Effects of interacting variables on the formulation of *Alstonia boonei* De Wild (Apocynaceae) tablets

Majekodunmi, S. O. and O. A. Odeku*

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria.

Abstract

The quantitative effects of formulation and processing variables on the mechanical and disintegration properties of *Alstonia boonei* tablets have been studied using a $2^3$ factorial experimental design. *Alstonia boonei* tablets were prepared by direct compression using Emcompress® and Avicel® as direct compression excipients, and by wet granulation using polyvinylpyrrolidone and corn starch as binders. The relative effects of the nature of excipient or binder (N), concentration of excipient or binder (C) and compression force (P) were evaluated. The result shows that *A. boonei* tablets can be successfully prepared by either direct compression or wet granulation methods. The type and concentration of excipients or binding agents employed and the method of preparation of the tablets need to be carefully selected to obtain tablets with adequate bond strength to withstand the rigors of handling and also release the active compound for biological action.

Key words: *Alstonia boonei*, direct compression excipients, binding agents, pharmaceutical tablets.

Introduction

*Alstonia boonei* De Wild (Apocynaceae), a widely distributed plant in the lowlands and rainforest areas of Nigeria, is employed for a variety of ailments in Africa. The stem bark is commonly used in the treatment of malaria and has been listed in the African Pharmacopoeia as an anti-malarial drug. The stem bark is an astringent, alternative tonic and a febrifuge for relapsing fevers. An infusion of the stem bark is used as anti-venom for snake bites and in the treatment of arrow poisoning. The leaves and latex of *A. boonei* are used topically to reduce swellings, for the treatment of rheumatic and muscular pains, and hypertension (Dalziel 1937, Irvine 1961, Oliver-Beer 1986, Iwu 1993). The stem bark of *A. boonei* (known as Ahun in Yoruba, Egbu-ora in Igbo, Uku in Edo and Ukpuku in Urobo) is also used in traditional medicine to treat fever, painful micturition, insomnia, chronic diarrhea and rheumatic pains (Dalziel 1937, Faparusi and Bassir 1972, Berry and Metzger 1980, Ojewole 1984, Awe and Opeke 1990, Asuzu and Anaga 1991, Iwu 1993). The chemical constituents include alkaloids, terpenes and steroids (Ojewole 1984, Kweifo-Okai et al. 1995). Over 90% of the isolated chemical constituents are alkaloids (Faparusi and Bassir 1972, Ojewole 1984, Kweifo-Okai et al. 1995). *In vitro* antiplasmodial activity of the alkaloids against both drug sensitive and resistant strains of *P. falciparum* (Wright et al. 1993) and *in vivo* activity against *P. berghei* in mice (Vasanth et al. 1990) have been reported. In another trial, the anti-inflammatory properties of the alcoholic extract *A. boonei* in rat hind paw edema has been used to justify its use in herbal medicine for the treatment of rheumatic and muscular pains (Olajide et al. 2000, Osadebe 2000).

*Corresponding author: pejuodeku@yahoo.com
In spite of their efficacy, herbal medicinal products have been widely criticized due to lack of standardization and poor-quality presentation. In traditional medicine, the stem bark of *A. boonei* is usually soaked in water and unspecified quantities of the decoction are ingested without regard to toxicological and other adverse effects. Therefore, formulation of *A. boonei* into tablet dosage form might ensure dosage precision and confer on it many of the good properties of tablets, which include ease of administration, patient acceptance due to better presentation, prolonged shelf life, and quality assurance in dispensing and reduction in cost arising from transportation of bulky dosage forms (Gunsell and Kanig 1986). Thus, the aim of the present study is to produce conventional tablet dosage form of the extracts of the stem bark of *A. boonei* for oral administration using direct compression and wet granulation methods.

In the present study, the quantitative effects of formulation and processing variables on the mechanical and disintegration properties of *A. boonei* tablets have been studied using the factorial experimental design (Woolfall 1964), which has already been proven useful in the analysis of the quantitative individual and interaction effects of various formulation factors on tablet properties (Itiola 1991, Itiola and Pilpel 1996, Odeku and Itiola 2003). *A. boonei* tablets were prepared by direct compression using Emcompress® and Avicel® as direct compression excipients, and wet granulation using polyvinylpyrroldione and corn starch as binding agents. The relative quantitative effects of the nature of excipient or binder (N), concentration of excipient or binder (C) and the compression force (P) on the mechanical and disintegration properties of *A. boonei* have been studied to determine the most suitable method for the preparation of the tablets.

**Materials and Methods**

The materials used were Emcompress® (dicalcium Phosphate, Mendell Co Ltd., Surrey, UK), Avicel® RH 102 (FMC International Co. Cork, Ireland), Lactose (DMV, Veghel, Netherlands), Polyvinylpyrroldione, PVP average molecular weight 360,000 (Aldrich Chemicals Co Limited, Gillingham, Dorset, UK), Corn starch B.P (BDH chemicals, Poole, UK), Magnesium stearate (Hopkin and Williams, Chadwell, Health, Essex, UK), and absolute ethanol 96% (BDH chemicals, Poole, UK).

The stem bark of *Alistonia boonei* was purchased from the herbal wholesalers at Oyingbo market, Lagos, Nigeria and authenticated by Mr. G. Ibamefebhoro of the Forestry Research Institute of Nigeria, Ibadan, Nigeria (Voucher FHI 107254).

**Extraction of the Powdered Stem Bark**

The stem bark was washed with distilled water to remove dirt and sand particles, and then dried in a GallenKamp Moisture Extraction Oven (Model: BS 250 GallenKamp Co., UK) at 40°C for four days. The dried bark was cut into pieces and then ground to a coarse powder using a laboratory mill. Six Kilograms of the powdered sample was exhaustively extracted with absolute ethanol by maceration. The solvent was removed at 30°C under reduced pressure and the dried extract was reduced to powder using a laboratory mill and then sieved with a 120 μm mesh sieve.

**Preparation of Powder Mixtures for Direct Compression**

Fifty gram batches consisting of *A. boonei* extract and Avicel® or Emcompress® in a ratio of 1:9 and 1:4 drug: excipient were thoroughly mixed and stored in airtight containers.

**Preparation of Granules**

Batches (200 grams) of a basic formula of *A. boonei* extract (10 or 20% w/w), lactose (70 or 80% w/w) and corn starch (10% w/w) were dry-mixed for five minutes in a Kenwood planetary mixer and then moistened with 1% (w/w) or 4% (w/w) concentration of binder solution (PVP or corn starch mucilage). Lactose and corn starch were used in the formulation as diluent and disintegrant respectively. Massing was continued for five minutes and the wet masses were granulated by passing them manually through a
No. 12 mesh sieve (1,400 μm), dried in hot air oven for 18 hours at 500C, and then sieved through a No. 16 mesh size (1,000 μm) to break aggregates. The granules were stored in airtight containers.

The moisture content of the powder and granule formulations was determined with an Ohaus moisture balance (Ohaus Scale Corporation, USA) and was found to be between 1.1 and 1.3% (w/w).

Preparation of Tablets

Tablets (500 mg) were prepared from the powder mixture and granules (500-1000 μm size fractions) by compressing the materials for thirty seconds with predetermined loads of 5 and 10KN using a Carver Hydraulic Hand Press (Model C, Carver Inc, Menomonee Falls, WI, USA). Before each compression, the die (10.5 mm diameter) and the flat-faced punches were lubricated with a 2%w/w dispersion of magnesium stearate in ethanol: ether (1:1 solution). After ejection, the tablets were stored over silica gel for 24 hours to allow hardening and elastic recovery.

Crushing Strength and Friability Tests

The load (N) required to diametrically break each tablet (crushing strength, CS) was determined at room temperature using a PTB 301 crushing strength testers (Pharmatest, Switzerland). Determinations were done four times and the results given are the means of four determinations.

The friability (F) of the tablets were determined using a scientific friabilator (Model TF 2D, Scientific Equipment Ltd., Bombay, India) operated at 25 revolutions per minute for 4 minutes.

Disintegration Test

The disintegration times (DT) of the tablets were determined in distilled water at 37±0.50C using an Erweka disintegration testing apparatus (Model: Copley ZT2, Erweka Apparatebau GMBH, Heusenstamm, Germany). All measurements were made four times and the results given are the means of four determinations.

Factorial Experimental Design

The Factorial experiment is a statistical method designed by Woolfall (1964) which has been used to study the effects of formulation variables on tablet properties (Itila and Pilpel 1996, Odeku and Itiola 2003). This method was used to study the effects of nature of excipient/binder (denoted by N), concentration of excipient/binder (denoted by C) and compression force (denoted by P), on the mechanical and disintegration properties of A. boonei tablets (Woolfall 1964). The basis of the experimental design was that each of the three variables was utilized at a “high” level (denoted by the subscript, H) and a “low” level (denoted by the subscript, L). The number of experiments in the design was $2^3 = 8$.

Using the above nomenclature the various combinations between the variables used in the design were:

\[
N_L C_L P_L, \quad N_L C_H P_L, \quad N_C P_H, \quad N_C P_L
\]

\[
N_H C_L P_L, \quad N_H C_H P_L, \quad N_H C_H P_H, \quad N_H C_L P_H
\]

where:

\(N_L\) = Nature of excipient/binder (emcompress/corn starch)

\(N_H\) = Nature of excipient/binder (aviceI/PVP)

\(C_L\) = Concentration of excipient (80%w/w)/ binder (1% w/w)

\(C_H\) = Concentration of excipient (90%w/w)/ binder (4%w/w)

\(P_L\) = Compression force (5KN)

\(P_H\) = Compression force (10KN)

By grouping the results into a number of sets, it was possible to assess the effects that each of the three variables had separately on the mechanical and disintegration properties of the tablets and also to determine whether the variables were interacting or acting independently of each other (Woolfall 1964).
For instance, the effects of increasing N, from its “low” level to its “high” level on the various parameters were found by summing all the results (crushing strength, CS or friability, F or crushing strength-friability ratio, CSFR or disintegration time, DT) of samples containing “high” level of N and subtracting the sum of the results of samples containing “low” levels of N. That is:

\[ \frac{1}{4} \left( N_1C_1P_L + N_1C_1P_H + N_0C_0P_H + N_0C_0P_H \right) - \left( N_1C_0P_L + N_1C_0P_H + N_0C_1P_L + N_0C_0P_H \right) \]  

(1)

The amount by which the result of this treatment departed from zero was a quantitative measure of the effect of N on the values of the relevant parameter. Similar expressions were used for finding the effects of C and P.

To determine whether there was any interaction between two variables, the CS (or F, CSFR or DT) results of the combinations in which they appear together at either “high” or “low” levels were summed and the sum of other combinations subtracted from this to obtain the interaction coefficient (Woolfall 1964). For example, for N and C:

\[ \frac{1}{4} \left( N_1C_1P_L + N_1C_1P_H + N_0C_0P_H + N_0C_0P_H \right) - \left( N_1C_0P_L + N_1C_0P_H + N_0C_1P_L + N_0C_1P_H \right) \]  

(2)

A result of zero indicates no interaction, but if the interaction coefficient was significantly removed from zero, it is concluded that the two variables concerned were interacting with each other. The extent of removal from zero is a measure of the magnitude of interaction (Iitola and Pipel 1996, Odeku and Iitola 2003). Similar expressions were used for estimating the interactions between N and P, and between C and P.

Statistical Analysis

Statistical analysis to compare the individual and interaction effects of the formulation variables on the mechanical and disintegration properties of A. boonei tablets was done with the Kruskal-Wallis test, a non-parametric multiple comparison test, using the computer software GraphPad Prism® 4 (GraphPad Software Inc., San Diego, USA). Individual differences between the formulations were performed using Dunn’s multiple comparison tests. At 95% confidence interval, \( p \) values less than or equal to 0.05 were considered significant.

Results and Discussion

The values of crushing strength (CS), friability (F), crushing strength-friability ratio (CSFR) and disintegration time (DT) at compression forces of 5 and 10 KN for A. boonei tablets prepared using direct compression and wet granulation, used for the factorial experiment are presented in Table 1.

<table>
<thead>
<tr>
<th>Variables and combination codes</th>
<th>CS (N)</th>
<th>F (%)</th>
<th>CSFR</th>
<th>DT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_1C_1P_L )</td>
<td>34.34</td>
<td>2.05</td>
<td>16.75</td>
<td>0.50</td>
</tr>
<tr>
<td>( N_1C_1P_H )</td>
<td>47.09</td>
<td>1.43</td>
<td>32.93</td>
<td>0.63</td>
</tr>
<tr>
<td>( N_1C_0P_L )</td>
<td>45.13</td>
<td>1.99</td>
<td>22.68</td>
<td>0.60</td>
</tr>
<tr>
<td>( N_1C_0P_H )</td>
<td>51.99</td>
<td>1.63</td>
<td>31.90</td>
<td>1.17</td>
</tr>
<tr>
<td>( N_0C_1P_L )</td>
<td>178.54</td>
<td>0.43</td>
<td>415.21</td>
<td>3.33</td>
</tr>
<tr>
<td>( N_0C_1P_H )</td>
<td>188.35</td>
<td>0.39</td>
<td>482.20</td>
<td>5.77</td>
</tr>
<tr>
<td>( N_0C_0P_L )</td>
<td>192.28</td>
<td>0.44</td>
<td>437.00</td>
<td>59.83</td>
</tr>
<tr>
<td>( N_0C_0P_H )</td>
<td>199.14</td>
<td>0.40</td>
<td>747.65</td>
<td>79.00</td>
</tr>
</tbody>
</table>
These values were used to calculate the individual and interaction coefficients for the variables using relevant equations. The individual and interaction coefficients are presented in Table 2.

Table 2. Individual and interaction effects of nature of excipient/binder (N), concentration of excipient/binder (C) and compression force (P) mechanical and disintegration properties of *A. boonei* tablets prepared by direct compression (A) and wet granulation (B) for factorial experimental design.

<table>
<thead>
<tr>
<th>Variables and combination codes</th>
<th>CS (N)</th>
<th>F (%)</th>
<th>CSFR</th>
<th>DT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N&lt;sub&gt;1&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;P&lt;sub&gt;1&lt;/sub&gt;</td>
<td>38.26</td>
<td>0.87</td>
<td>43.98</td>
<td>0.58</td>
</tr>
<tr>
<td>N&lt;sub&gt;1&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;P&lt;sub&gt;H&lt;/sub&gt;</td>
<td>47.09</td>
<td>0.69</td>
<td>68.25</td>
<td>0.77</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;P&lt;sub&gt;L&lt;/sub&gt;</td>
<td>81.42</td>
<td>0.67</td>
<td>121.52</td>
<td>0.75</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;P&lt;sub&gt;H&lt;/sub&gt;</td>
<td>114.78</td>
<td>0.65</td>
<td>208.69</td>
<td>1.07</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;P&lt;sub&gt;L&lt;/sub&gt;</td>
<td>101.04</td>
<td>0.62</td>
<td>162.97</td>
<td>1.32</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;P&lt;sub&gt;H&lt;/sub&gt;</td>
<td>108.89</td>
<td>0.57</td>
<td>191.04</td>
<td>1.60</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;H&lt;/sub&gt;P&lt;sub&gt;L&lt;/sub&gt;</td>
<td>161.87</td>
<td>0.51</td>
<td>317.39</td>
<td>9.83</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;P&lt;sub&gt;H&lt;/sub&gt;</td>
<td>178.54</td>
<td>0.41</td>
<td>435.46</td>
<td>10.17</td>
</tr>
</tbody>
</table>

The individual and interaction coefficient values provide a clear indication of the quantitative effects of the three variables studied on the mechanical and disintegration properties of *A. boonei* tablets. In comparing the formulations, the ranking of the individual (independent) coefficient values for formulations prepared by direct compression was N>>C>P on CS, N>>P>C on F and CSFR and N>C>>P on DT. For formulations prepared by wet granulation, the ranking was N>C>>P on CS, CSFR and DT and N>C>P on F. The individual effects on friability, F, were negative indicating that the values of that parameter decreased.

The effect of the nature of excipient or binder (N) on the mechanical and disintegration time of *A. boonei* tablets was positive; this result indicates that for tablets containing Avicel® as direct
compression excipient which represented the 'high' level, had higher CS, CSFR and DT than Emcompress® which represented the 'low' level of N. For tablets prepared by wet granulation, tablets containing PVP as binder which represented the 'high' level had higher CS, CSFR and DT than tablets containing corn starch which represented the 'low' level of N. The effect of N on F was negative indicating that the values of F decreased when the nature of N was changed from 'low' to 'high'. The results of the friability test indicated that the tablets generally passed the Pharmacopoeial requirement on friability (i.e. friability of ≤1% w/w of its weight) with the exception of tablets containing Emcompress® which failed the friability test. All the tablets complied with the Pharmacopoeial requirements on disintegration (i.e. disintegration within 15 minutes) (Odeku and Itiola 2003), with the exception of tablets containing high levels of Avicel® which had disintegration time of over 60 minutes. Statistical analysis showed that the effect of N was significantly (p<0.001) higher than those of other variables, C and P (Table 2). Furthermore, the effects of N was significantly (p<0.001) higher for formulations prepared by direct compression than for formulation prepared by wet granulation. This result indicates the need for careful selection of the type of binding agent and excipient used in the formulation of A. boonei tablets.

The effect of C indicates that increasing the concentration of the direct compression excipients from 80% to 90% and the binding agents from 1% to 4% (w/w) led to an increase in the plastic deformation of the formulation during compression and subsequently to the formation of more solid bonds in the tablet (Itiola and Pilpel 1986), leading to an increase in the crushing strength and disintegration time of the tablets. However, the effect of C on F was negative for formulations prepared by wet granulation but positive for those prepared by direct compression. This result indicates that the values of F for the formulation decreased with increase in binder concentration but increased with increase in excipient concentration. This result indicates that the presence of higher levels of binder at interparticulate junctions facilitates plastic deformation of the materials, resulting in tablets with more resistance to fracture and abrasion (Itiola and Pilpel 1986, Akin-Ajani et al. 2005). In general, the effect of concentration (C) on the mechanical properties of the tablets prepared by wet granulation were significantly (p<0.001) higher than the effects of C on tablets prepared by direct compression. This finding indicates that the concentration of binder used in tablet formulations prepared by wet granulation is a very important factor and should be given particular consideration when developing A. boonei tablet formulations (Odeku and Itiola 1998).

The compression force (P) generally had the least effect on the CS and DT of A. boonei tablets prepared by direct compression as well as tablets prepared by wet granulation. Thus, increasing the compression force from 5 KN to 10 KN led to an increase in the mechanical and disintegration properties of the tablets. This increase in properties may be due to the fact that as the compression force, P, is increased, the packing fraction of the tablets will also increase, leading to the formation of more solid bonds between the particles leading to an increase in crushing strength and disintegration time of the tablets (Itiola and Pilpel 1986, Itiola 1991, Akin-Ajani et al. 2005). The negative effect of P on F indicates that increasing the compression pressure decreased the friability of the tablet.

The result of the interaction coefficient values indicates the effect of the variables in combination (Table 2). It can be seen that nature of excipient/binder (N), concentration of excipient/binder (C) and compression force (P) interact with each other to alter the crushing strength, friability, crushing strength-friability ratio and disintegration times of the tablets. For the formulations prepared by direct compression, the ranking of the interaction effects on CS was N – C > C – P >> N – P, while that on F was N – P > N – C > C – P, on CSFR was N – P > C – P > N – C, and on DT was N – C >> N – P > C – P. For formulations prepared by wet granulation, the ranking of the interaction effects on CS was C – P >> N – C > N – P, while on
F was C – P > N – P > N – C, on CSFR was N – C > C – P >> N – P, and on DT was N – C >> C – P > N – P.

The interaction between N and C had the largest effect on the properties of A. boonei tablets, which suggests that P had the most independent influence on the mechanical and disintegration properties of A. boonei tablets. Furthermore, statistical analysis showed that the interaction between N and C was significantly (p<0.001) higher than those between N and P and those between C and P. This is probably due to the fact that the nature of excipient and binder determines the softness and plastoelastic properties of the material and in effect the amount of deformation the material undergoes under high compressional forces (Iitiola 1990). The number of bonds formed depends considerably on the concentration of the excipient or binder employed (Odeku and Iitiola 1998, 2003). Thus, the nature and concentration of excipients and binders employed in the formulation of A. boonei tablets needs to be carefully chosen to enable the production of tablets with adequate bond strength to withstand the rigors of handling and at the same time release the active compound for biological action. Furthermore, the methods of preparation of the tablets need to be carefully selected to ensure the production of suitable tablet formulation.

Conclusion

The result obtained suggests that A. boonei tablets can be successfully prepared either by direct compression or wet granulation method. The type of excipient or binder (N), concentration of excipient or binder (C) and the compression force of the tablets (P) significantly affect the mechanical and disintegration properties of the tablets. Thus, the nature and concentration of excipient and binder employed in the formulation of A. boonei tablets need to be carefully chosen during tablet formulation. This is important in order to obtain tablets with adequate bond strength to withstand the rigors of handling and at the same time release the active compound for biological action. Furthermore, the methods of preparation of the tablets need to be carefully selected to ensure the production of suitable tablet formulation. However, further work need to be done in characterizing the release of the active constituent from the tablets using one of the constituents as a marker in the formulation.

References


Received: 15.06.2008
Accepted: 10.06.2009