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Spray drying of *Eugenia dysenterica* extract: effects of in-process parameters on product quality

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Abstract: A 2^3 full factorial design was used to assess the impact of spraying air flow rate (30-50 L/min), drying air inlet temperature (90-150 ºC) and extract feed rate (4-6 g/min) on the quality of *Eugenia dysenteric*a DC., Myrtaceae, spray-dried extracts. Response surface methodology (RSM) was applied to analyze the significance of the effects of process factors on product quality and to obtain fitted equations to predict dry powder properties. Powder yields were satisfactory, ranging from 34.64 to 63.92%. The dried products showed moisture contents and water activities below 5% and 0.5, respectively. The recuperation ratios of total polyphenols, tannins and flavonoids ranged from 88.66 to 99.07%, 70.38 to 81.87% and 74.51 to 98.68%, respectively. Additionally, in some conditions the parameters related to dry product's flowability and compressibility varied over a range acceptable for pharmaceutical purposes. RSM proved that studied factors significantly affected most of the quality indicators at different levels. The spray drying technology is an attractive and promising alternative for the development of intermediate phytopharmaceutical products of *E. dysenterica.*

Article

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Introduction

A vast interest on the development of phytotherapics with proven efficacy, safety and quality has been recently demonstrated in Brazil (Rocha et al., 2008; Bueno & Bastos, 2009). From a phytopharmaceutical technology point of view, the drying of plant extracts is a crucial step to achieve a product suitable for industrial use and further therapeutic application (List & Schmidt, 1989). Within the widely used drying techniques, spray drying is the most commonly employed in the phytopharmaceutical industries (Georgetti et al., 2008).

Regarding industrial purposes, spray drying presents several advantages over the other drying technologies, such as operational flexibility, applicability for heat sensitive materials and affordability (Filková et al., 2007). Similarly, spray-dried extracts have a broad range of advantages over liquid forms, presenting a high stability and being easier to handle, standardize, transport and store (Oliveira et al., 2006). Furthermore, if these extracts were engineered with optimized properties, it is possible to manufacture solid dosage forms from it, which represents most of the medicines used worldwide (De Souza et al., 2006; Chaves et al., 2009). In this context, optimization statistical tools such as Response Surface Methodology (RSM) has being successfully applied in understanding the relationship between spray drying parameters and powder properties (Vasconcelos et al., 2005; Marquele et al., 2006; Souza et al., 2007; Jangam & Thorat, 2010; Toneli et al., 2010; Oliveira et al., 2011; Couto et al., 2011; Couto et al., 2012).

Eugenia dysenterica DC., Myrtaceae, commonly known as cagaita, was chosen for this research due to its importance in Brazilian folk medicine, as well as its valuable therapeutic potential described in the literature (Costa et al., 2000; Couto et al, 2009; Lima et al., 2010; De Souza et al., 2011; Lima et al., 2011; Vieira et al., 2012). Despite *E. dysenterica's* medicinal importance, there is a lack of information documenting its behavior during standardization and processing. In this work, RSM was used to investigate the effects of in-process set of conditions on the quality of *E. dysenterica* spray-dried extracts.

Materials and Methods

Chemicals

Rutin (98%) and tannic acid (98%) were purchased from Sigma-Aldrich® (Sigma-Aldrich Co., Steinheim, Germany). All other chemicals were of reagent grade and were used without further purification.

Herbal material

Samples of *Eugenia dysenterica* DC., Myrtaceae, leaves were collected from a specimen located in a region of Cerrado (Brazilian savannah), in Nova América City, State of Goiás, Brazil (674 m, 15º 00' 29,5" South, 49º 59' 00,5" West). Once identified, a voucher specimen was prepared and deposited in the Federal University of Goiás Herbarium under the registration identification FUG-41319. The leaves were dried at room temperature and ground in a knives mill TE-625 (Tecnal Ltda, Piracicaba-SP, Brazil). Powdered material was stored sheltered from light and moisture for subsequent use in the extraction procedure.

Feed extract

The hydroalcoholic *E. dysenterica* extract (HE) was obtained by percolation of the powdered material (mean particle size of 394.77±4.00 µm), using ethanol:water solution (70:30 v/v) as solvent mixture. Briefly, 1 kg of powdered material was placed in contact with 300 mL of solvent into a glass flask. After an incubation period of 2 h (pre-swelling phase), this material was carefully transferred to a 10 L percolator (Revitec Ltda, São Paulo-SP, Brazil) and solvent was added to volume. This system remained in contact with powdered material for 24 h (intermediate maceration phase). Next, it was extracted exhaustively (0.2±0.05 mL/min) at room temperature (percolation phase). The extractor solvent was throughout renewed until an albumin precipitation assay no longer detects tannins. The obtained extract was evaporated at 40±2 ºC using a rotary evaporator MA 120 (Marconi Ltda, Piracicaba-SP, Brazil) coupled to a vacuum pump Te-152 (Tecnal Ltda, Piracicaba-SP, Brazil). The concentrated extract (2 L) was stored in borosilicate flasks protected from light at temperature from -2 to 8 ºC prior to characterization and further use.

Density, alcoholic content and pH were determined according to the methodologies described in the Brazilian Pharmacopoeia (2010). Total solid content of 1.0 g sample was measured with a gravimetric method in a halogen lamp analyzer MB 35 (Ohaus Inc., Pine Brook, NJ, USA). Finally, the viscosity was measured using a viscometer Brookfield model DV-III+ (Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA).

Spray-dryer equipment and methodology

The drying process was performed in a laboratory-scale spray dryer model MSD 1.0 (Labmaq do Brasil Ltda., Ribeirão Preto-SP, Brazil) with concurrent flow regime and a pneumatic (two fluid) spray nozzle with inlet orifice diameter of 1.2 mm. The drying air was supplied by a blower (nominal flow rate of 1.0 m^3/min) and electrically heated. The cylindrical drying chamber was made of borosilicate glass with 160 mm in diameter and 645 mm in height. The following set of conditions was kept fixed for all experiments: nozzle air pressure was 0.4 MPa; mass of extract portion feed (W_E) was 150 g. The products of *E. dysenterica* extract spray drying (SDE) were separated from air by a stainless steel cyclone and collected in a glass flask. The products recovered were weighted, protected from light and stored in closed flasks in a desiccator at room temperature prior to quality determination.

Response surface methodology (RSM)

In the statistical design of experiments, RSM was used to investigate the effect of process variables on various powder properties. Spraying air flow rate (S_A, 30-50 L/min), drying air inlet temperature (IT, 90-150 ºC) and extract feed rate (E_F, 4-6 g/min) were selected as independent variables. Process variables were selected based on preliminary experiments and previous experience of the present research team. The 2^3 full factorial design matrices with coded and non-coded values of each factor studied are shown in Table 1. In Table 1 the factors were coded to allow the Analysis of Variance (ANOVA) by the RSM following the coding rule given by equation (**1**):

$$Coded.value = \frac{(uncode.value - 0.5 \times (high.value + low.value))}{0.5 \times (high.value - low.value)} \quad (1)$$

Table 1. 2^3 full factorial design matrices.

Run	X_1 . S_A	X_2 . IT	X_3 . E_F
1	30 (-1)	90 (-1)	4 (-1)
2	50 (1)	90 (-1)	4 (-1)
3	30 (-1)	150 (1)	4 (-1)
4	50 (1)	150 (1)	4 (-1)
5	30 (-1)	90 (-1)	6 (1)
6	50 (1)	90 (-1)	6 (1)
7	30 (-1)	150 (1)	6 (1)
8	50 (1)	150 (1)	6 (1)
9	40 (0)	120 (0)	5 (0)
10	40 (0)	120 (0)	5 (0)
11	40 (0)	120 (0)	5 (0)

X_i: Coded factors in the experimental design; -1, 0, +1: coded levels in the experimental design; S_A: Spray nozzle airflow rate (L/min); IT: Drying air inlet temperature (ºC); E_F: Extract feed rate (g/min).

The ANOVA/RSM was performed on the experimental data using the module Visual General Linear Model (VGLM) from the software Statistica 7 (Statsoft Inc., Tulsa, OK, USA). Only the factors with significance higher than or equal to 5% ($p \leq 0.05$) were considered. The response function applied was a linear polynomial equation, given by equation (**2**):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 \quad \textbf{(2)}$$

In equation (**2**), Y is the predicted response (dependent variable); β_0 is the model constant; X_1, X_2 and X_3 are independent variables; β_1, β_2 and β_3 are linear coefficients; and β_{12}, β_{13} and β_{23} are cross product coefficients.

Dry product quality determination

Process yield (P_Y, % w/w), or powder recovery, was calculated immediately after the drying experiments based on ratio of the powder mass (dry basis) collected in the flask (W) to the portion of the extract feed mass (W_E = 150 g) and its solid content (C_S, % w.b.) by equation (**3**).

$$P_Y = \frac{W}{W_E \times C_S} \times 100 \quad \textbf{(3)}$$

The powder moisture content (M_C, % w.b.) was measured from 0.5 g of sample employing a halogen lamp analyzer MB 35 (Ohaus Inc., Pine Brook, NJ, USA). Water activities (A_W) were measured using a thermo hygrometer Testo 650 (Testo AG, Lenzkirch, Germany) and a hermetic chamber.

Total polyphenol content (TP_C) and total tannin content (TT_C) in HE and SDE were determined following previously described methods (Mole & Waterman, 1987a, b), with some modifications. Ten mg (dry basis) of SDE were dissolved in 10 mL of 20% (v/v) methanol solution. HE was directly diluted 100 times with this same solution. In both TP_C and TT_C measurements, tannic acid was used to make the calibration curves.

Total flavonoid content (TF_C) was measured according to a modified method based on Rolim et al. (2005). Ten mg (dry basis) of SDE were dissolved in 10 mL of methanol:acetic acid 0.02 M (99:1). HE was directly diluted 200 times with the methanol:acetic acid 0.02 M (99:1) solution. The absorbances of 2 mL samples were measured at 361 nm with a SP220 UV/VIS spectrophotometer (Biospectro®, Curitiba-PR, Brazil). Rutin was used to make a calibration curve.

Bulk (ρ_b) and tapped (ρ_t) densities, Hausner Ratio (HR) and Carr's Index (CI, %) were determined according to the methods described elsewhere (USP, 2007). The product bulk density was determined by pouring 5 g of dry powder into a 25 mL graduated cylinder and measuring its volume. The tapped density was determined by controlled tapping of cylinder using a sieve shaker (Bertel Ltda, Caieiras-SP, Brazil) until a constant volume was achieved. Hausner Ratio and Carr's Index were used to indicate the compressibility and flowability properties of the powders and were calculated using the measured values of the tapped and the bulk density of the powders, according to their definitions:

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

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \quad \textbf{(5)}$$

The mean powder particles diameter (D50, μm) was measured from the cumulative size distribution, by sieving 20 g of powder with Tyler series sieves (710, 355, 300, 250, 180, 106 and 53 μm) and an electro-magnetic sieve-shaker (Bertel Ltda, Caieiras-SP, Brazil) for 20 min. (Brazilian Pharmacopoeia, 2010). Angles of repose (Θ,°) were determined according to the method described by Araújo et al. (2010). All of the above measurements, except P_Y, were performed in triplicate.

Results and Discussion

Characterization of the HE

The concentrated hydroalcoholic extract presented a density of 1.01±0.001 g/mL, a solids content of 10.69±0.55% (w/w), a pH of 5.003±0.075, an alcoholic content of 15.09±0.02% (v/v) and a viscosity of 6.67±0.14 mPas. The levels of TP_C, TT_C and TF_C were, respectively, 48.38±1.00, 22.12±2.09 and 60.82±4.28% (w/w). Many studies have shown that the nature of the feed material has important effects on the quality of the powder collected from the cyclone. However, these effects are difficult to assess in general terms, mainly due to the specific drying nature of most materials (Goula & Adamopoulos, 2004; Oliveira & Petrovick, 2010). Solids content, viscosity and surface tension of the liquid extract determine the type of particle drying behavior. They are directly correlated with the packaging and flowing properties of the dried powders, since they influence the droplet size and, consequently, the size and shape of the dry particles (Nath & Satpathy, 1998; Walton, 2000; Paramita et al., 2010). Accordingly, evaluation of the feed extract properties is required on experimental planning and, consequently, in obtaining dried products with optimized properties.

The efficiency of Eugenia dysenterica *extract spray drying (SDE)*

As shown in Table 2, P_Y values ranged from 34.64 to 63.92% (w/w). Powder recovery is an important variable to consider because it may indicate the adequacy of the drying parameters. The process yield in the spray drying of herbal extracts has shown to be variable, being dependent on several factors, *e.g.* in-process set of conditions (Souza & Oliveira, 2006; Jangam & Thorat, 2010; Toneli et al., 2010), as well as type, proportion and incorporation time of drying adjuvants in the liquid feed (Vasconcelos et al., 2005; Couto et al., 2011). It is interesting to note that, although the researchers of the present work did not have used drying aids, satisfactory levels of process yield were obtained. The significant product recovery may be associated with the HE properties, as well as the process parameters chosen for the experimental design, leading to a low adherence of the powders on the drying chamber walls.

The moisture contents were very low in most of the products obtained, ranging from 2.9±0.02 to 4.66±0.21% (w/w). According to the literature (USP, 2007), for pharmaceutical powders, including spray-dried extracts, moisture content values lower than 5% (w/w) are considered adequate. Therefore, it is possible to conclude that all the products shown in Table 2 presented suitable levels of residual moisture. Similarly to P_Y, the residual moisture is closely related to the efficiency of the drying process. Moreover, M_C has a considerable effect on the chemical and microbiological stability, as well as on the physical properties of the product, especially with regard to flow properties and particle size distribution (Telang & Thorad, 2010).

It can be observed in Table 2 that all powders showed water activity (A_W) below 0.5, which are considered acceptable for pharmaceutical purposes (USP, 2007). In powder engineering, A_W has been considered an important index because it can greatly affect the shelf life of the powder produced. By definition, A_W it is the ratio of vapor pressure of water in a dried system to vapor pressure of pure water at the same temperature. The lower the water activity, the lower will be the chemical potential of water and the driving force in chemical interactions involving water. Therefore, A_W is different from moisture content as it measures the availability of free water in a dried system that is responsible for any chemical and biochemical reactions, whereas the moisture content represents the water composition in a dried system (Quek et al., 2007).

In the obtained products, the levels of TP_C, TT_C and TF_C ranged, from 45.57±1.79 to 47.76±1.06, 17.47±0.43 to 18.78±1.05 and 53.27±4.76 to 58.13±6.11% (w/w), respectively. These values have recuperation ratios ranging from 88.66 to 99.07, 70.38 to 81.87 and 74.51 to 98.68%, respectively. From these results, it is possible to assert that the different sets of drying conditions used in this study affected the polyphenolic compounds differently, with the highest degradation ratio observed in TT_C. Polyphenols are assumed to be thermolabile (Marquele et al., 2006; Souza et al., 2007; Souza et al., 2008). However, in a recent publication, the present group of researches has proved that in addition to drying air temperature, other processing parameters affect the stability of these compounds (Couto et al., 2012). Undoubtedly, engineering a dried extract to present the desired content of bioavailable active compounds is the major challenge faced during the development of phytomedicines. Therefore, the correct selection of the drying set of conditions is required to guarantee the obtainment of products with suitable properties for therapeutical purposes.

In addition to drying performance evaluation and physicochemical quality control, the evaluation of several physico-mechanical properties is essential for a full characterization and validation of pharmaceutical powder technology process. In this context, HR, CI and Θ are widely accepted in the pharmaceutical field to predict the compressibility and flowability characteristic of the powders. In the established conditions, the Hausner ratios (HR) varied from 1.18±0.04 to 2.86±0.09, proving deficient rheological properties in most powders, since HR higher than 1.25 indicates cohesive and high internal friction powders (USP, 2007). The Carr's Index (CI) varied from 15±0.04 to 65.06±2.48%, which is within the range considered good (11-15%) to poor, very poor (>38%) flow and compressibility characteristics (USP, 2007). Low HR and CI values define powders with low packaging stability, which contribute to higher flow.

The angles of repose varied from 40.3±1.85 to 53.47±2.15º. The literature proposes the following classification of flowing properties of the angle of repose: excellent ($25º<\Theta<30º$), good ($31º<\Theta<35º$), fair ($36º<\Theta<40º$), passable ($41º<\Theta<45º$), poor ($46º<\Theta<55º$), very poor ($56º<\Theta<65º$) and very, very poor ($\Theta<66º$) (USP, 2007). Therefore, only one condition studied produced powders with suitable flowability ($\Theta<40º$). Free-flowing powders are essential to obtaining solid dosage forms. They assure the efficiency of filling capsules and in tablet manufacturing, where do the process of filling the matrix compression ("die filling"), which are fundamental steps in the determination of content uniformity and, therefore, are closely related to the bioavailability of pharmaceutical forms (Aulton, 2001). Finally, the mean powder particles diameter (D50) ranged from 208.24±9.18 to 481.32±13.67 μm.

Table 2. Results of powders characterization.

Run	P_Y	M_C	A_W	TP_C	TT_C	TF_C	HR	CI	Θ	D50
1	63.92	4.66±0.21	0.31±0.001	46.19±1.03	19.06±0.93	58.13±6.11	1.55±0.05	35.48±0.95	47.72±1.96	428.95±18.15
2	41.83	4.19±0.15	0.33±0.014	45.85±0.67	19.32±0.15	56.89±5.24	1.46±0.01	31.31±1.15	40.36±1.85	353.42±12.66
3	57.06	2.9±0.02	0.31±0.008	47.39±0.49	18.78±1.05	57.88±4.24	1.18±0.04	15±0.04	53.47±2.15	367.08±15.48
4	38.18	3.63±0.01	0.37±0.013	46.98±1.11	18.52±0.39	58.45±4.15	1.5±0.03	33.33±0.57	50.19±2.38	445.75±19.45
5	55.36	4.39±0.19	0.29±0.010	46.38±1.51	18.93±0.56	55.02±4.48	1.4±0.06	28.57±1.06	51.34±1.74	481.32±13.67
6	36.2	4.45±0.03	0.33±0.015	47.51±1.22	19.02±0.07	56.32±4.38	2.86±0.09	65.06±2.48	47.72±2.12	347.83±16.89
7	60.55	3.15±0.09	0.26±0.005	46.33±0.67	18.06±0.27	55.67±4.81	1.31±0.07	23.89±1.15	52.43±2.19	208.24±9.18
8	34.64	3.07±0.01	0.29±0.007	47.41±1.17	17.57±0.33	57.01±5.05	1.25±0.02	20±0.89	43.53±2.06	449.47±10.56
9	41.4	3.58±0.09	0.31±0.011	47.76±1.06	18.71±1.11	54.39±5.25	1.32±0.05	24.44±0.46	46.39±2.05	283.53±13.7
10	43.62	3.34±0.11	0.33±0.009	44.55±0.72	17.47±0.43	53.27±4.76	1.34±0.06	25.56±1.11	47.72±1.33	234.89±11.78
11	40.37	3.56±0.15	0.34±0.015	45.57±1.79	18.45±0.10	53.83±4.10	1.36±0.03	26.67±1.09	47.72±1.18	221.27±10.37

P_Y: Process yield (% w/w); M_C: Powder moisture content (% w.b.); A_W: Water activity (-); TP_C: Total polyphenol content (% w/w); TF_C: Total flavonoid content (% w/w); TT_C: Total Tannin Content (% w/w); HR: Hausner Ratio (-); CI: Carr's Index (%); Θ: Angle of repose (º); D50: Mean powder particles diameter (µm).

Table 3. Summary of factor effects and significances (*p*) on powder properties.

Factor	P_Y	M_C	A_W	TP_C	TT_C	TF_C	HR	CI	Θ	D50
S_A	↓0.001[a]	0.792	↑0.046[c]	0.725	0.808	0.318	0.24	0.289	↓0.027[c]	0.508
IT	0.393	↓0.009[b]	0.557	0.605	0.109	0.206	0.166	0.157	0.116	0.411
E_F	0.131	0.726	↓0.046[c]	0.768	0.258	↓0.021[c]	0.385	0.582	0.604	0.517
S_A x IT	0.644	0.292	0.557	0.977	0.519	0.343	0.393	0.657	0.846	↑0.037[c]
S_A x E_F	0.595	0.759	0.84	0.491	0.808	0.138	0.371	0.647	0.763	0.531
IT x E_F	0.133	0.742	0.095	0.559	0.472	0.986	0.307	0.453	↓0.046[c]	0.266

Significant at: [a]0.1%; [b]1%; [c]5%; Effects: ↑positive, ↓negative; S_A: Spray nozzle airflow rate (L/min); IT: Drying air inlet temperature (ºC); E_F: Extract feed rate (g/min); P_Y: Process yield (% w/w); M_C: Powder moisture content (% w.b.); A_W: Water activity (-); TP_C: Total polyphenol content (% w/w); TF_C: Total flavonoid content (% w/w); TT_C: Total Tannin Content (% w/w); HR: Hausner Ratio (-); CI: Carr's Index (%); Θ: Angle of repose (o); D50: Mean powder particles diameter (µm).

The size distribution of the particles is an important factor for the compression and flow of powders (Jangam & Thorat, 2010). Therefore, D50 is also directly related to the content uniformity, solubility, dissolution rate and bioavailability of the pharmaceutical dosage forms.

The effect of in-process parameters

The SDE had diverse properties when different sets of conditions were applied in the drying process (Table 2). In order to precisely determine the interactions of the process factors with the quality indicators, ANOVA and correlation analyses were performed. The tables with complete ANOVAs for each powder property are omitted, but a summary of the main effects and their significance values are listed in Table 3 where the levels of significance are displayed as percentages. Table 3 also displays comments on the interactions shown to be highly significant and arrows indicate the sign of the effect (positive or negative). The response surfaces of the parameters studied, as functions of the factors that were shown to be significant, are shown in Figures 1-6.

None of the factors studied had significant effects on TP_C, TT_C, HR or CI (Table 3). However, spraying airflow rate (S_A) exerted a strong effect on powder recovery (Table 3), with 0.1% of significance. It can be observed in the response surface shown in Figure 1 that increasing of S_A had a negative influence on powder recovery, which means that the higher the S_A, the lower the powder recovery will be. The higher the S_A, the lower will be the mean diameter of the atomizing drops during spray drying and, consequently, the finer the dried powder. It results in lower product recovery due to a decrease in the separation of dried particles from the air by the cyclone (Filková et al., 2007).

The surface response of the moisture content, M_C, as a function of IT and E_F, is shown in Figure 2. As shown in Table 3, IT had negative influence on the M_C at a significance level of 1%. This is because at higher inlet temperature, the rate of heat transfer to the particle is greater, providing greater driving force for moisture evaporation. This is in agreement with the results published by Vasconcelos et al. (2005), working with the spray drying of *Schinus terebinthifolius* Raddi, Anacardiaceae.

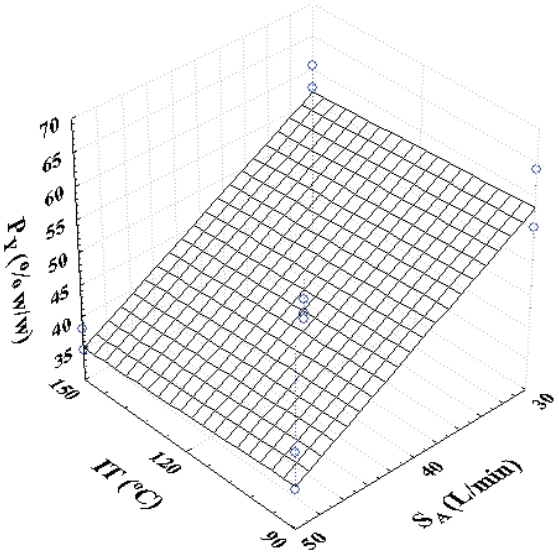

Figure 1. Surface response plot of process yield as a function of spraying airflow rate and drying air inlet temperature.

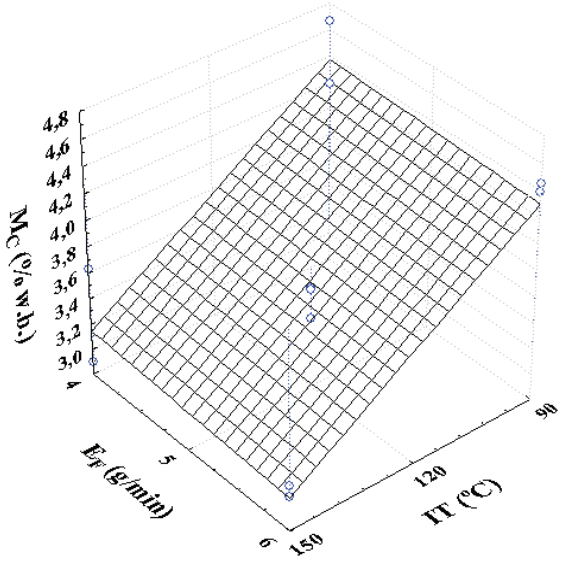

Figure 2. Surface response plot of moisture content as a function of drying air inlet temperature and extract feed rate.

The surface response plot of A_W as a function of the spray drying factors is presented in Figure 3. Typically, the increase in S_A and IT gives fine droplets, which results in a solid product with lower moisture content for constant values of other parameters. Hence, the water activity decreases as the S_A and IT are increased. However, an increase in E_F results in higher water activity values because the powder is partially dried and it retains more moisture (Filková et al., 2007). It is noteworthy to mention that a different trend regarding the effects of both spraying airflow rate and extract feed rate on the water activity was observed in this work. As shown in Figure 3, A_W increased with increasing S_A, and decreased with increasing E_F. The effect of the S_A and E_F on the water activity was confirmed by the ANOVA, which demonstrated a significance level of 5% for both the terms (Table 3). It may be explained by the occurrence of synergism between these parameters in the whole process, which makes the A_W dependent on the balance of the factors, besides its isolated effects.

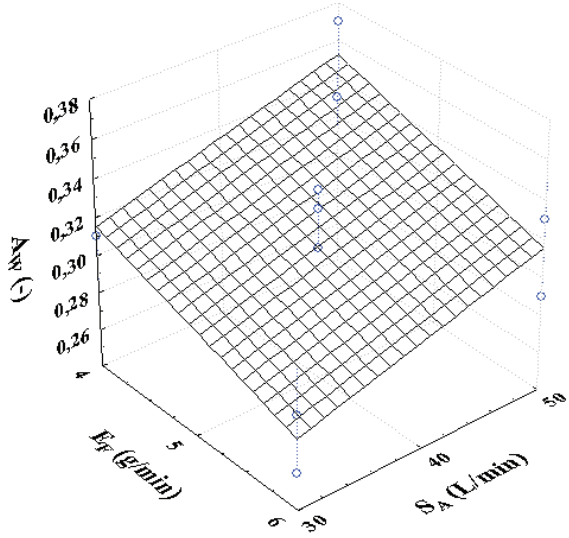

Figure 3. Surface response plot of water activity as a function of spraying airflow rate and extract feed rate.

The surface response of TF_C as a function of IT and E_F is shown in Figure 4. According to ANOVA (Table 3), only the E_F affected the TF_C, at a significance level of 5%. Neither S_A, IT nor the interactive terms were significant. It can be observed in the response surface shown in Figure 4 that increasing of E_F had a negative influence on total flavonoid content. An increase in E_F may have led to the formation of larger droplets, which present a greater tendency to form porous or hollow dried spheres (Mestry et al., 2011). Hence, an increase in the porosity of the particles may have facilitated the loss of flavonoids through an increase surface area in contact with the hot air.

The effect of spray drying factors on the angle of repose of the products, Θ, can be seen in Figures 5 a-c. As shown in Table 3, the angle of repose proved to be dependent on the S_A at a significant level of 5%. Furthermore, Θ depended on the interaction between IT and E_F, also at 5%. Both S_A and the interactive term had a negative influence on Θ.

As can be seen in Table 3, the mean powder particles diameter (D50) depended on the interaction between S_A and IT at 5% significance level. The surface response plot of D50 as a function of the S_A and IT

is presented in Figure 6. The surface shows that D50 increased with increasing S_A and IT. Indeed, both S_A and IT influences particle size distribution: higher S_A and IT would help to produce smaller particles and narrower distribution (Filková et al., 2007). In addition, small particles may form weak agglomerates, which lead to the production of particles with greater size (Fang et al., 2011). These results match to the trend observed to Θ, since better flowability and compressibility are expected to powders with higher particles (Jangam & Thorat, 2010).

Finally, RSM enables the fitting of polynomial equations of the dependent variables as a function of the studied factors for predicting quality indicators. As shown in Table 4, the high correlation coefficients observed in the fitted models confirm their ability to describe the experimental results. Accordingly, the spray drying technology is an attractive and promising alternative to development of intermediate phytopharmaceutical products of *E. dysenterica*.

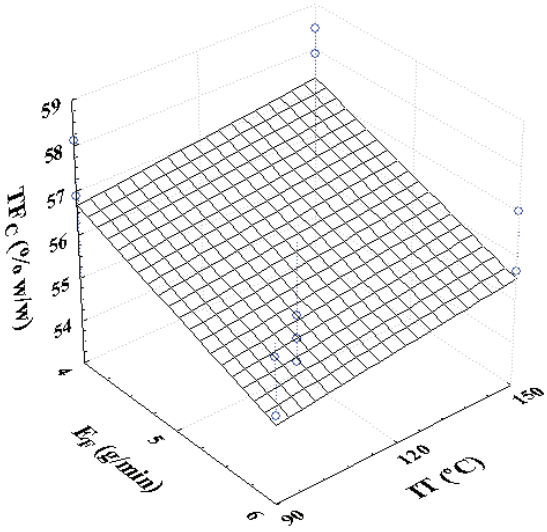

Figure 4. Surface response plot of total flavonoid content as a function of drying air inlet temperature and extract feed rate.

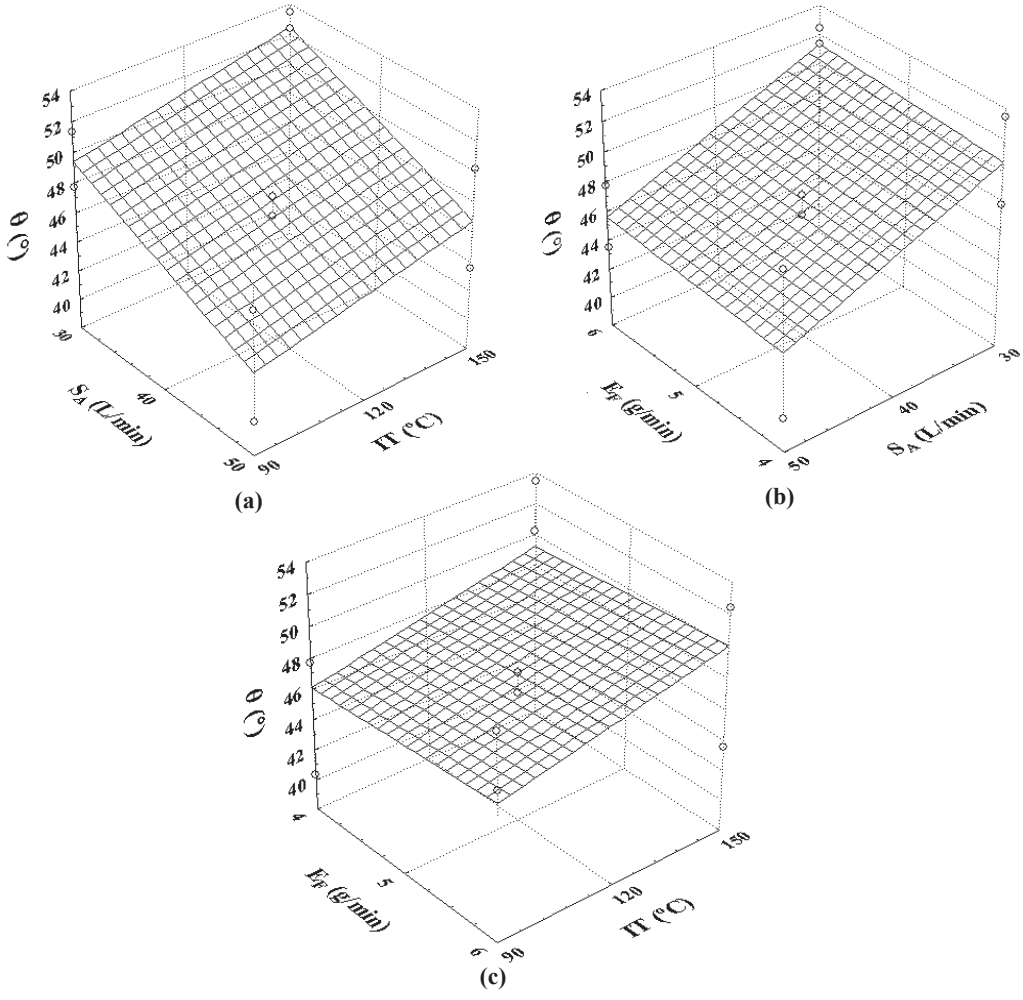

Figure 5. Surface response plot of angle of repose as a function of: (a) spraying airflow rate and drying air inlet temperature; (b) spraying airflow rate and extract feed rate; and (c) drying air inlet temperature and extract feed rate.

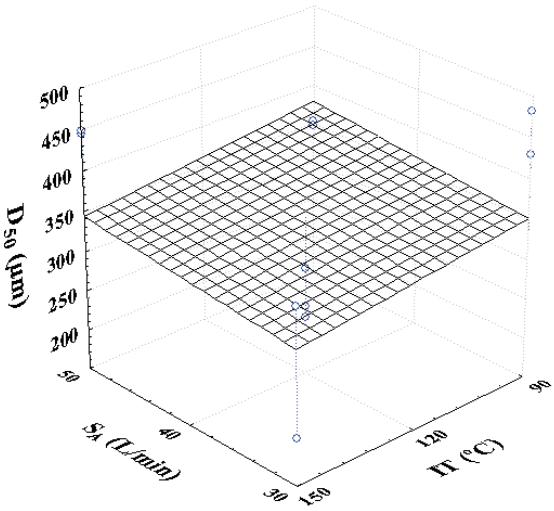

Figure 6. Surface response plot of mean powder particles diameter as a function of spraying airflow rate and drying air inlet temperature.

Conclusions

The impact of in-process factors during the spray drying of *E. dysenterica* hydroalcoholic extract was assessed using RSM on the basis of various responses. ANOVA/RSM proved that studied factors, *i.e.* spraying air flow rate, drying air inlet temperature and extract feed rate, significantly affected most of the quality indicators at different levels. Further optimization studies will provide useful data for a full developing and validation of a pilot spray drying method to achievement of standardized intermediate phytopharmaceutical products of *E. dysenterica*.

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Table 4. Fitted equations and correlation coefficients of the experimental results.

Fitted equations	R values	Eq.
$P_Y = 41.7967 - 10.755\ S_A - 0.86\ IT - 1.78\ E_F - 0.4425\ S_A \times IT - 0.5125\ S_A \times E_F + 1.7675\ IT \times E_F$	0.991824	(6)
$M_C = 3.493 + 0.03\ S_A - 0.6175\ IT - 0.04\ E_F + 0.1325\ S_A \times IT - 0.035\ S_A \times E_F - 0.0375\ IT \times E_F$	0.964274	(7)
$A_W = 0.326667 + 0.01875\ S_A - 0.00375\ IT - 0.1875\ E_F + 0.00375\ S_A \times IT - 0.00125\ S_A \times E_F + 0.01375\ IT \times E_F$	0.954023	(8)
$TF_C = 53.83 + 0.24625\ S_A + 0.33125\ IT - 0.91625\ E_F + 0.23125\ S_A \times IT\ 0.41375\ S_A \times E_F + 0.00375\ IT \times E_F$	0.983822	(9)
$\Theta = 47.27667 - 2.895\ S_A + 1.56\ IT + 0.41\ E_F - 0.15\ S_A \times IT - 0.235\ S_A \times E_F - 2.335\ IT \times E_F$	0.95777	(10)
$D_{50} = 246.563 + 13.86\ S_A - 17.6225\ IT - 13.5425\ E_F + 66.115\ S_A \times IT + 13.075\ S_A \times E_F - 25.2375\ IT \times E_F$	0.956736	(11)

P_Y: Process yield (% w/w); M_C: Powder moisture content (% w.b.); A_W: Water activity (-); TF_C: Total flavonoid content (% w/w); Θ: Angle of repose (°); D50: Mean powder particles diameter (µm); R = correlation coefficient.

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