Preparation of functionalized cotton fabrics by means of melatonin loaded beta cyclodextrin nanosponges

PREPARATION OF FUNCTIONALIZED COTTON FABRICS BY MEANS OF MELATONIN LOADED β-CYCLODEXTRIN NANOSPONGES

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Abstract

Biofunctional textiles are a new category of advanced materials which combine conventional textiles with advanced drug delivery systems to obtain fabrics able to release active principles through skin. The work presents the synthesis of hyper cross-linked β-cyclodextrins nanosponges with the carbonyl group acting as bridge between cyclodextrin molecules. The result of the synthesis is a 3-D porous structure, where melatonin molecules have been complexed. The complex has been characterized by elemental analysis, DSC, SEM, XRD and FT-IR spectroscopy and the results confirm that melatonin interacts with the synthesized nanosponge at molecular level. Melatonin loaded nanosponges has been dispersed on cotton fibres, which have proved to be a suitable substrate for durable nanosponge adsorption. The in-vitro release tests from the funtionalized fabrics have shown a zero order kinetics, which is typical of a reservoir diffusion controlled system.

Keywords: β-cyclodextrin nanosponges; cellulose fabrics; elemental analysis; melatonin; XRD.

Chemical compound studied in this article

β-cyclodextrin (PubChem CID: 24238); 1-1'-carbonyldiimidazole (PubChem CID: 68263); N,N-dimethylformamide (PubChem CID: 6228); melatonin (PubChem CID: 896).

1. Introduction

Over the past few decades the textile industry has experienced rapid development with enormous new applications, thanks to technological innovation. A new branch of textile research is focused on the health promoting aspects with advanced functional textile, among which textile designed for the transdermal delivery of active principles have attracted much attention in both academic and industrial community [Labay, Canal, Navarro & Canal 2014; Seib & al. 2014]. As with most areas of modern technology that address critical needs for mankind, exponential growth of functional textiles is drawing

upon an interdisciplinary vision that challenges the textile and biomaterial scientist with new approaches . Medical advances in drug delivery has been made as well through the development of controlled release dosage forms via transdermal delivery through the skin, as alternative to the oral route of administration, that allow the bypassing of hepatic and gastrointestinal side effects [Michalak 2012; Ming 2013; Numata & Kaplan 2010; Sintov 2015]. Numerous bioactive compounds and active pharmaceutical ingredients have been investigated to retain their activity when combined with textile fibres [Boateng, Matthews, Stevens & Eccleston 2007; Joshi, Butola & Saha 2014]. The major classes of naturally occurring bioactive molecules include enzymes, peptides, proteins, carbohydrates and lipids, which offer various potential applications to performance textiles [Ghosh & Sil 2015; Parraga, Zorzi, Diebold, Seijo & Sanchez 2014]. Among the variety of bioactive molecules, melatonin is a hormone found in animals, plants, and microbes. Within other medical and health care properties it has shown a sleep quality improvement in patients suffering from sleep diseases being this molecule functionally important in the nocturnal regulation of sleep and thermoregulation [Adamczyk-Sowa et al. 2014; Neubauer 2014]. Melatonin is also known to exhibit antioxidant properties against the deleterious effects of reactive oxygen and nitrogen species [Tan, Manchester, Terron, Flores & Reiter 2007].

In order to fulfill the bioactive function, a suitable system of transferring the active ingredient to the skin should be developed. Within the textile field several textile finishing methods are available for a prolonged release system including: active principles microencapsulation in polymer microcapsule and subsequent microcapsules fixation on textile substrates by impregnation or by exhaustion bath [Ghosh 2006]. Sudipta et al. [2014] have synthesized chitosan micro-particles which were subsequently applied on plasma activated polyester fabrics by a padding process. The microparticles can also be synthesized directly on the textile substrates. Salaun et al. [Salaün, Vroman & Elmajid 2012] have fixed polyamide microparticles on cellulosic substrates through interfacial polymerization method.

Cyclodextrin based nanosponges are proposed as cross-linked cyclodextrin-based nanostructured polymers with a three-dimensional network delivery system [Trotta, Zanetti & Cavalli 2012; Trotta, Dianzani, Caldera, Mognetti & Cavalli 2014]. Nanosponges are hyper-cross-linked cyclodextrins that can be synthesized from α-, β- and γ-cyclodextrins, either alone or as mixtures containing relevant amounts of linear dextrin, cross-linked with a suitable cross-linking agent. Interesting results have already been obtained as drug carriers by using an active carbonyl compound such as 1-1' carbonyldimiidazole, diphenyl carbonate, or organic dianhydrides [Conte et al. 2014; Olteanu, Aramă, Radu, Mihăescu & Monciu 2014]. This type of cyclodextrin polymer can form porous insoluble nanoparticles with a crystalline or amorphous structures and swelling properties. Submicron spherical nanosponges were obtained by using ultrasound-assisted synthesis and a suitable cross-linker molar ratio [Trotta & Cavalli 2009]. The final product is a kind of cyclodextrin based powder of cage-like structure with nanocavities. The cavities between the cyclodextrin units can be modulated by

changing the amount of cross-linking agent or the type of cyclodextrin, which affects the inclusion capacity and the solubilising ability of the nanosponges.

The most suitable textile substrates to be used in textile functionalization are the cellulose-based fibres. The main reason is that native cellulose is the most abundant natural polymer on earth, coming from renewable resources [Klemm, Heublein, Fink & Bohn 2005]. As a natural polymer, cellulose is environmentally friendly, biocompatible and renewable; in addition to that, cellulose can be easily modified to various derivatives useful in unlimited industrial applications, such as cellulose esters [Xiao et al. 2014] and cellulose ester/polyvinylidene fluoride blends used to prepare polymeric membranes with antioxidant activity [Jansen et al. 2011]. Among cellulosic fibers cotton is the dominant natural fibre and the purest form of cellulose available in nature. It is the most widely used natural textile fibre for its availability, low cost and for its properties. It combines high strength due to its highly fibrillar and crystalline structure with good absorbency and softness which gives cotton good human comfort properties [Gordon & Hsieh 2006]. This features make cotton one of the most suitable substrates to be used in the preparation of functionalized textiles.

In this work a bioactive functional fabric was prepared through cotton fibre functionalization with melatonin loaded β-cyclodextrin carbonate-nanosponge. Firstly, carbonate nanosponges were synthesized from β-cyclodextrin and 1-1' carbonyildiimidazole and then loaded with melatonin in water/ethanol suspension. Hereafter, the acronym CDI-NS will be used for the synthesized nanosponge. Melatonin loading capacity was checked through elemental analysis, formulation morphology was analyzed by SEM microscopy and the type of interactions between melatonin and the synthesized nanosponge was investigated by means of XRD and DSC measurements.

To check the feasibility of the finishing process, cotton fabrics were treated with plain CDI-NS through physical adsorption: phenolphthalein test and ATR-FT-IR spectra demonstrated that nanosponges are retained on the fabric even after two washing cycles. Afterwards, cotton fibres have been treated with the melatonin complex and the morphology of the treated cotton fibre surface was investigated through SEM microscopy.

Finally, in vitro release tests were carried out in a Franz diffusion cells system and the release kinetics of melatonin from a cotton fabric functionalized with the melatonin complex was compared with that of a cotton fabric treated with free melatonin.

2. Experimental

2.1 Materials and methods

β-cyclodextrin (β-CD, MW=1134.98 g/mol) was a gift of Roquette Italia (Italy). 1-1'-carbonyldiimidazole (CDI, MW=162.15), N,N-dimethylformamide (DMF) and melatonin (MW=232.278 g/mol), whose structure is shown in Figure 1, were supplied from Sigma-Aldrich (Italy). Knitted cotton fabrics (100% cotton, Nm 30/1, single jersey) were kindly supplied by Eusebio S.p.A. (Italy). The fabrics were scoured at 95°C for 30 min in a 4 g/L Na_2CO_3 water solution and rinsed under tap water for 10 min to remove impurities and waxes.

Synthesis of carbonate/β-cyclodextrin nanosponges

The nanosponge preparation was carried out in a 100 ml round bottom flask where 10 g (8.8 mmol) of β-CD (dehydrated in oven at 120°C for 12 hours) were dissolved in 60 ml of DMF and magnetically stirred at room temperature until a transparent solution was obtained. Then, 11.4 g (70.3 mmol) of CDI were added to have a large excess of crosslinker (β-CD/CDI molar ratio 1:8) and the suspension was heated to 80°C. After approximately 20 min, the gelation process was observed and the reacting mixture was kept at 80°C for 5 hours to complete the reaction. Once the condensation was completed, the monolith was crumbled washed with water and filtered under vacuum and finally grounded in a mortar. The nanosponge powder was purified by Soxhlet extraction in ethanol for 24 hours. A white powder of carbonate nanosponge was obtained after 24-hour drying. A schematic representation of the reaction between CDI and β-CD is shown in Figure 2.

2.2 Preparation of melatonin-loaded nanosponges

Melatonin loaded CDI-NS in the weight ratio 5:1 (CDI-NS/melatonin) were prepared according to the following procedure: 0.1 g of melatonin were dissolved in 10 ml of a 4:6 (v/v) ethanol/water solution. Then, the proper amount of CDI-NS was added to the solution. The suspension was stirred for 24 hours at room temperature, filtered under vacuum and rinsed in deionized water to remove any free melatonin, which has not been complexed in the NS cavities. The filtrate was then lyophilized at -50°C for 24 hours to obtain melatonin loaded CDI-NS powder.

2.3 Functionalization of cotton fabrics with plain and melatonin-loaded CDI-NS

Firstly, preliminary experiments were carried out to check the capability of cotton fabric to entrap plain CDI-NS and the resistance of the treatment to washing: a 2 cm diameter cotton sample (weight 66±2 mg) was dipped in 10 ml of 50 g/L CDI-NS suspension in deionized water. The system was left under magnetic stirring for 24 hours at room temperature. After the functionalization with melatonin loaded CDI-NS, the fabrics were dried in oven at 60°C for 48 h. The temperature was selected in order to not cause any detrimental effect on the fabrics neither on the loaded CDI-NS, so as 48 h was chosen in order to assure a complete water evaporation till the achievement of a constant weight.
Afterwards the fabric was removed from the bath and dried for 48 hours at 60 °C. Then, the amount of CDI-NS deposited on the fabric was estimated by the phenolphthalein test, as discussed in the results section.
Functionalization of cotton with melatonin loaded CDI-NS was carried out by dipping a 2 cm diameter cotton sample in 10 ml of a 50 g/L melatonin/CDI-NS suspensions in deionized water. The fabric was dipped in the suspension and magnetically stirred for 24 hours at room temperature. Afterwards the sample was removed from the bath and dried in oven at 60°C for 48 hours.

For comparison purposes, a fabric sample was loaded with free melatonin according to the following procedure: a 2-cm diameter cotton sample was dipped in a 0.8 g/L melatonin solution in deionized water. The fabric was left in the solution for 24 hours and then dried at room temperature.

2.4 Washing cycles

The treated fabric samples were hand-washed twice at 30°C in a 5 g/L mild soap solution to remove loosely adsorbed CDI-NS from the surface for 10 min. The fabrics were rinsed in running tap water. In between the two washing cycles, the fabrics were dried at room temperature for 24 hours and analyzed to assess the durability of the CDI-NS on the fabric.

2.5 Zeta Potential

The CDI-NS zeta potential was measured using a 90 PLUS instrument (Brookhaven instrument Corporation, USA).

Nanosponge dispersions in water were prepared and diluted with KCl (0.1 mM) and placed in the electrophoretic cell. Afterwards an electric field of 15 V/cm was applied. Each sample was analyzed in triplicate.

2.6 SEM analysis

Scanning electron microscopy (SEM) was used to examine the shape and particle size of the CDI-NS and the morphology and distribution of the CDI-NS on the fibres. The analysis was performed with a Leica Electron Optics 435 VP instrument (UK) with an acceleration voltage of 10 kV. The nanosponge suspensions were sprayed on a Formwar-coated copper grid and air-dried before observation.

2.7 Elemental analysis

Plain and melatonin-loaded CDI-NS were analysed by the CHNS-O Analyser (FLASHEA 1112 series). The loading capacity was estimated from the nitrogen signal.

2.8 XRD powder diffraction

X-rays analyses were carried out by Pananalytical X'Pert MRD PRO diffractometer (Almelo, Netherland), using Cu Kα radiation with Ni beta filter. All the scans were performed over an angular range $2\theta = 5\text{-}35°$ using a step size of 0.02°.

2.9 DSC Analysis

Thermal analysis were carried out by means of a Perkin Elmer DSC/7 differential scanning calorimeter (Perkin-Elmer, CT-USA) equipped with a TAC 7/DX instrument controller. The instrument was calibrated with indium for melting point and heat of fusion. A heating rate of 10°C/min was employed and an empty aluminum pan (Perkin-Elmer) was used as reference standard. Analyses were performed on 5 mg samples under nitrogen purge.

2.10 ATR-FT-IR spectroscopy

ATR-FT-IR spectra were acquired through a Perkin Elmer Spectrum Spotlight 300 FT-IR spectrophotometer with a Golden Gate attenuated total reflection attachment with a diamond crystal in the region from 4000 cm^{-1} to 650 cm^{-1}. Each spectrum was scanned with a resolution of 4 cm^{-1}.

2.11 Phenolphthalein test

The phenolphthalein test was employed to quantify the amount of the CDI-NS loaded on the functionalized cotton fabrics, before and after the washing cycles. A phenolphthalein solution was prepared by dosing 0.05 ml of 1% (w/w) of phenolphthalein in ethanol solution in 100 ml of 10 g/L Na_2CO_3 water solution. The final solution obtained showed the characteristic purple coloration, due to the alkaline environment (pH 10). The solution analysed through a UV-Vis spectrophotometer showed an absorption peak at 552 nm wavelength. pH was measured during the whole experiment. After the addition of the CDI-NS a discoloration of the phenolphthalein purple-colored solution was observed. The colour of the solution changed as a consequence of the CDI-NS/ phenolphthalein complex formation. Phenolphthalein complexation in the β-cyclodextrin cavity causes a decrease of the maximum absorption. A calibration line with $R^2 = 0.992$ allowed the estimation of the CDI-NS concentration in the phenolphthalein solution from its peak absorbance.

To estimate the concentration of CDI-NS distributed on the treated fabrics, an accurately weighted quantity of the CDI-NS loaded fabric was immersed into 5 ml of the phenolphthalein solution for 24 hours. Afterwards the fabrics were removed from the solution and the solution absorbance was measured. The CDI-NS amount loaded on the fabric was calculated assuming a 1:1 molecular complex between phenophtalein and β-cyclodextrin cavities by means of the calibration line.

2.12 In-vitro release test

Static vertical Franz diffusion cells (Bechenheim-Germany) were employed to assess in-vitro melatonin release from the functionalized fabrics. A scheme of the apparatus is shown in Figure 3.

The 12-ml capacity receptor chamber was filled with a phosphate buffer solution (pH 7.4) and kept at the standard skin temperature of 33°C, by circulating water through an external water jacket. The system was stabilized for 30 min before the test. A mixed cellulose ester membrane (0.45 µm pore size, Whatman) was placed in between the donor and receptor compartments. The membrane was boiled for 30 min to remove glycerol and impurities before use. The cotton fabric sample impregnated with melatonin loaded CDI-NS was placed on top of the membrane in the donor compartment. The entire receptor solution was withdrawn and substituted with fresh buffer solution at regular time intervals. As melatonin shows an adsorption peak at 254 nm, the receptor solution was analysed by the Spectrophotometer Evolution 300 UV-Visible (Thermo Scientific, USA) with a 2 nm band width.

3. Results and discussions

After CDI-NS synthesis and loading with melatonin, the resulting product was characterized to get insights of the types of interaction between melatonin and CDI-NS and between CDI-NS and cotton fibres. In this paragraphs the main findings of the investigation are reported.

3.1 Zeta-potential

The CDI-NS z-potential is shown in Table 1: CDI-NS are slightly negative, which suggests that particles have little tendency to aggregate and give stable nano or micro-suspensions over time.

3.2 Loading efficiency of melatonin in the CDI-NS

The drug encapsulation was performed accordingly to the post loading via swelling of the matrix and diffusion filling method, which allows nanocarriers to reach a swelling equilibrium in the drug solution. A water/ethanol solution was selected as the dissolution medium since melatonin is more soluble in ethanol and slightly soluble in water. The melatonin concentration was near to saturation since as reported in literature (Alam 2014, Gupta 2016) high drug concentration is a strategy to increase the drug loading profile of the matrix.

The elemental composition of melatonin-loaded CDI-NS is shown in Table 2.

Taking into account the ratio of melatonin to nitrogen molecular weights, melatonin loading in the CDI-NS can be estimated in approximately 8%.

3.3 Morphology of the CDI-NS loaded textiles

CDI-NS have colloidal size with a mean diameter of few microns and broad size distribution, as shown in Figure 4 (a). After complexation, the CDI-NS size and morphology did not change significantly.

In Figure 4 (b and C), cotton fibres with CDI-NS deposited on the surface are shown. Cotton fibres show the typical bean shaped cross section with a dip where CDI-NS can be housed. The distribution of CDI-NS on the fabric surface is not uniform on the fibre surface but aggregates of CDI-NS are visible.

3.4 XRD-diffraction analysis

XRD diffraction diagrams of pure melatonin, the physical mixture of CDI-NS/melatonin, plain CD-NS and the loaded CDI-NS are shown in Figure 5. For preparing the physical mixture, 8% w/w of melatonin was mixed with the CDI-NS powder in a mortar. Pure melatonin is a monoclinic crystal [Mostad & Romming 1974] and the typical peaks in the range 2θ 10-30° denote long-range order of its supramolecular structure. On the contrary, CDI-NS have amorphous nature with no sharp crystalline peaks and two broad humps suggesting only some degree of short-range organization. After complexation in the CDI-NS, no melatonin peaks were identified. This confirms the amorphization process of the formulation, which is indicative of the inclusion complex formation. The sharp peak in the melatonin-loaded CDI-NS is a reflection of the aluminium sample holder and is not ascribable to CDI-NS or melatonin.

3.5 ATR-FT-IR spectrophotometric analysis

Figure 6 shows the ATR-FT-IR spectrum of CDI-NS (Fig. 6a), with the prominent absorption of β-cyclodextrin: 3342 cm^{-1} (O-H stretching vibrations), 2923 cm^{-1} (C-H stretching vibrations), 1254 cm^{-1} and 1020 cm^{-1} (C-O stretch). The CDI-NS spectrum evidenced a typical peak at 1740 cm^{-1} corresponding to C=O stretching vibration of the cross-linking group.

The ATR-FT-IR spectra of plain cotton (Figure 6b) and cotton treated with CDI-NS (Figure 6c) show the typical vibration modes of cellulose: 3327 cm^{-1} (O-H stretching vibrations), 2893 cm^{-1} (CH_2 stretching), 1060 cm^{-1} (C-O stretching). The carbonyl peak at ca 1740 cm^{-1} which mark out the CDI-NS is missing in plain cotton while it appears in the spectrum of cotton treated with CDI-NS, confirming the presence of CDI-NS on the cellulose substrate.

3.6 Washing fastness

The estimation of the concentration of CDI-NS adsorbed on the fabric after one and two washing cycles is given in Table 3. The results show that CDI-NS adsorption on the fibres was durable to two washings. As demonstrated by Quian (2008) cyclodextrin based polymers are easily adsorbed on cellulose fibers and can also penetrate into the pores of the fibers and in the amorphous region. Mechanical entrapment between yarns and physical adsorption on the fibre structure are the proposed mechanisms for the retention of CDI-NS on the fabric. CDI-NS physically entrapped in the spaces between fibres are not easily detached from the fibre surface due to their small size and to hydrogen bonds formation with cotton fibres. Despite not being as permanent as chemical adsorption, hydrogen bonds contributes to the CDI-NS adesion on the fabric. In shaking and manipulating the fabrics, no powder is visibly detacted from the fabrics.

The CDI-NS retention on the cellulose substrates is moreover strengthen by the poor water solubility of the CDI-NS which favours the CDI-NS partition in the solid phase and confere a certain washing fastness.

3.7 DSC measurements

The results of DSC measurements are shown in Figure 7. The thermogram of pure melatonin shows a sharp melting temperature at 118°C, which is a sign of melatonin crystalline nature. The peak is detected also in the physical mixture whereas it disappeared in the loaded CDI-NS containing the same fraction of melatonin as the physical mixture. The nanosponges structure is amorphous as also demonstrated by the XRD analysis reported in Fig. 5 c), so no melting peak is shown. This was an expected results because nanosponges, as all crosslinked polymers, do not exhibit any melting point. The observation that also loaded CDI-NS do not show any melting peak deriving from melatonin suggests that it is dispersed at molecular level in the nanosponge cavities. This was also observed in the literature in case of cyclodextrin complexation and nanocapsules [Al-Marzouqi, Elwy, Shehadi & Adem 2009; Ribeiro, Figueiras, Santos & Veiga 2008; Zhao et al.2013].

3.8 Release kinetics of melatonin from the functionalized fabric

Figure 8 shows a comparison of the release kinetics from a cotton fabric sample impregnated with melatonin loaded CDI-NS (straight curve) and a cotton sample impregnated with free melatonin (dot-curve). The release test was performed in triplicate and the mean value was calculated. The release rate from the fabric treated with melatonin/CDI-NS complex shows a zero order kinetics (R^2=0.993), namely the amount of melatonin released from the fabric is proportional to time, whereas release kinetics from the fabrics impregnated with free melatonin shows a rapid release rate at the beginning and a progressive decay during time, which can be described by a power law (R^2=0.958). The release rate independent from melatonin concentration on the fabric is typical of reservoir diffusion-controlled system [Peppas & Narasimhan 2014] and allows the preparation of fabrics with multiple doses of melatonin to be released during several applications: the amount of melatonin of the first and the last administration will supply the same dose provided that the fabric is kept on the skin for the same time.

4. Conclusions

Carbonate nanosponges were successfully synthesized from β-cyclodextrin and 1 1'-carbonylimidazole and the loading efficiency of melatonin in the synthesized nano-porous structure was estimated in 8 wt%. DSC and XRD analysis highlighted that melatonin forms a molecular dispersion in the nanosponge cavities. Melatonin loaded nanosponges were charged on a knitted cotton fabric with the aim of developing a novel biofunctional fabric capable of controlling the release of melatonin through skin. The in vitro release study with the Franz cell equipment evidenced that melatonin release rate from the functionalized fabric can be described by a zero-order law, namely that the release rate is independent from melatonin concentration on the fabric. This finding might be the starting point for the development of biofunctional fabrics storing multiple doses of melatonin to be released over time.

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References

- Adamczyk-Sowa, M.; Pierzchala, K.; Sowa, P.; Mucha, S.; Sadowska-Bartosz, I.; Adamczyk, J.; Hartel, M. (2014). Melatonin Acts as Antioxidant and Improves Sleep in MS Patients. *Nurochemistry Research*, 39, 1585-1593.
- Alam N., Khare V., Dubey R., Saneja A. , Kushwaha M. , Singh G. , Sharma N., Chandan B. , Gupta P.N. (2014). Biodegradable polymeric system for cisplatin delivery: Development, in vitro characterization and investigation of toxicity profile. *Materials Science and Engineering C*, 38,85-93.
- Al-Marzouqi, A.H., Elwy, H.M., Shehadi, I., Adem, A.. (2009). Physicochemical properties of antifungal drug–cyclodextrin complexes prepared by supercritical

carbon dioxide and by conventional techniques. *Journal of Pharm. Biomed. Anal.*, 49, 227–233.

- Boateng, J. S.; Matthews, K. H.; Stevens, H. N.E.; Eccleston, G. M. (2007). Wound healing dressings and drug delivery systems: A review. *Journal of Pharmceutical Science,* 97, 2892-2923.
- Conte, C.; Caldera, F.; Catanzano, O.; D'Angelo, I.; Ungaro, F.; Miro, A.; Pellosi, D.S.; Trotta, F.; Quaglia, F., (2014). β-Cyclodextrin Nanosponges as Multifunctional Ingredient in Water-Containing Semisolid Formulations for Skin Delivery. *Journal of Pharmaceutical Science*, 103, 3941-3949.
- Ghosh, S. K., (2006) Functional coatings and microencapsulation: a general perspective. In K. Gosh Eds, Wiley-VCH Verlag GmbH & Co., *Functional Coating: By Polymer Microencapsulation* (pp. 1-28), Weinheim, Germany.
- Ghosh, J.; Sil, P. C., (2015)**.** Natural bioactive molecules: Mechanism of actions and perspectives in organ pathophysiology. *Studies of Natural Products Chemistry*, 45, 457-483.
- Gordon, S.; Hsieh, Y. L. (2006); *Cotton: Science and Technology* (1st ed).; Woodhead Publishing in Textiles, Taylor & Francis.
- Gupta M. K., Bajpai J., Bajpai A. K. (2016) Optimizing the release process and modelling of in vitro release data of *cis*-dichlorodiamminoplatinum (II) encapsulated into poly(2-hydroxyethyl methacrylate) nanocarriers, *Materials Science and Engineering C*, 58, 852-862.
- Jensen, J. C.; Cassano, R.; Trombino, S.; Cilea, A.; Picc,i N.; Driol,i E.; Giorno, L., (2011). Polymeric membranes with antioxidant activity based on cellulose esters and poly(vinylidene fluoride)/cellulose ester blends. *Cellulose*, 18, 359-370.
- Joshi, M.; Butola, B.S.; Saha, K., (2014). Advances in Topical Drug Delivery System: Micro to Nanofibrous Structures. *Journal of Nanoscience and Nanotechnology*, 14, 853-867.
- Klemm, D.; Heublein, B.; Fink, H. P.; Bohn, A., (2005). Cellulose: fascinating biopolymer and sustainable raw material. *Angewandte Chemie - International Edition*, 44, 3358-3393.
- Labay, C.; Canal, J. M.; Navarro, A.; Canal, C., (2014). Corona plasma modification of polyamide 66 for the design of textile delivery systems for cosmetic theraphy. *Applied Surface Science* 316, 251-258.
- Michalak I., Mucha M. (2012). The release of active substances from selected carbohydrate biopolymer membranes. *Carbohydrate polymers*, 87, 2432-2438.
- Ming K., Hyunjin P., Chao F., Lin H., Xiaojie C., Xiguang C. (2013). Construction of hyaluronic acid noisome as functional transdermal nanocarrier for tumor therapy. *Carbohydrate Polymers* 94, 634-641.

- Mostad, A.; Romming, C., (1974). The crystal and molecular structure of N-acetyl-5-methoxy-tryptamine (melatonin). *Acta Chemica Scandinavica*. *Series B: Organic chemistry and biochemistry*, 28, 564-572.
- Neubauer, D. N.; (2014). New and emerging pharmacotherapeutic approaches for insomnia. *International Review of Psychiatry*, 26, 214-224.
- Numata, K.; Kaplan, D.L., (2010) Silk-based delivery systems of bioactive molecules. *Advanced in Drug. Delivery Review*, 62, 1497–1508.
- Olteanu, A. A.; Aramă, C. C.; Radu, C.; Mihăescu, C.; Monciu, C. M., (2014). Effect of β-cyclodextrins based nanosponges on the solubility of lipophilic pharmacological active substances. *Journal of Encapsulation Phenomena and Macrocyclic Chemistry*, 80, 17-24.
- Parraga, J. E.; Zorzi, G. K.; Diebold, Y.; Seijo, B.; Sanchez, A., (2014). Nanoparticles based on naturally-occurring biopolymers as versatile delivery platforms for delicate bioactive molecules: An application for ocular gene silencing. *International Journal of Pharmaceutics*, 477, 12-20.
- Peppas, N.A.; Narasimhan, B., (2014). Mathematical models in drug delivery: How modeling has shaped the way we design new drug delivery systems. *Journal of Controlled Release*, 190, 75-81.
- Qian L., Guan Y. Ziaee Z., He B., Zheng A., Xiao H. (2009) Rendering cellulose fibers antimicrobial using cationic *b*-cyclodextrin-based polymers included with antibiotics, *Cellulose*, 16, 309-317.
- Ribeiro, A., Figueiras, A., Santos, D., Veiga, F. (2008). Preparation and Solid-State Characterization of Inclusion Complexes Formed Between Miconazole and Methyl-β-Cyclodextrin. *AAPS PharmSciTech* 9, 1102–1109.
- Salaün, F.; Vroman, I.; Elmajid, I., (2012). A novel approach to synthesize and to fix microparticles on cotton fabric *Chemical Engineering Journal*, 213, 78-87.
- Seib, F. P.; Herklotz, M.; Burke, K. A.; Maitz, M. F.; Werner, C.; Kaplan, D. L., **(**2014). Multifunctional silk–heparin biomaterials for vascular tissue engineering applications *Biomaterials*, 35, 83-91.
- Sintov, A. C., (2015). Transdermal delivery. *International Journal of Pharmaceutics*, 481, 471-478.
- Sudipta, C.; Salaün, F.; Campagne, C., (2014). Development of Multilayer Microcapsules by a Phase Coacervation Method Based on Ionic Interactions for Textile Applications. *Pharmaceutics*, 6, 281-297.
- Tan, D. X.; Manchester, L. C.; Terron, M. P.; Flores, L. J.; Reiter, R. J., (2007). One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species? *Journal of Pineal Research*, 42, 28-42.
- Trotta, F.; Cavalli, R., (2009). Characterization and Applications of New Hyper-Cross-Linked Cyclodextrins. *Composite Interfaces* 16, 39-48
- Trotta, F.; Zanetti, M.; Cavalli, R., (2012). Cyclodextrin-based nanosponges as drug carriers, *Beilstein Journal of Organic Chemistry*, 8, 2091-2099.

- Trotta, F.; Dianzani, C.; Caldera, F.; Mognetti, B.; Cavalli, R., (2014) The application of nanosponges to cancer drug delivery. *Expert Opinion in Drug Deivery.*, 11, 931-941.
- Xiao, P.; Zhang, J.; Feng, Y.; Wu, J.; He, J.; Zhang, J., (2014). Synthesis, characterization and properties of novel cellulose derivatives containing phosphorus: cellulose diphenyl phosphate and its mixed esters. *Cellulose*, 21 2369-2378.

Zhao, Y.; Wang, L.; Ma, C.; K.Zhao,Y. Liu, N. Feng (2013). Preparation and characyerization of tetrandine-phospholipid complex loaded lipid nanocapsules as potential oral carriers. *International Journal of Nanomedicine,* 8, 4169-4181.

Figures

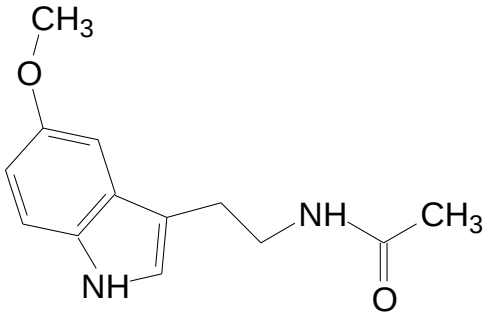


Fig 1: Melatonin chemical formula

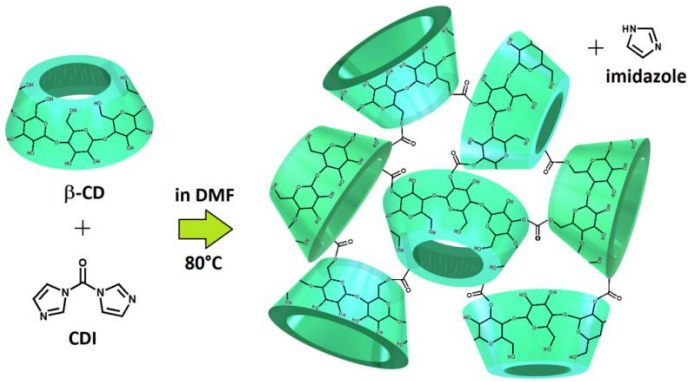


Fig 2: Molecular structure of CDI-NS

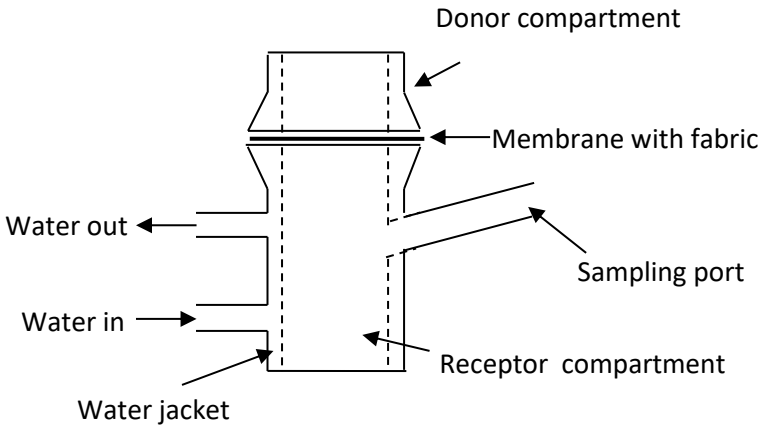
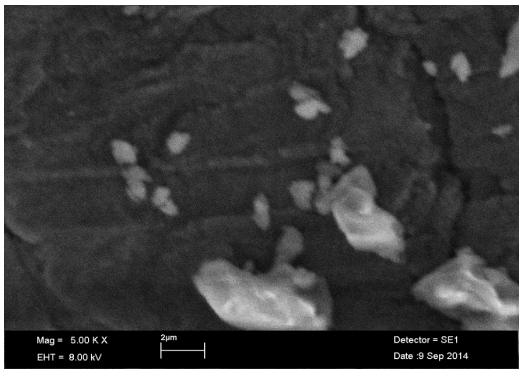
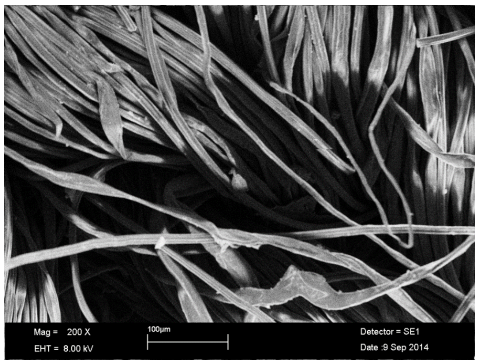
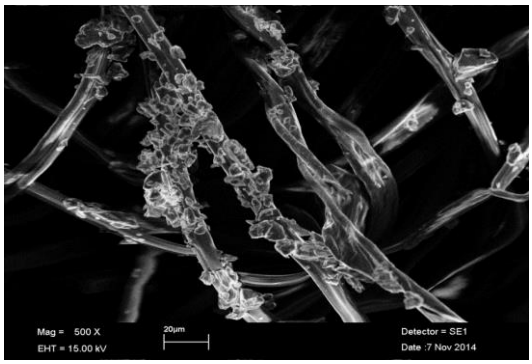


Fig 3: Scheme of the Franz diffusion cell



a)





b) c)

Fig 4: Morphology of the CDI-NS (a); Untreated cotton fibres (b); cotton fibre functionalized with the CDI-NS (c)

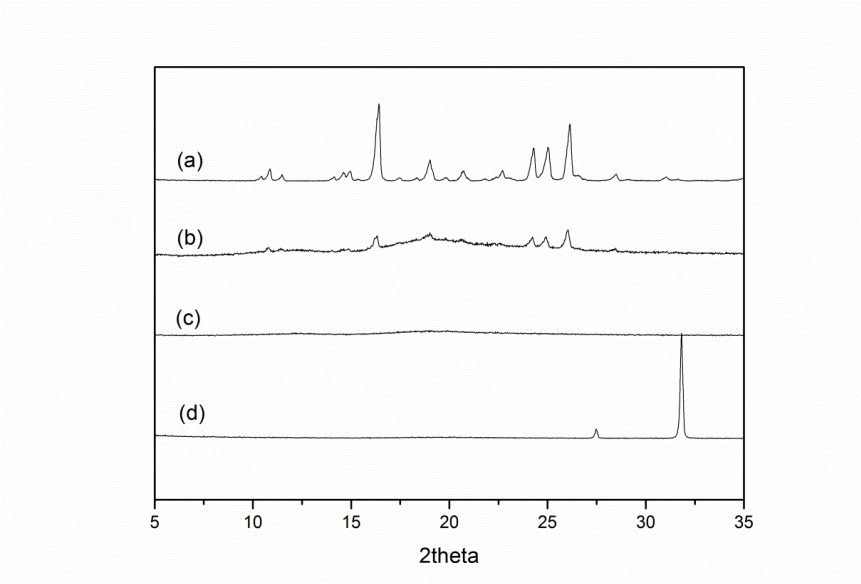


Fig 5: XRD diffraction analysis of melatonin(a), melatonin-CDI-NS physical mixture (b), plain CDI-NS (c) and melatonin loaded CDI-NS (d)

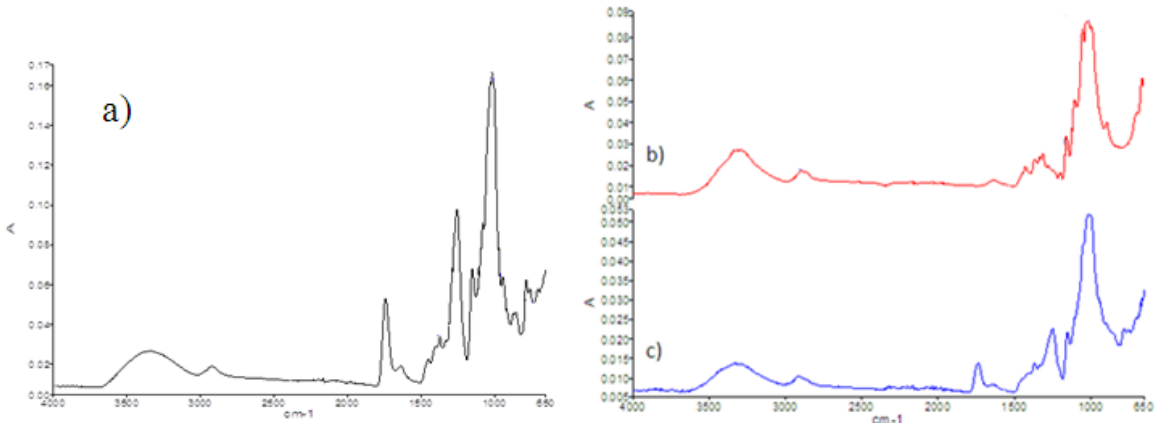


Fig 6: ATR-FTIR spectrum of the carbonate nanosponges (a); untreated (b) and carbonate nanosponges treated (c) cotton fabric

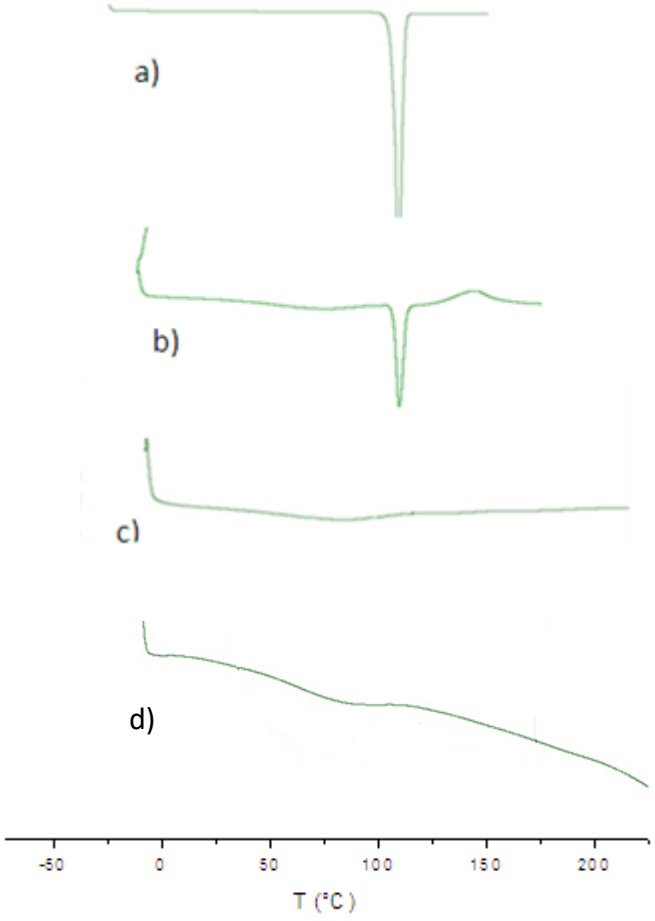


Fig 7: DSC thermogram of melatonin (a); melatonin-CDI-NS physical mixture (b) melatonin loaded CDI-NS (c) and only CDI-NS

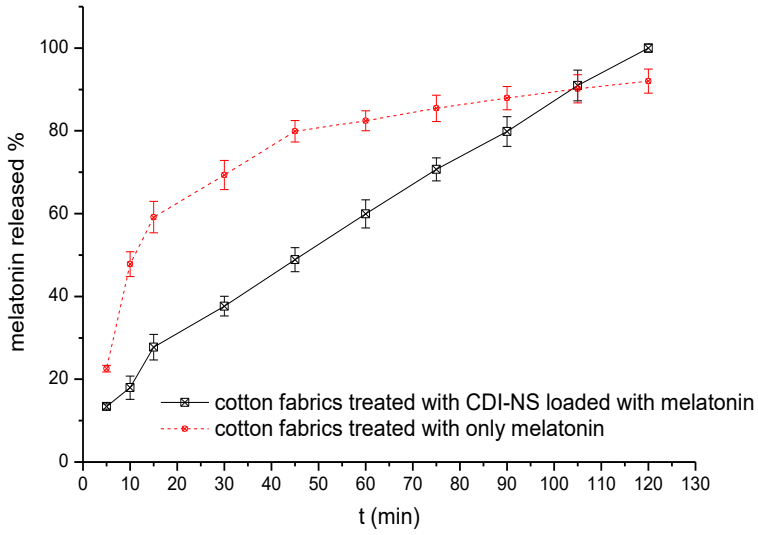


Fig 8: Release curves of the fabrics samples treated with free melatonin and with melatonin loaded CDI-NS

Tables

Table 1: z-potential of the CDI-NS.

Nanosponge	Zeta potential (mV)	Error (mV)
CDI-NS	-12.91	1.23

Table 2: Elemental analysis of the melatonin-loaded CDI-NS.

Sample	N%	C%	H%
Mel-CDI-NS	0.95	45,73	5,71

Table 3: Estimation of CDI-NS concentration on treated cotton fabrics after one and two washing cycles.

Sample	Fabric sample weight (mg)	CDI-NS amount on fabric (mg)[a]	Melatonin concentration on the fabric (mg/g)[b]
Plain cotton	68	-	-
Treated cotton (1 washing cycle)	66	16.7	20.0
Treated cotton	67	16.5	19.5

(2 washing cycles)

[a] The amount of CDI-NS on the fabric was calculated from the calibration curve $A = -0.006 \times c_{CDI-NS} + 0.104$ and the volume of phenolphthalein solution (5 ml).

[b] The amount of melatonin was estimated from the loading efficiency measurements.