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Delivery kinetics of natural active agents by PVA hydrogels intended for wound care

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ABSTRACT

Acute wound dressings can be based on PVA hydrogels, which present many characteristics of an ideal dressing, e.g., fluid uptake, a moisturized environment, etc. The lack of antimicrobial properties leads to the addition of natural active agents. The present work aims to manufacture and compare PVA gels loaded with Barbatimão bark extract, Leucaena bark extract, Aloe vera, and Lavender essential oil. They were characterized by FTIR, swelling tests, SEM, actives release. There were interactions between PVA and the active agents. The addition of Leucaena and Barbatimão increased the PVA ability to swell, but the opposite was found for Aloe vera and Lavender essential oil. PVA-Lavender essential oil samples presented interconnected pores, while samples with essential oil or extracts presented high crystallinity. Lavender essential oil and Aloe vera presented the highest release. The Barbatimão and Leucaena samples' release may be related to the samples' swelling, but the initial release of Aloe vera and Lavender samples was diffusion controlled by swelling. Their long-term release was dose-dependent for Aloe vera, while it was a non-Fickian diffusion for Lavender essential oil related to the hydrogel's relaxation step. There is a synergistic effect when Aloe vera and Lavender essential oil are loaded in PVA hydrogels.

Keywords: PVA hydrogels; Barbatimão extract; Leucaena extract; Lavender oil; Aloe vera.

1. INTRODUCTION

Wounds are the disruption of the skin continuity, which can be classified as open (characterized by bleeding), closed (characterized by internal bleeding), acute (following the normal stages of healing: inflammation, fibroblastic reparation, and remodeling), and chronic (prolonged healing which can also persist) wounds [1]. Polyvinyl alcohol – PVA is a classic material for preparing hydrogels (3D networks of crosslinked hydrophilic polymers) for acute wound dressings. PVA $[CH_2\ CH(OH)]_n$ hydrogels present most of the ideal dressing's characteristics, e.g., they keep a moist environment, absorb the wound exudates, prevent dryness, etc. [2] For treating chronic and acute skin wounds, in addition to burns, some tissue engineering techniques include using biomaterials capable of facilitating skin regeneration and wound healing [3]. One example is PVA-chitosan hydrogels functionalized with tea tree essential oil, which could synergistically affect the components, resulting in dressings with broad spectra of biological activity for repairing and healing injured tissues, such as burns [4]. Nonetheless, many polymeric hydrogels do not present antimicrobial activity to prevent infection [5], demanding the gels' loading with active agents [6].

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Several bark stem extracts can be used in wound care. *Jatropha curcas* L. bark, which contains glycosides, tannins, phytosterols, flavanoids, and steroidal sapogenins presented wound healing properties [7]; *Salvadora persica* L. bark extract promoted wound healing and antimicrobial activity [8]; The bark of *F. benghalensis* extract stimulated wound contraction [9]; stem bark of *Ficus racemosa* L. (rich in lupeol and β-sitosterol) showed enhanced cell proliferation and antimicrobial activity [10]; ethanol extract of stem bark of *Oroxylum indicum* presented an increased wound contraction according to the extract concentration [11]; among the bark extracts used in India for wound healing, there are also the extracts of *Kigelia pinnata* Sausage, of *Anthocephalus cadamba* Roxb and *Vernonia arborea* Buch.-Ham [12].

Stryphnodendron adstringens (Barbatimão) is a Brazilian species from Cerrado e Caatinga regions, which bark extract is used in Brazilian folk medicine for wound healing treatment [13, 14]. *Stryphnodendron adstringens* bark extract is rich in proanthocyanidin [$C_{31}H_{28}O_{12}$] polymers, specifically flavan-3-ol [$C_{15}H_{14}O_2$] [15] and its activity cicatrizing, anti-inflammatory, antioxidant, and antimicrobial would be due to the presence of tannins (proanthocyanidins) [16, 17]. Diabetic wounded rats treated with Barbatimao extract presented keratinocytes proliferation, replacement of type III by type I collagen, organized extracellular matrix, and the entire extent of the wound filled with new tissue [14]. Barbatimão barks can be considered effective in treating wounds [18], and ointment loaded with Barbatimão extract stimulated cell proliferation. Still, no effect was observed on wound contraction and keratinocyte proliferation [19].

Leucaena leucocephala (Leucaena) is a leguminous plant that is used as ruminant animal feed, but when there is over 30% of Leucaena in these animals' feed, they could present intoxication [20]. The Leucaena flowers and leaves extract present tannins and flavonoids, although flowers extract presents mimosine (alkaloids), while leaves extract has steroids and saponin. Leaves seem to have higher antioxidant activity than flowers, but both extracts were bactericides (active against *M. luteus* ATCC 4698, MSSA ATCC 25923, MRSA ATCC 33591, and MRSA (clinical isolate)) [21]. Leucaena methanol extract also showed the presence of antioxidant compounds: vitamin C, vitamin E, carotenes, xanthophylls, tannins, and phenols [22]. Leucaena extract showed rosmarinic acid [$C_{18}H_{16}O_8$] , resveratrol [$C_{14}H_{12}O_3$], o-coumaric acid [$C_9H_8O_3$], among others, as main substances [23].

Regarding essential oils, Lavandula officinalis (Lavender) essential oil was previously used for wound care, promoting collagen synthesis, fibroblast differentiation, and wound contraction [24, 25]. When in dressings, electrospun membranes of PVA/alginate/lavender oil were developed, showing limited aqueous solution absorption due to the oil hydrophobicity; the samples' inhibition zones of *S. aureus* were dose-dependent [26]. Lavender oil's active substances may be related to phenolic compounds, but its concentration varies per part of the plant used for the oil extraction and by its origin [27]. Lavender essential oil's main constituents are linalool [$CH_3C(CH_3) = CH(CH_2)_2C(OH)\ (CH_3)CH = CH_2$] and linalyl acetate [$CH_3CO_2C(CH = CH_2)(CH_3)\ CH_2CH = C(CH_3)_2$], besides 1,8-cineole [$C_{10}H_{18}O$], terpinen-4-ol [$C_{10}H_{18}O_3$] etc [28].

Aloe vera is a mucilaginous gel that is viscous and colorless, extracted from the plant's leaves. It consists mainly of water and polysaccharides, containing vitamins A, B, C, and E, calcium, potassium, magnesium, zinc, various amino acids, enzymes, and carbohydrates [29]. The main regulator of Aloe vera as a healing agent is the existence of a polysaccharide-rich in mannose (glucomannan [$C_{24}H_{42}O_{21}$]). It works together with gibberellin and growth hormone, stimulating fibroblasts to actively proliferate. By triggering fibroblast activation and proliferation, collagen biogenesis increases [30].

CAPES journals platform was searched, within the "Titles" search, using different combinations of keywords (on the 30th of May, 2023). The keywords "lavender" and "hydrogel" search showed four papers, none of them regarding PVA and lavender essential oil hydrogels [31–34]. No paper was found searching "Lavandula" or "L. officinalis" and "hydrogels". By searching "Stryphnodendron adstringens" and "hydrogel", two papers were found, one paper of silk fibroin hydrogel [35], and the second, a generic hydrogel (no mention of PVA), both loaded with Stryphnodendron adstringens bark extract [36]. "barbatimao" and "hydrogel" resulted in no paper found. Searching "Leucaena leucocephala" and "hydrogel", 2 papers were found, none regarding PVA hydrogels [37, 38]. 40 papers were found searching for "aloe vera" and "hydrogel"; among then, five were related to "aloe vera" and "PVA" and "hydrogel": PVA-aloe vera-graphene with antibacterial activity [39], PVA-aloe vera-curcumin for wound healing [40], PVA-aloe vera-salicylic acid for wound dressing [41], PVA-aloe vera-chitosan for skin needs [42], PVA-aloe vera-PVP gels prepared by radiation [43]. Since a few papers were available regarding the active agents used in the present paper and none related to a comparison, it highlights the novelty of the current work.

The goal of the present work is to manufacture, characterize and compare physic-chemically and *in vitro* PVA gels loaded with *Stryphnodendron adstringens* (Barbatimão) bark extract, *Leucaena leucocephala* (Leucaena) bark extract, Aloe vera mucilage and Lavender essential oil intended for wound care. In addition, the combination of both Aloe vera and Lavender oil was evaluated.

2. MATERIALS AND METHODS

2.1. Samples manufacturing

The woods extracts *Stryphnodendron adstringens* (Mart.), commonly named Barbatimão, and *Leucaena leucocephala* (Lam.), species grew in Seropédica/RJ, and UFRRJ donated them to the Institute of Forest/ UFRRJ. The bark extracts were prepared by methanol extraction in the Wood Technology Lab / Forest Institute / UFRRJ. Aloe vera mucilage was extracted from the donation of the plants' leaves by the Biology Institute / UFRRJ. The lavender essential oil was obtained from a local market (Laszlo®).

The PVA (Sigma-Aldrich, Mw 85000-124000 Da and degree of hydrolysis 99%) was dissolved in water (10% w/v, at 80°C under mechanical stirring for 4h). After dissolution, the solution was kept under stirring. For PVA hydrogels samples manufacturing, 10 ml of solution per petri dish (Φ 90 mm) were poured and freeze-thawed (1 cycle of 22h at –16°C and 2h at room temperature), followed by drying (room temperature). To prepare the PVA hydrogel loaded with active agents, when the PVA solution reached room temperature, the extracts were added to the PVA solution (2 mg of Barbatimão or Leucaena extract, or 2.6 mg of lavender essential oil, or 10 ml of Aloe vera mucilage per 100 mL of PVA solution) under stirring for 15 min. Then, the samples were poured into dishes, freeze-thawed, and dried, as mentioned before, Figure 1.

2.2. Physico-chemical characterization

The samples were evaluated by Fourier Transform Infrared Spectroscopy (FTIR, Vertex 70 equipment, Organic Chemical Lab/UFRRJ), in the ATR mode, with wavenumber range of 4000 cm^{-1} and 600 cm^{-1}, 32 scans per sample and a spectral resolution of 4 cm^{-1}).

2.3. *In vitro* analysis

The samples (n = 3) were immersed in 10 mL of distilled water for 4 days at room temperature, being weighed periodically (30 min, 1h 2h, 4h, 24h, 48h, 72h, and 96h). The samples' swelling degree (SD) was calculated according to equation (1). The W_S is the samples' weight at each time interval; W_D is the dry weight before the swelling test [44].

$$SD = 100 \times \frac{W_s - W_D}{W_D} \tag{1}$$

The media (water) of immersion was evaluated by Ultraviolet-Visible light spectrophotometry (UV-Vis, EVEN equipment, Materials engineering Lab/UFRRJ), the wavenumber of (360–370) nm. A standard curve of each active agent was plotted (0.1–10 mg/mL of active/water), and the amounts of active agents released by the samples were analyzed in the same wavenumber. The fitted linear curve of each reference plot served as the basis for quantification of each sample's media (n = 3), equations 2–5, where the reference curves are related to Barbatimao extract, Aloe vera mucilage, Lavender essential oil, and Leucaena extract, respectively. The PVA samples swelling media were evaluated in the same range.

$$\text{Concentration}_{\text{Barbatimao}}\,(\text{mg/ml}) = 1.91 * \text{Absorbance} - 0.16\ (R^2 = 0.996) \tag{2}$$

$$\text{Concentration}_{\text{Aloe vera}}\,(\text{g/ml}) = 0.54 * \text{Absorbance} - 0.07\ (R^2 = 0.994) \tag{3}$$

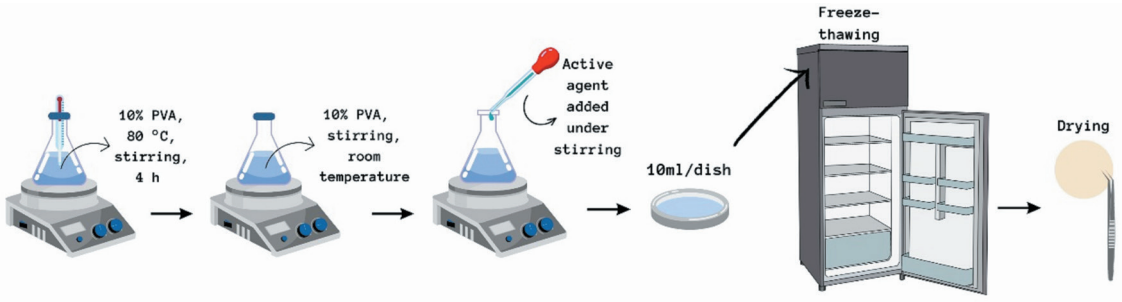

Figure 1: Scheme of hydrogels manufacturing methodology.

$$\text{Concentration}_{\text{Lavender}}\,(\text{g/ml}) = 0.12 * \text{Absorbance} - 0.02\ (R^2 = 0.998) \quad (4)$$

$$\text{Concentration}_{\text{Leucaena}}\,(\text{mg/ml}) = 0.95 * \text{Absorbance} - 0.06\ (R^2 = 0.988) \quad (5)$$

2.4. SEM analysis

The samples' morphology was evaluated using a Tm3030Plus Hitachi scanning electron microscope (SEM), operating under a high vacuum at 15kV. The samples were previously covered with silver (SCD 005 sputter BAL-TEC), CETEM/UFRJ.

3. RESULTS AND DISCUSSION

3.1. Physic-chemical analysis

The PVA spectrum revealed its characteristic bands, Table 1, while the "Barbatimão" extract mainly showed tannins, phenols, beta-carotene, saponin, stilbene, and alkaloids, Table 2 [45, 46]. The Leucaena extract exhibited alkaloids, tannins, flavonoids, alcohols, esters, and ethers, Table 2. Lavender presented 1,8 cineol. The curves of PVA and PVA-active agents were plotted together in Figure 2.

PVA-Barbatimão spectrum showed PVA bands (at 3264, 2938, 2907, 1654, 1413, 1378, 1329, 1235, 1143, 1088, 916) cm^{-1} and the band at 1453 cm^{-1} of the Barbatimão extract. The band intensity differed from the originals due to the influence of the materials in bond vibration [53]. Some of the PVA-Barbatimão bands, compared to PVA and Barbatimão extract, were shifted to different wavenumbers. The PVA-Barbatimão band at 847 cm^{-1} could result from the PVA band at 835 cm^{-1} displaced towards the Barbatimão band at 859 cm^{-1}, or these bands overlap. The PVA-Barbatimão band at 1524 cm^{-1} could have the Barbatimão band at 1509 cm^{-1} shifted due to interaction with PVA, Figure 3. In addition, two bands were identified in the PVA-Barbatimão sample that could be the results of PVA and Barbatimão bands displacement (Barbatimão's band at 1610 cm^{-1}

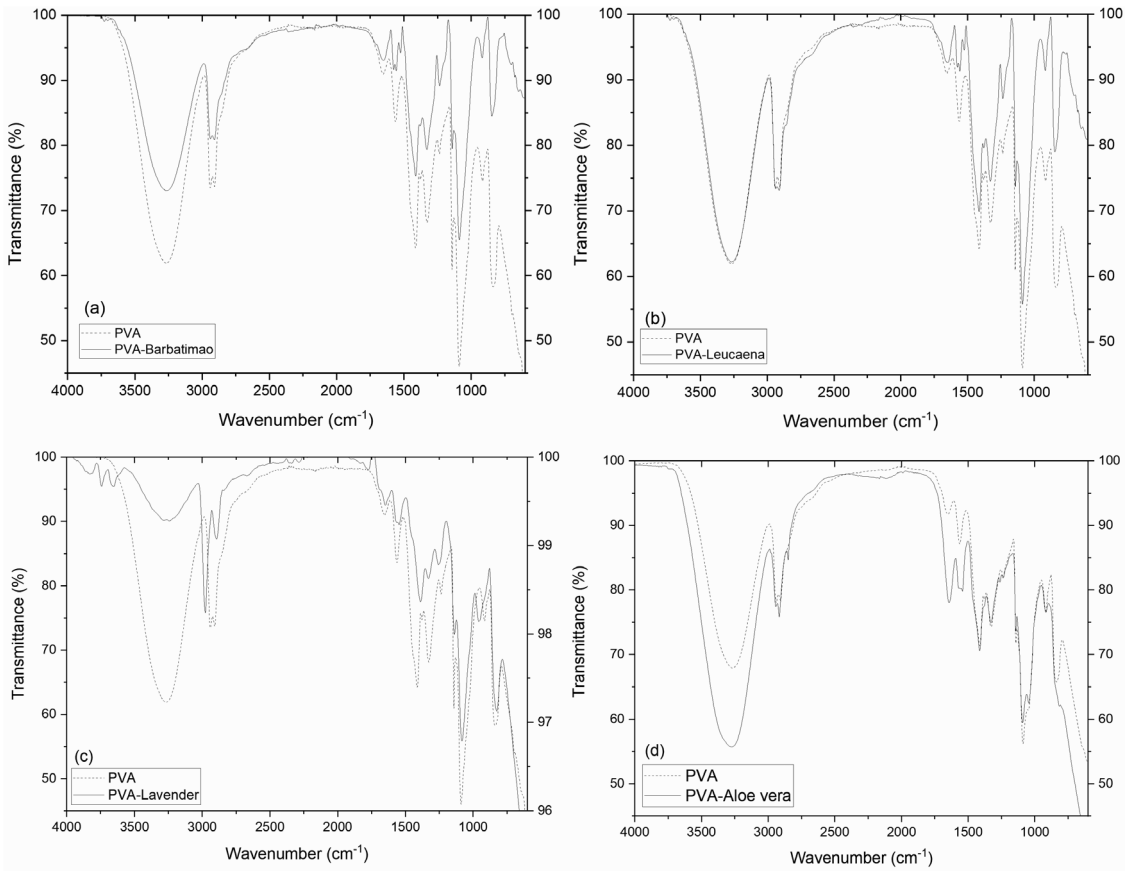

Figure 2: FTIR spectra of PVA samples loaded with (a) Barbatimao extract, (b) Leucaena extract, (c) Lavender essential oil, (d) Aloe vera mucilage.

Table 1: FTIR bands and vibrational modes of PVA. The Greek symbols mean υ = stretching; δ = bending; ω = wagging; ρ = rocking modes [47-52].

FTIR BANDS (cm^{-1})	VIBRATIONAL MODES
3268	$\upsilon(OH)$
2940	υ_{as} (CH_3); methyl groups of residual acetate groups
2910	υ_{as} (CH_2)
1654	$\delta(O-H)$ C = O vibration of residual acetate groups
1563	$C = C$ of residual acetate groups
1413	$\delta(C-H)$ of CH_2; $\delta(CH_3)$; $\delta_s(-CH_2)$ group
1378	$\omega(CH)$
1327	$\delta(C-H)$ of $C-CH_3$; $\delta(CH_2)$
1236	$\delta(C-O)$; $\upsilon(C-O-C)$ of ester group
1142	$\upsilon(C-C)$ and $\upsilon(C-O-C)$ related to the PVA crystallinity
1088	$\upsilon(C-O)$ *coupled with* $\delta(O-H)$; $\upsilon(C-O)$; $\upsilon(C-O)-C-OH$
915	CH_2 *of PVA atatic form*
835	CH_2 *of PVA atatic form;* $\omega(CH)$; $\upsilon(-CH_2)$

shifted to 1576 cm^{-1}, as well as PVA's band at 1563 cm^{-1} displaced to 1557 cm^{-1}), Figure 3. It could also indicate a strong interaction between PVA and some extract components since PVA can interact with plant extract [54]. PVA-Leucaena gel also revealed mainly PVA bands (3268, 2938, 2909, 1654, 1414, 1377, 1328, 1235, 1142, 1089, and 916) cm^{-1}. PVA-Leucaena sample also showed bands that could be the overlap of PVA and Leucaena bands, e.g., the band at 846 cm^{-1}. In addition, the Leucaena extract bands could be shifted to different wavenumbers due to PVA presence. It could also indicate the similar strong interaction mentioned in the PVA-Barbatimão sample, Figure 3, since PVA can interact with extracts components [54, 55].

PVA-Lavender showed mainly PVA bands (3268, 2909, 1654, 1563, 1328, 1142, 1089, 916) cm^{-1}, but Lavender essential oil bands were also observed, e.g., at 3747 cm^{-1}, related to water's υ_{as}(not H – bonded) [70]; 3673 cm^{-1}; 3652 cm^{-1} (free O-H bond of monomeric υOH) [71]; 2979 cm^{-1} of (CH of methyl groups) [72]; 1554 and 1542 cm^{-1} ($\upsilon_{as}(N-O)$) [73]; 1394 cm^{-1}, 1382 cm^{-1} of 1,8 Cineole ($\delta_s(CH_3\ (CO))$ [45, 46]; 1261 cm^{-1} ($\delta(N-H)$) [74]; 967 cm^{-1}, 954 cm^{-1} (υ_s (*glycosidic bond*)) [75]. There are PVA bands slightly shifted, probably due to physical interactions between PVA and Lavender essential oil. PVA-Aloe vera presented mostly all the PVA characteristic bands. The differences between PVA and PVA-Aloe vera were the bands at 2851, 1543 and 1258 cm^{-1}. These bands would be related to Aloe vera. The first band would be related to cellulose and $\upsilon_s(CH_2)$ [76, 77]; the band at 1543 cm^{-1} is related to amide II [78]; the last band would be due to $\upsilon(C-O)$ [79].

It was possible to correlate the samples' mechanical behavior to the samples' crystallinity degree (Xc). The Xc was calculated comparing the FTIR bands areas related to PVA main bands of crystalline (1139 cm^{-1}) and amorphous phases (1085 cm^{-1}) [80], Table 3. Since hydrogels with high crystallinity can be considered the ones with high strength [81], the gels loaded with Lavender, Leucaena, and Barbatimão would be the best choice for resistant dressings. When the PVA chains are in contact, inter and intramolecular hydrogen bonds can be formed, where crystallites are formed. These crystallites limit the mobility of the polymeric chains, increasing the strength of the gels [82].

3.2. SEM analysis

The gels morphology was evaluated under different conditions (Figure 4): unloaded PVA gels and PVA gels loaded with Lavender essential oil. The lavender samples presented a high degradation rate, probably a collaboration of two mechanisms: Lavender essential oil delivery and PVA chains leaching out. As expected, the porosity among them was different. The PVA gel seemed homogeneous and compact [83], while the Lavender sample presented open and interconnected pores. Interconnected pores would allow water diffusion and active agents' release, also contributing to oxygen permeation and hydrolytic degradation [84, 85].

3.3. *In vitro* analysis

The swelling analysis of the gels revealed that all reached a plateau (equilibrium of the swelling degree - ESD) after 48h of immersion, Figure 5, when there is a balance between the elastic forces and the fluid uptake forces

Table 2: FTIR bands of Barbatimao and Leucaena extracts.

BARBATIMÃO EXTRACT [56–65**]**	
3301	$\upsilon(O-H)$; $\delta(C-O-H)$ in phenols; hydrogen-bonding interaction
2921	$\upsilon(C-H)$
2852	$\upsilon(C-H)$
1773	tannins' $\upsilon(C=O)$ of the carbonyl group
1733	tannins' $\upsilon(C=O)$ of the carbonyl group (from moiety, acid, and beta-carotene)
1610	tannins' $\upsilon(C=O)$ of the aromatic rings; thymol's aromatic ring; aromatic fragments of stilbenes
1509	stretching of the tannins' aromatic ring; $C-H$; aromatic fragments of stilbenes
1450	tannins' $\upsilon(C=C)$ of the aromatic rings; $C-H$
1375	tannins' $\upsilon(C-O)$; $C=C$; $-COO$ group; stilbenes' $\delta(OH)$ in the aromatic ring
1281	tannins' asymmetric stretching vibration of the pyran ring
1202	tannins' $\upsilon(C-O)$
1160	tannins' aromatic $O-H$
1116	tannins' $(C-O)$
1068	–
1033	tannins' $\upsilon(C-O)$; saponin's $\upsilon(C-O-C)$ of glycoside linkage
1024	tannin's $\upsilon(C-O)$ of phenolic $O-H$ groups
1009	–
963	betacarotene's $\upsilon(CH=CH)$ of trans conjugated alkene
897	–
859	–
815	$\upsilon(C-H)$ of the tannins aromatic rings; thymol's aromatic ring
780	$\upsilon(C-H)$ of the tannins aromatic rings; thymol's aromatic ring
LEUCAENA EXTRACT [59, 60, 65–69**]**	
3324	$\upsilon(-OH)$ group
2920	$\upsilon(CH-)$ of alkane
2849	$\upsilon(C-H)$
1597	amino and aromatic $\delta(C=C)$ (including flavonoids)
1509	flavonoids aromatic vibration; tannins $\upsilon(C-O)$
1462	flavonoids vibration
1453	$\upsilon(C=C)$
1421	–
1375	tannins $\upsilon(C-O)$
1326, 1263, 1217, 1123	flavonoids; $\upsilon(C-O)$ of alcohols, carboxylic acids, esters, and ethers
1026	ether $\upsilon(C-O-C)$ groups
854	$\upsilon(C-O)$
813	flavonoids

imposed on the gels networks [86]. PVA-Barbatimao and PVA-Leucaena samples presented the highest swelling degree. The actives molecules are probably located between PVA chains, and by their release, more media enter, increasing the sample swelling [87]. It was expected that adding essential oil would diminish the hydrogel hydrophilicity [88], diminishing the samples' swelling ability. The PVA-Aloe vera did not reach a plateau due to the Aloe vera high release. Non-chemically crosslinked membranes with Aloe vera are expected to present weight loss during swelling [89]. Nonetheless, the ESD significantly differed between the samples ($p = 3{,}49$ E-14). Tukey test (level of significance of 95%) revealed that the $ESD_{leucaena} = ESD_{barbatimao}$, but they swell significantly more than PVA ($p < 0.05$), which also swell significantly more ($p < 0.05$) than $ESD_{Aloe\ vera} = ESD_{Lavander}$. It is known that the addition of actives to PVA alters the samples water uptake [90]. The actives probably interfered

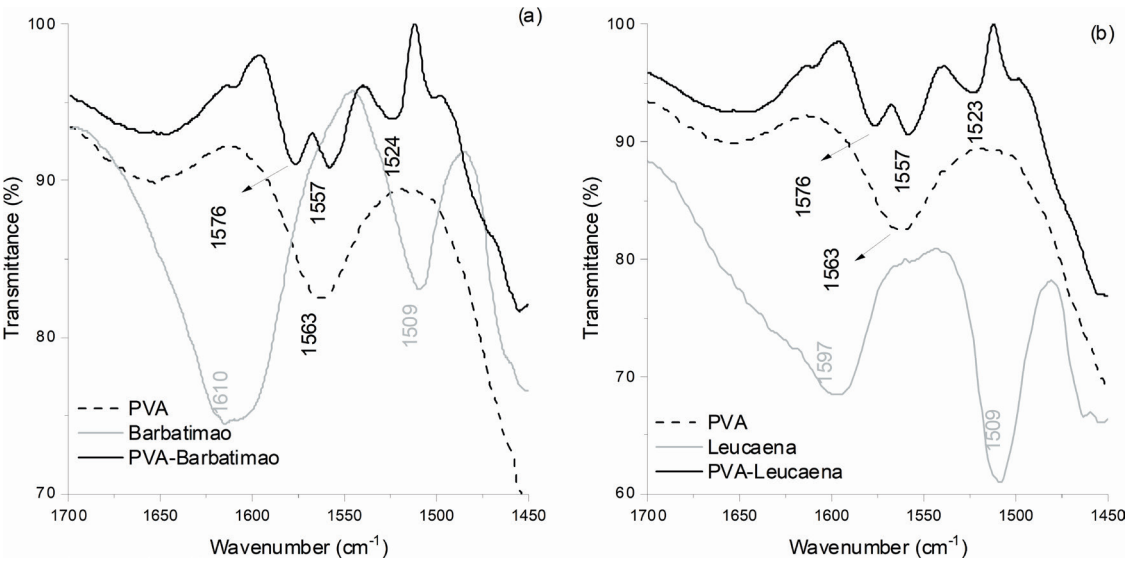

Figure 3: FTIR spectra of the raw materials, as well as (a) PVA-Barbatimão and (b) PVA-Leucaena, in the region of wavenumbers between 1700 and 1450 cm^{-1}.

Table 3: samples crystallinity degree (Xc).

SAMPLE	Xc (%)
PVA	17,92
PVA-lavender	27,93
PVA-barbatimao	24,65
PVA-Leucaena	25,72
PVA-aloe vera	16,91

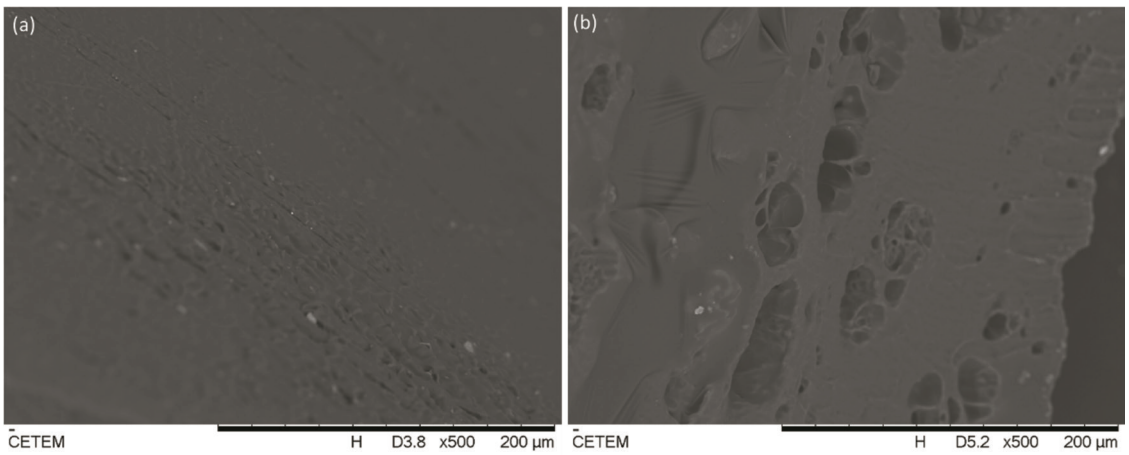

Figure 4: SEM analysis of (a) PVA hydrogel and (b) PVA-Lavender hydrogel.

with the PVA ability to crystallize and to entangle. In addition, PVA chains could be leached out to the media by the fluid uptake [86, 91].

Regarding the release of the actives, the standard curve of the Barbatimão extract was properly ($R^2 = 0.99$), as well as the Leucaena extract one ($R^2 = 0.98$), Lavender oil, and Aloe vera ones ($R^2 = 0.99$). It was observed that the samples delivered the active agents partially to the saline solution after 4 days of immersion, Figure 5. The ANOVA 1-way analysis (factor: type of active agent, 4 levels: Aloe vera, Barbatimao, Leucaena, Lavender)

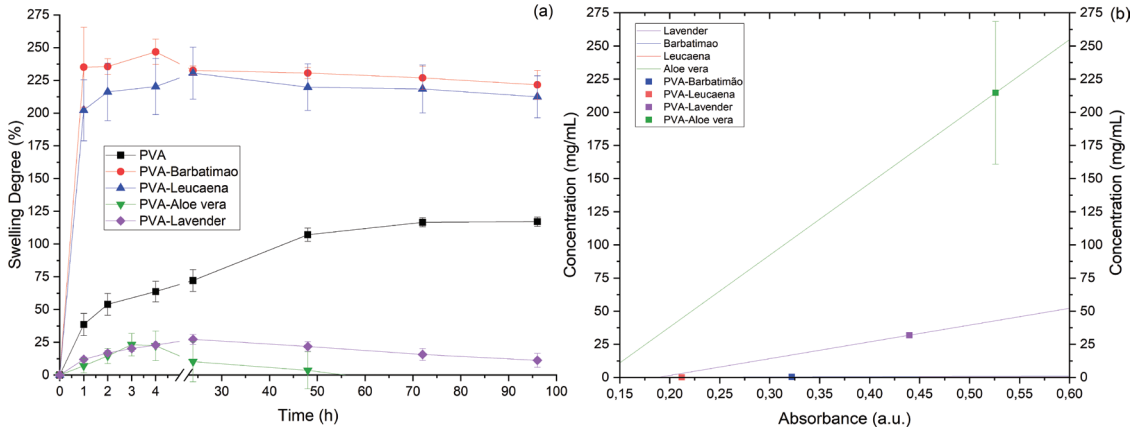

Figure 5: Samples' (a) swelling degree; (b) maximum release of each active.

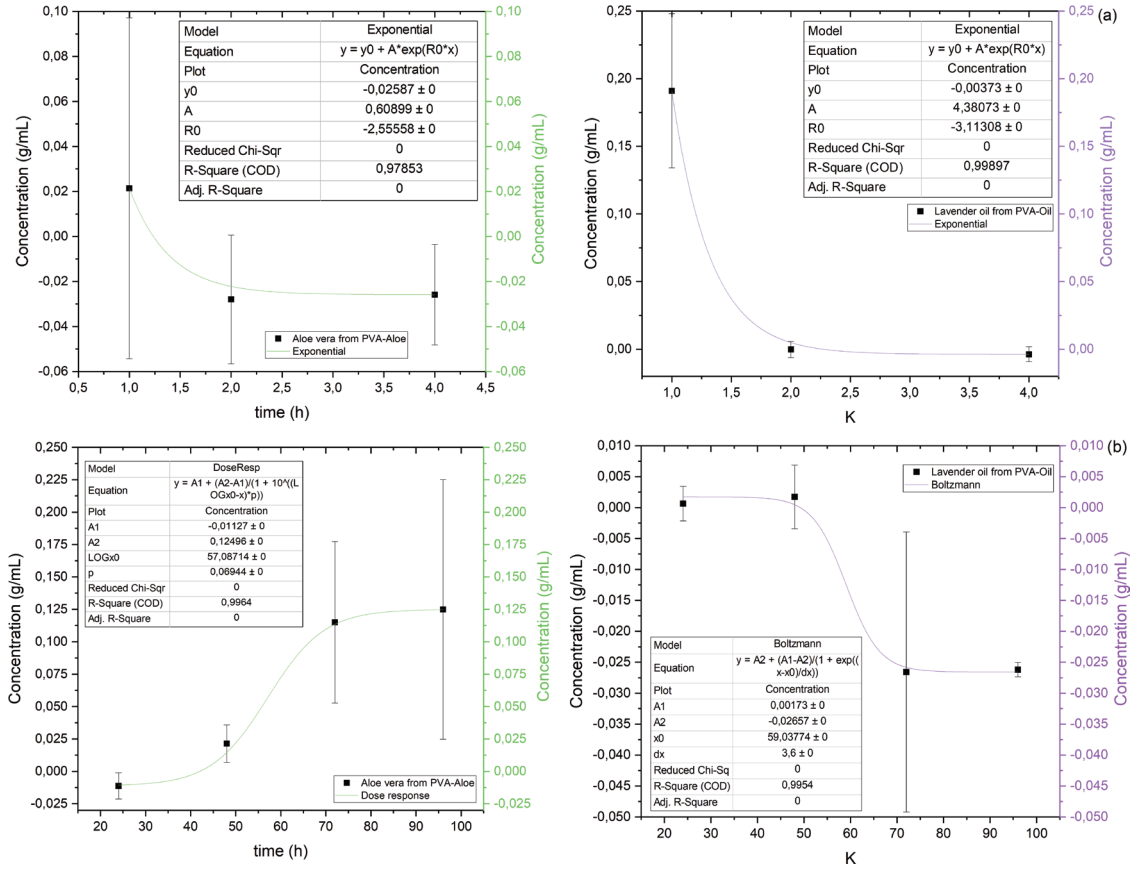

Figure 6: Aloe vera and Lavender essential oil: (a) initial and (b) long release.

revealed significative differences between actives release, where the PVA-Aloe vera released more active than the others ($p < 0.05$). There was a higher delivery of Barbatimão extract to the media than PVA-Leucaena hydrogels. Nonetheless, Lavender essential oil and Aloe vera had the highest release. The actives released by PVA gels could be related to the gels crosslinking density [92], PVA concentration and molecular weight [93], gels' ability to swell [94], etc.

Visually, Lavender essential oil and Aloe vera mucilage were the ones with the highest release and therefore are the ones evaluated. Aloe vera and Lavender initial release followed the Exponential model ($R^2 = 0.97$ and 0.99), respectively), Figure 6, similar to the diffusion-controlled release model related to swelling kinetics

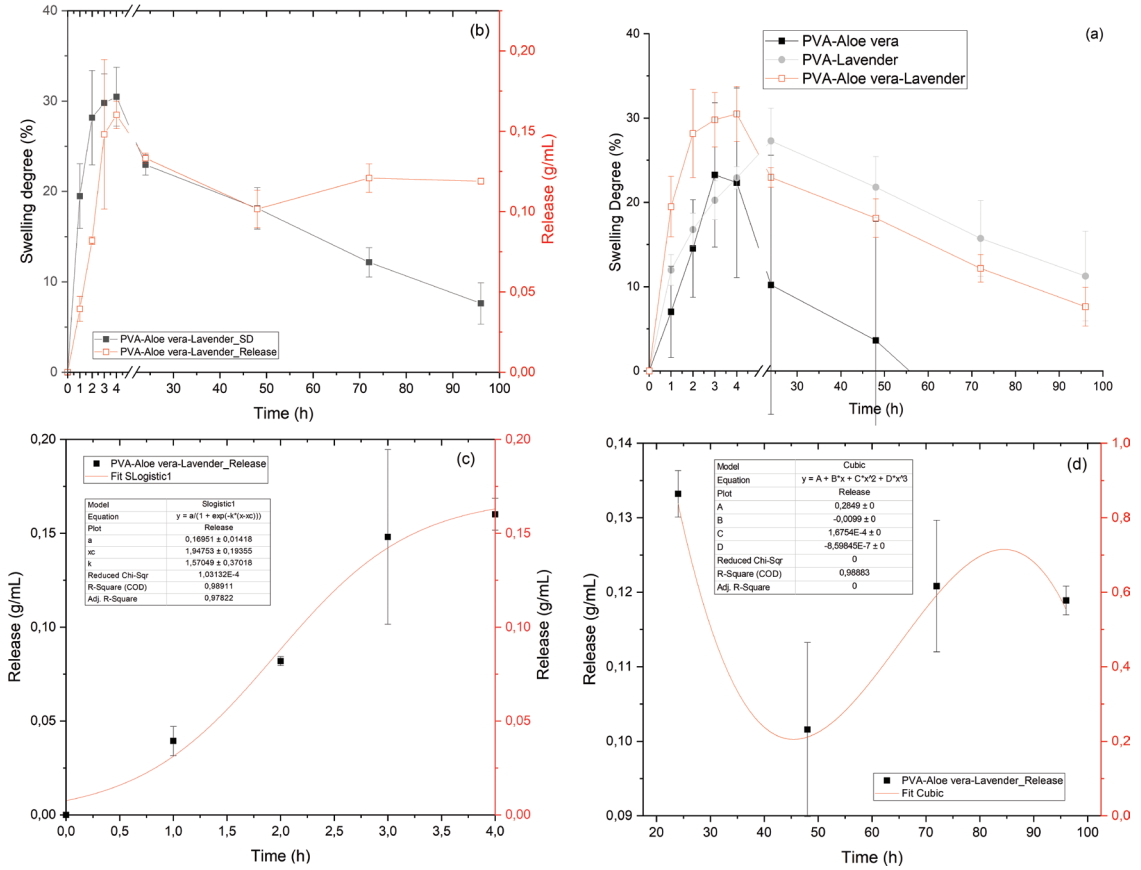

Figure 7: PVA-Aloe vera-Lavender essential oil (a) swelling degree, (b) swelling degree compared to the release of the combined actives; (c) initial release modeled; (d) long-term release modeled.

[95] [96]. Although Aloe vera release after ESD followed a dose-response model $R^2 = 0.99$, Lavender essential oil release followed a Boltzmann model $R^2 = 0.99$. The dose-response sigmoidal model for drugs delivery can be considered appropriated to identify regions of toxic effect and regions of therapeutical effect [97]. Boltzmann release can be associated with the hydrogel relaxation [98], related to-Fickian diffusion-controlled release [99]. Since Aloe vera mucilage can be quickly released to aqueous media [100], it is expected that the media exchange place with the Aloe vera mucilage (low swelling degree), destabilizing the integrity of the gel (high weight loss). Lavender essential oil presents burst release when in hydrogels, followed by diffusion mechanism and degradation of the hydrogel [101].

To further investigate, Aloe vera and Lavender essential oil were both loaded simultaneously to PVA gels. However, samples loaded with Lavender essential oil and Aloe vera presented low swelling, Figure 7, these agents were released in considerable amounts and presented potential as dressing materials. The swelling profile of the PVA-Aloe vera-Lavender sample was between PVA-Lavender essential oil and PVA-Aloe vera ones, indicating a synergistic effect of Aloe vera and Lavender essential oil [102]. If Aloe vera is not freely leached out of the gel by the media entrance, it might be retained by the presence of Lavender essential oil, a hydrophobic material [103]. In addition, the process of Lavender essential oil release occurs, but the release rate is affected by Aloe vera. Compared to PVA-Aloe vera gels, when Aloe vera gel does not release any more Aloe vera, the Lavender essential oil release increases. To properly fit, the release was fitted in two steps, the initial and the long-term. The initial delivery of these samples fits a logistic model ($R^2 = 0.98$). A logistic model for molecule delivery is usually attributed to chaotic behavior, where the molecule's delivery depends on time and many more variables [104]. the long-term release followed a cubic model [105]. It is observed that the agents' release might be modulated when they are combined in the hydrogel.

4. CONCLUSION

It was observed interaction between PVA and the added agents. The addition of Leucaena and Barbatimão increased the PVA's ability to swell. Aloe vera and Lavender essential oil did the opposite. Gels loaded with

Lavender essential oil presented interconnected pores, while PVA gels did not. Samples loaded with the essential oil or extracts showed high crystallinity. There was a high delivery of Barbatimão and Leucaena extracts, but Lavender essential oil and Aloe vera had the highest release. Although the Barbatimão and Leucaena samples' release may be related to the samples' swelling, it was possible to observe that the initial release of Aloe vera and Lavender samples was diffusion controlled by the swelling. Their long-term release was dose-dependent for Aloe vera, while it was a non-Fickian diffusion for Lavender essential oil related to the hydrogel's relaxation step. There is a synergistic effect when Aloe vera and Lavender essential oil are loaded in PVA hydrogels, modulating their release.

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