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Original article

Formulation factors affecting the binding properties of Chinese yam (*Dioscorea oppositifolia*) and corn starches

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Abstract

Objective: The quantitative effects of formulation and processing variables affecting the binding properties of Chinese yam starch (*Dioscorea oppositifolia*) in chloroquine phosphate tablet formulations have been investigated in comparison with corn starch using a 23 factorial experimental design. **Methods**: Chinese yam starch, representing the "low" level, and corn starch, representing the "high" level were used as binders at concentrations of 2.5 % w/w and 10 % w/w in chloroquine phosphate tablet formulations. The mechanical properties of the tablets, measured by the tensile strength (T) and brittle fracture index (BFI) as well as the release properties measured by the disintegration time (DT) and dissolution time (t_{80}- time for 80 % drug release), were used as assessment parameters. **Results**: The ranking of the individual coefficient values for the formulations on T was D > N ≫ C, on BFI was N > D ≫ C, on DT was D > N > C and on t_{80} was C > N > D while the ranking of the interaction coefficient on T was N-D > C-D ≫ N-C, on BFI was N-D > N-C = C-D, on DT and t_{80} was N-C > N-D > C-D. Changing the binding agent from Chinese to corn starch, led to a decrease in T, DT and t_{80} but increase in BFI of the tablets. There were significant ($P<0.001$) interactions between the nature of binder, N and the other two variables, C and D. **Conclusion**: The result showed that Chinese yam possessed stronger binding capacity than corn starch and could be useful as an alternative binder when tablets with high mechanical strength with minimal problems of lamination, and slow release are required.

Keywords: Starch; Binder; Chinese yam; Tensile strength; Brittle fracture index; Chloroquine phosphate

INTRODUCTION

Starches are of commercial importance in the food and pharmaceutical industries because of their inertness, abundance and cheapness. Commercial starches obtained from cereals (corn, waxy corn, high amylose corn, wheat and various rices), tubers and roots (particularly potato and cassava) are used as diluents, binders and disintegrants in drug formulation[1]. With the versatility of starches in various solid dosage forms, there is the need to continue to develop new starch excipients with suitable properties to meet the special needs of drug formulators.

Tropical yam tubers (Family Dioscoreaceae) are potential source of industrial starch because of their high starch content (about 50 - 80 % w/w)[2]. One of the species cultivated in many parts of Africa and Southeast Asia is *Dioscorea oppositifolia* (Chinese yam), which has been used in Chinese medicine as an invigorant[3]. *D. oppositifolia* L., (also known as *D. opposita* Thunb), is a perennial twining vine which has a deep, persistent root-like tuber that can be 1 m long and weigh up to several kilograms. Aboveground, it has round slender stems that twine

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dextrorsely upwards and leaves that are usually arranged oppositely. The species epithet "oppositifolia" refers to this opposite arrangement of its leaves. Recent studies on the physicochemical, material and tablet properties of Chinese yam starch have shown that the varied considerably from official corn starch and starches from other Dioscorea species[4]. Chinese yam starch has an amylose, protein, ash, lipid and phosphorus content of 21.61, 0.75, 0.21, 0.20 and 0.025 % respectively. When used as a directly compressible excipient, Chinese yam starch was observed to be highly compressible, forming tablets of acceptable crushing force [4]. The compactibility of the starch appeared to be related to the granule size, irregular shape and high specific surface area which facilitate more interparticulate contact and thus higher bond formation[4]. Further studies have shown that the starch could be useful at certain concentrations as disintegrants particularly where high mechanical strength and a good balance between binding and release properties of the tablets are required[5]. However, the quantitative effects of important formulation and processing variables on the binding properties of Chinese yam starch appear to be largely uninvestigated. Thus, in the present work, the quantitative effects of formulation and processing variables affecting the binding properties of Chinese yam starch (*Dioscorea oppositifolia*) have been investigated in comparison with corn starch using a 2^3 factorial experimental design[6]. The factorial experimental design has been found useful in the analysis of the quantitative individual and interaction effects of various formulation factors on the mechanical strength and drug release properties of tablets[7-9].

The mechanical properties of the tablet which are indicators of the ability of the tablets to withstand the rigors of handling involved in manufacture, transportation, dispensing and usage, has been assessed by two important properties: bond strength and brittleness [7,10]. The tensile strength of a tablet is a function of the area of contact between the particles and the strength of bonds produced between them [10]. The greater the degree of bonding, the greater is the tensile strength of the tablets. The brittle fracture index (BFI) on the other hand, was devised by Hiestand et al[11] and is obtained by comparing the tensile strength of a tablet with a hole to the tensile strength of the tablets without a hole, both at the same relative density. The hole serves as a built in stress concentrator "defect". A low value of BFI is desirable for the minimization of capping and lamination during tablet production.

Chloroquine phosphate, a 4- aminoquinoline antimalarial compound was used as the model drug. Chloroquine phosphate cannot be made into satisfactory tablets because of its poor compression properties and therefore requires a binder, among other excipients, to form satisfactory tablets.

MATERIALS AND METHODS

The materials used were chloroquine phosphate BP and corn starch BP (BDH Chemicals Ltd., Poole, U. K.), polyvinyl pyrrolidone, PVP Mol. Wt. 44,000 (BDH Chemicals Ltd., Poole, U. K.) and tubers of *Dioscorea oppositifolia* (Chinese yam) obtained from local farmers in Ibadan, Nigeria and authenticated. The starch was extracted from the tubers using established procedures[12].

Preparation of granules and tablets

Batches (200 g) of a basic formulation of chloroquine phosphate (60 % w/w), lactose (30 % w/w) and corn starch (10 % w/w) were dry mixed for 5 minutes in a planetary mixer (Model A120, Hobart Manufacturing Co, U. K) and then moistened with appropriate amounts of starch paste to produce granules containing different concentrations of the starches as binder (2.5-10 % w/w). Massing was continued for 5 minutes and the wet masses were granulated by passing them manually through a mesh 12 sieve (1 400 μm). These were dried in a hot air oven at 50 ℃ for 18 hours. Dried granules were sieved through a mesh 16 sieve (1 000 μm) and then stored in air tight container. The moisture content of the granules was determined and found to be between 2 - 4 % w/w. Particle densities were determined by the pycnometer method, using xylene as the displacement fluid.

Preparation of tablets

Quantities (500 mg) of granules within the size range of 710 - 1 000 μm were compressed for 30 seconds into tablets with predetermined loads on a Carver hydraulic press (model C, Carver inc. Menomonee Falls, WIS) using a 10.5 mm die and flat-faced punches lubricated with a 1 % dispersion of magnesium stearate in acetone before each compression. After ejection, the tablets were stored over silica gel for 24 hours to allow for elastic recovery and hardening. The weights (w) and dimensions of the

tablets were then determined to within ±1 mg and 0.01 mm respectively, and their relative densities, D, were calculated using the equation:

$$D = w/V_t \cdot \rho_s \quad (1)$$

where V_t is the volume, cm^3, of the tablet including the hole when present and ρ_s is the particle density, gcm^{-3}, of the solid material.

Testing

The tensile strength of the chloroquine phosphate tablets (T) was determined at room temperature by diametral compression [13] using a hardness tester (Ketan Scientific & Chemicals, Ahmedebad, India). The tensile strength of the tablet was then calculated from the equation:

$$T = 2L/\pi dh \quad (2)$$

where T is the radial tensile strength, L is the load needed to break the tablet, d is the tablet diameter and h is the tablet thickness[13]. Results were taken only from tablets which split cleanly into two halves without any sign of lamination. All measurements were made in quadruplicates and the results given are the mean of several determinations.

The brittle fracture index (BFI) values of the tablets were calculated from the equation:

$$BFI = 0.5[(T/T_o) - 1] \quad (3)$$

where T is the tensile strength of the tablet without a hole and T_o is the tensile strength of a tablet with a hole.

Disintegration and dissolution test

The disintegration time of the tablets was determined in distilled water at 37 ± 0.5 ℃ using a disintegration tester (Veego Scientific devices, Mumbai, Maharashtra, India). Determinations were done in quadruplicates.

Dissolution test was carried out on the tablets using the USPXX III basket method (Hanson Model 72RL, U. S. A) rotated at 100 rpm in 900 mL of 0.1 M HCL, maintained at 37 ± 0.5 ℃. Samples (5 mL) were withdrawn and replaced with equal amounts of fresh medium. The sample was diluted and the amount of chloroquine phosphate released was determined at wavelength of 255 nm, using a UV/visible spectrophotometer (Phillips Pye Unicam, PU 8610 Kinetics, Sarose scientific instruments, Cambridge, U. K.). Determinations were done in triplicates.

Factorial Experimental Design

A factorial experimental design was used to study the effects of nature of binder (denoted by N), concentration of binder (denoted by C) and relative density (denoted by D) on the mechanical and release properties of chloroquine phosphate tablets[6]. 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:

$N_L C_L D_L$, $N_L C_L D_H$, $N_L C_H D_L$, $N_L C_H D_H$
$N_H C_H D_H$, $N_H C_H D_L$, $N_H C_L D_H$, $N_H C_L D_L$
N_L = Nature of binder (Chinese yam starch)
N_H = Nature of binder (corn starch)
C_L = Concentration of binder (2.5 %)
C_H = Concentration of binder (10 %)
D_L = Relative density of 0.80
D_H = Relative density of 0.90

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 release properties of the tablets and also to determine whether the variables were interacting or acting independently of each other.

The effects of increasing N, from its "low" level to its "high" level on the various parameters were found by summing all the results (T or BFI or DT or t_{80}) of samples containing "high" level of N and subtracting the sum of the results of samples containing "low" levels of N. That is:

$$1/4[(N_H C_H D_H + N_H C_L D_H + N_H C_H D_L + N_H C_L D_L) - (N_L C_L D_L + N_L C_H D_L + N_L C_L D_H + N_L C_H D_H)]$$

The amount by which the result of this treatment departed from zero, irrespective of whether positive or negative 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 D.

To determine whether there was any interaction

between two variables, the T (or BFI or DT or t_{80}) 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. For example, for N and C:

$$1/4[(N_HC_HD_L + N_HC_HD_H + N_LC_LD_H + N_LC_LD_L) - (N_HC_LD_H + N_HC_LD_L + N_LC_HD_L + N_LC_HD_H)]$$

A result of zero indicates no interaction, but if the interaction coefficient is significantly removed from zero, it can be concluded that the two variables concerned are interacting with each other. The extent of removal from zero is a measure of interaction. Similar expressions were used for estimating the interaction between N and D, and between C and D.

Statistical analysis

Statistical analysis was carried out using the analysis of variance (ANOVA) and Tukey-Kramer multiple comparison tests on a computer software GraphPad Prism 4 (GraphPad Software Inc. San Diego, USA).

RESULTS

The representative plots of log tensile strength, brittle fracture index (BFI) and disintegration time (DT) versus relative density (RD) for chloroquine phosphate tablets containing 10 % w/w of the starch binding agents are presented in Figures 1, 2 and 3 respectively, while the dissolution profiles of the tablets are presented in Figure 4. The values of T, BFI, DT and t_{80} (the time required for 80 % of chloroquine phosphate to be released) at two selected relative density values of 0.8 and 0.9, which are representative of the range of relative density values normally achieved for commercial chloroquine phosphate tablets, used for the factorial experiment, are presented in Table 1. These values were used to calculate the individual and interaction coefficients for the variables using the relevant equations. The individual and interaction coefficient values are presented in Table 2. These values provide a clear indication of the quantitative effects of the three variables studied on the mechanical strength and the drug release properties of the chloroquine phosphate tablets.

Table 1 Tensile strength (T) brittle fracture index (BFI), disintegration time (DT) and dissolution time (t_{80}) of chloroquine phosphate tablets for the factorial experimental design.

Variables and combination codes	Tensile strength (MNm^{-2})	Brittle fracture index	Disintegration time (min)	t_{80} (min)
$N_LC_LD_L$	0.598	0.120	1.20	18.50
$N_LC_LD_H$	1.286	0.136	9.25	36.25
$N_LC_HD_L$	0.623	0.248	11.00	50.00
$N_LC_HD_H$	1.967	0.100	26.25	83.50
$N_HC_LD_L$	0.345	0.725	0.60	14.50
$N_HC_LD_H$	0.930	0.399	6.60	31.00
$N_HC_HD_L$	0.615	0.691	1.20	22.00
$N_HC_HD_H$	1.155	0.307	7.30	37.00

Table 2 Individual and interaction effects of nature of starch binder (N), concentration of starch binder (C) and relative density (D), on the mechanical and drug release properties of chloroquine phosphate tablets.

Variables		Tensile strength (MNm^{-2})	Brittle fracture index	Disintegration time (min)	t_{80} (min)
Independent coefficient	N	−0.36	0.38	−8.00	−20.94
	C	0.30	−0.01	7.03	23.06
	D	0.79	−0.21	8.85	20.69
	P	$P<0.001$	$P<0.001$	$P<0.01$	$P<0.01$
Interaction coefficient	N − C	−0.05	−0.06	−6.38	−16.31
	N − D	−0.23	−0.15	−2.80	−4.94
	C − D	0.15	−0.06	1.83	3.56
	P	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$

In comparing the formulations, the ranking of the individual (independent) coefficient values for the formulations on T was D > N ≫C, on BFI was N > D ≫C, on DT was D > N > C and on t_{80} was C > N > D while the ranking of the interaction coefficient on T was N-D > C-D ≫ N-C, on BFI was N-D > N-C = C-D, on DT and t_{80} was N-C > N-D > C-D. There were significant ($P < 0.001$) interactions between the nature of binder, N and the other two variables, C and D.

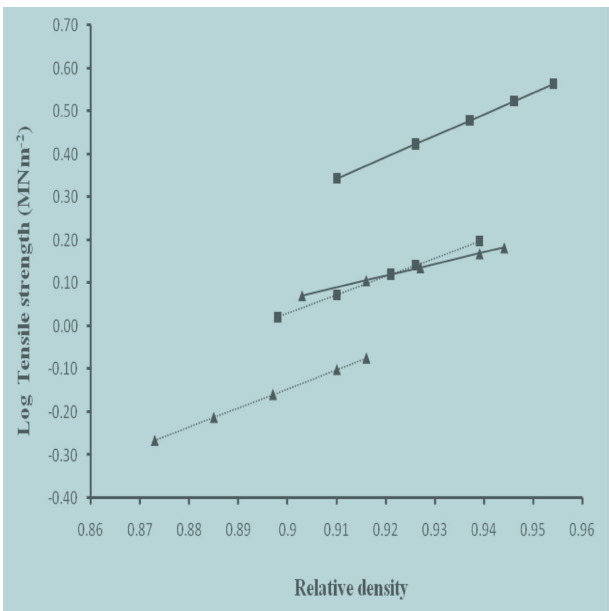

Figure 1 Plot of Logarithm of Tensile strength versus relative density for chloroquine phosphate tablets containing 10 % w/w of starch binder with hole (·····) and without a hole (___) at their center : ■, Chinese yam starch and ▲, corn starch.

DISCUSSION

The influence of N on T, DT and t_{80} was negative indicating that changing the binding agent from Chinese yam starch which represented the "low" level to corn starch which represents the "high", led to a decrease in T, DT and t_{80} but increase in BFI of the tablets. Thus, Chinese yam starch produced tablets with higher tensile strength and longer disintegration and dissolution times than the tablets containing corn starch as binding agent. The influence of N on BFI

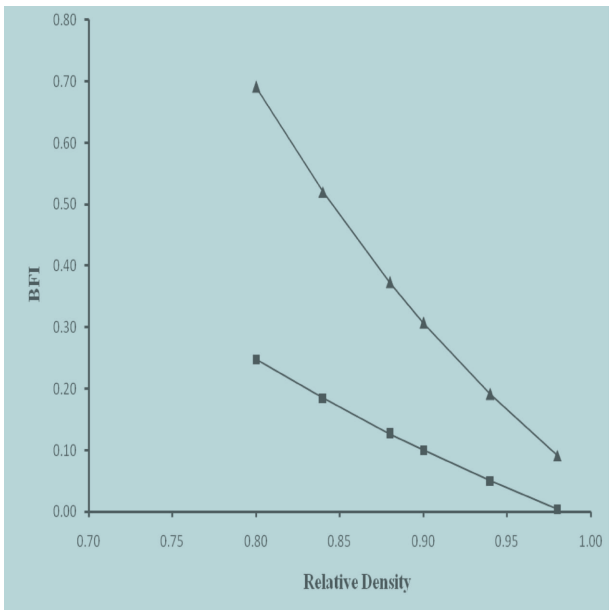

Figure 2 Plot of brittle fracture index versus relative density for chloroquine phosphate tablets containing 10 % w/w of binder: ■, Chinese yam starch and ▲, corn starch.

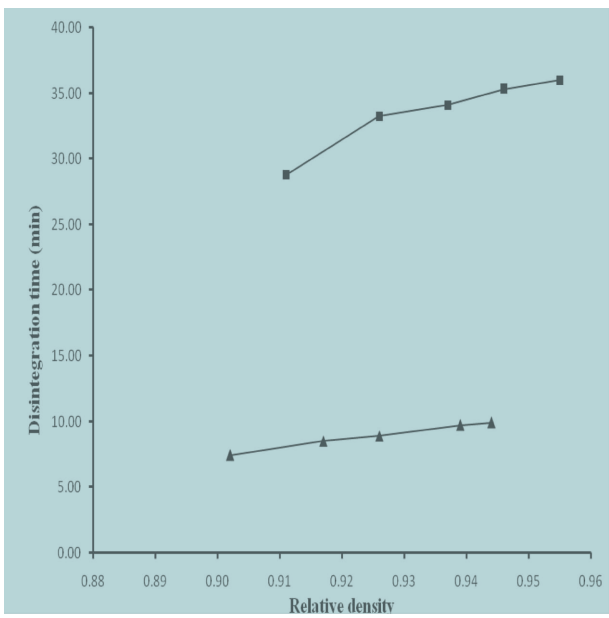

Figure 3 Plot of Disintegration time versus relative density for chloroquine phosphate tablets containing 10 % w/w of binder: ■, Chinese yam starch and ▲, corn starch.

was positive indicating that Chinese yam starch binder produced tablets with lower BFI values than corn starch. This indicates that the tablets containing Chinese starch has better ability to relieve stress and prevent capping and lamination during tablet production than tablets containing corn starch. Thus, Chinese yam starch appears to be a stronger binding a-

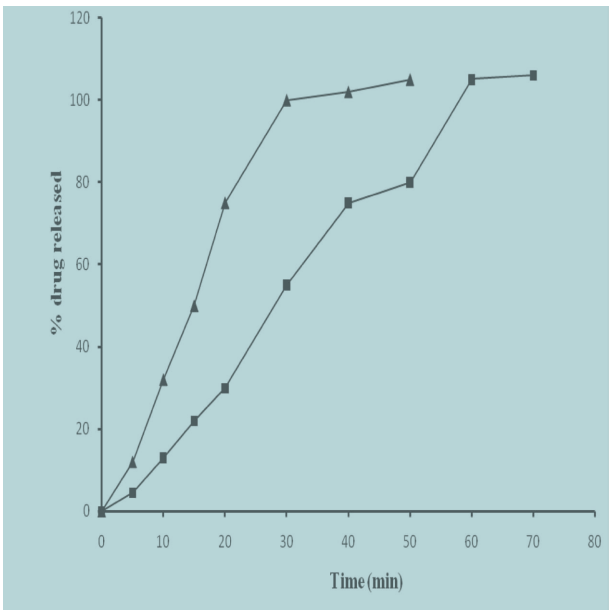

Figure 4 Dissolution profiles of chloroquine phosphate tablets containing 10 % w/w of starches as binders at relative density of 0.80: ■, Chinese; ▲, Corn.

gent than corn starch. However, all the tablets complied with the BP[14] requirement on disintegration (i.e. disintegration within 15 minutes) except formulations containing 10 % w/w Chinese yam starch which had a disintegration time of 26 minutes. Thus, Chinese yam starch could be more useful as a binding agent when stronger mechanical properties and longer disintegration and dissolution time is required.

The effects of C indicate that increasing the concentration of binder from 2.5 to 10 % w/w led to an increase in the tensile strength, disintegration and dissolution times of the tablet. However, the effect of C on the BFI was negative, indicating that there was a decrease in the tablet brittleness. It has been shown that the heat produced during compression would cause melting of the asperities and of the binders which on cooling would solidify to form strong solid bonds between the particles [15]. The amount of bonding would depend on the concentration of binding agent present. The decrease in BFI values with increase in C indicates that the presence of a binder at interparticulate points facilitates plastic deformation for the relief of localized stresses. Thus, the concentration of the starch binder has to be carefully selected to obtain tablets with adequate strength and with desired disintegration/dissolution times. This is in agreement with the results of other workers[15,16].

The relative density (D) had the highest effect on tensile strength and disintegration time but the least effect on dissolution time. Thus, increasing the relative density from 0.80 to 0.90 led to an increase in T, DT and t_{80}, but a decrease in BFI. For most pharmaceutical material, the relative density of the tablets generally increases with increase in compression pressure. This will lead to a decrease in porosity or reduction in capillary microstructure of the tablets[17] resulting in closer packing. Thus, more solid bonds will be formed between the particles leading to an increase in the mechanical strength of the tablets. Particle re-arrangement, fragmentation and deformation may also result in the closure of the inter and intragranular pore spaces, thereby reducing the capillary microstructure of tablets and the reduction in the size of the capillary spaces between the particles will reduce the rate of penetration of water, which will in turn lead to an increase in disintegration and dissolution times. There were significant ($P < 0.01$) differences in the effects of the individual variables on the mechanical and release properties of chloroquine phosphate tablets.

The interaction coefficient values (Table 2) indicate that all the variables interacted with each other to alter the mechanical and release properties of the tablets. The interaction between N and D had the largest effect on mechanical properties of the tablets while the interaction between N and C had the largest effect on disintegration and dissolution times of the tablets. Thus, the nature and concentration of binding agent used in tablet formulations need to be carefully chosen in order to obtain tablets of desired mechanical and drug release properties. In general, there were statistically significant ($P < 0.001$) interactions between the nature of binder, N and the other variables, C and D. The effect of N on tablet properties were shown to be strongly related to the concentration of the starch binder (C) and the relative density of the tablet (D) employed in the formulation[8]. Thus, there appears to be a strong interaction between Chinese yam starch and the other formulation and processing variables. Furthermore, changing the type of starch binder from Chinese yam starch to corn starch, and increasing the binder concentration (C), led to an increase in tensile strength, disintegration and dissolution times, but a

decrease in BFI of chloroquine phosphate tablets. Thus, the nature of binder (N), concentration of binder (C) and relative density (D) employed in a formulation need to be carefully chosen to enable the production of tablets with the adequate bond strength and afford the release of the drug in the desired time period and with the desired disintegration/ dissolution profile.

The results indicates that changing the binding agent from Chinese yam starch which represented the "low" level to corn starch which represents the "high", led to a decrease in T, DT and t_{80} but increase in BFI of the tablets. Thus, Chinese yam starch produced tablets with higher tensile strength and longer disintegration and dissolution times than the tablets containing corn starch as binding agent. The interaction between N and D had the largest effect on mechanical properties of the tablets while the interaction between N and C had the largest effect on disintegration and dissolution times of the tablets. Thus, the nature and concentration of binding agent used in tablet formulation need to be carefully chosen during tablet formulation in order to obtain tablets of desired mechanical and drug release properties. The result also showed that Chinese yam possessed stronger binding capacity than corn starch and could be useful as an alternative binder when tablets with high mechanical strength with minimal problems of lamination, and slow release are required. This study would be of immense value in developing tablet formulations for other drugs.

REFERENCES

1 **Gebre-Mariam T**, Schmidt PC. Some physicochemical properties of Dioscorea starch from Ethiopia. *Starch/Stärke* 1998; 50: 241-246.

2 **Farhat IA**, Oguntona T, Neale RJ. Characterization of starches from West African yams. *Journal of the Science of Food and Agriculture* 1999; 79: 2105-2112.

3 **Shujun W**, Jinglin Y, Wenyuan G. Hongyan L, Peigen X. New starches from traditional Chinese medicine (TCM) - Chinese yam (Dioscorea opposita Thunb) cultivars. *Carbohydrate Research* 2006; 341(2): 289-293.

4 **Odeku OA**, Picker-Freyer KM. Analysis of the material and tablet formation properties of four Dioscorea starches. *Starch/Stärke* 2007; 59: 430-444.

5 **Okunlola A**, Odeku OA. Comparative evaluation of starches obtained from Dioscorea species as intragranular tablet disintegrant. *Journal of Drug Delivery Science and Technology* 2008; 18(6): 445-4.

6 **Woolfall RC.** An approach to product formulation. *Soap Perfume Cosmetic* 1964; 37: 965-970

7 **Itiola OA**, Pilpel N. Tableting characteristics of metronidazole formulations. *International Journal of Pharmaceutics* 1986; 31;99-105.

8 **Odeku OA.** Effects of albizia gum and gelatin on interacting variables affecting the mechanical and release properties of paracetamol tablets. *Journal of Drug Delivery Science and Technology* 2008; 18(3): 215-217.

9 **Odeku OA**, Itiola OA. Effects of interacting variables on the tensile strength and the release properties of paracetamol tablets. *Tropical Journal of Pharmaceutical Research* 2003; 2(1): 147 - 153.

10 **Itiola OA**, Pilpel N. Formulations effects on the mechanical properties of metronidazole tablets. *Journal of Pharmacy and Pharmacology* 1991; 43: 145-147.

11 **Hiestand EN**, Wells JE, Poet CB, Ochs JF. Physical processes of tableting. *Journal of Pharmaceutical Sciences* 1977; 66: 510 - 519.

12 **Radley JA** ed. *Starch Production Technology*. London: Appl Sci Publ; 1976. 189 – 229, 1970.

13 **Fell JT**, Newton JM. Determination of tablet strength by diametral compression test. *Journal of Pharmaceutical Sciences* 1970; 59;688-691.

14 British Pharmacopoeia 1998. Vol. 1 & II. Her Majesty's Stationery Office, London.

15 **Kurup TR**, Pilpel N. The effects of binding agents on the tensile strength of powders and tablets. *Asian Journal of Pharmaceutical Science* 1979; 1;75-90.

16 **Itiola OA.** Compressional characteristics of three starches and the mechanical properties of their tablets. *Pharmacy World Journal* 1991; 8(3);91-94.

17 **Pilpel N**, Otuyemi SO, Kurup TRR. Factors affecting the disintegration and dissolution of chloroquine phosphate/ starch tablets. *Journal of Pharmacy and Pharmacology* 1978; 30: 214-219.

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