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Drug release from electrospun poly(lactic acid) membranes and their cell viability in vitro test

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In this study, the effect of a different drug-delivery system, which consists of different nanofiber membrane configurations, was examined. The membrane configuration was based on sandwiching the drug between two adherent layers of electrospun membranes in order to verify the mass transport behavior of the drug through different polymeric membrane configurations. These electrospun membranes were made of Poly(lactic acid) (PLA), because it is one of the most promising biodegradable polymers due to its mechanical properties, thermoplastic processability and biological properties, such as biocompatibility and biodegradability. The main advantages of electrospun membranes include providing very thin fibers in the order of magnitude of some nanometers with a large superficial area, and the possibility to be manipulated and processed for many different purposes. The electrospinning process was carried out in a prototypal device, developed by INTEXTER (UPC), and the operation conditions adjusted in this study were: voltage applied; polymeric solution flow; distance between spinneret and collector and spinneret opening diameter. When the first layer of the electrospun membrane was ready and dried, the drug was equally dispersed on the membrane surface. After placing the drug, a second layer of membrane was electrospun over the first one to cover the drug. The sandwich membrane configuration is illustrated in Figure 1.

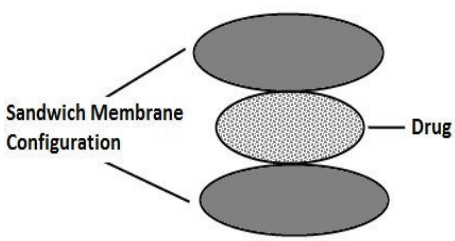

Figure 1: Sandwich membrane configuration.

The transport mechanism controlling drug delivery through the sandwich membrane was evaluated via release kinetics of a bioactive agent in physiological serum, used as a corporal fluid simulation. Drug release kinetics was carried out in batch methods for membranes with different operational conditions, such as: membranes obtained after different electrospinning times (5, 10 and 20 minutes) and sandwich membranes with different drug amounts (5, 10 and 15 mg of ibuprofen). The results of the amount of drug released from the PLA membranes during the kinetic tests are presented in Figure 2.

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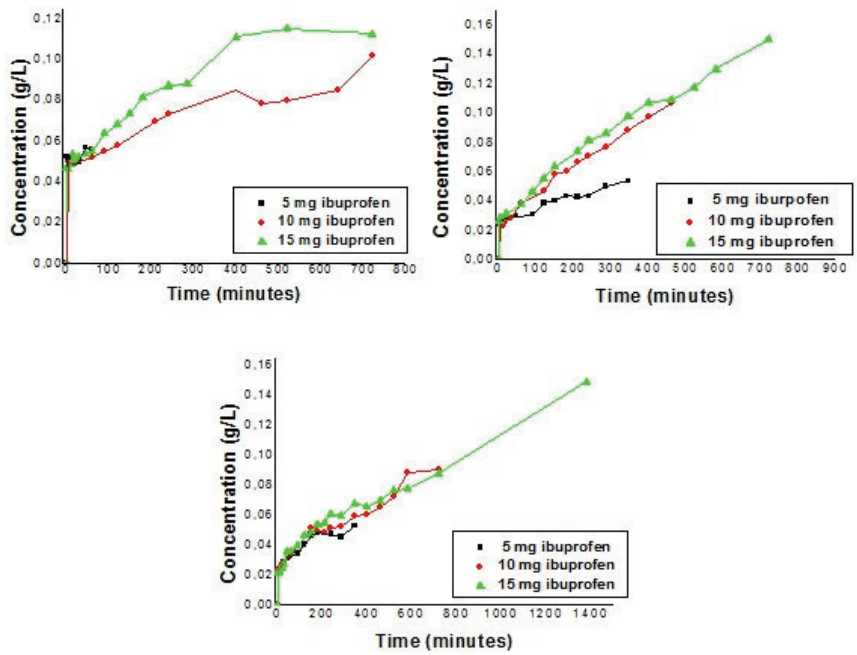

Figure 2 – Kinetics of ibuprofen release from PLA membranes obtained after 5, 10 and 20 minutes of electrospinning.

According to Mathiowitz (1999)[1], the kinetic curves of ibuprofen release showed typical behavior from reservoir-type membranes, then, it can be assumed that the drug transport mechanism through these membranes is usually a solution-diffusion mechanism. Drug transport occurs initially by drug dissolution through the membrane, followed by diffusion through the same membrane and desorption to the other side of the membrane. Therefore, assuming ibuprofen release is controlled by diffusion, it is possible to directly apply the classical Higuchi equation to find the mass transport coefficient of ibuprofen through PLA membranes[2].

The mass transport coefficient results showed that the influence of thickness in sandwich membrane systems (PLA-Ibuprofen) is a very important factor to be considered for controlling drug delivery. This is due to the reinforcement of fibers in 10 and 20 minute electrospinning membranes, which becomes denser and not easily penetrable. This fiber reinforcement reduces the empty spaces available for ibuprofen particle mobility, restraining its transference to the external medium. Increasing drug concentration decreases the empty spaces for mass transference even more, as a result the mass transport coefficient decreases. Therefore, the greater the thickness of the membrane, the less mass transference through it. Then, according to the kinetics studies, the choice of a proper PLA membrane thickness and ibuprofen concentration can be designed in accordance with the required treatment. If the treatment calls for less ibuprofen release control with a high initial dose, thinner membranes are appropriate. However, if it requires higher ibuprofen release control with a low dose rate, denser and thicker membranes are recommended.

The purpose of studying PLA membrane is to be used in medical applications, such as patches or implants in places where human serum can act as a swelling agent, and at the same time, a carrier of the active compound. Therefore, this new system can be used directly in the prophylactic period of recently operated patients, when *in situ* application is required. In some cases, this particular membrane can act not only as a carrier, but also as cavity filler with therapeutic agents. For that reason, the toxicity of the membranes had to be verified, once the polymer solvent used was dichloromethane (the least toxic of the simple organochloride compounds).

The cell viability tests, to check PLA membrane toxicity, were carried out with HeLa cells, a line derived from cervical cancer cells. The cells were cultivated in RPMI medium with fetal serum and antibiotics. After incubation period MTS solution (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) was added and a new incubation period was carried out.

The cell viability test result is shown in Figure 3.

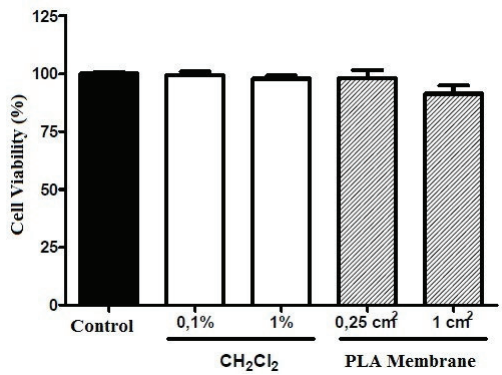

Figure 3 – Cell viability test.

The statistical analysis (ANOVA) results indicate no significant differences among the analyzed samples. For this reason, we can conclude that the material studied, such as dichloromethane and PLA membranes, do not present any toxicological harm to HeLa cells. Nevertheless, there is a tendency that the cell viability decreases when increasing the area of PLA membrane.

Keywords: electrospinning, drug delivery, poly(lactic acid), nanofiber