Development of tablets containing semipurified extract of guaraná (Paullinia cupana)

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Abstract: This study evaluated the technological feasibility of producing a semipurified extract of guaraná (Paullinia cupana Kunth, Sapindaceae) in tablet form, using a direct-compression process. Maltodextrin and gum arabic were used to produce the extract microparticles, in order to protect the microparticles against such factors as temperature, oxidation, and humidity. Using pharmacopoeial methodologies, technological and physicochemistry tests (determination of residual moisture, of bulk and tapped density, Hausner ratio, compressibility and compactibility index, appearance, mean weight, hardness, friability, disintegration time, determination of EPA amount in tablets and in vitro release profile) were conducted. The formulation containing 200 mg of microparticles, 170 mg microcrystalline cellulose, and 10 mg lactose gave the best results in terms of hardness (116 N), friability (0.28%), mean weight (0.3821 g), and disintegration time (25 min) for a tablet designed for oral administration. The results met pharmacopoeial specifications, and the tablets are suitable for oral administration.

Introduction

A dosage form is developed in several stages, including studies of pre-formulation and the formulation itself. These stages consist of physical, chemical, physicochemical, and biological analyses of all materials, including the drug used in the preparation of the product, as well as the anatomical and physiological characteristics of the route of administration and absorption, and finally the development of the pharmaceutical form (Ansel et al., 2000; Lachman et al., 2001; Aulton, 2007).

Some studies with phytopharmaceuticals aim to develop a suitable product for industrial use and further therapeutic application (Couto et al., 2012). Alves et al. (2011) investigated the feasibility of a co-processing technique for improving the manufacturing properties of extracts obtained from Maytenus ilicifolia (Schrad.) Planch., Celastraceae, and Cassia angustifolia Vahl, Fabaceae, in order to obtain tablets containing a high concentration of these extractive solutions. The spray-drying technology is an attractive and promising alternative for the development of intermediate phytopharmaceutical products (Bruschi et al., 2003; Bruschi et al., 2006; Dota et al., 2011; Couto et al., 2012).

The oral route is most often used in drug administration and is best accepted by patients. However, it is not always the most appropriate for administration of pharmaceuticals, since poorly soluble drugs may not be completely absorbed. Thus, in developing a new formulation, attention must be given to factors that improve the drug delivery in the gastrointestinal tract, including several related to the formulation: particle size, disintegration time, dissolution, the presence of hydrophobic and/or hydrophilic excipients, physicochemical properties, and other drug characteristics (Viana et al., 2006).

Considering that poorly soluble drugs can be readily absorbed if suitable excipients are used, the formation of microparticles can further enhance the availability of the drug for absorption in the...
gastrointestinal tract. The direct compression (DC) process is ideal for industrial-scale production of tablets (McCormick, 2005), and is suitable for substances that have free-flowing properties of cohesion and that can be compressed directly, without wet or dry granulation (Lachman et al., 2001). However, relatively few drugs can be compressed without prior granulation (Prista et al., 1995; Ansel et al., 2000; Yuan & Wu, 2001). Thus, in DC the excipients used must have appropriate properties of flow and compressibility (Palacios, 2000). The advantages of DC include speed, ease of manipulation, and reduced loss of the active ingredient. The method can be used with compounds that are unstable in humid and high-temperature conditions, and reduces the risks of contamination and oxidation, increases productive capacity, and is economical (Prista et al., 1995; Ansel et al., 2000; Palacios, 2000; Lachman et al., 2001).

Studies of the extract and semipurified fractions of guaraná by Audi & Mello (2000), Otobone et al. (2005), Otobone et al. (2007), and Roncon et al. (2011) demonstrated the pharmacological properties of the lyophilized extract (EBPC) and semipurified fractions (EPA and EPB) after acute or chronic oral administration in rats. One of the properties is an antidepressive effect, comparable to imipramine: cognition testing in the Morris water maze demonstrated that the EPA fraction has an antinociceptive effect, suggesting an antidepressant effect as observed with EBPC. EPA is orally active and has a panicolytic effect involving the serotonergic and dopaminergic systems.

Therefore, EPA can be useful in treating mood disorders such as panic disorder. Condensed tannins, which were isolated from the EPA fraction by Yamaguti-Sasaki et al. (2007), may be responsible for this activity, since Johnston & Beart (2004) showed that flavonoids can cross the blood-brain barrier and may act on the central nervous system. The promising activity of EPA encouraged us to attempt to develop the best technological features of this fraction, because its hygroscopic and electrostatic characteristics make it difficult to weigh accurately, and it is subject to degradation, mainly by oxidation. The need to protect this fraction led to an evaluation of microencapsulation as an alternative (Lachman et al., 2001; Bruschi et al., 2003). EPA also has poor solubility, suggesting the addition of excipients that facilitate dispersion and solubility.

The objective of this study was to develop and characterize tablets containing microparticles of EPA for oral administration. This is a monolithic system, where the asset is microencapsulated to protect it from degradation.

**Material and methods**

**Material**

The following materials were used: microcrystalline cellulose (FMC BioPolymer, Philadelphia, PA, USA), lactose (Reagen, Rio de Janeiro, RJ, Brazil), gum arabic (Synth, Diadema, São Paulo, SP, Brazil), maltodextrin (Aldrich, St. Louis, MO, USA), acetonitrile, methanol, trifluoroacetic acid, acetone, ethyl acetate (JT Baker, Mexico City, Mexico), and ultrapure water (Milli-Q gradient, Millipore, Billerica, MA, USA).

**Preparation of guaraná semipurified extract**

Seeds of *Paullinia cupana* Kunth, Sapindaceae (guaraná) were obtained from the municipality of Alta Floresta, Mato Grosso, Brazil. A voucher specimen was deposited in the Herbarium, Department of Biology, State University of Maringá under number HUEM 9065. The plant was identified by Professor Dr. Cássia Mônica Sakuragui. An extract was prepared in an acetone:water (7:3, v/v) 10% (w/v) solution by turbo extraction (UTC115KT Ultra-Turrax, Ika Works, Wilmington, NC, USA). The organic solvent was removed by a rotary evaporator under low pressure, and the material was lyophilized to yield the crude extract [EBPC; patent pending PI0006638-9 (Audi & Mello, 2000)]. EBPC was partitioned with ethyl acetate, resulting in an ethyl-acetate fraction (EPA), with a yield of 9.23% (w/w) relative to the dried seeds of guaraná (Antonelli-Ushirobira et al., 2010).

**Preparation of microparticles containing EPA**

Microparticles containing EPA were produced using a spray dryer (Mini Spray Dryer, Büchi B-191, Switzerland), with inlet temperature of 190 °C, 80% aspiration, pressure of 2 bars, 6% pumping, and spray nozzle with orifice diameter of 0.7 mm. The dispersion was prepared with 10% (w/v) total solids of a mixture of gum arabic (GA) and maltodextrin (MD) (1:1, w/w) in water, and EPA, corresponding to 80% polymers and 20% EPA. Initially, the polymer mixture (GA, MD) was dispersed in water, and EPA was dispersed in 10% ethanol. The EPA and the polymer mixture were stirred separately (20 min), and the EPA solution was added to the polymer dispersion, stirred for 5 min at room temperature, and dried in the spray dryer. The resulting dried products were collected and kept in the dark and protected from rehydration in desiccation chamber at room temperature until further tests. The choice of an appropriate formulation of microparticles, and its development and characterization will be reported separately (Klein, 2012).

**Physical and mechanical properties of microparticles**

Determination of residual moisture
To estimate the moisture content of spray-dried microparticles containing EPA, an aliquot of 3.0 g of sample was dried at 105 ºC for 30 min in an Ohaus-MB 200 infrared analytical balance. At least three replicates were performed, to estimate the inherent variability of the analysis.

**Determination of bulk and tapped density**

The bulk and tapped densities of microparticles containing EPA were determined according to the methodology proposed by Guo et al. (1985) and Cardoso (2002). A sample of approximately 10 g was placed in a previously weighed cylinder with a capacity of 50 mL. The tapped density was determined using a compression volumeter (Erweka® SVM 12, Heusenstamm, Germany). The powder was subjected to 1250 falls, according to DIN 53 194. The analysis was performed in at least three replicates, and the bulk density (db) and tapped density (dc) were calculated by equations (1) and (2) (Lachman, 2001; Aulton, 2007), respectively:

\[
\text{db} = \frac{M_a}{V_b} \quad \text{Equation (1)}
\]

\[
\text{dc} = \frac{M_a}{V_c} \quad \text{Equation (2)}
\]


**Determination of Hausner ratio, compressibility and compactibility index**

The sample used in the previous experiment was used to determine the Hausner ratio (HR), compressibility, and compactibility indexes, according to the methodology of Guo et al. (1985) and Cardoso (2002). The Hausner ratio was determined from the ratio between the bulk and tapped densities, according to equation (3):

\[
HR = \frac{dc}{db} \quad \text{Equation (3)}
\]

The compressibility index (CI) was determined according to equation (4):

\[
CI = (\frac{dc - db}{db}) \times 100 \quad \text{Equation (4)}
\]

Where: dc: tapped density (g/mL); db: bulk density (g/mL).

The compactibility (C) was calculated by the difference between the volumes at 10 (V10) and 500 falls (V500) by volume of compression, according to equation (5), using about 10 g of powder. The results were extrapolated to a mass of 100.0 g, obtaining the volume (mL) after 10 and 500 falls.

\[
C = V_{10} - V_{500} \quad \text{Equation (5)}
\]

**Preparation and characterization of tablets containing EPA microparticles**

During the development of tablets containing the microparticles, different formulations were tested (Table 1). The components of the tablet formulation were mixed in a glass mortar, and geometric dilutions of the powder were made.

Tablets were produced by direct compression in a compression machine (FELLC Compact 10, São Paulo, SP, Brazil), using a 10 mm round punch. Samples from different batches were individually weighed and placed in the compression chamber. For each formulation (Table 1), the compressive force was adjusted according to the properties of the material. The compression force of the machine was manually adjusted, i.e., for each material the behavior at a particular applied force was observed. To obtain the tablets, the machine engine was not engaged, so each form of the solid dosage was obtained individually by manual rotation of the punch. After compression, the formulations were collected and stored away from light and rehydration (in desiccation chamber) at room temperature until further analysis.

**Appearance**

The macroscopic characteristics of each formulation and pharmaceutical dosage form were observed, including the geometric shape, appearance, color, and presence of foreign material or particles.

### Table 1. Composition of the formulations tested for the development of tablets containing EPA microparticles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Microparticles (mg)</th>
<th>Microcrystalline cellulose (mg)</th>
<th>Lactose (mg)</th>
<th>Final tablet weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>0</td>
<td>0</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>25</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>90</td>
<td>10</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>140</td>
<td>10</td>
<td>350</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>170</td>
<td>10</td>
<td>380</td>
</tr>
</tbody>
</table>
Mean weight

The mean weight of each batch of tablets was determined using the methodology described in the Brazilian Pharmacopoeia (2010), using a range of tolerance of 5% for tablets with a mean weight above 250.0 mg. Twenty tablets were weighed individually, and the mean weight was determined.

Hardness

The hardness of the tablets was determined using an ERWEKA® durometer (Heusenstamm, Germany). Ten tablets were evaluated for each formulation (Brazilian Pharmacopoeia, 2010).

Friability

According to the procedure recommended in the Brazilian Pharmacopoeia (2010), twenty units were weighed and submitted to an Ethics® friability test (São Paulo, SP, Brazil). After 100 rpm for 5 min, the tablets were weighed again. The difference between the initial and final weights represents the friability (FR), as estimated by the percentage of powder lost.

Determination of EPA amount in tablets

For determination of the EPA concentration in the tablets, the quantification of chemical markers for EPA (catechin and epicatechin) was performed by High Performance Liquid Chromatography (HPLC) as developed by Klein et al. (2012). Briefly, chromatographic separation: Phenomenex® Synergi POLAR-RP 80A stainless-steel analytical column (250 mm×4.6 mm, 4 µm) and a Phenomenex C18 guard cartridge system (4 µm, 4.6 mm×20 mm). The mobile phases were: Phase A, water plus 0.05% TFA and Phase B, methanol:acetonitrile (25:75) plus 0.05% TFA, the gradient system established: 0 min, 80:20 (A:B); 20 min, 74:26 (A:B); 21 min, 80:20 (A:B); 24 min, 80:20 (A:B), 280 nm wavelength and 0.5 mL/min. For each formulation, at least three replicates were analyzed and the content of each EPA marker was determined in relation to the respective final formulation, using a calibration curve previously obtained using a catechin or epicatechin standard.

Evaluation of disintegration time

The disintegration test was performed following the method established by the Brazilian Pharmacopoeia (2010), using an Ethics® disintegration tester (São Paulo, SP, Brazil). In this test, a time limit of 30 min was used for the tablets.

In vitro release profile of EPA from formulations

The release profile of active substances (catechin and epicatechin) from the tablets was determined in a USP Apparatus 4 flow-through cell dissolution tester (SOTAX Smart AT7®, USA), using distilled water as the dissolution medium, at 37 °C, collection volume 5 mL, and flow 8 mL/min, with 22.6-mm cells. The analysis was carried out with at least three replicates. To prepare the sample for HPLC analysis, the volume was subjected to solid-phase extraction (SPE Strata C18-E) and completed to 10 mL in a volumetric flask. The catechin and epicatechin markers were quantified according to Klein et al. (2012).

Results and Discussion

The flow of powder during manufacturing dictates the quality of the product in terms of its weight and uniformity of content. However, the flow profile of a powder is complex and multidimensional, and depends on many characteristics of the powder. To address this multidimensional problem, several flow measurements are performed in order to obtain a more coherent flow classification (Alves et al., 2011).

The processing of plant extracts with pharmaceutical excipients could lead to the formation of materials with superior mechanical characteristics that are suitable for direct compression. The spray-drying technique has been used to obtain dried extracts with improved technological characteristics and a higher concentration of substances with biological activity (Oliveira & Petrovick, 2010). Thus, this technique was chosen to produce the microparticles containing the EPA semipurified extract, using GA and MD as polymers.

The moisture content of the EPA microparticle powder was determined as 5.16%±0.75. The bulk and tapped density were 0.3283±0.0084 and 0.4221±0.0136 g/mL, respectively. Thus, the Hausner ratio (HR) is 1.28±0.02, and high cohesiveness and internal friction are characteristics of powders that possess HR greater than 1.25 (USP, 2007). The compressibility index (CI) and rate of C are 22.18±1.48% and 7.33±2.36 mL, respectively. The CI indicates very poor flow and compressibility characteristics (USP, 2007).

In general, powders with a HR less than 1.25, CI less than 18% compactibility, and C less than 20 mL are easily compressible (Lachman et al., 2001; Aulton, 2007). Therefore, the EPA microparticle powder is not easily compressible. Because of this difficulty, other pharmaceutical compression excipients (microparticulate cellulose and lactose for direct compression) were used to assist in the preparation of tablets containing the EPA microparticles.

When developing a new formulation, all the physical characteristics and physicochemical
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Characteristics of the powders, including particle size, disintegration time, dissolution, presence of hydrophobic and/or hydrophilic excipients, physical and chemical properties, and other characteristics of the drug are determining factors in obtaining tablets that are suitable for administration (Viana et al., 2006; Alves et al., 2011).

First, the EPA microparticles were compressed directly, with no added excipients (Formulation 1). These tablets showed a hardness value of 55 N, but did not pass the friability test (Table 2) (Brazilian Pharmacopoeia, 2010).

In order to improve the flow properties of the EPA microparticles, which was necessary to achieve adequate flow while feeding the machine for filling and compressing the compression matrices (Aulton, 2007) and to decrease the friability of the tablets, lactose and microcrystalline cellulose were used as excipients, in different proportions.

These adjuvants were selected to provide certain attributes in order to obtain tablets with good physical characteristics and physicochemical properties. Cellulose is one of the materials most commonly used as a pharmaceutics adjuvant, and improves the flow characteristics of the powder and hence the uniformity of the final weight of the dosage (Toller & Schmidt, 2005). Lactose is also widely used in the pharmaceutical industry as a diluent in the production of tablets. The development of spray-dried lactose, with improved characteristics of compactibility and flow, has revolutionized the production of tablets, because it was one of the first excipients with a specific application to direct compression processes of solid oral forms (Toller & Schmidt, 2005). Although various raw materials are available, cellulose and lactose are still widely used, since they differ in particle size, degree of mixing, flow, density and other properties that allow the confection of dosage forms with suitable physicochemical characteristics and reproducible production on any scale (Toller & Schmidt, 2005). In this study, the proportions between these adjuvants were determined according to practical production needs. A lubricant was not used because preliminary tests indicated no adhesion of the powder on the punches.

The analysis showed that Formulation 2 was not adequate because the tablets showed a lack of cohesion between particles. Formulation 3 displayed a hardness of 493 N, but did not pass the friability test; while formulation 4 showed a hardness of 491 N and a 10.08% loss in the friability test (Table 3). On the other hand, Formulation 5 showed suitable characteristics, particularly hardness and friability, as shown by the test results in Table 3.

The mean weight of the tablets was appropriate, and all tablets were within ±5% of the mean, as specified by the Brazilian Pharmacopoeia (2010). This standard allows no more than two units outside the specified limits, in relation to the mean weight. The low relative standard deviations indicated that the improved flowability of the powder made it appropriate for machine feeding (Alves et al., 2011).

### Table 2. Results of hardness and friability analyses of the tablet formulations.

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Hardness (N)±SD</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation 1</td>
<td>55±2.51</td>
<td>n.d.</td>
</tr>
<tr>
<td>Formulation 2</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Formulation 3</td>
<td>493±2.08</td>
<td>n.d.</td>
</tr>
<tr>
<td>Formulation 4</td>
<td>491±3.05</td>
<td>10.08</td>
</tr>
<tr>
<td>Formulation 5</td>
<td>116±3.13</td>
<td>0.28</td>
</tr>
</tbody>
</table>

n.d: not detectable; SD: standard deviation

Tablets must be sufficiently hard to resist breakage during packaging, transport, or conventional handling (Ansel et al., 2000; Elkhalifa et al., 2009). However, tablets should be able to dissolve or disintegrate after they are properly administered, or be broken with the fingers if a partial dose is needed. Friability is the lack of resistance to abrasion, when subjected to the mechanical action of specific equipment. The friability determined for the tablets made from Formulation 5 was less than 1.5%, within the acceptable limit prescribed by the Brazilian Pharmacopoeia (2010). This ensured that the tablets were produced with appropriate characteristics of cohesion between the particles, to withstand the impact of manipulation and transport.

Regarding the content of the active ingredient, all the formulations were within the limits set by the Brazilian Pharmacopoeia (2010) to ensure a suitable dose (Viana et al., 2006; Alves et al., 2011).

With respect to disintegration, Formulation 5 disintegrated within 30 min. A 30-min time limit is used as a general criterion for testing the disintegration of tablets, unless otherwise specified (Brazilian Pharmacopoeia, 2010).

The development of immediate-release tablets that contain a high proportion of herbal product and still disintegrate within a reasonable length of time, less
than 10 min, is a difficult challenge and an important component of a successful scale-up. The disintegration time of Formulation 5 probably influenced the release of active substances. It would be useful to evaluate the use of disintegrants/superdisintegrants to improve the release time, with a view toward scale-up. However, the tablets disintegrated within the time limit prescribed by the Pharmacopoeia, and microcrystalline cellulose is itself a disintegrant, according to the Handbook of Pharmaceutical Excipients (Rowe et al., 2009).

To provide the antidepressant effect, the EPA dose for a normal adult weighing 70 kg was calculated as 80 mg per day. This value was based on the proportion of the body surface of the rats used in the pharmacological test (Roncon et al., 2011) and the body surface of an adult human weighing 70 kg. Therefore, the formulation contained 80 mg EPA in 400 mg of microparticles. For the other formulations it was not possible to use 400 mg of microparticles, and therefore the dose was divided into two tablets with 40 mg EPA each.

The drug manufacturing process and the formulation components used can influence dissolution and bioavailability. Tablets obtained by DC may display different in vitro and in vivo behavior. Dissolution testing is universally used in the development, production, and quality assurance of oral solid-dosage forms. During this testing, the dosage form is immersed in a flowing aqueous medium and the concentration of the drug released in the medium is measured at set time intervals, using techniques such as HPLC. The dissolution behavior of drugs is a critical quality attribute for oral solid-dosage forms, since in almost all cases their therapeutic efficacy depends on this behavior (Windbergs et al., 2009; Souza et al., 2011). The tablets obtained from Formulation 5 were slightly yellowish, round, flat, and free of foreign material (Figure 1).

Figure 2 shows scanning electron micrographs (SEM) of the spray-dried extract powder (microparticles) and the microparticles in Formulation 5, showing that the particles are spherical, and remain intact before and after compression. Spherical particles are a common result of the spray-drying process, and this shape is associated with adequate flowability and bulk density (Chaves et al., 2009).

Figure 3 shows the dissolution profiles of the tablets made with Formulation 5 and from EPA microparticles. The entire EPA content, with respect to the chemical markers catechin and epicatechin, was released from the tablets over a period of 120 min. The release from the microparticles occurred within 60 min.

We observed the same dissolution profile for both the microparticles and the tablets. However, the tablets required a longer time to dissolve. This occurs because the tablets were made by compression, and they dissolve through a process of erosion of the matrix together with swelling (Pezzini et al. 2007). The microparticles undergo the same process, but since their contact area with the dissolving liquid is much greater than that of the tablets, the microparticles dissolve much more rapidly.

For the conventional solid pharmaceutical dosage forms, a faster release of the active compounds was expected, but was not observed. A plausible explanation...
for this release profile is the disintegration time of the tablets, because for an immediate release, a disintegration time less than 10 min is recommended. Because in this case the disintegration time is longer (25 min), the release occurs more slowly in the beginning. Before the fraction is microencapsulated it has hygroscopic characteristics and good solubility; however in aqueous dispersion it is hard, and may tend to release more slowly.

In analyzing the results of the release profile, different values of n (release exponent), which characterizes the release mechanism were obtained. In the microparticles, catechin and epicatechin had n values of 0.4828 and 0.5428, with correlation coefficients of 0.9963 and 0.9982, respectively. For cylinder shapes, the ranges of n values are: Fickian diffusion (n≤0.45), non-Fickian diffusion (0.45<n<0.89) and transport mechanism type II (n>0.89). Therefore, the microparticles showed anomalous behavior, with a greater influence of Fickian diffusion and less relaxation of the polymer chains. This profile is a pseudo-first order, very close to Higushi model (Aulton, 2007).

The values of n for the tablets differed from those for the microparticles. In the tablets, the values of n and the correlation coefficients for catechin and epicatechin were 2.95 (r=0.9863) and 2.75 (r=0.9855), respectively. These values indicate a classification as transport mechanism type II.

The aqueous medium was chosen as a first step in assessing the release of markers in the dosage form, because freshly purified water lacks interfering attributes, i.e., has a pH close to neutral and contains no ions. For future studies, we intend to evaluate acidic media, simulating the environment of the gastric or even the intestinal tract.

**Conclusion**

Tablets were prepared with microparticles containing a semipurified extract of guaraná (EPA), in several formulations. The composition of each formulation influenced the physical and chemical characteristics. Only one formulation displayed characteristics that met pharmacopoeial specifications, and is therefore suitable for oral administration. The results of the *in vitro* drug release may be related to the more-complex structure of tablets, which hinders the delivery of the markers more than the microparticles, prolonging their release rate.

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**References**


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