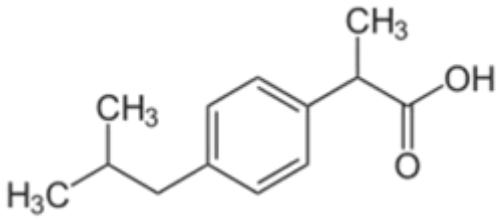
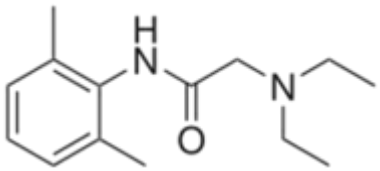
**Supporting information**

**Introduction**




Ibuprofen logP 3.97




Lidocaine logP 2.44

**Figure 1S**

**Methods**

**Vesicle preparation and purification**

The vesicles were obtained by the "film" method: the dried films were hydrated by addition of HEPES buffer (10 mM, pH7.4) alone or Hepes buffer (10 mM, pH 7.4) containing calcein (10 mM). The surfactant dispersion was mechanically stirred for about 5 min and then sonicated for 5 min at 60 °C with Vibracells VCX400 (Sonics), equipped with an exponential microprobe operating at 23 kHz and an amplitude of 6 mm.

**2.9 *In vitro* release**

Parallel measurements, carried out using IBU or LID without vesicles, proved that in no case the diffusion across the dialysis membrane was the limiting step of the overall diffusion process.

**2.10 *In vivo* experiments**

**Formalin test**

During the test, the mouse was placed in a Plexiglas observation cage (30×14×12 cm), 1 h before the formalin administration to allow it to acclimatize to its surroundings.

**3. Results**

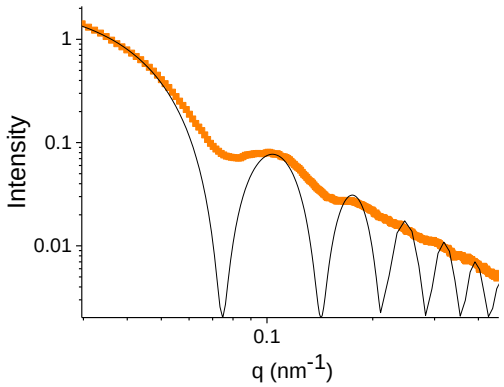



**Figure 2S.** SAXS intensity profile for Tween20 based niosomes with 5% Lidocaine. Fit of the particle form factor has been obtained with a spherical hollow particle, with multi-shell bilayer, accounting for hydrophilic and hydrophobic portion of the molecules : $P(q) \div ((4\pi r_1^3(\Delta\rho_1\, j_1(qr_1)/(qr_1))+(4\pi r_2^3(\Delta\rho_2\, j_1(qr_2)/(qr_2))+(4\pi r_3^3(\Delta\rho_3\, j_1(qr_3)/(qr_3))+(4\pi r_4^3(\Delta\rho_4\, j_1(qr_4)/(qr_4)))^2$, $r_1$ is the internal radius = 40 nm, $r_4$ is the external radius = 46 nm, $j_1(qr_i)$ are the Bessel functions, $\Delta\rho_i$ is the contrast in electron density of two adjacent shells (internal buffer, internal headgroups, hydrophobic core, external headgroups, external buffer). Differences with the experimental data are due to polidispersity.

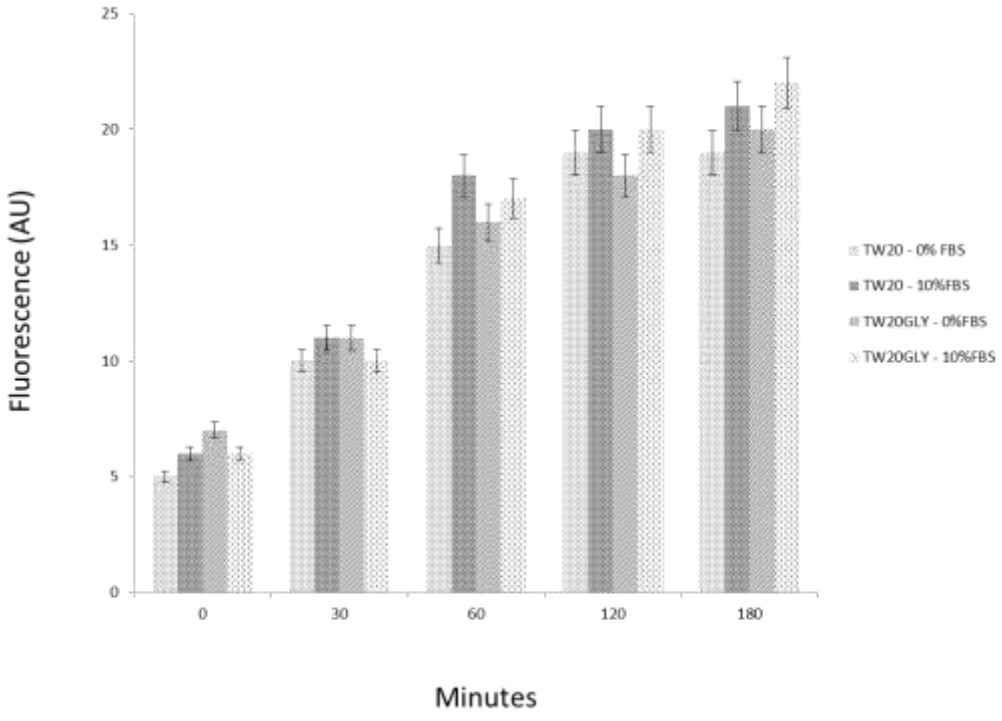


**Figure 3S**. Influence of FBS different concentrations on the in vitro stability of surfactant vesicles at 37 °C. The vesicles were incubated at pH 7.4 in absence (0% FBS) and in presence (10 %) of FBS. Samples were collected after 3 h and calcein leakage was measured by fluorimetry. Reported data represent the mean of three experiments; error bars=±S.D.