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# DEVELOPMENT OF AN INNOVATIVE FORMULATION THAT ASSOCIATES POLYMERIC NANOCAPSULES AND PECTIN FOR TOPICAL APPLICATION

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Trabalho de Conclusão de Curso apresentado ao Curso de Farmácia da Universidade Federal do Rio Grande do Sul, como requisito parcial para a obtenção do título de Farmacêutica

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# DEVELOPMENT OF AN INNOVATIVE FORMULATION THAT ASSOCIATES POLYMERIC NANOCAPSULES AND PECTIN FOR TOPICAL APPLICATION

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**Abstract**

This work aimed to developed and characterize a pectin hydrogel containing polymeric nanocapsules. This hydrogel was characterized in terms of rheological properties, drug release profile, adhesiveness, and permeation and penetration into the skin layers. For these experiments, imiquimod was used as a model drug. A pectin hydrogel without the nanocapsules and carbopol hydrogels (containing polymeric nanocapsules or not) were used as controls for the nanotechnological formulation developed. Regarding the rheological properties, the pectin hydrogel presented pseudoplastic behavior, which is suitable for topical application. The release profile study showed a more controlled drug release from the pectin hydrogel containing the nanoencapsulated imiquimod than from the other hydrogels. The adhesiveness was measured by two techniques: washability study and tensile stress study. By both techniques, the pectin hydrogel containing the polymeric nanocapsules presented as the most adhesive formulation. The penetration and permeation studies showed that the nanoencapsulated drug incorporated into the pectin hydrogel was able to penetrate the deeper layer of skin and to permeate the skin more effectively than the drug incorporated in the other formulations.

Key-words: Pectin hydrogel, polymeric nanocapsules, imiquimod, skin permeation, skin adhesiveness, *in vitro* release

## 1. Introduction

The skin is the largest organ of the human body and acts as a barrier against external factors that can cause damage to the body (McLafferty et al., 2012). In addition, the skin is responsible for controlling several essential parameters for the functioning of the organism, such as temperature and water loss. The skin is composed of two main layers, the epidermis and the dermis, and the stratum corneum is the uppermost layer of the epidermis (Tortora And Derrickson 2009A; Waugh and Grant 2010). Due to its composition and organization, the stratum corneum protects the skin from heat, microorganisms and chemical agents (McLafferty et al., 2012), minimizes the effects of UV and IR radiations (Baroli et al., 2010), and also controls the passage of particles through the skin.

The skin has been widely used for topical administration of drugs for both local and systemic effect. This administration route has several advantages, such as action only at the area affected by the disease, when a local effect is desired, and avoid the hepatic first-pass effect, when a systemic effect is desired. In addition, this administration route provides ease of application and acceptance by the patients.

Although the many advantages that this route of administration presents, there are limitations when penetration into and permeation through the skin is desired, due to the presence of the stratum corneum. The polymeric nanocapsules can be used as a strategy to solve this problem. These nanostructured systems have proven to be effective in increasing the transport of drugs through the skin, as already shown in many works (Alves et al., 2007; Teixeira et al., 2010; Contri et al., 2014). These studies show that nanoencapsulated drugs are able to penetrate the skin layers more effectively than the non-nanoencapsulated drug.

Moreover, studies described in the literature show that polymeric nanocapsules increase the adhesiveness of formulations, ensuring an adequate time of contact of the formulation with the affected area (Guterres et al., 2007; Contri et al., 2014; Frank et al., 2017; Chaves et al., 2017). This increase in the adhesiveness is probably related to the greater surface area that the nanocapsules present (Contri et al., 2014). This characteristic may be responsible, in part, for the increased penetration of the drugs into the skin when these nanocarriers are used.

The polymeric nanocapsules are obtained as an aqueous suspension, therefore, the application to the skin is difficult. Many works have already incorporated the polymeric

nanocapsules in hydrogels for topical application (Alves et al., 2007; Fontana et al., 2011; Zampieri et al., 2012; Contri et al., 2014; Frank et al., 2014). In these works, bioadhesive polymers were used for the production of the hydrogels, such as chitosan, carbopol and hydroxypropyl methylcellulose. In this work, the pectin was used to produce the hydrogel where the polymeric nanocapsules suspension was incorporated.

Pectin is a natural polymer, formed by a complex mixture of polysaccharides (Sriamornsak et al., 2017). Although it can be found in most plants' tissues, commercial pectin is extracted almost exclusively from citrus peel and apple pomace (Sriamornsak et al., 2017). This biopolymer is widely used in the food industry, as a thickening agent and gelling agent. It also has many applications in the pharmaceutical field, for example, for the treatment of disorders related to overeating (Di Lorenzo et al., 1988) and for cholesterol reduction (Mietinnen & Tarplia 1997). Some studies have evaluated this polymer as a controlled drug release system for oral administration (Ashford et al., 1994; Fernandez-Hervas et al., 1998). Although described as a bioadhesive polymer (Villanova et al., 2010), pectin has not yet been studied as a vehicle for administration of drugs to the skin.

This work aimed to develop an innovative gel that associates pectin and the polymeric nanocapsules for skin administration. The performance of this gel on the skin was evaluated in terms of penetration and permeation, and adhesiveness, using porcine ear skin.

## 2. Material and Methods

### 2.1 Materials

Poly(ε-caprolactone) (PCL, Mn 80 kg $mol^{-1}$) and sorbitan monostearate (Span 60®) were obtained from Sigma-Aldrich (Steinheim, Germany). Polysorbate 80 (Tween 80®) was obtained from Henrifarma (São Paulo, Brazil). Copaiba oil was donated by Inovam-Da Lamarta & Cia Ltda. Imiquimod was obtained from Chemical Goods (Guangdong, China). Carbopol 940 was obtained from Henrifarma (São Paulo, Brazil) and pectin was obtained from Labsul (Porto Alegre Brazil). The solvents were of analytical and high-pressure liquid chromatography (HPLC) grade.

### 2.2 Methods

### 2.2.1 Production of the imiquimod-loaded polymeric nanocapsules

The polymeric nanocapsules were prepared by the interfacial deposition of preformed polymer method (Fessi et al., 1988) and were done according to the methodology described by Frank and co-workers (2017). Briefly, an organic phase containing poly (ε-caprolactone) (100 mg), sorbitan monoestearate (38.4 mg), copaiba oil (334 μL) and imiquimod (5 mg), dissolved in acetone (25 mL) and ethanol (3 mL), was maintained under magnetic stirring and constant temperature (37ºC) until dissolution of all the components. Posteriorly, the organic phase was injected into an aqueous phase containing ultrapure water (53 mL) and polysorbate 80 (76.8 mg) under the same conditions. After 10 minutes, the solvents and part of the water were eliminated from this solution under reduced pressure in rotary evaporator and the final volume was adjusted to 10 mL. This formulation was named as NCimiq.

### 2.2.2 Production of the pectin hydrogel and control hydrogels for topic application

The pectin hydrogel was prepared by the incorporation of 10 ml of the formulation NCimiq into 0.3 g of pectin and these components were stirred until a homogeneous gel was obtained. This hydrogel was named as PEC-NCimiq. The free drug was obtained by the dissolution of imiquimod (5 mg) into 10 mL of acetate buffer (pH 3.7) and it was also incorporated into 0.3 g of pectin (PEC-imiq) in order to compare with the new developed formulation. Carbopol gels (3%) with the nanoencapsulated imiquimod (CARB-NCimiq) and with the free drug (CARB-imiq), both with 0.5 mg/mL of imiquimod, were used in this work as a control hydrogel, since this polymer is well-known for its use on the skin (Alves et al., 2005; Alves et al., 2007; Fontana et al., 2011).

### 2.2.3 Characterization of the polymeric nanocapsules

The polymeric nanocapsules had the following characteristics evaluated: pH, size, polydispersity and zeta potential. The pH value was determined by potentiometry without dilution of the formulation (B474 Micronal, Brazil). In order to guarantee the absence of microparticles on the formulation, the laser diffraction technique was used applying the refraction index of PCL (Mastersizer 2000, Nano ZS; Malvern Instruments, Malvern, UK). To determine the exact particle size of the nanocapsules and the polydispersity index

(PDI), the formulation was diluted in ultrapure water (1:500 v/v) and the dynamic light scattering technique was used (Zetasizer Nano ZS; Malvern Instruments). To analyze the zeta potential of the nanoparticles, the formulation was diluted in NaCl aqueous solution (1:500 v/v) and the electrophoretic mobility technique was used (Zetasizer Nano ZS; Malvern Instruments).

### 2.2.4 Characterization of the pectin hydrogels

The pectin hydrogel was characterized in terms of pH, rheological behavior, size and scanning electron microscopy. The pH value was determined by potentiometry diluting 1 g of the formulation in 9 mL of ultrapure water (B474 Micronal, Brazil). The rheological behavior was determined using a rotational viscometer (Brookfield® LV-DV-II+Pro, spindle SC4-25, 25ºC). In order to evaluate the presence of microparticles in the pectin hydrogel, the laser diffraction technique was used applying the refraction index of PCL (Mastersizer 2000, Nano ZS; Malvern Instruments, Malvern, UK). To analyze the shape and size of the nanocapsules in the pectin hydrogel, the scanning electron microscopy technique was used, and a water pectin hydrogel was used as a control.

### 2.2.5 Evaluation of the release profile

The release profiles of the pectin hydrogels (PEC-NCimiq and PEC-imiq) and Carbopol hydrogels (CARB-NCimiq and CARB-imiq) were performed in automated Franz Cell (MicroettePlus Multi-Group®; Hanson Research Corporation, Chatsworth, CA, USA) using cellulose, previously hydrated in ultrapure water, as a membrane (Sigma-Aldrich, dialysis tubing cellulose membrane, average flat width 25 mm). The formulation (100±2 mg) was added to the membrane surface (skin area of 1.76 $cm^2$) and the receptor compartment was filled with phosphate buffer (pH 6.8, 32ºC). At pre-determined times (1, 2, 4, 6, 8, 12, 24 hours), 2 mL samples were collected from the receptor medium, which was replaced by fresh buffer. These samples were analyze in HPLC-UV by previous validated method (Frank et al., 2017) in order to analyze the amount of drug that was released from the formulations over time. The sink condition was maintained throughout the experiment.

### 2.2.6 *In vitro* studies using porcine skin

The four hydrogels prepared (PEC-NCimiq, PEC-imiq, CARB-NCimiq and CARB-imiq) had their characteristics of skin adhesiveness and drug penetration and permeation analyzed using porcine ear skin as a membrane. For these studies, the porcine ears were obtained from a local slaughterhouse (Ouro do Sul, Brazil), the skin was removed using a scalpel and it was cut into circles (1,5 cm diameter, approximately). Then, the membrane samples were cleaned with ultrapure water, the hair was removed and the thickness was measured (only samples between 1.0 and 1.8 mm thick were used) using a dial thickness gauge (Nº 7301®; Mitutoyo, Kawasaki, Japan). The porcine skin samples were maintained at -4º until use.

### 2.2.7 Evaluation of the penetration and permeation in porcine skin

The permeability study was performed in automated Franz cell (MicroettePlus Multi-Group®; Hanson Research Corporation, Chatsworth, CA, USA). The hydrogel under study was weighed (100±2 mg) and applied to the skin surface (1.76 $cm^2$ area, n=3). The receptor medium was filled with 7 ml of phosphate buffer (pH 6.8) and it was maintained at 32 °C under magnetic agitation. Samples of 2 ml were collected from the receptor medium at 1, 2, 4, 6, 8, 12 and 24 hours after application and replaced by fresh buffer. These samples were analyzed in HPLC-UV and the amount of imiquimod that permeated through the porcine skin during the experiment was determined.

The separation of the skin layers was done according to methodology already described in other works (Contri et al., 2014; Menezes et al., 2017). The tape stripping technique was used to analyze the amount of drug that penetrated the stratum corneum, using 18 tape strips, and 5 mL of acetonitrile was used to extract the drug. The epidermis and dermis were obtained using heat separation technique at 60°C for 45 seconds and separated with a scalpel. To extract imiquimod from the epidermis and dermis, 1 mL and 2 mL of acetonitrile were used, respectively. The skin layers with acetonitrile were stirred for 2 minutes in vortex and for 30 minutes in ultrasound (USC-2850A model, Unique, 25kHz, 220 W; Indaiatuba, São Paulo, Brazil) with heat (37ºC). After the extraction process, the samples were filtered and injected in HPLC-UV and the amount of drug that penetrated into the skin layers was determined.

### 2.2.8 Evaluation of the adhesiveness: washability study in porcine skin

The adhesiveness of the developed formulation (PEC-NCimiq) and controls (PEC-imiq, CARB-NCimiq and CARB-NCimiq) was evaluated by the washability test (n=3). This test was performed in a modified Franz diffusion Cell, containing an input and output channel for the washing solution. The porcine skin was placed between the donor and the receptor medium. The gel under study was added to the skin surface (100±2 mg, skin area of 0.9 $cm^2$) and remained in contact for 1 hour before the study started. Phosphate buffer (pH 6.8, 32ºC) was used as the washing solution to simulate the flux of the skin (0.3 mL/min) and it was collected at predetermined times (15, 30, 45, 60, 90, 120, 150, 180 minutes) through the output channel. To extract the drug, 0.5 mL of acetonitrile was added to 1 mL of the collected washing solution, then it was agitated for 30 seconds in vortex followed by 30 minutes of sonication (USC-2850A model, Unique, 25kHz, 220 W; Indaiatuba, São Paulo, Brazil). After, the samples were centrifuged for 15 minutes at 5000 rpm (SIGMA 6-15, Nr. 10670, 230 V/50, 60 Hz) and 1 mL of the supernatant was injected in HPLC-UV in order to determine the amount of drug that was washed from the skin.

### 2.2.9 Evaluation of the adhesiveness: tensile stress study

The adhesiveness of the hydrogels ((PEC-NCimiq, PEC-imiq and CARB-imiq) was also analyze by tensile stress technique using texture analyzer (TA.XTplus Texture Analyzer; Stable Microsystem, Godalming, UK). The ear porcine skin (n=3) was placed in the probe using double-sided tape and the hydrogel under study was added in the equipment compartment until the base was completely covered with formulation. The porcine skin was left in contact with the formulation for 180 seconds using a force of 0.29 N. After, the probe with the skin was removed (0.10 mm/s) until the complete detachment. The force (mN) and distance (mm) needed to detach the formulation from the skin were analyzed.

## 3. Results and discussion

### 3.1 Characterization of the nanocapsules and the pectin hydrogel

The formulation NCimiq appeared as a homogenous white suspension. The pH value obtained was 6.3±0.07 (n=3). The nanocapsules suspension presented nanometric mean particle size (213±12 nm), as it can be seen in Figure 1, and a low value of polydispersity

index (0.12±0.03), which means proper homogeneity of size between the nanoparticles. The zeta potential obtained was -12.7±1.3, this low and negative value occurs due to the chemical structure of poly (ε-caprolactone) and the polysorbate 80 coating (Cattani et al., 2010). Therefore, this formulation presented adequate characteristics for incorporation into pectin and carbopol hydrogels.

The pectin hydrogels, PEC-NCimiq and PEC-imiq, had their pH measured and the values obtained were 3.8±0.04 and 3.9±0.12, respectively (n=3). Regarding the rheological behavior analysis, the pectin hydrogel containing the polymeric nanocapsules presented variation in viscosity according to changes in shear rate, as it can be seen in Figure 2, therefore, classified as a non-newtonian fluid. In order to determine the type of non-newtonian fluid that this formulation is, the rheograms were submitted to four different mathematical equations that represent different flow behaviors: Bingham (Ideal plastic), Casson (Plastic), Ostwald (Pseudoplastic) and Herschel-Bulkley (Yield-pseudoplastic). The evaluation of the determination coefficients for each one of the four models showed that the highest values correspond to the Herschel-Bulkley (Table 1). Moreover, the flow indices presented values less than 1 for this model. These results confirm that the PEC-NCimiq hydrogel presents pseudoplastic behavior, which is the proper behavior for gels. The size profile of PEC-NCimiq is also shown in the Figure 1. It is possible to see the same nanometric size profile in the hydrogel and in the NCimiq suspension. The micrometric population corresponds, possibly, to the pectin particles in the hydrogel.

Figure 3 shows the analysis of PEC-NCimiq and the control water pectin gel by scanning electron microscopy, confirming the presence of nanocapsules of homogeneous size and shape incorporated in the pectin hydrogel.

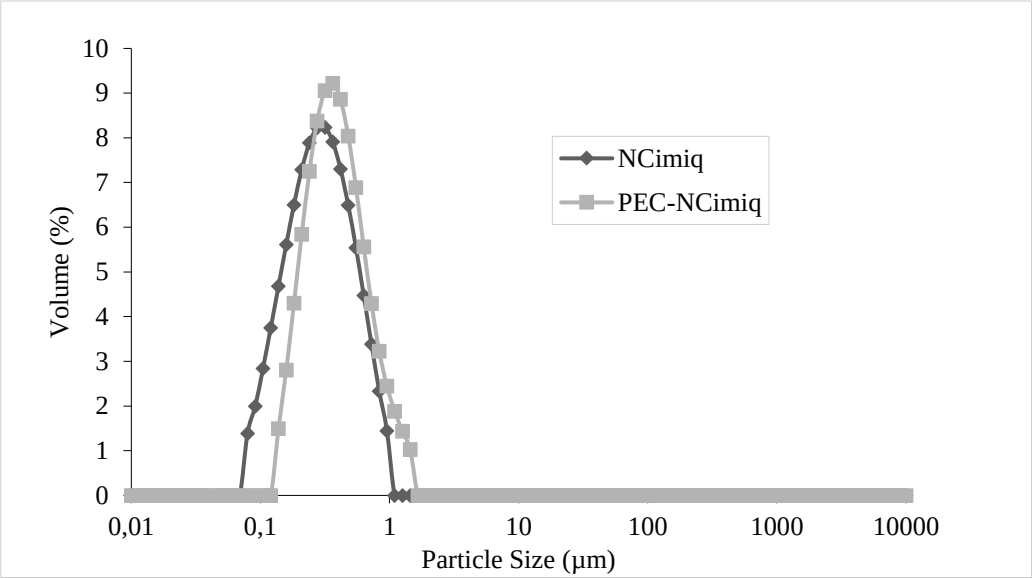


Figure 1 - Particle diameter profiles of the polymeric nanocapsules suspension (NCimiq) and the pectin hydrogel containing the polymeric nanocapsules (PEC-NCimiq) determined by laser diffraction.

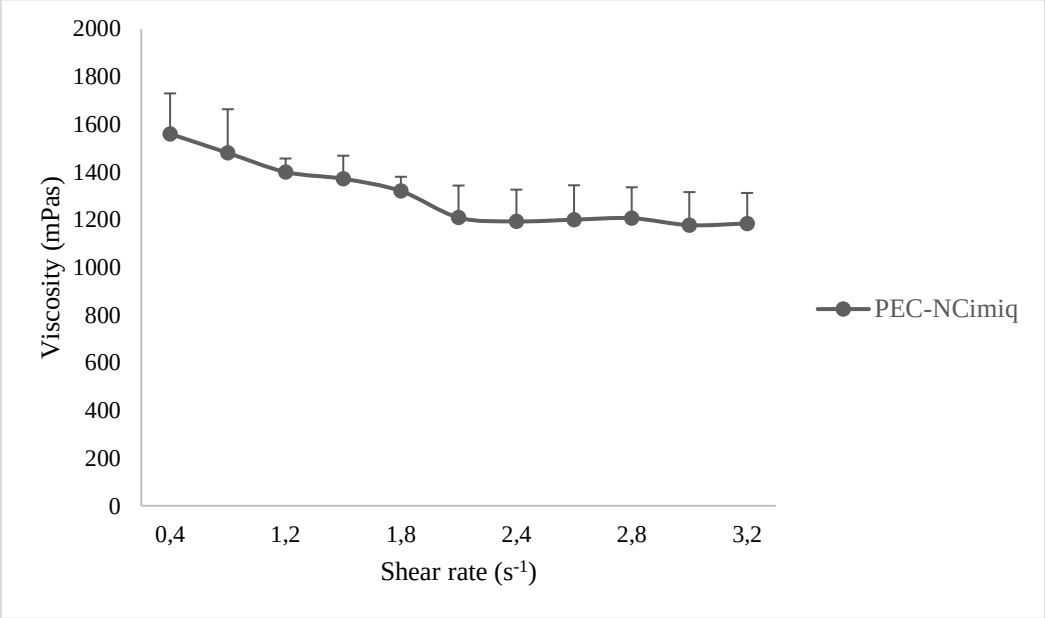


Figure 2 - Rheological behavior of the pectin hydrogel containing the polymeric nanocapsules.

Table 1 - Determination Coefficients for each flow model (Bingham, Casson, Otswald and Herschel Bulkley).

| Formulation | Bingham | Casson | Otswald | Herschel-Bulkley |
|---|---|---|---|---|
| PEC-NCimiq | 94.43±1.569 | 97.63±0.568 | 95.23±1.159 | 98.73±0.635 |

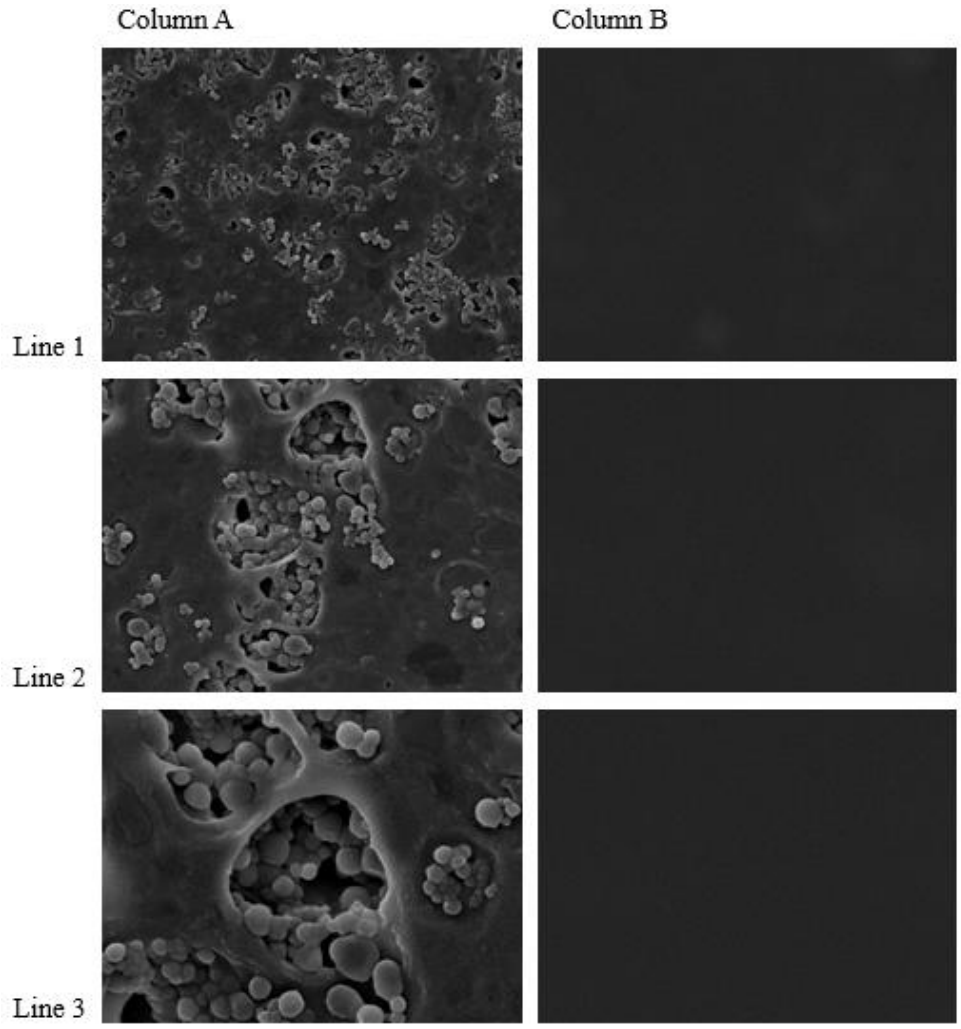


Figure 3 - Characterization of PEC-NCimiq (column A) and the control water pectin gel (column B) by scanning electron microcopy in 2000X (line 1), 4000X (line 2) and 8000X (line 3).

### 3.2 Evaluation of the release profile

The in vitro release profile of the pectin hydrogels (PEC-NCimiq and PEC-imiq) and Carbopol hydrogels (CARB-NCimiq and CARB-imiq) was performed in automated Franz Cell, according to already described methodology in the literature (Fontana et al., 2011). This experiment aimed to study the release profile of imiquimod from a pectin hydrogel, when nanoencapsulated or not. The carbopol hydrogels were used for comparison, since the release profile has already been studied and described in the literature (Marchiori et al., 2010; Fontana et al., 2011).

The Figure 4 shows the release profile of the four developed hydrogels. It is possible to see that the pectin hydrogels and the Carbopol hydrogels present different release profiles.

The formulation that presented the most controlled release profile of the drug during all experiment time was PEC-NCimiq, followed by PEC-imiq. Although PEC-imiq showed more immediate drug release in the first six hours of study than the carbopol hydrogels, in the following hours of experiment PEC-imiq started to show a higher control of the drug release and the carbopol hydrogels continued to release at the same rate. These results show that the pectin hydrogel has the capacity of controlling the drug release and this characteristic is improved when combined with nanotechnology.

Another important point to observe is that both pectin and Carbopol hydrogels containing the nanoencapsulated imiquimod presented more controlled release profile than the respective hydrogel containing the free drug. This result shows the importance of using nanotechnology when a controlled drug release is desired. This characteristic has already been described in several studies (Contri et al., 2010; Marchiori et al., 2010; Poletto et al., 2011).

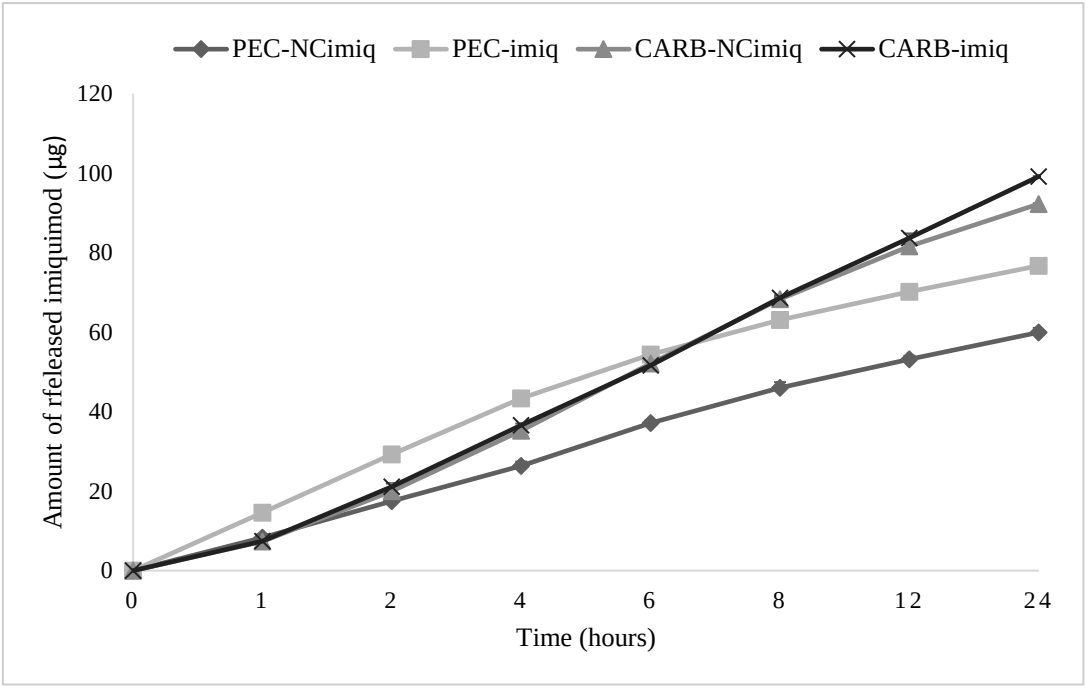


Figure 4 - Release profile of imiquimod during 24 hours when nanoencapsulated or not and when incorporated in pectin or Carbopol hydrogel. PEC-NCimiq: pectin hydrogel containing the nanoencapsulated imiquimod; PEC-imiq: pectin hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7); CARB-NCimiq: Carbopol hydrogel containing the nanoencapsulated imiquimod; CARB-imiq: Carbopol hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7).

### 3.3 Evaluation of the penetration and permeation in porcine skin

The in vitro penetration and permeation of the pectin and carbopol hydrogels (PEC-NCimiq, PEC-imiq, CARB-NCimiq and CARB-imiq) was carried out in automated Franz cell. In the Figure 5, is possible to see the imiquimod permeation, when the drug was incorporated in PEC-imiq and PEC-NCimiq hydrogels. As observed in this figure, the nanoencapsulated imiquimod incorporated in the pectin hydrogel was able to permeate the skin much more than the free drug incorporated in the pectin hydrogel. This result corroborates previous studies regarding the permeability of drugs through the skin using nanocarriers (Miyazaki et al., 2003; Guterres et al., 2007). Besides that, PEC-NCimiq started to permeate the skin after 8 hours of study, whereas PEC-imiq started after 12 hours. These results show that the nanoencapsulation of the drug not only improves the amount of drug that permeates the skin, but also makes the drug permeation faster. The Carbopol hydrogels did not permeate the skin during the 24 hours of study, results that agree with previous studies (Alves et al., 2007).

In the Figure 6, it is possible to see the penetration of the drug into the skin layers, when the drug was incorporated in PEC-NCimiq, PEC-imiq, CARB-NCimiq and CARB-imiq. As observed in this figure, the formulation that penetrated the most in the stratum corneum was CARB-NCimiq, followed by PEC-NCimiq, this suggests an affinity of the nanocapsules for this skin layer, when compared to the formulation containing the free drug. It can be observed, both in the epidermis and in the dermis, that the drug penetrated more when incorporated in the pectin hydrogels than when incorporated in the Carbopol hydrogels. This result can be partly explained by the fact that the pectin hydrogel presents lower viscosity. Furthermore, it is important to note that the imiquimod incorporated in the pectin hydrogels penetrated more into the skin layers when nanoencapsulated (PEC-NCimiq) than when free (PEC-imiq), showing the improvement in the delivery of drugs through the skin when nanocarriers are used.

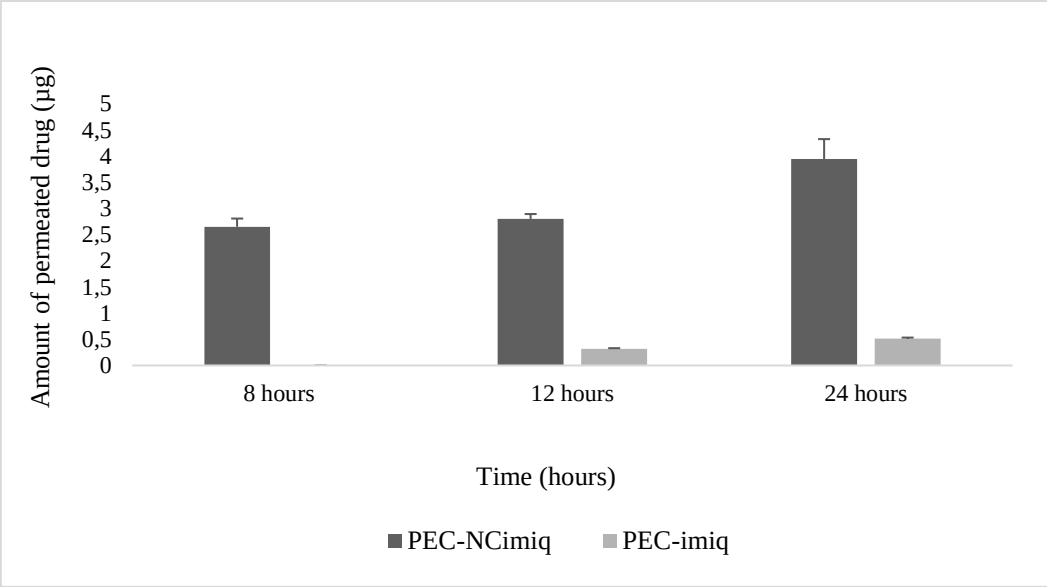


Figure 5 - Permeation of imiquimod through the skin in 8, 12 and 24 hours. PEC-NCimiq: pectin hydrogel containing the nanoencapsulated imiquimod; PEC-imiq: pectin hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7); CARB-NCimiq: carbopol hydrogel containing the nanoencapsulated imiquimod; CARB-imiq: carbopol hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7).

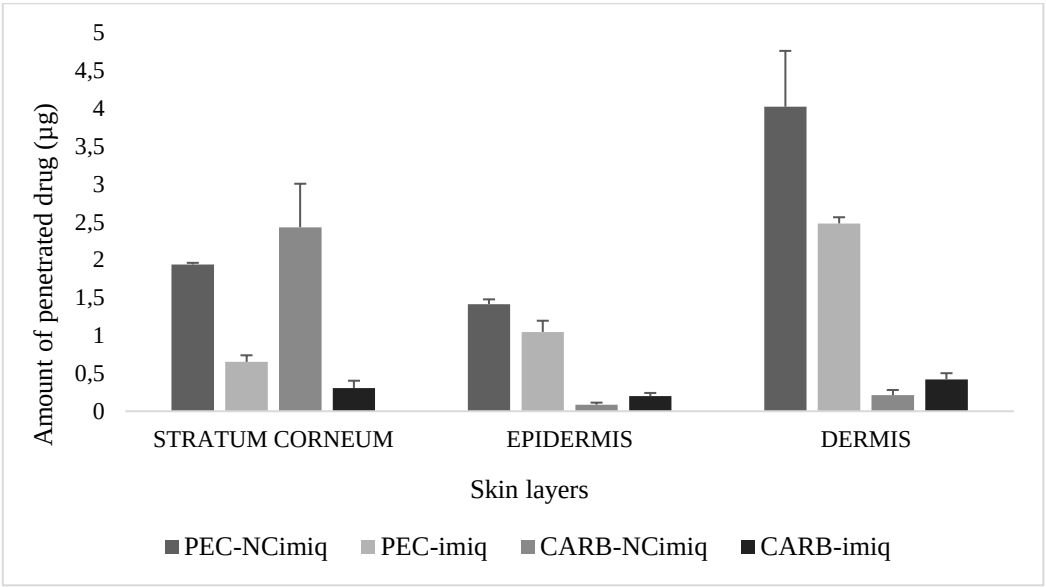


Figure 6 - Penetration of imiquimod in the layers of the skin after 24 hours of study. PEC-NCimiq: pectin hydrogel containing the nanoencapsulated imiquimod; PEC-imiq: pectin hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7); CARB-NCimiq: Carbopol hydrogel containing the nanoencapsulated imiquimod; CARB-imiq: Carbopol hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7).

### 3.4 Evaluation of the adhesiveness: washability study in porcine skin

The washability study was performed to analyze the adhesiveness of the formulations to the skin. This study is complementary to the tensile stress study. The difference is that on this experiment the hydrogels were submitted to a continuous flow (0.3 mL/min) that simulates the skin fluid. At the end of the experiment, each collected sample was analyzed in HPLC-UV and the amount of drug was determined. The amount of drug washed from the skin in each of the pre-determined times was summed and this value represents the total amount of formulation washed from the skin in 180 minutes. In the Figure 7, is possible to observe the cumulative percentage of drug washed from the skin of the four formulations (PEC-NCimiq, PEC-imiq, CARB-NCimiq and CARB-imiq), throughout the experiment time.

The formulation that presented the least amount of imiquimod washed was PEC-NCimiq (42%), therefore, it is the most adhesive hydrogel. On the other hand, the pectin hydrogel without the nanocapsules was the formulation that presented the highest amount of imiquimod washed (71%) and had a large amount of drug washed in the first 15 minutes of experiment (around 22%). These results show that the presence of the nanocapsules had great importance in the adhesiveness profile of the pectin hydrogel. The Carbopol hydrogels CARB-NCimiq and CARB-imiq presented 54% and 61% of imiquimod washed, respectively, also showing that the presence of the nanocapsules improved the adhesiveness, but not as significant as observed in the pectin hydrogel. These results corroborate previous studies (Contri et al., 2014; Guterres et al., 2007), which show that the use of polymeric nanocapsules increases the adhesiveness of formulations in the skin.

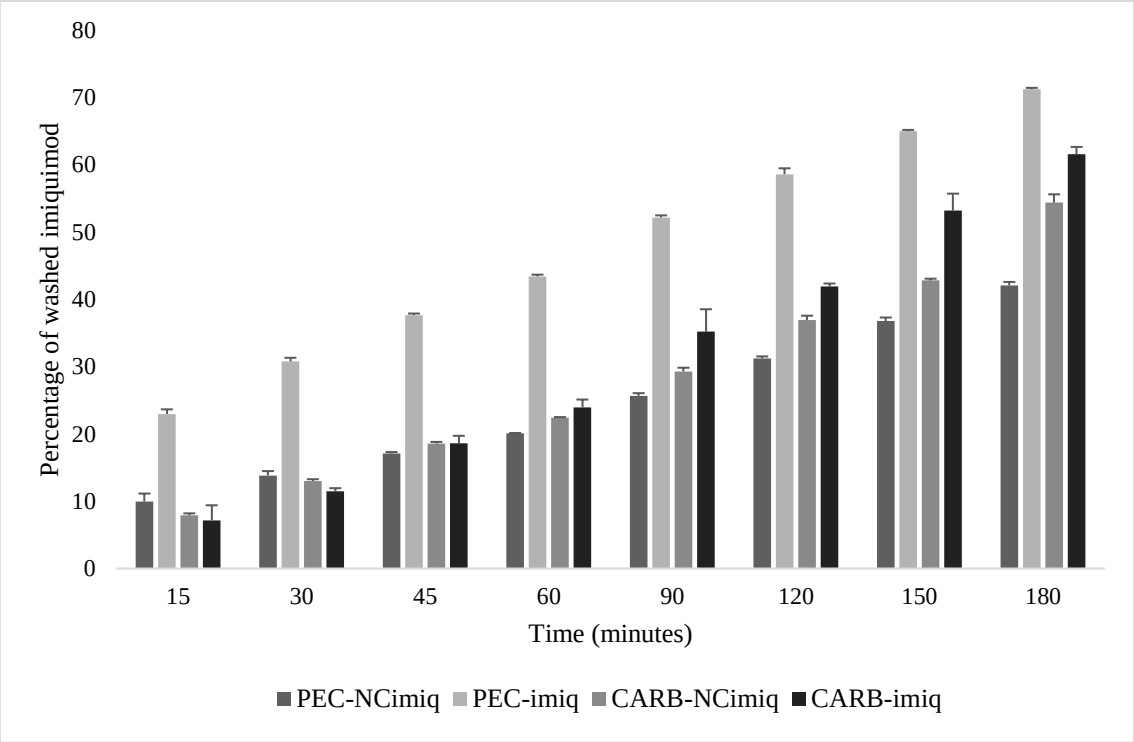


Figure 7 - Percentage of imiquimod washed from the porcine skin after 1 hour of contact. PEC-NCimiq: pectin hydrogel containing the nanoencapsulated imiquimod; PEC-imiq: pectin hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7); CARB-NCimiq: Carbopol hydrogel containing the nanoencapsulated imiquimod; CARB-imiq: Carbopol hydrogel containing imiquimod dissolved in acetate buffer (pH 3.7).

### 3.5 Evaluation of the adhesiveness: tensile stress study

The adhesiveness of the new hydrogel proposed in this work (PEC-NCimiq) was analyzed using a tensile stress tester and for comparison PEC-imiq and CARB-imiq were submitted to the same analysis. This experiment measures the force (F) and distance (D) required to remove the formulation from the skin.

The pectin hydrogel containing the polymeric nanocapsules presented the greatest detachment force (F=86,22±0,76), in comparison with PEC-imiq (F=31,06±4,33) and CARB-imiq (F=31,04±3,09), corroborating with the results found in the washability study. The pectin hydrogels presented similar detachment distances (PEC-NCimiq=4,14±0,79 and PEC-imiq=3,63±0,05), greater than the detachment distance for the carbopol hydrogel (CARB-imiq=3,03±1,36). Therefore, the most adhesive formulation is the pectin hydrogel containing the polymeric nanocapsules. These results agree with the ones found in the washability study, which showed that PEC-NCimiq was the most adhesive formulation to the skin when a flow was applied.

Analyzing these results and the ones found in the study described above, we can conclude that the PEC-NCimiq formulation has potential to be used for skin application since presented high adhesiveness and elastic characteristics, which is proper for topical formulations due to the easy spreadability and greater comfort for the patients.

## 4. Conclusion

The hydrogel developed in this work, which associates the polymeric nanocapsules and pectin, presented a low washing rate, which means a high adhesiveness of the formulation in the skin. Both the pectin and the polymeric nanocapsules were responsible for the high adhesiveness presented. This gel was able to penetrate all the layers of the skin, mainly the dermis, the deeper layer of the skin, and it was also able to permeate the skin significantly. In addition, the pectin hydrogel containing the polymeric nanocapsules was able to better control the drug release when compared to the other formulations. We conclude that this innovative gel presents promising characteristics to be used for the incorporation of lipophilic drugs aiming the transport through the layers of the skin and the systemic delivery.

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## Disclosure of interest

The authors report no conflicts of interest.

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