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Physicochemical equivalence of chloroquine phosphate tablets

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Summary

Seven brands of chloroquine phosphate tablets sourced from different retail outlets in the South-West Nigerian market were analysed in order to determine their physicochemical equivalence. The assessment parameters included uniformity of weight, friability, crushing strength, disintegration and dissolution tests and chemical assay of the tablets. All the brands passed the British Pharmacopoeia tests for weight uniformity, disintegration time and dissolution rate. Two brands, C and E passed the minimum criterion for crushing strength, four brands passed the friability test and two brands exceeded the specified amount of active drug content for chloroquine tablets. Only one brand C out of the seven brands that were analysed passed all the BP quality specifications. Hence none of the seven brands analysed could said to be physically and chemically equivalent. This study highlights the need for constant market monitoring of new products in order to ascertain their quality.

Keywords: *Physicochemical equivalence, comparative study, mechanical and release properties, chloroquine phosphate tablets*

Résumé:

Sept options des comprimés de phosphate de chloroquine aux vendeurs ambulant étaient analysé dans le but de déterminer leurs propriétés physicochemiques équivalence au Sud Ouest du Nigéria. Les paramétres évalués inclus l'uniformité du piuds, la friabilite, la solidite, la desintegration ,les testes de dissolution et l'analyse chimiques de ces comprimés. Tous les options avaient un poids uniforme , un meme taux de desintégration et de dissolution aux testes de la pharmacopée britanique. L'option C et E passaient le critére minimal de solidité, 4 options passaient le teste de friabilité et 2 options avaient une quantité excessive de la substance active. Seule l'option c sur les 7 passait tous les spécifications de qualité du BP, Mais n'avaient pas de meme proprites physicochimiques. Cette étude démontre le besion d'un contrôle constant et permanent des nouveaux produits pour assurer leur qualité.

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Introduction

There is an increase in the number of generic drug products from multiple sources; people involved in the delivery of health care are placed in a position of having to select one from among several seemingly equivalent products. Multisource interchangeability helps to contain the costs of drugs and reduces market monopoly by innovator manufacturers. Further, if therapeutic equivalence is established, preference will naturally be given to drugs with lower costs. For instance, in 1975 approximately 9% of all prescription drugs dispensed in the United States were generic versions and a higher percentage is believed dispensed in Sub-Sahara Africa[1]. Over 80% of the approximately 10,000 prescription drugs available in 1990 were obtained from more than one source and variable clinical responses to these dosage forms supplied by two or more drug manufacturers is documented[2]. The differences in responses may be due to formulation ingredients employed, methods of handling, packaging and storage and even the rigours encountered during in-process quality control. Hence, there is need to determine their therapeutic equivalence in order to ensure interchangeability.

Meanwhile, many developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. This situation informed the decision of the World Health Organization in issuing guidelines for global standard and requirements for the registration, assessment, marketing, authorization and quality control of generic pharmaceutical products[3]. The purpose of this was to give technical guidelines to national regulatory authorities such as the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria, which is responsible for drug administration and control in Nigeria and the quality of drug dosage forms generally available in the market. Generic drugs must satisfy the

same standards of quality, efficacy and safety as those applicable to the innovator products. Preliminary physicochemical assessment of the products is very important and *in vitro* dissolution testing can be a valuable predictor of the *in vivo* bioavailability and bioequivalence of oral solid dosage forms [4]. Previous work on other drugs has shown the need for this study[5,6].

Chloroquine phosphate is widely used as a first line drug in the suppression of susceptible *Plasmodium falciparum* malaria, which is a cause of high mortality among children in tropical Africa.

Several generic versions of chloroquine phosphate tablets are marketed in Nigeria, hence there is the need to assess the physical and chemical properties of these products as compared with the minimum standards as specified in the official books. In the present study the equivalence of seven brands of chloroquine phosphate tablets sourced from retail pharmacies in South-West Nigeria was determined using *in vitro* methods. This study is aimed at obtaining baseline data towards the establishment of bioequivalence of the tablets.

Experimental

Materials

Seven brands of Chloroquine phosphate tablets (A-G) were obtained from retail outlets in Nigeria. The manufacture and expiry dates are shown in Table 1.

Physical measurements

For each brand, twenty tablets selected at random were weighed individually and their average weight calculated to determine the weight uniformity [7]. The percentage deviation of each tablet from the average weight was determined.

Twenty tablets were caused to cascade in a friabilator (Ketan Model 12010, India) rotated at 25rpm for 4minutes. The weight loss was determined as a percentage of the initial weight.

Crushing strength of each of 5 tablets per brand was determined using the PTB 301 hardness tester (Pharmatest, Switzerland). The load required to break the tablets into two halves was determined.

The disintegration times of six tablets per brand were determined in distilled water at 37 ± 0.5°C using the Erweka tablet disintegration apparatus (Erweka Apparabetau, Germany). Determinations were done in triplicate. This was done in accordance with BP 1998 specifications.

Dissolution tests were carried out on the tablets using the Erweka dissolution test apparatus (Erweka Apparabetau, Germany) fitted with baskets rotated at 100 rpm. The dissolution medium, 900ml of 0.1M HCl, was poured into the vessel and maintained at 37± 0.5°C. One tablet from each brand was placed in the basket and lowered into the vessel containing the dissolution medium. 5ml samples were withdrawn at time intervals and replaced with fresh dissolution medium. The samples were filtered and diluted appropriately with 0.1M HCl and the absorbance of the solution measured at 344nm.

The graph of the amount of chloroquine phosphate dissolved versus time was plotted from which T_{50} and T_{80}, the time required for 50% and 80% of the active drug component to dissolve, and the amount dissolved in 45minutes was obtained for each brand. Determinations were done in triplicate.

Assay of active ingredient

Twenty tablets from each brand were weighed and powdered. A quantity of the powder containing 500mg Chloroquine phosphate was dissolved in 20ml of 1M sodium hydroxide and extracted with four successive 25mls of chloroform. The chloroform extracts were combined and evaporated to a volume of 10ml. 40ml of anhydrous acetic acid was added and non-aqueous titration carried out. The end-point was determined potentiometrically (BP). Perchloric acid (1ml if 0.1M) is equivalent to 25.79mg of $C_{18}H_{26}ClN_3, 2H_3PO_4$ (Chloroquine phosphate). 250mg of Chloroquine phosphate is approximately equivalent to 155mg chloroquine base.

Data analysis

Data for weight uniformity test, friability, crushing strength, disintegration and dissolution times of the tablets are presented as mean ± standard deviation.

Results and discussion

The present study was carried out to evaluate the physicochemical properties of different brands of chloroquine phosphate tablets having the same labelled content and to determine their pharmaceutical equivalence which is a precursor of bioequivalence. All the samples used were within their shelf lives at the time of investigation. Six out of the seven brands of chloroquine phosphate tablets have been registered by NAFDAC. The results of the physical properties of the various brands of chloroquine phosphate are presented in Table 2. All brands showed acceptable uniformity of weight as none had percent deviation in weight greater than 5% as stipulated by the British Pharmacopoeia 1998. The significance of the test is to ensure that the tablets in each Lot are within the appropriate size range.

Brands C, E, F and G passed the friability test while brands A, B and D failed (Table 2). This test is a measure

Table 1: Country of origin, manufacture and expiry dates of seven brands of chloroquine Figure

Brand	Country of Origin	Date of Manufacture	Expiry Date	NAFDAC* Registration
A	Nigeria	February, 2003	February, 2006	Yes
B	China	September, 2002	September, 2005	Yes
C	India	November, 2001	October, 2004	Yes
D	India	November, 2002	October, 2005	Yes
E	India	February, 2003	January, 2006	Yes
F	India	March, 2001	February, 2004	Yes
G	London	April, 2001	April, 2004	No

* *National Agency for food and drugs administration and control, Abuja, Nigeria*

of the tablet's ability to withstand abrasion during packaging, shipping and handling. The failure of some of the brands is possibly due to the use of insufficient amount of binder in the tablet formulation, inadequate moisture content during compression or insufficient compression pressure. A consequence of this is possible loss of drug content leading to insufficient dose delivered to the patient.

A direct correlation of this could be observed in the crushing strength determinations for the seven brands of tablets, where tablets that failed the friability test also had low crushing strength values. A crushing strength value of 4kgF is considered minimum for a satisfactory tablet [8] and brands A, B, D, F and G failed this test. Tablets with low crushing strength will not have ability to resist chipping, abrasion or breakage under conditions of transportation, storage and handling. The crushing strength of the tablets is an essential criterion in the determination of the ability of the tablets to resist chipping, abrasion or breakage under conditions of storage, transportation and handling before use. The results showed that the brands examined had mean crushing strength within the range of 2.2 – 4.3 kgF. These two tests, crushing and friability are now required for tablets as stipulated in the recent specifications in the official books.

The values of crushing strength CS and friability F provide measures of tablet strength and weakness, respectively. Thus, CS-F ratio (CSFR) can be used as a measure of the mechanical strength of the chloroquine phosphate tablets. The higher the CSFR, the stronger the tablet [10]. The values of CSFR are presented in Table 2. Brands C, E and G gave very high values which showed their good mechanical properties while brands A, B and D gave quite low values. It should be noted that both crushing strength and friability tests are now official requirements for tablets.

The disintegration test measures the time required for tablets to disintegrate into particles. This could be a necessary condition for dissolution and subsequently the rate-determining step in the process of drug absorption. The type and amount of excipients in a tablet formulation as well as the manufacturing process are all known to affect both the disintegration and dissolution parameters [9,11]. All brands however passed the BP 1998 standard which stipulates a disintegration time of not more

Table 2: Physicochemical properties of seven brands of chloroquine phosphate tablets

Parameter	Weight uniformity test, mg(mean ± sd)	Friability, % loss (mean ± sd)	Crushing strength, KgF (mean ± sd)	Crushing strength friability ratio (CSFR)	Disintegration time, min (mean ± sd)
Brand A	304.1 ± 3.4	2.8 ± 0.6*	2.2 ± 0.8	0.78	3.3 ± 0.5
Brand B	340.5 ± 4.7	1.4 ± 0.2*	2.7 ± 1.3	1.93	2.3 ± 0.4
Brand C	321.2 ± 1.5	0.4 ± 0.1	4.0 ± 1.8	10.00	11.2 ±0.2
Brand D	333.7 ± 3.6	1.6 ± 0.3*	2.4 ± 0.3	1.50	6.3 ± 0.5
Brand E	355.3 ± 1.5	0.4 ± 0.2	4.3 ± 2.2	10.75	10.1 ± 0.3
Brand F	318.3 ± 1.8	0.5 ± 0.1	2.2 ± 1.6	4.40	4.4 ± 0.2
Brand G	334.1 ± 1.4	0.4 ± 0.2	3.5 ± 2.2	8.75	5.3 ± 0.5

* *Failed to meet BP specifications*

Table 3: Active drug content of the seven brands of chloroquine phosphate tablets (mean ± sd)

Brand Code	%w/w (mean ± sd)
A	100.1 ± 0.4
B	93.4 ± 1.2
C	98.0 ± 0.1
D	97.0 ± 1.6
E	111.4 ± 0.3*
F	112.4 ± 2.1*
G	100.6 ± 0.1

**Failed BP specification*

than 15 minutes for uncoated tablets. All brands disintegrated within 12 minutes. This rapid disintegration may be due to the type and amount of disintegrant used in the formulations. It could be observed that tablets with low crushing strength also had low disintegration time. This could be accounted for by the use of a high amount of disintegrant and or low compression pressure.

The results of the assay of chemical content to determine the amount of chloroquine phosphate present in each formulation are presented in Table 3. Brands A, B, C, D and G had the stated amount of chloroquine phosphate in the tablets, having between 92.5 -107.5% while brands E and F failed. This failure could be due to poor preparation techniques during formulation and subsequent manufacturing. Incorrect weighing and non-satisfactory mixing can also be responsible for non-uniformity of active drug content. This test is of particular importance as good mechanical properties cannot make up for inadequate drug content. This could be a primary cause of treatment failure in malarial fever, although in this case the tablets had more than the stated amount of active ingredient. This may result in increased incidence of adverse drug reaction.

Table 4: Dissolution parameters of the seven brands of chloroquine phosphate tablets (mean ± sd)

Brand Code	T_{50}	T_{80}	% Dissolved at 45min
A	8.3 ± 1.2	43.2 ± 1.7	81.0 ± 1.5
B	14.0 ± 0.4	47.1 ± 1.1	78.2 ± 2.6
C	9.1 ± 0.1	31.8 ± 3.1	86.1 ± 0.3
D	18.3 ± 3.2	45.3 ± 2.1	80.3 ± 0.7
E	21.9 ± 0.4	44.2 ± 2.2	75.2 ± 0.4
F	24.3 ± 2.7	43.4 ± 5.4	83.1 ± 2.1
G	11.4 ± 0.6	29.2 ± 3.2	89.5 ± 3.2

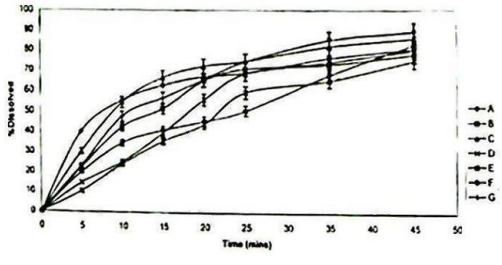

Fig. 1: Dissolution profiles of seven brands of chloroquine phosphate in 0.1M HCl at 344nm

The dissolution test is a measure of the amount of drug released into the dissolution medium with time. The United States Pharmacopoeia stipulates that at 45 minutes, 75% of the labelled amount of chloroquine phosphate should have been released into the dissolution medium. The dissolution profiles of the seven brands are presented in Figure 1. The time for 50% and 80% (T_{50} and T_{80}, respectively) of drug to be released and the amount of drug released at 45 minutes are presented in Table 4. This implies that all brands tested will release significant amount of the drug for absorption within the stated time and thus lead to good therapeutic response.

All brands passed the drug release tests while one failed at least one of the tests to determine the mechanical properties of the tablets.

Conclusion

Only brand C passed all the tests stipulated for uncoated tablets. Brands A, B, C, D and G passed the content uniformity test, Brands C and E passed the crushing strength test and brands C, E, F, G passed the friability test. The brands assessed were not equivalent using physical and chemical parameters hence cannot be interchanged in the treatment of malarial fever.

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