Technological development of *Cecropia glaziovi* extract pellets by extrusion-spheronization

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**Abstract:** *Cecropia glaziovi* Snethl., Urticaceae, is commonly used in South America and is one of the species included in the Brazilian Medicinal Plants Research Program. Pharmacological studies have led to reports of the potential of *C. glaziovi* as a hypotensive, antiasthmatic and anxiolytic agent. The strict requirements regarding the quality, safety and effectiveness of phytopharmaceutical products represent an enormous challenge in the search for products with a high level of uniformity, reproducibility and stability. The incorporation of dry extracts into multiparticulate dosage forms, such as pellets produced by extrusion/spheronization technology, is a suitable alternative to overcome the lack of technological properties of dry extracts, since they are associated with low flowability and high hygroscopicity. In this study, an optimized dry extract (ODE) of *C. glaziovi* was incorporated into pellets seeking to decrease the moisture sorption and increase the stability, safety and percentage of the extract in the final product. Pellets containing around 50% of ODE were considered the most technologically viable, offering a narrow particle size distribution, significant improvement in the flowability and compressibility properties, and decrease in the moisture compared with the ODE. In conclusion, pellets containing a high dose of the *C. glaziovi* extract were successfully prepared, achieving degrees of quality, physical stability and feasibility compatible with the desirable characteristics of a phytopharmaceutical.

**Keywords:** *Cecropia glaziovi* extrusion-spheronization moisture sorption pellets phytopharmaceuticals

**Introduction**

Herbal extracts are widely used to treat diseases in Traditional Brazilian Medicine. However, strict regulatory requirements in relation to the quality, safety and effectiveness of phytopharmaceuticals (Anvisa, 2010) result in significant challenges being associated with the search for products with a high level of uniformity, reproducibility and stability. Although dry herbal extracts are more stable in comparison to their aqueous form, they have a complex composition and contain a number of active components and hydrophilic ingredients with a tendency to absorb moisture leading to microbial growth and hydrolysis (Fischer, 2007). The highly hydrophilic characteristic of these compounds may facilitate the production of highly concentrated herbal extracts in aqueous and hydroalcoholic solutions. On the other hand, this characteristic also presents a challenge due to the significant effects on the physiochemical and technological properties as well as the biopharmaceutical properties of the extracts (Emery et al., 2009).

*Cecropia glaziovi* Snethl., Urticaceae, is a vegetal species commonly used by the South American population for anti-hyperlipidemic purposes (Silva et al., 2010). Several pharmacological studies have been reported in the past few years indicating the potential of *C. glaziovi* as a hypotensive (Ninahuaman et al., 2007), antiasthmatic (Delarcina Jr. et al., 2007) and anxiolytic (Rocha et al., 2002) vegetal drug. In preliminary studies conducted by our group, the presence of high amounts of both chlorogenic and caffeic acids were observed in hydroalcoholic extracts prepared with the leaves of *C. glaziovi*, which prompted the development and validation of an analytical method for the quantification of these chemical markers (Arend et al, 2011).

*C. glaziovi* is one of the species included in the Brazilian Medicinal Plants Research Program (Brasil, 2006), but the authors could find no reports available on studies related to the technological issues associated with the preparation of solid dosage forms containing *C. glaziovi* extract.

Oral solid dosage forms, such as tablets and...
capsules, containing dry herbal extracts have proved to be a suitable alternative for the use of medicinal herbs. However, the production of this type of dosage form requires the use of several adjuvants and additional operations due to the poor technological properties of the crude dry extracts, such as low flowability and density and high hygroscopicity (List & Schmidt, 1989; Petrovick et al., 2010; Sonaglio et al., 2010). The incorporation of dry extracts into granulated dosage forms is a suitable alternative to overcome such issues (List & Schmidt, 1989, Sonaglio et al., 2010). Pellets as a multiparticulate drug delivery system offer several technological and therapeutic advantages since they consist of a “multiple unit” dosage form with defined diameter of 0.5-2 mm and minimum surface/volume ratio, which ensures a good drug dissolution rate, less irritation of the gastro-intestinal tract and lower risk of side effects (Aguilar-de-Leyva et al., 2011). From the technological point of view, some characteristics of pellets, such as free flow properties, narrow particle size distribution and ideal surface for coating qualify them as a good solid dosage form (Chopra et al., 2002, Koester & Thommes, 2010, Sousa et al., 2002). In addition, this dosage form is appropriate to increase the amount of the active component in the formulation due to its high density (Di Pretoro et al., 2010), while the administration of a low density crude extract may become an issue when high amounts of herbal extract are necessary to achieve the therapeutic concentration of the active compounds.

Among several technologies available for pelletization, the extrusion-spheronization method (Kanbe et al., 2007) is one of the most commonly used. This method requires the preparation of a plastic mass by heating or moistening with a specific granulation liquid, shaping the wet mass into cylinders through extrusion, rounding the extrudates into spheres and drying the final product. Some properties of the raw materials have a strong influence on the quality of the pellets produced requiring formulation studies in order to determine the ideal formulation for extrusion-spheronization. Good wettability, ability to bind moisture, plastic behavior, good lubricity, and ability of the extruded material to separate are some of the important factors required of the raw materials used in pelletization (Kanbe et al., 2007).

In this study, a standardized Optimized Dry Extract (ODE) of C. glaziovii was incorporated into pellets as a solid oral dosage form in order to decrease the moisture sorption problem and enhance the technological properties of the product.

**Materials and Methods**

**Chemical reagents**

Chemical reagents and other materials were obtained from the following commercial sources: chlorogenic acid and caffeic acid (Sigma-Aldrich, St. Louis, MO, USA), methanol and acetonitrile (HPLC grade) (J.T. Baker, Phillipsburg, NJ, USA), acetic acid (Chemis, São Paulo, Brazil), LC grade water obtained with a Milli-Q system (Millipore, Bedford, MA, USA), and ethanol (Labsynth, São Paulo, Brazil). Microcrystalline cellulose 101 (Microcel® 101) and polyvinylpyrrolidone (Kollidon® VA64-Fine) were kindly donated by Blanver (São Paulo, Brazil) and BASF (São Paulo, Brazil) respectively. All samples and solutions were prepared with purified water. All other reagents and solvents were analytical grade.

**Plant material**

Dried leaves of *Cecropia glaziovii* Snethl., Urticaceae, were obtained from the Pluridisciplinary Center of Chemical, Biological and Agronomic Studies (CPQBA) of the University of Campinas (UNICAMP) in Campinas, São Paulo, Brazil. A specimen voucher is deposited at the CPQBA herbarium under number 78. The dried leaves were ground in a knife mill (Macmont) using a 3 mm mesh. The milled vegetal material was characterized according to the particle size distribution, loss on drying and total ash as described below.

**Vegetal drug characterization**

The particle size distribution of the vegetal drug was evaluated by a standard sieving method, for a period of 15 min (Sieve Shaker Bertel 1400), with 30 g of the dried milled plant material, using a series of sieves with screen sizes corresponding to 180, 355, 500, 710, 1000 and 1700 µm. The average particle size was calculated by means of Probito’s evaluation (Pasqualoto et al., 2005; Vila-Jato, 1997).

Loss on drying (LOD) analysis was carried out in order to determine the amount of water and volatile matter in the vegetal drug material. The LOD was determined gravimetrically by weighing 1.0 g of milled leaves in an aluminum plate and submitting the samples to a heat-generating halogen analyzer (MB35 Ohaus) at 105 °C until the weight reading stabilized. The results were expressed as percentage weight loss (w/w) considering the mean of three measurements (F. Bras. V, 2010).

The total ash (TA) content was determined after ignition of the dried leaves. This analysis was carried out gravimetrically by weighing 3.0 g of milled leaves in a porcelain crucible. The samples were submitted to calcination in an oven at 600 °C for 2 h. The results were expressed as percentage of the remaining weight (w/w) considering the mean of three measurements (F. Bras. V, 2010).
Preparation and characterization of the optimized dry extract (ODE)

The liquid hydroalcoholic extract was prepared according to previously optimized conditions (Dos Santos, 2012). The ground vegetal material was macerated at room temperature for three days. This operation was carried out in glass bottles with 18:100 (w/v) vegetal drug:27°GL ethanol solution ratio.

The optimized liquid extract (density 0.9504 g/mL) was concentrated under vacuum at 40 °C (MA-120, Marconi, Brazil) and freeze-dried for 48 h (LD1500, Terroni), obtaining as result the optimized dry extract (ODE).

The ODE was characterized according to the chlorogenic (CGA) and caffeic (CFA) acids contents and the Hausner and Carr indexes as described below.

Pellets formulation

Pellets were prepared by the extrusion-spheronization technique. Defined amounts of ODE were blended with microcrystalline cellulose 101 (MCC) achieving proportions of 20:80, 35:65 and 50:50 (MCC:ODE). The granulation liquid was water or polyvinylpyrrolidone (PVP) aqueous solution according to the need for binding agents. The amount of granulation liquid and concentration of PVP solution (0, 2 or 5%) required were determined experimentally.

The wet mass was transferred to a screen extruder (Extruder 20, Caleva Ltd.) and immediately extruded through a perforated screen of 1.0 mm diameter at a constant speed of 16 rpm.

The extrudates were transferred to a spheronizer (Spheronizer 120, Caleva Ltd.) equipped with a 3.0 mm square pitch cross-hatched friction plate and spheronized for 1 min at 1000 rpm. After complete spheronization, pellets were left to dry on a fluid bed (Mycrolab, Huttlin Ltd.) for 15 min (batch size 100 g; air flow 15 m³/h; inlet air temperature 60 ºC).

The particle size distribution of every formulation was carried out by a standard sieving method, for a period of 15 min (Sieve Shaker Bertel 1400), with 30 g of pellets, using a series of sieves with screen sizes corresponding to 180, 355, 500, 710, 800, 900, 1000, 1120, 1180, 1250, 1500 and 1700 µm.

Quantitative analysis

The chromatographic analysis was performed using a previously validated method (Arend et al., 2011) on a PerkinElmer high-pressure chromatograph equipped with a Series 200 auto sampler, Series 200 binary pump, Series 200 UV-Vis detector or Series 200 EP Diode Array Detector and Series 200 vacuum degasser. A Zorbax C HP C18 column (5 mm, 150 mm × 4.6 mm, Agilent Technologies) was used. The mobile phase consisted of acetonitrile (A) and 1.0% acetic acid (B) with a flow rate of 1 mL/min and was programmed as follows: 0-15 min, isocratic, 87% B; 15-25 min, gradient, 87-60% B; 25-34 min, isocratic, 60% B. Detection was set at 330 nm. The injection volume was 20 µL. The data were collected using TotalChrom® Workstation software.

The quantification of the chemical markers was carried out by comparison of their retention times and by coinjection of the standard solutions. Standard curves were plotted for chlorogenic (2.5-200 µg/mL) and caffeic (2.5-100 µg/mL) acids. The quantification of the individual compounds was performed using a validated regression curve (r²>0.9999). For the quantification of the dry extract, a known amount was dissolved in 10 mL of a methanol:water solution (50:50; v/v).

In order to obtain the pellets sample, a known amount of these was triturated and left under magnetic stirring in 50 mL of a methanol:water solution (50:50; v/v). The suspension was centrifuged (4K15, Sigma) at 1500 rpm for 5 min and the supernatant was collected for analysis.

The samples were filtered through a 0.45 mm HVLP membrane (Millipore) before injection. All of the chromatographic analysis was performed in triplicate and the average areas of the peaks were calculated.

Hausner and Carr indexes and aspect ratio

A 100 mL cylinder was filled with pellets of a known total weight and the mass to volume ratio of the pellets was calculated in order to determine the bulk density (ρb) of the pellets. The same samples were placed in a tapped density tester (Copley JV 1000) in order to compress the content. After 300 taps or when the volume remained constant, the mass to volume ratio of the compressed pellets was calculated in order to determine the tapped density (ρt).

The Hausner Index (HI) (Emery et al., 2009; Hauser, 1967; Soares et al., 2005), used as indicative of the packing capacity of powders and granules, was then calculated according to the following equation:

\[ HI = \frac{\rho_t}{\rho_b} \]

For comparison, the ODE was also characterized by the HI and CI as described above. Micrographs of pellets were taken using a Stereo-microscope coupled to the microscope.
a photographic camera (Olympus SZ 40). The aspect ratio (AR) of the pellets was determined by image analysis (Size Meter 1.1, LCP, UFSC) as the ratio between the longest caliper distance and the caliper distance perpendicular to it.

**Scanning electron microscopy (SEM)**

Scanning electron microscopy (SEM) analysis of all samples was carried out on a Philips XL-30 scanning electron microscope. The samples were coated with a fine gold layer before analysis. All samples were analyzed using an accelerating voltage of 10.0 kV and the magnification of images was set at 60x and 300x for C. glaziovi pellets and ODE, respectively.

**Moisture content of pellets and ODE**

The residual moisture content of the pellets and ODE was determined by a loss-on-drying method (F. Bras. V, 2010) using a halogen moisture analyzer (MB35 Ohaus). Approximately 1 g of material was deposited on an aluminum plate and dried at 105 °C under a heat-generating halogen source until the weight reading stabilized. The moisture content was expressed in percentage terms (%; w/w) as the mean of three measurements.

The capacity to gain moisture was determined through a controlled-humidity micro-environment exposure method (Hong et al., 2005). Samples of C. glaziovi pellets and ODE were sealed in a glass desiccator, containing a saturated solution of sodium chloride, at room temperature. This solution is capable of maintaining the relative humidity at 75% in a temperature range of 20 to 40 °C inside sealed enclosures (Hong et al., 2005; O'Brien, 1948). The relative humidity was monitored daily using a calibrated hygrometer and the maximum variation was only 1% at room temperature (25±2°C) during the whole experiment. The samples were analyzed at 15 and 30 days of exposure using a halogen moisture analyzer in order to determine the moisture gain potential of both the pellets and ODE. The results were expressed in percentage terms (%; w/w) as the mean of three measurements. Photographic images of the ODE and pellets before and after the moisture content study were obtained using a Fujifilm Finepix HS20EXR high-definition camera.

**Results and discussion**

**Vegetal drug characterization**

It is known that an excess of humidity enhances the enzymatic degradation of the chemical constituents of vegetal drug material during storage and allows the proliferation of micro-organisms (Fischer, 2007). In this study the volatile matter, including the humidity content, was determined through the LOD and the value found (13.10±0.44%) was considered to be satisfactory, according to the Brazilian Pharmacopoeia (F. Bras. V, 2010). The mean diameter of the crushed leaves was 0.946±0.798 mm and this is valuable information for the standardization since the reproducibility of the extractive process has a direct relation with the access of the extraction solvent to the vegetal material surface. The TA content was considered indicative of the degree to which the vegetal material could be considered as ‘clean’ (Fischer, 2007) and the value found (7.92±0.33%) was satisfactory (F. Bras. V, 2010).

**Pellets formulation**

The formulations were prepared in the order shown in the Table 1 by the extrusion-spheronization method. The amount of water added to the powder mixture of MCC and ODE was determined experimentally until the mass was sufficiently moist for extrusion.

The use of water as granulation liquid aimed to simulate the possibility of direct incorporation of the aqueous extract, without prior drying, reducing the number of production stages (concentration and drying of extract), optimizing time and cost in production.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Water (g)</th>
<th>PVP (%)</th>
<th>MCC:ODE</th>
<th>Viability*</th>
<th>Yield of usable fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM1</td>
<td>31.2</td>
<td>-</td>
<td>20:80</td>
<td>NV</td>
<td>-</td>
</tr>
<tr>
<td>FM2</td>
<td>46.9</td>
<td>-</td>
<td>35:65</td>
<td>NV</td>
<td>-</td>
</tr>
<tr>
<td>FM3</td>
<td>65.3</td>
<td>-</td>
<td>50:50</td>
<td>+</td>
<td>54.9%</td>
</tr>
<tr>
<td>FM4</td>
<td>66.2</td>
<td>2%</td>
<td>50:50</td>
<td>+++</td>
<td>68.2%</td>
</tr>
<tr>
<td>FM5</td>
<td>65.8</td>
<td>5%</td>
<td>50:50</td>
<td>+++</td>
<td>89.4%</td>
</tr>
</tbody>
</table>

*Viability: NV=not viable; +=slightly viable; +++=viable; ++++=highly viable.

The FM1 contained the highest amount of ODE in its composition, aimed at the incorporation of the maximum content of extract. Nevertheless, this formulation was not viable since the high amount of hydrophilic extract led to the formation of a goo due to the mucilage nature of the ODE (Lobova et al., 2003; Ribeiro & Mors, 1950). In comparison to other formulations, FM1 needed the lowest content of water (31.2 g) in order to achieve the necessary humidity for extrusion, but the tacky extrudates formed were inclined to agglomerate during spheronization hindering the formation of spherical granules.

A similar behavior to that shown by FM1 was observed for FM2, which contained a 35:65 MCC:ODE ratio. Although a higher amount of MCC was used, the high concentration of ODE also induced the formation of...
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In order to decrease the amount of fine particles, two concentrations of PVP solution (2 and 5%; FM4 and FM5, respectively) were added. The use of hydrophilic polymers, such as PVP, is an interesting strategy to improve the extrusion-spheronization process since they are capable to form solid bridges enhancing the cohesion of the wet mass. The use of PVP as a spheronization aid usually leads to higher yield and improvement on the sphericity of the particles (Law & Deasy, 1998; Otero-Espinar et al., 2010). As expected for these formulations, an improvement in the plasticity and cohesion of the wet mass was observed, and a narrow particle size distribution of pellets was achieved. The amount of granulation liquid was kept constant since the moisture content required for the formation of high amounts of fines. Table 1 shows the amount of pellets within the usable fraction of 0.5-1.0 mm determined in this study for comparison purposes.

Although FM3 was viable for the formation of granules with acceptable spherical shape, it was verified that the particle size distribution was too broad, with the formation of high amounts of fines. Table 1 shows the amount of pellets within the usable fraction of 0.5-1.0 mm determined in this study for comparison purposes.

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Table 2. Hausner and Carr indexes and aspect ratio for ODE and FM5.

<table>
<thead>
<tr>
<th></th>
<th>ρb (g/cm³)</th>
<th>pt (g/cm³)</th>
<th>HI</th>
<th>CI (%)</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODE</td>
<td>0.523±0.012</td>
<td>0.684±0.003</td>
<td>1.30±0.03</td>
<td>23.33±1.53</td>
<td>-</td>
</tr>
<tr>
<td>FM5</td>
<td>0.693±0.009</td>
<td>0.710±0.003</td>
<td>1.02±0.02</td>
<td>2.34±0.71</td>
<td>0.91±0.07</td>
</tr>
</tbody>
</table>

On comparing the HI and CI values, an enormous improvement in the technological properties of ODE was verified after incorporation into the pellets. The results obtained for the FM5 pellets of *C. glaziovi* were considered satisfactory for all indexes analyzed (Table 2). The ODE have a very small and irregular particle size (Figure 2), which produces a material with poor flow properties inherent to the high cohesiveness between particles. This behavior can adversely affect the content uniformity in the production of dosage forms, which leads to the need to incorporate poorly flowing powders, such as the ODE, into more elaborate intermediate dosage forms like pellets. The results obtained indicated excellent compressibility and flow properties for the FM5 pellet formulation (Aguilar-de-Leyva et al., 2011; Chopra et al., 2002). Good flow is important in the production of capsules and tablets, where satisfactory filling and content uniformity is necessary (Podczeck et al., 2008). The achievement of a technologically viable phytopharmaceutical product with good flow properties is important since this dispenses the need to introduce additional excipients, such as lubricants, which could modify the dissolution rate of the herbal extract. Moreover, the improvement of the technological properties allows a maximum drug per unit volume since
it would not be necessary the addition of high amounts (or no addition at all) of excipients in order to produce tablets or capsules. When it comes to the production of these final dosage forms using the crude ODE, the final concentration of the product would be diluted since the addition of high amounts of excipients is necessary in order to overcome ODE’s lack of technological properties. These results have considerable impact when a high drug dose is required, as commonly needed in the case of treatments with phytopharmaceuticals.

The aspect ratio (AR) of 0.91 (Table 2) can be considered satisfactory indicating that the pellets produced are acceptably spherical. Chopra et al. (2002) demonstrated that there is an important correlation between the amount of under-filled capsules and the pellet shape. The pellets do not necessarily need to be totally spherical to provide good filling results, but an increase in friction due to non-spherical shape and thus a more pronounced sensitivity to electrostatic charging can result from increased surface roughness and, consequently, influence the filling ability of the product.

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was also used to visualize the pellet surface morphology. Based on the photomicrographs, spherical and slightly rough beads without cracks were obtained (Figure 2). The comparison of the slight roughness of the pellets to the surface of the small non-regular-shaped particles of the ODE (Figure 2) indicates a significant improvement from the technological point of view, since the pellets flow properties appear to be a function of the surface roughness (Chopra et al., 2002).

These results indicate that the pellets obtained are suitable for its use as intermediate on the production of final solid dosage forms (e.g. capsules, tablets), due to their adequate flow and compressibility indexes and slightly rough surface.

Moisture content of pellets and ODE

One of the main difficulties associated with the use of dry herbal extracts is their high hygroscopicity. The moisture sorption can exert significant effects on the physicochemical and technological properties of the dry extracts. An improvement in the moisture resistance is desirable since the high hygroscopicity is one of the most critical issues in terms of the industrial production of phytopharmaceuticals. In relation to technological issues, an excess of moisture may decrease the ability of powders and granules to flow smoothly since the increased tackiness of the absorbed moisture layer increases the strength of liquid bridges formed between particles (Emery et al., 2009). In this regard, pelletization has the potential to improve this aspect, since the moisture sorption has much higher technological impact on small-particle products such as ODE in comparison to large particles, as in the case of pellets. The amount of water absorbed by pellets needs to be a lot higher in order to significantly influence the flow properties.

The moisture sorption is also a pharmacological issue since it accelerates the enzymatic degradation of chemical constituents, compromising the biological activity, and may also enhance the development of microorganisms decreasing the expiration time of the final product (Fischer, 2007).

Table 3. Percentage of water gain (w/w) of ODE and FM5 after 15 and 30 days.

<table>
<thead>
<tr>
<th>Percentage of water gain</th>
<th>Time zero</th>
<th>After 15 days</th>
<th>After 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODE</td>
<td>3.30±0.11</td>
<td>24.78±0.17</td>
<td>36.76±0.98</td>
</tr>
<tr>
<td>FM5</td>
<td>2.51±0.15</td>
<td>14.11±0.96</td>
<td>18.65±0.20</td>
</tr>
</tbody>
</table>

In relation to the water gain for ODE and FM5 (Table 3), in both cases an increase in moisture content
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was observed, however, the behavior differed. In the case of ODE, there was an important moisture increase for both periods evaluated, that is, 15 and 30 days, whereas for FM5, this increase was significantly lower, around half that observed for ODE (Table 3). In comparison with the crude ODE, the moisture resistance of the ODE incorporated into the pellets dosage form was clearly improved. In addition, the incorporation of ODE in pellets avoided the loss of the original structure after moisture sorption, such as noted in crude extract. This is evident in Figure 3, where there is the formation of a goo for the ODE, while the pellets presented only a slight change of color. This study showed that even though MCC has a known ability to retain water (Tomer et al., 2001), the incorporation of extremely hydrophilic dry extracts such as ODE into an MCC matrix exerts a beneficial effect in terms of decreasing moisture sorption. Along with this improvement in the moisture resistance achieved by pelletization, the water gain could be further enhanced by other technological resources, such as a polymeric coating.

Conclusions

Formulation variables were studied in order to determine the ideal parameters to produce pellets of a *Cecropia glaziovi* Snethl., Urticaceae, extract by extrusion-spheronization. Different proportions of extract were blended with MCC in order to incorporate the maximum content of ODE. It was verified that the 50:50 ratio using as a binder a 5% PVP solution led to the production of spherical granules with adequate technological characteristics. The flowability and compressibility of the optimized formulation was suitable. This formulation could be used as an intermediate dosage form to fill capsules or to be compressed into tablets. Moreover, it was verified that the incorporation of ODE into pellets increased significantly the moisture resistance enhancing the physical stability of the product.

In conclusion, pellets containing *C. glaziovi* extract were successfully prepared, achieving a degree of quality, physical stability and feasibility compatible with the characteristics required for the production of a phytopharmaceutical product.

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