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CHITOSAN MEMBRANES FILLED WITH CYCLOSPORINE A AS POSSIBLE DEVICES FOR LOCAL ADMINISTRATION OF DRUGS IN THE TREATMENT OF BREAST CANCER

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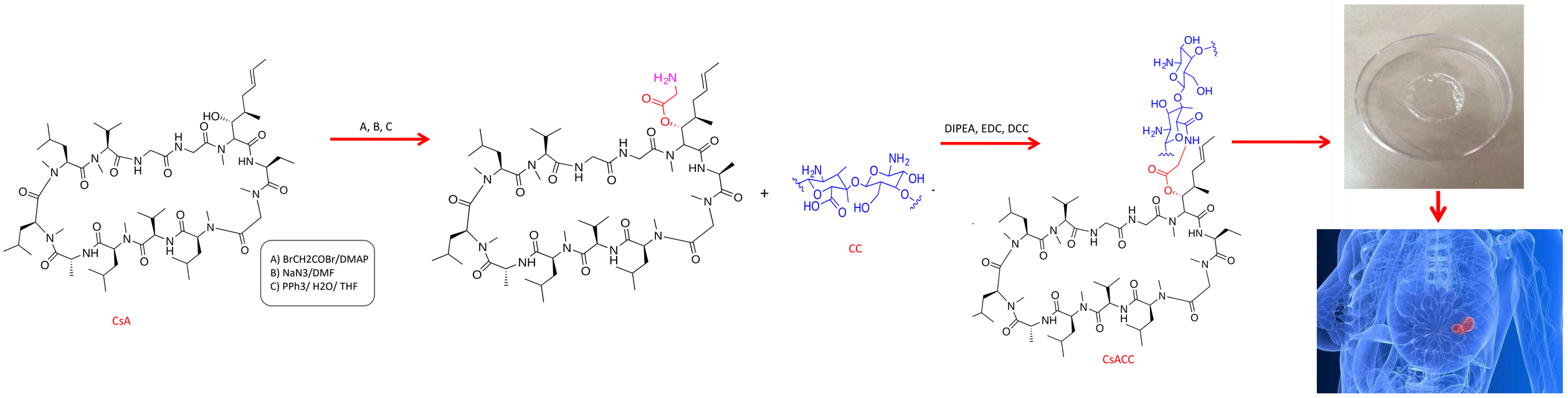
INTRODUCTION

Breast cancer is one of the most common neoplastic diseases among women, whose therapeutic approach involves various methods responsible for serious side effects, which reduce the quality of life of patients. One approach that reduces side effects is to locate the drug directly in tumors and cancer cells. Recently, it was discovered that CsA, an immunosuppressive drug used to prevent rejection in organ transplants, also possesses an anticancer activity that may inhibit the proliferation of breast cancer. The aim of the work was the design, preparation and characterization of dense polymeric membranes, based on cyclosporine A (CsA) and chitosan carboxylate (CC) useful as an implantable subcutaneous medical device for prolonged drug release when placed directly in contact with the neoplastic lesion. In particular, CsA was bound to CC through an amidation reaction to obtain a pro-drug dispersed inside a chitosan-based polymeric matrix.



MATERIAL AND METHODS

Amide, CsA and CC were characterized by Fourier Transform Infrared Spectroscopy (FT-IR) (Figure 1), Proton nuclear magnetic resonance ([1]HN-MR) (Figure 2) and Differential Scanning Calorimetry (DSC) (Figure 3). In particular the presence of amide was confirmed by FT-IR spectrum that showed the presence of a new band at 1621 cm-1 correlated to the stretching vibration of the C=O amide and by [1]H-NMR analysis that has provided a very broad and complex spectrum in CDCl3 in which are evident the signals of the N-methyl groups and those related to CH3 in the side chain of different amino acid residues. The DSC curves of CC showed an endothermic peak at 205 °C, the amide derivate at 207 °C, while the CsA (curve not shown) at 244° C.

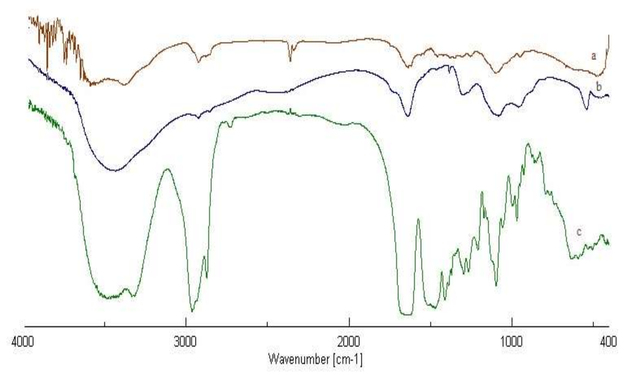


Figure 1. CsACC (a), CC (b) and CsA (c) FT-IR spectrum

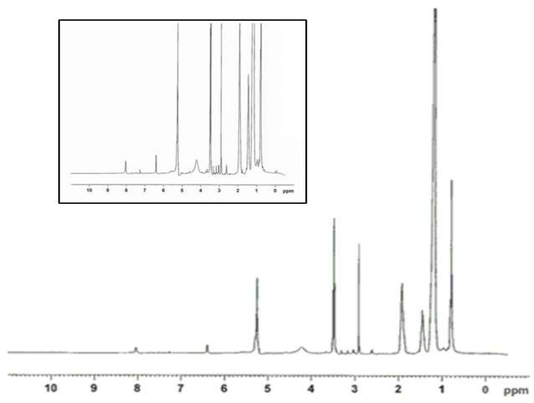


Figure 2. [1]H-NMR spectrum of CsACC

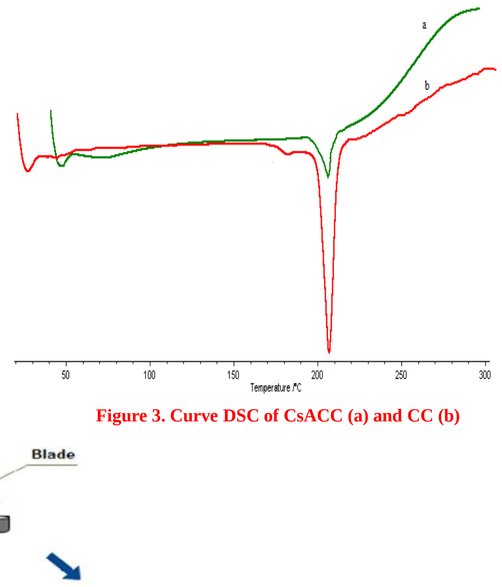


Figure 3. Curve DSC of CsACC (a) and CC (b)

Membranes were prepared using the phase inversion induced by solvent evaporation (Figure 4).

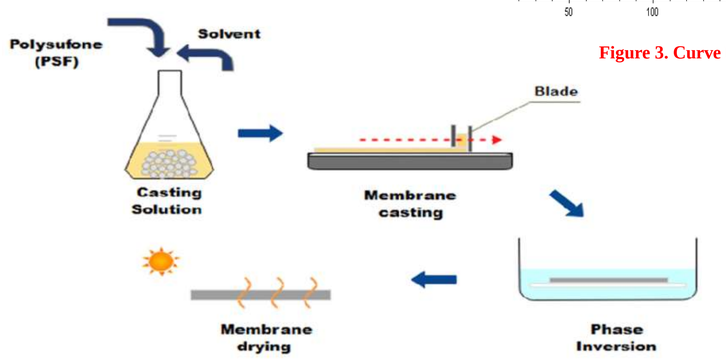


Figure 4. Method of phase inversion

RESULTS

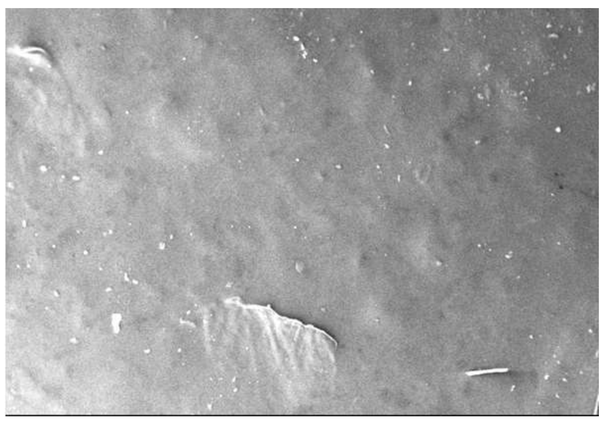


Figure 5. SEM micrography of membrane based on chitosan+CsACC

The morphological properties of membranes were analyzed using Electronic Scanning Microscopy (SEM) that showed a dense structure in which CsA appeares like filaments that protrude from the membrane (Figure 5).

The effects of CsACC membranes and CsA free on the viability processes of cellulose in human breast cancer cells MDA-MB-231 (triple negative carcinoma), were analyzed by cell proliferation assay. At the concentrations used in the experiment, after 72 hours of treatment, significant biological effects were observed in our experimental model. In particular, the results obtained showed a significant decrease in cell viability especially in cells treated with CsACC and with chitosan mixed with free CsA (Figure 6). This effect is not observed by treating the cells uniquely with CsA at the same concentration with which it is present in the membranes.

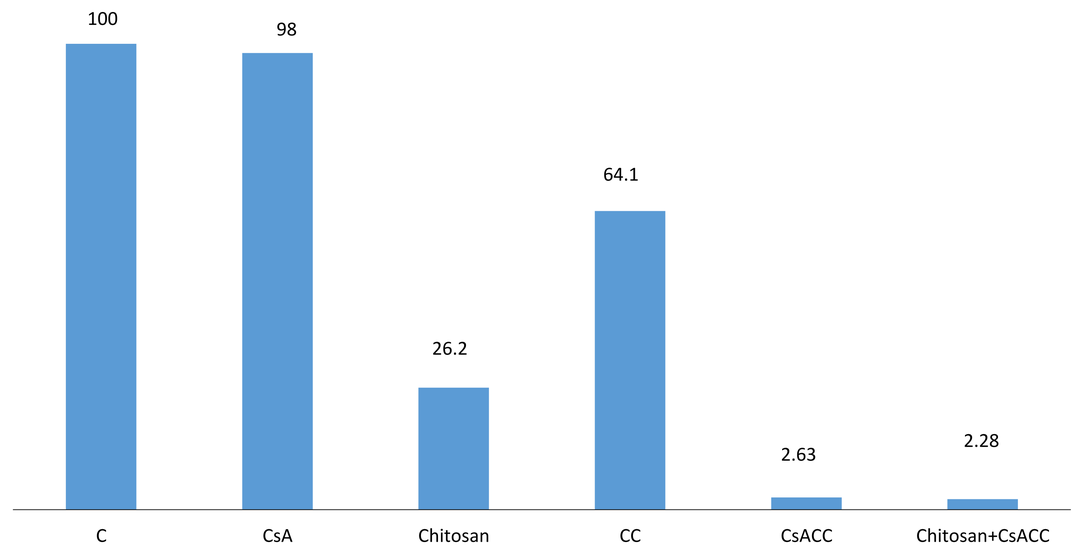


Figure 6. Cell proliferarion assay

CONCLUSION

The CsACC membranes were prepared by dispersing, inside a polymeric matrix, based on chitosan, the CsACC obtained by amidation reaction between derivatized CsA and carboxylated chitosan. In vitro tests showed a decrease in MDA-MB-231 cell viability 72 hours after treatment. For this reason, these devices could potentially be useful, in the form of subcutaneous implants, in the treatment of breast cancer.