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IN VITRO QUALITY ASSESSMENT OF FIVE BRANDS OF LOW DOSE ASPIRIN TABLETS MARKETED IN ENUGU, NIGERIA

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ABSTRACT

This study investigated the quality of low dose aspirin (acetyl salicylic acid) tablets marketed in Enugu, Nigeria. Five brands of low dose aspirin 75 mg and 81 mg (coded LDA-A, LDA-B, LDA-C, LDA-D and LDA-E) were purchased from different retail pharmacies within Enugu. Each of the brands was evaluated for wholesomeness of both the packaging materials and tablets, organoleptic, mechanical properties, disintegration time, content of active ingredient, and dissolution profile using standard methods. The results reveal that all the containers were intact and properly labelled while the weight of the tablets ranged from 0.108 ± 1.852 - 0.273 g ± 0.703 %, crushing strength (1.58 ± 0.333 – 6.57 ± 0.453 kgF), friabilities were ≤ 1 % (except brand LDA-D), disintegration time (< 15 min), content of active ingredient (95.672 ± 0.571- 98.177 ± 0.215 %) and dissolution (> 80 %) within 30 min. All the brands met the British Pharmacopoeia specifications for uniformity of weight, content of active ingredient and dissolution. Only batches LDA-A and LDA-E passed the crushing strength test. In conclusion, all the brands of low dose aspirin contained the labelled amounts and had good dissolution but only samples LDA-A and LDA-E were of good mechanical strength. Besides the challenge of possible loss of the physical integrity of the tablets during transportation and handling, all the brands of low dose aspirin tablets were of good quality and would be therapeutically beneficial to the consumers.

KEYWORDS: Low dose, aspirin, tablets, quality, assessment, British Pharmacopoeia.

INTRODUCTION

Quality control of medicines is important and remains one of the major processes of ensuring that pharmaceutical products are fit for their intended use, comply with the requirement of the marketing authorization and do not expose consumers to health risks.[1] Effective quality control procedures help to ensure the quality and consistency of pharmaceuticals from manufacturer to distributor, to consumers and even from batch to batch.[2,3] Poor quality medicines are serious public health problems, particularly in emerging economies and developing countries.[4] In an attempt to ascertain the enormity of the challenge, the increasing availability of deliberately falsified drugs has been on the front burner, although the problem is not limited to falsified drugs. It has also been found out that substandard medicines are also widely circulated and patients are exposed to them because of poor manufacturing and quality control practices during processing/manufacture of genuine medicines by the manufacturers of such medicines.[5,6] Many countries of the world especially the third world countries such as Nigeria are faced with the menace of substandard, fake or adulterated drugs, treatment failure, and drug toxicity amongst other undesirable adverse health implications arising from the circulation of unwholesome drug products.[7] An assessment of the situation by the World Health Organization (WHO) shows that between 2013 and 2017, an estimate of about 42 % of the world's pharmaceutical trade on fake drugs were reported from the African region.[8] An earlier report has documented that up to 25 % of all drugs consumed in poor countries are alleged to be counterfeit or substandard.[9] According to the WHO, counterfeit medicines are medicines that are deliberately and fraudulently mislabeled with respect to their identity and/or source. This definition is applicable to both branded and generic products.[10,11] The categorization of medicines regarded as counterfeit may include the medicines with correct ingredients, wrong ingredients, without active ingredients, with incorrect amounts of active ingredients or with fake packaging.[12] Generally, an assumption can be made that all counterfeit drugs could be substandard but a substandard drug may not be considered as counterfeit if there is no intent to deceive.[13]

Acetylsalicylic acid (aspirin) was discovered in 1853 by Charles Frédéric Gerhardt as an outcome of reacting acetyl chloride with sodium salicylate.[14] Aspirin is a non-steroidal anti-inflammatory drug that has been widely employed because of its analgesic and antipyretic activity for the reduction of pain and fever, prevention of clotting of blood as well as the reduction of inflammation when given at higher doses.[15] It also suppresses the normal platelet function. When a low dose of aspirin is used for a long term it could reduce incidences of heart attack or the prevention of further heart attacks in patients that have had a previous one.[16] Also, it could be beneficial in patients that have a high risk of blood clothing colorectal cancer.[17]

In 2016, the United States Preventive Services Task Force (USPSTF), recommended the use of low-dose aspirin in the primary prevention of cardiovascular disease and colon cancer in adults aged within 50 to 59 years. Such patients are supposed to have 10 % or greater than 10-year cardiovascular disease (CVD) risk, should not be at increased risk for bleeding, have a life expectancy of at least 10 years, and should be willing to take low-dose aspirin daily for at least 10 years.[18]

The scourge of fake, adulterated and substandard products across the globe and especially in countries such as Nigeria where the drug distribution chain has been infiltrated to a large extent by charlatans, coupled with the poor storage conditions and the deleterious effects of the environment such as increased humidity for a greater part of the year, post market surveillance on the quality especially in terms of the active pharmaceutical ingredient remains a major challenge to the health sector and the consumers of these products. In the past, some work has been done and reported on the quality assessment of some brands of 300 mg aspirin tablets marketed in some towns in Nigeria such as Maiduguri and Benin.[19-22] The data reported by these researchers show that a worrisome percentage of the products do not contain their label claims. This work was embarked upon to ensure that patients and especially geriatrics that are saddled with the risk of cardiovascular disease and whose health improvement may be dependent on the use of low dose aspirin are not exposed to fake, substandard or counterfeit of this drug which would invariably worsen their cardiovascular health and lead to morbidity and/or mortality.

MATERIALS AND METHODS

The following materials were used as procured: Five (5) brands of low dose aspirin (75mg and 81mg) tablets (Pharmacies within Enugu), pure aspirin powder (JT Bayer, USA), sodium acetate (Merck, Germany), acetic acid, hydrochloric acid, sodium hydroxide (JHD, China) and distilled water (Pharm. Tech. Lab., University of Port Harcourt, Nigeria).

Sourcing/collection of sample

Five low dose aspirin samples/brands coded LDA-A, LDA-B, LDA-C, LDA-D and LDA-E were randomly purchased from different retail pharmacies in Enugu, Nigeria. A total of 300 tablets of aspirin from each manufacturer was purchased. The label information on the packet of the different brands of aspirin tablets such as the name and address of the manufacturer, name and concentration/strength of the active pharmaceutical ingredient (API), dates of manufacture and expiry, batch/lot number and National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria, registration status were checked and recorded.

Physical appearance

The physical appearance of the tablets were visually examined for defects such as chips, stains and cracks or any other form of physical defect. The color and odor were also observed.

Identification test

Three tablets of each brand were pulverized to fine powder and 200 mg amount of each powder was collected and put into different test tubes. Four (4 ml) of sodium hydroxide was added to each of the test tubes, boiled for 3 min and cooled. To each tube was added 5 ml of dilute sulphuric acid, swirled to mix and filtered. The resultant residue was washed severally with distilled water, dried at 105 ˚ C until sufficiently dried. A portion of the dried powder was dissolved in sufficient distilled water and ferric chloride solution added to it. The aspirin solution was observed and color formed was noted.[23]

Weight uniformity test

Twenty tablets each of brands LDA-A, LDA-B, LDA-C, LDA-D and LDA-E were picked at random. The tablets from the same brand were individually weighed and the mean weight, standard deviation and coefficient of variance was calculated and recorded for each of the brands.

Crushing strength test

Ten tablets which were selected through a random picking of tablets from each brand were used for the crushing strength test. Each of the tablets was placed between the spindle and the anvil of the Monsanto-Stoke hardness tester (Singhla Scientific Industries, India) and pressure was applied by screwing the knob until the tablet cracked or was crushed. Readings were taken of the pressure at which breaking or crushing took place. The mean and standard deviation for each determination was recorded.

Disintegration time test

A model ZT 122 disintegration apparatus (Erweka, Germany) was used to determine disintegration time. Five hundred (500) ml of 0.1 N hydrochloric acid (HCl) was poured into the 1 L beaker of the disintegration tester. This was put in a water bath and both the disintegration media and bath temperatures were warmed

up to and maintained at 37 ± 0.5 ˚C. Six tablets that were selected at random from each brand of the aspirin tablets were individually placed into each of the six tubes of the basket rack assembly of the disintegration apparatus. The disintegration equipment was switched on and the disintegration time was recorded as the time when no particle of the tablet or its palpable core remained on the mesh of the tube of the basket.[24] Replicate determinations were done for each brand. The mean disintegration time and standard deviation for each brand of the tablets was determined and recorded.

Thickness and diameter determination

Ten tablets were picked at random from each brand of the aspirin tablets. The thickness and diameter of the tablets were individually determined using a micrometer screw gauge. The mean and standard deviation for each determination was recorded.

Friability test

Ten tablets from each brand of the aspirin tablets were chosen at random. The tablets were dusted, collectively weighed and the weight noted. The tablets were placed in the drum of a tablet friability testing machine, model TAR 200 (Erweka, Germany) and the friabilator was operated at 25 rotations per minute (rpm) for 4 min. At the end of the test, the tablets were removed, dedusted and reweighed.[24] Replicate determinations were done. The percentage friability for each brand was determined using equation 1.

$$F = [1 - \frac{Wf}{Wi}] \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where F is friability, W_i is the initial weight and W_f is the final weight.

Crushing Strength Friability Ratio

The crushing strength friability ratio of the tablets were calculated from the hardness and friability data. It is expressed as ratio of the two parameters and aids in determination of the mechanical strength of the tablets.

Determination of the wavelength of maximum absorption (λ_{max}) of aspirin

Some quantity of aspirin pure sample powder was pulverized into a fine powder using a mortar and pestle. A 100 mg quantity of this was weighed into a 100 ml volumetric flask. A stock solution of the aspirin was made with sodium acetate buffer solution (pH 4.8) to obtain a 100 mg/100 ml (1 mg/ml) solution. Serial dilutions of the aspirin stock solution was done using the acetate buffer solution to obtain 0.2, 0.4, 0.6, 0.8, and 1.0 mg % solutions. The 0.2 mg % solution was scanned in a model 6405 UV/Vis spectrophotometer (Jenway, England) to obtain the maximum wavelength of absorption at 264 nm.

Standard calibration curve of aspirin

The 0.2, 0.4, 0.6, 0.8 and 1.0 mg % solutions of aspirin obtained from the dilution of the stock solution of aspirin were scanned using the spectrophotometer at a wavelength of 264 nm to obtain their absorbance readings. A plot of the absorbance readings against their concentrations was made to obtain the standard calibration equation given as equation 2.

$$Y = mx + c \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$$

Where Y is the absorbance value, m is the slope, x is the concentration and c is the intercept.

Assay of aspirin tablets

A total of twenty tablets were randomly picked from the different brands of aspirin tablets. Each set of twenty tablets was weighed collectively and pulverized in a porcelain mortar. A quantity equivalent to the mean weight of the twenty tablets was weighed into a 100 ml volumetric flask where it was dispersed in 60 ml of acetate buffer (pH 4.5). The volume of the resultant aspirin dispersion was made up to 100 ml in the volumetric flask using the acetate buffer solution.[24] Filtration was done and the solution obtained was scanned through the spectrophotometer at a wavelength of 264 nm. The absorbance readings were fitted into the standard calibration equation which had been earlier established in order to calculate the concentration of the aspirin. This procedure was used for each of the five brands of aspirin being evaluated. Replicate determinations were done.

Dissolution test

A six station model DT 600 (Erweka, Germany) dissolution equipment was used to determine the dissolution or drug release profile of the different brands of aspirin tablets. The British Pharmacopoeia Apparatus I (Basket) method was employed. Five (500) ml of freshly prepared acetate buffer (pH 4.5) was placed in a 1 L beaker of dissolution equipment that was warmed up to 37 ± 0.5 ^{o}C. One tablet was put in each of the beakers and the speed of rotation of the basket was set at 50 rotations per minute.[24] The dissolution equipment was switched on and at 5 min intervals, 5 ml samples were withdrawn from the beaker which was immediately followed by 5 ml replacements using acetate buffer maintained at the same temperature. Filtrates obtained from the different withdrawn samples were scanned in the model 6405 UV/Vis spectrophotometer (Jenway, England) at wavelength of 264 nm. Conversion of the absorbance readings into concentrations were done by fitting the data obtained into the standard calibration equation that was earlier determined.

Statistical evaluation

Data were statistically evaluated using SPPS version 21 (SPSS Inc., Chicago, Illinois, USA). One way analysis of variance (ANOVA) was used for the determination of data sets and results were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Physical parameters

The physical inspection results of the different brands of aspirin tablets are shown in Table 1. They all contained

information on the name and locational address of the manufacturers and/or importers/representatives in the country, names and concentration or strength of the API, batch or lot number, NAFDAC registration number (except brand LDA-D), manufacturing date (except brand LDA-D and LDA-E) and expiry dates. These information were found conspicuously written on both the primary and secondary packaging of the different brands of aspirin tablets.

Some of the organoleptic test results show that brands LDA-A, LDA-C and LDA-D were white in color, tasteless and odorless while LDA-B was orange looking, odorless and had a sour taste. Brand LDA-E was yellowish in color, had no taste and odor.

All the brands did not have any physical defects such as capping or chipping on any of the tablets examined. This implies they were of reasonable mechanical strength, and were adequately protected by the packaging/containers where they were kept/stored.

Table 1: Some information on the aspirin tablets labels/containers.

Sample/batch code	Country of manufacture	NAFDAC registration	Date of Manufacture	Date of expiry	Label claim
LDA-A	Israel	Registered	06/2018	06/2021	81 mg
LDA-B	Nigeria	Registered	6/2018	06/2021	75 mg
LDA-C	Nigeria	Registered	05/ 2018	05/2021	75 mg
LDA-D	United Kingdom	Nil	Nil	07/2021	75 mg
LDA-E	Brooklyn, USA	Registered	Nil	03/2021	81 mg

Identification

The observation of a purple color after the addition of the Ferric chloride solution to the aspirin solution confirmed that all the brands contain acetyl salicylic acid (aspirin).

Weight uniformity

The results of the uniformity of weight test for all the tablets are shown in Table 2. All the brands of the aspirin tablets weighed less than 250 mg except brand LDA-A which had a greater weight (Table 2). The coefficient of variance for all the brands was less than 1 % implying that the tablets met with the British Pharmacopoeia (BP) requirements for such tablets. The BP stipulates that tablets weighing more than 84 mg but less than 250 mg, should have percentage coefficient of variance of not more than 7.5 % while for tablets weighing > 250 mg, the deviation in variance of their tablet weight should be within 5 %.[24] It was also observed that there was a significant difference in the weight of all the tablets ($p < 0.05$) and that all the tablets passed the test based on the British Pharmacopoeia set limits. Thus it is expected that they should contain their label claim of aspirin assuming proper blending/mixing of the API and excipients was done at the time of formulation by the manufacturer.

Crushing strength

The crushing test results are shown in Table 2. The crushing strength of LDA-A was 6.570 ± 0.453 kgF and this represents the highest value amongst the five brands of aspirin tablets being evaluated. Brand LDA-C had the least crushing strength of 1.580 ± 0.333 kgF. Statistical comparison shows that there was a significant difference ($p < 0.05$) in all the batches of the aspirin tablets. Conventionally, tablets are considered to be mechanically strong if they have crushing strength values of ≥ 4 kgF.[24] Since, brands LDA-C and LDA-D did not have crushing strength values up to 4 kgF, they are considered to have failed the crushing strength test implying that these brands may have their tablets crumbling when exposed to the stresses of handling and transportation. Brands LDA-A, LDA-B and LDA-E passed the crushing strength test. The crushing strength friability ratio results also show that the mechanical strengths were in the order of LDA-A > LDA-E > LDA-B > LDA-C > LDA-D (Table 2).

Disintegration time

The disintegration time results of the aspirin tablets are shown in Table 2. All the brands disintegrated within 15 min. There was a significant difference in the disintegration times of all the batches of aspirin tablets ($p < 0.05$) and these brands are considered to have passed the disintegration time test based on the British Pharmacopoeia specification. The British Pharmacopoeia stipulates an upper limit of 15 min as the disintegration time requirements for uncoated tablets.[24] The disintegration time of these tablets show that they will easily break up into smaller fragments upon oral ingestion and release their active ingredient for dissolution and absorbance to enable the eliciting of therapeutic effects in the body.

Friability

Table 2 contains the results of the friability of the different low dose aspirin tablets. Both brands LDA-A and LDA-E were not friable while the rest of the other brands of the low dose aspirin tablets had friability values that were less than 1 %. There was a significant difference ($p < 0.05$) in the friability values of all the batches except between batches LDA-A and LDA-E ($p > 0.05$). Conventionally, uncoated tablets are expected to have friability values of ≤ 1 % in order to pass this test.[24] When the friability values are less than 1 %, it is expected that such tablets would be able to overcome the abrasive stresses encountered during packaging, transportation and handling.

Crushing Strength Friability Ratio

The crushing strength friability ratio results (Table 2) shows that only batch LDA-D had a poor result implying poor mechanical strength. All other batches passed the test implying good inter particle bonding and mechanical strength within the tablet based on the surface area.

Table 2: Some physical properties of aspirin tablets.

Brands	Uniformity of weight {g ± CV[%]}	Crushing strength (kgF)	Disintegration time (min)	Friability (%)	*CSFR
LDA-A	0.273± 0.002	6.570 ± 0.453	6.202 ± 0.011	0.001 ± 0.000	6570.000
LDA-B	0.161±0.008	4.560 ± 0.171	1.105 ± 0.010	0.574 ± 0.001	4560.000
LDA-C	0.127 ±0.005	1.580 ± 0.333	2.114 ± 0.002	0.155 ± 0.001	10.194
LDA-D	0.145 ±0.003	2.430 ± 0.082	0.901 ± 0.001	1.648 ± 0.020	1.475
LDA-E	0.108 ± 0.002	5.190 ± 0.358	6.350 ± 0.100	0.001 ± 0.000	5190.000

*CSFR is Crushing Strength Friability Ratio

Content of active ingredient

The assay results showing the amount/quantity of aspirin contained in the tablets of the different brands of the commercial aspirin tablets coded LDA-A to LDA-E are shown in Figure 1. Their aspirin content ranged from 93.672 ± 1.492 – 98.331 ± 2.345 %. The BP stipulates that the aspirin content in aspirin tablets should not be less than 95 % or more than 105 % of the label claim.[24] Thus all the brands met with this specification except LDA-B implying that the label claims of the concentration contained by each brand on the package by the manufacturer was true except for brand LDA-B.

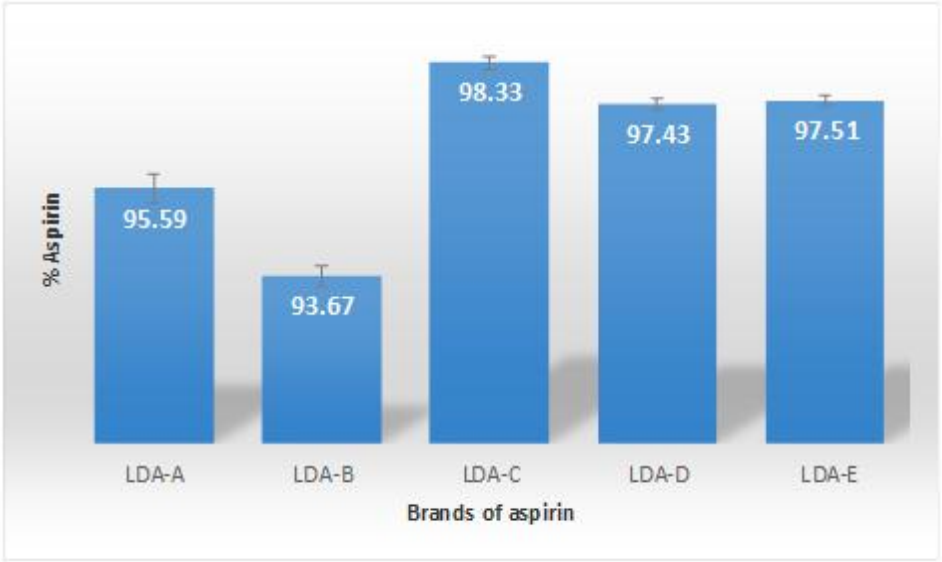

Fig.1: Assay results of some commercial brands of low dose aspirin tablets.

Dissolution/aspirin release from the tablets

The dissolution or release profile of aspirin from the different brand of aspirin tablets is shown in Figure 2. More than 80 % of the aspirin content of each tablet was released from all the brands within 30 min. Generally, there was a gradual increment in the release rate of aspirin as the time increased. Brand LDA-C had the highest dissolution while LDA-E had the least dissolution. This pattern was found to be consistent at all sampling times. The release pattern also conforms to the British Pharmacopoeia specifications for uncoated tablets which stipulates that not less than 80 % of the active pharmaceutical ingredient would be released within 30 min.[24] Therefore, the tablets passed the dissolution test and would release their aspirin content in good time when orally ingested to elicit its therapeutic response.

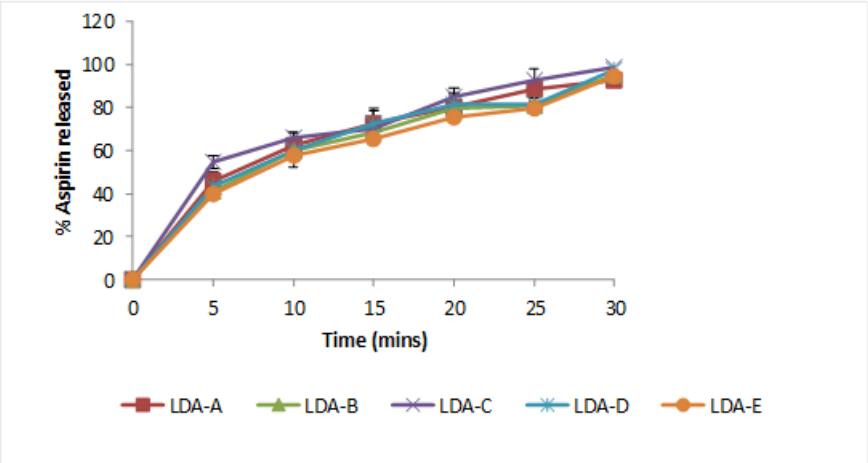

Fig. 2: Dissolution of aspirin from some commercial brands of low dose aspirin tablets

Time of drug release at T_{50}, T_{80} and T_{90} (%) concentration

The time for 50, 80 and 90 percentage concentration of aspirin release during dissolution designated as T_{50}, T_{80} and T_{90} % respectively are shown in Table 3. At 50 % aspirin release (T_{50} %), it was observed that it was attained at between 4.00 min (LDA-C) to 8.00 min (LDA-E). There was a significant difference ($p < 0.05$) for the time it took all the batches of the aspirin tablets to attain 50 % dissolution except for batches LDA-A and LDA-D, LDA-B and LDA-E that did not have a significant difference ($p > 0.05$) in the dissolution time. At $T_{80\%}$, the aspirin dissolution times were between 18.00 min (LDA-C) to 25.50 min (LDA-E). There was a significant difference ($p < 0.05$) in aspirin release for all the batches except between batches LDA-A and LDA-B ($p > 0.05$). At $T_{90\%}$, the times taken were between 23.00 min (LDA-C) to 28.50 min (LDA-E). Consistently, at the three concentrations that were considered, batch LDA-C had the least dissolution time while LDA-E had the highest time. Generally, the order of times taken to attain these concentrations were LDA-C < LDA-A < LDA-C< LDA-D < LDA-E.

Table 3: Time of aspirin release at T_{50}, T_{80} and T_{90} (%)

Batch	T_{50} (%)	T_{80} (%)	T_{90} (%)
LDA-A (min)	6.500	20.000	26.000
LDA-B (min)	7.500	20.500	27.500
LDA-C (min)	4.000	18.000	23.000
LDA-D (min)	7.500	19.000	27.500
LDA-E (min)	8.000	25.500	28.500

CONCLUSION

The physical inspection of the containers of the low dose aspirin tablets showed that they were intact and not tampered with. The necessary label information showing the name and the locational address of the manufacturer, number of tablets contained per pack, the strength/concentration of aspirin per tablet, manufacturing and expiry dates and the NAFDAC registration status were conspicuously indicated. The physical parameters showed tablets that had a minimum variation in weight for all the brands, good disintegration time and friability which met with the British Pharmacopoeia specifications, while two brands LDA-C and LDA-D failed the crushing strength test as their crushing strengths were < 4 kgF. The quantity of aspirin contained by each brand of tablets evaluated met with the specified British Pharmacopoeia amounts except brand LDA-B (93.672 ± 1.492 %). Aspirin release from the different commercial brand of tablets was more than 80 % within 30 min which was also compliant with the British Pharmacopoeia specification. Considering most of the evaluation parameters, it was observed that the aspirin tablets passed most of the assessment parameters except the crushing strength as observed in brands LDA-C and LDA-D. The different commercially available low dose aspirin tablets were found to be of good quality and would lead to good therapeutic response and good health of the consumers of these products.

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