Electronic Supplementary Information

Pickering emulsions for stimuli-responsive transdermal drug delivery: effect of rheology and microstructure on performance

Simona Migliozzi, Yiting He, Maryam Parhizkar, Yang Lan and Panagiota Ange

October 9, 2024

S1. Theoretical interfacial coverage of the Pickering droplets

In Table S.1, we report the summary of the theoretical interfacial coverage C, calculated as follows. First, the average droplet diameter (D_d) was determined by analysing at least 2000 droplets per sample, and calculated using the following equation:

$$D_d = \frac{\sum_i N_i D_i^3}{\sum_i N_i D_i^2} \tag{1}$$

where N_i is the total number of droplets with diameter D_i. Using the average droplet size, the total surface area of the water-oil interface can be obtained as

$$S = \frac{6V}{D_d} \tag{2}$$

where V is the volume of jojoba oil used to fabricate the emulsion. Next, the equivalent area theoretically covered by microgel particles is determined as:

$$S_{eq} = n_p V \pi \left(\frac{d_p}{2}\right)^2 \tag{3}$$

Here, d_p is the hydrodynamic diameter of the microgels in their swollen state, and n_p is the microgel number concentration, which is calculated from the microgel volume fraction, ϕ, assuming the following relation:

$$n_p = \frac{\phi}{\frac{4}{3}\pi\left(\frac{d_p}{2}\right)^3} \tag{4}$$

Finally, the theoretical coverage can be calculated as:

$$C = \frac{S_{eq}}{S} = \frac{\phi D_d}{4 d_p} \tag{5}$$

Table S. 1: Theoretical interfacial coverage of the Pickering droplets. The table reports the average droplet diameter D_d, the volume fraction ϕ of microgels in the whole formulation, evaluated using the rheological method reported in Section 3.2 of the main manuscript and C. A microgel diameter d_p equal to 348 nm and 796 nm is used for M300 and M800 samples, respectively.

		D_d (μm)	ϕ (-)	C (-)
M300	C1	6.21 ±2.6	0.25	2.27
	C2	5.64 ±2	0.17	1.36
	C3	25.07 ±7.1	0.084	3.03
M800	C1	4.33 ±0.75	0.25	0.69
	C2	11.73 ±1.7	0.17	0.92
	C3	15.4 ±3.1	0.084	0.81

S2. Drug release experiments

In-vitro transdermal release tests were performed using a Franz-cell. A schematic of the setup is reported in Fig. S.1A. To obtain cumulative release curves, a constant aliquot of receptor solution is withdrawn periodically using a needled syringe from the sampling port, and tested through UV-vis spectroscopy. To ensure proper calibration of the instrument, a calibration curve of levosimendan solutions in PBS buffer is built with 10 levosimendan solutions at known concentration. The final curve is reported in Fig. S.1B. Finally,

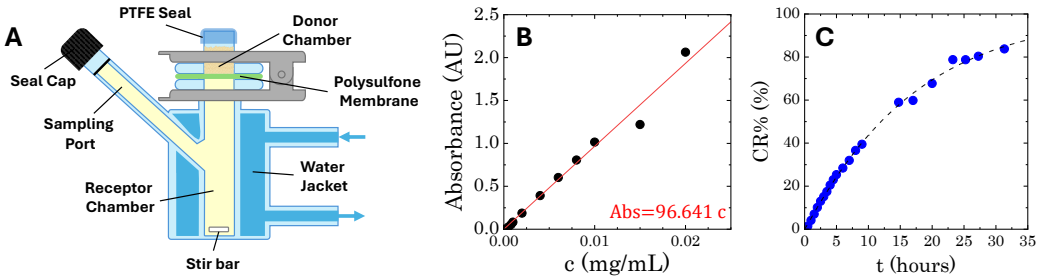
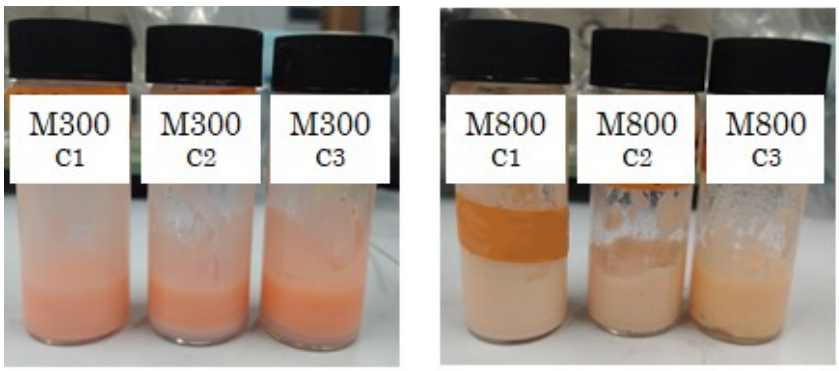


Figure S. 1: (A) Schematic of the Franz cell used for the transdermal release experiments. Donor chamber volume = 1 mL, Receptor chamber volume = 5 mL. Temperature control is obtained by submerging the cell in an oil bath, with temperature regulated with a hot plate. The temperature in the donor chamber was monitored during preliminary tests to ensure correct calibration of the oil bath temperature. To obtain T= 37 °C in the donor chamber, the oil bath should be set at T= 41 °C. (B) UV-vis calibration curve for levosimendan in PBS buffer. The red line is the linear fitting used as calibration law. (C) Normalised cumulative release of levosimendan from free jojoba oil. The data are fitted using $CR = 1 - \bar{c}(t) \sim \exp\left[-(t/\tau_0)\right]$. The fitting yields a characteristic diffusion time τ_0 of 17.03 hours.

S3. Pickering emulsions general aspect



	C1	C2	C3
M300	Liquid Smooth	Liquid Smooth *	Liquid Smooth *
M800	Solid Granular	Solid Granular	Solid Granular*

Figure S. 2: Pictures of the tested PEs, with a summary of the general characteristics. The asterisk (*) indicates the samples that show creaming. Creaming times observed: 1 week for samples M300-C1/C2, 3 days for sample M300-C3, 1 month for sample M800-C3).

S4. Zero-shear elastic plateau G'_0 and yield stress σ_y as a function of microgel loading

Figure S.3 reports the zero-shear elastic plateau G'_0 and the yield stress σ_y as a function of microgel loading for all PEs investigated. The yield stress is obtained from strain amplitude oscillatory sweep tests as $\sigma_y = G'_0\gamma_y$. Here γ_y is the strain amplitude at which the shear stress deviates from the linear relation $\sigma \sim \gamma_0$, hence the last point of the linear viscoelastic region.

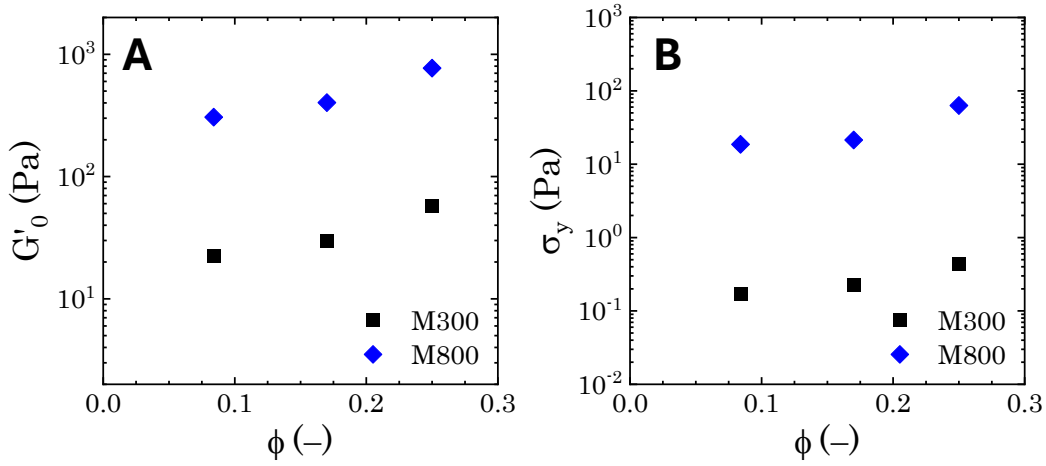


Figure S. 3: (A) Zero-shear elastic plateau G'_0 and (B) yield stress σ_y as a function of microgel volume fraction.

S5. Calculation of the effective droplet volume fraction and of the total dispersed phases volume fraction

The effective droplet volume fraction (ϕ_{EFF} of the formulations investigated is calculated using the method described by Kaganyuk et al. [1]. This method accounts for the increased size of the droplets due to the monolayer of particles at the droplets' interface, allowing to convert the initial volume fraction ϕ_o into ϕ_{EFF}, as follows:

$$\phi_{EFF} = \phi_o \left(1 + \frac{2x}{D_d}\right)^3 \tag{6}$$

In Eq. 1, x is a dimensional parameter that takes into account how much the particles protrude from the interface, and D_d is the average droplet diameter. For solid particles x can be calculated geometrically from the three-phase

contact angle of the system. For microgels, an exact value of x is extremely difficult to obtain, as microgels do not maintain a spherical shape at the interface, but rather they flatten and stretch, maintaining a more swollen core into the aqueous phase [2], with a thickness that will depend on the crosslinking degree of the microgel. Bochenek et al. [3] report that for similar microgels at the oil-water interface, the external layer, protruding in the aqueous phase, has a thickness $x \sim \frac{2}{3}d_p$. Hence, taking into account this estimate, we can calculate ϕ_{EFF} using Eq. 1, and considering that for all PEs ϕ_o is equal to 0.5. Table S.2 reports the values of ϕ_{EFF} for all PEs, together with the total volume fraction of the dispersed phases, $\phi_{TOT} = \phi_{EFF} + \phi_m$. This quantity, takes also into account the residual amount of microgels in the aqueous phase ϕ_m, obtained as follows:

$$\phi_m = \phi \left(1 - \frac{N_p}{N_{max}}\right) \tag{7}$$

where ϕ is the volume fraction of microgels added to the formulation, N_p is the total number of microgels in the formulation and N_{max} is the theoretical number of microgels required to obtain a coverage of 0.78 (i.e., limit of maximum random packing of spherical objects in 2D [4]).

Table S. 2: Effective droplet volume fraction ϕ_{EFF} and total dispersed phase volume fraction ϕ_{TOT} for all formulations investigated.

		ϕ_{EFF} (-)	$\phi_{TOT}(-)$	$\phi_m(-)$
M300	C1	0.652	0.817	0.165
	C2	0.634	0.707	0.073
	C3	0.528	0.59	0.061
M800	C1	0.967	0.967	–
	C2	0.65	0.65	–
	C3	0.611	0.611	–

S6. Interfacial tension of the oil/microgel dispersions interface

Table S.3 shows the equilibrium interfacial tension values (γ_{ow}) between jojoba oil and the different aqueous microgel suspensions used to fabricate the emulsions. All the measurements have been obtained using a DSA100 Drop Shape instrument (KRUSS SCIENTIFIC). For all experiments, an aqueous droplet containing a fixed microgel concentration is formed within a jojoba oil bath, and the interfacial tension is recorded in time until it reaches a stable value.

Table S. 3: Equilibrium interfacial tension γ_{ow} between jojoba oil and the different aqueous microgel suspensions used to fabricate the emulsions.

	γ_{ow} (mN/m)		
M300	C1	C2	C3
	6.72	6.71	6.79
M800	C1	C2	C3
	4.42	5.43	5.49

S7. Additional graphs from strain amplitude sweep tests

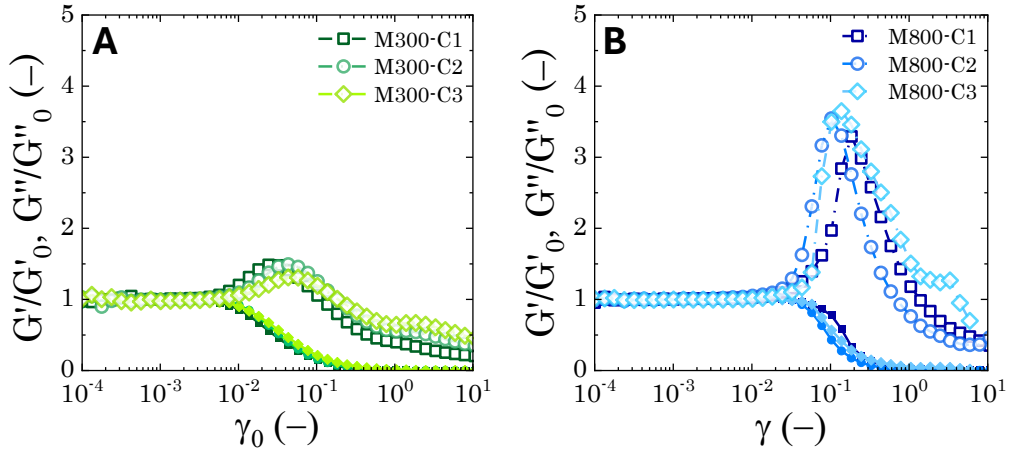


Figure S. 4: Viscoelastic modululi, G' (closed symbols) and G'' (open symbols), normalised by their corresponding zero-shear plateau values as function of the strain amplitude for (A) M300-stabilised PEs and (B) M800-stabilised PEs.

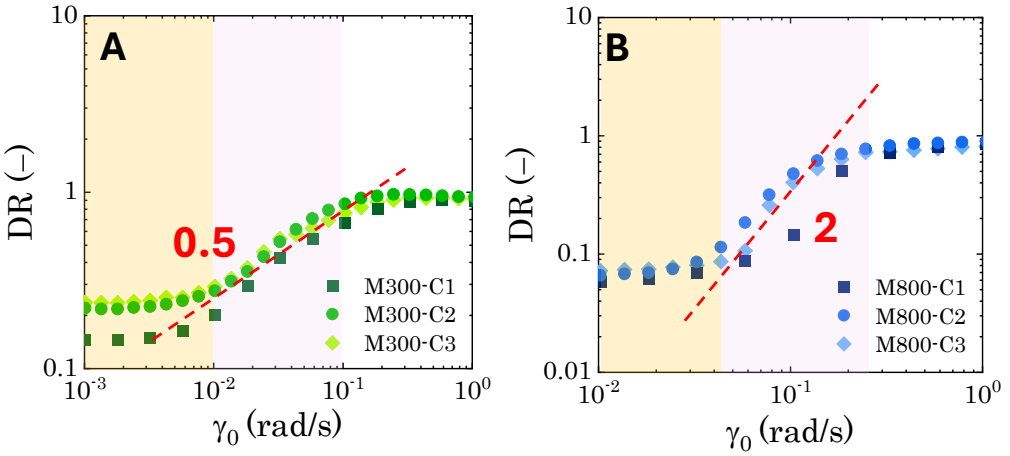


Figure S. 5: Log-log plot of the dissipation ratio DR as a function of the nominal strain amplitude γ_0, for PEs stabilised by microgels (A) M300 and (B) M800. The red dotted line indicate the slope of the power-law increase of DR in the yielding region.

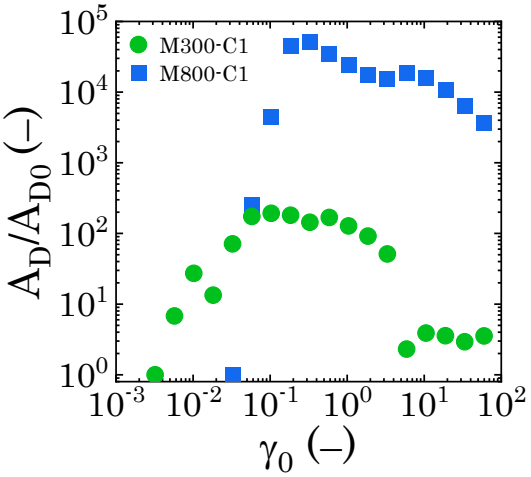


Figure S. 6: Evolution of the areas, A_D, of the deltoids reported in Fig. 8A-B of the main manuscript, normalised by the area in the LVER, A_{D0}

S8. Small-amplitude oscillatory sweeps

We report the trend of the viscoelastic moduli, G' and G'' with the angular frequency, obtained via small amplitude oscillatory frequency sweep experiments for four samples of reference. The tests were carried out in the same rheometer geometry and using the same pre-shearing procedure described for LAOS tests in the main manuscript. The experiments were performed using an amplitude strain of $3.5 \cdot 10^{-3}$ and sweeping the frequency from high to low values.

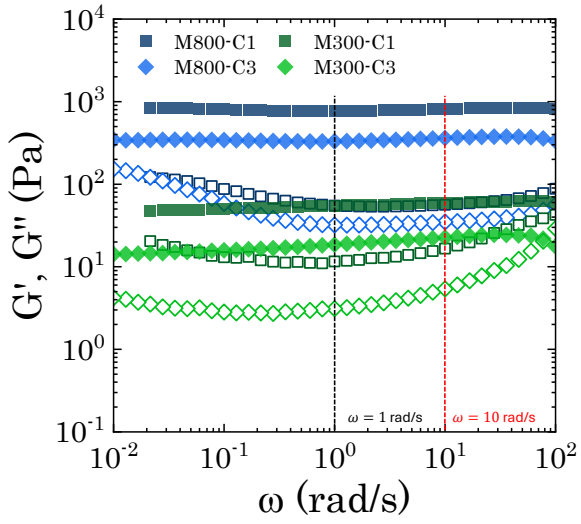


Figure S. 7: Frequency dependence of the storage (closed symbols) and loss (hollow symbols) moduli obtained from small-amplitude oscillatory frequency sweeps at $\gamma_0 = 3.5 \cdot 10^{-3}$ for samples M800-C1/C3 and M300-C1/C3.

References

[1] M. Kaganyuk, A. Mohraz, *Journal of Colloid and Interface Science* **540**, 197 (2019).

[2] M. Rey, M. A. Fernandez-Rodriguez, M. Karg, L. Isa, N. Vogel, *Accounts of Chemical Research* **53**, 414 (2020).

[3] S. Bochenek, *et al.*, *Langmuir* **35**, 16780 (2019).

[4] E. L. Hinrichsen, J. Feder, T. Jøssang, *Phys. Rev. A* **41**, 4199 (1990).