Research Article

EFFECT OF BINDER TYPE AND CONCENTRATION ON THE *IN VITRO* PROPERTIES OF *ALSTONIA BOONEI* TABLETS

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ABSTRACT

The objective of the work was to formulate a normal release *Alstonia boonei* tablet and to study the effect of binder type and binder concentration on the physico-chemical properties of the tablets. Sodium carboxymethyl cellulose (SCMC), gelatin and acacia at concentrations 1 %, 2 %, 4 % and 8 % w/w respectively were used as binders in formulating normal release tablets. The micromeritic properties of the granules prepared were studied in terms of flow rate, angle of repose, bulk and tapped densities, Carr's index and Hausner's ratio. The tablets were evaluated using the necessary official and unofficial tests. The results obtained from micromeritic studies showed that the granules had good flowability. Evaluation of the tablets showed that all the batches of tablets passed the uniformity of weight. The hardness of the tablets was significantly affected by the type of binder and concentration used during formulation ($p < 0.05$). Friability values (%) for all the tablet formulations were within the specified limit of acceptance. *A. boonei* tablets formulated with 1 % and 2 % binder passed the disintegration time test for normal release tablets of ≤ 15 min. The *in vitro* drug release properties of *A. boonei* tablets formulated with different binders and varying binder concentrations revealed that the performance of the binder could be ranked thus in decreasing order of drug release SCMC > gelatin > acacia.

Keywords: *Alstonia boonei*, gelatin, micromeritic, wet granulation, SCMC.

INTRODUCTION

In recent times, focus on plant research has increased all over the world and a lot of evidence has been collected to show immense potential of medicinal plants used in various traditional systems[1]. Medicinal plants will continue to provide a source for generating novel drug compounds[2]. Plants may become the base for the development of a new medicine or they may be used as phyto-medicine for the treatment of disease[3]. It is estimated that today, plant materials are present in, or have provided the models for 50 % Western drugs[4].

Alstonia boonei De Wild (Apocynaceae) has a history of use in traditional medicine of Nigeria and central Cameroon for malaria treatment but also for the prevention of the disease[5-6]. Alstonia consists of about 50 species widely distributed in the continents of Africa, Asia and America. The stem bark of *A. boonei* has been listed in the African Pharmacopoeia as an anti-malarial drug and it is used in traditional medicine for the treatment of fever, painful micturition, insomnia, chronic diarrhea, rheumatic pains, as anti-venom for snake bites and in the treatment of arrow poisoning[5, 7]. The chemical constituents of *A. boonei* include alkaloids, triterpenoids and steroids and more than 90 % of the isolated chemical constituents are alkaloids, many of which are the indole types. The major alkaloids are echitamine and echitamidine[5, 7]. *In vitro* antiplasmodial activity of *A. boonei* alkaloids against both drug sensitive and resistant strains of *P. falciparum* and *in vivo* activity against *P. berghei* in mice have been reported[5, 8-10]. The anti - inflammatory properties of the alcoholic extract *A. boonei* have also been reported[11].

The primary benefit of using plant-derived medicine is that they are relatively safer than synthetic alternatives, offering profound therapeutic benefits and more affordable treatments[12]. Plants with anti malarial and anti-inflammatory properties have been of immense ethnomedicinal use to mankind. In view of the popular and widespread use of herbal products used in such practice, important technical aspects such as standardization and quality control will be of immense benefit in order to enhance their efficacy and improve patients compliance[13-16]. Therefore the objective of this work is to formulate *A. boonei* tablets by wet granulation method and to study the effect of different binders on the *in vitro* properties of *A. boonei* tablets.

MATERIALS AND METHODS

Hydrochloric acid, lactose (Merck, Germany), maize starch, gelatin, acacia, ethanol 96% (BDH, England), sodium carboxy methyl cellulose and Magnesium stearate (May and Baker, England), distilled water (Lion water, Nsukka, Nigeria). *Alstonia boonei* extract was obtained from a batch processed in our laboratory. All other reagents and solvents were analytical grade and were used as supplied.

Methods

Extraction of *A. boonei* stem bark

Alstonia boonei stem bark was collected from the tree at a local forest in Nsukka, Enugu state, Nigeria. The plant sample had earlier been identified and authenticated in the herbarium section of the Department of Pharmacognosy and environmental medicine, University

of Nigeria, Nsukka. The stem bark was washed, cut into small sizes and then dried under a shed below 45°C. The dried bark was ground severally to a fine powder using a hammer mill. About 5 kg of the powdered sample was extracted with 10 L of absolute ethanol for 48 h by maceration. The solvent was removed at 30°C under reduced pressure and then evaporated to dryness. The dried extract was reduced to powder using an end runner mill (Pascal Engineering Co. Ltd., England) and then sieved with a 120 µm mesh sieve[5].

Preparation of granules

Granules were prepared by wet granulation method using three different binders at concentrations 1%, 2%, 4% and 8% w/w. Details of granulation are given in table 1. Lactose was used as filler (8% w/w) and maize starch BP as disintegrant (10% w/w) were dried and mixed for 10 min in a tumbler mixer. The powder mixtures were moistened with the appropriate amount of binder solution. The homogeneous wet mass was then screened through a 1.7 mm sieve and the wet granules dried in a hot air oven at 60°C for 1 h. Thereafter, the dried granules were screened through a 1.0 mm sieve[17-18].

Table 1: Composition of *A. boonei* tablets at different concentrations of the binder

Ingredients	Quantity/tablet (mg)			
	1 %w/w binder	2 %w/w binder	4 %w/w binder	8 %w/w binder
A. boonei extract	10.0	10.0	10.0	10.0
Acacia + gelatin + SCMC	3.0	6.0	12.0	24.0
Maize starch	15.0	15.0	15.0	15.0
Magnesium stearate	3.0	3.0	3.0	3.0
Lactose qs	300.0	300.0	300.0	300.0

Preparation of tablets

Initially granules were treated with lubricant i.e. magnesium stearate. Tablets were prepared by compressing the lubricated granules at 46-48 kgF using a 9.0mm punch and die set fitted into an automated F3 Manesty Single Punch tabletting machine[19].

Bulk and Tapped Densities

A 10 g of sample was placed in a 25 ml measuring cylinder; the volume occupied by the sample was noted as the bulk volume. The bulk density was obtained by dividing the mass of the sample weighed out by the bulk volume, as shown in Equation 1[19-22],

$$\text{Bulk density} = \frac{\text{Mass of Powder (M)}}{\text{Bulk volume of powder } (V_B)} \quad \text{------ (1)}$$

The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one inch at 2 seconds interval until there was no change in volume reduction. The volume occupied by the sample was then recorded as the tapped volume. The tapped density was calculated using the formula:

$$\text{Tapped density} = \frac{\text{Mass of sample (M)}}{\text{Tapped volume } (V_T)} \quad \text{------ (2)}$$

Flow rate and angle of repose

A funnel was properly clamped on to retort stand. The funnel orifice diameter, base diameter and efflux tube length were appropriately measured. A 30 g quantity of the granules was weighed out and gradually placed into the funnel with the funnel orifice closed with a shutter. The time taken for the entire sample in the funnel to flow through the orifice was noted. The flow rate was gotten by dividing the mass of the sample by the time of flow in seconds.

The static angle of repose was determined using the fixed base cone method[19-22]. A 30 g of the sample was transferred into an open-ended cylinder placed on a static base cone on a horizontal surface. The cylinder was gradually withdrawn vertically and the sample formed a cone-shaped heap. The height of the sample was determined using a cathetometer; the radius was gotten by dividing the fixed diameter by two. Angle of repose (Θ) for each sample was gotten using the equation;

$$\Theta = \tan^{-1} h/r \text{ ---------- (3)}$$

Compressibility index and Hausner's quotient

Carr's compressibility indices (%) of the lyophilized SLMs were obtained using the formula [19-22],

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \text{ ------- (4)}$$

While Hausner ratio was obtained using Equation 5,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \text{ ---------- (5)}$$

Evaluation of tablets

Disintegration time test

Disintegration time test was conducted using an Erweka ZT 120 basket and rack assembly and O. IN Hydrochloric acid maintained at 37.0 ± 1.0°C as the disintegration medium. Ten tablets from each batch were used for the test and the procedure being as stipulated in the BP 2009 for normal release tablets[23].

Uniformity of Weight

Twenty tablets were randomly selected from each batch. The tablets were weighed individually using an electronic balance (Ohaus Adventurer, China) and the individual

weights recorded. The mean weight, standard deviation and percentage deviation were calculated[23].

Tablet friability test

Twenty tablets were randomly selected from each batch of the tablet. The tablets were dedusted and weighed. The tablets were placed into the drum of the friabilator (Erweka GmbH, Germany) and rotated at 25 rpm for 4 min. The tablets were removed from the friabilator, dedusted and reweighed. The friability result was expressed as loss of mass expressed as a percentage of the initial mass[23]. The abrasion resistance B was calculated from the equation below:

$$B = 100\left[1 - \frac{W}{W_o}\right] \quad \text{---------- (6)}$$

where W_o and W are the initial weight and final weight of the tablets respectively.

Hardness/Crushing Strength Test

This test was carried out using a Monsanto-stokes hardness tester. Ten tablets from each batch were randomly selected. Each tablet was placed between the jaws of the hardness tester and force was applied by adjusting the knob of tester until the tablet integrity failed. The results were recorded in Kgf.

In vitro release studies

Beer's calibration curve was obtained at a concentration range of 0.1 – 1.0 mg% for *A. boonei* extract in 0.1 N HCl at a predetermined wavelength of 230 nm. The *in vitro* dissolution profile for each batch of tablet was determined using the paddle method[23], with an Erweka DT 600 Dissolution apparatus. The dissolution medium consisted of 900 ml of freshly prepared 0.1 N HCl. The temperature of the medium was maintained at 37 ± 1°C. A tablet from each batch was placed inside a tightly secured basket and the basket was placed in the bottom of the beaker. The paddle was rotated at 100 rpm. At various intervals, 5 ml sample was withdrawn from the dissolution medium, filtered with a non adsorbent filter paper (Whatman no. 1) and an aliquot of the filtrate was assayed using spectrophotometer (Jenway 6305 spectrophotometer, UK) at 230 nm. An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition. The amount of drug released at each time interval was determined with reference to the Beer's plot for *A. boonei* extract.

Statistical analysis

Statistical analysis was carried out using SPSS version 14.0 (SPSS Inc. Chicago, IL.USA). All values are expressed as mean ± SD. Data were analysed by one-way ANOVA. Differences between means were assessed by a two-tailed student's T-test. $P < 0.05$ was considered statistically significant.

Table 2: Micromeritic properties of *A. boonei* granules formulated with different binders and varying binder concentrations

Batch	ℓ_B (g/ml)*	ℓ_T (g/ml)*	A.R (°)*	H.R	C.I (%)	Flow rate (g/Sec)
A1(1 % acacia)	0.70 ± 0.07	0.80 ± 0.05	25.11 ± 0.21	1.14	12.3	13.7 ± 0.12
A2 (2 % acacia)	0. 71 ± 0.03	0.81 ± 0.07	24.64 ± 0.10	1.14	12.7	12.2 ± 0.11
A3 (4 % acacia)	0.70 ± 0.01	0.78 ± 0.01	23.94 ± 0.50	1.11	14.0	13.2 ± 0.17
A4 (8 % acacia)	0.60 ± 0.01	0.74 ± 0.01	24.24 ± 0.13	1.23	16.0	10.6 ± 0.23
B1 (1 % gelatin)	0.70 ± 0.05	0.80 ± 0.05	24.86 ± 0.27	1.14	12.5	15.5 ± 0.05
B2(2 % gelatin)	0.70 ± 0.03	0.79 ± 0.07	24.82 ± 0.36	1.13	11.5	16.6 ± 0.11
B3 (4 % gelatin)	0.68 ± 0.07	0.79 ± 0.05	24.90 ± 0.12	1.16	14.8	14.9± 0.23
B4 (8 % gelatin)	0.68 ± 0.06	0.77 ± 0.07	24.60 ± 0.17	1.13	12.2	13.6 ± 0.12
C1 (1 % SCMC)	0.72 ± 0.06	0.82 ± 0.05	23.60 ± 0.17	1.14	12.0	10.4± 0.07
C2 (2 % SCMC)	0.74 ± 0.03	0.82 ± 0.03	23.80 ± 0.11	1.11	10.0	12.6 ± 0.14
C3 (4 % SCMC)	0.73 ± 0.05	0.81 ± 0.06	24.68 ± 0.15	1.11	10.1	10.4 ± 0.23
C4 (8 % SCMC)	0.69 ± 0.06	0.80 ± 0.05	23.29 ± 0.17	1.16	14.1	8.3 ± 0.13

Values shown are mean ± SD (*n = 3); A - C: *A. boonei* granules prepared with different binder; ℓ_B and ℓ_T = Bulk and tapped densities, AR = Angle of repose, HR = Hausner's ratio, CI = Carr's compressibility index; SCMC: sodium carboxymethyl cellulose.

RESULTS AND DISCUSSION

The flow of powder during manufacturing dictates the quality of the product in terms of weight, hardness, and content uniformity of the tablets[22]. The measurement of the flow properties of powders is essential before tabletting because variation in particle flow will automatically cause variation in tablet weight and active ingredient variation. The flow property of bulk material results from the cohesive forces acting on individual particles such as vander Waals, electrostatic, surface tension, interlocking, and friction[22]. The results obtained from micromeritic studies presented in table 2 showed that *A. boonei* granules produced had good flowability. Angle of repose, flow rate, Carr's Index and Hausner's ratio were within the standard acceptable values required for formulation of quality tablets. Values for angles of repose ≤30° generally indicate a free flowing material and

angles ≥ 40° suggest a poorly flowing material[22, 24]. Angles of repose of the powder mixtures ranged between 23.29 ± 0.17° for batch C4 to 25.11 ± 0.21° for A2 granules formulated with 8 % SCMC and 1 % acacia respectively. CI indicates the flowability and consolidation properties of the powder mixtures. When the CI and HR are adequate, the powder flows at minimum bulk density and consolidates to maximum density inside the die, prior to compression[22]. A high bulk density, i.e. a low porosity, will result in a low deformation potential; a lack of space for deformation during compression will cause less intimate contact between the particles within the tablets, resulting in weaker tablets[22].

Table 3 shows the results obtained from the evaluation of the tablets formulated with different binders and varying binder concentrations. All the batches of tablets passed the uniformity of weight test and deviations obtained complied with BP standards of not more than 5 % for tablets weighing 250 mg or more[22, 25]. The hardness of the tablets was significantly affected by the type of binder and concentration used during formulation ($p<0.05$). Tablets formulated with 4 % and 8 % binder exhibited the highest crushing strength of 5.50 ± 0.12 to 5.70 ± 0.12 Kgf. However, *A. boonei* tablets containing acacia exhibited the highest crushing strength that ranged from 4.50 ± 0.17 to 5.70 ± 0.12 Kgf. Friability values (%) for all the tablet formulations were within the specified limit of acceptance. Friability values ranged from 0.33 to 0.90 %.

Table 3: Properties of tablets containing *Alstonia boonei* stem bark extract

Batch/Tablet code	Tablet Weight (mg ± CV)*	Hardness (Kgf)[a]	Friability (%)*	Disintegration Time (min)[a]
A1(1 % acacia)	309 ± 2.88	4.50 ± 0.17	0.60	15.3 ± 0.12
A2 (2 % acacia)	393 ± 2.35	5.00 ± 0.12	0.90	15.0 ± 0.12
A3 (4 % acacia)	306 ± 2.47	5.50 ± 0.23	0.62	88.0 ± 0.51
A1(8 % acacia)	298 ± 2.27	5.70 ± 0.12	0.33	95.0 ± 1.17
B1 (1 % gelatin)	306 ± 2.85	4.80 ± 0.21	0.50	4.1 ± 0.31
B2(2 % gelatin)	301 ± 2.23	4.75 ± 0.13	0.74	5.5 ± 1.23
B3 (4 % gelatin)	309 ± 2.11	5.35 ± 0.15	0.84	12.3 ± 0.12
B4 (8 % gelatin)	308 ± 2.41	5.50 ± 0.17	0.49	24.4 ± 0.50
C1 (1 % SCMC)	306 ± 2.00	4.45 ± 0.15	0.12	15.2 ± 0.23
C2 (2 % SCMC)	307 ± 2.04	4.45 ± 0.23	0.12	15.5 ± 0.11
C3 (4 % SCMC)	305 ± 2 .04	4.60 ± 0.11	0.90	29.4 ± 0.12
C4 (8% SCMC)	304 ± 1.46	5.50 ± 0.12	0.72	45.0 ± 0.32

*Mean for 20 tablets, [a]Mean for 10 tablets ± SD, CV: coefficient of variation SD: standard deviation, A1 – A4: tablets contain acacia as binder, B1 – B4: tablets containing gelatin as binder, C1 – C4: tablet containing SCMC as binder. P < 0.05 was considered significant.

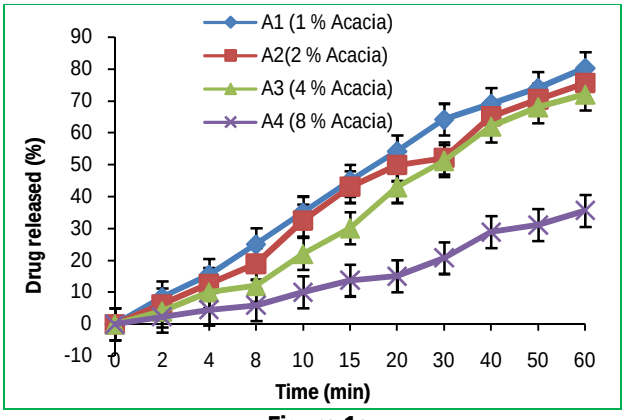

Figure 1a

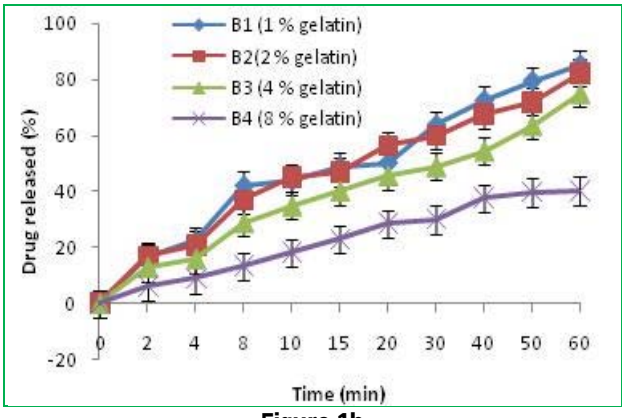

Figure 1b

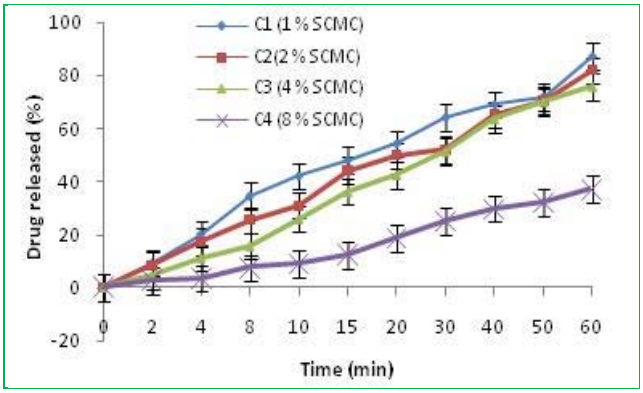

Figure 1c

Figure 1: Drug release from the formulations

The disintegration time of the tablet formulations was significantly affected by the type of binder and concentration used during formulation ($p < 0.05$). Disintegration time increased as the concentration of the binder increased. *A. boonei* tablets formulated with 1 % and 2% binder passed the disintegration time test for normal release tablets of ≤ 15 min. However tablets formulated with 4% and 8% binder failed the disintegration time test for normal release tablets except batch B3 containing 4% gelatin.

The *in vitro* release studies carried out in 0.1 N HCl indicated that the release profile was affected by both the

type and concentration of binder used in the formulation. Drug release decreased with increasing binder concentration as shown in Figs. 1(a – c). SCMC exhibited prolonged release of drug compared to other binders used. The results also showed that higher ratios of binder were more preferable in the formulation of sustained release preparations. The release profile of drug from the formulated tablets containing varying ratios of binders could be ranked in decreasing order of performance by the binder: SCMC > gelatin > acacia.

CONCLUSION

Alstonia boonei stem bark extract was successfully formulated as tablet dosage form. The results obtained from this work showed that Acacia, gelatin and SCMC could be used at low concentrations for the manufacture of normal release *A. boonei* tablets. However, high concentrations up to 8 % could be more useful in the manufacture of sustained release dosage form as shown in the work. Friability values (%) for all the tablet formulations were within the specified limit of acceptance. The disintegration time of the tablet formulations was significantly affected by the type of binder and concentration used during formulation ($p < 0.05$). The *in vitro* drug release properties of *A. boonei* tablets formulated with different binders and varying binder concentrations revealed that the performance of the binder could be ranked thus in decreasing order of release SCMC > gelatin > acacia. Drug release decreased with increasing binder concentration.

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