Vibrational and thermal study on the *in vitro* and *in vivo* degradation of a bioabsorbable periodontal membrane: Vicryl® Periodontal Mesh (Polyglactin 910)

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Fourier transform Raman (FT-Raman), attenuated total reflection/Fourier transform infrared (ATR/FT-IR) spectra and differential scanning calorimetry (DSC) measurements were performed on a biodegradable periodontal membrane, the Vicryl® periodontal mesh, in order to study its *in vitro* and *in vivo* degradation mechanism and kinetics. The hydrolitic *in vitro* degradation was investigated in two aqueous media: a saline phosphate buffer (SPB, pH = 7.4) and a 0.01 M NaOH solution. Moreover, a membrane implanted *in vivo* for 4 weeks for treatment of contiguous vertical bony defects, was examined.

Vibrational and thermal measurements show that the Vicryl® membrane presents a semicrystalline structure. It degrades faster in the NaOH solution than in the SPB and degradation occurs heterogeneously with a progressive increase in the percentage of crystallinity and shortening of the polymeric chains both *in vitro* and *in vivo*.

The trends of % weight loss and IR I_{627}/I_{1415} intensity ratio (identified as a marker of crystallinity) are discussed in comparison with the DSC results.

The IR I_{627}/I_{1415} intensity ratio and X_c% allow to determine the % weight loss undergone by the membrane degraded *in vivo*. The result obtained shows that the Vicryl® membrane degrades faster *in vivo* than *in vitro* with the formation of oligomers which are more easily absorbed by the surrounding tissues than they are soluble in the degradation media examined.

1. Introduction

Poly(glycolic acid) (PGA) was the first synthetic bioabsorbable polymer to be successfully used as biomaterial in wound closure [1], in the reconstruction of injured and diseased blood vessels [2] and, in general, in all temporary therapeutic applications [3–5]. Subsequently, many other bioabsorbable polyesters with different biodegradation properties [6] have been developed in order to meet the requirements of various aspects of reconstructive surgery. An example of this strategy is represented by the lactide-glycolide copolymers PLAGA which have been developed in order to decrease the biodegradation rate of PGA. In fact, it has been reported that Vicryl® sutures (Polyglactin 910, a copolymer of the PLAGA family) retain their mechanical strength longer than pure PGA sutures [7]. As far as degradation kinetics and mechanism is concerned, it is known from the literature that the PLAGA degrade much faster than poly(lactic acid) (PLA) homopolymers and the degradation rate increases with increasing glycolic acid (GA) content: PLA70GA30 (where 70 and 30 are the percentages of lactic acid, LA and GA units respectively) and PLA50GA50 have been reported to degrade much faster than PLA80GA20 and PLA90GA10 [8]. This behavior is due to the higher hydrophilicity of GA repeating units with respect to LA ones [9]. Therefore, degradation occurs preferentially on the GA ester groups [10].

In dental surgery, in treatment of periodontal defects, bioabsorbable polymers are used as barriers, in order to prevent epithelial migration and to promote the regeneration of new connective tissue attachment. The employment of these membranes has permitted the development of an innovative technique, the guided tissue regeneration (GTR) [11–15]. Moreover, these membranes are biodegradable and thus there is no need for a second operation to remove the device after healing.

The resorption process must be carefully controlled so

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that these membranes are truly effective. In fact, in the first phase of the healing process, the membrane must be integral in order to act as a barrier, then it must gradually degrade. Thus, the use of these membranes is mainly based on the programmed maintenance of their physical and mechanical properties for a fixed period of time and on their gradual and progressive degradation by simple hydrolysis [16, 17] into metabolic by-products (LA and GA) which are easily eliminated from the body. The physico-mechanical properties and the biodegradation mechanism and kinetics of the polymer depend on a series of factors which control water accessibility to ester linkages which are known to be involved in the degradation [16, 17]: composition (homo- or co-polymer), molecular weight, configurational structure, morphology, crystallinity, presence of residual monomer and low molecular weight compounds, processing, annealing, sterilization [16, 18–22].

The elucidation of the role played by these factors in the biodegradation mechanism of the polymer needs to be suitably evaluated at the molecular level after *in vitro* degradation at different pH and saline concentrations, and after *in vivo* implant in different sites.

Being non-destructive and non-invasive vibrational techniques, FT-Raman and ATR/FT-IR spectroscopies are particularly suitable for evaluating the molecular structure of biodegradable polymers and their degradation products. Therefore they can give a significant contribution to the characterization of this important class of biomaterials.

In the present work, Fourier transform Raman (FT-Raman), attenuated total reflection/Fourier transform infrared (ATR/FT-IR) spectroscopies coupled to differential scanning calorimetry (DSC) measurements were employed for the first time, as far as we know, in order to elucidate the *in vitro* and *in vivo* degradation mechanism and kinetics of a periodontal membrane used in the GTR technique [23–25], the Vicryl® periodontal mesh (Polyglactin 910, same composition as Vicryl® sutures).

Vibrational studies on GA [26, 27] and its polymerization process [26], on glycolates [26], on the ring-opening polymerization of glycolide [28], and on lactide-glycolide copolymers [29] are reported in the literature. DSC measurements on PGA and PLAGA copolymers as raw materials [10, 30, 31] and during *in vitro* [8, 21] and *in vivo* [32] degradation are reported as well.

2. Materials and methods

The commercial periodontal membrane studied is Vicryl® (Polyglactin 910) periodontal mesh (Ethicon – Johnson & Johnson). It is composed of a lactide-glycolide copolymer, PLA10GA90, where 10 and 90 are the percentages of LA and GA units respectively. The two surfaces of the membrane are chemically and physically identical.

In order to study the *in vitro* degradation kinetics, the membranes were weighed (20–30 mg) and immersed in 10 ml of two different aqueous media, at 37 °C:

- saline phosphate buffer (SPB, pH = 7.4) composed of 1.1830 g of KH_2PO_4, 4.3198 g of Na_2HPO_4 and 9 g of NaCl in 1 l of H_2O. This medium has been taken as a model of biological fluids.
- NaOH solution (0.01 M, pH = 12). This medium was used to accelerate the degradation since an OH^- catalytic effect on the simple hydrolisis mechanism is reported for poly(α-hydroxy acid)s [17, 33, 34].

For each degradation time, the specimens were recovered, washed with distilled water, vacuum-dried at room temperature and weighted before being subjected to the various analyses. The solutions were renewed every week.

The % weight loss (% wl) was calculated by comparing the dry weight (w_t) remaining at a given degradation time t with the initial weight (w_0) according to the equation:

$$\% \text{ weight loss} = 100(w_0 - w_t)/w_0 \qquad [1]$$

In order to study the *in vivo* degradation, the Vicryl® membrane was implanted for treatment of contiguous vertical bony defects according to the principles of GTR [11–13]. After explantation, it was immersed in Dentosan® (chlorhexidine gluconate, 0.1%), washed with water at 5 °C (1 l, 48 h) and vacuum-dried at room temperature.

ATR/FT-IR spectra were recorded on a Jasco Model 300E spectrophotometer using a KRS5 crystal. The spectral resolution was 4 cm^{-1}. FT-Raman spectra were measured on a Bruker IFS66 spectrometer equipped with a FRA-106 Raman module and a cooled Ge-diode detector. The spectral resolution was 4 cm^{-1}. The excitation source was a Nd^{3+}-YAG laser (1064 nm) in the backscattering (180°) configuration.

DSC thermograms were obtained by using a Mettler TA-STAR, Model 821^e calorimeter, covering 5–250 °C. The heating rate was 2 °C/min.

The crystallinity degree X_c% of different membranes was evaluated according to the equation:

$$X_c\% = \frac{\Delta H_m}{\Delta H_m^\circ} 100 \qquad [2]$$

where ΔH_m is the measured enthalpy of melting and ΔH_m° the enthalpy of melting of a theoretically 100% crystalline polymer (it was assumed to be 139 J/g, computed from the value of 72.3 J/g determined for a PGA100 with a crystallinity of 52% [30]).

In order to characterize the degradation products, the organic part of the solid residue was dissolved with CH_2Cl_2. The vacuum-dried extract was analyzed by FT-IR spectroscopy (KBr pellet technique).

3. Results and discussion

3.1. Weight loss

In Fig. 1A the % weight loss of Vicryl® membranes (w_0 about 20 mg) both in SPB and NaOH solution is reported versus time. As can be easily seen from the graphics, the Vicryl® membrane degrades faster in alkaline solution than in SPB. This result is in agreement with the literature where an OH^- catalytic effect on the simple hydrolysis mechanism is reported for poly(α-hydroxy

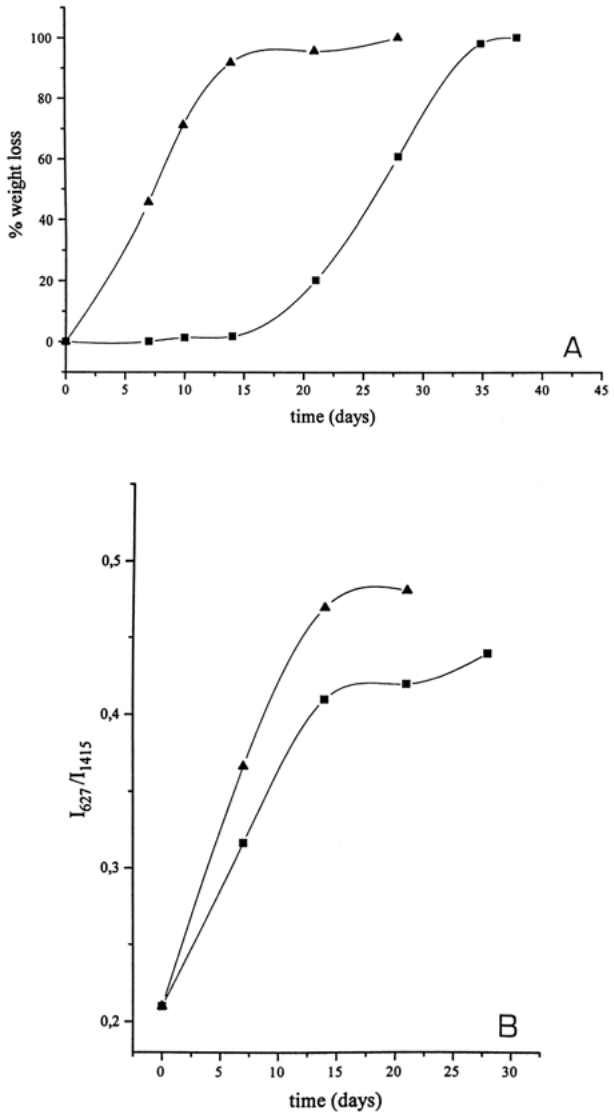

Figure 1 Percentage weight loss (A) and I_{627}/I_{1415} intensity ratio from the ATR/FT-IR spectra (B) of Vicryl® membranes (w_0 about 20 mg) during *in vitro* degradation at 37 °C in SPB, pH = 7.4 (square symbol) and in NaOH solution, pH = 12 (triangle symbol).

acid)s [17, 33, 34]. The trend of the curve corresponding to the degradation in SPB is typically sigmoidal: the Vicryl® membrane loses only about 2% of its weight in two weeks, then the % weight loss dramatically increases. The trend observed for the degradation in NaOH solution is comparable to that reported by Cam *et al*. [33] for PLA100 (where 100 is the percentage of L-LA) under the same conditions as ours: in the first phase of degradation the weight loss increases almost linearly with time, after which the degradation rate noticeably decreases. The linear increase in the weight loss can be explained by hypothesizing the presence of channels which allow degradation products to leave the bulk of the polymer immediately after their formation [33]. Moreover, it is possible that the earlier release of degradation products in the NaOH solution arises because solubility in this medium occurs for higher molecular weight species than in SPB. The decrease in the rate of the weight loss in the late phase of degradation can be explained, in agreement with Cam *et al*. [33], in terms of the morphology of the membrane. In fact, it is well known that the *in vitro* and *in vivo* degradation of semicrystalline polymers of the PLAGA family starts in

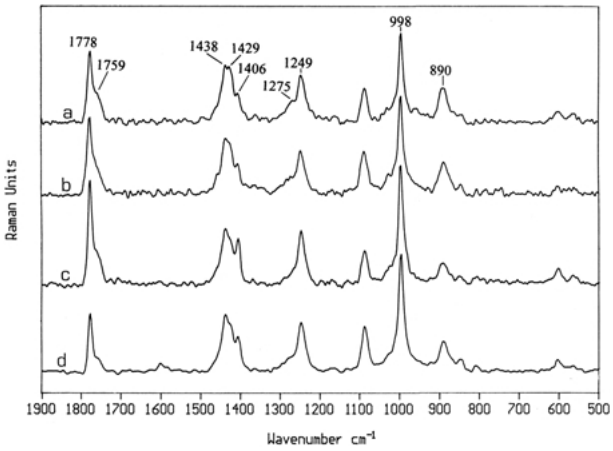

Figure 2 FT-Raman spectra of a Vicryl® membrane at different *in vitro* degradation times in SPB (pH = 7.4) at 37 °C: (a) $t = 0$; (b) $t = 2$ weeks (% wl = 2%); (c) $t = 4$ weeks (% wl = 61%) and (d) of a Vicryl® membrane implanted for four weeks.

the amorphous part of the polymer since water can enter more easily into these domains [34]. Therefore, if the amorphous parts of the polymer leaves its crystalline domains, the percentage of crystallinity increases. The degradation in the amorphous phase proceeds until it is exhausted and after that the rate of hydrolysis decreases since it involves the slow-degrading crystalline phase.

The trends of the curves of % weight loss versus time for the membranes of about 30 mg (not shown) are similar to those reported in Fig. 1A for the membranes of about 20 mg, even if with a time lag in agreement with the higher w_0/volume of degradation medium ratio. Therefore, under this consideration, the results reported for the two sets of membranes are comparable and do not depend on the initial weight.

3.2. Spectroscopic characterization of the membranes

In Fig. 2 we report the Raman spectra of an undegraded Vicryl® membrane (a) and of the same membrane treated by immersion in SPB (pH = 7.4) at 37 °C for 2 (b) and 4 weeks (c) (% wl = 2% and 61% respectively, see Fig. 1A). In the spectrum of the undegraded Vicryl® membrane (Fig. 2a), the bands characteristic of PLA are covered by the stronger bands of the GA component because of the low percentage of LA (10%) present in the copolymer (for example, the band at 1452 cm^{-1}, characteristic of PLA [35] is absent). This spectrum shows bands at 1778, 1438, 1406, 1249, 998 cm^{-1} which are characteristic of the crystalline PGA together with others at 1759, 1429, 1275, 890 cm^{-1} which are due to the amorphous PGA [29]. The spectra of Figs 2b and 2c show that, as immersion time increases, the bands characteristic of the amorphous state decrease in intensity, while the bands characteristic of the crystalline state increase in intensity.

The IR spectra reported in Figs 3a–c for the same membrane can be analogously explained. The spectrum of the undegraded Vicryl® membrane (Fig. 3a) shows bands at 1739, 1151, 1085, 973, 903, 808, 719 and 627 cm^{-1} which are due to the crystalline PGA [26]. As immersion time increases, some changes are observed in the spectra. The band at 627 cm^{-1} increases in intensity

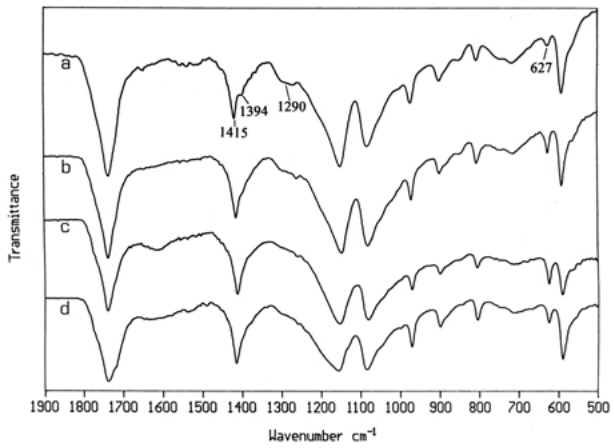

Figure 3 ATR/FT-IR spectra of a Vicryl® membrane at different *in vitro* degradation times in SPB (pH = 7.4) at 37 °C: (a) $t = 0$; (b) $t = 2$ weeks (% wl = 2%); (c) $t = 4$ weeks (% wl = 61%) and (d) of a Vicryl® membrane implanted for four weeks.

while the band at 1394 cm^{-1} and the broad shoulder at about 1290 cm^{-1}, which are not attributable to the crystalline PGA, decrease in intensity. According to the trend of the Raman spectra, which show an increase in the percentage of crystallinity of the membrane, the changes in the IR spectra can be reasonably attributed to the same behavior. Thus, the bands at 1394 and 1290 cm^{-1} can be tentatively assigned to the amorphous PGA, whose IR spectrum is not reported in the literature.

The Raman and IR spectra of Vicryl® membranes degraded by immersion in NaOH solution (pH = 12) at 37 °C show a trend analogous to that observed in SPB: the bands due to the crystalline PGA increase in intensity during the degradation process.

In Fig. 1B the I_{627}/I_{1415} intensity ratio between the IR marker band of crystallinity at 627 cm^{-1} and the IR band at 1415 cm^{-1} (CH_2 bending, taken as internal standard) is reported versus time for the membranes reported in Fig. 1A: it can be easily seen that this ratio, as well as % weight loss, increases faster in alkaline medium than in SPB. Moreover, by comparing the trends reported in Figs 1A and 1B for the degradation in SPB, it can be observed that, in the first two weeks of degradation, the trends of the two curves are different since the IR I_{627}/I_{1415} intensity ratio has already increased without a corresponding significant % weight loss increase. The early increase of the IR I_{627}/I_{1415} intensity ratio shows that more crystalline and organized structures – and thus of lower molecular weight – can develop. This behavior is in agreement with the *in vitro* observations [36]: the molecular weight of the polymer decreases immediately upon contact with water so that the polymeric chains can rearrange in structures with a higher I_{627}/I_{1415} intensity ratio; on the contrary, the weight loss does not start until a critical molecular weight of the polymer is reached. Regarding the degradation in NaOH solution, the curves of Figs 1A and 1B show comparable trends.

Regarding the *in vivo* degradation, we found behavior analogous to that observed for the *in vitro* degraded membrane: as can be seen in Figs 2d and 3d which report the Raman and IR spectra of a Vicryl® membrane implanted for four weeks, the bands due to the crystalline PGA increase in intensity with respect to the undegraded membrane (Figs 2a and 3a respectively); at the same time, those attributable to the amorphous PGA decrease in intensity. Regarding the I_{627}/I_{1415} IR intensity ratio it reaches a value of 0.40.

3.3. DSC measurements

In order to elucidate the degradation mechanism, DSC measurements were performed and the most significant results are reported in Fig. 4 and summarized in Table I.

In Fig. 4a we report the DSC thermogram for an undegraded Vicryl® membrane. It shows two unclear glass transitions at about 48 and 63 °C, in agreement with the literature where double glass transitions are often reported for semicrystalline polymers [37]. This is due to the presence of the same amorphous polymeric chains located in different regions: one region far from the crystallites and another one near them. In addition to the double glass transition, we observe a broad and weak endothermic peak at about 120 °C (whose attribution is unknown) and a significant endothermic melting peak at 202 °C from which a X_c% of about 31.5% was calculated. Gilding and Reed [10] reported for a PLA10GA90 a X_c% of 37% (calculated from X-ray and DSC measurements); this discrepancy may be due to the approximation in considering a ΔH_m° of 139 J/g calculated for a theoretically 100% crystalline PGA100 polymer, without taking into account the percentage of LA. In any case, in agreement with the spectroscopic results, the Vicryl® membrane has a semicrystalline structure.

In Fig. 4b we report the DSC thermogram of a Vicryl® membrane which lost 70.6% of its initial weight by degradation in NaOH solution at 37 °C. It shows a broad

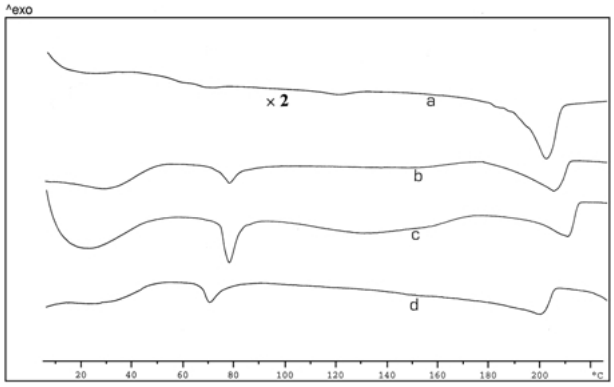

Figure 4 DSC thermograms of (a) an undegraded Vicryl® membrane; a Vicryl® membrane differently degraded in 0.01 M NaOH solution at 37 °C with (b)% wl = 70.6% and (c)% wl = 84.4%; (d) a Vicryl® membrane implanted for four weeks.

TABLE I Percentage weight loss, enthalpy of melting of oligomers (ΔH_m), T_{m2} and X_c% for differently degraded Vicryl® membranes

Percent weight loss	Degradation medium	ΔH_m oligomers (J/g)	$T_{m2(°C)}$	X_c%
0	—	0	202	31.5
54.6	SPB	18	202	32.7
70.6	NaOH	13	205	38.1
84.4	NaOH	28	210	39.3
	in vivo	14	200	39.6

glass transition at about 30 °C and two endothermic peaks at 78 °C (T_{m1}) and 205 °C (T_{m2}) respectively. The endothermic peak at 78 °C is attributable to the melting of oligomers (degradation products with lower molecular weight); from the endothermic peak at 205 °C a X_c% of 38.1% was calculated.

The DSC thermogram (Fig. 4c) of a Vicryl® membrane which lost 84.4% of its initial weight by degradation in NaOH solution shows further degradation of the polymeric chains: the broad glass transition decreases in temperature (T_g about 25 °C) while T_{m2} and X_c% further increase ($T_{m2} = 210$ °C and $X_c\% = 39.3\%$).

As can be seen from Table I and the thermograms a, b and c of Fig. 4, the increase in X_c% as well as the shift in the melting temperature as degradation proceeds, indicates that more crystalline and better organized crystallites can progressively develop because of the shortening of the polymeric chains revealed by the broadening and decrease in temperature of the glass transition. These results, in agreement with the spectroscopic findings, show that the percentage of crystallinity increases during degradation and support the interpretation given for the trend of % wl versus time.

Moreover, from Table I and the thermograms a, b and c of Fig. 4, it can be seen that for the membrane progressively degraded in NaOH solution, the enthalpy of melting of the degradation products increases from 13 J/g (% wl = 70.6%) to 28 J/g (% wl = 84.4%). This trend would show that the amount of oligomers entrapped in the membrane increases as degradation proceeds. For a Vicryl® membrane which lost 54.6% of its initial weight by degradation in SPB (see Table I), the enthalpy of melting of the oligomers is 18 J/g, that is, in this latter case, we found a higher value than we would expect on the basis of the % weight loss value which can be considered as a marker of the degree of degradation. This apparent incoherence can be explained considering that at pH = 12 the solubility of the anionic oligomers is higher than at pH = 7.4.

Regarding the *in vivo* degradation, in Fig. 4d we report the DSC thermogram of the Vicryl® membrane implanted for four weeks; the endothermic peak at about 70 °C can be assigned, as observed for the *in vitro* degraded membrane, to the melting of oligomers; from the broad endothermic peak at about 200 °C a X_c% of 39.6% was calculated. As can be seen from Table I, this X_c% value is comparable with that of 39.3% which corresponds to a membrane which lost 84.4% of its weight. Therefore, we can assume a similar % weight loss also for the *in vivo* degraded membrane. This result is also confirmed by the IR I_{627}/I_{1415} intensity ratio which reaches the same value (0.40) for the two degraded membranes. Thus, it is important to stress that spectroscopic and DSC measurements are in good agreement and lead to the same conclusion on the *in vitro* and *in vivo* degradation mechanism. However, they show that the Vicryl® membrane degrades faster *in vivo* than *in vitro* since the *in vitro* degraded membrane which is comparable to that implanted for four weeks required six weeks of immersion in NaOH solution.

It is interesting to note that, for the *in vivo* degraded membrane, we found a value of 14 J/g for the enthalpy of melting of oligomers, noticeably lower than that of 28 J/g found for the *in vitro* degraded membrane just mentioned (see Table I). This result can be explained by hypothesizing that the degradation products are more easily absorbed by the surrounding tissues than they are soluble in NaOH solution.

In any case, the presence, in the thermograms reported for the degraded membranes, of two melting peaks which point out different molecular weight polymeric chains, would suggest that degradation, both *in vitro* and *in vivo*, should be heterogeneous since the polymeric chains are not all degraded to the same degree. Parallelepiped devices (15 × 10 × 2 mm) made of various PLAGA polymers have been reported [21] to degrade heterogeneously with bimodal size exclusion chromatograms: the internal part of the sample degrades faster than its surface. Our measurements show heterogeneous degradation even if it was not possible to localize the more degraded polymeric chains because of the low thickness of the membrane (about 0.5 mm). Therefore no measurements were performed on the ''internal'' part or on the surface of the Vicryl® membrane.

3.4. Spectroscopic characterization of degradation products

The DSC findings lead us to reconsider the spectroscopic results. Since we detected the presence of oligomers by the DSC thermograms, we wondered whether the spectroscopic bands which increase in intensity as degradation proceeds could be attributable to degradation products. For this purpose, a spectroscopic characterization of the degradation products is in progress and here we report only our preliminary results. In the impossibility of separating the more degraded polymeric chains entrapped in the membrane, we tried to characterize the degradation products present in the degradation media by extraction. It may be that these degradation products do not perfectly coincide with those entrapped in the membrane, however, their study can provide useful information.

For example, in Fig. 5 we report the IR spectrum of the extract of the NaOH solution where a Vicryl® membrane lost 45.6% of its initial weight. The bands at 1600 (COO^- asymmetric stretching), 1390 (COO^- symmetric stretching), 701 (COO^- bending), 594 (COO^- wagging)

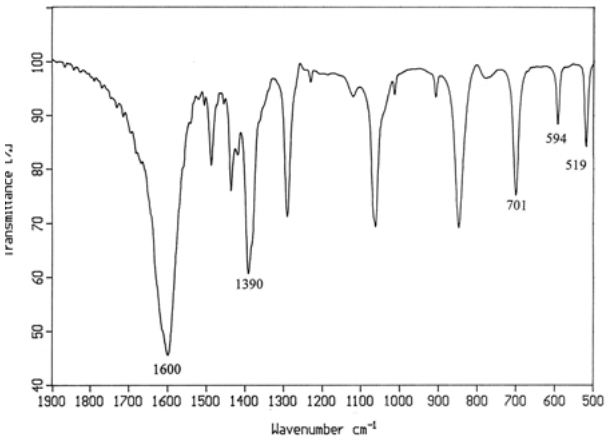

Figure 5 FT-IR spectrum of the extract of a NaOH solution where a Vicryl® membrane lost 45.6% of its initial weight.

and 519 cm^{-1} (COO^- rocking) reveal the presence of anionic species. These wavenumber values (in particular those corresponding to COO^- bending, wagging and rocking modes) are more similar to those of a glycolate ion [26] than of a lactate ion [38]. This result confirms that degradation preferentially involves glycolic subunits, as reported in the literature for copolymers where the LA content is higher than the GA content [10, 21]. Therefore, this is much more true for the Vicryl® membrane were GA represents 90% of the membrane composition. Actually, the spectrum of Fig. 5 is not perfectly comparable to that of the glycolate ion in aqueous solution [26] suggesting the formation of anionic oligomers rather than of glycolate ions. In any case, it can be seen that the 627 cm^{-1} marker band of degradation is not observed in the spectrum of Fig. 5. Therefore, it should be correct to attribute this band to the crystalline PGA.

4. Conclusions

The spectroscopic and DSC measurements show that the Vicryl® membrane presents a semicrystalline structure. This morphological characteristic strongly influences the mechanism and kinetics of the *in vitro* and *in vivo* degradation. The spectroscopic and DSC measurements show an increase in crystallinity during degradation as revealed by X_c% and the IR I_{627}/I_{1415} intensity ratio. These results are explained by hypothesizing that the amorphous parts of the membrane are the first to be degraded and to leave the crystalline domains leading to the observed increase in crystallinity. After that, the hydrolysis rate decreases since the slow-degrading crystalline phase is involved.

Moreover, the DSC measurements show heterogeneous degradation of the Vicryl® membrane both *in vitro* and *in vivo*, with the formation of oligomers which appear to be more easily absorbed by the surrounding tissues than they are soluble in the alkaline medium (the lower solubility was found at pH = 7.4).

Regarding the Vicryl® membrane implanted for four weeks, spectroscopic and DSC measurements are in good agreement and show that the Vicryl® membrane degrades faster *in vivo* than *in vitro*.

In conclusion, FT-Raman and ATR/FT-IR spectroscopies appeared to be a valid method for evaluating the molecular structure of biodegradable polymers and their degradation products.

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