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Evaluation Of Some Selected Brands of Iron Containing Liquid Preparations Marketed In Ilorin, Kwara State

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ABSTRACT

Background: The issues of continuous Quality control checks of medicines within our society cannot be over emphasized. These routine checks go a long way in providing information about the quality and efficacy of medicines being sold in the pharmaceutical market.

Objectives: This work focused on physical, chemical and microbiological quality control analysis of different brands of liquid preparations containing Ferric Ammonium citrate as one of its active ingredients marketed in Ilorin, Kwara State. It also examines the effect of the concentration of iron content of blood tonic on some physical parameters of the different brands of blood tonic.

Methods: A total of seventeen brands of liquid preparations containing Ferric Ammonium citrate as one of its active components was sourced from twenty major registered Pharmacies located in Ilorin, Kwara State. The assay of the Iron content of the samples of blood tonic was carried out using official titrimetric method. Microbiological analysis was done using pour plate method to determine bacterial and fungi counts of samples. Specific gravity and pH of the samples were done using viscometer (Brookfield, England) and digital pH meter (Jenway, UK) respectively.

Results: Analysis showed that four (equivalent to 23.5%) of the samples failed the chemical analysis according to specified standards in some official compendia while microbiological analysis showed that all the samples complied with stated official standards. Results also showed that the quantity of Ferric Ammonium citrate in the various samples had an effect on the pH of the blood tonic ($p = 0.005$) but does not have any effect on the specific gravity of the various samples used for this study ($p= 0.845$).

Conclusion: Generally, a substantial number of samples used for the study failed the chemical quality check carried out on them using official methods. Routine checks should be done on these medicines especially by regulatory bodies to ensure that these drugs comply with stated standards.

1. Introduction

The World Health Organization (WHO) defines a substandard medicine as an authorized medical product that does not meet quality standards or specifications, produced by a known manufacturer with no intent to fool or defraud the patient. Substandard medicines enter the legitimate supply chain and reach patients when the technical capacity to enforce good manufacturing practices (GMP) and good distribution practices (GDP) is limited. WHO also defines a falsified medicine as a medical product that is deliberately and fraudulently mislabeled concerning identity and source. Falsified medicines are produced in unsanitary and unregulated conditions by an unknown manufacturer. They can contain incorrect quantities of the active pharmaceutical ingredient (API), inert ingredients and dangerous contaminants. The packaging of falsified medicines is nearly always identical to the original medicine, making it challenging to identify without running a series of detection tests on the contents of the medicine[1-4].

One major area of concern is the growing number of substandard and falsified antimicrobials. The WHO Global

Surveillance and Monitoring System reported that 42% of the 1,500 cases of substandard and falsified medical products reported between 2013 and 2017 were from the Africa region[5]. The issue of substandard and falsified drugs cuts across all forms of medicines including antimalarial, antibiotics, antihistamine, analgesics as well as hematinics. Substandard and counterfeit medicines are a widespread problem in low-income and lower–middle-income countries. A systematic review showed that the median prevalence of substandard and counterfeit medicines was 28.5%. This ranged from 11% to 48% in individual studies[6].

Hematinics are nutrients that are required by the body for erythropoiesis, i.e. the production of red blood cells. Clinically, the most important hematinics are vitamin B_{12}, iron and folic acid because deficiency states of these three substances are much more common than for any other hematinic[7]. Use of hematinic or iron supplements has been found to be one way of prevention and treatment of iron deficiency. It has been reported that the most cost-effective way to prevent or treat iron deficiency is to give iron supplements particularly to pregnant women. These supplements can come in tablet, liquid preparations or parenteral. Different salts of Iron used in pharmaceutical preparations include ferrous fumarate, ferrous gluconate, ferrous sulphate, ferric ammonium chloride etc. However, it has been found that liquid preparations deteriorate in storage and may contain minerals and vitamins that are unnecessary for most patients[8].

The objective of this research work is to carry out some quality control analysis on different brands of liquid preparations containing Ferric Ammonium citrate as one of its active ingredients marketed in Ilorin, Kwara State, Nigeria and to determine the effect of the iron content on some physical parameters.

1. Methods

1.1 Materials

Water bath (Surgifield Medical, England), Digital pH meter (Jenway, UK), Viscometer (Brookfield, England), Digital colony counter (Labtech, Italy), Portable bench autoclave (Leaidal Medical, England), Laboratory Hot air oven (Meta lab, India), Bacteria Incubator (Leaidal Medical, England), Fungal Incubator (Leaidal Medical, England), Clean bench laminar flow (Leaidal Medical, England), Sulphuric acid (BDH Analar, England), Potassium Permanganate (BDH Analar, England), Sodium Thiosulphate (Oxford Lab, India), Potassium Iodide (Riedel-de Haen, Germany), Hydrochloric acid (Lobachemie, India), Starch mucilage (Kermel, China), Nutrient Agar (Acumedia, USA), Nutrient broth (Acumedia, USA), Sabourand Dextrose Agar (Lab M, UK), Sabourand Dextrose broth (Lab M, UK) and Deionized water (Peace Standard, Nigeria).

2.2 Sample size determination

Twenty out of the forty registered Pharmacy outlets in Kwara state were selected using simple random sampling. All the available brands of Ferric Ammonium citrate containing liquid preparations in the selected outlets were purchased. A total of seventeen brands were obtained and used for this study.

2.3 Assay of Iron content in samples of Iron containing liquid preparations

The assay was carried out using official titrimetric method for assay of Ferric Ammonium citrate in solutions as described in the Official Pharmacopeias[9,10]. The assay was done in duplicate for each sample. Using the label claim of each of the samples, average percentage content of FAC in each preparation was calculated and recorded.

2.4 Microbiological assay of samples of Iron containing liquid preparations

Bacterial and fungal culture media used for this study including Nutrient Agar and broth (Acumedia, USA); Sabourand Dextrose Agar and broth (Lab M, UK) were reconstituted with freshly prepared deionized water. The culture media were distributed into test tubes and bottles and sterilized at a pressure of 15psi and temperature of 121°C for 15 minutes in a portable bench autoclave (Leaidal Medical, England). The sterilized media were kept until ready for use. Screening for bacterial and yeast/ mold contamination of products were done in accordance with methods described in the British Pharmacopeia[11]. Plates were cultured in duplicate and average colony forming unit (cfu) for bacteria and yeast/mold for each sample were determined and recorded.

2.5 Measurement of pH and Specific gravity of samples of Iron containing liquid preparations

To determine the pH, 20ml of each sample was measured separately into beakers. Measurements of the pH of the samples were thereafter done using the manual instructions of digital pH meter (3510, Jenway, UK). The pH values displayed by the apparatus was recorded for each product.

To determine the specific gravity, 70ml of each sample was measured into the specific gravity bottle of the Viscometer apparatus. Measurement was thereafter done by following

the manual instructions of Viscometer (Brookfield, England). The specific gravity values displayed by the equipment after 30 minutes were recorded for each product.

2.6 Data analysis

Data analysis was done using Statistical Package for Social Sciences (SPSS) version 22 software. Results were presented in form of tables, mean and percentages. Inferential statistics was done using Pearson Correlation and the results obtained from the software were recorded. Obtained p-values of less than 0.05 were considered statistically significant.

2. Results

A total of seventeen different samples of liquid preparations containing Ferric Ammonium Citrate (FAC) were sourced from twenty registered Pharmacies in Ilorin, Nigeria. Each product was coded for confidentiality.

Table 1 shows the general characteristics of the Iron containing liquid preparations used for the study. Majority (8 of the samples) were manufactured in Kwara State, four samples from Ogun state, two samples from Lagos state and three samples were manufactured in India. All products are NAFDAC registered. The pack sizes of the products varied from 100ml to 300ml. The quantity of FAC per 5ml of product was between 32.18mg and 200mg. All products had not expired as at the time of the study.

Table 1: Characteristics of samples of Iron containing liquid preparations

Code	Batch number	Pack size (ml)	Label claim of FAC (mg/5ml)	Production date	Expiry date	Place of manufacture
BT01	PBT506	200	85	February, 2021	February, 2024	Kwara, Nigeria
BT02	1320	100	54	March, 2020	February, 2022	Ogun, Nigeria
BT03	10209	100	32.18	February, 2021	January, 2023	Ogun, Nigeria
BT04	HMA2102	200	80	February, 2021	January, 2024	Lagos, Nigeria
BT05	1121	200	200	January, 2021	December, 2022	Ogun, Nigeria
BT06	BL19I11	300	150	September, 2019	August, 2021	Mumbai, India
BT07	EVT075	200	85	March, 2021	March, 2024	Kwara, Nigeria
BT08	VRS08	200	200	February, 2021	February, 2023	Kwara, Nigeria
BT09	19036	200	53.33	December, 2019	November, 2021	Mumbai, India
BT10	ACI3406	200	200	January, 2021	December, 2023	Ogun, Nigeria
BT11	DS07	100	150	January, 2021	January, 2024	Kwara, Nigeria
BT12	BBT38	300	85	February, 2021	February, 2023	Kwara, Nigeria
BT13	KE20003	200	160	February, 2020	January, 2022	Sikkim, India
BT14	LO162	200	69	January, 2020	January, 2022	Lagos, Nigeria
BT15	VBT29	100	50	October, 2020	October, 2023	Kwara, Nigeria
BT16	PML121	200	85	March, 2021	March, 2024	Kwara, Nigeria
BT17	PSL105	100	85	February, 2021	February, 2024	Kwara, Nigeria

Table 2 shows the result of the physical and chemical analysis carried out on the various brands of Iron containing liquid preparations. The sample with the highest percentage of FAC as per the label claim is BT14 with 123.37% while BT09 had the lowest percentage of FAC in relation with the label claim (56.07%). The pH ranged from between 4.55 to 6.22 and the specific gravity were between 1.0955 to 1.3348.

Table 2: Chemical and physical analysis of samples of Iron containing liquid preparations

Code	Equivalent claimed quantity of Iron in mg/5ml	Average Percentage Content of Iron from Assay	pH	Specific gravity
BT01	17.00	99.05	5.91	1.1267
BT02	11.77	108.88	4.55	1.1928
BT03	7.02	95.31	4.55	1.1534
BT04	16.00	113.38	5.40	1.1129
BT05	40.00	101.68	6.45	1.2093
BT06	30.75	108.04	5.12	1.2069
BT07	17.00	102.35	5.61	1.1798
BT08	40.00	94.72	6.22	1.2781
BT09	10.93	56.07	5.29	1.3348
BT10	40.00	99.20	6.22	1.0955
BT11	30.75	96.03	4.91	1.2662
BT12	17.00	104.88	5.04	1.2836
BT13	32.80	81.56	5.74	1.3123
BT14	14.00	123.37	5.68	1.2671
BT15	10.00	105.86	4.85	1.2683
BT16	17.00	95.05	5.80	1.1301
BT17	17.00	99.75	5.64	1.1476

1. Pearson Correlation between quantity of Iron in mg/5ml and pH: 0.649
   p value: 0.005
2. Pearson Correlation between quantity of Iron in mg/5ml and Specific gravity: 0.051
   p value: 0.845

The microbial analysis conducted on samples of the Iron containing liquid preparations showed that none of the product had pathogen. Table 3 shows that the mean bacterial and yeast/mold count across the various samples. The Mean bacterial counts ranged from 0 to 230 cfu/ml while the mean yeast/mold counts ranged from 0 to 40 cfu/ml.

Table 3: Microbial analysis of samples of Iron containing liquid preparations

Code	Mean bacterial count (cfu/ml)	Mean yeast/mold count (cfu/ml)
BT01	30	40
BT02	100	0
BT03	10	0
BT04	230	0
BT05	0	10
BT06	10	10
BT07	10	10
BT08	40	20
BT09	0	20
BT10	150	10
BT11	0	40
BT12	40	10
BT13	0	40
BT14	180	10
BT15	40	20
BT16	0	10
BT17	30	0

3. Discussion

This is work focused on the evaluation of Iron containing liquid preparations marketed in Kwara state of Nigeria. Iron containing liquid preparations are fast moving medicines in Kwara state because they are Over the Counter (OTC) medicines which makes it easily accessible. Many people purchase them with the belief that they enhance blood volume and quality. It is also popularly prescribed by Prescribers mostly as an adjunct for the treatment and management of various ailments/ conditions. It is therefore, important that these liquid preparations are of the right quality and it must be ensured that manufacturers have incorporated within the formulation, the claimed quantity of active pharmaceutical ingredients which are usually the ingredients that are useful in blood formation.

Although there are various types of Iron containing liquid preparations in the market, preparations containing Ferric Ammonium Citrate (FAC) was chosen to ensure uniformity in the various brands of products being evaluated. This enables same method of analysis to be used on all samples as well as ensure easy comparison of the samples being studied. It was also observed that the preparation chosen for this study was the commonest type of Iron containing liquid preparation around the area under study.

According to the result obtained on Table 1, it was observed that majority (8 samples) were manufactured in Kwara State. This is not surprising because Kwara state is the area of study and has about six active Pharmaceutical Industries, some of which are into production of these iron containing preparations. It is therefore expected that the products of these indigenous Industries will be sold around the area of study. Results also showed that most other samples were manufactured in either Ogun state or Lagos state. This may be as a result of the proximity of these states to Kwara State. In addition, good concentration of Pharmaceutical Industries is found in these two states. Two samples however, were manufactured in India which shows that this class of product are among medicines imported into Nigeria.

All products evaluated had not expired as at the time of this study. A product is expected to maintain all its characteristics within its shelf life and as such, studies carried out on them gives a true reflection of the characteristics and quality of such sample. The pack sizes varied from 100ml to 300ml. It was observed that majority (10 samples) were 200ml pack size. This may be the most acceptable and affordable pack size among patients patronizing these medicines. Only two of the samples, had the largest pack size of 300ml. Again, the issue of affordability may be the reason why such pack sizes are not too common in the market. As earlier mentioned, all the liquid preparations contained FAC but it must be mentioned here that the samples had varying strength of the Active Pharmaceutical Ingredient (API) in the various products. Varying quantity of FAC may be incorporated in different product brands as long as those quantity or doses are within the therapeutic dosage range and are not toxic doses of Iron required by the body daily. The recommended dietary allowance for Iron ranges from 7mg to 45mg depending on age, gender and health conditions although dietary supplements may provide far much higher values and may be recommended by Physicians as required[12]. Moreover, since all the samples used for this study are registered by NAFDAC, it is believed that the regulatory body had evaluated these products at the point of registration and the quantity of active components therein approved before they are being allowed to be sold to the general public.

According to official Compendia, FAC containing hematinic should contain not less than 90% and not more than 110% of label claim of FAC calculated as the Iron content within the preparation[9,10]. Using this as our guideline, the result presented on Table 2 shows that four of the samples failed the assay of claimed Iron content in their respective preparations (sample BT14 containing 113.38% of claimed Iron in mg/5ml; BT09 containing 56.07%; BT13 containing 81.56% and BT14 containing 123.37%). Two of these samples had values less than the lower limit of 90% and two samples had values higher than the upper limit of 110%. Other samples had values within the official specification. Sample BT09 seem to contain just about half of the claimed FAC content in the preparation. The 56.07% is far below the specified official limit. This product falls under the category of substandard product and may not elicit the desired therapeutic effect when ingested. Sample BT14 was marginally above the official limit of 110%. During production, inclusion of overages on some of the APIs within a product may result in excessive quantity, if the overage is not properly weighed and incorporated into the product. This is a possible reason for the value of 113.8% obtained in sample BT14. In addition, improper calibration of the compounding vessel may also be a factor that may lead to obtaining excess or insufficient API(s) within a pharmaceutical product. If the compounding vessel is calibrated below the desirable mark, then we tend to have high content of the raw materials in the product and low yield of such product. The reverse is the case when the compounding vessel is calibrated above the desirable mark. Others factors that may possibly cause low content of active

component include deliberate weighing of insufficient or wrong quantity of the raw material, overshooting of the calibrated mark on the compounding vessel when making up the volume with product solvent and use of a substandard raw material during production. Raw materials should be certified to be of the desired quality before usage for production of medicines.

All the four samples which failed the chemical test can all be said to be substandard product since they are products which have failed the quality assessment and standards set for them[6]. Substandard medicines are also medicines which do not meet quality standards or specifications, produced by a known manufacturer with no intent to fool or defraud the patient[5]. In the case of this study, we assumed that all products used for the study are from known manufacturers since the samples were purchased from accredited Pharmacy outlets with medicines supplied to them through certified sources. Also from Table 2, it can be inferred that based on the Chemical test performed, about 23.5% of the total samples failed and are substandard. This percentage is quite substantial and as such, there is the dire need for regulatory body to intensify their efforts regarding routine checks of pharmaceutical products in the Nigerian market. This result is in line with a survey by the international health care organization which estimated that 25 to 50 percent of the pharmaceutical market is counterfeit in Africa as a whole, with Nigeria being the most affected[13].

The pH of all the samples fell between 4.55 and 6.22. This shows that all samples were acidic. From the analysis carried out, it showed that the pH of the samples tends to increase with increase in quantity of iron in the products. The Pearson correlation results as shown under Table 2 confirmed this (Value of 0.649 and a p-value of 0.005). A study that compared pH and absorbance of Ferric Ammonium citrate in preparations gave a similar result[14]. Higher pH values of the preparations corresponded to higher absorbance and vice versa. This in turn shows that the higher the quantity of Ferric Ammonium Citrate in the preparation, the higher the pH[14]. The pH of Ferric Ammonium Citrate in a water solution of 100g/L at 20°C is between 6 and 8[15]. Other chemicals or raw materials used for the production of iron containing liquid preparations may also have impact on the pH on the product. However, the analysis carried out has clearly shown that Ferric Ammonium Citrate in the product has a significant impact on the pH of the preparations under study.

In contrast, the result from the present study shows that FAC in the preparations has no correlation with specific gravity of the products. The Pearson Correlation revealed a value of 0.051 with a p-value of 0.845. Specific gravity can be influenced by certain components of the preparation. Components like the quantity and quality of thickener added to the preparation can affect the specific gravity and therefore, may be the reason why the quantity of FAC in the product does not necessarily affect its specific gravity.

The Microbial analysis of the various samples of iron containing liquid preparations under study showed that there was no trace of pathogenic organisms in all the products. Bacterial and yeast/mold count all fell within the official acceptable limit. These results are encouraging as all the product samples passed the official compendia specified standards. Official standards specify an average bacterial count of not more than 10^3 cfu/g or ml, fungal load of not more than 10^2 cfu/g or ml and the absence of pathogens in all oral pharmaceutical preparations [11,16,17].

Despite the fact that all the samples passed the stated standards, it is important to point out that manufacturers must strictly adhere to current Good Manufacturing Practice (cGMP) rules to ensure that products have minimal or no microbial contamination. Any form of microbial contamination of the product must be critically looked into even if it is within acceptable limits. If the cause of contamination, no matter how small, is not checked and curtailed immediately, such avenues may lead to higher contamination of samples until a time when the acceptable limits may be exceeded. Contamination may result from many sources including the Personnel, raw materials, equipment, the environment and even the method of production. Cleanliness and Good Manufacturing Practices must be adhered to at all times to minimize or/and eliminate contamination. Most Pharmaceutical Products have also been found to contain preservatives. Some of these preservatives also helps to ensure that microbial load of a product is checked even in a situation where such product has been minimally contaminated. Manufacturers must therefore always ensure that the right quality and quantity of preservative(s) are included in the formulations to help maintain high quality products.

Sterility is not a requirement for non-sterile Pharmaceuticals in official compendia for non-sterile pharmaceuticals but bio burdens need to be within acceptable limits. Contamination of pharmaceuticals with microorganisms irrespective whether they are harmful of non-pathogenic can bring about changes in physicochemical characteristics of the medicines[18]. They can cause spoilage of the product with loss of its therapeutic properties and if they are pathogenic, serious infections can arise[19].

4. Conclusion

This study revealed that the Ferric Ammonium Citrate content of four out of seventeen iron containing liquid preparations studied varied from their label claims using officially acceptable method and range. Microbial qualities of all products were within acceptable official range. The quantity of Ferric Ammonium citrate within the various products significantly affected the products' pH but had no significant effect on their specific gravities.

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