Anti-inflammatory cotton fabrics and silica nanoparticles for potential topical medical applications

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ABSTRACT: The preparation of functional cotton fabrics and silica nanoparticles by direct covalent linking of non-steroidal anti-inflammatory drugs (salicylic acid, ibuprofen and diclofenac) through an amide group is reported. Moreover, the coating of cotton fabrics with silica nanoparticles functionalized with such antiinflamatory agents is found to increase the roughness of the surface, providing hydrophobicity to the modified fabrics. This property is enhanced by the addition of fluorinated alkyl silane (FAS) in the co-condensation process to form the coating solution. Characterization of the functionalized nanoparticles and cotton textiles is accomplished by microscopic and spectroscopic techniques. The treatment of functionalized nanoparticles and cotton fabrics with model proteases and leukocytes from animal origin results in the *in situ* release of the drug by the selective enzymatic cleavage of the amide bond. Topical cutaneous applications in wound dressings and cream formulations for the acceleration of wound healing are envisaged.

INTRODUCTION

In recent years, some industrial companies have focused their research on the development of functional finishing for textile materials with high-added value and applications in different areas. The interest for antibacterial activity, ultraviolet protection, self-cleaning, and wrinkle-free properties has been rapidly increasing.[1-4] Cotton cellulose fibers are the most important in the apparel industry, since cotton-made clothes are the most comfortable garments. In addition, cellulose is a natural, low cost biodegradable material and the chemical and physical properties of cotton involve not only strength and elasticity, but also water affinity and permeability. Furthermore, functionalized cotton fabrics have also been envisaged for medical purposes. Recent strategies have focused on anti-inflammatory properties related to the acceleration of wound healing. In fact, wound dressings research has been set by the insights on wound healing process and by patient's demand. High expectations arise regarding the wound dressing, which must accelerate cicatrisation. In this context, Gedanken's group synthesized tannic acid nanoparticles, which were embedded into cotton fabric and presented inhibitory effect on myeloperoxidase from human leukocytes.[5] Moreover, biopolymers such as chitosan and sodium alginate mixtures were prepared and used for coating by pad-dry technique. Their healing ability was positively estimated using the carrageennan-induced rats paw oedema test.[6] Functionalization of gauzes with liposomes entrapping anti-inflammatory drugs has also been described as a strategy to improve wound healing.[7-8] Very recently, in 2019, the group of Pinho has reported a cotton textile functionalized with cyclodextrin-hydroxypropyl methyl cellulose-based hydrogel capable to encapsulate and release gallic acid with anti-inflammatory capacity.[9]

On the other hand, nanoscale biomaterials have been largely examined as agents for therapeutic and diagnostic (i.e., theranostic) applications.[10] Amongst them, silica-based nanoparticles (either dense or mesoporous) have deserved great attention as a biocompatible form of silica.[11-14] Particularly, mesoporous silica nanoparticles (MSNs)[15] present significant advantages for biomedical applications[16-20] due to their exclusive physicochemical properties (high surface area, tunable pore size, pore volume and hydrophilicity, good colloidal stability, enriched surface silanol groups) and facile surface modifications. In the past decade, they have exhibited high potential as stimuli-responsive drug delivery vehicles for targeted cancer treatment and as bioimaging devices.[21-26] The uptake of the drug and the controlled release upon an appropriate stimulus (pH, light, temperature, enzymes), takes place through the mesopores of the surface-modified MSNs with adjustable pore sizes and morphologies. Mou and Yang have

prepared positive-charge functionalized MSNs for pH-stimuli responsive oral drug delivery of sulfasalazine (an anti-inflammatory anionic prodrug used for inflammatory bowel disease) targeting at intestine.[27] Surface modification of ordered mesoporous SBA-15 nanoparticles with (3-aminopropyl)triethoxysilane has been found to significantly increase the loading of non-steroidal anti-inflammatory drugs (NSAID) and decrease their rate of delivery.[28-29] Periodic mesoporous ionosilica nanoparticles with ammonium walls can also be used as carrier vehicles for anionic drugs such as sodium diclofenac and are efficient in inhibiting lipopolysaccharides-induced inflammation.[30] Betamethasone, a synthetic anti-inflammatory corticosteroid, has been loaded via post-impregnation on MSNs (SBA-15-NH_2). Treatment of cotton fabric with the loaded-MSNs and the bacteriostatic polysaccharide chitosan afforded functional textiles with antibacterial activity, whose drug delivery properties have been described.[31]

It should be mentioned that in almost all the numerous studies on MSNs for drug delivery, the cargo is physically adsorbed into the pores and rarely covalently bound to the nanoparticles. Nevertheless, Kleitz and Qiao have designed a promising bacterial azo-reductase-responsive delivery system in which the prodrug sulfasalazine is covalently anchored to the surface of MCM-48 mesoporous silica nanospheres. The release of both 5-aminosalicylic and sulfapyridine is triggered by the reduction of the azo group of the prodrug by the enzyme inside the colon.[32] As an alternative to the drug encapsulation, dense hybrid silica nanoparticles containing the antimicrobial triclosan covalently linked to the ceramic matrix through carbamate functions have also been reported.[33] Such hybrid nanoparticles proved to be active against common bacterial pathogens such as *E. coli* (Gram-negative) and *S. aureus* (Gram-positive). On the other hand, Khashab's group proposed in 2016 a new strategy for drug delivery based on the biodegradation of drug-encapsulated MSNs with oxamide functions incorporated into the pore walls, in the presence of trypsin model proteins.[34]

Considering the mentioned precedents and taking advantage of the long experience of the group in carrying out sol-gel processes for the preparation of hybrid silicas[35-49] and in the coating of surfaces,[50-56] especially textiles,[50-55] we envisioned the covalent anchoring of anti-inflammatory agents on cotton fabric and silica nanoparticles. The functionalized non-porous or mesoporous silica nanoparticles would be dispersed on cotton fabrics for potential topical applications in medical textiles (bandages, gauzes or strips). The presence of functionalized silica nanoparticles in wound dressings would increase the roughness of the surface of the fabric and, consequently, its hydrophobicity and durability.[57-60] This is advantageous for keeping dry the gauze and wound, acting as a barrier to the microorganisms and helping the rapid wound healing. The repairing effect of anti-inflammatory drugs on human tissues can only take place if the drug is released from the fabric matrix and comes into direct contact with the cells involved in the inflammatory response in the wounded area. During inflammation a large number of leukocytes are recruited to the wounded area (chemotaxis), leave the blood vessels and activate metabolic processes resulting in increased phagocytic activity, a rise in the release of proteases, peroxidases and oxygen reactive species which contribute to the cleavage and elimination of external agents.[61] As proteases are capable of hydrolysing amide bonds found in peptides and proteins, our proposal is the connection of the drug to the linker by an amide functional group (**Figure 1**).

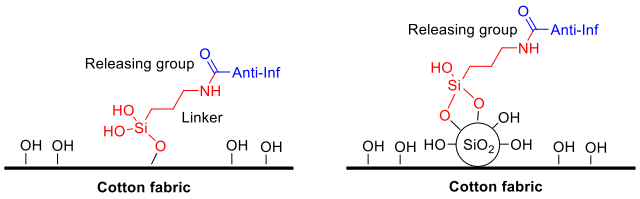


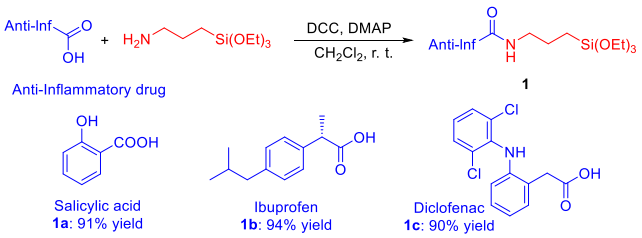
Figure 1. Schematic representation of the structure of the modified cotton fabrics.

Thus, we describe herein the preparation of cotton textiles and silica nanoparticles covalently functionalized with carboxyl-containing non-steroidal anti-inflammatory drugs through amide bonds, which will be cleaved by proteases to release the drugs in situ. Moreover, we report the loading of cotton fabrics with these functionalized silica nanoparticles by one-step-coating. We envisage potential topical applications in cutaneous chronic wounds.

RESULTS AND DISCUSSION

Some common topical non-steroidal anti-inflammatory drugs (NSAID) were selected: salicylic acid,[62] ibuprofen[63] and diclofenac[64] (sold under the trade name Voltaren, among others). They share as a common structural feature the presence of the carboxyl group, which is needed to form a covalent amide bond with the linker, and which will be the target for the subsequent enzyme-driven release of the drug. Moreover, a covalent chemical grafting of the anti-inflammatory agent onto the cotton fiber or silica nanoparticles should prevent the leaching of the drug derivative. The introduction of a triethoxysilyl moiety on the anti-inflammatory derivative was selected for that purpose. This reactive unit has been previously used for the dyeing of activated glass by grafting fluorinated azo dyes to obtain artificial water repellent surfaces,[50] for the attachment of proteins on germanium surfaces,[65] for the covalent link of antimicrobial compounds onto cotton textile,[66] and for the bonding of *N*-halamine to cotton swatches for antibacterial cellulose.[67]

In our case, the desired commercial anti-inflammatory agent was mixed with *N,N'*-dicyclohexylcarbodiimide (DCC, 1 equiv.), 4-(dimethylamino)pyridine (DMPA, 5 mol%) and 3-(triethoxysilyl)propylamine (1.2 equiv) in CH_2Cl_2 at room temperature overnight, affording compounds **1a-c** with excellent yields (90-94%) after chromatographic separation. These classical conditions gave excellent performance and the silylated derivatives showed good stability (**Scheme 1**).



Scheme 1. Coupling reaction of anti-inflammatory agents with 3-(triethoxysilyl)propylamine.

For the direct attachment of the drug to the textile, we took some pieces of commercial 100% cotton fabric (3 × 3 cm), which were first washed with water and non-ionic detergent under reflux, rinsed with distilled water, and dried in a vacuum oven at 55 ºC. The subsequent activation of the pieces of

cotton was carried out by treatment with 0.1 M NaOH and then the pieces were rinsed with anhydrous THF. Next, the fabrics were immersed in a 0.23% weight solution of the reactive anti-inflammatory drug in THF and the closed reaction tube was heated at 80 ºC for 48 hours. Afterwards, the pieces of cotton fabrics were washed with THF, followed by ethanol and dried in a vacuum oven at 55 ºC (**Figure 2**). This process of functionalization of the fabrics preserves their morphology, thus no appreciable differences were observed between the original fabrics and the modified ones (**Figure 3**). Moreover, the presence of diclofenac onto the surface of **Fabric-DiClfen** was confirmed by Scanning Electron Microscopy (SEM), X-Ray Photoelectron Spectroscopy (XPS), Energy-Dispersive X-Ray Spectroscopy (EDX) and mapping (**Figure 4**). The small signals in XPS and EDX corresponding to silicon, chlorine and nitrogen are indicative of the presence of the diclofenac attached to the cotton. Moreover, a distribution of these elements can be observed in the EDX mapping of **Fabric-DiClfen** surface**.**

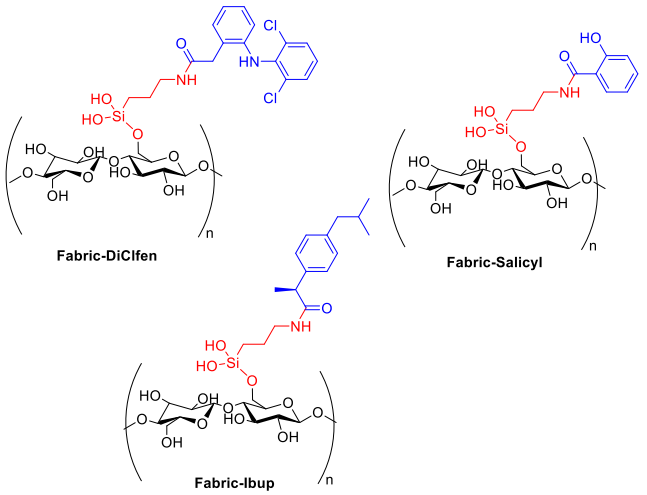


Figure 2. Schematic representation of covalently modified cotton fabrics.

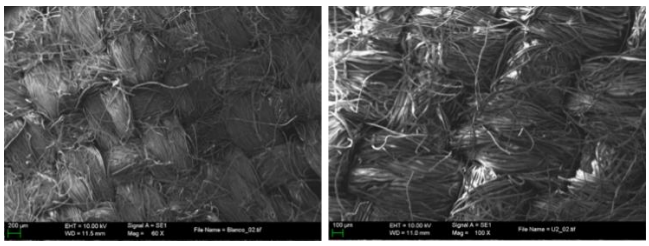


Figure 3. Representative SEM images of unmodified cotton (left) and **Fabric-Salicyl** (right)

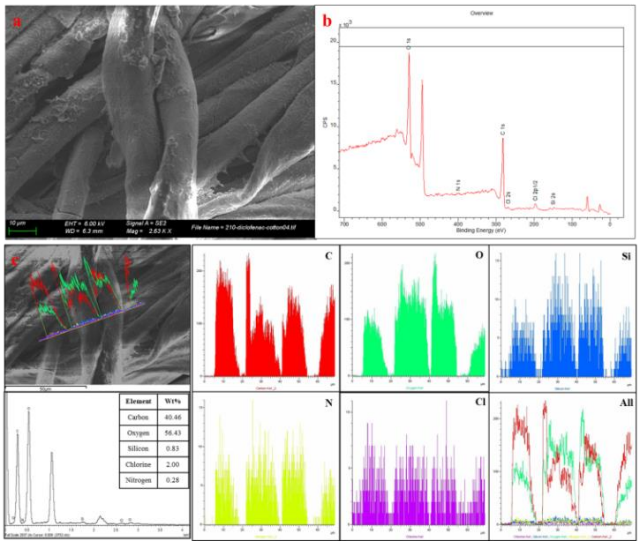
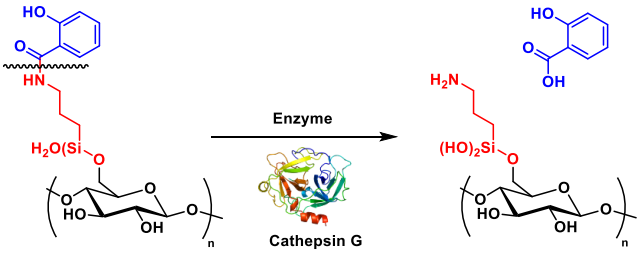


Figure 4. SEM image (a), XPS spectrum (b) and EDX and mapping (c) of **Fabric-DiClfen**.

As we have pointed out, the repairing effect of inflammation in human tissues can only take place if the drug is detached from the fabric and comes into direct contact with the damaged area. Thus, we have studied the release of the drug assaying a lysosomal enzyme, specifically we have used cathepsin G from human leukocytes. The experiment was carried out for each anchored anti-inflammatory agent. First, the modified fabrics was treated with cathepsin G in distilled water at 37 ºC under stirring for a given time. Next, we proceeded to its analysis by Gas Chromatography-Mass Spectrometry (GC-MS). In the case of **Fabric-Salicyl**, the corresponding molecular peak (m/z = 138.0) of the free salicylic acid was observed in the analysis of experiments involving 24 h and also 30 minutes of enzymatic treatment (**Scheme 2**). Moreover, no other fragments corresponding to other types of hydrolytic processes were detected. This fact is important, since it indicates that the silylated group correctly performs its function, remaining anchored to the surface of the cotton fabric. It is also indicative that the anti-inflammatory drug has been properly anchored.



Scheme 2. Exclusive amide hydrolysis on **Fabric-Salicyl** by cathepsin G.

In addition, salicylic acid exhibits fluorescence in the visible range when the product is irradiated with a UV lamp at 365 nm. Likewise, when this drug was anchored to the cotton fabric, irradiation of the fabric with 365 nm UV light also produced a bluish fluorescent luminosity. Although this behavior was constant throughout the days, once the experiment to evaluate the detachment of the drug from the cotton was finished (24 hours), the fabric no longer evidenced fluorescence under UV radiation, at least with the same intensity (**Figure 5**). This visual fact confirms both that the salicylic

acid is present in the **Fabric-Salicyl** surface and that it has been detached from the cotton surface after the treatment with cathepsin G.

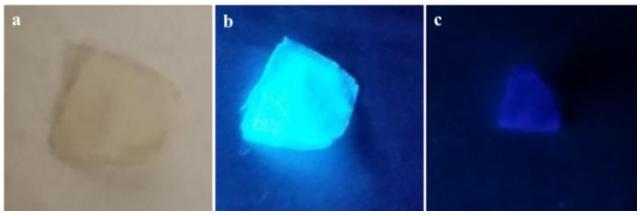
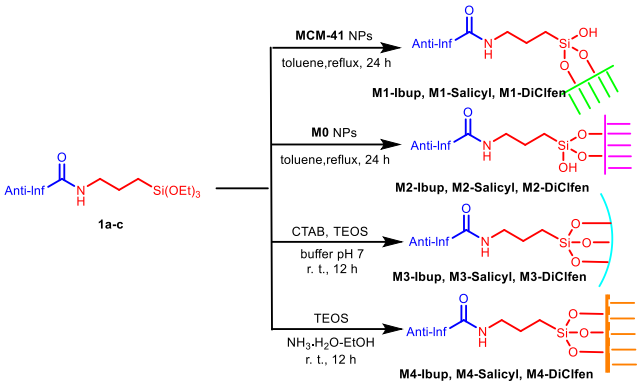


Figure 5. Unmodified cotton (a), **Fabric-Salicyl** irradiated with UV light at 365 nm before treatment with cathepsin G (b), **Fabric-Salicyl** irradiated with UV light at 365 nm after treatment with cathepsin G (c).

Analogous experiments were carried out with **Fabric-Ibup** and **Fabric-DiClfen**, the selective release of the anti-inflammatory drug under the action of cathepsin G being also confirmed by CG-MS. However, as ibuprofen and diclofenac do not exhibit fluorescence, visual confirmation of the release of the drug from the fabric under UV irradiation could not be obtained.

Next, a similar experiment was carried out using leukocytes of animal origin. Leukocytes were obtained from rat whole blood by centrifugation on a Percoll gradient. The resulting leukocyte suspensions were added to four vials containing 3 pieces of **Fabric-Salicyl** (1.5 × 1.5 cm) in a final volume of 2 mL PBS and were kept at 37 ºC for 150 minutes with continuous stirring. Once the experiment was finished, the samples were analysed by GC-MS after dichloromethane extraction of the aqueous phase. In the absence of leukocytes (blank experiment) and with the smaller number of cells (390.000), the release of salicylic acid was not detected. In contrast, in samples which contain approximately 1 and 2 × 10^6 cells, the release of the drug from the textile surface was confirmed by GC-MS analysis. To our delight, we have demonstrated that an amount of 10^6 cells are able to successfully release the salicylic acid through the hydrolytic cleavage of the amide bond. Thus, the anti-inflammatory agent detached and released from the dressing can exert its therapeutic effect on the injured tissue (wound).

After this successful result with cotton fabrics, we turned to the covalent anchoring of the drugs to silica nanoparticles. From the silylated anti-inflammatory precursors **1a-c (Scheme 1)**, different functionalized silica nanoparticles were prepared by grafting on MSNs of MCM-41 type[68] and **M0**[69] and by sol-gel co-condensation methodologies (**Scheme 3**) (for the synthesis of MCM-41 and **M0** NPs, see Supporting Information). Specifically, **M1** and **M2** were synthesized by anchoring the precursors to MSNs MCM-41 and **M0**, respectively, under standard conditions, in refluxing toluene for 24 h. Materials **M3** were obtained by co-condensation of precursors **1a-c** with tetraethyl orthosilicate (TEOS) using cetyltrimethylammonium bromide (CTAB) as template in an aqueous buffer solution of pH 7 from mixtures with the molar ratios CTAB : TEOS : **1** : H_2O = 5 : 40 : 2 : 30000.[70] The final solution was stirred at room temperature for 12 h and then the nanoparticles were collected by centrifugation (13500 rpm) at room temperature. The surfactant was removed from the obtained solid by treatment with an ethanolic solution of NH_4NO_3 and then the resulting material was washed successively with ethanol, Mili-Q water and ethanol. Materials **M4** were prepared by co-condensation of precursors **1a-c** with TEOS using a 28% aqueous ammonia solution in ethanol with the molar ratios TEOS : **1** : EtOH : NH_3 : H_2O = 100: 5 : 8587: 889 : 2160.[57] The mixed solution was stirred at room temperature for 12 h and then the nanoparticles were collected by centrifugation (13500 rpm) at room temperature and washed with ethanol until neutral pH was reached.



Scheme 3. Preparation of silica nanoparticles functionalized with anti-inflammatory drugs.

The modified silica nanoparticles **M1-M4** were characterized by elemental analysis, ^{13}C and ^{29}Si CP MAS solid state NMR, Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), nitrogen-sorption measurements, Dynamic Light Scattering (DLS), zeta-potential and Infrared Spectroscopy (IR). We present in **Table 1** some physical data of diclofenac modified silica nanoparticles. Some characterization data of the other functionalized nanoparticles are collected in the Supporting Information.

These silica NPs were first investigated by electron microscopies (TEM and SEM) to confirm their nanometric size and features (**Figure 6**). **M1-DiClfen,** obtained from MCM-41 type NPs by grafting, preserve the initial rod-like morphology with lengths about 145 ± 51 nm. The TEM images display the typical parallel channels throughout the rods. **M2-DiClfen,** obtained by grafting to **M0**, also preserved the initial spherical morphology, with diameters around 76 ± 5 nm. The TEM images clearly indicate the presence of pores, though they are not as organized as in MCM-41. Interestingly, the synthesis of **M3-DiClfen** by co-condensation of TEOS with 5 mol% of silylated diclofenac **1c** yielded small spherical NPs uniform in size (45 ± 4 nm), with similar porosity as for **M0**, as seen by TEM. **M4-DiClfen,** prepared by co-condensation in the absence of template, appeared as non-porous dense spherical nanoparticles with a narrow size distribution and an average diameter of 360 ± 25 nm. DLS measurements showed in all cases hydrodynamic diameters which are in good accordance with the TEM size of the corresponding dried particles, if we consider the likely adsorption of water molecules onto the nanoparticle surface (**Table 1**) (see in **Figure S1** in the Supporting Information the TEM statistical particle size distribution and DLS of **M4-DiClfen**).

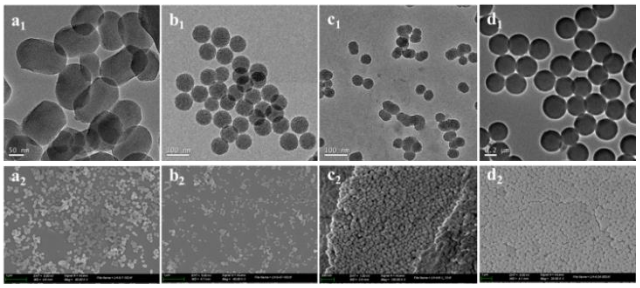


Figure 6. TEM and SEM images of diclofenac-functionalized silica nanoparticles: TEM (a_1) and SEM (a_2) of **M1-DiClfen**, TEM (b_1) and SEM (b_2) of **M2-DiClfen**, TEM (c_1) and SEM (c_2) of **M3-DiClfen**, TEM (d_1) and SEM (d_2) of **M4-DiClfen**.

Table 1. Some physical data of **M-DiClfen** and parent MSNs (**MCM-41** and **M0**).

Material	S_{BET} (m^2g^{-1})	V_{pore} (cm^3g^{-1}) [a]	$Ø_{pore}$ (nm) [b]	Drug loading ($mmolg^{-1}$) [d]	Particle size		Zeta potential (mV)
					TEM	DLS [e]	
MCM-41	1097	0.79	2.7	-	100-600	110, 450	-25
M1-DiClfen	771	0.37	2.6	0.65	145 ± 51	283	-30
M0	332	0.29	3.1	-	75 ± 8	100	-25
M2-DiClfen	256	0.18	1.9 [c]	0.49	76 ± 5	135	-15
M3-DiClfen	662	0.47	2.2	0.22	45 ± 4	169	-30
M4-DiClfen	9	0.007	nd [f]	0.26	360 ± 25	424	-50

[a] Determined from the uptake at saturation at p/pº = 0.8; [b] Determined by NLDFT(desorption); [c] Determined by BJH (desorption); [d] Calculated from the N elemental analysis; [e] Hydrodynamic diameters; [f] Non porous material. Not determined.

N_2-sorption experiments confirmed the porosity of the nanoparticles **M-DiClfen** (**Figure 7** and **Table 1**). As is usually observed, the surface area and pore volume for **M1-DiClfen** and **M2-DiClfen**, derived from grafting, were significantly reduced with respect to the parent MSNs, and the pore diameter was slightly decreased. **M3-DiClfen** obtained by co-condensation in the presence of template exhibited a significant surface area of 662 m^2g^{-1} and a pore volume of 0.47 cm^3g^{-1}. All of them displayed isotherms typical of mesoporous materials, whereas **M4-DiClfen** synthesized without surfactant was non-porous as expected.

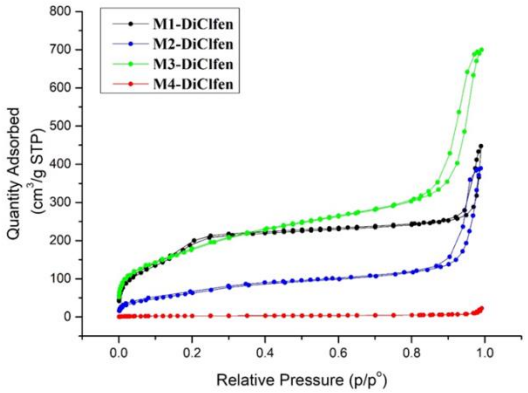


Figure 7. N_2-sorption isotherms of M1-DiClfen, M2-DiClfen, M3-DiClfen and M4-DiClfen.

The dispersibility of the NPs was checked in Mili-Q water and they were moderately aggregated after dispersion at 1 mg/mL. The zeta potential for the pure silica samples **MCM-41** and **M0** was -25 mV at pH 7, in agreement with the isoelectric point of *ca* 3.5 for silica. The modified silica NPs also

exhibited negative values from -15 to -50 mV, which are due to residual anionic silanol groups with some modulation from the functionalization with the drug (**Table 1**). The highly negative zeta potential means that the particles display good stability in suspension. The observation of negative values indicates that there is no protonation of the weakly basic diarylamino group present in **M-DiClfen** materials.

The presence of the organic moiety in the modified nanoparticles was ensured by the solid state ^{29}Si and ^{13}C NMR spectra. For example, the ^{29}Si CP MAS NMR spectrum of **M3-DiClfen** showed two groups of chemical shifts: T units from -59 to -67 ppm derived from the organosilane **1c**, and Q units ranging from -93 to -112 ppm resulting from TEOS (**Figure 8**, top). The presence of T signals indicated that the integrity of the Si-C bond was maintained during the formation of the nanomaterials, which was also confirmed by the ^{13}C CP MAS NMR spectrum with the signal at 10 ppm (**Figure 8**, bottom). The superposition of the ^{13}C-NMR spectrum of **1c** in solution and that of **M3-DiClfen** in the solid state shows a good similarity between the two spectra, supporting thereby the integrity of the organic framework. For the functionalized nanoparticles **M3-DiClfen**, the ^{29}Si CP MAS NMR spectrum exhibits mostly T^2 and T^3 environments (not T^1), which confirms the strong anchoring of the organic moiety within the silica network by two or three Si-O-Si linkages. This is also the case for **M2-DiClfen** and **M4-DiClfen**. However, whereas for the functionalized nanoparticles derived from co-condensation procedures (**M3-DiClfen** and **M4-DiClfen**) the intensity of T^3 signals are higher than those of T^2, for **M2-DiClfen** derived from grafting T^2 is more intense than T^3 (see Supporting Information for the data).

The drug loading was deduced from the nitrogen elemental analysis (**Table 1**).

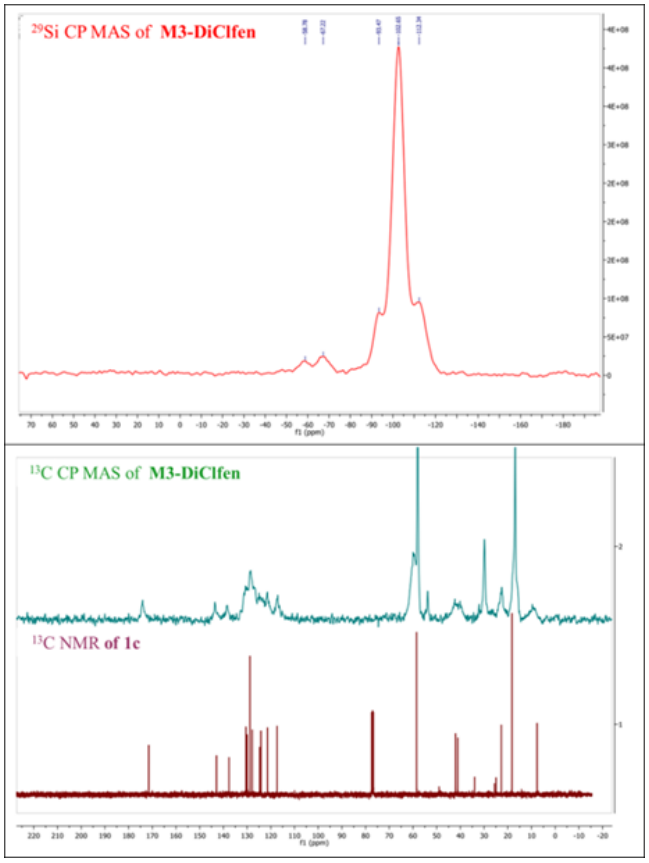


Figure 8. ^{29}Si CP MAS NMR spectrum of **M3-DiClfen** (top); ^{13}C CP MAS NMR spectrum of **M3-DiClfen** and ^{13}C NMR spectrum of **1c** (bottom).

With the drug-functionalized silica nanoparticles in hand, we turned to the loading of cotton fabrics with these nanoparticles. Preliminary essays using methods such as dip-coating,[60] or padding[71] with solutions of previously synthesized and isolated anti-inflammatory modified silica nanoparticles (**M1-Anti-Inf**, **M2-Anti-Inf** and **M3-Anti-Inf)** did not give the desired hydrophobicity for the textiles. Thus, we finally chose to prepare cotton fabrics loaded with **M4-Anti-Inf** by the one-step coating method[57] depicted in **Scheme 4**. The coating solutions were obtained by co-hydrolysis of TEOS with organosilanes **1a-c** (molar ratio 10:0.5) in aqueous ammonia in ethanol under stirring. Without any isolation and purification, the resulting milky solution was ultrasonicated for 30 min to produce a homogeneous suspension in which a piece of cotton textile was immersed and the whole system was ultrasonicated for half an hour. Then, the cotton textile was removed from the solution and dried at 120 ºC for one hour. The measured water contact angle (CA) was 140.5 ° for the fabric coated with **M4-DiClfen**. When the immersion process of the textile on the coating solution, sonication, removal and drying was repeated until three times, the contact angle achieved a value of 141.8 ° (**Figure 9**).

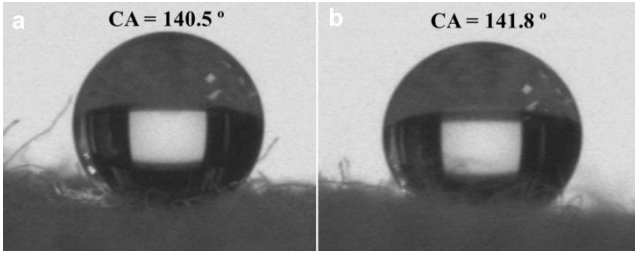
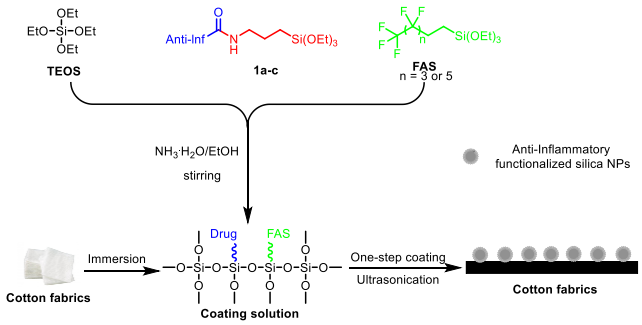


Figure 9. Pictures of water drops on the fabrics treated with **M4-DiClfen** (**Fabric-M4-DiClfen**).



Scheme 4. Schematic illustration of the silica sol preparation and coating procedure for highly hydrophobic cotton fabrics.

Table 2. Some physical data of cotton fabrics coated with **M4-DiClfen** and the corresponding silica nanoparticles.

Entry	FAS [a]		Cotton Fabrics **(Fabric-M4-DiClfen-x FAS-n)**							Silica NPs **(M4-DiClfen-x FAS-n)**		
	n	x mmol	CA (°) [b]	EDX [c]						DLS (nm) [d]	Zeta potential (mV)	Drug loading ($mmolg^{-1}$) [e]
				C	O	Si	N	Cl	F			
1	3	0	141	43.49	41.08	11.18	0.86	3.38	-	424	-50	0.264
2	3	0.25	148	30.97	37.92	19.60	1.28	3.66	6.57	167	-41	0.121
3	3	0.5	147	32.33	37.78	21.12	0.72	1.28	6.66	183	-42	0.104
4	3	0.75	147	41.35	41.39	9.78	0.63	1.21	5.63	312	-36	0.221
5	3	1	148	42.14	32.90	18.31	0.52	1.45	4.67	403	-37	0.096
6	5	0.25	156	41.76	37.01	13.76	0.89	2.93	3.64	229	-48	0.346

[a] Molar ratio TEOS:**1c**:FAS = 10:0.5:x. [b] The hydrophobic tests performed were the measurement of the contact angle of a water droplet (4 µL) deposited on top of each fabric; [c] EDX was taken on a SEM Zeiss Merlin with and INCA detector from Oxford Instruments; [d] Hydrodynamic diameters; [e] Calculated from the N elemental analysis.

In an attempt to increase the hydrophobicity, several textiles were also prepared by this one-step coating method by adding certain amounts of fluorinated alkyl silanes (FAS) of two different lengths, namely (1*H*,1*H*,2*H*,2*H*-nonafluorohexyl)-triethoxysilane[71] and (1*H*,1*H*,2*H*,2*H*-tridecafluorooctyl)triethoxysilane[72] in the co-hydrolysis process. With the silylated diclofenac derivative **1c** as a model, and keeping constant the molar ratio of TEOS:**1c** at 10:0.5, we have examined the influence of the amount of added FAS (n = 3) (x mmol) on the hydrophobicity of the resulting fabrics. Indeed, with x = 0.25, a higher water contact angle of 148 ° was found, but a further increase on the amount of added FAS did not give significant improvements (**Table 2** and **Figure S2** in Supporting Information). Interestingly, a superhydrophobic fabric (CA of 156 °, **Figure S3** in Supporting Information) was obtained by using the FAS with the longer fluorinated chain (n = 5, x = 0.25) (**Fabric-M4-DiClfen-0.25 FAS-5**). Some physical data of cotton fabrics prepared by one-step coating with **M4-DiClfen** and FAS and the corresponding functionalized silica nanoparticles are summarized in **Table 2**. The nanoparticles have high negative zeta potential values, indicative of stability. From the amount of fluorine (EDX) and the obtained loading of the drug derivative when increasing amounts of FAS were used (entries 2-6 of **Table 2**), we can infer that the fluorinated silane is not completely co-condensed, probably due to the lower solubility in the medium. This fact is more pronounced with the longer chain fluorinated silane (compare entries 2 and 6) which, in addition, acted as template.[73] Thus, the corresponding functionalized nanoparticles **M4-DiClfen-0.25 FAS-5** show some porosity (286 m^2g^{-1}, pore volume of 0.15 cm^3g^{-1}).

The presence of abundant silica nanoparticles on the surface of cotton fabric loaded with **M4-DiClfen** by one-step coating was clearly observed by SEM (**Figure 10**). The chemical composition of the surface of the fabrics was analyzed by EDX. As expected, in all cotton fabrics the EDX analysis showed peaks for the elements C, O, N, Cl, together with F when FAS was used (entries 2-6, **Table 2** and Supporting Information). As an example, we display in **Figure 11** the EDX spectrum and the corresponding element mapping of cotton fabric coated with **M4-DiClfen**. The peaks corresponding to silicon, chlorine and nitrogen clearly indicate the presence of the diclofenac-modified silica nanoparticles coating (see also **Figures S4** and **S5** in Supporting Information for the SEM image, EDX spectrum and the corresponding element mapping of the highly hydrophobic **Fabric-M4-DiClfen-0.25 FAS-5**).

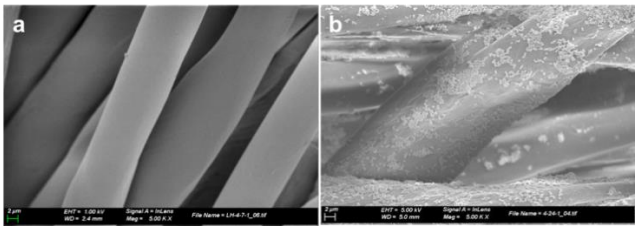


Figure 10. SEM images of uncoated cotton fabric (a) and cotton fabric coated with **M4-DiClfen** (**Fabric-M4-DiClfen**) (b).

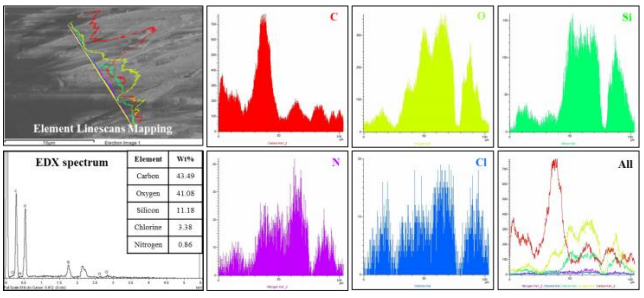


Figure 11. EDX spectrum and corresponding element mapping of the cotton fabric coated with **M4-DiClfen** (**Fabric-M4-DiClfen**).

This elemental composition is corroborated by XPS (**Figure 12**) and Fourier-Transform Infrared Spectroscopy (FTIR) (**Figure S6** in Supporting Information). The spectrum of uncoated fabric exhibited absorptions due to O-H stretching at around 3333 cm^{-1}, C-H stretching at 2900 cm^{-1} and C-O-C stretching at 1018-1100 and 1099 cm^{-1}, all of them consistent with those of typical cellulose.[74-75] In addition of these signals, in the IR spectrum of the coated cotton appeared a new absorption at 795 cm^{-1} corresponding to Si-C stretching. The typical absorption due to Si-O-Si moiety characteristic of silica nanoparticles, which should appear at 1100-1000 cm^{-1} region, was overlapped by the C-O absorption of cellulose.[71, 76] The intensity of the peaks at this region increases and becomes higher than in uncoated cotton fabrics, indicating the presence of Si-O-Si bond on the coating surface. These results confirm the successful coating of the cotton cellulose with modified silica nanoparticles.

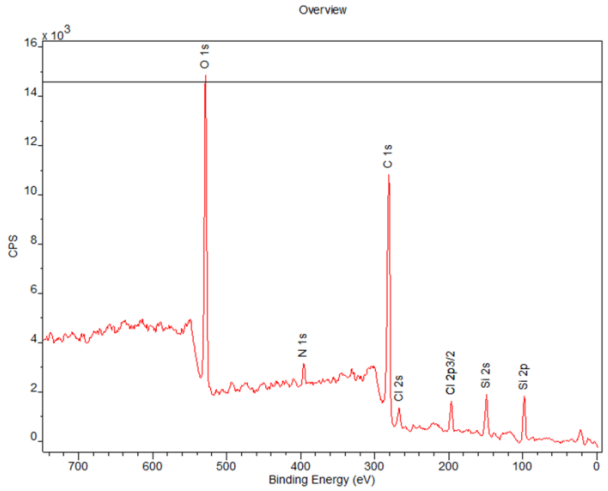
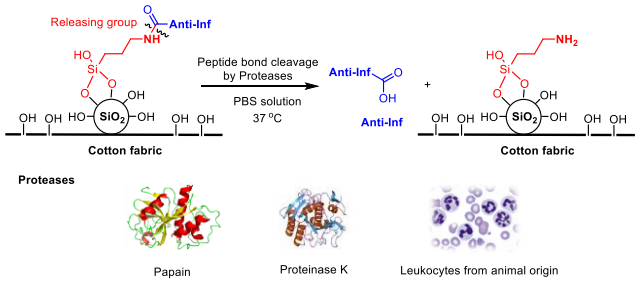


Figure 12. XPS spectrum of the cotton fabric coated with **M4-DiClfen (Fabric-M4-DiClfen)**.

Finally, the release of the drug from functionalized silica nanoparticles and the coated cotton fabrics was also assayed by proteases such as papain and proteinase K. We also used leukocytes from animal origin (**Scheme 5**). The experiments were performed in PBS buffer (pH = 7.4) at 37 ºC under stirring. After removal of the coated textile pieces or separation of the nanoparticles by centrifugation, the solutions were extracted with dichloromethane and analysed by GC-MS, the release of the anti-inflammatory drug being confirmed.



Scheme 5. Release of anti-inflammatory drug by enzymatic cleavage of amide bond.

Some silica NPs functionalized with ibuprofen and diclofenac, and cotton fabrics coated with **M4-DiClfen** were tested. Blank experiments were also performed to assure the need of the presence of the drug and the enzyme for the detection of the anti-inflammatory agent (**Table S1** and **Figure S7** in the Supporting Information). Release of the anti-inflammatory drug by enzymatic cleavage of the amide bond was confirmed in functionalized NPs and cotton fabric coated with **M4-DiClfen**. From the SEM images, we can confirm that the silica nanoparticles remain on the surface of the cotton fabrics, only the anti-inflammatory drugs were released (**Figure 12**).

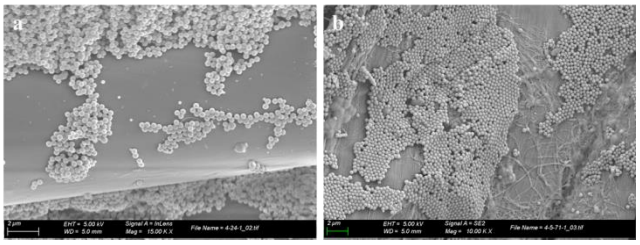


Figure 12. SEM images of **Fabric-M4-DiClfen**: a) before the protease treatment, b) after the protease treatment.

CONCLUSIONS

We have performed the covalent attachment of three carboxyl-containing non-steroidal anti-inflammatory drugs (NSAIDs) onto cotton surfaces and on mesoporous and non-porous silica nanoparticles through an amide functional group. We have used grafting and co-condensation procedures for the preparation of modified silica nanoparticles of different size. Salicylic acid, ibuprofen and diclofenac are the Food and Drug Administration (FDA)-approved anti-inflammatory agents selected. Furthermore, cotton fabrics have been coated with silica nanoparticles functionalized with such anti-inflammatory drugs by one-step procedure, which results in an increased roughness of the surface and provides hydrophobicity to the modified fabrics. This property is enhanced by the addition of a certain amount of fluorinated alkyl silane (FAS) in the co-condensation process to form the coating solution. The characterization of the functionalized nanoparticles and cotton textiles has been accomplished by microscopic and spectroscopic techniques. We have demonstrated that the corresponding anti-inflammatory drug is released *in situ* by the selective enzymatic cleavage of the amide bond in the presence of model proteases and leukocytes obtained from rat blood. High expectations arise for topical cutaneous applications in dressings intended to treat chronic wounds. The hydrophobicity would be advantageous for keeping the dressing and wound dry and promoting a rapid wound healing. Moreover, anti-inflammatory functionalized silica nanoparticles can find applications for ointment and cream topical formulations.

EXPERIMENTAL SECTION

General information. The ^{1}H and ^{13}C NMR spectra in solution were recorded at 298.0 K on a Bruker DPX-360 or 400 MHz Bruker Avance-III equipped with a BBFO probe with an automatic tuning. 1D ^{1}H and 2D ^{1}H-^{13}C HSQC experiments were performed using standard Bruker pulse sequences and acquired under routine conditions. All the spectra were calibrated using the residual solvent signal ($CHCl_3$, δ_H, 7.26 and δ_C, 77.16 ppm). Chemical shift data were expressed in ppm and coupling constant (*J*) values in Hz. Multiplicity of peaks was abbreviated as s (singlet), d (doublet), t (triplet), q (quartet) and dd (doublet of doublets). The ^{29}Si and ^{13}C CP-MAS NMR spectra were obtained from a Bruker AV400WB, the repeti-

tion time was 5 seconds with contact times of 5 milliseconds. These NMR instruments belong to the *Servei de Ressonància Magnètica Nuclear* of the Universitat Autònoma de Barcelona (UAB). From the *Servei d'Anàlisi Química* of UAB, the following experimental data were acquired: infra-red spectra (IR), mass-spectrometry (MS) and elemental analysis (EA). IR spectroscopy was recorded with a Bruker Tensor 27 spectrometer using a Golden Gate ATR module with a diamond window. Low- and high-resolution mass spectra were obtained by direct injection of the sample with electrospray techniques in a Hewlett-Packard 5989A and microTOF-Q instruments respectively. Elemental analysis of C, N and H were performed using Flash 2000 Organic Elemental analyser of Thermo Fisher Scientific with BBOT as an internal standard. Electron microscopy belongs to *Servei de Microscòpia* of UAB. Transmission electron microscopy (TEM) analyses were performed on a JEM-2011 Electron Microscope 200 Kv. Scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX) and element linescans mapping were taken on a SEM Zeiss Merlin with and INCA detector from Oxford Instruments. Microscopic investigations of the specimens were carried out using a ZEISS MERLIN scanning electron microscope (SEM). The specimens were mounted on conductive carbon adhesive tabs and images were taken after the specimens had been sputter-coated (K550X EMITECH) with a very thin layer of gold. To determine the elemental composition of the fabric surface, an INCA energy-dispersive X-ray (EDX) detector from Oxford Instruments was used. Dynamic light scattering (DLS) and zeta potential measurements have been performed by the ICTS "NANBIOSIS", more specifically by the Biomaterial Processing and Nanostructuring Unit (U6), Unit of the CIBER in Bioengineering, Biomaterials & Nanomedicine (CIBER-BBN) located at the *Institute of Materials Science of Barcelona* (ICMAB-CSIC). These analyses were performed on a Zetasizer Nano ZS (Malvern Instruments) with 8 mg silica NPs in 8 mL Mili-Q water, the pH of the solution was measured by CRISON pH METER Basic 20. The surface areas were determined at ICMAB-CSIC by the Brunauer-Emmet-Teller (BET) method from N_2 adsorption-desorption isotherms obtained with a Micromeritics ASAP2000 analyzer after degassing samples for 30 h at 55 °C under vacuum. The pore diameter distribution was calculated by Barrett-Joyner-Halenda (BJH) method, which relies on the Kelvin equation to relate the width of the pores to the condensation pressure. Contact angle (CA) measurements: the hydrophobic tests performed were the measurement of the contact angle of a water droplet (4 µL) deposited on top of each fabric. These experiments were carried out at ICMAB installations with a Contact Angle Measuring System DSA 100 from KRÜSS which is located in a physico-chemical laboratory (humidity and temperature control). X-ray photoelectron spectra (XPS) which belongs to *Catalan Institute of Nanoscience and Nanotechnology* (ICN2) was performed at room temperature with a SPECS PHOIBOS 150 hemispherical analyzer(SPECS GmbH, Berlin, Germany)) in a base pressure of 5 × 10^{-10} mbar using monochromatic Al Kalpha radiation (1486.74 eV) as excitation source.

When required, experiments were carried out with standard high vacuum and Schlenk techniques. Chromatographic purifications were performed under N_2 pressure using 230-400 mesh silica gel (flash chromatography). Dry toluene was purchased from Merck. Dichloromethane was from solvent processing equipment (PureSolv, Innovative Technology).

The proteases used in the experiments reported in this manuscript were proteinase K (50.7 units/mg), papain (20 units/mg) and cathepsin G (60 units/mg) (purchased from Sigma Chem). All of them have similar molecular weight (20-30 kDa) and are active in a quite wide pH range, including the physiological pH (7.4). Whereas papain is obtained from papaya, proteinase K is of bacterial origin and cathepsin G is a protease found in leukocyte lysosomes.

Whole blood was obtained from Sprague–Dawley rats of the university animal facility. The rats were exsanguinated as end-point procedure under anesthesia (ketamine-xylazine (80/20 mg / kg i.p.), a total of 15 mL of blood was collected with heparinized syringes. The pooled blood was diluted 1: 1 with physiological saline and centrifuged at 500 g at room temperature for 20 minutes on a percoll gradient. The layer containing leukocytes was collected, re-suspended in 50 mL cold PBS and centrifuged again at 500 g for 10 minutes. The supernatant was discarded and the pellet was incubated with lysis buffer to eliminate any residual red blood cells. The cells were washed with 50 mL cold PBS, centrifuged again and the resulting pellet was re-suspended in a small volume of PBS. The cells were then counted in a Neubauer chamber and the volume of the suspension was corrected to get the desired number of leukocytes.

*General procedure for the preparation of **1a-c***

The corresponding anti-inflammatory drug (1 mmol) was placed in a Schlenk under argon atmosphere. Then, DMAP (6 mg, 5 mol %), DCC (206 mg, 1 mmol) and dry dichloromethane (5 mL) were added and the solution was stirred until homogenization. Then 3-(triethoxysilyl)propan-1-amine (266 mg, 1.2 mmol) was introduced by syringe. The reaction was allowed to proceed under stirring at room temperature until completion (TLC monitoring). The crude mixture was poured into water and extracted with dichloromethane. The combined organic phase was washed with brine, dried with anhydrous sodium sulphate and evaporated under vacuum. The residue was purified by silica gel column chromatography (hexane-ethyl acetate mixtures) to afford the desired silylated derivative.

*General procedure for the preparation of **Fabric-Anti-inflammatory***

A piece of clean cotton fabric (3 × 3 cm) was activated by treatment with a 0.1 M solution of NaOH (10 mL) for 30 minutes at room temperature. Then, the cotton was rinsed with anhydrous THF and stored under vacuum in a sealed tube. Subsequently, a solution of the corresponding silylated anti-inflammatory derivative (**1a-c**) (0.068 mmol) in THF (8 mL) was added to the cotton and the mixture was refluxed for 48 h. Next, the piece of cotton fabric was thoroughly washed with THF and then with EtOH. Finally, the modified cotton was dried in a vacuum oven at 55 ºC for 60 min.

*General procedure for the preparation of **M1-Anti-inflammatory** and **M2-Anti-inflammatory**.*

In a 100 mL round bottom flask equipped with a Dean-Stark apparatus, the corresponding silylated anti-inflammatory derivative (**1a-c**) (0.15 mmol) and the corresponding mesostructured silica nanoparticles (**MCM-41** or **M0)** (180 mg, 3.0 mmol) were refluxed in dry toluene (30 mL) for 24 h. Then the suspension was centrifuged (13500 rpm at 25 ºC for 45 min). The solid was washed successively with ethanol (3 × 20 mL), acetone (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL) (30 min at 50 ºC under sonication, 30 min for centrifugation), then dried under vacuum and finally crushed to give the grafted material as a white solid.

*General procedure for the preparation of **M3-Anti-inflammatory***.

The functionalized MSNs were synthesized in an aqueous buffer solution of pH 7 from a mixture with the following molar ratios: CTAB:TEOS:**1**:H_2O = 5:40:2:30000. Initially, CTAB (455.5 mg, 1.25 mmol) was dissolved in the buffer solution [prepared from KH_2PO_4 (428.8 mg, 3.15 mmol) and NaOH (72.5 mg, 1.81 mmol) in H_2O (135 mL, 7500 mmol)], under vigorous stirring (1200 rpm) and heating at 95 ºC. When the solution became homogeneous, a mixture of TEOS (2.08 g, 10 mmol) and the corresponding silylated anti-inflammatory derivative (**1a-c**) (0.5 mmol) was added slowly. The reaction mixture was maintained for 12 hours under stirring (1200 rpm) at room temperature. The NPs were collected by centrifugation (13500 rpm at 25 ºC for 45 min). In order to remove the surfactant, 20 mL of an ethanolic solution of ammonium nitrate [NH_4NO_3, 6 g/L in 96% EtOH] was added to each tube, sonicated for 30 min at 50 ºC, then cooled and centrifuged (30 min at 13500 rpm at 25 ºC), the supernatant was discarded. This NH_4NO_3 washing was performed 3 times. Each solid in the tubes was washed successively with 96% ethanol, Mili-Q water and 96% ethanol using the same protocol (sonication for 30 min at 50 ºC, then centrifugation). The final white solid was dried for few hours under vacuum at room temperature.

*General procedure for the preparation of **M4-Anti-inflammatory***.

TEOS (2.08 g, 10.0 mmol) and the corresponding silylated anti-inflammatory derivative (**1a-c**) (0.5 mmol) were dissolved in absolute EtOH (25 mL). Then, an ammonium hydroxide-ethanol solution was added (6 mL of 28% $NH_3{\cdot}H_2O$ in 25 mL EtOH). The mixture was stirred intensively (1400 rpm) at room temperature for 12 hours. The functionalized nanoparticles were collected by centrifugation (12000 rpm for 10 min) and washed with ethanol until neutral pH was reached. Then, the obtained white solid was washed successively with Mili-Q water and 96% ethanol and was dried under vacuum for several hours.

*General procedure for the one-step coating of cotton fabrics with anti-inflammatory silica nanoparticles (**Fabric-M4-Anti-inflammatory-x FAS-n**)*.

TEOS (2.08 g, 10.0 mmol), the corresponding silylated anti-inflammatory derivative (**1a-c**) (0.5 mmol) and, in some cases, the corresponding FAS (x mmol) were dissolved in absolute EtOH (25 mL). Then, an ammonium hydroxide-ethanol solution (6 mL of 28% $NH_3{\cdot}H_2O$ in 25 mL EtOH) was added. The mixture was stirred intensively (1400 rpm) at room temperature for 12 hours. The resulting milky mixture was then ultrasonicated for 30 min to produce a homogenous suspension prior to the coating on the fabric. Then, a piece of cleaned cotton textile (3 × 3 cm) was immersed in the as-prepared coating solution and the whole system was ultrasonicated for 30 min. The coated cotton textile was dried at 120 ºC in an oven for 60 min.

Treatment of cotton fabrics modified with anti-inflammatory drugs with cathepsin G.

The lyophilized commercial sample of cathepsin G (0.5 mg) from human leukocytes was dissolved in 4 mL of water. Then, the corresponding cotton fabrics (4 pieces of 1.5 × 1.5 cm) were dispersed in the vial. The system was warmed up to 37 ºC for 24 h with gently stirring. Then, after removal of the cotton pieces, the water solution was extracted with dichloromethane (3 × 1 mL). The corresponding anti-inflammatory drug released was detected by GC-MS analysis of the combined extracts.

Treatment of cotton fabrics modified with anti-inflammatory drugs with leukocytes from animal origin.

The corresponding cotton fabrics (2 pieces of 1 × 1 cm) were dispersed in phosphate-buffered saline (PBS) (2.5 mL) in an eppendorf vial, leucocytes of animal origin (0.39×10^6, 1×10^6 or 2×10^6 cells) were added and the mixture was gently stirred at 37 ºC for 24 h. Then, after removal of the cotton pieces, the supernatant was extracted with dichloromethane (2 × 1 mL). The corresponding anti-inflammatory drug released was detected by GC-MS analysis of the combined extracts.

Treatment of anti-inflammatory functionalized silica nanoparticles with proteases.

The corresponding functionalized silica nanoparticles (10 mg) were dispersed in phosphate-buffered saline (PBS) (2.0 mL) in a centrifuge tube, the corresponding protease was added, and the mixture was gently stirred at 37 ºC for the given time. The final concentration of protease was 0.05 M. Then, the sample was centrifuged, and the supernatant was extracted with dichloromethane (2 × 1 mL). The corresponding anti-inflammatory drug released was detected by GC-MS analysis of the combined extracts.

Treatment of anti-inflammatory functionalized silica nanoparticles with leukocytes from animal origin.

The corresponding functionalized silica nanoparticles (35 mg) were dispersed in phosphate-buffered saline (PBS) (2.0 mL) in an *eppendorf* vial, leukocytes from animal origin (2×10^6 cells) were added and the mixture was gently stirred at 37 ºC for 24 h. Then, the sample was centrifuged, and the supernatant was extracted with dichloromethane (2 × 1 mL). The corresponding anti-inflammatory drug released was detected by GC-MS analysis of the combined extracts.

Treatment of cotton fabrics coated with anti-inflammatory functionalized silica nanoparticles with proteases.

The corresponding cotton fabrics (4 pieces of 1 × 1 cm) were dispersed in phosphate-buffered saline (PBS) (4.0 mL) in a tube, the corresponding protease was added, and the mixture was gently stirred at 37 ºC for 48 h. The final concentration of protease was 0.05 M. Then, after removal of the cotton pieces, the supernatant was extracted with dichloromethane (2 × 1 mL). The corresponding anti-inflammatory drug released was detected by GC-MS analysis of the combined extracts.

Treatment of cotton fabrics coated with anti-inflammatory functionalized silica nanoparticles with leukocytes from animal origin.

The corresponding cotton fabrics (2 pieces of 1 × 1 cm) were dispersed in phosphate-buffered saline (PBS) (2.5 mL) in a tube, leucocytes of animal origin (4×10^6 cells) were added and the mixture was gently stirred at 37 ºC for 24 h. Then, after removal of the cotton pieces, the supernatant was extracted with dichloromethane (2 ×1 mL). The corresponding anti-inflammatory drug released was detected by GC-MS analysis of the combined extracts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General procedure for the preparation of **1a-c**, preparation of silica nanoparticles functionalized with anti-inflammatory drugs, general procedure for the preparation of **Fabric-Anti-inflammatory**, general procedure for the one-step coating of cotton fabrics with anti-inflammatory silica nanoparticles (**Fabric-M4-Anti-inflammatory-x FAS-n**), some characterization data of functionalized silica nanoparticles and cotton fabrics , drug release procedures, NMR spectra of **1a-c**, NMR spectra of **1a-c**.

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Author Contributions

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Notes

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ABBREVIATIONS

Salicyl, salicylic acid. **Ibup**, ibuprofen. **Diclfen**, diclofenac. **Anti-Inf**, anti-inflammatory. **FAS**, fluorinated alkyl silanes.

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Table of Contents

Cotton fabrics and silica nanoparticles covalently functionalized with carboxyl-containing non-steroidal anti-inflammatory drugs through amide groups release the drug in the presence of proteases by selective enzymatic cleavage of the amide bond. Moreover, the coating of cotton fabrics with the functionalized silica nanoparticles provides hydrophobicity to the surface. Medical applications in wound dressings and topical formulations are envisaged.