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Optimization of heat and mass transfer, elucidation of reconstitution factors and assessing opportunities for liquid-liquid combination applications in dual chamber systems

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Dual-chamber systems (DCS) provide an option as drug/device combination product, when home care and emergency lyophilized products are intended. However, todayI today there are currently only a few products on the market, due to the challenges and limitations in manufacturability, product formulation and product stability in a dual-chamber configuration, as well as economic considerations. Initially we reviewed currently available DCS's and discusses challenges with emphasizes on established fill finish processes. After elucidating the challenges attributed with DCS, this work deals with potential solutions and strategies with special emphasizes on freeze-drying and reconstitution aspects in order to facilitate DCS availability in future. Last but not least potential liquid/liquid applications were discussed and mixing behavior within a DCS was elucidated.

Its complex and costly drug product manufacturing process (especially for freeze dried biologics) is presumably one of the reasons only few products have been launched in DCS so far. Within this work two improved processes (both based on tray filling technology) for freeze-drying pharmaceuticals in DCS are described. Challenges with regards to heat transfer were tackled by (1) performing the freeze drying step in a "needle-down" orientation in combination with an aluminum block or (2) freeze drying the drug product "externally" in a metal cartridge with subsequent filling of the lyophilization cake into the DCS. Metal mediated heat transfer was shown to be efficient in both cases and batch (unit to unit) homogeneity with regards to sublimation rate was increased. It was difficult to influence ice crystal size using different methods when in use with an aluminum block due to its heat capacity. Using such a metal carrier implies a large heat capacity leading to relatively small ice crystals. Compared to the established process, drying times were reduced by half using the new processes. The drying time was however, longer for syringes compared to vials due to the syringe design (long and slim). The differences in drying times were less pronounced for aggressive drying cycles. The proposed processes may help to considerably decrease investment costs into DCS fill finish equipment.

Reconstitution time is a critical quality attribute especially for products in a DCS. For emergency and home-care compliance short reconstitution times are desired. Homecare parenterals usually aim subcutaneous administration requiring relative small volumes. For biologics this circumstance leads to high concentrations, which are often attributed with long reconstitution times. This work addresses factors that may influence reconstitution time a DCS. As a pre-requisite a suitable method for reconstitution time determination had to be developed.

The reconstitution of freeze-dried products is usually determined by visual inspection with the naked eye. This can inevitably lead to significant variability in the ability to detect complete reconstitution of the dried solid. It was thus a goal of our work to assess an automated method to monitor reconstitution of a freeze dried protein drug product in its primary packaging. A newly developed measuring device was used to measure impedance. This was achieved by detecting minor changes in impedance of the reconstitution medium, which occurred due to solid material dissolving during the dissolution process. This measurement system was capable of consistently detecting the dissolution of the last visible residues of freeze dried lyophilisates. The endpoint of reconstitution was defined at an impedance change of less than 1 Ω for at least 7 s. Finally, we compared reconstitution times determined by the automated impedance method with results obtained by a visual method. In contrast to human operators, the new method delivered both accurate and precise results. Besides detection of the reconstitution endpoint, the impedance method and apparatus can monitor reconstitution endpoints as well as reconstitution kinetics. This standardized method can therefore advantageously be used for the determination of the reconstitution endpoint.

Reconstitution time of dried products is influenced by various factors including formulation, process and reconstitution method itself. This work describes factors affecting reconstitution time in a DCS using highly concentrated huMab and BSA model formulations. Freezing and drying conditions had only minor impact on the reconstitution time, whereas the primary container and thus the geometry of the lyophilization cake played a major role. Pre-warmed diluent and agitation decreased reconstitution time. For effective agitation, short displacements and high agitation frequencies were found to be desirable conditions to minimize reconstitution time for a given lyophilization cake while foam formation was minimized. This work also provides general strategies (e.g. reduction of lyophilized cake density, use of an optimized fill finish process and suitable method parameters) to reduce reconstitution time, especially for drug product presented in a DCS configuration.

DCS – originally designed to separate a solid substance and its diluent – can also be designed as liquid-liquid systems for applications where a co-formulation into one solution or product is not warranted. A liquid/liquid DCS can be designed to achieve homogenization and mixing of both solutions either shortly prior administration or can sequentially inject both solutions. While sequential injection can be easily achieved by a DCS with a bypass located at the very needle end of the syringe barrel, mixing of the two fluids may provide more challenges. In this work, we assessed the mixing behavior of surrogate solutions in a dual-chamber syringe head chamber. Furthermore, the influence of parameters like injection angle, injection speed and agitation were elucidated. We found that when the two liquids significantly differ in their physical properties (viscosity, density), mixing was poor for the commercial DCS with longitudinal ridge design bypass. In such cases improved mixing can be achieved using DCS with improved design such as multiple bypass channels.