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Original Article

Engineering spray-dried rosemary extracts with improved physicomechanical properties: a design of experiments issue

Luiza T. Chaul [a], Edemilson C. Conceição [a], Maria Tereza F. Bara [a], José R. Paula [a], Renê O. Couto [b,*]

[a] Faculdade de Farmácia, Universidade Federal de Goiás, Goiânia, GO, Brazil
[b] Departamento de Ciências Farmacêuticas, Centro de Ciências da Saúde, Universidade Estadual de Londrina, Londrina, PR, Brazil

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ABSTRACT

A 3^3 Box–Behnken design and Response Surface Methodology were performed to evaluate the influence of extract feed rate, drying air inlet temperature and spray nozzle airflow rate on the process yield, stability parameters (moisture content and water activity) and on several physicomechanical properties of spray-dried rosemary extracts. Powder yield ranged from 17.1 to 74.96%. The spray-dried rosemary extracts showed moisture content and water activity below 5% and 0.5%, respectively, which indicate their chemical and microbiological stabilities. Even without using drying aids, some sets of experimental conditions rendered dried products with suitable flowability and compressibility characteristics for direct preparation of solid dosage forms. Analysis of variance and Response Surface Methodology proved that studied factors significantly affected most of the spray-dried rosemary extract quality indicators at different levels. The main processing parameter affecting the spray-dried rosemary extract characteristics was inlet temperature. The best combination of parameters used to obtain a reasonable yield of stable dry rosemary extracts with adequate technological properties for pharmaceutical purpose involves an extract feed rate of 2 ml/min, 80 °C inlet temperature and 40 l/min SA. The design of experiments approach is an interesting strategy for engineering spray-dried rosemary extracts with improved characteristics for pharmaceutical industrial purpose.

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Introduction

Rosemary (*Rosmarinus officinalis* L., Lamiaceae), native to the Mediterranean, is a household specie used worldwide as a food preservative and food-flavoring agent. Over the last decades, the valuable medicinal properties of this herb have been in the spotlight of the scientific community. An evidence-based systematic review of rosemary's therapeutic use has been published (Ulbricht et al., 2010). Recently, preclinical surveys have contributed to evidence that rosemary has remarkable anti-inflammatory (Rocha et al., 2015), anti-proliferative (Cattaneo et al., 2015), and antibiotic (Barreto et al., 2014) activities, as well as antidepressant-like, anxiolytic, and antinociceptive effects (Abdelhalim et al., 2015).

Moreover, a clinical trial in humans reported the beneficial effects of rosemary for treatment of opium withdrawal syndrome during addiction treatment programs (Solhi et al., 2013). This broad range of relevant therapeutic properties is likely attributed to the antioxidant activity of this herb, which is a powerful source of antioxidant compounds *e.g.*, rosmarinic and carnosic acids, camphor, and 1,8-cineol (Barreto et al., 2014; Cattaneo et al., 2015; Lemos et al., 2015; Rocha et al., 2015; Li et al., 2016).

To become suitable for further therapeutic applications, herbal raw material typically undergoes several pharmaceutical processing technologies *e.g.*, the extraction of bioactive compounds and drying of plant extracts. In the latter, the dryer type and set of operating conditions used in the drying process of a liquid feed extract play important roles in determining the properties of co-processed products (Oliveira et al., 2006; Souza et al., 2008). As spray drying presents several advantages over other drying techniques such conventional air drying, freeze-drying and spouted bed drying, it is the most commonly employed in the pharmaceutical, food and flavor industry (Patel et al., 2014).

In brief, spray drying is a three-step unit operation (*i.e.*, atomization, dehydration, and powder collection) in which dry particulate products are recovered from a liquid solution or dispersion (suspension or emulsion) by spraying the liquid into a stream of drying gas under determined set of conditions (Oliveira and Petrovick, 2010). Due to its remarkable operational flexibility, spray drying offers a very accurate control over powder particle properties such as physicochemical stability, solubility, morphology and

* Corresponding author.
E-mail: rocouto@uel.br (R.O. Couto).

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flowability (Ameri and Maa, 2006; Vehring, 2008; Cortés-Rojas and Oliveira, 2012).

The equipment's operating variables have been widely studied during the spray drying of phytopharmaceuticals. Such variables include solution or dispersion feed rate, drying air inlet temperature, drying air outlet temperature, spray nozzle airflow rate, spray nozzle diameter, spray nozzle type, drying air flow rate, aspiration rate, drying air inlet humidity, drying air outlet humidity, compressed air flow, compressed air pressure, *etc.* (Oliveira and Petrovick, 2010).

Currently, our research group has struggled greatly to develop rosemary's phytopharmaceuticals intermediate products with greater aggregate value by spray drying (Couto et al., 2012a). The operating variables set up demonstrated an effect on the chemical profile and *in vitro* antioxidant activity of spray-dried rosemary extracts (SDRE). From a phytopharmaceutical technology point of view, besides the physicochemical quality control and biological activity assessments, determining the effects of spray drying process variables in the drying performance and physicomechanical properties of the products, is a starting point for the full and accurate validation and scale-up of rosemary's powder technology process.

Improving both chemical and microbiological stabilities, as well as their flowability and compressibility during the preformulation studies, may turn the SDRE into more inviting intermediate products for developing solid dosage forms (SDF), which represent the majority of medicines marketed worldwide. Multifactorial chemometric tools such as the design of experiments approach and Response Surface Methodology (RSM) may be useful strategies in this pursuit (Matero et al., 2013).

In this paper, we report the effect of extract feed rate (EF), drying air inlet temperature (IT) and spray nozzle airflow rate (SA) in several physicomechanical properties of SDRE. A 3^3 Box–Behnken design and RSM were performed. The correlations between the process adequacy indicators were also assessed. By using a determined set of experimental conditions, we engineered products with improved levels of stability, flowability and compressibility, which may enable the direct manufacture of tablets and/or capsules filling.

Materials and methods

Herbal drug

Samples of rosemary leaves (Rosmarinus officinalis L., Lamiaceae) were collected from specimens located in the medicinal plants garden of the Hospital de Medicina Alternativa da Secretaria Estadual da Saúde do Estado de Goiás (863 m, 16°43′50.3″ South, 49°14′32.9″ West/Goiânia, GO, Brazil). Once identified, a voucher specimen was prepared and deposited in the Universidade Federal de Goiás (UFG) Herbarium under the registration identification UFG – 43206. The leaves were dried at room temperature (25 ± 2 °C) and ground in a TE-625 knife mill (Tecnal Ltda, Piracicaba, SP, Brazil). A mean powder size of 437.94 ± 7.00 μm was achieved. Powdered material (herbal drug) was stored sheltered from light and moisture for subsequent use in the extraction procedure.

Feed extract

The hydroalcoholic feed extract was obtained at room temperature by percolation of the herbal drug, using as solvent an ethanol:water solution (80:20, v/v) as previously reported (Couto et al., 2012a). The extract was stored in closed flasks protected from light at a temperature between −2 and 8 °C prior to characterization and further use in the drying experiments. Extract density and alcoholic content were determined according to the methods described in the Brazilian Pharmacopoeia 5th edition (Farmacopeia Brasileira, 2010). Solid content (C_S, w.b.) of a 1 g sample was measured with a gravimetric method in an MB 35 halogen lamp analyzer (Ohaus Inc., Pine Brook, NJ, USA). The extract viscosity was measured at room temperature using a DV–III+ viscometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA). All experiments were performed in triplicate.

Table 1
Coded factors and their levels in the 3^3 Box–Behnken factorial design matrices.

Run	EF (ml/min)	IT (°C)	SA (l/min)
1	−1 (2)	−1 (80)	0 (40)
2	+1 (6)	−1 (80)	0 (40)
3	−1 (2)	+1 (140)	0 (40)
4	+1 (6)	+1 (140)	0 (40)
5	−1 (2)	0 (110)	−1 (30)
6	+1 (6)	0 (110)	−1 (30)
7	−1 (2)	0 (110)	+1 (50)
8	+1 (6)	0 (110)	+1 (50)
9	0 (4)	−1 (80)	−1 (30)
10	0 (4)	+1 (140)	−1 (30)
11	0 (4)	−1 (80)	+1 (50)
12	0 (4)	+1 (140)	+1 (50)
13	0 (4)	0 (110)	0 (40)
14	0 (4)	0 (110)	0 (40)
15	0 (4)	0 (110)	0 (40)

−1, 0 and +1: low, average and high coded values, respectively, in the factorial design matrices.
EF, extract feed rate; IT, drying air inlet temperature; SA, spray nozzle airflow rate.

Design of experiments

The spray drying experiments followed a 3^3 Box–Behnken design with three factors in three levels and three central point replicates as presented in Table 1, which shows the design matrices with the coded and non-coded values of each factor studied. The critical process parameters investigated (factors) were: (i) extract feed rate (EF, ml/min); (ii) drying air inlet temperature (IT, °C) and (iii) spraying airflow rate (SA, l/min). Their selection was based on our previous experiences.

The drying processes were performed at room temperature in a laboratory-scale spray dryer model MSD 1.0 (Labmaq do Brasil Ltda., Ribeirão Preto, SP, Brazil) with concurrent flow regime. The liquid extract feed system was composed of a peristaltic pump and a pneumatic (two fluid) spray nozzle with an inlet orifice diameter of 1.2 mm. The cylindrical drying chamber was made of borosilicate glass, 160 mm in diameter and 645 mm in height. The drying air was supplied by a blower (nominal flow rate of 1 m^3/min) and electrically heated. The temperature was maintained by a digital PID controller.

The following set of conditions remained fixed for all experiments: nozzle air pressure of 0.4 MPa; mass of extract portion feed (W_E) of 300 g and aspiration airflow of 100%. Before the extract was fed into the chamber, the drier was started with distilled water in order to reach thermal equilibrium. Then, if the inlet and outlet temperatures were constant, the feed extract was sprayed into the chamber. Drying air outlet temperatures (OT, °C) in each run were recorded in order to better understand the relations between factors studied and powder properties.

The SDRE were separated from air by a stainless steel cyclone and collected in a glass flask. The SDRE were weighed, stored in closed flasks protected from light and kept in a desiccator at room temperature for further characterization.

Characterization of the SDRE

The powder recovery or process yield (PY) was calculated immediately after the drying experiments based on the ratio of the mass

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