



Epoxidized natural rubber grafted with hyaluronic acid incorporated with *Matricaria chamomilla* L. extract for potential biomaterials applications

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Received: 7 February 2026 / Revised: 25 April 2026 / Accepted: 12 May 2026 /
Published online: 20 May 2026
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Abstract

The incorporation of plant extracts into polymeric matrices represents a promising strategy for the controlled release of bioactive compounds. In this study, the incorporation of chamomile flower extract (CHAM; *Matricaria chamomilla* L.) into epoxidized natural rubber grafted with hyaluronic acid (ENR-g-HA) at concentrations of 1.0%, 2.5%, and 5.0% was evaluated through physicochemical, morphological, and in vitro release analyses. FTIR spectra confirmed the absence of new absorption bands, indicating that the interaction between CHAM and the matrix is predominantly physical. Morphological analysis revealed increased surface roughness and structural heterogeneity with increasing extract concentration. Thermogravimetric analysis (TGA) showed that the presence of CHAM does not compromise the thermal stability of the polymeric matrix. In addition, DSC results demonstrated that extraction incorporation reduces the glass transition temperature, characterizing a plasticizing effect and increased segmental mobility of the polymer chains. Release assays exhibited a sustained profile, with similar behavior observed for the 2.5% and 5.0% CHAM samples and fitting to the Korsmeyer-Peppas model indicated a quasi-Fickian diffusion mechanism ($n \leq 0.5$). Collectively, the results demonstrate that the ENR-g-HA matrix enables stable physical incorporation of CHAM and promotes controlled extract release, highlighting its potential as a functional polymeric platform for biomaterial applications.

Keywords Polyisoprene · Polysaccharide · *Matricaria chamomilla* · Wound healing · *Hevea brasiliensis*

Introduction

The development of biocompatible and versatile biomaterials has become strategic for tissue engineering [1]. In this context, bioactive biomaterials have gained prominence due to their ability to interact with biological systems and release molecules that modulate processes such as angiogenesis and wound healing [2]. Among the different classes of biomaterials, natural polymers stand out for their biocompatibility, biodegradability, and versatility, enabling their application in tissue repair [3, 4].

Natural rubber latex (NR), a natural polymer derived from the rubber tree *Hevea brasiliensis*, has emerged as a promising material for biomedical applications. In addition to its low cost and ease of processing, NR exhibits biocompatibility as well as pro-angiogenic and wound-healing properties in both soft and hard tissues [2, 5]. Moreover, it can serve as a matrix for the sustained release of various natural and synthetic compounds [2, 6]. Chemical modifications of its structure can further enhance its properties for targeted biomedical applications [7]. In this context, the introduction of epoxy functional groups along the isoprene backbone through epoxidation can increase hydrophilicity and improve tissue adhesion and integration [8]. Furthermore, the presence of epoxy groups enables further functionalization [9]. Previous studies conducted by our group demonstrated the successful grafting of epoxidized natural rubber (ENR) with hyaluronic acid (HA), yielding ENR-g-HA, a material with enhanced hydrophilicity and potential for tissue repair applications [10]. HA is a natural polysaccharide of the extracellular matrix, composed of alternating units of N-acetyl-D-glucosamine and D-glucuronic acid. It is widely recognized for its biocompatibility, degradability, and hydrophilicity, and plays a crucial role in tissue hydration, wound healing, and the modulation of cellular processes [11–14].

Furthermore, natural compounds have been widely explored due to their bioactivity and potential synergistic effects with biomaterials [15–17]. In this context, chamomile (CHAM, *Matricaria chamomilla*) stands out as rich in bioactive metabolites, such as sesquiterpenes, polyacetylenes, coumarins, and flavonoids, conferring anti-inflammatory, antioxidant, and antimicrobial properties [18–20]. Its incorporation into polymeric systems has been associated with improved biological performance, particularly in wound healing applications.

Previous studies have demonstrated that the incorporation of CHAM enhances the physicochemical and biological properties of polymeric systems. Jamrozy et al. [21] reported improved physicochemical stability and increased cell viability in CHAM-containing acrylic hydrogels. Fazili et al. [22] observed enhanced cell adhesion in PLLA scaffolds coated with CHAM oil. Karam et al. [23] demonstrated the therapeutic activity of chitosan nanocapsules loaded with CHAM against *L. amazonensis*. Similarly, Shokrollahi et al. [19] showed that CHAM imparted antibacterial, antioxidant, biocompatible, and improved mechanical properties to nanofibrous membranes. More recently, Nezhad-Mokhtari et al. [24] reported increased cytocompatibility, cell proliferation, and antibacterial activity in PCL-chitosan membranes containing CHAM oil, effects attributed to bioactive compounds.

In this context, the present study aimed to investigate the physicochemical and morphological effects of incorporating dried CHAM flower extract into ENR-g-HA, as well as to evaluate its potential as a carrier system for the sustained release of bio-

active compounds. By combining the structural properties of the polymeric matrix with the bioactivity of chamomile, this approach seeks to develop multifunctional material. Thus, this study contributes to the development of polymeric biomaterials functionalized with natural bioactive, expanding the possibilities for innovative and sustainable biomedical applications, particularly in wound healing and tissue engineering. To the best of our knowledge, this is the first report on the incorporation of CHAM into ENR-g-HA.

Materials and methods

Materials

Natural rubber latex (NR) was supplied by Fábrica de Látex São Roque Ltda. (Brazil). Hyaluronic acid (1.56×10^6 g/mol) was obtained from Via Farma (Brazil). Chloroform (99.8%), methanol (99.8%), formic acid (88.0%), and Tween 20 (polyoxyethylene sorbitan monolaurate) were purchased from Synth (Brazil). Hydrochloric acid (0.2 and 2.0 M) and ammonium hydroxide (0.5 M) were obtained from Anidrol and Ecibra, respectively. Hydrogen peroxide, toluene (99.9%), and tin-2-ethylhexanoate ($\text{Sn}(\text{Oct})_2$) (95.0%) were obtained from Sigma-Aldrich. The dry chamomile flower extract (*Matricaria chamomilla* L./Asteraceae) was commercially obtained from Big Essências (Brazil) using a spray-drying method (Lot: 000672PAS).

Preparation of deproteinized, epoxidized, and graft copolymer with addition chamomile flower dry extract

The deproteinization by reprecipitation, epoxidation, and grafting of ENR with HA (ENR-g-HA) was performed following the methodology described by Quevedo et al. [10]. After the grafted material had cooled, 1.0%, 2.5%, and 5.0% (w/w) of CHAM were added separately under constant stirring 1 h at room temperature. The resulting mixture was then poured into 6 cm in diameter Petri dishes and dried in an oven at 40 °C for approximately 24 h. The dried samples, in membrane form, were subsequently stored in a vacuum desiccator.

Characterization

Fourier transform infrared spectroscopy (FTIR)

The FTIR-ATR analysis was conducted at room temperature using a Spectrum 65 spectrophotometer (Perkin Elmer), covering the range from 4000 to 500 cm^{-1} , with a resolution of 4 cm^{-1} and 32 scans.

Scanning electron microscopy (SEM)

The morphology of surface materials was evaluated using scanning electron microscopy (SEM) on (JEOL, JSM-6010LA) with a voltage parameter of 3 kV. The samples were previously coated with gold in a sputter (Denton Vacuum).

Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA), the TA Instruments Discovery TGA 55 equipment was obtained with a temperature range of 25 °C to 500 °C, under a dynamic atmosphere of nitrogen gas with a flow of 40 mL/min, with a heating rate of 10 °C/min. The CHAM sample was subjected to only a single heating, from 25 °C to 400 °C.

Differential scanning calorimetry (DSC)

The Differential Scanning Calorimetry (DSC) analysis was performed in a Discovery DSC 25 equipment from TA Instruments. The samples were firstly heated from 25° to 250 °C, with subsequent cooling down to -80 °C, followed by a 5 min isotherm. Finally, the samples were subjected to a second heating up to 250 °C. Simultaneously, the CHAM sample was subjected to only a single heating, from -80 °C to 250 °C. All events occurred under a dynamic nitrogen gas atmosphere with a flow rate of 250 mL/min, with a heating and cooling rate of 10 °C/min for all samples.

Chamomile flower extract release test

To quantify and evaluate the in vitro release profile of different concentrations (1.0%, 2.5%, and 5.0%) of CHAM incorporated into the grafted material (ENR-g-HA), previously weighed samples (0.2 g) were immersed in test tubes containing 6 mL of Phosphate Buffered Saline (PBS). The samples were kept in a thermostatic bath at 38 °C. Over a predetermined period of 165 h, 3 mL aliquots of the release medium were removed and replaced with an equal volume of pure PBS. The assay was performed in triplicate using quartz cuvettes for the readings. The readings were taken using a UV-Visible spectrophotometer, model CIRRRUS 80 (FEMTO), with a scanning resolution of 2 nm and a wavelength of 221 nm.

Study release mechanism The in vitro release data of CHAM were fitted to four mathematical models: Korsmeyer-Peppas, Higuchi, First-order, and Zero-order [25].

- Korsmeyer-Peppas (Eq. 1):

$$\frac{M_t}{M_\infty} k_k P t^n \quad (1)$$

- Higuchi (Eq. 2):

$$\frac{M_t}{M_\infty} = kH\sqrt{t} \quad (2)$$

- First order (Eq. 3):

$$M_t = \ln M_0 + k_1 t \quad (3)$$

- Zero order (Eq. 4):

$$M_t = M_0 + k_0 t \quad (4)$$

Where M_t is the amount of CHAM released at time t ; M_0 is the initial concentration of CHAM in the solution; k_H , k_0 , and k_1 are the Higuchi, First order and Zero order release constants, respectively. M_t/M_∞ is the fraction of CHAM released at time t and n is the diffusion exponent.

Results and discussion

Fourier transform infrared spectroscopy (FTIR)

The infrared spectrum of CHAM and ENR-g-HA samples incorporating different concentrations of CHAM (1.0%, 2.5%, and 5.0%) are presented in Fig. 1.

The FTIR spectrum of CHAM exhibited a broad absorption band at 3320 cm^{-1} , attributed to the stretching vibrations of -OH groups from phenols and alcohols present in quercetin, caffeic acid, chlorogenic acid, and apigenin [26]. The band at 2925 cm^{-1} was assigned to the asymmetric stretching vibration of aliphatic -CH groups, whereas the peak at 1645 cm^{-1} was associated with C = O. The band at 1409 cm^{-1} corresponds to the COO group, and the bands at 1346 and 1000 cm^{-1} are attributed to the C-O-C stretching vibration [27–29]. The presence of these characteristic bands confirms the occurrence of polyphenols, flavonoids, and terpenoid compounds in the chemical structure of CHAM [30].

As reported by Quevedo et al. [10], the FTIR spectrum of ENR-g-HA exhibited the main characteristic bands of ENR (1254 , 1030 , and 796 cm^{-1}) and HA (3400 , 1611 , and 1410 cm^{-1}), as well as evidence of grafting at 1770 cm^{-1} . In contrast, the spectra of ENR-g-HA incorporated with 1.0%, 2.5%, and 5.0% CHAM showed only the characteristic bands of the chemically modified material, with no additional bands detected. Therefore, no new absorption bands associated with chemical interaction were observed, indicating that the incorporation of CHAM into ENR-g-HA does not promote chemical bonding between the extract and the polymeric matrix. This finding suggests that the interactions between CHAM and ENR-g-HA are predominantly physical, occurring through adsorption mechanisms [31]. Such purely physical interaction is desirable, as they enable the controlled release of CHAM from the modified material into the lesion environment [32, 33].

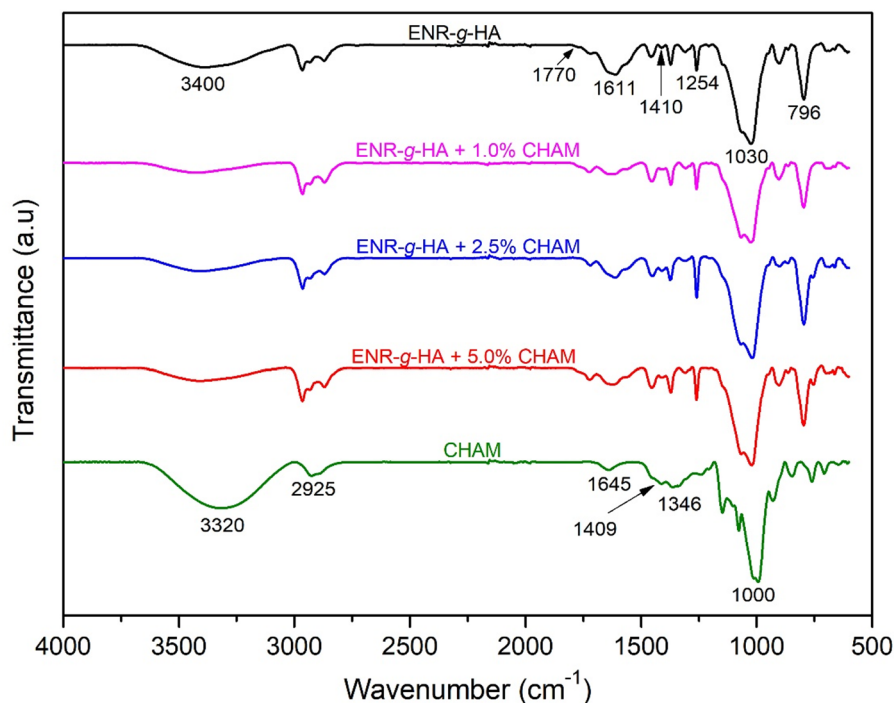


Fig. 1 FTIR spectra. The graph presents spectra of chamomile flower extract (CHAM), the modified material (ENR-g-HA), and ENR-g-HA incorporated with different CHAM concentrations (1.0%, 2.5%, and 5.0%)

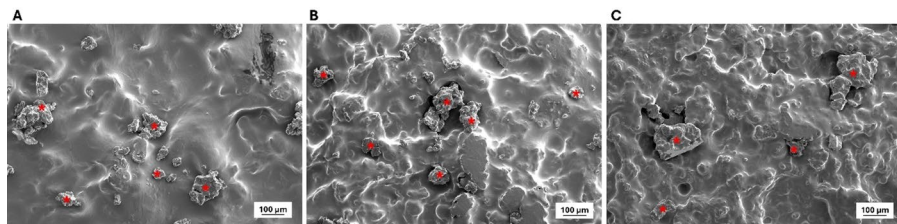


Fig. 2 SEM images. Micrographs of the surface morphology of the modified material (ENR-g-HA) incorporated with chamomile flower extract (CHAM). **(A)** ENR-g-HA + 1.0%CHAM, **(B)** ENR-g-HA + 2.5%CHAM, and **(C)** ENR-g-HA + 5.0%CHAM. (*) indicates CHAM distributed on the material surface. (Scale bar: 100 μm , Magnification: 100 $\times$)

Scanning electron microscopy (SEM)

SEM images of ENR-g-HA incorporated with different concentrations of CHAM (1.0%, 2.5%, and 5.0%), are shown in Fig. 2.

As evidenced in Fig. 2A, the ENR-g-HA membrane incorporated with 1.0% CHAM exhibited a predominantly smooth and continuous surface, which is a typical characteristic of the polymeric matrix, indicating proper film formation. However,

small agglomerates dispersed on the surface (indicated by *) were observed and can be attributed to the presence of the plant extract. The relatively homogeneous distribution of these domains suggests that, at this concentration, CHAM is largely well dispersed within the matrix, without significantly compromising the morphological integrity of the material.

With the increase in CHAM concentration to 2.5% (Fig. 2B), a gradual transition toward a more irregular, rough, and denser surface is observed. This behavior indicates partial saturation of the polymeric matrix, which may lead to the formation of CHAM-rich domains. In addition, the simultaneous presence of particles on the surface and potentially retained within the internal structure of the material suggests a mixed incorporation mechanism, involving surface dispersion and partial encapsulation.

In the sample containing 5.0% CHAM (Fig. 2C), the morphology becomes even more heterogeneous, with a significant increase in surface roughness, the presence of larger agglomerates, and regions exhibiting topographical discontinuities. This effect may be associated with spatial organization and interactions between the polymeric matrix and the extract at high concentrations during the membrane formation process. Similar phenomena have been widely reported in the literature for polymeric systems incorporated with plant-derived extracts [34, 35].

From a functional standpoint, the increase in surface roughness can be considered advantageous for biomedical applications, as rougher surfaces are often associated with a higher surface area, enhanced cell–material interactions, and a potential improvement in the controlled release of bioactive compounds [36, 37].

Thermogravimetric analysis (TGA)

The thermal properties of CHAM, ENR-g-HA, and ENR-g-HA incorporated with 1.0%, 2.5%, and 5.0% of CHAM were analyzed by TGA/DTG (Fig. 3). The results are summarized in Table 1.

As shown in Fig. 3 and summarized in Table 1, both CHAM and the ENR-g-HA samples incorporated with different CHAM concentrations (1.0%, 2.5%, and 5.0%) exhibited an initial mass loss of approximately 7% at temperatures below 100 °C, which can be attributed to the evaporation of water molecules present in both materials [28, 38]. In contrast, the plant extract (CHAM) displayed a pronounced thermal mass loss event (71%), which began at 256 °C and reached a maximum mass loss temperature ($T_{\max}$) at 304 °C. This event was attributed to the thermal decomposition of the organic constituents of the extract, such as flavonoids, phenolic compounds, and other secondary metabolites, in agreement with previous studies involving natural plant extracts [28]. In contrast, the ENR-g-HA without CHAM exhibited a single and intense mass loss event (96%), with an onset temperature of 368 °C and a $T_{\max}$ of 397 °C, which was attributed to the thermal degradation of the grafted polymeric backbone, corroborating previously reported results [10].

The modified polymeric matrices containing CHAM exhibited more complex thermal behavior. In addition to the initial event associated with water loss, three additional distinct thermal events were observed. The first event showed a mass loss of approximately 7%, with an onset temperature around 205 °C, which was attrib-

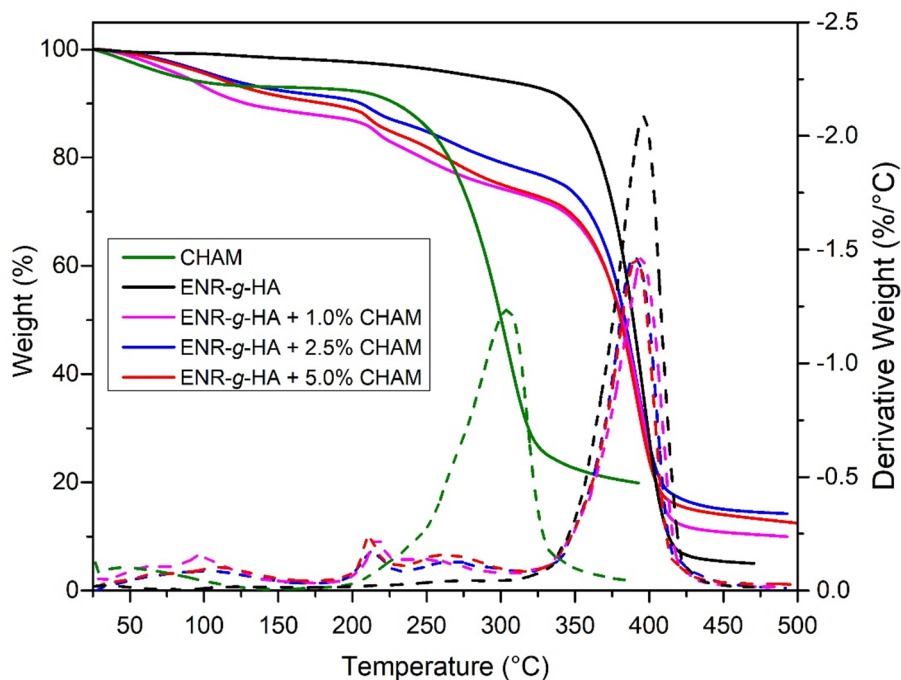


Fig. 3 Thermogravimetric analysis. TGA/DTG curves of chamomile flower extract (CHAM), the modified material (ENR-g-HA), and ENR-g-HA incorporated with different CHAM concentrations (1.0%, 2.5%, and 5.0%)

Table 1 Thermal properties obtained from TGA and DTG curves of chamomile flower extract (CHAM), the modified material (ENR-g-HA), and ENR-g-HA incorporated with different CHAM concentrations (1.0%, 2.5%, and 5.0%)

Sample	Events (n°)	T_{onset} ($^{\circ}\text{C}$)	T_{max} ($^{\circ}\text{C}$)	Weight loss (%)
CHAM	1	27	50	7
	2	256	304	71
ENR-g-HA	1	368	397	96
ENR-g-HA + 1.5% CHAM	1	47	97	10
	2	207	217	7
CHAM	3	249	256	8
	4	368	395	63
ENR-g-HA + 2.5% CHAM	1	57	95	7
	2	202	213	6
CHAM	3	248	266	6
	4	368	390	64
ENR-g-HA + 5.0% CHAM	1	66	100	8
	2	205	211	7
CHAM	3	249	260	9
	4	366	390	63

uted to the thermal decomposition of residual HA that did not react during the ENR grafting process. The occurrence of HA thermal degradation within this temperature range is well documented in the literature [39–41]. The presence of residual HA can be explained by the fact that the samples were not subjected to a washing step at the end of the synthesis, since such a procedure could promote the partial removal of the incorporated CHAM, thereby compromising the integrity and functionality of the system. This behavior was not observed in the ENR-g-HA sample without CHAM, which was subjected to a washing step after synthesis.

A third thermal event, characterized by a mass loss of approximately 7%, was observed, beginning around 249 °C with a $T_{\max}$ near 260 °C, and was attributed to the thermal degradation of CHAM incorporated into the polymeric matrix, consistent with the thermal profile observed for pure CHAM [28]. Finally, all ENR-g-HA+CHAM samples exhibited a prominent final thermal degradation event, with a mass loss of approximately 63%, starting around 368 °C and presenting a $T_{\max}$ close to 390 °C. This event was attributed to the thermal decomposition of the grafted polymeric matrix (ENR-g-HA), indicating that the incorporation of the plant extract did not significantly alter the main thermal stability of the polymer but introduced intermediate events associated with the incorporated natural component.

On the other hand, ENR-g-HA incorporated with different concentrations of CHAM exhibited a reduction in the DTG peaks (~ 390 °C) compared to the matrix without the plant extract. This behavior suggests that the incorporation of CHAM modulates the thermal degradation of the polymeric matrix, imparting a stabilizing effect on the structure of ENR-g-HA. Similar results were reported by Valero et al. [42], indicating that plant extracts can act as thermal protective agents in polymeric materials, delaying matrix decomposition.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) analysis (Fig. 4) was performed to evaluate the thermal behavior of CHAM, ENR-g-HA, and ENR-g-HA incorporated with different concentrations of CHAM (1.0%, 2.5%, and 5.0%). The DSC curve of CHAM exhibited three consecutive endothermic events at 170 °C, 211 °C, and 231 °C. These events were attributed to the thermal decomposition of constituents present in the plant extract. However, the literature reports that plant extracts are composed of a wide range of substances which, depending on their concentration, may influence the degradation of products observed in DSC analysis. Therefore, these thermal decomposition events may be associated with a broad variety of secondary metabolites, including phenolic compounds present in the dried extract [43].

The second heating ramp of ENR-g-HA revealed two events associated with glass transition temperatures (T_g), in addition to an additional endothermic event. The first T_g , observed at -45 °C, corresponds to the fraction of ENR that remained unmodified during synthesis. The endothermic event at -35 °C, close to the T_g (-45 °C), was attributed to the release of internal stresses that occur during the glass transition [10]. Furthermore, a second T_g was identified at 70 °C, which was attributed to the copolymeric phase formed during the grafting process, reflecting the grafting density and the interactions between the reactive groups of ENR and HA.

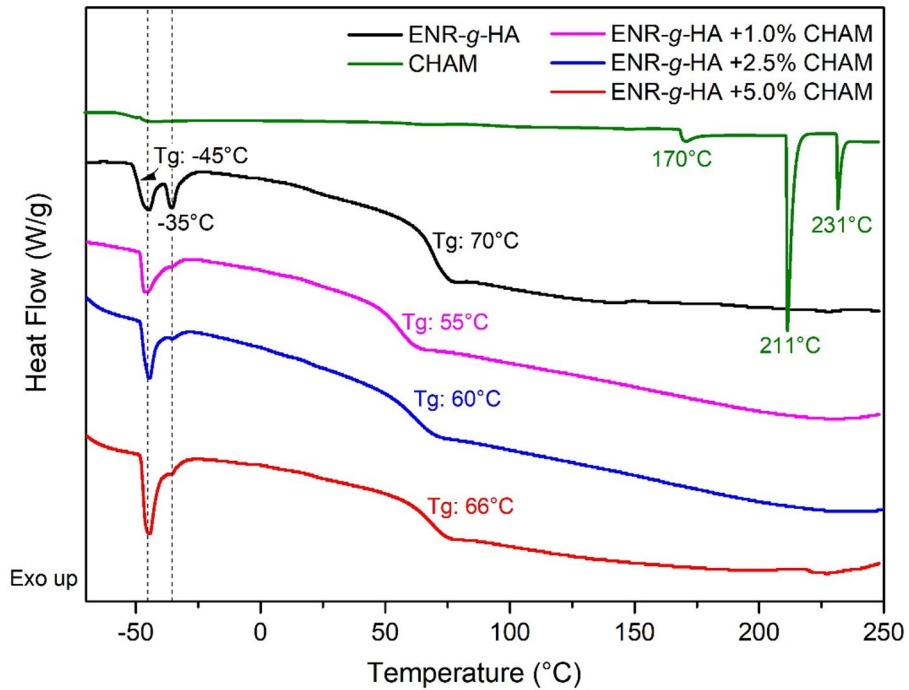


Fig. 4 DSC curves of chamomile flower extract (CHAM), the modified material (ENR-g-HA), and ENR-g-HA incorporated with different CHAM concentrations (1.0%, 2.5%, and 5.0%)

Similarly to ENR-g-HA, samples containing different concentrations of CHAM (ENR-g-HA+CHAM) also exhibited two T_g values in their DSC curves. The T_g at approximately -45 °C, accompanied by the endothermic event at -35 °C, was associated with an intrinsic characteristic of the modified polymer matrix that served as the base for CHAM incorporation. A clear reduction in the intensity of the endothermic peak at -35 °C was observed with CHAM addition, suggesting that its incorporation contributes to a decrease in internal stresses within the system. Additionally, a reduction in the higher-temperature T_g (70 °C) was observed after CHAM incorporation. The samples ENR-g-HA + 1.0%CHAM, ENR-g-HA + 2.5%CHAM, and ENR-g-HA + 5.0%CHAM exhibited T_g values of approximately 55 °C, 60 °C, and 66 °C, respectively. This behavior indicates that the presence of CHAM promotes a plasticizing effect in the modified material, reducing the stiffness of the polymer network [44, 45]. The dispersion of CHAM within the system may enhance segmental mobility of the polymer chains [46, 47], in agreement with the results obtained from TGA analyses.

Chamomile flower extract release test

The in vitro release profile of 1.0%, 2.5%, and 5.0% CHAM in the ENR-g-HA matrix is shown in Fig. 5.

The CHAM release profile for all samples exhibited a biexponential behavior, characterized by an initial burst release phase, followed by a slower and sustained

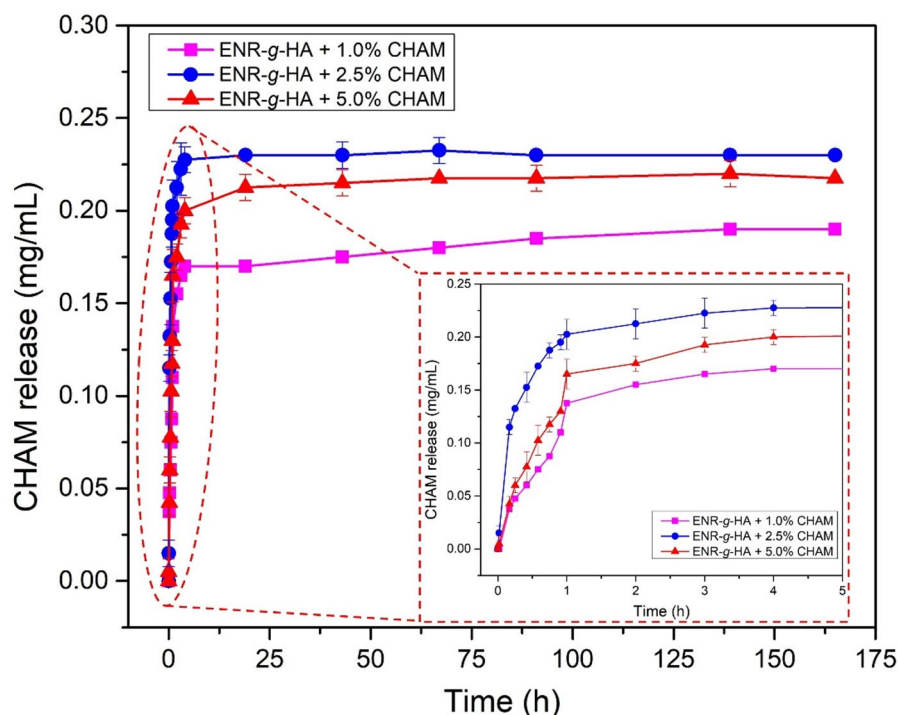


Fig. 5 In vitro release profile of 1.0%, 2.5%, and 5.0% chamomile flower extract (CHAM) from the ENR-g-HA matrix. The inset graph highlights the burst release profile observed during the first 5 h of analysis

release stage. The burst release occurred within the first two hours of the assay for all formulations. During the first hour, the samples containing 1.0%, 2.5%, and 5.0% CHAM released approximately 0.138, 0.203, and 0.165 mg/mL, respectively. This behavior is attributed to the rapid release of CHAM compounds dispersed on the surface of the material, which are more exposed to the liquid medium, facilitating the initial diffusion process [48, 49].

After approximately 4 h, the release process became progressively slower for all samples until approaching a near-stabilization regime. At the end of the experiment (165 h), the released amounts were 0.190, 0.230, and 0.218 mg/mL for the samples containing 1.0%, 2.5%, and 5.0% CHAM, respectively. This slower release stage is associated with the diffusion of the active compound encapsulated within the inner regions of the polymeric matrix, where CHAM is less exposed to the liquid medium, particularly in samples containing higher concentrations of the plant extract (2.5% and 5.0%), as supported by SEM micrographs (Fig. 2B and C) [48, 50, 51].

In polymeric systems, release kinetics are generally proportional to the concentration of the incorporated active compound, such that higher loadings typically result in greater released amounts [19, 29]. However, a distinct behavior was observed in the present study, as the samples containing 2.5% and 5.0% CHAM exhibited similar release profiles. This finding suggests that, in the 5.0% formulation, the plant extract

may be heterogeneously distributed and poorly dispersed within the matrix, hindering its diffusion into the surrounding medium. In contrast, the sample containing 2.5% CHAM appears to present improved dispersion within the polymeric matrix, providing a larger effective surface area for exposure. As a result, even with a lower CHAM content, the released amount becomes comparable to that of the higher-concentration sample, explaining the deviation from the behavior commonly reported in the literature. Overall, the results demonstrate that the ENR-g-HA-based matrix can promote sustained CHAM release across different concentrations, highlighting its potential as a controlled delivery system for bioactive compounds.

Study release mechanism

The release mechanism was investigated during the initial hours (burst release) of CHAM release. Table 2 presents the mathematical models - Korsmeyer-Peppas, Higuchi, First-order, and Zero-order - fitted to the CHAM release profile.

As shown in Table 2, the Korsmeyer-Peppas mathematical model provided the best fit among the analyzed models, exhibiting the highest correlation coefficient (R^2) of 0.98 compared to the other models. The Korsmeyer-Peppas model is widely used due to its simplicity and its ability to describe drug release from a broad range of systems, providing valuable insights for the development and optimization of controlled-release formulations.

The diffusion exponent (n) obtained using the Korsmeyer-Peppas model represents the drug release mechanism. The model indicates that when $n \leq 0.5$, quasi-Fickian transport occurs, and the release is primarily controlled by the diffusion of the drug through the polymer (diffusion-controlled release). Conversely, if $0.5 < n < 1.0$, the release is governed by a non-Fickian process, involving both diffusion and matrix relaxation. Finally, when $n > 1$, the transport mechanism is referred to as Super Case-II, which can occur through polymer matrix relaxation and erosion [19, 52, 53]. In the present study, the obtained n values ($n \leq 0.5$) indicate that the release of 1.0%, 2.5%, and 5.0% CHAM from the polymer (ENR-g-HA) occurred via quasi-Fickian diffusion. Figure 6 shows the Korsmeyer-Peppas fitting to the release profiles of different CHAM concentrations in ENR-g-HA.

Table 2 Mathematical models of Korsmeyer-Peppas, Higuchi, First-order, and Zero-order fit the CHAM release profile

Mathematical models	Parameters	1.0% CHAM	2.5% CHAM	5.0% CHAM
Korsmeyer-Peppas	R^2	0.980	0.900	0.970
	n	0.500	0.400	0.500
Higuchi	R^2	0.970	0.780	0.940
	k	0.016	0.008	0.004
First order	R^2	0.590	0.300	0.440
	k	0.510	0.390	0.620
Zero order	R^2	0.770	0.520	0.750
	k_0	0.007	0.003	0.002

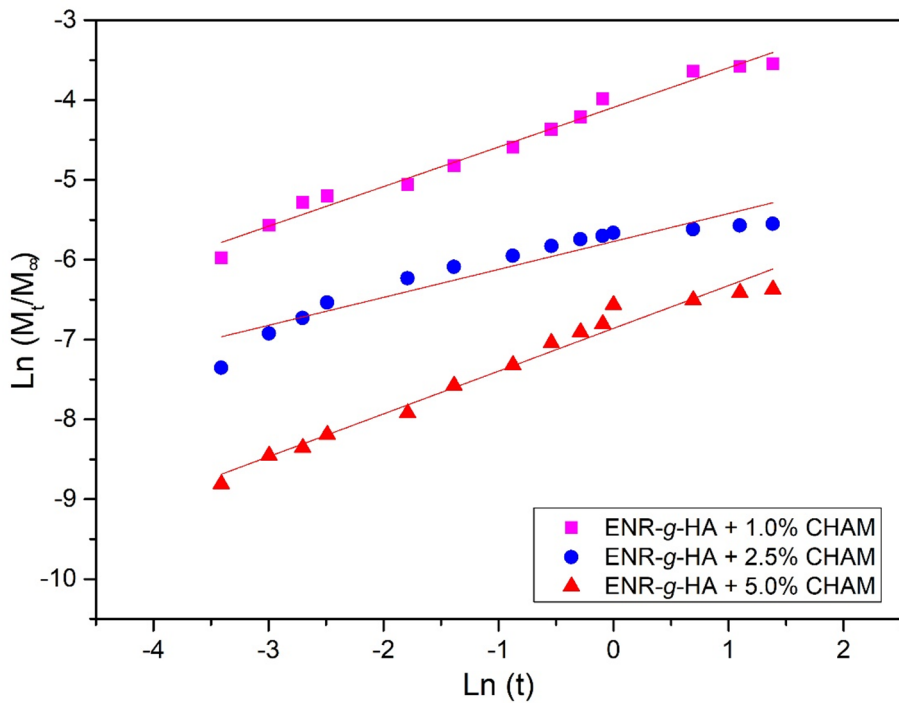


Fig. 6 Korsmeyer-Peppas mathematical model applied to the release mechanism of 1.0%, 2.5%, and 5.0% CHAM

Conclusion

The incorporation of different concentrations of CHAM into the ENR-g-HA matrix was successfully achieved, resulting in a hybrid material with preserved structural characteristics. FTIR analyses indicated the absence of new absorption bands, demonstrating that the interaction between CHAM and the polymeric matrix is predominantly physical, a condition favorable for controlled release of the bioactive compound, as confirmed by the release profile and fitting to the quasi-Fickian diffusion model. Morphological analyses revealed increased surface roughness and greater structural heterogeneity with higher extract concentrations, features that may enhance the exposure area and diffusion of the active compound. From a thermal perspective, CHAM incorporation induced only a slight reduction in the initial degradation temperature without compromising the overall stability of the material, while also decreasing the glass transition temperature, indicating a plasticizing effect and increased segmental mobility of the polymer network. Collectively, these results demonstrate that the ENR-g-HA matrix can physically incorporate natural compounds and act as a potential system for sustained bioactive release.

As a limitation, this study focused exclusively on physicochemical and morphological characterizations, without biological evaluations. Therefore, *in vitro* and *in vivo* investigations are essential to confirm biocompatibility, applicability, and effi-

cacy of the new material, representing critical steps to validate its use as a biomaterial in clinical contexts.

Acknowledgements The authors acknowledge the Brazilian funding agencies CAPES (Coordination for the Improvement of Higher Education Personnel; Process No. 88887.492777/2020-00) and the São Paulo Research Foundation (FAPESP; Grant Nos. 2023/17083-8 and 2023/12039-0) for the financial support essential to this work.

Author contributions Bruna V. Quevedo: Conceptualization; Formal analysis; Investigation; Data curation; Visualization; Methodology; Writing – original draft; Writing - Review & Editing; Funding acquisition. Daniel Komatsu: Conceptualization; Validation; Visualization; Methodology; Writing - Review & Editing. Maira de Lourdes Rezende: Conceptualization; Validation; Visualization; Supervision; Writing – review & editing. Eliana Aparecida de Rezende Duek: Conceptualization; Visualization; Validation; Methodology; Resources; Funding acquisition; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Funding The Article Processing Charge (APC) for the publication of this research was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) (ROR identifier: 00x0ma614).

Data availability Data will be made available on request.

Declarations

Competing interests The authors declare no competing interests.

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