

Development of magneticresponsive poly(ϵ -caprolactone) nanoparticles with potential applications in advanced cancer therapeutics

Fátima Fernández-Álvarez *, Laura Marín-Gil, Ana Medina-Moreno and José L. Arias

1 Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, Granada, Spain.

2 Institute of Biopathology and Regenerative Medicine (IBIMER), Center of Biomedical Research (CIBM), University of Granada, Granada, Spain

3 Biosanitary Research Institute of Granada (ibs.GRANADA), Andalusian Health Service (SAS), University of Granada, Granada, Spain

INTRODUCTION & AIM

Cancer continues to be a major global health challenge and remains one of the leading causes of mortality. Early diagnosis and targeted treatment are essential, but often limited by insufficient precision and specificity. In this context, pharmaceutical nanotechnology has emerged as a promising field, offering significant advances in cancer diagnostics and therapy. Among the nanomaterials being investigated, iron oxides have garnered considerable interest due to their favorable magnetic properties and versatile biomedical applications.

The aim of this work was to define a reproducible procedure to formulate haemocompatible maghemite/poly(ϵ -caprolactone) (γ -Fe₂O₃/PCL) nanoparticles (NPs) with potential applications against cancer.

METHOD

Nanoparticle preparation

- Preparation of Fe₃O₄ particles by chemical co-precipitation and oxidation into γ -Fe₂O₃.
- γ -Fe₂O₃/PCL particles were prepared by emulsion/solvent evaporation.

Physicochemical characterization

Particle size and surface electrical charge were characterized by *photon correlation spectroscopy* and *electrophoresis*, respectively

Magnetic responsiveness of the particles were evaluated through visual analysis at two levels: **macroscopic** and **microscopic**.

Blood compatibility assays

The colloids were kept in contact with blood aliquots to evaluate their impact on **erythrocytes**, **coagulation**, and the **complement system**.
It was followed a previously described procedure appropriate to nanopharmaceutics.

Hyperthermia capacity evaluation

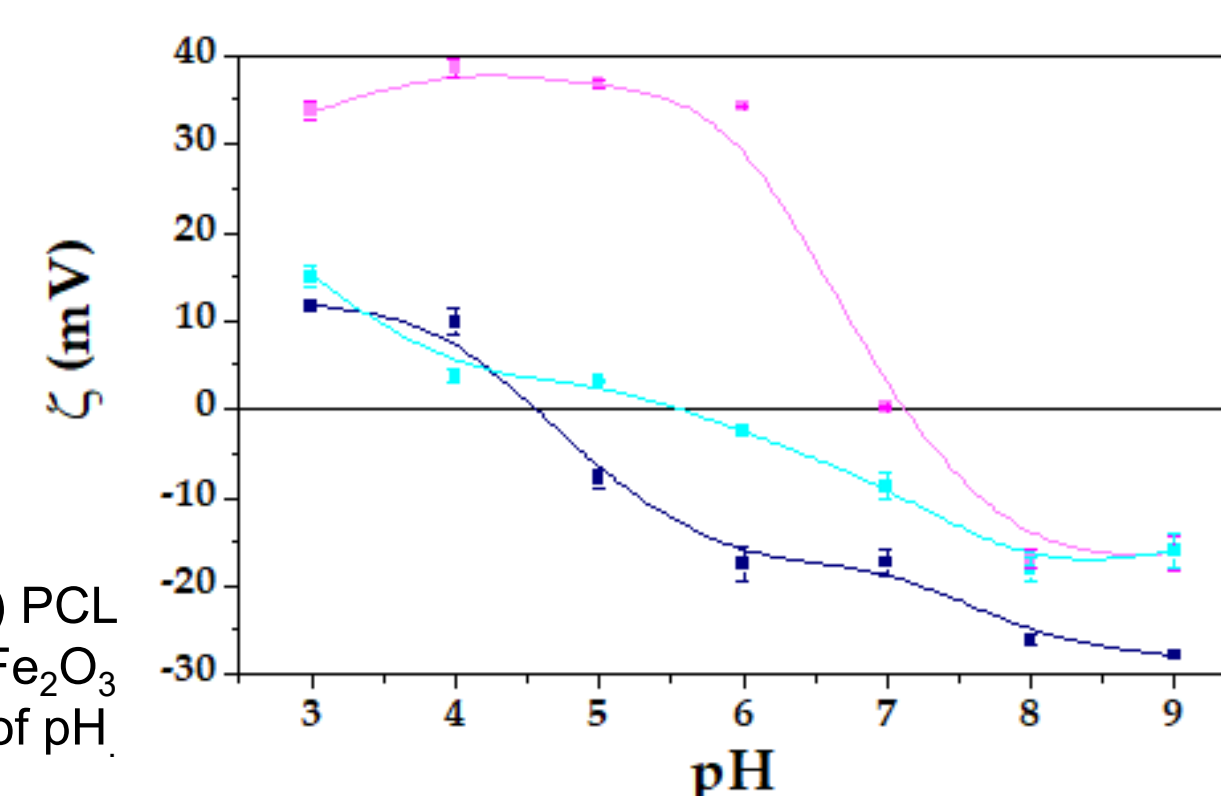
The *in vitro* heating behaviour of a nanoparticles dispersion at 20 °C was evaluated under **four alternating magnetic field** conditions with variations in **intensity** and **frequency**.
The temperature increase was measured using high-resolution sensors.

RESULTS & DISCUSSION

1 The γ -Fe₂O₃/PCL nanocomposites were in the **colloidal range** (370 ± 30 nm).

2 Electrokinetic analysis confirmed the **successful formation of the core/shell structure** (Figure 1).

Figure 1. Zeta potential (ζ , mV) of (■) PCL NPs, (■) γ -Fe₂O₃ NPs, and (■) γ -Fe₂O₃/PCL NPs as a function of pH.



3 Negligible effect of NPs on haemolysis, platelet activation (sP-selectin release), complement system activation (C3a desArg), and plasma clotting time ($T_{1/2 \text{ max}}$) (Table 1).

Sample	Haemolysis (%)		sP-selectin release (ng/mL)	C3a desArg (ng/mL)	$T_{1/2 \text{ max}}$ (min)
	Incubation time				
	4 h	48 h			
γ -Fe ₂ O ₃ /PCL	1.1 \pm 0.6	1.2 \pm 0.5	104 \pm 2	317 \pm 9	11.8 \pm 1.9
Control (PBS solution)	0	0	103 \pm 3	303 \pm 6	10.2 \pm 2.7

Table 1. Ex vivo blood compatibility of the γ -Fe₂O₃/PCL NPs.

4 In addition, the nanohybrids demonstrated **favorable magnetic responsiveness** (Figure 2) and **heating capacity** (Figure 3). The experiment showed ΔT^a above 38 °C depending on the applied frequency. This suggests that, starting from 37 °C, minimum antitumour hyperthermia temperature ($\approx 41^\circ\text{C}$) could be easily reached. It was confirmed that the exposure time depends on the frequency.

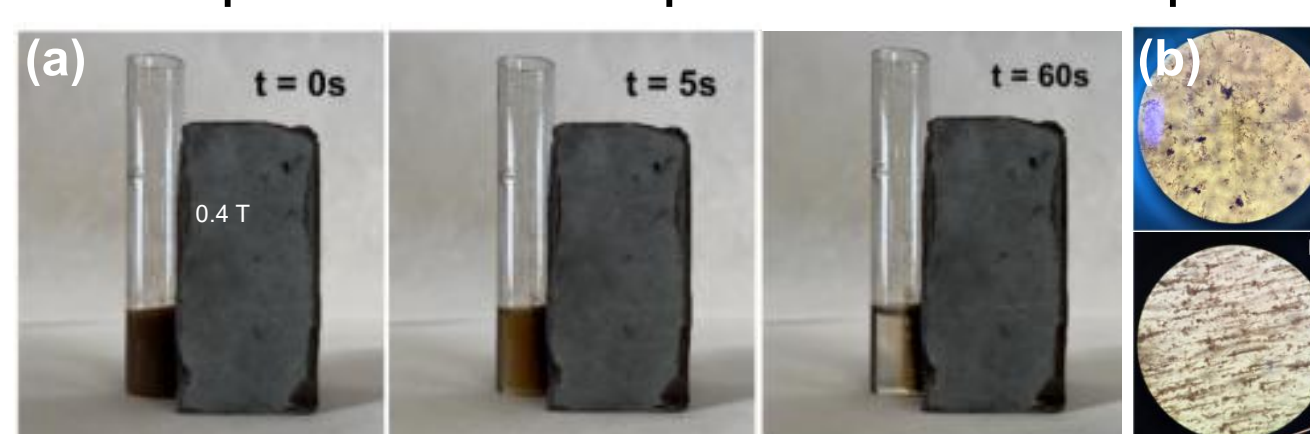


Figure 2. Macroscopic (a) and microscopic (b) visual analysis of the magnetic responsiveness of NPs exposed to a static (a) and moving (b) magnet.

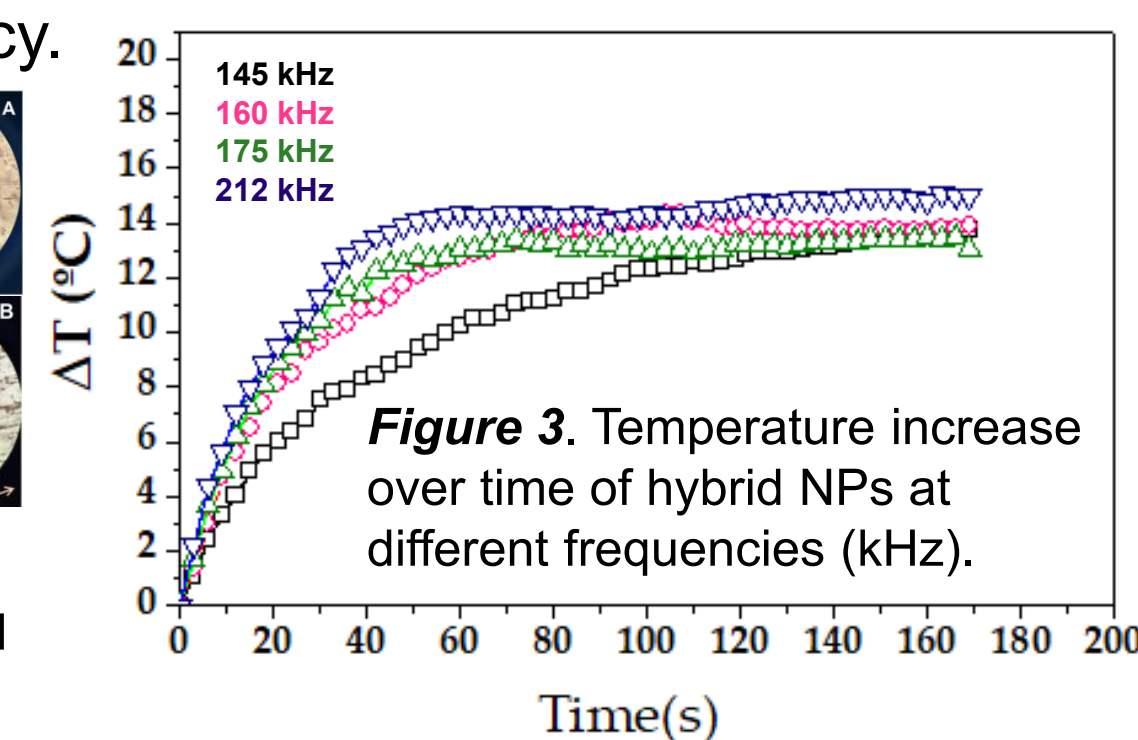


Figure 3. Temperature increase over time of hybrid NPs at different frequencies (kHz).

CONCLUSION

The γ -Fe₂O₃/PCL nanohybrids may enable magnetic-driven accumulation into the site of action and, probably, multifunctional capabilities for cancer therapy.

REFERENCES

- García-García, G., Caro, C., Fernández-Álvarez, F., García-Martín, M. L., & Arias, J. L. (2023). *Nanomedicine: Nanotechnology, Biology and Medicine*, 52, 102695.
- Fernández-Álvarez, F., Caro, C., García-García, G., García-Martín, M. L., & Arias, J. L. (2021). *Journal of Materials Chemistry B*, 9(24), 4963–4980.

BioRender®