

EVALUATION OF *KHAYA GRANDIFOLIA* GUM AND EFFECT OF TEMPERATURE OF GRANULATION ON THE PROPERTIES OF CHLOROQUINE DIPHOSPHATE GRANULES.

AREMU OI AND ITIOLA GA

Department of Pharmaceutics and Pharmaceutical Technology,
Olabisi Onabanjo University, Shagamu and
Department of Pharmaceutics and Industrial Pharmacy,
College of Medicine, Ibadan.

ABSTRACT

A study has been made on the effects of temperature of granulation and the nature and concentration of binding agent on the size distribution of chloroquine diphosphate granules.

Chloroquine diphosphate granules were prepared at varying concentrations, 0.0% w/w (Basic formulation), 0.5% w/w, 1.0% w/w, 2.0% w/w, and 4.0% w/w, at temperatures 250C, 500C and 750C respectively for both Khaya gum and official Gelatin B.P. Determinations were later carried out on the weights and granule size distribution.

The mean granule size (G) of the formulation depends on the nature and concentration of binder used and also on the temperature of granulation. *Khaya grandifolia* gum (family Meliaceae) was compared with official Gelatin BP. Formulations containing gelatin as binder generally have higher values of (G) than formulations containing Khaya gum as binder. The value of G generally decreases as the temperature of granulation is raised from room temp (250C) to 500C. When the temperature is raised further to 750C the value of G for formulations containing gelatin generally decreased further while those containing Khaya gum exhibited a general increase in the value of G. The results are explained in terms of various possible mechanisms that may be operative at higher temperatures including evaporation of liquid films during granulation, asperity melting, lowering melting point and softening of materials.

The granule size distribution of chloroquine diphosphate formulations granulated by wet method depends on the nature also on the temperature of granulation.

INTRODUCTION

Khaya gum is obtained from the incised trunk of the tree *Khaya grandifolia* (family Meliaceae), a typical West African mahogany tree largely available in Western Nigeria. The gum is normally secreted as a colourless liquid which hardens on exposure to air and changes colour from yellowish white to a dark brown mass after some time.

It is believed that Khaya gum contains galactose, rhamnose and galacturonic acid residue. Hence in terms of composition, it is similar to Karaya gum rather than Acacia. The exudate contains a highly branched polysaccharide consisting of D-galactose, L-rhamnose, D-galacturonic acid and 4-O-methyl-D-glucuronic acid¹.

It is a translucent amorphous substance about 80% of which is soluble in water with no clear separation of the components being observed. A concentration of the gum greater than 4% is a semisolid mass. The gum is liable to oxidation and it may change colour from colourless to brown on aging. The gum has been found to be resistant to hydrolysis and is precipitated by high concentration of alcohol and electrolytes². The purified gum is usually a white powder.

Khaya gum has been shown to possess binding properties in tablet formulations³. This gum has also been investigated for its effect on the compressional characteristics of certain pharmaceutical materials⁴

Binding agents are usually plasto-elastic in nature and are known to soften under the high compressional forces employed for tableting¹⁴. Presumably due to the heat generated in the die during tableting process. Khaya gum which has been shown to possess binding properties in tablet formulations³ would therefore be expected to possess plasto-elastic properties.

It is well known that the physico-chemical properties of tablets are determined to a large extent by the properties of the granulations from which they are made¹⁵. While some work have been done on the effect of temperature on the tableting process^{10,16}, little work appears to have been done on the effect of temperature on the process of granulation.

In the present work, the various studies^{3,4} have been extended to investigate the effect of temperature of granulation using Khaya gum and official Gelatin BP on certain physico chemical properties of chloroquine diphosphate granules.

MATERIALS AND METHODS

Materials

The materials used were chloroquine diphosphate (Bayer, Germany), Gelatin B.P. (BDH Chemicals Ltd, England), Khaya gum (from *Khaya grandifolia*, Botanical garden, University of Ibadan), lactose B.P. (DMV, Veghel Holland), Corn Starch B.P. (Lot 703 26, Pfizer Nigeria Ltd, Lagos, Nigeria).

Collection and Purification of Khaya Gum

Khaya gum from *khaya grandifolia*, family meliaceae was collected from the trunk of the mahogany tree, at the Botanical garden, Un

Evaluation of khayaiversity of Ibadan. The hardened exudates from the trunk was hand picked and sheared from the bark. The dried exudate was then oven-dried at about 400C until brittle. This was crushed in a mortar with a pestle and then pulverised in a blender (Model 857, Chrome white, osterizer, U.S.A.) to produce the powder of the gum. The gum powder was hydrated in double strength chloroform water for five days with intermittent stirring. The resultant mucilage was screened through a clean calico cloth to remove extraneous materials and undissolved gum.

The pure gum was precipitated from solution with 95%w/v Ethanol at the ratio of 2:3. The precipitated gum was then filtered and washed with diethylether and then dried in hot air oven at 400C for 24 hours. The purified gum was then pulverised and packed in air - tight container.

Preparation of Granules

250g batches of the basic formulation comprising chloroquine diphosphate (65%w/w), lactose (25% w/w) and corn starch (10% w/w) were dry mixed for

about 3 minutes at room temperature (?250C) in a Kenwood planetary mixer fitted with a calibrated temperature regulator. The mixture was then moistened with 0.0%w/w, 5% w/w, 1.0% w/w, 2.0% w/w, and 4.0% w/w, amounts of mucilages (Khaya gum) and solutions (gelatin) of the binding agents of mucilages (Khaya gum) and solutions (gelatin) of the binding agents.

Massing was continued for about 5 minutes. Thereafter, the wet masses were granulated manually by passing them through a No.12 Mesh (1400 μ m) sieve. The granules were dried in trays in a hot air oven for about 24 hours at 600C and then screened through a No. 16 mesh (1000 μ m) sieve. The granules were then stored in air tight containers.

The granulation process was repeated twice, but with the Kenwood planetary mixer regulated to temperatures 500C and 750C respectively.

Granule Size Distribution

In order to perform size distribution, standard sieves with the following sizes were used: 12 mesh (1400 μ m), 16 mesh (1000 μ m), 22 mesh (710 μ m), 30 mesh (500 μ m), 44 mesh (355 μ m), 60 mesh (250 μ m), 88 mesh (180 μ m) and the receiver (pan).

The sieves were arranged in descending order of aperture size with the receiver below all the sieves. 100g of the granules was weighed on an electronic balance and poured into the uppermost sieve. The cover of the sieves was placed firmly in position and the stack of sieves was shaken for 10 minutes on a sieve shaker (J. Englishmann AG, ludwigshatanlphan, Germany). The granules retained by each sieve were removed carefully and the stuck ones removed with a brush.

The weights of the granules were determined. Determinations were carried out in duplicate.

RESULTS AND DISCUSSION

The temperature of granulation of pharmaceutical powdered formulations is of considerable importance. This is largely because it is a well known fact that countries in the tropics arid zones can exhibit weather conditions that can be very harsh, producing sometimes ambient temperatures much in excess of 350C, especially during the dry season. This would appear to pose a threat to the preparation and storage of pharmaceuticals whose components

are either thermolabile or susceptible to fluctuations in temperature.

In the present work, the chloroquine diphosphate formulations have been granulated at different temperatures to see the effect of temperature of granulation on granulation and granule properties. The behaviour of Khaya gum, the binding agent being developed, under these conditions was also monitored and compared with the behaviour of official gelatin BP, particularly whether there are changes in granule properties under the various conditions of granulation.

The particle size distributions of the chloroquine diphosphate granules are presented in Tables I to VII for formulations containing no binder, for those containing gelatin as binder and those containing Khaya gum as binder respectively and in the same order of presentation as plots of cumulative percentage oversize versus granule size in figures 1 to 7. Fig. 1 shows the distributions for granules containing no binder and prepared at room temperature (25°C), 500°C and 750°C. Tables II to IV and figures 2 to 4 show the distributions for granules containing various concentrations of gelatin showing data for granules prepared at room temperature 25°C, 500°C and 750°C respectively. The same order of presentation is shown for distribution of granules, containing various concentrations of Khaya gum in Tables V to VII and figures 5 to 7. the mean granule size (G) is of importance in tableting since granule size distribution will affect flowability, compression characteristics, and tablet properties such as weight variation and mechanical strength⁵. Thus the effect of temperature on granulation could be very important in relevant production processes. The particles of most powdered materials, metals, inorganic and organic solids and glasses, tend to soften and become more plastic as their temperature is increased towards their melting points⁶. Also, that certain polymers and thermosetting resins soften on heating but harden subsequently due to cross-linking and other chemical reactions. The increase is usually accompanied by increase in tensile strength of any bed of compact into which the powder may have been formed irrespective of whether the tensile strength is measured at the elevated temperature or after the specimen has been allowed to cool. This would affect the flow rates of powders⁷ and other physical characteristics of the compacts⁸.

From Table VIII, it is seen that, at the various con-

centration of binder employed in the granules, granules containing gelatin have higher values of mean granule size (G) than the granules containing Khaya gum as binders, at all temperatures of granulations. Furthermore, for formulations containing Khaya gum as binder at room temperature, the mean granule size (G) generally increased as the concentration increased up to 2% concentration of Khaya gum.

This could be attributed to the strengthening of bonds between particles, as there are more binder per bond. It has been discovered that there could be general increase in granule diameter of glass spheres with increase in binder concentration⁹. Khaya gum exhibits this established trend. This same trend was obtained for formulations containing gelatin as binder as the concentration increased, up to a maximum value of G at 2%. At 4% concentration of Khaya gum or gelatin, however, the mean granule size decreased. This could be useful information in the choice of concentration of binder in pharmaceutical preparations.

For higher temperatures, granules containing Khaya gum and prepared at 500°C and 750°C, showed a continuous increase in the value of G with increase in concentration of Khaya gum.

Granules containing gelatin and prepared at 500°C and 750°C, exhibit a general increase in granule size with increase in concentration of binder up to 2% is observed for granules prepared at room temperature as mentioned earlier. But here also, there is a decrease in granule size at 4% concentration of gelatin as observed for granules prepared at room temperature (25°C)

At the same concentration of gelatin as binders, it is observed that with increase in temperature of granulation, the granule size generally decreased. This tends to contradict the theory that material becomes increasingly cohesive as the temperature is raised. However, it has been shown that as the homologous temperature of material increases, the melting point of the material could increase by 20 - 300°C¹¹. It has also been suggested that the flow rates of three powders, Behenic acid, stearic acid and glyceryl monostearate altered at temperature closer to their melting points¹¹. Hence during granulation at higher temperatures, it should be expected that gelatin would first of all soften followed by lowering of melting point of the formulations.

To attempt to analyse the observed results further, the stages in the development of moist granules described by Newitt & Conway - Jones¹² need to be considered. At wetting of powders during the initial stages, liquid films are formed on the surface and combine to produce discrete liquid bridges at points of contact. This results in pendular stage, with low mechanical strength. Increase in content leads to the funicular stage with a modest increase in the strength of moist granules. Therefore, increase in liquid content leads to the capillary stage. This is the point of maximum strength of wet granules. The particle at this stage are brought into closer proximity, bonding being effected by interfacial forces at the granules surface and by negative capillary pressure throughout the interior of the liquid filled space. Further addition results in droplet formation, the granules hereby formed are weaker.

Considering the various stages described above, as the temperatures of granules preparation is increased to 500C and 750C for formulations containing gelatin as binding agent liquid films (in this case water) which provide surface tension and capillary forces, would probably have evaporated to some extent, leaving in larger amounts the weaker vander Waals forces. It could be suggested therefore that the evaporation of liquid films could result in the reduction of the quantity of the liquid present and the liquid bridges between the particles held together by surface tension and capillary forces which are stronger and act over greater distances than vander waals forces leading to production of weaker granules and probably a lot of fines.

These findings are of great importance in compression since certain amounts of fines are necessary for optimal tablet strength. However, for granules containing Khaya gum, the findings were, to some extent, different from those observed for granules containing gelatin. At higher temperature of granulation (500C), the mean granule size of granules containing Khaya gum decreases as for formulation containing gelatin. This could also be attributed to loss liquid (water) available for formation of liquid bridges during granulation, due to evaporation, which enhances only modest increase in strength and size of granules¹².

However, when the temperature of granulation was raised to 750C, the granule size increased. It is possible that Khaya gum at the much higher temperature of 750C could exhibit appreciable softening

which results in greater plasticity of powdered particles which on cooling results in the formation of larger granules and thereby compensating for loss of liquid by evaporation.

Hence this apparent property of Khaya gum could be very useful in the preparation of formulations with specific granule size distributions. From the foregoing, it can be reasonably concluded that the granule size distributions for the formulations depend largely on the nature and concentration of the binding agent used, and also on the temperature of granulation.

CONCLUSION

The granule size distribution of chloroquine diphosphate formulation granulated by wet method depends on the nature and concentration of binder used and also on temperature of granulation.

Khaya gum appears to be a weaker binding agent than gelatin in chloroquine diphosphate formulations generally giving smaller granules, which may lead to formation of softer tablets. Khaya gum may however be useful in formulation of chewable tablets like antacids.

Table I: Distribution of Granules of Chloroquine Diphosphate Containing no Binding Agent, Prepared at Different Temperature

Sieve Size	Cumulative weight % oversize (C.B)		
(µm)	25 °C	50 °C	75 °C
1400	0	0	0
1000	0	0.20	0.53
710	11.31	7.27	12.26
500	27.08	10.45	27.25
355	41.54	31.45	38.74
250	58.57	47.79	53.31
180	78.29	72.32	75.07
Receiver (01)	100.00	100.00	100.00

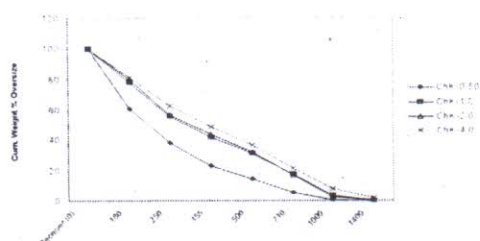
Simple Code Representative

C.B = Chloroquine granules containing 0% binder

Table II: Size Distribution of Chloroquine Diphosphate Granules with Gelatin As Binder Prepared at Approx. 25 °C (Room Temperature)

Sieve Size(µm)	Cumulative weight % oversize			
	Ch(G-5)	Ch(G-1)	Ch(G-2)	Ch(G-4)
1400	0.10	0.61	35.88	9.94
1000	5.16	11.8	64.65	22.24
710	29.60	37.12	78.69	40.84
500	48.04	54.45	87.12	55.90
355	61.97	67.66	91.03	68.23
250	75.04	80.50	95.46	80.80
180	80.12	92.07	97.00	90.05
Receiver (01)	100.00	100.00	100.00	100.00

Fig. 7: Size Distribution of Chloroquine Diphosphate Granules with Khaya Gum at 75°C



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Fig. 1: Size distribution of chloroquine diphosphate Granules using no binder

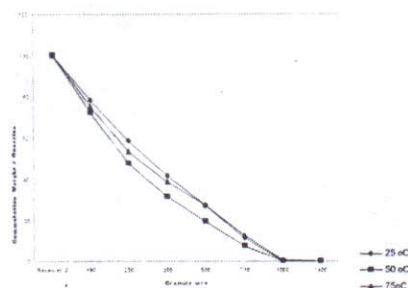


Fig. 2: Size Distribution of Chloroquine Diphosphate Granules with Gelatin at 25oC

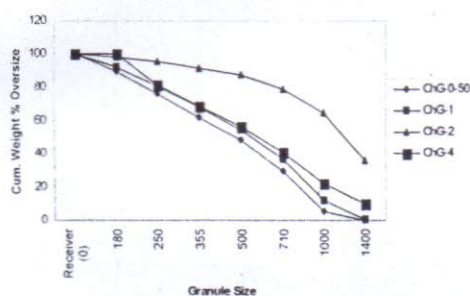


Fig. 3: Size Distribution of Chloroquine Diphosphate Granules with Gelatin at 50oC

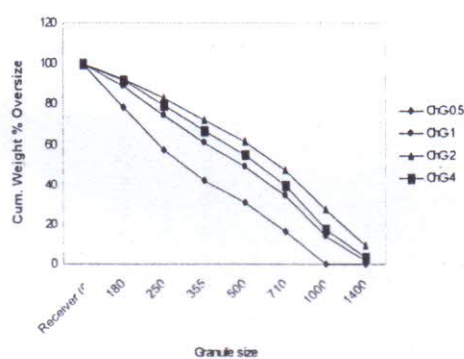


Fig. 4: Size Distribution of Chloroquine Diphosphate Granules with Gelatin at 75oC

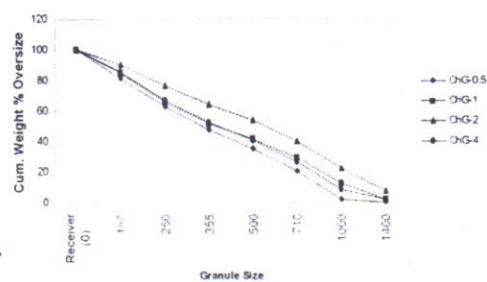


Fig. 5: Size Distribution of Chloroquine Diphosphate Granules with Khaya Gum at 25oC

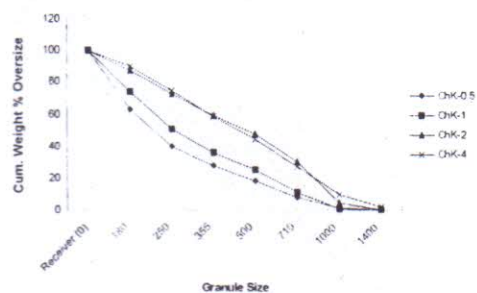


Fig. 6: Size Distribution of Chloroquine Diphosphate Granules with Khaya Gum at 50oC

