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NANOCOMPOSITES FILMS BASED ON POLY (LACTIC ACID) FOR CONTROLED RELEASE OF RIFAMPICIN

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ABSTRACT

Polymer nanocomposites have been successfully used as excipients in pharmaceutical technology, due to its various applications and features, especially in therapies for controlled drug release. The aim of this work was to prepare and characterize PLA nanocomposites by solution casting mode, with two different clays, sodic (NT25) and organoclay (Viscogel B8), focusing being possible used as matrices for controlled release of an important drug for tuberculosis, rifampicin. The systems were characterized by conventional technique such as XRD and by unconventional one, low-field NMR technique, relaxation, employing the determination of proton spin-lattice relaxation. The nanoscomposites obtained showed good dispersion and formation of nanomaterials containinga mixed morphology with different degrees of intercalation and exfoliation. Nanostructured poly(lactic acid) films were developed for modified Rifampicin release and based on the results, it can be concluded that both materials employing NT25 clay or Viscogel B8 clay exhibited a modified release of Rifampicin.

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INTRODUCTION

Tuberculosis (TB) is one of the main causes of mortality and morbidity globally. According to World Health Organization (WHO), *M. tuberculosis* has infected approximately more than 7 million people and causes 1.2 million deaths annually (WHO, 2019). Effective drug treatments were first developed in the 1940s. The currently recommended treatment for cases of drug-susceptible TB disease is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. These drugs are administered orally and have outstanding effectiveness against *M. tuberculosis* (NASIRUDDIN *et al*., 2017). Rifampicin is a semi-synthetic rifamycin antibiotic used for the treatment of tuberculosis. It works by inhibiting DNA-dependent RNA polymerase, in which it forms a stable complex that prevents the formation of bacterial RNA. It is effective in combating most gram-positive bacteria as well as many gram-negative species (MELO *et al*., 2020; SOUZA, 2005).

Due to its complex structure, it exhibits polymorphism and exists in two polymorphic forms, form I and form II. Recent studies have shown that these forms have different solubilities in aqueous media and thus may affect drug absorption and bioavailability from oral solid dosage forms. Rifampicin presents low solubility and low permeability, and could be classified by the Biopharmaceutical Classification System (SCB) as a class IV drug (KHADKA *et al*., 2020, MARIAPPAN & SINGH, 2006). Modified drug release aims to improve these characteristics, leading to greater use of the active principle, reducing toxic and subtherapeutic doses. It also provides a longer administration interval, reducing the number and frequency of doses required to maintain the desired therapeutic response, which brings greater comfort and improves patient compliance with treatment (KAMALY *et al*., 2016; UCHEGBU, 2006). For the development of a modified release system the appropriate material must be capable of controlling drug release, sustaining its therapeutic action over

time and releasing the drug into a specific tissue or organ. Being a biodegradable polymer, PLA looks very attractive for biomedical applications. Its biocompatibility is due to its α-hydroxy acid group, which undergoes hydrolysis in living organisms, resulting in a metabolite that is incorporated into the tricarboxylic acid cycle which is subsequently excreted. In addition, PLA degradation products are non-toxic, making them a natural choice for biomedical purposes (FARAH *et al*., 2016; SURYANEGARA *et al*., 2009). Clay-based nanocomposites are commonly referred to as aluminosilicate-based nanocomposites, including montmorillonite, which is composed of layered silicates that were used to prepare the nanocomposites of this work. A complete dispersion of layered silicate within the polymeric matrix can result in exfoliated structure formation. This allows to increase the benefits of layered silicates, leading to significant improvements in mechanical and physical properties for the polymer matrix and the mechanical properties, with respect to barrier properties, allow controlled or sustained release of some drugs (RAY & OJIJO, 2018; MITTAL, 2009). Aiming at the application of these materials in modified release therapies, the objective of the present work was to develop nanostructured films based on clays and poly(lactic acid) for modified rifampicin release.

MATERIAL AND METHODS

Material: Nature Works ®PLA Polymer 2002D sample was supplied by Nature Works LLC, the organophylic clay Viscogel B8 was supplied by Bentec and the sodic clay NT25 by Bentonit União Nord. Ind. e Com. Ltda.

Nanocomposites Preparation: The PLA nanocomposites were prepared by solution casting mode, employing chloroform as the solvent. First, a PLA solution was prepared and was stirred at room temperature for 24 h, using a magnetic stirrer. Then suspensions of montmorillonite containing 1, 3 and 5% clay were added. After blending the samples, the new solutions with 100 mg of rifampicin were stirred again with the magnetic stirrer at room temperature for 24 h. This solution was poured into a glass plate and the solvent was evaporated, using an oven with forced air circulation for three days. Solvent elimination was confirmed by its band disappearing using infrared spectroscopy. After the solvent was completely removed, the film was taken out for further analyses (BRITO & TAVARES, 2012).

X-ray diffraction: X-ray analyses were carried out in a Rigaku D/Max 2400 diffractometer, with nickel-filtered CuKα radiation of wavelength 1.54 Å, at room temperature. The 2θ scanning range was varied from 2° to 30º, with 0.02º steps, operated at 40 KV and 30 mA.

Low-Field NMRMeasurements: The relaxation measurements were performed with a Maran NMR spectrometer (Resonance Instruments, Oxford, UK), operating at 23 MHz for the hydrogen nucleus. Proton spin-lattice relaxation times, with a time constant T_1H, were determined directly by the traditional inversion-recovery pulse sequence (recycle time 180°–τ–90º acquisition), using 40 data points, with 4 scans for each and a range of τ varying from 0.1 to 2 s, with 10 s of recycle delay and 90° pulse of 4.5 ms, calibrated automatically by the instrument's software. The T_1H values and relative intensities were obtained by fitting the exponential data with the aid of the WINFIT program. Distributed exponential fittings as plots of relaxation amplitude versus relaxation time were performed by using the WINDXP software.

Dissolution tests

Rifampicin Calibration Curve: The calibration curve was constructed using five concentration points: 20 µg / mL, 40 µg / mL, 60 µg / mL, 80 µg / mL and 100 µg / mL. Five Rifampicin solutions with their respective concentrations were prepared from a 100 mg / mL stock solution. The solutions were analyzed by ultraviolet spectrophotometer using 333 nm as wavelength.

Dissolution in simulated gastric fluid: The simulated gastric fluid (SGF) was prepared according to the specifications of U.S. Pharmacopeia 30 (USP, 2007). NaCl (2.0 g) were solubilized in sufficient amount of distilled water. 7.0 ml of HCl and the solution adjusted to 1.0 liter volume with distilled water were added. The pH of the solution was monitored during the addition calibrated potentiometer acid and adjusted to 1.2 ± 0.1. For the test in simulated gastric fluid in each vat was added one tablet. Aliquots of 10 ml were taken every 1h for each of the vats, replenishing the volume of gastric medium removed at a temperature of 37 °C. Assays were performed in a total time of 24 hours (VALADARES *et al*., 2006).

Evaluation of release kinetics: The release kinetics of a formulation is a parameter of great importance and should be assessed during the development phase, because from this analysis it is possible to evaluate the influence of certain parameters, such as crystallinity, solubility of active, particle size in the same release (MANADAS, PINA & VEIGA, 2002).

RESULTS AND DISCUSSION

X-ray diffraction: Figure 1 shows the X-ray diffractogram of rifampicin. In the angular range analyzed from 2° to 40°, intense peaks are observed, indicating a high degree of crystallinity of this drug (PORTO, 2014).It is known that rifampicin can be found in various polymorphic forms and the solubility between them varies mainly by its particle size, crystal purity, electrostatic interactions and pH of the medium, at pH 6.8 the amorphous form presents higher intrinsic dissolution than isoforms I and II, and at pH 2.0 isoform II presents less intrinsic dissolution than the amorphous form and is slightly less than isoform I (ESMAEILI & KHODAEI, 2018). The use of XRD shows that the analyzed sample has predominantly crystalline characteristic peaks, with peaks that indicates the presence of polymorphs I and II.

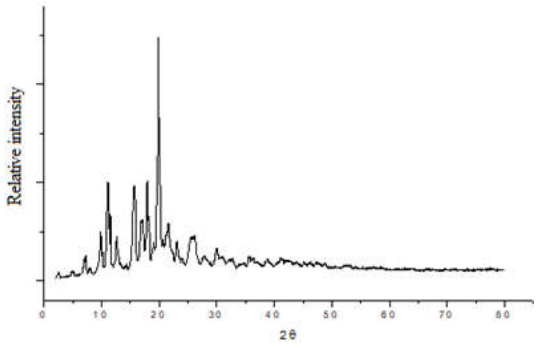

Figure 1. Rifampicin X-ray Diffractogram

Rifampicin polymorph I is characterized by of peaks located at 2θ angles in 13.65 and 14.65° while polymorph II has 2θ angles in 9.93 and 11.1° (Figure 2), which explains the different peaks found in this work, which is in agreement with the literature, showing that the drug used is a polymorph (AGRAWAL *et al*., 2004). Two clays were used and both of them, sodic one (NT25) and organic modified (Viscogel B8), have in their XRD patterns, characteristic peaks of intensity between angles of 0 to 10 corresponding to their basal spacing lamellae and can be observed in Figure 2 (BRITO & TAVARES, 2012).

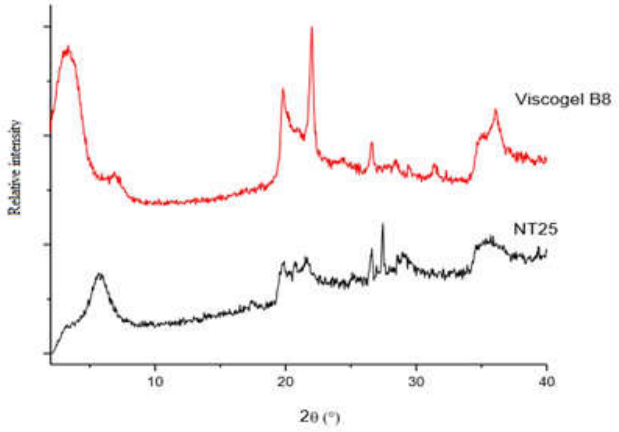

Figure 2.Viscogel B8 and NT25 clay diffract grams.

Evaluating the material formed by PLA, Rifampicin and NT25 sodium clay, Figure 3 shows the diffractograms of the PLA, Rifampicin and NT25 sodium clay composites at concentrations of 1, 3 and 5%.

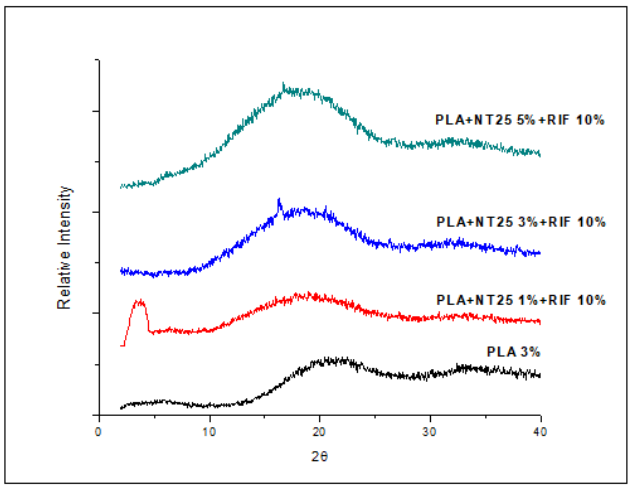

Figure 3. X-ray diffractograms of PLA/Rif/NT25 films at concentrations 1%, 3%, 5% and PLA 3% film

From the results one can see a significant decrease in peak intensity in all materials formed when compared to the Rifampicin diffractogram, indicating that the interaction between the phases occurred in newmaterials with lower crystallinity degree. When the datas were analyzed in relation to basal peak of NT25 sodium clay, it is noted that at when 3 and 5% of NT25 were added to the PLA the peaks related to the clays were not observed, while at 1% concentration the peak was shifted to lower angles. The behavior of pure PLA on film shows no peak in the diffract gram; this can indicate that the sample shows new intermolecular interaction.

Figure 4 shows the composites and PLA diffractogram profile, however, using Viscogel B8 clay at concentrations of 1, 3 and 5% and Rifampicin. There is a decrease in peak intensity, but with more intense ones remaining at concentrations 3 and 5%. Regarding the clay basal peaks, the peaks did not disappear, but were shifted to lower angles in the three composites obtained, which is a result of predominance of intercalation morphology in the systems obtained.

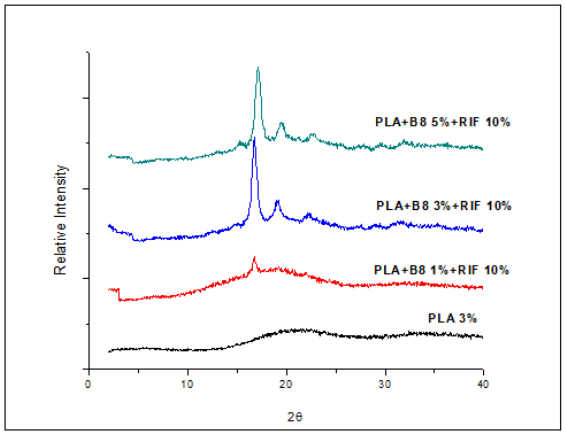

Figure 4. X-ray diffratogram of PLA/Rifampicina/ViscogelB8 films in the concentration varying from 1 to 5% and for the film of PLA at 3%

Table 1.Degree of crystallinity of composites containing clays NT25 and Viscogel B8

Nanocomposite Crystalinity		
Clay Concentration	Viscogel B8 (%)	NT25 (%)
1%	44.25	21.89
3%	31.29	9.73
5%	24.32	5.67

According to Bernardi *et al* (2013), the technique of X-ray diffraction is most appropriate in determining crystalline phases present in pharmaceuticals. As shown in Figure 1, Rifampicin is a drug with a high degree of crystallinity and its use in the nanocomposite PLA and clays system has made this feature take milder dimensions. As observed, in both cases where NT25 and Viscogel B8 clay were used, the materials presented lower crystallinity values. Once a high degree of crystallinity of a drug affects its absorption, the more amorphous it appears will be more efficiently absorbed (GILMAN, 2005). Thus, it is believed that the formed materials have a great potential to improve the absorption and bioavailability of rifampicin.

In terms of comparison, the composites formed with NT25 clay had the most significant decrease in crystallinity. This result indicates that there was a better solubility of rifampicin and better interaction of clay with PLA. Viscogel B8 clay has an organophilic characteristic, similar to the polymer; its interactions were more effective, even when clay concentrations were increased and this result in a material with a higher proportion of amorphous characteristic (VOSSEN, 2009). According to Ferreira (2013), Voussen (2009) and Alexandre& Dubois (2000), low-angle X-ray diffractograms allow the identification and quantification of interlamellar spacing of clay minerals. This is possible due to the stacked layered morphology of silicates that makes X-rays diffract by showing the distance from the top of one layer to the top of the next layer, and this distance is called basal spacing.

Therefore, it is possible to use this parameter to study and compare this spacing before and after mixing with the polymer. As this spacing increase, the characteristic clay peaks corresponding to the basal spacing are detached to lower angles, suggesting possible intercalation or exfoliation. When none of these peaks are observed, it is indicated that the clay lamellae have become disordered, losing their structural layers, leading to the formation of an exfoliated material.

In NT25 clay-containing composites, the basal clay peak appears at lower angles in the material containing the 1% concentration, while at the 3 and 5% concentrations they completely disappeared. This result may be associated with a possible intercalation for the composite containing 1% clay composite and exfoliation to 3 and 5%, respectively. In the composites containing the Viscogel B8 clay, it is noted that the basal peaks of the clay are present in all employed concentrations, being attributed only the displacement to lower angles. The explanation is based on affinity, where the polymer and clay have organophilic characteristics and thus can have a good interaction, allowing a polymer intercalation between the clay lamellae (BRITO & TAVARES, 2012).

Low Field Nuclear Magnetic Resonance (NMR): Table 2 shows the values of proton spin-lattice relaxation time,T_1H, values calculated with 1 exponential that correspond to the relaxation time of the hydrogens of the material as a whole, and 2 exponentials that show that the hydrogens of different areas of the material relaxed at different times. NMR analyzes were performed for pure PLA film, PLA/RIF film and the three composites containing PLA/RIF/NT25 and PLA/RIF/B8 at concentrations of 1.3 and 5%.

Table 2. Values of$T_1H$of pure PLA film, PLA/RIF film and PLA/RIF/NT25 films at concentrations from 1 to 5%.

It can be observed in the values obtained from 1-exponential that when added only to RIF thevalues of hydrogen relaxation time decreases. In PLA/RIF/NT25 1% composites time increased, while in 3% and 5% concentrations time also decreased. Using the calculation with 2 exponentials, it can be noted that the addition of rifampicin induced an increase in the difference between relaxation times. The same happened with the composites and was more evident and accentuated in the 5% concentration. Bovey & Miaru (1996) describe that in the case of heterogeneous materials such as this one, the relaxation times can be used to evaluate the dispersion quality, that is, the interaction in the interface of the different components that results in differences in the relaxation times. Relaxation time analyzes can provide a variety of information such as molecular mobility, polymer and nanocharge compatibility, and material organization. When the relaxation time increases, a good interaction between the polymer and the nanocarbon is suggested, which indicates good dispersion of the mnanoparticle in the polymer matrix, makingthe material more rigid; resulting in a decrease in the molecular mobility. When the relaxation time decreases, the opposite happens (ALMEIDA *et al.*, 2012).

In the case of an exponential calculation, when gradually added to the NT25 clay concentrations, there is a decrease in the relaxation time. This can be explained by the affinity between the polymer and the nanocarb, since the polymer has organophilic characteristic and hydrophilic characteristic clay. This data, added to the results obtained in the XRD, indicate the formation of an exfoliated material. According to Almeida (2012), when the nanoparticle is clay, it is possible to observe the degree of its intercalation or exfoliation. When the relaxation time increases, there is a formation of an intercalated material with decreased molecular mobility due to the coletivemovents of polymer chains when beingintercaledin the clay lamellae, generating a narrower domain curve. On the other hand, when the relaxation time decreases, there is a material in which the interlamellar spaces of the clay are enlarged to the point of losing their organization. Thus, the domain curve is wider because the material assumes a random morphology due to the predominance of exfoliated materials that become more heterogeneous. The domain curves of nanocomposites are exibit in Figure 5.

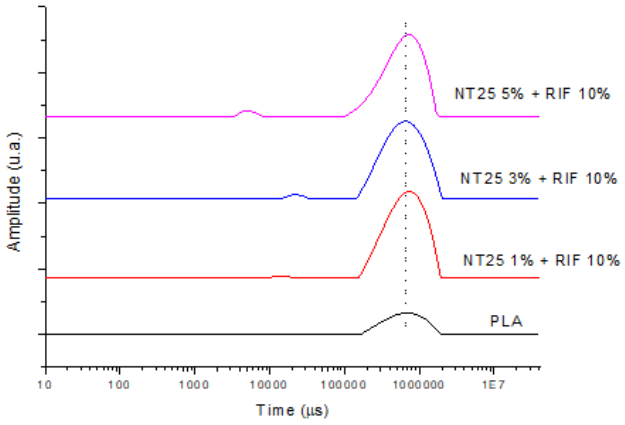

Figure 5. Domain curves of relaxation data of PLA/RIF/NT25 nanocomposites 1, 3 and 5%

Based on the pure PLA domain curve (Figure 6), it is observed that the composites curves are differentiated and as the clay concentration increased, the curves were adopting the broader bases, indicating the increasing material disorder, and then the formation of an exfoliated material. Figure 6 shows the domain curves of pure PLA, rifampicin and PLA/Rif 10%.

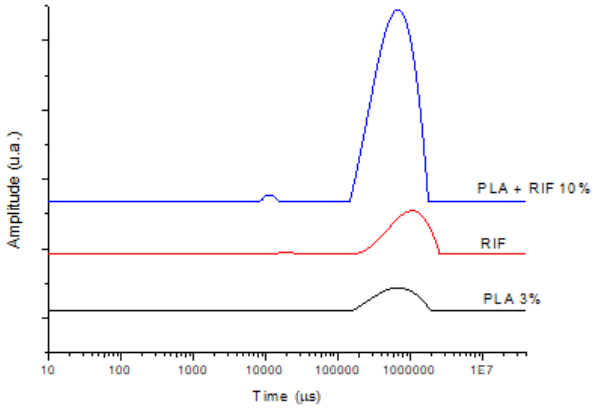

Figure 6. Domain curves of PLA 3%, RIF and PLA+RIF 10%.

Figure 7 shows the domain curves of the nanocomposite obtained with the Viscogel B8 clay. It can be seen that at concentrations 3 and 5% the formation of a material with different relaxation times, indicating the formation of a more heterogeneous material, when compared to nanocomposites with NT25 clay. This result is corroborated with analyzes obtained in X-Ray Diffraction, where it is possible to observe the formation of a material with greater crystallinity, in addition to indicating the formation of a preferentially intercalated material.

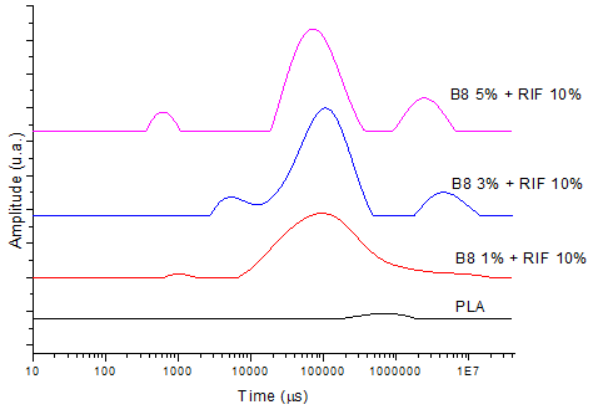

Figure 7. Domain curves of PLA/RIF/B8 nanocomposites 1, 3 and 5%.

Dissolution Tests: In order to be able to calculate the Rifampicin concentration through the measured aliquot absorbance values, it was necessary to obtain the standard calibration curve, as shown in Figure 8.

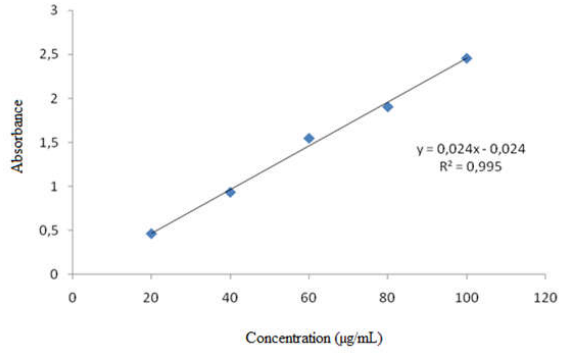

Figure 8. Rifampicin calibration curve

Figure 9 shows the concentration of Rifampicin released during the 120 minute time corresponding to the gastric transit time of PLA/RIF/NT25 composites at concentrations 1, 3 and 5%.

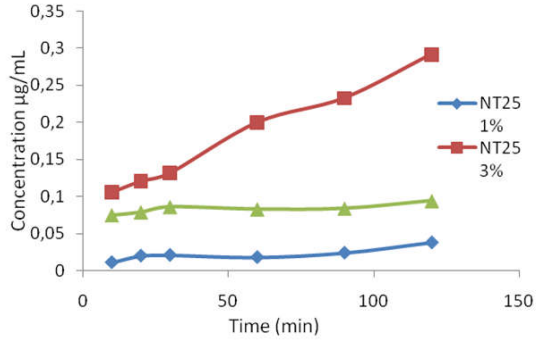

Figure 9. Release profile of PLA/RIF/NT25 composites at concentrations of 1%, 3% and 5%.

The composite containing 1% NT25 sodium clay released low concentrations of rifampin when compared to the other two composites. Nanocomposite at a concentration of 3% released the drug steadily. The composite containing 5% clay initially released a larger amount than the previous two with a peak of greater release in approximately 60 minutes, and another in 120 minutes. The release profile analysis of composites containing PLA/Rif/Viscogel B8 at concentrations 1, 3 and 5% is shown in Figure 10.

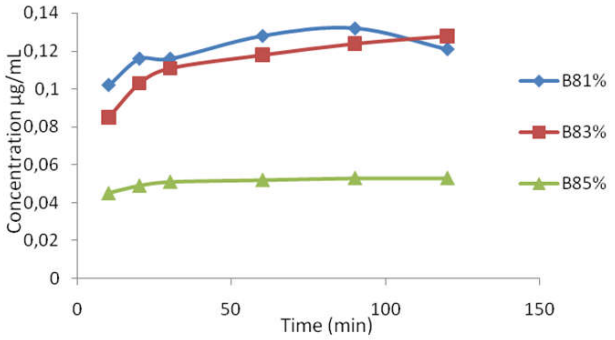

Figure 10. Release profile of PLA/RIF/ViscogelB8 composites at concentrations of 1%, 3% and 5%

The release profile of Viscogel B8 clay composites was generally more constant. The composites containing concentrations of 1 and 3% began to release increasingly and then stabilized maintaining a more uniform release. Finally, the 5% clay composite retained a uniform release, but significantly reduced the amount of Rifampicin when compared to the 1 and 3% films.

There is a delay in the release process in both NT25 and Viscogel B8 clay. This can be explained by the difficulty of water to access the drug molecules due to the hydrophobic characteristics of the polymer, suggesting a release by the diffusion mechanism. Added to this effect, for the case of NT25 clay, it is believed that increasing its concentration also increased the disorder and molecular mobility in the material. This factor is due to the divergence of affinity with the polymer, which facilitated water penetration and drug loading, and can be clearly seen at a concentration of 5%. In the case of Viscogel B8 clay, it indicates that polymer affinity generated better dispersion and interaction of the polymer chains between the clay lamellae, resulting in a more organized and rigid material capable of keeping the drug more entrapped and making it difficult for water to infiltrate, since the higher the clay concentration, the longer the drug release time (BARCELOS, 2016).

Conclusion

Nanostructured poly(lactic acid) films were developed for modified Rifampicin release and based on the results, it can be concluded that both materials employing NT25 clay or Viscogel B8 clay exhibited a modified release of Rifampicin. In the characterization analysis, it can be seen that the components were able to interact physically with each other. Both exfoliated and intercalated composites are capable of promoting control of rifampicin release. In addition, the crystallinity of rifampicin decreased when used in composites. Because of this it represents a promising material to increase the bioavailability of rifampicin.

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