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Article

Comparative study of mucoadhesive vaginal tablets of *Schinopsis brasiliensis* Engler extract formulated with different polymers with antifungal activity

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Candida albicans is the main fungus responsible for acute and recurrent vaginal infections. Low adherence to treatment is due to dosing frequency and available topical medications. Thus, we developed mucoadhesive tablets based on *Schinopsis brasiliensis* Engler extract composed of Carboxymethylcellulose (F1), Hydroxypropylmethylcellulose (F2), or Pluronic (F3), against *C. albicans*. The extract metabolites determination showed presence of polyphenols (15 $\mu g.mg^{-1}$), flavonoids (5.51 $\mu g.mg^{-1}$), and tannins (4.80 $\mu g.mg^{-1}$). The *in vitro* antifungal activity was performed by broth microdilution method. Quality control tests were performed according international pharmacopeias. Regarding the mucoadhesion test, in terms of the force expressed between the tablet:mucin disc, the average values were approximately 0.1267 N (F1), 0.0411 N (F2) and 0.814 N (F3), while in the tablet:vaginal mucosa, the average values were approximately 0.0294 N (F1), 0.0166 N (F2) and 0.0365 N (F3). The dry extract showed a minimum inhibitory concentration of 62.5 $\mu g.mL^{-1}$. In evaluating the *in vitro* release of tablets, polymers derived from cellulose released 100% in less than 4 hours, while Pluronic released around 56.3% in 72 hours. It is concluded that F1 has greater mucoadhesion while F3 has a modified release rate, providing promising results for future application of the formulation in the clinical assay.

Keywords: Vaginal fungal infections. Mucoadhesion. Carboxymethylcellulose. Hydroxypropylmethylcellulose. Pluronic.

INTRODUCTION

Preventing the invasion of pathogens is one of the essential functions performed by the body's mucous membranes (Harris-Tryon, Grice, 2022). The natural microbiota of these regions acts as a barrier that protects them against infections, especially those with an intense flow of microorganisms, such as the vaginal cavity (Kennedy *et al*., 2019; Chee, Chew, Than, 2020). The imbalance of this microbiota is responsible for favoring the pathogenic development of microorganisms, such as the fungus *Candida albicans*, historically responsible for at least 70% of clinical records of candidiasis in the world (Gonçalves *et al*., 2016). Usually, these infections are treated with topical dosage forms, such as creams, tablets, gels, ointments, and suppositories, as they allow greater concentration and distribution of the active ingredient in the affected tissue (Edmans *et al*., 2020; Şenel, Özdoğan, Akca, 2021). However, individualities

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of the mucosa are responsible for compromising therapy, since secretion flow and tissue thickness interfere with mucoadhesion and retention of the drugs, requiring an increase in dosage, which results in the possibility of toxic effects to the patient (Şenel, Özdoğan, Akca, 2021; Dedeloudi *et al*., 2022).

Regarding adhesion, mucoadhesive tablets are a good alternative, when compared to non-mucoadhesive forms, as they allow greater contact and adherence with the mucosa without the risk of removal of therapeutic agents by local fluids, a fact that stimulates greater permeability of the active ingredient avoiding the action of first-pass metabolism and enzymes responsible for the chemical degradation of the drug (de Sá *et al*., 2018; Sette-DE-Souza *et al*., 2020). The main challenge for these formulations is the selection of the ideal inert polymer that will perform the adhesive action at the desired site (Chaiya, Patomchaiviwat, Phaechamud, 2023). In contrast, the literature demonstrates the possibility of beneficial use of polymeric compounds, with emphasis on cellulose derivatives, such as Carboxymethylcellulose (CMC), Hydroxypropylmethylcellulose (HPMC), and Pluronic (PLU), as they are biocompatible and hydrophilic, providing good mucoadhesion when formulated for topical use in the vaginal cavity (da Silva *et al*., 2021; Dedeloudi *et al*., 2022).

The mucoadhesive interaction between cellulose derivatives may occur with certain similarities, according to studies (Watchorn *et al*., 2022a, 2022b). CMC and HPMC would possess an affinity to the mucosal tissue proposed by bonds reinforced through the protons of the Carbohydrate ring present in cellulose. In addition, there would also be the influence of molecular weight on the impact of mucoadhesion. Low molecular weight CMC (90 kDa) would not be able to form significant bonds with mucin compared to high molecular weight CMC (131 kDa), given the higher proton-binding availability for the latter (Watchorn *et al*., 2022b). In contrast, low molecular weight HPMC has better mucoadhesion than high molecular weight HPMC, which suggests a relationship with its lack of ability to rearrange spatially indicating immobility (Watchorn *et al*., 2022b). While for Pluronic, its relationship in mucoadhesion is related to its chemical affinity with the tissue, which considers several theories about its fixation, mentioning hydrogen bridges and hydrophobic-hydrophilic electrostatic attractions (Calori *et al*., 2020; da Silva *et al*., 2021).

In this perspective, a promising alternative for treating infections is the use of medicinal plants in the form of Plant Active Pharmaceutical Ingredients (PAPIs), due to their chemical reserve of bioactive compounds, appreciable efficacy, and safety (AlSheikh *et al*., 2020; Sawicka *et al*., 2022). As a highlight, we can mention *Schinopsis brasiliensis* Engler (Anacardiaceae), a medicinal plant typical of the Brazilian semiarid region, present in the Caatinga biome located in the northeast of the country, popularly known as "baraúna", "braúna", "braúna-parda" and "baraúna-do-sertão" (Barreto Linhares *et al*., 2022). The plant is rich in secondary metabolites such as condensed tannins, phenols, flavonoids, triterpenes, saponins, polyphenols, quinones, alkaloids, gallic and phenolic acids, which justifies the use of leaves, fruits, stems, bark, seeds, and the root of this plant in traditional medicine (Barreto Linhares *et al*., 2022; Sampaio *et al*., 2023).

Studies address the antimicrobial activity of *S. brasiliensis* against fungi of the genus *Candida spp.* (Saraiva *et al*., 2013), Gram-positive bacteria of the genus *Streptococcus* (*S. mutans*, *S. oralis,* and *S. mitis*) (Sette-DE-Souza *et al*., 2020) and Gram-negative of the genera *Escherichia*, *Pseudomonas,* and *Klebsiella* (*E. coli*, *P. aeruginosa*, *K. pneumoniae*) (de Lima-Saraiva *et al*., 2017). In this sense, given the antimicrobial potential of *Schinopsis brasiliensis* Engler together with the need to reduce the risks of toxic effects by drugs in the treatment of infections in the vaginal mucosa, the development of drugs with PAPIs from this plant is something promising and innovative. However, there is no formulation available that uses this PAPI and allows a temporal and spatial release to optimize therapy.

In the present study, we developed and compared three types of mucoadhesive tablets, intended for the treatment of vaginal infections, based on CMC, HPMC, or PLU, incorporated with *Schinopsis brasiliensis* Engler extract.

MATERIAL AND METHODS

Material

Carboxymethylcellulose (CMC) (L-10/2459), Hydroxypropylmethylcellulose (HPMC) obtained by Unna Derme Comércio de Produtos Farmacêuticos Ltda (REQ. 020521; REG. 20057), Pluronic (PLU) (Lot # BCBK2015V), disintegrating agent Starch (L-11/26050) and lubricating agent Magnesium Stearate (EXT) (L- C014668), were obtained from Henrifarma Produtos Químicos e Farmacêuticos Ltda (located in Cambuci, Brazil). Lactose powder diluent agent (LACT) (L-11040090) was obtained from Galena Química e Farmacêutica Ltda (located in São Paulo, Brazil). Ethyl alcohol 99.5% obtained from Dinâmica Química Contemporânea Ltda (L- 118092).

Plant material

The plant was registered in Brazil's Sistema Nacional de Patrimônio Genético e Conhecimento Tradicional Associado (SISGEN) under the number A31EB7A. The leaves of *Schinopsis brasiliensis* Engler were collected in the semi-arid region of Paraíba, Brazil (7° 16' 73.26''S, 35° 97'93.50''W) on March 26, 2019 at 09:00 hours. Botanical identification (macro and microscopic) was performed at the Center for Agrarian Sciences of the Federal University of Paraíba (UFPB) in the Jaime Coelho de Moraes Herbarium. The exsiccate was deposited with the registration number EAN-14049

Obtaining the *S. brasiliensis* Engler dried extract

The leaves were cleaned and dried in a forced air circulation drying oven at 40°C until they reached a constant weight. They were then pulverized in a knife mill with an output of 10 mesh. The plant drug was then stored in Kraft paper bags.

The ultrasound method was used to obtain the hydroalcoholic extract. Briefly, 620 mL of a 50% (v/v) hydroalcoholic solution composed of water and 99.5% ethanol (1:1) was used as the solvent, and 20% (w/v) of the plant drug (124 g) was added. The sample was positioned in an ultrasonic cleaner (Ultrasonic Cleaner - UNIQUE) in a water bath at 40°C for 60 minutes. Finally, the liquid extracts were filtered, concentrated under reduced pressure in a rotary evaporator (50°C), and then dried in an oven at 40°C. The dried extracts were stored in individual hermetically sealed vials at room temperature (± 25°C) until further analysis.

Phytochemical prospecting

Determination of total polyphenol concentration

The calibration curve was constructed using variable concentrations between 4 $\mu g.mL^{-1}$ and 40 $\mu g.mL^{-1}$ of gallic acid, by spectrophotometry in the visible region, using a spectrophotometer (Shimadzu Uvmini-1240) (Fernandes *et al*., 2015). The readings were performed with samples of the plant extract solutions in the presence of the Folin-Ciocalteau reagent in an alkaline medium, relating the absorbance values found to the concentration of polyphenols in the solution through a mathematical relationship obtained by the calibration curve.

According to the technique, 0.5 mL of 1N Folin–Ciocalteau solution was dispensed into test tubes, and 0.5 mL of the extract solution was subsequently added. The tubes were left to stand for 2 minutes at room temperature (± 25°C). Then, 1 mL of a 20% (w/v) Na_2CO_3 solution was added. The tubes were left to stand again for 10 minutes until the colorimetric reaction was completed. Measurements were obtained in triplicate at a wavelength set to 757 nm.

Determination of total flavonoid concentration

The calibration curve was constructed using concentrations between 2 $\mu g.mL^{-1}$ and 28 $\mu g.mL^{-1}$ of quercetin, analyzed in a previously described device with absorbance reading at 415 nm (Broadhurst, Jones, 1978). The readings were performed with extract samples in the presence of aluminum chloride solution, relating the absorbance values found with the concentration of flavonoids in the solution through a mathematical relationship obtained by the calibration curve.

For this method, 1.5 mL of a 2% (w/v) methanolic solution of 1.5% methanol was distributed in test tubes,

and 1.5 mL of methanolic solution of the extract was then added. The tubes were left to stand for 10 min at room temperature (25°C). The measurements were obtained in triplicate, at a wavelength adjusted to 415 nm.

Determination of total condensed tannin content

The calibration curve was constructed using concentrations between 10 $\mu g.mL^{-1}$ and 45 $\mu g.mL^{-1}$ of catechin, analyzed in a previously described device, with absorbance reading at 500 nm (Broadhurst, Jones, 1978). The readings were performed with samples of the plant extract in the presence of a vanillin solution, in an acidic medium, relating the absorbance values found with the concentration of condensed tannins in the solution through a mathematical relationship obtained by the calibration curve.

An aliquot of 1.5 mL of 4% (w/v) vanillin methanolic solution was dispensed into test tubes, followed by 0.25 mL of methanolic solution of the extract and 0.75 mL of HCl. The tubes were left to stand for 20 minutes, immersed in water at approximately 22°C. Measurements were obtained in triplicate at a wavelength adjusted to 500 nm.

Evaluation of antifungal activity

The antifungal activity of *S. brasiliensis* dried extract was evaluated *in vitro* by broth microdilution method, determining the extract's Minimum Inhibitory Concentration (MIC). American Type Culture Collection (ATCC) standard strains of *Candida albicans* (10231) were used. Briefly, the microbial suspension was standardized on a UV-VIS spectrophotometer (UVmini-1240 – Shimadzu, Tokyo) at a wavelength of 530 nm to contain the equivalent of 5.0 x 10^6 CFU/mL (equivalent to the absorbance of 0.08 to 0.10 (McFarland (0.5)).

The PAPI at 1000 to 7.8 $\mu g.mL^{-1}$ concentrations was diluted in 10% dimethyl sulfoxide (DMSO). Fluconazole was used as a positive control. The plates were incubated at 35 ± 2 °C for 24 hours. The MIC was confirmed after 1 hour of adding 20 µL of resazurin to each well of the plate. The analyses were performed in triplicate. In parallel, the viability of the strain (growth control) and the sterility control of the medium were performed.

Formulation development and synthesis of *S. brasiliensis* Engler tablets

The tablets exploited the mucoadhesive characteristics presented by CMC (F1), HPMC (F2), and PLU (F3), which were obtained by the wet granulation technique. First, all excipients were mixed, including PAPI, LACT (powder diluent agent), and starch (powder disintegrant agent), followed by agglutination caused by the addition of ethanol 50% v/v until the formation of a moldable mass. With the aid of a 2.36 mm granulator (mesh 8 - Lawes), the granules were produced, followed by the addition of EXT (lubricating agent). Finally, the compression necessary to produce the tablets was caused by a Lemaq Monopress LM-1 compressor.

Table I shows the proportion of each agent in the formulation. It is possible to observe that F1 refers to the tablet containing Carboxymethylcellulose polymer, while F2 Hydroxypropylmethylcellulose and F3 refer to the pharmaceutical form containing the Pluronic polymer.

TABLE I - Percentage concentrations of components and their classes in formulations with CMC (F1), HPMC (F2), and PLU (F3)

Components	F1 (%)	F2 (%)	F3 (%)	Classification
Dry extract	40.00	40.00	40.00	PAPI
CMC/HPMC/PLU	15.00	15.00	15.00	Adhesive
EXT	02.00	02.00	02.00	Lubricant

TABLE I - Percentage concentrations of components and their classes in formulations with CMC (F1), HPMC (F2), and PLU (F3)

Components	F1 (%)	F2 (%)	F3 (%)	Classification
Lact	33.00	33.00	33.00	Diluent/Sweetener
Starch	10.00	10.00	10.00	Binder/Disintegrant

Caption: CMC: Carboxymethylcellulose; HMPM: Hydroxypropylmethylcellulose; PLU: Pluronic; Lact: Lactose; EXT: magnesium stearate. F1: Formulation with Carboxymethylcellulose; F2: Formulation with Hydroxypropylmethylcellulose; F3: Formulation with Pluronic.

Preformulation studies

Determination of bulk and compaction densities, Hausner ratio, compressibility index, and densification index

Using 10 g (m) of each formulation arranged in different 50 mL beakers, the Bulk Volume (BV) was measured by measuring the new volume after 10, 50, and 1250 successive drops. In this perspective, the compaction volume was determined after the fall of number 1250, in which the realization of two subsequent readings obtained a variation less than or equal to 0.1 mL.

Based on the BV and compaction volume (CV) values, the Bulk Density (DB) and Compaction Density (DC) could be calculated using equations A and B, respectively.

$$DB = \frac{m}{BV} \quad \text{(A)}$$

$$DC = \frac{m}{CV} \qquad DB = \frac{m}{BV} \quad \text{(B)}$$

Using the density values, the Hausner Ratio (HR), Carr Index (CI), and Densification Index (DI) were determined using the equations shown in C, D, and E.

$$HR = \frac{DC}{DB} \quad \text{(C)}$$

$$\mathrm{CI} = \frac{\mathrm{DC} - \mathrm{DB}}{\mathrm{DC}} \times 100 \quad \text{(D)}$$

$$\mathrm{DI} = \mathrm{V10} - \mathrm{V500} \quad \text{(E)}$$

Investigation of the Angle of repose

10 g of the powder of each developed formulation was subjected to the fixed funnel height method. For this, the sample was positioned in a funnel at 8.00 cm from the millimeter paper base with powder allowed to pass through. The tangent of the angle of repose was calculated from the equation F.

$$\mathrm{tg}\alpha = \frac{\mathrm{h}}{\mathrm{r}} \quad \text{(F)}$$

Assuming that α corresponds to the angle of repose, h the height, and r the radius of the cone formed. In addition, the test was performed in quintuplicate with flow times paused by a stopwatch (ASTM-C1444, 2000).

Quality control

Investigation of average weight

A total of 20 tablets of each formulation were weighed and the mean values were calculated, considering the parameters established by the Brazilian Pharmacopoeia (Farmacopeia Brasileira, 2019).

Investigation of friability

Under the parameters of the Brazilian Pharmacopoeia (Farmacopeia Brasileira, 2019), 20 tablets were weighed and, without sequence, subjected to about 100 rotations with the aid of a type 300 friabilometer (Ethik), ending

with the elimination of any powder residues and subsequent weighing. The percentage of powder lost was measured according to equation G.

$$Mi - Mf = Mp \quad \text{(G)}$$

Admitting that, Mi corresponds to the mass of the tablets before submission to the test, Mf is the final mass of the tablets after the step promoted by the friabilometer, and Mp is the mass of the total powder lost.

Hardness investigation

With the aid of a digital durometer type 298/DGP, the hardness was measured based on the values demarcated by the test with 10 tablets, according to the parameters of the Brazilian Pharmacopoeia (Farmacopeia Brasileira, 2019).

Dissolution evaluation of S. brasiliensis mucoadhesive tablets

The dissolution test of the formulated tablets was performed in accordance with the Brazilian Pharmacopeia (Farmacopeia Brasileira, 2019). Three tablets of each formulation (HPMC, CMC or PLU) were placed in a dissolution paddle-type apparatus (Nova Ética) with a three vats capacity. The tablets were immersed in 900 mL of acetate buffer solution (pH 4.0) at 37 ºC while being agitated at 50 rpm. At predetermined times of up to 72 hours, aliquots of 3 mL were collected and submitted for reading in Spectrophotometry UV-vis.

Investigation of mucoadhesive potential

In the first step, a tablet compressor (123 mm diameter) was used to prepare mucin-type disks from the compression of 250 mg of mucins moistened with 50 µL of 8% (w/w) mucin dispersant, with subsequent placement of the object on cow mucosa from the slaughterhouse. The mucoadhesive strength for both formulations were determined using a TAXT plus texture analyzer (Stable Micro Systems®).

For the experiment, 50 µL of acetate buffer was applied to the mucin disks while the model mucosa (cow vagina) was immersed in the same type of buffer for 30 seconds, to simulate the vaginal physiological environment. Then, the mucosa was fixed horizontally to the equipment on a cylindrical probe of the texturometer and immobilized by a double tape. Adjacent to this process, the disk was adhered to the surface of the acrylic plate in the lower position and positioned below the cylindrical probe, generating a lowering on the scale of 1 mm s^{-1} until the experimental length was reached.

For 60 seconds, the cylindrical probe was held to facilitate contact between the mucin disk and tablet, allowing the result to be read at 1 mm s^{-1} (Oshiro Junior *et al*., 2015). The process was performed in triplicate (37 ± 1 °C) and the data generated were treated using the Expert Texture Exponent 32 software, and a force-distance curve was generated during the withdrawal phase, while the peak adhesion was measured by Wad.

In vitro release of S. brasiliensis tablets containing CMC, HPMC, or PLU

The *in vitro* release test was carried out using a paddle-type apparatus along with the dissolution test. Aliquots of 3 mL were collected at the pre-established times of 15, 30, 45 minutes, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours, proceeding in reading in the spectrophotometric equipment (Shimadzu UVmini-1240). The percentage of PAPI released was analyzed according to a protocol pre-established by the group, according to the correlation between the concentration of polyphenol available in the medium per Gallic Acid Equivalent (%) (EAG) by time (h).

RESULTS AND DISCUSSION

Obtaining *S. brasiliensis* Engler extracts

The final weight of the oven-dried leaves was 195.28 g, of which only 63.5% (124.00 g) was kept after grinding (Figure 1S (b and c)). During the whole cycle to obtain the dry extract (Figure 1S), it was possible to observe the standardization and uniformity of the particle size of the plant drug after the grinding process. In addition, there was no proliferation of microorganisms, and the dry extract presented as a fine powder, dark in color and

without solvent odor (Figure 1S (f)), indicating that all processes were performed properly. Thus, after drying, a mass of 23.56 g of the dry extract was obtained, which represented an extraction yield of 19.0% of the PAPI per plant drug from the pulverized dry leaves.

Phytochemical prospecting

As presented in Table II, the line equation results of all analytical curves were found to be linear as all correlation coefficient (r^2) values were above 0.98. Thus, the unknown concentrations of the proposed metabolites in the screening were identified per 100 g of dry extract. The results showed a concentration of 1500 mg of polyphenols (or 15 $\mu g.mg^{-1}$ of extract), 551 mg of quercetin (or 5.51 $\mu g.mg^{-1}$ of extract), and 480 mg of tannins (or 4.80 $\mu g.mg^{-1}$ of extract) compared to the standard of gallic acid, quercetin, and catechin, respectively. Among them, polyphenols showed the highest concentration followed by flavonoids and tannins.

TABLE II - Phytochemical Screening

Metabolite	Concentration (mg per g of dry matter)	Analytical curve (line equation)	r^2
Polyphenols	0.1500	y = 0.0315x + 0.0046	0.9963
Flavonoids	0.0551	y = 0.0317x + 0.0778	0.9850
Tannins	0.0480	y = 0.0041x + 0.0930	0.9820

The presence of these three metabolites is noticeable in other literature dealing with the same plant. As an example, the study carried out by Sette-de-Souza *et al.* (2020), demonstrated the quantification of metabolites of the ethanolic extract of *S. brasiliensis* obtained from the bark of the plant and revealed the presence of polyphenols (598.55 $\mu g.mg^{-1}$ of extract), tannins (15.83 $\mu g.mg^{-1}$ of extract) and flavonoids (6.94 $\mu g.mg^{-1}$ of extract). Another example of the presence of these metabolites is in the study by Fernandes *et al.* (2015), who obtained a concentration of polyphenols (24.52 $\mu g.mg^{-1}$ of extract) and flavonoids (1.43 $\mu g.mg^{-1}$ of extract) also by the extraction performed by the stem barks of *S. brasiliensis*. These findings not only demonstrate that polyphenols predominate in parts of the plant other than the leaves, but also suggest that polyphenols are appreciable markers for the identification of *Schinopsis brasiliensis* Engler.

Evaluation of antifungal activity

The dry extract showed inhibitory activity at a concentration of 62.5 $\mu g.mL^{-1}$, while the positive control was 7.8 $\mu g.mL^{-1}$ (Table IS). Previous research has shown the fungicidal activity of an ethanol/water (90:10 v/v) hydroalcoholic extract by ultrasound-assisted method against *Candida albicans* (ATCC 10231) at a concentration of 54 $mg.mL^{-1}$ by the diffusion in agar cylinder method, with an inhibition halo of 20.00 ± 0.57 mm (Sampaio *et al*., 2023). Other studies have also reported the antimicrobial activity of *S. brasiliensis* against *E. coli* (ATCC 25922) at a concentration of 250 $\mu g.mL^{-1}$, using CIM assay (de Oliveira *et al*., 2020). These results show the potential use of *S. brasiliensis* extracts in the treatment of infections caused by various species.

The review by Hsu *et al*. (2021), on the activity against *Candida albicans* of herbal extracts and their metabolites, addresses that there are studies that demonstrate the antifungal action of phenols, for example, gallic acid, which probably occurs by the binding of the compound with the ergosterol present in the cell membrane with consequent formation of pores and distrust of enzymes, causing damage to the cell structure.

In the case of flavonoids, as far as is known, the mechanism of action of antifungal activity has not been

fully clarified, but it is believed that this metabolite interferes with ergosterol synthesis or, like catechin, causes oxidative stress and production of Reactive Oxygen Species (ROS). ROS are closely linked to the deactivation of molecular mechanisms, the degradation of the fungal matrix, and the consequent breakdown of cellular homeostasis. As for tannins, it is suggested that their antifungal action involves the formation of complexes, between tannins and flavonoids, with nucleophilic amino acids in membrane and cell wall proteins, leading to inactivation and loss of function (Hsu, Sheth, Veses, 2021).

Preformulation studies, tablet development and quality control

To analyze whether the mixture of constituents had suitable characteristics for direct compression, studies of the rheological properties were carried out, related to the ease or resistance to general flow, flow itself, compaction, and compression.

Flowability is a property of powders that depends on factors such as particle size and shape, particle shape, roughness and porosity, and cohesive and frictional forces (Leturia *et al*., 2014). In tablet development, flowability is a determining factor for the uniformity and compactness of powders, which guarantees the homogeneity and strength of the final pharmaceutical form (Wu, Armstrong, Vlachos, 2012). In this study, it was not possible to measure the angle of repose values for the F1, F2 and F3 powder mixtures, due to the poor flow. In addition, the Carr's ratio values were 16.66%, 9.42% and 21.87% for F1, F2 and F3 respectively. The Hausner ratio data obtained for F1, F2 and F3 were 1.20, 1.10 and 1.28, in that order. Therefore, the values suggest a reasonable and poor flow for direct compression of the formulations, indicating the need for flow refinement.

Dry or wet granulation techniques can be used to improve the flow properties of powders. Larger, uniform granules with a smooth surface have better fluidity and are more suitable for compression (Yamashita, Sun, 2019). Wet granulation can improve the properties of powders used to produce solid pharmaceutical forms, such as modified-release tablets (Fujimoto *et al*., 2016). Given its advantages for improving the flexibility of powders, wet granulation was the technique chosen for the preparation of granules to obtain F1, F2 and F3 tablets.

The visual characteristics of the tablets obtained with different polymers can be seen in Figure 1.

FIGURE 1 - Visual aspects of tablets containing Carboxymethylcellulose (a), Hydroxypropylmethylcellulose (b), and Pluronic (c).

Regarding the quality control of the tablets, Table III shows the mean results, standard deviation, and coefficient of variation of the average weight, friability, and hardness tests. The average weight test for tablets with CMC polymer (F1) was 262.69 mg, HPMC (F2) was 324.23 mg, while the formulation with PLU (F3) obtained a result of 298.26 mg. In this aspect, the values found comply with the parameters established by the Brazilian Pharmacopoeia (Farmacopeia Brasileira, 2019) since the active ingredient amount selected is directly proportional and uniformly distributed by each weight unit in the formulation.

TABLE III - Results of means, standard deviation, and coefficient of variation for average weight, friability, and hardness

	F1	F2	F3
AVERAGE WEIGHT (mg)			
Mean	262.69	324.23	298.16
Standard deviation	6.03	7.57	9.52
Coefficient of variation	2.29	2.33	3.19
FRIABILITY (mg)			
Mean	261.2	322.62	296.89
Standard deviation	7.49	8.89	10.99
Coefficient of variation	2.87	2.75	3.70
HARDNESS (N)			
Mean	24.43	25.19	23.49
Standard deviation	1.90	3.88	5.34
Coefficient of variation	7.78	15.40	22.74

The friability test was performed to observe the mechanical resistance to wear, mechanical abrasion, and loss of mass. The results show variant values between 0.56% (F1), 0.49% (F2), and 0.42% (F3), being below the standard acceptance limit established by the Brazilian Pharmacopoeia of ≤1.5% (Farmacopeia Brasileira, 2019).

The hardness test determines resistance to crushing force and may presume physical integrity in the face of mechanical shocks, packaging, coating, and transportation. Thus, unsatisfactory hardness values compromise the physical stability of the product (Alves, Prado, Rocha, 2020). For this analysis, tablets F1, F2, and F3 showed results of 24.41 ± 1.90, 25.19 ± 3.88 and 23.49 ± 5.34, respectively. The results showed a low standard deviation (> 6), however, the hardness test is considered only as informative data and does not present official reference values (Alves, Prado, Rocha, 2020).

Investigation of mucoadhesion

The mucoadhesion mechanisms of the polymers used for this purpose, start from a chemical assumption of molecular interaction between the synthetic form inserted and the tissue, which can be modified by the nature of the tablet, such as molecular weight or type of polymer and chemical bond between compound:mucosa, or by internal factors such as pH, mucus runoff, level of secretion, among other factors that can affect the ionic strength (Sette-DE-Souza *et al*., 2020). Table IV shows the mucoadhesion strength results for the tablets with the mucin disk and cow vagina mucosa polymers.

TABLE IV - Results of the means, standard deviation, and coefficient of variation of the mucoadhesion test

	F1	F2	F3
	MUCIN DISK (N)		
	0.1361	0.0413	0.0868
	0.1120	0.0389	0.0852
	0.1320	0.0432	0.0721
Mean	0.1267	0.0411	0.0814
Standard deviation	0.0105	0.0018	0.0066
Coefficient of variation	8.31	4.28	8.09

TABLE IV - Results of the means, standard deviation, and coefficient of variation of the mucoadhesion test

	F1	F2	F3
	COW VAGINA (N)		
	0.0315	0.0124	0.0062
	0.0273	0.0190	0.0102
	0.0294	0.0183	0.0930
Mean	0.0294	0.0166	0.0365
Standard deviation	0.0017	0.0029	0.0400
Coefficient of variation	5.83	17.87	109.71

According to the literature, several methods for characterizing mucoadhesive systems exist, but none are considered official. Different theories can explain the process of mucoadhesion, based mainly on the principles of interfacial, electrostatic, wetting, adsorption, and fracture forces (Asati, Jain, Choubey, 2019;). In this study, the adhesion forces on cow vaginal mucosa tissue and on a mucin disk were compared between the formulations produced with CMC, HPMC, and PLU, with the use of a texturometer (Table IIS).

The three polymers selected for the formulations showed more relevant mucoadhesive properties on the mucin disk compared to the vaginal mucosa tissue, with an average strength between 0.0411 and 0.1267 N. The differences in mucoadhesive capacity between the polymers can be explained by their chemical structures and the higher or lower presence of hydrogen bond-forming chemical groups, which improve the properties of swelling, water loading, and flexibility for mucus entanglement (Chatterjee *et al*. 2017).

In this sense, CMC stands out as an anionic polymer with a greater ability to form hydrogen bonds than non-ionic cellulose polymers such as HPMC. In contrast, the acidic pH of the vaginal mucosa causes the adhesion strength of CMC to be considerably reduced because the carboxylate ion passes into the acidic COOH form and intermolecular hydrogen interactions increase within the CMC chain, resulting in a decrease in its interaction with vaginal mucus (Gunathilake *et al*., 2020).

In the vaginal mucosa, physiological factors, such as humidity, the amount of mucus present in the cavity and its composition, pH and vascularization of the region, can influence the mucoadhesive capacity of the formulations and reduce the strength of adhesion in relation to the mucin disc. Therefore, formulation F3 was more suitable when the conditions at the site of administration of the pharmaceutical form were simulated.

Dissolution and *in vitro* release of *S. brasiliensis* from HPMC and PLU tablets

The dissolution was validated by Snedecor's F test, which was used to analyze the fit of the model, therefore, it did not present a lack of fit and demonstrated significance of the regression, validating the model given by the straight-line equation. The residue graph can be seen in Figure 2b.

According to Figure 2, the results showed that the type of polymer used can influence and control PAPI release. Being F1 and F2 resulting from the total release of the amount of PAPI (15 mg of EAG per 100 g of extract) in a conventional way, that is, 100% of the concentration before 4 hours. However, the formulation using Pluronic (F3) showed a prolonged release profile, detaching 56.3% of the PAPI from the matrix after 72 hours of testing, corresponding to 8.44 mg of EAG per 100 g of extract (84.4 $\mu g.g^{-1}$) exceeding the value found in the MIC test, suggesting the applicability of the pharmaceutical form at a reduced dosage frequency.

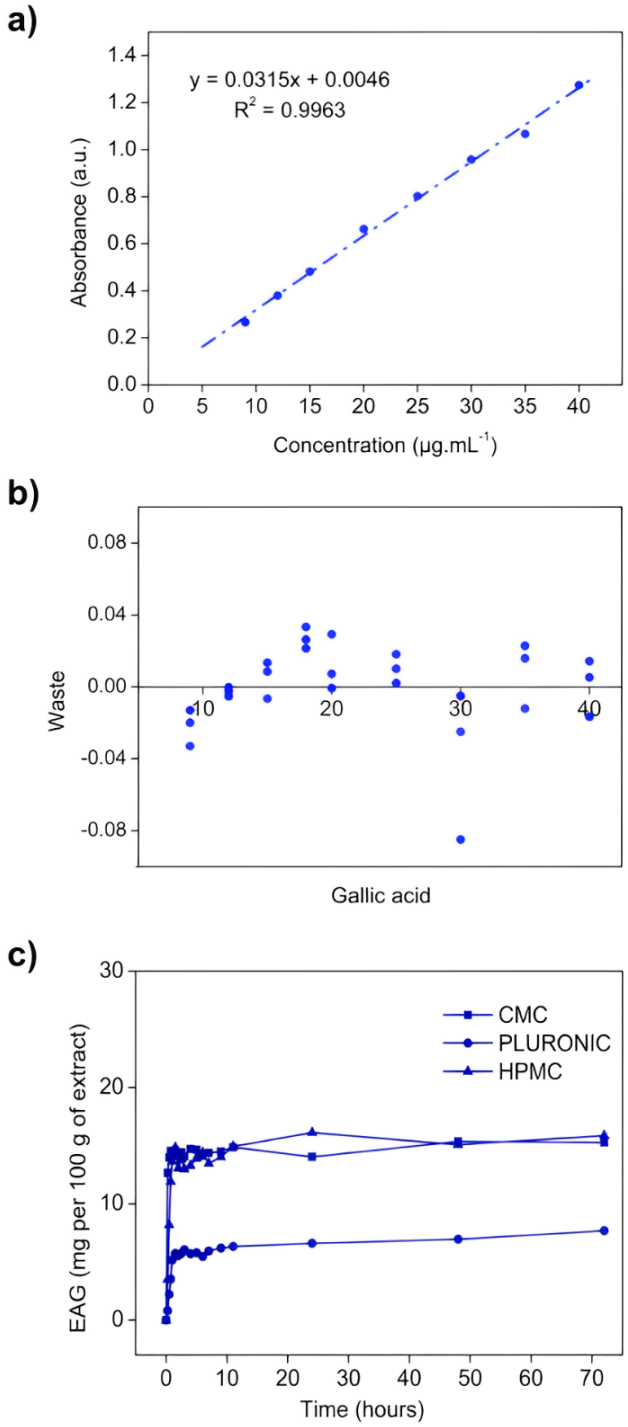

FIGURE 2 - Gallic Acid Equivalent Release per 100 g dry extract (c), gallic acid residue plot (b), and linearity curve under Snedecor's F-Test (a).

Such behavior is justified by the chemical individualities of each compound, combined with the degree of swelling and physical degradation of the matrix, the latter also responsible for the release of the active ingredient (Hirun, Kraisit, 2022). For Pluronic, the literature already demonstrates formulations with this polymer to promote a sustained release by a geometric decrease of the released concentration over time, which suggests the formation of a compact network with smaller channels that reduce the passage of aqueous fluids, as well as the formation of the gel phase, resulting from swelling, stabilizes the diffusion barrier controlling the release (Shoukat, Pervaiz, Rehman, 2022; Kalogeropoulou *et al*., 2023). For CMC and HPMC, their high hydrophilic profiles allow the penetration of the aqueous solvent through the edges towards the core of the tablet, which results in hydration, loss of rigidity, increased malleability, and consequent erosion of the swollen fraction (Tudoroiu *et al*., 2021).

In addition, among the cellulose derivatives, the formulation with Carboxymethyl cellulose (F1) showed rapid dissolution, compared to the others, which suggests a manifestation of its high solubility in an aqueous medium, combined with the ability to retain moisture, a fact that justifies the use of the polymer by the pharmaceutical industry in forms that absorb heavy exudates, being common the application with other polymers that modulate the behavior of the matrix, in solid pharmaceutical forms, which require a prolonged release of their assets in a humid environment (Kanikireddy *et al*., 2020; Tudoroiu *et al*., 2021). In turn, the formulation containing Hydroxypropylmethylcellulose also showed significant release, but not as much as CMC, since its hydrophilic/hydrophobic profile is directly related to its degree of substitution and molarity, as well as its greater stability at lower pH values (Tudoroiu *et al*., 2021).

CONCLUSION

In this study, the initial step emphasizes the physicochemical control of *Schinopsis brasiliensis* Engler extract and its anti–Candida properties. The results showed that the extraction process was adequate, reaching a satisfactory yield of 63.5%, which suggests an efficient obtaining of the extract for pharmaceutical purposes. Furthermore, the antifungal activity, evaluated by the microdilution method, showed promising results, with a minimum inhibitory concentration of 62.5 µg.mL^{-1} against *Candida albicans*. This result is related to the

presence of a high concentration of polyphenols, as identified in the phytochemical screening.

Subsequently, three mucoadhesive tablet formulations containing PAPI were developed and compared. The mucoadhesion tests revealed that CMC (Carboxymethylcellulose) polymer showed the highest adhesion strength, followed by Pluronic and HPMC (Hydroxypropylmethylcellulose). However, the controlled release capacity of PAPI was observed only in tablets with Pluronic. This suggests that despite showing better adhesion to mucus, CMC-containing tablets may not be ideal for the controlled release of PAPI.

Thus, the overall results indicate that Pluronic is the most suitable polymer for this purpose. These findings open promising perspectives for the development of new pharmaceutical formulations, contributing to the advancement of antifungal therapy and the efficient use of natural resources in medicine. However, further studies are needed to deepen the knowledge about the safety and efficacy of these tablets in preclinical models and subsequently in clinical trials for their eventual therapeutic application in humans.

AUTHOR

Contributions Conceptualization A.C.D.M., and J.A.O-Jr; methodology, M.M.D., N.F, and J.A.O-Jr.; software; validation and formal analysis, M.M.D., N.F., J.O.A-Jr., J.A.O-Jr, B.M.S.B., S.E.D.M.A., and A.C.D.M.; writing—original draft preparation, M.M.D., J.A.O-Jr., J.O.A-Jr., B.M.S.B., S.E.D.M.A., and A.C.D.M. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

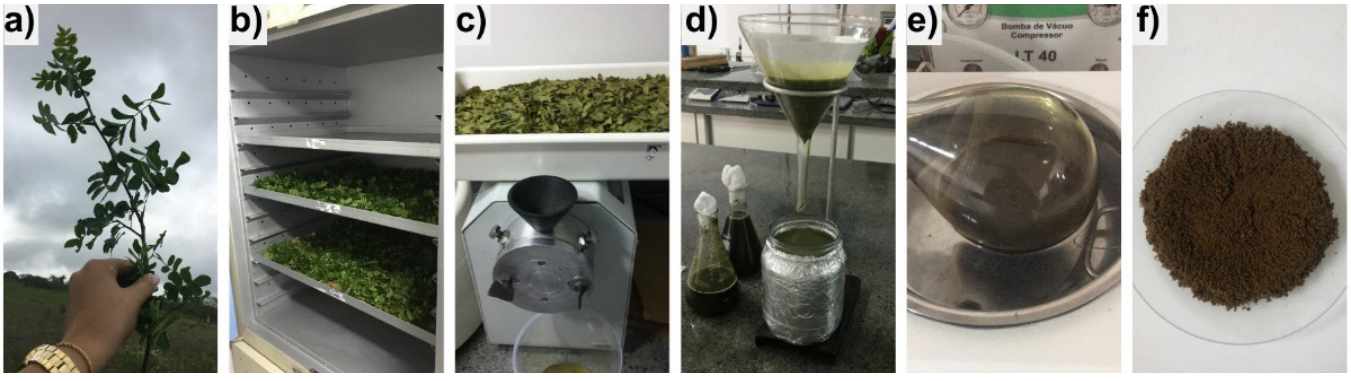

FIGURE 1S - Cycle of obtaining dry extracts of *S. brasiliensis* ((a) harvesting, (b) drying, (c) grinding, (d) extracting, (e) rotary evaporation and (f) dry extract).

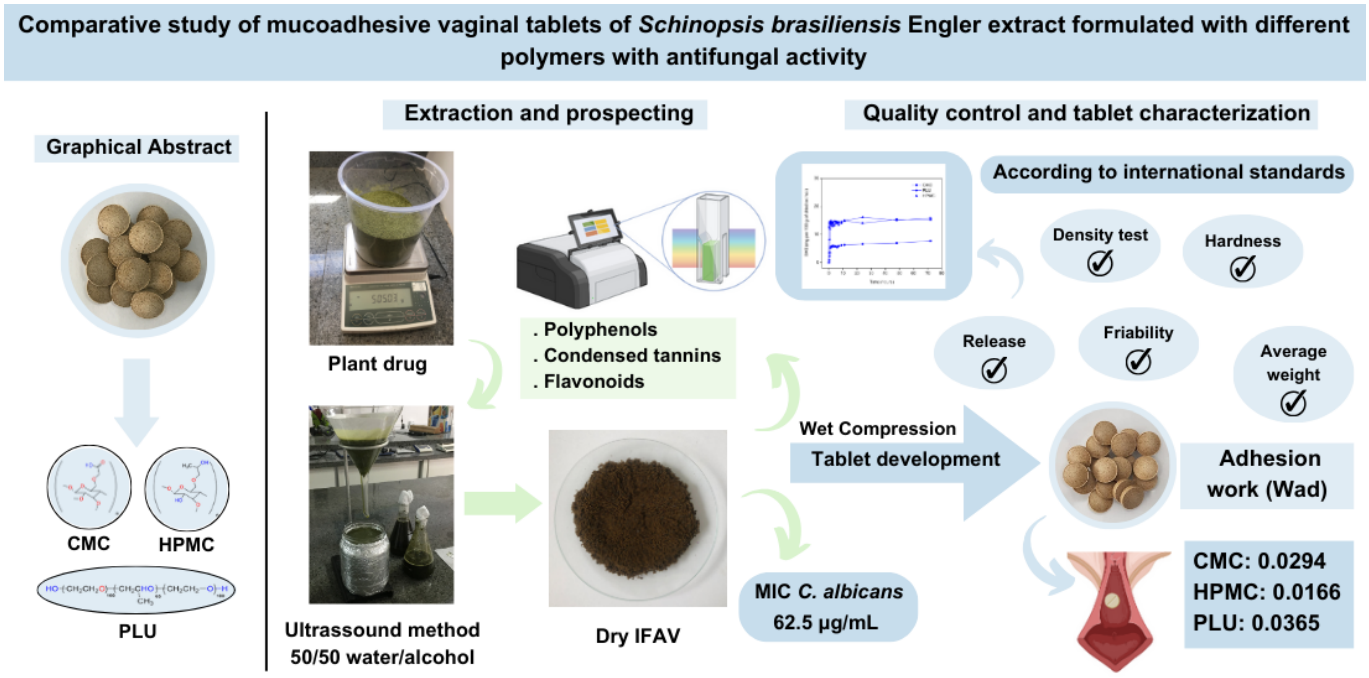

FIGURE 2S -

TABLE IS - Minimum Inhibitory Concentration (MIC) of extracts of *S. brasiliensis*

Groups	MIC (µg mL^{-1})
S. brasiliensis	62.5
Positive control	≤ 7.8

TABLE IIS - Mucoadhesive strength values (Wad) for tablet when in contact with mucin discs and vaginal mucosa

	Word of mucoadhesion (N)	
	Mucin disc	Vaginal mucosa
Tablet	0.12 ± 0.0098	0.0294 ± 0.0014

Results are expressed as mean ± SD for n = 3.