

Full Length Research Paper

Comparative utilization of visual, potentiometric titrations and UV spectrophotometric methods in the determination of Ibuprofen

Benjamin U. Ebeshi*, Kehinde E. Oseni, Augustine A. Ahmadu and James O. Oluwadiya

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, Niger Delta University, P. M. B. 071, Wilberforce Island, Bayelsa State, Nigeria.

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The accuracy and reliability of the analytical results are critical in ensuring quality, safety, and efficacy of pharmaceutical products. However, to ensure these criteria, the choice of appropriate analytical method is required. This study sets out to compare the efficacy of visual, potentiometric titrations and UV spectrophotometric methods in the determination of the quality of Ibuprofen tablets in Nigeria. Eight different brands of Ibuprofen tablets were purchased from local pharmacies and drug stores. Visual, potentiometric titrations and UV spectrophotometric methods were utilized in the quantification of the different brands. The label claims of the various brands were assessed base on the different methods. The results obtained were compared with the official specification for uniformity. All the eight different brands of Ibuprofen tablets conform to the USP specification for the percent purity of the active principle using the visual titration, whilst one out of the eight brands did not conform to the USP specification with potentiometric titration as well as four out of the eight brands also, did not meet the official compendium specification using the UV spectrophotometric method. It can be inferred from this study that the choice of analytical method is critical in ascertaining the exact quality of pharmaceutical products.

Key words: Visual titration, potentiometric titration, UV spectrophotometry, analytical methods, Ibuprofen.

INTRODUCTION

The proliferation of substandard and adulterated pharmaceutical products is a global phenomenon, which has been of great concern to many countries including Nigeria (Clarke, 2002). The resurgence of substandard drug products especially, in Nigeria is as a result of a number of factors, which include poor drug procurement and distribution practises, low literacy level, inadequate information on the circulation of substandard products, lack of facilities for effective quality control analyses as an important element in quality surveillance and ineffectiveness of drug regulatory authorities. These problems have being further compounded in that Nigeria imports most drugs to meet its healthcare need from far-east Asia countries such as, China and India. It was not too long

ago that the World Health Organisation (WHO) rose to the challenge of recommending that all importing countries should protect themselves from this menace by undertaking sampling of products within the distribution network as an important element in quality surveillance (WHO, 1988).

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) is a propionic acid derivative of Iso-butyl benzene and chemically known as, (\pm)-2-(p-Isobutylphenyl)propionic acid (Figure 1). It has analgesic, antipyretic and anti-inflammatory activity. It is formulated into different dosage forms such as, tablets, gel pellets and syrups which, are widely used due to its high efficacy and tolerance when compared with other substances e.g. Aspirin, Indomethacin and Pyrazolone derivatives such as Dipyron, Antipyrine, Aminopyrine and Propyphena-zone (Lopez et al., 1999).

Many methods, both official and non-official, have been used to analyze the active pharmaceutical ingredients as

*Corresponding author. E-mail: benebeshi@yahoo.com. Tel: +234-8059817538.

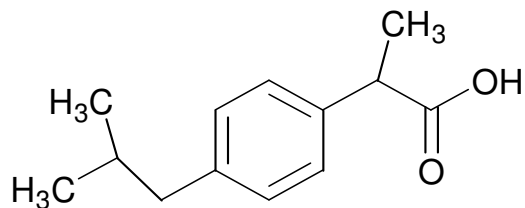


Figure 1. Structure of Ibuprofen.

well as the pharmaceutical preparations of Ibuprofen. These methods include; direct titration using sodium hydroxide in methanol, potentiometric titration, high performance liquid chromatography, UV spectrophotometry (Satheesh-Manikandan et al., 2001) and flow injection infrared analysis. Capillary electrophoresis and isotachopheresis have also been used to analyze the drug and other NSAIDs. The visual titration method with sodium hydroxide is simple, cost-effective and it is found in British Pharmacopoeia (BP) as a method for the quantification of raw Ibuprofen (BP, 2008). However, coloured and insoluble excipients contained in the tablets might interfere in the observation of the endpoint of the reaction. In the potentiometric titration, the interference of the excipients is avoided since the end point of the reaction is detected through the slope change of the electromotive force (EMF) or the pH versus the volume of the titrant. This method is suitable for the analysis of ibuprofen tablets using tetrabutylammonium salt in aceto-nitrile (Cakirer et al., 1999; Issopoulos, 1995). The high performance liquid chromatography (HPLC) is a very versatile technique for the quantitative determination of pharmaceuticals. The method allows for the analysis of both ibuprofen and its degradation product such as 4-Isobutylacetophenone (Lampert and Stewart, 1990). The off column pre-treatment of the sample might constitute a limitation in the utilization of this method, if the excipients or the active ingredients are insoluble in the mobile phase. Furthermore, capillary electrophoresis and isotachopheresis methods are economic, easily applicable, selective and accurate for the analysis of ibuprofen (Donato et al., 1994; Persson-Stubberud and Astrom, 1998). However, the method requires experienced technologist and not acceptable by regulatory agencies (Sadecka et al., 2001). Also, Garrigues et al. (1993) developed a method for the quantitative analysis of ibuprofen by measuring the carbonyl absorption of the acid function in an FT IR spectrometer on line injection device, though; the device is not commercially available. Many official documents describing the criteria of validation are available. However, these concern mainly chromatographic analysis and bio-analytical methods of pharmaceutical products, but they do not propose any experimental protocol for direct potentiometric methods using ion-selective electrodes applied in pharmaceutical analysis. In this work, we are proposing a simultaneous

utilization of more than one analytical strategy based on the normative and regulatory guidelines applied in quality surveillance of pharmaceutical products.

MATERIALS AND METHODS

Materials

Secondary standard of Ibuprofen extracted from Brustan-N, Ethanol 96%, Chloroform, distilled water, Sodium hydroxide (0.1M), Phenolphthalein solution, Eight (8) different Brands of Ibuprofen 400 mg tablets were purchased from Pharmacies and Patent medicine shops in Amassoma and Yenagoa, Bayelsa State, Nigeria and were coded A to H. Their batch and official registration (NAFDAC) numbers and the address of the manufacturer for each brand as well as their corresponding manufacturing and expiry dates were duly documented.

Methods

Uniformity of weight

Ten (10) tablets of each product were accurately weighed individually on an analytical balance (Shimadzu, Japan) and the average weight calculated. The percentage deviations of the individual weights from the average weight were computed.

Isolation and assay of pure Ibuprofen

Ten tablets of Ibuprofen (Brustan N[®]) were accurately weighed and powdered in a mortar. The powdered Ibuprofen was dissolved in 100 ml of water and stirred gently for about 10 min. The resultant solution was poured into a separation funnel and shaken with 100 ml chloroform. The organic layer was removed. More chloroform (50 ml) was added to the aqueous layer and the mixture further shaken. The chloroform layer was separated and added to the already separated chloroform layer. The total chloroform layer was filtered through a sintered glass and upon evaporation of the solvent a needle-like crystals, which weighed 9.2 g was obtained. The ¹³C and ¹H NMR were performed on the crystals to ascertain the structural composition of Ibuprofen. The extracted ibuprofen, weighing 0.216 g was dissolved in 50 ml ethanol by warming in a boiling water-bath, after which 8 drops phenolphthalein solution was added. The solution was titrated with standardize 0.1M NaOH solution, until colour change was observed.

Assay of Ibuprofen tablets by visual titration

Powdered Ibuprofen tablets weighing 0.303 g of the sample A was dissolved in 25 ml ethanol and warmed on a boiling water-bath. Phenolphthalein solution (4 drops) was added and the solution titrated with 0.1 M NaOH until the end-point. The titration was repeated two times and the volume of titrant used (0.1 M NaOH) as well as the mean values are as shown in Table 1. A blank titration was carried out without Ibuprofen. The same procedure was repeated for Ibuprofen tablet samples B to H. The amount of sodium hydroxide consumed by each sample A to H was noted. The percentage content of each sample was then calculated.

UV calibration curve for Ibuprofen

A stock solution of Ibuprofen (1 mg/ml) was prepared by weighing accurately 100 mg of the extracted Ibuprofen as the secondary

Table 1. Titre values obtained from the visual titration for samples A to H.

Sample	Titre value of 0.1M NaOH				Mean titre value \pm SD (ml)	(Purity \pm deviation) %
	First titration (ml)	Second titration (ml)	Third titration (ml)			
Isolated standard Ibuprofen	9.90	9.80	9.80		9.83 \pm 0.06	
A	9.60	9.70	9.50		9.60 \pm 0.1	97.66 \pm 1
B	9.50	9.40	9.40		9.43 \pm 0.06	95.93 \pm 0.6
C	9.40	9.50	9.60		9.50 \pm 0.1	96.64 \pm 1
D	9.60	9.50	9.50		9.53 \pm 0.06	96.95 \pm 0.6
E	9.50	9.60	9.70		9.60 \pm 0.1	97.66 \pm 1
F	9.50	9.40	9.40		9.43 \pm 0.06	95.93 \pm 0.6
G	9.70	9.60	9.50		9.60 \pm 0.1	97.66 \pm 1
H	9.70	9.60	9.60		9.63 \pm 0.06	97.96 \pm 0.6

standard into a 100 ml volumetric flask. Approximately, 50 ml of 0.1 M NaOH was measured and transferred into the volumetric flask containing Ibuprofen with shaking to dissolve the drug. The volumetric flask containing the dissolved Ibuprofen was made up to the 100 ml mark with 0.1 M NaOH. Serial dilutions of the stock solution were made to give the following concentrations; 0.05, 0.10, 0.15, 0.20, 0.25, 0.30 and 0.35 mg/ml in aq. NaOH (0.1M). The UV absorbance of each concentration was measured at the wavelength (λ_{max}) of 265 nm using a UV-VIS Spectrophotometer (Shimadzu, Japan). The graph of absorbance was plotted against the concentrations to give the standard curve using Microsoft excel 2007.

UV analysis of Ibuprofen tablet samples

A stock solution of Ibuprofen tablet powder (1 mg/ml) was prepared by accurately weighing amount equivalent to 100 mg of the active principle for the various samples A – H into a 100 ml volumetric flask using the same procedure as in the calibration curve except that the solution was filtered before it was made up to 100 ml mark with 0.1M NaOH. Two concentrations (0.15 and 0.20 mg/ml) were prepared from the stock solutions by serial dilution for each sample and their respective absorbance was taken. The absorbance was extrapolated on the calibration curve to determine the unknown concentration and the percentage content of each sample was calculated.

Potentiometric titration

The pH meter (Gallenkamp, England) was standardized against a buffer solution of pH 4. The burette was filled with sodium hydroxide solution (0.1 M). The Ibuprofen tablet powder was dissolved in 50 ml of 96% ethanol in a beaker and pH of the drug solution was initially determined. Sodium hydroxide solution (0.1 M, 1 ml), was added drop-wise with stirring into the beaker and the pH change noted. As the pH rises, the amount of titrant added was reduced to 0.5 ml as the end-point is approached by a sharp drop in the pH. This approach was repeated for all the samples. The Mean profiles of pH of the samples A - H was plotted against the volume of the titrant following potentiometric titration as shown in Figure 2.

RESULTS

Uniformity of weight

The percentage deviation of each tablet from the average

weight for the samples A –H ranged from 0.83 to 2.81%.

Assay of Ibuprofen in tablet samples by visual titration

The titre values of 0.1 M NaOH after three titrations for the samples A to H, the mean titre values, percent purity as well as the standard deviation obtained from the visual titration are as shown in Table 1. The upper percentage standard deviation for all the samples following titration with 0.1 M NaOH is approximately 1%. This indicates a good control of the manual operation of the titration. The percentage purity was calculated by taking the ratio of the mean titre value of sample against the mean titre value of the standard Ibuprofen and multiplied by a 100. All the samples had percentage purity within the official compendium limit (BP, 2008) which, specified that the Ibuprofen content should be within 95 – 105%.

UV spectrophotometric assay for samples A-H

The percentage purity for Samples A–H determined by UV spectrophotometry is shown in Table 2. Only sample B showed outright low percentage purity compared to the official requirement (BP, 2008) as its percentage deviation of approximately 27% from the mean of all the samples is quite high and can be considered to be substandard. On the other hand, the percentage purity of samples C and F can say to be substandard on account of overage with percentage deviation of approximately 19 and 49% respectively.

Potentiometric titration of Ibuprofen tablets samples A-H

The percentage purity for samples A–H determined by potentiometric titration is shown in Table 3 and the result indicates a correlation with the visual titration except for

Table 2. The percent purity of samples A-H following UV analysis.

Sample	% Purity	% Deviation
A	100.00	9.1
B	75.00	26.78
C	140.00	19.18
D	103.00	6.98
E	100.00	9.1
F	182.00	48.88
G	100.00	9.1
H	103.00	6.98

Table 3. The percent purity of samples A-H after potentiometric titration.

Sample	Titre value of 0.1M NaOH (ml)	% Purity	% Deviation
A	11.5	115.32	9.31
B	10.5	105.31	2.23
C	9.7	97.27	3.46
D	10.0	100.29	1.32
E	10.0	100.27	1.34
F	9.5	95.29	4.86
G	9.8	98.27	2.75
H	10.5	105.29	2.21

sample A, where overage is found with high percent deviation of 9.3%. The mean profiles of samples A-H indicating the titration curve of the change in pH against the volume of titrant (0.1 M NaOH) added after the potentiometric titration is shown in Figure 2. The equivalence point which, is the point at which the end point of potentiometric titration is determined, can be seen when the average volume of titrant added for all the samples was slightly less than 11 ml. Thereafter further volume addition of the titrant produced a gradual plateau as change in pH becomes insignificant.

DISCUSSION

The standards for uniformity of weight are applied to tablets which are supplied in unit dose forms because they are subject to more variations than comparable preparations supplied in multi dose forms. For tablets with average weight above 250mg, the percentage deviation from the average weight permissible in the official compendia (BP, 2008; USP, 2006) is $\pm 5\%$. The eight different brands (samples A - H) of ibuprofen tablets passed the test for uniformity of weight. Though sample G exceeded the 5% deviation from the average weight of the tablet, it still conformed to the official compendia specification that not more than one tablet must deviate by 5% from the average weight if ten tablets are used for the test.

The implication of a tablet deviating by more than 5% from the average weight is an indication of an increase in the quantity of the active ingredient above permissible average and this could result in higher plasma concentration of such tablet beyond the maximum safe concentration when administered. It is therefore important to carry out the uniformity of weight test in order to assess the uniformity of the content of the active ingredient in each unit dose. Although the weight of a tablet is not necessarily equal to the amount of active ingredient present, but it is a reflection of the amount of active principle expected to be contained in each tablet.

Analytical assay methods were carried out on the various ibuprofen tablets samples to ascertain that the products contain the required amount of the active ingredient and to investigate the possibility that passing or failure to pass a quality control analysis by a pharmaceutical preparation may result from the inefficiency or limitation of the analytical method employed. The samples were assayed volumetrically by visual titration, an official compendia method of assay and two additional techniques, which include UV spectrophotometry and potentiometric titration.

The eight brands of Ibuprofen brands conform to the official limits of 90 –110% (USP, 2006) following the use of visual titrimetric method. Sample H has the highest percentage content of 97.8%, while Sample B has the least percentage content of 95.7% when visual titrimetric method was employed as shown in Table 1. The percent

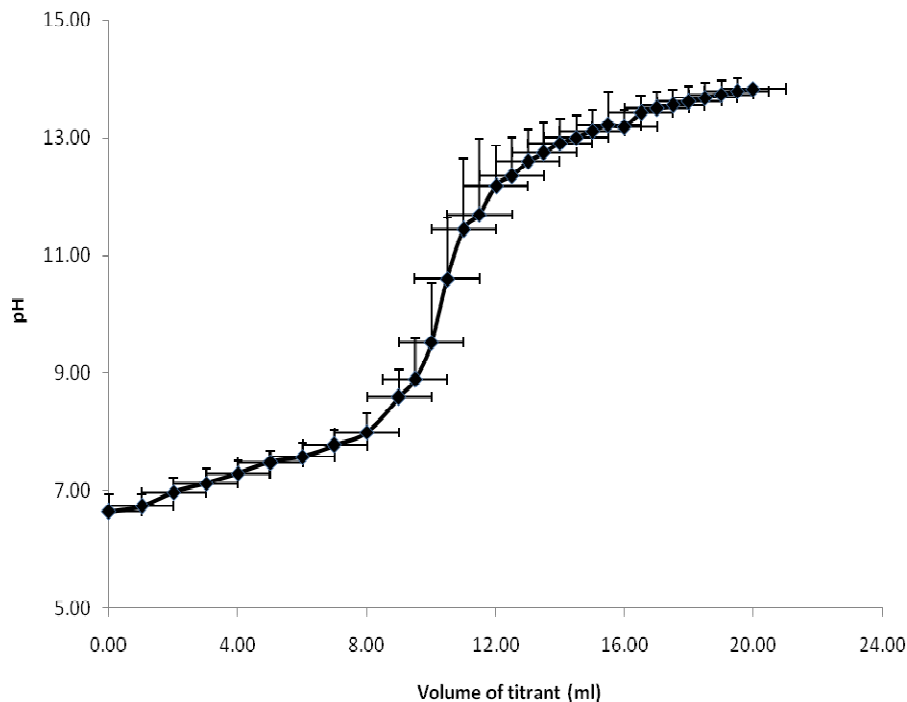


Figure 2. Mean profiles of Samples A-H following potentiometric titration with 0.1M NaOH.

deviation (approximately 1%) for all the samples after the visual titration shows that the manual operation of the titration was highly sensitive and reproducible.

UV spectrophotometric method is suitable for the analysis of ibuprofen tablets since it contains suitable chromophore that absorbs radiation in the UV region of the electromagnetic wavelength (λ_{\max} 265nm). It has been used for the assay of drugs quantitatively. The calibration curve for reference ibuprofen was linear over a concentration range of 0.05 to 0.35 mg/ml with the regression line equation obtained as $Y = 1.8679x - 0.0263$ is in line with the Beer-Lambert's law. The correlation coefficient ($R^2 = 0.998$) allows for accurate reading of the concentrations of all the test samples. The UV spectrophotometric method was therefore sensitive and reproducible. The assay of Samples A – H by UV spectrophotometric method gave results that showed that not all the samples fall within the BP limits. This implies that not all the samples contain the required amount of the active ingredients as specified by the BP. Samples A, D, E, G and H fell within the BP range while samples B, C and F fell outside the BP range as shown in Table 2. The amount of active ingredient of 75% in sample B fell far below the BP, 2008 range of 95 – 105% and can be said to be substandard whereas the amount of the active principles in samples C and F are well above the BP range and could also be said to be substandard on the ground of overage. The implication of overage of this nature is grave since drug products are potential poison and therefore when administered at dosages exceeding their limits may predispose patients to adverse drug

reactions. The failure of samples B, C and F to pass quality assurance tests may stem from under incorporation of active ingredient or over-incorporation of active principles to probably meet the accelerated stability testing, poor formulation, poor storage facilities since presence of chromophores in drug substances makes them light sensitive and possible adulteration.

In potentiometric titration, the change in pH is measured as a function of the volume of the titrant added. The equivalence point of the reaction is shown by a sudden change in the pH. This is indicated by the plot of the pH reading against the volume of the titrant as shown in Figure 2. Potentiometric assay showed that seven out of the eight samples conform to the stated limit as required by the BP (Table 3). Sample A gave a value of 115.3% with 9% deviation from the mean percent purity of all the samples. Sample A fail to conform to the stated limits on account of overage which, may result from over-incorporation of the active principles or poor formulation.

Comparing the three methods used for the analysis of the drug samples, it is obvious that the classical visual titration method shows that all the samples passed the quality control analysis unlike the instrumental methods that indicates otherwise. This may be because; the visual titrimetric method, though relatively inexpensive and simple but it is less sensitive and less selective than the UV spectrophotometry and the potentiometry methods. Also, recalibration of equipment is essential towards obtaining a reproducible and precise results, which is always the case with the instrumental methods use but recalibration is not required with the visual titrimetric method, thus

limiting its efficiency. Potentiometric method offer additional advantage of quantitation, especially where the endpoint is masked and no indicator is suitable (e.g. where analyte solution is coloured or turbid). Also, spectrophotometric analytical method is very useful where a large number of sample determinations are required.

Compliance with officials' standards as stipulated in the monographs is a measure of the authenticity of a preparation. Therefore, the efficacy of these methods to validate all the test samples is essential. The implication of our findings is that no single method is adequate to authenticate the quality of particular drug samples, especially when large numbers of such samples are involved.

We suggest that in carrying out post market surveillance of the quality of pharmaceutical products, manufacturers or regulatory authorities should employ the use of more than one analytical method to authenticate the quality of such products, since in such cases; large amounts as well as wide range of products are considered for evaluation.

Conclusion

The assay of the eight different brands of Ibuprofen tablets from different manufacturer using the analytical methods as highlighted may serve as a necessary panacea when quality surveillance of large number of drug samples are being considered. Simplicity and cost-effectiveness of an analytical method may not be the overriding factors for the choice of analytical method to validate label claims of manufacturers by regulatory authorities.

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