

Title: Prevention and Control of Fungal Contamination in Tablets					
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Prevention and Control of Fungal Contamination in Tablets

Introduction

What steps can be taken to prevent and control of fungal contamination in tablets?

The presence of water is the key element in the growth of fungal contamination. This document discusses the prevention and control of fungal contamination in tablets production to include: raw material and API testing, manufacturing processes, environmental monitoring, and final product testing.

Recommendations & Rationale for Recommendations

Tablets are generally considered to be a self-preserved dosage form that possesses an inhospitable environment to most microorganisms because of the lack of available water. Still, many fungi (mold) populations, if introduced before or during manufacturing, can potentially survive (in a static state) or proliferate on or within the final tablet dosage form if the correct conditions are present. These conditions center on the presence of water, which is considered the key element in the proliferation of any fungal contamination. Fungal contamination is most commonly introduced into a tablet via the following:

1. Steps of the manufacturing process of the tablet where water is present (*e.g.*, wet granulation, coating solutions).
2. Contaminated raw materials, excipients or active pharmaceutical ingredients (API).
3. The lack of good manufacturing practices (*e.g.*, water quality, processing equipment sanitization).
4. Inappropriate storage, handling, and transport conditions where humidity may be problematic.

The primary concern of fungal contamination in a tablet is generally not the direct medical hazard it may cause the patient, but the possible spoilage of the product itself and non-compliance with contemporary regulatory expectations (cGMP) regarding microbiological quality of non-sterile dosage forms. It should also be noted that fungi are ubiquitous in nature and that their mere presence does not necessarily indicate that microbial control has been lost in the manufacturing process. The topics discussed below will provide more detailed information on the prevention and control of fungal contamination in tablets.

Raw Materials and Active Pharmaceutical Ingredient (API) Quality and Testing

solution holding tanks and the spraying apparatuses should also be evaluated. Poor equipment design that allows for the coating solution to be trapped (*e.g.*, piping dead legs, spray heads) may also affect the microbial quality of the final product.

Compaction:

Although the bioburden of a tablet can be reduced during the tablet compression process, this should not be relied upon as a kill step in tablet manufacturing (Baird and Bloomfield).

Sanitization:

It is important to sanitize the direct product contact surfaces of processing equipment. Typically, hot water alone (usually around 80°C.) is considered sufficient. Purified Water should be used for the final rinse with equipment sanitization procedures. Tablet manufacturing equipment (*e.g.* coating solution tanks, spray lines, spraying apparatus) that is sanitized with hot water should be dried after cleaning. Water should not be allowed to stagnate in tanks or piping as this may also lead to the proliferation of fungal contamination. Periodic inspections of equipment and processing lines can also assist in detecting potential problems before they arise.

Utilities:

The processing, packaging and storage areas should be equipped with ventilation systems to adequately control humidity and temperatures. Purified Water should be used in tablet manufacturing processes. Compressed air and other gases used in tablet processing steps should have the same microbiological requirements as the surrounding room air. Environmental Monitoring of Non-Sterile Manufacturing Environmental monitoring of the manufacturing areas for tablets should be performed on a periodic basis to assure an adequate level of microbiological control over the facility. Environmental monitoring for this type of manufacturing is not performed on a frequent basis, as it is primarily used to establish an historical database to determine if adverse trends in the environment are occurring. Preservation and Water Activity

Considerations in Tablet Formulation

Preservatives are not typically used in tablet formulations because of the low water activity. Water activity (A_w) is defined as the amount of bound versus available water that can be utilized for microbial/fungal growth. The lower water activity, the less likely microbial growth will occur. Fungi typically can grow at low water activity levels (approximately 0.6 A_w), which are much lower than available water requirements for bacteria or non-osmophilic yeasts. These types of microorganisms require water activity levels above 0.85 for growth to occur. Dry, uncoated tablets typically have lower water activities than those tablets that utilize water in the tableting process. It should be noted that a low water activity may prevent the proliferation of fungi, but unlike a preservative, it does not kill those microorganisms that may be present in the tablet. Typically, fungi and fungal spores can survive at extremely low water activity levels.

Water activity measurements of the final product tablets can assist in determining the quality of the tablet and potential processing problems that may be conducive for possible fungal growth.