Research Article

PRELIMINARY EVALUATION OF CHLOROQUINE PHOSPHATE TABLETS OBTAINED USING DEFATTED *DETARIUM MICROCARPIUM* (SQUILL & SPERR) GUM AS A BINDER

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ABSTRACT

The defatted seed gum of *Detarium microcarpium* (Squill and Sperr),a naturally occurring hydrophilic polymer was investigated as a normal release binder matrix for the formulation of chloroquine phosphate tablet and was compared with sodium carboxymethylcellulose (NaCMC) as a standard. Matrix formulations of chloroquine phosphate were prepared with 1%$^{w}/_{w}$, 2% $^{w}/_{w}$, 3%$^{w}/_{w}$ and 4%$^{w}/_{w}$ of Chloroquine of both the defatted *Detarium microcarpium* seed gum and NaCMC respectively. The granules prepared were standardized by evaluating their micromeritic properties using indices such as bulk and tapped densities, flow rate, angle of repose, Carrs index, Hausners ratio and percentage of fines. Tablets compressed there from were evaluated using the necessary unofficial and official indices (B.P. 2009) for normal uncoated compressed tablets. Results showed that both defatted *Detarium microcarpium* seed gum and NaCMC had good binding properties and tablet hardness which improved with increase in binder concentration (4% > 3% > 2% > 1%$^{w}/_{w}$).

Keywords: Defatted *Detarium microcarpium* gum (DDMG), Sodium Carboxymethylcellulose (NaCMC), micromeritics.

INTRODUCTION

Binders are pharmaceutical excipients which are often employed in the formulation of tablets to impact cohesion on the powder mix and thus improve the granule and tablet charateristics[1-3]. They have the ability to modify or impact cohesiveness to granules by promotion of strong cohesive bonds between particles[4]. They can be used either as solutions or in dry forms depending on the physicochemical properties of other ingredients in the formulation and the method of preparation chosen[5]. Binders could be obtained from natural, semisynthetic and synthetic sources. Gums from plants are mainly long chain, straight or branched chain polysaccharides that contain hydroxyl groups which bond to water molecules[6]. Investigations show that *D. microcarpium* (Family Caesalpinaeceae) is the most common member of its three known species and grows best in the Savannah forest of the drier type[7]. The seed is very hard, wrinkled and swells up on the absorption of water. The fruit is edible and rich in Vitamin C[8]. In Nigeria the seed is used traditionally amongst the different ethnic groups as a delicacy in soup thickening.

Pharmaceutically, the defatted seed gum can serve as a bioadhesive agent in the formulation of muco-adhesive and sustained release tablets and the oil as a matrix for depot injections, emulsions, creams and ointments[9,10].

Chloroquine Phosphate has a wide application as an antimalarial, as it kills the erythrocytic forms of malaria parasites at all stages of development[11]. It also has beneficial effects in rheumatoid arthritis and Lupus erythromatosus on prolonged administration although its use for such is not popular because of its toxic effects on the eye and hair pigments[12] and its use as an antimalarial is on the decline because of resistant plasmodium strains. However, it remains one of the most popular antimalarial remedies because of its fast onset of action.

This study was embarked upon because of the prevailing need to develop cheaper, safer and more accessible materials (binders or adhesives) for local drug production especially in the developing countries of the world such as Nigeria in order to reduce the cost of production.

MATERIALS

Chloroquine Phosphate B.P., NaCMC and Magnesium stearate (May & Baker, England), Lactose (Merck, Germany), Corn starch (BDH, England), Hydrochloric acid and Acetone (Sigma), *Detarium microcarpium* seed (locally sourced). All chemicals were of analytical grade.

METHODS

Gum extraction

Ripe *Detarium microcarpium* seeds sourced locally were properly identified and authenticated at the University of Nigeria, Nsukka herbarium. The seeds were sorted, cured by oven drying at 50^{0}C for 24 hours, pulverized to a coarse powder and was hydrated with water when needed. The gum was precipitated from the slake by repeated application of acetone and air dried. Comminution to fine powder was done with an End runner mill. The powder was put in a Soxhlet apparatus and the oil extracted with Pet-ether (40-60^{0}C) for 8 hours. The defatted *Detarium microcarpium* gum was air dried, milled to fine powder which was collected through a No 180 sieve size and stored in an appropriate container.

Formulation of Chloroquine Phosphate Tablets

Three batches each of one hundred tablets containing 250mg of Chloroquine Phosphate were prepared at

binder concentrations of 1% $^{w}/_{w,}$ 2% $^{w}/_{w,}$ 3% $^{w}/_{w}$ and 4% $^{w}/_{w}$ respectively of both the DDMG and NaCMC. The quantities of the ingredients used are as shown in table 1.

Table 1: Formulation composition of Chloroquine Phosphate tablets ingredients

Batch	Quantity/tablet (mg)			
	I	II	III	IV
Chloroquine Phosphate	250	250	250	250
Lactose	30	30	30	30
Polymer/Binder (%$^{w}/_{w}$)	1	2	3	4
Corn Starch	13	13	13	13
Magnesium Stearate	3	3	3	3
Talc	3	3	3	3

The accurately weighed out and mixed ingredients were wet granulated using mucilages of the DDMG and NaCMC according to the individual batch requirements. The homogeneously blended damp masses formed were screened through a 1.8mm stainless steel sieve and the granules dried in the oven at a temp of 50^{0}C for 6 hours. Further screening of granules through a 1.0mm stainless sieve was done. The talc and magnesium stearate were added extra granularly.

Compression into tablets was done at 46-48 kgf using a 9.0mm punch and die set fitted into an automated F3 Manesty Single Punch tabletting machine. The same procedure was used for all the batches.

EVALUATION OF GRANULES (micromeritic properties)

Determination of Percentage of Fines

A 10g quantity from each batch of granules was further screened through a No. 52 sieve. Both the fines and coarse granules were collected and weighed. The Percentage of Fines was calculated as

$$\frac{\text{Weight fine granules}}{\text{Weight coarse granules}} \times 100\% \text{ ---------(1)}$$

Bulk and Tapped Densities

A 10g quantity of granules was poured freely into a dry 100ml measuring cylinder and the volume (V_b) noted. The cylinder was tapped mechanically using a constant velocity rotating cam on a flat table surface until no further decrease in volume (V_t) was noted.

The bulk and tapped densities were calculated thus:

$$\text{Bulk density} = \frac{\text{Mass / weight of granules (M)}}{\text{Poured volume } (V_b)} \text{ ----------(2)}$$

$$\text{Tapped density} = \frac{\text{Mass / weight of granules (M)}}{\text{Final volume of tapped granules } (V_t)} \text{ ---------- (3)}$$

Hausners ratio and Carrs Index

Both were calculated from the data of bulk and tapped densities thus[13]

$$\text{Hausners ratio} = \frac{\text{Tapped densities } (D_t)}{\text{Bulk density } (D_b)} \text{ ----------(4)}$$

$$\text{Carrs Index, (I)} = \frac{\text{Tapped density } (D_t) - \text{Bulk density } (D_b) \times 100)}{\text{Tapped density } (D_t)}$$

$$= [1 - D_b/D_t] \times 100 \text{ ----------(5)}$$

Angle of Repose and Flow Time of Granules

A 10g quantity of granules was poured into a glass funnel whose orifice is fixed at a height of 15cm above the flat table platform. The time of flow, the height and diameter of granules heap were determined.

The angle of repose (ϕ) was calculated from the formula[14]

$$\phi = \tan^{-1}\left(\frac{\text{Height of Granules heap (h)}}{\text{Radius of granules heap (r)}}\right) \text{ ----------(6)}$$

$$\text{Flow Rate} = \frac{\text{Mass (weight) of granules}}{\text{Flow Time (sec)}} \text{ ----------(7)}$$

EVALUATION OF TABLETS

The tablets were allowed a 24 hours post compression relaxation time before the following tests were conducted.

Hardness Test

Ten tablets randomly selected from each batch were used for this test using a Monsanto Hardness tester. Each tablet was placed between the anvil and spindle of the tester and the knob screwed until the tablet broke and the value read off recorded in Kgf units. The mean of the ten determinations was taken as the value.

Uniformity of weight/mass test

As recommended by the BP, 2009 twenty tablets were randomly selected from each batch and weighed individually using an analytical balance (Adventurer®). The mean, variation were also calculated.

Friability Test

Twenty tablets were randomly selected from each batch, dusted and were collectively weighed (Wo). The tablets were put in a twin drum friabilator (Erweka TAR 200) with each drum containing ten tablets. The drums were rotated at 25 rpm for 4 mins, after which the tablets were collected, dedusted and any broken tablets rejected. The final weight (w) was determined and the abrasion resistance (B) calculated thus[15]:

$$B = 100\left(1 - {}^{w}/_{wo}\right) \quad \text{or} \quad 100\left(\frac{W_o - W}{W_o}\right) \text{ ------ (8)}$$

The mean value from both drums is the value of the test.

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^{0}C as the disintegration media. A minimum of six tablets from each batch was used test and the procedure being as stipulated in the BP 2009 for normal release or uncoated tablets.

Dissolution rate test

The in-vitro dissolution profile for each batch of tablet was determined using the paddle method (BP 2009) with an Erweka DT 600 Dissolution apparatus. Dissolution medium was 900ml of freshly prepared 0.IN Hydrochloric acid maintained at 37.0 ± 1.0^{0}C. Paddle speed was set at 50.0±1.0rpm. Samples of 5ml each were withdrawn at 10mins intervals over a 60 min. period, and absorbances read at 251nm using an SP – 6 – 450 UV/VIS Pye Unicam spectrophotometer. A 5ml volume of 0.1N HCL maintained at 37.0±1.0^{0}C was used to replace the 5ml samples withdrawn for tests. The concentration of the samples were calculated using the Beer Lamberts equation,

$$A = KC \quad \text{---------- (9)}$$

(where A = absorbance, C = concentration and K = Beers constant) from a Standard Beers plot for Chloroquine Phosphate using pure sample.

Beers Plot

A 100mg quantity of pure Chloroquine Phosphate powder was dissolved in sufficient freshly prepared 0.IN HCL to obtain 100ml of stock solution, from where further serial dilutions were made. These were scanned and absorbances read at 251nm using a UV/VIS Spectrophotometer and the slope (Beers constant K) was determined from plot of the absorbance (A) against concentration C in mg%.

RESULTS AND DISCUSSION

Results obtained from the evaluated granules prepared with DDMG as binder matrix compared favorably with granules prepared from NaCMC as binder matrix. These applied to all concentrations of both binders used in the formulations as shown in table 2. Values obtained for angle of repose, flow rate, Carrs Index, Hausners ratio, percentage fines fell within the standard acceptable values required for formulation of quality tablets.

Table 3 shows the results obtained from the evaluation of the tablets formulated with DDGM in comparison with NaCMC. All the batches of tablets passed the uniformity of weight test and deviations obtained complied with BP standards of not more than ± 7.5% for tablets weighing 300mg or more.

Table 2: Micromeritic properties of the Chloroquine Phosphate granules

Name of Polymer	Conc ($\%^w/_w$)	Fines (%)	Flow Rate g/s	Carrs Index %	Hausner's Ratio	Angle of Repose (ϕ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)
DDMG	1	36. 50 ± 1.00	7.30 ± 0.16	3.84 ± 0.01	1.04 ± 0.01	27.10 ± 1.50	0.50 ± .01	0.52 ± 0.01
	2	37 .30 ±1.00	7.16 ± 0.20	11.86 ± 0.01	1.13 ± 0.01	26.50 ± 1.82	0.52 ± 0.11	0.59 ± 0.01
	3	39.40.± 1.00	6.95 ± 0.25	14.28 ± 0.55	1.17 ± 0.55	25.0 ± 1.00	0.54 ± 0.01	0.63 ± 0.02
	4	41.10.± 1.00	6.80 ± 0.10	13.63 ± 0.61	1.16 ± 0.61	25.00 ± 1.00	0.57 ± 0.02	0.66 ± 0.00
NaCMC	1	35.40.± 1.00	6.85 ± 0.10	8.77 ± 0.51	1.09 ± 0.51	25.40 ± 1.00	0.52 ± 0.01	0.57 ± 0.02
	2	38.60.± 1.00	6.00 ± 0.15	10.34 ± 0.02	1.11 ± 0.02	25.80 ± 2.00	0.52 ± 0.01	0.58 ± 0.02
	3	41.50.± 1.00	5.97 ± 0.11	10.94 ± 0.50	1.12 ± 0.50	26.30 ± 1.20	0.49 ± 0.01	0.55 ± 0.00
	4	43.30.± 1.00	5.70 ± 0.20	10.54 ± 0.01	1.27 ± 0.01	26.00 ± 1.50	0.51 ± 0.01	0.65 ± 0.01

Values are mean ± SEM; Levels of significance (Student t – Test) P < 0.5

Table 3: Evaluation of Chloroquine Phosphate tablets

Properties	DDMG				NaCMC			
Binder Conc. (%W/W)	1	2	3	4	1	2	3	4
Mean Tab. Weight (mg)	295±0.50	304±0.02	310±0.02	320±0.02	294±0.01	298±0.62	305±0.06	315 ±0.52
Friability (%)	1.5 ± 0.01	1.0 ± 0.01	0.8± 0.02	0.5 ±0.00	1.7 ±0.01	1.1 ±0.02	1.0 ±0.00	0.8± 0.01
Hardness (kgf)	4.5 ± 0.35	5.3 ± 0.50	6.2± 0.02	7.0± 0.25	4.8± 0.20	5.6 ± 0.40	6.8 ±0.21	7.3± 0.39
Disintegration Time (min)	4.0 ± 0.55	9.0 ± 0.42	8.5 ± 0.7	8.8± 0.02	7.0± 0.03	17.0 ± 0.01	26.0±0.02	34.0±0.01

Values are mean ± SEM, levels of significance (student t – test) P < 0.05

Friability values fell within acceptable criteria <2.00 and was found to decrease as the binder concentration increased.

The mean hardness values of the tablets for all the batches fell within the acceptable criteria for standard compressed tablets (4.0 to 7.0 kgf). The disintegration time for all the DDGM matrix tablets batches fell within the acceptable official criteria of ≤ 15 mins., with values increasing as the binder concentration increased (ie 4% > 3% > 2% > 1%) whereas values for NaCMC ranged from 6 – 34 mins. Therefore tablets formulated with DDGM performed better in terms of disintegration.

The dissolution data (Fig 1) shows that matrix tablets formulated with defatted *Detarium microcarpium* gum had dissolution profile in all the batches with more than 70% of the total drug content available for absorption within 60 mins. The availability of the dissolved drug decreased with increase in binder concentration. 1% $^w/_w$ had the least release performance.

Tablets formulated with NaCMC (Fig 2) also had a release rate of more than 70% dissolution within 60 mins. However a comparison of both binders shows that defatted Detarium gum had a better release rate profile for all the batches of the tablets except for tablets formulated with 1% $^{w}/_{w}$ NaCMC.

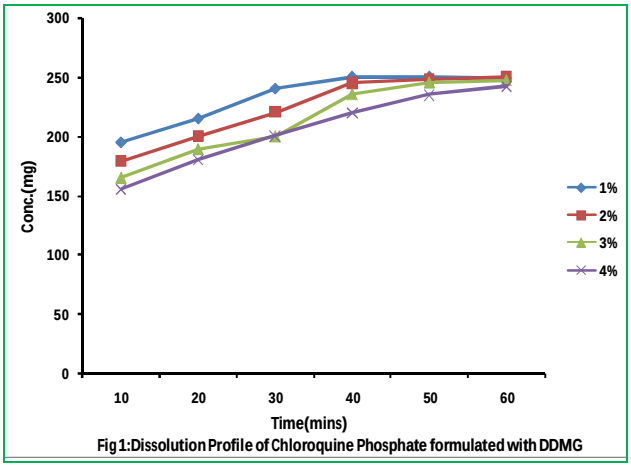

Fig 1:Dissolution Profile of Chloroquine Phosphate formulated with DDMG

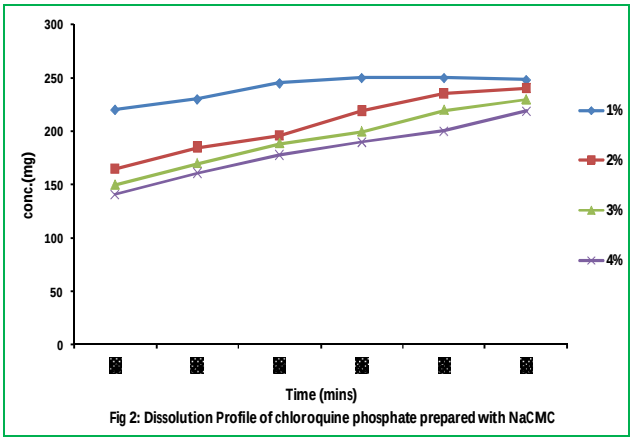

Fig 2: Dissolution Profile of chloroquine phosphate prepared with NaCMC

CONCLUSION

Though DDMG showed an insignificant better binding characteristics,all indices used for evaluation showed a favourable competition with NaCMC and the tablets produced met with acceptable B.P standards. Therefore DDMG can be recommended for use as an alternative to NaCMC or other binders in the formulation of normal release tablets.

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