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# Vibrational and thermal study on the *in vitro* and *in vivo* degradation of a poly(lactic acid)-based bioabsorbable periodontal membrane

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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 poly(lactic acid)-based biodegradable periodontal membrane in order to study its *in vitro* and *in vivo* degradation mechanism and kinetics. For this purpose, the hydrolitic *in vitro* degradation of the membrane was investigated in two aqueous media: saline phosphate buffer (SPB, pH = 7.4) and 0.01 M NaOH solution. Moreover, a membrane implanted *in vivo* for four weeks for treatment of contiguous vertical bony defects, was examined.

Vibrational and thermal measurements show that the membrane has a prevalently amorphous structure and is composed of low molecular weight polymeric chains. The degradation is faster in NaOH solution than in SPB and occurs heterogeneously without any significative increase in crystallinity.

The DSC and spectroscopic measurements are discussed in comparison with the trend of % weight loss and show a progressive decrease in molecular weight. Regarding the Raman analysis, the $I_{875}/I_{1452}$ intensity ratio was identified as a marker of the degree of degradation. Regarding the *in vivo* degradation, the presence, spectroscopically revealed, of a biological component entrapped in the membrane proves the good integration of the membrane with the surrounding tissues. The membrane seems to degrade faster *in vivo* than *in vitro*.

A comparison with the degradation mechanism and kinetics of a periodontal membrane previously studied, Vicryl® periodontal mesh, is made.


## 1. Introduction

Biodegradable polyesters such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and their copolymers (PLAGA) have found numerous clinical applications in various areas of surgery (suture material, devices for internal bone fracture fixation etc.) [1, 2] and pharmaceuticals (sustained drug delivery systems) [3].

In treatment of periodontal defects, these polymers are used as membranes; their employment has permitted the development of an innovative technique: the guided tissue regeneration (GTR) [4–8]. The bioabsorbability of these membranes does not require their surgical removal after healing.

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 [9, 10] into metabolic by-products (lactic and glycolic acids, LA and GA) which are easily eliminated from the body.

The degradation rate mainly depends on molecular weight, composition, configurational structure and crystallinity of the polymers since these factors [11–15] control water accessibility to ester linkages which are known to be involved in the degradation [9, 10].

In a previous work [16] we studied the *in vitro* and *in vivo* degradation mechanism and kinetics of a commercial biodegradable membrane, Vicryl® periodontal mesh (a PLA10GA90 copolymer where 10 and 90 are the percentages of LA and GA units respectively) by Fourier transform Raman (FT-Raman), attenuated total reflection/Fourier transform infrared (ATR/FT-IR) spectroscopies coupled to differential scanning calorimetry (DSC) measurements.

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Here we present an analogous study on a PLA-based periodontal membrane in order to elucidate the role played by the factors above reported in the degradation mechanism. The membrane studied is Guidor® matrix barrier. Even if this membrane is, at present, off of the market, our work can give a significant contribution to the characterization of this material which still arouses the interest of the literature [17, 18] together with PLA-based periodontal membranes [19, 20]. Moreover, the employment of vibrational techniques coupled to DSC measurements may represent a general and valid approach to the study of the degradation mechanism and kinetics of PLA-based materials.

Since lactic acid (LA) is a chiral compound, different stereocopolymers can be obtained. High or low molecular weight, semicrystalline or amorphous, isotactic, syndiotactic or atactic polymers can be synthesized depending on the polymerization method (conditions and starting materials) [21, 22].

Vibrational studies on the ring-opening polymerization of L-lactide and D,L lactide [23], on L-lactic and D,L lactic acid oligomers [24], on poly(L-lactic acid) in amorphous and semicrystalline states [25] and on the morphology, conformation and configuration of various PLAs [26] are reported in the literature together with their thermal characterization as raw materials [27–32] and during *in vitro* [12, 15, 33, 34] and *in vivo* [35, 36] degradation.

Moreover, Raman studies on PLA devices used in orthopedics have been recently carried out [37, 38] while analogous studies on PLA membranes used in dentistry are reported here for the first time.

## 2. Materials and methods

The commercial periodontal membrane studied is Guidor® matrix barrier (Guidor AB-Huddinge, Sweden). It is composed of a PLA containing both enantiomers of LA, but their relative amounts are not specified by the producer. It contains acetyl tri-*n*-butyl citrate added as plasticizer. The two surfaces of the Guidor® membrane are chemically identical, but physically different. The outer surface is characterized by wide rectangular perforations, the inner one is characterized by many smaller circular perforations.

In order to study the *in vitro* degradation kinetics, the membranes were weighed (about 20 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 hydrolysis mechanism is reported for PLA [10, 33, 35].

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

The percentage 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 Guidor® membrane was implanted for treatment of contiguous vertical bony defects according to the principles of GTR [4–6]. After explanation, 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. The laser power at the sample position was 190 mW. The spectroscopic measurements were performed on both surfaces.

DSC thermograms were obtained by using a Mettler TA-STAR, Model 821$^e$ calorimeter, covering 5–230 °C. The samples were heated at 2 °C/min (1st run), then cooled at −2 °C/min (2nd run) and finally newly heated at 2 °C/min (3rd run).

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

$$X_c\% = \frac{\sum \Delta H_m - \sum \Delta H_c}{\Delta H_m^\circ} \times 100 \qquad (2)$$

where $\Delta H_m$ is the measured enthalpy of melting, $\Delta H_c$ is the measured enthalpy of crystallization, and $\Delta H_m^\circ$ the enthalpy of melting of a theoretically 100% crystalline polymer calculated in the literature [27] ($\Delta H_m^\circ = 93.6$ J/g).

## 3. Results and discussion

### 3.1 *In vitro* degradation

#### *3.1.1. Weight loss*

In Fig. 1 the percentage weight loss (calculated according to the equation (1)) of Guidor® membranes both in SPB

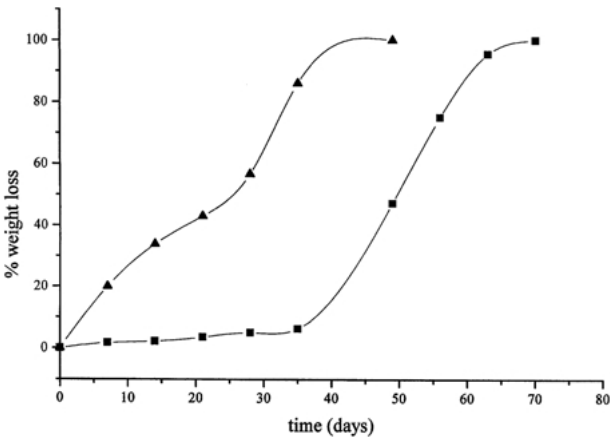


*Figure 1* Percentage weight loss of Guidor® membranes during *in vitro* degradation at 37 °C in SPB, pH = 7.4 (square symbol) and in NaOH solution, pH = 12 (triangle symbol).

and NaOH solution is reported versus time. As can be easily seen from the graphics, the Guidor® membrane completely degrades in 10 weeks in SPB and in seven weeks in NaOH solution. This result is in agreement with the literature where an $OH^-$ catalytic effect on the simple hydrolysis mechanism is reported [10, 33, 35].

Regarding the degradation in SPB, the trend of the curve is typically sigmoidal as observed for the Vicryl® membrane [16]; the Guidor® membrane has lost only about 6% of its weight in five weeks, after which the percentage weight loss dramatically increases. The trend observed for the degradation in NaOH solution is more complex. Cam *et al*. [33] reported that various PLAs100 (where 100 is the percentage of L-LA) of different molecular weights had lost their weight almost linearly with time up to 100 days, then the degradation rate noticeably decreased. The authors explained the linear rate of weight loss by hypothesizing the presence of channels which allowed degradation products to leave the bulk of the polymer immediately after their formation. For the Guidor® membrane, the trend observed is more complex and will be discussed in relation to the DSC measurements; however, according to Cam *et al*. [33], in the first phase of the degradation, the percentage weight loss increases almost linearly with time. In any case it must be recalled that weight loss occurs because the degradation products generated are characterized by a sufficiently low molecular weight which allows them to solubilize in the degradation medium and leave the membrane. Therefore, it is possible that the earlier release of degradation products in NaOH solution arises because solubility in this medium occurs for higher molecular weight species than in SPB. For this purpose, measurements on the products solubilized in the degradation medium are in progress.

### 3.1.2. Spectroscopic characterization

In Figs 2 and 3 we report the FT-Raman and ATR/FT-IR spectra respectively of an untreated Guidor® membrane (a) and of the same membrane treated by immersion in SPB ( pH = 7.4) at 37 °C for 4 weeks (b) and 8 weeks (c). The spectra refer to only one surface since the spectra of the two surfaces of the Guidor® membrane coincide at all degradation times. Thus, there is no preferential chemical degradation of one surface with respect to the other.

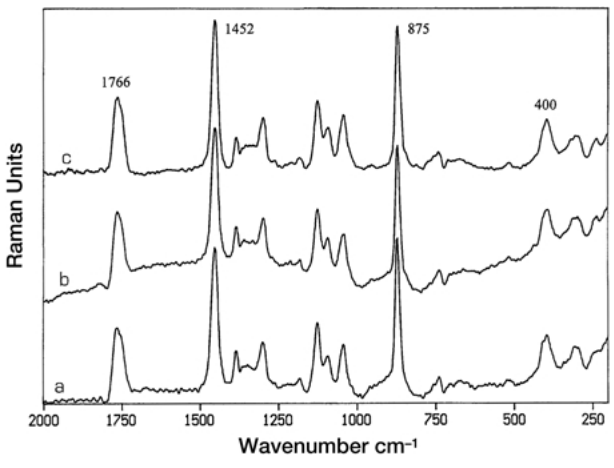


*Figure 2* FT-Raman spectra of a Guidor® membrane at different *in vitro* degradation times in SPB ( pH = 7.4) at 37 °C: (a) $t = 0$; (b) $t = 4$ weeks; (c) $t = 8$ weeks.

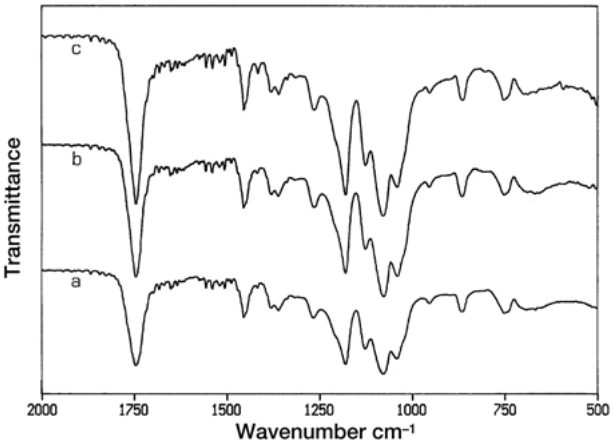


*Figure 3* ATR/FT-IR spectra of a Guidor® membrane at different *in vitro* degradation times in SPB ( pH = 7.4) at 37 °C: (a) $t = 0$; (b) $t = 4$ weeks; (c) $t = 8$ weeks.

The Raman spectrum of the untreated Guidor® membrane (Fig. 2(a)) shows that the specimen has a prevalently amorphous character. In fact, the band at 1766 $cm^{-1}$ (C=O stretching) and the band at about 400 $cm^{-1}$ (CCO bending) are poorly structured also at 2 $cm^{-1}$ resolution, while in the crystalline PLA100 both bands are split [25, 26]. Moreover the bands at 923 $cm^{-1}$ (helical backbone mixed with $CH_3$ rocking modes) and 520 $cm^{-1}$ ($C–CH_3$ bending mixed with that of CCO), characteristic of the α-helix structure of the crystalline polymer, are not observed [25, 26].

The prevalently amorphous character of the Guidor® membrane can be deduced also from the IR spectrum (Fig. 3(a)). In fact the crystallinity marker band [25, 26] at 925 $cm^{-1}$ is not present.

Previous studies on PLA biomaterials used in orthopedics showed that the Raman $I_{875}/I_{1452}$ intensity ratio constitutes a spectroscopic marker of the polymeric chain length [37, 38]. In fact, the 875 $cm^{-1}$ band is characteristic of the C–COO stretching modes in the chain, while the 1452 $cm^{-1}$ band, attributable to the $CH_3$ symmetric bending, can be taken as internal standard. In confirmation, the $I_{875}/I_{1452}$ intensity ratio noticeably decreases in the Raman spectrum of the D,L oligomer [38]. As reported in Table I, for the undegraded Guidor® membrane, the Raman $I_{875}/I_{1452}$ intensity ratio is considerably lower than those of the crystalline PLA100 of high molecular weight, the amorphous PLA50 of lower molecular weight and the D,L oligomer [38]. This behavior would show, although only qualitatively, that the Guidor® membrane is composed of low molecular weight polymeric chains.

The Raman and IR spectra of the degraded membrane (Figs. 2(b), (c) and 3(b), (c)) do not show valuable changes if compared with that of the untreated membrane (Figs. 2(a) and 3(a)).

Regarding the Raman spectra, the structure of some bands changes a little, but the splitting of the 1766 and 400 $cm^{-1}$ bands, typical of the crystalline polymer, is not observed. The Raman $I_{875}/I_{1452}$ intensity ratio does

TABLE I Raman $I_{875}/I_{1452}$ intensity ratios

| Sample | $I_{875}/I_{1452}$ |
|---|---|
| D,L oligomer | 1.30* |
| PLA50 | 1.63* |
| PLA100 | 1.78* |
| undegraded Guidor® | 1.15 |
| Guidor® degraded for 7 weeks in SPB | 1.13 |
| Guidor® degraded for 8 weeks in SPB | 0.97 |
| Guidor® degraded for 4 weeks in NaOH solution | 1.13 |
| Guidor® degraded for 4 weeks *in vivo* | 0.98 |

*Calculated from the spectra of Ref. 38 recorded under the same experimental conditions as the Guidor® membrane.

not noticeably decrease up to seven weeks of degradation in SPB; after eight weeks, when the percentage weight loss reaches 75%, it decreases (see Table I) and the trend of the spectrum remains the same as that after seven weeks. Regarding the degradation in NaOH solution (pH = 12), the Raman and IR spectra (not reported) show an analogous behavior; the Raman $I_{875}/I_{1452}$ intensity ratio does not noticeably decrease up to four weeks. The spectrum of the membrane degraded for five weeks was not recorded because of the exiguity of the sample.

From the spectroscopic results, the Guidor® membrane seems to degrade without any significant change in crystallinity. Regarding the chain length, it seems to not vary up to seven weeks of degradation in SPB (and up to four weeks in NaOH solution), while after eight weeks of degradation in SPB, the Raman $I_{875}/I_{1452}$ intensity ratio suggests a decrease in chain length (see Table I).

### 3.1.3. DSC measurements

In order to elucidate the degradation mechanism, DSC measurements were performed. In Figs 4 and 5 we report the most meaningful DSC thermograms for the Guidor® membrane. The thermogram 4a, referring to the 1st run of the undegraded membrane, shows a glass transition at about 60 °C ($T_g$) according to the literature where a representative value for the $T_g$ of PLA is reported to be (55 ± 5) °C, independently of the stereoregularity of the polymer or of the molecular weight of the specimen [28]. Actually, we observe another glass transition at about 20 °C; this behavior was reported for low molecular

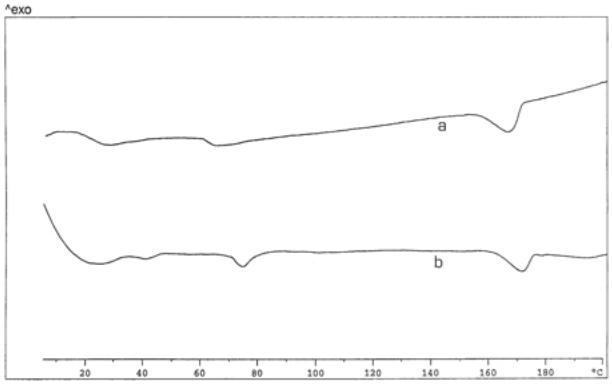


*Figure 4* DSC thermograms (1st runs) of a Guidor® membrane: (a) undegraded; (b) after degradation in 0.01 M NaOH solution at 37 °C for five weeks (% wl = 86%).

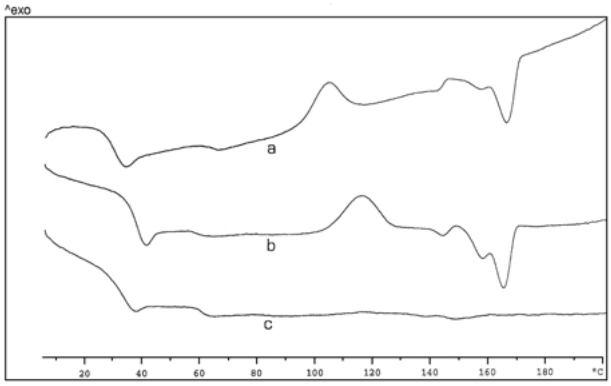


*Figure 5* DSC thermograms (3rd runs) of a Guidor® membrane: (a) undegraded and after degradation in 0.01 M NaOH solution at 37 °C for: (b) two weeks (% wl = 30%) and (c) three weeks (% wl = 43%).

weight D,L-PLA microspheres and was attributed to fast and slow degradation regions in the microsphere [34]. Moreover we observe an endothermic melting peak ($T_m$ = 167 °C, $\Delta H_m$ = 5.24 J/g) from which a $X_c$% of 5.6% was calculated. Therefore, according to the spectroscopic results, the Guidor® membrane has a prevalently amorphous character.

The 2nd run for the undegraded membrane (not reported) shows no signs of crystallization and only a glass transition at about 30 °C is observed: evidently, the polymer is unable to crystallize, despite the low cooling rate used. The 3rd run, reported in Fig. 5a, shows a sharp glass transition at about 30 °C, which looks like an endothermic melting peak, and another one less clear at about 60 °C, a large exothermic crystallization peak at 105 °C and another one complex and weaker at about 145 °C; regarding melting, we observe a broad and double endothermic peak at 158 and 167 °C. The broadening of the melting peak is typically displayed by low molecular weight polymers [29] and is indicative of different sized crystallites. The clear and sharp glass transition at 30 °C, the endothermic peak generated near it (attributed to the enthalpy stress-relaxation effect [30]) and the large crystallization exotherm observed in the 3rd run are indicative of a polymer that contains a large amorphous phase; in fact, we calculated $X_c$% from the 3rd run (under the assumption that the melting enthalpy has the same value for the different crystallites) and we found a value close to 0% indicating that the polymer at the end of the 2nd run was completely amorphous.

Regarding the degradation in NaOH solution, the 1st and the 2nd runs (not shown) of a membrane degraded for two weeks and which lost about 30% of its weight, show trends analogous to those of the undegraded membrane. In particular, for the 1st run, according to the spectroscopic results, no significant $X_c$% change with respect to the undegraded membrane was observed; moreover, no presence of oligomers or lactic acid was detected because of the absence of the endothermic peak at about 80 °C [34] indicating that, at this stage, the degradation products are solubilized in the degradation medium, according to the spectroscopic results.

Regarding the 3rd run of the above mentioned membrane (Fig. 5b), some changes are observed in the exothermic and endothermic peaks with respect to the thermogram of Fig. 5a: the main exothermic crystal-

lization peak occurs at a higher temperature ($T_c = 116\,^{\circ}C$), indicating that the degraded chains have become more difficult to crystallize. Another exothermic crystallization peak occurs at about 150 °C. Moreover, the components at 144, 158 and 165 °C of the endothermic melting peak are better resolved than in thermogram 5a indicating that the range of the size of the crystallites – and thus the range of molecular weights – becomes larger. This result seems to indicate a certain molecular weight dispersion not detected by the Raman $I_{875}/I_{1452}$ intensity ratio which remains unchanged with respect to the undegraded membrane. In spite of the changes observed with respect to the undegraded membrane, the 3rd run shows that the degradation products remain capable of crystallizing. On the contrary, for a membrane which has lost 43% of its weight, the 3rd run (Fig. 5c) shows only a double glass transition at 33 and 60 °C (the 1st and the 2nd runs were unchanged with respect to those of the undegraded membrane) and no sign of crystallization is observed indicating that, at this stage of degradation, the polymeric chains have become too short to crystallize. It is interesting to notice that this inability to crystallize is observed for the first time at the beginning of the second dramatic increase of percentage weight loss (see Fig. 1). This result shows that percentage weight loss dramatically increases only when the molecular weight of the polymeric chains decreases to some extent.

The 1st run for the membrane degraded for five weeks in NaOH solution (% wl = 86%) shows further degradation of the polymeric chains (Fig. 4b); in fact, besides a glass transition at 38 °C and the endothermic melting peak at about 170 °C, it shows another endothermic peak at 76 °C attributable to the melting of degradation products with lower molecular weight [34].

An analogous trend was observed for the degradation in SPB even if with a time lag in agreement with a slower degradation; the inability to crystallize in the 3rd run appears for the Guidor® membrane degraded for five weeks (% wl = 6%), that is at the beginning of the dramatic increase of percentage weight loss (see Fig. 1). At a later stage, as well as in NaOH solution, the polymeric chains undergo further degradation: the 1st run (not shown) for the membrane degraded for eight weeks in SPB (% wl = 75%) is comparable to that of Fig. 4b and shows the endothermic peak at 76 °C due to the melting of the degradation products of lower molecular weight together with the other endothermic peak at 167 °C. The presence of the melting peak at 76 °C suggests that, at this stage, the degradation products of lower molecular weight should be entrapped in the membrane; the decrease in the Raman $I_{875}/I_{1452}$ intensity ratio in the corresponding spectrum of Fig. 2c confirms this result, even if the 830 $cm^{-1}$ (C–COOH stretching mode [24]) reported as the main marker band of oligomers and LA as well as the bands due to their anions [39] are not observed. Moreover the presence of complex melting peaks corresponding to different molecular weight polymeric chains, would suggest that, both in NaOH solution and in SPB, the degradation should be heterogeneous since the polymeric chains are not all degraded to the same degree. Parallelepiped devices (15 × 10 × 2 mm) made of various PLA/PGA polymers and copolymers were reported [13–15] to degrade heterogeneously with bimodal size exclusion chromatograms: the internal part degrades faster than the surface leading, in the case of amorphous materials, to hollow structures. Moreover, a size-dependence of the degradation mechanism was reported [40]: 0.3 mm thick PLA50 films degrade homogeneously with monomodal size exclusion chromatograms. For the Guidor® membrane (about 0.5 mm thick), our measurements show heterogeneous degradation; it was not possible to localize the more degraded polymeric chains since no hollow structures were detected because of the low thickness of the membrane. Therefore, no measurements were performed on the ''internal'' part or on the surface of the membrane.

## 3.2. *In vivo* degradation

In Fig. 6 we report the Raman spectrum of a Guidor® membrane implanted for four weeks; it does not show significant changes with respect to that of the untreated membrane, except for the bands at 1661 and 1605 $cm^{-1}$ attributable to νC═O stretching modes of a biological component, not removed despite the washing treatment. In fact, at the time of explantation, the membrane appeared strongly integrated with the surrounding tissues.

The Raman $I_{875}/I_{1452}$ intensity ratio reaches about the same value as that after eight weeks of degradation in SPB (see Table I). Probably this value appears to be an underestimation, since the intensity of the band at 1452 $cm^{-1}$ could be increased by the contribution of the biological component. Therefore the percentage weight loss should be lower than 75% but probably higher than 5% (values found for the membrane degraded for eight weeks and four weeks respectively in SPB, see Fig. 1). Therefore the Guidor® membrane should degrade faster *in vivo* than *in vitro*. For this purpose, the enzymatic contribution to the *in vivo* degradation represents a much discussed question [35, 41]; however, the presence of enzyme molecules is known to affect the degradation of PLA and PGA.

As well as for the *in vitro* degraded membranes, the Raman spectrum of the *in vivo* degraded membranes do

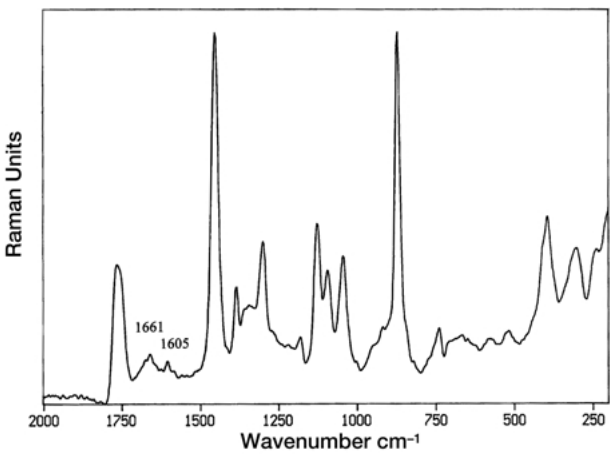


*Figure 6* FT-Raman spectrum of a Guidor® membrane implanted for four weeks.

not show the presence of oligomers and lactates because of the lack of their marker bands. As was stressed for the Guidor® membrane degraded for eight weeks in SPB, this result does not allow us to exclude the presence of degradation products with lower molecular weight entrapped in the membrane even if they could be more leachable *in vivo* than *in vitro* because they could be more easily absorbed by the surrounding tissues, as observed for the degradation of the Vicryl® membrane [16]. The impossibility of recording the DSC thermograms for the *in vivo* degraded membrane does not allow any predictions.

## 4. Conclusions

Vibrational and thermal studies point out that the Guidor® membrane has a prevalently amorphous structure; from the Raman $I_{875}/I_{1452}$ intensity ratio it can be deduced that it is composed of low molecular weight polymeric chains. These structural and morphological characteristics strongly influence the mechanism and kinetics of the *in vitro* and *in vivo* degradation of the membrane: the Guidor® membrane seems to degrade without any significant increase in cristallinity, differently from the Vicryl® membrane previously studied [16].

The degradation rate is higher in NaOH solution than in SPB and is lower than for the Vicryl® membrane [16] in both the media. This result can be explained by considering the different compositions of the membranes: in fact, the Vicryl® membrane contains a high percentage of the more hydrophilic GA unit.

The trends of percentage weight loss versus time in both the media were discussed in relation to DSC and spectroscopic measurements which showed a progressive decrease in molecular weight during degradation.

Regarding the *in vivo* degradation, it seems to occur faster *in vivo* than *in vitro*, as observed for the Vicryl® membrane [16]. Moreover, the presence, spectroscopically revealed, of a biological component entrapped in the membrane proves the good integration of the Guidor® membrane with the surrounding tissues, already after four weeks; this early integration is greatly appreciated since it eliminates or reduces epithelial downgrowth and thus minimizes gingival recession and device exposure. This result reveals the efficacy of the Guidor® membrane which is a good material even if off of the market, as revealed by the interest in this membrane [17, 18] and in those based on PLA [19, 20] in the recent literature.

It is interesting to notice that the Guidor® membrane degrades in 10 weeks in SPB (pH = 7.4, 37 °C), that is the degradation rate is noticeably higher than for other PLAs which are reported to degrade, under the same conditions, in one to two years [2, 13].

The degradation kinetics found for the Guidor® membrane is strongly dependent on its low molecular weight and on its prevalently amorphous morphology, resulting from its composition based on both enantiomers of lactic acid. Therefore, the Guidor® membrane represents a good example in the strategy of modulating the degradation properties of biomedical materials, by varying the structural and morphological characteristics of the polymer. Obviously, this modulation is required because different materials with different degradation properties need to be available depending on the biomedical application. For this purpose higher molecular weight PLA100 (composed of only the L-enantiomeric form) which retains its mechanical properties for a longer period of time will be used in orthopedic applications, while amorphous low molecular weight fast-degrading PLAs and PLAGA will be used in all the applications where only a temporary maintenance of the physical and mechanical properties of the polymer is required.

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