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Synthesis and Characterization of Stealth Liposomes for *Acmella oleracea L.* Encapsulation

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Liposomes have been proven to be an excellent tool for drug delivery and cosmetic use, minimizing side effects, for example, allergic reactions, making them more precise and effective in delivering active ingredients. This study aims to develop and investigate the composition of the liposome and the possible interactions between its constituents: lipoid S75, cholesterol, and polyvinylpyrrolidone. Formulations and laboratory analyses were conducted to characterize and maximize the mechanical strength and stability of the liposomes, also assessing the viability of encapsulating medicinal herbs. The thin-film hydration method was used in the formulation of the liposomes. For characterization, instrumental analysis techniques such as mid-infrared spectroscopy, differential scanning calorimetry, dynamic light scattering, field emission scanning electron microscopy, and chemometrics for data optimization were employed. The results show spherical particles at the nanometric scale and good integration between cholesterol, polyvinylpyrrolidone, and the lipid matrix, providing greater stability and strength to the liposomal matrix. Therefore, the formulations developed in this study demonstrated reliability in the control of components as well as the encapsulation of the medicinal herb jambu, enabling the potential for new developments in pharmaceuticals for future therapeutic and cosmetic applications.

1. Introduction

Herbal medicines have been widely recognized as some of the oldest forms of therapeutic intervention, which are documented across diverse cultures and historical periods.[1] The bioactive compounds may be extracted from plant-based sources such as leaves, roots, flowers, and seeds, including alkaloids, flavonoids, and phenolic acids. Depending on plant-based taxonomy, the pharmacological properties can vary significantly, as different plant families and species produce unique bioactive compounds with distinct therapeutic effects. The pharmacological properties may include anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory effects.[2] Among medical herbs, *Acmella oleracea L.* (commonly known as jambu) has kept much attention due to its wide range of applications. This plant is native to the Amazon rainforest and exhibits a broad spectrum of bioactive properties, including pain relief, anti-inflammation, antiflu, digestion, healing, antimutagenic properties,[3] antioxidant properties, vasorelaxation, and wound-healing effects, which have been attributed to its high concentration of flavonoids and other secondary metabolites.[4] The plant's extract is particularly rich in phenolic compounds and flavonoids, which are key contributors to its potent antioxidant activity. Given its pharmacological potential, *Acmella oleracea L.* has garnered increasing attention in evidence-based therapeutic practices as well as for dermatology applications.[5]

Despite its promising medicinal properties, the therapeutic application of *Acmella oleracea L.* extracts faces several challenges, primarily related to their physicochemical instability. Factors such as oxidation, light exposure, and enzymatic degradation can compromise their efficacy and stability, leading to the loss of bioactivity.[6] To address these challenges, encapsulation techniques such as liposomes have gained prominence. Liposomes provide advantages such as improved bioavailability, controlled release, and facilitated targeted delivery, becoming an excellent tool in preserving and optimizing the therapeutic benefits of herbal extracts, making them a versatile tool in pharmaceutical and cosmetic applications. Liposomes are vesicular structures composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic compounds, making them highly effective carriers for bioactive molecules. In addition, the pharmaceutical applications of liposomes include cancer treatment and diagnosis, ocular drug administration, neurological disorders, and Alzheimer's disease treatment, where their ability to cross the blood–brain barrier enables drug delivery to brain cells.[7–9] Recent research has investigated mRNA lipid vesicles used for nucleic acid delivery in the vaccines for COVID-19.[10] Also, applications in the cosmeceutical area, such as sunscreens, vitamins, and essential oils, due to their natural, biodegradable,

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and low toxicity properties. Besides enhancing solubility and permeability, one can administer them dermally, subcutaneously, intravenously, orally, nasally, or transmucosally.[7,11,12]

Liposome structures can be composed of phospholipid vesicles, which can be formed by one or more lipids produced naturally or synthetically.[13,14] Lipids are responsible for the formation of the lipid bilayer and may be associated with other molecules to enhance the membrane's resistance against breakage.[15] Various types of liposomes have been developed, including conventional liposomes, PEGylated liposomes (stealth liposomes), cationic liposomes, immunoliposomes, and stimuli-responsive liposomes, each offering distinct advantages depending on the application.[14] The structural integrity of liposomes can be further optimized through the incorporation of excipients such as cholesterol and polyvinylpyrrolidone (PVP). This study aims to synthesize and characterize stealth liposomes composed of lipoid S75, cholesterol, and PVP for the encapsulation of *Acmella oleracea L*. extract. Cholesterol plays a crucial role in enhancing membrane stability as it allows an increase in mechanical strength[16] and influences drug release profiles in liposomal formulations.[17] PVP acts as a stabilizing agent for the carrier in its amorphous state, minimizing its molecular mobility. This occurs because PVP forms intermolecular interactions (such as hydrogen interactions) with active compounds, serving as efficient steric protectors for liposomes.[18] The phosphatidylcholine-based liposomes enriched with cholesterol and stabilized with polyvinylpyrrolidone (PVP) exhibit advanced features such as biocompatibility, structural integrity, and the ability to encapsulate both hydrophilic and lipophilic compounds. Thus, the physicochemical properties of the liposomes were evaluated using dynamic light scattering (DLS), Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). Although both excipients have been used in liposomal systems, the novelty of this work resides in the detailed structural and thermal characterization of stealth liposomes developed specifically for the stabilization and encapsulation of *Acmella oleracea L*., a medicinal plant that remains scarcely explored in nanocarrier-based systems. In addition, the experimental section is provided in the Supporting Information.

2. Results and Discussions

Due to the spherical approximation inherent in DLS mathematical modeling, accurate determination of liposome morphology is essential for validating DLS results. Therefore, liposome size and shape were evaluated using scanning electron microscopy (Figure 1a,b), corroborating with the spherical shape described in the literature.[19–24] This result allows the correct interpretation of DLS data that is more accurate due to its ability to provide accurate size distribution and particle stability measurements in their natural, hydrated state. The Z-average is an intensity-weighted mean hydrodynamic diameter derived from the first cumulant of the autocorrelation function in DLS measurements, providing a reliable estimate of the overall particle size in relatively monodisperse systems. As shown in the histogram of Figure 1c, the liposomal formulation exhibited a monomodal distribution, with particle sizes ranging from approximately 50 to 300 nm and a calculated Z-average of 153 nm. Liposomes within this size range are widely recognized as ideal for biomedical applications, including drug delivery and cosmetic formulations. In addition, particles between 100 and 200 nm are known to efficiently encapsulate active compounds and promote enhanced cellular uptake and passive accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect.[19] In contrast to SEM, which requires sample drying and coating processes that can alter liposome structure.[17] Thus, Figure 1c shows liposomes hydrodynamic size distribution, polydispersity index (PDI), and zeta potential values measured by DLS. In addition, micrography was collected from a standard liposome made from lipoid S75 used to interpret the changes that will occur by the incorporation of PVP and cholesterol.

The PDI is a quality measurement of particle size distribution and can range from 0 (homogeneous size) to 1 (polydisperse size).[25] Thus, PDI results of 0.18 reveal a liposome dispersion size with uniform distribution, which is essential for ensuring consistent bioavailability and controlled drug release.[25] Zeta potential represents the surface charge of the particle, which influences its stability.[15] The colloidal solution with a zeta potential lower than −30 mV and higher than 30 mV is considered stable.[21,26] The negative value of −49.9 mV indicates strong electrostatic repulsion among particles due to radical charges, such as hydrogen bonds of the second liposomal bilayer. These interactions result in a negative charge on the surface of the liposomes, reducing molecular mobility and increasing the stability of the formulation, which contributes to enhanced colloidal stability and prolonged shelf life.[21]

Figure 2a shows the FTIR spectra changes as a function of cholesterol incorporation in the liposome matrix. The liposome made from lipoid S75 is represented by the spectrum with the black line, which is a reference for further modification. The main spectral contribution can be assigned to the 2923–2853 cm^{-1} stretching of C-H from CH_3 and CH_2 radical, 1376 cm^{-1} symmetric bending of CH_3 and CH_2 radical, 1466 cm^{-1} antisymmetric bending of CH_3 and CH_2 radical, 1736 cm^{-1} symmetric stretching of C═O; 1200 cm^{-1} antisymmetric stretching of P═O and, 1237–1061 cm^{-1} are related to symmetric stretching of PO_2.[27–29] From cholesterol, a vibrational band at 1055 $cm^{-1}$is assigned to ring deformation.[30] In this graphic was also observed a proportional increase at band 1061 cm^{-1} as a function of cholesterol incorporation. A linear fit was made between the 1087 cm^{-3} and 1061 cm^{-3} bands' intensities as a function of cholesterol incorporation, suggesting a strong positive linear relationship between two variables, reinforcing the role of cholesterol in enhancing liposomal membrane rigidity and reducing permeability. The results showed a correlation of $R = 0.9416$ (Figure 2b). In addition, the increase in cholesterol leads to an increase in hydrodynamic size, except for 5% which causes increased uniformity in the hydrodynamic size as well as an increase in the zeta potential value.

Figure 3a shows the change of FTIR spectra as a function of PVP incorporation. The main PVP band is at 1643 cm^{-1}, which

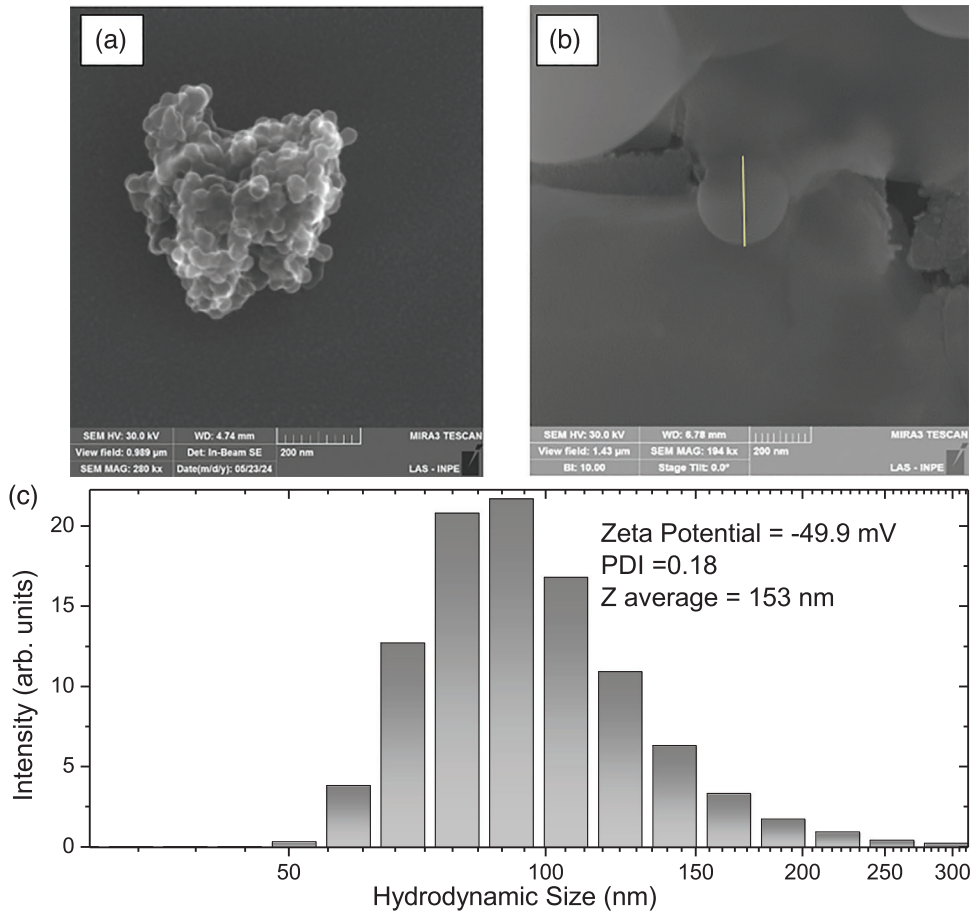

Figure 1. Characterization of raw liposome: a) and b) SEM images showing morphology and spherical shape at different magnifications. c) Hydrodynamic size distribution by DLS, indicating average particle size in aqueous suspension.

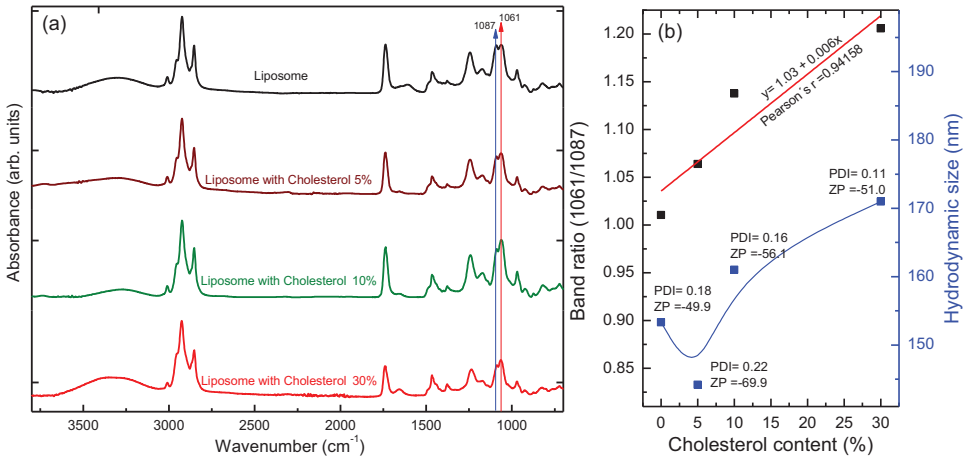

Figure 2. The influence of cholesterol content in the liposome structure: a) FTIR spectra of liposomes with increasing cholesterol content (0%–30%). b) Linear regression analysis of the FTIR band ratio (1061/1087) and hydrodynamic diameter as a function of cholesterol content, indicating structural and size modifications induced by cholesterol incorporation.

is an assignment for symmetric stretching of C=O from the *N*-vinyl pyrrolidone. A shift in the bands was also observed due to the increase in the PVP content added to the liposome. A linear fitting was done based on the band ratio at 1738 and 1652 cm^{-1}, revealing a correlation among the PVP proportions of 1%, 1.5%, 3%, and 4.8%. These data were plotted in Figure 3b, which showed a correlation of $R = 0.9687$, evidencing the incorporation of PVP into the liposomal matrix. The hydrodynamic size also had changes as a function of PVP, overall an increase in size.

At 1%, PVP enhances the liposome stability (ZP = −54.1 mV) and decreases the PDI that is in the range of 0.05–0.2, where particle sizes are very uniform and ideal for many applications

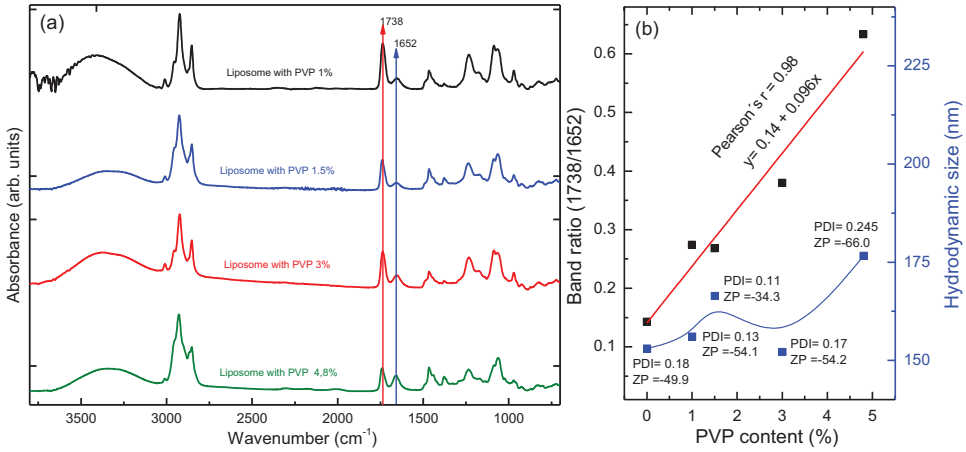

Figure 3. The influence of PVP content in the liposome structure: a) FTIR spectra of liposomes with PVP content ranging from 1.0% to 4.8%. b) Band ratio (1738/1652) with linear fitting (red line) and hydrodynamic size as function as PVP content (%).

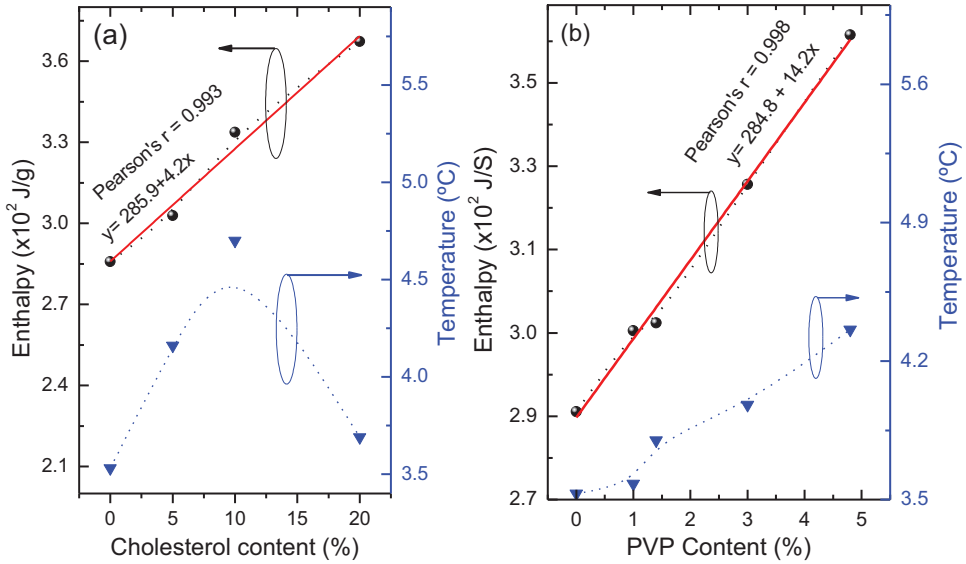

Figure 4. Characterization of liposomes by thermal analysis (DSC): a) enthalpy (black, left axis) and phase transition temperature (blue, right axis) as a function of cholesterol content. b) Enthalpy (black, left axis) and phase transition temperature (blue, right axis) as a function of PVP content. In both graphs, the red line represents a linear fit, with the corresponding function equation and Pearson's r value.

such as drug delivery.[31] The comparison between cholesterol and PVP incorporations shows similar results with an increase in liposome size and zeta potential. Indeed, incorporating cholesterol into liposomes generally increases their size by stabilizing the membrane and reducing fluidity.[32] Also, PVP into liposomes can enhance their stability, biocompatibility, and performance in drug delivery applications.[33] In addition, PVP was added in the hydration process of the thin film during liposome preparation, allowing its interaction with the liposome surface as they form.

Figure 4a depicts the effect of cholesterol on the liposome structure, whereas Figure 4b demonstrates the impact of PVP. The incorporation of cholesterol and PVP in the liposome matrix significantly enhances the structural integrity of the liposomes, which can be explained by the increase in enthalpy values.[34] An increase in enthalpy also indicates a change in the energy associated with the lipid bilayer's phase transitions, and more energy is required to induce the phase transition. Thus, higher enthalpy indicates a more stable or ordered lipid bilayer, which may affect the liposome's permeability, fluidity, and mechanical properties. Also, the vesicle size-dependence has a strong influence on enthalpy, considering that cholesterol and PVP incorporations lead to an increase in size, which corroborates with enthalpy values.[35] For both graphics, there is a strong correlation between enthalpy values as a function of the PVP or cholesterol contents, showing a linear correlation with values of *R* at 0.998 and 0.993, respectively.

The angular coefficient of the linear equation is the first derivative and represents the slope or rate of change of the equation. For cholesterol, the slope is 4.2, whereas for PVP, it is 14.2. This indicates that PVP increases at a much faster rate than cholesterol in the liposome. The accumulation of PVP occurs more rapidly compared to cholesterol, suggesting a higher affinity or incorporation efficiency of PVP in the system. These results suggest that both excipients contribute significantly to membrane stabilization, reducing lipid bilayer fluidity and enhancing the mechanical resilience of the vesicles.[35] However, Figures 2

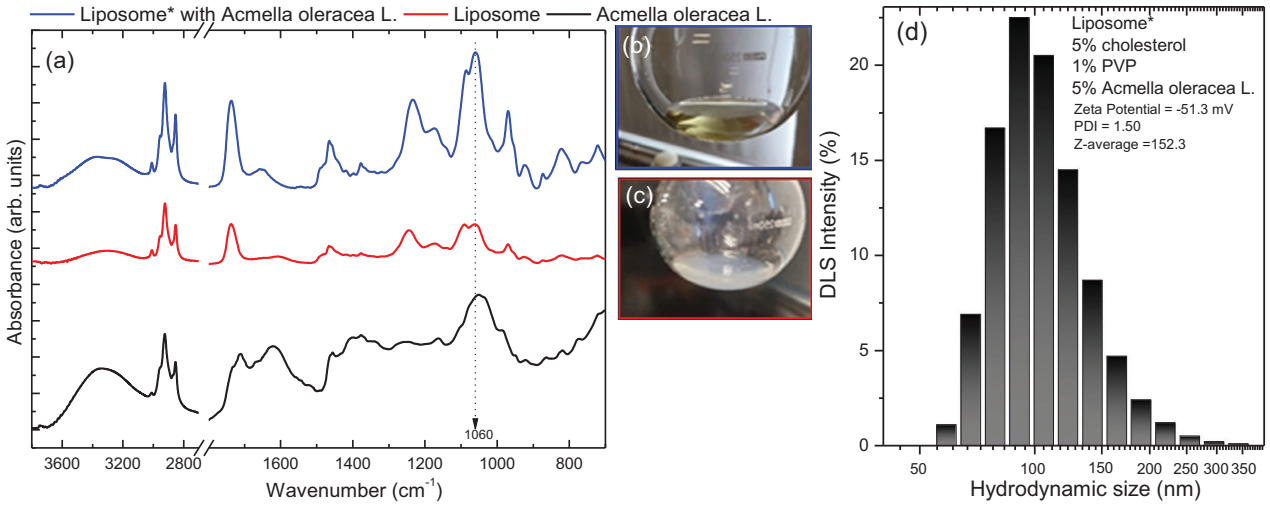

Figure 5. Encapsulation of *Acmella oleracea L*: a) FTIR spectra of individual components. b) Photograph of raw liposome. c) Photograph of liposome loaded with *Acmella oleracea L.* . d) Hydrodynamic size distribution of liposome containing *Acmella oleracea L.*

and 3 have shown that liposome hydrodynamic size is influenced by the incorporation of PVP and cholesterol, as well as nanoparticle uniformity and stability. Indeed, liposomes with a size of ~180 nm loaded with ATP act as an effective transport platform for delivery of drugs to protect ischemic myocardium from the ischemia damage[36] or smaller ones are ideal for use in the treatment of cancer and dermal applications,[37] and maintaining a low PDI is often essential for optimal performance in biomedical and industrial applications.

Among medicinal herbs, *Acmella oleracea L.* is a plant native to the Amazon region commonly known as jambu, with origins in Peru, Brazil, and West Tropical Africa.[4] Studies have demonstrated that jambu leaves possess notable antioxidant effects, primarily attributed to their flavonoid content.[38] Despite their therapeutic potential, herbal extracts are often prone to degradation, particularly during storage, due to factors such as temperature, light exposure, and enzymatic activity, which can compromise their efficacy and stability.[6,39] To address these challenges, encapsulation techniques like liposomes have gained prominence. Indeed, liposomes are widely recognized for their potential to enhance bioavailability, improve controlled release, and facilitate targeted delivery, making them a promising tool for preserving and optimizing the therapeutic properties of herbal extracts.[40] Thus, the results of *Acmella oleracea L.* in liposome are shown in Figure 5.

A visual inspection of the addition of *Acmella oleracea L.* into liposomes shows a change in color, as observed in Figure 5b. The FTIR spectra also confirm the incorporation of medicinal herb, leading to a shift in the stretching bands from 1070 to 1061 cm^{-1}[41] due to the bending of C—O—C and the elongation of C—O—H functional groups (Figure 5a). The parameters set for liposome* were 5% cholesterol, 1% PVP, and 5% of herb extract at 0.3 mg/mL, which has a hydrodynamic size distribution in the nanometric range (Figure 5d). The hydrodynamic size is a monomodal distribution with a Gaussian shape with the highest intensity value below 100 nm with values of PDI very homogeneous.[15] The capsulation efficiency was calculated using the mathematical model approach, which considers that each 1% decrease in ΔH corresponds to approximately 12.2% of active incorporation in systems composed of S75 and cholesterol.[42] In this work, the enthalpy of the empty liposomes was 317.9 J/g, whereas the value after encapsulation of *Acmella oleracea L.* extract was 296.4 J/g, representing a 6.76% reduction. By applying the correction factor ($k = 12.2$), the encapsulation efficiency was approximately 82.5%. According to Barbosa et al., a concentration of 0.33 mg/mL promotes a 63% increase in tyrosinase activity,[43] which is the base for the development of melanogenesis inhibitors.[44] Thus, the concentration of 0.3 mg/mL is the range of potential application, which provided a reference point for selecting a relevant and effective concentration for encapsulation studies.

In addition to its physicochemical performance, the liposome formulation developed here presents important advantages in terms of sustainability when compared to other delivery technologies for herbal compounds. The thin film hydration method is relatively simple and energy-efficient and does not require specialized or high-cost equipment, unlike techniques such as supercritical assisted Liposome formation.[45] Moreover, the materials used in this formulation, including lipoid S75, cholesterol, and PVP, are all biocompatible, commercially available, and economically viable. These characteristics make the method attractive for large-scale production, especially in settings with limited infrastructure or resources.

3. Conclusions

In this study, FTIR, DLS, SEM, and thermal analysis were used to characterize liposomes based on lipoid S75 incorporating PVP and cholesterol. The results showed that cholesterol incorporation strongly correlates with spectral changes (Pearson ~0.94), improving particle size and zeta potential at 5%, whereas PVP enhances stability at 1% with a low PDI (0.05–0.2). Thermal analysis revealed enthalpy changes associated with lipid bilayer stability, with PVP exhibiting a higher rate of incorporation than cholesterol. Additionally, liposomes effectively encapsu-

lated *Acmella oleracea L.*, preserving its antioxidant properties while maintaining a hydrodynamic size below 100 nm, making them suitable for biomedical applications. Moreover, the liposome system and the methodology employed in this study offer potential advantages in terms of sustainability. The use of readily available and biocompatible materials, combined with a relatively low-energy preparation method such as thin-film hydration, contributes to a cost-effective and environmentally friendly approach.

Supporting Information

The Supporting Information contains detailed experimental procedures for the synthesis and characterization of the nanoparticles.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: *Acmella oleracea L* · Lipoid S75 · Liposome

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