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STORAGE IMPLICATIONS ON THE MICROBIOLOGICAL QUALITY OF SOME LOCALLY MANUFACTURED PHARMACEUTICALS

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ABSTRACT

Pharmaceutical products non-sterile are expected to have a minimal microbial load which must not exceed the limits as stated in pharmacopoeia monographs. This study attempted to evaluatestorage implications on the microbiological quality of some non-sterile pharmaceutical products manufactured locally in some states in south east Nigeria. Twenty brands of pharmaceutical products comprising 13 tablets, 5 capsules and 2 suspension procured from patent medicine and local drug markets in Aba and Enugu states were stored at room temperature (25^{o}C) for 6 months. Microbial growth was evaluated at 0 and 6 months using standard microbiological procedures including Total aerobic bacteria plate count, isolation, characterization and identification of microbial contaminants. The results from the study showed that 55% and 30% of the pharmaceutical products had bacteria and fungi contamination at 0 month which increased to 70% and 50% at 6 months storage period respectively. Statistical analysis showed there was a significant increase ($p < 0.05$) in growth of micro-organisms at 6 months for both bacteria and the fungi/moulds ($p < 0.05$). The isolated bacteria were Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli while the fungi include Trichosporonasahii, Curvularia bothriochloae, Candida albicans, Candida parapsilosis. All contaminated samples had microbial counts above the British Pharmacopoeia (BP) acceptabl limit of 10^3 and 10^2 CFU/ml for bacteria and fungi respectively. This can be attributed to poor adherence to current Good Manufacturing Practice (cGMP) by the manufacturers. Thus, it is recommended that manufacturers adhere strictly to cGMP and storage conditions stated on these pharmaceutical products followed strictly during distribution and storage to reduce the levels of microbial contamination.

Keywords: Non-sterile pharmaceutical products, Contamination, Storage, Microbiological Quality

INTRODUCTION

Pharmaceutical products are grouped into two in microbiological terms; sterile and non-sterile (Salem et al, 2021). Sterility is not a requirement for non-sterile pharmaceutical products however they must meet the appropriate microbiological purity criteria as stated in pharmacopoeia monographs (Noor et al, 2015; Ratajezak et al., 2015). Microbial

contamination of pharmaceutical products can result in breakdown of the active pharmaceuticalingredients (APIs) and excipients which affects the potency, stability and efficacy of the products (Khana et al., 2018). This breakdown in active pharmaceutical ingredients can lead to a loss of therapeutic effect and sometimes drug-induced infections in patients (Gamal et al., 2011). The use of contaminated pharmaceutical products is unsafe to patient's health and there have been reports of drug-borne human infections (Khana et al., 2018). The quality of pharmaceutical products is thus crucial for patient safety (Kiron et al., 2013).

Contamination of pharmaceutical products may arise from the raw materials (pharmaceutical actives and excipients), packaging materials, manufacturing machines and equipment, production environment, persons handling the production, improper handling of materials, packaging, distribution and storage (Kamil and Lupuliasa, 2011; Yasir et al., 2017; Olaitan and Muhammad, 2018) Environmental parameters such as temperature, relative humidity and differential air pressure can also promote microbial contamination (Rashed et al., 2015). During manufacturing, the viability of microbial cells can be seriously affected by the drying process of granules and by compaction of tablets (Al-Shikli et al., 2010). The availability of water also plays an important role (Al-Shikli et al., 2010).The level of contamination is likely to increase as a result of poor adherence to Good Manufacturing Practices by the manufacturers of pharmaceutical products (Yasir et al., 2017).Non- sterile pharmaceutical products are also prone to post manufacturing contamination as a result of poor handling practices and the environment (Obuekwe et al., 2002).

The stability of a pharmaceutical preparation or product refers to the ability of a formulation in a specific container or closure system to remain within its physical, chemical and microbiological, therapeutic and toxicological specifications throughout its shelf life (Bajaj et al., 2012; Kiron et al., 2013. It can be affected by microbial contamination (Bajaj et al., 2012). In many tropical countries like Nigeria, pharmaceutical raw materials and finished products are stored in transit or during use under uncontrolled conditions (Al Shikli et al., 2010). Factors such as moisture, heat and light promote degradation of drugs (Obitte et al., 2009). In hot and humid conditions in tropical countries, growth of micro-organisms cannot be overlooked (Al-shikli et al, 2010). Temperatures and relative humidity (RH) beyond limit leads to product degradation and microbial growth (Kumar &Ajeya, 2017).

Various studies have been conducted on commercially available and extemporaneously prepared pharmaceutical products which showed microbiological quality concerns in different countries and locations (Mugoyela & Mwambeta, 2010). In tropical countries like Nigeria, the risk of microbial contamination of pharmaceutical preparations is increased as a result of storing it under uncontrolled conditions where average temperature is up to 31^{o}C and relative humidity 75% (Obi and Nwannunu, 2010). Thus, it is of great importance to evaluate the microbiological quality of these pharmaceutical products and determine the effect of storage condition over time on bioburden. Evaluation of microbiological quality of pharmaceutical preparations on the basis of quantitative and qualitative tests that will determine the extent of microbial contamination and detection of specified objectionable microorganisms (Anie & Okafo, 2021). The aim of this study therefore was to evaluate the microbiological quality of some locally manufactured oral dosage forms (tablets, capsules, suspensions) upon storage over a period of time.

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MATERIALS AND METHODS

Sampling and Sample Processing

Different brands of pharmaceutical products were randomly sampled from retail pharmacies, patent medicine stores and local market drug stores located in different parts of Abia and Enugu states in south east Nigeria. A total of twenty (20) non-sterile oral dosage forms which consists of 13 tablets, 5 capsules and 2 suspensions were randomly sampled. The tablets and capsules were in blister packs. Samples collected were stored in an air conditioned environment and analysed within 48 hours. Samples were procured in duplicates on the basis of availability of the products manufactured by the local pharmaceutical companies in the south east zone. Samples collected were physically examined to ensure that products were intact. Date markings, batch number, National Agency for Food and Drug Administration and Control (NAFDAC) registration number, appearance and colour were checked and recorded. The total bacteria and fungal load as well as presence of specific pathogens were determined in line with standard methods (Anie and Okafor, 2021). Samples were analyzed in duplicates and the mean Total aerobic microbial counts (TAMC) and Total yeast and mold count (TYMC) obtained.

Enumeration of Total Viable Bacterial and Fungal Count

The blister pack of each product was thoroughly wiped with isopropyl alcohol and four tablets each of the pharmaceutical products were crushed in a sterile glass mortar and pestle. One gram (1g) each of the products was weighed out aseptically. Peptone water was prepared and sterilized by autoclaving for 15 minutes at 121^0C. One gram of drug sample was placed in 9ml of sterile peptone water used as diluent in a sterile test tube. Serial dilution was made to the 6^{th} dilution (10^6).

The procedures stated in the British Pharmacopoeia (BP) 2020 were used for assessment of microbiological quality of samples of pharmaceutical preparations. Pour plate method was used hence one milliliter (1ml) of each dilution was placed in sterile Petri dishes and 40 ml of nutrient agar added to each Petri dish. Test samples were prepared in duplicates. The Nutrient agar plates were incubated at 37^o C in an incubator for 48 hours and observed for growth. The procedure was repeated for the Sabourauds dextrose agar (SDA), sterile media was poured into the Petri dishes. Test samples were prepared in duplicates and plates incubated at 25^o C in a different incubator for five days before observing the plates for growth.

Estimation of viable aerobic mesophillic bacteria count of each sample was carried out using the standard plate count method described in the British Pharmacopoeia 2020 and expressed in CFU/ml. The colony counts for bacteria and fungi/mold were taken independently and the arithmetic mean calculated. The number of colony forming units per milliliter (CFU /ml) was calculated as follows:

CFU/ml = (Number of Colonies / Volume of Sample in ml)

Enumeration of Specific Pathogens

The colonies observed on the Nutrient agar plates were gram stained using the procedure described by Willey et al. (2007). The aerobic bacteria growth observed were further screened for identification and tested for presence or absence of objectionable micro-organisms (*Salmonella sp., Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli*).

Salmonella spp.

A pure culture from Nutrient agar was inoculated onto Xylose Lysine Deoxycholate agar and incubated at 33^o C for 48 hours. The growth of red colonies with black centers that indicates the presence of *Salmonella spp.* was not observed for all samples tested.

Pseudomonas aeruginosa

A pure culture from Nutrient agar was inoculated onto Cetrimide agar and incubated at 37^{o} C for 48 hours. The growth of colonies with characteristic green colour that indicates the presence of *Pseudomonas aeruginosa* was observed in 1 out of 20 samples tested.

Staphylococcus aureus

A pure culture from Nutrient Agar was inoculated onto Mannitol salt agar and incubated at 33^{o} C for 72 hours. The growth of white colonies surrounded by yellow zones indicates the presence of Staphylococccus aureus for all samples tested was not observed.

Escherichia coli

A pure culture from MacConkey agar was inoculated onto Eosin Methylene Blue agar to selectively isolate *Escherichia coli.* The culture plate was incubated at 33^{o} C for 72 hours and observed. The growth of colonies with dark centers and greenish metallic sheen indicative of *Escherichia coli* was observed in two of the samples tested.

Candida albicans

Growth of small round moist, white to colourless colonies with even edges on Sarbourauds dextrose agar plates were considered to be *Candida albicans*. Further microscopic identification was done using the wet mount preparation with Lactophenol cotton blue stain (Olaitan& Muhammad, 2018). For confirmation, pure cultures were inoculated into 10 ml sterile Potato dextrose broth prepared according to manufacturer's instructions.

Gram stain and biochemical tests which included catalase, oxidase and indole tests were carried out.

Effect of Storage on Microbial load- The samples of pharmaceutical products were stored at room temperature of 25^{o} C for 6 months and the microbial load of the samples were evaluated at 0 and 6 months**.**

Statistical Analysis

Data were recorded on excel and analyzed using the statistical software IBM SPSS version 26.

RESULTS AND DISCUSSION

The total aerobic microbial count (TAMC), total yeast/mold count (TYMC) and specific pathogens isolated are shown in Tables 1 and 2. At 0 month, findings from this study shows that 11(55%) and 6 (30%) of all samples analyzed were contaminated with bacteria and fungi respectively. The results show that after 6 months of storage bacterial population that contaminated the samples increased to 14(70%) and that of fungi increased to 10(50%). All contaminated samples had microbial counts which exceeded the acceptable limit in BP which is 10^3 and 10^2 CFU/ml for bacteria and fungi/mold respectively. Table 2 and 4 show that *Klebsiella pneumonia* (35%) had the highest frequency of occurrence among the pharmaceuttical products analysed. Objectionable bacteria species identified as *Escherichia coli* was isolated from two (2) products and *Candida albicans* was isolated from four (4) products. Statistical analysis of the results are shown in tables 3 and 4. Results of statistical analysis showed that the growth of microbes at 6 months increased significantly ($p < 0.05$) 0 month for both bacteria and fungi/mould (Table 3). The results presented in Table 5 shows that microbial growth from the samples at 6 months was higher than the values recorded at 0 month for the different dosage forms, however there was no significant difference; $p > 0.05$ in all cases.

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Table 1: Microbial Count for the Different Pharmaceutical Oral Dosage Forms

S/N	Brand/Active Ingredient	Quantity of Powder	TAMC CFU/ml (Market sample) 0 month	TAMC CFU/ml 6 months	TYMC CFU/ml (Market sample) 0 month	TYMC CFU/ml 6 months
1	Ampicillin 250mg capsules	1g	$1x10^4$	$4X\ 10^5$	$1x10^4$	$1X\ 10^5$
2	Ampicillin 250mg+Cloxacillin 250mg capsules (I)	1g	0	0	0	0
3	Amoxycillin 250mg capsules	1g	$5X10^4$	$4.8X10^6$	0	$4X10^6$
4	Acetaminophen 500mg tablets	1g	0	0	0	0
5	Ciprofloxacin 500mg tablets (I)	1g	$4x10^4$	$1.6X\ 10^6$	$4.0x10^5$	$2X10^6$
6	Paracetamol 500mg +caffeine 30mg tablets	1g	$1.1X\ 10^6$	$4X10^5$	$1X\ 10^4$	$1X\ 10^5$
7	Paracetamol 500mg tablets	1g	$1X\ 10^6$	$2.0X\ 10^5$	0	0
8	Cotrimoxazole 480mg +Trimethoprim 80mg tablets	1g	$1.35x10^6$	$7\ X10^6$	$1.0x10^4$	$1.2x10^4$
9	Piroxicam 20mg capsules	1g	$2x10^4$	$2X\ 10^5$	$1.0x10^5$	$2X10^6$
10	Hydrochlorothiazide 250mg tablets	1g	$5x10^5$	$3.4\ X10^7$	0	$6X10^6$
11	Acetyl Salicylic Acid 75mg tablets	1g	$1x10^4$	$6X10^6$	0	$7X10^6$
12	Metronidazole 200mg tablets	1g	$2.2\ X10^6$	$9X\ 10^6$	$6X10^3$	$1X10^5$
13	Ampicillin 125mg +Cloxacillin 125mg capsules (II)	1g	0	0	0	0
14	Artemether 80mg + Lumefantrine 480mg tablets	1g	0	0	0	0
15	Ampicillin 750mg + Cloxacillin 250mg oral suspension	1g	0	$1.0X\ 10^7$	0	0
16	Artemether 180mg +Lumefantrine 108mg oral suspension	1g	0	$2.6X10^7$	0	0
17	Ciprofloxacin + Tinidazole tablets	1g	0	0	0	0
18	Ciprofloxacin 500mg tablets (II)	1g	$1.7X\ 10^6$	$1.3X10^7$	$2.6x10^6$	$2x\ 10^6$
19	Diclofenac Sodium 100mg tablets	1g	0	$4.6X10^7$	0	0
20	Ibuprofen 200mg tablets	1g	0	0	0	0

Table 2: Microbial Species Isolated from Different Brands of Non-sterile Oral Dosage Forms

S/N	Brand/Active Ingredient	Isolated Micro-organisms	
		0 month	6 months
1	Ampicillin 250mg capsules	*Klebsiella pneumoniae, Curvularia bothriochloae*	*Klebsiella pneumoniae, Curvularia bothriochloae*
2	Ampicillin 250mg+Cloxacillin 250mg capsules (I)	NG	NG
3	Amoxycillin 250mg capsules	*Klebsiella pneumoniae*	*Klebsiella pneumonia, Candida albicans*
4	Acetaminophen 500mg tablets	*NG*	*NG*
5	Ciprofloxacin 500mg tablets (I)	*Klebsiella pneumoniae, Candida albicans*	*Klebsiella pneumoniae, Candida albicans*
6	Paracetamol 500mg +caffeine 30mg tablets	*Escherichia coli, Candida albicans*	*Escherichia coli, Candida albicans*
7	Paracetamol 500mg tablets	*Escherichia coli*	*Escherichia coli*
8	Cotrimoxazole 480mg +Trimethoprim 80mg tablets	*Candida albicans, Trichosporan asahii*	*Candida albicans, Trichosporon asahii*
9	Piroxicam 20mg capsules	*Klebsiella pnuemoniae , Candida tropicalis*	*Klebsiella pneumonia, Candida tropicalis*
10	Hydrochlorothiazide 250mg tablets	*Klebsiella pneumoniae*	*Klebsiella pneumonia , Candida tropicalis*
11	Acetyl Salicylic Acid 75mg tablets	*Klebsiella pneumoniae*	*Klebsiella pneumonia , Candida parapsilosis*
12	Metronidazole 200mg tablets	*Klebsiella pnuemoniae, Candida parapsilosis*	*Klebsiella pneumonia , Candida parapsilosis*
13	Ampicillin 125mg +Cloxacillin 125mg capsules (II)	NG	NG
14	Artemether 80mg + Lumefantrine 480mg tablets	NG	NG
15	Ampicillin 750mg + Cloxacillin 250mg oral suspension	NG	*Pseudomonas aeruginosa*
16	Artemether 180mg +Lumefantrine 108mg oral suspension	NG	*Pseudomonas aeruginosa*
17	Ciprofloxacin + Tinidazole tablets	NG	NG
18	Ciprofloxacin 500mg tablets (II)	*Proteus mirabilis, Candida albicans*	*Proteus mirabilis, Candida albicans*
19	Diclofenac Sodium 100mg tablets	NG	*Klebsiella pneumonia*
20	Ibuprofen 200mg tablets	NG	NG

NG: No Growth

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Table 3: Paired Samples T-Test Statistics

		Mean	N	Std. Deviation	p value
Aerobic microbes	Mean Aerobe count at 0month	3.14E+05	20	6.14E+05	0.016
	Mean Aerobe count at 6months	7.93E+06	20	1.29E+07	
Fungi/Moulds	Mean fungi/mould count at 0month	1.57E+05	20	5.82E+05	0.049
	Mean fungi/mould count at 6months	1.17E+06	20	2.13E+06	

Table 4: Occurrence of Microbial Species Isolated from Samples

S/N	Micro-organisms	Number of samples	
		0 month	6 months
1	*Curvularia bothriochloae*	1	1
2	*Proteus mirabilis*	1	1
3	*Klebsiella pneumoniae*	6	7
4	*Trichosporon asahii*	1	1
5	*Candida parapsilosis*	1	2
6	*Candida tropicalis*	1	1
7	*Escherichia coli*	2	2
8	*Candida albicans*	4	4

Table 5: Paired T-Test comparing tablets, capsules and suspensions at, 0 months and 6 months.

		Tablets(mean ± Std dev) and p value				Capsules (mean ± Std dev and p value)				Suspensions (mean ± Std dev and p value)			
mean aerobic count	0 months	4.77E+05	±	7.17E+05	0.057	1.60E+04	±	2.07E+04	0.314	0.00E+00	±	0.00E+00	0.266
	6 months	9.02E+06	±	1.46E+07		1.08E+06	±	2.09E+06		1.80E+07	±	1.13E+07	
mean mould	0 months	2.33E+05	±	7.20E+05	0.135	2.20E+04	±	4.38E+04	0.203	0.00E+00	±	0.00E+00	
	6 months	1.32E+06	±	2.42E+06		1.22E+06	±	1.77E+06		0.00E+00	±	0.00E+00	

Klebsiella pneumoniae is an opportunistic pathogen and its presence indicates possible contamination from handling or the environment. *Escherichia coli* and *Candida albicans* which are objectionable micro-organisms were recovered from 3 out of 6 brands in the study carried out by Anie & Okafo (2021) to evaluate antacid suspensions marketed in Delta State, Nigeria. Fauzeeyah & Kabiru (2022) also isolated *Escherichia coli* from a study carried out to determine the microbial quality of some commonly administered non-sterile drug types from hawkers and pharmacy outlets within Lafia metropolis. *Proteus mirabilis* was recovered in the study conducted by Itah et al. (2004) in the study aimed at evaluating the bacteriological quality of some pharmaceutical products marketed by drug vendors in Uyo, Nigeria. *Pseudomonas aeruginosa* was reported by Obuekwe et al. (2002) and El- Houisseny et al. (2013) in

studies which investigated the microbial contamination of pharmaceutical products in a tropical environment and detection of microbial contaminants in some non-sterile pharmaceutical products respectively.

The isolation of pathogenic organisms and their presence in levels higher than the microbial limits as stated in BP indicates a possible health hazard. The bacteria and fungi counts increased after 6 months which is similar to results obtained in a study carried out by Gad et al. (2011) to determine the types and incidence of predominant micro-organisms in certain non-sterile pharmaceuticals immediately after collection. Bacteria counts were significantly different at 6 and 12 months from that at 0 month. Also in the study by Khana et al. (2018) to evaluate the effect of packaging system and storage on the microbial quality of non-sterile oral liquid dosage form, the population of micro-organisms in the product increased as well as the bacterial counts after storage for 6 and 12 months.

CONCLUSION

The results from this study show that the microbiological quality of these locally manufactured pharmaceuticals is a challenge which can be attributed to poor adherence to cGMP as well as poor distribution and storage practices. Thus, there is a need for the manufacturing companies and regulatory bodies in Nigeria to pay closer attention to the manufacturing processes, handling, distribution and storage of these pharmaceuticals.

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