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Comment on "D-Poly(lactide) and LHRH decapeptide stereointeractions investigated by vibrational spectroscopy"

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Abstract

This note is a response to Zhang et al. [Zhang J, Beshra A, Domb AJ, Ozaki Y. D-Poly(lactide) and LHRH decapeptide stereointeractions investigated by vibrational spectroscopy. Eur Polym J 2007;43:3016–27] who reported spectroscopic data for blends of poly-D-lactide and LHRH (a leuprolide decapeptide analog). These authors concluded to the presence of a stereocomplex between those two species but it is shown, in this note, that the results obtained as well as literature results do not support this conclusion.

Keywords: Polylactide; LHRH; IR spectroscopy; Sterecomplexation

In 2001 [1], 2003 [2–4] and 2004 [5], Slager et al. reported the formation of a complex between poly(D-lactide) and luteinising hormone releasing hormone (LHRH), a leuprolide analog of L-configuration. This phenomenon, which is quite interesting if it is the case, was based on the formation of a white precipitate consisting of spherical particles when the polymer and the peptide were mixed together in acetonitrile, and on the presence, in the DSC curves, of a dual endotherm for the mixture, the lower temperature peak being assigned to the less stable β-helical form of PDLA [1,3,5]. The ^{1}H NMR results showed no additional peaks that could be assigned to LHRH, and no deviation in the polymer signals even at a LHRH loading of 20% or higher [1,2]. The same negative observation was made using FT-IR spectroscopy [1,2]. In NOESY experiments, no cross-peak corresponding to intermolecular correlation was found [5]. Moreover, no structural modification was detected by X-ray diffraction [1,2] and solid-state ^{13}C NMR spectroscopy [1,2,5] in contradiction with the presence of a β-form. Therefore, we may question the validity of the authors' conclusion in terms of stereocomplexation.

In 2005, we have analyzed the same system by DSC, X-ray diffraction, FT-IR and Raman spectroscopy [6]. The clear conclusion was that there is no peptide incorporated in the precipitate obtained from acetonitrile solutions containing 5% (w/w) LHRH, and no evidence of the presence of any kind of stereocomplex. A very important point of that

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paper was the observation of a similar behaviour between poly(D-lactide)/LHRH and poly(L-lactide)/LHRH mixtures.

Recently, Zhang et al. published another paper on the PDLA/LHRH mixture and, using FT-IR, Raman and FT-NIR spectroscopy, concluded to the presence of stereocomplexation between these two molecules [7]. This conclusion is not supported by the experimental data.

Let's begin by defining what a stereocomplex is. With Zhang et al., we agree that it involves interactions between two complementary stereoregular polymers, "forming a new composite with altered physical properties in comparison with their parent polymers" (Ref. [7] p. 3016). A clear example is the PDLA/PLLA mixture that has been exhaustively described in the literature [8–18]. The stereocomplex formed between PDLA and PLLA exhibits a melting temperature 50 °C above that of the pure parent polymers, which is accompanied by a crystalline structure modification from the α form (10_3 helix) to the β form (3_1 helix), as confirmed by X-ray diffraction and spectroscopic measurements (IR, Raman and NMR). The same kind of observation was made for the stereocomplex formed between poly(α-methyl-α-ethyl-β-propiolactones) of opposite configurations that show a melting temperature 30 °C above that of the parent polymers and significant differences in their X-ray diffraction profiles [19,20].

What do we get when PDLA and LHRH are mixed together, is a new compound with altered physical properties formed? The DSC curve of the precipitate shows two distinct endothermic peaks, the high temperature melting peak clearly corresponding to pure PDLA. Domb et al. first suggested that the low temperature melting peak could correspond to the melting of the β form of the stereocomplex [1,3,5], but we now all agree [6,7] that the double melting peak merely indicates the presence of crystals of different perfections as is frequently the case with polymers [21–23].

Let's also consider the other evidence shown in Ref. [7] in which IR spectroscopy was used to characterize the precipitate. The IR spectrum (Fig. 6) of the mixture loaded with 10% LHRH (sample prepared in a KBr pellet) does not exhibit any characteristic band corresponding to the peptide; the conclusion that "PDLA just stereocomplex with LHRH on a fixed ratio" (p. 3020) is intriguing because, if the complex really exists, band shifts and/or peak broadenings are expected. At 20% LHRH loading, signals from the peptide show up (in Ref. [1] p. 108, they were not visible under the same conditions) but there is still no broadening or shift for the PDLA peaks. The LHRH peaks are more intense at 30% loading, as expected.

Samples for IR analysis were also prepared in the form of films, with spectra different from those prepared in the KBr pellet (at the same LHRH loading). Fig. 4 of Ref. [7] shows the transmission IR spectrum of a 10% LHRH loading thick film exhibiting two amide I bands at 1668 and 1615 cm^{-1} and one amide II band at 1516 cm^{-1}, all characteristic of the presence of LHRH; the authors' conclusion is that "*LHRH does exist and complexes with PDLA*" (p. 3020) but, since no band shift is observed, this conclusion seems excessive because the results merely describe the formation of a blend (simple addition of the individual spectra of the two species involved).

In summary, all IR spectra shown in Ref. [7] merely correspond to blend spectra, as was the case for the numerous IR and NMR results described in Refs. [1–5]. If specific interactions would occur between the two species, the resulting spectrum should exhibit significant differences, i.e., band shifts and/or broadenings, intensity changes, in comparison with the co-addition of the spectra of the pure components. Ref. [7] does not present a spectrum of the PLLA/LHRH mixture, which is unfortunate because we have shown, in Ref. [6], that in many instances, the spectra of the PDLA/LHRH and PLLA/LHRH mixtures are indistinguishable.

In view of these results, let's come back to the initial question: were interactions leading to altered physical properties (in comparison with the parent polymers) observed between PDLA and LHRH? The answer is clearly no. DSC measurements do not indicate the presence of a peak corresponding to a new species. Spectroscopic (IR) measurements exhibit no peak shift or peak broadening that could be assigned to any kind of interactions. There is clearly no stereocomplexation between these two species. However, we have shown in Ref. [6] that the presence of LHRH in the blend slightly changes the crystallization process of PDLA, but it does not only with the addition of LHRH but also with the addition of poly(L-lysine), poly(L-glutamic acid) and water. Moreover, the same phenomenon is observed with blends of PLLA and LHRH which, in any case, cannot lead to the formation of a stereocomplex since these two molecules are of the same configuration.

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