

Development of Tablets Based on *Lannea microcarpa* Engl. Et K. Krause (Anacardiaceae) Extracts for Arterial Hypertension Therapy



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Abstract

In context of hypertension, research in African traditional medicine allows the identification of safe and effective recipes that lead to the development of phytomedicines or the isolation of molecules that can be used in managing of hypertensive patients.

Objectives: This study aims at formulating and evaluating tablets based on *Lannea microcarpa* Engl. et K. Krause (Anacardiaceae) extracts for arterial hypertension therapy.

Methodology: Formulations of conventional release tablets containing 250mg and 500mg of extract were made. Several excipients were tested in several steps and wet granulation was performed. A formulation containing a diluent/disintegrant (corn starch), a binding agent (PVP K30) and a lubricant (magnesium stearate) was made. Then a flow agent (colloidal silica) was associated with the formulations of the first step. Finally, the colloidal silica of the previous formulations has been replaced by an anti-adhesive, the talc.

Discussion: The average masses of the 250 mg tablets varied from 263.187 mg \pm 16.4 to 379.979 \pm 13.1 with coefficients of variation between 2.72% and 6.23%. The average masses of the 500mg tablets varied from 561.047mg \pm 15.13 to 783.388 \pm 33.82 with coefficients of variation between 2.05% and 4.95%. These tablets had disintegration times of less than 15 minutes. The friability indices (< 1%) of the tablets of formulations FA6, 11, 17 and 18 as well as FB1, 2, 7, 8 and 15 alone complied with the specifications of the European Pharmacopoeia 10th edition. The mean contents were 0.378900 \pm 0.010609 mg gallic acid equivalent (GAE)/tablet and 0.757 0.0211 mg GAE/tablet, respectively for the 250mg and 500mg tablets. The individual content of each tablet unit of both strengths was between 85 percent and 115 percent of the mean content and complied with the requirements of the European Pharmacopoeia 10th edition. These analyses led to the choice of FA6 and FB2 as the optimal formulation.

Conclusion: These results show the feasibility of the extracts of the plant in pharmaceutical form for the treatment of arterial hypertension.

Keywords: Arterial hypertension; Extracts; Formulations; *Lannea macrocarpa*; Tablets

Introduction

High blood pressure (HBP) is leading chronic disease in the world [1]. It is currently a public health problem worldwide, because of its burden. It also increases the risk of stroke, coronary heart disease, heart failure, kidney failure and cognitive impairment [2]. Its management considers the environmental factors, the genetic capital, the medical staff with all the available therapeutic arsenal (drug treatments, biological analyses,

traditional and alternative medicine etc.) [3]. In terms of drug treatment, there are five main classes of antihypertensive drugs that have demonstrated their effectiveness in terms of morbidity and mortality in managing uncomplicated essential hypertension. These include thiazide diuretics, beta-blockers, angiotensin II antagonists (ARBs), ACE inhibitors and calcium channel blockers (CCBs). For these treatments, it is often necessary to take several

combinations of drugs under specific conditions (Long-term treatment, restrictive schedules, etc.) [4]. Therefore, solid oral forms that are easy to use, and store improve compliance and offer significant advantages. Despite the recommendations of national and international learned societies on the management of hypertension, it remains insufficiently detected, treated, and controlled, indicating that the impact of these recommendations remains insufficient or even weak in the general population [5,6].

Despite considerable progress in managing hypertension in recent years, a large proportion of hypertensive subjects still have uncontrolled hypertension, especially in Africa. This is justified by problems of fragmentation, distribution, combined with difficulties in terms of availability, geographical accessibility and affordability resulting from an increased lack of universal health coverage. Because of these socio-cultural and economic barriers, Africa is becoming more active in developing traditional medicine in the fight against hypertension [7]. The research developed in this sense aims to enhance the value of traditional medicine through actions such as the involvement of herbal healers, the discovery of new molecules, the formulation of accessible and usable drugs to treat priority diseases [8]. These plants are used by traditional practitioners in old liquid forms derived from macerations, infusions, and decoctions etc., with stability problems. Possibilities of formulation in several forms (capsules, tablets, creams, gels, ointments etc.) are studied. Some are more innovative in modified release or microcapsule forms [9]. Among these conventional forms, solids such as capsules and tablets have higher stability, are easier to standardize [10] and represent two-thirds of the world market for drugs [11]. *Lannea microcarpa* Engl. et K. Krause (Anacardiaceae), a medicinal plant found in the Sahelo-sudanian and Sudanian savannahs, [12] is one of the antihypertensive medicinal plants used by herbal healers [13,14], and which present some efficacy and safety. Indeed, ethnobotanical studies have indicated the use of its trunk bark in the form of decoction in the treatment of hypertension in Burkina Faso [14-16]. Experimental studies (in vitro, ex vivo and in vivo) have demonstrated the safety and Anti-hypertensive properties of freeze-dried aqueous decoct of the bark of the plant trunk [17-22]. Also studies of physicochemical characterization, quality

control and galenic formulation have allowed the development of capsule forms based on standardized extracts dosed at 250mg [23-25]. Characterization studies showed that the freeze-dried aqueous extract was hygroscopic and had poor physico-mechanical properties [23]. This justified the initial choice of using the capsule form in order to ensure protection against moisture. Moreover, the process of obtaining the capsules is simple and less expensive. However, the development of a capsule form dosed at 500 mg of extract, for use in adult subjects, could not be achieved because of technological difficulties related to the high quantity of powder necessary for a capsule of size less than or equal to 0. Indeed, for pharmaceutical products, it is unusual to use capsules of size greater than "0", because of the difficulty to swallow large capsules [26]. This study aims to develop a formulation of conventional release tablets based on lyophilized aqueous extracts of *Lannea microcarpa* with as few excipients as possible using a simple process. It aims to provide practitioners and patients with an easy-to-use alternative treatment based on extracts of the plant.

Methodology

Materials

Plant material: The plant material consisted of trunk bark of *Lannea microcarpa* (Anacardiaceae), collected in the commune of Loumbila (Burkina Faso), a locality located 20 km from Ouagadougou. A sample of the plant was identified by a botanist of the Laboratory of Ecology of the Joseph KI-ZERBO University concerning the herbarium N° 1544 deposited at the Department of Forest Production of the National Center of Scientific and Technological Research (CNRST, Ouagadougou, Burkina Faso). The harvested bark was dried in a sunlight and dust-free environment and then pulverized with a Gladiator blade mill. The pulverized barks were subjected to an extraction by aqueous decoction and then lyophilized using the CHRIST® benchtop freeze dryer type ALPHA 1-2.

Excipients: Different types of excipients have been used and their characteristics studied to achieve an optimal formulation. The raw materials used, and their features shown in Table 1.

Table 1: Characteristics of the pharmaceutical raw materials used.

Raw Materials	Role	Reference	Batch	Suppliers
Freeze-dried extract	Active ingredient	Internal	-	IRSS
Corn starch	Thinner and disintegrant		3406	CERESTAR GL, Germany
Magnesium stearate	Lubrifiant	Ph. Eur	14.153.874	FAGRON, Belgium
Colloidal silica	Flow agent	Ph. Eur	14.235.129	FAGRON, Belgium
Talc	Flow agent	Ph. Eur	P 657980	FEDERA, Belgium
Polyvinylpyrrolidone K30	Binding agent	Ph. Eur	14G04-B05-298548	FAGRON, Belgium

Methods

Characterization of lyophilisates

Residual moisture content: The residual moisture

content of the extracts and the excipients were determined using the thermogravimetric method [27,28]. One (01) g of each powder is weighed in triplicate and placed in a previously tared watch glass in an infrared moisture Analyser (MF-50, US).

Hygroscopicity

Hygroscopicity was determined using 1.0 g of extract according to the method described in European Pharmacopoeia 6.0 [28]. The extract was introduced into a suitable desiccator containing a saturated ammonium chloride solution at 25°C for 24 hours. The percentage increase in mass was calculated according to the expression: $((m^3 - m^2) / (m^2 - m^1)) \times 100$

m^1 : mass of the container

m^2 : mass of container + powder at T 0 hour

m^3 : mass of vessel + powder at T 24 hours

Solubility test

The solubility study was performed in distilled water. Solubility was determined by gradually adding increasing volumes. The maximum amount of substance required for this assay was 111 mg and the maximum solvent volume was 30 mL according to the European Pharmacopoeia 5th edition [21]. The mixtures were stirred vigorously with a magnetic stirrer for 1 minute and then placed in a thermostatically controlled chamber at a temperature of 25.0 ± 0.5 °C for 15 minutes.

Suitability for extract flow

The flowability of the extracts was realized through the determination of the compressibility index (Carr index) and the Hausner index. The compressibility index (Carr's index) and the Hausner index (Hausner's index) were determined by measuring the apparent non-packed volume called bulk density and the tapped density after compacting the granules until a constant final volume. It was carried out with test piece according to the method described in European Pharmacopoeia 6.0 [29,30]. Both bulk density (BD) and tapped density (TD) were determined by pouring 10 g of granules from each formula into a 50 mL measuring test piece. The test piece was tapped three times onto a hard surface from the height of 2 cm at 2-second intervals. This volume was considered as a bulk volume. The tapping was continued until no further change in volume was noted.

This volume was considered as a tapped volume. BD and TD [30] were calculated using the following formulas:

Compressibility index or Carr's index (%) = $[(TD - BD) \times 100] / TD$ [30]

BD = weight of the granule/volume of the packing

TD = weight of the granule/tapped volume of the packing

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TD = weight of the granule/tapped volume of the packing.

Hausner's ratio was determined using the following formula: Tapped density / Bulk density. A Hausner ratio greater than 1.25 is considered of poor flow ability [31,32].

Development of tablet formulas

a) Justification of the dosage form

This study aimed to develop conventional release tablets containing 250mg and 500mg of extract. The orientation of the galenic form was based on the one hand, on the physicochemical properties of the extract and the other hand on the chronic character of the disease, requiring ease of administration and conservation to improve the observance of the treatment. These characteristics were also determining factors in the choice of excipients and the process to be used to produce the tablets. The amount of extract per tablet was based on the work of Nitiema et al., [18]. Mixing tests of excipients alone without extracts and excipients with extracts have oriented the retained proportions. The wet granulation technique was used with freeze-dried aqueous extracts of *Lannea microcarpa* trunk bark powders as active substance according to the evaluated characteristics and properties.

b) Formulation strategy

The strategy was to develop formulations that meet the standards with as few excipients as possible for formulation development. Therefore, it was, necessary to evaluate the relevance and the possible need to use or restrict certain excipients in the formulation. Several excipients were used to study their impact on the formulations and to arrive at an optimal formulation. The wet granulation method was chosen because the properties evaluated were not optimal for direct compression. The granulation having improved the flow of powders, the influence of three (03) lubricants (magnesium stearate, colloidal silica, talc) has been studied.

The first step was to make a series of formulations containing increasing amounts (10-50% w/w based on total extract weight) of diluent/disintegrant (corn starch), 4% w/w binding agent (PVP K30), and 1% w/w lubricant (magnesium stearate), corresponding to formulations F1 through F6 in Table II. The quantity of diluent was determined in these proportions of the theoretical mass of the tablet in order to obtain a homogeneous powder. In the second set of formulations (F7 to F12), 0.5% flow agent (colloidal silica) was incorporated into each of the initial formulations F1 to F6. Finally, in the third set of formulations (F13 to F18), colloidal silica was replaced with 1% w/w of another flow agent with anti-adhesive properties, talc..

The theoretical mass was constituted by the mass of the internal phase associated with the mass of the external phase with a mass of internal phase constituted by the mass of the extract + half of the mass of diluent/disintegrant + the mass of binder. The mass of the external phase consisted of half the mass of the diluent/disintegrant + mass of lubricants.

c) Preparation of granules

The granulation was carried out with a Frewitt (Switzerland) oscillating pelletizer, equipped with an ERWEKA motor type AR

400 n°48581 (Switzerland). Ethanol at 96° was used as wetting liquid. Its volume varied from thirteen (13) for F1 to Twenty-one (21) mL for F18. The mass to be granulated was weighed, mixed, and wetted with ethanol until a wet mass was obtained. This mass was introduced into the granulator and then subjected to an oscillatory movement forcing the paste to pass through the diameter sieves (1, 25mm). The obtained granules were dried in a Memmert oven (Germany) at a temperature of 45° C for 12 hours. The dried grains were sifted to retain grains of homogeneous size. The quality controls of the granules were carried out according to the official tests of the European Pharmacopoeia, namely, the macroscopic characteristics, the residual moisture content, the compressibility index and the Hausner index per methods 2.2.1.1, 2.2.1.2 and 2.2.1.3 [33].

d) Preparation of tablet

The mixtures of grains and lubricants were made in a Stephan® mixer in order to obtain a homogeneous product with

a uniform distribution of the lubricant. The theoretical masses of the tablets were calculated, to compare them with the real masses obtained after compression. They were calculated according to the addition of the masses of the internal phases associated with the masses of the external phases. The tablets were manufactured with a manual rotary tablet press. Adjustments were made to the filling volume of the compression chamber and the compression force. The intervention on the volume of the compression chamber made it possible to obtain the mass of the tablet containing the calculated active dose of the extract. These adjustments made it possible to modulate the mass and hardness of the tablets to the desired values that meet the standards of the European Pharmacopoeia. Among the formulations made, the one meeting all the required qualities of the tablets were retained. The quality controls of the tablets were carried out according to the official tests of the European Pharmacopoeia, namely, the tests of mass uniformity, hardness, friability, disintegration time and chemical tracer content [33].

Table 2: Qualitative and quantitative formulations of tablets based on freeze-dried aqueous extracts of *Lannea microcarpa* trunk bark powders.

Components	Formulations																	
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12	F 13	F 14	F 15	F 16	F 17	F 18
Extract (PA, mg)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cornstarch (%m/m of PA)	10	15	20	30	40	50	10	15	20	30	40	50	10	15	20	30	40	50
Magnesium stearate (%m/m of PA + diluent + binder + disintegrant)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Colloidal silica (%m/m of PA+ diluent + binder + disintegrant)	0	0	0	0	0	0	0.5	0.5	0.5	0.5	0.5	0.5	0	0	0	0	0	0
PVP K30 (%m/m of PA+ thinner)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc (%m/m of PA+ thinner + binder + remover)	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
TM 500	577.72	603.98	630.24	682.76	735.28	787.8	580.6	606.99	633.39	686.17	738.95	791.73	583.49	610.02	636.54	689.58	742.63	795.67
TM 250	288.86	301.99	315.12	341.38	367.64	393.9	290.3	303.5	316.7	343.09	369.48	395.87	291.75	305.01	318.27	344.79	371.32	397.84

TM = Theoretical mass

Pharmaceutical controls of tablets

Macroscopic characteristics: The macroscopic and organoleptic characteristics of the tablets obtained were described. It is about the appearance, the homogeneity of the colour, the taste and the smell of the tablets. Tablet dimensions such as diameter and thickness were also determined using a caliper [34,35].

Mass uniformity test: This test was performed on twenty (20) tablets taken randomly from each batch and weighed individually with a precision balance (Sartorius, France). The average mass (M), the mass deviations, as a percentage [100 (mi - M)/M] from the average mass and the coefficient of variation (CV)

were calculated. These parameters were compared to the limits specified in the European Pharmacopoeia 10th edition (2.9.5) [36], which states that the individual mass of not more than 2 of the 20 tablets may deviate from the average mass by more than the percentage given in Table 3 but the mass of no tablet may deviate by more than twice that percentage.

Hardness test : This test was carried out on 6 tables taken at random and introduced individually into the tubes of the disaggregation apparatus (Pharma test, France). A disc was placed on each table and the disaggregation medium used was distilled water at 37°C. The time of complete disintegration of the first and last tablet was noted (2.9.8) [36].

Table 3: Standards for the mass uniformity test of tablets

Pharmaceutical Form	Average Weight	Limit Deviations in % of the Average Mass
Uncoated tablets and Film-coated tablets	≤ 80 mg	10
	> 80 mg et < 250 mg	7.5
	≥ 250 mg	5

Disintegration time : This test was carried out on 6 tablets taken at random and introduced individually into the tubes of the disaggregation apparatus (Pharma test, France). A disc was placed on each tablet and the disaggregation medium used was distilled water at 37°C. The time of complete disintegration of the first and last tablet was noted. and the calculated average disintegration time. The results were compared to the limits specified in the European Pharmacopoeia 10th edition (2.9.1) [36].

Friability test : A number of whole tablets with a mass of approximately 6.5 g ($m < 650$ mg) and 10 tablets ($m > 650$ mg) was taken at random and placed in a friabilizer (Erweka, France) rotating at 25 rpm for 4 min. The tablets were weighed together before and after the test. The friability index determined must be less than 1%. The test was repeated 3 times according to the European Pharmacopoeia 10th edition (2.9.7) [36].

Determination of the uniformity of total phenolic compound content

A sample of 10 tablets was taken at random. Each tablet was weighed, pulverized with a mortar, and macerated individually for 10 min, by magnetic stirring, in a beaker containing 50 ml of distilled water. A 1 ml volume of the filtrate from each sample was prepared according to the method of Singleton et al and determined spectrophotometrically at 380 nm [37]. The content (% m/m) of phenolic compounds in each tablet was determined by calculation, and the content of the powder used as raw material for tablet manufacturing. The test was repeated 3 times according to the European Pharmacopoeia 10th edition (2.9.6) [36].

Results and Discussion

Physicochemical characteristics of lyophilisates

The physicochemical characterization tests of the freeze-dried extracts showed that the residual moisture content was $4.39 \pm 0.15\%$ (m/m) with a value ($17.42 \pm 0.36\%$ %) higher than 15 percent for the hygroscopicity test which indicates that the extract is very hygroscopic according to the European Pharmacopoeia 10. The solubility in water at 25°C of the extract was classified as easily soluble and those of the mixtures and granules were partially soluble according to the indications of the European pharmacopoeia 6.0. The flow properties realized by the tests of compressibility index (Carr's index) was superior 38% and the Hausner index (Hausner's index) superior at 1.6. This indicates according to the European Pharmacopoeia that the extracts have

very poor flow properties. In contrast, the properties of powders to flow under given circumstances (fluidity) affects a large number of industrial applications [38]. One of the most advantageous processes for manufacturing of tablets is the direct compression of the active ingredient with suitable excipients [39,40]. However, for its realization, the active ingredients and excipients must demonstrate, good fluidity, compressibility and wettability [41]. Indeed, hygroscopicity plays an essential role in particle-particle interactions and can contribute to a poor fluidity of the powder and negatively affect the physical and chemical stability of the powder [42]. Previous studies have shown that freeze-dried extracts of *Lannea microcarpa*, like dry plant extracts in general, are complex materials that tend to be hygroscopic and sticky with poor physical and mechanical properties [43]. Therefore, the addition of suitable excipients and/or the use of appropriate processing technologies prior to compression is necessary. Thus, the amount of excipients that can be added becomes a critical step to manufacture tablets of reasonable size by compression [44,45]. Therefore, pre-treatment becomes almost mandatory to obtain dry plant extracts suitable for compression [46-48]. Granulation is then an alternative to this pre-treatment to improve the flow with fewer excipients.

Physicochemical characteristics of the granules

The physicochemical characterization tests of the *Lannea microcarpa* based granules showed that granules were uniform, brown in colour, with a weak, uncharacteristic odour and a slightly bitter taste (Figure 1). The granules had almost homogeneous grains because they were prepared using the same process with a sieve of the same mesh size. This is probably related to the fact that in the mixture some constituents, namely the excipients, are not soluble in water [49;50]. The residual moisture contents (RMC) are respectively $7.26 \pm 0.38\%$ for the extracts and recorded in Table 4 for the granules formulations. All granules had a residual water content of less than 10%. This low moisture content could indicate better stability because it avoids possible enzymatic reactions and the development of microorganisms [51,52]. The compatibility tests performed by settling were classified into indices according to Table 4. They gave Hausner indices that ranged from 1.06 ± 0.03 to 1.13 ± 0.02 from F1 to F18, respectively, and Carr indices that ranged from 7.60 ± 0.01 to 11.63 ± 0.09 from F1 to F18. Therefore, all granules had good flow properties according to the European Pharmacopoeia. These indices are useful for characterizing the fluidity of granules and predicting their compressibility's. Among

parameters, flow of powders within these processes play a critical role in obtaining desirable characteristics of end products [53].

These analyses indicated that these granules could be used for compression.

Table 4: Pharmacotechnical characteristics of granules.

Designations	Residual Moisture Contents (RCM)	Carr's Index	Hausner Ratio
F1	6.42±0.24	10.11±0.01	1.11±0.01
F2	6.25±0.75	10.76±0.03	1.12±0.03
F3	7.05±0.32	7.60±0.01	1.08±0.06
F4	7.4±0.11	11.60±0.02	1.13±0.02
F5	7.6±0.08	9.78±0.05	1.11±0.01
F6	6.05±0.06	8.93±0.05	1.10±0.02
F7	7.12±0.24	10.02±0.03	1.11±0.01
F8	6.17±0.09	10.07±0.07	1.11±0.01
F9	6.76±0.91	11.63±0.09	1.13±0.02
F10	7.22±0.39	10.28±0.02	1.11±0.02
F11	6.41±0.17	10.20±0.01	1.06±0.02
F12	5.85±0.13	9.55±0.03	1.10±0.01
F13	6.51±0.37	11.31±0.01	1.09±0.03
F14	7.81±0.31	10.27±0.03	1.08±0.02
F15	7.11±0.62	10.38±0.05	1.09±0.02
F16	8.04±0.45	7.65±0.04	1.09±0.03
F17	6.28±0.54	9.00±0.01	1.10±0.01
F18	7.39±0.20	10.63±0.06	1.06±0.03

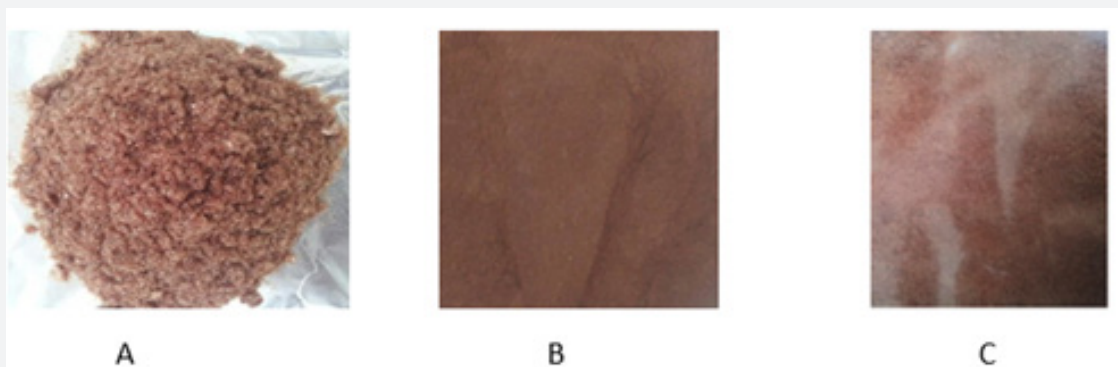


Figure 1: Photographic Image of Extracts (A), Mixtures (B) and Granules (C).

Pharmacotechnical characteristics of the tablets

The results of mass uniformity, hardness and friability are presented in Tables 5 & 6.

The average masses of the tablets dosed at 250mg are recorded in Table 5 and varied from 263.187 mg ± 16.4 for FA1 to 379.979 ± 13.1 for FA18 with coefficients of variation between 2.72% and 6.23%. The average masses of the tablets dosed at 500mg are recorded in Table 6 and varied from 561.047mg ± 15.13 for FB1 to 783.388 ± 33.82 for FB18 with coefficients of variation ranging from 2.05% to 4.95%. As a percentage of the average mass, the

deviations in individual tablet mass fell within limits allowed by the European Pharmacopoeia. These parameters make it possible to know if the tablets have the desired masses. The coefficients made it possible to measure the degree of dispersion of masses of the tablets around each average mass. Also, this parameter could be used in stability studies because any increase in mass during the storage period indicates absorption of moisture highlighting unsuitable conditions. The mass uniformity ensures that, the distribution of the powder mixture in the setting unit is uniform and sufficiently precise during the manufacturing process [54]. The analysis of mass variations shows that the

250 mg formulations had coefficients of variation that were relatively higher than those dosed at 500 mg. This indicates that the 500mg tablets had more homogeneous masses [55]. The mean hardness ranged from 24.9 N \pm 0.61 to 57.32 N \pm 2.35 for the 250 mg tablets and from 27.9 N \pm 0.64 to 61.9 N \pm 2.91. This variation could be related to the compatibility of each mixture but also a variation of the compression force. Indeed, during the use of a manual press, the compression force could be more or less important during each operation since development processes often focus on improving tablet characteristics such as hardness, disintegration time, stability and friability. This also provides an opportunity for the manipulator to set certain parameters to the desired characteristics. The understanding of the impact of the characteristics of the raw materials and the different parameters related to the manufacturing process allows to quickly solve the problems encountered, optimize the production of tablets and adapt to any modification (raw material, equipment, etc.) [56,57]. The analysis of the crumbling rates indicates that for the 250 mg tablet formulations, only the FA6, 11, 12, 17 and 18 tablets had crumbling rates within the norms according to the European Pharmacopoeia 10th edition (33). This friability rates (< 1%) of the tablets indicates that these tablets will have good shock resistance during storage and distribution operations (35,58). These crumbling rates of less than 1% indicate good resistance to crumbling and good cohesion of the particles during compression. It is related to the quality and quantity of the binding agent used (PVP) and or the variation of the compression force. This is made possible by pelletizing, which has a number of advantages, including improved particle compactibility, reduced dust emission and air entrapment during compression,

and better homogenization of the mixture (59). Other studies confirm the improved mechanical performance of tablets by wet compression compared to conventional tablet forming routes (60, 61). For example, Bi et al., (60) show that lactose tablets are ten times stronger mechanically when made with the wet compression process than with conventional methods. In addition, the water added to the mixture to be compressed plays a key role because it allows the binder to dissolve and coat the particles in the mixture more easily. In addition, solid bridges are formed within the tablet during the drying period. These bridges allow the tablet to acquire a better mechanical strength than that obtained by other compression methods, where only Van der Waals forces and hydrogen bonds intervene to ensure the bonds between the particles, the solid bridges possibly present being created during the preceding stages (granulation in particular) (60,62). The disintegration times of the tablets took place in an acceptable conditions. All formulations had disintegration times of less than 15 minutes, although some had relatively high values close to 15 minutes. They were, therefore, in conformity with the requirements of the European Pharmacopoeia 10th edition. (Table 6). Into the overall analysis, the formulations had different disintegration times depending on their composition. This disintegration of all the tablets, lower than 15 minutes, was linked to the nature of the excipients, in particular corn starch, which leads to a sufficient disintegration in the proportions used. Indeed, corn starch is also used as disintegrating agents in order to accelerate the disintegration of the tablet, thus the release of the active ingredient in water and digestive juices. This suggests a relatively rapid release of the active substances contained in these tablets in the digestive tract (52).

Table 5: Pharmacotechnical characteristics of 250 mg tablet formulations.

Designation	References	FA 1	FA 2	FA 3	FA 4	FA 5	FA 6	FA 7	FA 8	FA 9	FA10	FA11	FA12	FA13	FA14	FA15	FA16	FA17	FA18
Thickness (mm)	2.68	2.71	2.91	2.96	2.98	2.98	3.11	3.18	3.23	3.26	3.31	3.42	3.47	3.49	3.46	3.75	3.83	3.91	3.96
Diameter (mm)	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9
RML* %	Ph. Eur	6.01 \pm 0.19	5.82 \pm 1.06	6.92 \pm 1.23	8.06 \pm 2.33	7.31 \pm 1.79	5.83 \pm 1.05	8.09 \pm 2.06	5.27 \pm 0.88	6.38 \pm 1.85	6.17 \pm 0.89	6.01 \pm 0.20	5.82 \pm 1.07	6.92 \pm 1.24	8.06 \pm 2.34	7.31 \pm 1.80	4 \pm 0.760	6.44 \pm 0.32	7.25 \pm 1.06
Delayed (min)	(2.9.1): Ph. Eur.	3.21	4.18	4.32	5.35	4.45	4.05	3.49	3.55	3.47	3.25	4.22	4.16	4.44	5.42	5.34	4.26	5.34	5.34
		5.11	5.25	5.16	6.45	6.52	6.56	5.15	5.46	5.16	5.51	6.21	6.17	6.45	7.36	7.1	7.38	8.25	8.38
Hardness N	(2.9.8): Ph. Eur.	24.9 \pm 0.61	26.1 \pm 1.12	28.32 \pm 0.86	46.25 \pm 1.24	52.27 \pm 2.17	32.6 \pm 1.53	38.11 \pm 0.85	42.38 \pm 1.22	48.8 \pm 3.17	48.75 \pm 1.62	32.12 \pm 1.74	27.9 \pm 0.88	42.3 \pm 1.33	57.25 \pm 2.47	57.32 \pm 2.35	49.17 \pm 1.82	55.36 \pm 2.65	49.23 \pm 1.97
Friability (%)	(2.9.7): Ph. Eur	4.18 \pm 0.91	4.02 \pm 0.63	3.06 \pm 0.25	3.16 \pm 0.19	1.01 \pm 0.04	0.82 \pm 0.05	4.51 \pm 1.08	2.43 \pm 0.52	2.95 \pm 0.44	2.85 \pm 0.78	0.94 \pm 0.06	0.86 \pm 0.08	3.76 \pm 1.11	3.72 \pm 1.42	2.93 \pm 0.92	1.85 \pm 0.56	0.77 \pm 0.09	0.82 \pm 0.07

Average mass (mg)	(2.9.5): Ph. Eur.	263.187	279.317	306.447	328.707	355.967	380.2	268.631	279.82695	299.7283	316.4139	343.8052	374.1965	279.0756	302.3369	309.5982	322.044	359.5664	379.979
SD		16.4	12.7	15.3	11.6	12.1	10.3	15.3	13.5	11.7	15.1	15.8	13.9	13.5	13.5	15.6	14.5	14.71	13.1
Cv %		6.23	4.55	4.99	3.53	3.4	2.72	5.7	4.82	3.9	4.77	4.6	3.71	4.84	4.47	5.04	4.5	4.09	3.42

RML = Residual Moisture Level, SD = Standard deviation, Cv = Coefficient of variation

Table 6: Pharmacotechnical characteristics of the 500 mg tablet formulations

Designation	References	FB 1	FB 2	FB 3	FB 4	FB 5	FB 6	FB 7	FB 8	FB 9	FB 10	FB 11	FB 12	FB 13	FB 14	FB 15	FB 16	FB 17	FB 18
Thickness (mm)		4.32	4.36	4.40	4.51	4.57	4.65	4.72	4.86	4.93	5.1	5.22	5.36	5.36	5.42	5.48	5.56	5.56	5.63
Diameter (mm)		13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9	13.9
RML* %	Ph.EU	6.01 ±0.19	5.82 ±1.06	6.92 ±1.23	8.06 ±2.33	7.31 ±1.79	5.83 ±1.05	8.09 ±2.06	5.27 ±0.88	7.41 ±0.25	7.63 ±0.75	6.01 ±0.20	5.82 ±1.07	6.92 ±1.24	8.32 ±.17	7.91 ±0.92	8.64 ±0.71	6.28 ±0.32	7.21 ±0.46
Delayed (min)	(2.9.1): Ph. Eur.	4.21	4.23	4.35	11.35	9.45	4.25	3.47	4.42	3.22	3.455	4.52	5.16	5.28	5.38	4.45	3.22	4.18	4.56
		7.11	6.25	7.16	13.45	13.52	6.38	5.36	5.28	5.11	5.48	6.21	6.17	6.45	7.19	6.54	7.11	6.28	7.39
Hardness N	(2.9.8): Ph. Eur.	54.9 ±1.52	56.1 ±2.01	28.32 ±0.72	46.25 ±1.25	52.27 ±1.83	32.6 ±0.49	38.11 ±1.06	42.38 ±2.18	54.9 ±3.11	49.68 ±1.75	32.12 ±1.09	27.9 ±0.64	42.3 ±1.05	61.9 ±2.91	60.17 ±2.75	54.26 ±1.47	61.11 ±2.25	58.43 ±2.11
Friability (%)	(2.9.7): Ph. Eur.	0.93±0.04	0.86 ±0.06	3.22 ±1.05	3.01 ±1.12	4.12 ±1.09	6.82±	0.91±0.21	0.87 ±0.04	2.51±1.24	2.43±1.18	3.62±1.32	4.22±1.63	3.76±0.97	1.16 ±0.75	0.92±0.6	2.06±1.28	3.24±1.44	3.62 ±1.06
Average mass (mg)	(2.9.5): Ph. Eur.	561.047	588.3	609.567	626.087	721.607	774.127	572.9356	600.3269	622.4239	673.5008	715.2834	770.066	579.8242	601.3468	623.8694	676.4776	729.8528	783.388
SD		15.13	12.05	17.03	23.6	32.5	38.3	21.7	21.02	22.54	29.32	32.41	34.17	24.06	24.28	21.41	22.73	31.71	33.82
Cv %		2.70	2.05	2.79	3.77	4.50	4.95	3.79	3.50	3.62	4.35	4.53	4.44	4.15	4.04	3.43	3.36	4.34	4.32

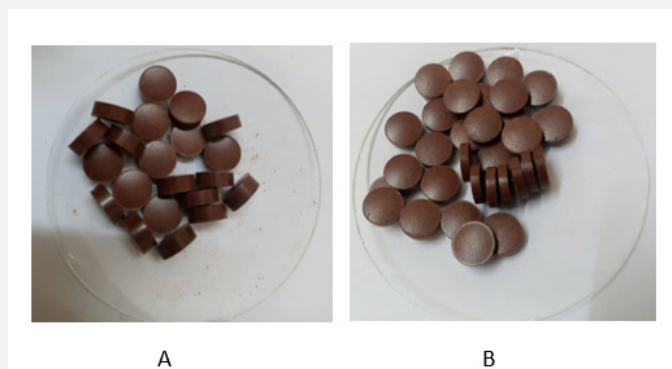
RML = Residual Moisture Level, SD = Standard deviation, Cv = Coefficient of variation

Table 7: Uniformity of content of 250mg tablets.

N° Tablets 250mg	Mass (mg) of powder per tablet	Content in mg of GAE/tablet	Percentage content (%) of the average content
1	372	0.363	95.8036421
2	386	0.378	99.7624703
3	374	0.372	98.178939
4	368	0.365	96.3314859
5	388	0.376	99.2346266
6	369	0.384	101.346002
7	376	0.384	101.346002
8	386	0.393	103.721298
9	401	0.395	104.249142
10	382	0.379	100.026392
mean (mg)	380.200000	0.378900	100.000000
standard deviation	10.336559	0.010609	2.799867
coefficient of variation %	2.718716	2.799867	2.799867

Table 8: Uniformity of content of 500mg tablets.

N° Tablets 500mg	Mass (mg) of powder per tablet	Content in mg of GAE/tablet	Percentage content (%) of the average content
1	586	0.74	97.6253298
2	595	0.76	100.263852
3	601	0.78	102.902375
4	563	0.78	102.902375
5	581	0.74	97.6253298
6	603	0.72	94.9868074
7	577	0.76	100.263852
8	594	0.77	101.583113
9	593	0.74	97.6253298
10	590	0.78	102.902375
mean (mg)	588.3	0.757	99.8680739
Standard deviation	12.05	0.0211	2.7847
Coefficient of variation%	2.05	2.7884	2.78839986

**Figure 2:** Photographic Image Of 500mg (A) and 250mg (B) Extract Tablets.

Determination of the content of phenolic compounds as a marker

The phenolic compound contents of the tablets were determined by calculation, from the calibration line whose equation is $y = 10.459x + 0.0335$ with a regression coefficient $R^2 = 0.9993$. This resulted in an average content of 0.378900 ± 0.010609 mg gallic acid equivalent (GAE)/tablet and 0.757 ± 0.0211 mg GAE/tablet, respectively for the 250mg and 500mg tablets. From the content uniformity study represented by (Tables 7 & 8) the unique content of each tablet unit of both strengths is between 85 percent and 115 percent of the average content, which indicates that these tablets comply with the requirements of the European Pharmacopoeia. In effect, this pharmacopoeia indicates that tablets fail the test if the individual content of more than one unit is not within these limits or if the unique content is outside the limits of 75 percent to 125 percent of the average content.

Conclusion

The present study was conducted to develop tablets for the treatment of hypertension. The formulation strategy used in

this work allowed to realize mixtures of the active ingredient (lyophilized aqueous extract of *Lannea microcarpa*) with corn starch, PVP, colloidal silica, talc and magnesium stearate. The tablets were obtained by compression after wet granulation of the mixtures. The comparative analysis of the pharmacochemical characteristics of the different formulations indicates that the FA6 and FB2 formulations showed the best properties such as disintegration, disintegration and hardness and meeting the requirements of the European Pharmacopoeia 10th edition. Additional studies such as the dissolution test and the stability study are necessary to conclude on the quality of the formulation. These pharmaceutical forms dosed at 250mg and 500mg in addition to being new will offer an alternative, because the use of mixtures in the form of powder and granules followed by a filling of capsules did not allow to obtain quickly a galenic form dosed at 500mg and meeting the recommendations of the pharmaceutical standards. This alternative in the management of the disease, allows reducing the production cost by compressed forms resulting from fast and straightforward manufacturing process with the least possible excipient and which do not use empty capsules.

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