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Evaluation of disintegration and dissolution of chloroquine tablets in some States in Northern Nigeria

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Abstract
The biological performance of tablets is commonly assessed by disintegration time and dissolution rates, which ascertains how much of the orally administered tablet may be bioavailable. This study seeks to assess the quality of chloroquine tablets in some States in Northern Nigeria by determining their disintegration and dissolution parameters. The Vanderkamp tablet disintegration tester was used to assess the disintegration time, while the dissolution rate test was carried out according to British Pharmacopoeia specifications. Five tablets of each coded sample were singly placed in a dry basket of the dissolution tester and the contents of which were immersed in a vessel containing one litre dissolution medium of de-aerated 0.1 HC1 at a constant temperature of 37±0.5°C. The stirring motor operated at 100 revolutions per minute for 45 minutes. The absorbance was measured in an UV spectrophotometer at a wavelength of 344 UM. Twenty-six (26), 36, 50 and 16 of the samples from states A, B, C and D respectively had normal disintegration times of less than 15 minutes. About 86% of the total samples from the 4 states disintegrated within 14 minutes thus conformed to the official requirement. States A (42.86%), B (67.57%), C (80.77%) and D (90.91%) samples had dissolution rate values above 70%. The disintegration time and dissolution rates of the sampled chloroquine tablets were assessed and found to have a good quality. However, quantitative drug assays need to be carried out that will measure the actual amount of active chloroquine in a tablet sample.

Keywords: Chloroquine tablet, Disintegration, Dissolution

INTRODUCTION

Disintegrants are excipients added to tablet formulations to facilitate its disintegration in an aqueous environment or after administration (Jaiyeoba *et al*., 1998). Disintegrants are mostly added intragranularly, though they may also be added extragranularly just before compression. They are usually added in concentration of 5-20% w/w of the granules (Jaiyeoba *et al*., 1998; Rubinstein, 1988). Substances used as disintegrants in tablet formulation include starches, carboxymethyl cellulose, Avicel®, alginic acid, sodium alginate, cross-linked PVP and colloidal silicon. The most popular however are the starches (corn and potato). Starches of plantain (*Musa paradisiacal*), African bitter yam (*Dioscorea dumeforum*) and Cassava (*Manihot utilssima*) were used as disintegrants by Esezebo (1991). Their effectiveness on disintegration and dissolution

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rates were ranked as follows: Plantain starch, <Cassava, <Yam, <Maize. Though plain starches are the most commonly used disintegrants, at low concentrations however, they are not very effective. A number of studies by various researchers (Deshpande and Panya, 1987; Esezebo, 1991; El-khawas and El-khodiory, 1995; Duru *et al.*, 1995) have been carried out in search for more effective disintegrants. In combination with starch, sodium lauryl sulphate, a surfactant, has been found to be an effective disintegrant. Akande (1988) postulated the apparent effectiveness of some surfactants in improving tablet disintegration to be due to an increase in wetting rate. Mechanism of action of disintegrants is a subject of controversy (Rubinstein, 1988). According to Jaiyeoba *et al* (1998) disintegration time is a measure of the ability of the tablet to break down into smaller particles when in contact with fluids. However, Lowenthal and Wood (1973) have studied a number of mechanisms of tablet disintegration. Water absorption capillary and porosity theory (Curlin, 1955; Khan and Rhodes, 1975) explained that by virtue of a disintegrant's relative incompatibility especially starch, they form chains around the granules (drug) forming capillaries. The capillaries increase with increase in the concentration of the starch. The most widely accepted mechanism of tablet disintegration is swelling (Curlin *et al.*, 1986; Takewiech and Kawashiima, 1987; Esezebo, 1991). Starch, the most commonly used disintegrant, acts by this means. Aspirin tablet (a water insoluble drug) has been said to disintegrate by swelling (Caramella, 1991). Starch grains undergo elastic or plastic deformation, which tend to return to the original shape when pressure is removed. When exposed to water, the deformed grains swell rapidly releasing the energy gained (Fahrer, 1977). In effervescent tablets, carbon dioxide gas is produced from the reaction of sodium bicarbonate with citric acid in the presence of water. As carbon dioxide is released within the tablets, an internal pressure develops until the tablet disintegrates; carbon dioxide dissolves or disappears from the reaction vessel. Dissolution test is a measure of the time it takes the active ingredient in the tablet to go into solution. Itiola and Pilpel (1996) showed that for tablet that are formulated to disintegrate, disintegration positively influence dissolution, since the tablet must disintegrate before dissolution. Before a drug is absorbed in the G.I.T, it must go into solution. A tablet may meet the disintegration standards yet be therapeutically inactive. Tablets are therefore subjected to dissolution test in case of suspected problem of active ingredient dissolution. The standard requires that 70% of the stated amount of drug must be found to be in solution within minutes. Therefore, effective performance of oral tablets can be evaluated through disintegration and dissolution studies in which the present study seeks to address.

EXPERIMENTAL

Disintegration test: The Vanderkamp tablet disintegration tester is an apparatus which consists of a basket rack holding six plastic tubes, which are open at both ends. The bottom of the tubes is covered with 10-mesh screen. For testing, one tablet was placed in each of the six tubes and covered with a plastic disc which forced the soft mass of disintegrating tablets through the bottom screen. For operation the disintegration tester was placed in a water bath at 37±0.5°C. The time needed for the tablets to completely disintegrate was noted and recorded (King, 1980). Good quality products disintegrated within 15 minutes, while poorly manufactured tablets did not disintegrate within the stipulated norm of 15 minutes.

Dissolution rate test: This test was carried out according to B.P. specifications (BP, 1988). Five tablets of each coded sample were singly placed in a dry basket of the

dissolution tester. The basket consists of a 40-mesh cy1indrical container, the contents of which were immersed in a vessel containing one litre dissolution medium of de-aerated 0.1 HC1 at a constant temperature of 37±0.5°C (King, 1980). The stirring motor operated at 100 revolutions per minute for 45 minutes. At the end of that period, 10 ml of the dissolution medium were filtered and diluted in 25 or 50 ml of fresh medium. The absorbance of the final dilution was measured in an UV spectrophotometer at a wavelength of 344 UM. The averaged absorbance for the 5 single tablets was taken as the final result and the percentage amount of CQ that went into solution was determined by use of calibration curves. The percentage amount of CQ moiety present in the medium after 45 minutes should not be less than 70%. Care was taken that for each test the basket was dry and the medium was kept at a steady temperature of 37±0.5°C. Sampling at the end of 45 minutes was carried out at a position half-way between the surface of the dissolution medium and the top of the rotating basket. For the purpose of determining the amount of CQ phosphate (or sulphate) present in solution during the dissolution rate test, a calibration curve was prepared. About 0.0125 g of pure chloroquine phosphate powder were accurately weighed and dissolved in 25 ml 0.1M HCl. This stock solution contained 0.5 mg/ml of CQ phosphate. From the stock solution six different concentrations were prepared by serial dilutions. Thus the least and highest concentrations were 0.5 µg/ml and 20 µg/ml. The absorbance of each of the six dilutions was measured by UV spectrophotometry at a wavelength of 344 nm. Gradient 'B' and correlation coefficient 'r' were determined. Similarly, 0.0125g of pure chloroquine sulphate powder was subjected to the same procedure. Serial dilutions were prepared such that the lowest and the highest concentrations were 5µg/ml and 30µg/ml respectively. Absorbance was measured at the same wavelength. The gradients of the two calibration curves were employed to determine the amounts of phosphate and sulphate in the dissolution medium.

RESULTS

Disintegration time. The results of tablet disintegration are shown in Table 1 and Figure 1. Table 1 illustrates that 26 (74.3%), 36 (97.3%), 50 (96.2%) and 16 (72.7%) of the samples from states A, B, C and D respectively had normal disintegration times of less than 15 minutes. For the remaining samples from the 4 states, disintegration times were above 15 minutes. About 86% of the total samples from the 4 states disintegrated within 14 minutes thus conformed to the official requirement, while the remaining 14% of the samples had disintegration times beyond 15 minutes and therefore did not comply with official standards. The respective mean disintegration times for samples from the 4 states (Figure 1) were 10.37±1 7.61, 5.41±1 3.02, 7.28±4.59 and 11.83±5.80 minutes. Thus these fell within the normal range.

Dissolution rate testing of tablets. The dissolution rate testing of tablets is presented in Table 2 and Figure 2. It can be seen from Table 2 that in states A, B, C and D, 15(42.86%), 25(67.57%), 42(80.77%) and 20(90.91%) samples had dissolution rate values above 70%, while the remaining samples had values of less than 70%. Thus the former complied with the official requirements, whereas the latter did not. About 73% of all the samples from the 4 states had dissolution rates above 70% and therefore all passed the test. Also about 26% had dissolution rates ranging between 35-69.9% and the remaining 1% between 0 and 34.9%, both categories therefore failed the dissolution rate test. The mean dissolution rates of samples in states A, B, C and D were found to be 66.36±27.22%, 82.30±21.30%,

81.38±20.30% and 88.26±11.70% respectively (Figure 2). All except state A had mean dissolution rate values above 70% and therefore passed the dissolution rate tests. State A, however, did not meet this requirement.

DISCUSSION

The biological performance of tablets is commonly assessed by disintegration time and dissolution rates (Deshpande and Panya, 1987; Esezebo, 1991; El-khawas and El-khodiory, 1995; Duru *et al.*, 1995; Itiola and Pilpel, 1996). The two parameters describe how much of the orally administered tablet may be bioavailable. Samples that comply with good manufacturing practice disintegrate within 15 minutes. For the study area, the average disintegration time of all the samples was found to be 8.72±5.26 minutes, with a range of 3.46 - 13.98 minutes. On the average therefore samples disintegrated within the expected period of 15 minutes (BP, 1988). Disintegration time of tablets from the 4 states was rated as follows; B, C, A and D, thus state D had the highest disintegration time as opposed to state B with the lowest.

Table 1: Disintegration of some brands of chloroquine tablets in study states

Disintegration Time (min)	*Number and Percentage per State*				*Total*
	A	*B*	*C*	*D*	
<15	26 (74.3%)	36 (97.3%)	50 (96.2%)	16 (72.7%)	128 (88%)
>15	9 (25.7%)	1 (2.7%)	2 (3.8%)	6 (27.3%)	18 (12%)
Total	35 (100%)	37 (100%)	52 (100%)	22 (100%)	146 (100%)

Table 2: Dissolution rates of some brands of chloroquine tablets in study states

Range of % dissolution	*Number and percentage of dissolution rates*				*Total*
	A	*B*	*C*	*D*	
>70%	15 (42.86%)	25 (67.57%)	42 (80.77%)	20 (90.91%)	102 (70%)
35-69.9%	16 (45.71%)	12 (32.43%)	10 (19.23%)	2 (9.09%)	40 (27%)
0-34.9%	4 (11.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (3%)
Total	35 (100%)	37 (100%)	52 (100%)	22 (100%)	146 (100%)

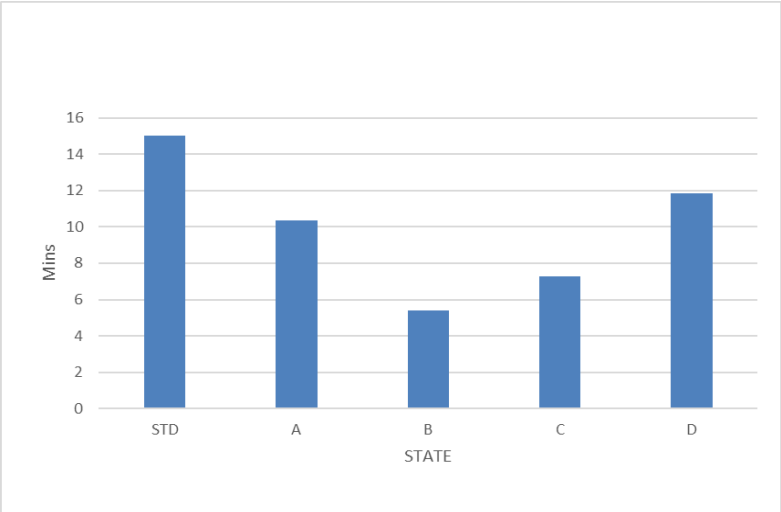

Figure 1: Mean disintegration time of some brands of chloroquine tablets in study states.

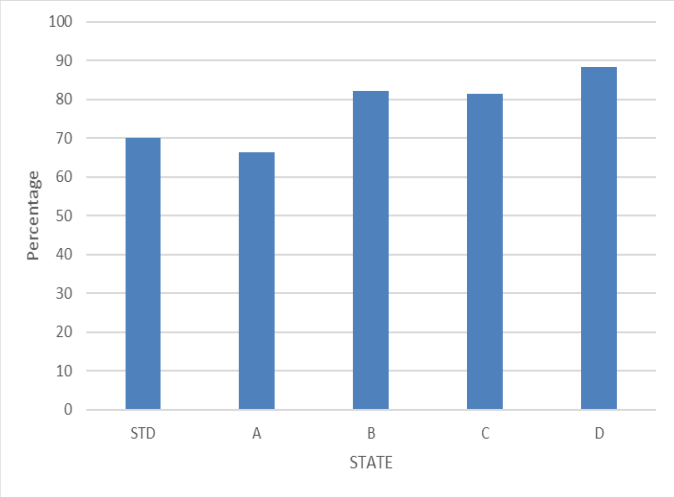

Figure 2: Mean dissolution rate of some brands chloroquine tablet in study states

In general, if disintegration time is below 5 minutes, high concentrations of the active ingredients are made available in blood within a short time causing toxicity. Samples from states B, C and A are therefore likely to cause toxicity more often than those of state D. On the other hand, when disintegration time is long (i.e. greater than 15 minutes), only small concentrations of drug are bioavailable within the expected time and such concentrations may be inadequate. Such sub- therapeutic concentrations bear the risk of selecting resistant strains from a sensitive parasite population promoting the emergence of CQ resistance. This is in agreement with several literature reports in which inappropriate use of disintegrants in pharmaceutical tablets affect pharmacological outcome (Curlin *et al.*, 1986; Esezebo, 1991; Itiola and Pilpel, 1996; Jaiyeoba *et al.*, 1998). Examples are 27.27% and 25.71% of the samples from States D and A, respectively. Disintegration time solely depends on the amount of disintegrants in the tablets. The smaller the amounts, the longer the time of disintegration will be and as the amounts increase the disintegration time is shortened until a critical value is reached which provides optimum disintegration (WHO, 1986). On the average, all 4 states performed creditably in this regard. Dissolution rates encompass complete or partial dissolving of tablet samples in a medium (0.1M HCl or distilled water) maintained at body temperature (37±0.5°C). The extent of dissolution predicts the bioavailability state of the tablet sample. In general, dissolution rate is considered to be a better parameter of bioavailability than disintegration (WHO, 1986). In this study, 90.91% of the samples from state D passed the dissolution rate tests, meaning that at least 70% of active CQ was released within 45 minutes. Similarly, only 42.86% samples of state A passed the tests, i.e. more than 50% of the samples could not release up to 70% active CQ into the medium forecasting poor bioavailability leading to low CQ blood concentrations. Such low concentrations will induce the development of resistant parasite strains from a sensitive population. Of the 4 states, only state A had mean dissolution rates below 70% (66.36±27.22%). This value differs significantly from those obtained for states B ($p<0.00l$), C ($p<0.01$) and D ($p<0.001$). When pairs of states B and C, B and D and C and D were compared with each other, no statistical difference was found ($p>0.05$). Therefore, samples from state A were statistically different from those of states B, C and D, while samples of states B, C and D performed uniformly with no significant differences. The

correlation suggests that in this study low quality chloroquine tablets were mostly supplied from South-Eastern Nigeria. This finding together with the fact that in Nigeria chloroquine resistance *Plasmodium falciparum* (CRPF) was first reported from that part of the country (Eke, 1979) suggest that the use of low quality chloroquine preparations might have played an important role in the emergence of CRPF in Nigeria.

Conclusion

Comprehensive performance study using disintegration time and dissolution rates of the sampled chloroquine tablets from northern Nigeria were assessed and found to be of good quality. However, quantitative drug assays need to be carried out that will measure the actual amount of active chloroquine in a tablet sample.

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