



Preparation of pH sensitive poly(vinylidene fluoride) porous membranes by grafting of acrylic acid assisted by supercritical carbon dioxide

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ABSTRACT

Free radical grafting of acrylic acid (AA) on poly(vinylidene fluoride) (PVDF) porous membranes was studied at 65 °C using supercritical carbon dioxide (scCO₂) as a solvent and delivery agent. The process was initiated by the thermal decomposition of benzoylperoxide (BPO).

Spectroscopic analyses confirmed the presence of poly(AA) chains linked to treated membranes. The mass fraction of grafted AA increased with grafting time and BPO concentration while it decreased when the density of the fluid phase was enhanced. A not-monotonic trend was obtained when the effect of the initial AA concentration was studied. The grafting process was accompanied by a reduction of the crystallinity of the PVDF matrix.

Flow measurements and caffeine release experiments performed using PVDF membranes with proper grafting degree exhibited a pH dependent behaviour.

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1. Introduction

Poly(vinylidene fluoride) (PVDF) is known for its excellent mechanical and physicochemical properties. Moreover, because of its chemical inertness and good processability, PVDF has been extensively investigated for the preparation of membranes [1–3]. However their utilization for biomedical applications, such as selective permeation and controlled drug release and delivery, is limited to some extent by the hydrophobic nature of the polymer. Moreover, for these applications, it could be important to impart the matrix a stimuli-responsive behaviour allowing reversible changes in their properties in response to some environmental stimuli, such as temperature and pH [4–11].

Several approaches have been developed to endow the conventional hydrophobic membranes with hydrophilic properties and pH-sensitivity [12–18]. An interesting method to reach this goal was based on the preactivation of the fluoropolymer, dissolved in N-methylpyrrolidone (NMP) or N,N-dimethylformamide, by ozone treatment. After precipitation and drying, the PVDF matrix containing peroxide groups is redissolved in the solvent and reacted in homogeneous phase with acrylic acid (AA) or 4-vinylpyridine [15–17]. A similar approach in the presence of 1-phenylethyl

dithiobenzoate as chain transfer agent was also used to graft living poly(acrylic acid) on PVDF [18]. These methods are anyway based on the utilization of low-volatile toxic solvents that must be thoroughly removed from the polymer before its utilization in biomedical applications. A different tested approach was the activation of PVDF by ionizing or UV-vis radiation and subsequent modification of the matrix by heterogeneous grafting of AA in bulk or from aqueous solutions [19–27]. By this route purification concerns have been decreased and are mainly related to the removal of unreacted monomer, anyway non-uniform grafting levels can be obtained.

Supercritical carbon dioxide (scCO₂) has been already adopted to perform modification of polymers by grafting of several vinyl monomers [28–39]. By this choice one would take benefit of scCO₂ peculiar properties, i.e. biocompatibility, easy recovery from the processed polymer by depressurization, inertness to chain transfer reaction and good swelling capability towards amorphous polymers that imparts fast mass transfer rate of low molecular weight species inside the CO₂ plasticized polymer [40–43]. Moreover, initiator efficiency is improved in scCO₂ because solvent-solute cage effects are negligible relative to liquid solvents [44–46]. Furthermore, CO₂ can be used also for the purification of the matrix at the end of the grafting process by supercritical extraction of unreacted species [47].

Last but not least it must be underlined that the modified PVDF matrix is a specialty polymer for a market segment that

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is characterized by small volume of production and high added value of the product thus creating favourable conditions for the industrial adoption of an unconventional technology such that based on the utilization of dense gases.

In this work we have studied the preparation of hydrophilic and pH-sensitive PVDF membranes by free radical grafting of the AA monomer using scCO₂ as solvent and swelling agent and benzoyl peroxide as thermal initiator at mild temperature condition. The effect of selected operative parameters such as the grafting time, the initial concentration of monomer and initiator and the density of the fluid phase was investigated. The modified membranes (PVDF-g-PAA) were also characterized in terms of their flow behaviour at different pH levels and for what concern their ability to modify the dissolution rate of caffeine, adopted as a model bioactive compound, in aqueous phase in response to modifications of environmental pH.

2. Experimental

2.1. Materials

Durapore PVDF hydrophobic membranes were used as model substrates. They have an average pore size of 0.22 μm, a diameter of 47 mm, a thickness of about 100 μm and 75% (vol/vol) porosity. Acrylic acid (AA) 99% anhydrous (with 200 ppm of monomethyl ether hydroquinone as inhibitor) and ethanol (ACS, 99.8%) were purchased from Aldrich; CO₂ was Air Liquide 99.998 pure. All these chemicals were used without further purification. Benzoyl peroxide (BPO), purchased from Aldrich (75% remainder water, USP grade), was recrystallized from methanol (HPLC grade, Riedel-de Haën).

2.2. Apparatus for the study of phase behaviour of the CO₂/AA/BPO system

In order to study qualitatively the phase behaviour of the ternary mixture of CO₂, acrylic acid and organic peroxide in the adopted reaction conditions, a three ports high pressure AISI 316 view cell equipped with two 1.25 in. diameter sapphire windows with 180° orientation (Thar SCF, nominal volume of 50 mL) was used. The fluid mixture was stirred by a Teflon coated magnetic bar. The reactor was fitted with a pressure transducer (Barksdale UPA 3, estimated accuracy by calibration with a high-precision manometer of ±0.05 MPa) and a Pt100 thermal sensor, with an accuracy of ±0.3 °C both mounted on the same port. One other port of the vessel was fitted with a Swagelock male connector closed by a cap to allow the loading of condensed components. The last opening was fitted with a high pressure needle valve to convey CO₂. The reactor temperature was kept constant by a heating mantle controlled by a PID electronic controller (Eurotherm).

After addition of the selected amounts of AA and BPO, the system was carefully washed with gaseous carbon dioxide and then the proper quantity of CO₂ was delivered by an ISCO model 500D syringe pump up to reach the selected nominal density. The total amount of CO₂ introduced was measured weighing the vessel with an electronic scale (Mettler PM34 max 30 kg, precision 0.1 g). Then the cell was carefully covered with the heating mantle and it was subjected to a thermal cycle consisting of a progression of stepwise increase of temperature over the transition temperature, and a similar gradual cooling down to room temperature, both achieved with variation of temperature having amplitude of 5 °C. After each step the attainment of equilibrium was waited for the acquisition of the pressure and temperature values inside the cell. Blank experiments with pure CO₂ demonstrated that the equilibrium condition is reached within a few minutes from the thermal perturbation.

2.3. Grafting procedure

The experiments were carried out in an AISI 316 fixed volume (27 mL in the completely assembled set-up) batch reactor, stirred by a magnetic bar and heated by an electronically controlled electric tape. The proper amounts of AA and initiator were charged in the reactor together with the PVDF pristine membrane, the vessel was then purged by a controlled flow rate of low pressure CO₂ maintained for at least 10 min to remove air. After sealing the reactor, CO₂ was added at room temperature by using an ISCO syringe pump. The total amount introduced was measured weighing the vessel with an electronic scale (Sartorius LP 8200S, precision 0.01 g). The vessel was then inserted in the control system and heated at the reaction temperature (65 °C). The time interval to reach the operative temperature was roughly 20 min in each run. At the end of the reaction the reactor was cooled in an ice bath to room temperature and slowly depressurized. The reactor was then opened to recover the membrane. It was firstly washed at room temperature with ethanol for 1 h to remove unreacted monomer and initiator and after at 90 °C with the same solvent for 2 h in a closed stainless steel vessel to remove poly(AA) homopolymer. Then the treated membrane was dried under vacuum at 40 °C overnight and weighed. Such procedure was repeated until constant weight of the sample was obtained. Constant weight was always reached after the second washing.

At this point it was assumed that unreacted species and poly(AA) homopolymer were completely removed. The amount of grafted PAA, termed degree of grafting (DG), was gravimetrically estimated using an electronic scale Sartorius CP 225 D, accuracy 0.01 mg, with the following equation:

$$DG (\%) = \frac{W_1 - W_0}{W_0} 100 \quad (1)$$

where W_0 stands for the weight of virgin PVDF membrane and W_1 is the weight of modified membrane after aforementioned washing procedure.

2.4. Grafted membranes characterization

Horizontal attenuated total reflectance infrared (HATR-FTIR) spectra of the membranes were obtained from a Perkin-Elmer Spectrum 2000 Explorer FTIR. Each spectrum was collect by cumulating 6 scans at a resolution of 1 cm⁻¹ using a near-IR fast recovery deuterated triglycine sulphate detector.

Selected samples of PVDF membranes were kindly analyzed by ¹H NMR and ¹⁹F NMR spectroscopy in the NMR laboratory of Solvay-Solexis Bollate. Analyses were performed in deuterated DMSO at 50 °C using a Varian S 500 instrument working at 470.291 MHz for fluorine. H and F chemical shifts were referred to TMS and CFC1₃ used as external standards, respectively.

The surface morphology of the matrixes was studied by the scanning electron microscopy (SEM), using a Philips scanning electron microscope. The membranes were putted on the sample stubs by means of double-sided adhesive tapes and then were sputter-coated with gold to a thickness of about 200 Å.

Calorimetric analyses of copolymers were performed with a PerkinElmer Jade-DSC calorimeter. A pre-weighed amount of the copolymer (c.a. 3–5 mg) was loaded into an aluminium pan. Then, the sample pan was sealed with an aluminium lid pressed slightly using a metal plunger and placed in the differential scanning calorimeter (DSC) holder under a N₂ flow of 20 mL/min. The sample was heated twice from 18 °C up to 220 °C with a heating rate of 10 °C/min. The cooling rate between the two scans was 10 °C/min too. Melting enthalpies, Δ*H*_m, were determined from the peak areas and melting temperatures, *T*_m, at the maximum of the peaks. The

percent of crystallinity of the grafted and pristine membranes, χ_c , was then calculated from melting enthalpies values by using:

$$\chi_c = \frac{\Delta H_m \times 100}{\Delta H_{100\% \text{ crystalline}}} \quad (2)$$

where $\Delta H_{100\% \text{ crystalline}}$ is the heat of fusion of pure crystalline PVDF, which is reported to be 104.6 J/g [48]. It seems interesting to highlight that the grafted PAA chains do not contribute to sample crystallinity so that in principle a reduction of χ_c could be induced also by sample dilution with grafted PAA. This effect could justify a decrease of crystallinity of 6% when the DG is 15% (w/w). To take into account this effect all crystallinity values reported in this work have been referred to the effective amount of PVDF (M_{PVDF}) in the polymer sample (M_{sample}) estimated according to Eq. (3):

$$M_{\text{PVDF}} = \frac{M_{\text{sample}}}{1 + (\text{DG}/100)} \quad (3)$$

The thermal stability of the copolymers was studied by thermogravimetric analysis (TGA). The samples were heated from 30 °C to 700 °C at a rate of 10 °C/min under a nitrogen atmosphere using a Perkin-Elmer STA 6000 simultaneous thermal analyzer.

The water permeability of grafted membranes was investigated by measuring the flux through the membranes of aqueous solutions at different values of pH. Before each measure the membrane was soaked in an aqueous HCl solution of predetermined pH value for about 30 min. Then it was inserted in a vacuum filtration unit and a known volume of aqueous HCl solution of the same pH value was added to the filtration system. The ionic strength of the solution was adjusted to 0.1 mol/L by addition of sodium chloride. The flux was calculated from the volume of solution permeated per unit time and unit area of the membrane surface.

The release kinetics of caffeine from PVDF-g-PAA membranes was studied in vitro at 37 ± 0.3 °C. Several bags of modified polymer were prepared by cutting slices that were a quarter of a modified membrane and that were closed on the cut edges by hot pressure welding. A weighed amount of the drug (3 mg) was loaded in the bag through the open side that was then closed with the same method.

The bags were immersed in aqueous buffer solution prepared by mixing suitable amounts of sodium chloride, sodium phosphate dibasic and potassium phosphate monobasic (pH = 6.8) and sodium chloride, potassium phosphate monobasic and phosphoric acid (pH = 2.5) in water. The solution was stirred by a magnetic stir bar and the drug release was monitored using a PC controlled Avantes fiber optic UV-vis spectrophotometer equipped with a DH2000 light source and a reflection dip probe (optical path 1 cm) that was immersed in the aqueous phase. All connections between components and optical fibers were made with SMA 905 connectors. The signal from each spectrometer was recorded as transmitted intensity and converted in absorbance spectra by the spectrometer manufacturer's software (AVA-Soft version 5, Avantes) running on the PC, using a previously recorded blank spectrum of the buffer solution at the typical operating conditions. Dissolution curves were recorded in terms of the absorbance at 272 nm without any calibration for the absolute amount of dissolved compound.

3. Results and discussion

3.1. Phase behaviour of the CO₂/AA/BPO system

Solubility of acrylic acid in supercritical carbon dioxide is quite high. Up to 40% (w/w) concentration of the vinyl monomer can be dissolved in CO₂ at 65 °C and pressure higher than 13 MPa [49].

The phase behaviour of the CO₂/AA/BPO mixture was investigated at 0.6M concentration of AA and with the highest BPO concentration used to perform grafting reactions, at the lowest

Table 1

Recipes adopted to perform preliminary tests to study the effect of scCO₂, BPO and AA on PVDF membranes.

Entry	[BPO], mM	[AA], M	$\rho_{\text{CO}_2}^a$, g/mL	DC ^b , % w/w
1	0	0	0.53	0
2	0.24	0	0.51	0
3	0.50	0.20	0.52	14.8

T = 65 °C, soaking or reaction time 16 h.

^a CO₂ density,

^b Degree of grafting.

value of investigated CO₂ density, i.e. 0.5 g/mL, by visual observation in a view cell. We observed that, at temperature higher than the critical one of CO₂, the system was initially constituted by two fluid phases that merged in a single one at temperature between 60 and 65 °C with the corresponding pressure changing from 12 to 13 MPa in agreement with data reported in the literature [38]. On the other hand to dissolve low molecular weight PVDF ($M_n = 3031$ g mol⁻¹, $PDI = 3.65$) in scCO₂ pressure of 150 MPa and temperature of 140 °C were necessary [50]. This means that under operative conditions adopted to perform grafting experiments, an heterogeneous reaction system was obtained constituted by a solid PVDF membrane contacted with an homogeneous fluid phase formed by the supercritical solvent, BPO and AA.

3.2. Grafting of AA on PVDF membranes

A set of experiments was performed to obtain preliminary information on the grafting process. In this stage of the research we prepared three different membranes that were treated in scCO₂ with experimental conditions summarized in Table 1.

Sorption and/or swelling of PVDF contacted with scCO₂ has been investigated using different experimental techniques [51–53] and it has been found that CO₂ has a significant solubility in the amorphous domains of the fluoropolymer thus inducing a swelling of the matrix that increases the mass transfer rate of chemical species inside the amorphous polymer [54]. In fact it is commonly accepted that crystallites constitute a nonsorbing, nonpermeable phase [55].

The role of each phase as reaction locus in heterogeneous free radical polymerization systems has been recently discussed [56]. From the comparison of molecular weight distribution of polymer samples that were characterized by very different values of specific area it was found that the role of the polymer phase as reaction locus cannot be neglected when high polymer interfacial area and hold-up are present in the polymerization reactor.

The BET surface area of Millipore PVDF membranes similar to that adopted in this study was estimated to be in the range 2–3 m²/g that is a value considerably larger than the apparent geometrical surface of the membrane [57,58]. Under this condition it could be possible that free radicals generated in the fluid phase can be transported in the amorphous portions of the PVDF membrane while they are still active so that AA grafting can occur not only on the surface of the pore walls but also in the bulk of the matrix.

To this regard it seems relevant to underline that grafted chains buried inside the polymer should not affect the local environment inside pores thus playing a negligible role in determining the pH sensitive behaviour of the membranes while it cannot be ruled out an effect on the permeability in itself since the lumen of channels could be changed by restriction of pore walls induced by volume effects arising from the polymerization occurred in the polymer phase.

On the other hand only one membrane was loaded in the reactor for each experiment and then the volume fraction of PVDF in the reactor is quite limited. For this reason the main locus of AA homopolymerization should always remain the continuous fluid phase [56] as clearly indicated by the significant amount of

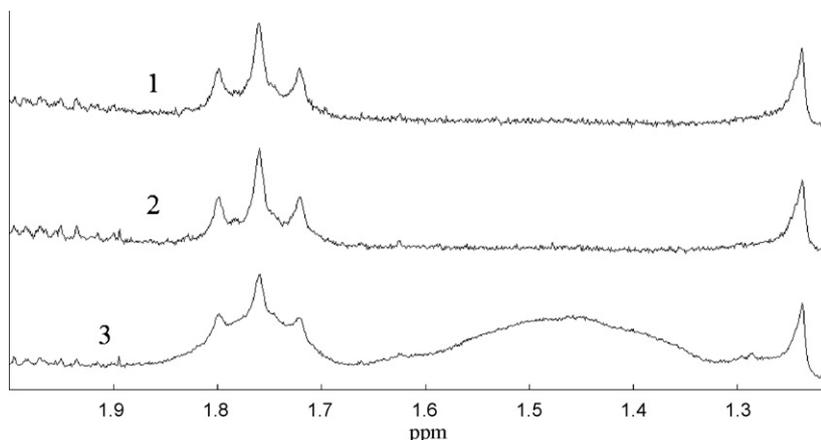


Fig. 1. ^1H -NMR spectra of selected PVDF samples in d_6 -DMSO. Pristine PVDF membrane (1), PVDF membrane contacted with BPO in scCO_2 (entry 2, Table 1) (2), PVDF membrane contacted with BPO and AA in scCO_2 (entry 3, Table 1) (3).

poly(acrylic acid) that was collected at the end of each experiment on the wall of the high pressure vessel.

The membranes were characterized by ^1H NMR, ^{19}F NMR and HATR-FTIR spectroscopy. Spectra of samples taken from PVDF membranes soaked in dense CO_2 both in the absence and in the presence of BPO were undistinguishable from those obtained with the pristine PVDF membrane (spectra 1 and 2 in Figs. 1 and 2). Also DSC thermograms were substantially the same and we could conclude that calorimetric crystallinity was not significantly affected both by the swelling of the matrix in dense CO_2 and by the action of free radicals generated from BPO decomposition.

In the case of the membrane treated in the presence of AA (entry 3, Table 1), after three washing cycles with hot ethanol we obtained a constant weight of the polymer sample that was considered an indication that unreacted monomers and ungrafted poly(AA) were completely removed.

Since the washing procedure is crucial to obtain reliable grafting data we challenged its efficacy. To this purpose a sample of poly(AA) was prepared by precipitation polymerization in scCO_2 at 0.65 g/mL and 65 °C with AA and BPO initial concentration of 1.0 M and 0.5 mM, respectively, polymerization time was 16 h. This polymer was dissolved in ethanol in order to prepare 20 mL of solution 10% (w/w) in poly(AA) in which a virgin PVDF membrane, initial mass 125 mg, was soaked at 35 °C overnight. Then the solvent was fully evaporated at reduced pressure obtaining a membrane physically impregnated with the polyacid.

This membrane was then treated with hot ethanol with a procedure similar to that adopted to clean grafted membranes. After the first washing, 95% of the mass in excess of the initial weight of the membrane was removed; after the second treatment the dry membrane reached a mass that was only one milligram higher than the initial value. From this test we can conclude that residual ungrafted poly(AA) chains can induce an uncertainty of less than 1% in the gravimetric grafting level.

Additionally, when grafting of maleic anhydride on PVDF was studied in scCO_2 at 100 °C using BPO as initiator, signals at 7.29 ppm were detected in ^1H NMR analyses of the modified fluoropolymers that were attributed to $-\text{CH}=\text{CF}-$ double bonds arising from dehydrofluorination of the macromolecular chains [39]. These signals were not detected in the spectra of all PVDF samples obtained with recipes reported in Table 1 probably owing to the milder adopted temperature. In the ^1H NMR spectra of PVDF membrane contacted with BPO and AA one peak was detected at about 1.47 ppm indicative of the AA units of poly(AA) grafted chains [59] (spectrum 3 in Fig. 1). The amplitude of this peak suggests that relatively long grafted chains were obtained. Moreover signals indicative of the presence of branches were not observed in the ^{19}F NMR spectrum. These two elements may be indicative that a low density of active centres was generated in the PVDF matrix leading to relatively long poly(AA) chains attached to each of them.

The presence of poly(AA) chains was further confirmed by HATR-FTIR that showed an absorption band at 1715 cm^{-1} in the spectrum of the modified PVDF membrane, that corresponds to the resonance of the carbonyl group of AA units [21] and was absent both in the spectrum of the membrane simply soaked in scCO_2 and in that of the sample treated only with BPO (Fig. 2).

A tentative schematic description of the grafting process coherent with the results of spectroscopic analyses above reported and useful for the discussion of the experimental results collected in this study is depicted in Fig. 3.

3.3. Effect of reaction time and AA concentration

The graft copolymerization of AA on PVDF porous membranes was studied changing the reaction time with initial concentration of monomer and initiator fixed at 0.2 M and 0.16 mM, respectively. The polymerization temperature was kept constant at 65 °C and, within the accuracy of the temperature sensor, no drift of its value was observed.

The amount of grafted chains increased with time with a non linear trend that suggests an auto-acceleration of the polymerization kinetics (Fig. 4).

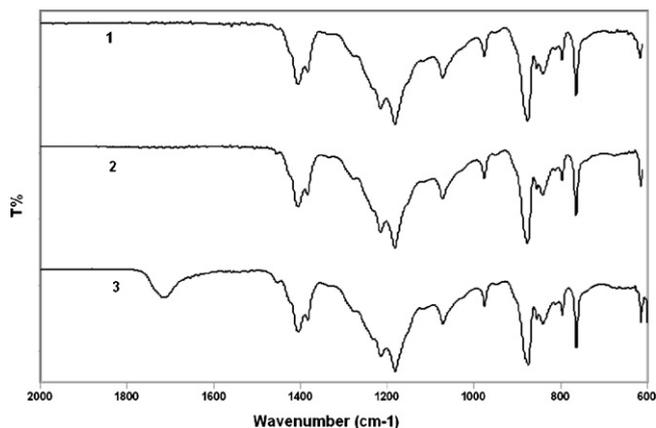


Fig. 2. HATR-FTIR spectra of PVDF membranes obtained in experiments reported in Table 1. Pristine PVDF membrane (1), PVDF membrane contacted with BPO in scCO_2 (entry 2, Table 1) (2), PVDF membrane contacted with BPO and AA in scCO_2 (entry 3, Table 1) (3).

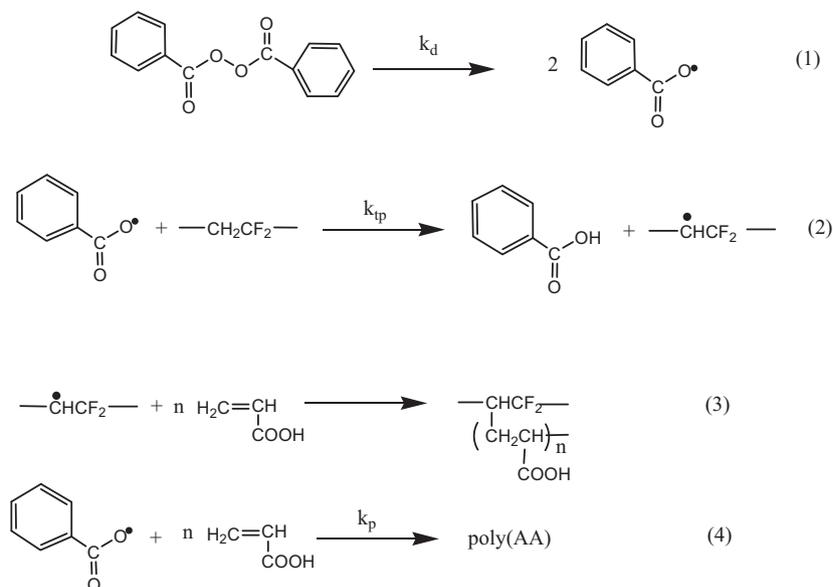


Fig. 3. Schematic description of postulated grafting process.

Selected samples of modified membranes (PVDF-g-PAA) were analyzed by DSC. Crystallinity of as polymerized samples was not drastically affected by the grafting process considering uncertainty in the technique ($\pm 5\%$ in the absolute value of crystallinity). Differently we found that the 2nd heating melting enthalpy of the modified membranes decreased significantly with the grafting level (Fig. 5).

This trend could be attributed mainly to the accumulation of grafted poly(AA) chains in the amorphous domains of the fluorinated polymers that could prevent the melt crystallization of VDF segments without significant alteration of the initial crystallinity of the modified membranes since crystallites are considered to be impermeable to mass transport of chemical species [55]. The accumulation of grafted poly(AA) tails could also lead to a decrease of local mobility of repeat units incorporated in macromolecular chains decreasing the rate of termination of active species under grafting conditions and originating the autoacceleration effect.

In the perspective of modulating the pH sensitivity of the modified matrix: the initial loading of AA could be an important operative parameter to change the surface concentration of grafted chains.

When grafting experiments were carried out changing the initial concentration of the carboxylated monomer from 0.02 to

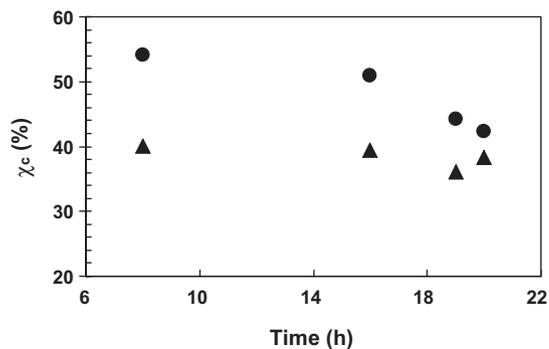


Fig. 5. Effect of reaction time on the melting enthalpy (χ_c , %) calculated (▲) in the first heating (as polymerized samples) and (●) in the second heating (melt crystallized samples) of grafted membranes obtained in experiments reported in Fig. 4.

0.4 M, a not-monotonous trend was obtained in the examined range of concentration (Fig. 6). In particular, the grafting level increased from 2 to 7% (w/w) when the initial concentration of AA changed from 0.03 to 0.06 M. The concentration of grafted

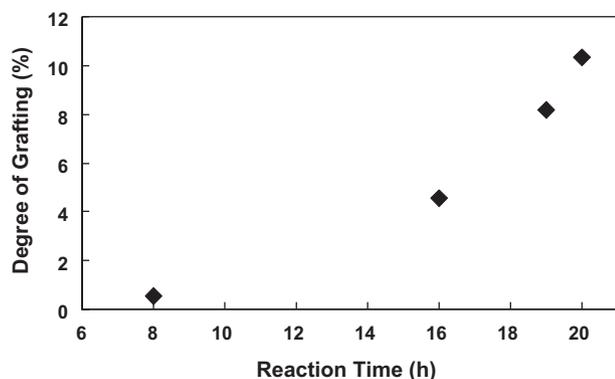


Fig. 4. Effect of reaction time on the grafting of AA on PVDF membranes in scCO_2 . Experimental conditions: [BPO]=0.16 mM, [AA]=0.2 M, CO_2 density 0.51 ± 0.02 g/mL, reaction temperature 65°C .

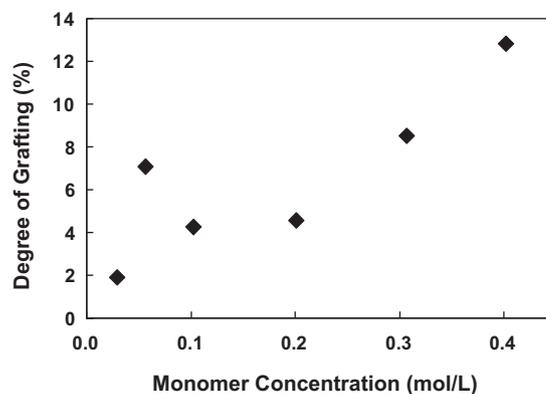


Fig. 6. Effect of initial concentration of AA on the grafting of AA on PVDF membranes in scCO_2 . Each point is the average of two experiments. Experimental conditions: [BPO]=0.16 mM, CO_2 density 0.51 ± 0.02 g/mL, reaction temperature 65°C , reaction time 16 h.

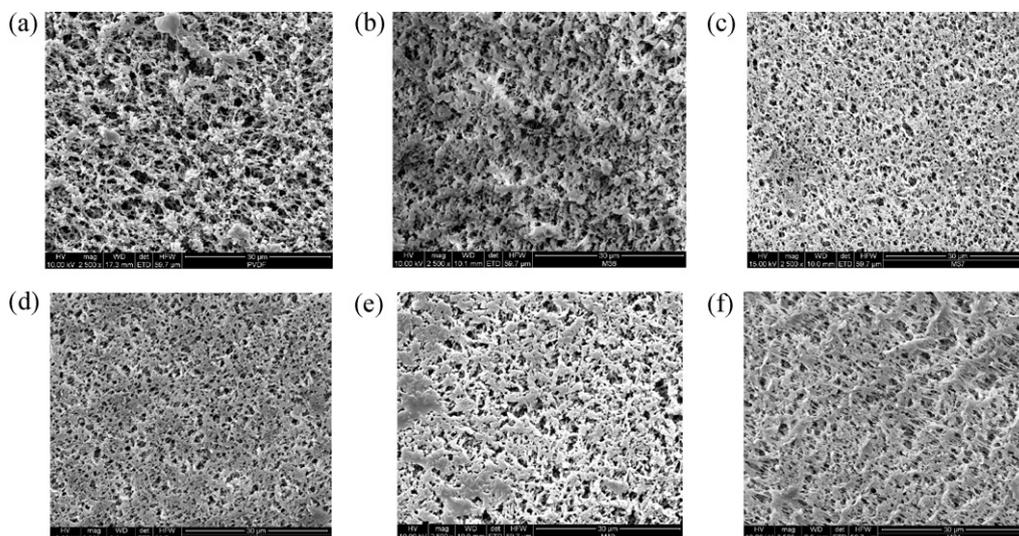


Fig. 7. SEM micrographs of membranes obtained with different grafting time and initial concentration of AA: (a) pristine PVDF membrane, (b) membrane grafted for 16 h with 0.03 M AA, DG 1.9% (w/w); (c) membrane grafted for 16 h, 0.1 M AA, DG 4.3% (w/w); (d) membrane grafted for 19 h, 0.2 M AA, DG 8.2% (w/w); (e) membrane grafted for 20 h, 0.2 M AA, DG 10.3% (w/w); (f) membrane grafted for 16 h, 0.4 M AA, DG 12.8% (w/w). Other experimental conditions: [BPO]=0.16 mM, CO₂ density 0.51 ± 0.02 g/mL, reaction temperature 65 °C.

monomer decreased to about 4% (w/w) when the concentration of AA in the feed was augmented to 0.1 M and negligibly changed for further augmentation to 0.2 M. Further increases in the initial loading of the reactor with the vinyl monomer were accompanied by a clear enhancement of the grafting degree. The reproducibility of the observed behaviour was verified by repeating twice each experiment. Relative variations in the grafting degrees between two duplicated tests were always lower than 10%.

The previously described trend of grafting degree as a function of the initial monomer concentration (Fig. 6) was already found in the maleation of polyolefins both in scCO₂ [35,60] and in conventional reaction systems [61]. This behaviour could be tentatively attributed to the kinetic competition between graft copolymerization and AA homopolymerization. In fact, primary radicals arising from peroxide decomposition that add to acrylic acid dissolved in the fluid phase cannot generate macroradicals on the PVDF backbone. At low monomer loading the graft polymerization prevails and an increase in the DG with the AA concentration is observed. By increasing the AA loading the fraction of primary radicals trapped in the homopolymerization route becomes so large that a depression of the grafting level is induced. By further increasing the monomer concentration, aforementioned effect could be compensated by the fast propagation of active centres efficiently replenished with

acrylic acid dissolved in the polymer matrix whose diffusivity is enhanced by CO₂ swelling. In this scenario the novel increase of the grafting degree at [AA] higher than 0.2 M would be mainly the effect of an increase in the length of grafted chains.

It could be observed that in the case of grafting of maleic anhydride the branch of the curve corresponding to the increase of the grafting level at the higher investigated vinyl monomer concentrations was not clearly detected [60]. This different sensitivity of the grafting level on the concentration of the vinyl compound could be due to the fact that acrylic acid is characterized by a fast rate of homopolymerization in scCO₂ [62] while maleic anhydride has a lower tendency to homopolymerize at temperature adopted in the grafting process [60].

All membranes modified changing the reaction time and the initial concentration of acid monomer were analyzed by SEM. We observed that the surface fraction of void space of the macromolecular matrixes, estimated through the fraction of darker zones on the micrographs, decreased when the grafting level increased independently from the fact that this result was obtained increasing the reaction time or changing the AA concentration (Fig. 7).

The thermal stability of the grafted membranes was compared with that of pristine PVDF membrane and polyacrylic acid homopolymer by thermal gravimetric analyses (Fig. 8). PVDF

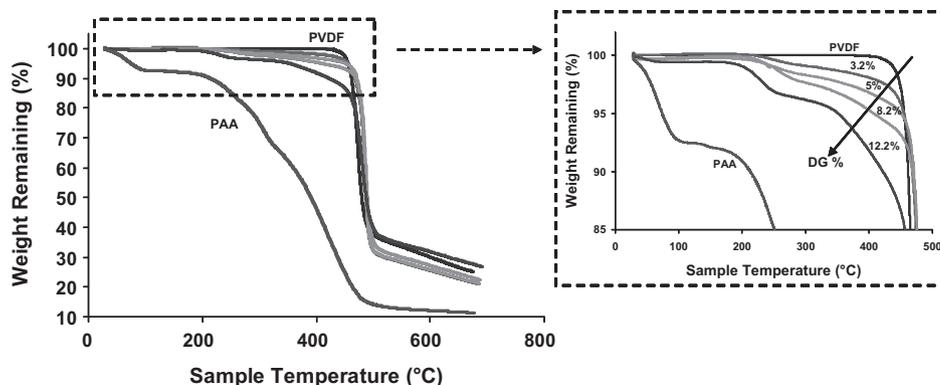


Fig. 8. Thermal gravimetric curves of the pristine membrane (PVDF), of poly(acrylic acid) synthesized in scCO₂ according to recipe reported in Section 3.2 (PAA) and of PVDF-g-PAA membranes obtained in experiments performed changing reaction time or initial concentration of AA.

Table 2
Effect of BPO concentration and CO₂ density on DG and crystalline content of PVDF membranes modified in scCO₂.

Entry	Time, h	[BPO], mM	$\rho_{\text{CO}_2}^{\text{a}}$, g/mL	DG ^b , % w/w	χ_c^{c} , %	$A_{\text{COOH}}/A_{\text{CF}_2}^{\text{d}}$
1	16	0.16	0.53	4.6	51	0.10
2	16	0.50	0.52	14.8	46	0.21
3	20	0.16	0.48	10.3	42	0.18
4	16	0.16	0.71	2.1	52	0.05
5	16	0.50	0.78	3.4	51	0.07
6	20	0.16	0.70	5.0	52	0.10

[AA] = 0.2 M, reaction temperature 65 °C.

^a CO₂ density.

^b Degree of grafting.

^c Calorimetric crystallinity referred to the effective amount of PVDF, 2nd heating.

^d HATR-FTIR absorbance of carbonyl group of grafted poly(AA) chains normalized with respect to the absorbance of CF₂ unit of PVDF.

resulted thermally stable up to about 430 °C while PAA starts to decompose at about 200 °C. The grafted membranes showed an intermediate behaviour that in this case too was essentially correlated with the grafting level independently from the operative conditions used to process the membrane. In particular the extent of the weight loss at about 280 °C, corresponding to the degradation of PAA grafted chains, increased with the gravimetric degree of grafting of the sample, while the global thermal stability was comparable to the one of pristine PVDF.

3.4. Effect of the BPO concentration and of the density of the CO₂

A set of experiments was designed to study the effect of the initial concentration of organic peroxide ([BPO]). This aspect was investigated at different levels of the density of the fluid phase, namely 0.5, 0.7 and 0.8 g/mL. A higher concentration of BPO would lead to a faster rate of generation of free radicals. This should correspond to a higher rate of generation of macroradicals in the polymer matrix accompanied by a shorter lifetime of active species that would lead to shorter length of the grafted chains. The entity of the effect should be dependent also on the density of the fluid phase that fixes the chemical potential of species in the fluid and polymer phase thus affecting the driving force for interphase mass transfer. In particular it should be expected that higher density of the CO₂ should bias the partitioning of low molecular weight species towards the fluid phase thus decreasing the grafting level.

When the initial concentration of BPO was changed from 0.16 to 0.50 mM the degree of grafting increased from 4.6 to 14.8% (w/w) (entries 1–2, Table 2). This effect was accompanied by a decrease of the calorimetric crystallinity of the matrix as already observed when the grafting level increased as a consequence of longer reaction time (entry 3, Table 1 and Fig. 5).

When the density of the fluid phase was increased (entries 4–6, Table 2), at fixed value of any other operative parameter, the degree of grafting decreased coherently with the theoretical considerations mentioned at the beginning of this section. Moreover, the crystalline content of the membranes processed at high density was sensibly less affected also at the highest investigated initiator concentration and grafting time (entries 3, 5 and 6, Table 2).

Quite interestingly, SEM micrographs showed a similar coverage of the membrane surfaces in spite of the much lower gravimetric grafting level obtained in denser reaction system (Fig. 9).

To obtain additional information on the distribution of grafted AA inside the polymer, modified PVDF membranes were also analyzed by HATR-FTIR. The absorbances of the 1715–1720 cm⁻¹ carbonyl group, normalized using the 875 cm⁻¹ band relative to the CF₂ unit of the PVDF backbone as internal reference, were compared for samples of Table 2. The reason for this approach lies on the fact that the HATR IR spectrum detects energy absorption in a finite thickness of the outermost layer of the sample as the depth of penetration can be estimated in the range 0.5–1 μm.

We have found that the ratio of normalized absorbances of membranes obtained in experiments carried out under similar operative conditions but the value of the density, are quite close to the ratio of the corresponding gravimetric grafting levels. This result suggests that similarity among membranes is only achieved at the very external surface.

Results described in this section considered together with those obtained studying the water permeability of grafted membranes reported in the following section, indicate that the density of the supercritical solvent is the most effective parameter to control the performances of grafted membranes.

3.5. Water permeability of grafted membranes and investigation of their release behaviour

The flux of water solution of NaCl through the PVDF-g-PAA membranes was examined at different pH, keeping constant the ionic strength of the solution.

The modification in the flow as a consequence of change in solution pH can be attributed to the different conformation of the grafted poly(AA) tails located in the proximity of the pore surface of modified membranes.

At pH higher than 4, poly(AA) chains assume an extended conformation, driven from their strong interaction with the aqueous environment and the electrostatic repulsion among dissociated side groups. This phenomenon decreases the effective pore dimension and the permeation rate. Differently, the poly(AA) chains collapse assuming a helical conformation at low pH [63] thus allowing the opening of the pores.

The virgin PVDF membranes were characterized by extremely low values of flux at all investigated pH values.

When we studied the behaviour of PVDF-g-PAA membranes we found that their water permeation depends on the grafting level of the hydrophilic monomer AA (Fig. 10). Indeed, for lower DG (<2–3%) the fluxes resulted very low probably because the pore surface was not enough hydrophilic. When DG increased at intermediate values (4–8%) the water permeability increased notably, while decreased for the higher DG (>8%) that were obtained in this study at high grafting time and/or at the highest investigated initial concentration of AA and BPO.

The observed behaviour could be attributed to a blocking effect of the PAA grafted chains anchored onto the pore surface of the PVDF substrate when the grafting level is too high so that a larger surface concentration of PAA grafted chains could lead to smaller active pore size with respect to matrixes modified with lower DG. This result indicates that the control of the DG is a crucial aspect to obtain pH sensitive membranes with desired permeability.

Some preliminary experiments of drug release from PVDF-g-PAA membranes obtained in this study were carried out using caffeine as model drug. This bioactive compound belongs to class 1 in the biopharmaceutical classification system [64] which means

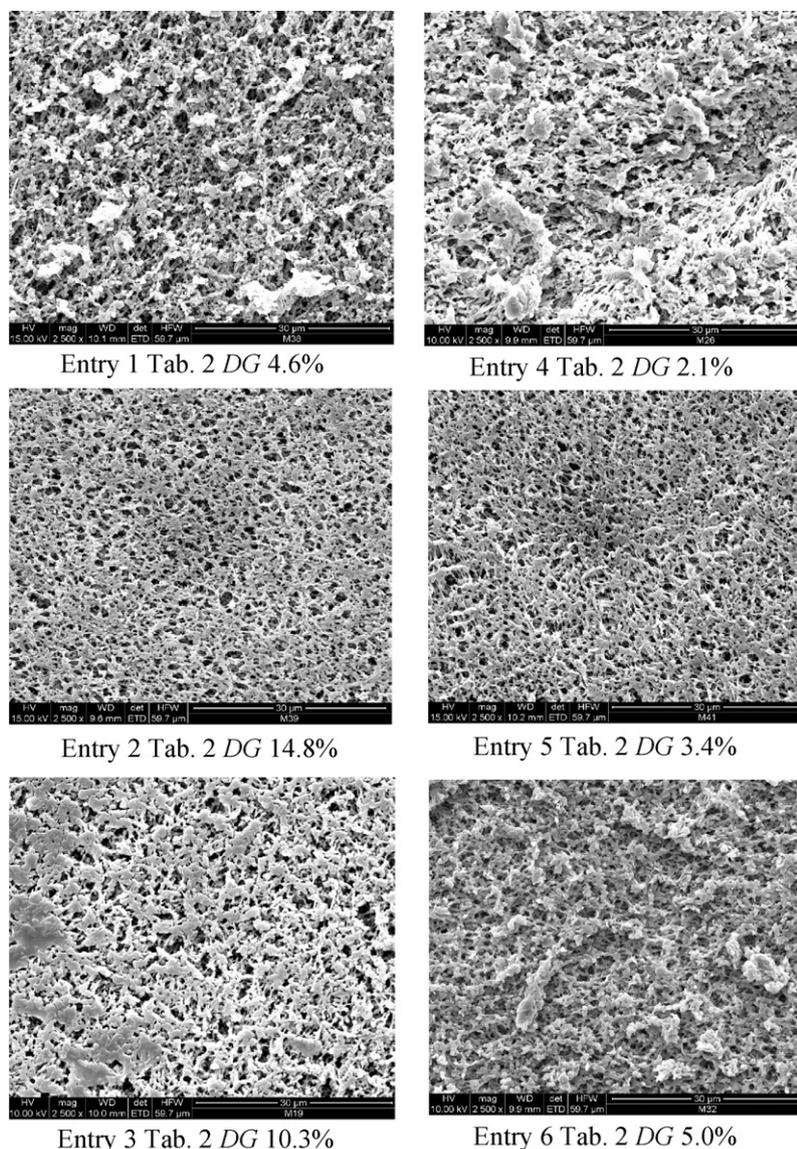


Fig. 9. SEM micrographs of PVDF-g-PAA membranes obtained in experiments reported in Table 2.

that it has high bioavailability because of high water solubility and good intestinal permeability.

In Fig. 11 are shown the release profiles recorded at 37 °C of pure caffeine and of the model drug encapsulated in a pristine PVDF membrane and in a PVDF-g-PAA membrane in buffer solutions at pH 2.5 (curve a) and 6.8 (curve b). The membrane selected

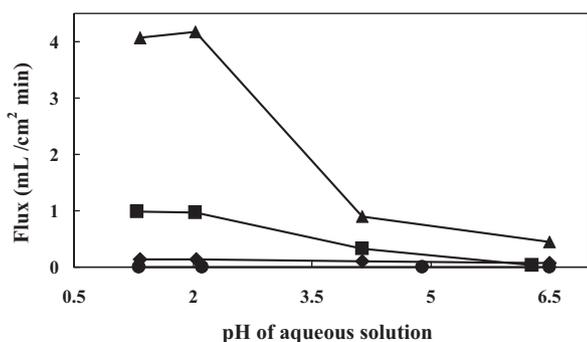


Fig. 10. Water permeability of grafted membranes with a DG of (●) 0.6%, (◆) 2.7%, (■) 8.2%, and (▲) 4.6%.

for the experiments presented an intermediate level of grafting (4.6%, w/w) and gave higher water permeation in acid environment (curve (▲) in Fig. 10). The dissolution rate of caffeine encapsulated inside the PVDF membranes, estimated from the slope of the

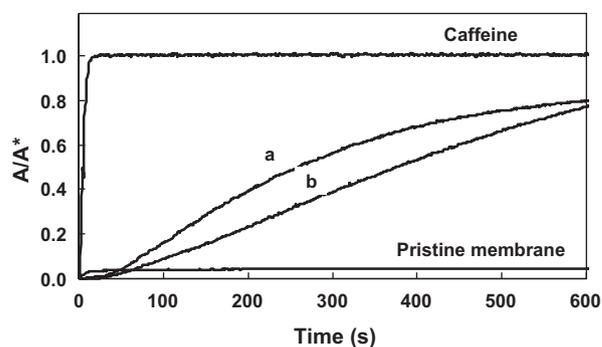


Fig. 11. Release profiles at 37 °C of caffeine encapsulated in a grafted PVDF membrane (DG of 4.6%) in buffer solutions at pH (a) 2.5, (b) 6.8, compared with that from pristine membrane (curves obtained at both pH are substantially overimposed). A is the actual absorbance of caffeine in the dissolution medium and A^* is the absorbance of pure caffeine measured at infinite release time.

absorbance vs time curves, was significantly lower than that of the free drug. In particular very low dissolution rates were obtained when caffeine was encapsulated in unmodified hydrophobic Durapore PVDF membrane at both investigated pH in agreement with its low wettability and pH insensitive behaviour.

The dissolution rate of encapsulated drug was significantly accelerated when the grafted membrane was used to entrap the drug and quite interestingly faster release rate were recorded at pH = 2.5 where PAA chains should be present under collapsed conformation thus widely opening the pores of the membrane. These results clearly confirm that modified membranes can exhibit a pH sensitive behaviour in the release of caffeine.

4. Conclusions

Free radical grafting of AA on PVDF membranes was successfully performed in scCO₂ using the initiator benzoyl peroxide as source of radicals to initiate the process at mild temperature condition. Results collected from ¹H NMR, ¹⁹F NMR and HATR-FTIR analyses of treated membranes thoroughly extracted with hot ethanol indicated the presence of PAA chains with no evidence of dehydrofluorination of the PVDF chains.

The results collected studying the influence of selected operative parameters indicated that the grafting degree can be significantly changed by adjusting the monomer and initiator concentrations, the reaction time and the density of carbon dioxide.

Flux measurements across the pristine and the grafted membranes at different pH-values demonstrated that a pH-sensitive behaviour was obtained after the grafting process and that the level of grafting notably influences the water permeability that was adversely affected by DG higher than 8% and lower than 3% (w/w).

Preliminary results of release experiments performed with caffeine as model drug suggested that it is possible to use PVDF membranes modified by graft copolymerization of AA in scCO₂ as matrixes to induce pH sensitive dissolution rate to drugs with high water solubility.

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