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Sol–Gel Treatment of Textiles for the Entrapping of an Antioxidant/Anti-Inflammatory Molecule: Functional Coating Morphological Characterization and Drug Release Evaluation

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Abstract: The growing interest towards textile-based drug delivery systems is due to their potential innovative medical and well-being applications. In recent years, the technique of encapsulation or inclusion of the medicine/active principle into a polymer functional matrix has been employed in order to obtain textile materials with controlled drug release. In this study, a sol–gel-based coating was developed and used as an entrapping polymeric cross-linked network for a *N*-Palmitoyl-ethanolamine (PEA) derivative, 2-methyl-pentadecanoic acid (4-nitro-phenyl)-amide or *N*-Palmitoyl-(4-nitro-phenyl)-amine (PNPA), whose anti-inflammatory and antioxidant properties have already been shown. A wide series of chemical-physical methods have been used to characterize the silica-based functional sol and to ascertain the efficient and temporary deposit of PNPA on the sol–gel coated cotton fabrics. The medicine release system achieved was shown to ensure biocompatibility, PNPA reservoir and its subsequent releasing under the action of cutaneous stimuli, thus providing useful insights in the design of medical textiles.

Keywords: sol–gel coating; medical textiles; antioxidant; anti-inflammatory; PEA derivative; drug release

1. Introduction

The research field dealing with the development of controlled drug delivery systems has been of relevant scientific interest since the 1970s and has grown and diversified rapidly in recent years, in

particular thanks to the benefits it brings to healthcare; furthermore, it covers a large market segment [1]. In general, the effectiveness of drug therapy is the main objective of controlled release systems [1,2], with a corresponding (i) reduction of the number of drug administrations; (ii) improvement in therapeutic activity [3,4]; (iii) consequent reduction of the intensity of side effects; and (iv) elimination of specialized drug administration [5]. This pharmaceutical technology, especially in recent years, has seen application in other fields ranging from cosmetics [6] to agriculture [7], including textiles [8,9], as an interesting and innovative application. Indeed, textile fabrics, thanks to their biocompatibility, breathing structure and absorptive capacity, are of great interest as a medium (for ex vivo applications) for controlled release of drugs, active principles or aroma substances of particular comfortability [10]. Several examples are nowadays in common use, such as the well-known transdermal patches or textile costumes, generally characterized by different layers in which the release of a specific drug substance, deposited on the textile surface, is activated by stimuli such as temperature, humidity, enzyme, perspiration types or friction [11].

In general, in controlled release systems, biocompatibility and controllability are important features; furthermore, in terms of biocompatibility, the carcinogenicity, toxicity, teratogenicity and mutagenicity are important elements to be controlled [10]. The use of textile fabrics for the realization of controlled release systems presents several advantages but on the other hand, some disadvantages with respect to the oral administration of substances. Indeed, this administration represents an attractive and easier therapy for the patient due to its efficacy since the drug avoids both the digestive apparatus and the hepatic metabolism that reduce the concentration of the drug. Furthermore, it requires lower dosages due to the higher diffusion through tissues, which correspond to lower social costs of therapies [11]. On the other hand, the disadvantages are related to the diffusion rate of the drug as function of its molecular structure and body surface administration [11]. Different methods have been employed in order to develop better textile-based delivery systems (i.e., bandages, patches), with good controllability, biocompatibility and active species entrapment/release by use of host-guest molecules (cyclodextrins [12], aza-crown ethers, fullerenes) or doping functional molecules (ion-exchange; drug-loaded hollow; nanoparticles; bioactive) [10]. Several C–C polymer heteroatom-containing (i.e., N, P, Si) backbones for controlled release applications have been tested and considered in order to improve the drug therapy effectiveness [5]. All the developed release polymeric systems have been shown to act through mechanisms of temporal controlled release, such as drug-delayed dissolution, diffusion-controlled, and drug solution flow control after interaction with environmental water or by reacting to specific skin stimuli.

The sol–gel method has been shown to be a useful method in the preparation of functional nanostructured coatings for textiles, thus combining the entrapment/encapsulation of bioactive compounds, biomolecules and their controlled release [13].

In our previous studies, we have already shown that nano-hybrid sol–gel-based coatings feature abrasion resistance, tensile strength and elongation properties of the treated fabrics [13,14]. These peculiar characteristics may be combined with a proper doping molecule, such as a dye [15–21], an antimicrobial [22], a hydrophobic [23–25] or a flame-resistant molecule [26,27], with the aim of improving the textile surface properties and making a functional nano-hybrid coating.

With the aim of developing a functional sol–gel-based coating suitable for medical application, we thought worthwhile to make a silica sol containing the 3-glycidoxypropyltriethoxysilane (GPTES, hereafter "G"), as silica cross-linker precursor, and a PEA derivative, the *N*-Palmitoyl-(4-nitro-phenyl)-amine (hereafter PNPA), whose anti-inflammatory and antioxidant properties have already been tested and compared with other analogue molecules [28]. The sol was successfully applied on cotton surfaces and, after drying and curing, a stable and uniform PNPA-containing silica-based coating was obtained, as confirmed by morphological studies (SEM and AFM microscopy). As already shown in previous studies for halochromic dyestuff [20], the PEA derivative results firmly encapsulated into the 3D hybrid silica layer in absence of external stimuli (i.e., variable pH conditions), thanks to non-covalent and weak interactions (i.e., hydrogen bonds

and van der Waals interactions) acting between the non-polar active molecule and the alkoxysilane hosting network.

Finally, the functionally coated cotton samples were employed for in vitro diffusion studies with the aim of testing their ability to release the synthesized PEA derivative in a controlled manner compared to a standard solution of the molecule. This effectively prepared functional hybrid system, based on the non-covalently immobilized PNPA, showed good results so that it can be considered a suitable scaffold for fabrics in drug release applications, thus providing useful insights in the design and the development of medical textiles.

2. Materials and Methods

N-Palmitoyl-(*4*-nitro-phenyl)-amine (PNPA) was synthetized according to a synthetic strategy described in previous researches [28]. *3*-glycidyloxypropyltriethoxysilane (GPTES) and methanol were purchased from Wacker and Aldrich, respectively, and used without further purification. Two cotton scoured and bleached 100% plain-weave textile fabrics (coded CO_L and CO_H) kindly supplied by Albini S.p.A. (Albino, Italy) and Mascioni S.p.A. (Cuvio, Italy), respectively, were used for this research. The fabrics showed different mass per unit area (CO_L = 119 g/m^2 and CO_H = 331 g/m^2, respectively). Cotton fabrics were washed before treatment at pH 7 and at 40 °C for 20 min in a non-ionic detergent, rinsed several times with de-ionized water and then dried. The cleaned samples were conditioned at 20 (± 1) °C and under standard atmospheric pressure at 65 (± 2)% relative humidity for at least 24 h prior to all experiments.

PNPA (25 mg) was dissolved in 40 mL of methanol through ultrasonication and left under continuous stirring. Then 2 mL of a 1 M aqueous sol–gel solution of GPTES were added drop by drop to the clear methanol solution of antioxidant molecule, thus resulting in a final GPTES sol concentration of 0.05 M (1:0.034 molar ratio with respect to PNPA). The obtained solution (G-PNPA sol) was ultrasonicated and left at room temperature under stirring for at least 90 min. The same reaction was also carried out in absence of the antioxidant molecule in order to obtain a reference GPTES sol sample. Both solutions were applied separately onto cotton textile (10 cm × 10 cm) through a two-roll laboratory padder (Werner Mathis, Zurich, Switzerland) at a nip pressure of 2 bar, then dried (80 °C for 5 min) and cured (100 °C for 1 min) in an electric laboratory oven.

PNPA, G-PNPA and G sols were fully investigated through FT-IR spectroscopy and Nuclear magnetic resonance (NMR). Untreated and treated textiles were characterized by FT-IR spectroscopy, Scanning Electron Microscopy (SEM) coupled to energy dispersive X-ray (EDS) and Atomic Force Microscopy (AFM).

The PNPA controlled release from the two prepared textiles, CO_L_G-PNPA and CO_H_G-PNPA, was investigated by performing in vitro diffusion studies using Franz diffusion cells and according to the experimental protocol reported in a previous work [29]. For this purpose, Strat-M® membranes (25 mm discs, Cat. No. SKBM02560, Merck Millipore, Darmstadt, Germany) were positioned between the donor and the receptor compartments of each Franz cell and the experiments were carried out at 37 ± 0.5 °C. The two tested items, CO_L_G-PNPA and CO_H_G-PNPA, were placed on the Strat-M® membrane with the GPTES layer facing towards the acceptor chamber. Then, the Franz cell compartments were fixed together and filled with 0.5 and 5.5 mL of phosphate buffer at pH 7.4 (10^{-3} M), respectively. The content of the receptor chamber was withdrawn at different times, such as 1, 2, 4, 6 and 24 h, for UV-Vis analysis and replaced with phosphate buffer. The same experimental conditions were applied to a control sample consisting of a standard PNPA solution. The in vitro diffusion studies were carried out in triplicate and the obtained results were expressed as diffused amount (%).

FT-IR spectra were performed by a Thermo Avatar 370 equipped with an attenuated total reflection (ATR) accessory and using a diamond crystal as internal reflectance element. Spectra were acquired with 32 scans and in the range from 4000 to 550 cm^{-1} with a resolution of 4 cm^{-1}.

One- and two-dimensional NMR experiment were recorded in methanol-d_4 at 298.2 (±0.1) K on Bruker ARX-300, equipped with a 5 mm gradient probe and operating at 300.1 MHz for 1H nucleus. All chemical shifts are shown in parts per million (δ/ppm), downfield to tetramethylsilane (Me_4Si) as an internal standard (δ = 0.0 ppm), or referenced to the residual protiated solvent signal such as in methanol-d_4 (^{1}H NMR: 3.30 ppm). ^{1}H NMR signals were assigned by means of two-dimensional homonuclear NMR gradient experiments (gCOSY, gNOESY), acquired using standard Bruker pulse sequences.

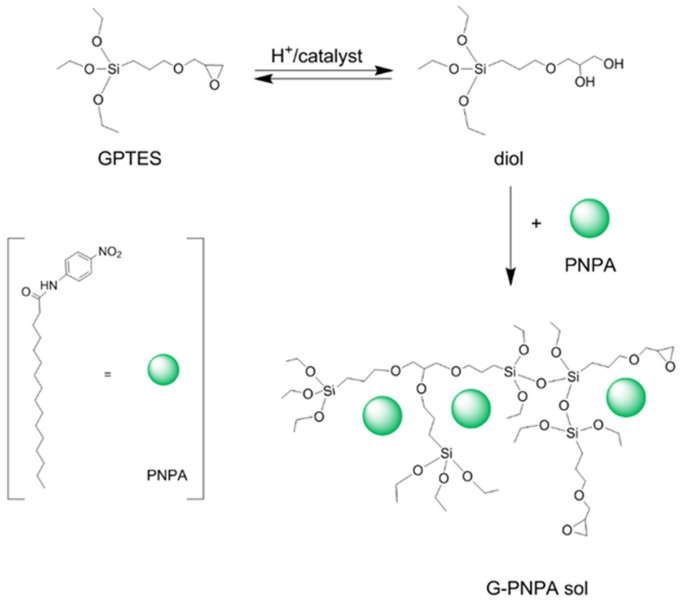
SEM morphology and SEM-EDS of the investigated samples were obtained using a FEI Quanta FEG 450 microscope. An operating voltage of 5 kV in low vacuum was used for SEM images. EDS analysis was conducted with an operating voltage of 20 kV, always in low vacuum. Samples were fixed on aluminum sample holders by means of a graphitic adhesive.

AFM characterization was performed using a stand-alone SMENA head by NTMDT, equipped with a Bruker silicon probe model NCHV working in semi-contact mode. The samples were fixed onto metallic stubs using a small piece of double-sided scotch tape and studied at RT.

3. Results

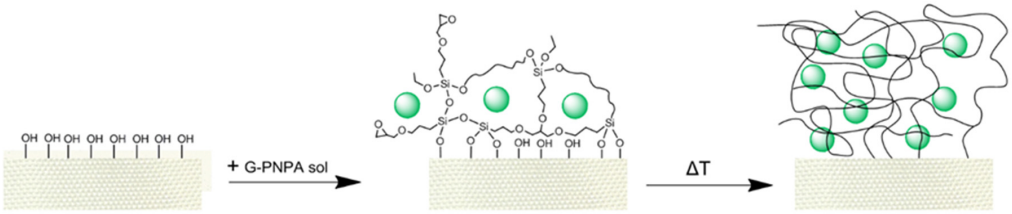
3.1. Sol–Gel Synthesis and Coating Application

To obtain a controlled drug release fabric, 3-glycidoxypropyltriethoxysilane (GPTES) was employed in a sol–gel synthesis in the presence of an antioxidant/anti-inflammatory molecule, the N-Palmitoyl-(4-nitro-phenyl)-amine (PNPA) [28]. The simultaneous presence of both an epoxy group and a triethoxysilane functionalities makes this specific silica precursor able to cross-link to other GPTES molecules, to entrap the antioxidant doping molecule and still to coat the textile surface, respectively. In this regard, a GPTES-based sol was synthesized in acidic aqueous medium by addition of slight amount of HCl, as catalyst, and then added to a methanol solution containing the PNPA molecule. As reported in previous studies [15–21], the sol–gel synthesis leads to the formation of a hybrid polymeric 3D network through the opening of the epoxy ring of GPTES and interaction of the triethoxysilane end to form an extended polyethylene oxide network (PEO) [20], in whose holes the PNPA is physically and stably entrapped (Scheme 1).



Scheme 1. Reaction pathways toward the formation of the G-PNPA sol, as obtained in methanol solution at room temperature in slight acid conditions.

The so obtained G-PNPA functional sol was applied by padding on cotton fabrics and cured thermally with the aim to prepare a nano-hybrid coating for controlled release application (Scheme 2).



Scheme 2. Schematic representation of the application of the G-PNPA sol on cotton surface and the formation of the coating xerogel.

3.2. Sol NMR Characterization

A reaction mixture relative to the G-PNPA sol as obtained in methanol for coating application, has been achieved in situ (1:0.1 = [GPTES]:[PNPA] molar ratio) in methanol-d_4 and characterized by means of ^{1}H one- and two-dimensional NMR spectroscopy. Figure 1 shows the ^{1}H NMR spectra as recorded at time zero and after 24 h (in methanol-d_4 at 298 K, 300 MHz). The comparison of the aliphatic regions of the ^{1}H NMR spectra of the reaction mixtures recorded at different times clearly reveal the presence of the protonic pattern expected for the diol/PEO silylated (red squares in Figure 1) derivatives and the starting GPTES (black squares in Figure 1, [20]) as shown in Scheme 1. In particular, the aliphatic regions of the ^{1}H NMR spectra in Figure 1 clearly show: (i) the presence of the expected protonic pattern for the GPTES open ring derivative, bringing a hydroxyl and an ether group bonded to two vicinal carbon C_e and C_f atoms (δ = 0.68, CH_{2a}; 1.71, CH_{2b}; 3.48, CH_{2c} + CH_{2d} + CH_{2f}; 3.88 CH_{2e}, red squares in lower spectrum) [30] (ii) the proton peaks relative to the starting GPTES in a decreased concentration (δ = 0.67, CH_{2a}; 1.68, CH_{2b}; 2.61+2.78, CH_{2f}; 3.16, CH_{2e}; 3.32 + 3.76, CH_{2d}; 3.49, CH_{2c}, black squares in upper spectrum); (iii) the presence of the upper-field methylene and the methyl proton resonances relative to free ethanol moieties, compared to those relative to the ethylic groups of GPTES (δ = 3.63, CH_2, 1.19, CH_3 vs 3.84, CH_2, 1.22, CH_3; cut signals in both spectra).

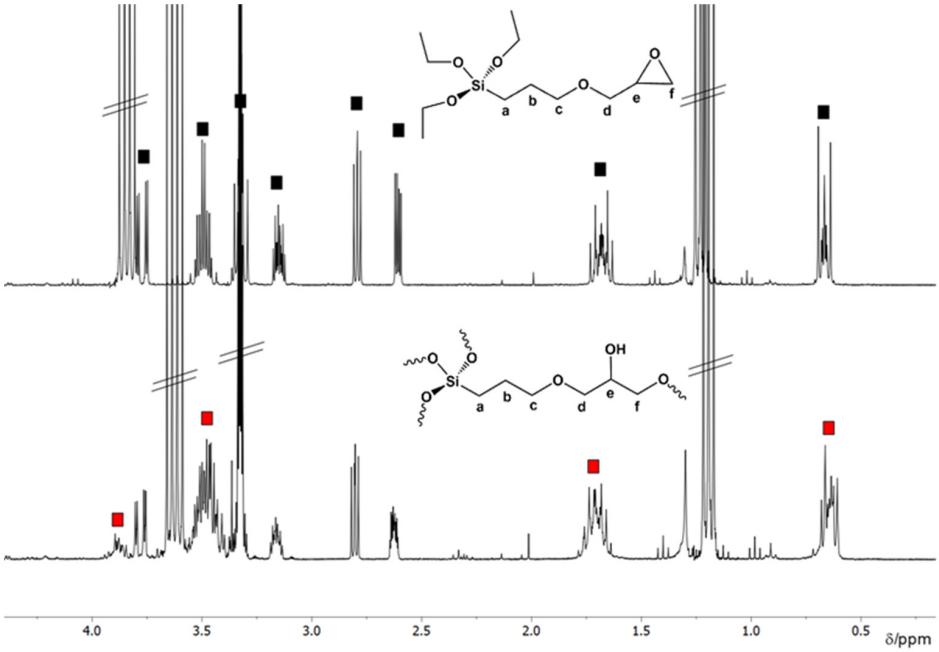


Figure 1. ^{1}H NMR spectra relative to solutions of the G-PNPA sol, as obtained in methanol-d_4 at 298 K, 300 MHz, at time zero (upper spectrum) and after 24 h reaction time in the presence of slight amount of HCl (lower spectrum).

Unfortunately, the long penta-decanoic protonic chain is buried under other signals, also due to the strong molar ratio exceed of GPTES. The aromatic region shows the expected and unchanged pattern of broad signals for para-substituted phenyl ring of the PNPA molecule.

The ^{1}H NMR experiments clearly show that the GPTES epoxy ring opening reaction by a suitable nucleophilic group of the PNPA molecule is not occurring, as well as the formation of a stable ether covalent bond. As previously shown [20], the stable encapsulation of the PNPA molecule into the PEO silylated GPTES derivative is most likely due to the formation of weak bonds (i.e., van der Waals or electrostatic) between the polymerized GPTES (i.e., ether oxygen and hydroxyl group) and the N-Palmitoyl-(4-nitro-phenyl)-amine (i.e., nitrogen, oxygen, long alkyl chain, phenyl group).

3.3. ATR FT-IR

FT-IR spectra of untreated and treated cotton fabrics were analyzed after the normalization at 1362 cm^{-1}, absorption band relative to the CH bending of cellulose. In Figure 2, FT-IR of CO_L untreated and treated samples with GPTES sol and G-PNPA sol (CO_L_UT, CO_L_GPTES and CO_L_G-PNPA, respectively) are reported and compared with those relative to CO_H untreated and treated fabrics with the same solutions (CO_H_UT, CO_H_GPTES and CO_H_G-PNPA, respectively). In particular, in all spectra, it is possible to distinguish clearly the characteristic absorption bands relative to cellulose moieties, such as: the broad bands around to 3331 cm^{-1} and 2894 cm^{-1} (stretching mode of OH and CH, respectively), and the absorption bands between 1097 cm^{-1} and 895 cm^{-1} relative to the asymmetric in-plane ring stretch and to C–O stretch and asymmetric out-of-phase ring stretch (C_1–O–C_4) [31]. In particular, in the inset in Figure 2A,B the presence of a silica coating is evident through the increase of the bands in the range 1145 cm^{-1}–895 cm^{-1} for the CO_L, assigned to the asymmetric stretching of the -Si–O–Si, and in the range between 995 cm^{-1}–760 cm^{-1} for the CO_H, due to the Si–O–Si absorption bending (852 cm^{-1}) and stretching (790 cm^{-1}).

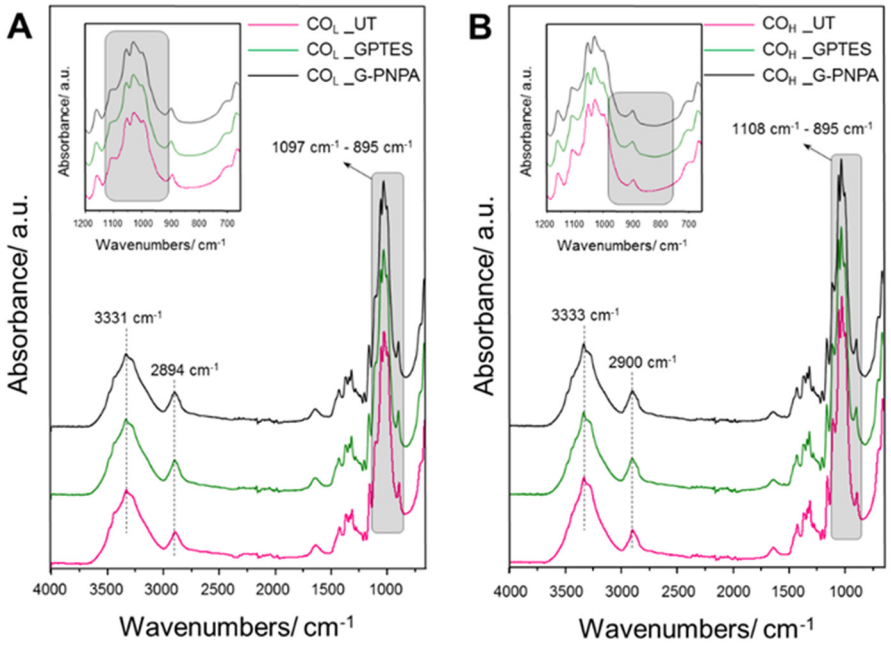


Figure 2. FT-IR spectra of CO_L and CO_H untreated and treated with GPTES sol and G-PNPA sol (**A** and **B**, respectively). (**A**) FT-IR spectra of CO_L untreated and treated with GPTES sol and G-PNPA sol; (**B**) FT-IR spectra of CO_H untreated and treated with GPTES sol and G-PNPA sol.

With the aim of investigating the chemical structure and interactions between silica precursor and antioxidant molecule without the interference of the intense absorption bands of cotton fabrics, the FT-IR spectra of each sol was carried out on the pure xerogel. The latter was obtained by depositing

a few drops of each solution onto optical glass slides further subjected to a thermal treatment (100 °C) to remove the solvent [26]. Indeed, by analyzing the FT-IR spectra of PNPA, it was possible to identify the characteristic peaks in order to establish its interaction with the GPTES sol. Spectra of the GPTES sol (Figure 3, green line) clearly shows the formation of the inorganic network due to the absorption bands relative to: asymmetric (1093–1010 cm^{-1}) and symmetric stretching of Si–O–Si (756 cm^{-1}) and its bending mode (850 cm^{-1}) [17,18,20]. Furthermore, the absorption bands at 3072–3000 cm^{-1}, 1255 cm^{-1} and 906–850 cm^{-1} were assigned to asymmetric and symmetric C–H stretch, ring breathing, as well as the asymmetric and symmetric ring deformation, respectively [17,18], indicating that some unopened epoxy ring remain in GPTES sol.

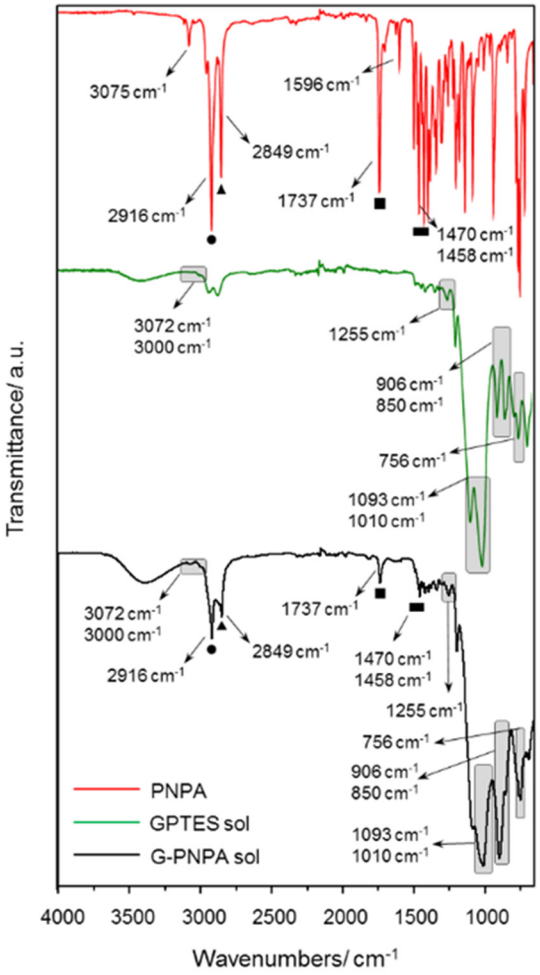


Figure 3. FT-IR spectra of PNPA, GPTES sol and G-PNPA sol.

These peaks relative to the GPTES sol are also evidenced in the sol containing PNPA (Figure 3, black line), in which the main characteristic absorption bands of the antioxidant molecules are present. As shown in Figure 2 (red line), PNPA is featured by the asymmetric and symmetric CH_2 stretching mode of alkyl chain (2916 and 2849 cm^{-1}, respectively) with relative bending (1470–1458 cm^{-1}), the C=O and C–N stretching of the secondary amide (1737 and 3075 cm^{-1}, respectively) and the C–N stretching mode (1596 cm^{-1}) [32].

3.4. Morphological Characterizations

All untreated and treated cotton samples were investigated by SEM and AFM microscopy, in order to characterize the morphology of the coated textile fabric and to underline structural differences before and after the coating application.

SEM analysis shows that the two analyzed tissues have two different weaves: CO_H_UT samples have a larger weave than CO_L_UT ones, and the fibers appear less ordered compared with CO_L_UT ones and more threadbare (compare Figure 4a,b). Both samples do not show modifications after treatment and the morphology appears unchanged also at higher magnification (Figure 5). This demonstrates that, after treatment, no changes at micrometer scale occur.

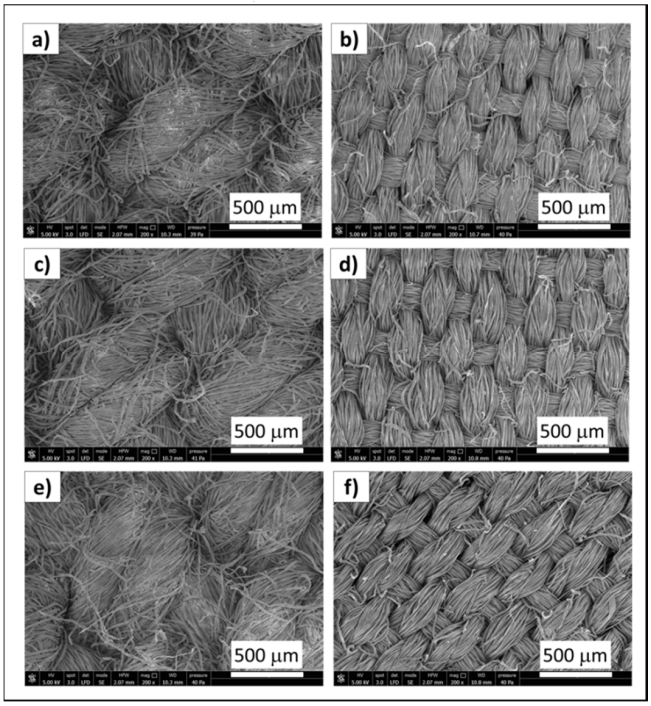


Figure 4. SEM analysis of investigated samples: CO_H_UT (**a**), CO_L_UT (**b**), CO_H_GPTES (**c**), CO_L_GPTES (**d**), CO_H_G-PNPA (**e**), CO_L_G-PNPA (**f**).

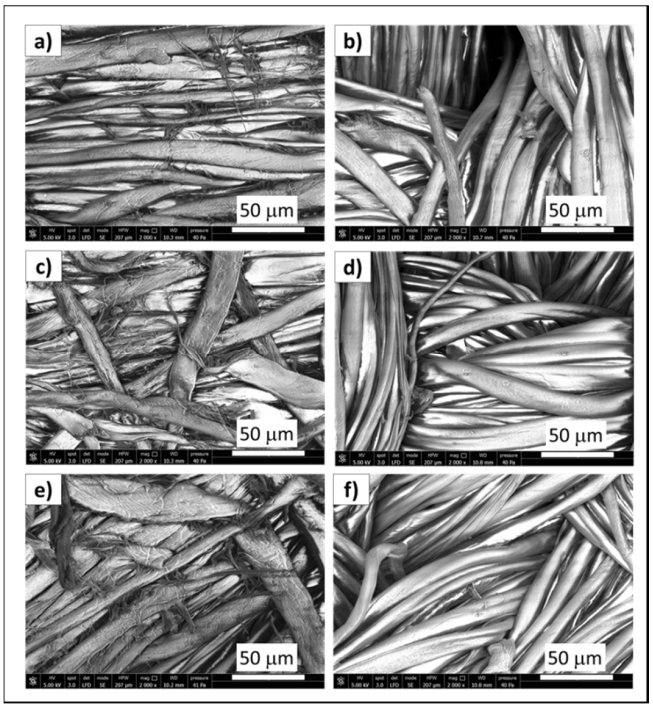


Figure 5. SEM analysis of investigated samples at higher magnification: CO_H_UT (**a**), CO_L_UT (**b**), CO_H_GPTES (**c**), CO_L_GPTES (**d**), CO_H_G-PNPA (**e**), CO_L_G-PNPA (**f**).

EDS analysis shows Si peak only in samples treated with GPTES (CO_H_GPTES, CO_L_GPTES) and subsequently with PNPA (CO_H_G-PNPA, CO_L_G-PNPA) (Figure 6, only two treated samples are reported for briefness, because the other ones exhibited a similar spectrum). The other peaks refer to carbon, present in the analyzed tissues but also in graphite adhesive used for SEM analysis, oxygen, present also in vapor-low vacuum atmosphere, and aluminum, derived from the SEM stub.

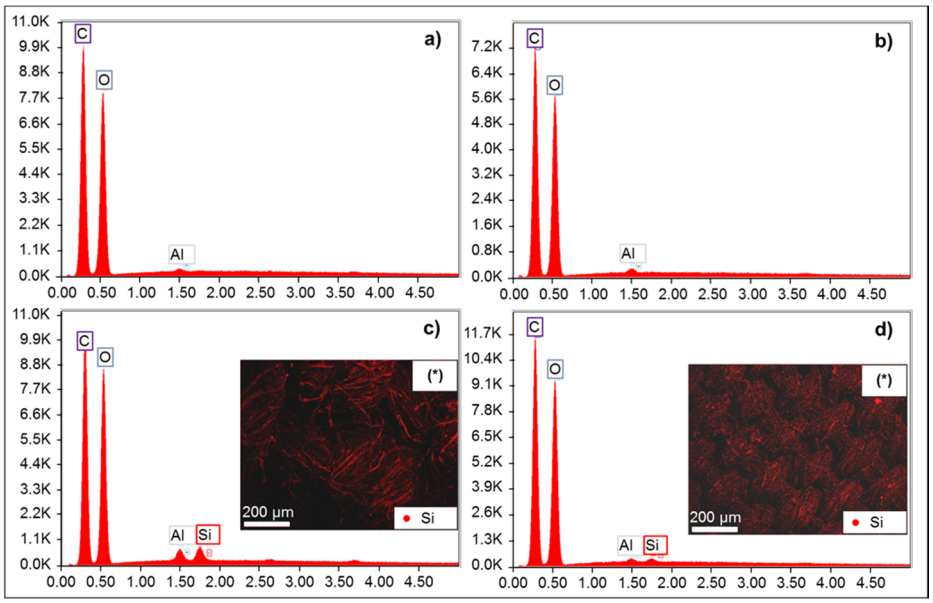


Figure 6. EDS analysis of investigated samples: CO_H_UT (**a**), CO_L_UT (**b**), CO_H_G-PNPA (**c**), CO_L_G-PNPA (**d**), and mapping of CO_H_G-PNPA (inset **c***) and CO_L_G-PNPA (inset **d***).

The mapping presented in Figure 6 (inset c* and d*) shows that distribution of Si element (present in GPTES) is very uniform and no phase separation occurs.

3.5. AFM Characterizations

Figure 7 shows that all the studied sampled are characterized by the typical filamentary structure of the tissue fibers on the nanoscale.

Thanks to the high resolution achieved by the AFM technique, it is possible to notice that both the two sample pairs CO_L_GPTES (Figure 7c), CO_H_GPTES (Figure 7d) and CO_L_G-PNPA (Figure 7e), CO_H_G-PNPA (Figure 7f) are rougher than the untreated tissues CO_L_UT (Figure 7a), CO_H_UT (Figure 7b), indicating that the GPTES and PNPA intimately and homogeneously wrap the fibers. This result is in good agreement with the EDS Si mapping. In the lower right corner of Figure 7f, it is possible to observe the presence of a lack in the coating; the study of the line profiles in that area allows us to evaluate the thickness of the coating that ranges between 2.5 and 4 nm.

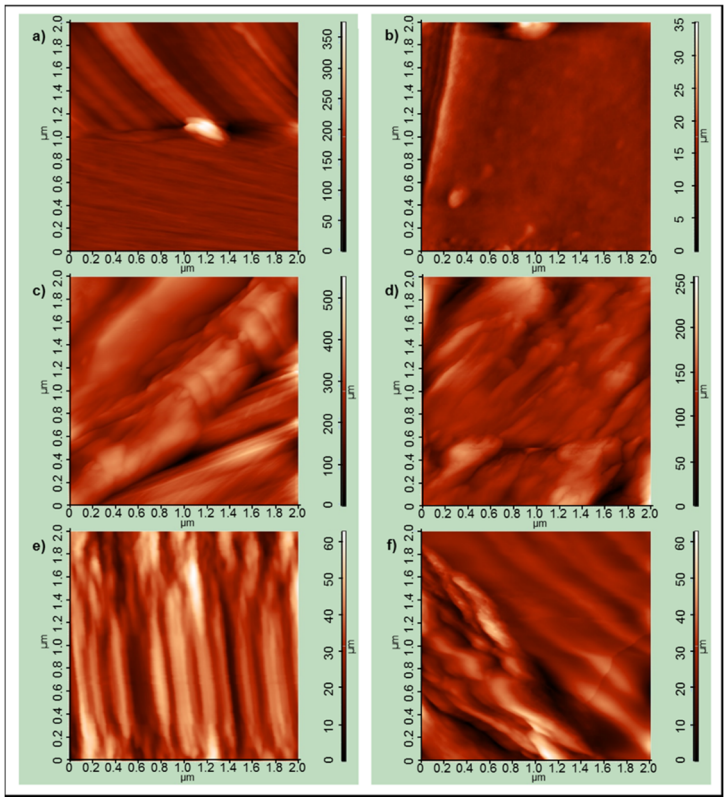
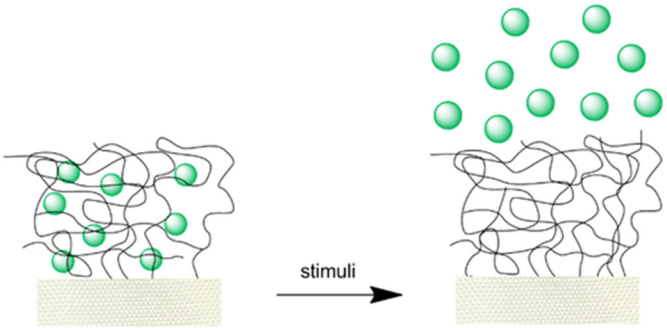


Figure 7. AFM micrograph of CO_L_UT (**a**), CO_H_UT (**b**), CO_L_GPTES (**c**), CO_H_GPTES (**d**), CO_L_G-PNPA (**e**), and CO_H_G-PNPA (**f**).

3.6. PNPA in Vitro Diffusion Studies

In vitro diffusion studies on the developed cotton-based textiles were carried out with the aim of evaluating their ability to release in a controlled manner the synthesized PEA derivative compared to a standard solution of the molecule (Scheme 3).



Scheme 3. Schematic representation on the PNPA controlled release from the functional sol–gel coated cotton by stimuli effect.

In the performed experiments, Strat-M® membranes were used as a synthetic alternative, which is predictive of the diffusion process occurring through human skin. The studies involved two different textiles, such as CO_L_G-PNPA and CO_H_G-PNPA, prepared employing the obtained G-PNPA functional sol. The obtained results are expressed as cumulative diffused amount (%) and the diffusion profiles for the tested items are reported in Figure 8.

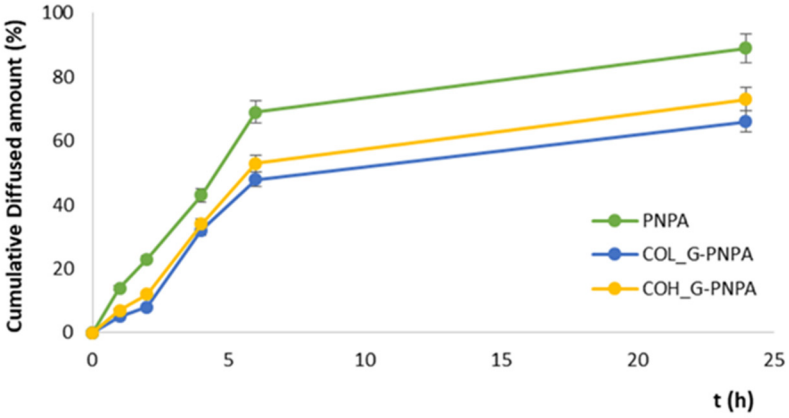


Figure 8. In vitro diffusion profiles.

The two G-PNPA-coated cotton textiles, CO_L_G-PNPA and CO_H_G-PNPA, show similar results in the performed in vitro diffusion studies. In the case of the CO_L_G-PNPA sample, indeed, the amount of released PNPA is equal to 5% within the first hour reaching the 48% and 66% in 6 and 24 h, respectively, while the CO_H_G-PNPA sample exhibits a value of 7% after the first hour achieving the 53% and 73% at the time points of 6 and 24 h. On the other hand, the 14% of PNPA is released after the first hour from the control solution reaching the 69% and 89% at 6 and 24 h. The experimental data confirm the ability of both the developed textiles to release in a controlled way the synthesized PEA derivative. These results could be related to the rate-limiting steps in drug release reported in the literature [33,34]: the drug diffusion within the polymer matrix and the rate of polymer swelling. Depending on the presence of sweat, simulated with the buffer solution in contact with the PNPA-treated fabric, the weak interactions between the treated fabric and the antioxidant molecule slowly disappear until the drug is completely released. The presence of the sol–gel matrix increases the bonding interactions between the network and the drug, slowing down its release.

4. Conclusions

The N-Palmitoyl-(4-nitro-phenyl)-amine, PNPA, a PEA derivative that already showed good anti-inflammatory and antioxidant properties, was firmly entrapped in a sol–gel-based matrix obtained by polymerization reaction of the epoxy-alkoxysilane GPTES, as cross-linker compound. NMR studies run on the sol evidenced that the GPTES epoxy-ring opening and the subsequent polymerization give rise to a polyethylene oxide 3D network grafted on textile with the PNPA immobilized into it. After the textile drying and curing the xerogel was morphologically studied on the treated cotton samples by SEM and AFM microscopy, revealing that no changes in the fiber morphology occurred at the micrometer scale, and that GPTES and PNPA intimately and homogeneously wrap the fibers. Furthermore, SEM mapping revealed a uniform distribution of the silica-based coating on the cotton fibers. In vitro diffusion studies were realized on the developed functionalized cotton-based textiles in order to check their ability to release the PEA derivative in a controlled manner in comparison to a standard molecule solution. As a matter of fact, this functional textile has been shown to be a suitable system for PNPA release, thanks to the chemical binding weakening of PNPA with the sol–gel polymer matrix by mean of medium effect, thus opening the way to the design of similar functional hybrid coatings for biomedical application. Although parameters of sol particles (e.g., hydrodynamic radius and electrokinetic potential) as well as the porosity of systems were not investigated, the obtained results confirmed the potential of the nanoengineered procedure as a versatile method for preparing stable and tunable drug-releasing materials. The combination of the functionality and transparency provided by the hybrid coating with its easy processability could represent an innovative route to fabricate biomaterials for healthcare. Future work will focus on the comparison of silica sols characteristics with release properties of this delivery system.

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References

1. Langer, R. Drug delivery and targeting. *Nature* **1998**, *392*, 5–10.
2. Brouwers, J.R.B.J. Advanced and controlled drug delivery systems in clinical disease management. *Pharm. World Sci.* **1996**, *18*, 153–162. [CrossRef]
3. Sinicropi, M.S.; Iacopetta, D.; Rosano, C.; Randino, R.; Caruso, A.; Saturnino, C.; Muià, N.; Ceramella, J.; Puoci, F.; Rodriquez, M.; et al. N-thioalkylcarbazoles derivatives as new anti-proliferative agents: Synthesis, characterisation and molecular mechanism evaluation. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 434–444. [CrossRef]
4. Saturnino, C.; Caruso, A.; Longo, P.; Capasso, A.; Pingitore, A.; Caroleo, M.C.; Cione, E.; Perri, M.; Nicolò, F.; Nardo, V.M.; et al. Crystallographic study and biological evaluation of 1,4-dimethyl-N-alkylcarbazoles. *Curr. Top. Med. Chem.* **2015**, *15*, 973–979. [CrossRef]
5. Uhrich, K.E.; Cannizzaro, S.M.; Langer, R.S.; Shakesheff, K.M. Polymeric systems for controlled drug release. *Chem. Rev.* **1999**, *99*, 3181–3198. [CrossRef]
6. Brannon-Peppas, L. Controlled Release in the Food and Cosmetics Industries. In *Polymeric Delivery Systems—Chapter 3*; El-Nokaly, M.A., Piatt, D.M., Charpentier, B.A., Eds.; American Chemical Society: Washington, DC, USA, 1993; pp. 42–52.
7. Levy, R.; Nichols, M.A.; Miller, T.W., Jr. Encapsulated Systems for Controlled Release and Pest Management. In *Polymeric Delivery Systems—Chapter 13*; El-Nokaly, M.A., Piatt, D.M., Charpentier, B.A., Eds.; American Chemical Society: Washington, DC, USA, 1993; pp. 202–212.
8. Radu, C.D.; Parteni, O.; Popa, M.; Muresan, I.E.; Ochiuz, L.; Bulgariu, L.; Munteanu, C.; Istrate, B.; Ulea, E. Comparative study of a drug release from a textile to skin. *J. Pharm. Drug Deliv. Res.* **2015**, *4*. [CrossRef]
9. Hashemikia, S.; Hemmatinejad, N.; Ahmadi, E.; Montazer, M. A novel cotton fabric with anti-bacterial and drug delivery properties using SBA-15-NH 2/polysiloxane hybrid containing tetracycline. *Mater. Sci. Eng. C Mater.* **2016**, *59*, 429–437. [CrossRef]
10. Ten Breteler, M.R.; Nierstrasz, V.A.; Warmoeskerken, M.M.C.G. Textile slow-release systems with medical applications. *Autex Res. J.* **2002**, *2*, 175–189.
11. Radu, C.D.; Popa, M.; Parteni, O.; Salariu, M.; Lupușoru, E.C.; Ghiciuc, C.; Foia, L.; Chiriac, A.; Lupusoru, R.; Oproiu, L.; et al. Achievements and limits on the controlled release of a drug from a textile fabric to dermis. *Open Conf. Proc. J.* **2014**, *5*, 1–8. [CrossRef]
12. Radu, C.D.; Parteni, O.; Ochiuz, L. Applications of cyclodextrins in medical textiles—Review. *J. Control Release* **2016**, *224*, 146–157. [CrossRef]
13. Mahltig, B.; Haufe, H.; Böttcher, H. Functionalisation of textiles by inorganic sol-gel coatings. *J. Mater. Chem.* **2005**, *15*, 4385. [CrossRef]
14. Plutino, M.R.; Colleoni, C.; Donelli, I.; Freddi, G.; Guido, E.; Maschi, O.; Mezzi, A.; Rosace, G. Sol-gel 3-glycidoxypropyltriethoxysilane finishing on different fabrics: The role of precursor concentration and catalyst on the textile performances and cytotoxic activity. *J. Colloid Interf. Sci.* **2017**, *506*, 504–517. [CrossRef] [PubMed]
15. Caldara, M.; Colleoni, C.; Guido, E.; Re, V.; Rosace, G. Development of a textile-optoelectronic pH meter based on hybrid xerogel doped with methyl red. *Sens. Actuators B Chem.* **2012**, *171–172*, 1013–1021. [CrossRef]
16. Van der Schueren, L.; De Clerck, K.; Brancatelli, G.; Rosace, G.; Van Damme, E.; De Vos, W. Novel cellulose and polyamide halochromic textile sensors based on the encapsulation of Methyl Red into a sol-gel matrix. *Sens. Actuators B Chem.* **2012**, *162*, 27–34. [CrossRef]

17. Guido, E.; Colleoni, C.; De Clerck, K.; Plutino, M.R.; Rosace, G. Influence of catalyst in the synthesis of a cellulose-based sensor: Kinetic study of 3-glycidoxypropyltrimethoxysilane epoxy ring opening by Lewis acid. *Sens. Actuators B Chem.* **2014**, *203*, 213–222. [CrossRef]
18. Caldara, M.; Colleoni, C.; Guido, E.; Re, V.; Rosace, G. Optical monitoring of sweat pH by a textile fabric wearable sensor based on covalently bonded litmus-3-glycidoxypropyltrimethoxysilane coating. *Sens. Actuators B Chem.* **2016**, *222*, 213–220. [CrossRef]
19. Plutino, M.R.; Guido, E.; Colleoni, C.; Rosace, G. Effect of GPTMS functionalization on the improvement of the pH-sensitive methyl red photostability. *Sens. Actuators B Chem.* **2017**, *238*, 281–291. [CrossRef]
20. Rosace, G.; Guido, E.; Colleoni, C.; Brucale, M.; Piperopoulos, E.; Milone, C.; Plutino, M.R. Halochromic resorufin-GPTMS hybrid sol-gel: Chemical-physical properties and use as pH sensor fabric coating. *Sens. Actuators B Chem.* **2017**, *241*, 85–95. [CrossRef]
21. Trovato, V.; Colleoni, C.; Castellano, A.; Plutino, M.R. The key role of 3-glycidoxypropyltrimethoxysilane sol-gel precursor in the development of wearable sensors for health monitoring. *J. Sol-Gel Sci. Technol.* **2018**, *87*, 27–40. [CrossRef]
22. Poli, R.; Colleoni, C.; Calvimontes, A.; Polášková, H.; Dutschk, V.; Rosace, R. Innovative sol-gel route in neutral hydroalcoholic condition to obtain antibacterial cotton finishing by zinc precursor. *J. Sol-Gel Sci. Technol.* **2015**, *74*, 151–160. [CrossRef]
23. Avnir, D.; Coradin, T.; Lev, O.; Livage, J. Recent bio-applications of sol-gel materials. *J. Mater. Chem.* **2006**, *16*, 1013–1030. [CrossRef]
24. Cardiano, P. Hydrophobic properties of new epoxy-silica hybrids. *J. Appl. Polym. Sci.* **2008**, *108*, 3380–3387. [CrossRef]
25. Cardiano, P.; Lo Schiavo, S.; Piraino, P. Hydrorepellent properties of organic–inorganic hybrid materials. *J. Non-Cryst. Solids* **2010**, *356*, 917–926. [CrossRef]
26. Brancatelli, G.; Colleoni, C.; Massafra, M.R.; Rosace, G. Effect of hybrid phosphorus-doped silica thin films produced by sol-gel method on the thermal behavior of cotton fabrics. *Polym. Degrad. Stabil.* **2011**, *96*, 483–490. [CrossRef]
27. Grancaric, A.M.; Colleoni, C.; Guido, E.; Botteri, L.; Rosace, G. Thermal behaviour and flame retardancy of monoethanolamine-doped sol-gel coatings of cotton fabric. *Prog. Org. Coat.* **2017**, *103*, 174–181. [CrossRef]
28. Saturnino, C.; Popolo, A.; Ramunno, A.; Adesso, S.; Pecoraro, M.; Plutino, M.R.; Rizzato, S.; Albinati, A.; Marzocco, S.; Sala, M.; et al. Anti-inflammatory, antioxidant and crystallographic studies of N-Palmitoyl-ethanol Amine (PEA) derivatives. *Molecules* **2017**, *22*, 616. [CrossRef]
29. Parisi, O.; Scrivano, L.; Amone, F.; Malivindi, R.; Ruffo, M.; Vattimo, A.F.; Pezzi, V.; Puoci, F. Interconnected PolymerS TeChnology (IPSTiC): An effective approach for the modulation of 5α-reductase activity in hair loss conditions. *J. Funct. Biomater.* **2018**, *9*, 44. [CrossRef]
30. Castellano, A.; Colleoni, C.; Iacono, G.; Mezzi, A.; Plutino, M.R.; Malucelli, G.; Rosace, G. Synthesis and characterization of a phosphorous/nitrogen based sol-gel coating as a novel halogen- and formaldehyde-free flame retardant finishing for cotton fabric. *Polym. Degrad. Stabil.* **2019**, *162*, 148–159. [CrossRef]
31. Chung, C.; Lee, M.; Choe, E.K. Characterization of cotton fabric scouring by FT-IR ATR spectroscopy. *Carbohyd. Polym.* **2004**, *58*, 417–420. [CrossRef]
32. Peng, Y.D.; Wang, F.; Gao, L.; Dong, W.K. Structurally characterized dinuclear Zinc(II) bis(salamo)-type tetraoxime complex possessing square pyramidal and trigonal bipyramidal geometries. *J. Chin. Chem. Soc. Taipei* **2018**, *65*, 893–899. [CrossRef]
33. Ma, Z.H.; Yu, D.G.; Branford-White, C.J.; Nie, H.L.; Fan, Z.X.; Zhu, L.M. Microencapsulation of tamoxifen: Application to cotton fabric. *Colloid Surf. B* **2009**, *69*, 85–90. [CrossRef] [PubMed]
34. Messaritaki, A.; Black, S.J.; van der Walle, C.F.; Rigby, S.P. NMR and confocal microscopy studies of the mechanisms of burst drug release from PLGA microspheres. *J. Control Release* **2005**, *108*, 271–281. [CrossRef] [PubMed]