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Quality assessment of some commercial brands of Acyclovir tablet marketed in Abuja, FCT, Nigeria.

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ABSTRACT

Background: Acyclovir is a widely used medication for treating herpes simplex and varicella-zoster virus infections, including herpes encephalitis. This study aimed to evaluate the quality of different acyclovir tablet brands available in Abuja, Nigeria.

Methods: Four brands of acyclovir tablets were purchased from community pharmacies and assessed for quality control parameters, including weight variation, active ingredient content, hardness, thickness, diameter, friability, disintegration time, and dissolution.

Results: All samples met the USP specification limits for weight variation, active ingredient content, friability, thickness, and diameter. Except for brands A and D, which failed to meet hardness specifications, all samples passed the hardness test. All samples fulfilled disintegration time and dissolution tolerance limits, indicating that none of the samples were counterfeit or substandard.

Conclusion: This study demonstrated that all acyclovir brands evaluated met quality specifications for most parameters, ensuring their efficacy and safety for use in treating herpes infections.

1. Introduction

Acyclovir (a synthetic purine nucleoside analogue), which belongs to the Class III Biopharmaceutical Class System, is a widely used antiviral medication for treating herpes simplex virus (HSV) infections, including herpes encephalitis, genital herpes, and cold sores[2]. It is also effective against varicella-zoster virus (VZV) infections, such as shingles and chickenpox[3]. Acyclovir's selective inhibitory activity against herpes viruses is attributed to its affinity for viral thymidine kinase, an enzyme encoded by HSV and VZV[4]. This enzyme converts acyclovir into its active form, acyclovir triphosphate, which inhibit viral DNA replication[5]. The drug's greater efficacy against HSV compared to VZV is due to more efficient phosphorylation by viral thymidine kinase[6]. Acyclovir's pharmacokinetics have been extensively studied[7]. It dissolves well in bodily fluids but has difficulty passing through biological membranes, which can affect how much of the drug is absorbed and becomes available in the body[8]. The drug is primarily eliminated unchanged through the kidneys via

glomerular filtration and tubular secretion[9]. Only a small fraction (8-14 %) is metabolized to 9-carboxymethoxymethylguanine, which is excreted in the urine. Oral administration results in approximately 20 % bioavailability[10]. The plasma elimination half-life of acyclovir ranges from 2.5 to 3.3 hours, and protein binding is relatively low, between 9 % and 33 %[11]. Despite its long-term use, there is a need for ongoing evaluation of its efficacy and safety, particularly in the context of generic medications[12]. Ensuring the quality of generic acyclovir tablets is crucial, especially in low- and middle-income countries where substandard or falsified medicines can have devastating consequences[13]. In sub-Saharan Africa, the World Health Organization estimates that at least 1 in 10 medicines are substandard or falsified, resulting in significant economic and health burdens[14]. This study aims to evaluate the quality of four brands of acyclovir tablets purchased from retail pharmacies in Abuja, Nigeria, providing baseline data for potential bioequivalence studies and informing regulatory bodies and manufacturers about the importance of post-marketing surveillance. By assessing the quality of these essential medications, this study can contribute to ensuring the efficacy and safety of acyclovir tablets and promoting public health in Nigeria.

Materials and Methods

Materials

Four commercial brands of acyclovir tablets (400 mg), 2M hydrochloric acid (Merc Germany), 0.1M sodium hydroxide (CDH, India).

Acyclovir tablets were obtained from the retail outlets mainly from private pharmacies and drug stores in Abuja, Nigeria. The drug samples were anonymously purchased in their original package as supplied by the manufacturers and protected from direct sunlight.

The sample information with respect to physical requirement for packaging and labelling was observed and recorded. Information such as batch number, NAFDAC number, expiration date, label claim and manufacturing date was observed and recorded in table 1.

Table 1. Sample information and packaging requirements for the commercial brands of Acyclovir tablets assessed.

	BATCH NO.	NAFDAC NO.	MFG. DATE	EXP. DATE
A	CC09579	04-1935	09/2022	08/2025
B	DFD2669A	NIL	NIL	05/2025
C	V1956	NIL	NIL	10/2025
D	MG8W	NIL	11/2022	11/2023

Instrument and equipment

A UV/VIS spectrophotometer (Agilent Carry 60 UV-VIS-G6860A, Malaysia), Analytical balance (Ohaus MC 173467, USA), Friabilility tester (Karl Kolb D-6072 Dreieich. West Germany), Dissolution tester (BioBase BK-RC8), Tablet thickness & Diameter tester (Mosanto, West Germany), Disintegration tester (BioBase BK-BJ2, China), Hardness tester (Karl Kolb D-6072 Dreieich. West Germany), Water bath & mechanical shaker (SHZ-82, China).

Methods

Four brands of Acyclovir 400 mg tablets were used in the study. Weight uniformity, dissolution, hardness, thickness & diameter, friability and disintegration test were done as described in the United State Pharmacopeia. While the assay for the content of active ingredients was done as described in the British Pharmacopoeia. Dissolution profiles were constructed for each drug product.

Weight uniformity test

The test for uniformity of weight for each brand of Acyclovir tablets was carried out as described in pharmacopoeia[15]. The weights of twenty tablets were determined individually using an analytical balance. The mean tablet weight and relative percent standard deviation were calculated.

Assay of Acyclovir tablet

The acyclovir content in the four brands was analyzed using UV/VIS spectrophotometry, following the British Pharmacopoeia method[16]. The process involved weighing and powdering ten tablets. To a quantity of the powdered tablets containing 0.1g of Acyclovir, 60ml of 0.1M sodium hydroxide was added and dispersed with the aid of a sonicator for 15 minutes. Sufficient quantity of 0.1M sodium hydroxide was added to produce 100ml, which was filtered. To 15ml of the filtrate, 50ml of water and 5.8ml of 2M Hydrochloric acid and sufficient water was added to produce 100ml. To 5ml of the solution, 0.1M HCl was added to produce 50ml, and was mixed well. The absorbance of the resulting solution was measured at the maximum at 255nm, using 0.1M HCl in the reference cell. The content of $C_8H_{11}N_5O_3$ was calculated taking 560 as the value of A (1%, 1cm) at the maximum at 255nm.

Hardness test

Six tablets were randomly selected from each brand. The crushing strength of tablets from each brand was tested by applying increasing pressure until the tablet broke, using a tablet tester. The pressure at the point of breakage was recorded as the crushing strength[17].

Friability test

Tablets from each batch were tested for friability by rotating them in a friabilator for 4 minutes at 25 rotation per minute. The weight loss was calculated as a percentage to determine the tablets' durability and resistance to abrasion[17].

$$f=w1-w2/w1 \times 100$$

Disintegration test

The disintegration time of tablets from each brand was tested in a disintegration tester filled with 600mL of 0.1N HCl at 37 ± 2°C. The time it took for the tablets to break apart and pass through the basket mesh was measured[15].

Dissolution test

The dissolution test was conducted using a paddle apparatus with 900 ml of 0.1 N HCl as the medium at 37 ± 0.5°c. tablets were added, and samples were withdrawn at intervals to measure the amount of drug released using UV/VIS spectrophotometer at 254 nm[15]. The percentage of drug released was calculated, and a dissolution profile was plotted.

Prior to the dissolution testing, a stock solution of acyclovir (1000 g/ml) was prepared by dissolving 10 mg of the standard drug in 0.1N HCl in a 10 ml volumetric flask, sonicating for 5 minutes, and then making up the volume to the mark. This stock solution was then diluted to in two steps: first, 1 ml was diluted to obtain a 100 g/ml solution, and then 5 ml of this solution was further diluted to 10 ml to achieve a final concentration of 50 g/ml. Then, further five dilutions (25, 20, 15, 10, 5) g/ml were made. These concentrations were measured at wave length of maximum absorbance of 254 nm, and the absorbance values obtained were plotted against their respective concentrations[18] (figure 1), to obtain the calibration equation

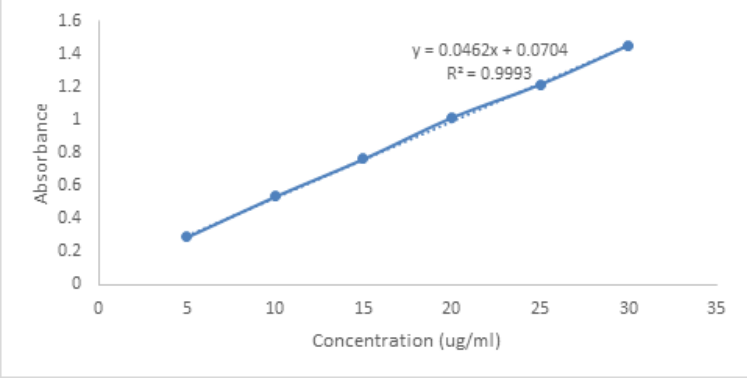

Figure1. Calibration plot for acyclovir

Results

Table 2. Thickness (T), diameter (D), weight variation (WV), hardness (H), friability (F), disintegration time (Dist) and assay (A) values for brands of acyclovir tablets. (Results expressed as standard deviation where applicable).

	T (mm)	D (mm)	WV (g)	H (KgF)	F (%)	Dist (min)	A (%)
A	3.85±0.26	11.21±1.16	0.525±0.35	11.21±1.16	0.02	3.86±0.80	98.3
B	5.57±0.54	8.39±0.36	0.608±0.29	8.39±0.36	0.08	0.5±0.00	98.9
C	4.02±0.25	12.16±0.66	0.580±0.28	6.20±11.61	0.07	0.3±0.00	98.2
D	3.92±1.28	12.27±1.14	0.551±1.28	12.20±0.80	0.07	1.43±0.06	98.9

A summary of the properties of the various brands whose quality were assessed is shown in table 2 and figure 2.

The results for the weight uniformity test shows that tablet weight across brands tested ranges from 0.525 g to 0.608 g, and all products met the USP specification limitation, with a relative standard deviation of not more than 5 %.

All brands met the BP specification for drug content for acyclovir tablet. The highest content recorded was for sample B (98.9 %), while sample C contains the least amount of the active drug (98.2 %)

The average value of hardness of the various brands tested ranged from 3.07 KgF to 12 KgF. Values for samples B and C were within the limit range of 4-10 KgF.
All samples met accepted criteria for tablet thickness and diameter (less than 2 % relative standard deviation).

All samples met the specification for friability testing with values ranging from 0.02 % to 0.07 %.
Mean disintegration time for brands tested were less than 4 minutes, meeting the pharmacopoeia limit of not more than 15 minutes for conventional tablets.
All samples met the dissolution testing specification for acyclovir, releasing at least 80 % of the stated amount within 45 minutes.

Discussion

Although, specific studies on acyclovir tablets are limited, research on similar medications highlights the importance of rigorous quality assessment and regulatory oversight. In our evaluation of four acyclovir tablets (400 mg) brands, all met official packaging requirements, including proper labeling with essential information. However, two brands lacked manufacturing date, and notably, three brands were not registered with NAFDAC, Nigeria's drug regulatory agency (Table 1).
The absence of a regulatory number on a medication raises serious concerns, including: Potential lack of rigorous testing and approval, compromising safety, efficacy, and quality; None adherence to good manufacturing practice regulations; Risk of counterfeit or substandard products; Difficulty tracking the medication's origin and distribution chain; and a Potential for treatment failure, adverse effects, and public health impacts[19,20,21,22].
These findings underscore the significance of our study and the need for strict regulatory oversight to ensure medication quality and safety.

Disparity in tablet weights within a batch could affect the extent of drug release[18]. A weight uniformity test is required to assure that the drug content in each unit dose is distributed in a narrow range around the label strength. If the drug substance forms the greater part of the oral solid dosage form, any weight variation obviously reflects variation in the content of active ingredient. The average weight of the tablets ranged from 525 mg to 608 mg for the 400 mg acyclovir brands, while their weight uniformity test results showed that all products met the USP specification limits, indicating acceptable uniformity of weight[15]. The relative standard deviation was less than 5 %, across batches.

In the pharmaceutical industry, hardness of the tablets is an important parameter because pharmaceutical tablets must have sufficient ability to survive the handling forces during packaging and shipping. If a tablet is too hard, disintegration time and drug release may be slowed, while a

too soft tablet may not withstand handling. Several factors influence tablet hardness, including: lubricant type and concentration; powder density and particle size; tableting speed; compression force; storage conditions; binder type; and drug concentration[17]. These factors can impact the tablet's overall quality and performance. Although the brands of Acyclovir tablets which had failed the hardness test still exhibited very good quality control parameters such as dissolution profile, disintegration time and drug content.

Uniform thickness and diameter don't guarantee uniform active pharmaceutical content, but significant variations in these parameters can lead to differences in disintegration, dissolution, and weight variation, affecting tablet quality[3]. Although, all brands contain the right amount of active ingredient, our study's assay results still underscore the importance for regular quality assessments for pharmaceutical products on the market, as some brands may not meet quality standards.

Friability is a measure of tablet strength assessed via resistance to fracture and abrasion[17]. Our data indicated that the entire tablet samples showed impressive friability values. A separate study has reported friability value for an orally disintegrating acyclovir tablet to be less than 1 % as well[3]. Tablets need to withstand wear and tear during handling and transportation to prevent damage like chipping or fragmentation[17]. A tablet's friability is influenced by its surface roughness and moisture content, with rougher surfaces and higher moisture levels increasing the likelihood of breakage[18].

Disintegration is the breakdown of the interparticulate bonds which holds tablets together upon contact with the disintegration fluid[15]. Disintegration testing ensures lot-to-lot uniformity in formulation development and is linked to dissolution rate[3]. A disintegration test can serve as a surrogate for dissolution testing under specific conditions. Factors like excipients, storage conditions, and manufacturing processes affect disintegration time, which is crucial for drug absorption and efficacy[3]. These factors that typically affect tablet disintegration didn't seem to impact the brands tested, as all disintegrated within the specified time frame for conventional tablets.

The dissolution test measures the proportion of drugs dissolving in a prescribed time under standardized in vitro condition[3]. Same products with different formulations, different inactive ingredients, and different formulation design may have different dissolution profiles or release characteristics and therefore may have different bioavailability[23]. In this study, the mean percentage dissolution when calculated on the basis of time showed that none of the brand released less than 80 % of the stated amount in 45 minutes as stipulated in the USP. Our findings correlate Sakore and Chakraborthy's study on the in vitro-in vivo correlation of immediate-release acyclovir[23].

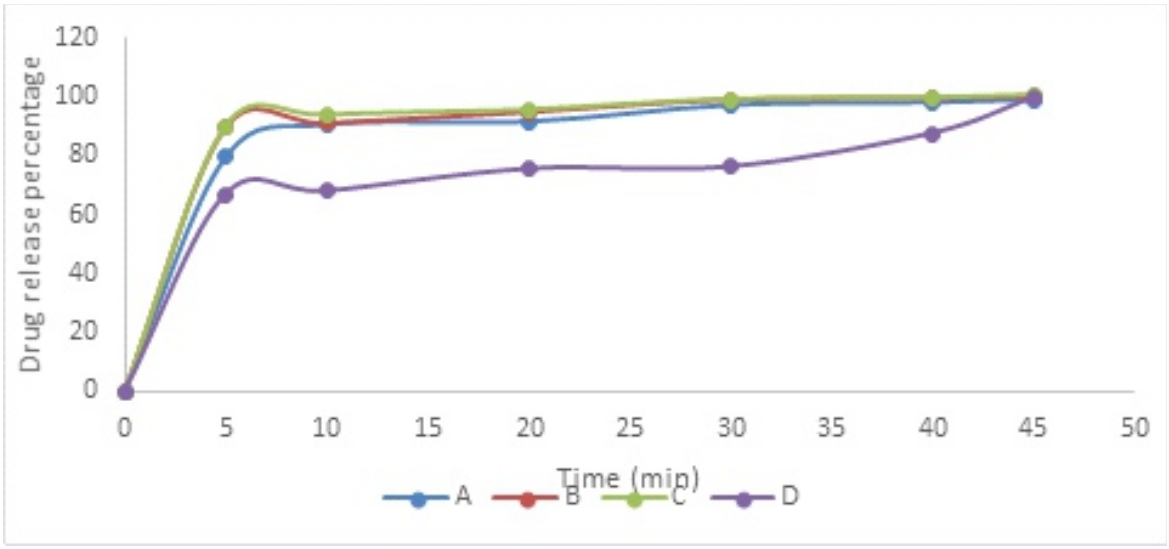

Fig 2. Drug percentage release curve of sample A-D

Conclusion

This study evaluated the quality of four brands of acyclovir tablets and found that all brands met pharmacopoeia specifications for active ingredient content, weight uniformity, disintegration time, thickness, diameter, friability, and dissolution. However, two brands failed to meet the hardness test specification. Despite this, all brands complied with USP dissolution tolerance limits. To further ensure the quality and efficacy of essential drugs, continuous post-marketing surveillance is necessary. Additionally, further studies should investigate the correlation between in vitro dissolution and in vivo bioavailability to validate the specification limits.

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