Maslinic Acid Nanoparticles: a drug to carry others

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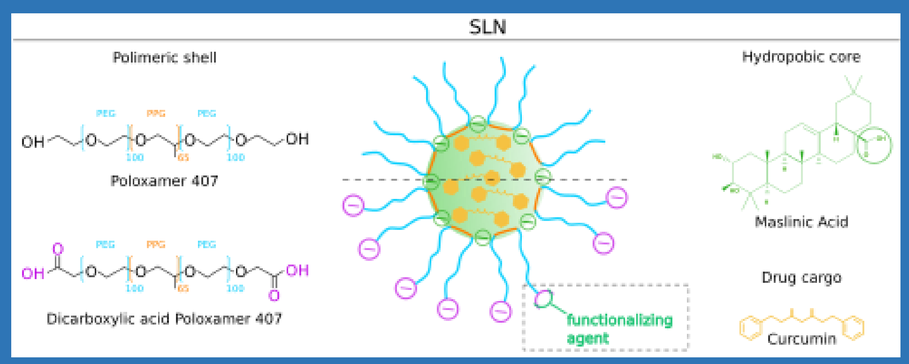
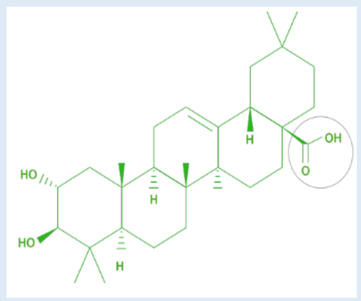
Maslinic acid is a potent antitumor agent, but its insolubility in water has limited its therapeutic use. By creating nanoparticles, Maslinic Acid can be solubilized by a factor of a million and, in addition, a novel hydrophobic drug transporter nanosystem with inherent therapeutic efficacy is generated.



Introduction

Maslinic Acid (MA), is a gaining interest molecule due to its multiple therapeutic potentials and **lack of harmful effects**. Strong evidence reinforces its potential as an **anticarcinogenic agent**. It can be extracted in large amounts and by an **economic** method from olive oil milling byproducts.



MA is practically **insoluble** in water. Its solubility in aqueous solutions is 3,6 µg/L. To solve this limitation, we developed **MA-based Solid Lipid Nanoparticles (SLNs)** by a modified solvent-displacement method. Two types of particles were prepared by using two types of poloxamers: P407, and a synthesized terminal carboxylated P407-C; namely, PMA, and PCMA SLNs.

Methods

MA SLNs were prepared by adapting a **solvent-displacement method**. Particle hydrodynamic diameter (D_H), polydispersity index (PDI) and ζ-potential were determined by dynamic light scattering (DLS). Measurements were performed on a Zetasizer Nano-S system (Malvern Instruments, UK).

The morphological characterization of MA SLNs was performed by Transmission Electron Microscopy (**TEM**) and Scanning Electron Microscopy (**SEM**).

Ionic strength and pH effect were evaluated by titration experiments, performed using the Malvern MPT-2 **Autotitrator**.

Results

D_H, PDI and ζ-potential and morphology

SLNs have an adequate D_H, are highly monodisperse, and have negative ζ-potential values (Table 1). SEM and TEM micrographs (Figure 1) revealed that particles are spherical or near spherical in shape

Table 1. D_H, PDI and ζ-potential of PMA and PCMA SLNs at pH 7.

	D_H (nm, mean ± SD)	PDI (mean ± SD)	ζ-potential (mV, mean ± SD)
PCMA	133 ± 3	0.13 ± 0.04	-20.2 ± 1.1
PMA	133 ± 3	0.10 ± 0.02	-6.5 ± 0.6

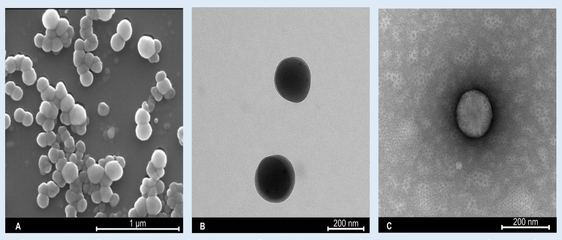


Figure 1. A) SEM visualization of MA SLNs, B) TEM micrographs without staining samples and C) with negative stained samples.

Synthesis Optimization

❑ Effect of the organic phase composition

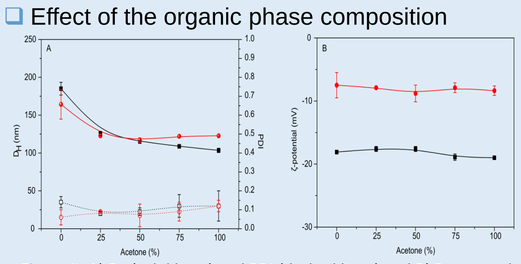


Figure 2. A) D_H (solid lines) and PDI (dashed lines) and B) ζ-potential of PCMA (black squares) and PMA (red circles) as function of the acetone proportion included in the organic phase.

❑ Effect of the MA:Poloxamer ratio

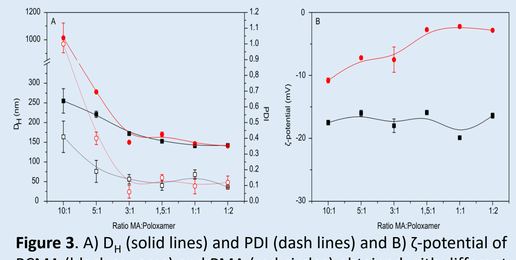


Figure 3. A) D_H (solid lines) and PDI (dash lines) and B) ζ-potential of PCMA (black squares) and PMA (red circles) obtained with different MA:Poloxamer ratios.

Colloidal Stability

❑ Effect of the ionic strength

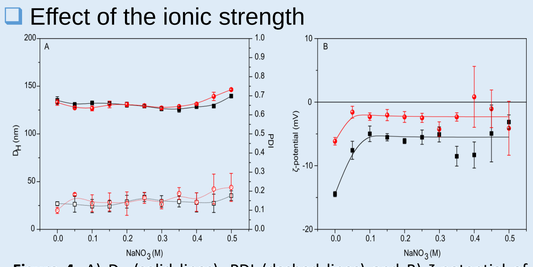


Figure 4. A) D_H (solid lines), PDI (dashed lines) and B) ζ-potential of PCMA (black) and PMA (red) at different $NaNO_3$ concentrations.

❑ Effect of the pH

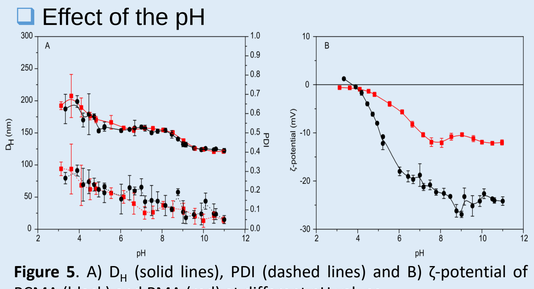


Figure 5. A) D_H (solid lines), PDI (dashed lines) and B) ζ-potential of PCMA (black) and PMA (red) at different pH values.

Curcumin entrapment

Formulations presented the following curcumin Encapsulation Efficiency (EE) and Drug Loading (DL), respectively:

86 ± 4 % and **5.6 ± 0.3 %** for PCMA-Cur
93 ± 2 % and **6.1 ± 0.2 %** for PMA-Cur

The incorporation of curcumin had no negative effect on the colloidal properties of SLNs.

Table 2. Curcumin retention in PCMA-cur and PMA-cur, expressed as the EE, over time.

Time (days)	PCMA-Cur EE (%, mean ± SD)	PMA-Cur EE (%, mean ± SD)
0	**86 ± 4**	**93 ± 2**
1	**77 ± 1**	**86 ± 3**
7	**75 ± 2**	**79 ± 1**
30	**72 ± 3**	**78 ± 2**
60	**70 ± 5**	**75 ± 1**

Conclusions

- MA SLNs increase the aqueous solubility of this bioactive compound by a 10^6 factor.
- MA SLNs are stable under the conditions of pH and ionic strength analysed, thanks to the steric stabilization offered by the adsorbed poloxamers.
- MA SLNs exhibited high encapsulation efficiency and curcumin loading capacity. MA SLNs could be used as therapeutic vehicles for this type of compounds.

Acknowledgments

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