

Independent co-delivery of model actives with different degrees of hydrophilicity from oil-in-water and water-in-oil emulsions stabilised by solid lipid particles via a Pickering mechanism

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1 **Independent co-delivery of model actives with different degrees of hydrophilicity from**
2 **oil-in-water and water-in-oil emulsions stabilised by solid lipid particles via a Pickering**
3 **mechanism: a-proof-of-principle study**

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11

12 **Abstract**

13 *Hypothesis*

14 The development of vehicles for the co-encapsulation of actives with diverse characteristics and their
15 subsequent controllable co-delivery is gaining increasing research interest. Predominantly centred
16 around pharmaceutical applications, the majority of such co-delivery approaches have been focusing
17 on solid formulations and less so on liquid-based systems. Simple emulsions can be designed to offer a
18 liquid-based microstructural platform for the compartmentalised multi-delivery of actives.

19 *Experiments*

20 In this work, solid lipid nanoparticle stabilised Pickering emulsions were used for the co-
21 encapsulation/co-delivery of two model actives with different degrees of hydrophilicity. Lipid particles
22 containing a model hydrophobic active were prepared in the presence of either Tween 20 or whey
23 protein isolate, and were then used to stabilise water-in-oil or oil-in-water emulsions, containing a
24 secondary model active within their dispersed phase.

25 *Findings*

26 Solid lipid nanoparticles prepared with either type of emulsifier were able to provide stable emulsions.
27 Release kinetic data fitting revealed that different co-delivery profiles can be achieved by controlling
28 the surface properties of the lipid nanoparticles. The current proof-of-principle study presents
29 preliminary data that confirm the potential of this approach to be utilised as a flexible liquid-based

30 platform for the segregated co-encapsulation and independent co-release of different combinations of
31 actives, either hydrophobic/hydrophilic or hydrophobic/hydrophobic, with diverse release profiles.

32

33 **Keywords:** co-encapsulation; co-delivery; solid lipid nanoparticles; Pickering stabilisation;
34 water-in-oil or oil-in-water emulsions; hydrophobic or hydrophilic actives

35

36 **1. Introduction**

37 The co-encapsulation and co-delivery of two or more active substances within the same vehicle has
38 emerged as an attractive research area, with the majority of published work focusing on applications in
39 combination drug therapy for cancer treatment [1,2], delivery of bioactives and nutraceuticals [3,4], and
40 anti-ageing agents in the cosmetics sector [5]. Combining multiple actives within the same system
41 diminishes the need for individual intake of different active ingredients, while co-delivery offers the
42 benefit of improved physiological functions of the actives due to potential synergistic effects arising
43 from co-administration [6,7]. Wang *et al.* [8] were able to simultaneously and independently deliver to
44 a target tissue two water-insoluble drugs from single multicompartiment polymeric hydrogel composed
45 of PEGylated hydrocarbon (triblock copolymer based on PEG and poly(ϵ -caprolactone) (PECT)) and
46 fluorocarbon (copolymer of mPEG and PPFEMA (PEPF)) nanoparticles, thus achieving improved
47 tumour growth inhibition in cancer therapy over single drug treatment using the two actives
48 individually. The benefits of multimodal drug delivery in cancer treatment were also demonstrated
49 following a multicompartimental nanostructure approach, where polymeric PLGA (poly(lactic-co-
50 glycolic acid)) nanocapsules incorporating a hydrophobic active were coated with a phospholipid
51 bilayer encapsulating a secondary hydrophobic active, showing very high entrapment efficiencies and
52 sustained release profiles [9].

53 Even though multi-delivery has been already successfully employed for solid dosage forms,
54 realising such approaches in liquid-based formulated products, despite the benefits offered (e.g. dosage
55 flexibility, better patient compliance, rapid absorption of the encapsulated actives at the target site), is
56 much more challenging [10–12]. Simple oil-in-water (o/w) or water-in-oil (w/o) emulsions constitute a
57 widely used liquid platform for the encapsulation and delivery of actives, as they can be designed to

58 offer protection against degradation, increased bioavailability of the actives, and encapsulation of both
59 hydrophobic and hydrophilic molecules [13,14]. Further exploring their functionality, fabrication of
60 multiple emulsions (e.g. w/o/w) has been shown to allow for controlled delivery of encapsulated actives
61 as a response to changes in formulation parameters (e.g. type of oil) or environmental conditions (e.g.
62 temperature), and oil-drug interactions [13,15,16]. In terms of co-encapsulation/co-delivery, a triple
63 emulsion (water-in-oil-in-(oil-in-water)) with a highly compartmentalised structure was previously
64 employed for the segregated co-encapsulation of three photosensitive compounds with varying degrees
65 of hydrophilicity, resulting in their improved stability and protection [17]. Winkler *et al.* [18] employed
66 biphasic PLGA/PCL (poly(lactic-co-glycolic acid)/polycaprolactone) Janus particles for the
67 co-encapsulation of either two hydrophobic actives, using a single o/w emulsion method, or a
68 combination of hydrophilic/hydrophobic compounds, using three different methods to enhance the
69 solubility of the hydrophilic active; single o/w emulsion with partially water-miscible solvent, single
70 o/w emulsion using a co-solvent or double w/o/w emulsions. Dual release was achieved, with high
71 encapsulation efficiencies for the two hydrophobic compounds, while for the combination of
72 hydrophilic/hydrophobic compounds, the double emulsion method yielded the highest encapsulation
73 efficiency. In another study [19], sodium caseinate/chitosan (NaCAS/CS, protein/polysaccharide)
74 co-precipitated complexes (containing a hydrophilic active) were used to stabilise oil-in-water emulsion
75 droplets (containing a secondary hydrophobic active). This approach enabled the segregated
76 co-encapsulation and independent co-release of two incompatible actives from a simple emulsion
77 microstructure.

78 The present proof-of-principle work aims to demonstrate that the approach of Spyropoulos *et al.* [19]
79 can be successfully applied to emulsions stabilised by solid lipid nanoparticles (SLNs). SLNs have been
80 extensively utilised as single- and multi-drug delivery systems for actives with different characteristics
81 [20–22], but also investigated for their capacity to stabilise (Pickering) emulsions [23–26]. As multi-
82 drug delivery systems, SLNs offer limited control over manipulating the individual release profiles, due
83 to the fact that the encapsulated actives have to migrate out of a crystalline network. As Pickering
84 particles, thus far SLN-stabilised Pickering emulsions have only been utilised for the encapsulation of
85 a single active within their included phase; in this case the lipid nanoparticles principally act as

86 stabilising agents [26]. Harnessing the advantages offered by the individual components of such a
87 compartmentalised system, could potentially result in the development of an ideal delivery vehicle for
88 the co-encapsulation of different combinations of actives, that could simultaneously address issues
89 associated with controlled delivery. These advantages are introduced by the presence of two different
90 phases that the incorporated actives can release from; a crystalline network offered by the SLNs and a
91 liquid phase provided by the emulsion. In the current study, SLNs fabricated in the presence of two
92 types of surface active species, are utilised for a two-fold purpose; encapsulating a model hydrophobic
93 active (active 1), while at the same time stabilising w/o or
94 o/w emulsion droplets, containing a secondary model hydrophilic or hydrophobic active (active 2),
95 respectively. The findings reported here offer evidence that depending on the type of emulsifier used
96 during their fabrication, SLNs can provide significant stability to both w/o and o/w emulsions, while in
97 tandem facilitating the generation of a variety of co-delivery profiles. By altering the surface properties
98 of the lipid nanoparticles and in turn the properties of the stabilised emulsions, release kinetics can be
99 controlled. This work not only proposes a novel method to achieve co-encapsulation and co-delivery of
100 different combinations of hydrophobic and hydrophilic actives through the development of a
101 compartmentalised vehicle, but also highlights the impact of the SLN characteristics upon obtaining
102 stable Pickering emulsions with tuneable release profiles.

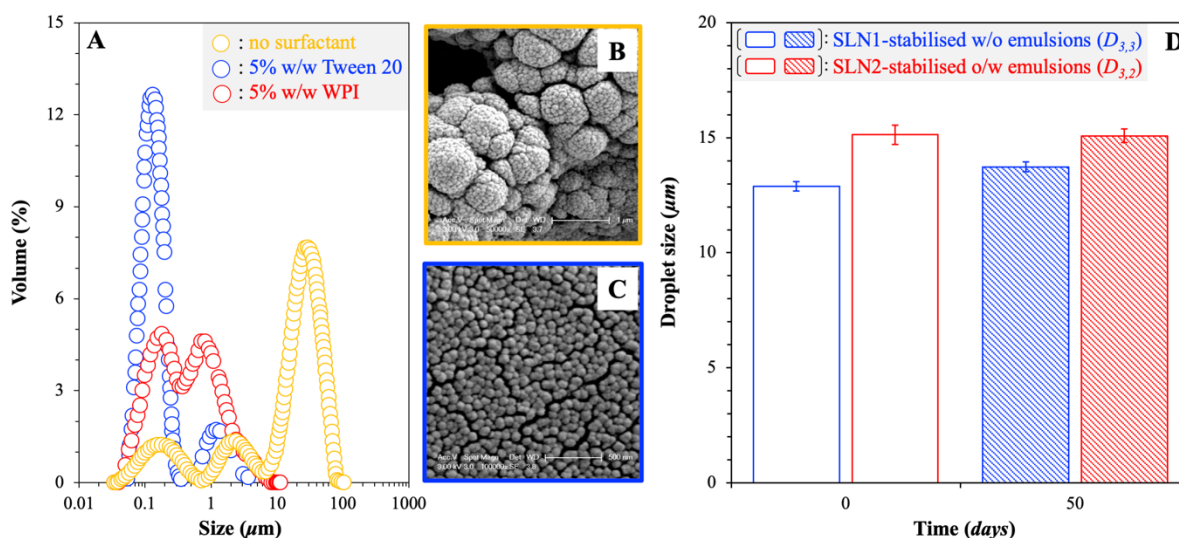
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104 **2. Results and Discussion**

105 **2.1 Effect of active encapsulation on the size and stability of SLN and SLN-stabilised** 106 **emulsions structures**

107 Tripalmitin SLNs were prepared in the presence of either a low molecular weight non-ionic
108 surfactant (Tween 20; SLN1) or a globular protein (whey protein isolate, WPI, SLN2). SLN1 and SLN2
109 were subsequently used to stabilise w/o and o/w emulsions, respectively, via a Pickering mechanism.
110 Based on theoretical calculations used to estimate the amount of SLN particles necessary to fully cover
111 the surface of the emulsion droplets, it was found that there was excess of SLN particles present in both
112 systems. The possibility of utilising Pickering emulsions for the co-encapsulation and co-delivery of

113 two segregated actives was assessed by incorporating actives, with different degrees of hydrophilicity,
114 within both the SLNs and the emulsion droplets. Sudan III was used as the model hydrophobic active
115 encapsulated within either type of SLNs (SLN1 or SLN2), while NaCl and dimethyl phthalate (DMP)
116 acted as the model hydrophilic and hydrophobic actives encapsulated within the w/o and o/w emulsion
117 droplets, respectively. Blank tripalmitin SLN1 and SLN2 have been employed in a previous study [25]
118 as Pickering particles for the stabilisation of emulsions prepared with sunflower oil. SLN1 formed w/o
119 emulsions, whereas SLN2 showed an inclination towards providing o/w emulsions. The latter was
120 explained by the overall relative hydrophilic character of the particles, and the tendency of WPI to form
121 a thick layer at the particle interface affecting the polymorphic state of the lipid crystals, and
122 consequently the polarity of the particles. Similar observations were made in the current study when
123 the same type of particles, but with Sudan III encapsulated within them, were assessed for their
124 Pickering functionality. Size measurements of SLN1 and SLN2 showed that entrapment of Sudan III
125 did not affect particle dimensions. Both types of particles were characterised by bimodal size
126 distributions, which remained unchanged over a storage period of 9 weeks at 4°C. SLN1 showed two
127 distinct size populations at 150 nm and 1.3 μm , while SLN2 displayed two peaks at 150 and 700 nm
128 (*Figure 1A*). The presence of the surface active species had a significant effect on both the average size
129 of the particles, and their size distribution profile, which was further supported by SEM imaging
130 (*Figures 1B & C*). Stability of the SLN-formed Pickering emulsions was confirmed as the average
131 droplet size, $D_{3,3}$ (measured using pulsed field gradient NMR) or $D_{3,2}$ (measured using laser diffraction)
132 for the w/o or o/w Pickering systems, respectively, did not change significantly over a storage period
133 of 50 days (*Figure 1D*). The long-term storage stability of the SLN-stabilised emulsions could be the
134 result of a synergistic mechanism between the surfactant and the colloidal lipid particles present in the
135 system [27–29].



136
 137 **Figure 1. A.** Particle size distribution of 5% w/w tripalmitin SLNs with no surfactant, and in the presence of 5% w/w Tween
 138 20 (SLN1), and 5% w/w WPI (SLN2); Data reproduced from [25] - Published by The Royal Society of Chemistry. Cryo-SEM
 139 images of tripalmitin SLN particles fabricated with no surfactant (B), or in the presence of 5% w/w Tween 20 (C; SLN1). D.
 140 Droplet size measurements over a storage period of 50 days for SLN1-stabilised w/o Pickering emulsions ($D_{3,3}$; measured
 141 using pulsed field gradient NMR) and SLN2-stabilised o/w Pickering emulsions ($D_{3,2}$; measured using laser diffraction).

142

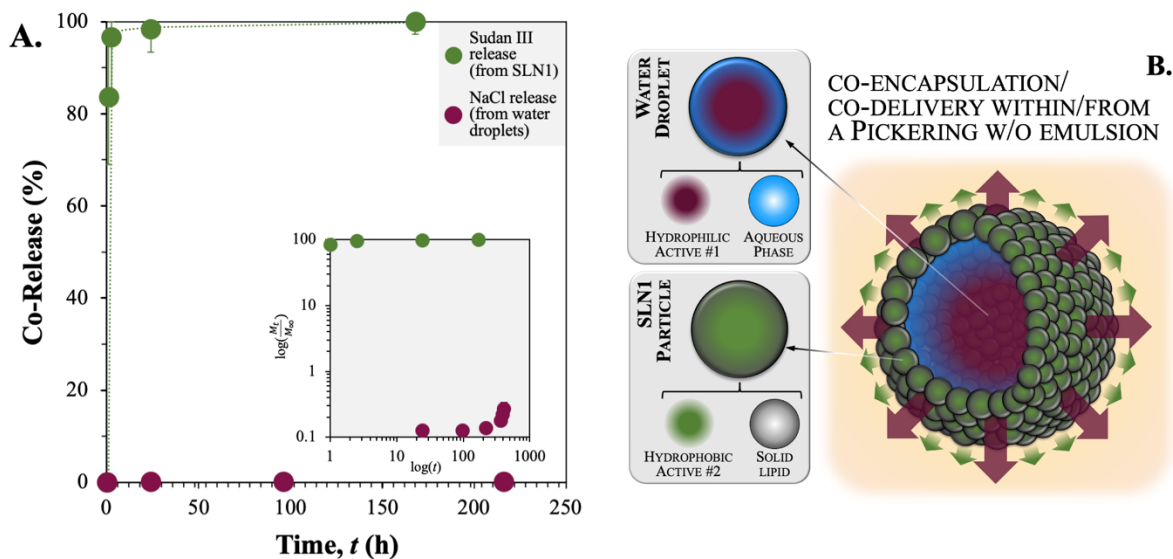
143 2.2 Co-delivery of hydrophobic/hydrophobic combination of actives

144 The co-release of Sudan III and DMP co-encapsulated within the SLN1-stabilised w/o emulsions,
 145 prepared using sunflower oil as the continuous phase, was investigated (Figure 2A and B). The
 146 discharge of Sudan III in sunflower oil serving as the dissolution medium, displayed a burst release
 147 with 96% of the active being liberated within the first 2-3 hours. The overall release percentage achieved
 148 corresponds to active discharge from both adsorbed and unadsorbed SLNs onto the water droplets'
 149 interface. Similar observations of burst release have been made in other studies [30,31], which were
 150 attributed to active enrichment of the particles' outer shell (suggesting a drug-enriched shell model) and
 151 the large surface area of the nanoparticles. Subsequent slow release could be the result of diffusion of
 152 the remaining active in the inner regions of the lipid matrix [32]. Fitting the release data into various
 153 empirical and semi-empirical kinetic models showed that the release of Sudan III is best described by
 154 the Weibull model (Figure S2 & Table S2). According to a previous study [33] relating the α and β
 155 Weibull model parameters to diffusivity, it is expected that for low diffusion coefficient values,
 156 parameter α is also low, which was indeed the case here (Table S2). Regarding parameter β , also known
 157 as the shape parameter, the predicted value ($\beta > 1$) denotes that the position of the active near the leak
 158 boundaries allows for an increasing release rate, averting the creation of a depletion zone. The relatively

159 low D values calculated here align with the hypothesis that the burst release profile of Sudan III is
160 potentially due to the presence of the active near the particles' surface.

161 Data fitting to the mechanistic models proposed by Crank [34] and Guy *et al.* [35], suggest that
162 diffusion was the rate-limiting step for the release of Sudan III from SLN1; both models gave diffusion
163 coefficient (D) values in the range of 10^{-14} $\text{cm}^2 \text{s}^{-1}$. Literature data regarding the diffusion coefficients
164 of actives releasing from SLNs is limited. Emami *et al.* investigated the use of glycerin monostearate
165 and cholesterol-based solid lipid nanoparticles for the delivery of budesonide. Fitting the Crank and
166 diffusion-limited models used here to the release data reported for the optimised SLN (~218 nm)
167 formulation in the latter study, give diffusion coefficients of 1.43×10^{-16} and 3.70×10^{-16} $\text{cm}^2 \text{s}^{-1}$,
168 respectively. In another study with relevance to cosmeceutics [36], Tiyaboonchai *et al.* monitored the
169 release of curcuminoids from stearic acid-based solid lipid nanoparticles (~450 nm). Fitting (by the
170 current authors) the release data obtained after incorporating the curcuminoid-loaded SLNs into a cream
171 formulation (as reported by Tiyaboonchai *et al.*) gave D values of 8.41×10^{-16} and 5.23×10^{-16} $\text{cm}^2 \text{s}^{-1}$
172 for the Crank and diffusion-limited models, respectively. The larger D values determined for the
173 systems studied here could be the result of poor distribution of Sudan III within the lipid matrix of the
174 SLN1 particles. Overall, fitting of either type of kinetic model indicates that the previously hypothesised
175 disproportional positioning of Sudan III near the particles' surface could be responsible for the
176 exaggerated diffusion coefficients calculated by the models.

177 On the other hand, NaCl release (carried out in water as the dissolution medium and quantified by
178 conductivity measurements over a period of 17 days) was negligible; only exhibiting 0.3% discharge at
179 the end of the monitoring period (inset *Figure 2A*). This could have been caused by sintering of
180 tripalmitin particles at the interface of the water droplets. As it has been previously shown [25], even
181 though tripalmitin particles covered with Tween 20 were able to stabilise w/o emulsions over long
182 storage periods, they could not provide sufficient steric protection against particle sintering.
183 Consequently, formation of a tripalmitin solid lipid layer around the emulsion droplets could be the
184 reason behind the release inhibition of the encapsulated active.



185
 186 **Figure 2.** A. Co-release profiles of NaCl and Sudan III contained within the aqueous droplets of a w/o emulsion and the SLN1
 187 lipid particles stabilising these, respectively. B. Schematic representation of the segregated co-encapsulation of a hydrophilic
 188 and a hydrophobic active within a lipid particle (SLN1) stabilised w/o Pickering emulsion microstructure.

189
 190 Particle sintering could potentially emerge from emulsifier-related events at the surface of the lipid
 191 particles; such as adsorption of the surface active species to the tripalmitin crystals in such a way, that
 192 the non-polar groups of the emulsifier are incorporated within the lipid crystal structure, leaving the
 193 polar groups exposed [25]. Interaction between the polar groups of the emulsifier present onto
 194 neighbouring lipid particles, such as hydrogen bonding, can lead to effective Pickering stabilisation
 195 [37], and therefore also to release hindrance caused by the inability of the active to permeate the dense
 196 lipid layer barrier.

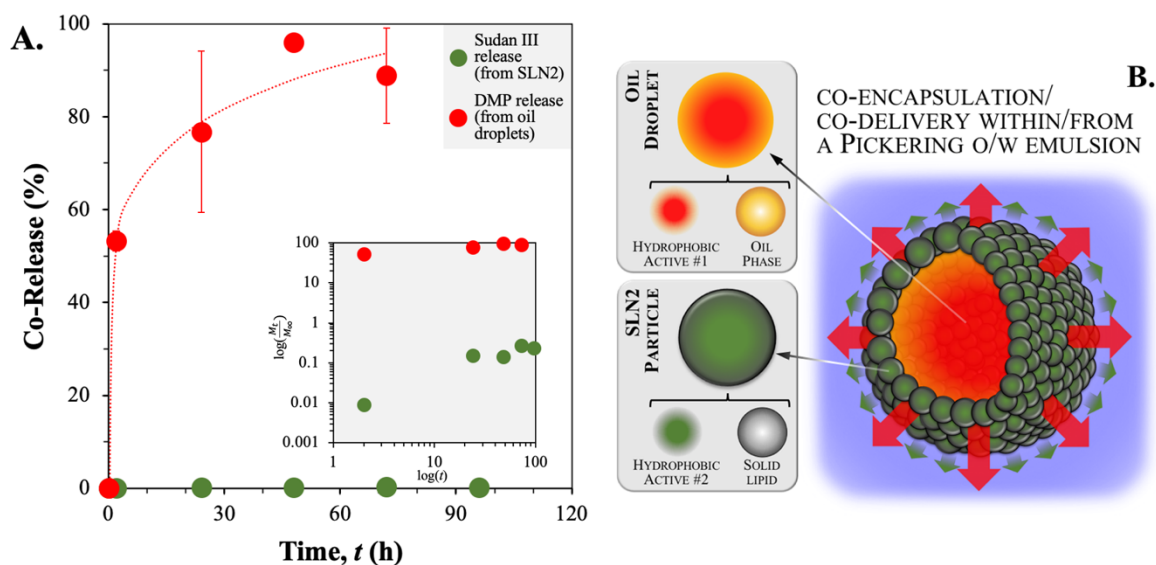
197 To further assess the effect of the type of oil on the release kinetics of the incorporative active from
 198 SLN1, three different oils with varying values of relative polarity were studied. Mineral and silicone
 199 oils have polarity indices of 43.7 and 26.6 mN m^{-1} respectively, while sunflower oil has a lower value
 200 of 19.3 mN m^{-1} [38]. w/o emulsions were prepared using either mineral or silicone oil as the continuous
 201 phase (in a similar manner to those formed with sunflower oil) and the release of NaCl was measured.
 202 The overall NaCl release percentage for all types of oils remained below 1% (Figure S1). However, a
 203 slight increase in the rate of release could be observed for the two alternative oil types compared to that
 204 of the previously used sunflower oil, suggesting that choosing an oil with different properties (e.g.
 205 higher polarity) could potentially result in sustained release profiles. An enhancement of sintering

206 phenomena and the higher affinity of the Tween 20 covered tripalmitin particles for sunflower oil could
207 be responsible for the greater NaCl release reduction in this case. Heating the systems to a temperature
208 above 40°C, the melting point of the lipid particles, resulted in emulsion destabilisation and subsequent
209 complete release of the encapsulated NaCl to the external water phase.

210

211 **2.3 Co-delivery of hydrophobic/hydrophilic combination of actives**

212 In addition, the co-release of two model hydrophobic actives encapsulated within Pickering o/w
213 emulsions stabilised by the SLN2 particles was studied. DMP (0.2% w/w) served as a model
214 hydrophobic active encapsulated within the sunflower oil droplets of the o/w emulsions, while Sudan
215 III (secondary model hydrophobic active) was contained within the SLN2 particles. Sudan III release
216 into sunflower oil (serving as the acceptor phase) was shown to be practically non-existent; 0.2% of the
217 active was detected after 4 days (inset *Figure 3A*). DSC and microscopic analysis previously [25]
218 performed on SLN2 particles had indicated that WPI adsorbs onto the lipid particle interface, rather
219 than penetrating into the lipid crystal network, while there were no signs of particle sintering. The
220 presence of a thick layer of WPI around the particles, in combination with the α polymorphic form of
221 tripalmitin further supported the increased polarity of SLN2 compared to SLN1 [25,39]. The
222 hydrophilicity of the emulsifier used, which is effectively exerted onto the lipid entities it stabilises, is
223 an important parameter affecting the release kinetics of particle-enclosed species [40]. This, in tandem
224 with the presence of a thick WPI layer at the surface of the particles, enhances the barrier that the
225 encapsulated hydrophobic active needs to overcome in order to cross over into the external phase, and
226 thus significantly hinders the rate of its release [41]. The obtained release profile could also indicate a
227 drug-enriched core model regarding the incorporation and distribution of the active within the lipid
228 crystal matrix [42]. It is therefore apparent that altering the surface active component used in the
229 fabrication of the lipid particles, not only changes the type of emulsion that the latter can provide, but
230 also results in a profound shift in the release kinetics of the same encapsulated species (Sudan III).



231
 232 **Figure 3.** A. Co-release profiles of DMP and Sudan III contained within the oil droplets of an o/w emulsion and the SNL2
 233 lipid particles stabilising these, respectively. B. Schematic representation of the segregated co-encapsulation of two
 234 hydrophobic actives within a lipid particle (SLN2) stabilised o/w Pickering emulsion microstructure.

235

236 Regarding the release kinetics of DMP contained within the oil droplets of the SLN2-stabilised o/w
 237 emulsions, the active was almost entirely discharged within 48 hours (*Figure 3A*). In current literature,
 238 active release from emulsion droplets has been discussed using two mechanisms; a diffusion-limited
 239 model or an interfacial barrier-limited model [35,43]. Application of the diffusion-limited and the Crank
 240 models gave diffusion coefficients in the range of $10^{-13} \text{ cm}^2 \text{ s}^{-1}$. However, these values are significantly
 241 lower to the diffusion coefficient estimated using the Stokes-Einstein equation ($D = 8.5 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$).
 242 What is more, a study [44] on the release of tetracaine, a moderately hydrophobic molecule, from
 243 medium chain triglyceride emulsion droplets stabilised by lecithin reported a diffusion coefficient value
 244 of $5.46 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. Therefore, there is clear indication that DMP release in the current systems is not
 245 limited by diffusion (*Table S2 & Figure S3*). Instead, applying the interfacial barrier-limited model to
 246 the DMP release profile gave an interfacial rate constant (k_i) of $3.09 \times 10^{-12} \text{ cm}^2 \text{ s}^{-1}$, which is slightly
 247 higher but comparable to the value reported for DMP-loaded o/w Pickering emulsions stabilised by
 248 NaCaS/CS co-precipitates, which also followed an interfacial barrier controlled release [19], in addition
 249 to other literature on the release of hydrophobic actives from emulsions [40,43]. It is therefore evident,
 250 that the SNL2 fabricated in the presence of WPI offer a significant barrier for the passage of DMP into
 251 the external phase (*Figure 3B*).

252 **3. Conclusions**

253 In conclusion, the present proof-of-principle study demonstrates that the approach proposed by
254 Spyropoulos *et al.* [19] can be applied to SLN-stabilised emulsions to enable the co-encapsulation and
255 independent co-delivery of two segregated actives. The current work significantly extends previous
256 research efforts in the area of compartmentalised multi-delivery of actives using liquid-based systems
257 [8,9,17,18], by confirming that the employed co-encapsulation strategy is applicable to both w/o and
258 o/w simple emulsions and can be utilised for the co-delivery of different combinations of actives with
259 varying degrees of hydrophilicity/hydrophobicity. In addition, the current preliminary findings
260 underline the effect of the emulsifier used during fabrication of SLNs on the attainment of different
261 release profiles from the SLN-stabilised Pickering emulsions, a concept that has been previously
262 described only for o/w emulsions [14]. Overall, this exploratory work greatly enhances the versatility
263 and flexibility of the co-encapsulation/co-delivery simple emulsion strategy reported previously [19],
264 and thus significantly aid research efforts towards the realisation of multi-active delivery approaches
265 from liquid formulations. Further research should focus on confirming and fully understanding the
266 release mechanisms proposed here, studying additional Pickering colloidal species that can be
267 functionalised in the same manner and investigating means to expand the currently-realised co-release
268 kinetics arsenal. The ultimate research goal is to be able to routinely and robustly fabricate such liquid-
269 based formulations and to realise their potential applications in the foods, pharmaceuticals, agrochemical
270 and cosmetics sectors.

271

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277

278

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280

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Supplementary Data for:

Independent co-delivery of model actives with different degrees of hydrophilicity from oil-in-water and water-in-oil emulsions stabilised by solid lipid particles via a Pickering mechanism: a-proof-of-principle study

S1. Experimental Section

S1.1 Materials

Tripalmitin (purity $\geq 85\%$), Sudan III, silicone oil, mineral oil, dimethyl phthalate (DMP, $\geq 99\%$), potassium sorbate ($\geq 99\%$) and Tween 20 (HLB = 16.7) were purchased from Sigma Aldrich (UK). Whey protein isolate (WPI) was kindly gifted by Davisco (Davisco Foods International). Sodium chloride (NaCl, technical grade) was purchased from Fischer Scientific (UK). Commercially available sunflower oil was used for emulsions preparation. Distilled water (pH = 6.8, $1.63 \mu\text{S cm}^{-1}$) was employed throughout this study. All materials were used without further purification. All compositions are reported as weight of the individual substance per weight of the total system; % (w/w).

S1.2 Methods

S1.2.1 Preparation of solid lipid nanoparticles

For the preparation of solid lipid nanoparticles (SLN), a melt-emulsification-ultrasonication method was followed that has been previously described elsewhere [S1]. SLN particles were fabricated in the presence of either Tween 20 (SLN1) or WPI (SLN2), both at 5% (w/w). Briefly, 5% (w/w) of tripalmitin used as the solid lipid was heated up to 75°C (approximately 10°C higher than the melting point of the lipid) and was added to the aqueous phase containing the surfactant heated at the same temperature, while mixed with a magnetic stirrer. The hot premix was then homogenised using a high intensity ultrasonic processor (Vibra Cell VCX 500, Sonics, USA) operating continuously for 3 min using a 12 mm probe (20 kHz, 95% amplitude). The dispersions formed were subsequently cooled down to $\sim 4^\circ\text{C}$ using an ice bath. SLNs were prepared with 0.05% (w/w) of the hydrophobic model active Sudan III. To ensure complete solubilisation of the active in the lipid phase, Sudan III and tripalmitin were stirred together above the melting point of the lipid for approximately 0.5 h. 0.01% (w/w) of potassium sorbate was used as a preserving/antimicrobial agent in all formulations. To avoid phase inversion due to the presence of excess Tween 20, the aqueous SLN1 dispersions used as the included phase in the preparation of w/o emulsions were dialysed using distilled water by immersing the colloidal suspensions in pre-hydrated cellulose tubing (35 mm width, 12 kDa MW cut-off; Sigma Aldrich, UK). To ensure full removal of the excess surfactant, the distilled water was refreshed until a constant surface tension value was obtained. Unless otherwise stated, all SLN aqueous dispersions were kept at 4°C .

S1.2.2 Preparation of Pickering emulsions

All w/o and o/w emulsions were prepared using commercially available sunflower oil, silicone oil or mineral oil without further purification. Unless stated otherwise, sunflower oil was the oil phase used for emulsion production. For w/o emulsions, 20% (w/w) of the aqueous phase containing SLN1 were combined with 2% (w/w) of the model hydrophilic active NaCl (10% w/w solution) and 78% (w/w) oil phase. For o/w emulsions, 80% (w/w) of the aqueous phase containing SLN2 were combined with 19.8% (w/w) of oil phase and 0.2% (w/w) of the model hydrophobic active DMP. The mixtures were then homogenised using a high-shear mixer (Silverson L5M, Silverson Machines Ltd, UK) at 10,000 rpm for 2 minutes, while cooled in an ice bath to avoid shear-induced heating of the samples and melting of the lipid particles. The final composition of the SLN-stabilised Pickering emulsions is given in *Table S1*. Based on theoretical calculations, the quantity of SLNs used in either systems is enough to provide complete surface coverage of the emulsion droplets. Unless otherwise stated, all emulsions were stored at 4°C.

Table S1. Composition of Pickering stabilised w/o and o/w emulsions by tripalmitin solid lipid nanoparticles (SLN).

SLN1-stabilised w/o emulsions			SLN2-stabilised o/w emulsions		
Phase	Component	Composition (%)	Phase	Component	Composition (%)
SLN1-containing aqueous phase	<i>Tripalmitin</i>	1	Oil phase	<i>Sunflower oil</i>	19.8
	<i>Tween 20</i>	1*		<i>Dimethyl phthalate (DMP)</i>	0.2
	<i>Sudan III</i>	0.01	SLN2-containing aqueous phase	<i>Tripalmitin</i>	4
	<i>Potassium sorbate</i>	0.01		<i>WPI</i>	4
	<i>NaCl</i>	0.2		<i>Sudan III</i>	0.04
	<i>Distilled H₂O</i>	19.78		<i>Potassium sorbate</i>	0.01
Oil phase	<i>sunflower, mineral, or silicone oil</i>	78	<i>Distilled H₂O</i>	71.95	

*The % composition of Tween 20 refers to the amount used for the production of SLN1 before dialysis.

S1.2.3 Microstructure characterisation

Characterisation of the SLN and emulsion microstructures formed in this work was carried out following the procedures used by Pawlik *et al.* [S1] *Size measurements*. Laser diffraction (Mastersizer[®] Hydro 2000SM, Malvern, UK) was performed to measure the size of the lipid nanoparticles and the droplet size of o/w emulsions, and pulsed field gradient NMR (Bruker Minispec, UK) to measure the size of the w/o emulsions. *Microscopy*. Images of the tripalmitin particle dispersions were obtained using a Phillips XL30 FEG Cryo Scanning Electron Microscope (SEM) equipped with a Gatan low temperature unit. An emulsion drop was placed on an analysis slide and dipped into nitrogen at -198°C.

The slide was then directly inserted into a preparation chamber at -180°C , where it was fractured and etched for 5 min at -90°C . The surface was subsequently coated in gold and imaged at -130°C .

S1.2.4 Release measurements

Release experiments for the lipophilic active Sudan III encapsulated within the SLN1 or SLN2 particles were carried out by placing a known quantity (40-45 g) of the SLN-stabilised Pickering emulsions, either the o/w or w/o systems, at the bottom of a beaker and gently topping it up with 50 g of excess (pure) oil (sunflower, silicone, or mineral oil) serving as the acceptor phase. Aliquots (~ 1 mL) were withdrawn at timed intervals from the acceptor phase (oil phase), passed through a syringe filter ($0.2\ \mu\text{m}$ pore size) and analysed using ultraviolet-visible (UV-VIS) spectroscopy (Thermo-Scientific[®], UK) at $\lambda = 510\ \text{nm}$. The release of NaCl from the SLN1-stabilised w/o emulsion droplets was studied by gently adding ~ 45 g of the emulsion on top of ~ 70 g of distilled water which were already placed in a beaker (external phase). A probe (S30 SevenEasy[™] fitted with an InLab[®] 710 platinum 4-plate electrode, Mettler Toledo, UK), which was pre-positioned at the bottom of the beaker, was used to measure the conductivity of the external aqueous phase at regular time intervals. DMP release from the SLN2-stabilised o/w emulsion droplets was measured by placing ~ 10 g of the emulsion inside a pre-hydrated cellulose tube (Sigma Aldrich Company Ltd., UK, 35 mm width, M.W. cut-off of 12 kDa) and dialysed to a large quantity (~ 100 g) of water (acceptor phase) in order to create sink conditions. Aliquots of ~ 1 mL were withdrawn from the acceptor phase at regular time intervals, pressed through a syringe filter ($0.2\ \mu\text{m}$ pore size) and analysed using UV-VIS spectroscopy (at $\lambda = 290\ \text{nm}$). During preliminary studies, it was shown that the DMP release rate from the oil droplets was controlled by transfer across the interface of the emulsion rather than limited by the passage of the active across the dialysis membrane. In all cases, the amount of active released into an acceptor phase was determined using previously obtained calibration curves. All release experiments were performed at room temperature.

S2. Results

S2.1 Effect of oil type on the release kinetics

The effect of the type of oil used as the continuous phase in the w/o emulsions on the release kinetics of NaCl encapsulated within the water droplets was investigated. A number of oils with different polarities were chosen; sunflower oil, mineral oil and silicone oil. NaCl release was monitored over a period of 17 days (*Figure S1*).

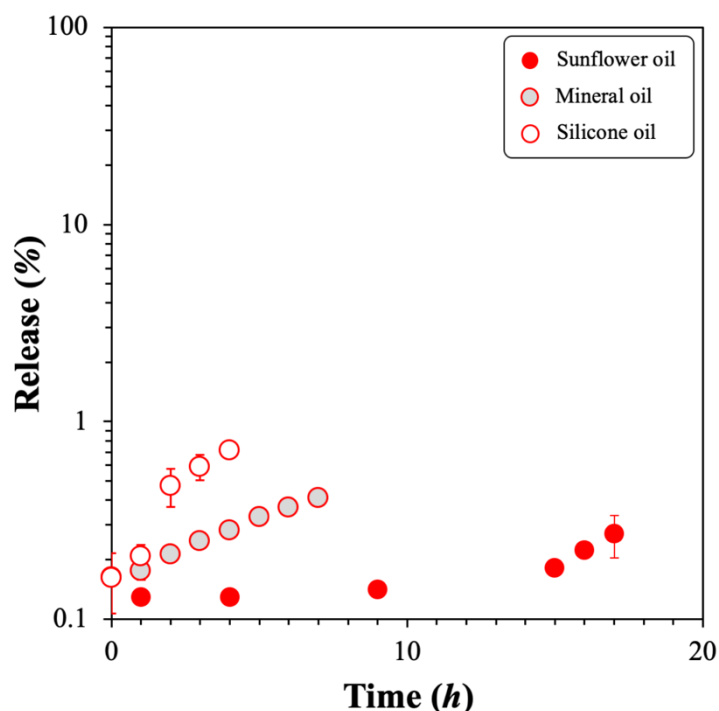


Figure S1. Release profile of model hydrophilic active NaCl from w/o Pickering emulsions prepared using three different types of oils, sunflower, mineral and silicone oil, stabilised by solid lipid nanoparticles (SLN1) containing a hydrophobic active (Sudan III).

S2.2 Modelling of release data

Various empirical and semi-empirical release kinetic models (First order, Higuchi, Hixson-Crowell, Baker-Lonsdale, Makoid-Banakar, Weibull) were evaluated for their capacity to describe the individual release profiles obtained for only those actives exhibiting appreciable release; these were Sudan III (encapsulated within the SLN1 particles stabilising w/o Pickering emulsion droplets) and DMP (encapsulated within the oil droplets of the SLN2-stabilised o/w emulsions). Fitting was performed using the Curve Fitting ToolboxTM 3.5.11 in Matlab[®] R2020a (MathWorks Inc., Natick, MA, USA). The coefficient of determination (R^2), the adjusted coefficient of determination (R_{adj}^2) and the root mean square error (RMSE) were used as model selection indicators. Only the Makoid-Banakar and Weibull models were deemed capable of providing satisfactory fits to the experimental data; the results for these models are presented in *Table S2*.

Mechanistic models were also examined for their ability to describe the Sudan III and DMP release profile data. Regarding the release of Sudan III from SLN1, the expression proposed by Crank [S2] gave ($R^2 = 0.99$) an effective diffusion coefficient (D) of $3.12 \times 10^{-14} \text{ cm}^2 \text{ s}^{-1}$ (*Table S2*). Guy *et al.* [S3] developed a diffusion-limited model that assumes that the release of an active is predominantly governed by its diffusion through the matrix of the spherical enclosure containing it. The diffusion coefficient calculated in this case gave a D value of $3.11 \times 10^{-14} \text{ cm}^2 \text{ s}^{-1}$ ($R^2 = 0.98$); thus very close to the diffusion coefficient determined by the Crank model (*Table S2*).

Release of actives encapsulated within emulsion droplets (as in the case of DMP discharge from the SLN2-stabilised o/w emulsions studied here) has been discussed using two limiting mechanistic models [S3]. According to these, release can either be limited by diffusion of the active through the phase that constitutes the emulsion droplet, or driven by transfer across the interfacial barrier present at the surface of the droplet [S3,S4]. Application of the diffusion-limited model ($R^2 = 0.94$) lead to a diffusion coefficient value of $6.98 \times 10^{-13} \text{ cm}^2 \text{ s}^{-1}$ (Table S2); fitting the Crank model gave a similar value of $7.22 \times 10^{-13} \text{ cm}^2 \text{ s}^{-1}$ ($R^2 = 0.93$). Fitting of the empirical and semi-empirical models revealed that the Weibull and Makoid-Banakar models were able to provide good fits to the experimental data (Table S2).

The release profiles for both Sudan III and DMP, as generated using the model parameters given in Table S2, are presented (together with the experimental release data) in Figures S2 and S3, respectively.

Table S2. Best fit parameters to relevant empirical, semi-empirical and mechanistic kinetic models for the release of Sudan III (encapsulated within the SLN1 particles stabilising w/o emulsion droplets) and DMP (encapsulated within the oil droplets of the SLN2-stabilised o/w emulsions).

Model	Equation	Sudan III				DMP			
		Parameters	R^2	R^2_{adj}	RMSE	Parameters	R^2	R^2_{adj}	RMSE
<i>Makoid-Banakar</i> [S5]	$Q_t = k_{MB} t^n \exp(-kt)$	$k_{MB} = 82.28$ $n = 0.08$ $k = 0.001$	0.78	0.55	28.69	$k_{MB} = 86.10$ $n = 0.21$ $k = 0.06$	0.93	0.78	8.88
<i>Weibull</i> [S5]	$\frac{Q_t}{Q_\infty} = 1 - \exp\left(-\frac{t^\beta}{\alpha}\right)$	$\alpha = 0.55$ $\beta = 3.26$	0.99	0.99	2.14	$\alpha = 0.59$ $\beta = 0.36$	0.92	0.87	6.68
<i>Crank</i> [S2]	$\frac{Q_t}{Q_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{Dn^2\pi^2 t}{r^2}\right)$	$D =$ 3.12×10^{-14}	0.99	0.99	15.57	$D =$ 7.22×10^{-13}	0.93	0.93	11.67
<i>Guy Diffusion-limited</i> [S3]	$\frac{Q_t}{Q_\infty} = 1 - \frac{6}{\pi^2} \exp\left(-\frac{\pi^2 D}{r^2} t\right)$	$D =$ 3.11×10^{-14}	0.98	0.98	20.80	$D =$ 6.98×10^{-13}	0.94	0.94	6.18
<i>Guy Interfacial barrier-limited</i> [S3]	$\frac{Q_t}{Q_\infty} = 1 - \exp\left(\frac{-3k_I}{r^2} t\right)$	$k_I =$ 5.62×10^{21}	0.34	0.34	45.88	$k_I =$ 3.09×10^{-12}	0.94	0.94	20.76

R^2 : coefficient of determination; R^2_{adj} : adjusted coefficient of determination; RMSE: root mean square error; Q_t : amount of active released at time t ; Q_∞ : total amount of active released when the formulation is exhausted; k_{MB} : release constant (*Makoid-Banakar*); n , k : empirical parameters (*Makoid-Banakar*); α : scale parameter (*Weibull*); β : shape parameter (*Weibull*); n : dummy variable (*Crank*); r : particle/emulsion droplet radius, D : apparent diffusion coefficient of the active within the system, k_I : interfacial rate constant. The values for D and k_I are given in $\text{cm}^2 \text{ s}^{-1}$.

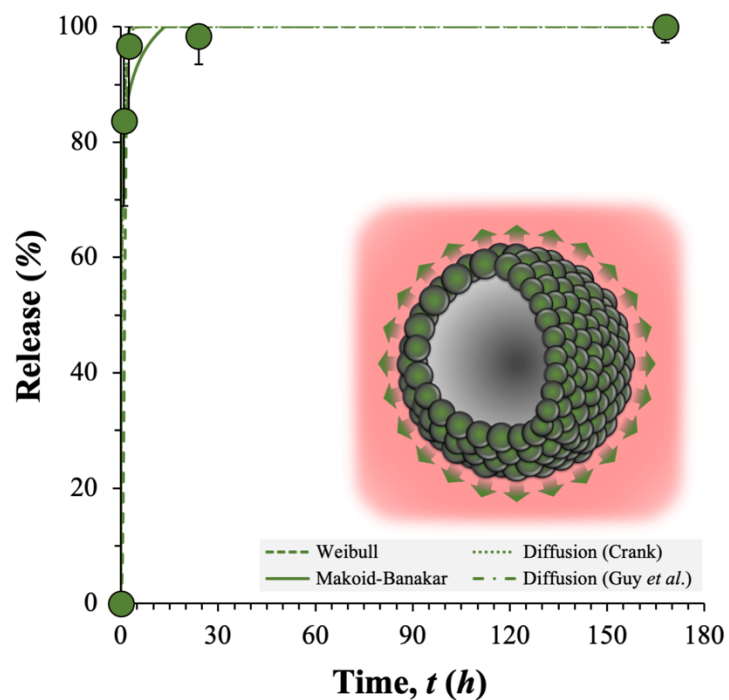


Figure S2. Release kinetic model fitting for Sudan III (encapsulated within the SLN1 particles stabilising w/o emulsion droplets) for the empirical and semi-empirical Weibull and Makoid-Banakar models, and for the mechanistic models for diffusion-controlled release proposed by Crank [S2] and Guy *et al* [S3].

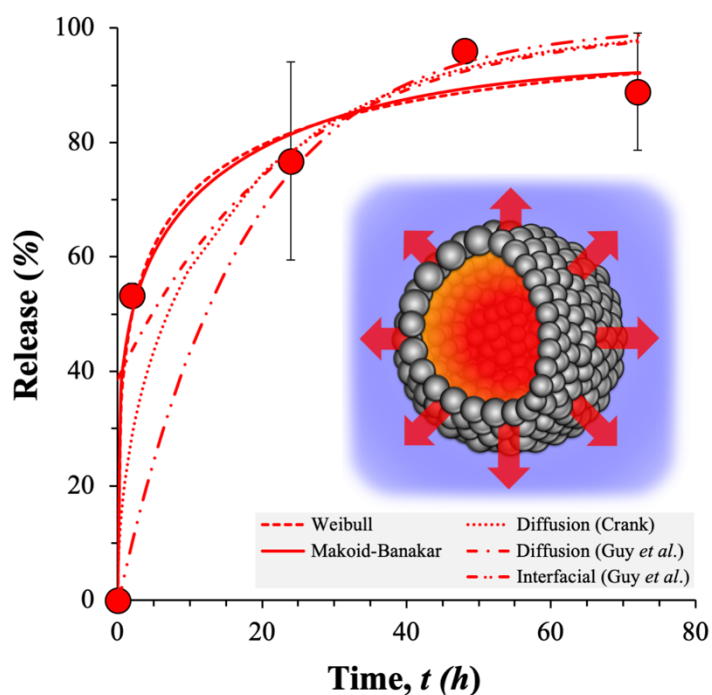


Figure S3. Release kinetic model fitting for *DMP* (encapsulated within the oil droplets of the SLN2-stabilised o/w emulsions) for the empirical and semi-empirical Weibull and Makoid-Banakar models, and for the mechanistic model for interfacial barrier-limited release proposed by Guy *et al*. [S3].

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