SHORT COMMUNICATION

Water soluble microparticles of Sambucus nigra L. (elderberry) as a potential herbal medicine

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ABSTRACT

Although traditional use of elderberry flowers is recognized by Medical Agencies, there are not suitable products on the Brazilian market. To overcome poor stability of tinctures of Sambucus nigra flowers, we aimed to develop spray dried microparticles. Statistical experimental design was applied taking inlet temperature and maltodextrin\% at five different levels. Next, we applied a stability study for 60 days under accelerated conditions (40°C/75% RH) and 180 days at room temperature (15–30°C). We monitored flavonoid content as markers. The best drying condition was 188°C and 65% of carrier and enabled microparticles with more than 90\% of markers recovery. After 180 days, the dried extract remained with 90.8\% at room temperature. The markers were released from microparticles in two minutes. In conclusion, the spray drying process and formulation enabled elderberry flowers to be easier to apply in solid pharmaceutical forms.

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1. Introduction

*Sambucus nigra* L., belonging to the family Adoxaceae, has traditional use approved by regulatory agencies (Brasil 2014, EMA. 2018). The infusion and tincture of dried flowers, syrup and coated tablet are used for the treatment of fever, chills and as an expectorant in the case of mild inflammation of the upper airways (WHO Monographs on Selected Medicinal Plants 2002; Brasil 2014; EMA 2018). The use of this herbal drug in the treatment of viral infection has also been exploited. A lyophilized infusion of *S. nigra* L. flowers, *Hypericum perforatum* L. aerial parts and *Saponaria officinalis* L. roots (100 g; 70 g; 40 g) exhibited antiviral effect, inhibiting the reproduction of different strains of influenza virus types A and B, *in vitro* and *in vivo*, and the herpes simplex virus type 1, *in vitro* (Serkedjieva et al. 1990). Recently, our research group proved *in vivo* that *S. nigra* lyophilized extract represents an important tool for the management of acute inflammation (Santin et al. 2022). These results, together with the traditional use of elderberry flower in improving flu states, pointed out the importance of phytomedicines in coping with viruses that can aggravate the situation of patients affected with coronavirus, acting to relieve pressures in hospitals which are treating patients with COVID-19, as is occurring in the current pandemia (WHO. 2020).

However, the poor chemical stability of the tincture represents a problem to obtain products using this herbal preparation in industrial scale (Prosen and Pendry 2016; Testoni et al. 2019). This problem can be overcome by using drying process, since dry extracts can be used to obtain a greater number dosage forms, as well as by improving storage and use (Vidović et al. 2014; Baccarin et al. 2016; Lockwood 2016; Di Battista et al. 2017; Gabbay Alves et al. 2017). For that choice, it is essential to find the operation conditions to overcome problems such as physicochemical stability, solubility, as well as product yield.

Among drying and microencapsulation techniques for dehydration and protection of the herbal medicines compounds, by using carrier matrix, spray drying has been applied to convert aqueous solutions, emulsions or suspensions, in powders with accurate specifications, such as moisture, particle size and morphology. Operating conditions and formulation feed composition might be studied to optimize the process. Both are related to be dependent of the herbal medicine composition (Cortés-Rojas et al. 2015).

The use of spray drying of extracts, containing flavonoids, has widely been described in the literature, specially how it can improve the solubility, bioavailability, and stability of such extracts (Outuki et al. 2016; Zokti et al. 2016). Experimental design, response surface and multiple response analysis have been employed to evaluate and optimize the operating conditions.

Although traditional use of elderberry flowers is known and recognized by European Medical Agency (EMA. 2018), there are not products on the Brazilian market, and there are still few studies about the microencapsulation of elderberry extracts (Ribeiro et al. 2019). Therefore, the aim of this study was the optimization of spray drying conditions and the formulation feed composition to develop a dried extract of *S. nigra* flowers, to be taken as an instant tea instead of its tincture.
2. Results and discussion

Mostly herbal preparations for therapeutic use from *S. nigra* dried flowers have been reported as a tea obtained from 2 to 5 g of the flowers, or alternatively, 3 to 5 mL of the 1:1 fluid extract and 10 to 25 mL of the 1:5 tincture (Blumenthal et al. 1998; EMA. 2018; WHO. 2020). In both cases, problems related to stability should be concerned, as related by Prosen and Pendry (2016) and Testoni et al. (2019). Based on that, a dried extract would be a promising form to enhance the storage time of the *S. nigra* products, as well as, facilitating its storage.

In this study, spray drying technique was employed to convert the tincture (see supplemental results) in dry extract, using maltodextrin as drying carrier and a pre-concentration step before drying. The solid content in formulation feed solution was adjusted to 5.5% (w/v) since this concentration had shown to be appropriate in previous tests.

Maltodextrin was chosen as carrier for the development of *Sambucus nigra* dry extract, at first, to be instantaneous soluble in water. Also, because of its low cost, film-forming property, reduced oxygen permeability in the formed matrix (Rowe et al. 2009; Sansone et al. 2011; Medina-Torres et al. 2016).

To prepare the microparticles spray drying was chosen as process, by setting the inlet temperature ($X_1$) and carrier agent ($X_2$), at five levels. All the results about optimization conditions for moisture content, flavonoid recovery and product yield are shown in supplemental results.

The extract corresponds to microparticles of reduced size, spherical shape, hollow, quite agglomerated, and a slight roughness taken at 5000x of increase by SEM (supplementary materials). The reduced size, spherical shape and hollow are typical characteristics of spray dried particles (Vidović et al. 2014). The mean size diameter was $2.83 \pm 2.55 \mu m$ with 60% of the particles with sizes between 1 and 4 mm. The bulk density of microparticles was beyond 0.11 g/ml, but usually, all those properties lead to low bulk density. Density values have an important meaning for planning of solid formulation, especially the package volume for extemporaneous powders. In fact, the values obtained are like other ones, which were either obtained by adding maltodextrin or using spray drying process (Vidović et al. 2014; Baccarin et al. 2016).

The water solubility index was near to 100%, higher than other extracts using maltodextrin as a drying aid, such as *Theobroma cacao* L. dry extract, with a WSI of 75.3% (Gabbay Alves et al. 2017). Indeed, after two minutes flavonoids release profile reached a plateau (supplementary materials), which is highly desirable for immediate release pharmaceutical forms.

About flavonoid content during stability study, under accelerated conditions and at room temperature, in comparison, at accelerated conditions, there were small differences between the tincture and the dried extract after 30 and 60 days of storage (supplementary materials). After 60 days, losses about 19.7% and 22.6% for tincture and dry extract were observed, respectively. Besides that, at room temperature the dried extract remained with 90% of the flavonoid content while the tincture lost more than 30%.

During the stability study, the initial moisture content of the dried extract was 4.98%. After 60 days, under accelerated condition, this value increased to 9.00% and to
9.25% after 180 days at room temperature. These results also suggest the use of another packaging material, originally packed in plastig bag and aluminum sealed sachet, to overcome stability problems related to moisture and improve the stability of dried extract during storage.

However, at room storage conditions, the dried extract showed better chemical stability than the tincture, remaining with 90.8% after 180 days.

3. Experimental

See supplementatory material.

4. Conclusion

The results herein obtained demonstrate a promising step for herbal medicines development containing *S. nigra*, specially to obtain instantaneous powder preparations, which can be applied in substitution to the infusion and the tincture, aiming to preserving its stability.

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Disclosure statement

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