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Production of gastro-resistant coated tablets prepared from the hydroethanolic standardized roots extract of *Harpagophytum procumbens* DC.

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This project aimed at developing a gastro-resistant coated tablet using traditional herbal medicine dry extract from the secondary roots of the plant species *Harpagophytum procumbens* DC. (Pedaliaceae), standardized in harpagoside 20%, popularly known as "devil's claw". The tablets were produced by direct compression and coated with the gastro-resistant dispersion. Accelerated and long-term stability studies were performed to define the period of use and validity. The tablets present a high dose of chemical markers differently from the usual pharmaceutical forms, diminishing the daily doses to 1 or 2 tablets. The hardness, friability, weigh and thickness were in agreement with the Brazilian Pharmacopeia 5th Edition. The analytical method used was validated to confirm the assays. The gastro-resistant coated tablets, obtained from the dried extract of *H. procumbens* DC., standardized in harpagoside 20%, was stable after the accelerated study and the analytical methodology was validated.

Key words: Pedaliaceae, *Harpagophytum procumbens* DC., devil's claw, traditional herbal medicine, gastro-resistant coated tablets.

INTRODUCTION

Harpagophytum procumbens DC. belongs to the family Pedaliaceae. This perennial herbaceous plant, popularly known as "devil's claw", grows naturally in the Kalahari desert and in the steppe region of Namibia in southwestern Africa. Its secondary tubular roots, commonly associated with the term "devil's claw" by its shape, have been widely used in traditional medicine with several therapeutic indications, especially as anti-inflammatory and analgesic (Baghdikian et al., 1997).

According to the Brazilian Resolution of the Collegiate Board of Directors (RDC) n° 26 (Brazil, 2014a), "traditional herbal products are those obtained with the

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Table 1. Stability study of the traditional herbal product.

Storage condition	Packing	Temperature (accelerated)	Temperature (long-term)	Relative humidity
15-30°C	Impermeable	40 ± 2°C	30 ± 2°C	60 ± 5%

exclusive use of vegetal active raw materials whose safety and effectiveness are based on data of safe and effective use published in the technical-scientific literature, and which are designed to be used without supervision by a physician for diagnostic, prescription or monitoring purposes". Thus, in Brazil, the dry extract produced from the roots of the *H. procumbens* DC. plant species, standardized on harpagoside, is classified as a traditional herbal product, and indicated for the relief of moderate joint pain and acute low back pain, according to the ethnopharmacological use described in the literature. In addition, advances in the scientific area have allowed the development of proven medicines and herbal products of safety and efficacy, as well as an increase in the population's search for less aggressive therapies for primary health care (Ribeiro et al., 2005). Given the importance of herbal medicines worldwide, the study of plant species such as *H. procumbens* DC. has been considered to be of extreme relevance for the development of new therapeutic alternatives with efficacy and low adverse effects compared to synthetic drugs.

H. procumbens DC. extract has been constantly investigated as a potential therapeutic agent because of its analgesic and anti-inflammatory activities, and favorable adverse effects profile compared to available synthetic alternatives such as non-steroidal anti-inflammatory drugs (Ahmed et al., 2005). The prescription usually is from 3 to 6 tablets per day, which makes the acceptance of the product very low. Therefore, in view of the increasing use of natural products as a form of medicinal therapy, the research area aimed at the development of traditional phytotherapeutic products obtained from standardized plant extracts, with high content of phytochemical markers, with validated analytical methodologies and pharmacotechnical developments of stable pharmaceutical forms, in order to develop safe and effective products with low adverse effects in high therapeutic doses, which can diminish the quantity of tablets daily, is extremely promising.

MATERIALS AND METHODS

Pharmacotechnical development

The tablet cores developed from the dried extract prepared from the secondary roots of *H. procumbens* DC. (Pedaliaceae) were produced by direct compression. The dried extract of *H. procumbens* DC., standardized on harpagoside (20%) according to the European Pharmacopoeia monograph (France, 2013), was furnished by Naturex Inc (France, Avignon). The plant was acquired from Africa and the extract prepared in Avignon (France). The design of the experiment (DOE) was used to study the influence of composition and optimization of the formulation through experimental mixing design using the Design Expert® statistical program. Physical-chemical tests, described in the Brazilian Pharmacopoeia 5th edition (Brazil, 2010) were applied to evaluate the tablet cores. For that, individual and medium weight, toughness, friability, and disintegration were determined. Subsequently, the tablet cores were coated with the Acryl-EZE® coating dispersion in Vector equipment, model LDCS-30, with 8 L drum, using a Schlick type pistol, 1.0 mm exit hole, with distance between the bed of cores and pistol equal to 8 cm for the aqueous coating, with four Fischer type blades and peristaltic pump. Additionally, the critical parameters of the coating process with the determined dispersion were evaluated, which included: energy consumption, coating uniformity and yield (Alcorn et al., 1988; Smith et al., 2003; Ho et al., 2008).

Stability studies

Accelerated and long-term stability studies were designed according to the parameters defined in Table 1 to define the shelf-life and period of use in packaging and storage conditions specified for the traditional herbal product developed from the dry extract, standardized in harpagoside (20%) according to European Pharmacopoeia monograph (France, 2013), coming from the secondary roots of the plant species *H. procumbens* DC., popularly known as "devil's claw."

Analytical validation

Sample preparation

The sample used for analytical validation, that is the 702 mg gastro-resistant coated tablets developed, were ground into porcelain grains with a pistil until a homogeneous powder was formed.

Placebo preparation

For the validation analysis, a placebo was produced containing all the components used in the development of the formulation, except the dry extract of *H. procumbens* DC.

Standard solution preparation

Exactly 5 mg of harpagosides were weighed and quantitatively transferred to a 50 ml volumetric flask. The volume was quenched with methanol and the volumetric flask was subjected to ultrasonic bath for 10 min. A final concentration of 0.250 mg/ml was obtained.

Sample solution preparation

About 175.5 mg of the sample were weighed and quantitatively

transferred to a 50 ml volumetric flask. The volume was quenched with methanol and the volumetric flask was subjected to the ultrasonic bath for 10 min to solubilize the sample completely. A final concentration of 0.250 mg/ml was obtained.

Placebo solution preparation

About 113 mg of the placebo were weighed and transferred quantitatively to a 50 ml volumetric flask. The volume was quenched with methanol and the volumetric flask was subjected to the ultrasonic bath for 10 min in order to solubilize the placebo completely.

Specificity and selectivity

In order to evaluate the influence of excipients on the assay method studied, absorption spectra in the ultraviolet-visible region of the placebo solution, the standard solution and the sample solution were checked.

Linearity

In order to evaluate the linearity (L) of the method, a calibration curve was constructed at concentrations equivalent to 80, 90, 100, 110, and 120% of the reference standard concentration, prepared as specified previously. The final concentrations of harpagoside were 0.200, 0.225, 0.250, 0.275, and 0.300 mg/mL, respectively. All solutions were prepared in triplicate.

Accuracy

The solutions corresponding to 80, 100 and 120% of the standard harpagoside reference solution concentration were evaluated for their concentration obtained, and the mean of the three concentrations was calculated as:

$$A = \frac{Co \times 100}{Ct} \quad (1)$$

Where, A refers to the accuracy; Co refers to the concentration obtained; and Ct refers to the theoretical concentration.

Repeatability

In order to evaluate the repeatability of the method, the solutions corresponding to 80, 100 and 120% of the reference standard concentration of the harpagoside were evaluated for coefficient of variation (CV), which was calculated from the following formula:

$$CV = \frac{SD \times 100}{Mean} \quad (2)$$

Where, ST refers to the standard deviation.

Harpagoside content

Calculation of harpagoside content in the *H. procumbens* DC tablets was carried out during the study of stability in three different periods. The first assay was performed at the initial stage of the procedure, the second calculation was checked after 3 months of onset of stability, and finally the last assay was performed 6 months after tablet stability had begun. In order to verify the harpagoside content in the tablets of *H. procumbens* DC., the following calculation was carried out:

$$[C]obtained = \frac{y - b}{a} \quad (3)$$

Where, [C] obtained refers to the concentration obtained by the calibration curve and the peak area of the chromatographic peak; y refers to the area of the chromatographic peak relative to the harpagoside; b refers to the linear coefficient of the curve and a refers to the angular coefficient of the curve.

Chromatographic conditions

They are as follows: Column: C_{18} 250 × 4.6 mm × 5 µm; temperature: 35°C; flow rate: 1.2 ml/min; injection volume: 10 µl; detection: ultraviolet at 280 nm; mobile phase: H_2O:MeOH (50:50, v/v); retention time, 13.0 ± 0.5 min.

Statistical analysis

The statistical analyses were established using analysis of variance (ANOVA) followed by the Tukey-Kramer multiple comparison tests (Sokal; Rohlf, 2012). Results with $P < 0.05$ were considered to be significant. The data were expressed as mean (M) ± standard deviation (SD).

RESULTS AND DISCUSSION

The results were analyzed qualitatively and quantitatively. The internal and external validity of the experiments were observed, as well as the statistical methodology to be used in each test. The development of a formulation from the standardized extract of the plant species *H. procumbens* DC., popularly known as "devil's claw," which can be manufactured by direct compression is very convenient commercially. For that, the main limitations are the low flow property, low compression ability and tendency for capping to be exhibited by the extract, whose therapeutic dose is high, which does not allow the addition of a large amount of excipient to correct these characteristics. In view of such difficulties, a preliminary study was conducted to collect data, such as the size, thickness, and average weight of the tablets.

The development of the tablet cores from the extract of the plant species *H. procumbens* DC., with a final weight of 650 mg, by direct compression was a great challenge. For this, statistical techniques were used to obtain the desired formulations with the lowest number of experiments, based on preliminary study subsidies.

In order to develop formulations that met the pharmacopoeial specifications and to study the influence of the composition on the physico-chemical characteristics of the cores, the experimental design of

Table 2. Formulation proposed for the tablet cores.

Ingredient	Percentage	Quantity per dose (mg)
H. procumbens DC.	38.46	250.00
Colloidal silicon dioxide	0.77	5.00
Croscarmellose sodium	2.00	13.00
Microcrystalline cellulose	42.77	278.00
Atomized lactose	15.00	97.50
Magnesium stearate	1.00	6.50

the mixture was used through the statistical program Design Expert®. For experimental planning of mixing, the amount of extract of plant species *H. procumbens* DC., was set at 250 mg. On the other hand, the total amount of excipients constituting the mixture amounted to 400 mg. The maximum and minimum values of the variation were determined according to the normal amount of use of each excipient described in literature. Design Expert® program provided the formulation proposals through the mixing technique, resulting in the formulation shown in Table 2.

Direct compression is a technique widely used in the production of tablets and its use has increased considerably (Nada and Graf, 1998; Eissens et al., 2002; Hauschild and Picker, 2004). The main advantages of this technique are related to: the reduction in the time of manufacture, increasing productivity, elimination of several processing steps, reducing the likelihood of cross-contamination, low moisture, the reduction of energy consumption and the reduction of the final cost of the product (Prista et al., 1995).

Direct compression also requires a smaller physical area and a reduced number of equipment, since it involves only three stages: the weighing of the powders that make up the formulation, the mixing of the powders, and the compression (Prista et al., 1995; Shangraw, 1989). In addition, the direct compression method is the one that best preserves the stability of the components of the formulation when compared to procedures that include granulation, since it does not use moisture (addition of binder solution) and heating (drying) during the production. Therefore, it is considered suitable for the processing of hygroscopic and thermolabile substances. Another advantage of direct compression is the optimization of tablet disintegration, where each drug particle is released from the tablet mass and becomes available for dissolution (Shangraw, 1989).

The choice of the excipients or adjuvants for the composition of a formulation for direct compression deserves careful attention so that the physical stability of the resulting tablets is maintained. Diluents are inert and stable products, added to the formulation to give tablets suitable weight in the case of active substances in small dosages. Lactose is an example of a soluble diluent and microcrystalline cellulose is an insoluble diluent (Prista et al., 1995; Lachman et al., 2001). As the excipients are only dry blended prior to compression, it is critical that the binder excipients have certain characteristics as good compaction, so that the tablets conform to the requirements of hardness and friability; smooth flow to meet content uniformity specifications; be inert so that there is no interaction with other substances; are stable to meet the established shelf-life and non-toxic to reconcile regulatory requirements (Eissens et al., 2002). The determination of the hardness of a tablet evaluates its resistance to breakage. It is based on an indirect evaluation of the degree of consolidation of the tablets, that is, the formation of solid-solid bonds due to the reduction of the free surface energy of the solid particles (Lachman et al., 2001).

On the other hand, the determination of the friability of a tablet evaluates its rolling resistance. In addition, friability provides useful indications as the resistance to frictional strength of the tablets in the packaging, transportation and other technological operations, as coating. In general, friability is an indicator of the compaction of the material, besides being a conditioning factor for the consumer's acceptance of the pharmaceutical form (Prista et al., 1995).

Microcrystalline cellulose is presented as a white, odorless, tasteless, relatively free flowing powder practically free from inert and non-toxic inorganic and organic contaminants. It is insoluble in water, dilute acids and most organic solvents. It is practically insoluble in sodium hydroxide solutions (Merck Index, 2001). Due to its characteristics of excellent compaction, good flowability and disintegration ability, microcrystalline cellulose is one of the most widely used excipients in tablet formulations by direct compression, and is easily obtained by several suppliers in several countries (Wu et al., 2001).

Lactose is a disaccharide composed of one unit of galactose and one unit of glucose. It can be found in various solid forms, such as α-lactose monohydrate, anhydrous α-lactose, anhydrous β-lactose or atomized lactose, according to the manufacturing process (Busignies et al., 2004). Atomized lactose is the oldest and most widely used diluent in direct compression. Atomized lactose presents good flow characteristics and is frequently used as a direct compression diluent associated with microcrystalline cellulose (Prista et al., 1995). Disintegrants, such as sodium croscarmellose, are

Table 3. Determination of the mean weight of the cores.

1	2	3	4	5	6	7	8	9	10	Mean	SD**
654	656	653	649	651	650	648	648	654	651	651.4	2.76
652	650	650	648	651	653	649	649	656	653	651.1	2.42

**Standard deviation.

Table 4. Determination of the thickness of the cores.

1	2	3	4	5	6	7	8	9	10	Mean	SD
42	42	43	43	43	42	44	43	42	44	42.8	0.79
43	44	42	42	43	43	43	42	43	44	42.9	0.74

added to the tablet formulation to provide breakdown or disintegration in the presence of water. The function of the disintegrant is to neutralize the action of the diluent and the physical compressive forces required to form the tablet. They comprise a group of materials that, in contact with water, swell, hydrate, change in volume or position, or chemically react (Prista et al., 1995; Lachman et al., 2001).

Lubricants, such as magnesium stearate, are added to the pharmaceutical formulations in order to reduce the friction of the powder mixture with the matrix walls and the puncture surfaces, allowing for easy ejection of the tablets (Prista et al., 1995). Slippers, such as colloidal silicon dioxide, are added to the pharmaceutical formulation to improve flow properties by reducing interparticular friction, facilitating the filling of the die of the compression machine. The effects produced by sliders depend on their physical and chemical nature, such as particle size and shape, moisture content and temperature (Prista et al., 1995).

Determination of the mean weight

The mean weight of the cores, in milligrams (mg), was determined according to the results presented in Table 3.

Determination of thickness

The thickness of the cores, in millimeters (mm), was determined according to the results presented in Table 4.

Determination of friability

The friability (F) of the cores was determined according to the results presented with the equation:

$$F = \frac{P1 - P2}{P1} \quad (4)$$

Where, P1 refers to the mean weight of twenty tablets before the test; P2 refers to the mean weight of twenty tablets after the test.

Therefore, for P1 = 650.8 mg and P2 = 650.4 mg, the friability of the cores is equal to 0.06%. This value is in accordance with the specification of friability, which recommends that values below 1% are satisfactory (Brazil, 2010).

Coating of the tablet cores

The cores were coated with the Acryl-EZE® coating dispersion, and critical process parameters were evaluated as shown in Table 5. The coating gave protection to the dried extract obtained from the secondary roots of the plant species *H. procumbens* DC. against the destructive exposure of air, light and moisture and also masked the flavor thereof. From the application of the dispersion of the Acryl-EZE® coating, it was possible to obtain a modified, if any, gastro-resistant release profile, and additionally to provide aesthetic and differentiated qualities to the traditional herbal product. It is essential in the gastro-resistant protection of the harpagoside, since this molecule has a sugar moiety which can be hydrolyzed in acids, such as the stomach.

Stability study

The accelerated stability study plan was performed according to the results presented in Table 6. The long-term stability study plan was performed according to the results presented in Table 7.

Table 5. Critical parameters of the coating process.

Process time (min)	Input temperature (°C)	Output temperature (°C)	Product temperature (°C)	Nebulization rate (g/min)	Weight gain (%)
0	65.3	46.3	45.0	-	0.00
5	65.2	45.5	43.6	4.6	0.46
10	65.0	45.2	42.8	4.4	0.90
15	65.4	45.6	43.2	4.2	1.72
20	65.7	46.2	44.0	4.0	2.14
25	63.2	45.6	43.8	4.4	2.86
30	64.3	45.8	43.9	4.0	3.56
40	63.0	45.4	43.5	4.1	4.38
50	62.6	45.0	43.0	4.2	5.42
60	62.3	45.3	43.2	4.3	6.92
70	63.2	45.6	43.5	4.6	8.00

Table 6. Accelerated stability study plan.

Test	Specification	Initial	90 days	180 days
Aspect	Coated, circular and biconvex tablet	In accordance	In accordance	In accordance
Toughness	Informative	26.2 kP	27.5 kN	26.4 kN
Content	45 mg and 55 mg	50.8 mg	50.2 mg	49.7 mg
Bacteria	Max. 10.000 UFC/g	< 10.000 UFC/g	-	< 10.000 UFC/g
Yeasts	Max. 100 UFC/g	< 100 UFC/g	-	< 100 UFC/g
Salmonella sp.	Absent	Absent	-	Absent
S. aureus	Absent	Absent	-	Absent
E. coli	Absent	Absent	-	Absent

Table 7. Long-term stability study plan.

Test	Specification	Initial	3 months	6 months
Aspect	Coated, circular and biconvex tablet	In accordance	In accordance	In accordance
Toughness	Informative	26.2 kP	26.4 kP	26.9 kP
Content	45 mg a 55 mg	50.8 mg	50.2 mg	49.7 mg
Bacteria	Max. 10.000 UFC/g	< 10.000 UFC/g	-	< 10.000 UFC/g
Yeasts	Max. 100 UFC/g	< 100 UFC/g	-	< 100 UFC/g
Salmonella sp.	Absent	Absent	-	Absent
S. aureus	Absent	Absent	-	Absent
E. coli	Absent	Absent	-	Absent

According to the "Guide to Stability Studies" (Brazil, 2005), "the stability of pharmaceuticals depends on environmental factors such as temperature, humidity and light, and others related to the product itself, such as the physical and chemical properties of active substances and pharmaceutical excipients, form and composition, manufacturing process, type and properties of the packaging materials". The shelf-life of a solid pharmaceutical form in Brazil should be determined by the long-term stability study, according to the parameters defined in the table. However, since the accelerated stability study (6 months) accompanied by preliminary results from the long-term study was successful; an interim period of validity of 24 months may be conferred

Table 8. Evaluation of the linearity parameter.

Samples (%)	Theoretical concentration (mg/ml)	Concentration obtained (mg/ml)	Recovery (%)	Average recoveries (%)
	0.202	0.205	101.5	
80	0.199	0.198	99.5	101.0
	0.196	0.200	102.0	
	0.222	0.225	101.3	
90	0.219	0.217	99.1	100.4
	0.226	0.228	100.9	
	0.251	0.256	102.0	
100	0.254	0.258	101.6	101.6
	0.246	0.249	101.2	
	0.277	0.274	98.9	
110	0.274	0.279	101.8	99.9
	0.280	0.277	98.9	
	0.298	0.303	101.7	
120	0.294	0.293	99.7	100.8
	0.292	0.295	101.0	

on the product.

Analytical validation and standardization

The coated tablets obtained from the dried extract of *H. procumbens* DC., were standardized in harpagoside, according to Normative Instruction (IN) nº 02, of May 13, 2014 (Brazil, 2014b), by high performance liquid chromatography (CLAE) with ultraviolet (UV) detection, according to the European Pharmacopoeia monograph (France, 2013), and the analytical methodology was validated according to the criteria established in the "Guide for validation of analytical and bioanalytical methodologies" published in Resolution nº 899 (Brazil, 2003). In this way, validation ensured that the method met the requirements of the analytical applications, thus ensuring the reliability of the results. In order to do so, it presented selectivity, linearity, interval, precision, accuracy and robustness, according to "Guidance for registration of herbal medicine and registration and notification of traditional herbal product", published in Normative Instruction No. 04, June 18, 2014 (Brazil, 2014c).

Specificity and selectivity

Specificity and selectivity can be defined as the ability of the method to accurately measure a compound in the presence of other components, such as impurities or degradation compounds. The method used to determine harpagoside content in *H. procumbens* DC. Tablets is specific and selective, since there was no influence of placebo, that is the excipients used in the preparation of the tablet, at the maximum absorption peak of the harpagoside at 280 nm.

Linearity

Linearity may be defined as the ability of an analytical method to present a response directly proportional to the analyte concentration in the sample, within a specific range. In Table 8, it was inferred that the individual recovery varied between 98.9 and 102.0%, while mean recovery varied between 99.9 and 101.6%. These values are considered acceptable by Resolution n^{o} 899 (Brazil, 2003). In order to construct the calibration curve (Figure 1), the averages of the theoretical concentrations and the concentrations obtained were used, as shown in Table 9. The method is considered linear. A straight line with coefficient of determination (R^2) equal to 0.99857 was obtained, as observed in Figure 1.

Accuracy

Accuracy can be defined as the proximity of the results obtained by the method under study to the true value.

Table 9. Average of theoretical and obtained concentrations.

Samples (%)	Mean of theoretical concentrations (mg/ml)	Mean of concentrations obtained (mg/ml)
80	0.199	0.201
90	0.222	0.223
100	0.250	0.254
110	0.277	0.277
120	0.295	0.297

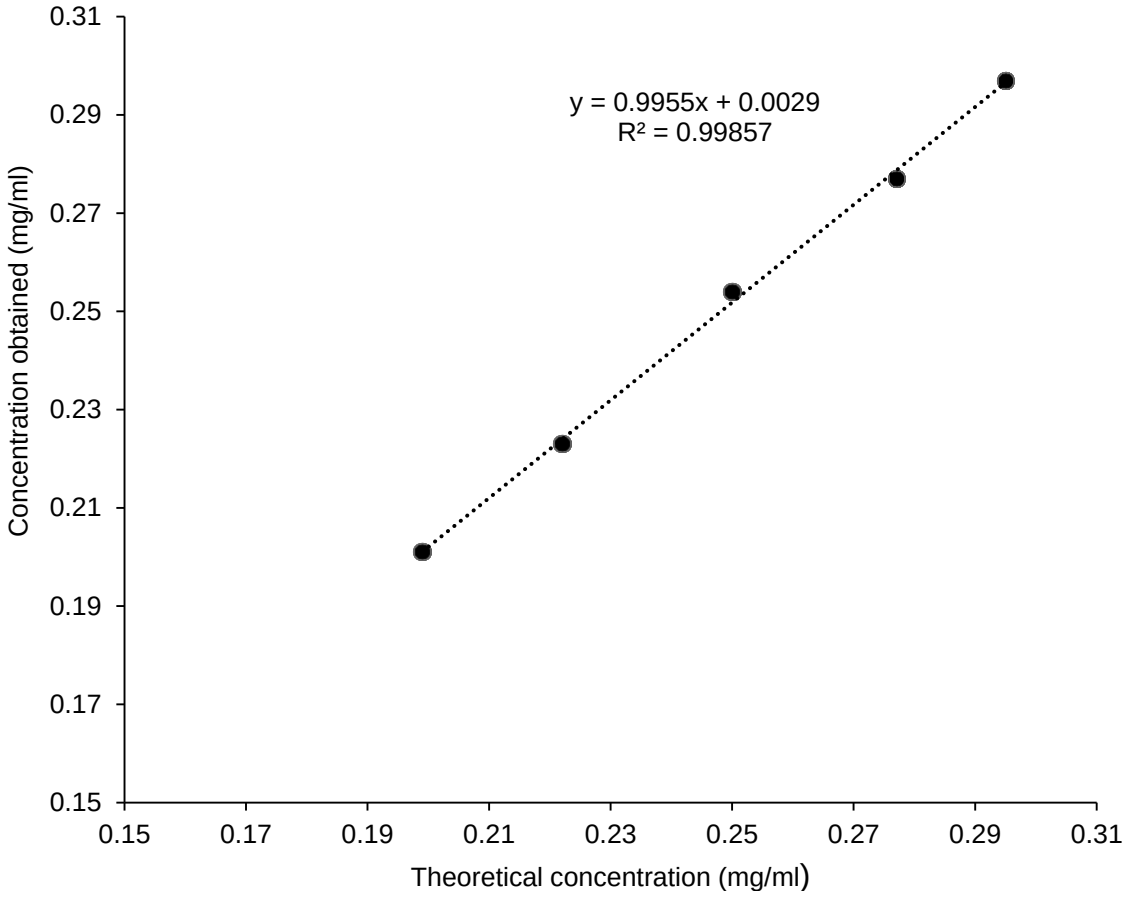

Figure 1. Calibration curve.

The solutions corresponding to 80, 100 and 120% of the standard harpagoside reference solution concentration were evaluated for the concentration obtained and theoretical, as well as the average of the three concentrations. From the results obtained in Table 10, it was verified that the variation of the individual recovery was of 99.5 to 102.0% and the mean of the recoveries was of 100.8 to 101.6%. These values are considered satisfactory, according to Resolution (RE) nº 899, of May 29, 2003 (Brazil, 2003) and therefore, prove the accuracy of the method under analysis.

Precision

Precision can be defined as the evaluation of the proximity of the results obtained in a series of measurements of a multiple sample of the same sample. The accuracy can be evaluated in three different modalities: Repeatability: accordance between results within a short period of time with the same analyst and the same instrumentation; intermediate precision: agreement between results within the same laboratory, however, obtained on different days and with different

Table 10. Evaluation of parameters accuracy and precision.

Samples (%)	Recovery (%)	Average recoveries (%)	CV (%)
80	101.5 99.5 102.0	101.0	1.31
100	102.0 101.6 101.2	101.6	0.39
120	101.7 99.7 101.0	100.8	1.01

analysts and equipment and reproducibility: agreement between the results obtained by different laboratories.

In the study in question, only the repeatability of the method was evaluated in accordance with the requirements of Resolution (RE) No. 899, of May 29, 2003 (Brazil, 2003). The solutions corresponding to 80, 100 and 120% of the standard harpagoside reference solution concentration were evaluated for the coefficient of variation. Observing Table 10, it was verified that the results found were 1.31, 0.39 and 1.01%, respectively. Coefficients of variation below 5% are considered acceptable and prove the accuracy of the method under analysis.

Conclusion

In the pharmacotechnical development of gastro-resistant coated tablets produced by direct compression from the standard extract of *H. procumbens* DC., the presence of a glidant, such as the excipient colloidal silicon dioxide, was required to have sufficient flow to fill the matrix. Microcrystalline cellulose, in turn, constituted a suitable binder for this type of formulation, giving adequate compaction properties to the manufacturing process. Experimental mixing planning was an extremely useful statistical tool in obtaining formulation of the tablets produced by direct compression from the standard extract of *H. procumbens* DC. Through the use of this technique, it was possible to develop an optimized formulation, in which all physicochemical characteristics met the pharmacopoeial specifications. The development of the supplements allowed evaluating the influence of each excipient on the majority of the physical-chemical characteristics of the formulations. In addition, the use of this technique allowed to reduce the number of tests, and consequently to reduce the cost of the research. From the analytical validation, it was possible to verify that the analytical methodology used to determine the harpagoside content in the tablets is specific, selective, linear, accurate and precise. Finally, through the assays performed and the process used, the results have presented a high performance tablet, with high content of the chemical marker and stability after the study, meeting the requirements for good manufacturing practice.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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