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# Preparation of bio-functional textiles by surface functionalization of cellulose fabrics with caffeine loaded nanoparticles.

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**Abstract:** In recent years transdermal drug delivery has aroused significant interest as a sustained and non-invasive way of administering active substances. The development of nanotechnology allowed the development of novel pharmaceutical formulations overcoming skin barrier. Furthermore, such nano-system can be combined with conventional fabrics to pave the way to a new generation of wearable drug delivery devices: bio-functional garments. First the NP were produced by flash nanoprecipitation technique (FNP), the production process was optimized to produce particles with suitable size for transdermal applications. The nanoparticles were characterized in terms of drug content by UV-visible spectroscopy and of antioxidant activity by Electron Paramagnetic Resonance spectroscopy (EPR) coupled with spin trapping technique. The NPs were used to functionalized cotton and viscose-micromodal fabrics and the transdermal release properties were tested in vitro by Franz's Cell experiment. FNP was proven to be an effective technique to produce tunable size particles. Moreover, the nanoencapsulated drug exhibited antioxidant activity. The release test evidenced a controlled release behavior effect providing evidence that the bio-functional textile is suitable for applications where sustained release and antioxidant properties are required.

**Keywords:** Antioxidant activity, Bio-functional textiles, Caffeine, Drug delivery, Encapsulation, Flash Nanoprecipitation, Hydrophilic, Nanoparticles.

## I. INTRODUCTION

Nowadays many efforts of pharmaceutical research have been focused on the development of innovative tools and approaches to administer drugs in "smart" way i.e. improving therapeutic efficacy while minimizing side effects [1]. Among these innovative approaches to drug delivery, the possibility of delivering active substances through skin aroused significant interest [2]. In fact skin is the largest tissue of the human body and has significant surface area available for drug administration; moreover, it plays the important role of protecting the body from external factors, which could significantly reduce side effects during drug administration [3]. Therefore, skin can be used as a route of administration for local and systemic

drugs; according to Food and Drug Administration the first case is defined as topical administration and consists in the application of a drug to a particular area on the outer surface of the body, while the latter is defined as transdermal administration and involves the delivery through the dermal layer of the skin to the systemic circulation. Despite the numerous advantages in using skin for topical and transdermal drug delivery, such administration route is challenging for several compounds because of the structural complexity of the skin barrier [4]. Recent developments in nanotechnology and nanomedicine offer several approaches to overcome the above mentioned problem [5-8].

In addition, these advanced drug delivery systems can be combined with conventional textiles to develop wearable

drug delivery devices [9], this new class of material defined as bio-functional textiles has shown the capability to improve the transdermal administration of active molecules [10]. Among of bio-functional textiles much attention has been gained by transdermal patches that employ nano-carrier based drug delivery systems [11]. These patches aim to enhance drug permeation through the skin barrier in order to reach the blood circulatory system; such approach allows to obtain a sustained and constant drug release in a non-invasive way, while reducing the drug toxicity [12]. Cellulosic substrates and derivatives are the main potential candidates used in this technology, due to their natural biocompatibility, the absence of side effects, such as allergies and skin irritations. Moreover, they are readily available and biodegradable, making them a suitable substrate for bio-functional textile preparation [13]. Due to skin barrier complexity only a limited number of active compounds with a lipophilic character can penetrate the outer layers of the skin. Thus, the preparation of a bio-functional textile usually requires encapsulation of the active substance before functionalizing the textile [14], the use of properly designed nanoparticles protects the drug from surrounding agents until it reaches the target tissue. Polymeric nanoparticles (NPs) are among the most studied nanocarriers given the large availability of polymeric materials that fulfill the requirements of biological applications such as non-toxicity, biodegradability and biocompatibility [15]. Furtherly, these carriers have been proved to effective in entrapping and releasing active substances [16], [17]. Poly- $\epsilon$ -caprolactone (PCL) has peculiar features that made it widely applied in tissue engineering, implantable devices, cell cultures and drug delivery [18], [19]. This Polymer is commonly biodegraded in body fluids by cleavage of the ester bond, the degradation mechanism consists in a first step in which the molecular weight decreases due to chain scission and a second one where an actual weight loss is observable, the overall process can take several weeks to be completed. Thus this material is suitable for applications where long lasting releases are needed [20], and it has been also successfully employed in transdermal applications [21], [22].

Unfortunately, a wide application of such polymeric devices is still a challenging issue due to the scarce productivity and scalability of NPs production processes [23], and this issue is even more critical dealing with bio-functional textiles given the high amount of NPs that would be required in textile functionalization.

The Flash Nanoprecipitation technique (FNP) [24] is a suitable process to overcome the above mentioned issue given its simplicity, fastness, productivity and good reproducibility of the obtained results [25]. FNP exploits the difference of solubility of a polymer in two miscible fluids and partition coefficient in polymer-solvent system.

The polymer, dissolved in an organic solvent, collides against a water jet in a micro reactor to generate a highly turbulent mixing, the low affinity of the polymer for the aqueous phase leads to its precipitation in the form of nanoparticles [26]. The factor governing particle formation phenomenon is mainly the mixing conditions. Reactors such as the confined impinging jet mixer (CIJM) have been appositively designed in order to control the process conditions [27]. On the other hand, the chemical nature of the active substance also influences the encapsulation yield. Thus, several studies have shown that the entrapment of hydrophobic substances ( $\text{LogP} > 3.2$ ) such as curcumin, paclitaxel, menthol and vitamin E [25–28] can be realized with FNP, while to our knowledge few works deal to encapsulate hydrophilic substances.

The aim of this study is to determine the process parameters allowing for encapsulating a hydrophilic substance, caffeine (CAF), which represents an opportunity for transdermal delivery, due to its potential application in dermatology [28]. CAF is able to protect skin from damages caused by UV light, and displays antioxidant activity. Furthermore, it was found that CAF can promote the lipolysis at cellular level and act as an anti-cellulite drug [29], [30].

In the present work a FNP methodology is proposed to produce CAF loaded PCL nanoparticles. The process parameters as well as the formulations were studied in order to achieve NPs of a size similar to the one skin annexes. The tested formulations were characterized by measuring their encapsulation efficiency (EE) and loading capacity (LC), while the antioxidant activity of the NPs was determined by Electron Paramagnetic Resonance Spectroscopy (EPR) coupled with spin trapping technique. The particles were then used to functionalize two different textiles substrates, a cotton and a viscose-micromodal blend. The release properties of the functionalized textile were tested *in vitro* in a vertical Franz diffusion cell.

## II. MATERIALS AND METHODS

### *Materials*

Poly- $\epsilon$ -caprolactone (PCL) (molecular weight of 14000 g/mol), and caffeine (CAF), selected as shell and core component, respectively were purchased from Sigma Aldrich. Acetone with purity  $\geq 99,5\%$  meeting European Pharmacopedia standards (Sigma Aldrich) was used as solvent. Phosphate Buffer solution used in the release test was prepared from Sodium Chloride anhydrous  $\geq 99\%$ , Potassium Chloride ACS grade  $\geq 99,5\%$ , Sodium phosphate dibasic dehydrate  $\geq 99\%$  and Potassium Dihydrogen Phosphate ACS reagent  $\geq 99\%$ , also purchased from Sigma Aldrich. For the spin trapping reaction 5,5-Dimethyl-1-pyrroline N-oxide (DMPO), Hydrogen Peroxide (30%) and Iron (II) Sulphate were purchased from Sigma Aldrich. Ultrapure water was produced by mean of a Milli-Q RG system by Millipore R (Billerica, MA) and employed in all

the experimental procedures. Textile materials tested were knitted cotton fabrics single jersey made of 100% cotton and a blend of viscose/micromodal 70/30%; they were kindly supplied by Eusebio S.p.a (Varese, Italy).

#### A. Nanoparticle preparation

The nanoparticles were prepared by FNP in a CIJM (1mm inlet tube diameter, 5 mm chamber diameter, 11.2 mm chamber height). A stream of polymer organic solvent solution was mixed with an anti-solvent, water (Fig. 1). The collision of the two jets induced polymer precipitation in the form of nanoparticles.

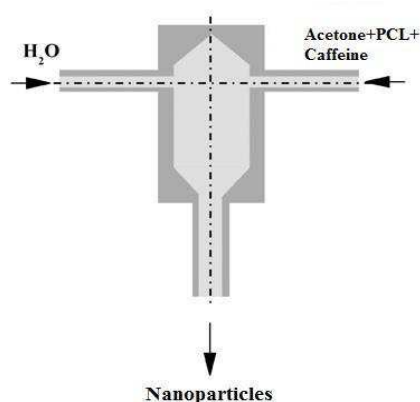


Fig. 1. Scheme of the FNP employed for the production CAF loaded PCL Nanoparticles.

Defined volumes of acetone solution with the proper concentration of PCL and CAF, and water were placed in syringes and fed to the CIJM micro-mixer by a syringe pump (KDS200, KD Scientific, Holliston, MA) at a flow rate varying from 20 to 80 ml/min; the concentration of CAF and PCL used in the inlet solutions are shown in Table I. Samples of 6 ml (3 ml for each stream) were taken, collected in a glass vial containing 3 ml of quenching water placed downstream of the mixer. The collected suspension and the quenching water were kept under magnetic stirring for two minutes. The collected nanoparticle suspension was used for further characterizations.

TABLE I  
FORMULATIONS TESTED.

Formulation	PCL concentration (mg/ml)	CAF concentration (mg/ml)
F1	4.5	9.0
F2	6.0	9.0
F3	10.0	7.6

#### B. Fabrics Functionalization

Fabrics were functionalized by imbibition. The NPs were firstly separated from liquid, in order to obtain about 2 ml of concentrated NP suspension. 0.5 ml of each suspension were then added dropwise over a disk of textile material of

about 2 cm in diameter. Particular care was taken to spread the NPs uniformly over the textile surface and to let the fabric dry between the drop additions.

#### C. Characterizations and analytical methods

- Particle size analysis

Particles size distribution was measured by means of DLS Zetasizer Nanoseries ZS90, Malvern Instruments (Malvern, UK). Samples were prepared by diluting 0.1 ml of as produced nanoparticles suspensions in 1 ml of ultrapure water. All samples were measured in triplicate under controlled temperature at  $25.0 \pm 0.1$  °C.

- Determination of Loading Capacity and Encapsulation Efficiency.

LC is defined as the mass of encapsulated ( $m_{en}$ , in g) drug divided by the mass of the whole polymeric nanoparticles system ( $m_{tot}$ , in g) as given by (1); it is an indicator of the amount of drug that can be incorporated in a given amount of nanoparticle formulation. EE is defined as the amount of encapsulated caffeine over its input quantity of in the process ( $m_{in}$ , in g) as expressed by (2); it is an index of the efficiency of the nanoparticles production process.

$$LC(\%) = \frac{m_{en}}{m_{tot}} \times 100 \quad (1)$$

$$EE(\%) = \frac{m_{en}}{m_{in}} \times 100 \quad (2)$$

In order to calculate LC% and EE% a methodology based on the one described in [11] with slight modification was employed. Briefly the NPs suspension was placed in a rotary evaporator RE 300 at 50 °C, under vacuum for 15 min, to remove acetone; then, it was centrifuged for 30 min at 15.777 g in a SL 16 Thermo scientific centrifuge in order to separate the liquid from the solid NPs. 0.1 mL supernatant sample was diluted in 25 ml of water and analyzed by UV-Vis spectroscopy in a 6850 UV/Vis spectrophotometer, Jenway (Stone, Staffordshire, UK).

EE% and LC% were calculated indirectly after measuring the amount of unencapsulated caffeine in the supernatant.

- Antioxidant activity

The antioxidant activity of nanoparticles was studied by EPR coupled with the spin-trapping technique. For this analysis an appositively prepared sample with equal CAF and PCL concentration of F2 but produced by dissolving CAF in water was used; the NP was accurately separated from the liquid, taking also care of removing all traces of acetone. Hydroxyl radicals were generated in situ by Fenton reaction and trapped using the spin-trap DMPO. H<sub>2</sub>O<sub>2</sub> (20 μL, 10mM), DMPO (100 μL, 50 mM) an aqueous solution of nanoparticles at different concentrations (78 μL) and FeSO<sub>4</sub> (2 μL, 10 mM) were mixed in an Eppendorf tube. The resulting solution was mixed, transferred to a quartz

microcapillary tube and placed in the EPR cavity for measurement. After 5 minutes since the addition of  $\text{FeSO}_4$ , the spectra were recorded on a Bruker EMXnano X-Band spectrometer (Bruker, Billerica, MA, USA). The EPR measurements conditions were as follows: Frequency, 9.74 GHz; scan width, 100 G; receiver gain, 60 dB; time constant, 1.28 ms; sweep time, 80 s; scan, 1. After acquisition, the spectra were processed using the Bruker Xenon software (Bruker, Billerica, MA, USA) for baseline correction and the total number of hydroxyl radicals trapped was quantified using the SpinFit software (Bruker, Billerica, MA, USA).

- *In vitro* release Test

The release test from the functionalized fabrics was conducted on static vertical Franz diffusion cells (PermeGear, Hellertown, PA, USA). The Franz cells were constituted by an upper donor chamber and a lower receptor chamber (volume 11.4 mL) with a contact surface of 1.5  $\text{cm}^2$ . The acceptor compartment was filled with pH 7.4 phosphate buffer solution kept at temperature of 33°C by a heating jacket. A cellulose acetate membrane with porosity of 0.45  $\mu\text{m}$  was used to mimic skin. Prior release test the membrane was boiled in water for 1 h to enhance its wettability. 1 ml samples of the acceptor fluid were withdrawn at a fixed time intervals and analyzed for caffeine by spectrophotometry; thereafter, an equal volume of the fresh PBS solution was replaced into the cell. Experiments were performed in quadruplicate.

### III. RESULTS AND DISCUSSION

#### A. Particle size

To be suitable for a transdermal administration, NPs size should be less than the one of skin annexes (approximately 450 nm). The results of the production of the three formulations at varying inlet flow rate are plotted in Fig. 2.

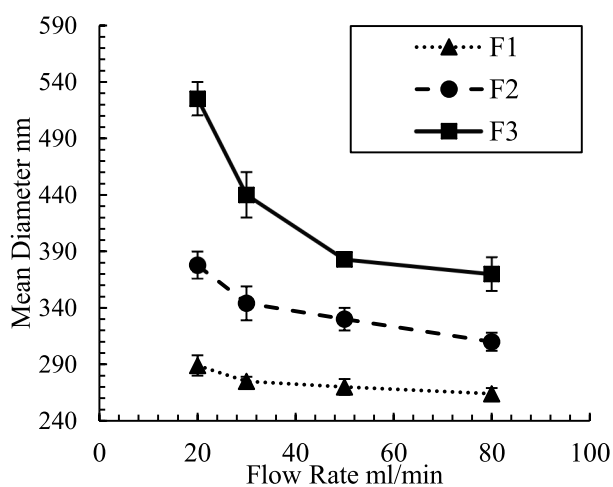


Fig. 2. Trends in particle diameter at varying flow rate for the different formulation tested.

The particle size tends to decrease as the flow rate is increased. Such result is in accordance with theoretical works in which particle formation occurs by two successive steps of nucleation and growth [31]. As a matter of facts, increasing solvent and antisolvent flow rate (FR) causes a higher turbulence inside the reactor chamber, which in turns increases the number of nuclei formed. Therefore less polymer are available for the secondary growth stage. Comparing different formulations, it is noticeable an inverse correlation between the initial PCL concentration and the diameter, this mainly due to greater amount of polymer that can precipitate over the already formed nuclei causing the particles to enlarge during the growth stage.

#### B. Development of textile treatment

Given the suitability of the NPs systems for the transdermal release in terms of diameter, the choice of the optimal formulation was mainly based on the particle content. In Table II the values of EE and LC for the different formulations prepared at FR= 80 ml/min are reported.

TABLE II  
EE AND LC OF THE DIFFERENT FORMULATIONS AT FR = 80 ML/MIN.

Formulation	EE%	LC%
F1	11.3	7.7
F2	17.4	10.4
F3	13.1	7.6

The values of the EE below 20% are an expected results give the high affinity of caffeine with water; as previously reported FNP is commonly used to encapsulated hydrophobic drug that precipitate together with the polymer due to their scarce water solubility. In this study, instead the CAF can be encapsulated only by a mechanical entrapment that occurs during the precipitation of the polymer and such phenomenon lead to lower EE values. The F2 displays the highest results both in term LC and EE, this mainly due to the good balance between initial caffeine and polymer concentration. The low PCL concentration in F1 does limit the available polymer chains for the entrapment while the high PCL content in F3 increases the overall mass of the system reducing the LC.

Because of its capability of incorporating higher amounts of caffeine F2 was chosen as optimal formulation for the textile functionalization and release test.

The effectiveness of the imbibition protocol was already proved in our previous work by SEM analysis [11].

#### C. Antioxidant activity

Hydroxyl radical is a highly reactive chemical specie with very short half-life in the order of nanoseconds [32]. It is known to be the most biologically active free radical, damaging DNA and initiating lipid peroxidation [33]. In

this study, the antioxidant activity of CAF loaded nanoparticles in scavenging hydroxyl radicals was studied. Hydroxyl radicals were generated using the Fenton reaction ( $\text{Fe}_2^+ + \text{H}_2\text{O}_2 \rightarrow \text{Fe}_3^+ + \text{OH}\cdot + \text{HO}^-$ ) and the oxidation of DMPO spin trap by  $\text{OH}\cdot$  was studied by EPR [34]. Results are shown in Table III. Addition of empty PCL nanoparticles did not significantly protect the spin-trap DMPO from oxidation by Fenton-generated  $\text{OH}\cdot$  radicals: indeed, the acquired DMPO-OH signal intensity did not vary upon the addition of the nanoparticles. On the contrary, addition of CAF-loaded PCL nanoparticles protected the spin-trap DMPO from oxidation, markedly reducing the spin-adduct DMPO-OH signal. The protective effect is concentration dependent over the range 1 mg/mL - 4.5 mg/mL CAF-loaded nanoparticles, reaching 49% of DMPO-OH signal decrease for the highest NPs concentration. Notably, the corresponding higher amounts of empty PCL nanoparticles displayed negligible  $\text{OH}$  radicals scavenging activity, thus suggesting that the observed hydroxyl radical scavenging ability was only due to the CAF loaded in the nanoparticles. Overall, these data show that the encapsulation of CAF in PCL nanoparticles results in a marked hydroxyl radical scavenging ability, thus suggesting PCL-loaded NPs as innovative nanoparticle-based antioxidants.

TABLE III  
OH RADICALS CONCENTRATION NORMALIZED TO THE CONTROL

Water (Control)	Empty NPs (4,6 mg/mL)	CAF-loaded NPs (5,75 mg/mL)
100%	98%	49%

#### D. In vitro release test

The Franz's Cell experiment aimed to assess the potential of the developed bio-functional textile as a transdermal delivery device. The normalized cumulative release curves are plotted in Figure 3, a sample obtained by functionalizing the fabric with a solution of free caffeine were used as reference (labeled as CAF COT and CAF MIC). The NP used for the release test were formulation F2 produced at a FR of 80 ml/min.

It is noticeable that two factors play a role in slowing and controlling the release. One is ascribable to the textile substrate, as the CAF MIC sample present a slower and release compared to CAF COT, which reaches a plateau in less than 2 hours. This fact is mostly due to the smaller diameter of micromodal fibers, which means higher surface; this will make the fabric act as a reservoir that control the diffusion from the fabric toward the membrane. Under the same substrate (micromodal), it can be observed that the encapsulation process furtherly slows down the release as the kinetics is slower for caffeine-PCL nanoparticles than free caffeine. This is due to a series of phenomena occurring: first, the particle must be released from the textile and interact with the membrane, then the

NP may either pass through the membrane delivering CAF to the acceptor fluid or get stuck in the membrane pores, in this case CAF has to diffuse out the NP that may act as a reservoir inside the skin.

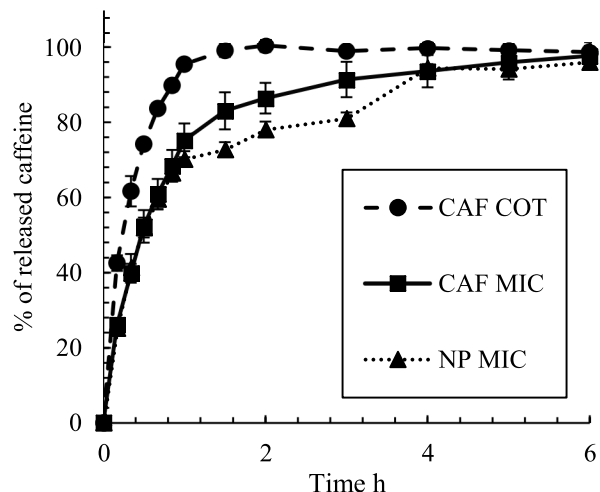


Fig. 3. Cumulative release curves for textiles functionalized with CAF and NP F2 formulation.

During the first hour the CAF MIC and NP MIC curve present the same slope, and this is due to CAF diffusing out of the particles and passing directly through the membrane. Between 1h and 4h the kinetic of the NP system becomes slower, here the particles get stuck in the membrane and CAF is released from the NP facing higher resistance to mass transfer.

The overall contribution of those different phenomena make the micromodal-NP system the most effective in controlling the drug release.

#### IV. CONCLUSIONS

The present research inquired the preparation of a bio-functional textile. The employment of the polymeric nanoparticle a transdermal delivery system combined with the proper textile material showed an effective control of the drug release kinetic. The use of FNP as a high productivity process was proven suitable even with dealing with a hydrophilic drug. The assessment on the antioxidant properties of the NP combined with the transdermal release of the textile-NP system provides interesting preliminary results about the possibility of administering caffeine through daily worn garments. This could represent an improvement with respect to conventional transdermal systems such as creams and ointments that must be locally applied several times a day. Once worn next to skin, the fabric can deliver CAF for several hours without any further action of the patient to be taken.

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#### REFERENCES

- [1] F. Leone and R. Cavalli, "Drug nanosuspensions: a ZIP tool between traditional and innovative pharmaceutical formulations," *Expert Opin. Drug Deliv.*, vol. 12, no. 10, pp. 1607–1625, Oct. 2015.
- [2] L. F. Santos, I. J. Correia, A. S. Silva, and J. F. Mano, "Biomaterials for drug delivery patches," *Eur. J. Pharm. Sci.*, vol. 118, pp. 49–66, Jun. 2018.
- [3] R. Goyal, L. K. Macri, H. M. Kaplan, and J. Kohn, "Nanoparticles and nanofibers for topical drug delivery," *J. Controlled Release*, vol. 240, pp. 77–92, Oct. 2016.
- [4] T. W. Prow *et al.*, "Nanoparticles and microparticles for skin drug delivery," *Adv. Drug Deliv. Rev.*, vol. 63, no. 6, pp. 470–491, May 2011.
- [5] L. A. DeLouise, "Applications of Nanotechnology in Dermatology," *J. Invest. Dermatol.*, vol. 132, no. 3, pp. 964–975, Mar. 2012.
- [6] B. Dumontel *et al.*, "Enhanced biostability and cellular uptake of zinc oxide nanocrystals shielded with a phospholipid bilayer," *J. Mater. Chem. B*, vol. 5, no. 44, pp. 8799–8813, 2017.
- [7] G. Canavese *et al.*, "Nanoparticle-assisted ultrasound: A special focus on sonodynamic therapy against cancer," *Chem. Eng. J.*, vol. 340, pp. 155–172, May 2018.
- [8] M. Argenziano *et al.*, "Vancomycin-loaded nanobubbles: A new platform for controlled antibiotic delivery against methicillin-resistant *Staphylococcus aureus* infections," *Int. J. Pharm.*, vol. 523, no. 1, pp. 176–188, May 2017.
- [9] U.-C. Hipler and P. Elsner, Eds., *Biofunctional Textiles and the Skin*, vol. 33. S. Karger AG, 2006.
- [10] M. Mihailiasa, F. Caldera, J. Li, R. Peila, A. Ferri, and F. Trotta, "Preparation of functionalized cotton fabrics by means of melatonin loaded  $\beta$ -cyclodextrin nanosponges," *Carbohydr. Polym.*, vol. 142, pp. 24–30, May 2016.
- [11] D. Massella, F. Leone, R. Peila, A. Barresi, and A. Ferri, "Functionalization of Cotton Fabrics with Polycaprolactone Nanoparticles for Transdermal Release of Melatonin," *J. Funct. Biomater.*, vol. 9, no. 1, p. 1, Dec. 2017.
- [12] S. A. Joshi, S. S. Jalalpure, A. A. Kempwade, and M. R. Peram, "Fabrication and in-vivo evaluation of lipid nanocarriers based transdermal patch of colchicine," *J. Drug Deliv. Sci. Technol.*, vol. 41, pp. 444–453, Oct. 2017.
- [13] E. Pinho, M. Henriques, R. Oliveira, A. Dias, and G. Soares, "Development of biofunctional textiles by the application of resveratrol to cotton, bamboo, and silk," *Fibers Polym.*, vol. 11, no. 2, pp. 271–276, Apr. 2010.
- [14] M. Martí, V. Martínez, L. Rubio, L. Coderch, and J. L. Parra, "Biofunctional textiles prepared with liposomes: *in vivo* and *in vitro* assessment," *J. Microencapsul.*, vol. 28, no. 8, pp. 799–806, Dec. 2011.
- [15] A. Kumari, S. K. Yadav, and S. C. Yadav, "Biodegradable polymeric nanoparticles based drug delivery systems," *Colloids Surf. B Biointerfaces*, vol. 75, no. 1, pp. 1–18, Jan. 2010.
- [16] M. Bazzano *et al.*, "Synthesis of polymeric nanocapsules by radical UV-activated interface-emulsion polymerization," *J. Polym. Sci. Part Polym. Chem.*, vol. 54, no. 20, pp. 3357–3369, Oct. 2016.
- [17] F. Artusio *et al.*, "Polymeric nanocapsules via interfacial cationic photopolymerization in miniemulsion," *Polymer*, vol. 139, pp. 155–162, Mar. 2018.
- [18] F. Cesca *et al.*, "Fabrication of biocompatible free-standing nanopatterned films for primary neuronal cultures," *RSC Adv.*, vol. 4, no. 86, pp. 45696–45702, 2014.
- [19] T. Limongi *et al.*, "Laboratory injection molder for the fabrication of polymeric porous poly-epsilon-caprolactone scaffolds for preliminary mesenchymal stem cells tissue engineering applications," *Microelectron. Eng.*, vol. 175, pp. 12–16, May 2017.
- [20] V. R. Sinha, K. Bansal, R. Kaushik, R. Kumria, and A. Trehan, "Poly- $\epsilon$ -caprolactone microspheres and nanospheres: an overview," *Int. J. Pharm.*, vol. 278, no. 1, pp. 1–23, Jun. 2004.
- [21] K. Madhaiyan, R. Sridhar, S. Sundarajan, J. R. Venugopal, and S. Ramakrishna, "Vitamin B12 loaded polycaprolactone nanofibers: A novel transdermal route for the water soluble energy supplement delivery," *Int. J. Pharm.*, vol. 444, no. 1–2, pp. 70–76, Feb. 2013.
- [22] C. Alonso, M. Martí, C. Barba, M. Lis, L. Rubio, and L. Coderch, "Skin penetration and antioxidant effect of cosmeo-textiles with gallic acid," *J. Photochem. Photobiol. B*, vol. 156, pp. 50–55, Mar. 2016.
- [23] A. Lamprecht, "Nanomedicines in gastroenterology and hepatology," *Nat. Rev. Gastroenterol. Hepatol.*, vol. 12, no. 4, pp. 195–204, Mar. 2015.
- [24] B. K. Johnson and R. K. Prud'homme, "Flash NanoPrecipitation of Organic Actives and Block Copolymers using a Confined Impinging Jets Mixer," *Aust. J. Chem.*, vol. 56, no. 10, p. 1021, 2003.
- [25] C. J. Martínez Rivas *et al.*, "Nanoprecipitation process: From encapsulation to drug delivery," *Int. J. Pharm.*, vol. 532, no. 1, pp. 66–81, Oct. 2017.
- [26] A. A. Barresi, M. Vanni, D. Fissore, and T. Zelenková, "Synthesis and Preservation of Polymer Nanoparticles for Pharmaceutical Applications," in *Handbook of Polymers for Pharmaceutical Technologies*, V. K. Thakur and M. K. Thakur, Eds. Hoboken, NJ, USA: John Wiley & Sons, Inc., 2015, pp. 229–280.
- [27] F. Lince, D. L. Marchisio, and A. A. Barresi, "Strategies to control the particle size distribution of poly- $\epsilon$ -caprolactone nanoparticles for pharmaceutical applications," *J. Colloid Interface Sci.*, vol. 322, no. 2, pp. 505–515, Jun. 2008.
- [28] M. Dias, "Topical delivery of caffeine from some commercial formulations," *Int. J. Pharm.*, vol. 182, no. 1, pp. 41–47, May 1999.
- [29] G. Ginsberg, D. Hattis, A. Russ, and B. Sonawane, "Physiologically Based Pharmacokinetic (PBPK) Modeling of Caffeine and Theophylline in Neonates and Adults: Implications for Assessing Children's Risks from Environmental Agents," *J. Toxicol. Environ. Health A*, vol. 67, no. 4, pp. 297–329, Feb. 2004.
- [30] C. Puglia *et al.*, "Design of solid lipid nanoparticles for caffeine topical administration," *Drug Deliv.*, vol. 23, no. 1, pp. 36–40, Jan. 2016.
- [31] A. D. Lavino, N. Di Pasquale, P. Carbone, and D. L. Marchisio, "A novel multiscale model for the simulation of polymer flash nanoprecipitation," *Chem. Eng. Sci.*, vol. 171, pp. 485–494, Nov. 2017.
- [32] L. A. Pham-Huy, H. He, and C. Pham-Huy, "Free radicals, antioxidants in disease and health," *Int. J. Biomed. Sci. IJBS*, vol. 4, no. 2, pp. 89–96, Jun. 2008.
- [33] B. Lipinski, "Hydroxyl Radical and Its Scavengers in Health and Disease," *Oxid. Med. Cell. Longev.*, vol. 2011, pp. 1–9, 2011.
- [34] Y. Qiu *et al.*, "Antioxidant chemistry of graphene-based materials and its role in oxidation protection technology," *Nanoscale*, vol. 6, no. 20, pp. 11744–11755, 2014.