



EVALUATION OF MICROCRYSTALLINE STARCH FROM SWEET POTATO IN DIRECT COMPRESSION OF RELATIVELY HIGH DOSE POORLY COMPRESSIBLE DRUGEmmanuel O. Olorunsola^{1*}, Adamu B. Isah¹, Teryila S. Allagh¹¹Department of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University, Zaria - Nigeria.**ABSTRACT**

This study was designed to evaluate the suitability of microcrystalline starch from sweet potato as a direct compression excipient for a relatively high dose poorly compressible drug. The microcrystalline starch was produced by acid hydrolysis of sweet potato native starch. Tablets containing 250 mg chloroquine phosphate and 375 mg direct compression excipient binary mixture were produced. The different proportions of the microcrystalline starch (MCS) and microcrystalline cellulose (MCC) in the binary mixtures were :- 0:100, 25:75, 50:50, 75:25 and 100:0. Tablets' weight uniformity, thickness, diameter, mechanical properties (crushing strength and friability) and release properties (disintegration and dissolution) were evaluated. The results showed that the crushing strength decreased significantly ($P < 0.05$) and friability increased with increase in the proportion of the microcrystalline starch. Also, disintegration time decreased and dissolution rate increased significantly ($P < 0.0005$) with increase in the proportion of the microcrystalline starch in the binary mixture. This work has shown that while microcrystalline cellulose has better mechanical effects, microcrystalline starch has better release effects on chloroquine phosphate. Binary mixture of the microcrystalline starch and microcrystalline cellulose in the ratio 3:1 is suitable for direct compression of a relatively high dose poorly compressible drug.

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effect, sweet potato.

INTRODUCTION

An obvious way to reduce production time and hence cost is to minimize the number of operations involved in the pretreatment of powder mixture before tableting. Tablet production by direct compression involves only two operations in sequence:- powder mixing and tableting^[1]. The main advantage of direct compression is reduced production cost. As heat and water are not involved, product stability can be improved by this method of tablet production. However, specially designed fillers and binders are normally required which usually are more expensive than the traditional ones^[1-3].

Native starch from various botanical sources have been investigated as pharmaceutical excipients for over four decades^[4]. A lot of efforts have been applied to develop locally produced starches as binders and disintegrants. However, their use as directly-compressible excipients is limited by their poor functional properties of flow, compressibility and compactability. In order to improve these properties, starch modification has been introduced^[5]. The various types of modification are:- heat gelatinization, acid hydrolysis, enzymatic hydrolysis and various forms of chemical modification^[6].

Formerly, direct compression was reserved for tablet manufacture of crystalline chemicals (for example potassium salts) having all the physical characteristics needed for manufacture of good tablets. Today, poorly compressible drugs can be formulated and manufactured via this process with the use of modified starch as a filler-binder^[2].

This study was designed to evaluate the suitability of microcrystalline starch derived from sweet potato for direct compression of relatively high dose poorly compressible drug. Chloroquine phosphate is an example of water soluble drugs with these properties^[2,4].

MATERIALS AND METHODS

Materials

Ipomoea batatas tubers obtained from Zaria - Nigeria and identified by the herbarium unit of University of Abuja, Abuja – Nigeria where voucher number TOYIN-UNIABUJA I26 was allocated to the specimen were used as the starch source. Maize starch B.P, polyvinylpyrrolidone, magnesium stearate, talc, hydrochloric acid and sodium hydroxide were all obtained from BDH chemicals Ltd. Poole-England; while chloroquine phosphate powder was obtained from May and Baker, Lagos-Nigeria.

Extraction of starch and production of microcrystalline starch

The starch extraction from sweet potato tubers was carried out using the method described by Ibezim et al.^[7]. Microcrystalline starch was produced by subjecting the native starch obtained to acid-hydrolysis using the method described by Mohammed et al.^[8]. To 450 g of 36 % w/w starch suspension, 28 ml of 6 N HCl was added and the reaction was allowed to take place at 54 °C for 6 h. The reaction was terminated by adjustment of pH to 6 using 0.1N NaOH and the microcrystalline starch suspension was dehydrated using 800 ml ethanol.

Determination of dilution potential

The dilution potential of the microcrystalline starch was evaluated in comparison with that of avicel[®]. Graded portions of excipient and chloroquine phosphate were compressed at 6.0 kgf using single punch tableting machine (Erweka Apparatebau, Germany). The varying proportions of the excipient and the drug in the 500 mg directly compressed tablets were: 100:0, 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, 10:90 and 0:100. The mechanical strength (crushing strength and friability) of the tablets were determined to establish the maximum proportion of the drug in the mixture that will ensure formation of tablets with acceptable mechanical properties (crushing strength greater than 4 kgf and friability less than 1 %).

Tablet production

Chloroquine phosphate tablets were prepared by direct compression using tablet formula in table 1. The binary

mixture of the direct compression excipients was made by weighing appropriate amount of the microcrystalline starch and microcrystalline cellulose, transferring into a rotor mixer (Forster Equipment Co. England) and mixing for 5 min. The chloroquine phosphate was weighed and added to the binary mixture followed by further mixing for a period of 5 min. Finally, the powder mixture was

lubricated with magnesium stearate over a period of 2 min. Tablets were compressed on a single punch tableting machine (type AR 400, Erweka Apparatebau, Germany) set at a compaction pressure of 6 kgf. The batches were labelled based on the proportion of the microcrystalline starch and microcrystalline cellulose in the binary mixture of direct compression excipients.

Table 1. Tablet formula

Material/tablet	B a t c h e s				
	S0/C100	S25/C75	S50/C50	S75/C25	S100/C0
Chloroquine phosphate (mg)	250	250	250	250	250
Microcrystalline starch (mg)	0.00	93.44	186.875	280.31	373.75
Microcrystalline cellulose (mg)	373.75	280.31	186.875	93.44	0.00
Magnesium stearate (mg)	1.25	1.25	1.25	1.25	1.25
Total weight (mg)	625	625	625	625	625

Table 2. Properties of tablets

Binary mix of MCS:MCC	Mean weight (mm)	Thickn. (mm)	Diam. (mm)	CS (kgf)	FR (%)	DT (min)	CS-FR	CSFR /DT
0:100	630.35 ±2.99	5.08 ±0.04	12.07 ±0.02	12.1	0.48	84.7	25.2	0.29
25:75	621.2 ±2.63	5.07 ±0.062	12.06 ±0.01	11.0	0.63	57.3	17.5	0.30
50:50	624.5 ±2.83	4.99 ±0.06	12.06 ±0.01	9.6	0.79	32.5	12.2	0.37
75:25	638.45 ±4.05	5.24 ±0.01	12.07 ±0.01	9.4	0.96	7.5	9.8	1.30
100:0	637.45 ±5.03	5.24 ±0.01	12.08 ±0.01	9.2	2.08	3.2	4.4	1.38

Abbreviations

MCS = Microcrystalline starch MCC = Microcrystalline cellulose (Avicel[®])

CS = Crushing strength FR = Friability DT = Disintegration time

Evaluation of tablets

A 24-hour period was allowed for the tablets produced to undergo stress relaxation before subjecting them to quality control tests. The tests carried out include:

Uniformity of weight: Twenty tablets were weighed individually from each batch using analytical balance (Explorer E02140, Ohaus Co., U.S.A). The mean weight was computed as total weight divided by 20.

Thickness and diameter measurements: The thickness and diameter of 5 tablets per batch were measured using digital caliper (Z540-1, U.S.A). The mean and standard error of the mean were calculated.

Crushing strength: The crushing strength of five tablets selected at random from each batch was determined using Monsanto hardness tester. The load was gradually increased until the tablet just fractured. The value of the load gives a measure of the crushing strength.

Friability test: Ten tablets were dusted, weighed together and then subjected to abrasion test in Erweka friabilator (Erweka, Germany) operated at 25 rpm for 4 min. The tablets were then dusted properly and weighed again collectively. The friability was calculated as percent loss in weight of the tablets.

Disintegration time studies: The disintegration time of the produced tablets was determined using Erweka disintegration tester, type ZT3. Distilled water thermostatically maintained at 37 ± 0.5 °C was used as the disintegration medium. A tablet was placed in each of the six tubes, of which the lower end was fitted with a gauze disc made of rust-proof wire. The disintegration apparatus was calibrated to operate at thirty cycles per minute. The time for each of the six tablets to disintegrate and pass through the mesh was determined using a stop clock.

The values of the crushing strength, friability and disintegration time were used to compute the CS-FR and CF-FR/DT indices.

Dissolution test: It was carried out using the B.P method [5]. One litre of 0.1 M hydrochloric acid thermostatically maintained at 37.0 ± 0.5 °C was the medium in Erweka dissolution rate apparatus. A tablet was placed in the dry basket and the apparatus was set to a rotational speed of 100 rpm. A 10 ml sample was taken out at 10 min interval with subsequent replacement with equal volume of buffer solution. Withdrawn sample was filtered and 1 ml of the filtrate was diluted to 10 ml. The absorbance of the resulting solution was taken at the maximum wavelength of 343 nm. A graph of percentage drug dissolved was plotted against time.

The data obtained from dissolution test were subjected to Kitazawa et al. analysis [9] which involves the integrated form of Noyes-Whitney equation [10] written as:

$$\ln [C_s/(C_s-C)] = kt \dots\dots\dots(1)$$

where C_s is the concentration of the solute at saturation, C is the concentration at time t and k is the dissolution rate constant. The values of $\ln [C_s/(C_s-C)]$ were plotted against t . Dissolution rate constants k_1 and k_2 which are the slopes of two straight regression lines of each plot; and time t_1 which is the point of intersection of the two lines were calculated for each plot.

Data analysis

The mean values were compared using 1-way analysis of variance (ANOVA). At 95 % confidence interval, p values less than 0.05 were considered significant.

RESULTS AND DISCUSSION

The microcrystalline starch had a dilution potential of 40 % (60 % MCS combined with 40 % chloroquine phosphate). At this proportion, the tablet had a crushing strength of 8.9 Kgf and friability of 0.99 %. The microcrystalline cellulose had a higher dilution potential (70 %). The dilution potential of the MCS is comparable with that of microcrystalline cassava starch which has a dilution potential of 40 % for both metronidazole and ascorbic acid [11]. It is also comparable with those of modified starches of maize, rice, cassava and cocoyam which individually has dilution potential of 40 % for chloroquine phosphate [2]. Therefore, the various batches were formulated to contain 40 % chloroquine phosphate and 60 % binary mixture of MCS and MCC as shown in table 1.

The mean weight of 630.35, 621.2, 624.5, 638.45 and 637.45 mg all fall within the ± 5 % weight variation specified by B. P [5] for tablets of theoretical weight > 250 mg.

The crushing strength of tablets decreased significantly ($P < 0.05$) with increase in the proportion of microcrystalline starch in the binary mixture (Table 2).

Crushing strength of tablet depends on the magnitude of plastic deformation occurring during compression^[12]. Therefore, microcrystalline cellulose may undergo higher plastic deformation than microcrystalline starch.

The friability of tablets increased with increase in the proportion of microcrystalline starch in the binary mix. In other words, increase in the proportion of microcrystalline cellulose led to decrease in friability. This can be attributed to the fact that microcrystalline cellulose forms stronger bond which confers resistance to fracture and abrasion compared to microcrystalline starch^[4]. All the tablets passed friability test except the batch containing 100 % MCS in the binary mixture (Table 2).

The disintegration time decreased with increase in the proportion of microcrystalline starch in the binary mixture. MCS (like other starches) works via the swell-rupture theory^[12]. Therefore, with increase in the proportion of the MCS, more starch particles are available for swelling, exerting high pressure and forcing the tablet to break resulting to faster disintegration of tablet. The difference in the disintegration time of tablets containing different proportions of MCC and MCS is statistically significant ($p < 0.0005$). Only two batches passed the disintegration test. These are : batch S100/C0 containing 100 % MCS as the direct compression excipient and batch S75/C25 containing 75 % MCS and 25 % MCC in the binary mixture. The B. P

specifies 15 min disintegration time for uncoated tablets^[5].

The crushing strength – friability index (CSFR) which is a measure of the mechanical strength of tablet^[13] decreased with increase in the proportion of MCS (Table 2). This shows that MCC confers better strength than MCS. It has been established that microcrystalline cellulose possesses high CSFR index having bonding index of 4.3, strain index of 2.2 and brittle fracture index of 0.04^[14].

Conversely, the crushing strength – friability / disintegration time index (CSFR/DT) increased with increase in the proportion of MCS. Therefore, microcrystalline starch is superior to microcrystalline cellulose in this regard. The higher the value, the better the tablet as it take into consideration the ability of the tablet to disintegrate in an aqueous environment^[13].

The dissolution plots of chloroquine phosphate tablets containing various proportions of MCS and MCC are shown in figure 1. The rate of dissolution increased with increase in the proportion of MCS in the binary mixture (Table 3). This trend is the same as with disintegration time and is in consonance with disintegration – dissolution theory which states that disintegration plays a vital role and determines the area of contact between the drug and dissolution medium^[15].

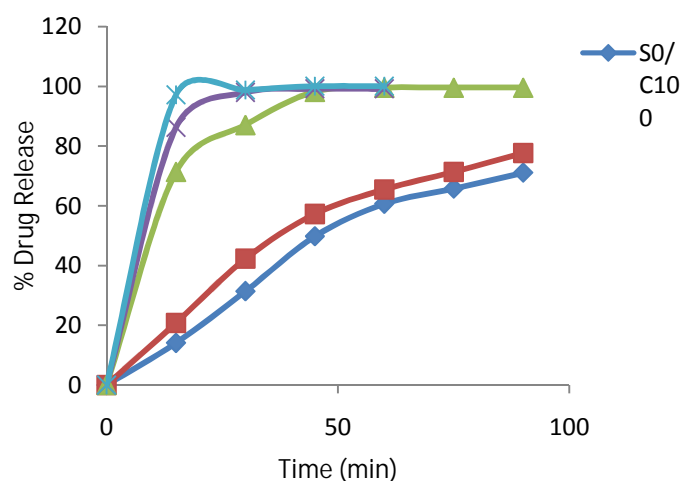


Figure 1. Graph showing dissolution profile of chloroquine phosphate tablets containing various proportions of MCS and MCC.

Table 3. Dissolution characteristics of chloroquine phosphate tablets containing various proportions of MCS and MCC

Proportion of MCS :MCC	D.R _{45min} (%)	t _{50%} (min)	t _{90%} (min)	t ₁ (min)	k ₁ (min)	k ₂ (min)
0/100	45.80	45.27	>90.00	73.82	0.014	0.035
25/75	57.30	37.70	>90.00	60.00	0.017	0.036
50/50	99.20	10.50	33.92	28.33	0.064	0.088
75/25	99.20	8.69	19.74	15.00	0.087	0.113
100/0	100.00	7.72	13.89	-	0.153	0.153

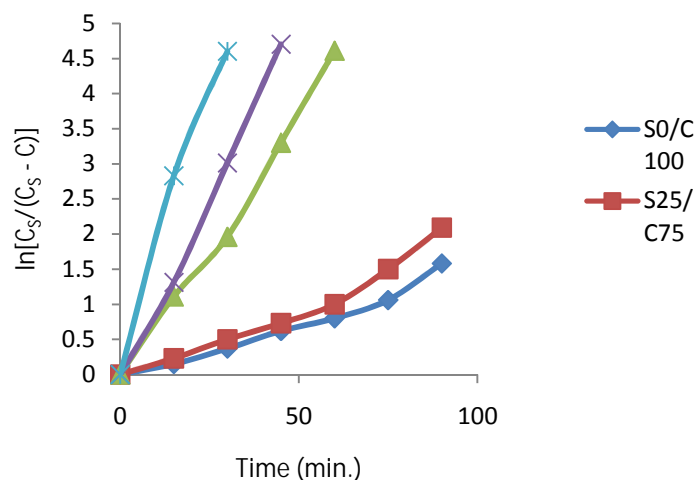
Abbreviations

D.R = Drug release t = Time k = Dissolution constant

The t_{50%} and t_{90%} decreased with increase in the proportion of the MCS. Also D.R_{45min} which is the amount of drug release in 45 min increased with increase in the proportion of MCS. Therefore MCS confers better release effect than MCC. The B. P states that at least 70 % of the drug must be in solution in 45 min^[5]. Only three batches passed the test. These are :- batches S50/C50, S75/C25 and S100/C0 containing 50 %, 75 % and 100 % MCS respectively in the binary mixture of the directly compressible excipients.

Kitazawa plots based on the concentration of chloroquine phosphate at various times of dissolution for the different formulations are illustrated in figure 2. The regression lines of slope K₁ and K₂ intersecting at time t₁ were obtained for all the formulations and shown in table 3. The value of k₂ was higher than that of K₁ for all the formulations showing that the dissolution rate was faster after t₁. It would appear that increase in the surface area of the dissolving particles brought about by the disintegration and deaggregation of the tablets were manifested in the substantial increase in dissolution rate after t₁^[4]. The values of k₁ and k₂ increased with increase in the proportion of microcrystalline starch; implying better dissolution and release effects. Tablets containing pure microcrystalline starch as the directly compressible excipient had a very

high dissolution rate and the curve could not be differentiated into two regression lines. .

Figure 2. Ln[C_s/(C_s-C)] versus dissolution time for chloroquine phosphate tablets.

CONCLUSION

The results of this study showed that while microcrystalline cellulose possesses better mechanical effects than the microcrystalline starch, the microcrystalline starch possesses better release effects. The binary mixture containing MCS and MCC in the ratio 3:1 produced chloroquine phosphate tablets that passed all tests and is suitable for direct compression of relatively high dose poorly compressible drug.

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