

Research Article

Development of a Capsule Formulation Containing Dry Bark Extract of *Annickia Polycarpa*: Laboratory to Pilot Scale-up

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Abstract

This study focuses on the development and scale-up of a capsule formulation based on the dry extract of *Annickia polycarpa* bark, a West African medicinal plant known for its antimalarial, antibacterial, and antioxidant properties. The objective was to adapt the process, initially optimized at laboratory scale, to a pilot scale for pharmaceutical valorization. Hot maceration followed by drying yielded a higher extraction rate at pilot scale (24%) compared to laboratory scale (18.46%). Powder characterization revealed very fine particles ($D_{x50} < 125 \mu\text{m}$), residual moisture within pharmacopeial limits (4%), and good solubility (100-200 g/L). However, the powders exhibited poor flowability, requiring wet granulation with pregelatinized starch or carboxymethylcellulose as binders. This step significantly improved flow properties and particle cohesion. Capsules produced from the granules met uniformity of mass requirements according to the European Pharmacopeia and displayed a rapid disintegration time (< 7 minutes), ensuring efficient release of active compounds. The human equivalent dose (HED), extrapolated from animal studies, was estimated at 3,402 mg/day for a 70 kg adult, allowing the definition of capsule size 2 with 247-296 mg of extract per unit. Overall, these findings demonstrate the technical feasibility and robustness of the encapsulation process for *Annickia polycarpa*, providing promising perspectives for industrial development and the production of standardized phytomedicines. However, further studies on long-term stability, bioavailability, and clinical efficacy are required to ensure the quality, safety, and therapeutic effectiveness of the final product.

Keywords

Annickia Polycarpa, Pilot-Scale Extraction, Capsule Formulation, Phytomedicine

1. Introduction

The valorization of African plant resources for therapeutic purposes constitutes a strategic issue for the development of improved traditional medicines and phytomedicines. *Annickia polycarpa* (DC.) Setten & Maas (Annonaceae), commonly used in traditional pharmacopeias of West Africa, is renowned for its antimalarial, antibacterial, antifungal, antioxidant and anti-inflammatory properties [15, 16]. The

barks of this plant contain alkaloids, flavonoids, terpenes and phenols, which justify its documented pharmacological activity [7].

The development of a phytomedicament requires rigorous control of the transformation process, from the extraction of bioactive compounds to the galenic formulation. The dry extract represents a stable and concentrated form, compatible

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with putting in capsules, which is one of the most common oral forms in herbal medicine for its acceptability, dosage accuracy and ease of packaging [2, 4]. However, the transition from small-scale production to pilot or industrial scale poses several technological challenges, particularly with regard to reproducibility of yield, stability of assets, physical characteristics of the powder (particle size, hygroscopicity, compressibility) and the suitability with the capsule packaging process [5].

The formulation of capsules is based on strict criteria, including the fluidity of the powder, the uniformity of the filling, the absence of reactions between excipients and active ingredients, as well as the stability of the content over time [14, 18]. Moreover, scaling up in the production line requires applying galenic engineering principles (such as respecting drying, grinding, mixing and encapsulation conditions), while maintaining the pharmaceutical specifications of the finished product [3, 6].

The present study aims to develop a formulation in capsules based on dry extract of *Annickia polycarpa* bark, starting from the experimental conditions of the laboratory to adapt them to the pilot scale. It is part of an approach to the industrial

valorization of traditional pharmacopoeia, by combining quality, stability and pharmaceutical compliance requirements.

2. Material and Methods

2.1. Material

2.1.1. Plant Material

The plant material was bark of *Annickia polycarpa*.

They were harvested about 75 km from Daloa on the way to Zoukougbeu, in the Classified forest of Haut Sassandra de Daloa on Sunday, August 22, 2021. The sample was authenticated by a morphological identification at the National Center of Floristics of the FELIX HOUPHOUËT-BOIGNY University (FHBV). The herbarium is kept there under number UCJ001184. The collected bark were dried at room temperature (25 °C), away from the sun, for two weeks. They were then ground (Retsch GM 300 Mill) at 2000 rpm to obtain a fine powder.

2.1.2. Technical Equipment and Materials

- | | |
|--|---|
| <ol style="list-style-type: none"> 1) Agitator KIKA WERKE 2) Bain marie 3) Precision balance O'HAUS 4) Beakers 3 liters 5) Timer 6) Sieve 100µ 7) Grinder Retsch GM 300 8) Granulometer MASTERSIZER 3000^E 9) Manual capsule maker 10) Delitest PHARMATEST PTZ | <ol style="list-style-type: none"> 1) Evaporator E1400v3 FF3 2) Tilting cooker (Reactor 80 L) 3) Porcelain tray 4) Rotavapor Heidolph 5) Filter 90µ in canvas 6) Homemade gas oven 7) Oven MEMMERT 8) Semi-automatic capsule maker MULTIGEL MS-6 AUT 9) Granulator ERWEKA FGS equipped with an engine ERWEKA AR400 |
|--|---|

2.2. Methods

2.2.1. Extraction Method by Hot Maceration, Followed by a Concentration by Evaporation and Drying

The hot maceration operation consisted of letting the *Annickia polycarpa* bark powder stay in water heated to 80 °C for 1 hour 30 minutes and twice 1 hour, to extract the active metabolites.

The extraction yield was calculated according to the Equation: *Determination of dry extract yield:*

The dry extract yield (EY%) was calculated from the following formula:

Equation (1): Extraction yield

$$EY\% = \frac{\text{mass of dry extract}}{\text{mass of bark powder}} \times 100 \quad (1)$$

(i). Laboratory Scale

100 g of *Annickia polycarpa* bark powder was placed in a beaker with a capacity greater than 3 L. The water bath was run up to 80 °C. 800 mL of osmosis water was added to the beaker containing our sample, then placed in the water bath with stirring for 1 hour. Using a sieve, the resulting mixture was filtered.

Twice, 800 mL of 80 °C RO water was added to the bark powder residue, and the same operation was carried out to exhaust the drug, this time with stirring for 1 hour.

The liquid extraction yield was calculated.

The resulting macerate was then concentrated to one-third volume using a rotavapor.

The concentrated liquid extract was dried in a MEMMERT oven at 50 °C. The dry extract obtained was weighed and the extraction yield calculated.

(ii). Pilot-Scale Maceration

3000 g of *Annickia polycarpa* bark powder were placed in a tilting cooker filled with 80 L of osmosis water heated to 80 °C. The mixture was stirred for 1 h 30 min, then filtered through a sieve with a mesh less than 90 µm in diameter.

Twice, we added 80 L of RO water to the bark powder residue and performed the same operation to exhaust the drug, this time stirring for 1 hr.

The filtrate obtained is concentrated in a vacuum evaporator to about 1/3 of its volume.

The concentrated liquid extract was dried in a gas oven at 80 °C. The dry extract obtained was weighed and the extraction yield calculated.

2.2.2. Characterization of Extract Powders

The characterization of extract powders enabled us to compare the pharmaco technical properties of powdered extracts and to deduce the extract most suitable for galenic formulation.

Due to the low yield of extract obtained in the laboratory, we were only able to carry out tests that did not require a large quantity of extract. The table below shows all the tests carried out on each sample. The cages marked with a tick are the tests we carried out.

Our standards were obtained from the 9th edition of the European Pharmacopoeia.

NB: the flow test requires 100 g of powder.

Table 1. Tests carried out on the different powder samples.

Characterization tests of powders	Extracted at the laboratory scale oven	Extract at pilot scale
Macroscopic and organoleptic examination	X	X
Flowability test		X
Laser particle size analysis	X	X
Residual moisture test	X	X
Solubility test	X	X

(i). Macroscopic and Organoleptic Characterization of the Extracts

The organoleptic characteristics of the extracts were determined by an observation of color, taste and smell.

(ii). Flowability Test

100 g of powder was weighed and put into the standardized funnel previously plugged with the finger. The powder flow time was timed after clearing the funnel. The test was repeated 3 times. The results are expressed as flow times of 100 g of powder.

(iii). Laser Particle Size Analysis

The passage of the extracts to the MALVERN laser particle sizer type MASTERSIZER 3000 E made it possible to plot the histograms of the percentages of the simple masses and the cumulative percentages of the powders as a function of the size of the particles, to determine the particle size distribution profile of the powder, then the median particle size (50% of the powder). The fineness of the powders was defined according to the following table:

Table 2. Classification of powders according to their fineness.

Descriptive term	X ₅₀	Cumulative volume distribution Q ₃ (x)
Coarse	>355	Q ₃ (355) <0,50
Moderately fine	180-355	Q ₃ (180) <0,50 et Q ₃ (355) ≥0,50
Fine	125-180	Q ₃ (125) <0,50 et Q ₃ (180) ≥0,50
Very fine	≤125	Q ₃ (125) ≥0,50

(iv). Residual Moisture Test: Gravimetric Method

3 test shots of 1 to 3 g (m) of powder were introduced, respectively in 3 pre-calibrated watch glasses. The masses of the test shots plus the tares have been noted. After 2 hours in the oven at a temperature of 102 ±2 °C, the test samples were weighed again. Mass constancy was checked by heating 1 h more each time, until the difference in mass is less than 0.5 mg. The mass of water contained in the powder of each watch glass was noted M and given by the formula: $M = m - m'$. The mass after drying is: m' [9].

The residual moisture content (RM%) was calculated according to the Equation

$$RM\% = \frac{m - m'}{m} \times 100 \quad (2)$$

The standard states that it must be between 3 and 5%.

(v). Solubility Test [8]

The method was that of the OECD (Organization for Economic Cooperation and Development) 105. Increasing volumes of water were gradually added to approximately 0.1 g of sample (sprayed), at room temperature, in a 10 ml graduated bottle closed with a glass stopper. After each addition of water, the mixture was stirred for 10 minutes. It was then visually checked if the sample was completely dissolved. If undissolved parts of the sample remained after adding 10 ml of water, the test should continue in a 100 ml graduated flask.

Table 3 below gives the volume of water that completely dissolves the sample, the approximate solubility. If the solubility is low, the time required to dissolve the substance may be long and at least 24 hours. If after 24 hours the

substance is still not dissolved, it is necessary to wait up to 96 hours or proceed with further dilution.

Table 3. Different types of solubility according to the OECD.

ml of water for 0,1 g soluble	0,1	0,5	1	2	10	100	> 100
Approximate solubility (g/l)	> 1000	1000 à 200	200 à 100	100 à 50	50 à 10	10 à 1	< 1

2.2.3. Wet Granulation of the Extracts and Characterization

Determining the dose to be administered [17]

The determination of the dose to be administered was made using a factor-based dose approach. In this approach, the no

observed adverse effect level (NOAEL) of the drug in the animal undergoes simple allometric extrapolation to obtain the Human Equivalent dose (HED). The United States Food and Drug Administration (FDA) has formulated a table of conversion factors (Table 4) that allow for proper calculation of the HED.

Table 4. Conversion factors in the determination of HED.

Species	HED (mg/kg) = Divide animal dose by...	HED (mg/kg) = Multiply animal dose by...
Mouse	12,3	0,081
Hamster	7,4	0,135
Rat	6,2	0,162
Guinea pig	4,6	0,216
Rabbit	3,1	0,324
Dog	1,8	0,541
Marmoset	6,2	0,162
Baboon	1,8	0,541

To account for size-independent effects of pharmacokinetics and pharmacodynamics, the DHE is then multiplied by the mass of a standard adult (70 kg) and divided by a safety factor equal to 10. The FDA approach uses 0.67 as an exponent to extrapolate doses between species.

Choice of excipients

The excipients were selected on the basis of the results of the rheological characterization, their availability and the fact that they were obtained from our natural resources.

Table 5. Excipients description.

Raw materials	Function	Proportion	Description
Carboxymethyl cellulose	Binder	2.5%	White, odorless, tasteless powder. Hygroscopic after drying
Pregelatinized corn starch	Binder	5%	White to off-white, medium-coarse to fine powder. It is painless and has a slight, characteristic taste
Osmosed water	Dampening solution	Sqt	Purer, odorless water, free of chlorine aftertaste and other undesirable, polluting substances.

Wet granulation was chosen because the flow of powder extract was infinite.

In view of the low yield of the powder extracts obtained in the laboratory, and given that after the various characterization tests, the two extracts presented practically the same characteristics (see results), we carried out wet granulation with the powder extract obtained on a pilot scale (720 g).

Wet granulation

It was carried out in the following stages:

- 1) Weighing: The various raw materials were crushed and weighed using a mortar and pestle combination and a precision balance.
- 2) Mixing: The raw materials required for the internal phase of the granules (dry extract + binder) were mixed. The binder was added dry, to optimize the amount of water required for wetting.
- 3) Wetting: Once the mixture was homogeneous, we proceeded to the wetting stage, a critical step in the granulation process. This involved adding osmosed water at 75 °C to the mixture until a paste of optimum consistency was obtained.
- 4) Granule formation: This was carried out on the BONALS oscillating granulator. The wet mass was passed through a screen. The wet granulated mass was weighed.
- 5) Drying: The granulated mass obtained was placed in the MEMMERT oven for 48 h at 50 °C.

Residual moisture was measured using the loss-on-drying method.

Two formulas were produced: formula 1 with 5% pregelatinized starch as binder, and formula 2 with 2.5% carboxymethyl cellulose.

Formula 1:

Table 6. Formula 1 (First granulation formula).

Raw materials	Function	Quantity
Annickia polycarpa bark extract	Active ingredient	20 g
Pregelatinized corn starch	Binder	5%
Osmosed water	Dampening solution	Sqt

Formula 2:

Table 7. Formula 2 (Second granulation formula).

Raw materials	Function	Quantity
Annickia polycarpa bark extract	Active ingredient	20 g
Carboxymethyl cellulose	Binder	2.5%
Osmosed water	Dampening solution	Sqt

We performed the following tests on formulas 1 and 2:

- 1) Particle size analysis: sieve method
- 2) Flow tests
- 3) Residual moisture test

(i). Particle Size Analysis: Sieve Method [11]

The test was carried out using a sieve shaker with 7 sieves of mesh sizes 4000, 2000, 1000, 600, 300, 150, 100 and 50 µm on a sample of 25 to 100 g of powder. The powder was placed on the top sieve and agitated for 10 min at a speed of 40 vibrations per minute. The rejects from each sieve and the base were weighed. Histograms of single and cumulative mass percentages of powders as a function of particle size were plotted. D₁₀, D₅₀ and D₉₀ deciles were determined. The classification of powders is shown in Table 2.

(ii). Flowability Test [10]

100 g of granules were weighed and placed in the standardized funnel, which had previously been plugged with a finger. The time taken for the powder to flow was measured after the funnel had been cleared. The test was repeated 3 times. Results were expressed as flow times for 100 g of granules.

(iii). Residual Moisture Test: Gravimetric Method [9]

3 test doses of 1 to 3 g (m) of granules were introduced into 3 pre-weighed watch glasses. The masses of the test samples plus the tares were noted. After 2 h in the oven at a temperature of 102 ± 2 °C, the test samples were weighed again. Mass consistency was checked by heating for a further 1 h each time, until the difference in mass was less than 0.5 mg (m'). The mass of water contained in the powder of each watch glass was noted M and given by the formula: M = m-m'. The mass of the test sample is: m.

2.2.4. Human Equivalent Dose of *Annickia Polycarpa*

An in vivo study evaluated the antimalarial activity of *Annickia polycarpa* extract in mice infected with *Plasmodium berghei*. The doses administered ranged from 200 to 600 mg/kg/day. At 600 mg/kg, parasitaemia was suppressed by 75.8%, with no apparent toxicity at oral doses of up to 4,000 mg/kg [15].

$$\text{HED} = \frac{\text{Animal dose (mg/kg)}}{\text{Conversion factor animal/human}} \quad (3)$$

Human Equivalent Dose (HED):

Animal dose = 600 mg/kg

Human body weight = 70 kg

Conversion factor (mouse → human) = 0,081 (see Table 4)

HED = 600 mg/kg × 0,081 = 48,6 mg/kg (human)

Total dose for 70 kg = 48,6 × 70 = 3 402 mg/day

2.2.5. Theoretical Extract Masses per Capsule

Formula 1

In 3000 mg of granules (2000 mg of extract + 1000 mg of binder), there are 2000 mg of plant extract.

For a size 2 capsule with a theoretical average weight of 370 mg, there are 247.67 mg of plant extract.

Formula 2

In 2500 mg of granules (2000 mg of extract + 500 mg of binder), there are 2000 mg of plant extract.

For a size 2 capsule with a theoretical average weight of 370 mg, there are 296 mg of plant extract.

2.2.6. Capsule Manufacturing and Capsule Control

The quantities required for capsule filling were determined using the filling table.

Formula: granules obtained from Formula 1 and Formula 2.

The extract dose per capsule was determined. Then, using the filling table, the amount of granule-exipient mixture required to fill 20 size 2 capsules was defined for both formulas. In a mortar, a homogeneous mixture was prepared and distributed into capsules by scraping level.

Capsule filling: The body of each capsule was opened and placed in the capsule filler, with the caps set aside. The capsules were filled by scraping level (without tamping). Once filling was complete, the capsule filler was gently tapped and carefully lowered, the upper part turned a quarter turn. The capsules were closed and ejected by turning the upper part of the capsule filler a quarter turn (same direction).

(i). Uniformity of Mass [12]

Method: We individually weighed the 20 filled samples, then emptied and weighed the contents of each capsule, and finally weighed the cleaned empty capsule. We then determined:

- 1) Net weight.
 - 2) Mean ($\bar{X}$)
 - 3) Confidence Interval (CI)
- CI = $\bar{X} \pm P\bar{X}$ P = Acceptance limit
CC' = $\bar{X} \pm 2P\bar{X}$

(ii). Disintegration Test [13]

Capsules were placed in each basket compartment, a disk was added (specific immersion medium: $37 \pm 2^\circ\text{C}$), the test duration was set, and the device was started. At the specified time, the basket rack was lifted out of the liquid.

Upon complete disintegration, the soft mass contained no palpable core.

Table 8. Acceptance criteria for the disintegration test.

LEVEL	SAMPL ES	Acceptance criteria (at the end of specific time)
Test 1	06	All units disintegrated: Test compliant

LEVEL	SAMPL ES	Acceptance criteria (at the end of specific time)
		1 ou 2 units not disintegrated: Perform Test 2
		More than 2 units not disintegrated: Test non-compliant
Test 2	12	16 out of 18 disintegrated

3. Results

3.1. Extraction Yield

Table 9. Drying results of the extracts at different scales.

	Laboratory scale	Pilot scale
Powder quantity	100 g	3000 g
Extract mass obtained	18,46 g	720 g
Yield %	18,46%	24%

3.2. Characterization of Extract Powders

3.2.1. Macroscopic and Organoleptic Characterization

Both extracts were brown in color, in flake form, slightly bitter, with a characteristic plant odor.

Table 10. Macroscopic and organoleptic examination of the two extracts.

CHARACTERISTIC	RESULT
Color	Brown
Odor	Characteristic
Taste	Slightly bitter



Figure 1. *Annickia polycarpa* extract.

3.2.2. Flowability Test

Both extracts were classified as very fine powders based on Dx50 values below 125 μm . Both showed almost identical D_{10} values (1.60-1.61 μm), meaning that 10% of particles had a diameter below this size. The “pilot extract” had slightly finer particles (2.35 μm) and a narrower distribution ($D_{90} = 5.78 \mu\text{m}$) compared to the “oven extract” ($D_{90} = 6.06 \mu\text{m}$).

The “laboratory extract” had the largest mean particle size (3.35 μm), indicating overall larger particles.

Both extracts had D_{90}/D_{10} ratios greater than 1, indicating heterogeneous size distribution, which may influence their rheological behavior.

Table 11. Particle size distribution of the different extracts.

PARAMETER	Laboratory Pilot
D_{10}	1,61 μm 1,60 μm
Median: D_{50}	2,39 μm 2,35 μm
D_{90}	6,06 μm 5,78 μm
Mean	3,35 μm 3,24 μm
D_{90} / D_{10}	3,78 3,61

3.2.3. Residual Moisture Content

Table 12. Residual moisture content test results.

SAMPLES	m (g)	After 2 h m 1	After 3 h m'	RESULTS
Oven extract	1,00	0,98	0,96	m-m'= 0.04 g RM % = 04
Pilot extract	1,00	0,98	0,96	m-m'= 0.04 g RM % = 04

The residual moisture content of both extracts complied with standards (3-5%) (Table 12).

3.2.4. Solubility Test

Both extracts were soluble in water, with an approximate solubility of 100-200 g/L, and showed similar solubility profiles.

Table 13. Solubility test.

SAMPLE	ml water dissolving 0,1 g	Approximate solubility (g/l)
Oven extract	1	100 à 200
Pilot extract	1	100 à 200

3.3. Wet Granulation

3.3.1. Determination of HED

- 1) Animal dose = 600 mg/kg (*Annickia polycarpa*)
- 2) Human weight = 70 kg
- 3) Conversion factor (mouse $\rightarrow$ human) = 0,081
- 4) HED = 600 mg/kg $\times$ 0,081 = 48,6 mg/kg (human)
- 5) Total dose for pour 70 kg = 48,6 $\times$ 70 = 3 402 mg/day

3.3.2. Particles Size Analysis Granules

Table 14. Particle size distribution of *Annickia polycarpa*.

D_{10}	2,332	€ [100-200]
Median: D_{50}	11,6	€ [300-600]
D_{90}	20,988	€ [600-1000]

Mean	3.887
Standard deviation	3.993

Both formulas exhibited excellent flow through the funnel, with complete discharge and flow times ≤ 10 s (0.45 s for Formula 1, 0.30 s for Formula 2). Flow occurred in a funnel-shaped stream..

3.3.3. Flowability Test

Table 15. Flowability test.

SAMPLES	<i>Polycarpa</i>
1 st test	0,47 s
2 nd test	0,45 s
3 rd test	0,43 s

3.3.4. Residual Moisture Content

The residual moisture content of the granules complied with the standard (between 3 and 5%). Formula 1 and Formula 2 granules had substantially equal values (04 and 03% respectively).

Table 16. Residual moisture content of Formulas 1 and 2.

Formula	m (g)	After 2 h	After 3 h	RESULT
		m	m'	
Formula 1	1	0,99	0,96	m-m'= 0.04 g RM %= 04
Formula 2	1	0,99	0,97	m-m'= 0.03 g RM %=03

3.3.5. Capsule Manufacturing and Quality Control

(i). Uniformity of Mass

No capsule mass fell outside the confidence interval. Capsules showed good uniformity of mass.

Table 17. Uniformity of mass.

	Mass of the full capsules (mg)	Mass of the empty capsules (mg)	Mass of the content of the capsules (mg)
m1	370	55	315
m2	350	66	284
m3	350	60	290
m4	350	70	280
m5	370	55	315
m6	320	60	260
m7	350	66	284
m8	330	60	270
m9	320	61	259
m10	370	55	315
m11	340	67	273

	Mass of the full capsules (mg)	Mass of the empty capsules (mg)	Mass of the content of the capsules (mg)
m12	340	70	270
m13	360	60	300
m14	340	60	280
m15	350	56	294
m16	330	58	272
m17	390	55	335
m18	360	57	303
m19	350	55	295
m20	350	55	295
Total	6990	1201	5789
Mean	349,5	60,05	289,45

- 1) Mean ($\bar{X}$): $\bar{X}=289,45$ mg
- 2) Confident interval (CI)
 - a. $CI = \bar{X} \pm P\bar{X}$, $P =$ Acceptance limit, $P = 10\%$ because $X < 300$ mg
 - b. $CI = [260,54-318,36]$
 - c. $CI' = \bar{X} \pm 2P\bar{X}$
 - d. $CI' = [231,56-347,34]$

(ii). Disintegration Test

All 6 capsules disintegrated in less than 7 minutes (below the 15 min limit). Test passed.

Table 18. Disintegration test.

SAMPLE	<i>A. polycarpa</i>
1 st test	6 min 30
2 nd test	6 min 10

4. Discussion

4.1. Extraction Yield

The extraction yield was significantly higher at pilot scale (24%) than at laboratory scale (18.46%). This difference can be attributed to a more favorable solvent-to-material ratio, more homogeneous agitation, and better thermal control at the pilot scale, enabling more complete diffusion of active metabolites [6, 5, 2]. Large-scale processes often benefit from optimized mass and heat transfer parameters, which favor the extraction of polar compounds such as alkaloids and flavonoids from *A. polycarpa* [16, 7]. Shorter drying times

and controlled temperature at pilot scale also help limit thermal degradation of actives, as reported in several phyto-extraction studies [1, 15].

4.2. Particles Size Characterization

Both extracts showed very fine particle sizes ($D_{50} < 125$ μm), with slightly finer particles and a narrower distribution at pilot scale ($D_{90} = 5.78$ μm) compared to laboratory scale ($D_{90} = 6.06$ μm). Finer particle sizes generally increase surface area and dissolution rate [14, 4, 18]. However, heterogeneous size distribution ($D_{90}/D_{10} > 3$) can affect blend uniformity and rheology, often requiring pre-processing such as granulation to improve flowability [11, 5, 3]. Similar findings have been reported for polyphenol-rich plant powders, where excessive milling may cause electrostatic charging and poor flow [6, 14, 2].

4.3. Residual Moisture and Solubility

Residual moisture levels (4% for both extracts) complied with European Pharmacopoeia standards (3-5%), ensuring microbiological and chemical stability [9, 4, 18]. Excess moisture can promote enzymatic degradation or microbial growth, while too little moisture can increase friability and dust formation [5, 2, 14]. Solubility values (100-200 g/L) were favorable for oral bioavailability of hydrophilic extracts [8, 6, 1] and consistent with the high alkaloid and polyphenol content reported in *A. polycarpa* [16, 7, 15].

4.4. Granulation and Flowability Improvement

Wet granulation transformed non-flowing powders into granules with excellent flow (≤ 0.45 s for 100 g). This is consistent with pharmaceutical engineering principles, where

granulation increases bulk density, reduces interparticle cohesion, and improves flow [14, 4, 2]. The choice of pregelatinized starch and carboxymethylcellulose as binders aligns with their ability to provide good interparticle cohesion while maintaining rapid disintegration [18, 13, 5]. Post-granulation moisture content (3-4%) remained within recommended limits, ensuring granule stability [9, 4, 6].

4.5. Capsule Quality Control

Capsules met European Pharmacopoeia criteria for mass uniformity [12] and disintegration (< 7 min, well below the 15 min limit [13]). These results reflect good filling performance, homogeneous blending, and excipient-extract compatibility [2, 5, 4]. Rapid disintegration is essential for prompt release and absorption of active ingredients [3, 18, 14].

5. Conclusion

This study successfully developed a capsule formulation containing dry extract of *Annickia polycarpa* bark, scaling the process from laboratory to pilot production. The pilot-scale process achieved a higher extraction yield (24% vs. 18.46% at laboratory scale) while maintaining physicochemical quality, particularly in terms of residual moisture (4%), solubility (100-200 g/L), and fine particle size ($D_{50} < 125 \mu\text{m}$).

Wet granulation significantly improved powder flowability, ensuring uniform capsule filling and mass uniformity in line with European Pharmacopoeia standards. The capsules also showed short disintegration times (< 7 minutes), favorable for rapid release of active compounds.

From an industrial perspective, these results confirm the technical feasibility and robustness of the process, offering promising prospects for the pharmaceutical valorization of *A. polycarpa*. However, further studies on long-term stability, bioavailability, and clinical evaluation of antimalarial efficacy are required to finalize development into a phytomedicine that meets quality, safety, and efficacy standards.

Abbreviations

CI	Confidence Interval
Eq	Equation
EY%	Extraction Yield
FDA	Food and Drug Administration
FHB U	Felix Houphouët-Boigny University
HED	Human Equivalent Dose
NOAEL	Non Observed Adverse Effect Level
OECD	Organization for Economic Cooperation and Development
RM%	Residual Moisture Content
Sqt	Sufficient Quantity To

Author Contributions

Lia Gnahoré Jose Arthur: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing

Kone Sounan Serge Alain: Investigation, Writing – original draft

Dally Laba Ismaël: Supervision, Validation, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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