

# Preparation of cellulose aerogels from ionic liquid solutions for supercritical impregnation of phytol: loading capacity study

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## Abstract

The use of natural polysaccharides is especially attractive to the pharmaceutical industry because of their stability, availability, renewability and low toxicity. In this study, cellulose aerogels obtained from cellulose/ionic liquid solutions were prepared by supercritical drying with surface areas ranged from 154 to 434 m<sup>2</sup> g<sup>-1</sup>, pore volume from 0.3 to 2.4 cm<sup>3</sup> g<sup>-1</sup> and pore diameter from 7.9 to 34 nm. Drug loading capacity was

investigated by impregnating phytol as model compound into the aerogels, using supercritical CO<sub>2</sub> at 100 bar, 40°C and mass ratio of phytol per gram of aerogel 10:1. The quantity of drug present is consistent in each aerogel. The aerogel prepared from 2 wt% cellulose in [Emim][DEP] solution showed the highest loading capacity. The high amount of drug loaded (approx 50% w/w) in the cellulose aerogels prepared from ionic liquid solutions shows their potential uses in the pharmaceutical or medical industry.

*Keywords: Supercritical, Impregnation, Phytol, Aerogel, Cellulose, Ionic liquids*

### **Abbreviations**

[Amim][Cl]: 1-allyl-3-methylimidazolium chloride;

BET: Brunauer-Emmet-Teller;

BJH: Barret-Joyner-Halenda;

[Bmim][Cl]: 1-butyl-3-methylimidazolium chloride;

DSC: differential scanning calorimetry;

[Emim][Ac]: 1-ethyl-3-methylimidazolium acetate;

[Emim][DEP]: 1-ethyl-3-methylimidazolium diethyl phosphate;

[HOemim][Cl]: 1-(2-hydroxyethyl)-3-methylimidazolium chloride;

ILs: ionic liquids;

LiCl/DMAc: lithium chloride/dimethylacetamide;

MCC: microcrystalline cellulose;

NMMO: N-methylmorpholine-N-oxide;

SC-CO<sub>2</sub>: supercritical carbon dioxide;

SEM: scanning electron microscopy

## 1. Introduction

Natural polymers are promising materials for preparing polysaccharide-based aerogels with high surface area (70 – 680 m<sup>2</sup>/g) [1]. Among them, cellulose extensively used for the preparation of aerogels [2] namely cellulose aerogels [3-7]. Different applications of cellulose aerogels have been proposed: as carriers of bioactive compounds [8], for protein adsorption [9], oil absorption [4], lightweight shielding material [10] or as food additives [11]. In general, their applications depend on the material properties which can vary with the type of biomass, IL and drying technique. The production of cellulose-based aerogels consists of three main steps:

- 1) Dissolving cellulose in non-derivatizing solvents such as lithium chloride/dimethylacetamide (LiCl/DMAc), *N*-methylmorpholine-*N*-oxide (NMMO) or ionic liquids (ILs), among other solvents. ILs are a group of salts that are fluid below or around 100°C. An important advantage of working with ILs is their low vapor pressure: ILs do not evaporate like organic solvents. The most studied cations in cellulose processing are those derived from imidazolium. ILs with alkylmethylimidazolium-based cations combined with chloride, acetate and phosphate anions are known to be good solvents of cellulose [12-17]. There are a number of works in which cellulose aerogels are prepared from ILs. Some works include the study of the different preparation parameters (biopolymer concentration, dissolution time, coagulation temperature) of the cellulose solution and coagulation process on the properties of these aerogels [18, 19].

- 2) The second step in the preparation of the aerogel is the formation of a gel. A cellulose hydrogel can be obtained by soaking homogeneous mixtures of cellulose with ionic liquid into water [20] to cause the coagulation of cellulose. If the solution is soaked into an alcohol (e.g. ethanol) the gel obtained is known as alcogel. The morphology of coagulated microcrystalline cellulose (MCC) in water is similar to the morphology in ethanol as showed by FTIR spectra of regenerated cellulose from the IL 1-ethyl-3-methylimidazolium acetate ([Emim][Ac]) [21].
- 3) After the formation of the hydrogel/alcogel the last step is the removal of the coagulation solvent by drying. Different drying methods can be used in order to obtain materials with different properties for different applications. These methods include air drying, oven drying, nitrogen freeze drying, regular freeze drying, reduced pressure and supercritical carbon dioxide (SC-CO<sub>2</sub>) drying. To obtain cellulose as aerogels, freeze drying and SC-CO<sub>2</sub> drying have been used. As water is not compatible with CO<sub>2</sub>, the aerogel's pore structure can collapse, thus the water present in the coagulation solvent media has to be exchanged with an alcohol (usually ethanol) prior drying. To avoid damages to the hydrogel, water replacement is usually performed stepwise using water-ethanol solutions of increasing ethanol concentration.

In this work the influence of different operational parameters on the properties of cellulose aerogels produced using ILs is studied: various alkylmethylimidazolium-based ILs are employed, at low dissolution temperature, and with several cellulose concentrations. In the second part of this work, an impregnation study was performed to determine the loading capacity of the cellulose aerogels with the bioactive compound phytol. Phytol is an acyclic diterpene alcohol, present in green plants and, which is claimed to have antibacterial and anti-inflammatory properties [22-24]. Recently an

investigation on SC impregnation of phytol in silica and alginate aerogels resulted in a method to obtain higher loading capacity without the use of organic solvent [25]. The method consists on the adsorption of the active compound to it into a SC-CO<sub>2</sub> saturated with the active compound. The impregnation of cellulose aerogel with phytol has not been described in the literature, but a study has been reported on cellulose acetate aerogels loading capacity with thymol which showed morphology changes with high impregnation yields [26]. In this second part, the cellulose aerogels morphology was analysed before and after the SC impregnation with phytol for possible swelling and/or plasticizing effect of SC-CO<sub>2</sub> and excess of solute on the biopolymer.

## **2. Experimental section**

### **2.1 Materials**

Microcrystalline cellulose was supplied by Alfa Aesar and dried for 5h at 60°C under vacuum before the dissolution. Ionic liquids 1-butyl-3-methylimidazolium chloride ([Bmim][Cl]) with purity >99 % and moisture of 0.140 wt%, 1-(2-hydroxyethyl)-3-methylimidazolium chloride ([HOemim][Cl]) with purity of >99 % and moisture of 0.214 wt%, 1-ethyl-3-methylimidazolium acetate ([Emim][Ac]) with purity of >95% and moisture of 0.385 wt% and 1-ethyl-3-methylimidazolium diethyl phosphate ([Emim][DEP]) with purity of 98% and moisture of 0.067 wt%, were provided by Iolitec (Germany). 1-allyl-3-methylimidazolium chloride ([Amim][Cl]) was purchased from Alfa Aesar with purity of 98% and moisture content of 0.247 wt%. The water content was measured by Karl-Fischer titration (Mettler Toledo C20 Coulometric KF titrator).

### **2.2 Methods**

The complete procedure for aerogels preparation is summarized in Fig. 1. Each step is described in following sections.

### 2.2.1 Preparation of cellulose alcogel

The cellulose solution was prepared by dissolving MCC in IL at 80°C. Samples were handled under N<sub>2</sub> atmosphere to avoid water absorption. After heating and stirring a clear solution was obtained indicating the total dissolution of cellulose. Then the cellulose/IL solution was transferred to cylindrical moulds (15 mm of diameter and 3 mm high) and washed with an aqueous solution of ethanol at room temperature to extract the IL. The volume of the solution employed was 10 times higher than the IL volume in order to remove the most of it. As a sudden change of the solvent composition can damage the gel structure, the gels were successively soaked in solutions of increasing ethanol concentration: 10, 30, 50, 90 and 100%, in 2 h cycles. The exchanges with 100% ethanol were done twice to ensure that there is no water residuals left in the alcogel.

### 2.2.2 Supercritical drying

Cellulose aerogels were produced by SC-CO<sub>2</sub> drying at 120 ± 5 bar and 40°C. The procedure employed is similar to the method described elsewhere [25, 27] where the drying was done in 3 cycles of CO<sub>2</sub> flow, each one lasting 2 h. At the end of each cycle, the extracted ethanol was collected and fresh CO<sub>2</sub> was introduced. After completing the total period of 6 h of SC drying, the system was depressurized at rate of 2 bar/min to avoid shrinkage of cellulose aerogels.

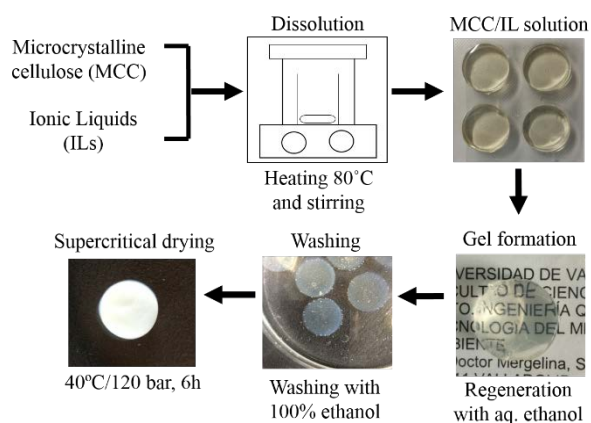


Fig. 1 Scheme of cellulose aerogel preparation in ionic liquid and supercritical drying

### 2.2.3 Supercritical Impregnation

The impregnation study was performed to determine the loading capacity of the cellulose aerogels with bioactive compounds. A 70 mL stainless steel high pressure autoclave with a maximum working pressure of 150 bar was used. A known mass of pure phytol with respect to mass of aerogel was placed at the bottom of the autoclave. Meanwhile a known mass of dried cellulose aerogels was wrapped in metal filters and separated from the phytol by lifting them up from the bottom of the autoclave applying a cylindrical metal platform. The autoclave was heated to 40°C and pressurized with CO<sub>2</sub> to 100 bar at rate of 2 bar/min. The pressure was maintained for 24h to ensure that adsorption equilibrium was reached. Magnetic stirrer was employed to additionally enhance the dissolution of phytol. After that time, the system was slowly depressurized at a rate of 2 bar/min to avoid aerogels shrinkage or collapse of the mesoporous structure of the aerogels. The impregnated aerogels were recovered from the autoclave and the loading of compounds was determined gravimetrically and calculated as indicated in the following equation:

$$\frac{w_a (g) - w_b (g)}{w_b (g)} \times 100\%$$

where  $w_a$  is the mass of cellulose aerogels after impregnation,  $w_b$  is the mass of cellulose aerogels before impregnation (g). This is a common method to determine the weight of such amounts of non volatile compound impregnated in aerogels. Thus, the measurement is precise as phytol does not evaporate after impregnation and before the weight was recorded the impregnated aerogels were placed in a dessicator to let the CO<sub>2</sub> to be properly release from the pores and avoid absorbing moisture from the ambient. The measurement was repeated three times and reported as means  $\pm$ SD.

### 2.3 Characterization

Textural properties (surface area, pore volume, pore size) of aerogels were determined by gas N<sub>2</sub> adsorption-desorption analysis. All experiments were carried out at -196°C and prior to the analysis the samples were degassed under vacuum at 70°C for 660 min. The samples from experiments number 1, 2, 4 and 5 were analyzed using a Micrometrics ASAP 2020MP instrument and all the other samples with an ASAP 2420 V2.09 instrument. The method applied for measuring the textural properties of the aerogels was the same regardless the instrument used. The specific surface areas were calculated from the Brunauer-Emmet-Teller (BET) equation and the average mesopore diameter distributions were determined from desorption isotherms by the Barret-Joyner-Halenda (BJH) method.

The melting point was measured with a differential scanning calorimetry (DSC) apparatus (DSC 822e Mettler Toledo SAE) equipped with a ceramic sensor FSR5, under a stream of N<sub>2</sub> at a flow rate of 50 cc min<sup>-1</sup>. The analysis was carried out over a temperature range of 25 to 300°C, at a heating rate of 10°C min<sup>-1</sup>.

The surface morphology of the cellulose aerogels was examined by scanning electron microscopy (SEM) using a SEM JEOL JSM 820 equipment. The samples were splattered-coated with gold layer prior to the scanning at voltage of 2-4kV.

The FTIR spectra were recorded on a Fourier Transform infrared instrument (Bruker Platinum-ATR) equipped with software of OPUS Optik GmbH in the range from 400 to 4400 cm<sup>-1</sup> of wavelength.

Elementary analysis was performed in the University of Burgos (Spain) with a EA Flash 200 Elementary Analyzer (Thermo Fischer Scientific), using a TCD detector. The temperature of the combustion oven was 900°C with an oxygen flow of 250 mL/min.



Helium was used as a carrier with a flow of 140 mL/min, and sulfanilamide was used as a standard. The samples were prepared by weighting amounts between 1000 and 2000 mg using a microbalance Mettler Toledo XP6.

### 3. Results and Discussion

#### 3.1 Textural and morphological properties of cellulose aerogels

Cellulose aerogels were prepared from cellulose/IL solutions with MCC concentration between 1 and 4 wt% in five alkylmethylimidazolium-based ILs. The results of surface area, pore volume and pore size are presented in Table 1.

**Table 1** Experimental data of cellulose aerogels characterization: surface area ( $\text{m}^2 \text{g}^{-1}$ ), pore volume ( $\text{cm}^3 \text{g}^{-1}$ ) and average pore diameter (nm) obtained from ionic solutions after supercritical drying

Exp. No.	Ionic liquid	wt% <sup>a</sup>	Surface area ( $\text{m}^2 \text{g}^{-1}$ )	Pore volume ( $\text{cm}^3 \text{g}^{-1}$ )	Average pore diameter (nm)
1	[Amim][Cl]	1	434	0.7	8.7
2	[Amim][Cl]	2	426	0.8	9.4
3	[Amim][Cl]	4	278	2.4	34
4	[Bmim][Cl]	2	428	1.1	11.7
5	[HOemim][Cl] <sup>b</sup>	2	154	0.3	7.9
6	[Emim][Ac]	2	282	1.9	27

7	[Emim][DEP]	2	326	1.4	22
8	[Emim][DEP] <sup>c</sup>	2	280	1.9	28
<sup>a</sup> Concentration of cellulose in ionic liquid by weight; <sup>b</sup> Cellulose dissolution at 100°C; <sup>c</sup> Cellulose dissolution at 40°C					

154 - 434 m<sup>2</sup> g<sup>-1</sup> is the range of surface area obtained from the characterization of the cellulose aerogels prepared with cellulose/IL solutions. Similar surface area range have been reported for other cellulose solutions, e.g. 200 - 300 m<sup>2</sup> g<sup>-1</sup> in NaOH aqueous solutions at lower temperatures [28] and 100 - 400 m<sup>2</sup> g<sup>-1</sup> in *N*-methyl-morpholine-*N*-oxide (NMMO) [29]. In the latter study, it was found that the internal surface area was mainly influenced by choosing the appropriate regeneration and critical drying conditions. It could be the case where, slightly lower surface areas (315 ± 35 m<sup>2</sup>g<sup>-1</sup>) have been reported for cellulose/[Amim][Cl] solutions in the range of concentration 2 – 3 wt%, after coagulation with methanol and SC drying at 200 bar [30]. The experiments (Table 1) were performed with the same SC drying conditions, resulting in cellulose aerogels with similar properties with the exception of the one prepared from the solution cellulose/[HOemim][Cl] which presented a significantly lower surface area and pore volume. The surface area in this experiment could have been affected by the low ability of [HOemim][Cl] to dissolve MCC without previous pretreatment [31]. Hydroxyl group in [HOemim][Cl] alkyl side chain makes it a lower hydrogen-bond basicity IL [32] and thus lowers its cellulose solvation capacity. In addition the high viscosity of this IL hinders the complete dissolution of cellulose. From Table 1 it is observed that aerogels with higher surface area are produced with [Amim][Cl] and [Bmim][Cl], being the first one easier to handle due to its lower viscosity and melting point [33, 34]. On the other

hand, aerogels prepared from low viscosity IL, [Emim][DEP] showed high surface area as well even at low dissolution temperature of 40°C.

Another important aspect from these experiments is the shrinkage. After SC drying shrinkage was observed (Table 2) in all aerogels, being lower for the highest concentration (4 wt%).

Table 2 Experimental average aerogel diameter ( $d_A$ ) after coagulation and supercritical drying

Ionic liquid	wt% <sup>a</sup>	$d_A$ (mm)
[Amim][Cl]	1	12
[Amim][Cl]	2	13
[Amim][Cl]	4	14
[Emim][DEP]	2	13
[Emim][DEP] <sup>b</sup>	2	13
[Emim][Ac]	2	13
<sup>a</sup> Cellulose concentration in ionic liquid, <sup>b</sup> Cellulose dissolution at 40°C		

Different factors can affect the aerogels shrinkage. It is known that for polysaccharide gels, lower gelation temperature increases the shrinkage after solvent exchange and SC drying [1] and higher biopolymer concentration leads to lower shrinkage [7, 35]. Although SC drying maintains the pore structure, some shrinkage is always present.

As shown in Fig. 2 the alcogel from cellulose/IL is transparent. After SC drying all the aerogels were sticky (due to static electricity) with a white opaque appearance.



Fig. 2 Cellulose alcogel and aerogel prepared from cellulose/[Amim][Cl] solution (1, 2, 4 wt%)

In Fig. 3 DSC of a cellulose aerogel prepared in [Amim][Cl] and the DSC of pure [Amim][Cl] are compared. A peak at 55°C corresponds to the melting point of the IL. The DSC of the aerogel (solid line) does not have this peak point of [Amim][Cl], nevertheless an elemental analysis revealed  $0.9\pm 0.1\%$  of N in the cellulose aerogel (2 wt% MCC/IL) and  $0.8\pm 0.3\%$  of N (1 wt% MCC/IL). Thereby, contamination of aerogels with IL produced by this method is a possibility. Additionally, a small weight loss below 100°C is observed, which could be due to evaporation of absorbed water. Furthermore, the endothermic peak observed at 310°C corresponds to the decomposition of cellulose [36].

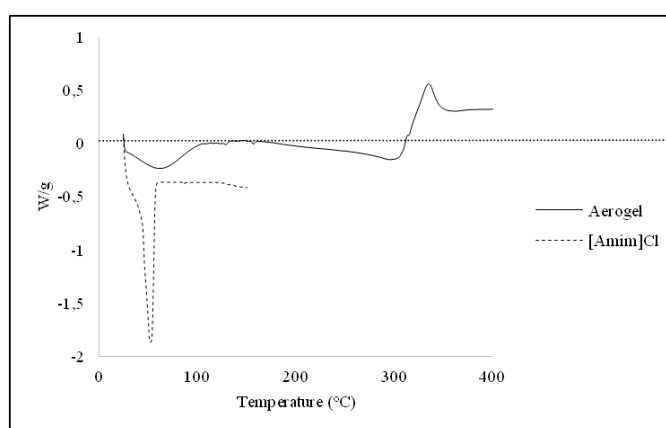


Fig. 3 Comparison of DSC between cellulose aerogel and pure ionic liquid

### 3.2 Supercritical impregnation onto cellulose aerogels

Table 3 Loading capacity of cellulose aerogels impregnated with phytol by supercritical CO<sub>2</sub>

Aerogels regenerated: Ionic liquid / wt% cellulose	Specific surface area <sup>a</sup> (m <sup>2</sup> /g)	Pore volume <sup>a</sup> (cm <sup>3</sup> /g)	Pore diameter <sup>a</sup> (nm)	Loading (wt%)	Reference
[Amim][Cl] / 2	426	0.8	9.4	48.7±0.5	This work
[Amim][Cl] / 4	278	2.4	34	52.3±0.9	This work
[Emim][DEP]/2	326	1.4	22	55.4±0.3	This work
Silica aerogels	882	2.9	12.9	30.1±0.6	[24]
Alginate aerogels	126	0.8	25.5	22.1±0.2	[24]
<sup>a</sup> Textural properties before the supercritical impregnation					

Impregnation of phytol as model bioactive compound was performed to determine the loading capacity of the produced cellulose aerogels. The impregnation was performed using SC-CO<sub>2</sub> at 100 bar and 40°C during 24 h. The amount of phytol employed for impregnation is based on its solubility in SC-CO<sub>2</sub> reported by Lazo [37]. The mass ratio of cellulose aerogel/phytol was kept at 0.1 for all the series of phytol impregnation, in order to ensure that excess phytol is present in order to be not limited by this factor. It was shown that increasing the cellulose concentration in IL for aerogel preparation resulted in a decrease of the specific surface area and increase in aerogel pore size and

pore volume. However, the loading capacity of the aerogels was higher with the increase of the cellulose concentration for the same IL. Higher phytol loading of  $52.3 \pm 0.9$  wt% in aerogel produced from 4 wt% cellulose solution in [Amim][Cl] could be due to the larger pore volume and size, in comparison to the one produced in 2 wt% cellulose solution in [Amim][Cl], which enhance the penetration of SC-CO<sub>2</sub> into the inner parts of the cellulose aerogels. On the other hand, aerogels made from 2 wt% cellulose solution in [Emim][DEP], exhibited slightly higher loading capacity with  $55.4 \pm 0.3$  wt% of phytol compared to the loading in cellulose aerogels regenerated from 2 and 4 wt% cellulose solutions in [Amim][Cl]. Although the latter has the highest surface area, its lower pore volume and pore size reduced the overall drug load capacity. This indicates that pore volume and pore size are the properties with a stronger influence on the compound loading into aerogels by SC-CO<sub>2</sub> impregnation. Furthermore, lower phytol loading content was achieved in the aerogel produced from 2 wt% cellulose solution in [Amim][Cl] than in the one generated from 2 wt% cellulose solution in [Emim][DEP] with a lower surface area. Nevertheless the behavior of these effects needs further investigation for different polymer or biopolymer materials. The reason for the variation of loading capacity for different regenerated cellulose by IL is still unknown and to the best of our knowledge there is no literature on these aspects. In contrast, Mustapa and co-workers [25] performed SC impregnation of phytol at 200 bar and 40°C, obtaining loading of  $20.1 \pm 0.2$  to  $30.1 \pm 0.6$  wt% for alginate and silica aerogels, respectively. The phytol loading in silica and alginate aerogel are lower even though the impregnation was performed at higher pressure and in the case of silica aerogel pore volume and pore size are higher than of cellulose ones. Thus, higher loading in cellulose aerogel could be due to different biopolymer materials used that lead to different affinity of the compound for the materials.

Regarding characterization, all the cellulose aerogels produced in this work show a similar IR spectrum after impregnation with phytol, indicating that the phytol could have similar interaction (formation of hydrogen-bonding) with the cellulose material regardless the type of IL used in the regeneration process. The IR spectrum of the non- and impregnated aerogels regenerated from 2 wt% cellulose solution in [Amim][Cl] are presented in Fig. 4. The appearance of the vibration peak at  $2900\text{ cm}^{-1}$  that corresponds to the  $-\text{CH}$  groups and the increment of the absorbance intensity at  $1380$ ,  $1440$  and  $3400\text{ cm}^{-1}$  due to the vibration band of C-H, C-C and  $-\text{OH}$ , respectively indicates the presence of phytol loaded in the cellulose aerogels.

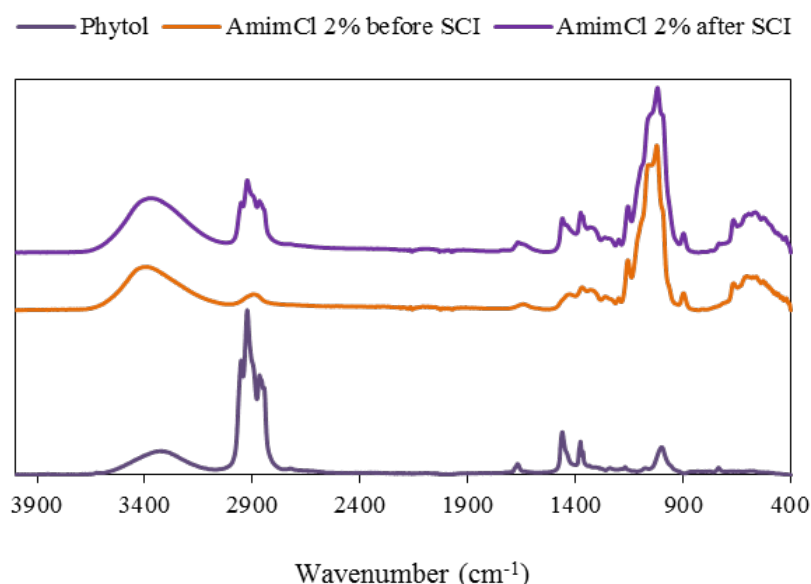


Fig. 4 FTIR spectrum of non- and impregnated cellulose aerogels with phytol by supercritical CO<sub>2</sub> at 100 bar and 40°C

Furthermore, the morphology of cellulose fibrils was maintained indicating that the high impregnation yield of phytol (range from  $48.7 \pm 0.5$  to  $55.4 \pm 0.3$  wt%) by SC-CO<sub>2</sub> did not change or swell the surface morphology of the biopolymer as observed from SEM images. An image of a sample impregnated with phytol is presented in Fig. 5 SEM images. The SEM analyses the cross-sectional images of the samples. it is noticed that

the pore morphology became coarser after the impregnation with phytol. In contrast a previous work [28] in which cellulose acetate with thymol was impregnated by SC-CO<sub>2</sub> at 100 bar and 35 °C in 24h, it was demonstrated that after impregnation the morphology of the biopolymer significantly changed by swelling and melting, especially when the impregnation yield was increased, due to the impact of thymol on the structure of cellulose acetate.

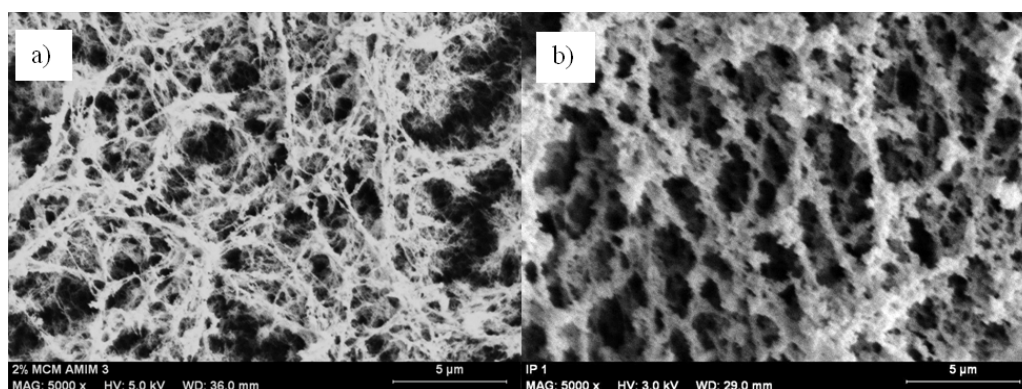


Fig. 5 SEM images of the a) non- and b) impregnated cellulose aerogels regenerated from 2% cellulose solution in [Amim][Cl]

#### 4. Conclusions

Cellulose aerogels have been prepared from high and low melting point ILs. Despite the lower viscosities and melting points of acetate or phosphate anions-based ILs, higher surface areas were obtained with high melting point ILs (chloride anion). The properties of these types of ILs and the solvent exchange method may have contributed to a small percentage of salt in the aerogels. Selected aerogels were loaded with phytol as a model compound, obtaining loads of approximately 50 wt%. These values are much higher than loadings in phytol of SiO<sub>2</sub> or alginate aerogels achieved in previous works. The drug loading capacity of the cellulose aerogels was positively influenced by the pore size and volume. Results of IR spectra showed that the cellulose aerogels regenerated from



different IL has similar interaction with the phytol model compound and SEM showed no changes in the morphology of the aerogels after SC impregnation.

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