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Article

Process optimization of physicochemical properties of spray-dried *Hydrocotyle umbellata* L. extract

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Hydrocotyle umbellata L., Araliaceae, is a species that is recommended in Ayurvedic medicine for its effects on the central nervous system, such as anxiolytic and memory-stimulant effects. Despite the medicinal potential of this species, its phytopharmaceutical and technological potential to produce standardized extracts has not been investigated. This study analyzes the influence of spray drying parameters on the contents of the chemical markers (total phenolic, total flavonoid, and hibalactone) and the functional properties of *H. umbellata* extract. The optimization of drying conditions was performed using a central composite design combined with response surface methodology and desirability function approach. The mathematical models fitted to experimental data indicated that all the evaluated drying parameters significantly influenced the chemical contents. The optimal conditions were: inlet temperature of 120 °C, feed flow rate of 4 mL min^{-1}, and colloidal silicon dioxide:maltodextrin ratio of 16%:4%. Under these conditions, the powder samples had spherical particles and desirable physicochemical and functional properties, such as low water activity and moisture content, good product recovery, reconstitution, and flowability. Thus, spray drying might be a promising technique for processing standardized *H. umbellata* extracts.

Keywords: Anxiety. Medicinal plants. Phytotherapy. Powder properties. Spray drying.

INTRODUCTION

Natural medicines not only fulfill the primary healthcare needs of the majority of the population in developing countries but have also attracted attention in developed countries due to rising healthcare costs (Moreira *et al*., 2014). Studies have shown that many people seek herbal products to treat different types of psychiatric disorders. Some have focused on validating popular medicinal plants with therapeutic applications on central nervous system disorders (Petrovska, 2012).

Hydrocotyle umbellata L., Araliaceae, is a perennial herbaceous plant that is found mainly in the American continent and is well known for its benefits for human health. It is also recommended in Ayurvedic medicine for its anxiolytic and memory-stimulant effects (Rocha *et al*., 2011). A previous study showed the antinociceptive, anti-inflammatory, and anxiolytic effects of its ethanolic

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extract and the lignan hibalactone as a chemical marker of its activities (Oliveira *et al*., 2017). Despite the medicinal potential of *H. umbellata*, few studies have investigated its phytopharmaceutical applications.

Transforming raw herbal material into a product suitable for industrial processing and further therapeutic application is a complex operation that requires specific technologies, including dry plant extracts (Thamkaew, Sjöholm, Galindo, 2021). The production of herbal powders is a promising approach for reducing the costs of packaging, storage, transportation, and curtailment, due to the higher stability of the powder form compared with its liquid counterpart (Rocha, Melo, Radünz, 2011).

The spray drying technique has been successfully employed for these purposes. The small droplets generated by the atomization of the liquid feed increase the surface area in contact with the heated airflow, causing the fast and efficient evaporation of the solvent (Gallo, Bucalá, 2019). Due to its remarkable operational flexibility, spray drying offers accurate control over powder particles and optimizes its properties. The demand for spray-dried herbal powders has considerably increased due to the multiple benefits of the application of these products on a variety of pharmaceutical formulations (Grasmeijer *et al*., 2013).

On the other hand, the physicochemical properties of the powder depend on the parameters of the spray drying process, such as inlet temperature, feed flow rate, and the type and concentration of the carrier agent (Gunjal, Shirolkar, 2020). Thus, the process must be optimized to obtain products with the desired chemical and functional characteristics and drying performance. Accordingly, multivariate statistical analyses, such as response surface methodology (RSM), have been used to assess the impact of the processing factors and to optimize the drying conditions (Patil, Chauhan, Singh, 2014).

To advance the development of phytopharmaceutical products with this species, this study investigated the possibility of producing standardized dried *H. umbellata* extracts with optimized properties through spray drying. The RSM was employed to evaluate the influence of process variables on the analyzed responses (chemical markers). The desirability function approach was used to identify the optimal conditions for all significant responses.

MATERIAL AND METHODS

Herbal material

Samples of subterranean *H. umbellata* parts were collected in Hidrolândia, GO, Brazil, at 16°54'01.0''S and 49°15'32.5''W. The plant material was identified at the herbarium of the Federal University of Goiás, where a voucher specimen was deposited (UFG-22394). The material was washed with water, desiccated at 40 °C, and ground in a Willye mill. The powder was protected from light and moisture.

Feed extract

The hydroethanolic feed extract was obtained through percolation of the powdered herbal material using ethanol and water (70:30 w/w) as the solvent at a plant to solvent ratio of 1:5 kg L^{-1}. After a pre-swelling period of 2 h, the material was transferred into a 10 L percolator. The material remained in contact with the solvent for 24 h in an intermediate maceration stage. Then, it was exhaustively extracted (0.2 mL min^{-1}) at room temperature. The extract was concentrated in a rotary evaporator at 40 °C and stored in closed flasks protected from light at −2 °C before the characterization and further use in the drying experiments.

The density and pH were measured according to the Brazilian Pharmacopoeia (Brazil, 2019). The total solids content was measured with a halogen moisture analyzer (MB 45, Ohaus Co., Pine Brook, NJ). The viscosity was measured with a viscometer (DV-III+, Brookfield Engineering Laboratories Inc., Middleboro, MA). All of these measurements were performed in triplicate.

Quantification of total phenolic and total flavonoid content

The total phenolic content (TPc) was measured in triplicate according to Mole and Waterman (1987). For this purpose, 1 mL of *H. umbellata* extract was dissolved in 5 mL of ethanol 70% in a volumetric flask. Ferric chloride was added to the extract under alkaline conditions to result in a colored complex with phenols. After the solution had

rested for 30 minutes, the absorbance was measured at 510 nm with a digital spectrophotometer (Biospectro®, Curitiba, Brazil). The standard curve was constructed with tannic acid 98% (Sigma-Aldrich Brasil Ltda., São Paulo, Brazil) dissolved in 50% (v/v) methanol and diluted to 0.05, 0.10, 0.15, 0.20, 0.25, and 0.30 mg.mL^{-1}. The total flavonoid content (TFc) was determined in triplicate following the method by Rolim *et al*. (2005). To do so, 50 µL of *H. umbellata* extract was dissolved in 5 mL of ethanol 70% in a volumetric flask. The absorbance was measured at 361 nm with a digital spectrophotometer (Biospectro®, Curitiba, Brazil). The standard curve was constructed with rutin 95% (Sigma-Aldrich Brasil Ltda., São Paulo, Brazil) dissolved in a 0.02 M methanol:acetic acid (99:1) solution and diluted to 0.01, 0.015, 0.02, 0.025, 0.03, and 0.035 mg.mL^{-1}.

Quantification of hibalactone

The quantification of hibalactone was done through high-performance liquid chromatography (HPLC) using the chromatographic conditions established by De Oliveira et al. (2019). The Waters HPLC Alliance system (e2695 separation module, 2998 photodiode array detector (PDA)) and the Empower software (version 2.0) were used. Chromatographic separations were performed using a Zorbax Eclipse XDB-C18 reverse phase column (250 mm × 4.6 mm, 5 µm). The column oven temperature was maintained at 25 °C, the injection volume was 10 µl, the mobile phase was acetonitrile/methanol/water (10:65:25), the detection wavelength was 290 nm, and the flow rate was 0.8 ml min^{-1}. The hibalactone content (Hc) was measured by comparing it with the standard (isolated hibalactone, 93% purity) obtained in our previous study (De Oliveira *et al*., 2019). Stock solutions of the standard were prepared in the range of 25–200 µg mL^{-1}. The mean of the three calibration curves and the equation resulting from the linear regression were used to measure the Hc. The method followed the Brazilian Health Regulatory Agency guidelines (data not shown) (Brazil, 2017).

Spray drying

The drying processes were performed in a spray dryer (LM MSD 1.0 Labmaq) with a concurrent flow regime and a pneumatic (two-fluid) spray nozzle with an inlet orifice diameter of 1.2 mm and air pressure fixed at 60 psi. The outlet temperature varied between 52 and 71 °C. The spray-dried extracts were collected from the dryer outlet, weighed, and stored at room temperature in closed flasks protected from light and humidity before the characterization.

Previous assays for spray drying optimization

Based on Navarro-Flores *et al*. (2020), the influence of the following parameters on the production of spray-dried extracts was investigated: inlet temperature (IT) of 100–120 °C, extract feed rate (EF) of 2-6 mL min^{-1}, and spray nozzle air flow rate (SA) of 30–50 L min^{-1}. Maltodextrin with a dextrose equivalent (DE) 4.0–7.0 (Sigma-Aldrich, Saint Louis, Missouri, USA) was added to the extracts at the proportion of 20% of the solids content. The experiments were carried out following the Box–Behnken design (BBD) combined with the response surface methodology (RSM). The conditions that provided the highest contents of chemical markers (TPc, TFc, and Hc) formed the basis for the optimization design.

Experimental design

Based on the information obtained from BBD, a central composite design (CCD) combined with RSM was employed to optimize the drying conditions. The CCD contains a fractional factorial design with centerpoints and a group of axial points which establish new extremes for the low and high settings of all factors (Fukuda *et al*., 2018). The following factors were studied: IT (X_1), EF (X_2), and Aerosil® 200 (colloidal silicon dioxide; Sigma-Aldrich, Saint Louis, Missouri, USA) and Maltodextrin DE at a ratio of 4.0–7.0 (A:M, X_3), as shown in Table I. The spray nozzle air flow rate was fixed at 50 L min^{-1}. The complete design consisted of 8 factorial points, 6 axial points, and 3 central points, carried out in random order. A second-order polynomial regression model (Eq. 1) was used to express the contents of the chemical markers as a function of the independent variables.

TABLE I - Levels of each variable in the central composite design (CCD)

Symbols	Independent variables	Levels				
		- α	**-1**	**0**	**+1**	**+α**
X_1	Drying air temperature (°C)	93.2	100	110	120	126.8
X_2	Extract feed rate (mL min^{-1})	1.32	2	3	4	4.7
X_3	Aerosil:Maltodextrin ratio (%)	0:20	4:16	10:10	16:4	20:0

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X^2{}_i + \sum\sum \beta_{ij} X_i X_j \quad (1)$$

Where y is the predicted response (chemical marker content), β_0 is a constant, and βi, βii, and βij are the linear, quadratic, and interactive coefficients of the model, respectively. Accordingly, *xi* and *xj* represent the independent variables. The statistical analyses were conducted using the software Statistica, version 7.0.

To obtain the best values for responses analyzed simultaneously, the desirability function approach was employed. Derringer's approach consists of converting each response (*y*k) into individual desirability (*d*k). The desirability scale ranges from 0 to 1, where, if the response is outside an acceptable region, *d*k is set to 0, and, if the response is fully desirable, *d*k is set to 1. The scoring weight was 3.0 for Hc and 1.0 for TPc and TFc. The individual desirability functions from the analyzed responses were then combined to obtain the overall desirability D (Eq. 2), which is the geometric average of the individual desirability values.

$$D = (d_1, d_2, \ldots, d_k)^{\frac{1}{k}} \quad (2)$$

The *D* value ranges from 0 to 1. A high D value is regarded as the best solution for the system (Costa, Lourenço, Pereira, 2011).

Assessment of the physicochemical properties of the spray-dried extract

Chemical marker content

The TPc and TFc were measured according to Mole and Waterman (1987) and Rolim *et al*. (2005), respectively. To measure the TPc and TFc, respectively, 100 mg and 10 mg of dried extract were dissolved in 5 mL of ethanol 70% in a volumetric flask. The Hc was measured according to De Oliveira *et al*. (2019). To do so, 100 mg of dried extract was dissolved in 5 mL of methanol. After the RSM and desirability function analysis, the spray-dried extract with the optimal chemical marker content was selected to assess the following properties.

Powder recovery

The process yield (PY) was calculated immediately after the drying experiments, based on the ratio of the mass of the powder (dry basis) in the flask (W) to the extract's mass flow rate (WE) and solids content (CS, %), as shown in Eq. 3.

$$PY\ (\%) = \frac{W}{W_E\ x\ C_S}\ x\ 100 \quad (3)$$

Moisture content

The moisture content was measured in triplicate with an MB 35 halogen lamp analyzer (Ohaus Inc., Pine

Brook, NJ, USA). To do so, 1 g of powder was submitted to a heat of 105 °C until the mass remained constant.

Water activity

The water activity was measured in triplicate using a thermo-hygrometer (AquaLab PRE Cap) and a hermetic chamber with 0.5 g of powder.

Flow properties

The bulk (ρ_b, g mL^{-1}) density, tapped (ρ_t, g mL^{-1}) density, Hausner ratio (HR), and Carr's compressibility index (CI, %) were measured according to the methods described in the United States Pharmacopeia (United States, 2008). The ρ_b was determined by pouring 1.5 g of dry powder into a 10 mL graduated cylinder and measuring its volume. The ρ_t was determined through the controlled tapping of the cylinder using a sieve shaker (Bertel Ltda, Caieiras, SP, Brazil) until the volume was constant. The HR and CI were calculated using Eq. 4 and Eq. 5, respectively.

$$HR = \frac{\rho_t}{\rho_b} \quad (4)$$

$$CI(\%) = \frac{\rho_t - \rho_b}{\rho_t} x\ 100 \quad (5)$$

The angles of repose (θ°) were measured according to the method described by Araújo, Teixeira, and Freitas (2010). All of these measurements were done in triplicate.

Water solubility

The water solubility was measured in triplicate according to Cano-Chauca *et al.* (2005). To do so, 100 mg of powder was added into a Falcon tube containing 10 mL of distilled water and centrifuged at 1000 rpm for 5 min. Then, the supernatant was transferred to pre-weighed Petri dishes and oven-dried at 105 °C until the weight was constant. The solubility (%) was calculated according to the percentage of dried supernatant in relation to the amount of powder initially added.

Dispersibility

The dispersibility was measured in triplicate according to the A/S Niro Atomizer method (GEA Niro, 1978). To do so, 1 g of powder was added to a beaker containing 10 mL of distilled water. The sample was then stirred vigorously with a spoon for 15 s, making 25 complete movements back and forth across the whole diameter of the beaker. Next, the reconstituted powder was passed through a 250 μm Tyler sieve into a pre-weighed Petri dish and dried until the weight was constant. Dispersibility was calculated using Eq. 6.

$$Dispersibility = \frac{[(10+a)\ x\ TS]}{a\ x\ (100-b)/100} \quad (6)$$

In Eq. 6, *a* is the amount of powder (g) taken, *b* is the moisture content of the powder, and TS (%) is the percentage of dry matter in the reconstituted powder after it has been passed through the sieve.

Wettability

The wettability was measured in triplicate according to Fuchs *et al.* (2006). To do so, 100 mg of powder was sprinkled over the surface of 100 mL of distilled water in a beaker without agitation. The time, in seconds, taken until the last powder particles submerged was recorded.

Powder size distribution

The powder size distribution was performed in triplicate according to the method described in the Brazilian Pharmacopoeia (Brazil, 2019). Briefly, 25 g of the powder was sieved through standardized and superimposed Bertel® sieves (125, 180, 250, 355, and 710 mesh) for 15 min with proper vibration. Then, the

powders were weighed, and the percentage held in each sieve was calculated.

Scanning electron microscopy (SEM)

The morphology of the spray-dried powders was evaluated using a scanning electron microscope (JEOL, JSM – 6610) equipped with energy-dispersive X-ray spectroscopy (Thermo Scientific NSS Spectral Imaging). Before the SEM analysis, the sample was put on a metal stub with double-sided adhesive tape and then recovered with a gold layer of 200 Å thickness in a vacuum using a metallisator (Denton Vacuum, Desk V). Photomicrographs with magnifications of 500×, 1,500×, and 3,000× were recorded at 5 kV. The images were analyzed using the software Scandium, version 5.1.

Thermal analysis

Thermogravimetry (TG) and differential scanning calorimetry (DSC) analyses were performed in a DTG-60H and a DCS-60 system (Shimadzu, Japan), respectively. The analyses of dried extracts were conducted at a heating rate of 10 °C min^{-1} at the temperature range of 25–600 °C, using alumina crucibles, 2.8 mg of TG, and 2.5 mg of DSC. The experiments were carried out under a nitrogen atmosphere at a flow rate of 50 mL min^{-1}.

RESULTS AND DISCUSSION

Characterization of the feed extract

The concentrated hydroethanolic extract presented a density of 0.967 g mL^{-1}, pH of 6.02, solids content of 12%, and viscosity of 1.63 mPa. The levels of TPc, TFc, and Hc were 3.15%, 1.40%, and 0.09 %, respectively. In the spray drying process, the characteristics of the dried particles depend on the features of the atomized droplets. Therefore, assessing the properties of the feed extract is essential to verify the stability and standardization of the obtained dried extracts. However, from a phytopharmaceutical technology perspective, producing a standardized extract with the desired bioactive compounds for therapeutic applications is a great challenge (Coimbra, Cardoso, Gonçalves, 2020). Thus, the contents of the chemical markers (TPc, TFc, and Hc) were used as physicochemical parameters to assess the quality of the obtained dried extracts.

Effects of the drying parameters on the contents of the chemical markers

The screening of the main parameters affecting the TPc, TFc, and Hc in the drying process indicated significant linear and quadratic effects of *IT* in the range of 100–120 °C, *EF* in the range of 2–6 mL min^{-1}, and *SA* in the range of 30–50 L min^{-1}.

It is well established that the addition of carrier agents to the liquid feed improves the drying of sticky products, increases the drying yield, and reduces the moisture content of spray-dried products (Gallo, Bucalá, 2019). However, dried extracts with high hygroscopicity were obtained in the preliminary drying experiments, even using maltodextrin as a carrier agent, which is considered a polysaccharide with a low hygroscopic character. Moreover, maltodextrin was used with a DE value of 4.0–7.0. The amount of low sugar content is defined by the DE value. It has been reported that lower DE values are related to the low hygroscopic character of maltodextrin, since the contact surface is decreased (Castro *et al*., 2016).

To reduce the hygroscopicity of dried extracts, colloidal silicon dioxide (Aerosil® 200) was included as a carrier agent, which is considered suitable for hygroscopic powders (Charoo, 2020). The experimental design of CCD with colloidal silicon dioxide yielded low hygroscopic powders, which suggests that, combined with maltodextrin, it reduces the hygroscopicity of the powders. Similar findings were shown in spray-dried *Rhamnus purshiana* D.C. bark extract and *Physalis peruviana* L. fruit extract reported by Gallo *et al.* (2011) and Bernal, Ramos, and Baena (2019), respectively, where increasing the concentration of colloidal silicon dioxide decreased the hygroscopicity of powders.

Table II presents the data of chemical marker contents from the 17 experiments generated by the CCD design. The conditions for experiment 8 provided the highest Hc, TFc, and TPc, which were optimized

by the desirability approach. The influence of process factors on chemical marker contents was evaluated by ANOVA, and Table III shows a summary of their effects on interactions and their significance. Table IV presents the fitted equation obtained for TPc, TFc, and Hc with the correlation coefficients.

TABLE II - Central composite design (CCD) for spray drying parameters and the response of chemical marker contents

Run	IT (°C)	EF (mL min^{-1})	A:M (%)	TPc (%)	TFc (%)	Hc (%)
1	100	2	4:16	1.970	1.272	0.055
2	120	2	4:16	1.755	1.240	0.019
3	100	4	4:16	1.901	1.256	0.048
4	120	4	4:16	1.839	1.330	0.032
5	100	2	16:4	3.016	1.442	0.084
6	120	2	16:4	2.889	1.769	0.153
7	100	4	16:4	3.360	1.485	0.113
8	120	4	16:4	2.881	1.813	0.189
9	93.182	3	10:10	2.419	1.211	0.080
10	126.817	3	10:10	2.493	1.441	0.080
11	110	1.318	10:10	2.503	1.416	0.108
12	110	4.681	10:10	3.080	1.354	0.099
13	110	3	0:20	1.515	1.290	0.093
14	110	3	20:0	3.597	1.702	0.123
15	110	3	10:10	2.563	1.333	0.118
16	110	3	10:10	2.694	1.330	0.107
17	110	3	10:10	2.671	1.345	0.111

TABLE III - Summary of factor effects and significance (*p*) on spray-dried extract

Factor	TPc	TFc	Hc
Linear			
IT	ns	0.0001*	ns
EF	0.0498*	ns	ns
A:M	< 0.0001*	< 0.0001*	0.0952**
Quadratic			
IT^2	0.0745**	ns	0.0083*
EF^2	ns	ns	Ns
$A:M^2$	ns	0.0015*	Ns

TABLE III - Summary of factor effects and significance (*p*) on spray-dried extract

Factor	TPc	TFc	Hc
Interactions			
IT x EF	ns	ns	Ns
IT x A:M	ns	0.0013*	0.0011*
EF x A:M	ns	ns	0.0981**

Significant at: *5% and **10%; ns: not significant.

TABLE IV - Fitted equations and correlation coefficients (r) of the chemical marker contents of the spray-dried extract

Equations	r
TPc= 2.61 - 0.056*IT* + 0.097*EF* + 0.60*A:M* - 0.089*IT*²	0.941
TFc= 1.37 + 0.079*IT* + 0.15*A:M* + 0.077*IT x A:M* + 0.060*A:M*²	0.940
Hc= 0.11 - 0.000008027*IT* – 0.002893*EF* + 0.008949*A:M* + 0.003446*IT* x *EF* + 0.025*IT x A:M* + 0.007371*EF x A:M* - 0.012*IT*² - 0.004119*EF*² + 0.012*IT*² *x EF* + 0.039*IT*² *x A:M* + 0.012*IT x EF*²	0.981

Concerning TPc, the factors *EF*, *A:M,* and *IT*² showed significant effects. The interactions of the factors did not show a significant influence on TPc. Regarding TFc, the factors *IT*, *A:M*, *A:M*², and the interactive effects between *IT* x *A:M* were significant. As for Hc, the factors *A:M*, *IT*², and the interactive effects between *IT* x *A:M* and *EF* x *A:M* were significant. Figure 1A–B shows the surface response plot for TFc and Hc as a function of *IT* and *A:M*. The plot shows that higher levels of *IT* (120 °C) can increase the levels of TFc and Hc, which are also associated with higher levels of *A:M* (16%:4%).

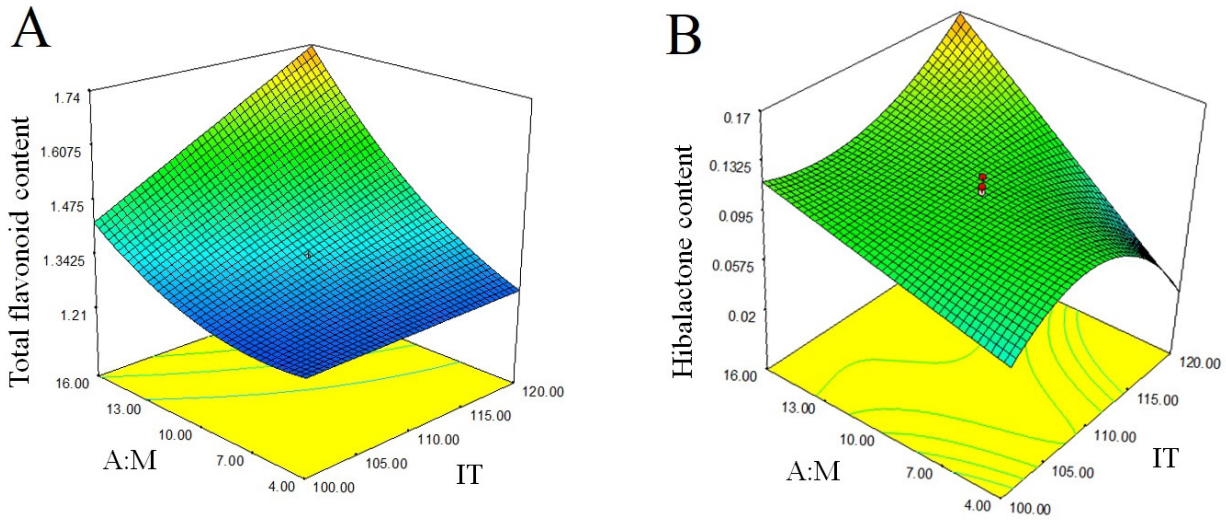

FIGURE 1 - Surface plot of total flavonoid content (TFc) (A) and hibalactone content (Hc) (B) as a function of inlet temperature (IT) and Aerosil® 200: Maltodextrin DE 4.0-7.0 ratio (A:M).

However, some drying conditions resulted in decreased levels of chemical markers (Table II), which might be caused by thermal degradation. The TPc, TFc, and Hc ranged from 1.515 to 3.597%, 1.211 to 1.813%, and 0.019 to 0.189%, respectively. These values have degradation ratios ranging from 2.222% to 51.904%, 3.285% to 13.500%, and 6.670% to 78.890%, respectively.

One of the most important elements of a spray drying system is air temperature. This variable is directly related to mass and heat transfer. It might promote fast evaporation, a rapid crust formation, and, in the case of thermo-sensitive compounds, it might lead to either the preservation or degradation of these compounds (Gallo, Bucalá, 2019). Some studies have analyzed the effect of temperature on the retention of bioactive compounds during the drying process (Teles *et al*., 2018; Özdikicierler, Dirim, Pazır, 2019; Dao *et al*., 2021).

In this study, the possible effect of high air temperature on the reduction of chemical marker contents was observed mainly when a lower ratio of A:M was used, suggesting that a higher ratio of A:M (16:4) was more efficient in preserving the chemical markers. This might be related to the film-forming capacity and plastic properties of the carrier agents. The higher retention of compounds provided by colloidal silicon dioxide compared with maltodextrin was also verified by Georgetti *et al.* (2008). Moreover, the higher feed flow rate (4 mL min^{-1}) might decrease the exposure of compounds to high temperatures.

The feed flow rate relies on the speed of the atomizer. A higher pump speed causes a higher feed flow rate. Under this condition, the extract inside the drying chamber achieves lower temperatures, and the occurrence of degradation reactions probably decreases (Gallo, Bucalá, 2019). Similarly, with the spray-dried extract of *Bidens pilosa* L. (Cortés-Rojas, Souza, Oliveira, 2015) and *Myracrodruon urundeuva* Allemão (Leite *et al*., 2017), the increase in extract feed rate promoted higher concentrations of bioactive compounds.

Based on the RSM analysis and the desirability optimization approaches, the best spray drying conditions were determined (theoretically optimal conditions): inlet temperature of 120 °C, feed flow rate of 4 mL min^{-1}, and colloidal silicon dioxide:maltodextrin ratio of 16%:4%. Under these conditions, the values predicted for TPc, TFc, and Hc were 3.163%, 1.736%, and 0.195%, respectively. The independent experiments, conducted in triplicate, resulted in an average of TPc, TFc, and Hc of 3.052%, 1.701%, and 0.191%, respectively, which corresponds to 96.49%, 97.98%, and 97.94% of the predicted value, respectively, demonstrating that the model was appropriate to predict the data.

Physicochemical properties of the optimized spray-dried extract

In addition to quality control, evaluating the functional properties of chemical markers is essential for a better characterization of pharmaceutical powder technologies and processes. Table V presents a summary of the results of chemical marker contents, powder recovery, moisture content, water activity, flow properties, water solubility, wettability, dispersibility, mean powder size, and mean particle length of the optimized spray-dried extract.

TABLE V - Physicochemical properties of the spray-dried *H. umbellata* extract

Property	Result
TPc	3.052%
TFc	1.701%
Hc	0.191%
Powder recovery	75.550%
Moisture content	2.360%
Water activity	0.214
Bulk density	0.440 g mL^{-1}
Tapped density	0.500 g mL^{-1}
Hausner's ratio	1.130
Carr's index	12%
Angle of repose	27°
Water solubility	70%
Dispersibility	73%
Wettability	95 s
Mean powder size	125 µm
Mean particle length	4.670 µm

Powder recovery (yield) might indicate the success and affordability of the process. The high product recovery obtained might be mainly associated with low feed extract viscosity and the carrier agents' properties, leading to a low adherence of powders on the drying chamber and cyclone walls (Maury *et al*., 2005).

The obtained low moisture content (< 5%) and water activity (< 0.5), which might be related to the effects of high air temperature and the carrier agents' properties, increase powdered products' resistance to microbiological and oxidative degradation, enhancing their stability during packaging and storage. Moreover, it might indicate the efficiency of the drying process (Ribeiro, Da Costa, Afonso, 2019).

The rheological properties of the dried extract were also evaluated to contribute to its further manufacturing by applying specific unit operations, such as granulation, tableting, and capsule filling. The HR, CI, and angle of repose were used to estimate the compressibility and flowability (cohesiveness) characteristics of the dried powders. The obtained HR (< 1.25) might indicate non-cohesive and low internal friction powders. The obtained CI (11% < CI < 15%) might predict good flowing properties (Shah, Tawakkul, Khan, 2008). Moreover, the obtained angle of repose ($25° < \theta° < 40°$) might indicate that the cohesiveness of the powder is within the acceptable limit according to the pharmaceutical needs (Geldart *et al*., 2006). Colloidal silicon dioxide has been reported as an effective carrier agent for improving the flow properties of spray-dried extracts (Majerová *et al*., 2016).

The obtained small powder size and particle length might contribute to the solubility of the powders, due to the increased surface area interacting with the surrounding solvent during dissolution. Solubility, dispersibility, and wettability are related to the reconstitution behavior of spray-dried products (Fang *et al*., 2007). Although the literature has reported that higher levels of maltodextrin afforded better values of these characteristics, compared with colloidal silicon dioxide (Nortuy, Suthapakti, Utama-ang, 2018), it has been reported that colloidal silicon dioxide is also effective at improving these characteristics (Kamble, Mahadik, 2014).

The morphology of the spray-dried extract particles analyzed by SEM is shown in Figure 2A–C. The particles were mostly spherical with a rough surface, some cracks, and inter-particle adhesion. The length of the particles varied between 1.05 and 16.19 μm, with a mean length of 4.67 μm. Dried extracts with a rough surface are reported in the literature on colloidal silicon dioxide (Mokale *et al*., 2020). Moreover, high drying temperatures could cause cracks on the surface of particles due to the rapid formation of a crust on the surface of droplets (Boel *et al*., 2020). The presence of irregularities on the surface of the dried extract might have partially contributed to the degradation levels observed in the chemical markers in the drying process, which might be caused by the higher exposure of compounds to thermal degradation.

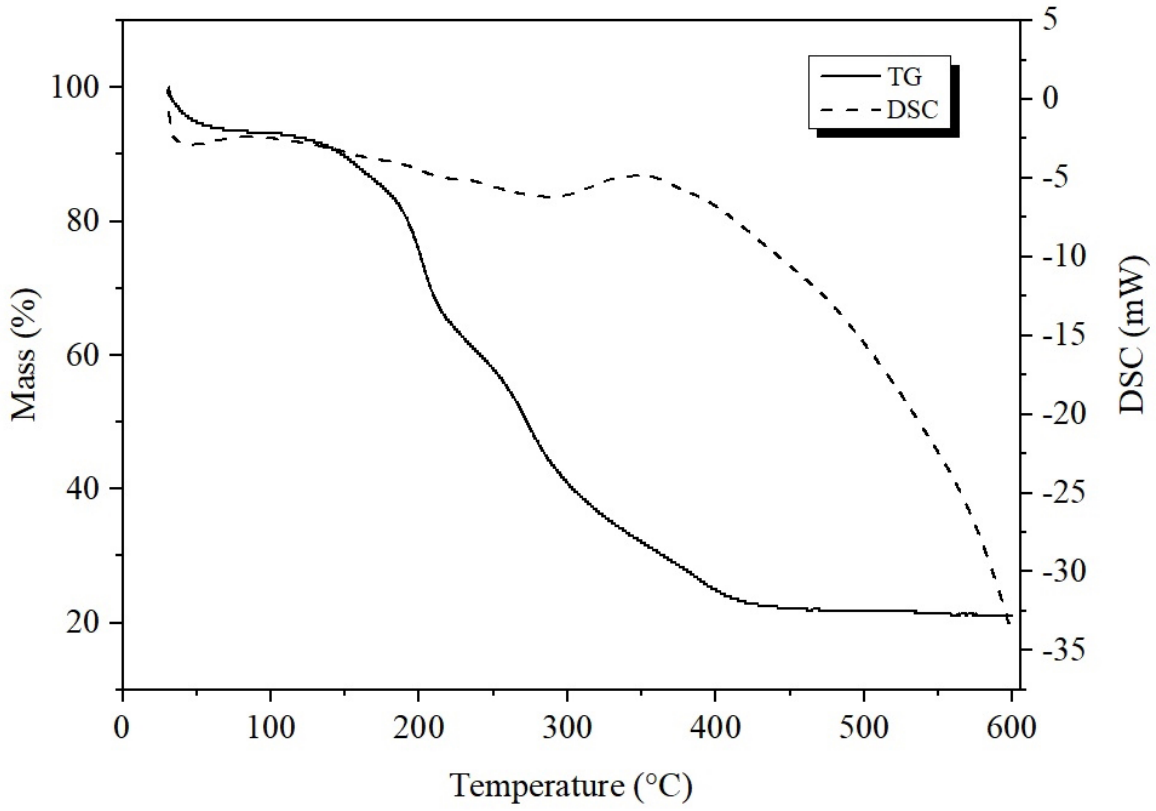

FIGURE 2 - Scanning electron microscopy (SEM) micrographs of the spray-dried *H. umbellata* extract. The images correspond to magnifications of ×500 (A), ×1500 (B), and ×3000 (C).

The thermal analysis indicated that the higher thermal stability of the dried extract occurred until approximately 120 °C, as observed in the TG curve (Figure 3), which corresponds to the highest inlet temperature used in drying experiments. The mass loss until that temperature, which was approximately 7%, might be attributed to water extract dehydration and loss of other volatile constituents (De Andrade *et al*., 2019). From the onset temperature, at 150 °C, a great mass loss was observed and proceeded further until 420 °C, leaving approximately 20% of the residual mass.

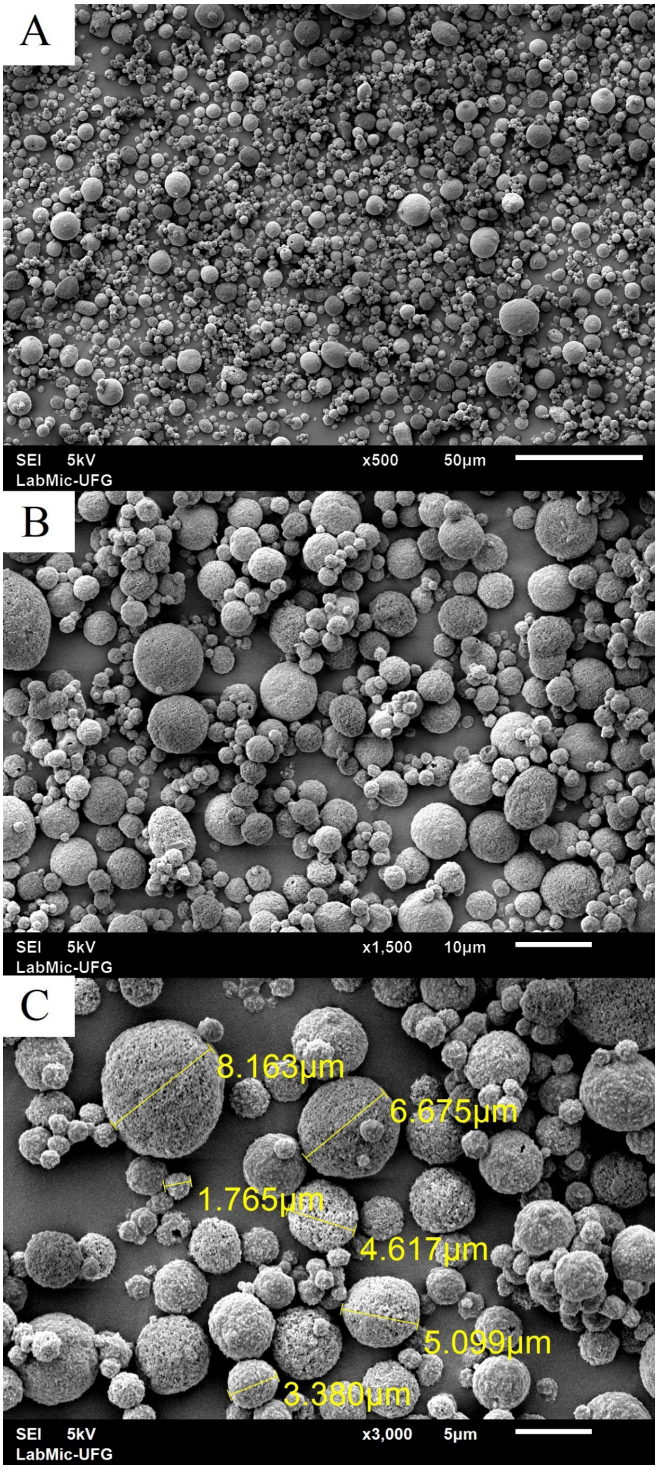

FIGURE 3 - Thermogravimetry (TG) and differential scanning calorimetry (DSC) curves of the spray-dried *H. umbellata* extract.

The main exothermic event started at 280 °C and had a maximum peak temperature of 330 °C, as shown in the DSC curve (Figure 3). It may represent the beginning of the main organic matter decomposition of the sample, probably due to the degradation of the complex formed between extract and maltodextrin, as suggested by the literature (Hijo *et al*., 2017). Similar thermal behavior was found for *Curcuma zerumbet* Roxb. (Zingiberaceae)

rhizome extracts (Castro *et al*., 2018). More studies should be carried out to improve the thermal stability of the spray-dried extract obtained in this study, including a better evaluation of other carrier agents to better preserve its chemical marker contents.

CONCLUSION

This study demonstrated the influence of spray-drying parameters on the preparation of standardized spray-dried *H. umbellata* extracts. The optimal conditions for obtaining optimized chemical marker contents were an inlet temperature of 120 °C, a feed flow rate of 4 mL min^{-1}, and a colloidal silicon dioxide:maltodextrin ratio of 16%:4%. Moreover, these conditions provided powders with spherical particles and desirable physicochemical and functional properties, such as low water activity and moisture content, good product recovery, reconstitution, and flowability. However, the improvement of its thermal stability is still necessary. Thus, our results reveal the technological potential of *H. umbellata,* indicate that spray drying is an attractive and promising technology for manufacturing products of this species in the pharmaceutical sector, and support future industrial process scale-up studies.

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