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Research Article

EFFECT OF CONCENTRATION ON THE RELEASE PROPERTY OF *KHAYA SENEGALENSIS* GUM IN CHLOROQUINE PHOSPHATE TABLET FORMULATION

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ABSTRACT

Khaya gum gotten from the bark of *khaya senegalensis* was used as disintegrant in chloroquine phosphate tablets and was evaluated and compared to maize starch and microcrystalline cellulose. Batches of 5, 7.5 and 10%w/w were formulated for the three excipients.

Khaya gum was observed to swell to about ten (10) times its weight in water. The granules of all the batches were observed to have good flow properties. Tablets of all the batches containing *khaya* gum were observed to be softer, disintegrated faster and had greater dissolution than the tablets of the MCC batches. An increase in the concentration of the *khaya* gum led to slower disintegration of the tablets. The dissolution profile showed that an increase in the concentration of *khaya* gum led to a retardation in the release of the drug and the effective concentration for fast disintegration and quick drug release was found to be 5%w/w.

The mechanism of disintegration and drug release was attributed to the gum's water uptake and swelling capacity.

Keywords: Disintegrant, gum, *khaya senegalensis*, chloroquine phosphate.

INTRODUCTION

Pharmaceutical excipients control physicochemical properties as well as the release profiles and availability of the drug in the system. It has been reported that 83% of the excipients used to manufacture drugs in Nigeria are imported[1]. This great dependency brings about great use up of the Nigeria foreign exchange reserves thus bringing about an increase in production costs and prices of drugs. Therefore it has become necessary to source for excipients that are cheap, readily available and meet the quality of pharmaceutical grade excipients. Plant products serve as an alternative to synthetic products because of local accessibility, eco-friendliness and lower prices compared to the imported synthetic products. Most researches carried out on the utility of plant-based materials as pharmaceutical excipients have been centered on polysaccharides and proteins due to their ability to provide a wide range of materials and properties based on their molecular structures[2].

Khaya senegalensis is genus specie of tree in the mahaogany family *meliaceae*. It has been recommended for planting in the Sahel to provide shade and fodder and to improve pasturage. It is considered useful in the fight against desertification[3]. This tree can be found in most part of Africa and is especially found in the northern parts of Nigeria; Katsina, Kaduna and in other states in Nigeria like Oyo and Anambra.

The timber of *khaya* is the only timber widely accepted as mahogany besides that of the true mahogany of the genus *swieteria*. In West Africa, Fulani herdsmen prune the tree during the dry season to feed their cattle. The wood was used for making drums and is still used in making canoes, high grade carpentry and joinery, wide-scale use for furniture, gun-stocks, boat-construction and conversion into plywood and veneers[4]. The stem-bark and leaves have been used in northern Nigeria in form of decoction and concoction for the cure of mucus diarrhoea, syphilis, pyrexia and malaria fever.

Khaya gum is gotten from the bark of *Khaya senegalensis* and is a pale greenish yellow to golden yellow gum. *Khaya senegalensis* gum is a polysaccharide with a galactan in which the 1,-3 linked β –D galactopyranosyl residues are concentrated in the inner chain. It has also been reported to contain both D-glucoronic and D- galatoronic acid. Analysis of the gum showed that approximately 5% was in the free acid form and the remainder was largely the calcium salt[5]. It has been said that methylation of the gum and other study of the gum reveal many similarities to acacia gum[6]. It is slightly soluble in water and this is a peculiar characteristic of the meliaceae gum producers. *Khaya* gum swells to about ten times its original weight in water and it has been reported that swelling of the linear polymer without dissolution is an indication that it is crossed linked[7]. The swelling ability of *khaya senegalensis* gum may provide potential for it use as a disintegrant in tablet owing to its psuedoplastic and thixotropic properties[8].

MATERIALS AND METHODS

Materials

Chloroquine phosphate B.P, magnesium stearate, microcrystalline cellulose, talc powder (BDH chemicals Ltd, Poole, England). Absolute Ethanol, Diethyl ether (sigma-Aldrich, Germany). Double strength chloroform water, Gelatin (May and Baker Ltd, Dagenham, England) and Khaya gum (prepared in the department of Pharmaceutics, Ahmadu Bello university, Zaria).

Khaya senegalensis gum was obtained from the trunk of *Khaya* trees grown around Samaru, Zaria town of Kaduna state, Nigeria. The gum was collected around mid-November during the day time. The plant material was identified, authenticated and assigned a voucher number 872 in the herbarium of the department of Biological sciences of Ahmadu Bello University, Zaria, Nigeria.

The crude gum was dried in an oven at 40^{o}c for 2hrs and size reduced using a blender. It was hydrated in double strength chloroform water for five days with intermittent stirring to ensure complete dissolution of the gum and then strained through a 75µm sieve to obtain particulate free slurry which was allowed to sediment. Thereafter, the gum was precipitated from the slurry using absolute ethanol, filtered and defatted with Di-ethyl ether. The precipitate was dried in the oven at 40^{o}c for 48 hours. The dried flakes were pulverized using a blender and stored in an air tight container.

Methods

Physicochemical properties of gum

Solubility

The extracted gum was evaluated for solubility in cold and hot water, acetone, chloroform and ethanol. One (1g) of the gum was added to 50ml of the mentioned solvents and left overnight. Twenty-five (25ml) of the clear supernatant was heated to dryness over a water-bath in an evaporating dish. The solubility was expressed in

terms of "parts" representing the number of milliliters (ml) of the solvent in which 1 g of the solid is soluble.

Moisture sorption capacity

Two grams (2g) of the powder (W) was weighed and put into a tanned petridish. The sample was then placed in a dessicator containing distilled water at room temperature and the weight gained by the exposed sample at the end of a five day period (Wg) was recorded and the amount of water absorbed (Wa) was calculated from the weight difference. Wa=Wg-W…..2

Flow indices

Bulk density was measured by taking accurately weighed powder into a graduated cylinder of tapped density apparatus and the volume was measured and recorded as bulk volume. The cylinder was tapped until powder bed volume reached a constant value and the volume was recorded as tapped volume. The bulk density was calculated using the equation mass/bulk volume; tapped density= mass/tapped volume; and compressibility index= [tapped density-bulk density]/tapped density. Also, the Hausner's ratio was calculated as tapped density/ bulk density. The angle of repose was used to characterize a flow property of powder material and it was computed as $\tan^{-1}\frac{h}{r}$, where h=height of heap and r=- radius of heap.

Preparation of chlorquine phosphate granules and tablets

Chloroquine phosphate granules containing 250mg chloroquine phosphate where prepared with *khaya* gum and microcrystalline cellulose as disintegrant at 5%, 7.5% and 10%w/w (Table I). The wet granulation method of massing and screening was employed in the formulation of the granules. The required quantities of chloroquine phosphate powder and disintegrants were weighed and mixed with the binder solution (gelatin 5%w/w). The resulting masses were screened through a 1.7mm mesh size and then dried for 1hour at 40oc in an oven and then screened again through a 0.88mm mesh size and then dried to constant weight. The granules were then mixed with 1.1g of extragranular excipient (1g of talc and 0.1g of magnesium stearate) and then compressed into tablets at 4.5metric tonnes using the Erweka type G. M B. H machine. The tablets produced were stored for 24hours before the tablet evaluation.

Table 1: Shows the formula for preparing chloroquine phosphate granules and tablets

Ingredients (g)	Batches					
	KGa	MCCa	KGb	MCCb	KGc	MCCc
Chloroquine phosphate	25	25	25	25	25	25
Lactose	18.9	18.9	17.65	17.65	16.4	16.4
Khaya gum	2.5	-	3.75	-	5.0	-
MCC	-	2.5	-	3.75	-	5.0
Gelatin	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	0.1	0.1	0.1	0.1	0.1	0.1
Talc	1.0	1.0	1.0	1.0	1.0	1.0

Key: KGa= *Khaya* gum, MCC= microcrystalline cellulose, a, b, c= 5.0%w/w, 7.5%w/w, 10.00%w/w.

Granule analysis

The granule analysis carried out were moisture content and flow indices determination (bulk, tapped densities, compressibility index, Hausner's ratio and angle of repose).

Characterisation of tablets

The following tests were carried out to evaluate the tablets formulated: Tablet thickness, Weight uniformity, Crushing strength, friability, Disintegration test, Dissolution test.

Calibration curve for chloroquine phosphate

A stock solution of 100mg of Chloroquine phosphate was dissolved in 100ml of 0.1 N HCL. Various dilutions of the stock were made and the absorbances of the various dilutions were taken at 343nm using a UV spectrophotometer. A plot of the absorbance, A against concentration, C was made and the calibration curve was determined from the slope of the graph.

Dissolution test

The dissolution rates of the Chloroquine phosphate were determined using the DGN multipurpose drug test machine (China) Shanghai. The dissolution media was 0.1N HCL at 37 ± 0.5ºC. Samples (10ml) were withdrawn at certain intervals and these were replaced with equivalent volume of the dissolution media. The withdrawn samples were diluted 1 in 10 and analysed at a wavelength of 343nm using the B.Bran Scientific Spectrum Lab 752s spectrophotometer.

RESULTS AND DISCUSSION

The percentage yield was 64%w/w**.** This gives the amount of purified *khaya* gum obtained from the crude gum. This could be due to the nature of the gum as it formed two phase: the supernatant and the residue (marc) which may not be readily soluble after soaking in the extraction medium. The organoleptic properties of *khaya* gum shown in Table II describes the gum as yellowish to brown in colour, coarse in texture, mildly acidic in taste and possess a cocoa-like smell.

The sparing solubility of *khaya* gum in water may be due to the linear nature of the polymer which has been reported to be less soluble compared with branched molecules[9]. The slight solubility of *khaya* gum in water is most likely perculiar to members of the meliaceae gum producers. For example it has been reported that *khaya grandifoliola* has only limited solubility in water but dissolves in sodium carbonate with removal of calcium ions[5]. The gum was not soluble in acetone, chloroform and ethanol because organic solvents precipitate gums[8]. The swelling capacity of *khaya* gum was observed to be high and this could be an indication that the gum contains linear polymers which is an indication that the gum is a cross-linked polymer[7]. The cross-links tie the macromolecular chains together by primary covalent bonds thereby transforming each particle into a single giant molecule.

Table 2: Organoleptic and physicochemical properties of *khaya* gum.

Parameters	Results
%Yield	65
Colour	Yellowish-brown
Odour	Cocoa smell
Texture	Coarse
Taste	Mild Acidic
Swelling Capacity	10
Moisture Sorption Capacity	42.8%

The swelling ability of polymers enables them to absorb water and they are suitable for use as disintegrants because they form hydrogels. The moisture sorption studies indicates that when the gum is stored in damp environment, the gum quickly gets hydrated but has the ability to rapidly loose such water molecules in the presence of desiccants. This property makes the gum susceptible to microbial and physicochemical deterioration.

Analysis of granules

The range of angle of repose obtained for all the batches of granules was 22.78°-26.70° and this indicates that the granules possess good flow property as low values of < 25 ⁰ are indicative of monosize spherical particles with smooth surfaces which flow extremely well[10]. Good flow property indicates that the granules would fill the die uniformly and produce a uniform weight of tablets.

The result of the moisture content of the granules was observed to be similar at the concentrations used (Table III). The flow rate of granules which is a measure of flowability has been said to be necessary for successful tableting[10]. The flow rates were observed to increase with increase in disintegrant concentration and this shows that an increase in concentration improved the flow of the granules. The flow rates of KG formulations were slightly less than those of MCC and this implies that MCC formulations would flow better than those of KG (Table III).

Table 3: Properties of chloroquine phospahte granules

Parameters	Batches					
	KGa	MCCa	KGb	MCCb	KGc	MCCc
Angle of Repose(⁰)	26.07	23.54	26.7	22.78	26.15	24.8
Bulk Density(g/cm^3)	0.52	0.48	0.51	0.51	0.46	0.51
Tapped Density(g/cm)	0.57	0.54	0.57	0.56	0.53	0.58
Flow Rate(g/sec)	4.68	4.94	4.83	4.87	4.80	5.13
Moisture Content(%)	7	4	6	6	3	3
Hausner's Ratio	1.10	1.13	1.12	1.10	1.15	1.14
Carr's Index	8.77	11.11	10.53	8.77	13.21	12.07

The percentage compressibility (Carr's index) and Hausner's ratio express the difference between the bulk and tapped densities and the ratio of tapped to bulk density. These indices give a measure of the ability of a material to be reduced in volume under pressure and the indication of the likely flow behaviour of granules when subjected to compression forces to form compact mass. The higher the Hausner's ratio, the greater the propensity of the granules to form a compact mass.

The Carr's indices of the MCC granules were observed to decrease with increase in concentration while those of KG granules increased slightly with increase in concentration indicating that MCC produced granules with slightly better flow property than KG This agrees with the report that low compressibility index predicts better flow of the granules[11]. The Hausner's ratio increased as disintegrant concentration increased but not beyond 1.2. Generally the granules of both formulations had good flowing property.

Tablet evaluation

The mean uniformity of weight of the tablets produced (Table IV) were within the acceptable limits of the official specification[12] which says that not more than two (2) tablets should deviate from the mean by 10%. This therefore implies there was uniform filling of the die as a result of good flow characteristics of the granules.

The result of the tablet thickness obtained shows that tablet thickness varied with the varying mean weight thereby giving no particular trend. Tablet thickness is said to vary with no change in weight because of difference in the density of the granules, pressure applied to the tablets as well as speed of tablet compression[13].

The crushing strength of tablets is used as a measure of the cohesiveness or structural strength of a tablet as provided by the binding agent; gelatin (in this case) and other forces that interplay in the formation of a compact mass during formation of a tablet. As shown in Table IV tablet crushing strength was observed to increase as the concentration of each disintegrant increased. This could be due to more particle-particle contact points of the disintegrants as well as with the particles of the drugs which help create more solid bonds; the increase could also be attributed to the intragranular disintegrants which are starch, cellulose and gum. These when wetted may have had a fraction turned into mucilage and gels thereby acting as a binder[14].

From Table IV, there was a general decrease in the friability of the tablets with increase in disintegrant concentration. The resistance of a tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before use has been attributed to its hardness. In both formulations irrespective of the disintegrant concentration used, friability index remained well within 1%w/w, an upper level of acceptability for pharmaceutical products.

MCC formulations were observed to have the higher crushing strength than those of KG formulations due to its characteristic high crushing strength-friability ratio. MCC has been observed to have a bonding index of 4.3, strain index of 2.20 and brittleness index of 0.04 which indicates superior compaction[15]. This could explain the reason for the hardness of the tablets and therefore its high crushing strength-friability ratio. The disintegration time was observed to increase with increase in disintegrant concentratio. It was also observed that for both formulations, the tablets slowly eroded rather than break into smaller fragments. This increase in disintegration time with increase in disintegrant concentration could also be due to the swellable nature of KG in aqueous medium which upon hydration form a gel-like barrier around the granules and or the tablet core, thereby retarding fast disintegration[16].

Table 4: Tablet properties

Batch	Mean tablet weight (mg)	Tablet thickness (mm)	Tablet friability (%)	Tablet hardness (kgf)	Tablet disintegration (mins)
Kga	495.40	4.296	1.00	7.30	13.25
Kgb	494.75	4.062	0.80	10.63	19.48
Kgc	496.55	4.172	0.308	11.58	20.23
Mcca	491.80	4.136	0.993	12.50	22.24
Mccb	497.95	4.112	0.67	13.00	21.18
Mccc	500.65	4.106	0.33	14.5	46.52

Conventionally, uncoated tablets are required to disintegrate within 15min but on the basis of this, only the tablets containing 5% KG could be considered acceptable. Hence the correlation between tablet parameters such as crushing strength, friability and disintegration time is dependent on the type of disintegrant.

It was observed that 5% w/w KG formulations had a faster initial release of the drug than with the other concentrations of KG and MCC (Fig. I). The lower release of the drug from the highest concentration (10%w/w) of KG (Fig. III) could be attributed to the gel-forming nature of the gum upon hydration which acts as an obstacle to quick release of the drug. The 5%w/w KG formulations were able to give a desirable initial burst of drug and steady release to the end of the dissolution time. However, all the KG formulations released the specified amount of drug (70%) within the specified time (30mins[12] but the MCC formulations did not meet this specification (Fig. I, II, III).

It has been said that for a given tablet formulation, a critical amount of disinetgrant is required to cause quick release of the drug[17]. The shortest disintegration time for the formulated tablets was for KG 5%w/w, hence, this may be the critical concentration for KG formulation by wet granulation. It is believed that this concentration may represent a certain threshold value in which the polymer occupies minimum distances apart in the tablet which permits rapid liquid penetration. It has been shown that a slight increase in the volume of disinetgrant particles which may not be a visible increase in the diameter of the particle granules could display sufficient force to activate disintegration.

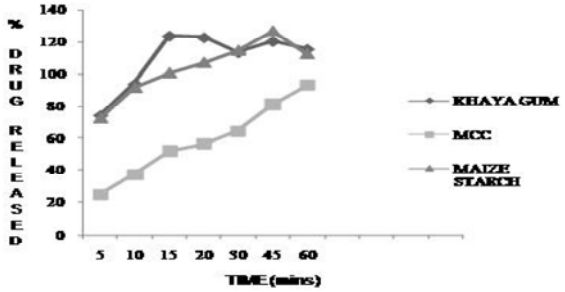

Fig. 1: Dissolution profile of chloroquine phosphate tablets formulated using 5%w/w disintegrant.

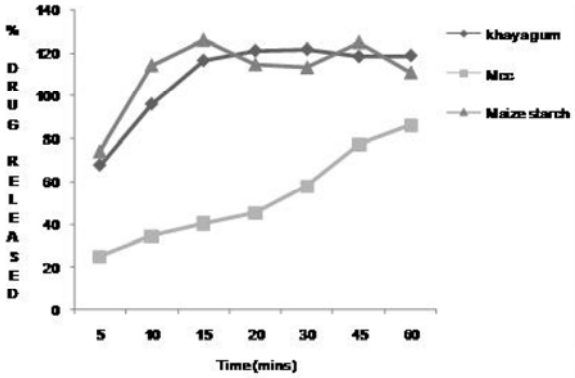

Fig. 2: Dissolution profile of chloroquine phosphate tablets formulated using 7.5%w/w disintegrant.

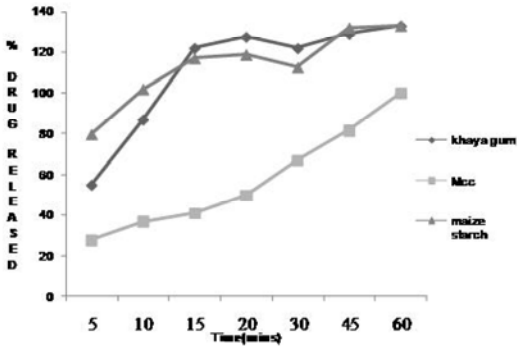

Fig. 3: Dissolution profile of chloroquine phosphate tablets formulated using 10%w/w disintegrant.

CONCLUSION

This study discusses the evaluation of *Khaya* gum as a possible tablet disintegrant. It has shown that *Khaya* gum exhibits great ability to swell in aqueous medium and even though forms gels during swelling, its initial swelling is capable of eliciting the break-up of tablets which is essential in promoting the release of the drug. An increase in concentration of the gum resulted in an increase in tablet crushing strength, disintegration time but a decrease in friability index. This study suggests that *Khaya* gum may be a potential disintegrant in Chloroquine phosphate tablet formulation at 5%w/w which is the threshold in which the gum is able to occupy the little distances apart in the tablet and thus permit liquid penetration.

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