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PAPER

## **Organic–inorganic hybrid polysilsesquioxane nanospheres as UVA/UVB** absorber and fragrance carrier<sup>†</sup>

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To avoid the photocatalysis property of inorganic UV absorbers, such as TiO<sub>2</sub> and ZnO nanoparticles, and to utilize the minimal transdermal penetration and non-sticky nature of particulate silica particles, whilst at the same time fully harnessing the UV absorption characteristics of organic chromophores, hybrid organic–silica particles with UVA/UVB absorptive chromophores as part of their network structures were synthesized. Two UV absorptive hybrid nanospheres, poly[propyl-4methoxycinnamamide silsesquioxane] (PTES4C) and poly[propyl-2,4-dimethoxycinnamamide silsesquioxane] (PTES24C), were synthesized through the hydrolysis-polycondensation of triethoxysilylpropyl-4-methoxycinnamamide (TES4C) and triethoxysilylpropyl-2,4-dimethoxycinnamamide (TES24C), respectively. Optimization of the catalyst type (acid, base or self-catalysis) and solvent (ethanol) and monomer concentrations, led to a high yield (71–73%) preparation of the two nanospheres. The two spheres displayed good sun protection factor (SPF) and UVA protection factor (UVA-PF) when used in a gel based formulation. The labile and volatile fragrant citronellal could be effectively loaded into the PTES4C spheres at 35–48% (w/w) *via* the *in situ* hydrolysis–polycondensation reaction under self-catalysis conditions, and the obtained citronellal-loaded nanospheres demonstrated clear sustained controlled release of the citronella characteristics.

#### Introduction

It is well accepted that both UVB (280–315 nm) and UVA (315–400 nm) are harmful to human skin,<sup>1,2</sup> and so the use of sunscreen is seriously recommended.<sup>3,4</sup> Sunscreen, both organic types, such as 2-ethylhexyl-*p*-methoxycinnamate (EHMC), benzophenone, dibenzoylmethane and 2,4-bis{[4-(2-ethyl-hexyloxy)-2-hydroxyl]-phenyl}-6-(4-methoxyphenyl)-(1,3,5)-triazin, and inorganic types, such as titanium dioxide (TiO<sub>2</sub>) and zinc oxide (ZnO), are used at high percentages in sunscreen formulations. Advancements in organic synthesis and photochemistry have made available organic UV filters with adequate photostability.<sup>5-8</sup>

However, the systemic absorption of small organic UV filtering molecules across the skin is still a problem that needs more attention, since the materials are used daily over a large skin surface area<sup>9-11</sup> and the xenoestrogen-like activity of many

organic filters has been reported.<sup>12-14</sup> The idea of using organic polymers with a UV absorptive property to minimize systemic absorption has been demonstrated earlier. Examples of proposed polymeric UV filters include UV absorptive silicone,<sup>15</sup> oligoesters based on poly(*p*-alkoxycinnamate) and poly(pentaethylene glycol cinnamate)<sup>16</sup> and UV absorptive chitosan nanospheres.<sup>17</sup> Encapsulation of organic filters into either polymeric carriers<sup>18,19</sup> or inorganic silica particles<sup>20</sup> is another strategy used to lessen the transdermal absorption problem.

Inorganic filters, such as TiO<sub>2</sub> and ZnO, on the other hand, promise minimal systemic absorption due to their insoluble particulate nature, but raise concern over their potential safety due to their photocatalytic properties.<sup>21-27</sup> Organic–TiO<sub>2</sub> composite particles were recently fabricated using poly(methyl methacrylateco-sodium sulfopropyl lauryl maleate-co-2-hydroxy-4-(3-methacryloxy-2-hydroxylpropoxy) benzophenone).<sup>28</sup>

In order to appreciate the non-sticky nature and minimal transdermal penetration of silica particles, and at the same time fully harness the UV absorption characteristics of organic chromophores without concern over their systemic absorption and stickiness nature, covalent linkage between the two was proposed. To this end the UV absorptive chromophore, benzophenone 3, was linked to triethoxysilyl monomer, producing 2-(hydroxyl-4-(3-triethoxysilylpropoxy))diphenylketone and then this monomer was polymerized together with tetraethyl

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orthosilicate into hybrid organic–silica particles.<sup>29</sup> Subsequently, UVB absorptive trimethoxysilylpropyl-*p*-methoxycinnamamide and triethoxysilylpropyl-*p*-methoxycinnamamide were synthesized and then polymerized into UV absorptive spherical particles.<sup>30</sup> These two organic–silica hybrid UV filters were prepared using the ammonia catalyst process.<sup>31</sup>

We propose that UV filters in the form of nanoparticles can be made to function not only as UV filtering agents but also as carriers for volatile, labile or photo-unstable active molecules. The use of UV absorptive carriers for topical drugs or cosmetics should i) help protect the unstable active molecules from environmental threats (*e.g.* reactive oxygen species and light) and ii) reduce the use of unnecessary carriers for other active molecules in the formulation. With no unnecessary carrier, the skin will be in less contact with unnecessary chemicals. In addition, the UV absorptive spheres will serve not only as good reservoirs for delivering the loaded active molecules to the skin, but will also provide UV protection to both the skin and the encapsulated molecules.

Therefore, here we show the synthesis of organic-silica hybrid particles which possess UVA/UVB absorption characteristics and at the same time can be used as labile fragrance reservoirs. The work involves the synthesis of poly[propyl-2.4-dimethoxycinnamamide silsesquioxane] (PTES24C) and poly[propyl-4methoxycinnamamide silsesquioxane] (PTES4C) particles from triethoxysilane monomers containing the chromophoric 2,4dimethoxycinnamoyl and 4-methoxycinnamoyl moieties, using the sol-gel process. Evaluation of the catalysis conditions (base, acid and self-catalysis) was performed and optimized to obtain a process that gave a high yield but under mild enough conditions to be able to perform in situ polycondensation in the presence of labile fragrant molecules. The obtained spheres were evaluated for their UVA/UVB filtering efficiency in a gel based formulation. The encapsulation of the volatile and labile fragrant citronellal into the PTES4C nanospheres was carried out, and its controlled release was investigated and is reported.

#### **Result and discussion**

#### Synthesis of hybrid monomers

Two chromosphores, 4-methoxycinnamoyl moiety (UVB absorptive chromosphore,  $\lambda_{max} = 290-300$  nm) and 2,4-dimethoxycinnamoyl moiety (UVA/B absorptive chromosphore,  $\lambda_{\rm max} = 320-330$  nm) were successfully condensed with 3-aminopropyltriethoxysilane (APTES) to produce two UV absorptive hybrid monomers, triethoxysilylpropyl-4-methoxycinnamamide (TES4C) and triethoxysilylpropyl-2,4-dimethoxycinnamamide (TES24C), using a conventional amide bond formation reaction via acid chloride (Scheme 1). The purity of the synthesized TES4C, in terms of the amount of residual APTES was deduced from the <sup>1</sup>H-NMR spectrum of the product using the integration of peaks at 7.56 ppm (Ar-CH=) and 0.67 ppm (-CH<sub>2</sub>-Si-), and revealed a 2% (by mole) APTES residue (Fig. 1). Similarly, the amount of residual APTES in the TES24C was deduced from the <sup>1</sup>H-NMR spectral information (integration of peaks at 7.74 ppm (Ar-CH=) and 0.67 ppm  $(-CH_2-Si-)$ , Fig. 1) and found to be 8% (by mole) (see full NMR spectral interpretation in ESI<sup>+</sup>).

#### Polycondensation and sphere formation

The polysilsesquioxane products, PTES4C or PTES24C, in the form of spheres, as obtained from the hydrolysis–polycondensation of TES4C or TES24C in the presence of external catalysts (0.1% (v/v) HCl, 3% or 5% (v/v) NH<sub>4</sub>OH) and under self-catalysis conditions, were compared (Table 1). In addition, the amount of ethanol used in the reaction was also optimized.<sup>32,33</sup>

For both PTES4C and PTES24C, the acid-catalysis process gave the highest synthesis yields at 87.4% and 77.9%, respectively, but required by far the longest reaction time at 14 and 3 days, respectively. Self-catalysis gave the second highest synthesis yield at 74.2% and 73%, respectively, and only required 24 h to obtain stable and more uniform spheres compared with the other catalysts. Polymerization under the two basic conditions (3% and 5% (v/v) NH<sub>4</sub>OH) proceeded much faster, being complete within 1 h, but gave significantly lower yields (Table 1).

As the volume of ethanol used (as the monomer solvent) was increased, the particle size (anhydrous and hydrated) of the product increased and the product yield decreased (Table 1). The decrease in the product yield was usually accompanied by a more sticky mass being observed in the reaction. It should be noted here that the process with less than 20% (v/v) ethanol could not be carried out for TES4C in PTES4C synthesis, because the monomer solution was too viscous.

Considering the product yield, reaction time, morphology and uniformity of the spheres, the self-catalysis process was considered the most convenient process for the synthesis of both PTES4C (at 20% (v/v) ethanol) and PTES24C (at 10% (v/v) ethanol) nanospheres. Unlike with the acid catalysis, which gave a little higher yield for PTES4C synthesis (87.4% vs. 74.2%), but not for PTES24C (72.9% vs. 73%), the self-catalysis process required no neutralization nor washing of the product. The mild conditions of the self-catalysis process also provided a good possibility to perform encapsulation of labile compounds through *in situ* polymerization without harming the labile material.

The monomer concentration was then optimized for the selfcatalysis process where it was found that the higher the monomer concentration was, in general, the lower the obtained yield was, except for the 0.01 g ml<sup>-1</sup> and the 0.02 g ml<sup>-1</sup> TES4C that gave comparable yields and particle morphologies. Thus, a concentration of 0.02 g ml<sup>-1</sup> and 0.01 g ml<sup>-1</sup> of the respective monomer was chosen as the most appropriate condition for the synthesis of PTES4C and PTES24C nanoparticles under self-catalysis, respectively. It should be noted here that all the PTES24C spheres prepared did not disperse well in water, except those prepared at a monomer concentration of 0.01 g ml<sup>-1</sup>. In fact, those spheres settled down very quickly in water, thus preventing the measurement of their hydrodynamic diameter by dynamic light scattering (DLS).

Instead of using ethanol to dissolve the monomer and then slowly dispersing the monomer solution in water, Triton X-100, a non-ionic surfactant, was used in place of ethanol, at a 5% (w/v) final concentration. Polymerization was carried out by self-catalysis at a final monomer concentration of 0.02 g ml<sup>-1</sup> and 0.01 g ml<sup>-1</sup> for PTES4C and PTES24C synthesis, respectively. Compared to the process with ethanol, the process with Triton



Scheme 1 Synthesis of triethoxysilylpropyl-4-methoxycinnamamide (TES4C) and triethoxysilylpropyl-2,4-dimethoxycinnamamide (TES4C), and the hydrolysis-polycondensation of TES4C and TES24C into poly[propyl-4-methoxycinnamamide silsesquioxane] (PTES4C) and poly[propyl-2,4-dimethoxycinnamamide silsesquioxane] (PTES4C).



**Fig. 1** <sup>1</sup>H NMR of **TES4C** (top) and **TES24C** (bottom). The percentage of residual APTES could be deduced from the ratio of integration of peaks a and b.

X-100 gave much larger PTES4C spheres (anhydrous, as DLS could not be performed) and at a much lower yield (Table 1, Fig. 2). In addition, it was accompanied with a more sticky solid mass formation. In contrast, the preparation of PTES24C spheres in the presence of 5% (v/v) Triton X-100 gave more uniform spheres at a comparable spherical size and yield to the process using ethanol (Table 1, Fig. 2).

Thus, it was concluded that PTES4C was best prepared under self-catalysis using 20% (v/v) aqueous ethanol with a final monomer concentration of 0.02 g ml<sup>-1</sup>, whilst PTES24C was best prepared under self-catalysis condition at a final monomer concentration of 0.01 g ml<sup>-1</sup> with either 5% (v/v) Triton X-100 or 10% (v/v) ethanol. Under these optimized conditions, the synthesis yield was 71% and 73% for PTES4C and PTES24C, with average sphere sizes of ~420 nm and ~210 nm, respectively.

The PTES4C and PTES24C spheres obtained under such conditions were subjected to solar protection factor (SPF) and UVA-protection factor (UVA-PF) measurements, and were also

used to encapsulate citronellal. An aqueous suspension of PTES4C spheres showed obvious absorption of UVB radiation ( $\lambda_{max} \sim 290$  nm), while those of the PTES24C possessed both UVB and far UVA absorption characteristics ( $\lambda_{max} \sim 292$  and 322 nm) (Fig. 3a). The dry spherical products (solid) also showed expected UV absorption characteristics (Fig. 3b). It should be noted here that the UV absorption spectra of TES4C and TES24C shown in Fig. 3a, were acquired from the solution samples and, therefore, their absorbances corresponded well with their molar absorption coefficients. However, since the spectra of PTES4C and PTES24C were obtained from the spherical suspension, their absorption spectra did not follow Beer's law and should not be compared to the spectra of the diluted monomer solutions. Nevertheless, the absorption spectra of the suspensions gave good qualitative information and agreed well with the absorption profiles of the dry particles.

#### Solar protection factor (SPF)

The SPF and UVA-PF of PTES4C and PTES24C nanospheres were evaluated and compared with those of EHMC, a widely used UV filter that is accordingly used as a reference standard here. All samples were prepared at 34.5 mM chromophores in aqueous polyacrylic acid gel (Table 2). The molar concentrations of the chromophore for PTES4C and PTES24C were estimated from the polysilsesquioxane network structures assuming similar percentage loss of APTES and TES4C or TES24C at the 71 and 73% yield. No SPF booster was used in the gel formulation, and so the SPF and UVA-PF values obtained should directly correspond to the amount of UVB and UVA light filtered by the tested gel. The SPF and UVA-PF values are usually affected by various factors, including the light absorption property (molar extinction coefficient) of the UV filter chemical used, the homogeneity of the UV filter chemical in the formulation, the concentration of

Table 1	Morphology	and vield c	of PTES4C	and PTES24C	nanospheres	obtained und	ler various sv	nthesis conditions

Monomer	Catalysis	[Monomer] (g ml <sup>-1</sup> )	Reaction time	%EtOH (v/v)	Synthesis yield (%)	Average diameter by SEM <sup>a</sup>	Hydrodynamic diameters <sup>b</sup>	PDI <sup>c</sup>
TES4C	HC1	0.02	14 days	20	87.38	449 + 40	$610 \pm 10$	0.23
		0.02	14 days	30	74.45	$625 \pm 52$	$798 \pm 10$	0.23
		0.02	14 days	40	69.27	837 + 81	$907 \pm 13$	0.22
	3% NH4OH	0.02	1 h	20	47.89	$868 \pm 82$	$910 \pm 44$	0.19
		0.02	1 h	30	41.99	$1252 \pm 164$	$1987 \pm 203$	0.16
		0.02	1 h	40	30.56	$2361 \pm 202$	$3028 \pm 299$	0.95
	5% NH₄OH	0.02	1 h	20	37.30	513 + 87	$687 \pm 54$	0.34
	4	0.02	1 h	30	17.20	$826 \pm 184$	$1456 \pm 81$	0.25
		0.02	1 h	40	11.88	$2254 \pm 212$	$2694 \pm 114$	0.14
TES4C + 20%	Self-catalysis	0.02	1 dav	20	71.11	$419 \pm 64$	$559 \pm 9$	0.09
APTES	Sell editalysis	0.02	1 day	30	64.21	$788 \pm 139$	$1354 \pm 44$	0.16
		0.02	1 day	40	X	X	X	X
		0.01	1 day	20	74.15	$423 \pm 65$	$588 \pm 4$	0.20
		0.04	1 day	20	53.76	$437 \pm 57$	$564 \pm 8$	0.15
		0.06	1 day	20	41.34	$465 \pm 49$	$566 \pm 6$	0.14
		0.02	1 day	Triton X 100	<20	$1227\pm198$	nd	nd
TES24C	HCI	0.02	3 days	10	77 91	$576 \pm 78$	$768 \pm 12$	0.13
115240	nei	0.02	3 days	20	75.11	$570 \pm 70$ $615 \pm 58$	$811 \pm 5$	0.15
		0.02	3 days	30	56 70	$755 \pm 84$	$1177 \pm 30$	0.09
	3% NH OH	0.02	1 h	10	24.95	$451 \pm 48$	$482 \pm 17$	0.20
	5701114011	0.02	1 h	20	38.50	$956 \pm 291$	$929 \pm 27$	0.10
		0.02	1 h	30	31.64	$1792 \pm 377$	2142 + 122	0.10
	5% NH OH	0.02	1 h	10	22 34	$402 \pm 977$	$471 \pm 16$	0.20
	570 14114011	0.02	1 h	20	40.68	$535 \pm 64$	$706 \pm 9$	0.14
		0.02	1 h	30	20.05	$1557 \pm 132$	$1316 \pm 26$	0.14
TES24C + 20%	Self-catalysis-	0.02	1 day	10	66 36	$448 \pm 66$	$1310 \pm 20$	nd
APTES	Sen-catalysis-	0.02	1 day	20	64.48	$465 \pm 00$	nd	nd
AFIES		0.02	1 day	30	v0	405 ± 71	nu v	v
		0.02	1 day	10	73.04	210 + 67	229 + 19	0.18
		0.04	1 day	10	51 70	$409 \pm 99$	nd	nd
		0.04	1 day	10	x	x	X	x
		0.00	1 day	Triton	73.15	228 + 30	232 + 14	0.12
		5.01	1 duy	X-100	, 5.15	220 ± 50	252 ± 17	0.12

<sup>*a*</sup> Average anhydrous size (nm)  $\pm$  SD, from SEM photographs. <sup>*b*</sup> Average hydrated size (nm)  $\pm$  SD, as determined by DLS. <sup>*c*</sup> The cumulant analysis -polydispersity index (PDI) where a value of 0.08–0.7: means a mid-range polydispersity, the range over which the distribution algorithm based on NNLS best operates. x = no spherical product was formed, and not determined.



Fig. 2 SEM and TEM (inset) photographs of a) PTES4C spheres prepared at 0.02 g ml<sup>-1</sup> monomer and 20% ethanol under self-catalysis, b) PTES4C spheres prepared at 0.02 g ml<sup>-1</sup> monomer and 5% Triton X-100 under self-catalysis, c) PTES4C spheres prepared at 0.02 g ml<sup>-1</sup> monomer with 20% ethanol under base catalysis, d) PTES24C spheres prepared at 0.01 g ml<sup>-1</sup> monomer and 10% ethanol under self-catalysis, e) PTES24C spheres prepared at 0.01 g ml<sup>-1</sup> monomer and 5% Triton X-100 under self-catalysis, and f) PTES24C spheres prepared at 0.01 g ml<sup>-1</sup> monomer with 10% ethanol under base catalysis.

the UV filter, and the ability of the tested sample to either absorb or scatter the incoming radiation. Note that the values obtained take into account neither the transdermal penetration of the UV filters nor the stability of the UV filters.

When used at the same molar concentration of chromophore (4-methoxycinnamoyl moiety) in the gel (34.5 mM), PTES4C gave slightly higher ( $\sim$ 1.1-fold) SPF and UVA-PF values than the reference standard EHMC (Table 2). As mentioned earlier, the SPF and UVA-PF values are affected by how well the UV filter chemicals are dispersed in the formulation and the ability of the formulation to either scatter or absorb the incoming radiation. In this case, it is likely that the ability of the PTES4C spheres to scatter light compensates well for their lower homogeneity compared to those of the EHMC.

In contrast, the PTES24C gel under the same conditions gave just over ~1.3-fold lower SPF and UVA-PF values than that for the reference standard EHMC. However, the lower SPF and UVA-PF values for PTES24C were expected since PTES24C's chromophore (2,4-dimethoxycinnamoyl moiety) possesses only half the molar extinction coefficient when compared to that of EHMC. In fact, when taking into account the molar extinction coefficients of each UV filter's chromophore, the SPF and UVA-PF values of the PTES24C are higher than the expected values.



**Fig. 3** UV absorption spectra of (a)  $1.28 \times 10^{-5}$  M TES4C and TES24C solutions (in ethanol), 120 ppm PTES4C particle suspension in 20% (v/v) aqueous ethanol, and 80 ppm PTES24C particle suspension in 20% (v/v) aqueous ethanol, and (b) dry PTES4C and PTES24C spherical solids.

This was likely to be due to the light scattering effect caused by the (230 nm diameter) PTES24C spheres.

The better UV filtering efficiency of the PTES4C over the PTES24C spheres could also be explained through a more effective light scattering of the bigger PTES4C spheres (560 nm) compared to the smaller PTES24C spheres (230 nm).

Usually, when the organic UV absorptive chromophore is in the solution state (normal organic UV filter), the UV filtering mechanism involves the absorption of UV radiation by the ground state electrons (electrons in their highest occupied molecular orbital, HOMO), the jumping of those electrons to the higher energy levels (the excited state which usually is the lowest unoccupied molecular orbital, LUMO), the return of the excited electrons to the ground state energy levels ideally via non-radiative pathways (e.g. vibrational relaxation and internal conversion which usually are accompanied with the release of infrared radiation). The energy gap between the excited and ground states determine the absorption wavelength of that particular filter. In the case of the hybrid organic-inorganic UV filtering particles, the particulate nature of the materials will cause light scattering, while the organic chromophores in the siloxane network structure will absorb photons of the right energy (here the energy will be in the UVB and UVA regions). Therefore, the particulate nature of the hybrid UV filtering spheres acts synergistically with the cinnamoyl chromophores by scattering the photons around, resulting in an increased chance for any given photon to be absorbed by the organic chromophores of the spheres. In other words, the particulate nature of the hybrid UV filtering spheres increases the time and path-length of each photon in the gel layer,

thus increasing their probability of being absorbed by the organic chromophores. This rationalization helps explain the high SPF and UVA-PF values of the PTES24C spheres despite the low molar extinction coefficient of their chromophore.

It should be noted here that the two cinnamoyl moieties, 4methoxycinnamoyl and 2,4-dimethoxycinnamoyl, were chosen as the organic chromophoric part of the hybrid filters based on not only their UV absorption wavelengths, but also their appropriate photochemical and photophysical properties, *e.g.*, short lived excited state, low barrier for non-radiative decay and low fluorescent quantum yield.<sup>34,35</sup>

In addition to their good UV filtering property and easy preparation, the two hybrid UV filtering nanospheres could disperse well in water, contributed no oiliness to the personal formulations and did not act as photocatalyst, therefore, applications in personal care and cosmetic products should be possible.

#### PTES4C as carrier for controlled release of citronellal

PTES4C spheres were evaluated for their role as a suitable carrier for the controlled release of the volatile fragrant citronellal. Encapsulation of the citronellal was carried out at a TES4C : citronellal (w/w) ratio of 2 : 1 and 1 : 1. Assuming complete polycondensation (80% by wt TES4C and 20% by wt APTES) and 100% citronellal entrapment, the 1 : 1 and 1 : 2 citronellal loaded PTES4C (citro-PTES4C-1 and citro-PTES4C-2, respectively) would possess a citronellal loading of 39 and 56% (w/w), which corresponds to a mole ratio between the cinnamoyl

 Table 2
 The solar protection factor (SPF) and UVA protection factor (UVA-PF) values of a polyacrylic acid gel containing PTES4C, PTES24C and EHMC

UV Filters	[UV Filter] (g 100 ml <sup>-1</sup> )	[Chromophore] (M)	$\epsilon$ of the chromophore (M $^{-1}$ cm $^{-1})$	SPF (mean $\pm$ SD) <sup><i>a</i></sup>	UVA-PF (mean $\pm$ SD) <sup>4</sup>
PTES4C	10.8	0.0345	24 000	$22.0 \pm 1.5$	$7.9 \pm 0.8$
PTES24C	11.9	0.0345	14 000	$14.4 \pm 1.4$	$5.5 \pm 0.5$
EHMC	10.0	0.0345	24 000	$19.8\pm1.4$	$7.3\pm1.2$
<sup>a</sup> obtained f	rom at least five measureme	ents			

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moiety : citronellal of 1.00 : 0.96 and 1.00 : 1.91, respectively. Analyzing the two encapsulated products gave an actual citronellal loading of slightly less than the theoretical level at 35% (w/ w) (citro-PTES4C-1) and 48% (w/w) (citro-PTES4C-2), which corresponded to the mole ratio of the cinnamoyl moiety : citronellal at 1.00 : 0.81 and 1.00 : 1.40, respectively. This high loading level indicated that during the *in situ* hydrolysis–polycondensation of the TES4C monomers in the presence of citronellal molecules, the hydrophobic citronellal molecules delocalized themselves away from the increasing polar water medium, towards the forming nanospheres where they would have good hydrophobic interactions with the cinnamoyl moieties in the siloxane network structure.

With higher citronellal loadings, the spheres became smaller and more aggregated (Fig. 4). It was speculated that at high loading levels, more citronellal would be displaced to the particle's surface, therefore, causing more aggregation of the spheres. The presence of citronellal moieties at the particle's surface also prevented the contact between the growing particles and the new incoming TES4C monomer resulting in spheres of a smaller size.

Citronellal-loaded PTES4C spheres showed a clear controlled release property compared to the free citronellal at the same concentration (Fig. 5). The polysilsesquioxane spheres (sizes of approximately  $115 \pm 20$  and  $100 \pm 10$  nm for citro-PTES4C-1 and citro-PTES4C-2, respectively) certainly acted as a physical barrier, slowing down the diffusion of citronellal molecules. The hydrophobic interaction between citronellal molecules and the cinnamoyl moieties of the silica network structure probably helped retard the release of the volatile citronellal molecules, resulting in an obvious slower release of citronellal from both the citro-PTES4C-1 and citro-PTES4C-2 spheres. However, the fast initial release of citronellal located at the surface of citro-PTES4C-1 and the citro-PTES4C-2 nanoparticles, in addition to any concentration dependent release kinetics.

#### Conclusions

PTES4C and PTES24C nanospheres with UVB and UVA/B absorption properties, respectively, were prepared successfully from TES4C and TES24C hybrid monomers using a hydrolysis–polycondensation reaction. The catalyst type (acid, base or self-catalysis), the concentration of the ethanol (solvent of monomer) and the respective monomer used during the particle formation and the presence of the non-ionic surfactant Triton X-100, all



Fig. 4 SEM images of (a) citro-PTES4C-1 (35% (w/w) citronellal-loaded PTES4C spheres) and (b) citro-PTES4C-2 (48% (w/w) citronellal-loaded PTES4C spheres).



Fig. 5 Release profiles of citronellal from citro-PTES4C-1 (35% (w/w) citronellal loading) and citro-PTES4C-2 (48% citronellal loading) in aqueous suspensions at a final citronellal concentration of 2% and 3% (w/ v) for citro-PTES4C-1 and citro-PTES4C-2, respectively. The profiles are displayed as % citronellal remaining. Releases of free citronellal at the same concentrations are also shown. The release experiment was conducted at 45 °C. The data are shown as the mean derived from two repeats.

affected the particle size and product yield. Optimization led to a mild self-catalysis process that gave PTES4C and PTES24C products with a high yield (71 and 73%, respectively) and acceptable nanoparticle size (~400 nm PTES4C and ~200 nm PTES24C). Both PTES4C and PTES24C spheres gave acceptable SPF and UVA-PF values despite the fact that the molar extinction coefficient value of the 2,4-dimethoxycinnamoyl chromophore in PTES24C was 1.71-fold lower than that for the 4-methoxycinnamoyl chromophore in PTES4C. A synergistic effect between the UV absorption of the cinnamoyl chromophore in the siloxane network and the light scattering caused by the particulate nature of the UV filtering spheres was likely to be responsible for the good UV filtering efficiency of the obtained materials. Encapsulation of volatile citronellal into PTES4C nanoparticles could be carried out successfully by in situ polycondensation under self-catalysis conditions. The citronellal-loaded PTES4C spheres with a loading of 35% (w/w) (citro-PTES4C-1) and 48% (w/w) (citro-PTES4C-2) showed sustained release characteristics.

#### Materials and methods

APTES, 4-methoxycinnamic acid and 2,4-dimethoxy benzaldehyde were purchased from Acros Organics (Geel, Belgium). EHMC (Eusolex 2292) was obtained from Merck (Darmstadt, Germany). All other chemicals were reagent grade and were used without additional purification.

FT-IR analysis was carried out using a Nicolet Fourier transform Infrared spectrophotometer: Impact 410 (Nicolet Instruments Technologies, Inc., Madison, WI, USA). <sup>1</sup>H- and <sup>13</sup>C-NMR analyses were carried out using a Varian Mercury spectrometer which was operated at 400.00 MHz for <sup>1</sup>H and 100.00 MHz for <sup>13</sup>C nuclei (Varian Company, Palo Alto, CA, USA). UV analysis was done with the aid of a UV 2500 UV-Vis spectrophotometer (Shimadzu Corporation, Kyoto, Japan), using a quartz cell with a 1 cm pathlength. Transmission Electron

Microscopy (TEM) was carried out using a JEM-2100 (Jeol, Ltd., Japan) and Scanning Electron Microscopy (SEM) was performed on a JEM-6400 (Jeol, Ltd., Japan). The hydrodynamic particle sizes of the nanoparticle suspensions were determined without prefiltering on a Zetasizer nanoseries (Mulvern Instruments, Worcestershire, UK).

#### Synthesis of hybrid monomers

2,4-Dimethoxycinnamic acid was synthesized using Knoevenagel-Doebner condensation between 2,4-dimethoxybenzaldehyde and malonic acid.36 TES4C and TES24C were obtained from a condensation reaction between APTES and 4-methoxycinnamic acid and 2,4-dimethoxy cinnamic acid (via acid chloride), respectively (Scheme 1). 4-Methoxycinnamoyl chloride (or 2,4dimethoxycinnamoyl chloride) was first prepared by reacting 4methoxycinnamic acid (or 2,4-dimethoxycinnamic acid) with thionyl chloride (2.5 folds) in 200 ml of dry toluene. The mixture was refluxed for 6 h under an N<sub>2</sub> atmosphere. Then, the solvent and excess thionyl chloride were removed by vacuum pump. Finally, toluene (5 ml) was added to remove the trace amount of thionyl chloride by rotary evaporation under reduced pressure. The obtained 4-methoxycinnamoyl chloride (or 2,4-dimethoxycinnamoyl chloride) (0.1 mol) was dissolved in 250 ml of dry toluene. Then, 0.1 mol APTES and 0.1 mol triethylamine (TEA) were added. The mixture was refluxed for 3 h under N2 atmosphere. The solid salt of TEA-HCl was separated by suction filtration. The solvent and TEA were removed by rotary evaporation under reduced pressure. The obtained viscous liquid product was dried under vacuum to constant weight. NMR and IR spectra of the products are shown in the ESI.†

*TES4C*: Red-brown oil. Yield: 96.5%. FT-IR (cm<sup>-1</sup>): 3276 (N–H stretching), 2966 (C–H stretching), 1655 (C=O stretching), 1602 (C=C Ar stretching), 1545 (N–H bending), 1509 (C=C Ar stretching), 1061 (C–O stretching) and 947 (Ar bending). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 7.56 (d, *J* = 15.6 Hz, 1H, Ar–CH=), 7.42 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.88 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.24 (d, *J* = 15.6 Hz, 1H, =CH–CONH), 5.91 (br, s, 1H, –CONH), 3.83 (m, 2H, –OCH<sub>2</sub>–CH<sub>3</sub>), 3.82 (s, 3H, –OCH<sub>3</sub>), 3.38 (m, 2H, –OCH<sub>2</sub>–CH<sub>3</sub>), and 0.68 (m, 2H, –CH<sub>2</sub>–CH<sub>2</sub>–Si–).

*TES24C*: Yellow-brown oil. Yield: 95.0%. FT-IR (cm<sup>-1</sup>): 3259 (N–H stretching), 2965 (C–H stretching), 1649 (C=O stretching), 1601 (C=C Ar stretching), 1562 (N–H bending), 1502 (C= C Ar stretching), 1079 (C–O stretching) and 836 (Ar bending). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 7.74 (d, *J* = 16 Hz, 1H, Ar–CH=), 7.38 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.47 (d, *J* = 8.8 Hz, 1H, Ar–H) 6.44 (s, 1H, Ar–H), 6.41 (d, *J* = 16.4 Hz, 1H, =CH–CONH), 5.86 (br, s, 1H, –CONH), 3.84, 3.82 (s, 2 × 3H, 2 × OCH<sub>3</sub>), 3.82 (m, 2H, –OCH<sub>2</sub>–CH<sub>3</sub>), 3.37 (m, 2H, –NH–CH<sub>2</sub>–CH<sub>2</sub>–CH<sub>2</sub>–), 1.68 (m, 2H, –CH<sub>2</sub>–CH<sub>2</sub>–CH<sub>2</sub>), 1.22 (m, 3H, –OCH<sub>2</sub>–CH<sub>3</sub>) and 0.67 (m, 2H, –CH<sub>2</sub>–CH<sub>2</sub>–Si–).

#### Polycondensation and particle formation

Hydrolysis coupled with polycondensation and particle formation were carried out simultaneously. Three external catalyst systems, acid catalysis with 0.1% (v/v) HCl, base catalysis with 3% or 5% (v/v) NH<sub>4</sub>OH<sup>37,31</sup> and self-catalysis<sup>38</sup> were compared. Reactions were carried out with various percentages of ethanol solvent (Table 1). In addition, the effect of surfactant on the sphere formation was investigated.

### Acid and base catalyst (0.1% (v/v) HCl, 3% and 5% (w/w) $\rm NH_4OH)$

PTES4C spheres were prepared from the hydrolysis–polycondensation of TES4C in the presence of 20, 30 and 40% (v/v) of ethanol. TES4C (0.4 g) was dissolved in 4, 6 or 8 ml of ethanol and the obtained clear solution was dropped slowly (1 ml min<sup>-1</sup>) into stirred (700 rpm) water (16, 14 or 12 ml) containing the appropriate acid or base catalyst. The obtained suspension was further stirred at room temperature to complete the condensation. Completion of the reaction was checked by confirming that the obtained spheres were not soluble in ethanol. The PTES4C spherical suspension was then dialyzed against 20% (v/v) aqueous ethanol to remove residual monomers and catalyst, followed by dialysis against water. The suspension product was dried under vacuum to a constant weight and the synthesis yield was evaluated.

PTES24C spheres were prepared in a similar manner to PTES4C spheres with slight modification, from the hydrolysis– polycondensation of TES24C in the presence of 10, 20 or 30% (v/ v) of ethanol. The hybrid monomer TES24C was dissolved in ethanol (2, 4 or 6 ml) to obtain a clear solution. The appropriate volume (18, 16 or 14 ml) of water was then dropped slowly (1 ml min<sup>-1</sup>) into the obtained TES24C solution whilst stirring at 700 rpm, and thereafter stirred at room temperature (see Table 1 for times and amounts of TES24C used). Residual monomers and catalysts were then removed by the same dialysis process used in the PTES4C preparation and the dry product was also obtained similarly.

#### Self-catalysis

PTES4C and PTES24C self-catalysed polymerization was carried out as above (acid/base catalysis) except that 1) APTES was mixed with the monomer at 20% (w/w) and 2) the water phase contained neither HCl nor NH<sub>4</sub>OH.

#### Surfactant

Polymerization of TES4C and TES24C by self-catalysis was also carried out in a presence of 5% (v/v) of the non-ionic surfactant, Triton X-100. The reaction was carried out with no added ethanol. Monomer (0.40 g for TES4C or 0.20 g for TES24C) was added to 1.0 ml of Triton X-100 and then stirred. Then the same procedure as described above was used except that the amount of water used was 19 ml and the monomer solution in the surfactant was used in placed of the monomer solution in ethanol. The residual monomer and surfactant residues were removed from the product by dialysis against 20% (v/v) aqueous ethanol, and then water. The obtained product was dried under vacuum to a constant weight and the synthesis yield was evaluated.

#### Encapsulation

Citronellal was encapsulated into PTES4C nanospheres by the *in situ* polycondensation of TES4C in the presence of citronellal

using the method modified from the works of Lapidot<sup>20</sup> and Ahn.<sup>39</sup> The encapsulation was carried out at a 1 : 2 and 1 : 1 (w/w) ratio of citronellal : TES4C. For encapsulation, at (w/w) ratio of 1 : 2 citronellal : TES4C, citronellal (0.20 g), TES4C (0.40 g) and APTES (0.08 g) were co-dissolved in 4 ml ethanol. The obtained clear solution was dropped slowly (1 ml min<sup>-1</sup>) into the stirred water (16 ml, stirring rate ~700 rpm), and the suspension stirred for 24 h at room temperature, before being centrifugally filtered (MWCO 100,000, Amicon Ultra-15, Millipore, Ireland) to collect the citro-PTES4C-1 spheres. The obtained spheres were then redissolved in water to a final volume of 20 ml. Encapsulation at a citronellal : TES4C (w/w) ratio of 1 : 1 was carried out similarly, except that 0.40 g of citronellal was used instead of 0.20 g and the obtained product was called citro-PTES4C-2.

Citronellal loadings in citro-PTES4C-1 and citro-PTES4C-2 were determined by directly evaluating the amount of citronellal in the obtained particles following extraction of the encapsulated citronellal nanoparticles with hexane. Five ml of hexane was added to 1.0 ml of the obtained suspensions, vigorously shaken, sonicated for 30 min, and left at 30 °C for 12 h before the hexane layer was withdrawn and the amount of citronellal in the hexane layer was determined by UV absorption spectroscopy with the aid of a calibration curve. The loading capacities were then calculated as follows:

$$\%$$
Loading =  $\frac{\text{Weight of citronellal found spheres} \times 100}{\text{Weight of citronellal loaded spheres}}$ 

#### **Release of citronellal**

Five ml of the aqueous suspension of citro-PTES4C-1 spheres (0.286 g) at the final citronellal concentration of 2% or 3% (w/v) (or 0.313 g of citro-PTES4C-2), were loaded into a 20 ml flat bottom-headspace-vial (five vials). The vials were left uncovered at 45 °C. Due to water evaporation, water was added to each vial everyday to maintain a near constant volume throughout the 4day experiment. At the indicated times (0, 1, 2, 3 and 4 days), one of the five vials was filled with 15 ml of hexane, capped with headspace aluminium crimp caps with PTFE/silicone septa and then vigorously vortexed, sonicated, and left to stand at 30 °C for 12 h. The hexane layer was then subjected to citronellal quantification using UV-Vis spectroscopy with the aid of a calibration graph constructed from the freshly prepared citronellal solutions. Control vials (unencapsulated citronellal of similar concentration) were prepared using standard citronellal in 20% (v/v) aqueous ethanol, i.e., 0.1 g of citronellal at the final volume of 5 ml and 0.15 g of citronellal at the final volume of 5 ml. Each experiment was carried out in duplicate and the average values were reported.

## Sun protection factor (SPF) and UVA protection factor (UVA-PF)

Cosmedia SP gel, containing 10.8% (w/v) PTES4C, was prepared by dispersing the PTES4C in the gel (1% (w/v) sodium polyacrylate in water with 0.05% di-sodium EDTA) with stirring. The freshly prepared sample gel was then subjected to SPF and UVA- PF measurement using an SPF Analyzer (Optometrics, SPF-290s, MA, USA). PTES24C and EHMC were also subjected to the same measurement using the same protocol (see Table 2 for the amount of PTES24C and EHMC used).

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