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Formulation and evaluation of granules based on trunks barks extracts of *Anogeissus leiocarpus* (DC) Guill. et Perr. (Combretaceae) intended for the development of phytomedicines for the treatment of hypertension

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Abstract
Quality control as well as the appropriate integration of modern scientific technique and traditional knowledge are important for promoting traditional remedies. Thus, preliminary quality control studies of extracts of *Anogeissus leiocarpus* concluded that there was a need to improve the rheological properties. Granulation improves properties such as texture, porosity or wettability. It reduces the amount of dust during handling. Ten (10) formulations were produced, the compositions of which were varied by the content of corn starch, Polyvinylpyrolidone and magnesium stearate. All the granules were prepared by wet granulation. After the drying process, the granules were sieved through a 1.6 mm mesh screen to standardize the particle size. The dust was sieved through 1.2 mm and these particles were again granulated. All quality control tests have been carried out in accordance with the European Pharmacopoeia 6.0. The average disintegration times of the formulations prepared were all less than 10 minutes. The residual humidity of the various pellets was less than 10%. The granules formulated F2 and F3 were less friable. The granules had a good flow time. All the granules were hygroscopic. The solubility tests carried out on the formulations showed that the content of F3 tracer was greater than 85% after 45 min. Microbial controls met the standards of European Pharmacopoeia 6.0 for preparations for oral administration containing raw materials of natural origin. The F3 formulations had the best characteristics in accordance with the recommendations of the European Pharmacopoeia 6.0.

Keywords: Formulation, exctract, *anogeissus leiocarpus*, arterial hypertension, granulation

Introduction
According to the World Health Organization, traditional medicine or herbal medicine is the accumulation of the skills, knowledge and practices based on the theories, beliefs and indigenized by different cultures, to maintain health. Nature always stands as a golden mark to exemplify the outstanding phenomena of symbiosis. Natural products from plant, animal and minerals have been the basis of the treatment of human disease [1-3].
In the last few years, there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter.
Arterial hypertension is a major cause of morbidity and mortality because of its association with coronary heart disease, cerebro-vascular disease and kidney disease. The hypertension optimal treatment study indicates that the treatment goal is to reduce blood pressure to 140/85 mm Hg. Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality [4, 5].
The plants provide a potential source of arterial hypertension drugs because many plants and plant derived compounds have been used in the treatment of arterial hypertension. Plant drugs such as extracts of *Anogeissus leiocarpus* have an important role in the treatment of the disease [6-8].
Quality control as well as the appropriate integration of modern scientific techniques and

traditional knowledge are important for promoting traditional remedies to combat certain chronic diseases. This is how preliminary studies of quality control of the extracts concluded that there was a need to improve the rheological properties [9,10].

Indeed, the granulation process is carried out to give the powdered substances the granular form, with a similar particle size, which also leads to reducing the amount of dust [11]. Granulation also improves properties such as surface texture, porosity or wettability. It has a positive influence on the disintegration time and the solubility of the active substance [12].

The main objective of this study was to develop a solid oral form based on freeze-dried extract of *Anogeissus leiocarpus* while minimizing the indirect costs of production, accessible, with a reproducible process and conforming to standards. In view of the available technologies at the level of the study laboratory and the physicochemical characteristics of the extracts, the granules were retained as to be developed.

The quantities of excipients have been determined with reference to the recommendations of the Handbook of pharmaceutical excipient [13]. Several series of formulations have been produced in the absence of lubricant, with lubricant alone, without binding agent and with lubricants associated with the binding agent.

Materials and methods

Plants materials

Fresh trunks's barks of *Anogeissus leiocarpus* (Combretacaea) were harvested at Loumbila commune (Burkina Faso) in February 2015 and identified by a botanist from the ecology laboratory of the university of Joseph KI-ZERBO in reference to the herbarium N° 1544. The barks have been dried and crushed to powder.

Preparation of extracts

Hundred (100) grams of vegetable powder have been boiled with 1L sterile distilled water while 30 minutes. The extracts obtained were frozen for 24 hours and then lyophilized at 96 hours.

Galenic formulation test

The formulation methodology was based on the one hand by the results of the preformulation study ($ED_{50\%}$, $LD_{50\%}$, physicochemical and stability properties of the lyophilized extracts) and on the other hand, by the availability of equipment at within the different laboratories. Mixtures followed by capsule-setting tests as well as pharmacotechnical controls were studied on batches of 100 grams of variable qualitative and quantitative composition: Corn starch 30 to 100%, PVP 0.5 to 5%, and magnesium stearate 0.25 to 5% (Table 1).

Table 1: The composition of granules (amounts of the substances are given in parts)

Formule/ gram	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Polyvinylpyrolidone K25 (PVP)	0	0.28	0.12	0.25	0.38	0.5	0.63	0.75	0.88	0.53
Magnesium stearate	0.12	0.12	0.12	0.25	0.37	0.59	0.39	0.72	0.87	0.97
Extract	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Corn starch	11.12	10.9	11	10.7	10.5	10.2	10.2	9.77	9.49	9.74

Manufacturing process

the herbal granules were prepared by wet granulation method. *Anogeissus leiocarpus* trunks's barks extract (active ingredient) was triturated in a mortar and pestle to make powder then mixed with calculated amount of the other components. It was carried out using an GLA-ORY FREWITT type granulator. The mass to be granulated was weighed, mixed and wetted with ethanol until a crumbly paste was obtained. The dough was introduced into the granulator and then subjected to an oscillatory movement forcing the crumbly dough to pass through the sieves of diameter (1.25 mm). The granules obtained were dried in a MEMMERT oven at a temperature of 45 ° C for 12 hours.

Evaluation of granules

Residual moisture content

The residual moisture content of the granules was determined according to the thermogravimetric method of the European Pharmacopoeia 6th edition in an oven (Memmert, Germany). The assay was performed in triplicate on one (01) g of granules. The mean and standard deviation were calculated (n = 3, mean, standard deviation).

Determination of pH

pH was determined by immersing the pH-meter electrode (Eutech, Singapore) in 1% (mass / volume) aqueous solutions of each vegetable material. The test was performed in triplicate and the mean and standard deviation were calculated (m ± standard deviation, n = 3) [14].

Flow test

The flow test was determined by measuring with a stopwatch the time that 100 g of granules to flows completely through a funnel of defined size in the European Pharmacopoeia [15].

Compressibility Index and Hausner's Ratio

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 (BD) and the tapped density (TD) 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.

The 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 [16].

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

BD = weight of the granule/volume of the packing

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

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

Compressibility index or Carr's index (%) = [(TD – BD) × 100] /TD [17]

Haushner's ratio was determined using following formula: H = Tapped density / Bulk density. A Hausner ratio greater than 1.25 is considered of poor flow ability [18].

Hygroscopicity
Hygroscopicity was determined using 1 g of granules according to the method described in European Pharmacopoeia 6.0. The granule was introduced into a suitable desiccator containing a saturated solution of ammonium chloride at 25 ° C. for 24 hours. The increase in mass allowed the calculation of the ratios expressed as a percentage.

Disintegration of granules
A sample of 1.0 g of granules was placed into the conical flask filled with 50.0 mL distilled water at 37 ± 2ºC. The disintegration time was measured using a stopwatch and the test was considered completed when no granules was observed [19].

Friability test
Granules friability was measured as the percentage of weight loss of 1 g in a friabilator. After 5 minutes of rotation at 25 rpm, any loose dust was removed and the granules were reweighted. The weight loss (%Friability) was calculated through the following equation:
%Friability = (Wi −Wr) ×100/ Wi) [20].

Dissolution test
Dissolution tests were carried out with the type II paddle apparatus. It concerned six (06) masses weighed individually and each corresponding to the quantity of granules necessary to fill a capsule. The dissolution media used were:

Water R
PH 1.2 buffer (European Pharmacopoeia 6.0 (2.9.3) p292-293)
- 0.2 M NaCl (11.69 g / l) 250 ml
- 0.2 M HCl (17.3 ml / l) 425 ml
- Water R qs 1000 ml

PH 6.8 buffer (European Pharmacopoeia 6.0 (2.9.3) p292-293)
- KH_2PO_4 0.2 M (27.22 g / l) 250 ml
- 0.2 M NaOH (8.4 g / l) 112 ml
- Water R qs 1000 ml

The volume of the dissolution medium was 600mL and temperature set at 37 ± 0.5 ° C. The rotational speed of the paddles was 75 rpm. During dissolution, 5 mL samples were removed from the dissolution baths at regular intervals of 10, 20, 30, 40, 50 and 60 minutes. The volumes taken from each vase are replaced by distilled water previously thermostatically controlled at 37 ± 0.5 ° C. The samples taken were filtered through cellulose acetate filters with a porosity of 0.45 µm. The filtrate obtained was used to measure the phenolic compounds which were used as a tracer.

Dosage of phenolic compounds
Previous studies have shown that lyophilized aqueous extracts of the trunk bark of both plants contained abundant phenolic compounds [21]. These compounds are known for their positive effects against hypertension [22]. In view of this, the phenolic compounds are retained as tracers in this study. The phenolic content was determined according to the method of Singleton by using Folin-Ciocalteu as reactive reagent [23]. The reaction mixture consisted of 1 mL of granule, 1 mL of 2N FCR and 2 mL of a 20% sodium carbonate solution. A control solution referred to as white identical to the reaction mixture except that the granules was replaced with distilled water was used. The solutions were allowed to stand at room temperature for 40 min and then the absorbance was measured at 760 nm using the Visible UV spectrophotometer. A standard curve was plotted with gallic acid (1-5 µg / ml). The trials were carried out in triplicate. The results are expressed in microgram gallic acid equivalents / mg granule (µGAE / mg) with reference to the gallic acid calibration curve.

Microbiological quality
The germs sought were total flora, salmonella and thermo-tolerant coliforms. Total flora and salmonella were determined by the method of the European Pharmacopoeia 6th edition. Thermo-tolerant coliforms were determined according to ISO 7218 standards. Colony counts were performed to calculate the number of colony forming units per gram (CFU / g).

Stability test
The stability study was carried out for six (06) months at 25° C temperature in the laboratory. The samples were packaged in food sachets. The color, the taste, the pH and the phenolic compounds were determined according to the methods described above.

Results and discussion
Macroscopic and organoleptic characteristics
The granules were brown, not very astringent, and slightly bitter in taste (fig 1).

Fig 1: Photograph of granules

Pharmacotechnical characteristics of granules
The results of the pharmacotechnical characteristics of granules were interpreted according to the European pharmacopoeia and represented by Table 2.
The results of the residual moisture contents of the granules were less than 10%. this residual content. The compressibility index and the Hausner ratio have long been used to characterize powder flowability. The flow property has been classified in terms of compressibility index of repose and Hausner ratio as follows [24,25]: excellent (1-10 and 1.00-1.11, respectively), good (11-15 and 1.12-1.18), Pretty good (16-20 and 1.19-1.25), fair (21-25 and 1.26-1.34), and poor (>25 and >1.34). The Hausner ratio of most granules prepared ranged from 1.12 to 1.18, while the compressibility index ranged from 12.43 to 15.01%. Consequently, granules exhibited good flow properties. contributes to improving the flow properties of the granules [26].

Table 2: Pharmacotechnical characteristics of granules

Desig-nations	THR	Flow	Carr's index	Hausner ratio	Hygros-copicity	Disinte-gration	Friability	pH
F1	7.23	<10 s	14.11%	1.18%	19	19min	0.78	7.42±0.86
F2	6.24	<10 s	12.85%	1.13%	28	18 min	0.52	7.29±0.131
F3	6.83	<10 s	14.26%	1.13%	24	22 min	0.62	7.32±0.273
F4	7.2	<10 s	12.53%	1.16%	>30	16 min	1.16	7.04±0.092
F5	5.21	<10 s	15.01%	1.12%	>30	19 min	1.01	7.36±0.174
F6	8.14	<10 s	13.21%	1.18%	>30	18 min	1.82	7.33±0.213
F7	8.56	<10 s	12.43%	1.16%	>30	19 min	1.51	7.22±0.18
F8	7.12	<10 s	12.55%	1.16%	>30	16 min	2.43	7.35±0.21
F9	6.33	<10 s	14.86%	1.12%	>30	18 min	1.08	7.19±0.17
F10	8,69	<10 s	12,73%	1.13%	>30	20 min	2,12	7,34±0,29

Flow rate

The flow times of granules are less than 10 seconds and according to European Pharmacopoeia 6.0, they have a good flow (Table 2). The granulation process is carried out to give the powder substances the granular form, with similar particle size, which leads also good flow reduce the amount of dust [27].

Hygroscopicity

Percentage of hygroscopicity are all above 15%, indicating that the granules studied are microporous and very hygroscopic, the rehydration of which is almost instantaneous according to the European pharmacopoeia 6.0 (Table 2). The granules can thus absorb the humidity of the air, by absorption or by adsorption during the manipulations at ambient temperature.

Test of disintegration

The test of disintegration time of granules showed that the granules of formulas comply with the pharmacopoeia with regard to this property. All the prepared granules were disintegrated in less than 30 minutes (Table 2). These observations indicate strong strength and interparticle adhesion with visible particles in solution which is probably related to hydrophobic character of lubricant, properties of Magnesium Stearate.

Friability

the granules prepared showed a disintegration which discharges almost immediately. They had very fine grains, which crumble on drying except for formulas F2 and F3. Their granules were found to be satisfactory in terms of mechanical properties with a fairly low friability, of less than 1% (Table 2). This is important so that the granules are resistant to mechanical stresses during handling (fall, vibration, fluidization, etc.) [20].

Dissolution test

- **Content of phenolic compounds in the 3 formulations**

The results of the contents of phenolic compounds dosed as a tracer are shown in Table 3.

Table 3: Results of content of phenolic compounds in the formulations

Designations	Average content in mg of gallic acid equivalent
F1	0.044625± 0.002365
F2	0.04172± 0.0014
F3	0.06146± 0.00362

The table 4 show the results of dissolution tests on granule formulations. Whatever the dissolution medium, the release of gallic acid (tracer) from the F3 formulations was greater than 85% after 45 min. These results have shown that the F3 formulation complies with the dissolution test described by the European Pharmacopoeia [26].

Table 4: *In vitro* release profile of phenolic compounds from granules formulated

	Designations	15 minutes	30 minutes	45 minutes	60 minutes
Water R Percentage (%)	Extract	0.9214µg/mg	0.94µg/mg	0.9510µg/mg	0.9421µg/mg
	F1	11.26	23.6	32.42	56.18
	F2	9.17	19.53	27.15	42.25
	F3	31.22	58.15	85.36	97.71
PH 1.2 buffer Percentage (%)	Extract	0.961µg/mg	0.943µg/mg	0.914µg/mg	0.941µg/mg
	F1	13.24	21.52	34.5	49.88
	F2	12.24	18.76	30.11	36.55
	F3	40.33	72.25	98.27	99.42
PH 6.8 buffer Percentage (%)	Extract	0.9096µg/mg	0.9212µg/mg	0.946µg/mg	0.928µg/mg
	F1	10.9	21.33	32.77	49.52
	F2	11.25	17.21	28.12	55.36
	F3	38.62	66.31	90.06	98.14

Microbial control.

The microbiological control of the formulations F1, F2 and F3 gave the results presented in table 5. The assessments of the bacteria contamination of granules have concerned thermo-tolerant the coliforms and salmonella were not detected in any samples. These results were in accordance with the recommendations of the European Pharmacopoeia 6.0 [26].

Table 5: microbiological control in the formulations

	Parameters (UFC/g)		
Designations	Totale Flora	Thermo-tolerant Coliforms	Salmonella/25g
F1	$1.3.10^3$	Absence	Absence
F2	$2.11.10^3$	Absence	Absence
F3	$4.22.10^3$	Absence	Absence

Granules stability

After 6 months of storage at room temperature in the laboratory, we found that the granules retained the same colors and the same tastes. the content of phenolic compounds in the formulations was not significantly changed after 6 months of storage. (Table 6).

Table 6: Content of phenolic compounds in formulations

Désignations	**0 month**	**1 month**	**2 months**	**4 months**	**6 months**
Temperature	(29°C)	(31°C)	(30°C)	(31.5°C)	(30.5°)
F1	0.045± 0.0017	0.044± 0.0036	0.044± 0.0025	0.040± 0.0038	0.042± 0.0075
F2	0.041± 0.0023	0.028± 0.0027	0.041± 0.0013	0.041± 0.0062	0.039± 0.0028
F3	0.061± 0.0048	0.060± 0.0072	0.059± 0.0061	0.060± 0.0056	0.058± 0.0091

Conclusion

In this study, granules were prepared based corn starch, Polyvinylpyrrolidone and magnesium stearate. All the granules were prepared by wet granulation. The study of physical properties made it possible to determine that all the granules were hygroscopic. The dry granules could therefore absorb moisture from the air during handling and during their storage. They should therefore be manufactured in areas with controlled humidity and stored in tight containers. F3 formulation is considered as the best according to the obtained results. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges.

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