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Mini Review

Technology, Applications, and Process Challenges of Dual Chamber Systems

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ABSTRACT

Dual-chamber systems provide an option as a drug and device combination product, when home care and emergency lyophilized products are intended. Nevertheless, until today, there are 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. This review serves to describe currently available dual-chamber systems and to discuss factors to be considered for appropriate selection and establishing fill-finish processes.

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Introduction

Therapeutic proteins for parenteral administration are most commonly presented in vials—either as a liquid formulation or as a freeze-dried powder. However, as administration from the vial requires many handling steps, it is prone to errors, even when carried out by trained professionals.[1]

Looking at today's pharmaceutical market, there is a clear trend to reduce the time and number of handling steps required before administration by using prefilled syringes and auto injectors.[2] The predominant driver for this development is patient convenience and reduced health care costs because such systems facilitate self-injection and home care use, despite the higher unit dose cost of a dual-chamber prefilled system (DCS).[3] However, freeze-dried products cannot be simply combined with standard syringes because they need a reconstitution step before administration. Devices that allow both—reconstitution in place and administration—are dual-chamber systems (Fig. 1).[4] As approximately 1 of 2 approved biopharmaceutical products is freeze-dried, DCSs are expected to be on the rise and have the potential to become the first choice for emergency and home care markets.[5]

Although these systems are very convenient from the end-user perspective, their development provides a number of significant challenges: these include the increased complexity with respect to freeze-drying and reconstitution. Both processes depend on the container geometry which should provide a big surface area for optimal product drying and wetting. Thus, the use of DCSs with their intrinsically small cross-sectional area is a challenge. Consequently, a critical and controversial discussion tends to (over) emphasize limitations of the technology: scarcity of published data, patent restriction, and technical difficulties. This might impact the need for changes in product formulation or the use of special diluents. Other challenges are caused by an increased moisture migration from the diluent chamber and the rubber parts (plunger and closure) to the dried product which might affect stability and

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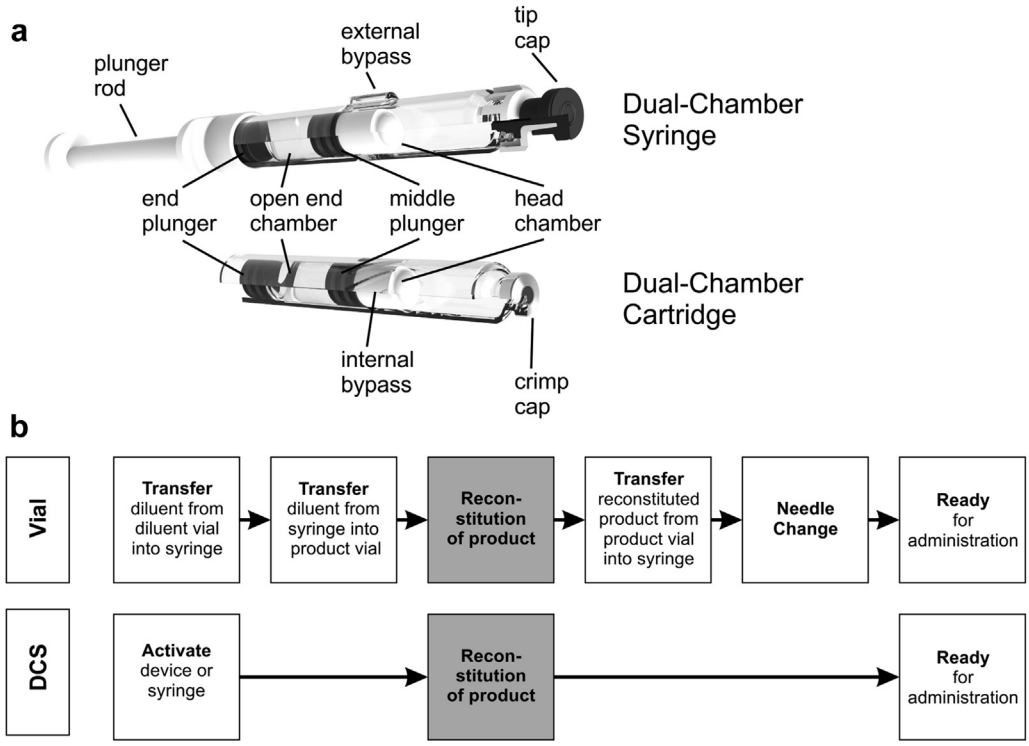

Figure 1. DCS design and working principle: (a) marketed DCS variations can be broken down to a single design with variation in the bypass region. Additional parts define whether the system is termed cartridge (to be used in a device; head closure is pierced by a needle) or syringe (used without device, usually a needle is attached to the head closure). The drawings are based on information provided in references.[7-10] (b) Necessary steps for dried product reconstitution before administration for a vial and a DCS.

by the presence of silicone oil which can introduce silicone particulates or opalescence.[6] Numerous other challenges need to be overcome when developing a DCS, including extractables and leachables, product compatibility, ensurance of device functionality (also and especially over the product shelf life), ensurance and adequate setup for testing of container closure integrity, and other challenges typically encountered when developing drug and device combination products.

Given all mentioned challenges for the development and commercialization of dual-chamber syringe development, there are only a few facilities available globally to process dual-chamber systems today, and the market potential is still far from being exhausted.

With this minireview, we aim to provide a detailed overview on the current technology available, its potential applications, and known process limitations. DCSs can be used for home care and self-administration, resulting in less hospitalization and patients' convenience improvement and thus are important to be considered.

Scope of Literature Search

A thorough review and keyword search of US patents, scientific literature, and recent conference reports was conducted. Specific studies were selected according to the following criteria: reporting of stability data in dual chambers, freeze-drying behaviors in syringes, disclosed processes and equipment for processing vials, dual-chamber systems, and prefilled syringes. The present review article focuses on technologies which were used for the production of commercial products presented in DCS. Other strategies, mainly described in patents, were excluded because they were never implemented and therefore had no visible impact on contemporary production processes or the market situation. Noncommercial technologies, products, and processes that are under development were not considered. These included Unifill (Unilife), LyoGo (LTI), as well as nonglass-containing dual-chamber systems. Systems that significantly differ from cartridges or syringes, for example, Act-O-Vial (Pfizer) or dual-container bag (B Braun) were also not further discussed.

Technology—Design and Working Principle of the DCS

Among the many designs known for dual-chamber systems, those being marketed with a drug product can be categorized by their bypass (i.e., internal or external) and head design (i.e., syringe or cartridge). Figure 1a illustrates a typical DCS design. All DCSs consist of a glass barrel which is divided into 2 chambers via a plunger. In some cases, barrels consisting of plastic can also be considered, provided that extractables and/or leachables are manageable, DCS washing and sterilization is feasible, product stability is warranted, and that likely occurring oxygen and water permeation would lead to still acceptable product. The DCS usually contains the freeze-dried drug product in the head chamber and a diluent in end chamber opposite to the head chamber. When pressing the plunger rod, the middle plunger moves into a bypass position that allows the diluent to reconstitute the drug product. Most marketed products use an external bypass DCS which is formed as a longitudinal ridge in the outer wall of the barrel. One marketed product (Genotropin, Pfizer) is presented in a DCS with an internal bypass consisting of a plurality of lands and grooves.[7] An advantage of the internal design is that the external form remains a radial body and thus does not need any geometric alignment for processing. Furthermore, it is claimed to allow a slim barrel for both the DCS and injection devices the DCS is

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