Original Article

A self-assembling prodrug approach emerges as the most efficient strategy to produce nanoparticles with high payloads of pipemidic acid, a poorly soluble crystalline antibiotic

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Supplementary Information

List:

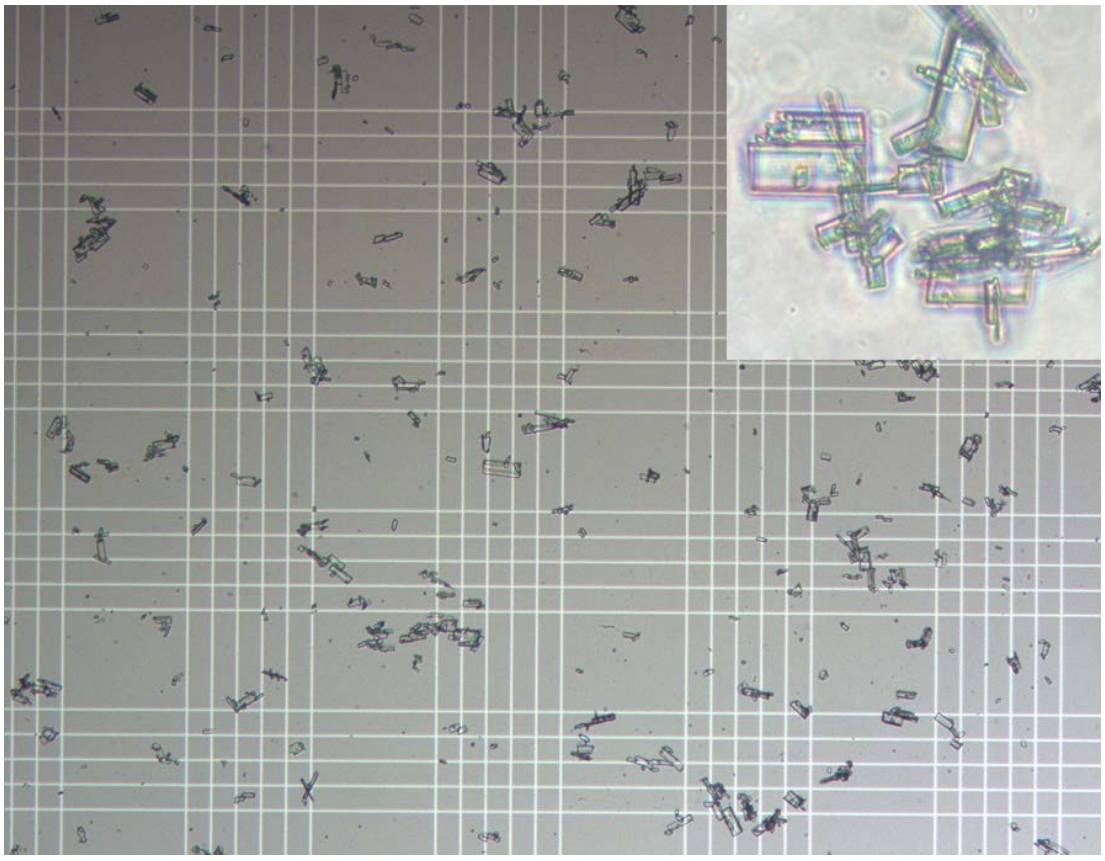

Figure S1. Optical image of PIP crystals in PLA/PLGA NPs. Typical example of PIP crystals formed in NPs suspension observed with 10 times and 40 times (zoomed panel) magnification in an inverted optical microscope over a Malassez chamber.

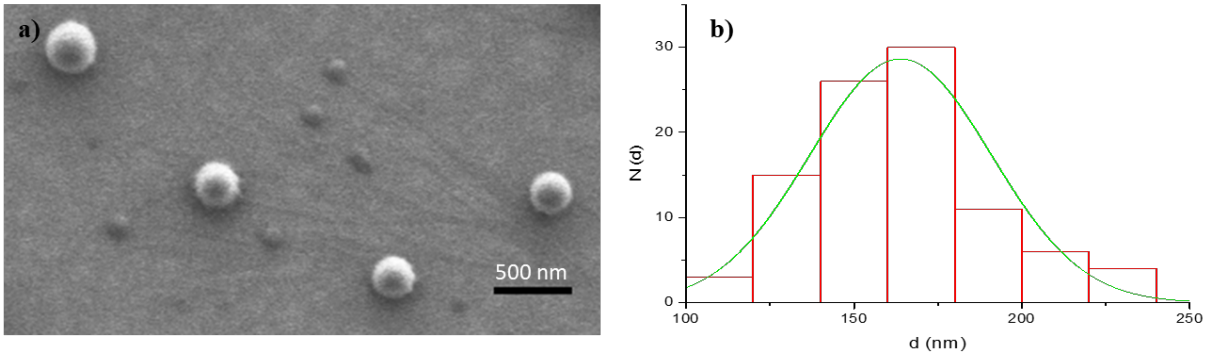

Figure S2 PLGA PIP-loaded NPs observed by SEM. a: SEM micrograph. b: Histogram of the size distribution of the NPs showing a mean diameter d = 164 ± 27 nm. N(d) refers to the total counts and the scale bar corresponds to 500 nm.

Nanoemulsion method - PIP release upon dilution

The release of PIP from NPs was thoroughly studied after progressive dilution in water and PIP content was lost within less than 5 min. Interestingly, there was a correlation between the amount of burst-released drug and the dilution factor. For example, the DL of NPs made using polymer P33 (see Main text - method section 4.1) decreased from 8.7% to 4.1%, 2.4% and 1.7% (*w*/*w*) after 0, 10, 20 and 50 times dilution, respectively.

Nanoprecipitation method supplementary information

The P19 NPs were formulated in presence and in absence of PIP. Interestingly, the size measurement of the obtained particles highlighted a 50–60 nm difference in the mean size of empty and loaded NPs. For example, in the case of a final P19 concentration of 5 mg/mL, the empty NPs displayed a size of 170 ± 1.3 nm while the loaded ones of only 117 ± 1.6 nm (PIP/P19 ratio =1:10). The same behavior was evidenced also when increasing P19 final concentration to 10 mg/mL (or higher) (empty NPs= 212 ± 2.3 nm, PIP NPs= 150 ± 2 nm). The same tendency was evidenced also when formulating the NPs by using other polymers.

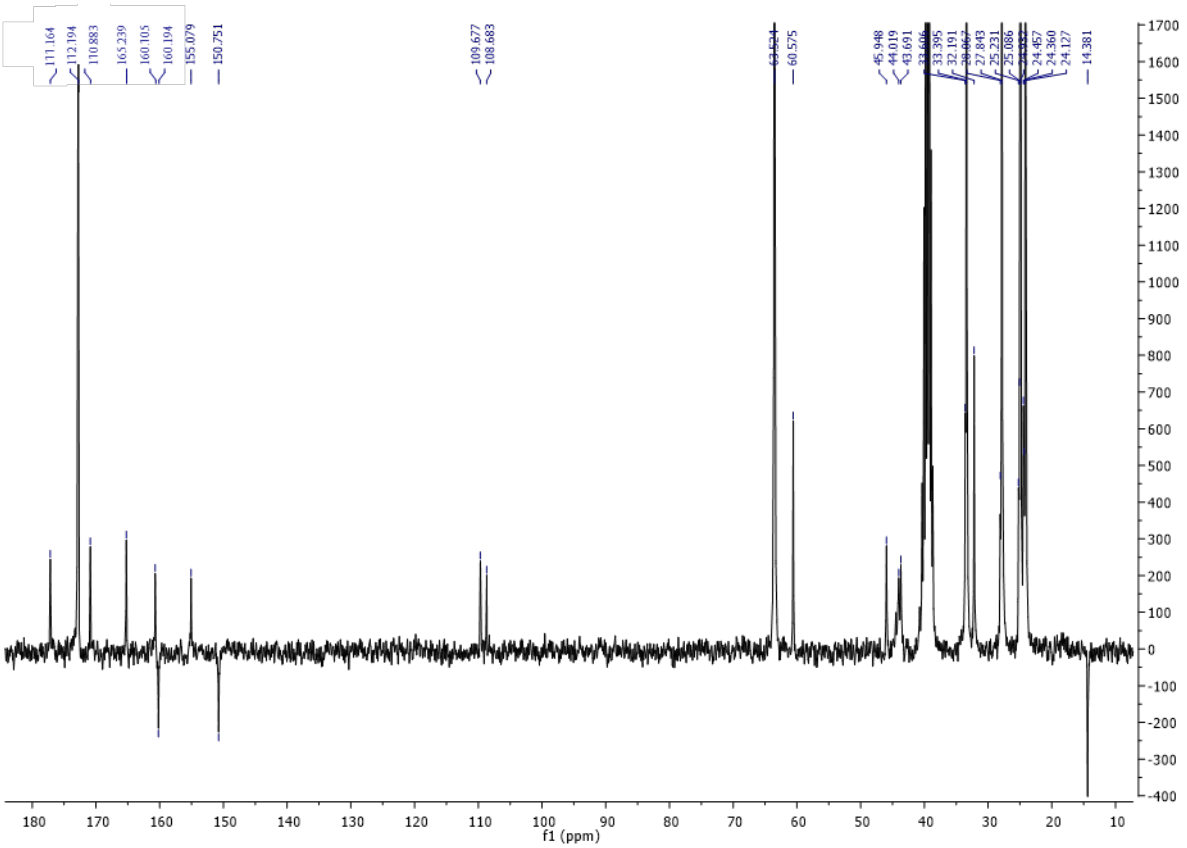

Figure S3 ^{13}C NMR spectrum of PCL-PIP in DMSO-d_6.

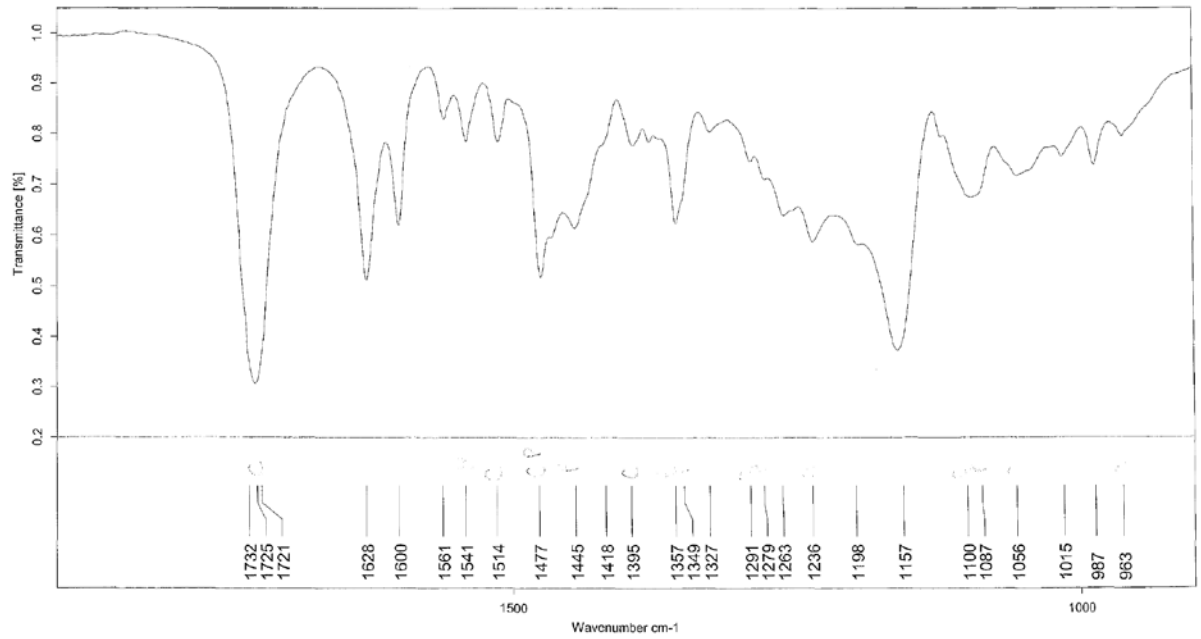

Figure S4 IR spectrum of PCL–PIP.

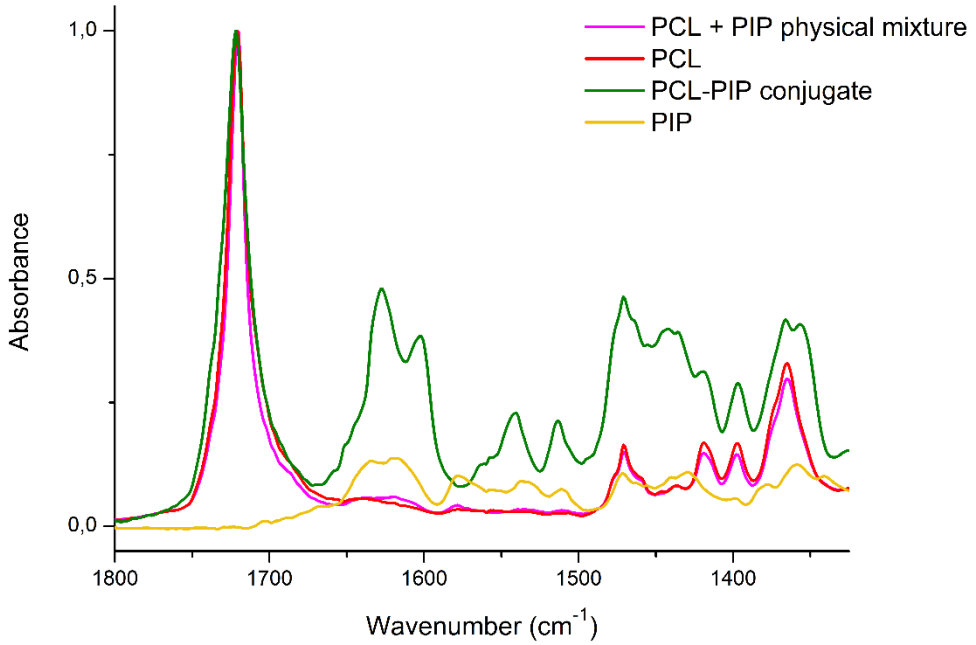

Figure S5 IR spectra of PCL, PIP, PCL–PIP conjugate and a physical mixture of PCL and PIP.

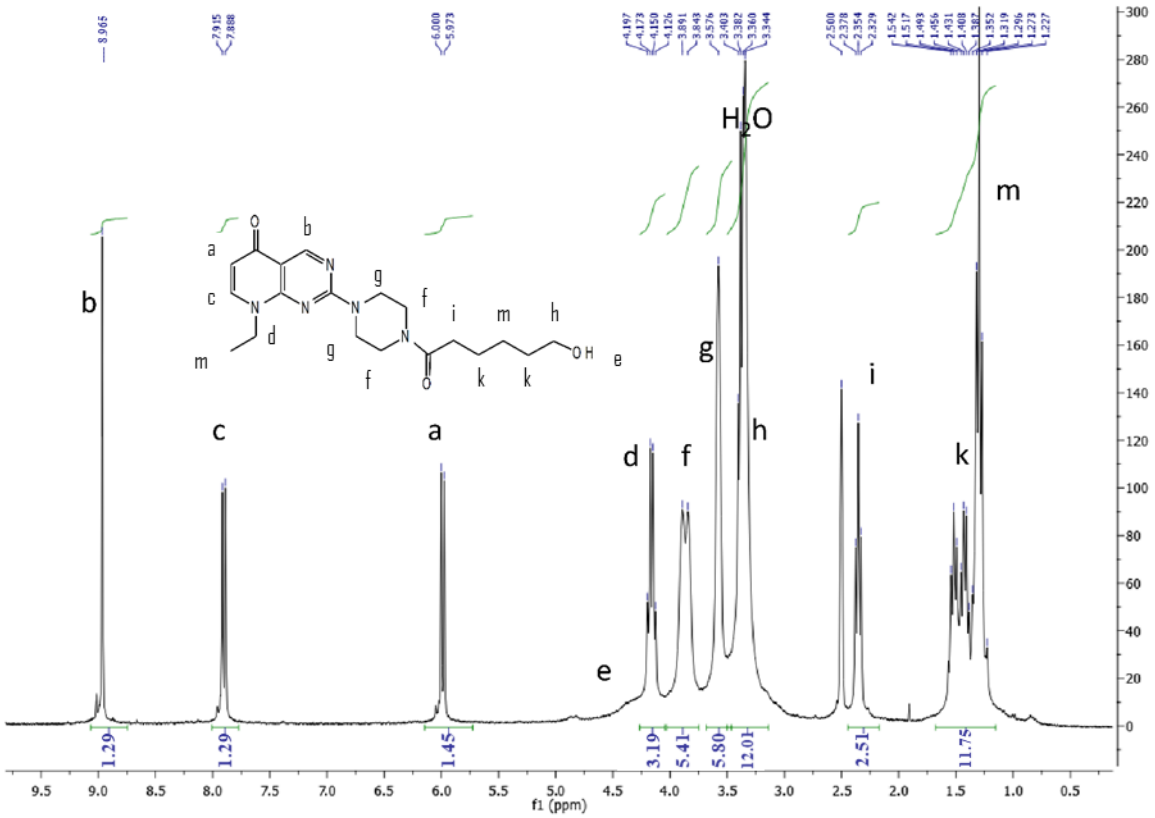

Figure S6 ^{1}H NMR of decarboxylated caprolactone adduct (**4**) (see Fig. 2 main manuscript).

Supplementary Information