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Enhanced geranylgeraniol stability and dissolution from self-emulsifying pellets containing the sucupira (*Pterodon emarginatus* Vogel) standardized extract

Dissolução e estabilidade aprimoradas do geranilgeraniol em pellets autoemulsionáveis contendo o extrato padronizado de sucupira (*Pterodon emarginatus* Vogel)

Dissolución e estabilidad mejoradas de geranilgeraniol en péletes autoemulsionantes que contienen el extracto estandarizado de sucupira (*Pterodon emarginatus* Vogel)

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Abstract
The vegetal species sucupira (*Pterodon emarginatus* Vogel) presents some diterpenes that have anti-inflammatory activities. However, diterpenes are poorly water-soluble compounds. The development of Self-Emulsifying Drug Delivery Systems (SEDDS) allows for obtaining a solid dosage form that maximizes the release of *P. emarginatus* constituents in an aqueous medium. This work aimed to obtain and characterize pellets containing the SEDDS prepared from *P. emarginatus* extract using the extrusion-spheronization technique. Formulations PF1 to PF6 were tested. Then, self-emulsifying formulations were prepared (SES1 to SES5) based on the mixture of poloxamer 188 (Pluronic® F-68) and sorbitan triolate (Span®85) with *P. emarginatus* extract. Next, formulation PF6, containing microcrystalline cellulose: *P. emargitus* extract: aerosil®200: polyvinylpyrrolindone K-30 (50: 54.25: 4: 4) was used in the preparation of pellets containing the self-emulsifying systems. These pellets had a homogeneous surface and average sphericity of 0.52. When encapsulated in hard gelatin capsules, it was noted that the formulations PF6, PSES3 and PSES4 were statistically different from each other at the 5% level. In the first 10 min of dissolution, PSES3 and PSES4 showed a higher level of geranylgeraniol released compared to the PF6 (p=0.000117). However, after 20 min of dissolution, no significant difference was observed in relation to the content of this compound. In the accelerated stability study, the average content of the geranylgeraniol was 85.6% and 81.8% for PSES3 and PSES4, respectively, whereas it was only 34.4% for PF6. Under the studied conditions, obtaining the self-emulsifying systems made it possible to achieve the desired dissolution and chemical stability of geranylgeraniol.
Keywords: Medicinal plants; Bioproducts; Phytopharmaceutical technology; SEDDS.

Resumo
A espécie vegeta*l sucupira* (*Pterodon emarginatus* Vogel) apresenta alguns diterpenos que possuem atividades anti-inflamatórias. No entanto, os diterpenos são compostos pouco solúveis em água. O desenvolvimento de sistemas de liberação de fármacos autoemulsionáveis (SEDDS) permite a obtenção de uma forma farmacêutica sólida que maximize a liberação de constituintes de *P. emarginatus* em meio aquoso. Este trabalho visou obter e caracterizar *pellets* contendo SEDDS preparados a partir do extrato de *P. emarginatus* pela técnica de extrusão-esferonização. As formulações PF1 a PF6 foram testadas. Em seguida, formulações autoemulsionáveis foram preparadas (SES1 a SES5) com base na mistura de poloxamer 188 (Pluronic® F-68) e triolato de sorbitano (Span®85) com extrato de *P. emarginatus*. Posteriormente, a formulação PF6, contendo celulose microcristalina: extrato de *P. emargitus*: aerosil®200: polivinilpirrolindona K-30 (50: 54,25: 4: 4) foi utilizada na preparação dos *pellets* contendo os sistemas autoemulsionáveis. Esses *pellet*s apresentaram superfície homogênea e esfericidade média de 0,52. Quando encapsulado em cápsulas de gelatina dura notou-se que as formulações PF6, PSES3 e PSES4 foram estatisticamente diferentes entre si ao nível de 5%. Nos primeiros 10 min de dissolução, PSES3 e PSES4 demonstraram uma maior liberação de geranilgeraniol comparado à PF6 (p=0.000117). Porém, após 20 min de dissolução, nenhuma diferença

significativa foi observada em relação ao conteúdo desse composto. No estudo de estabilidade acelerada, o teor médio do geranilgeraniol foi de 85,6% e 81,8% para PSES3 e PSES4, respectivamente, enquanto foi de apenas 34,4% para PF6. Nas condições estudadas, a obtenção dos sistemas autoemulsificantes possibilitou a obtenção da dissolução e estabilidade química desejadas do geranilgeraniol.
Palavras chave: Plantas medicinais; Bioprodutos; Tecnologia fitofarmacêutica; SEDDS.

Resumen
La especie vegetal sucupira (*Pterodon emarginatus* Vogel) presenta algunos diterpenos que tienen actividades antiinflamatorias. Sin embargo, los diterpenos son compuestos poco solubles en agua. El desarrollo de sistemas de administración de fármacos autoemulsionantes (SEDDS) permite obtener una forma farmacéutica sólida que maximiza la liberación de los constituyentes de *P. emarginatus* en un medio acuoso. Este trabajo pretendia obtener y caracterizar pellets que contengan SEDDS preparados a partir del extracto de *P. emarginatus*. Se probaron las formulaciones PF1 a PF6. Luego, se prepararon formulaciones autoemulsionantes (SES1 a SES5) a base de la mezcla de poloxámero 188 (Pluronic® F-68) y trilato de sorbitán (Span®85) con extracto. Posteriormente, la formulación de PF6, que contiene celulosa microcristalina: extracto de *P. emargitus*: aerosil®200: polivinilpirrolindona K-30 (50: 54,25: 4: 4), se utilizó en la preparación de gránulos que contenían los sistemas autoemulsionantes. Cuando se encapsuló en cápsulas de gelatina dura, se observó que las formulaciones de PF6, PSES3 y PSES4 fueron estadísticamente diferentes entre sí al nivel del 5%. En los primeros 10 min de disolución, PSES3 y PSES4 demostraron una mayor liberación de geranilgeraniol en comparación con PF6 (p=0,000117). Sin embargo, luego de 20 min de disolución, no se observó diferencia significativa en relación al contenido de este compuesto. En el estudio de estabilidad acelerada, el contenido medio de geranilgeraniol fue de 85,6% y 81,8% para PSES3 y PSES4, respectivamente, mientras que para PF6 fue solo de 34,4%. En las condiciones estudiadas, la obtención de sistemas autoemulsionantes permitió obtener la disolución y estabilidad química deseadas del geranilgeraniol.
Palabras clave: Plantas medicinales; Bioproductos; Tecnología farmacéutica; SEDDS.

1. Introduction

Pterodon emarginatus Vogel (Fabaceae) is a tree species of the Brazilian flora, which has proven pharmacological activities, especially anti-inflammatory (Pascoa et al., 2015; Goes et al., 2020; Lorenzi & Matos, 2021; Oliveira et al., 2023). *P. emarginatus* has an oil resin composed of sesquiterpenic and diterpenic compounds that confer lipophilic characteristics (Oliveira et al., 2017; Lemos et al., 2021).

Few innovative products developed from active constituents of the Brazilian biodiversity are commercially available in Brazil (Calixto, 2019; Trindade et al., 2021). Technological innovations are very important to improve the limited technological properties of plant extracts and their physicochemical and biological properties (Hoscheid et al., 2015; Vieira et al., 2020; Lemos et al., 2021; Silva et al., 2021; Garcia et al., 2022).

In this context, incorporating a lipophilic plant extract in self-emulsifying drug delivery systems (SEDDS) is an exciting strategy to improve the solubilization of the active compounds and the bioavailability of the drug (Tang et al., 2008). From this, a solid dosage form can be obtained, maximizing the active constituents' release in an aqueous medium (Lemos et al., 2021). The solid dosage form combines the advantages of SEDDS and solids. It can be prepared by including a self-emulsifying mixture into microcrystalline cellulose (MCC) followed by producing pellets using extrusion/spheronization (Clarke et al., 2000). To date, there are no reports on incorporating of *P. emarginatus* in pellet formulations containing self-emulsifying systems, which motivated this study.

This work investigates ways to overcome the low aqueous solubility of terpenic compounds, in particular, geranylgeraniol, from *P. emarginatus*. Therefore, it aimed to develop pellets containing a self-emulsifying release system containing the standardized extract of *Pterodon emarginatus.* The dissolution profile of the geranylgeraniol from the pellets and its accelerated stability for the self-emulsifying systems were determined.

2. Methodology

2.1 Obtaining *P. emarginatus* extract

Pterodon emarginatus Vogel fruits were collected in Campestre-GO, Brazil (16º 46' 01" Sul and 49º 42' 06"; 612 m). An exsiccate was deposited in the UFG Herbarium (number 41714). The fruits were crushed in a knife mill Willye (Tecnal®) and were subjected to percolation in 95% ethyl alcohol, in a drug: solvent ratio of 1: 20. Then, the extract was concentrated in a rotary evaporator (Buchi® R-220 SE) under reduced pressure (30 rpm, 40ºC, -600 bar).

The solids content was determined (Brazil, 2010), and the quantification of geranylgeraniol was performed (Oliveira, 2014), on a Waters® Chromatographic System with a diode array detector. Chromatographic separations were carried out on a Zorbax Eclipse XDB C18 column (5 µ, 250x4.6 mm, Agilent®) at 210 nm, in gradient elution mode, the mobile phase being composed of acetonitrile acidified with 0.2% phosphoric acid (v/v) (A), methanol (B) and 0.5% phosphoric acid (v/v) in water (C), in the following proportion: 65:15:20 for 10 min; then changed to 90:0:10 for 5 min, holding for another 17 min; returning to 65:15:20 by 4 min, holding for another 4 min and ending with a 40 min of the chromatographic run. The mobile phase flow rate was 1 mL.min^{-1}, the column oven was maintained at 30 °C and the injection volume was 10 µL.

2.2 Preparation of *P. emarginatus* pellets

The extrusion and spheronization technique was used to prepare pellets containing *P. emarginatus* extract and pellets containing the extract in a self-emulsifying system. The extruder (Caleva® Extruder 20, UK) was equipped with a 0.8 mm mesh, operating at 30 rpm. The spheronizer (Caleva® MBS 250, UK) was equipped with an 85 mm diameter disc with 3 mm grooves operating at 1000 rpm for 1 min. Microcrystalline cellulose (CMC – Avicel® PH 101, FMC, USA) and colloidal silicon dioxide (Aerosil®200, Degussa, Germany) were used in the pellet formulation in different proportions (w/w) (Table 1). The mixing of the constituents was carried out manually. The standardized extract, with or without the polyvinylpyrrolidone binder (Kollidon® K-30, BASF), was used as a wetting liquid for the powders to form an extrudable wet mass. The pellets were dried at room temperature until they had residual moisture below 5% (w/w).

Table 1 describes the constituents of the studied pellet formulations.

Table 1 - Composition of pellets containning *P. emarginatus* extract standardized in geranylgeraniol.

Formulation code	Constituents ratio (w/w)	Constituents % (w/w)	Solids (g) *P. emarginatus* extract
PF1	MCC: Extract (50: 34.52)	MCC: Extract (51.6: 35.6)	12.38
PF2	MCC: Extract (50: 59.2)	MCC: Extract (38.9: 46.1)	19.17
PF3	MCC: Extract: PVP K-30 (50: 49.3: 2.5)	MCC: Extract: PVP K-30 (42.4: 41.1: 2.12)	15.97
PF4	MCC: Extract: A: PVPK-30 (50: 69.0: 4: 4)	MCC: Extract: A: PVPK-30 (33.5: 46.2: 2.7: 2.7)	22.36
PF5	MCC: Extract: A: PVPK-30 (50: 49.3: 4: 4)	MCC: Extract: A: PVPK-30 (40.5: 40: 3.2: 3.2)	15.97
PF6	MCC: Extract: A: PVPK-30 (50: 54.2: 4: 4)	MCC: Extract: A: PVPK-30 (38.5: 41.8: 3.1: 3.1)	17.57

PF: pellets formulation: MCC: microcrystalline cellulose; PVP: polyvinylpyrrolidone; A: aerosol. Source: Authors.

2.3 Preparation of self-emulsifying formulations

The preparation of the self-emulsifying formulations involved mixing the surfactant Poloxamer 188 (Pluronic® F-68) and the co-surfactant sorbitan triolate (Span®85) (Table 2) with a standardized extract of *P. emarginatus* at 37 ºC in a magnetic stirrer. The extract solid: excipient ratio was 1:1. The hydrophilic-lipophilic balance (HLB) was calculated according to Griffin's Theory for the combinations of Pluronic® F-68 with HLB of 20.5 and Span®85 with an HLB of 1.8. After the dispersion of the surfactant and co-surfactant in the extract, the formulations were stored at room temperature for 24 hours to observe phase separation or any change in the system. To evaluate the self-emulsification ability of the different formulations, 1 g of each formulation was dispersed in 200 mL of distilled water under constant stirring in a mechanical stirrer (IKA® C-MAG HS7) kept at 70 rpm (37 ºC).

Table 2 - Composition of self-emulsifying systems.

	Composition of the self-emulsifying mixture (% w/w)	
Formulation code	Pluronic®F-68	Span®85
SES1	90	10
SES2	80	20
SES3	70	30
SES 4	60	40
SES5	50	50

SES: self-emulsifying systems. Source: The authors.

Table 2 describes the studied self-emulsifying systems.

The emulsification process was visually monitored and the diameter and polydispersity index (PdI) of the droplets were determined by the dynamic light scattering technique in the ZetaSiser Nano-S equipment (Malvern Instruments, New York, USA). The SES1 to SES5 formulations were evaluated regarding their physical stability during 24 h. The average diameter and the polydispersity index (PdI) of the droplets were evaluated.

2.4 Preparation and characterization of pellets containing the self-emulsifying systems

The pellet formulation (Table 1), which presented the best morphological properties, was selected to prepare pellets containing the self-emulsifying systems. The pellets containing the self-emulsifying systems (PSES1 to PSES5) were produced as described in section 2.2, using the SES instead the standardized extract as liquid binder. The resulting pellets were analyzed in a stereomicroscope coupled to a camera (Leica MZ, Germany), and the images were recorded using the Leica MJ software (Leica, Germany). The area and Feret diameter of the pellets were determined by analyzing the images obtained using the Image J software (NIH, USA). The data obtained were used to calculate the projected sphericity.

2.5 Determination of the solubility of geranylgeraniol

Geranylgeraniol solubility was determined in 0.1 M HCl solution (pH 1.2); 0.1 M HCl containing 0.5% (w/v) sodium lauryl sulfate (SLS); 0.05 M dibasic sodium phosphate buffer (pH 6.8); dibasic sodium phosphate buffer pH 6.8 containing 0.5% (w/v) SLS.

Ten milliliters of *P. emarginatus* extract (equivalent to 3.2 g of total solids and 160 mg of geranylgeraniol) were added to 10 mL of test media under constant stirring at 250 rpm in a planar shaker incubator with orbital shaking platform (IKA® KS 4000 ic control). The experiment was conducted at 37 °C for 24, 48, and 72 h. Aliquots of 1 mL were taken at each period, filtered through a 0.2 µm filter (Millex®), and had the geranylgeraniol content determined by HPLC. This test was performed in triplicate.

2.6 Preparation and characterization of capsules containing the pellets

The selected pellet formulations containing *P. emarginatus* extract (Table 1) and the self-emulsifying systems that presented the most suitable HLB (Table 2) were added to hard gelatin capsules. Next, capsules were evaluated for average weight, geranylgeraniol content (HPLC), and *in vitro* dissolution profile.

2.7 Dissolution profile of the geranylgeraniol from pellets

To evaluate the geranylgeraniol dissolution from the selected *P. emarginatus* pellet formulations, 0.05 M sodium phosphate buffer pH 6.8 with 0.5% SLS was used. A dissolution flask containing 500 mL of the medium, equipped with a paddle apparatus operating at 100 rpm, was used. A Hanson dissolution model Vison Elite 8 was used, and the experiments were conducted at 37 ± 0.5°C Aliquots of 3 mL were withdrawn each time (5, 10, 20, 30, 40, 50, 60, and 90 min). The dissolution profile was determined with six capsules. The concentration of geranylgeraniol was determined by HPLC (Oliveira, 2014). Analyzes were performed in triplicate.

2.8 Accelerated stability study

The selected *P. emarginatus* pellet formulations were stored at 75 ± 5% relative humidity (UR) for six months in a climatic chamber (Solab SL-206), according to the official guidelines (Brazil, 2005). Geranylgeraniol was quantified at 0, 1, 2, 3, and 6 months of study. The mass of 0.2 g of pellets was transferred to a 25 mL volumetric flask, the volume was completed with HPLC-grade methanol, and the dispersion was subjected to ultrasonic extraction for 40 min. The results were expressed in % geranylgeraniol remained in the pellets as a function of storage time.

2.9 Statistical analysis

Analysis of variance of the dissolution and stability data was performed using the Statistica 7 Software (Statsoft Inc., Tulsa, OK) Two-way analysis of variance was used with p value less than 0.01.

3. Results and Discussion

3.1 Obtaining *P. emarginatus* extract

The concentrated extract of *P. emarginatus* fruits showed a total solids content of 32.39 g per 100 g extract. Quantification of geranylgeraniol by HPLC showed an average content of 5.55% (w/w). Isolation and characterization studies of oils and extracts produced from fruits of species of the genus *Pterodon* identified the compound geranylgeraniol as a component of relevance to the identity of the genus and as a constituent of analytical monitoring (De Omena et al., 2006; Menna-Barreto et al., 2008; Spindola et al., 2010; Spindola et al., 2011; Alves et al., 2020).

3.2 Preparation of *P. emarginatus* pellets

The formulations developed (Table 1) resulted in pellets with different surface properties. PF1 and PF2 showed low mechanical resistance. Thus, polyvinylpyrrolidone K-30 was added to increase the binding property of the system (PF3). Formulations PF4, PF5, and PF6 had silicon dioxide (Aerosil®200), which was included to adsorb the oily fraction of the extract, allowing the formation of a homogeneous system. PF5 and PF6 formed more resistant and homogeneous pellets.

The PF6 formulation composed of microcrystalline cellulose, standardized extract (solids content in the formulation of 17.57%), aerosil® and polyvinylpyrrolidone K-30 (50: 54.2: 4: 4 respectively) were selected for further studies since it had a higher amount of the standardized extract and allowed the particles not to be aggregated during spheronization. The pellets presented a reasonable sphericity.

In recent years, the development of pellets from plant extracts has shown promise in producing phytomedicines (Rabisková et al., 2012; Beringhs et al., 2013; Silva Filho et al., 2015; Zhang et al., 2015; Silva et al., 2021).

3.3 Preparation of self-emulsifying formulations

The extract: excipient ratio of the PF6 pellet formulation was used to obtain pellets containing self-emulsifying constituents. In addition, the hydrophilic-lipophilic balance (HLB) was used to obtain stable emulsions. Formulations SES1 to SES5 presented HLB from 11.15 to 18.63 (Table 3). The SES3 formulation showed an HLB close to 15. According to Pascoa et al. (2015), microemulsion systems containing the oil resin extracted from the fruits of *P. emarginatus* showed an HLB value of approximately 15. Oliveira et al. (2016) developed nanoemulsions from the fixed oil of *P. emarginatus* fruits and observed that emulsions with HLB of 14 and 15 had adequate stability.

In the present study, the formulations SES1 to SES5 did not show phase separation when dispersed in water. However, based on the HLB values recommended in the literature (Pascoa et al., 2015; Oliveira et al., 2016), further studies were performed using SES3 and SES4 formulations.

Table 3 - Hydrophilic-Lipophilic Balance (HLB) calculated for the formulations of emulsified systems.

	Composition of the self-emulsifying mixture (% w/w)		
Formulation code	Surfactant Pluronic®F-68	Co-surfactant Span®85	HBL
SES1	90	10	18.63
SES2	80	20	16.76
SES3	70	30	14.89
SES4	60	40	13.02
SES5	50	50	11.15

Source: Authors.

Table 3 presents the HBL value of the studied self-emulsifying systems.

SES3 and SES4 formulations had the average diameter of the particles and polydispersity index (PdI) determined by the dynamic light scattering technique. These results are presented in Table 4. The polydispersity index indicates the droplet size distribution and determines the physical stability of the colloidal dispersion (Cazo et al., 2012). The mean diameter and PdI values found in this study showed that the SES gave rise to homogeneous emulsions in the nanometric range.

Table 4 - Mean diameter and polydispersity index of the emulsified droplets from SES3 and SES 4 formulations.

Formulation code	Mean diameter (nm)	PdI
SES3	302.1	0.437
SES4	208.8	0.344

Source: Authors.

Table 4 presents the mean particles diameter and polydispersity index (PdI) of the selected self-emulsifying systems.

3.4 Preparation of pellets containing the self-emulsifying systems

Incorporating the selected SES formulations in MCC resulted in compact pellets with a more homogeneous surface than pellets consisting only of the standardized extract without surfactants and co-surfactants. In any case, the *P. emarginatus* pellets presented a rounded shape. Additionally, the pellets showed a non-agglomerated aspect and enough mechanical resistance to support the encapsulation process. The pellet's sphericity was approximately 0.52 ± 0.13 and showed an average size from 662 to 1100 (Table 5).

Table 5 - Sphericity and average size of *P. emarginatus* pellets (containing SEDDS or not) obtained by extrusion/spheronization

Formulation code	Mean sphericity ± SD	Mean size (µm) ± SD
PF6	0.52 ± 0.13	662 ± 0.25
PSES3	0.52 ± 0.14	877 ± 0.37
PSES4	0.53 ± 0.14	779 ± 0.35

Source: Authors.

Table 5 presents the sphericity and average size of the pellets containing the selected self-emulsifying systems (PSES 3 and PSES4) or not (PF6).

Studies have been carried out with the production of pellets containing self-emulsifying systems containing poorly soluble synthetic drugs (Tuleu et al., 2004; Abdalla et al., 2008; Krstic et al., 2015). However, this technological strategy has yet to be explored for complex natural mixtures like plant extracts.

It is important to note that due to the complex chemical composition of plant extracts, the development of stable formulations is challenging. In this context, developing solid self-emulsifying systems with the standardized extract of *P. emarginatus* is an exciting alternative to overcome the low solubility of the extract in aqueous media, favoring the dissolution of its active compounds in biological systems and potentially improving its biological actions.

Studies with species of the genus *Pterodon* have shown the promising ability of micro and nanostructured systems to increase the pharmacological efficacy of their oil and extracts (Alves et al., 2014; Hoscheid et al., 2015; Vieira et al., 2020; Zamora et al., 2020; Kawakami et al., 2021; Lemos et al., 2021). However, the development of self-emulsifying drug delivery systems (SEDDS) with *P. emarginatus* extracts has yet to be explored.

3.5 Determination of the solubility of geranylgeraniol

The solubility test aimed to select the dissolution medium in which the geranylgeraniol showed excellent solubility allowing the definition of the sink condition. It was possible to observe that the marker solubility in 0.1M HCl and pH 6.8 was

low. The surfactant's presence led to higher geranylgeraniol concentrations, with phosphate buffer pH 6.8 plus 0.5% SLS selected as the dissolution medium (Table 6).

Table 6 - Mean solubility values (mg mL^{-1}) of geranylgeraniol.

Liquid media	Concentration (mg mL^{-1}) ± SD		
	24h	48h	72h
0.1M HCl pH 1.2	0.0	0.0	0.0
0.1M HCl pH 1.2 + 0.5% SLS	0.37 ± 0.02	0.37 ± 0.04	0.42 ± 0.08
0.05M phosphate buffer pH6.8	0.28 ± 0.06	0.29 ± 0.10	0.60 ± 0.27
0.05M phosphate buffer pH6.8 +0.5% SLS	1.51 ± 0.09	1.65 ± 0.15	2.31 ± 0.66

Source: Authors.

Table 6 presents the solubility of geranylgeraniol in the tested dissolution medium.

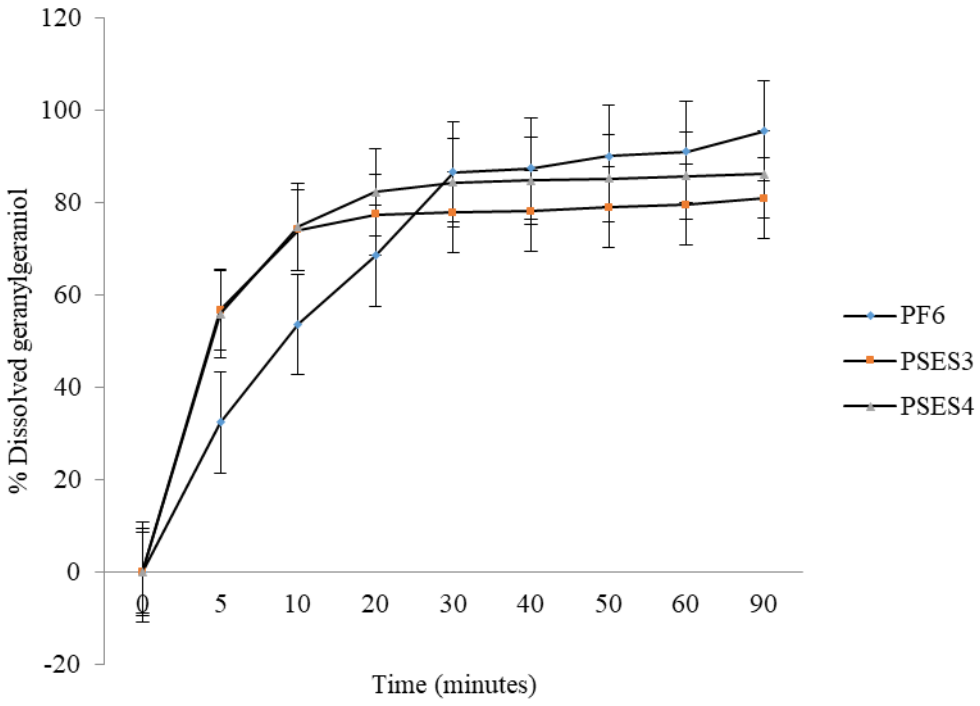
Additionally, the liquid medium containing surfactant can better simulate the conditions of the gastrointestinal tract than that containing organic solvents or other non-physiological substances (Noory et al., 2000). The concentration of SLS commonly used in dissolution media is 0.1 to 3% (Zhao et al., 2004).

3.6 Characterization of capsules containing the *P. emarginatus* pellets

The capsules containing *P. emarginatus* pellets had an average weight of 263 mg and presented acceptable weight variation (less than ± 10%).

Analysis of variance showed that geranylgeraniol dissolved from the studied formulations, significantly increase ($p < 0.01$) as a function of time (Figure 1) and shows that the formulations PF6 and those containing the self-emulsifying systems (PSES3 and PSES4) were statistically different from each other at the 5% level. In the first 5 and 10 min of dissolution, the PSES3 and PSES4 formulations showed a higher level of geranylgeraniol dissolution compared to the PF6 formulation ($p=0.000117$). However, after 20 min of dissolution, no significant difference was observed between the analyzed formulations. These data indicate that the dissolution rate of geranylgeraniol from self-emulsifying formulations was significantly higher in the first minutes,

Figure 1 - *In vitro* dissolution of geranylgeraniol from capsules containing *P. emarginatus* pellets (PF6) and pellets in self-emulsifying systems (PSES3 and PSES4 formulations) at pH 6.8 at 37 ± 0.5ºC. Data are expressed as mean ± SEM, with standard deviation for $p < 0.01$.



Source: Authors.

Figure 1 demonstrates the geranylgeraniol dissolved from the studied formulations (in the pellets - PF6 - or those containing the selected self-emulsifying systems - PSES 3 and PSES4).

We highlight that the higher percentage of dissolution of the pellets containing the self-emulsifying systems contributes to developing a solid pharmaceutical form that allows the release of the lipophilic marker geranylgeraniol in aqueous media.

The superior geranylgeraniol dissolution from the pellets containing the self-emulsifying systems is because, in these systems, the free energy required to form an emulsion is low, thus allowing the spontaneous formation of the oil/water interface. It is proposed that the oil/surfactant/co-surfactant and water phases effectively swell by decreasing particle size and eventually increasing the rate of release of the compound from the dosage form (Dash et al., 2015).

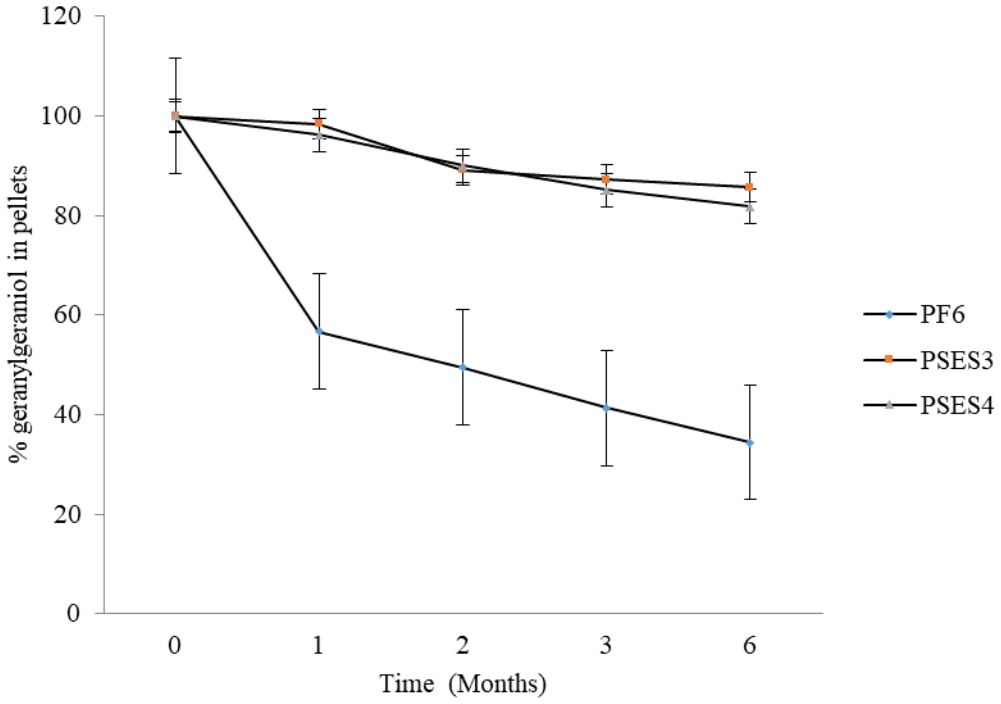
The use of self-emulsifying systems allows for better solubility and dissolution conditions, contributing to the more excellent stability of the systems (Vasanthavada & Serajuddin, 2007). Furthermore, using a solid multiparticulate dosage form may also improve the technological properties of the plant extract. It may favor the dissolution rate (Beringhs et al., 2013) and contribute to improving the bioavailability of the drug due to the control or modification of its release rate (Bhaskaran & Lakshmi, 2010). The importance of associating self-emulsifying systems with pellets to convey the *P. emarginatus* extract is highlighted in this context.

3.7 Accelerated stability study

Stability study of the *P. emarginatus* pellets showed that the geranylgeraniol content from the PF6 formulation was significantly lower than the marker content in PSES3 and PSES4 formulations ($p < 0.01$) (Figure 2). In the first month of the

study the PF6 pellets showed a decrease of 43.28% of the marker content, while the PSES3 and PSES4 formulations had the drug content slighty decreased (1.60% and 3.79%, respectively). At the end of 6 months, the self-emulsifying systems had a geranylgeraniol content of 85.6% (PSES3) and 81.8% (PSES4), while for PF6 it was only 34.4% (Figure 2).

Figure 2 - Stability of geranylgeraniol in pellet formulations containing *P. emarginatus* extract (PF6) and in *P. emarginatus* pellets containing the self-emulsifying systems (PSES3 and PSES4) in the 6-month period. Data are expressed as mean ± SEM, with standard deviation for $p < 0.01$.



Source: Authors.

Figure 2 provides data from the stability study in relation to the geranylgeraniol content of *P. emarginatus* pellets (PF6, PSES3 and PSES4).

The results show that the self-emulsifying systems, under the conditions studied, contribute to the physicochemical stability of the marker, a lipophilic compound of the *P. emarginatus* standardized extract.

4. Conclusion

Associating SEDDS and pellet technologies contributed to developing a new technological platform for *P. emarginatus*-based bioproducts, favoring the geranylgeraniol *in vitro* dissolution and increasing its stability.

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