Tuning nanophase separation and drug delivery kinetics through spray drying and self-assembly†

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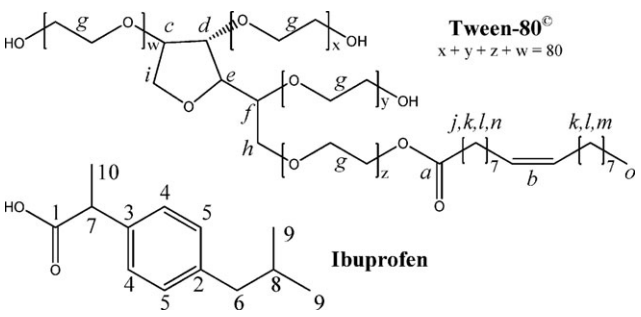
A new one-pot synthesis route associating sol–gel, self-assembly and spray drying allows the formation of microspheres with tuneable textures (worm-like mesophases, separated spheroid nanodomains, core–shell organisation) and drug delivery properties (from burst to delayed release).

Sol–gel methods associated with self-assembly and spray drying processes[1,2] open up new possibilities for the formation of drug delivery systems (DDSs). Several advantages are indeed related to these methods, among which are the versatility of their chemical composition, the promotion or inhibition of nanometre-scale phase separations and the control of their final morphology. Until now, these methods have often been used separately and in two distinct directions. The first direction associates sol–gel (hydrolysis and condensation of alkoxide precursors) and spray drying (alcoholic solutions containing the drug and the intermediate oxo-alkoxide oligomers).[3] The drug release kinetics of the resulting oxide-based microspheres then depend on the spatial distribution of the drug, and to some extent on the matrix's dissolution processes. The second direction consists of the adsorption of drugs by mesoporous materials, preliminarily formed by sol–gel and self-assembly,[4,5] and more recently by spray drying.[6] In theses cases, the drug confined in the mesopores forms nanoscale connected domains, and the kinetics of drug release depend on the porous texture and surface chemistry.[7,8]

Here, we have chosen a third direction that allows full investigation of the potential of sol–gel, self-assembly and spray drying processes to directly form new textured materials, acting as DDSs with tuneable properties. Spray drying also has the advantages of being a scalable process, and reducing the number of steps. In addition, we consider a one-pot synthesis in which oxo-alkoxide oligomers, drug and surfactant molecules are mixed together in solution. Spray drying of these solutions leads to fast solvent evaporation from the atomised droplets, during which the chemicals interact together, eventually phase-separate inside the droplets and form the final microspheres. In particular, we show how simple tuning of the drug and surfactant content can lead to very different drug dispersions at the nanometre scale, and consequently to very different drug release profiles.

The new spray dried microspheres were obtained by adapting a preliminary one-pot synthesis[9] to incorporate a poorly water-soluble model drug, ibuprofen, and to use a non-ionic surfactant, polysorbate Tween-80©, a known pharmaceutical excipient (Scheme 1). Firstly, hydrolysis and condensation of the siloxane precursor was promoted by mixing together tetraethoxysilane (TEOS), isopropanol (^{i}PrOH) and an aqueous acidic solution (HCl, 0.1 M) by stirring for 24 h. Ibuprofen and Tween-80© were then added and the solution spray dried. The collected powders were further dried for 6 d (for more details see the Experimental section and ESI 1†). This synthesis procedure gave reproducible results, and a series of spray dried samples was prepared by varying the molar ratio $r_{ibu/tw}$ between ibuprofen and Tween-80© from 0 to 7. From this series, we focused on the properties of two representative samples, **A** and **B**, for which $r_{ibu/tw}$ = 2 and 5, respectively (Table 1). Sample **C**, without surfactant ($r_{ibu/tw} = \infty$) and an identical amount of ibuprofen as in sample **A**, was also synthesised. All the drug and surfactant molecules present in the solution were incorporated into the final microspheres, as confirmed by elemental, thermogravimetric and NMR analyses. Isolated or slightly agglomerated spherical particles were observed by SEM, with their size distribution modelled using a log-normal function (see ESI 2†), in agreement with previous work.[9,10] The geometric mean diameters, D_{GM}, were in the 1.4–2.0 μm range (see ESI 1†).

The spray dried microspheres possessed very contrasting delivery properties. The differences in the *in vitro* drug release profiles between samples **A**, **B** and **C** can be appreciated in Fig. 1.‡ As a general trend, the greater the surfactant content



Scheme 1

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† Electronic supplementary information (ESI) available: Supplementary characterisation data, SEM, variation of d_{corr} and TEM. See DOI: 10.1039/b9nj00773c

Table 1 Synthesis conditions and release properties (Weibull model)

Sample	A	B	C
Synthesis			
Ibuprofen/mg g^{-1} SiO_2[a]	156	286	156
$r_{ibu/tw}$	2.0	5.0	∞
Release properties			
Q_0 (%)	60	59	48
b	0.85	1.50	2.60
t_{lag}/min	0.8	2.2	8.5
t_{scale}/min	8	118	6483
r^2	0.999	0.998	0.998

[a] The amount of ibuprofen introduced into the sol over the amount of SiO_2 formed after condensation.

(or the smaller the $r_{ibu/tw}$ ratio), the faster the release is. We also observed that the shape of the release curve strongly depends on $r_{ibu/tw}$: from a near exponential increase for **A** to a sigmoidal curve for **C**. Herein, the release kinetics can be finely tuned by varying $r_{ibu/tw}$.

These contrasting release profiles can be fitted remarkably well (Fig. 1, high correlation coefficients r^2) using the empirical Weibull model adapted to heterogeneous systems.[11] Within this model, the ratio $Q(t)/Q_0$ between the cumulative percentage of drug released at time t and at infinite time is:

$$Q(t)/Q_0 = 1 - \exp[-(t - t_{lag})^b/t_{scale}] \quad (1)$$

where t_{lag} is the lag time before drug release takes place, t_{scale} is indicative of the timescale for the release process and b characterizes the shape of the release curve. All the resulting values for the kinetic parameters (Table 1) show a gradual increase with $r_{ibu/tw}$ and are consistent with preliminary qualitative observations: burst release for **A** ($b < 1$), sigmoidal release for **C** ($b > 1$) and an intermediate release profile for sample **B**.

The effect of $r_{ibu/tw}$ on the kinetic parameters cannot be explained by the small differences in morphology.§ Therefore, the explanation is more likely to be found in the spatial distribution and accessibility of the ibuprofen and/or in its

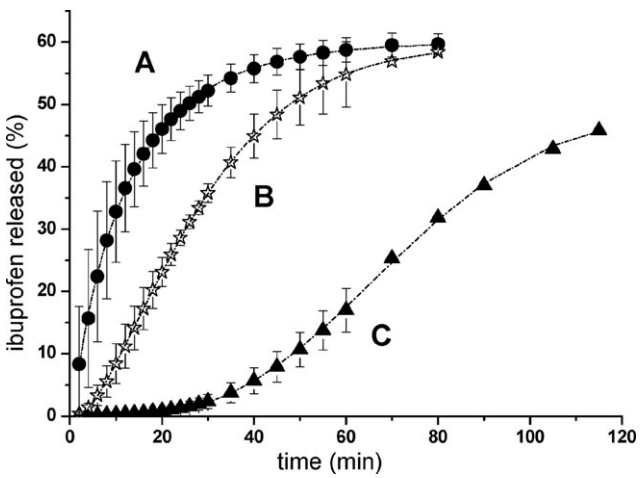

Fig. 1 Cumulative *in vitro* release profiles of ibuprofen in simulated intestinal fluid (pH = 7.4, 310 K). Error bars represent the standard deviation for three measurements; lines are obtained by fitting the experimental data points using the Weibull model described in the text.

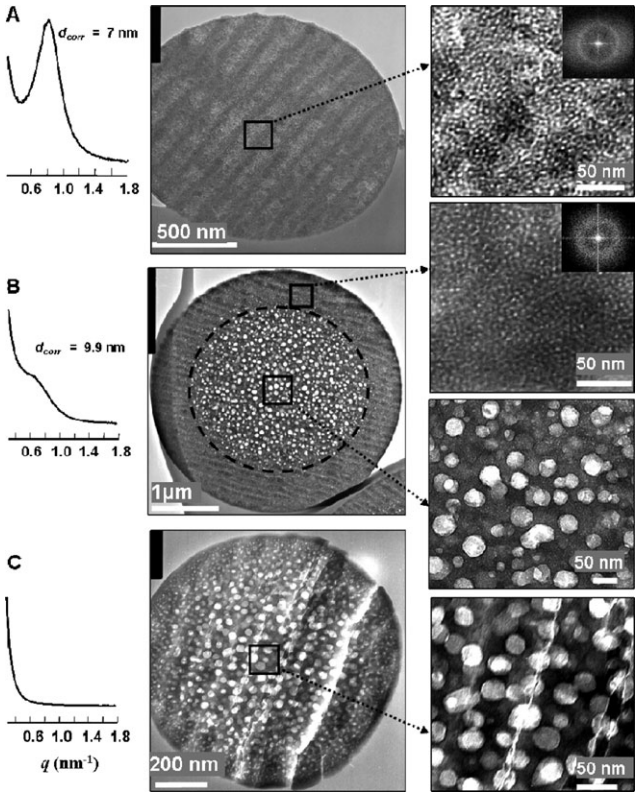

Fig. 2 SAXS patterns (left) and TEM micrographs (middle and right) of samples **A**, **B** and **C**. 2D FFTs of the TEM micrographs are also shown to illustrate the uniformity of the worm-like mesophase.

physical state. From a TEM analysis (middle/right-hand side of Fig. 2), it clearly appears that the three samples have very different textures. In the case of sample **A**, a worm-like mesophase is observed throughout, consistent with the scattering peak observed by SAXS (left-hand side of Fig. 2). The SAXS and TEM correlation distances, d_{corr}, are almost identical (7 and 6.8 nm, respectively), and are also close to the micelle size of the Tween-80© surfactant measured in parallel by DLS in acidic water (pH = 2, average diameter 9 ± 1 nm). Therefore, the texture of sample **A** corresponds to a non-ordered worm-like mesophase composed of surfactant aggregates and formed by self-assembly during spray drying.[1,2] In parallel experiments, we have also noticed that d_{corr} increases linearly with $r_{ibu/tw}$ in the range $0 \leq r_{ibu/tw} < 6$ for our series of samples prepared under the same conditions (see ESI 3†). This observation suggests that the surfactant's aggregates solubilize the drug molecules within this worm-like mesophase.

On the contrary, sample **C** does not present this texture. Instead, we observe in the TEM micrographs clear spheroid domains with diameters (20–100 nm) that decrease radially from the core to the surface of the spheres. Such domains, never previously observed in microspheres made solely from siloxane oligomers, are assigned to phase-separated amorphous ibuprofen (no crystal phase detected by wide angle XRD). The phase separation at this nanometre scale occurs during the fast solvent evaporation step, probably when the ibuprofen becomes less soluble in the residual medium. The

presence of larger domains in the core signifies that the solvent content during the evaporation step can be more important at the surface after the thermal equilibration of the droplets, as discussed previously.[10]

For sample **B**, with an intermediate $r_{ibu/tw}$, the texture is more complex. At the sphere surface, a worm-like texture similar to that of sample **A** and leading to a scattering peak, is observed. Meanwhile, the sphere cores exhibit a spheroid domain of amorphous ibuprofen, similar to that of sample **C**. An explanation for this complex core–shell texture is the preferential location of the surfactant molecules at the air–liquid interface during droplet drying. The surfactant content at the core of the droplets is then definitively reduced, ibuprofen is no longer solubilised and phase separation occurs.

Additional information about the local molecular environment of the drug can be obtained by ^{13}C solid-state NMR spectroscopy (Fig. 3). The isotropic chemical shift, δ_{iso}, and width, $\Delta\nu_{\frac{1}{2}}$, of the ibuprofen peaks vary between samples. In particular, significant differences are noticed for COOH (no. 1 in Fig. 3), the more hydrophilic and reactive group of the drug. A single narrow peak is observed for sample **C** ($\Delta\nu_{\frac{1}{2}} = 32$ Hz), whereas a broad peak is observed for sample **A** ($\Delta\nu_{\frac{1}{2}} = 158$ Hz) and two overlapping narrow and broad peaks are observed for sample **B**. Neither narrow nor broad peaks were easily observed by $^{13}C\{^1H\}$ cross-polarisation MAS, suggesting a high level of mobility.[12] Narrow peaks have been observed for neat ibuprofen, either when forming macroscopic crystals[12] or when confined in the nanoscale-connected domains of mesoporous samples.[12,13] Here, we assign the narrow peak to neat ibuprofen forming separated nanodomains, similar to those observed by TEM for samples **B** and **C**. The broad peak more likely corresponds to a distribution of chemical shifts related to a distribution of local environments. This can be assigned here to ibuprofen molecules solubilised by surfactant aggregates present in samples **A** and **B**.

From all of these textural and structural data, we are able to propose a general model for the tuneable release properties observed. These properties are driven by the accessibility of ibuprofen to the aqueous medium. In the case of high surfactant content samples such as **A**, the fast ibuprofen release ($b < 1$, small t_{lag} and t_{scale} values) observed is related to the diffusion of the drug through the worm-like mesophase formed by the surfactant's aggregates. In the case of samples not containing surfactant, such as **C**, the ibuprofen is not homogeneously distributed and forms nanodomains whose size increases from the surface to the core of the microspheres. The accessibility of these nanodomains implies a delayed and longer release (increased t_{lag} and t_{scale} values) associated with a sigmoidal profile ($b > 1$). Intermediate sample **B** shows intermediate structural and kinetic properties, demonstrating the tuning capability of our synthesis procedure.

In summary, the combination of sol–gel, self-assembly and spray drying in an easily scalable and reproducible one-pot synthesis route allows the formation of siloxane-based microspheres containing the model drug ibuprofen. Drug nanodomains within inorganic networks can be easily obtained by this one-pot procedure. Moreover, depending on the application aim (*e.g.* fast *vs.* sustained release), the properties of these DDS materials can be easily tuned by changing the synthesis parameters, such as the drug content and surfactant molecules, as well as the chemical surface of the siloxane network. Tuning the hydrophilic–hydrophobic balance of the drug and/or the surfactant will also modify the extent and nature of the nanometre-scale phase separation, leading to additional possibilities in terms of release properties. We are currently working on these further developments, which, in particular, will demonstrate higher percentages of release.

Experimental

Synthesis

The described one-pot synthesis procedure consists of mixing together TEOS, ^{i}PrOH and an aqueous acidic solution (HCl, 0.1 M); the molar proportions were fixed at TEOS : ^{i}PrOH : H_2O of 1 : 10 : 10 (2×10^{-2} moles of TEOS were employed). The solution was stirred for 24 h in a closed vessel maintained at 298 ± 1 K. Tween-80© and ibuprofen were added and

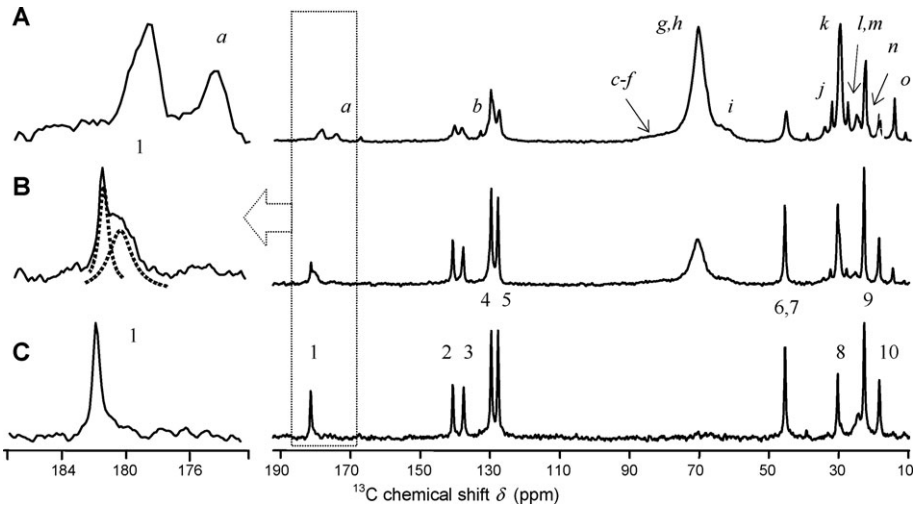

Fig. 3 $^{13}C\{^1H\}$ NMR solid-state spectra of **A**, **B** and **C**. The numbers and letters correspond to the ^{13}C NMR signals of ibuprofen and Tween-80©, respectively, using the notation shown in Scheme 1.

dissolved with vigorous stirring 15 min before spray drying. The amount of ibuprofen incorporated and the molar ratio between ibuprofen and Tween-80©, $r_{ibu/tw}$, are presented in Table 1.

Spray drying was undertaken using a Büchi Mini-Spray Dryer B-290 apparatus fitted with a two-fluid nozzle (inner diameter of 0.7 mm, sol and compressed air volumic flow rates fixed at 0.34 and 357 L h^{-1}, respectively) and an inert loop containing a de-humidifier and a solvent condensation unit. The spray drying gas was dried nitrogen. The inlet and outlet temperatures were 373 and 338 K, respectively. An overpressure of 3×10^3 Pa before gas filtering insured small particle residence times ($\approx$1 s). Particles were collected by a cyclone and the gathered powder dried for 6 d at 328 K. The final yields were between 50 and 80%. All the drug and surfactant molecules present in the solution were incorporated in the final microspheres, as confirmed by elemental, thermogravimetric and NMR analyses. This synthesis procedure gave reproducible results.

Characterisation methods

SAXS. X-Ray scattering experiments were carried out on solid powders in 1.5 mm diameter glass capillaries within a transmission configuration and 2D detection (image plate). A copper rotating anode X-ray source operating at 4 kW with a monochromator giving high flux (10^8 photons s^{-1}) and punctual collimation was employed. Diffracted intensity was corrected by exposition time; transmission and intensity background coming from diffusion by an empty capillary.

SEM. Micrographs were obtained from metallized samples using a Hitachi 4800 S microscope.

TEM. A JEOL 1200 EX2 microscope operating at 100 kV was used for TEM analysis. The microspheres were trapped in a resin and cut into slices ($\sim$70 nm thick) by ultramicrotome.

Solid-state NMR. Solid-state $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian 400 spectrometer ($\nu_0\{^{13}C\} \equiv 100.6$ MHz) using 7.5 mm zirconia rotors spun at 5.5 kHz MAS frequency with 90° single pulses, ^1H decoupling during acquisition and a 30–60 s recycle delay. RF field strengths were kept close to 50 kHz.

Release assay. The *in vitro* release of ibuprofen was performed in simulated intestinal fluid (pH = 7.4) for 80–120 min using dissolution in a flow-through Sotax cell in order to simulate the behaviour of the material after oral administration.[14] A Shimadzu HPLC apparatus with a UV-visible adsorption detector was used to obtain the dosage (λ = 260 nm).

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‡ After release experiments, the morphology and texture showed no clear modification, as verified by SEM, SAXS and TEM, indicating the macroscopic stability of the microspheres.
§ Moreover, the slightly agglomerated and larger microspheres (ESI,† sample **A**) have the fastest release, although their surface-to-volume ratio is lower.

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