

ASSESSMENT OF MICROBIOLOGICAL QUALITY OF SYRUP AND WATER USED IN PHARMACEUTICAL INDUSTRIES IN KANO STATE, NIGERIA

Olaitan, Morufat O.^{1*} and Muhammad, Bashir²

^{1,2}Department of Microbiology, Bayero University, Kano, Nigeria

*Corresponding author: oluwatorworship2010@gmail.com (+2348139682860, +2349029135352)

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ABSTRACT

The pharmaceutical industry is an essential element of health care system all over the globe, in as much as discovery, development, manufacturing and marketing of pharmaceuticals for human health is of paramount importance. This research was conducted to evaluate the microbiological quality of syrups and water used in pharmaceutical industries selected in Kano State, Nigeria. The selected industries are coded as: Industry A and B. Parameters such as aerobic mesophilic bacterial and fungal count, coliform count and identifications were carried out. Data obtained from the study showed that all the syrup sampled were bacteriologically safe. All plate count of syrups did not exceed the United States Pharmacopoeia acceptable criteria, negative for *Salmonella*, *Shigella*, *Pseudomonas*, and *Escherichia coli*. The levels of coliform contamination in all the analyzed samples (water and syrup) were within the acceptable limit of Most Probable Number (MPN) ≤ 10 . Analyzed water samples also did not exceed the World Health Organization suggested microbial limit for facility water except one which gave 1.2×10^2 , but yet, within the limit for alert. Objectionable organisms were as well not detected except *Alcaligenes faecalis* and *Providencia sp.* Fungi isolated from this study includes *Aspergillus niger*, *A. amstelodami*, *Mucor raemosios*, *Penicillium spinulosum* and *Saccharomyces cerevisiae*. It can be concluded that the microbial limit of the industries assessed are within the limit stipulated by pharmacopoeia.

Keywords: Pharmaceutical industries, Microbiological quality, Pharmacopoeia.

INTRODUCTION

The pharmaceutical industry is an important element of health care systems all over the world, (Uddin *et al.*, 2016). The poor qualities of medicines are not only a health hazard, but also a waste of money for both government and consumers (Bhaskar *et al.*, 2011). Therefore, the maintenance of quality with continuous improvement in facilities is very important in pharmaceutical industries (Bhaskar *et al.*, 2011). To achieve the quality objective, it is necessary to control all stages of drugs, which covers all matters, which individually or collectively influence the quality of a product, including raw materials, manufacturing process and the evaluation of finished product (Ratajczak *et al.*, 2015). One of control stages is the assessment of microbiological quality of medicinal products (Tyski, 2011; GGMPMP, 2013). Water is a reagent that is used in the manufacture of medicinal products (WHO, 2010). Processed water should at minimal meet World Health Organization requirements for drinking quality unless otherwise justified. Inability of water to meet such standards should not be permitted in the potable water

system (NAFDAC, 2010). Water is sufficiently important to be worthy of special attention, not only because it is the most commonly used raw material but also because it is used extensively for cleaning (Hanlon and Hodges, 2013). If water with high level of microorganisms is used as rinsing detergents it might negate the sanitizing effects of any disinfectants that may have been used earlier (Hanlon and Hodges, 2013).

Syrups are viscous oral liquids that may have one or more active ingredients in solution which usually contain large amounts of sucrose or other sugars to which certain polyhydric alcohols may be added to inhibit crystallization or to modify solubilisation, taste and other properties (Uddin *et al.*, 2016). Sugarless syrups may contain sweetening and thickening agents with 95% ethanol being preservative solvent that incorporate flavouring agents, in addition antimicrobial agents are also added into syrups (Uddin *et al.*, 2016). The presence of microbes in syrups is a great public health concern globally (Islam *et al.*, 2015). Contamination of pharmaceutical preparations with

microorganisms irrespective of being pathogenic or non pathogenic can bring about changes in the drugs physical characteristics, including the breaking of emulsions, fermentation of syrups, and appearance of turbidity or deposit; besides producing possible odours and colour changes. The pharmaceutical manufacturing and packaging environment, raw materials as well as the manufacturing water may attribute to the microbiological spoilage of the finished products (Islam *et al.*, 2015; Kabir and Dulal, 2013). The presence of high number of non-pathogenic microorganisms in pharmaceutical products is objectionable as the organisms may deteriorate active ingredients and interfere with the desired activity of the product or generate toxic metabolites (Gad *et al.*, 2011). Since non – sterile pharmaceuticals are not produced by aseptic processes and, thus not expected to be totally free from microbial contaminations which can lead to significant economic loss to the industry as well as morbidity and mortality of the consumers (Hanlon and Hodges, 2013). Therefore, the aim of this research work is to evaluate the microbiological quality of syrup, treated and raw water used in two pharmaceutical industries selected in Kano state, Nigeria.

MATERIALS AND METHODS

Sampling Site

Samples were sourced from two different pharmaceutical industries selected in Kano State, Nigeria and coded as letters A and B.

Sample size and collection

Samples were collected in three (3) batches with two weeks interval for each industry. Samples obtained from the same industry on different days or batches were considered different samples. Therefore, a total number of 18 samples were collected from the two industries.

Study Site and Processing

All samples collected were transported to Microbiology Laboratory, Bayero University, Kano, Nigeria and analyzed within hours of collection. All samples were obtained between September and October, 2016. Serial dilutions were carried out for enumeration methods and isolation and identification was done for detection

of pathogenic microorganisms (Khanom, *et al.*, 2013)

Microbiological Assessment

Aerobic mesophilic bacterial count was done using pour plate technique in accordance to Kabir and Dulal (2013), APHA (1992, 1998), Mbaeyi – Nwaoha and Egbude (2012) and Mbah (2015). Pour plate technique was as well used for the enumeration of aerobic mesophilic fungi count as modified by fatema *et al.*, (2014) and Kabir and Dulal (2013).

The multiple tube fermentation technique was performed to enumerate coliform bacteria count using tubes containing MacConkey broth and inverted Durham tubes (Amira *et al.*, 2012 and as modified by Mbaeyi – Nwaoha and Egbude 2012). Inoculation was carried out as follows:

- i. To each of 3 double-strength MacConkey broth tubes, 10 ml of the original sample was added.
- ii. To each of 3 single-strength MacConkey broth tubes, 1 ml of the original sample was added.
- iii. To each of 3 single-strength MacConkey broth tubes, 0.1 ml of the original sample was added.

All tubes were incubated at 37 °C for 48 hours for the observation of gas production. First reading was taken after 24 hours to record positive tubes, and the negative ones were incubated for another 24 hours. Each gas positive presumptive tube was inoculated into a tube containing 10 ml Brilliant green lactose broth medium.

Identification of the Bacterial isolates

The sample of syrups and water was placed on various selective media such as MacConkey agar, mannitol salt agar, *Salmonella – Shigella* agar, and eosine methylene blue agar and then incubated. The biochemical tests used were catalase, coagulase, methyl red (MR), Voges – Proskauer (VP), indole, triple sugar iron (TSI), citrate utilization (Leboffe *et al.*, 2011; Al – Kaf *et al.*, 2015).

Identification of Fungi

Where possible, fungi were identified to specie

level directly from colonies on PDA media using well – established techniques of macroscopic and microscopic examination and standard reference works for the identification of moulds using lactophenol blue stain (Gautam, and Bhadauri 2012; Obi and Nwannunu 2010). A portion of the obtained culture was placed and teased out into a clean glass slide upon a drop of lactophenol cotton blue using sterile inoculating needles and covered with clean cover slip (El – Gali and Abdulrahman, 2014). The light microscope depended on studying the morphological characteristic and microscopic characteristic which was compared to the mycological atlas for confirmatory identification (Hassan *et al.*, 2014, and Gautam and Bhadaur 2012).

Statistical Analysis

The statistical analysis was done with PC using GraphPad InStat – [DATASET1.ISD], Version 3.05 (2000). Student's t – test statistics was used for comparing the geometric means of the bacterial and fungal counts in the two industries.

RESULTS

Table 1 showed aerobic mesophilic bacterial and fungal counts present within the analyzed syrup, treated water and the raw water samples, of all which were within the stipulated limit except industry A having highest (1.2×10^2 CFU/ml) aerobic mesophilic bacterial count in the treated water. Table 2 further shows the coliform bacterial count of all the three batches of samples with almost all the analyzed syrups, water having 0 – 0 – 0 which is equivalent to 4 MPN/ml on MPN table for all the two industries except raw water of industry B showing the highest count of 1 – 0 – 1 equivalent to 7 MPN/ml. A comparison of the two industries using data obtained showed no significant difference between them ($p > 0.05$). Table 3 reveals the biochemical characteristics of the isolated microorganisms namely *Alcaligenes faecalis* and *Providencia* sp. Table 4 indicates the identified fungal isolates which involved *Mucor racmosios*, *Aspergillus amstelodami*, *A. niger*, *Penicillium spinulosum* and *Saccharomyces cerevisiae*.

Table 1: Aerobic Mesophilic Bacterial and Fungal Counts of the Samples

Parameter	Sample	Industry	Mean of 1st batch	Mean of 2nd batch	Mean of 3rd batch	Acceptance Criteria
AMBC	Syrup (CFU/ml)	A	6.0×10^1	4.0×10^1	<10	10^2 (EP, USP)
		B	3.0×10^1	2.0×10^1	<10	
AMBC	Treated water (CFU/ml)	A	8.0×10^1	7.0×10^1	1.2×10^2	100(WHO)
		B	6.0×10^1	3.0×10^1	<10	
AMBC	Raw water (CFU/ml)	A	2.0×10^2	1.6×10^2	1.7×10^2	200(WHO)
		B	1.6×10^2	7.0×10^1	<10	
AMFC	Syrup (CFU/ml)	A	2.0×10^1	2.0×10^1	1.0×10^1	10^1 (EP; USP)
		B	<10	2.0×10^1	<10	
AMFC	Treated water (CFU/ml)	A	3.0×10^1	3.0×10^1	3.0×10^1	10(USP; EP; BP)
		B	3.0×10^1	3.0×10^1	2.0×10^1	
AMFC	Raw water (CFU/ml)	A	5.0×10^1	6.0×10^1	5.0×10^1	
		B	5.0×10^1	7.0×10^1	3.0×10^1	

Keys: AMBC = Aerobic Mesophilic Bacterial Count; AMFC = Aerobic Mesophilic Fungal Count

Table 2: Coliform Count for the Three Batches of Samples

Sample	Industry	Mean of 1st batch	Mean of 2nd batch	Mean of 3rd batch	Acceptable value
Syrup	A	0 – 0 – 0 = 4	0 – 0 – 0 = 4	0 – 0 – 0 = 4	MPN ≤10
	B	0 – 0 – 0 = 4	0 – 0 – 0 = 4	0 – 0 – 0 = 4	
Treated water	A	0 – 0 – 0 = 4	0 – 0 – 0 = 4	0 – 0 – 0 = 4	
	B	0 – 0 – 0 = 4	0 – 0 – 0 = 4	0 – 0 – 0 = 4	
Raw water	A	0 – 0 – 0 = 4	0 – 0 – 0 = 4	0 – 0 – 0 = 4	
	B	1 – 0 – 0 = 7	1 – 0 – 1 = 7	0 – 0 – 0 = 4	

Table 3: Biochemical Characteristics for all the three batches of samples

Samp	Ind	T S I											Inference
		GS	I	M	VP	C	S	B	G	H ₂ S	Cat		
T ₁	A	–	–	–	–	+	R	R	–	–	+	<i>Alcaligenes faecalis</i>	
R ₁	A	–	–	–	–	–	R	R	–	–	+	<i>Alcaligenes faecalis</i>	
	B	–	+	+	–	+	R	Y	–	–	+	<i>Providencia</i> sp	
T ₂	A	–	–	–	–	+	R	R	–	–	+	<i>Alcaligenes faecalis</i>	
R ₂	A	–	–	–	–	+	R	R	–	–	+	<i>Alcaligenes faecalis</i>	
T ₃	A	–	+	+	–	+	R	Y	+	–	+	<i>Providencia</i> sp	
R ₃	A	–	+	+	–	+	R	Y	+	–	+	<i>Providencia</i> sp	

Keys: Samp = Sample; T = Treated water; R = Raw water; (the subscript indicate the batch of sample); I = Indole; M = Methyl red, VP = Voges – Proskauer; C = Simmon citrate; S = Slant; B = Butt; G = Gas, H₂S = Hydrogen Sulphide; Cat = Catalase; TSI = Triple Sugar Iron; R = Red (Alkaline); Y = Yellow (Acid); GS = Gram stain; Ind = Industry; + = Positive; – = Negative

Table 4: Fungi Isolated from the two pharmaceutical industries in Kano State

Sample	Industry	Fungi specie
Syrup	A	<i>Penicillium spinulosum</i> <i>Aspergillus amstelodami</i> <i>Saccharomyces cerevisiae</i>
	B	NG
Treated water	A	<i>Aspergillus niger</i> <i>Aspergillus amstelodami</i>
	B	<i>Aspergillus amstelodami</i> <i>Aspergillus niger</i> <i>Penicillium spinulosum</i> <i>Mucor racemosus</i>
	A	<i>Aspergillus amstelodami</i> <i>Penicillium spinulosum</i> <i>Aspergillus niger</i>
	B	<i>Aspergillus niger</i> <i>Penicillium spinulosum</i> <i>Saccharomyces cerevisiae</i> <i>Aspergillus amstelodami</i>

NG = No Growth

DISCUSSION

Results obtained from this work have revealed that all the syrup samples conform to the official requirement for microbiological quality of syrup in the total viable aerobic count levels, according to the USP (2007) specification. This is in agreement with the work of other investigators (Sudeshika *et al.*, 2010; El-Housseiny *et al.*, 2013). The low levels of microbial contamination in tested syrup samples could be due to the adoption of Current Good Manufacturing Practice (CGMP), effective preservative agents and adequate quality control program (Ogbulie *et al.*, 2009) as observed in the industries during study. The lower total count of bacteria and fungi recorded in the syrups may be attributed to the sugar content of the syrups that provide high osmotic pressure that is inhibitory to many microorganisms (Al – Kaf *et al.*, 2015). Moreover, syrups are usually filtered prior to bottling (Tukur *et al.*, 2012).

The USP (2007) recommends *Salmonella* sp., *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* as indicators of pathogenic microbial contamination of syrups. All the analyzed samples of syrups were found to be free from the pathogenic microorganisms and

passed the USP (2007) specifications. Similar observation was reported by Shaikh *et al.* (1988), Khanom *et al.* (2013) and Al – Kaf *et al.* (2015). Absence of coliform and pathogenic bacteria indicated that fecal contamination of water might not have occurred (Al – Kaf *et al.*, 2015). Some of the fungi isolated from the syrup sample include species of *Aspergillus amstelodami*, *Penicillium spinulosum*, and *Sacharomyces cerevisiae* which are possible allergic and toxin producers. *Aspergillus* sp. causes Aspergillosis while *Aspergillus flavus* produces aflatoxin that is carcinogenic (Prescott *et al.*, 2008). The types of microorganisms isolated in this study suggest contamination from air, processing unit, during handling, and packaging materials (Al – Kaf *et al.*, 2015).

According to Pelizar *et al.* (1986), water of good quality is expected to give a low count, less than 100 CFU/ml. Third batch water sample of Industry A had the highest count of 1.2×10^2 but are still within the range of WHO's recommendation (300 CFU/ml). Also, all analyzed raw water of both industries is within the range of WHO target for raw water. High plate counts are indicative of poor, unhygienic handling and processing practices. Bacterial growth in water may be unnoticed and the presence of some of

these microorganisms may pose a potential risk ((Obiri-Danso *et al.*, 2003). According to World Health Organization report (2002), a high plate count concentration does not itself present a risk to human health. Nevertheless, aerobic mesophilic counts are used as good indicators of the overall quality of production (Ferreira *et al.*, 1994; Obiri-Danso *et al.*, 2003). All water samples analysed are within the limit permissible by NAFDAC and WHO for potable water. This is in line with the work done on water by Enwere and Ade (2006). WHO (2008) water standard stated that in all water directly intended for drinking, *E. coli* and thermotolerant coliform bacteria must not be detectable in any 100 ml of sample. The suggested bacteriological standard for drinking water from unchlorinated water, and other sources (also applicable to food and syrups samples), is MPN value 0, which is rated excellent and desirable; values between 1 and 10 are however still acceptable but value ≥ 50 signify gross pollution or contamination (Chukwuemeka *et al.*, 2011).

The presence of *Alcaligenes faecalis* and *Providencia* sp in water might be due to the fact that the bacterium (*Alcaligenes faecalis*) is commonly found in the environment. Though was originally named for its first discovery in feces, but was later found to be common in soil, water and environment in association with human. While *Providencia* species are also found in soil, water and sewage. In humans, it has been isolated from urine, stool and blood as well as from sputum, skin and wound culture (Edward, 2015).

CONCLUSION AND RECOMMENDATION

It can be concluded from this study that the microbiological quality parameters of the analysed syrup samples agree with established standard, free from indicator of pathogenic microorganisms and thus conform to USP (2007) specifications for bacteria. Also water used in the sampled pharmaceutical industries is within NAFDAC and WHO quality specifications.

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