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Microfibrillated cellulose coatings as new release systems for active packaging

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ABSTRACT

In this work, a new use of microfibrillated cellulose (MFC) is highlighted for high-added-value applications. For the first time, a nanoporous network formed by MFC coated on paper is used for a controlled release of molecules. The release study was carried out in water with caffeine as a model molecule. The release process was studied by means of (i) continuous, and (ii) intermittent diffusion experiments (with renewal of the medium every 10 min). The effect of the MFC was first observed for the samples impregnated in the caffeine solution. These samples, coated with MFC (coat weight of about 7 g/m^2), released the caffeine over a longer period (29 washings compared with 16), even if the continuous diffusions were similar for both samples (without and with MFC coating). The slowest release of caffeine was observed for samples coated with the mixture (MFC + caffeine). Moreover, the caffeine was only fully released 9 h after the release from the other samples was completed.

This study compared two techniques for the introduction of model molecules in MFC-coated papers. The latter offers a more controlled and gradual release. This new approach creates many opportunities especially in the food-packaging field. A similar study could be carried out with an active species.

1. Introduction

The development of new food packaging materials is being driven by increased consumer demand. Specifically, research is being focused on (i) the use of renewable resources, (ii) the improvement of barrier properties, and (iii) the introduction of new functionality to enhance the shelf-life of food products (Johansson et al., 2012). This study tries to address these three objectives.

Fiber-based materials such as paper seem to be the most promising packaging materials to address consumers' needs for renewable, biodegradable, lightweight, and recyclable packaging. However, the intrinsic properties of paper are not sufficient for some packaging applications, so that specific treatments are necessary by using polymers or multilayer materials. However, the general non-recyclability and non-biodegradability of many petroleum polymers limits interest in these current solutions. Thus, researchers are trying to avoid this issue by using new biopolymers or materials. Among the latter, the new family of nanocelluloses greatly interests such researchers, as proven by the recent increase in books (Dufresne, 2012) and reviews (Eichhorn et al., 2010; Klemm et al., 2011; Moon, Martini, Nairn, Simonsen, & Youngblood, 2011) on them. In particular, microfibrillated cellulose (MFC) is being increasingly studied (Lavoine, Desloges, Dufresne, & Bras, 2012; Siró & Plackett, 2010).

In 1985, Turbak, Snyder, and Sandberg (1985) patented a manufacturing process for MFC. Due to its nanometer scale, its high surface energy and its ability to form a nanoporous network, MFC was studied for use in nanocomposites as a mechanical reinforcement (Siqueira, Bras, & Dufresne, 2010; Siró & Plackett, 2010) and as a dispersion stabilizer (Andresen, Johansson, Tanem, & Stenius, 2006). Since then, research in this area has increased, and new applications are targeted: films (Ahola, Salmi, Johansson, Laine, & Österberg, 2008; Andresen et al., 2007; Aulin, Gällstedt, & Lindström, 2010; Fukuzumi, Saito, Iwata, Kumamoto, & Isogai, 2009), aerogels (Aulin, Netrval, Wagberg, & Lindström, 2010; Fischer, Rigacci, Pirard, Berthon-Fabry, & Achard, 2006), electronic devices (Shah & Malcolm Brown, 2004; Torvinen, Sievänen, Hjelt, & Hellén, 2012), etc. Increasingly, the combination of MFC and cellulosic materials such as papers and boards is being investigated (Lavoine et al., 2012). The first such study investigated the coating of MFC on papers to improve their barrier properties (Aulin, Gällstedt, et al., 2010; Syverud & Stenius, 2009). Others have focused on MFC coatings with polymers or resins such as starch, wax or shellac (Hult, Iotti, & Lenes, 2010; Spence, Venditti, Rojas, Pawlak, & Hubbe, 2011) to obtain a homogeneous MFC coat with a better barrier performance. The use of MFC suspensions as coating slurries is also advantageous for the printing industry (Ankerfors, Lindström, Hoc, & Song, 2009; Hamada, Beckvermit, & Bousfield, 2010; Ridgway,

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2011) and, more recently, in the food packaging sector (Rodionova, Lenes, Eriksen, & Gregersen, 2010; Spence, Venditti, Rojas, Habibi, & Pawlak, 2010). The enhancement of barrier and mechanical properties is thus the main motivation for using MFC with paper. Its ability to form a nanoporous network (Fukuzumi et al., 2011; Nemoto, Soyama, Saito, & Isogai, 2012) can be considered to be an advantage for other applications in comparison with classical films. One further possibility, investigated in this study, is the use of MFC in drug release applications.

To our knowledge, very few papers have discussed the use of MFC as a drug release system, and even when it has been attempted, a different strategy has been employed in each study. The first such work in 2011 highlighted the ability of MFC to immobilize and protect well the drug nanoparticles in a suspension and in a freeze-dried MFC matrix (Valo et al., 2011). Thus, the nanoparticles could be stored for more than ten months without inducing major changes in their morphology. Dissolution tests were also carried out since there was an indication that the binding of the drug with the MFC could have controlled the release. Nevertheless, the authors did not establish any positive role of the MFC in slowing down release. Another recent study used MFC as a carrier for the encapsulation of drugs (Kolakovic, Laaksonen, Peltonen, Laukkanen, & Hirvonen, 2012). Here, drug-loaded MFC microparticles were produced using a spray drying process. The objective of doing this was to use the tight, nanoporous network of the MFC around the drug to release it progressively. Long-term studies showed sustained drug release profiles over a period of two months. Thus, it was proven that the MFC had played a significant role in limiting the drug diffusion.

These both studies employed MFC as a new technology for drug dissolution. However, the present study focused rather on the release of active compounds from insoluble support, such as paper substrate. Such systems dealing with the release of active agents (e.g. drugs, flavors) from insoluble support (e.g. proteins, acrylic coatings) are already well-known (Chen, Remondetto, & Subirade, 2006; Madene, Jacquot, Scher, & Desobry, 2006). Technologies such as coating, extrusion or spray-drying (Gouin, 2004; Guillard, Issoupov, Redl, & Gontard, 2009) have been indeed used with different insoluble matrices (e.g. starch, carbohydrate, whey gluten, wax etc.) for the encapsulation and the controlled release of active compounds.

The use of MFC as insoluble matrix for controlled release system is, nevertheless, very new. It was firstly developed by Kolakovic, Peltonen, Laukkanen, Hirvonen, and Laaksonen (2012). They published a study emphasizing the diffusion-control role of the nanoporous network of MFC (Kolakovic, Peltonen, et al., 2012). They produced MFC films that were impregnated with the drug, using a filtration process. They studied different drug release periods up to a maximum of three months and showed the utility of MFC for controlled-release applications. Nevertheless, they also noticed that the release rate was slow and that small quantities of the drug were released within 24 h. The latter observation limits the use of MFC for the sustained release of drugs over a long time.

In this study, we developed a new strategy. For the first time, we availed of the nanoporous network structure of MFC, which is formed during the paper coating process, to induce the controlled release of an active species. The study was carried out with a model species, caffeine, which was introduced using three different techniques in the paper. Caffeine was chosen as it is classically used as a simulator of hydrophilic drug release systems with a high solubility in water (Efentakis, Pagoni, Vlachou, & Avgoustakis, 2007), UV detectable, and, in our case, has no chemical interactions with the cellulosic substrate. The effect of the MFC coats on caffeine release was then investigated to identify its positive impact.

2. Experimental

2.1. Materials

Two MFC suspensions (E-MFC-MIC and E-MFC-H) were supplied by the FCBA (France). The first suspension, E-MFC-MIC, was produced from eucalyptus pulp, enzymatically pre-treated (during 2 h with an endoglucanase) and passed through a Microfluidizer® M-110EH-30 (5 passes through the 100 nm chamber, 4 passes through the 200 nm chamber). The concentration was 2% (w/w).

The second suspension, E-MFC-H, was produced from sulfite pulp (Domsjö®), also enzymatically pre-treated as described above, and passed through a GEA Ariete® homogenizer (4 passes, at 1400 bars). The concentration was 2% (w/w).

Both MFC suspensions are considered similar, since diameter dimensions are closed.

The base paper material was calendered paper with a basis weight of 41 g/m^2 made with non-bleached pulp. Caffeine (99%), $C_8H_{10}N_4O_2$, was purchased from Sigma–Aldrich (France) and used as received.

2.2. Methods

2.2.1. Paper coating process

The MFC suspensions were coated onto paper samples (A4 format) with a bar coating process (Endupap, France). A 0.9 mm Mayer bar was used with a coating speed of 5 cm/s. The coated papers were then dried with a contact drying system (Allimand, France) at 105 °C for 3 min. These steps were repeated five times in order to deposit five MFC layers on the sample.

Reference samples (water-treated papers) were obtained by impregnation of one side of the base paper in deionized water followed by drying under the same conditions described above. They were treated the same number of times as the MFC-coated samples, i.e. five water impregnations, each one followed by a drying at 105 °C for 3 min.

2.2.2. Determination of the caffeine absorption

Paper samples of 10 cm × 10 cm were first dried at 105 °C for 1 h. Their dried mass (M_i) was then determined. An aqueous caffeine solution of 21 g/L was then prepared at room temperature. Each paper sample was impregnated for different times (1, 5, 10, 20 30, 40, and 60 min) in the solution. After removing the excess solution by manually squeezing, the samples were dried at 105 °C for 1 h in a ventilated oven. The impregnated dried mass (M_f) was then determined.

The adsorbed amount of caffeine for each sample was calculated as follows:

$$C\,(\%) = \frac{(M_f - M_i)}{M_i} \times 100$$

2.2.3. Preparation of the samples for the release study

The tested samples were prepared using three different strategies as shown in Fig. 1.

The first strategy (i) was the preparation of the reference samples by impregnation of paper samples in the caffeine solution (21 g/L) over the time determined. The full quantity of caffeine introduced was calculated using the mass difference between the dried impregnated samples after and before impregnation using a precision scale at ±0.001 g.

The second strategy (ii) involved the impregnation of the paper samples according to strategy (i), followed by coating with five MFC layers. The full quantity of caffeine was determined as described previously, so that the authors could assess the hypothesis that little caffeine was released during the coating process.

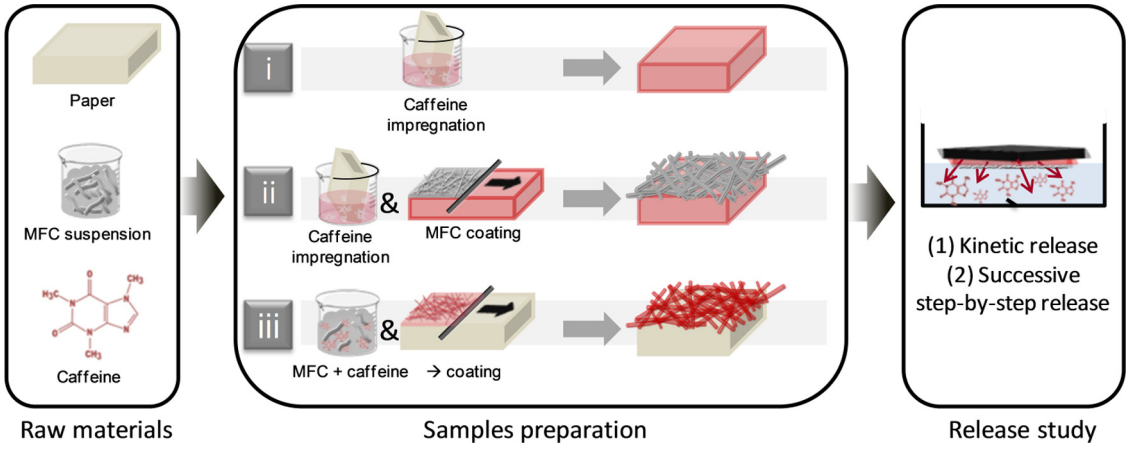

Fig. 1. The caffeine release study – samples preparation. Preparation of the tested samples using three different strategies: (i) impregnation of papers samples in the caffeine solution, (ii) impregnation of papers samples in the caffeine solution followed by coating with MFC and, (iii) papers samples coated with the mixture caffeine/MFC.

The final strategy (iii) involved coating of the paper with the MFC suspension, in which the caffeine was previously introduced, to obtain a concentration of about 21 g of caffeine per liter of MFC suspension. The samples were coated five times with this slurry. In this case, the quantity of caffeine has been calculated from its initial quantity introduced in the slurry with MFC. The share of caffeine in the slurry caffeine/MFC is known and the coat mass of the slurry caffeine/MFC on paper samples is also measured. Supposing that the coating process is homogeneous and caffeine is homogeneously mixed with MFC, the share of caffeine in the slurry will be identical to the share in the coat on paper samples. The dried coat mass of each sample was determined by mass difference after drying each sample for at least 1 h at 105 °C. The full quantity of caffeine coated on the sample was then calculated from the percentage of caffeine introduced initially in the slurry and the dried coat mass of the sample.

2.2.4. Release protocols

Two protocols were developed for analyzing the caffeine release.

Each sample was adhered to a light expanded polystyrene support using scotch tape in order to study only the release of caffeine from the sample's surface. These experiments were repeated on three specimen of each sample, at room temperature and under sink conditions.

2.2.4.1. Continuous diffusion experiments. The continuous diffusion was studied in 500 mL of deionized water that was continuously stirred with a magnetic stirring-bar. The samples were placed at the surface of the aqueous media. At successive intervals, 3 mL of the solution was taken for UV analysis at a wavelength of 272 nm. Using a calibration curve, the concentration of the caffeine released was then determined as a function of time.

2.2.4.2. Intermittent diffusion experiments. This protocol was similar to the continuous diffusion protocol, except that between each 10 min sampling step, the aqueous media was renewed.

Analysis of the solution absorbance was carried out with a UV spectrophotometer SHIMADZU UV1800 at a wavelength of 272 nm.

2.2.5. Samples characterization

Before each test, the paper samples were maintained at a temperature of 23 °C, and a relative humidity of 50% for at least 24 h.

Scanning Electron Microscopy (SEM) and Field Emission Gun Scanning Electron Microscopy (FE-SEM) images of the base or coated papers, and of the MFC suspensions, were taken using a Quanta200® and a Zeiss® Ultra-55, respectively. The MFC suspensions were spread onto a metal substrate using carbon tape, allowed to dry for two nights at room temperature, and coated with a thin layer of gold. The working distance used with the FE-SEM was 5.5 mm for an accelerating voltage of 2.00 kV at a magnitude of ×20.00 K. The respective surfaces of the base and coated papers were precisely cut, and mounted onto a similar support to be analyzed with SEM, using the back-scattered electron (BSE) detection mode. The working distance employed was 9.9 mm with a voltage of 12.5 kV at a magnitude of ×100. The respective cross-sections of the base and coated papers were also analyzed with SEM at a working distance of 10.2 mm, a voltage of 15.0 kV and at a magnitude of ×600.

The basis weight of the 10 cm × 10 cm samples was determined by weighing samples with a precision scale (±0.001 g). Each value was expressed as an average of at least five measurements.

Their thickness was measured by image analysis of the cross-sections analyzed with SEM. The ImageJ® software was used to obtain thickness average values of at least 50 measurements.

The Young's modulus of the samples was determined according to the standard ISO 1924 – 2/3 using a Lorentzen & Wettre Tensile Tester at a speed of 100 mm/min, at 23 °C and 50% RH. The same device also allowed the measurements of the strength-at-break and the elongation of each sample. At least five measurements were carried out to obtain the average value. At the same conditions of temperature and humidity, the bending stiffness was measured using a Kodak stiffness tester (ISO 5629). This measurement was also repeated on at least five specimens.

The air permeability tests were carried out using Mariotte vases (ISO 5636) with each sample having an area of 2 cm^2, at a vacuum of 2.5 kPa. The results were expressed as an average of at least five measurements.

3. Results and discussion

3.1. Characterization of MFC

Fig. 2a shows a FE-SEM image of the E-MFC-GR suspension used to coat the paper samples. An average diameter of MFC of 60 ± 16 nm was determined after image analysis, using the ImageJ® software, after at least 50 measurements. This value agrees well with dimensions for similar MFC fibers found in the literature (Lavoine et al., 2012; Siqueira, Bras, & Dufresne, 2009; Siró & Plackett, 2010). Currently, different types of MFC are produced. However, depending on the MFC source and the treatment that is applied, the aspect ratio and dimensions of each type of MFC fiber will differ. Thus, FE-SEM was used to verify that the MFC

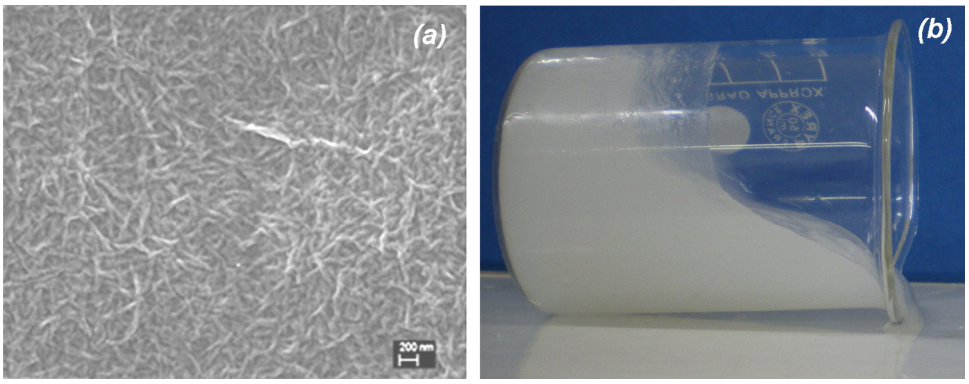

Fig. 2. FE-SEM image of the E-MFC-GR suspension (dried) from eucalyptus pulp (a) and picture of E-MFC-GR (2% w/w) as gel (b).

suspensions were homogeneous and that it had no large fibers (with diameter higher than 100 μm). Moreover, the suspension used for coating clearly resembles a gel (Fig. 2b) because of the high specific area and homogeneity observed in the suspension, both of which are characteristic of nanoscale features.

3.2. Characterization of the MFC-coated papers

As shown in Fig. 1, three kinds of samples were prepared for investigating the influence of the nanoporous network (shown in Fig. 2a). The impact of MFC coatings was first assessed by studying the mechanical and barrier properties of each sample: the base paper, the water-treated samples and the MFC-coated samples. As the MFC-coating contained about 98% of water and only 2% of dried MFC, wet reference samples (water-treated samples) were also prepared to compare and highlight the influence of the wetting and drying processes (during the coating steps). Indeed, it is well-known that wetting and drying steps influence paper structure (Thomson, Lowe, & Ragauskas, 2008).

Due to the viscosity of the suspension, the coating was not homogeneous after one coat. Fig. 3 presents SEM images of the surfaces of the coated papers between the first and fifth coats. In BSE detection mode, the fillers (calcium carbonate, kaolin) are represented by white and the cellulosic parts are represented by black. As the number of coats increases, more filler is progressively recovered. After five coats, the MFC coating was assumed to be homogeneous. Thus, for the release study, all the samples were coated with five MFC coats. This choice was further justified by the positive mechanical and barrier properties obtained in this case and detailed later in Table 1.

Fig. 4 shows the differences between the base paper and the one with the 5-layer MFC coating. The MFC is well distinguished on the surface of the sample (Fig. 4b and c) but do not penetrate through the whole thickness of the paper. A homogeneous thickness of about 7 ± 2 μm is observed for the MFC layer on the surface.

With five MFC coats, the coat mass obtained was 7 g/m^2, which is the expected value for barrier coating. Table 1 summarizes the mechanical properties of the samples. The water-treated samples had a similar basis weight than the reference paper (from 41 ± 1 to 43 ± 1 g/m^2) when taking into account the standard deviations.

However, the thickness values indicated a swelling of the paper samples after the water treatment, i.e. the successive wetting/drying cycles. Thickness values of water-treated samples measured by image analysis are indeed increased by about 25% demonstrating structural changes induced by the coating process. With the addition of MFC, this value increased again by 46%. As the thickness of MFC layers is about 7 μm, this thickness increase is also explained by the water coating induced during MFC coating.

These structural changes have consequences on mechanical properties. Compared to base paper properties, values of Young's modulus and strength were indeed decreased after the water treatment (−36% and −17% in machine direction respectively). However, the addition of MFC counterbalanced these damages. MFC-coated paper samples have indeed similar mechanical properties than base paper. The use of MFC is here interesting as it reinforced the mechanical properties of base paper damaged during the coating process.

The mechanical reinforcement is also concluded with the bending stiffness values. Nevertheless, the enhancement is the same for water-treated and MFC-coated samples. Thus, this improvement is mainly due to the coating process, and especially to shrinkage, which confers a better elongation to paper samples. More details for this type of experiment have been reported recently (Lavoine, Desloges, & Bras, 2011).

The MFC coating has significant effect on the air permeance. With five MFC coats, i.e., with about 7 g/m^2 of the MFC suspension, the air permeance decreases drastically to 70% of the uncoated value (Table 1). These results are significant, even when the MFC-coated samples are compared to water-treated samples, whose air permeance values are two to three times higher than those of the base paper. These results are in agreement with those of a study published by (Syverud & Stenius, 2009).

The characterization of the MFC-coated papers proved the positive effect of MFC-coatings (i.e., slightly better mechanical properties with a strong reduction in air permeability), as expected

Table 1
Mechanical properties and air permeability of the base paper and the MFC-coated papers compared to the mechanical properties and air permeability of the water-treated papers (at 23 °C and 50% of relative humidity). Measurements in machine (MD) and cross-direction (CD) were carried out on at least five specimens.

	MFC coat weight (g/m^2)	Thickness (μm)	Young's modulus (Gpa)		Bending stiffness (mN m)		Strength (N)		Elongation at break (%)		Air permeance (μm/Pa s)
			MD	CD	MD	CD	MD	CD	MD	CD	
Base paper	00 ± 00	42 ± 2	7.3 ± 0.5	2.3 ± 0.1	0.06 ± 0.01	0.03 ± 0.001	47 ± 4	15 ± 1	1.2 ± 0.1	1.7 ± 0.3	2679 ± 139
5 H_2O treatments	00 ± 00	52 ± 7	4.7 ± 0.2	1.7 ± 0.1	0.10 ± 0.002	0.03 ± 0.001	39 ± 2	13 ± 1	1.5 ± 0.1	1.7 ± 0.1	6441 ± 801
5 MFC coats	6.8 ± 1.3	72 ± 4	5.8 ± 0.1	2.4 ± 0.4	0.11 ± 0.01	0.05 ± 0.0002	48 ± 1	16 ± 1	1.4 ± 0.1	1.2 ± 0.2	787 ± 166

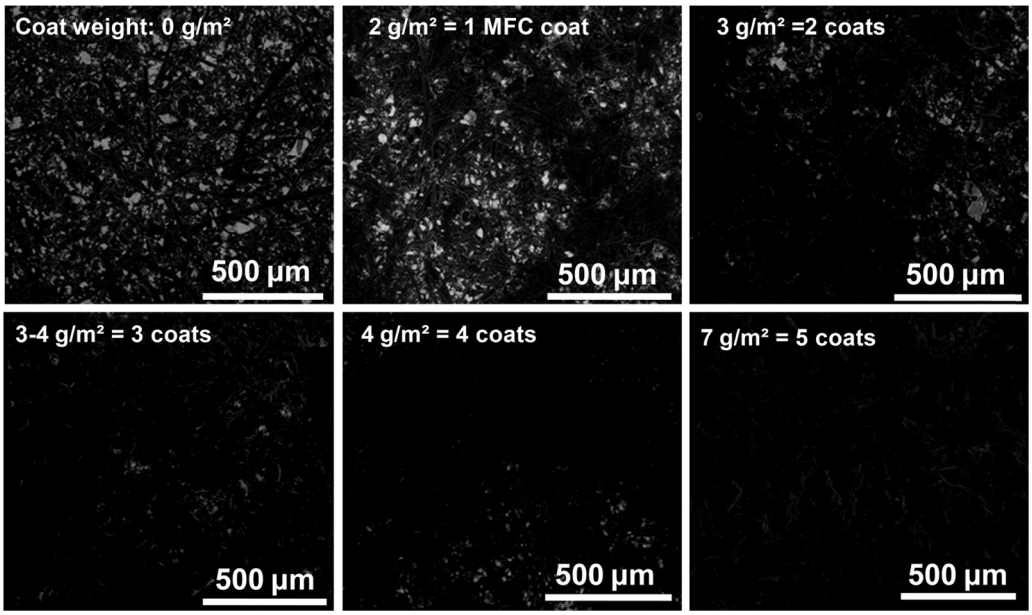

Fig. 3. SEM images of the surfaces of MFC-coated papers between the first (coat mass of 2 g/m^2) and fifth passes (coat mass of 7 g/m^2 – bottom right corner) compared to the base paper (upper left corner) using the BSE detection mode at a magnitude of ×100.

from recent papers (Aulin, 2009; Aulin, Gällstedt, et al., 2010; Nygårds, Aulin, & Ström, 2011). However, whether this interesting biobased, nanoporous network significantly affects the rate of molecule release and whether it can be used to control such a release still needs to be investigated.

3.3. Continuous diffusion

The caffeine release study comprises three steps: (1) the paper absorption, (2) the continuous diffusion experiments, and (3) the intermittent diffusion experiments of the species into an aqueous media. At the end, a comparison is made between (i) the base paper impregnated in caffeine, (ii) the same paper subsequently coated with MFC, and (iii) the base paper coated with the mixture of MFC and caffeine, as previously described in Fig. 1.

Caffeine was selected as the release molecule because it is highly soluble in water, detectable by UV–vis, and classically used as a simulator of drug release systems (Efentakis et al., 2007; Nicoli, Colombo, & Santi, 2005; Santander-Ortega et al., 2010; Sriamornsak & Kennedy, 2007).

The absorbed amount of caffeine was determined for different times of impregnation in the caffeine solution. After 10 min, no more absorption occurred with further increase in time. Accounting for standard deviation with a relative error between 5% and 15% (results not shown), the values were indeed similar and converged to an absorbed amount of caffeine of approximately 7%. Thus, in our next studies, each paper was impregnated for a minimum of 10 min in the caffeine solution.

After preparation, each sample surface was placed on the meniscus with an aqueous solution to study the release of the caffeine. It is important to note that caffeine is very soluble in water and should be released into aqueous solution very quickly compared with the release of classical drug medicines or antimicrobial molecules (which are usually less soluble) (Sriamornsak & Kennedy, 2007).

The continuous diffusion experiments for the three kinds of samples are plotted in Fig. 5. The release rate of caffeine with time in the case of the paper impregnated in caffeine reaches a plateau after 40 min of release in water. A similar trend is observed for a similarly impregnated sample coated with five MFC layers. The MFC coats do not seem to prevent the caffeine from releasing or to slow this release. Even if the slope at the origin is slightly slower for the MFC-coating, the gradients of the curves for both samples are approximately identical (Fig. 6). Moreover, both curves do not indicate 100% caffeine release (they are 80% and 60%, respectively). This observation could be explained if little caffeine were released during the coating process. The coating of the MFC suspension involves the coating of 98% of water for only 2% of dried MFC. Consequently, the caffeine previously introduced into the paper structure during impregnation already has an opportunity to be released. UV analysis (not presented here) of the support placed

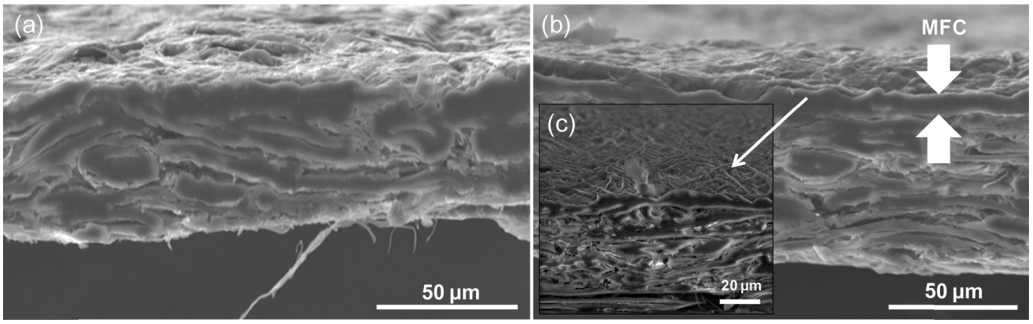

Fig. 4. SEM images of the base paper (a) and paper with five MFC coats (b and c) slices (WD: 10.2 mm, HV: 15.0 kV, Mag: ×600). The picture (c) highlights the nanoporous MFC network formed at the surface of the paper surface (WD: 9.9 mm, HV: 12.5 kV, Mag: ×1200; BSE detector).

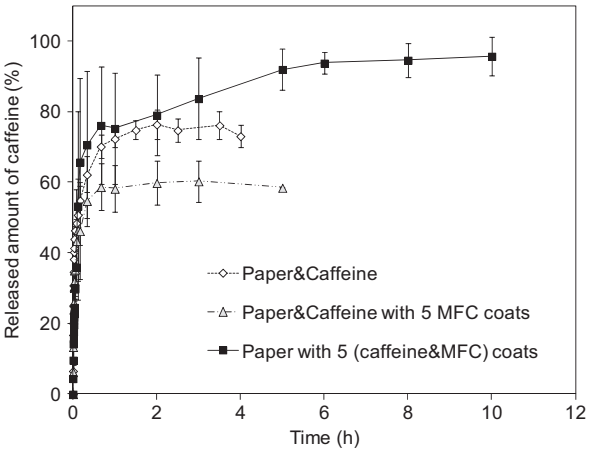

Fig. 5. Continuous diffusion of caffeine in the case of three kinds of samples: (1) paper impregnated in caffeine solution [Paper&Caffeine ◊], (2) paper impregnated in caffeine solution and coated with five MFC coats [Paper&Caffeine with 5 MFC coats △] and, (3) paper coated five times with the slurry caffeine/MFC [Paper with 5 (caffeine&MFC) coats ■]. The mass of caffeine released divided by the mass of caffeine previously introduced into the paper samples (%) is plotted as a function of the time of release (h). This experiment has been carried out on three specimens, at room temperature.

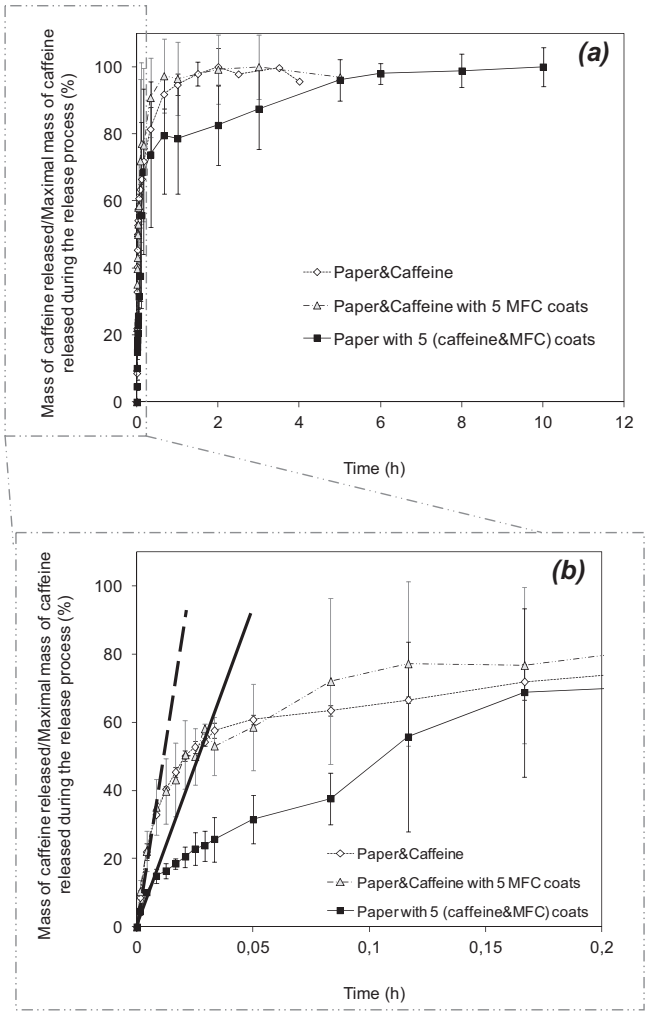

Fig. 6. (a) Continuous diffusion of caffeine with the mass of caffeine released with time divided by the maximal quantity of caffeine released during the release process (plateau value) (%). (b) Zoom of the graph (a) on the gradient of each curve.

under the samples during the coating process proved the presence of caffeine that was released prematurely during the coating process. Unfortunately, the process has not allowed a precise measurement of this quantity despite several tentative efforts. This can lead to an inaccuracy when quoting the initial mass of caffeine. It is also important to note that the concentration of caffeine released into the solution is still very low and continuous diffusion into the aqueous media occurs. Indeed, the volume of the release media was chosen so that the equilibrium concentration of caffeine in water would never be reached (sink conditions Gibaldi and Feldman, 1967). Nevertheless, as no chemical grafts or hydrogen bonds are possible between paper or MFC, and caffeine, it is possible to test the hypothesis that all the caffeine within the samples is released when the plateau is reached. For these two reasons, the results have also been expressed with the assumption that the maximal mass of caffeine released during the release process is equivalent to the whole mass introduced initially in the sample (Fig. 6).

Indeed, considering the diffusion of the sample coated with the mixture (caffeine and MFC suspension), the release lasts longer and is slower. The curve indicates almost 100% caffeine release after 10 h compared to the previous 40 min for the two other samples (15 times longer duration). Its release is thus clearly more progressive without being blocked by the MFC. These results tend to prove that MFC forms a nanoporous network since (i) the caffeine can still be released and (ii) the release is much slower.

In other studies, however, this nanoporous MFC network was most of the time considered as a dense layer (Kolakovic, Peltonen, et al., 2012; Cozzolino et al., 2013). In these previous works, indeed, a model based on the Fickian diffusion was established to understand the diffusion phenomenon of molecules released through a neat MFC films. In our case, when assuming a nanoporous MFC network, and consequently a swelling-controlled system (even for paper substrate), we can suppose that the molecule release is non-Fickian in nature. Frequently, the drug release in a swelling-controlled system is expressed by:

$$\frac{M_t}{M_\infty} = kt^n$$

where is the fractional drug release, is the diffusional exponent, and is the pre-exponential factor (Huang & Brazel, 2001).

Such representation of the caffeine release was performed so that a diffusion pattern can be deduced for each kind of our samples (graph not shown). For the first two paper samples impregnated in the caffeine solution, the molecule release seems to be dominated by the caffeine diffusion ($n = 0.5$). In the case of the paper samples coated with the caffeine/MFC mixture, however, the diffusional exponent was slightly higher than 0.5 presuming a possible anomalous diffusion, i.e. a process involving both the caffeine diffusion and the swelling of the MFC network.

This last point still needs to be confirmed with further analyses to confirm the nanoporosity of the MFC network formed at the paper surface.

It is, indeed, still difficult to exactly determine the diameter of the nanopores formed by the MFC-coating since the paper itself has its own specific porosity. However, considering the MFC layers alone without the paper substrate, we can compare them to a neat MFC film. The porosity of such MFC films has recently been studied and published for TEMPO-oxidized cellulose nanofibrils films (Fukuzumi et al., 2011). A diameter of 0.47 nm was determined using the PALS equipment. As already said, depending on MFC source and treatment, different types of MFC will have different properties and, consequently, will form different types of networks. In our study, we worked with enzymatically pre-treated MFC, which usually have larger fiber diameters than those of the TEMPO-oxidized MFC (ca. 40 nm vs. a few nm), and carry less negative charges. In an additional study about enzymatically

pre-treated MFC films, we measured an average pore diameter of about 5 nm (results not shown). This value was determined by the mercury porosimetry method. A comparison of our value with that of (Fukuzumi et al., 2011) remains inconclusive since the method of determination is different, as well as the manufacturing process of the films. We can, however, consider these two values as an approximation of the range (maximum and minimum) of pore dimensions for comparison with the dimensions of the caffeine molecule. The size of the latter (0.376 nm (Rosenberg & Dan, 2010)) is lower than the porosity of the neat MFC films. However, the caffeine tends to crystallize, and according to (Edwards, Lawson, de Matas, Shields, & York, 1997), the volume of one crystalline pattern of the caffeine hydrate is about 0.98 nm^3. Considering that the pores of the nanoporous network are non-continuous, and approximating each pore to a sphere, the MFC pore volume ($V = 65\ nm^3$) is about 65 times bigger than the volume of the crystal lattice of caffeine in dried state. If caffeine can be released through dried pores, it is obvious that it will be released through wet-state materials, which have larger pores than in dry state. The release of caffeine is thus possible through the nanoporous network. Then, mixing the MFC and the caffeine jointly establish a tighter network due to both the entanglement of nanofibers and the caffeine that can then be trapped in these networks. Thus, the water can less easily open this network, which explains the longer and slower release of caffeine observed in the data. The gradient of the curve is indeed slightly lower than those of the two other samples, but there is also a two-phase phenomenon observed that can be associated with the two other curves. First, the caffeine that is not trapped by the entanglement is released at almost the same speed as that released from the reference sample (Burst effect (Raso et al., 2010)). Then, the "trapped" caffeine is released. However, for the samples impregnated and then coated with MFC, no caffeine has been "trapped" by the entanglement of MFC, and a classical release due to nanoporosity is observed.

These continuous diffusion experiments highlight the ability of MFC to slow down the release of caffeine when it is directly introduced into the MFC network and then coated on paper. This is in accordance with the results of a simultaneous study reported very recently (Kolakovic, Peltonen, et al., 2012), which deals with more concentrated 100% MFC films.

This study established for the first time a model describing the release behavior of drugs introduced into MFC films. They used the Higuchi model Eq. (1) supposing that diffusion is the only release mechanism:

$$Q = A\sqrt{\frac{D_\varepsilon}{\tau}(2\rho - \varepsilon C_s)C_s t} \quad (1)$$

where Q is the amount of drug released, A is the surface area of the film, D is the diffusion coefficient of the drug inside the film, ε is the porosity of the film, is the tortuosity of the film, is the density of the drug material in the film, is the saturated solubility of drug inside the film, and t is time.

This model fitted well to their experiments as they used hydrophobic drugs. Indeed, the Higuchi model is used for monolithic dispersions, i.e. when drug is homogeneously distributed within a matrix former at an initial concentration that exceeds drug solubility in the wetted system (Siepmann & Siepmann, 2011). Moreover, one other assumption of this model is that swelling or dissolution of the polymer carrier is negligible. The authors did not considered the possible swelling of MFC films in contact with water.

Although this approach could be used in our study, the two previous assumptions cannot be applied for our samples. Caffeine was indeed introduced at an initial concentration lower than its solubility. This assumption is the most important, because it provides the basis for the justification of the applied pseudo-steady state approach (basis of Higuchi model) (Siepmann & Peppas, 2012). Then, we cannot assume in our case that swelling of the matrix is negligible. Swelling of paper as well as MFC is a significant phenomenon, as it contributes the molecule release into aqueous medium.

It is also worth noting that this Higuchi model was applied considering the MFC films as a dense material. However, in the case of our study, the paper substrate as well as the MFC layer cannot be considered as dense materials (as explained previously). Indeed, the first studies on this topic demonstrated that the MFC film tends to be a porous substrate (Fukuzumi et al., 2011).

Nevertheless, this hypothesis can in a first step be taken into account to better understand the release mechanism. In this case, mathematical models based on the Fick diffusion can be applied. This was indeed done by a very recent study also dealing with the use of MFC films as carrier and delivery system of lysozyme (Cozzolino et al., 2013).

Although we could assume that the MFC coating is a MFC film in the present study, it seems however sensitive to only consider the Fick diffusion. We indeed tried previously to apply a classical law for swelling-controlled systems. Nevertheless, to our knowledge, this model was only applied for polymeric matrices, excluding cellulosic substrates.

Consequently, other models could be investigated and compared such as the Darcy/Poiseuille mechanisms or the Knudsen diffusion. These models are also developed for porous substrates, but usually consider diffusion of gases or vapors (Spence et al., 2011).

Many parameters have thus to be considered in the case of our substrates such as the presence of amorphous and crystalline parts in MFC, the porosity and the swelling of the MFC coating and of the paper substrates, which make it difficult to establish a fitted model. Modeling of molecules from delivery systems based on paper substrates and MFC is currently in progress and consider the all previous models introduced.

3.4. Intermittent diffusion

The protocol of intermittent diffusion is generally used for the study of drug release in the pharmaceutical field (Cusola, Tabary, Belgacem, & Bras, 2012; Hoang Thi et al., 2010), It allows the determination of the quantity of drug released at the end of an exact period and measures the time taken for the release to occur. This protocol was also established to highlight the positive effect of MFC on the controlled release of caffeine. As described previously, the continuous diffusion was similar for paper samples impregnated in the caffeine solution and paper samples impregnated in caffeine and MFC-coated. Intermittent diffusion experiments will emphasize the prolonged release obtained using MFC.

In contrast to the usual period used (24 h), the protocol was adapted here because the release of the caffeine is more rapid. The measurement of the release was carried out every 10 min, and between each sampling point, the aqueous media was renewed to simulate saliva or blood.

With the replacement of the aqueous media, the equilibrium of the system is shifting toward increased diffusion of caffeine in one direction and the molecules of caffeine are attracted by the new aqueous media, which accelerates their release. The intermittent diffusion is considered to be complete when the measured absorbance of the solution reaches the zero value. The released amount of caffeine is plotted as a function of the number of washing steps (Fig. 7).

In the paper impregnated in the caffeine solution, the release lasts 16 washings and about 90% of the caffeine was released after five washings (Fig. 7). In the two other kinds of samples (papers

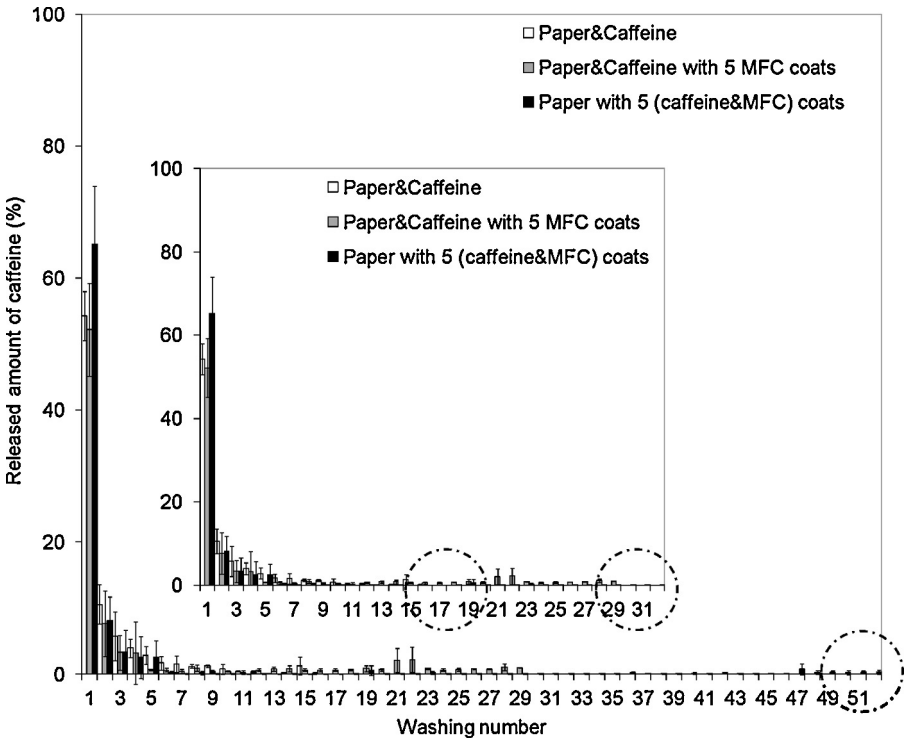

Fig. 7. Intermittent diffusion of caffeine in the case of the three following samples: (1) Paper samples impregnated in the caffeine solution □ [Paper&Caffeine], (2) paper samples impregnated in the caffeine solution and coated with ■ 5 MFC coats [Paper&Caffeine with 5 MFC] and, (3) paper samples coated five times with the mixture caffeine/MFC [Paper with 5 (caffeine&MFC) coats ■]. The graph plots the mass of caffeine released dividing by the total amount of caffeine introduced in paper samples.

impregnated in caffeine and coated with MFC and, papers coated with the mixture caffeine/MFC), the release lasts much longer. Paper samples impregnated in caffeine and MFC-coated released 87% of caffeine introduced during 29 washing steps. Contrary to continuous diffusion experiments, which showed a similar release kinetic for both samples, the intermittent diffusion experiments underline a more controlled and progressive caffeine release thanks to MFC.

The influence of the MFC coating was also highlighted by Fig. 8 representing the cumulative amount of caffeine released as a function of the number of washing step. In comparison with the paper impregnated in the caffeine solution, the samples coated with the MFC released more progressively the caffeine: the proportion of caffeine released between each washing step was indeed smaller than the proportion released by the samples without MFC. Consequently, the caffeine was more progressively released with a higher number of washing steps owing to MFC, as confirmed in Fig. 7. Fig. 8 also displayed the effect of the caffeine gradient. We concluded in Fig. 6 that the caffeine was released following a similar kinetic without and with the MFC coating. The graph (Fig. 8) confirmed this observation: when considering the gradient after the burst effect (i.e. after the first washing step), the gradients of the curves of the samples impregnated in the caffeine and then coated or not with MFC are similar.

In conclusion, the MFC coating did not slow down the release of caffeine, but controlled its release by releasing about 15–20% less than samples without MFC.

Considering the release of samples coated with the mixture caffeine/MFC, the release lasts 52 washings, releasing 88% of caffeine (Fig. 7). Here again, the method consisting in the coating of mixture caffeine/MFC is the most efficient as controlled release system. This confirms the continuous diffusion experiments and supports the hypothesis of a tighter network obtained with the caffeine/MFC mixture. Fig. 8 gathers the conclusions drawn from Figs. 6 and 7: the caffeine/MFC mixture slowed down the release of the caffeine and also released it more progressively. The gradient of the curves (Fig. 8) is indeed constant, and from a certain number of washing steps (9 and 27 for the paper impregnated in the caffeine solution, and the same paper coated with MFC, respectively), the proportion of caffeine released is the smallest.

One explanation for the latter release behavior could be the effect of the coating technique used to apply the MFC suspension. The viscosity and fiber nanoscale dimensions of the MFC suspension have an effect on the quality of MFC coating achieved. However,

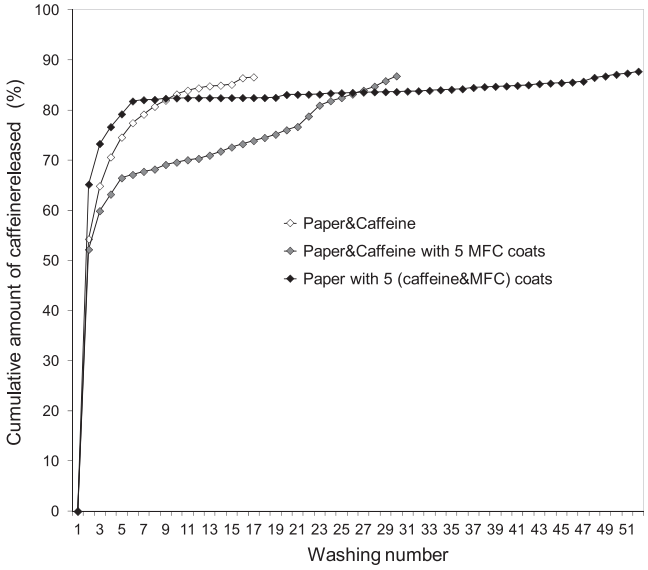

Fig. 8. Cumulative amount of caffeine released (%) as a function of the number of washing step. In white, the paper impregnated in caffeine is represented and compared with the paper impregnated in the caffeine solution and then coated with the MFC (in gray) and with the paper coated with the caffeine/MFC mixture (in black).

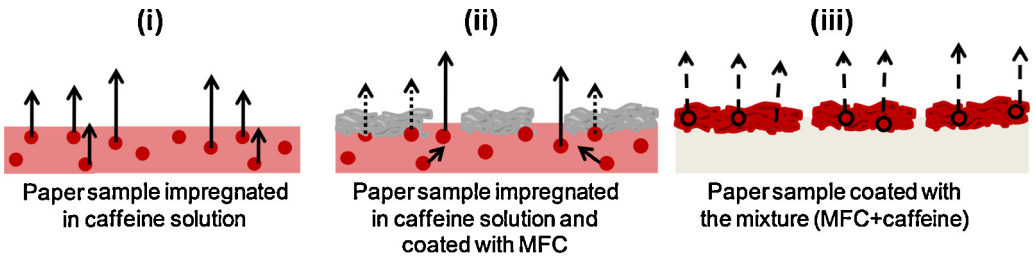

Fig. 9. Scheme of diffusion of caffeine introduced in the three kinds of samples (i), (ii) and (iii). This scheme explains why the paper samples coated with the mixture caffeine/MFC release slower and longer caffeine than the two others.

during the bar-coating process, good homogeneity of the coating is not necessarily realized. Inspecting the SEM images of the coated papers' surfaces, which were obtained in the BSE mode (Fig. 4), we suppose that systems with more than five MFC coats are perfectly coated. However, at a higher magnification, some minute areas that are not entirely covered by the MFC still exist. In general, when paper is impregnated in the caffeine solution and then coated with MFC, the caffeine can be released through (i) the MFC network but also more easily through (ii) these non-covered areas (Fig. 9). By contrast, when the paper is coated with the mixture (caffeine and MFC), the caffeine has no other choice but to diffuse through the MFC network. Moreover, even if the coating is not homogeneous across the entire surface of a sample, the caffeine remains trapped in the MFC network and it will require a longer period to be released.

This study emphasizes the positive effect of employing MFC networks for the controlled release of caffeine. In particular, for paper impregnated with 5 MFC coats, the caffeine was released over a longer time (twice longer duration) than it was through paper without MFC. Furthermore, by mixing MFC with caffeine, the release was prolonged of 23 washing steps, i.e. about 4 h, and caffeine was entirely released over a longer time (15 times longer duration).

These results clearly prove the concept that the nanoporous network formed by the MFC could be useful for the development of a more progressive and controlled release of active molecules when coated on cellulosic materials.

4. Conclusion

The use of MFC with cellulosic materials has recently begun to increase in importance. In this study, MFC is applied to obtain better mechanical properties. Specifically, it improves the air resistance of a base paper significantly, without using components other than the MFC suspension. This biobased material is already a high-performance material, but an added novelty of this study is in the idea of employing the nanoporous network, formed by the MFC during the coating process, to facilitate a controlled release of active molecules. Results obtained here demonstrate for the first time that MFC coatings effectively slow the release of active molecules. Of the two different strategies studied for applying MFC, samples coated with the mixture (caffeine and MFC) showed better results than the samples that were firstly impregnated in the caffeine solution and then coated with MFC. This was due to the entanglement of nanofibers that clearly trapped diffusing species with molecular sizes as small as that of the model compound caffeine. It will be interesting to apply this solution to a final application.

In general, these initial results clearly create further research opportunities. For example, other tests could be performed with an active molecule, to demonstrate a controlled and progressive antimicrobial action for application in the food-packaging field.

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