Beyond traditional methods: the versatility of microfluidic for the synthesis of drug delivery devices

S. Gimondi[1,2], D. Mendanha[1,2], C. Guimarães[1,2], R. L. Reis[1,2], H. Ferreira[1,2], N. M. Neves[1,2]

[1] 3B's Research Group, I3Bs – Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, AvePark, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, 4805-017 Barco, Guimarães, Portugal;

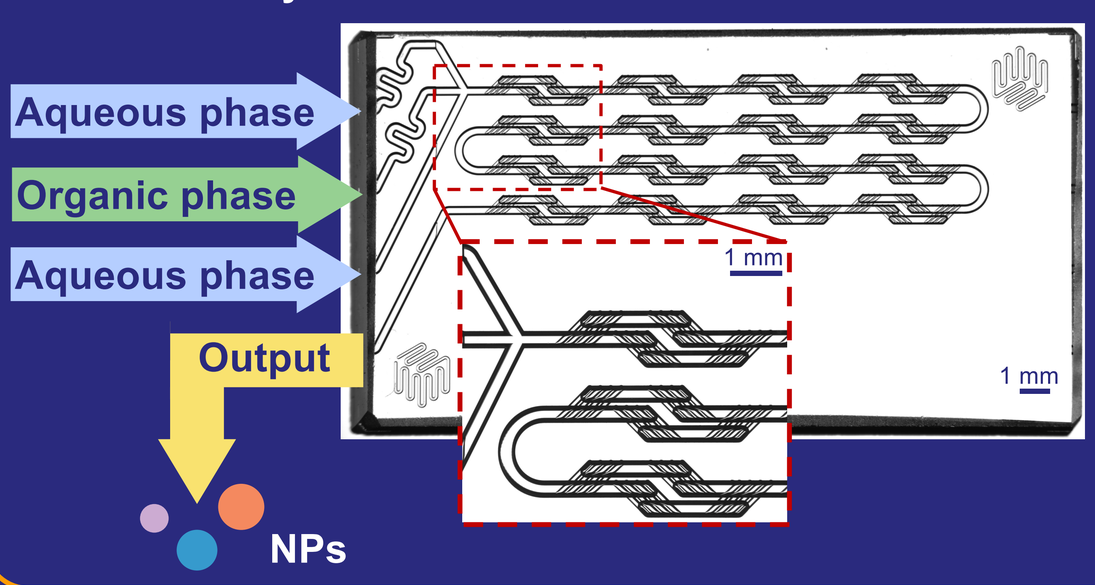
[2] ICVS/3B's–PT Government Associate Laboratory, Braga/Guimarães, Portugal;

INTRODUCTION

Traditional nanoparticles (NPs) synthesis methods often suffer from limited reproducibility, scalability, and control over physicochemical properties. Microfluidic technology presents an unconventional alternative, enabling the rapid, precise, and tuneable synthesis of NPs with well-defined characteristics. Here, we demonstrate the versatility of a novel herringbone-architecture microfluidic platform for the synthesis of diverse NP types, including polymeric, polysaccharide-based, and lipidic NPs such as large unilamellar liposomes (LUVs). We further highlight their impact on drug delivery for cancer and inflammation treatment.

MATERIALS AND METHODS

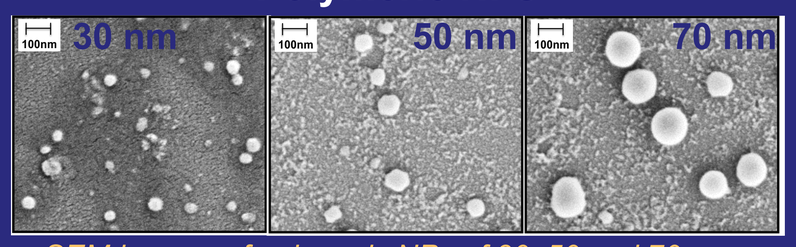
Microfluidic synthesis of NPs via micromixer device



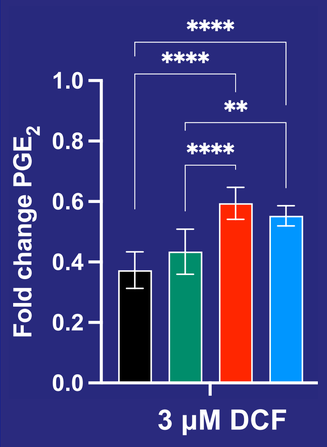


RESULTS AND DISCUSSION

Polymeric NPs

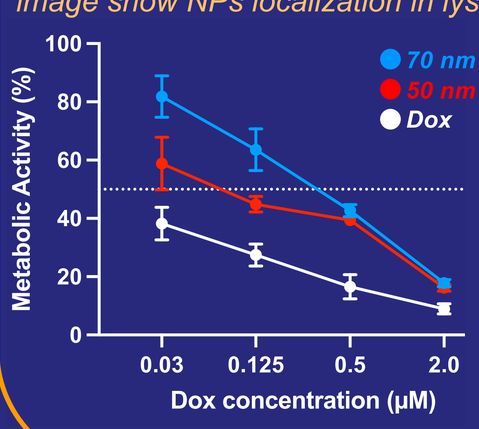


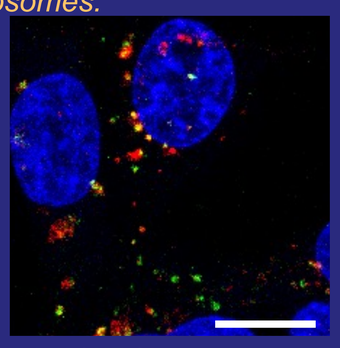
SEM images of polymeric NPs of 30, 50 and 70 nm



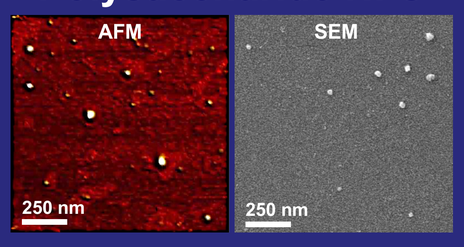
Human macrophages were treated with NPs of 30, 50, and 70 nm loaded with diclofenac (DCF) or with free DCF. The graph shows the reduction in prostaglandin E_2 (PGE_2) production.

Human breast cancer cells were treated with 50, and 70 nm doxorubicin (Dox)-loaded NPs or free Dox. Graph shows size-dependent reduced cell viability. Confocal image show NPs localization in lysosomes.

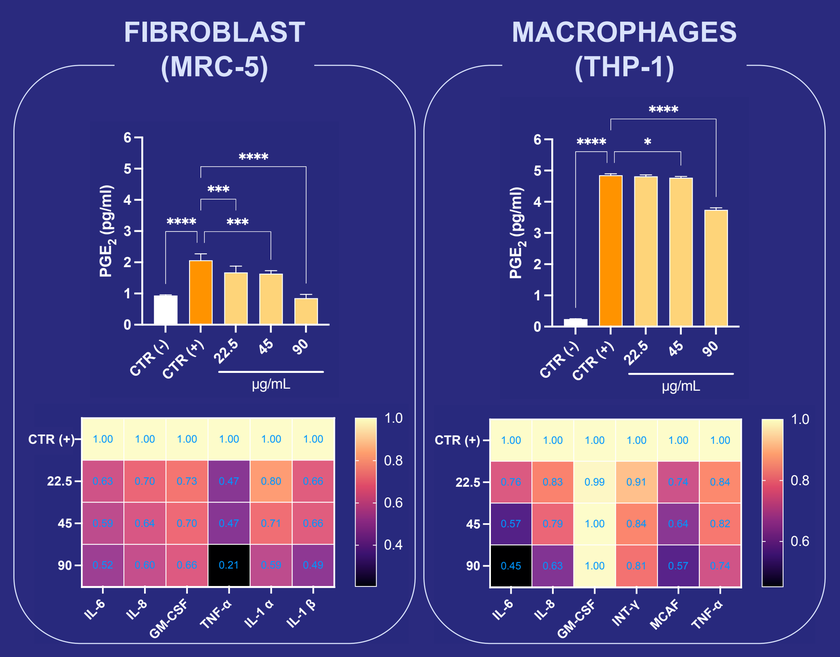




Polysaccharide NPs

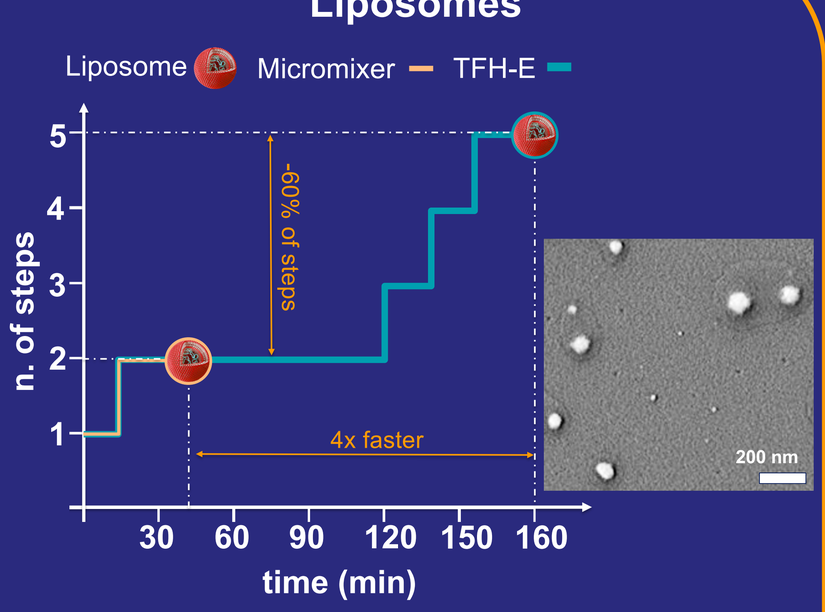


AFM and SEM images of chitosan and high molecular weight (HMW) hyaluronic acid (1.3 MDa) polyelectrolyte complex NPs.
***Size:** 113.1 nm; **PDI:** 0.15; **Zeta potential**: +20.7 mV.*

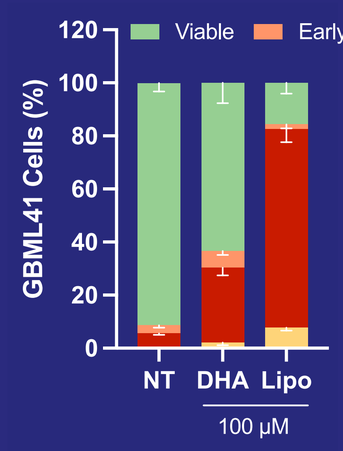


LPS-stimulated macrophages and fibroblasts exposed to a pro-inflammatory cytokine-enriched medium were treated with NPs to evaluate the native anti-inflammatory potential of high molecular weight hyaluronic acid. The modulation of the inflammatory response was quantified by ELISA.

Liposomes



Schematic comparison of liposome production methods: microfluidic-assisted synthesis versus conventional thin-film hydration and extrusion (THF-E). On the right, SEM micrograph of docosahexaenoic acid (DHA)–loaded liposomes produced by the microfluidic approach.
***Size:** 127 nm; **PDI:** 0.15; **Zeta potential**: -25 mV.*



Glioblastoma cells were treated with either free DHA or DHA encapsulated in liposomes. Flow cytometry (FACS) analysis shows the distribution of viable, early apoptotic, late apoptotic, and necrotic cell populations, demonstrating the enhanced efficacy of DHA when delivered via liposomal formulation.

CONCLUSIONS

Microfluidic technology successfully enabled the synthesis of various NP types, including polymeric, polysaccharide-based, and lipidic NPs. For liposome synthesis, the microfluidic approach significantly simplified production, reducing processing time and complexity. By overcoming the limitations of conventional techniques, this method allows precise tailoring of NPs to meet specific biological needs. Its adaptability to diverse materials positions microfluidics as a highly versatile tool for nanomedicine applications.

*This work was also supported by FCT through the Sara Gimondi Individual Scientific Employment Stimulus grant (**https://doi.org/10.54499/2023.06754.CEECIND/CP2841/CT0014**), the LA ICVS/3B's (**LA/P/0050/2020**). and the project "TERM RES Hub – Scientific Infrastructure for Tissue Engineering and Regenerative Medicine" (**PINFRA/22190/2016, Norte-01-0145-FEDER-022190**)*