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Microbiological quality of non-sterile pharmaceuticals in Egypt

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Abstract

Background: The context and purpose of the study are as follows: Drug-borne infections may arise from non-adherence to strict microbiological quality of pharmaceuticals products. Moreover, presence of exceeding levels of microorganisms in non-sterile pharmaceuticals may lead to change of their organoleptic characteristics and loss of effectiveness. The aim of the study is to evaluate the microbiological quality of commonly used non-sterile pharmaceuticals in Alexandria, Egypt.

Results: Average microbiological quality of the studied products, where 17.03% and 19.23 % of samples had exceeded the maximum acceptable limit of TAMC and TYMC, respectively. No *E. coli* was isolated from oral products. None of *S. aureus* nor *P. aeruginosa* were isolated from topical products. Bacterial growth was recovered from 19 (10.44%) of the studied 182 samples, four *Bacillus* spp. had been recovered from topical products, two *P. aeruginosa* isolates were recovered from tablets and other two were isolated from syrups dosage forms. Other isolates were *Pseudomonas stutzeri*, *Stenotrophomonas maltophilia*, *Acinetobacter Achromobacter denitrificans*, *Ochrobactrum anthropic* and *Aeromonas salmonicida*.

Conclusion: Average microbiological quality of the tested pharmaceuticals used in Alexandria.

Keywords: Acceptable limits, Indictor organisms, Microbial burden, Pharmaceuticals, US pharmacopeia

1 Background

In microbiological terminology, pharmaceutical products are classified into two classes, sterile and non-sterile. Sterile production involves creating medication in an area free from microorganisms, such as production of intravenous injections and eye drops, while the production of non-sterile pharmaceuticals (NSP) requires a clean area which is not completely free from microorganisms and allows the presence of non-objectionable organisms within permissible limits. NSP include oral dosage forms (syrups, suspensions, and emulsions) and topical dosage forms (creams, gels, and ointments) [1]. Microbiological quality of non-sterile pharmaceuticals should be assessed as an important quality control step especially in developing countries, where the climatic conditions may support the proliferation of microorganisms in medical products. Moreover, many products may be stored or dispensed under uncontrolled conditions [2].

In Egypt, with an average-low socio-economic standard, serious effects may be superadded on debilitated patients by drug-borne infections [3]. Outcomes of these infections depend on the product types, route of administration, and patient immune status [4]. In addition, the presence of exceeding levels of microorganisms in non-sterile pharmaceuticals may lead to loss of effectiveness and change of organoleptic characteristics including breaking of emulsions, syrups fermentation, and odors changes [5].

Regardless their dosage forms, the presence of microbial charge is conceptually allowed in NSP; however, they must satisfy the appropriate microbiological quality criteria and normal ranges of a recent edition of pharmacopeia. According to US Pharmacopeia (USP), the microbial bioburden, total aerobic microbial count

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(TAMC), and total yeast and mold count (TYMC) should be within acceptable microbiological limits and they should be free of certain specified microorganisms such as *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), and *Candida albicans* (*C. albicans*) [6]. To our knowledge, few studies had been conducted in Egypt to identify the microbiological quality of different types of non-sterile pharmaceuticals. The aim of the current study was to evaluate the absence of specified microorganisms in non-sterile pharmaceutical preparations and to assess the microbial bioburden of these products.

2 Methods

The study protocol was approved by Ethical Committee at the High Institute of Public Health (HIPH).

2.1 Study area

This prospective cross-sectional study was conducted over a period of 4 months from the beginning of August to the end of November 2019.

2.2 Sampling

A total number of 182 NSP were tested, the samples comprised 21 herbal cough syrup samples which contain botanical substance as active ingredients, and 161 non-herbal preparations which included oral products (79 tablets, 6 capsules, 47 syrups, 8 suspensions, and 4 emulsions) and 17 topical products (7 creams and 10 gels). A total of 47 different registered trade names were tested (18 tablets, 4 capsules, 13 syrups, 4 suspensions, one emulsion, 2 creams, and 5 gels). All product trade names are listed in Table 1.

Samples were purchased from three districts in Alexandria, East, El Amreya, and Sidi Bishr areas. Governmental and non-governmental pharmacies were randomly selected. The selected drugs were over the counter (OTC) products that were representative to those readily available and commonly used in the community.

2.3 Laboratory investigation

Sample preparation was done as per the USP and according to physical characteristics of each tested product. To achieve acceptable microbial recovery from each product, the lowest possible dilution factor was used (1: 10 dilution). Tryptic soy broth or phosphate buffer solution (pH 7.2) was used as diluents. Five units of tablets were ground in a sterile bag using mortar; 1 gm of powder was dispersed in 10 ml diluent to obtain 1:10 sample dilution. Enough capsule units to obtain the required quantity (1 gm) were dissolved in 10 ml diluent using water bath in a temperature not less than 30 °C and not more than 45 °C [6].

Counting method suitability testing was conducted to test for inhibitory effects of any of tested products on possibly present microorganisms. Standard test strains were used, *S. aureus* (American Type Culture Collection (ATCC) 6538), *P. aeruginosa* (ATCC 9027), and *C. albicans* (ATCC 10231) to obtain the correct inoculum of not more than 100 colony forming unit (CFU) at specific incubation temperatures and durations. Enough volumes of each microbial strain suspension were added to the diluted product samples and control tubes (only broth, no drug). The number of CFU recovered from the diluted product was compared to that recovered from the control tubes; it should be not less than 50% of the control. If colony count was decreased by more than 50%, then the drug had an inhibitory effect on multiplication of microorganisms and neutralization of antimicrobial activity was done using dilution method [7].

TAMC and TYMC were conducted using the spread plate technique. Tryptic soy agar was used for TAMC and Sabouraud dextrose agar for TYMC. About 0.1 ml of 1:10 dilution of the tested product was dispensed onto the center of the appropriate agar plates using sterile graduated pipette; duplicate plates were performed for each sample. After the appropriate incubation conditions, the recovered colonies from each plate were enumerated and the mean count of the duplicate plates was used for calculating the TAMC and TYMC of the test sample (CFU/ml or g). Acceptable criteria of each dosage form are illustrated in Table 2. Tests for absence of

Table 1 All products trade names

Tablets	**Deltavit, captopril, aspirin, paracetamol, egypro, newbezim, moxen, lessuric, noflam, paramol, ranitidine, alertam, pharocal, iverzine, salbovent, silymar, allerfen, rivo**
Capsules	Ketofan, calcimate, relax, nitrotard
Non-herbal syrups	Pharovit syrup, hemojet, maxilase, zylofen, prednisolone, loratidine, zincoria, apidone, hi-cal
Herbal syrups	Tussin, oplex, bromohexin, bronchoterol
Suspensions	Ketofan, fluver, alertam, bendax
Emulsion	Simethicone
Creams	Marpelene, novacortin
Gels	Romafen, ascizadex-N-gel, herbaril, adapalene, diclofenac sodim

Table 2 Acceptance criteria for microorganism's enumeration tests of non-sterile pharmaceutical products according to USP

Route of administration	TAMC (CFU/ml or g)	TYMC (CFU/ml or g)	Specified microorganisms
Non-aqueous oral preparations	10^3	10^2	Absence of *E. coli* (1 g or 1 ml)
Aqueous oral	10^2	10^1	
Topical preparations	10^2	10^1	Absence of *S. aureus* and *P. aeruginosa* (1 g or 1 ml)
Recommended USP microbial limits for botanical ingredients			
Herbal products	10^4	10^3	

specified microorganisms according to routes of administration were done using MacConkey's agar, acetamide agar, and mannitol salt agar plates [6]. All isolated colonies were identified according to the standard microbiological procedures following their morphology in Gram stain, cultural characteristics, and biochemical properties [8].

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (version 21). Chi-square test (χ^2) was used to test association between qualitative variables. Monte Carlo corrections were carried out when indicated (n × m table or expected cells less than 5). Fisher exact (FE) correction and correction for chi-square was done when more than 20% of the cells have expected count less than 5. An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

3 Results

Out of 182 tested samples, 31 (17.03%) and 35 (19.23%) had exceeded the maximum acceptable limits of TAMC and TYMC, respectively. None of the specified organisms by USP had been isolated from the studied pharmaceuticals. Bacterial growth was recovered from 19 (10.44%) of the studied 182 samples and 15 (78.95%) of them were gram-negative isolates, while 4 (21.05%) were gram-positive and had been correctly identified by routine biochemical tests as *Bacillus* spp. Four (26.67%) out of 15 recovered gram-negative bacterial isolates were correctly identified as *P. aeruginosa*, while 11 (73.33%) were inconclusively identified by routine biochemical methods and were identified by VITEK® 2 automated system as illustrated in Table 3.

Differences of microbiological quality of herbal and non-herbal products were assessed; 2 (9.52 %) and 3 (14.29 %) out of 21 herbal pharmaceuticals had passed the permissible limits of TAMC and TYMC, respectively. Regarding non-herbal products, it appears that 29 (18.01%) and 32 (19.88%) out of 161 non-herbal products were off limits of TAMC and TYMC, respectively. The differences between these results were not statistically significant. About 7 (8.86%) out of 79 tablets and 16 (34.04%) out of 47 syrups were off limits of TAMC. The majority of capsule samples, 5 (83.33%) out of 6, had unsatisfactory TYMC.

Regarding topical products, 3 (30.00%) out of 10 gels and none of creams had passed the permissible limit of TAMC. One (14.29%) out of 7 creams and 3 (30%) out of 10 gel had exceeded TYMC limits.

Nineteen isolates were recovered from the studied products, two of them (10.53%) were recovered from herbal products, and 17 (89.47%) were from non-herbal samples. Table 4 illustrate microbial contaminants from different tested dosage forms.

The differences between microbial bioburden of pharmaceuticals purchased from governmental pharmacies and non-governmental pharmacies were not statistically significant.

4 Discussion

Microbial burden of non-sterile pharmaceuticals must be regularly monitored according to international standards. The validity of microbial count tests relies on verification of any inhibitory effects of tested products on the present microorganisms. In the present study, method suitability verification was conducted using three standard strains, *S. aureus* (ATCC 6538), *P. aeruginosa* (ATCC 9027), and *C. albicans* (ATCC10231). All 47 brands, except four tablet trademarks, recovered valid counts (> 50% of the initial inoculums used). Neutralization procedure by dilution method was performed for these four brands; then, valid microbial recovery was achieved from all of them (> 50%). The inhibitory effect was neutralized by dilution method. This observation was parallel to that reported by Shaqra

Table 3 VITEK compact system identification of inconclusively identified bacterial isolates

Isolates	No.	%
Pseudomonas stutzeri	3	27.3
Achromobacter denitrificans	1	9.1
Stenotrophomonas maltophilia	3	27.3
Acinetobacter baumannii complex	2	18.2
Ochrobactrum anthropi	1	9.1
Aeromonas salmonicida	1	9.1
Total	11	100

Table 4 Distribution of recovered microbial contaminants from different tested dosage forms

Dosage form	Isolates		χ^2	$p_{(MC)}$
	No.	%		
Gram-negative isolates (n = 15)				
Tablet	8	53.33	25.218	0.004*
Capsule	1	6.67		
Syrup	4	26.67		
Suspension	2	13.33		
Emulsion	0	0.00		
Total	15	100.00		
Gram-positive isolates (n = 4)				
Cream	2	50.00		
Gel	2	50.00		
Total	4	100.00		

*Statistically significant

et al. from Jordan who confirmed the effectiveness of the neutralization procedure [9]. On the contrary, El-Housseiny et al. from Egypt failed to obtain valid recovery counts for 6 samples after using several neutralization methods, consequently they had omitted these samples from further testing [10].

Manufacturers had a good adherence to good manufacturing practices and this was reflected on the average microbiological quality of the tested pharmaceuticals in the current study, where 17.03% and 19.23% out of the 182 tested products had exceeded the maximum acceptable limit of TAMC and TYMC, respectively. These results were in accordance of those reported by Nawas and Alkofahi [11], where 21% of the items tested were found to exceed the acceptable limits. On the other hand, Gad and Ashour from Egypt reported adequate to excellent quality of the examined products, where the proportion of the products with exceeding TAMC was small (5.8% in syrups and 10% in suspensions) [12]. El-Houssieny et al. reported more satisfactory results regarding TYMC, where only 1.1% of the products had exceeded the acceptable limit [10]. Much higher microbial loads were recorded by Mugoyela and Mwambete from Tanzania (50%) and Mehmood et al. from Pakistan (76%). Observed microbial load may be due to ineffective or incorrect amounts of preservatives in formulations, active excipients, low quality raw, packaging materials or water used, faulty apparatus, poor aseptic handling of personnel operating the equipment, improper storage, and unhygienic environment [13, 14].

In the current study, most of the products that had passed the permissible TAMC USP limit were oral preparations. This may be attributed to limited numbers of the examined topical samples. These findings corroborate well with the observations made by El-Housseiny et al. [10] and Gad et al. from Egypt [12]. On the contrary, in a study conducted in Brazil, only topical preparations had exceeded TAMC limit, while all oral samples were within the acceptable limit [15].

Oral and topical pharmaceutical products come in contact with areas bearing natural microbial flora; hence, it is important to control the final microbial charge present in these products. Oral medicines such as tablets and capsules constitute a large proportion of products dispensed in all health facilities. Tablets are usually presented in blister packs that prevent contamination. However, in some developing countries, such drugs are supplied in bulk packs and the prescribed amount counted from them which could result in serious health hazards due to highly contaminated drugs [16]. Reduced water activity of tablets (< 0.6) causes self-preservation and decreases the liability of microbial proliferation. Moreover, moisture level determines the type of bacteria that can survive [17].

Syrups are the most convenient alternative oral liquid forms for babies, children, and elderly who cannot take solid forms conveniently. Although high sugar content of syrups increases osmotic pressure and prevents the growth of microorganisms, added sweetening agents increases water activity and predispose to microbial contamination [18].

In the present study, these parameters had been reflected, where 7 (8.86%) out of 79 tablets and 16 (34.04%) out of 47 syrups, 3 (30.00%) out of 10 gels, and none of the creams were off limits of TAMC. These observations were parallel with the findings of Opoku et al. from Ghana and Rauf et al. from Pakistan [19, 20].

Presence of fungi in NSP changes the physicochemical characteristics of medicines and may cause invasive fungal infections with high mortality rates. The current study revealed that the majority of capsule samples, 5 (83.33%) out of 6, had unsatisfactory TYMC. This may be due to high gelatine content that may support fungal growth. Aghili et al. from Iran found higher fungal bioburden in ointments. They attributed their finding to the availability of fungal growth requirements in ointments with fatty base or water-in-oil emulsions [21].

The risk of microbial contamination may increase in herbal products due to the organic nature of these products, non-feasibility of antimicrobial pre-treatment, and use of less preservatives. On the other hand, Ratajczak et al. found only three samples out of 40 herbal medicinal products that did not comply with the European Pharmacopeia requirements [1]. This agreed with the current study, where only 2 (9.52 %) and 3 (14.29 %) out of 21 herbal pharmaceuticals had passed the permissible limits of TAMC and TYMC, respectively. On the other hand, de Sousa Lima et al. examined larger sample size of herbal products and reported that 42 (31.8%) and 31 (23.5%) out of 132 herbal samples had exceeded TAMC and TYMC, respectively [22].

Pharmaceuticals contamination may arise from ineffectiveness of preservatives, water system, equipment used, and low standard post-production storage or transport. According to USP, oral non-sterile pharmaceuticals should be free of *E. coli*, while those used topically should be free of *S. aureus* and *P. aeruginosa*. The results of the current study revealed that none of the specified organisms by USP had been isolated from the studied pharmaceuticals; no *E. coli* was isolated from oral products. None of *S. aureus* nor *P. aeruginosa* were isolated from topical products. Only 4 isolates of *P. aeruginosa* had been isolated, 2 were recovered from tablets, and the other two were isolated from syrups. Two *Bacillus* spp. were isolated from gels and 2 from cream samples. On the other hand, El-Houssieny et al. had recovered *E. coli from* a syrup (1.1%); one *P. aeruginosa* isolate (1.1%) was recovered from a capsule was recovered from a syrup [10]. Contrary to the present study, Al-Charrakh reported the isolation of *E. coli* (5.7%), *S. aureus* (20.8%), and *P. aeruginosa* (1.9%) from a range of pharmaceutical products [23].

In the current study, the percentage of contaminated samples was low (10.44%). On the other hand, higher incidence of contamination was documented by El-Houssieny et al. (32%) [10]. Relative low percentage of recovered microorganisms in the present study may be due to the method used in cultivation which involved direct culture of the product without enrichment techniques; higher contamination rates would be expected with enrichment methods. In the current study, 11 bacterial isolates were isolated, mainly from tablets and syrups, which were inconclusively identified by routine biochemical methods and had been identified by VITEK automated system, 3 (27.3%) of them were *Pseudomonas stutzeri*, 3 (27.3%) were *Stenotrophomonas maltophilia*, two (18.2%) were *Acinetobacter baumannii complex*, and the remaining three isolates were *Achromobacter denitrificans*, *Ochrobactrum anthropic*, and *Aeromonas salmonicida*.

5 Conclusion

The microbiological quality of the examined samples was satisfactory. Syrups were the most common dosage form to exceed the TAMC limit, while capsules were the commonest to exceed the TYMC. Recovered microorganisms were ubiquitous in nature, such as *Bacillus* spp., *Pseudomonas* spp., and *Acinetobacter baumannii* complex.

Abbreviation

C. albicans: *Candida albicans*; CFU: Colony forming units; *E. coli*: *Escherichia coli*; NSP: non-sterile pharmaceuticals; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus*; TAMC: Total aerobic microbial count; TYMC: Total yeast microbial count; USP: US Pharmacopeia; OTC: Over the counter

6 Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43088-021-00127-6.

Additional file 1.

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High Institute of Public Health (Microbiology Department) staff members. Studies involving plants must include a statement specifying the local, national, or international guidelines and legislation and the required or appropriate permissions and/or licenses for the study: not applicable as the study used over the counter ready-made herbal products not plant parts.

Authors' contributions

MAE: Participated in the design of the study and approval of the final version of manuscript. NFA: Interpretation of laboratory results and statistical analysis of data, and drafting of manuscript. NMA: Implementation of laboratory investigation and acquisition of data. The authors have read and approved the manuscript.

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Availability of data and materials

All datasets on which the conclusions of the manuscript rely with all authors in excel sheets and to be presented the journal if needed.

Declarations

Ethics approval and consent to participate

The study protocol was approved by Ethical Committee at the High Institute of Public Health (HIPH). Reference no. not applicable.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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