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**Keywords:** mucoadhesive film, macroporous ureasil–polyether material, triamcinolone, oral disease treatment

## Abstract

The aim of this study was to develop macroporous mucoadhesive films from ureasil–polyether materials for future application in oral disease treatment. The films were prepared via the sol–gel route by using polyethylene oxide (PEO) and polypropylene oxide (PPO) polymers; triamcinolone was used as a model drug for *in vitro* release testing. The *in vitro* drug release assay revealed that Ureasil-PEO500 films containing 3% and 6% of the model drug released 56% and 33% of the initial mass, respectively. This difference in release is probably due to a higher amount of the drug, making relaxation of polymer chains difficult, causing reduced swelling. For Ureasil-PPO400 films the amount of the drug did not influence the release; the rate of release was 5.1% after 12 hours and this lower release can be explained by the hydrophobic character of Ureasil-PPO400 polymeric chains. These results are in agreement with the swelling results. The swollen behavior of the films was monitored by small-angle x-ray scattering measurements (SAXS). Atomic force microscopy demonstrated that all the films are macroporous (pores around 400 nm) but the Ureasil-PEO500 film possesses more pores than Ureasil-PPO400. Mucoadhesion force assessment revealed that all ureasil–polyether films with or without a model drug have higher mucoadhesion values than the commercial product. These results indicate that macroporous ureasil–polyether mucoadhesive films are promising candidates for oral disease treatment considering their cost, biocompatibility, drug release and ease of handling, and they have more adhesion force to oral mucosa than the commercial product.

## 1. Introduction

Mucoadhesive systems have been used to promote intimate contact between the formulation and the administration site, with the help of interfacial forces [1]. The formation of a mucoadhesive bond between the pharmaceutical device and the mucosa is explained by the following theories: (i) adsorption theory, where the polymer adheres to the mucosa by weak forces, such as Van der Waals forces, hydrophobic or hydrogen bonds [2]; (ii) electronic theory, where the mucoadhesive material and mucosa possess different electronic structures and when contact occurs the electric double layer is responsible for attractive force; (iii) diffusion theory, which suggests that formation of the mucoadhesive bond is due to interpenetration between the polymeric chains of the material and the polymeric chains of the mucus; (iv) wetting theory, the ability of a material to spread on the mucus in relation to its surface tension; (v) mechanical theory, which suggests that a rougher surface benefits adhesion between surfaces due to the larger contact area; (vi) fracture theory, where force is necessary to detach the two surfaces after they are adhered [3, 4].

Thereby, for a material to be applied as a mucoadhesive system some features are necessary, such as: (a) a sufficient amount of chemical moieties able to establish hydrogen bonds with the biological substrate; (b) flexibility of the polymer chain, which allows its adaptation to changes in the oral mucosa; (c) anionic

charges on the surface that reduce the surface tension generated by saliva [5–9].

The oral mucosa when compared to other mucous membranes has the advantage of being more tolerant to allergens, with less tendency for irreversible tissue damage to occur, and also allows drug permeation, favoring both local and systemic effects [10]. This administration route also avoids the hepatic first pass effect [11]. However, in the oral mucosa there are factors such as humidity, temperature and mucosal movements that can easily remove conventional treatments based on creams, solutions and lotions [11].

In this context, research has been dedicated to the development of new materials that can, due to their features, interact with the mucosal surface, improving adhesion and drug release and optimizing oral disease treatment. Organic–inorganic hybrid materials whose inorganic phase is formed by silica, a class called ureasil–polyether, in particular, meet some of these important characteristics to act as mucoadhesives, such as mechanical resistance (flexibility), thermal resistance, transparency, the ability to release drugs and chemical groups (-OH, -COOH) in its structure capable of making hydrogen bonds with the oral mucosa. They can be applied to a variety of drugs, are low cost and easy to apply, increasing patients' adherence to therapy [12–17]. The macroporous feature allows the presence of compartments in the system, which could represent special molecular encapsulation and release capabilities [18]. Macroporous drug delivery systems have been used for systemic-delivery and also implantable local-delivery devices; in this case, we suggest the oral delivery of drugs [19].

Furthermore, previous studies of biocompatibility *in vitro* and *in vivo* showed that these materials are biocompatible [9, 11, 17].

Thus, in this paper we have developed macroporous ureasil–polyether mucoadhesive films (Ureasil-PPO400 and Ureasil-PEO500) containing triamcinolone and we evaluated the possibility of use for oral mucosa treatment. Triamcinolone was used as a model drug, chosen due to its anti-inflammatory and immunosuppressive properties. This drug is often used in the treatment of oral lichen planus, which requires repeated application over a long period, due to the chronic characteristic of this disease [7, 20]. Thus, the development of mucoadhesive films capable of releasing triamcinolone in a controlled manner in the oral mucosa is an important way to optimize oral disease treatment.

## 2. Materials and methods

### 2.1. Preparation of ureasil–polyether mucoadhesive films

The ureasil–polyether mucoadhesive films were prepared according to our previously reported protocol [12–14]. Briefly, mucoadhesive films were prepared by the sol–gel process, using in the synthesis of precursor a functionalized polyether, based on poly(ethylene oxide) ($NH_2$-PEO-$NH_2$) (MW 500 g $mol^{-1}$) or poly (propylene oxide) ($NH_2$-PPO-$NH_2$) (MW 400 g $mol^{-1}$), and adding a modified alkoxide, 3-(isocyanatopropyl)-triethoxysilane (IsoTrEOS) (molar ratio of the polymer:alkoxide = 1:2). Ethanol was used as solvent. The solution remained under reflux for 24 hours at 80 °C, to promote the formation of the hybrid precursor $(EtO)_3Si(CH_2)_3NHC(=O)NHCHCH_3CH_2$-(polyether)-$CH_2CH_3CHNH(O=)NHC(CH_2)_3Si(OEt)_3$ [15]. Subsequently, the solvent was removed by heating under reduced pressure to form the hybrid precursor.

For mucoadhesive film formation, it was subjected to hydrolysis and condensation reactions, and the desired proportion of the model drug was solubilized in ethanol. During these reactions, the OH groups were progressively eliminated, and the inorganic–organic networks were joined by covalent bonds [21].

### 2.2. Determination of pH

The assessment of changes in pH induced by the films was determined by immersion in an artificial saliva composite of NaCl, KCl, $CaCl_2.2H_2O$, citric acid, urea, $Na_2S.9H_2O$, $NaH_2PO4 \cdot H_2O$, $(NH_4)_2SO_4$ and $NaHCO_3$ with an initial pH of 7.4. The films used were 6 mm in diameter and 0.3 ± 0.5 mm in thickness. Each sample was packaged into a glass flask containing 6 ml of saliva. A digital pH meter (PG1800 Gehaka) was used to make these measurements which were performed in triplicate at a temperature of 37 ± 0.5 °C.

### 2.3. *In vitro* drug release assay

The Ureasil-PPO400 and Ureasil-PEO500 mucoadhesive films containing 3% and 6% of triamcinolone acetonide (m/m) were immersed in dissolution apparatus (Agilent Technologies 708-DS) containing 500 ml of receptor medium (phosphate buffer 7.2 pH with 0.5% of Procetyl® AWS to ensure sink conditions) at 37 ± 0.5 °C and stirred with a USP paddle at 50 rpm. At given time intervals, 2 ml of filtered medium was removed for analysis and replaced with the same volume of receptor medium. The triamcinolone acetate amount in the extracted solution was analyzed by measurement of absorbance at 240 nm, using a UV–vis Cary 60 spectrophotometer. The cumulative percentage of drug release was calculated from the average of three parallel monitoring experiments. The results were expressed as mean ± SD of three experiments.

### 2.4. Small-angle x-ray scattering measurements

Changes in the nanoscopic structure of the ureasil–-polyether mucoadhesive films imbibed in artificial saliva were assessed by small-angle x-ray scattering

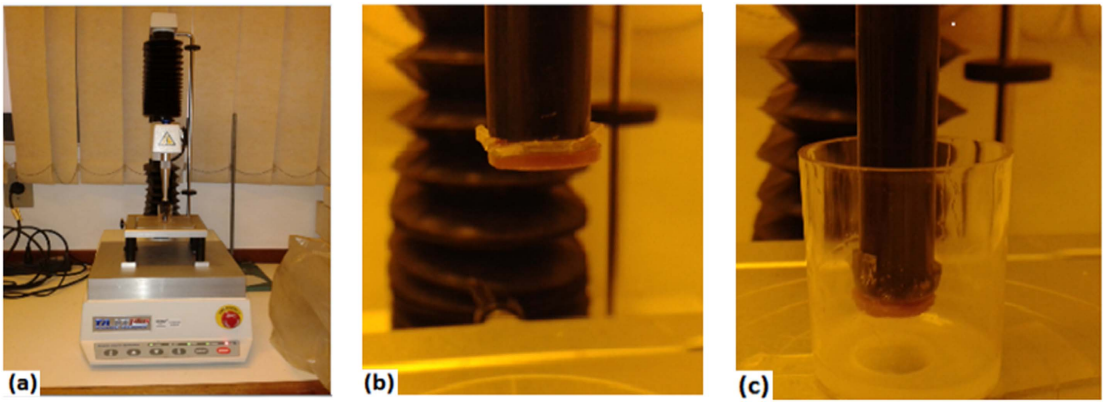


**Figure 1.** Scheme for mucoadhesion force assessment using mucin discs. (a) Texture analyzer; (b) mucin disc on the analytical probe; (c) position of the mucoadhesive film during the test.

(SAXS) measurements. Data were recorded at the synchrotron SAXS 1 beamline at LNLS (Campinas, Brazil). This beamline is equipped with an asymmetrically cut and bent Si (111) monochromator that produces a horizontally focused beam ($\lambda = 0.1608$ nm). A vertical position-sensitive x-ray detector and a multichannel analyzer were used to record the SAXS intensity, I($q$), as a function of the modulus of the scattering vector $q = (4\pi/\lambda)\sin(\varepsilon/2)$, $\varepsilon$ being the scattering angle. The SAXS patterns of dried mucoadhesive films were recorded at 37 °C. Monitoring of the *in situ* swelling process was performed by immersing discs of the samples in artificial saliva heated at 37 °C, with SAXS patterns being recorded every 30 s.

### 2.5. Atomic force microscopy (AFM)

AFM experiments were carried out under environmental conditions using a standard commercial AF (Multimode III, Brucker), working in contact mode. Image data were analyzed using WSxM software [22]. Olympus silicon nitride cantilevers with a nominal spring constant of 0.06 N m and a nominal tip radius of 20 nm were used.

### 2.6. Mucoadhesion force assessment

Adhesion force assessment was used to verify the peel force between the mucoadhesive film and a mucin disc or pig buccal mucosa. The mucin discs were prepared by compression of mucin (250 mg) from a porcine stomach (Sigma-Aldrich, São Paulo, Brazil) using a tablet compressor with a diameter of 123 mm. Freshly excised pig buccal mucosa was obtained from a local slaughterhouse, cleaned and frozen at −30 °C until the day of the experiment.

The test was performed in a texturometer (TA.XT Plus Texture Analyser System) equipped with a ring for mucoadhesion testing and a cylindrical probe of 10 mm diameter.

The mucin discs or pig buccal mucosa were adhered onto the cylindrical probe of the texturometer with double-sided tape to keep them static. The tests were performed on neat films and on films incorporated with triamcinolone, with the drug in cylindrical plastic devices. The devices were fixed with double-sided tape onto the table of the machine, as shown in figure 1. The cylindrical probe with mucin discs or pig buccal mucosa was then lowered at a speed of 1 mm$s^{-1}$ until it reached the hybrid material. The probe was kept in contact with no force applied for 300 seconds; this time was considered ideal, since a time less than 120 seconds does not occur in the training system [12] and a time longer than 300 seconds caused discomfort in waiting for the gel formation [23]. After this time the test was removed with a speed of 0.5 mm $s^{-1}$ and, thus, the resistance of removing the mucin or pig buccal mucosa from the mucoadhesive film was measured (figure 1).

## 3. Results and discussion

### 3.1. Preparation of precursors and ureasil–polyether mucoadhesive films

The ureasil–polyether mucoadhesive films were prepared by the sol–gel process. This process is ideal for inserting the material non-invasively into the mucosa, because it allows the precursor in the sol state (liquid state, see figure 2(a)) to be inserted into mucosa and results in a rigid gel structure that immobilizes the liquid part in its interstices, adhering to the mucosa during this process [24]. The films were obtained from 0.75 mg of the precursor that was placed in an acrylic plate covered by Teflon® using a film extensor (slot cavity of 0.254 mm). However, the shape of the films is determined according to the mold used.

These ureasil–polyether materials have functional groups such as OH that are correlated with mucoadhesive binding to the oral mucosa; the high moisture content favors the formation of hydrogen bonds between water and COOH groups. The choice of Ureasil-PPO400 and Ureasil-PEO500 materials was due to their lower molecular weight in relation to

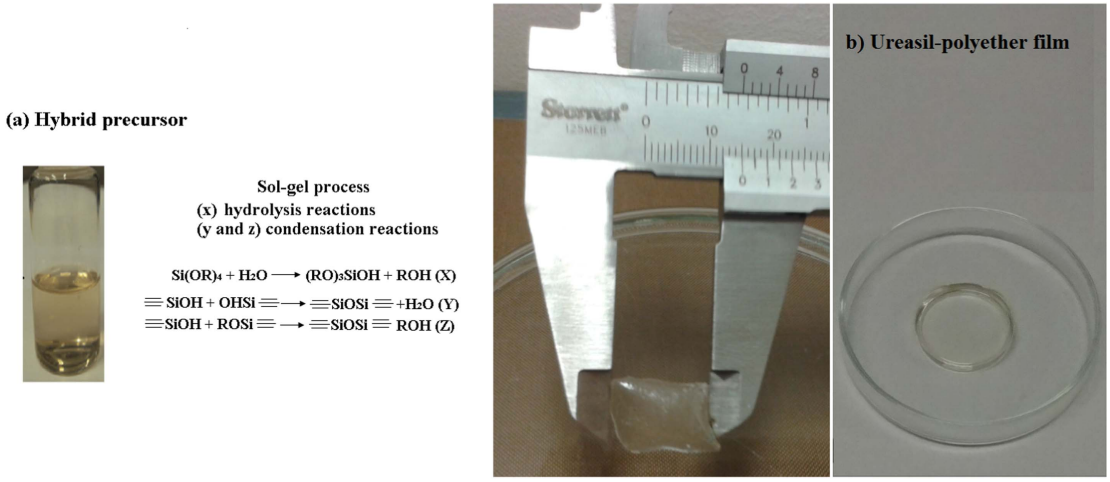


**Figure 2.** Aspects of ureasil–polyether precursor (**a**) and mucoadhesive film (**b**) after the hydrolysis and condensation step.

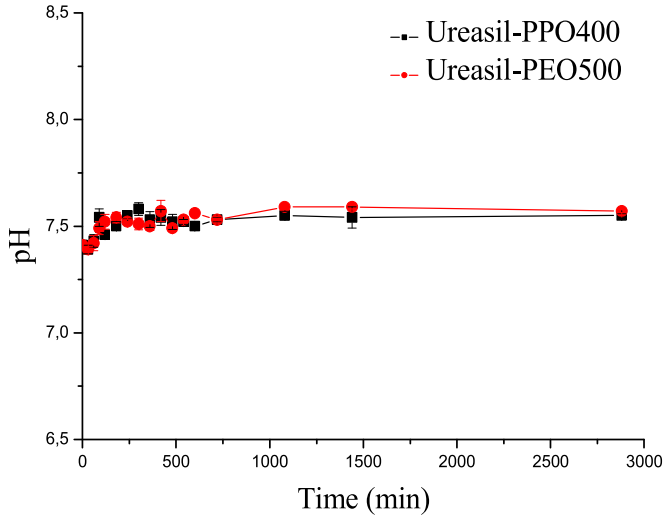


**Figure 3.** pH evolution as function of immersion time of Ureasil-PEO500 and Ureasil-PPO400 films in artificial saliva.

other ureasil–polyethers found in the literature [12, 14], resulting in a greater amount of functional groups able to bind to the biological substrate; this is important to maintain film adherence for a long time, while suffering the action of humidity and mucosal movements.

The visual appearance of the films prepared from polyether ureasil hybrid precursors is shown in figure 2. The films exhibited well-defined macroscopic characteristics, such as transparency, flexibility and no cracks. Therefore, the material after hydrolysis and condensation reactions acquired structural uniformity. Such structural uniformity leads to the formation of a homogeneous film that can be spread uniformly across the mucosa. These characteristics were observed for Ureasil-PPO400 and Ureasil-PEO500 films containing up to 6% m/m of triamcinolone.

### 3.2. Determination of pH

The oral mucosa pH may not undergo extreme changes after contact with ureasil–polyether mucoadhesive films, since high or low values of pH, differing from biological values, can cause cytotoxic effects. The pH range considered appropriate is $6.0 \leqslant \text{pH} \leqslant 8.5$ [25].

Thus, the *in vitro* pH values of the artificial saliva as a function of immersion time of ureasil–polyether films were measured. The pH evolution of the artificial saliva in the presence of films is shown in figure 3.

We can observe from figure 2 that the artificial saliva containing Ureasil-PPO400 or Ureasil-PEO500 presented similar pH evolution during the studied period (2 days) with pH values remaining between 7.38 and 7.64, considered appropriate for oral application. The pH of artificial saliva without the films is 7.4 so we can conclude that the films do not significantly alter the pH of the artificial saliva.

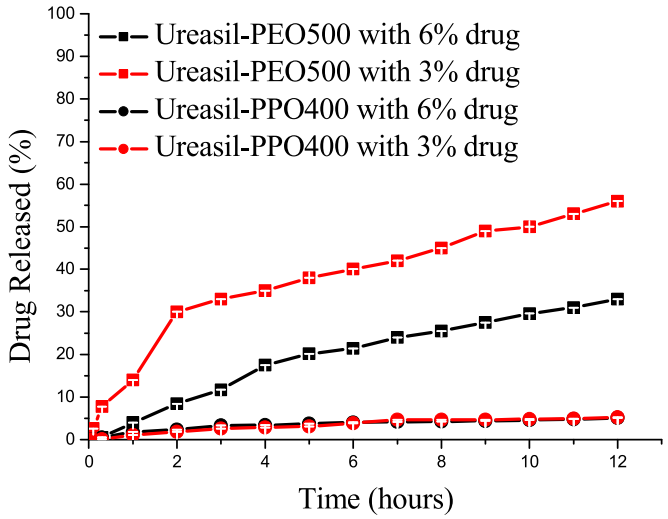


**Figure 4.** Triamcinolone release profile at 3% and 6% in Ureasil-PEO500 and Ureasil-PPO400 films.

### 3.3. *In vitro* drug release assay

Drug release from polymeric materials can occur through physical and chemical processes such as diffusion, swelling or erosion of the matrix or by a combination of these mechanisms. However, when using a mucoadhesive system, erosion of the matrix is not desirable because it changes the time the material remains at the site of action. Ureasil–polyether films are formed by a crosslink network that forms an insoluble system, avoiding erosion of the matrix and, consequently, the material is kept in the mucosa longer. Considering the macroporous feature of these films, the erosion is not necessary, due to the release of the drug through the macropore channels of the film being possible [18].

Figure 4 shows the release profile of triamcinolone incorporated at two different concentrations (3% and 6%) in Ureasil-PEO500 and Ureasil-PPO400 films.

For Ureasil-PEO500 films (hydrophilic character) the results reveal that a higher drug release rate occurs when compared with Ureasil-PPO400 films (hydrophobic character), independent of the drug concentration. The hydrophilicity of the material increases the affinity with the dissolution medium, resulting in greater relaxation of the polymer chains of the matrix, favoring the release of the drug through the macropore channels of the film.

However, Ureasil-PEO500 films containing 3% and 6% of the drug have different delivery behavior; the film containing 3% of the drug released 56%, while that containing 6% released only 33% of the initial mass. This behavior could be due to the fact that the drug is located in the polymer chain between the crosslinking nodes, which makes relaxation of polymer chains difficult, causing less swelling. As the higher amount of the drug (6%) in the film results in less swelling, consequently the release value is lower. Results of SAXS measurements confirmed this reduced swelling of the matrix (see 3.4 SAXS measurements).

The Ureasil-PPO400 film has a different behavior to Ureasil-PEO500 films, presenting the same rate of release (5.1%) after 12 hours for the films containing 3% and 6% of the drug.

This behavior can be explained by the hydrophobic character of Ureasil-PPO400 films that decreases the affinity of films for water; the swelling rate remained unaltered at 0% for Ureasil-PPO400 films with 3% and 6% triamcinolone (see 3.4. SAXS measurements).

Previous studies conducted by our research group revealed that the transport mechanisms involved in control of the drug in Ureasil-PPO400 and Ureasil-PEO500 occur by Fickian diffusion and anomalous transport (where swelling and Fickian diffusion are the transport mechanisms that release the drug from the matrix to the medium), respectively [13, 16, 26]. Thus, in Ureasil-PPO400 the amount of the drug does not influence the behavior as it does in Ureasil-PEO500.

The release profile was evaluated during 12 hours, considering the suggestion of application site for this film. The permanence of the film in the oral mucosa is unlikely to occur for a longer period, considering the need for food and oral hygiene. Also, in the same way that happens with conventional pharmaceutical formultations, these special formulations suffered with movement, contact with biological fluids, and other factors, which reduces the residence time of the formulation [27].

### 3.4. Small-angle x-ray scattering measurements

These ureasil–polyether materials are formed by an organic polymeric chain and an inorganic phase containing crosslinking nodes (Si–O–Si). Thus, from the maximum scattering vector peak ($q$max), the correlation distance ($d$) between two 'nodes' of silicon can be calculated, using the relation $d = 2\pi/q\text{max}$,

**Table 1.** *q*max values, correlation distance (*d*) and swelling of the crosslinked nodes ($\Delta d$) for Ureasil-PPO400 and Ureasil-PEO500 materials containing 3% and 6% of triamcinolone.

| | Ureasil-PEO500 (triamcinolone 3%) | | | Ureasil-PEO500 (triamcinolone 6%) | | | Ureasil-PPO400 (triamcinolone 3% and 6%) | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min) | *q*max | *d* (nm) | $\Delta d$ (%) | *q*max | *d* (nm) | $\Delta d$ (%) | *q*max | *d* (nm) | $\Delta d$ (%) |
| 0 | 3.00 | 2.09 | 0 | 2.2 | 2.85 | 0 | 2.66 | 2.36 | 0.00 |
| 5 | 2.68 | 2.34 | 10.68 | 2.05 | 3.06 | 6.86 | 2.66 | 2.36 | 0.00 |
| 10 | 2.54 | 2.47 | 15.38 | 1.96 | 3.20 | 10.93 | 2.66 | 2.36 | 0.00 |
| 20 | 2.15 | 2.92 | 28.42 | 1.91 | 3.28 | 13.10 | 2.66 | 2.36 | 0.00 |
| 30 | 1.95 | 3.22 | 35.09 | 1.88 | 3.34 | 14.67 | 2.66 | 2.36 | 0.00 |

where *q*max is the value of the scattering vector *q*, corresponding to the position of the maximum correlation peak.

Furthermore, the evolution of the distance between the crosslinked nodes as a function of the swelling of the matrix ($\Delta d$) is an important structural parameter, which is relative to the elongation ratio $\Delta d = (dt - ds)/dt$. The relative elongation ratio was calculated from the SAXS curves by the average distance between crosslinking nodes measured in the dry state (d*s*) and after different time *t* of contact with the release medium periods (d*t*) [13–16, 26].

Table 1 shows the values for the parameters *q*max, correlation distance (*d*) and evolution of the distance between the crosslinked nodes ($\Delta d$) for Ureasil-PPO400 and Ureasil-PEO500 films containing 3% and 6% of the drug.

In Ureasil-PEO500 films with 3% and 6% of the drug a shift to low *q*max values occurred and, consequently, the distance between the two 'nodes' of silicon increased (table 1). However, the swelling rate varied; the Ureasil-PEO500 films containing 3% and 6% of the drug revealed 35.09% and 14.67% of swelling, respectively. These results corroborate the *in vitro* drug release assay, since Ureasil-PEO500 films with 3% of the drug had a higher swelling rate in relation to Ureasil-PEO500 with 6%. The Ureasil-PPO400 films with 3% and 6% of triamcinolone did not present a shift to low values of *q*max (table 1), indicating that the correlation distance between the silicon 'nodes' remained unaltered at 3.95 nm and the swelling rate for Ureasil-PPO400 was 0%.

This difference in swelling rate is based on the more hydrophobic character of Ureasil-PPO400. The $CH_3$ moieties exert protection in the oxygen ether type and decrease the affinity of films with water, which is not verified in Ureasil-PEO500.

### 3.5. Atomic force microscopy

The surface topography of Ureasil-PEO500 and Ureasil-PPO400 films loaded with 3% triamcinolone was characterized by contact-mode AFM and is shown in figure 5. Both films were laterally homogeneous, with height variations of the order of 10 nm. No characteristic feature which could be directly attributed to the presence of triamcinolone on the surface/near surface regions could be distinguished from the images.

In the loaded Ureasil-PEO500 (figure 5(a)), the presence of several surface pores of about 400 nm in diameter are apparent (black arrows). The presence of those pores confirms the macroporous character of this material, and constitutes a factor that may strongly influence its drug release behavior, facilitating the penetration of the medium into the material and dissolution of the drug. Even though some pores may also be observed in the loaded Ureasil-PPO400 (figure 5(b)) it is clear from our study that Ureasil-PEO500 presents more pores in the surfaces of the films. Until now the presence of pores in ureasil–polyether hybrid polymeric matrices had not been demonstrated. In previous studies, the differences in drug release profiles from Ureasil-PEO500 and Ureasil-PPO400 were attributed only to differences in the balance between the hydrophilic/hydrophobic character [13–16] of the matrices or to drug–matrix interactions [28, 29]. The present study reveals that the presence of a greater amount of pores in Ureasil-PEO500 may also strongly contribute to facilitating entry of the release medium into the films and facilitating transport of the drug out of the polymer matrix.

### 3.6. Mucoadhesion force assessment

Table 2 shows the adhesive strength values (*W*ad) for Ureasil-PPO400 and Ureasil-PEO500 films with and without drug when in contact with mucin discs.

When the adhesion values of Ureasil-PPO400 were compared with Ureasil-PEO500 films (with and without drug), it was observed that Ureasil-PEO500 films had statistically higher adhesion values; this fact can be related to their hydrophilic character, since hydrophilic materials tend to have a greater adhesion to the oral mucosa compared to hydrophobic materials. Another influence can be derived from the swellability capacity of Ureasil-PEO500, which occurs when in contact with artificial saliva. This capacity allows greater interpenetration between the polymeric chains of the material and the polymeric chains of the mucus, besides the swelling increasing the flexibility of the material which favors mucoadhesion (mucoadhesive theories, see Introduction). Another factor is that the Ureasil-PEO500 material has a greater roughness

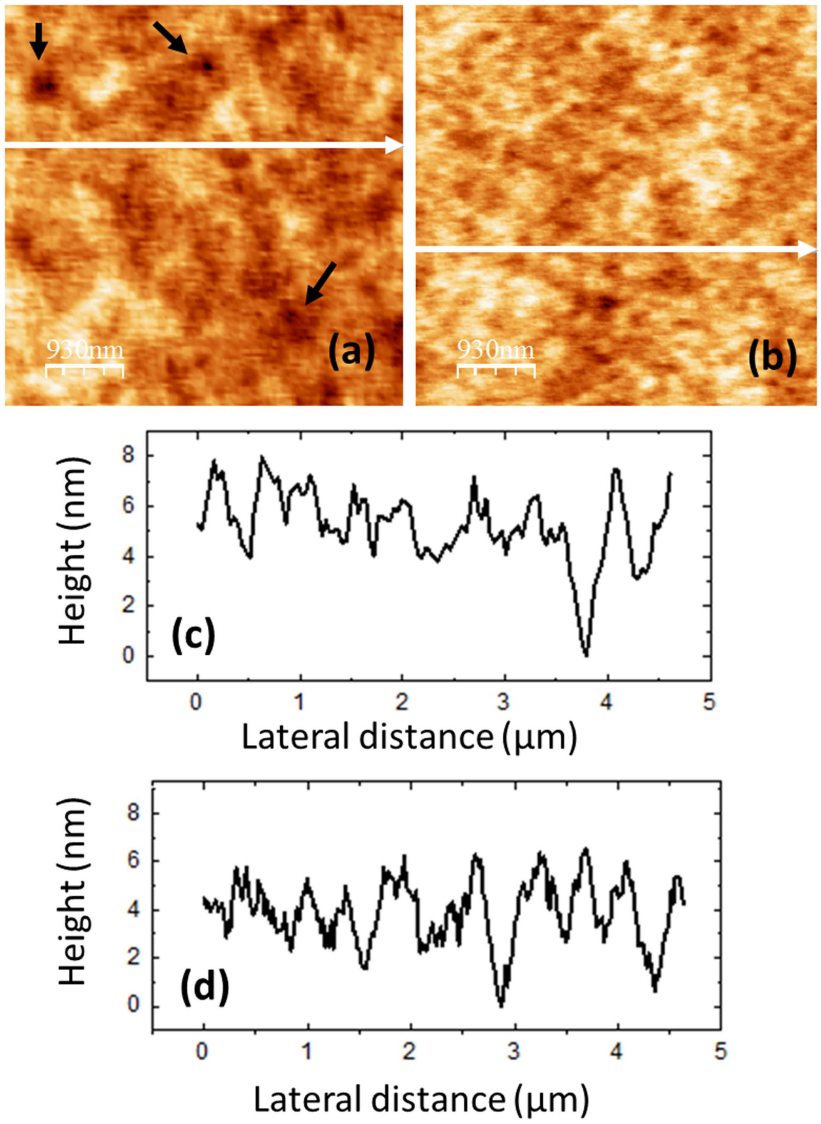


**Figure 5.** Surface topography of Ureasil-PEO500 (a) and Ureasil-PPO400 (b) films loaded with 3% triamcinolone. (c) and (d) topographic contours along the white arrows in (a) and (b), respectively.

**Table 2.** Adhesive strength values (*W*ad), for Ureasil-PEO500 and Ureasil-PPO400 films and commercial mucoadhesive formulations when in contact with mucin discs.

| Ureasil–polyether film | Work of adhesion (*W*ad)[1] |
|---|---|
| Ureasil-PPO400 without drug | 7.32 ± 0.35 |
| Ureasil-PEO500 without drug | 8.47 ± 0.31 |
| Ureasil-PPO400 with 3% of drug | 5.80 ± 0.29 |
| Ureasil-PEO500 with 3% of drug | 6.58 ± 0.27 |
| Ureasil-PPO400 with 6% of drug | 4.62 ± 0.04 |
| Ureasil-PEO500 with 6% of drug | 5.22 ± 0.27 |
| Triamcinolone Orabase (EMS®) | 0.93 ± 0.19 |
| Ad-Muc (Avert®) | 0.12 ± 0.007 |

[1] Results are expressed as mean ± SD for $n = 5$.

than Ureasil-PPO400 (see figure 5(c)); as suggested by mechanical theory, the greater the roughness of the material, the greater its strength adhesion (see Introduction).

When the values for Ureasil-PPO400 and Ureasil-PEO500 films without drug and with the addition of 3% drug were compared, a decrease in the adhesion values to the films with drug was observed. In the films with 6% drug, this decrease was more pronounced, probably due to the smaller amount of swelling (SAXS results) and the possibility of the drug binding to the chemical groups (-OH, -COOH), which also are responsible for the formation of hydrogen bonds between the system and the mucosa.

Table 3 shows the adhesive strength values (*W*ad) for Ureasil-PPO400 and Ureasil-PEO500 films with and without drug when in contact with pig buccal mucosa.

We can verify that all materials analyzed with the pig buccal mucosa presented values statistically lower than those presented with the mucin discs (table 2). However, the results followed the same pattern, i.e., Ureasil-PEO500 films had higher mucoadhesion values than Ureasil-PPO400 films, and as the amount

**Table 3.** Adhesive strength values (*Wad*) for Ureasil-PEO500 and Ureasil-PPO400 films and commercial mucoadhesive formulations when in contact with pig buccal mucosa.

| Ureasil–polyether film | Work of adhesion (*Wad*)[1] |
|---|---|
| Ureasil-PPO400 without drug | 2.88 ± 0.21 |
| Ureasil-PEO500 without drug | 6.49 ± 0.48 |
| Ureasil-PPO400 with 3% of drug | 2.49 ± 0.20 |
| Ureasil-PEO500 with 3% of drug | 4.05 ± 0.27 |
| Ureasil-PPO400 with 6% of drug | 1.82 ± 0.09 |
| Ureasil-PEO500 with 6% of drug | 3.66 ± 0.28 |
| Triamcinolone Orabase (EMS®) | 0.73 ± 0.04 |
| Ad-Muc (Avert®) | 0.13 ± 0.02 |

[1] Results are expressed as mean ± SD for $n = 5$.

of drug incorporated in the films increased the adhesion value decreased. The lower values in relation to the experiment performed with mucin discs may be due to this glycoprotein (mucin), which has the main responsibility for conferring gel resistance to the mucus, being at a higher concentration in the discs.

However, comparing the adhesion values of all ureasil–polyether films with values of commercial mucoadhesive formulations, all films have statistically higher adhesion than the commercial materials, supporting the proposal of using these materials as mucoadhesive systems.

The high adhesion values obtained for the ureasil–polyether films are related to a sum of mechanisms, such as swelling, hydrophilic/hydrophobic character and the amount of chemical groups (-OH, -COOH) available to make hydrogen bonds with the oral mucosa.

## 4. Conclusions

In conclusion, this research demonstrated that the use of Ureasil-PPO400 and Ureasil-PEO500 macroporous materials for oral disease treatment deserves to be highlighted. For the first time the presence of pores in the surface of ureasil–polyether hybrid materials and their influence on the swelling and drug release profile was evidenced. The ureasil–polyether mucoadhesive films assessed in this work are macroporous, biocompatible and release drug in a controlled manner. *In vitro* studies of adhesion to the oral mucosa demonstrated that they are more efficient than the commercial model. The combination of these properties endorse the use of these materials as a mucoadhesive. The next step will be to conduct clinical trials in animals and humans. If successful, this approach would minimize clinical adverse effects and disadvantages of conventional systems increasing patient adherence to treatment.

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**Author contributions**

João Augusto Oshiro Júnior and Neima Jamil Nasser characterized the ureasil–polyether materials by Small-angle x-ray scattering measurements, *in vitro* evaluation of the mucoadhesion force and *in vitro* drug release. Bruna Galdorfini Chiari-Andréo performed the pH experiments and analyzed the data of *in vitro* drug release. M Teresa Cuberes analyzed the data of Atomic Force Microscopy. Leila Aparecida Chiavacci supervised the authors and developed the systems. All authors assisted in drafting the paper.

## Conflicts of interest

The authors declare no conflict of interest.

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