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RESEARCH ARTICLE

Controlled release of drugs from cellulose acetate matrices produced from sugarcane bagasse: monitoring by square-wave voltammetry

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ABSTRACT

In this paper, cellulose triacetate (CTA) was produced from sugarcane bagasse and used as matrices for controlled release of paracetamol. Symmetric and asymmetric membranes were obtained by formulations of CTA/dichloromethane/drug and CTA/dichloromethane/water/drug, respectively, and they were characterized by scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). Different morphologies of membranes were observed by SEM, and the incorporation of paracetamol was confirmed by lowering of the glass transition temperature (T_g) in the DSC curves. This indicates the existence of interactions between the matrix and the drug. The evaluation of drug release was based on the electrochemical monitoring of paracetamol through its oxidation at a glassy carbon electrode surface using square-wave voltammetry (SWV), which provides fast, precise and accurate *in situ* measurements. The studies showed a content release of 27% and 45% by the symmetric and asymmetric membranes, respectively, during 8 h.

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Introduction

Controlled release systems are, ideally, devices that disseminate an active agent when and where it is required at a level of concentration sufficient to generate the expected effect[1]. Controlled release systems are designed to prolong the release time of the drug in the organism, to sustain its plasma concentration and to control the temporal and spatial location of molecules *in vivo* through biological and chemical principles. In this way, cyclical changes in the concentration are eliminated and the bioavailability of the drug is increased. Furthermore, drug toxicity can be reduced, and controlled release systems can suppress adverse reactions, decrease the number of doses administered, increase the safety of drugs and can increase the plasma concentration of active principles with a short half-life[1].

The improvement in the development of controlled release systems depends on the selection of an appropriate agent that is capable of controlling drug release, maintaining the therapeutic action over time and/or releasing the drug at a specific target tissue or organ. Given the various options, polymers are versatile and promising agents to perform such functions[2]. Cellulose acetate is one of the components used in systems for controlled release of drugs and are used in the form of membranes[3–19].

In previous work[6], symmetric and asymmetric membranes of cellulose triacetate, produced from sugarcane bagasse were used as matrices for the controlled release of drugs. The drug incorporated was doxycycline and the release was evaluated by spectrophotometric analysis in the ultraviolet visible region. The study showed that the morphology of the membranes has a great influence on the desorption of the drugs and that the release occurs predominantly by diffusion.

Beyond spectrophotometric technique, voltammetry has been cited in the literature for drugs quantitation[20–37], which have electroactive groups that can be detected voltametricamente[7]. We recently have demonstrated that SWV is a very attractive analytical technique for studying naproxen controlled releasing from cellulosic materials. This technique is especially useful to real-time monitoring of the fast initial release stages, which cannot be accessed by analytical techniques usually employed in controlled drug releasing studies, such as spectrophotometry or chromatography. In addition, SWV can be successfully used to follow naproxen releasing profiles from cellulosic microparticles, which is difficult by spectrophotometry in the UV region.[7]

In this work, cellulose acetate produced from sugarcane bagasse was used in the production of membranes as matrices for the incorporation of paracetamol. The study of drug release from the polymer matrix was made by SWV, which is a fast and accurate electroanalytical technique that is able to monitor paracetamol in real time once the electrochemical sensor is placed inside the subject of the drug release experiment. SWV presents several advantages over the traditional ultraviolet visible spectrophotometry technique, including higher sensitivity and selectivity, wider linear concentration range, and no need for sample collection (*in situ* monitoring).[20]

Experimental

Purification of sugarcane bagasse and production of cellulose triacetate

Sugarcane bagasse was delignified and further acetylated according to the methodology described. Delignified bagasse is composed of

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87.59% cellulose, 12.00% hemicellulose and 0.41% lignin. The produced cellulose acetate presents a degree of substitution of 2.80 ± 0.09 and is classified as cellulose triacetate and a viscosity average molecular weight of 39 000 g mol^{-1}, as previously reported.[6]

Membrane production and paracetamol incorporation

The casting solution was prepared by dissolving CTA (10.0% w/w) and paracetamol (5.0% m/m) in dichloromethane (MB-SYMpara). For the asymmetric membrane, the same formulation was utilized, and 10% water was added as a pore-forming agent (MB-ASYpara).

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to analyze the membrane surfaces and cross sections. In order to obtain cross sections, the membranes were fractured in liquid nitrogen. The samples were gold coated, and then, micrographs were obtained in a Carl Zeiss, EVO MA 10 scanning electron microscope, (Oberkochen, Germany) operating at 10 kV.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) measurements were carried out in a TA Q-20 equipment (New Castle, DE) at 10 °C min^{-1}, using a nitrogen inert atmosphere at 50 cm^3 min^{-1}. The scan first was carried out from 20 °C up to 350 °C. In second scan, the samples were heated to 250 °C and immediately cooled to 70 °C and heated again up to 280 °C, in order to determine the glass transition (T_g) of the polymer.

Study of paracetamol release from cellulose triacetate membranes by square-wave voltammetry

In the evaluation of drug release, a thermostatic bath was used in order to ensure that the temperature of the experiment was maintained about 36.5 °C, and phosphate buffer solution (pH 7.4) was used[6]. Drug release was monitored in the solution from a Type III μAutolab potentiost at connected to a microcomputer. For controlling the equipment, GPES software, (Low Countries, Netherlands) version 4.9, was used. The drug-release measurements were obtained using square-wave voltammetry.

The microcell consisted of a 50-mL beaker, a platinum wire as a counter electrode, a glassy carbon disc electrode (2 mm diameter) as the working electrode and a miniaturized Ag/AgCl (sat. KCl) electrode built on a micropipette tip as a reference electrode[20].

The glassy carbon-working electrode was polished in alumina suspension and then washed with deionized water. For the analysis procedure, 25 mL of a phosphate buffer solution preheated to 36.5 °C and a portion of the membrane containing the incorporated drug was introduced into the micro cell. Next, the three electrode system was introduced and held the first voltammogram ($t = 0$). From this voltammogram, others were performed every 20 min. All voltammograms were made using the following conditions: initial = 0.0 V; final = 1.00 V; step potential = 0.01995 V; amplitude = 0.04995 V; frequency = 20 Hz; scan rate = 0.399 Vs^{-1}.

Results and discussion

Membrane characterization

SEM study

The membrane morphology, which plays a key role in the drug release kinetics, can be studied by SEM. Figure 1 shows the results for cross section and surface structures.

The results show that symmetric membranes form dense structures, aspect observed both on the surface, as in the fracture. In these membranes, structures without pores and the presence of areas with uniformity and a high density of polymer could be seen. With the addition of paracetamol, the membrane had practically the same morphology.

In the asymmetric membranes, which are produced with water as a nonsolvent, pores on the surface and throughout their thickness could be seen. The pores were of nonuniform size and were distributed irregularly along the membrane.

These morphological differences are directly related to the processing used. During the membrane formation from solution (CTA/dichloromethane/water), the solvent (dichloromethane) and nonsolvent (water) evaporate at different rates. The solvent evaporates faster than the water, causing two effects: an increase in the time of coalescence of the membrane, leading to phase separation and increased water concentration in the polymer structure, causing pore formation.

The addition of paracetamol to the formulation causes a reduction in the number of pores formed on the surface and in cross section. The water typically causes a destabilization in the system and consequently, the phase separation. The drug interacts with both the membrane and the water and hence reduces the intensity of phase separation, which occurs in a smaller proportion.

DSC study

One fundamental aspect on the employment of thermal analysis when evaluating matrices for drug controlled-release is the fact that this method permits the investigation of thermal stability of both matrix and drug, as well as the nature of dispersion of the drug in the matrix[6]. An important parameter to study the interaction between paracetamol and polymer is the glass transition temperature (T_g), which is obtained from the second scan DSC curves. Figure 2 shows the first and second scan DSC curve of all membranes.

Figure 2(A) and (B) present DSC curves of first scan for cellulose triacetate symmetric and asymmetric membranes with and without the incorporation of paracetamol. The thermograms presented are typical of cellulose triacetate, in which an endotherm between 60 °C and 100 °C may be observed, along with the desorption of water associated with the polymer structure. An exothermic peak at approximately 192 °C relative to the crystallization of the polymer during the scan, and an endotherm at approximately 300 °C due to CTA fusion[6].

The data of Figure 2(B) and (C) show that the glass transition temperature decreased with the addition of paracetamol in membranes. The drug molecules, which are usually small, are retained between the polymer chains. This reduces the intermolecular forces of attraction between the polymer molecules, thus increasing mobility of the chains, which results in a reduction in the T_g value[38].

In asymmetric membrane, the paracetamol caused a decrease in the value of T_g of 33 °C, while in the symmetric membrane, the reduction was less significant (6.5 °C). This difference in values shows that the interaction between the membrane and paracetamol is more pronounced with MB-ASYpara. The drug has a plasticizing

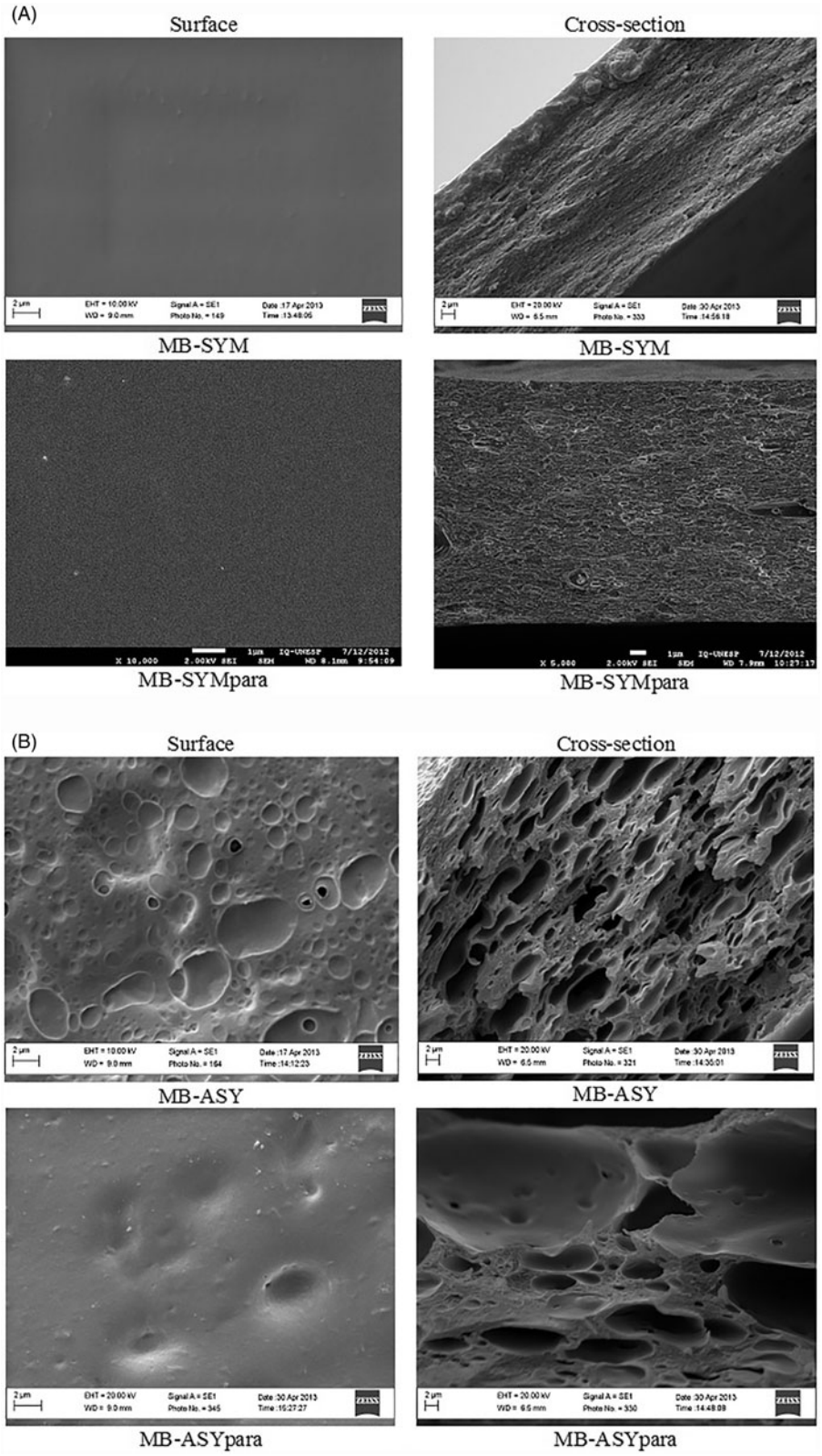

Figure 1. SEM of the fracture and surface, symmetric membranes (A) without drug (MB-SYM) and with drug (MB-SYMpara); asymmetric (B) without drug (MB-ASY) and with drug (MB-ASYpara).

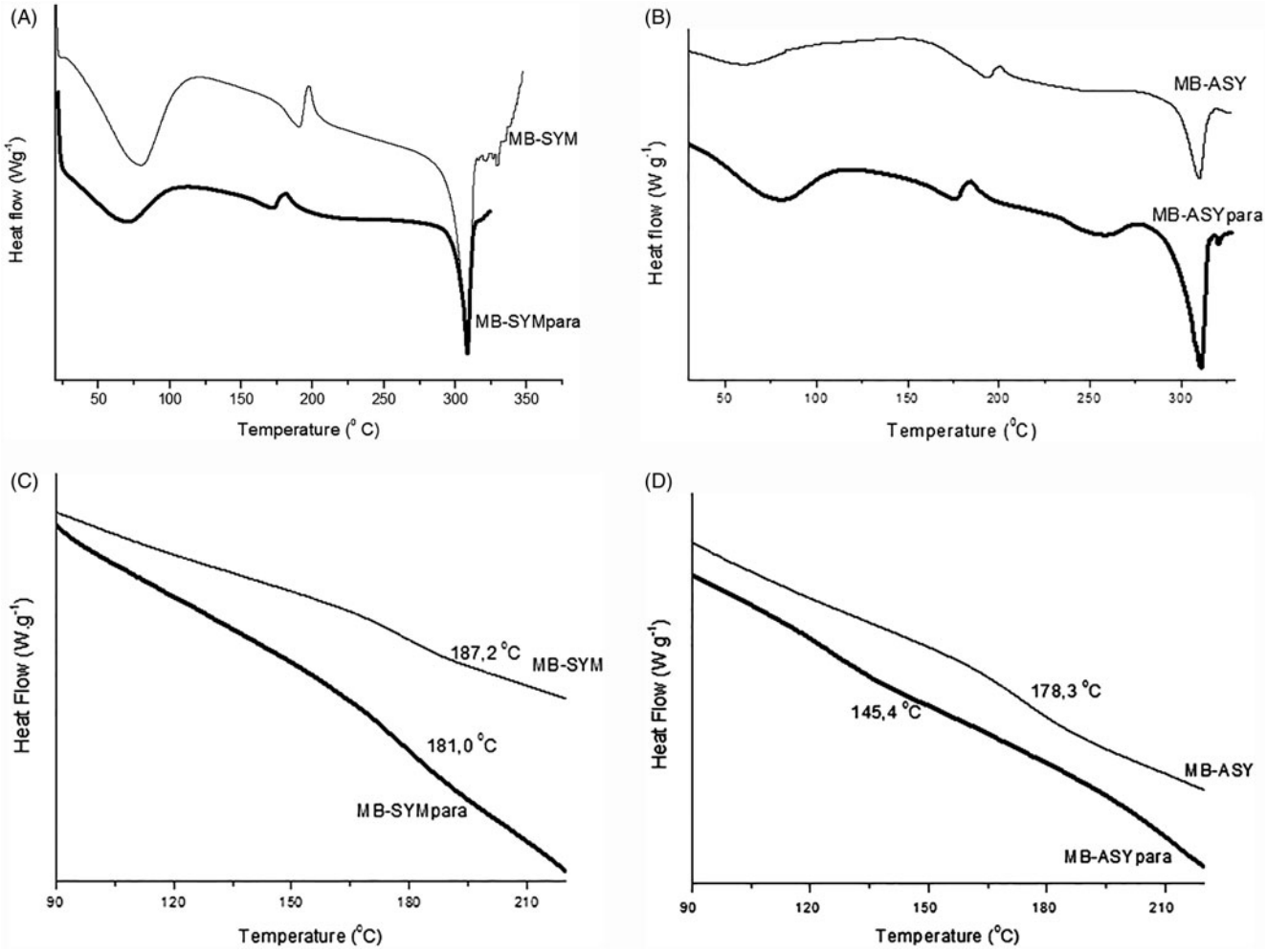

Figure 2. First and second scan DSC curves. Symmetric membranes (A and C), asymmetric membranes (B and D).

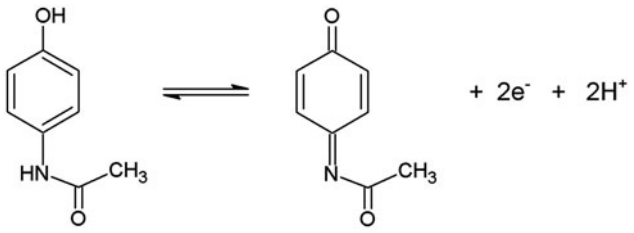

Figure 3. Mechanism of the electrochemical oxidation of paracetamol.

effect on the system. These results are in agreement with those of SEM both the surface and substructure of the membrane.

Monitoring of paracetamol release by square-wave voltammetry

Paracetamol is a phenolic compound that undergoes electrochemical oxidation by electrolytic etching on the aromatic ring with irreversible removal of two electrons and two protons, producing *N*-acetyl-*p*-quinoneimine according to the mechanism shown in Figure 3.

The monitoring of released paracetamol content was made using the SWV technique. Initially, a calibration curve was carried out, in which equal amounts of a stock solution of 10 mM paracetamol were added to a buffer solution under the same conditions in which the analysis of drug release was made. By measuring the height of the peaks formed (current responses) at the different concentrations of added paracetamol, a highly linear ($R^2 = 0.9989$) calibration curve (in the range of 5 to 100 μmolL^{-1}) was obtained with the following equation: $I(\mu A) = 0.035 + 0.1154x$ [Paracetamol] (μmol L^{-1}). This calibration curve was used to calculate the amount of paracetamol released from the membranes and then converted into percentage of drug release. Figure 4 shows voltammograms obtained with symmetric and asymmetric membranes.

Shift of the oxidation potential of paracetamol is observed in both experiments of drug release presented in Figure 4. Repetitive voltammograms for the standard solutions of paracetamol in 0.1 mol/L phosphate buffer pH 7.5 showed a similar displacement of the oxidation peak of paracetamol. Therefore, the shift of oxidation potential may be due to partial passivation of the electrode surface related to the adsorption of paracetamol or its oxidation product. However, this potential shift did not affect the linear range of the voltammetric determination of paracetamol. Therefore, the equation for the calibration curve obtained before drug release experiment can be used to determine the content of paracetamol in solution. The drug release experiment was performed in a medium that simulates the biological conditions of paracetamol absorption in human body (0.1 mol/L phosphate buffer pH 7.5).

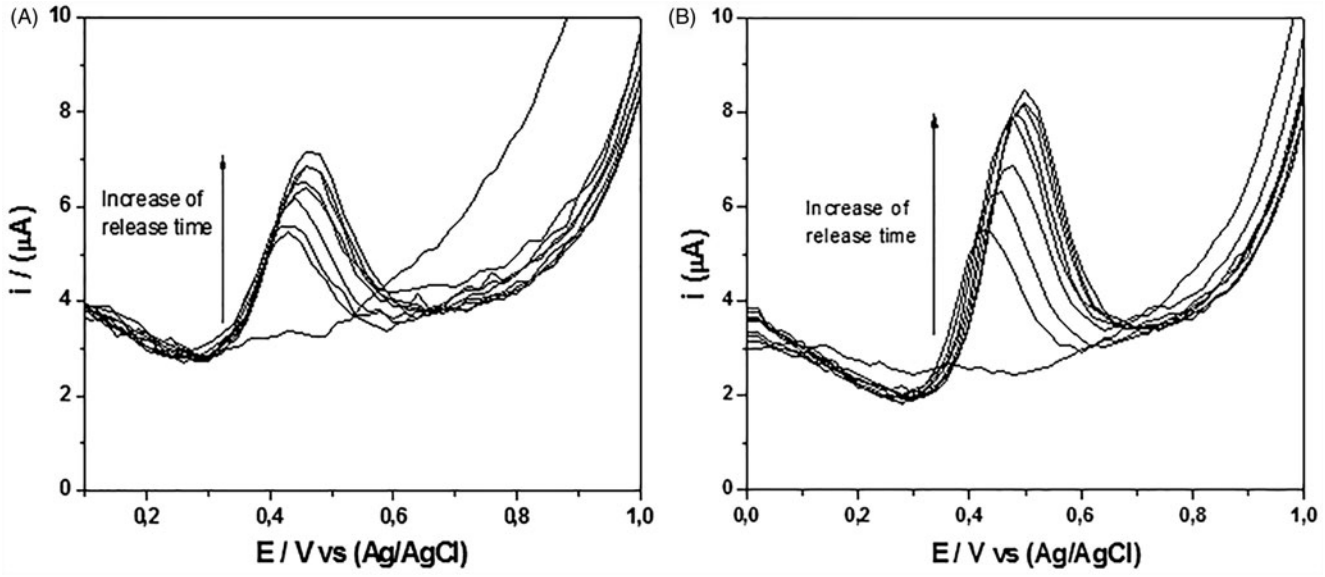

Figure 4. Voltammograms obtained from the paracetamol released from symmetric (A) and asymmetric (B) membranes.

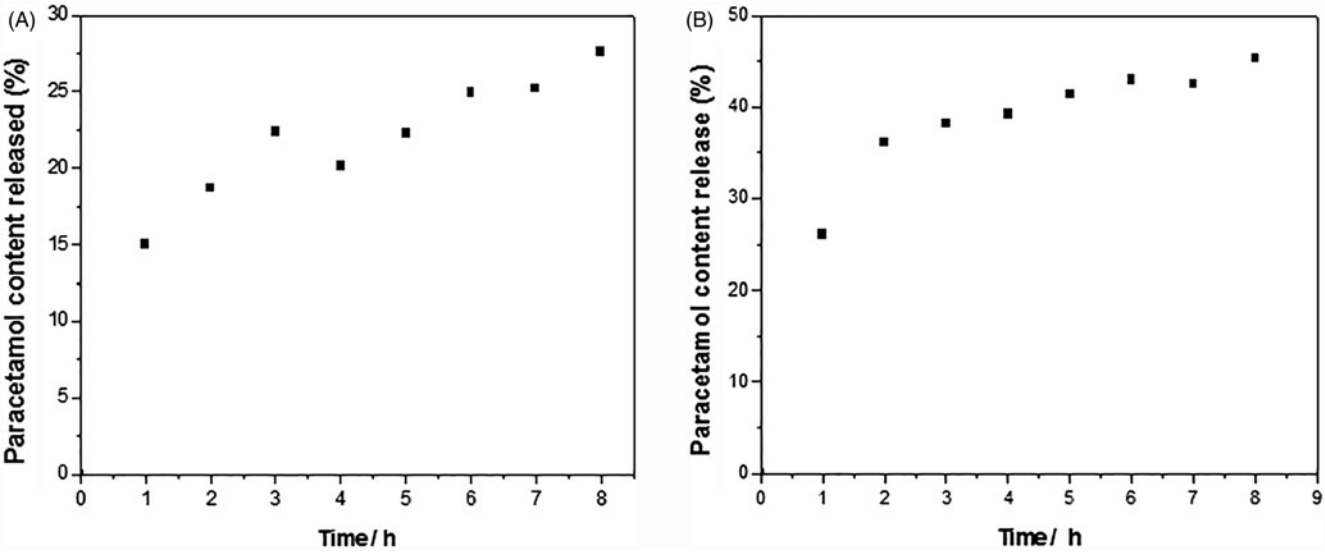

Figure 5. Curves of paracetamol released from symmetric (A) and asymmetric (B) membranes.

The analysis of the voltammograms reveals that the drug release occurs differently on each membrane, since the peak height formed is directly proportional to the concentration of analyte in the solution. Obtaining the height of the peaks and using the equation of the calibration curve, it was possible to determine the concentration of paracetamol released from the membranes (Figure 5).

The paracetamol is soluble in water, and the release occurs as the solution comes into contact with the polymer system, resulting in relaxation of the polymer chains with volume expansion, which facilitates the diffusion of the drug through the matrix. The values of paracetamol release versus time indicate the influence of the membrane structure in the release of the drug.

Confirming the data from the voltammograms, with the asymmetric membrane, a large amount of drug that was incorporated into the matrix was released, reaching approximately 45% of the paracetamol at around 8 h of the experiment. This differs from that observed in the symmetric membrane, where only 27% of the drug was released.

An aspect that accounts for the difference in the percentage of released drug by each membrane is the existence of pores in the asymmetric membrane. The pores on the surface and throughout the thickness of the membrane control the transfer and facilitate the movement of the drug across the membrane. When the pores are achieved, they do not offer resistance to the paracetamol flow.

Paracetamol has a plasticizing effect on the system, as demonstrated by DSC studies, resulting in increased mobility of the polymer chains. This increase in mobility favors the transport of the drug across the membrane and its subsequent release.

The tests showed that it is possible to use square-wave voltammetry in the study of controlled drug release systems. Its main advantages over the spectrophotometric technique include: *in situ* monitoring, making it unnecessary to handle samples for reading, thus avoiding temperature loss, and there is less chance of contamination by other materials; easy system handling and low cost of operation; rapid stabilization of the apparatus; analysis in a short time; the dispensability of dilutions for sample reading (wide

linear range, from 5 to 100 μmolL^{-1}), high sensitivity and reduced spending of reagent and sample.

Conclusion

The SEM results indicated the formation of a symmetric (MB-SYM) and asymmetric (MB-ASY) membrane. The paracetamol incorporation in membranes was confirmed by the changes in the thermal properties of the matrix with a reduction in the value of the T_g in the presence of the drug, showing a strong interaction with the polymer matrix in the case of asymmetric membranes. Quantitative analysis of drug release using square-wave voltammetry showed that 27% and 45% of the drug was released from symmetric and asymmetric membranes, respectively, after 8 h of analysis. The results show that the membranes produced from the use of sugarcane bagasse have potential for application in controlled release of paracetamol. Additionally, square-wave voltammetry is an important technique in studies of drug release for these systems, especially when *in situ* and real time monitoring is required.

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Declaration of interest

The authors report no declarations of interest.

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