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Original Article

THERMAL DEGRADATION KINETICS OF KAEMPFEROL AND QUERCETIN IN THE PRE-FORMULATED OF THE STANDARDIZED EXTRACTS OF POINCIANELLA PYRAMIDALIS (TUL.) L. P. QUEIROZ OBTAINED BY SPRAY DRYER

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ABSTRACT

Objective: The aim of this work was to evaluate the stability and determine the kinetic parameters of degradation of biomarkers kaempferol and quercetin, present in the pre-formulated of the extract of Poincianella pyramidalis obtained by a spray dryer.

Methods: A 2^3experimental design coupled with RSM was applied to evaluate and optimize the effects of processing parameters on the content of chemical markers in dry extracts by a spray dryer. Stability testing was performed to verify the influence of temperature on the degradation of kaempferol and quercetin present in the pre-formulated. The markers contents were determined by HPLC.

Results: Surface response analysis showed the influence of the independent variables on the responses of the concentration kaempferol and quercentin biomarkers on the process. The variables of the inlet air temperature, flow feed rate and the adjuvant ratio presented negative responses with significant difference ($p<0.05$). According to the data obtained in the stability of the pre-formulated studied zero and second orders kinetics models the for degradation of the kaempferol and only second order kinetic model for the quercetin. It was also evaluated reducing the concentration of both biomarkers studied throughout the study.

Conclusion: In the present study, it was observed that all independent variables of the drying process by spray dryer showed the greatest influence on the concentration of the studied markers. Two markers had a different thermal behavior compared to the different excipients studied and there was degradation of both the quercentin biomarker and kaempferol during the study period.

Keywords: *Poincianella pyramidalis*, Spray dryer, Excipients, Stability

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INTRODUCTION

Poincianella pyramidalis (Tul.) L. P. Queiroz is an arboreal species belonging to the family Fabaceae, endemic to the northeastern region of Brazil, mainly in the caatinga biome, popularly known as “catingueira”, “pau de porco”, “catinga de porco”, “pau de rato”, “mussilaba” e “catingueira-das-folhas-largas”[1]. It is used in tradicional medicine for the treatment of gastritis, colic, diarrhea, asthma, bronchitis, diabetes, as an expectorant, cicatrizant, anti-inflammatory and diuretic [2-5].

Due to the great diversity of traditional uses and the importance of this species to the caatinga biome, several researchers from different areas of knowledge have shown interest in the study of this species. Phytochemical investigations have demonstrated the presence of secondary metabolites, such as flavonoids, diterpenes, tannins and lignans [6-10]. Several biological activities have already been tested with this species, among which we can highlight the antimicrobial activity against Staphylocus aureus, Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae, *Salmonella spp., S. Aureus e Pseudomonas aeruginosa,* antioxidant, gastro protective, anti-inflammatory, anti-nociceptive and anthelmintic activity, which corroborates many of its traditional uses. Due to these proven pharmacological properties, this species has a great potential for the development of a herbal medicine with ample spectrum of action [11-16].

Obtaining standardized plant extracts has been one of the major challenges for the development of herbal medicines, especially in Brazil, and the herbal industry has sought alternatives to solve this problem, one of which would be the production of standardized dried extracts of medicinal plants aiming establishment of quality control parameters for the vegetable raw material [17-19].

Spray drying is one of the most commonly used drying techniques in the preparation of dried vegetable extracts, providing products with suitable technological properties in a short time of drying and with a high production capacity [20-21], however this process can also be affected significantly by parameters such as air inlet temperature, feed flow rate and concentration of carrier agent in the mixture [22-23]. Response surface methodology (RSM) is a widely used tool to evaluate the effects of the various factors in the process and to define the best conditions for the desired responses [23-25].

Ensuring the stability of the plant extracts is essential to preserve the quality, safety and efficacy of the final product, accelerated stability studies are considered predictive tools with emphasis on qualitative results, but of great use for the design of new formulations and products. Since from the first signs of instability of a drug or marker, it is possible to assist in the identification of potential problems of development, as well as to articulate strategies of stabilization and to suggest ways to optimize the manufacturing processes [26].

The aim of this work was to determine the thermal degradation kinetics of the biomarkers kaempferol and quercetin in the preformulated dry extract of Poincianella pyramidalis.

MATERIALS AND METHODS

Herbal material and chemicals

Leaves of Poincianella pyramidalis, were collected in the city of Serra Branca, State of Paraíba, Brazil. (7°30’51.1”S 36°41’91.5”O). The voucher specimen are deposited at the herbarium Lauro Pires Xavier of the Federal University of Paraíba, Brazil, under number NC36. The herbal material was dried in an oven with circulating air

(Tecnal ®, Model TE-394-4), at 40°C. After drying the material was reduced in an industrial mill to obtain the powder.

In the present study, the ethanol absolute (Toscano®, Brazil), chloroform and hexane, analytical grade (Vetec®, Brazil), methanol grade HPLC (Tedia Brazil, Rio de Janeiro, RJ, Brazil) Anhydrous phosphoric acid (Merck®, Germany) were used. The water was purified using aMilli-Q system (Millipore, Massachusetts, USA).

The analytical standards kaempferol (purity: 98%) and quercetin (purity: 97%) were obtained from Sigma-Aldrish®. The pharmaceutical excipients: microcrystalline cellulose 102 (MC) starch (ST), lactose (LC), maltodextrin (MD) and carrier agent colloidal silicon dioxide 200 (CSD) were all purchased from Brazilian suppliers.

Preparation of hydro alcoholic extract

The leaf powder was subjected to maceration with ethanol-water 50:50 (v/v) at plant: solvent ratio of 20:100 (w/v), for a period of 120 h at room temperature. The extractive conditions were previously studied and optimized by our research group, in order to obtain the best yield of the biomarkers kaempferol and quercetin.

Spray drying

The spray-drying process was carried out in a mini Spray-Dryer (LabPlant®, model SD-05, Huddersfield, UK), with a concurrent flow regime, equipped with a peristaltic pump connected to a two-fluid atomizer, with a internal orifice of 1.2 mm, which operated with an air flow rate, W_g=40L/min and constant pressure of 2.0 bar. The operating parameters of the process were following: drying air inlet temperature (160, 170 and 180 °C), air flow feed rate of the drying composition fed to the spray drying (4, 6 and 8 ml/min) and proportion of colloidal silicon dioxide in the drying composition (10, 15 and 20%).

Experimental design

A 2^{3+1}factorial experimental design coupled with surface response methodology (RSM) was applied to evaluate and optimize the effects of processing parameters on the content of chemical markers kaempferol (Y_1) and quercetin (Y_2). Therefore were investigated the individual and interactive effects of the following independent variables: drying air inlet temperature (X_1), air flow feed rate of the drying composition fed to the spray drying (X_2) and proportion of colloidal silicon dioxide in the drying composition (X_3). Table 1 shows the coded and encoded values in the design experimental.

Statistical analysis

The experimental data were analyzed with the aid of the Statistica 13.1 software program (Dell Inc., Tulsa, USA). The results were expressed as mean±SD and coefficient of variation. The means were compared using ANOVA/SRM. Differences were considered statistically significant at $p<0.05$ and larger values were not considered. A total of 9 experiments runs were performed, including the medium point, with nine, replicates for each of them.

The parameters of the kinetic models and the arrhenius equation were obtained by linear regression. The order of reaction was chosen by comparing the correlation coefficients.

Table 1: Factors coded and non-coded and their levels in fractional factorial design (2^{3+1})

Runs	X_1 (IT)	X_2 (FFR)	X_3 (CSD)	IT (°C)	FFR (ml/min)	CSD (%)
1	-1	-1	-1	160	4	10
2	-1	+1	-1	160	4	10
3	-1	-1	+1	180	8	20
4	-1	+1	+1	180	8	20
5	+1	-1	-1	180	4	10
6	+1	+1	-1	160	4	10
7	+1	-1	+1	180	8	20
8	+1	+1	+1	180	8	20
9	0	0	0	170	6	15

IT: air inlet temperature, FFR: air flow feed rate of the drying composition, CSD: the proportion of colloidal silicon dioxide.

Pre-formulated

Pre-formulated were prepared from fisical mixtures of the nebulized extract (NE) and the following pharmaceutical excipients: starch (ST), microcrystalline cellulose 102 (MC), maltodextrin (MD) and lactose (LC) in the proportion of 1:1. The powder of the blends was calibrated in 48 mesh sieves and mixed mechanically for 15 min. The tests were performed in 9 replicates.

Quantification of chemicals markes quercetin and kaempferol

The quercetin and kaempferol contents were determined using High-performance liquid chromatography (Shymadzu, Tokyo, Japan), equipped with LC-20 AT multi-solvent supply system, DGU-20A5 degassing system, SIL-20A auto-sampler, CTO-20A column furnace and detection by electron spectrometry in the ultraviolet-visible region with SPD-M20A UV-VIS diode array, at 370 nm. The mobile phase used was a mixture of methanol: phosphoric acid 1% (47%: 53%) in the isocratic system, pH 3.1 and flow of 1.2 ml/min. The stationary phase was a C-18 Gemini 5µ, 150 x 4.6 mm x 0.5µm (Phenomenex) column.

Samples were prepared according to the previously described methodology [27]. A standard solution 4µg/ml of de kampferol and quercetin was prepared with methanol: water (70:30). All sample and standard solutions were filtered through 0.45 µm PTFE membrane (Millipore, Massachusetts, USA).

The method was previously validated by our working group. Parameters of validation, such as selectivity, linearity, detection and quantification limits and precision were established according to ICH Q2B [28]. The calibration curve was found to be linear over a kaempferol and quercetin concentration range of 0.4 to 7.6 µg/ml presenting a coefficient of the linear regression analysis was within>0.999. The Limit of Detection (LOD) for kaempferol and quercetin were 0.07 and 0.18 µg/ml, respectively. The Limit of Quantification (LOQ) for kaempferol and quercetin were 0.22 and 0.56 µg/ml, respectively. The method proved to be robust for small, deliberate changes in temperature, flow and pH of the mobile phase with RSD % <3.0%. The Relative Standard Deviation (%) values for markers (intra-and inter-day precision studies) were<5.0% and the accuracy was>95%.

Stability testing

Stability testing was performed to verify the influence of temperature on the degradation of bioactive compounds, present in the pre-formulated. Kaempferol and quercetin were used as chemicals markers. The tests were carried in a B. O. D (Tecnal TE-371) incubator with temperature control, for a period of 180 d under a temperature 40±2 °C. Approximately 3g of samples was placed in hermetic PVC-aluminum sachets. The amount of the kaempferol and quercetin markers were periodically analyzed (90 and 180 d) by HPLC and compared to that present at zero time. The assays were carried out in 9 replicates.

For the determination of kinetic parameters of reaction order (n) and decomposition rate constant (k) the Arrhenius equation was used:

$$\kappa = Ae^{-\frac{E_a}{RT}} (1)$$

Where:

κ is the chemical reaction rate, Ae is the pre-exponential factor, E_a is the activation energy (J/mol), R is the ideal gas constant (8.314J/mol. K) and T is the absolute temperature.

Experimental data of kaempferol and quercetin degradation were fitted by zero and second-order kinetic models, given by Eqs. (2) and (3), respectively [29].

The zero-order reaction rate was obtained directly from the mass data and plotted against time according to the following equation:

$$C = C_0 - \kappa t (2)$$

Where:

C is concentration at time t, C_0 is initial marker concentration, and κ′ is the reaction constant zero-order.

The second-order reaction, the inverse of the concentration is plotted versus at time t, according to the following equation:

$$\frac{1}{[C]} = \frac{1}{[C_0]} + \kappa'' t (3)$$

Where:

C is concentration at time t, C_0 is initial marker concentration, and κ′′ is the reaction constant second-order.

RESULTS AND DISCUSSION

Effect of drying operating conditions on the concentration of monitored chemical markers

According to the data obtained, it was verified that the operational conditions of drying by dry spray influenced the concentration of the two chemical markers studied, kaempferol and quercetin, a fact explained by the physicochemical characteristics. Table 2 shows the total number of experiments that were carried out and the concentrations of the chemical markers obtained in each of them, where it was observed that the highest concentration obtained for the kaempferol and quercetin markers, respectively, was in experiment 7 (0.87 mg/g±0.02 and 1.55 mg/g±0.04), corroborating with the response surface graphs (fig. 1), which show that the concentrations of the markers increase with minimum levels of the three factors studied, whereas the lowest concentrations recorded were obtained in experiments 1 and 5 for kaempferol and 1 and 8 for quercetin.

Table 2: Experimental design for spray drying runs, independent variables, with their corresponding response values

Run	Independent variables			Response 1	Response 2
	IT (°C)	FFR (ml/min)	SDC (%)	Kaempferol content (mg/g)*	Quercetin content (mg/g)*
1	180	4	20	0.68±0.02	1.28±0.05
2	180	8	20	0.70±0.02	1.34±0.03
3	180	4	10	0.75±0.03	1.39±0.05
4	160	8	10	0.79±0.03	1.44±0.06
5	160	8	20	0.68±0.02	1.31±0.04
6	180	8	10	0.74±0.03	1.35±0.06
7	160	4	10	0.87±0.02	1.55±0.04
8	160	4	20	0.75±0.01	1.28±0.05
9	170	6	15	0.79±0.03	1.45±0.06

*Values represent the mean±Standard deviation (n = 9), IT: air inlet temperature, FFR: air flow feed rate of the drying composition, CSD: proportion of colloidal silicon dioxide

Table 3 and fig. 1 shows the effects between the selected independent variables (IT, FFR and CSD) on the development and optimization of the drying process of the *P. pyramidalis* extract, using as a response the concentration of the markers kaempferol and quercetin.

Statistical analysis of the experimental data (table 3) showed that both the quercetin and kaempferol concentrations were significantly influenced by all the independent variables when the primary effects were evaluated, being the air inlet temperature (X_1) and the carrier ratio (X_2)were the most important variables in the analysis of the responses. The secondary effects were too observed for both responses in the following interactions: IT (X_1) x FFR (X_2) and IT (X_1) x CSD (X_3), with significance level p<0.05. The tertiary interaction between IT x FFR x CSD factors exerted significant influence only on quercetin label. This shows that the concentrations obtained are also influenced by the nature of chemical markers.

Surface response analysis was used to evaluate the individual variables and interactive effects on drying process investigated in this study. A 3D response surface plot (fig. 1) showed the influence of the individual and secondary effects studied on the responses. The negatives effects of the inlet air temperature (X_1) and the adjuvant ratio (%) on the responses showed a significant difference (p<0.05). This can be explained by the fact that at a higher temperature has a direct impact in the degradation of chemical compounds of the extract. Similar results were described by Thirugnanasambandham and Siva Kumar in the study of the influence of process conditions on the physicochemical properties of pomegranate juice in spray drying process [30] and by Patil, Chauhan and Singh, who performed a work for optimization of the spray-drying process for developing guava powder using response surface methodology [24]

Table 3: Summary of significant factor effects according to ANOVA

Independent variable	p-value	
	Kaempferol content	Quercetin content
IT (X_1)	0.000000*	0.000000*
FFR (X_2)	0.000972*	0.000444*
CSD% (X_3)	0.000000*	0.000000*
IT (X_1) x FFR (X_2)	0.001395*	0.000665*
IT (X_1) x CSD% (X_3)	0.000624*	0.015135*
FFR (X_2) x CSD% (X_3)	0.342668	0.129123
IT (X_1) x FFR (X_2) x CSD% (X_3)	0.280519	0.030913*

*p<0.05significant effect

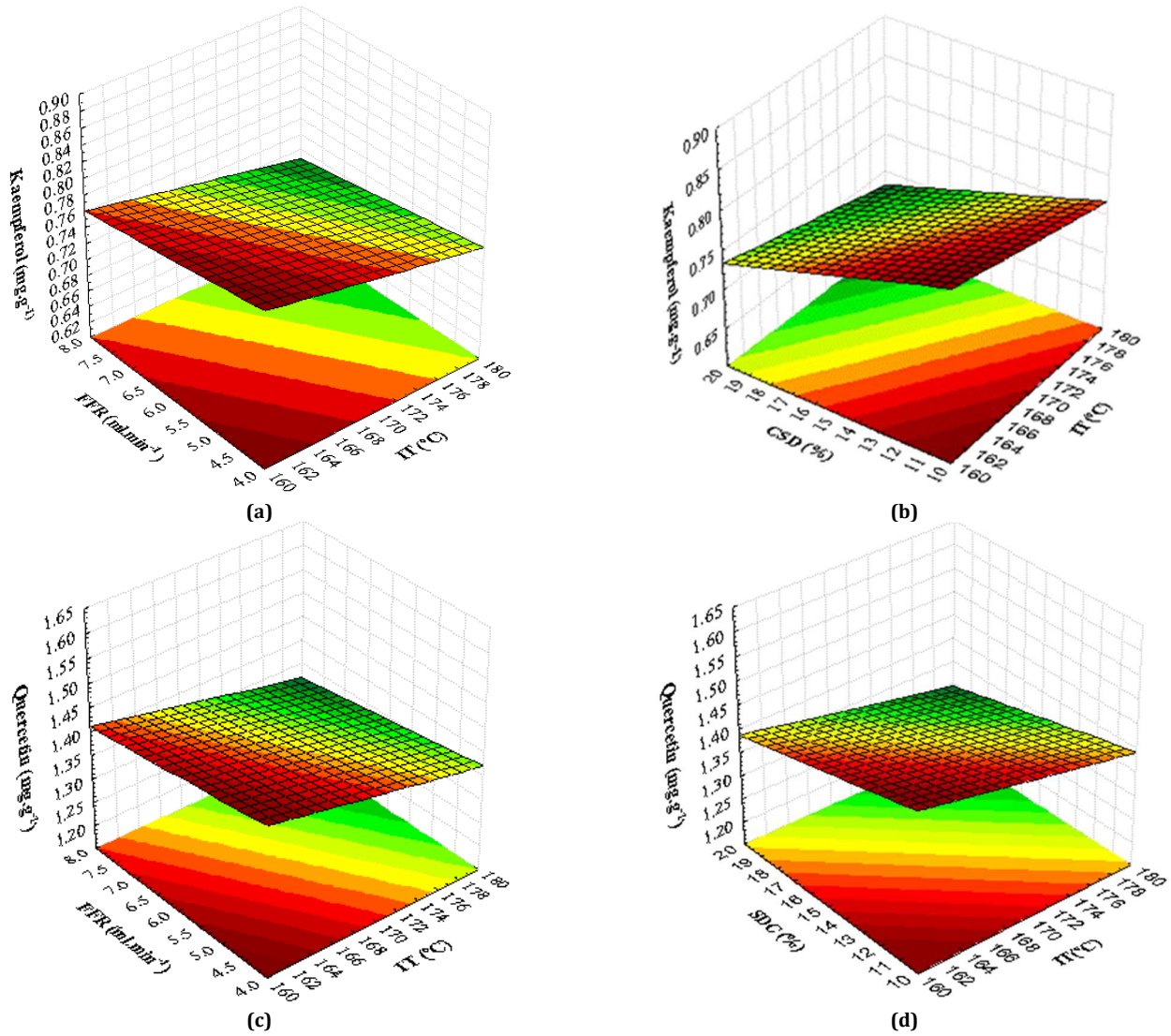

Fig. 1: Response surface showing the effects of the process parameters, air inlet temperature, air flow rate of the drying composition, proportion of colloidal silicon dioxide in kaempferol and quercetin contents

Stability testing

The Arrhenius method was used to determine the decomposition kinetic parameters following: reaction order (n), decomposed fraction $\alpha_{0.9}$ and rate constant (*k*).

Table 4 shows the kinetic parameters and regression coefficients (R^2) that defined two kinetic models for the biomarker kaempferol, zero order kinetic model for the preformulated NE: ST and NE: LAC and second order model kinetic for following binaries mixtures: NE: MC 102, this shows that the excipients directly influenced in the kaempferol degradation kinetics.

The values of the degradation constants of kaempferol marker are in accordance with the laws of classical kinetics, which showed an exponential progression in relation to the temperature (fig. 2). According to the results obtained in the kinetic study, the times corresponding to the fraction decomposed $\alpha_{0.9}$ of the concentrations of the marker studied presented values in the range 50.90 to 64.68 d, demonstrating a variation in the stability of the pre-formulated, with the following order of stability: NE: ST<NE: MC 102<NE: MD<NE: LAC.

The pre-formulations showed a second order kinetic degradation for the marker quercetin since the rate constants presented an exponential behavior based on correlation coefficients (R^2) (fig. 3). The quercetin biomarker, a second-order kinetic model was defined for all preformulated, thus suggesting that the quercetin marker has a similar thermal behavior for the four excipients studied. The degradation constants showed that the kinetic decomposition profiles of ESN: ST, ESN: MMC 102 and ESN: MD showed differences in the times corresponding to the decomposed fraction $\alpha_{0.9}$ with variations between 67.31 to 107, 3 d (table 4).

The mechanism of flavonoids thermal degradation was explained by Scibisz, who suggested that under the influence of heat, glycosidic bonds in dye molecules undergo hydrolysis leading to unstable aglycones [31]. Also, it has been explained that polyphenols stability, eg. Anthocyanin, a decreases with increasing number of free hydroxyl groups in the B-ring increase [32]. The results obtained in this study are in agreement with others studies reported and indicate that the spouted bed and spray dryer extracts of medicinal plants, eg. *Passiflora alata* tended to be hygroscopic and have a short shelf life. The dried extracts of a medicinal plants are a very complex mixture of chemical substances and each one likely degrade at a different rate. However, the use of packaging with low water vapor permeability, for example, laminated aluminium film, and lower storage temperatures would significantly increase the product stability [33].

Table 4: Kinetics parameters of the chemical markers on the preformulated on conditions storage 40°C during 180 d

Samples	Kaempferol				Quercetin			
	k (d^{-1})	R^2	Decomposed fraction $\alpha_{0,9}$ (d)	Kinetic model	*k* (d^{1})	R^2	Decomposed fraction $\alpha_{0,9}$ (d)	Kinetic model
ESN: ST	-2.85E-02	0.999	64,42	Zero-Order	1.00E-03	0.964	67,31	Second-Order
ESN: MMC 102	7.00E-05	0.993	63,21	Second-Order	1.00E-03	0.950	70,52	Second-Order
ESN: MD	5.00E-05	0.999	50,90	Second-Order	1.00E-03	0.898	107,3	Second-Order
ESN: LAC	-5.74E-02	0.970	64,68	Zero-Order	2.00E-03	0.988	248,5	Second-Order

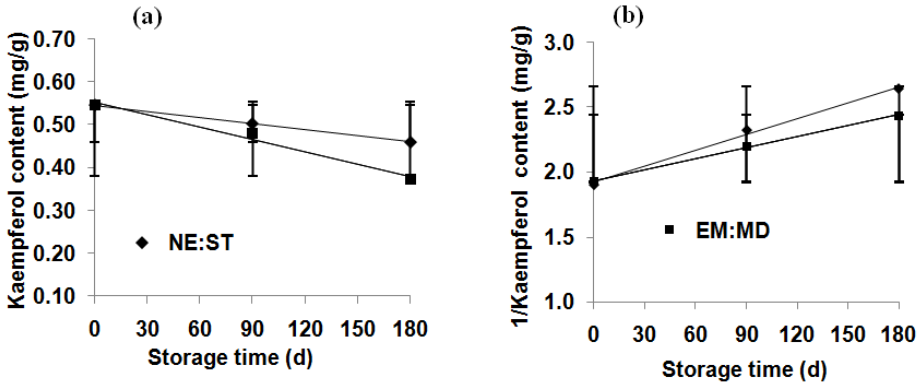

Fig. 2: Degradation kinetic kaempferol of the preformulateds during times storage: (a) nebulized: starch, nebulized: lactose zero-order model (b) nebulized: maltodextrin, nebulized: microcrystalline cellulose, second-order model

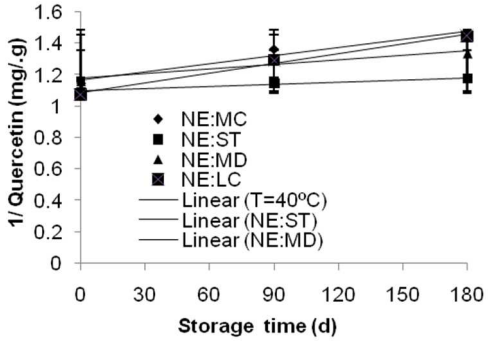

Fig. 3: Degradation kinetic quercetin of the preformulateds during times storage

CONCLUSION

In the present study, the effects of the spray dryer process conditions, such as IT, FFR and CSD, on the following responses were evaluated: the levels of the phytochemical markers quercetin and canferol in obtaining the dry extract of *Poincianella pyramidalis* and the results showed that all the responses studied were significantly affected by the process conditions, and the IT and CSD were the independent variables that showed the greatest influence on the concentration of the studied markers. The analysis of the surface methodology allowed to define the optimum conditions of the process, to obtain the maximum concentrations of the monitored markers.

The stability study of the preformulateds showed a king different degradation kinetics for the kaempferol phytochemical marker, with zero order and second order kinetics, while the quercetin marker showed second order degradation kinetics, thus demonstrating that the two markers have a different thermal behavior compared to the different excipients studied.

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AUTHOR CONTRIBUTION

Oliveira AH, performed analysis of all samples, interpreted data, wrote the manuscript and acted as the corresponding author; Leite, RS, Souza VG and Júnior, JVC and Dantas, FH, helped to carry out the experiments, data analysis, collection, and interpretation. Macêdo, RO, Souza, FS, supervised the development of work, helped in data interpretation and manuscript edition and evaluation, performed a critical revision of the article.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests

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