Adsorption and localization of nanoparticles at fluid interfaces are key factors in processes like transport through membranes or emulsion stabilization. Adsorption of poly(lactic-co-glycolic acid) (PLGA) and Pluronic coated PLGA nanoparticles (NPs) were studied at three different fluid interfaces. The effect of particle surface modification and type of interface was investigated with the aim of fine tuning interfacial interaction of the nanoparticles.

**Experiments:** Surface tension measurements were carried out to determine the surface activity and adsorption kinetics of the particles. Particles layers at the air/water interface were further studied using the Langmuir balance technique by recording the surface pressure–area isotherms. Interfacial rheological measurements were performed to characterize the structural properties of the nanoparticle interfacial films.

**Findings:** Interfacial adsorption and its kinetics were explained by the diffusion controlled adsorption theory and considering the energy barrier of particle transport to the interface. Surface modification by Pluronic increased the interfacial activity of nanoparticles at all interfaces. Surface activity of PLGA-Pluronic particles could be described by the contributions of both the PLGA NPs and the effective portion of their Pluronic shell. Both particle films present mainly elastic dilatational properties suggesting that particles are in kinetically separated state.

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## 1. Introduction

Accumulation of nanoparticles at fluid or solid interfaces has great influence on their applicability in various fields of technology [1]. The self-assembly of particles at fluid interfaces have been investigated to create nanoporous membranes [2] and the

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fabrication of surface coatings with tuneable electrical, optical properties [3,4]. The adsorption layer of nanoparticles at fluid interfaces are used for the stabilization of emulsions and foams in the cosmetic, pharmaceutical and metallurgy fields [5–8] as well as flotation of minerals [9]. Hydrophobic silica nanoparticles [10] and various types of polymeric microgels [11–13] have shown great potential as stabilizers of Pickering emulsions. More recently biodegradable polymeric nanoparticles have been investigated as biocompatible alternatives for these materials to be used as stabilizer for medical emulsions [14].

Poly(lactic-co-glycolic acid) (PLGA) nano- and microparticles have been described as convenient platforms to carry drug molecules in the body [15–17]. Surface modification of these biodegradable particles with polyethylene oxide containing molecules has been shown to increase the biocompatibility of these systems [18–21]. Interfacial interactions play an essential role in drug delivery as drug carrier particles have to pass several interfaces in the body before they reach the site of action. The knowledge how these particle systems interact with various fluid and fluid-solid interfaces is crucial in the rational design of new therapeutic methods.

The behavior of particles at fluid interfaces was investigated in recent works to get information on the emulsion stabilizing properties. These studies mainly focus on the systems like soft microgels [11,22], micrometer scaled solid particles [23] or small inorganic nanoparticles [24,25].

In the present study biocompatible PLGA nanoparticles (NPs) in the size range of 100–200 nm designed for drug delivery were studied. A comparative investigation was carried out to analyze the effect of a polymeric surfactant surface modifier on the interfacial properties and interactions of the particles at three interfaces, air/water, *n*-octane/water and 1-octanol/water representing a series of interfaces between phases of different polarities. The above interfaces are considered as simple, well defined models of biointerfaces allowing the usage of physicochemical methods to follow the adsorption and interfacial interactions.

## 2. Experimental

### 2.1. Materials

Poly(dl-lactic-co-glycolic acid), PLGA with 50% of lactic and 50% of glycolic content ( $M_w$ : 50,000–75,000), was obtained from Sigma-Aldrich, Hungary. Poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide), PEO-PPO-PEO triblock copolymer, Pluronic F127 ( $M_w$ : 12,700) (provided by BASF Hungaria Kft.), was applied as received. The composition of the Pluronic 127 is on average 202 EO units and 56 PO units according to the manufacturer.

All organic solvent were of analytical grade. Acetone was used in the preparation of nanoparticles. Dichloromethane was used for cleaning the Langmuir trough and its barriers. Aqueous sols of NPs were mixed with 2-propanol for the spreading on the aqueous surface. *n*-octane and 1-octanol were equilibrated with water for one day prior interfacial tension measurements.

Doubly distilled water checked by its conductivity (<5 mS) and surface tension (>72.0 mN/m at  $25 \pm 0.5$  °C) was used as medium for aqueous solutions and as the subphase in the Langmuir balance experiments.

### 2.2. Preparation and characterization of PLGA nanoparticles

PLGA nanoparticles with a narrow size distribution were prepared using the nanoprecipitation method as described previously

[26,27]. Briefly PLGA was dissolved in acetone at a concentration of 10 g/L. 5 mL of the organic solution was added dropwise to either 50 mL of pure water or 50 mL of 1 g/L Pluronic F127 aqueous solution under magnetic stirring (500 rpm) to create pure PLGA or Pluronic stabilized PLGA NPs. After the complete evaporation of acetone PLGA sol was centrifuged at 3500g for 10 min to remove possible particle aggregates. The supernatant, containing the nanoparticles, was separated and concentrated to a final volume of 5 mL by membrane filtering. Pluronic stabilized NPs were further purified by centrifugation at 12000g for 20 min. The supernatant was removed and the pellet containing the particles was redispersed in bidistilled water. This purification procedure was repeated 4 times, when the surface tension of the supernatant was >72 mN/m. The mass concentration of the sols was determined by dry mass measurement.

Average hydrodynamic size and polydispersity of the PLGA NPs were determined using a dynamic light scattering (DLS) system (Brookhaven Instruments, USA) consisting of a BI-200SM goniometer and a BI-9000AT digital autocorrelator. As a light source a Coherent Genesis MX488-1000STM laser-diode system operating at 488 nm wavelength and emitting vertically polarized light was used. Measurements were carried out at a detection angle of 90° and a temperature of 25 °C with nanoparticle sample appropriately diluted with doubly distilled water. The recorded autocorrelation functions were analyzed by the second order cumulant expansion and Contin method.

### 2.3. Zeta potential measurement

The determination of electrophoretic mobility of nanoparticles was carried out by means of Malvern Zetasizer Nano Z apparatus at 25 °C. For calculations the zeta potential of octane/water and octanol/water emulsions were also determined. Oil droplets were formed according to the method described by Marinova et al. [28]. The oil and water were added to a glass container that was heated to 60 °C for 1 h while the solvents were stirred gently. Samples were taken from the aqueous phase that became cloudy upon cooling to 25 °C indicating the formation of oil droplets from the oversaturated solution. Measurements were carried out immediately. Smoluchowski approximation was used to calculate zeta potential ( $\zeta$ ) from mobility values. Results were collected in triplicates, the  $\zeta$  values were reproducible to  $\pm 1$  mV.

### 2.4. Surface activity of nanoparticles

Adsorption of nanoparticles at fluid interfaces was monitored through the measurement of surface/interfacial tension [29]. Axisymmetric drop shape analysis of droplets of the aqueous sols was carried out in an OCA15+ (Dataphysics, Germany) optical contour analysis instrument. 10  $\mu$ L droplets were created in air, octane or 1-octanol outer phases, at 25 °C. The octane and octanol media were presaturated with water. Surface and interfacial tension values were followed for 1 h at various sol concentrations in the range of 0.25–4 g/L. The measurement time was limited to 1 h to allow the particles to approach their equilibrium surface tension but decrease the risk of possible trace contaminants influencing the measured values. Three parallel measurements were carried out for all systems and surface tension values were reproducible to  $\pm 0.5$  mN/m.

### 2.5. Langmuir monolayer studies

Monolayer studies of the NPs were performed in a Langmuir trough, KSV MiniMicro ( $5 \times 20 \times 0.6$  cm<sup>3</sup>) with two moving

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