Research Article

Evaluation of Three Grades of Binders as Matrices in Chloroquine Phosphate Tablets

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ABSTRACT

Three hydrophilic polymers as binder matrices in the formulation of chloroquine phosphate tablets were evaluated. *Detarium microcarpium* seed gum (DMSG), a natural gum was compared with acacia (a natural gum) and sodium carboxymethylcellulose (NaCMC), a synthetic gum as matrices in the formulation of conventional release chloroquine phosphate. Both acacia and NaCMC served as standards. Chloroquine phosphate tablets were formulated with 1% w/w, 2% w/w, 3% w/w and 4%w/w of DMSG, acacia (AC) and NaCMC using the wet granulation method. Granules prepared on evaluation showed flow rate of 5.80 ± 0.22 g/s to 10.40 ± 0.00 g/s, angle of repose values of 26.00 ± 0.05 to 30.05 ± 0.10°, Carrs Index values of 3.64 ± 0.00 to 7.94 ± 0.01, and Hausner's quotient values 1.05 ± 0.00 to 1.09 ± 0.01 for all batches. The tablets obtained from the compressed granules were evaluated for uniformity of weight, hardness, friability, content of active ingredient and *in vitro* dissolution profile. Tablets were found to conform to British Pharmacopoeia standards. DMSG was found to compare favorably with both AC and NaCMC.

Keywords: *Detarium microcarpium* seed gum (DMSG), acacia (AC), sodium carboxymethyl cellulose (NaCMC), chloroquine phosphate.

INTRODUCTION

The inability of some powders in their native form to compress into firm tablets on the application of pressure makes it pertinent that binders be incorporated into such formulations. Binders do not only impact cohesion on a powder mix but also improve both granule and tablet characteristics[1 – 3]. The choice of a binder and its method of incorporation depend to a large extent on their compatibility with the physico-chemical properties of other excipients /active ingredients in the formulation. The form, quantity and method of incorporation can lead to either a normal release or sustained release formulation. Gums can be defined as polymeric materials that can be dissolved or dispersed in water to give viscous solutions or dispersions[4]. Natural gums are gelatinous substances exuded by plants and is composed of complex organic acids or its salts which on hydrolysis yield sugars[5]. Such sugars are mainly long, straight or branched chained that contain hydroxyl groups that can bond to water molecules[6]. *Detarium microcarpium* (Family : Caesalpinaceae) is a dry savannah forest plant whose seed is used traditionally amongst the different ethnic groups in Nigeria as a soup thickener and delicacy[7]. Investigations show that its seed gum can serve as a bioadhesive agent in the formulation of conventional release and sustained release tablets, and its oil as a matrix for depot injections, creams and emulsions[1]. Acacia is a natural gum that has wide pharmaceutical application as binder, suspending agent, or emulsifier[8]. Sodium carboxymethylcellulose (NaCMC), is a semi synthetic gum that has been widely used as binder, suspending agent, and emulsifier in the pharmaceutical industry[9]. Both AC and NaCMC were used as standards. Chloroquine phosphate is an antimalarial that has a fast onset of action. It is known to combat and destroy the erythrocytic forms of malaria at all its stages of development[10] although incidences of resistance by some strains of plasmodium parasite as well as unpleasant side effects have made the artemisinin combination therapy (ACT) group of drugs more popular in this decade.

This study was embarked upon because of the dire need to develop local raw materials and increase local content in the pharmaceutical and food industry in Nigeria. This would reduce manufacturing costs and impart positively on the country's economy.

MATERIALS AND METHODS

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), Acacia, Sodium carboxymethylcellulose (NaCMC). 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 and passed through a No 180 sieve size. The gum was stored in an appropriate container.

Formulation of Chloroquine Phosphate Tablets

Table 1 shows the ingredients used for the formulation. Four batches each of one hundred tablets containing 250 mg of chloroquine phosphate and tablet target weight of 300 mg ± 7.5% were prepared using 1%, 2%, 3% and 4% w/w each of DMSG, AC and NaCMC as matrices. Accurately weighed powders were triturated to a homogeneous blend in a wedgewood mortar and wet granulated using mucilages of DMSG, AC and NaCMC in sufficient quantities to form wet damp masses. These were screened through a 1.8 mm stainless steel sieve and the resultant granules were dried in an oven (Mermett®, England) at 60˚C for 6 h. The dried granules were further screened through a 1.0 mm stainless sieve. Magnesium stearate and talc were added to the granules and tumble mixed in a powder bottle for the 10 min.

Table 1: Formulation composition of chloroquine phosphate tablets

Ingredients	Quantity / Tablet (mg)			
	Batch I	Batch II	Batch III	Batch IV
Chloroquine Phosphate	250	250	250	250
Lactose	25	25	25	25
Polymer/Binder ($\%^{w}/_{w}$)	1	2	3	4
Corn Starch	18	18	18	18
Magnesium Stearate	3	3	3	3
Talc	3	3	3	3

The powder mix (granules) were compressed into tablets using a single punch tabletting machine (Manesty F-3, England) fitted with a 9.0 mm biconcave punch and die set. Target tablet weight was 300 mg ± 20 mg. Compressional force was kept constant as much as possible by setting compression pressure at 43 – 46 units of the machine during tabletting.

Some Micromeritic Properties of Chloroquine Granules

Flow Rate and Angle of Repose

A 5.0 g quantity of granules was freely poured into a glass funnel with orifice and base diameters of 1.1 cm and 5.5 cm respectively. It was allowed to flow freely under gravity from the funnel orifice height of 10.0 cm above a flat surface. The time of flow of granules and the height of the granule heap formed were determined. The flow rate and angle of repose were calculated as [11].

Flow Rate = M / F.T. (sec) 1

Angle of Repose (θ) = $\tan^{-1}$ (h/r) 2

Where M = mass of granules, h = height of granules, r = radius of granules heap, and F.T. = flow time of granules.

Bulk and Tapped Density

A 5.0 g quantity of granules was freely poured into a dry 100 mL glass measuring cylinder kept on a flat surface and the volume (V_b) noted. The cylinder was tapped mechanically using a constant velocity rotating cam on a flat surface until no further decrease in volume (V_t) was noted. The bulk and tapped densities were calculated as below:[12]

Bulk density (D_b) = M / V_b 3

Tapped density (D_t) = M / V_t 4

Hausner's quotient and Carr's Index

Both Hausner's quotient and % compressibility (Carr's Index) were calculated from Carr's equation [13] using the values of D_b and D_t

Hausner's quotient (H.Q.) = D_t / D_b 5

Carr's Index = D_t - D_t / D_b x 100

= {1 – Db /Dt } x 100 6

Evaluation of Tablets

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

Uniformity of weight/mass test

Twenty tablets randomly selected from each batch of tablet formulation were individually weighed using an analytical balance (Adventurer®). The mean, standard deviation, and coefficient of variation were also calculated.

Hardness Test

The tablet crushing strength was determined on a Monsanto Hardness tester. Ten tablets randomly selected from each batch were used. Each tablet was placed between the anvil and spindle of the tester and the knob screwed until the tablet broke and the value recorded in kg/F units. The mean of the ten determinations was taken as the value [14] .

Friability Test

Ten tablets randomly selected from each tablet batch were after dedusting and weighing collectively used for the test in a friabilator (Erweka TAR 200). The drum was rotated at 25 rpm for 4 mins after which the tablets were collected, dedusted and any broken tablets rejected. The initial weight (w_o) and final weight (w) were determined and the abrasion resistance (B) calculated thus[15]:

B = 100 (1 – $^{w}/_{wo}$) or 100 [w_o – w/w_o] 7

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 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.

Determination of wavelength of maximum absorption (λ max) and 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. The λ max of 251 nm was determined from the scan of a 1 mg% solution using a UV/Vis spectrophotometer. Solutions of 0.2, 0.4, 0.6, 0.8, and 1.0 mg% were scanned at 251 nm and absorbances read, and the slope (Beers constant K) was determined from the plot of the absorbances (A) against concentration (C) in mg % using the Beer Lamberts equation,

$$A = KC \quad \ldots\ldots 8$$

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

Assay of tablet

Each batch of tablets was assayed for content of active ingredient using the BP 2009 method[16]. The *in-vitro* dissolution profile for each batch of tablet was determined using the BP 2009[16] paddle method with an Erweka DT 600 dissolution apparatus. Dissolution medium was 900ml of freshly prepared 0.IN Hydrochloric acid maintained at 37.0 ± 1.0 °C. Paddle speed was set at 50.0 ± 1.0 rpm. Samples of 5ml each were withdrawn at 5 min. intervals over a 60 min period, and absorbances read at 251 nm using an SP – 6 – 450 UV/Vis Pye Unicam spectrophotometer. A 5ml volume of 0.IN HCL maintained at 37.0 ± 1.0°C was used to replace the 5ml samples withdrawn for tests. The concentration of the samples were calculated from equation 8.

RESULTS AND DISCUSSION

Micromeritic evaluation of chloroquine phosphate (Table 2) show that for all granule batches DMSG had good and comparable values with those of AC and NaCMC as binder matrices. Flow rate of granules increased from 6.75 ± 0.15 g/s to 8.00 ± 0.01 g/s as the polymer concentration increased from 1% to 4 % w/w for DMSG. Similar behaviors were observed with AC and NaCMC. Other indices such as Carr's Index values, Hausner's quotient, angle of repose, bulk and tapped densities were indicative of good flowing granules that would enhance the production of high quality tablets.

In vivo tablet evaluation results as shown in Table 3, show that all tablet batches passed the weight variation tests for uncoated tablets[17]. Friability values were ≤ 1.0 % for all tablet batches except at 1 % w/w DMSG and decreased with increase in polymer concentration. Tablet hardness values were within conventionally acceptable range (4 – 7 kg/F) for uncoated tablets[18 - 20].

Table 2: Some micromeritic properties of chloroquine phosphate granules

Name of polymer	Conc (% w/w)	Flow Rate (g/s)	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's quotient
DMSG	1	6.78 ± 0.15	30.05 ± 0.10	0.58 ± 0.15	0.61 ± 0.10	4.92 ± 0.01	1.05 ± 0.01
	2	6.89 ± 0.10	28.80 ± 0.05	0.55 ± 0.10	0.59 ± 0.01	6.78 ± 0.03	1.07 ± 0.01
	3	7.25 ± 0.25	27.30 ± 0.02	0.53 ± 0.10	0.56 ± 0.01	5.36 ± 0.15	1.06 ± 0.01
	4	8.00 ± 0.01	25.00 ± 0.05	0.52 ± 0.05	0.56 ± 0.01	7.14 ± 0.01	1.08 ± 0.00
Acacia	1	9.00 ± 0.00	28.10 ± 0.90	0.59 ± 0.00	0.62 ± 0.00	4.84 ± 0.01	1.05 ± 0.00
	2	10.00 ± 0.00	27.05 ± 0.50	0.59 ± 0.01	0.60 ± 0.05	5.00 ± 0.01	1.05 ± 0.01
	3	10.40 ± 0.00	26.55 ± 0.10	0.56 ± 0.01	0.59 ± 0.00	6.78 ± 0.01	1.05 ± 0.01
	4	10.62 ± 0.01	26.00 ± 0.50	0.53 ± 0.02	0.55 ± 0.02	3.64 ± 0.00	1.05 ± 0.01
NaCMC	1	5.80 ± 0.22	26.90 ± 0.80	0.60 ± 0.02	0.64 ± 0.01	6.25 ± 0.01	1.07 ± 0.01
	2	6.35 ± 0.30	26.50 ± 1.00	0.58 ± 0.01	0.63 ± 0.01	7.94 ± 0.01	1.09 ± 0.01
	3	6.95 ± 0.10	26.25 ± 1.00	0.55 ± 0.01	0.59 ± 0.01	6.78 ± 0.01	1.07 ± 0.11
	4	7.80 ± 0.20	25.55 ± 0.40	0.53 ± 0.02	0.56 ± 0.01	5.36 ± 0.00	1.06 ± 0.01

Values are mean ± SEM (levels of significance (student t test) p ≤ 0.5

Table 3: Some *In vitro* Chloroquine phosphate tablet properties

Name of polymer	Conc (% w/w)	Weight (mg)	Friability (%)	Hardness (kg/F)	Disintegration time (min)
DMSG	1	298.00 ± 0.50	1.08 ± 1.00	5.60 ± 1.50	5.00 ± 0.31
	2	305.00 ± 0.15	0.70 ± 0.80	6.02 ± 1.00	8.00 ± 0.25
	3	307.00 ± 0.20	0.45 ± 0.50	6.80 ± 1.20	10.00 ± 0.10
	4	313.00 ± 0.20	0.20 ± 0.00	7.50 ± 1.00	15.00 ± 0.50
Acacia	1	290.00 ± 0.30	0.95 ± 0.20	5.80 ± 0.70	7.00 ± 0.41
	2	296.00 ± 0.10	0.67 ± 0.10	5.95 ± 0.90	7.80 ± 1.20
	3	302.00 ± 0.15	0.33 ± 0.30	7.00 ± 0.50	7.85 ± 0.20
	4	310.00 ± 1.00	0.18 ± 0.50	7.60 ± 0.60	9.80 ± 0.20
NaCMC	1	295.00 ± 0.60	1.00 ± 0.50	5.50 ± 0.15	6.00 ± 0.30
	2	298.00 ± 0.40	0.82 ± 0.00	6.25 ± 0.20	10.00 ± 0.30
	3	308.00 ± 0.25	0.53 ± 0.10	7.30 ± 0.25	13.00 ± 0.15
	4	317.00 ± 0.20	0.22 ± ±0.15	8.00 ± 0.05	28.00 ± 0.10

Disintegration test values were ≤ 15 min for all batches of tablets except for batches containing 3% and 4% w/w NaCMC. Thus most tablets batches conformed to BP acceptable standards[21]. Also both hardness and disintegration increased with increase in the binder concentration. Figs. 1 – 3 show the dissolution profile of chloroquine phosphate in DMSG, AC, and NaCMC.

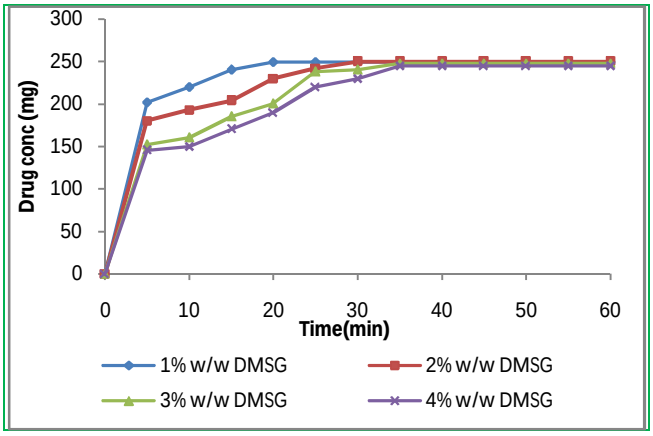

Figure 1: Dissolution Profile of chloroquine phosphate tablets formulated with DMSG

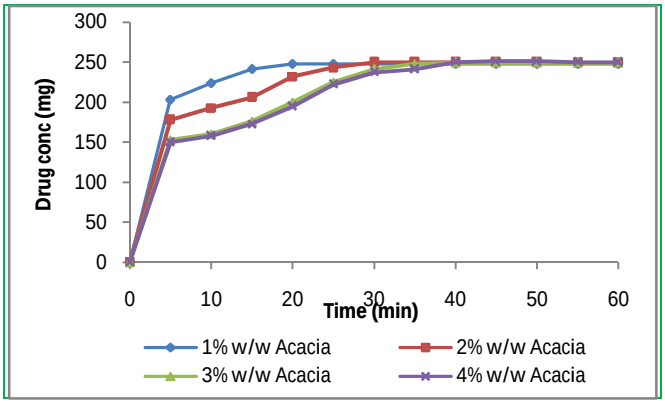

Figure 2: Dissolution Profile of chloroquine phosphate tablets formulated with acacia

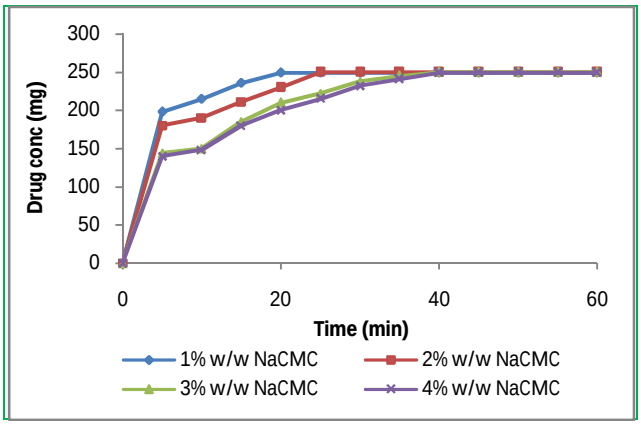

Figure 3: Dissolution profile of chloroquine phosphate tablets formulated with NaCMC

There was a gradual retardation of drug release as the binder concentration increased. All batches exhibited more than 220 mg (88%) drug release at 40 min which complies with BP specification for conventional release tablets [22]. Drug was maximally released at 20, 30 and 35 min for 1%, 2%, and both 3% and 4% w/w DMSG respectively. However drug release was fastest in acacia and DMSG than NaCMC at all concentrations employed.

CONCLUSION

The three gums/binders evaluated showed good granule characteristics and tablets compressed from such granules showed good tablet characteristics at all concentrations of the binders used. The dissolution profile of the three binders conformed to BP specification for uncoated tablets[22]. *Detarium microcarpium* seed gum (DMSG) compared favorably with AC and NaCMC and is recommended as a possible replacement for both binders in the formulation of normal release chloroquine phosphate tablets. This would increase local content input of pharmaceutical raw materials in the local industry and thus impact positively in the Nigerian economy.

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