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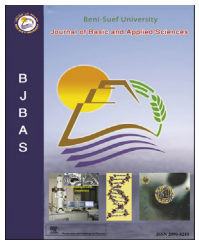

Full Length Article

Distribution of bacterial contamination in non-sterile pharmaceutical materials and assessment of its risk to the health of the final consumers quantitatively

Mostafa Essam Eissa *

Quality Compliance Section Head in HIKMA Pharma Pharmaceutical Company, P.O. Box 1913, Cairo 11511, Egypt

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ABSTRACT

Bacterial contamination control in pharmaceutical products is a critical aspect in the field of drug manufacturing industry due to the encountered risk to the patients' health and possibly their life. The application of commercial bacterial identification system is crucial to identify the type of contamination and its source to anticipate the impact of bioburden on the products and setting corrective and preventive actions. During the period of one year, random samples from raw materials and final products were tested according to United States Pharmacopeia, and those that showed suspect results for specified microorganisms and/or out-of-specification limits or showed out-of-trend results were subjected to further identification by using miniaturized biochemical identification system after performing Gram stain. From the total bacterial isolates of the investigated products, more than 60% were primarily belonging to *Micrococcaceae* 16.98% (empty hard gelatin capsules), *Enterobacteriaceae* 18.86% (vaginal cream applicator, plastic caps for bottles, Sorbitol solution, finished hard gelatin capsule product, topical cream and oral suspension) and *Bacillaceae* 24.53% (Talc powder, liquid oral preparation and finished hard gelatin capsule product). Gram Positive and Negative samples were 56.60% and 41.51% respectively from the total investigated sample products and materials. Finished pharmaceutical products constituted 53.33% and 68.18% from Gram-positive and Gram-negative microorganisms respectively. An approach to quantitative risk assessment for pharmaceutical products was conducted on selected medicinal items and showed that *Enterobacteriaceae* followed by *Burkholderiaceae* contributed by more than 80% to the major hazard that could be delivered to patients through drugs. The applied risk can be used as a milestone for setting goals by pharmaceutical companies to improve the safety of medicinal products microbiologically and to identify the major sources of the risk to work on it in order to deliver safe drugs to the customers.

* Microbiological Quality Control Department, Hikma Pharma Pharmaceutical Company, P.O. Box 1913, Cairo 11511, Egypt. Fax: +20238331791.
E-mail address: mostafaessameissa@yahoo.com.

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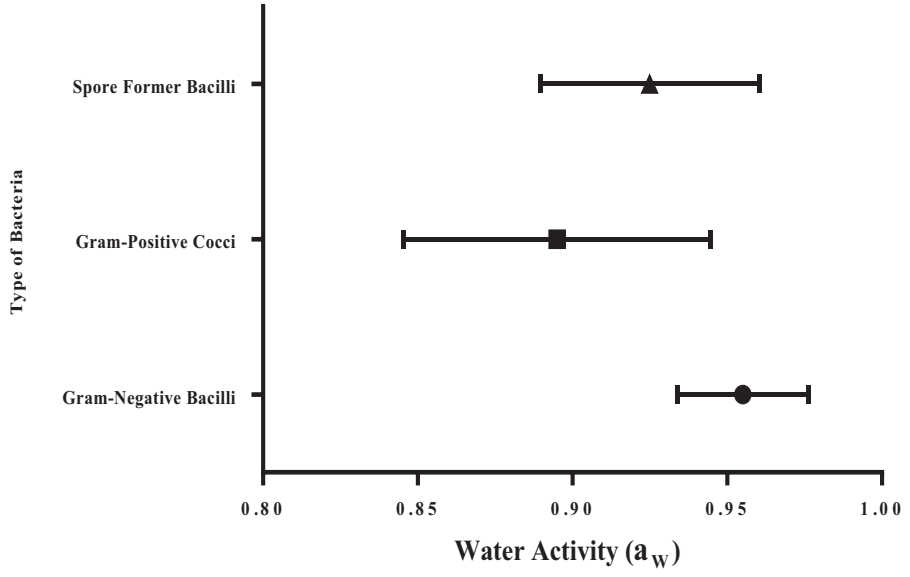
1. Introduction

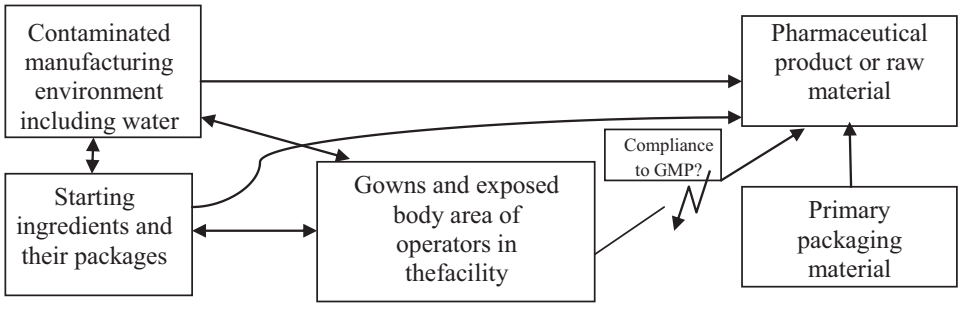
Microbial contamination and spoilage cost pharmaceutical companies huge financial loss annually through equipment malfunction, production stoppage, drug contamination, investigations and loss of energy. The target of most reputable pharmaceutical firms today is centered on determining the different sources of contamination (Eissa et al., 2014). The quality of product is assessed through testing and monitoring of the environmental conditions and manufacturing activities in the firms where they are processed, packaged, stored and tested as well as through sampling and analysis of the finished dosage forms. Products that are found to be contaminated with microorganisms are recalled from the market. A product can also be recalled if there is evidence that a deviation occurred during its manufacture or distribution, resulting in a possible risk to public health. Such incidences typically occur in small numbers of batches. However, if a product is found to be unsafe for continued marketing, it must be withdrawn completely (Clontz, 2008).

The moisture level available for microbial proliferation determines the type of bacteria that most probably can survive in the pharmaceutical material. The application of water activity (a_w) in the pharmaceutical and biopharmaceutical industries was first addressed in the USP Stimuli to the Revision Process article, "The Application of Water Activity Measurement to the Microbiological Attributes Testing of Nonsterile Over-the-Counter Drug Products," by Friedel and Cundell (1998). The USP Chapter <1112>, *Application of Water Activity Determination to Non sterile Pharmaceutical Products*, was finally made official on August 1, 2006, in USP 29, Supplement 2. Generally, Gram-negative bacilli require relatively higher moisture contents compared to Gram-positive bacteria as shown in Fig. 1a.

Another factor that should not be overlooked is the length of time the bacteria can survive before losing cultivability either in the product or on the dry surface. Most gram-positive bacteria, such as *Enterococcus spp.* (including Vancomycin resistant enterococci), *Staphylococcus aureus* (including MRSA), or *Streptococcus pyogenes*, survive for months on dry surfaces. Many gram-negative species, such as *Acinetobacter spp.*, *Escherichia coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *Serratia marcescens*, or *Shigella spp.*, can also survive for months (Kramer et al., 2006). Fig. 1b illustrates the possible modes of contamination of either raw materials or pharmaceutical products.



(a)



(b)

Fig. 1 – (a) Water activity (a_w) levels required to support bacterial growth (Modified from USP <1112>, 2014a). (b) The major modes of contamination of pharmaceutical dosage forms and their ingredients (Modified from Kramer et al., 2006).

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