

# Preparation of pellets containing a standardized *Artemisia annua* L. extract by extrusion-spheronization

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## Abstract

Artemisinin, the major substance with antimalarial activity of *Artemisia annua* L., is a poorly water-soluble drug. The development of pellets containing a standardized hydroethanolic extract of *A. annua* may overcome these drawbacks while offer an intermediate product with good technological properties for subsequent tablet manufacture. This work aimed to obtain and characterize *A. annua* pellets using the extrusion-spheronization technique. The extract was prepared by percolation and artemisinin content was determined using a validated HPLC method. The standardized extract was then used as a liquid binder in the preparation of pellets with different liquid: solid ratio. The formulation PF5 containing microcrystalline cellulose: *A. annua* extract (40:58) resulted in pellets with  $1.49 \pm 0.02$  % (w/w) artemisinin, average size of approximately 500  $\mu\text{m}$  and sphericity of  $0.82 \pm 0.08$ . These pellets were encapsulated in hard gelatin capsules and the percentage released was higher than 80% in 10 min using 0.1N HCl and phosphate buffer media. These data allow to suggest that the pelletizing strategy used made it possible to achieve the desired artemisinin dissolution and generates perspectives for the potential further use of the *A. annua* pellets as a solid dosage form for malaria treatment.

**Keywords:** Herbal medicinal. Artemisinin. Multiparticulate solid dosage form. Phytopharmaceutical technology.

## Introduction

*Artemisia annua* L. (Asteraceae) is an herb widely used in traditional medicine to treat malaria with a relatively safe toxicity profile<sup>[1-3]</sup>. Artemisinin is a sesquiterpene lactone isolated from the aerial parts of *A. annua*. This compound has an endoperoxide bridge crucial for its potent antimalarial activity at nanomolar concentrations<sup>[3,4]</sup>. The flavonoid content of the leaf powder can vary between 9% and 11% (w/w) and has already been shown to exert antimalarial and antioxidant activity<sup>[5]</sup> and enhance the activity of artemisinin<sup>[6]</sup>. Other phytochemicals in this genus are therapeutically active<sup>[2]</sup> denoting the relevance of administering the phytotherapeutic complex for treating malaria and other diseases. Additionally, artemisinin is a poorly water-soluble compound with low oral bioavailability<sup>[7]</sup> when administered alone, however, its use from *A. annua* extracts is related to an improvement in bioavailability<sup>[2]</sup>.

However, the use of *A. annua* in the form of infusion as self-medication, prepared with plants from different sources can result in treatment failure and the occurrence of high recrudescence of malaria. This may occur due to high variation of artemisinin content between different cultivars ranging from 0.01 % to 1.5 % (dry mass), because it depends on the altitude conditions, climate, nutrients, soil pH, among other factors<sup>[8]</sup>. In addition, storage in inappropriate conditions can also reduce artemisinin content of the vegetable drug. For these reasons, in 2012, the World Health Organization took a cautious approach to the use of home-grown plants to treat and prevent malaria as an infusion<sup>[9]</sup>.

Accordingly, the best approach seems to be the use of phytotherapeutic products prepared from standardized vegetable extracts which should present an appropriate content of the active ingredient, as well as adequate flowability, density and hygroscopicity<sup>[10,11]</sup>. Industrial production of pellets is a promising strategy to improve the technological properties of vegetable extracts<sup>[11-14]</sup>. Additionally, pellets can ensure a proper drug dissolution rate with less irritation of the gastrointestinal tract<sup>[15]</sup>. Lastly, pellets are especially advantageous when the active component is in great amounts in the formulation, because of its high density<sup>[16]</sup>. Among the technologies available for pelletization, the extrusion-spheronization technique is one of the most commonly used and has been successfully applied to herbal products<sup>[11-13]</sup>.

With a view of producing *A. annua* intermediate products with good technological properties and physicochemical properties, pellets were developed and characterized using the extrusion-spheronization technique. To do so, a standardized extract of *A. annua* was used as granulation liquid and the resulting pellets were characterized.

## Materials and methods

The anhydrous artemisinin (98%) was purchased from Sigma Aldrich (São Paulo, Brazil). Desiccated aerial parts of *Artemisia annua* L. (Asteraceae) were kindly provided by Divisão de Agrotecnologia do Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agrícolas (CPQBA) of the Universidade de Campinas (UNICAMP), Brazil, in march 12, 2012 (block F1). Identification of the botanical material was done by Pedro Melillo de Magalhães (CPQBA). The plant material was grounded in a crusher with a helix (Siemens, Brazil). Particle size analysis was carried out by sieving (BecTel Granulometer, Brazil). The volatile content was determined on the Ohaus MB35 infrared balance (NJ, USA). Solvents were of analytical grade (for extraction purposes) or HPLC grade (for chromatographic analysis). Microcrystalline cellulose PH 101 (Blanver, São Paulo, Brazil), lactose monohydrate (Milkaut, Santa Fé, Argentina), polyvinylpyrrolidone K30 (Ashland, São Paulo, Brazil) and Kollicoat<sup>®</sup> (BASF, Ludwigshafen, Germany) were used for pellet preparation.

### Extraction of *A. annua* leaves and extract characterization

Grounded *A. annua* leaves were extracted with ethanol 95% (v/v) using a percolation procedure at 1:10 drug: solvent ratio. The solvent was added in four steps to a 10 L percolator containing the plant material. The total extraction time was 72 h. The four fractions obtained were combined and the solvent was evaporated under reduced pressure in a rotary vacuum evaporator (Buchi<sup>®</sup> R-220 SE, Flawil, Switzerland) at 40°C and 70 rpm. The concentration step was performed until a small precipitation was observed (1.25: 1 extract: plant ratio).

The total solid content of the percolate and concentrate was then determined, as well as the ethanol content, relative density, pH and viscosity<sup>[17]</sup>. The content of artemisinin was determined by HPLC using a Waters HPLC (Massachusetts, USA) system equipped with a separation module (e2695), a PDA absorbance detector (Waters 2998), and the software Empower<sup>®</sup>. Separations were performed on a Zorbax Eclipse XDB-C18 reverse phase column (Agilent, Santa Clara, USA) (150 x 4.6 mm, 5 µm) and guard column RP18 Security Guard Phenomenex (California, USA). The mobile phase consisted of a mixture of acetonitrile: 0.2% formic acid (v/v) followed a gradient of 35:65 for 8 min, then changed to 60:40 for 5 min, returning to 35:65 and ending with a 20 min run. The flow rate was 1.2 mL/min and the detection wavelength was 255 nm. The column temperature was 30°C. The analytical validation was reported elsewhere<sup>[18]</sup>.

### Preparation of *A. annua* pellets by extrusion-spheronization

Polyvinylpyrrolidone (PVP) was slowly dispersed in the *A. annua* extract, under constant mechanical stirring at 750 rpm for 10 min. Next, the PVP-containing extract was used as liquid binder by adding it to the microcrystalline cellulose at different liquid: solid ratios (**TABLE 1**). For some formulations (PF1 and PF5, **TABLE 1**) no PVP was added. The wet mass was formed using a planetary mixer Stinfer<sup>®</sup> (São Paulo, Brazil). Extrusion was performed with a Caleva<sup>®</sup> Extruder 20 (Caleva Process Solutions Limited, United Kingdom). The wet mass was fed into the extruder set at 30 rpm. The wet mass was forced through a plate containing 0.8 mm diameter holes. The extrudates were then spheronized in a Caleva Multi Bowl Spheronizer MBS 250 (Caleva Process Solutions Limited, United Kingdom) set at 1500 rpm for 60 s. Pellets were then dried in a Hüttlin<sup>®</sup> Mycrolab fluidized bed, with air inlet temperature of 60°C.

**TABLE 1:** Composition of *A. annua* pellets.

Formulation code	MCC: <i>A. annua</i> extract ratio (w/w)	Mass of PVP K30 % (w/w)
PF1	0.88:1	-
PF2	0.57:1	8
PF3	0.57:1	5
PF4	0.57:1	2
PF5	0.69:1	-

### Pellet characterization

Pellets containing *A. annua* extract had their projected sphericity (PS) determined using the ImageJ software, version 1.47v (NIH, Maryland, USA)<sup>[19]</sup>. Their residual moisture content was evaluated in an infrared balance (Ohaus MB35, NJ, USA) at 105°C up to constant weight. The size distribution analysis was performed on a Beckman Coulter<sup>®</sup> LS I3 320 diffraction particle size analyzer (Indianapolis, USA). The pellet size amplitude (d90/d10) was calculated<sup>[20]</sup>. Artemisinin content was determined by HPLC, as previously reported<sup>[18]</sup>. The analyses were performed in triplicate.

### Preparation and characterization of the pellet-containing capsules

Gelatin capsules (size 00) containing *A. annua* pellets were prepared using a manual capsule filler. The capsules were evaluated for disintegration (Nova Etica 301 AC disintegrator, São Paulo, Brazil), mean weight, artemisinin content (HPLC) and *in vitro* dissolution profile. Dissolution study was performed on a

Vankel VK 7000 dissolutor (Varian, USA) with an USP apparatus II kept at 100 rpm. Dissolution tests were performed in 0.1N HCl solution (pH 1.2) and 0.05M potassium phosphate buffer (pH 6.8) which were prepared according to the United States Pharmacopoeia<sup>[21]</sup>.

## Results and Discussion

The proper control of neglected diseases can significantly reduce morbidity, social exclusion and mortality rates<sup>[22]</sup>. Among the neglected diseases, malaria stands out in the Brazilian Legal Amazon region, as it is one of the most common diseases<sup>[23]</sup>. Similarly, malaria has great relevance in Africa and others tropical countries<sup>[24]</sup>.

The use of *Artemisia annua* is an important therapeutic option for the treatment of malaria; however, an adequate control of the artemisinin content should be performed because it is affected by geographical, seasonal and growth conditions<sup>[4,25,26]</sup>. Selection of hybrids with good artemisinin production<sup>[27]</sup> has been performed to overcome these drawbacks. In the present study, a hybrid specimen was collected and submitted to a standard extraction process with a view of obtaining a standardized extract of *A. annua* which was further used in developing *A. annua* containing-pellets.

The artemisinin content in the non-concentrated percolate was  $0.084 \pm 0.01\%$  and dry residue was  $2.09 \pm 0.05\%$ . Artemisinin is a poorly water-soluble drug<sup>[7]</sup>, therefore, to avoid its precipitation during ethanol removal, the concentration step was interrupted at the first signal of precipitation. The final *A. annua* extract obtained had  $1.47 \pm 0.05\%$  of artemisinin, and  $30.78 \pm 0.43\%$  of dry residue. The relative density of this extract was  $0.93 \pm 0.00$  g/mL, pH 6.3, viscosity of  $3.13 \pm 0.06$  cP and 23.5% (v/v) ethanol content.

The use of *A. annua* extract instead neat artemisinin may be therapeutically beneficial, because the plant extract may increase the antimalarial effect, since it has other phytochemicals that could act synergistically. For instance, flavonoids of *A. annua* have proven antimalarial activity<sup>[5]</sup> and can improve the solubility of artemisinin, together with glycosides, saponins and other phenolic compounds<sup>[8,28,29]</sup>. In this context, Meshnick *et al.*<sup>[4]</sup> showed that patients receiving 600 mg/day neat artemisinin reached a degree of upsurge equal to or less than 10%, whereas a dose of only 11.1 mg of artemisinin (from *A. annua* extract) plus 7.4 mg of neat artemisinin, led to a 9.1% recrudescence rate<sup>[30]</sup>.

With a view of improving the technological properties of the standardized *A. annua* extract, pellets were prepared using the extrusion-spheronization technique. To do so, the extract of *A. annua* was used as the granulation liquid at different solid: liquid ratios. The characterization data are shown in **TABLE 2**. The dried pellets had sphericity from 0.77 to 0.82, average diameter and size amplitude from 551 to 1465  $\mu\text{m}$  and from 1.8 to 2.8, respectively. The artemisinin content was from 1.49 to 1.89% (**TABLE 2**).

PF1 formulation did not form pellets because the amount of liquid binder was not enough to achieve a minimum powder agglomeration. Consequently, the amount of liquid binder was increased (PF2 to PF5 pellets, **TABLE 1**). PVP was used as a binder and when it was present at high concentration (PF2, **TABLE 1**) an excessive growth was observed preventing pellet formation. Lower PVP concentrations were then used (PF3 and PF4, 2.86 and 1.15% PVP, respectively) which allow pellet production, however, average size was too high for a subsequent tablet production. In the PF5 formulation, the amount of liquid was slight reduced and PVP was suppressed. As a result, pellets with the highest sphericity value and average size of approximately 500  $\mu\text{m}$  were obtained. This formulation was then encapsulated in hard gelatin capsules. We emphasize that the pellets

of *A. annua* achieved through PF5 formulation presented an artemisinin content close to that of the standardized extract used, making both interesting for future studies of antimalarial activity.

**TABLE 2:** *A. annua* pellets obtained by extrusion-spheronization technique.

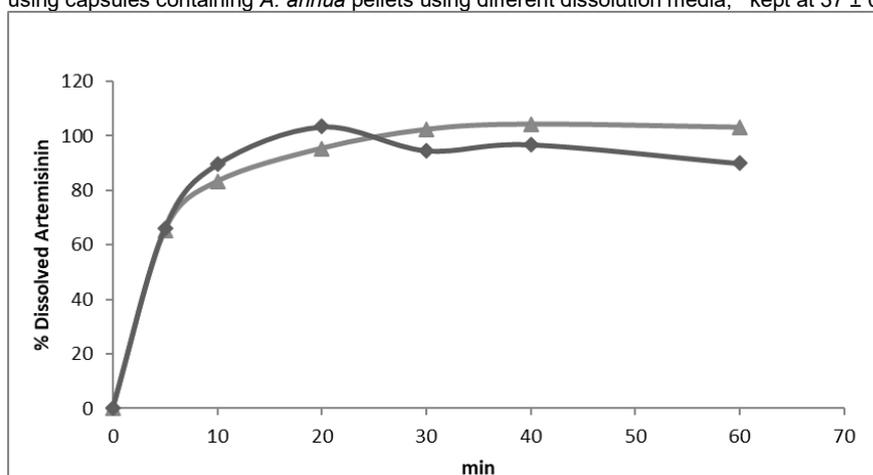
Formulation code	Residual moisture (%)	Sphericity	Average diameter ( $\mu\text{m}$ )	Size amplitude (d90/d10)	Artemisinin content (%)
PF1 <sup>1</sup>	-	-	-	-	-
PF2 <sup>1</sup>	-	-	-	-	-
PF3	2.57 $\pm$ 0.05	0.79 $\pm$ 0.09	1340	1.9	1.89 $\pm$ 0.03
PF4	2.49 $\pm$ 0.11	0.77 $\pm$ 0.09	1465	1.8	1.86 $\pm$ 0.09
PF5	2.28 $\pm$ 0.13	0.82 $\pm$ 0.08	551	2.8	1.49 $\pm$ 0.02

<sup>1</sup>not characterized

There are herbal medicines with *A. annua* extract available in the market (tablets, capsules and suppositories), however, they are comprised by non-standardized plant drug<sup>[4]</sup>. Diawara *et al.*<sup>[24]</sup> prepared granules from the hydroalcoholic extract of *A. annua* containing 0.23% (w/w) of artemisinin. These authors reported adequate weight and content uniformity, but other tests were not performed. On the other hand, we used standardized raw material for developing pellets, which were not yet described for this medicinal plant. The use of a multiparticulate solid dosage form may improve technological properties of the herbal extract. Additionally, pellet administration can improve dissolution rate and decrease tissue irritation<sup>[11]</sup> and contributes to improving the drug bioavailability due to the control or modification of their release rate<sup>[31]</sup>. The low flowability and high hygroscopicity of the herbal extracts can also be overcome by their incorporation into pellets<sup>[10,32]</sup> allowing the development of other solid dosage forms, like capsules and tablets<sup>[33]</sup>.

Capsules containing *A. annua* pellets were characterized. These capsules had 605.6 mg average weight and showed acceptable weight variation (lower than  $\pm 7.5\%$ ). Capsules containing pellets were fully disintegrated in less than 5 min in both purified water and 0.1N HCl (pH 1.2). The mean artemisinin content was 95.8% of the predicted amount. The uniformity of content test resulted in an acceptance value of 14.0 (that is,  $8.64 \pm 0.4$  mg per capsule), below the limit recommended by the US pharmacopoeia<sup>[21]</sup>. Artemisinin release from the *A. annua* capsules was very rapid in both media, reaching more than 80% up to 10 min (**FIGURE 1**).

**FIGURE 1:** *In vitro* artemisinin dissolution at pH 6.8 (gray color) and 1.2 (black color). The dissolution test was performed using capsules containing *A. annua* pellets using different dissolution media, kept at  $37 \pm 0.5^\circ\text{C}$ .



After 60 min of dissolution the amount of released artemisinin was significantly lower in HCl solution pH 1.2 ( $89.9 \pm 5.9\%$ ) ( $p = 0.014$ ) than in phosphate buffer (pH 6.8) ( $103.2 \pm 3.4\%$ ). This difference may be explained by the deposition of a resinous material in the dissolution vessel containing acidic medium. This insoluble material may contain a certain amount of artemisinin. Despite the differences in artemisinin, the dissolution efficiency (ED) did not show a significant difference ( $p = 0.26$ ) between the dissolution media.

Artemisinin solubility in water is very low<sup>[7]</sup> and values of  $49.7 \mu\text{g/mL}$ ,<sup>[29]</sup>  $44.7 \mu\text{g/mL}$ <sup>[34]</sup> and  $30.1 \mu\text{g/mL}$ <sup>[35]</sup> were reported. Despite this, artemisinin release from cellulose pellets was very fast, which can be explained by the presence of the other plant compounds, mainly the phenolic ones<sup>[29]</sup>.

The dissolution studies were carried out with 900 mL of dissolution medium (pH 1.2 and 6.8) using 100 rpm paddle speed under sink conditions. The paddle speed were in accordance to Hoa *et al.*<sup>[36]</sup> and Balducci *et al.*<sup>[34]</sup> whose performed studies on pure artemisinin, although these authors used water as dissolution medium. To the best of our knowledge, no *in vitro* dissolution studies have been reported with *A. annua* extract.

Nijlen *et al.*<sup>[37]</sup> studied the dissolution of 20 mg neat artemisinin in water: ethanol: sodium dodecyl sulfate medium (90:10:0.1, v/v/v). Even using a dissolution medium capable to increase the solubility of artemisinin, less than 7 mg were dissolved after 60 min. Capsules containing pellets of standardized extract of *A. annua* prepared in this study released all of the artemisinin content after 30 min. These results reinforce the effect of other substances present in *A. annua* hydroalcoholic extract on artemisinin dissolution.

A proper dosage form development can circumvent the poor technological properties of herbal extracts allowing to explore the unique advantages of these products, mostly representing by the synergistic action of their constituents. In this sense, the *A. annua* pellets developed here have potential to be used as an herbal platform for the treatment of malaria.

## Conclusion

The incorporation of *A. annua* L. extract into microcrystalline cellulose allowed the obtention of uniform pellets by extrusion-spheronization technique. The pellets showed high sphericity, and average size adequate for subsequent tableting. Additionally, the artemisinin dissolution from pellets was rapid in acidic and neutral media suggesting its potential for further studies.

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