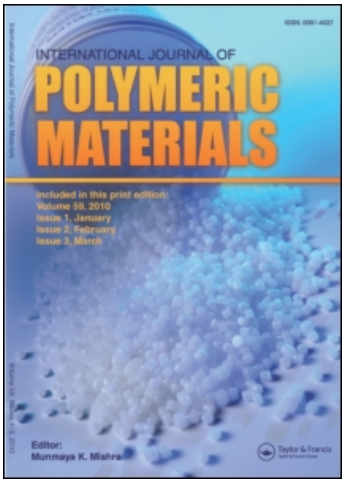

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Synthesis and Characterization of a Novel Zn-polycarboxylate Ocular Adhesive

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A Zn-polycarboxylate biocompatible adhesive was synthesized from polyacrylic acid and Zn-acetate solutions. The influence of reactant concentration, from 1 to 3 N, on the properties of this compound, was studied. The reaction product was characterized by both infrared (IR) and Raman spectroscopies and scanning electron microscopy. Adhesion behavior was evaluated by 90° and 180° peel-out testing using wood and cow-hide as substrates, to simulate bonding to living tissue. The measured adhesion strength increases with reactant concentration. *In-vivo* tests were performed in dogs. Preliminary results show a transparent and flexible polymer material with very good adhesion to cornea tissue.

Keywords: Polycarboxylate; Adhesives; Biomaterials

INTRODUCTION

Ocular surgeries, especially retinopexy techniques, have significant practical limitations which jeopardize proper healing procedures for patients. None of the available methods neither reestablishes retinal continuity nor provide significant adhesive strength. Most of the methods currently used must be combined with procedures that relieve

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traction or that will temporally protect the surgical wound until a retinal scar develops. However, those procedures may result in cataract, glaucoma, and corneal opacification [1]. Aiming to overcome those problems, cyanoacrylate polymers have been extensively studied as synthetic adhesives [2–5]. In spite of the fact that cyanoacrylates have shown successful anatomic reattachment in clinical test after 6 months [6], they have also been found to have some degree of toxicity in tissue culture [7]. Moreover, they are difficult to handle, for the surgeon requires a very specific applicator, are mildly exothermic and some cyanoacrylates monomers may be carcinogenic [8].

Conversely, polycarboxylates are the product of the polyacrylic acid (PAA)-metal oxide reaction. As a result of such reaction, a crosslinking process occurs between the polymeric and the inorganic phases. During the first stages of the reaction, hydrogels with interesting properties are formed [9, 10]. These hydrogels have found practical applications in dentistry, since they were first synthesized in the late 1960s [11], due to their good biocompatibility and adhesion.

In the present study, a novel Zn-polycarboxylate adhesive to be used in ocular surgery is synthesized; its adhesion properties, studied by peel-out testing, are presented herein. *In vivo* preliminary results are presented as well.

EXPERIMENTAL

97-w% zinc acetate (ZnAc) was synthesized from zinc oxide (ZnO) and 30 w% solution of acetic acid (HAc). Polyacrylic acid (PAA) 1, 1.5, 2, 2.5 and 3 COOH equivalents/ml aqueous solutions were prepared from 38.75 w% PAA (Aldrich). The PAA molecular weight was 132,000 g/mol, as measured by viscosimetry.

The adhesives samples were prepared by reacting varying amounts of equimolar concentration solutions of PAA and ZnAc, as indicated Table I. The reaction was carried out at room temperature. The ZnAc solution was added dropwise to thoroughly stirred PAA solution. In order to avoid agglomeration, the reaction was allowed to set after each drop was added to the ZnAc sol. The reaction was stopped when a fluid gel mixture was achieved, prior to complete gelation. Each reaction product was washed with deionized water. Each sample was

TABLE I Molar relations of prepared samples

Formulation	*ZnAc*	*PAA*
I	1	1
II	1	1.5
III	1	2
IV	1	2.5
V	1	3

in two parts, one was used in adhesion and preliminary *in vivo* tests; the other was dried in a vacuum oven at 70°C prior to be characterized by infrared (IR) and Raman spectroscopy, and scanning electron microscopy (SEM).

IR, Raman and SEM samples were prepared from dried powder ground in a mortar. IR spectra were run in a FTIR Nicolet 5 PC in the range 4000 to 300 cm^{-1}, with resolution of 4 cm^{-1}, and were analyzed in a Nicolet 680-work station. Powder of PAA and adhesives formulations were mixed with KBr (1 : 1000 = to form a tablet using a pressure of 5000 psi). Raman spectroscopy was carried out in a Nicolet 910-FT Raman bench equipped with a YAG-Nd infrared laser (1064 nm). The SEM micrographs were obtained in JEOL JSM-5200 machine in the range 1 – 40 kV on gold covered samples.

Adhesion properties were measured by peel-out testing 90° and 180°, peeling tests were performed using cow hide, and cow hide and wood as substrates, respectively. Ten specimens of each formulation were tested in a DY test machine according to ASTM 1876 and 903.

Preliminary *in vivo* tests were carried out in dogs' ocular muscle, conjunctiva and cornea tissue. 1 mm scissions were made on the cornea surface and then a small amount of adhesives was applied. On conjunctiva tissue and ocular muscle, 2 mm scissions were made, and then slight pressure was applied. In all those cases drying time and adhesion were carefully observed.

RESULTS AND DISCUSSION

FTIR spectra of PAA, ZnAc, samples V and I are shown in Figure 1, and were chosen as typical examples of the set of specimens prepared. As observed there, the carbonyl 1719 cm^{-1} band present in PAA

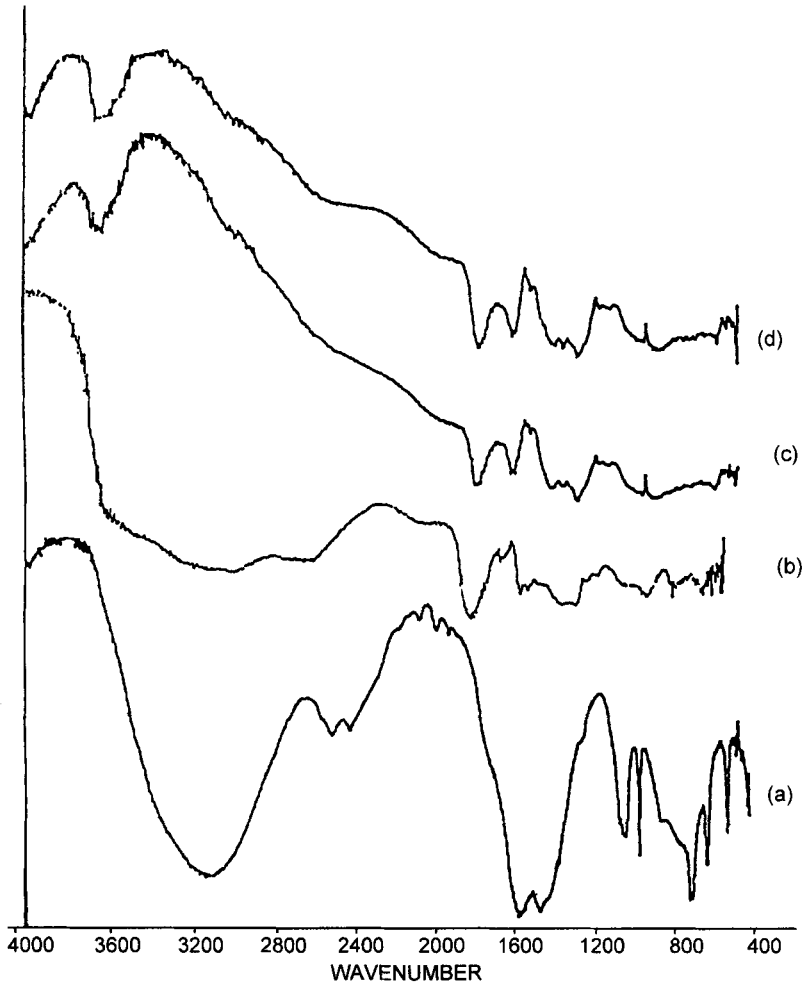


FIGURE 1 FTIR Spectra of (a) AcZn, (b) PAA, (c) Formulation I and (d) Formulation V.

spectrum remains in the spectra of both Zn-polycarboxylate formulations shown. As we have discussed previously, the reaction was not carried out up to complete crosslinking since it is impossible to use completely crosslinked formulations as adhesives. The $1717\,cm^{-1}$ band shows the presence of PAA reactive still of the final product. The $1546-1555\,cm^{-1}$ band corresponds to the C—O bond stretching in the salt. Those bands, clearly absent in PPA spectrum,

show the reaction between ZnAc and PAA. The 1175 cm^{-1} band, corresponding to hydrogen bridging between OH in PAA, disappears due to the Zn salt produced during the reaction. IR spectra clearly

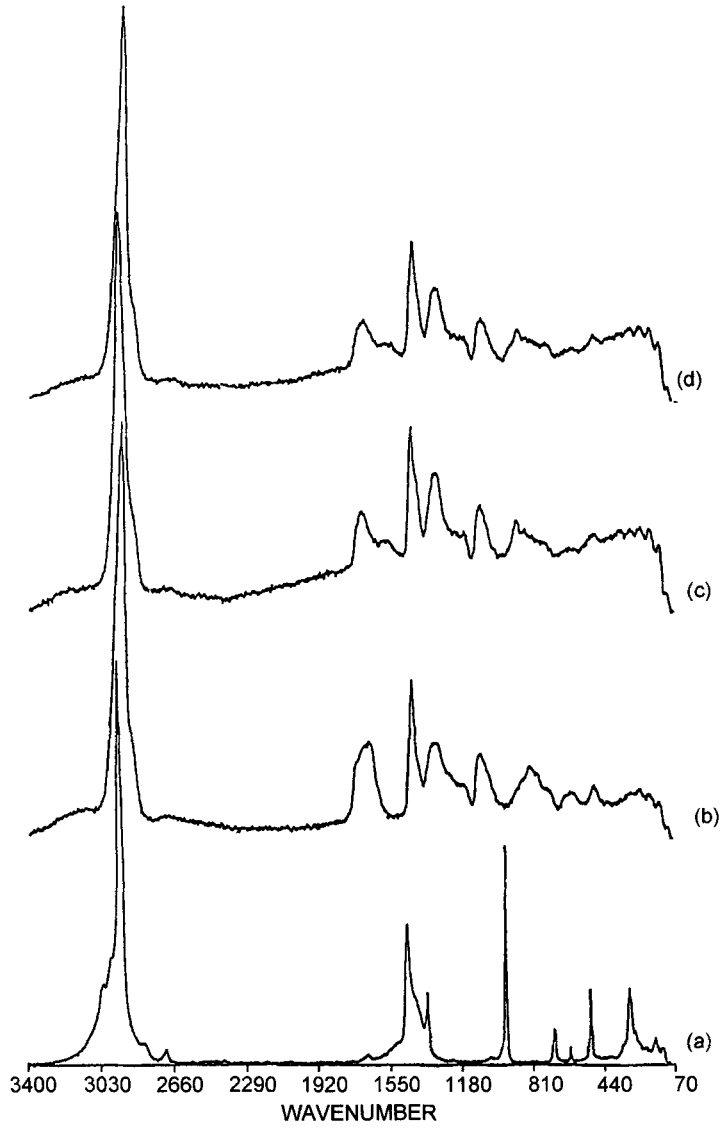


FIGURE 2 RAMAN Spectra (a) AcZn, (b) PAA, (c) Formulation I and (d) Formulation V.

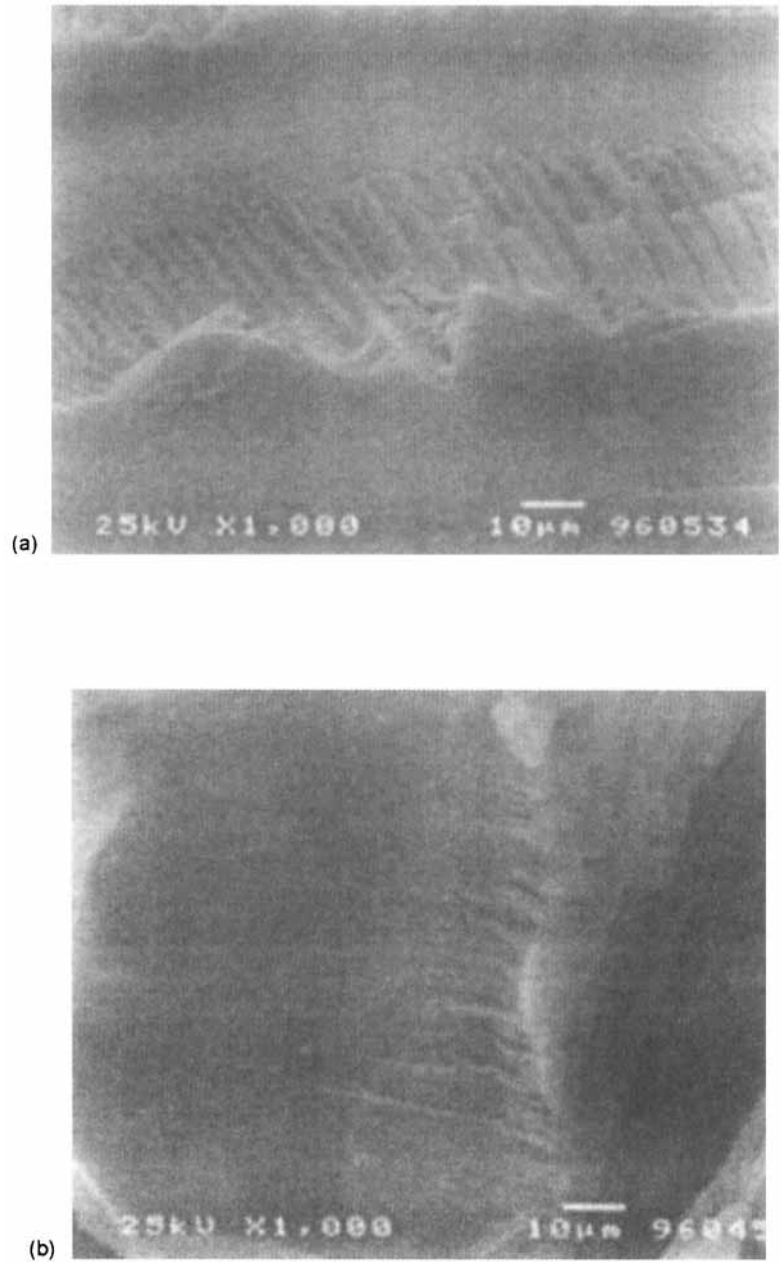
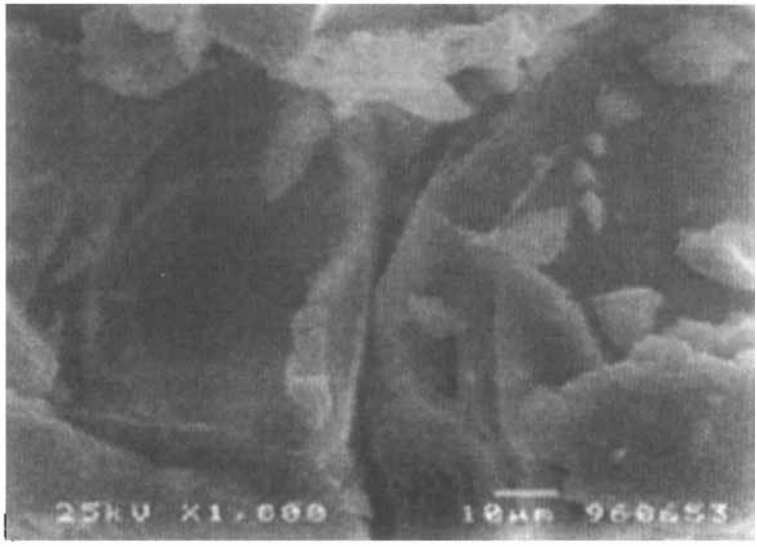


FIGURE 3 SEM micrographs of (A) PAA, (B) Formulation I and (C) Formulation V.



(c)

FIGURE 3 (Continued).

show chemical interaction between PAA and Zn as the crosslinking proceeds. It is important to point out that the spectra shown in the above figures correspond to different amounts of samples. Upon normalizing with respect to the sample weight, large differences between samples I and can be appreciated.

Figure 2 shows the Raman spectra of PAA, ZnAc, I and V formulations. The —COOH stretching band at $1707\,cm^{-1}$ is shown by both formulations spectra. At $1575-1586\,cm^{-1}$, a new band can be seen corresponding to —(COO)Zn asymmetric stretching. Raman spectrometry confirms the above IR results, showing chemical bond between Zn and PAA but not complete reaction.

Typical SEM micrographs are shown in Figure 3. The morphology of PAA and samples V and I is shown there. Sample I and PAA look like rigid materials. However, sample V shows higher porosity and roughness as compared to PAA.

Peel-out testing shows clear difference among formulations. 180° peel test results are higher than 90° because of the porosity of wood used as a substrate. For each formulation, the higher the substrate porosity, the higher the adhesion, which is the well-known

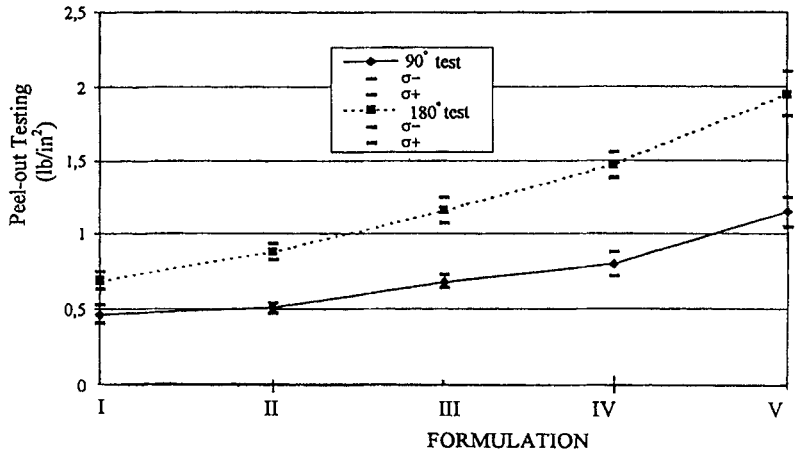


FIGURE 4 Peel-out testing using wood as substrate.

"mechanical keying effect". However, not only the substrate but also the more concentrated solutions increase adhesion. In the range of concentration studied, adhesive force increases 150% and 185% in 90° and 180° peel test respectively (Fig. 4).

Preliminary *in vivo* tests show very good results in cornea. Poorer results were obtained in conjunctiva and ocular muscle. Less adhesion was due to the higher humidity of conjunctiva and ocular muscle as compared to cornea. To enhance adhesion properties, completely or almost completely dried surfaces are needed. Upon adhesive curing, the surfaces remain weakly joined in wet environment. Although drying time was 30 min, which is longer than usual surgery times, after drying the adhesives form a transparent and flexible layer, suitable for surgery applications.

CONCLUSIONS

The synthesis of a novel polymeric ocular adhesive, based on the homogeneous reaction of two liquid components (namely the PAA and the ZnAc) was achieved. The results show both the production of a new material with controllable crosslinking degree and its feasibility to be employed as a non-toxic ocular adhesive, since carboxylates have been extensively used in oral surgery.

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