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Short communication

Filter formulation interactions during filtration of a benzodiazepine solution for injection

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Introduction

Sterile filtration is a critical step in the manufacturing of parenteral drug products, ensuring microbiological quality while maintaining the physicochemical stability of the product. Membrane filtration is widely applied as a sterilization method, particularly for head-sensitive solutions, and is especially important for active substances sensitive to elevated temperatures, due to its ability to effectively remove microorganisms without thermal degradation of the product.

Interactions between the drug product and filter materials may occur during the filtration process (McBurnie et al., 2004). These interactions, including adsorption of active substance or excipients onto the filter surface, as well as potential incompatibility between the formulation and filter components, may affect the quality, safety and efficacy of the final product. The extent of adsorption depends on several factors such as membrane material, pore size, physicochemical properties of the formulation and process conditions.

Compatibility and adsorption studies are performed to ensure that contact between the solution and the filter does not alter the filter's critical characteristics or adversely affects its performance (WHO, 2022). Such studies are particularly important for complex formulations containing organic solvents and multiple excipients, where interaction with filter material may be more pronounced.

Benzodiazepine solution for injection is a complex formulation containing a benzodiazepine active ingredient, organic solvents and stabilizing excipients, which may potentially interact with filtration material.

Therefore, the aim of this study was to evaluate the compatibility and adsorption characteristics of Benzodiazepine solution for injection during filtration through nylon membrane filters with pore sizes of 0.45µm and 0.2µm under full scale production conditions, as a part of validation study performed following the introduction of a new active ingredient manufacturer.

Materials and methods

The study was conducted during manufacturing of three consecutive validation batches of Benzodiazepine solution for injection, each with a batch size of 400 L under routine production conditions. Based on formulations characteristics, benzodiazepine active ingredient and selected excipients were identified as critical components with potential adsorption risk.

The filtration process was performed in two stages using cartridge Nylon membrane filters: a 0.45µm filter for bioburden reduction followed by 0.2µm sterilizing-grade filter. Samples were

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collected before filtration, during filtration (beginning, middle and end) and after filtration.

Adsorption was evaluated by comparing assay values of critical components in filtered and unfiltered samples. Compatibility was assessed through filter integrity testing, including bubble point and diffusing tests, performed before and after exposure to the process solution. Additionally, the impact of the filtration on product quality was evaluated through physicochemical and microbiological testing according to specifications requirements.

Results and discussion

The consistency of assay values before, during and after filtration confirms that the filtration process does not cause loss of the active substance or excipients. This is important for formulation containing organic solvents, where potential interactions with polymeric filter materials could lead to partial adsorption or selective retention of certain components. The results further confirm that neither the active substance nor the excipients exhibit affinity towards the Nylon membrane surface that could impact the composition of the solution.

Filter integrity testing showed that all parameters met acceptance criteria before and after filtration, confirming that exposure to the solution did not compromise filter performance or structure. The stability of integrity test parameters further supports the conclusion that no physicochemical interaction occurs between the formulation components and the filter material that could alter membrane properties.

The filtered product complied with all specification requirements, including appearance, pH, sterility particulate matter and impurity profile, confirming that the filtration process maintains both physicochemical and microbiological quality of the product.

The absence of changes in critical quality attributes demonstrates that the filtration process is well controlled and does not introduce variability that could affect product compliance with specification requirements. In addition, the obtained results are representative of full-scale manufacturing conditions providing assurance that the process is robust and reproducible in routine production.

Conclusion

The results of this study demonstrate that Benzodiazepine solution for injection is compatible with Nylon membrane filters (0.45µm and 0.2µm) used in the sterilization process. No adsorption of the active substance or excipients was observed under full-scale manufacturing conditions.

Filter integrity remained unchanged after exposure to the solution and all tested quality attributes of the product complied with predefined specification limits.

The filtration process does not affect filter integrity or product quality and can be considered robust and suitable for routine industrial applications. The results confirm the reliability of the sterilizing filtration process in ensuring consistent product quality, safety and efficacy in line with GMP requirements for sterile medicinal products (European Commission, 2022).

Furthermore, stability studies demonstrated that all quality parameters remain within specified limits over time, confirming the absence of long-term incompatibility between Benzodiazepine solution for injection and the Nylon membrane filters.

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