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Research paper

On the needle clogging of staked-in-needle pre-filled syringes: Mechanism of liquid entering the needle and solidification process

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ABSTRACT

Staked-in-needle prefilled syringes (SIN-PFS) are widely used for the parenteral administration of drug product solutions. During stability studies, clogging of the injection needle was observed in syringes filled with concentrated antibody solution. A prerequisite for this phenomenon is that liquid has entered the needle. In this study, we characterized the mechanism causing the entry and movement of liquid in the needle using neutron imaging without manipulating the container closure integrity of the syringe. The gas pressure difference between inside and outside of the syringe was identified as the major cause of liquid movement. The influence of external factors, such as temperature fluctuation and physical pressure on the stopper, were tested and were confirmed to have a relevant impact on the processes of liquid entering and moving inside the injection needle. In a second step, the solidification process of the liquid segments inside the needle via solvent evaporation was further investigated, and the process was found to be dependent on storage time, environmental climate and interaction between the drug product solution and the needle surface. The presence of air/liquid segments was identified as a further factor for the stochastic behavior of needle clogging. For the first time, this fundamental mechanism behind the needle clogging issue was investigated in depth and the results will help to reduce the defect rate for clogged SIN-PFS products.

1. Introduction

Pre-filled syringes (PFS) are a widely used primary container for parenteral administration of vaccines or protein therapeutics [1–3]. Thereby, the syringe is delivered pre-filled with a drug product solution (DPS). A special variant of PFS are staked-in-needle pre-filled syringes (SIN-PFS), in which the metal cannula is already attached to the glass barrel and protected by a rigid needle shield (RNS). Hence, the SIN-PFS is ready for injection after removal of the RNS. The relevance of PFS as a primary container for parenteral drugs has increased during recent years due to the simplicity of use. No transfer from the vial to a disposable syringe is necessary, which reduces the risks for microbial contamination and dose errors. SIN-PFS are usually assembled in needle safety devices (NSD) or auto-injectors (AI) [4]. The main functionality of a NSD is to prevent needle stick injuries. AI provide additional functionality to the user, such as automated delivery of the dose or end-of-dose indication, and allow a simple and controlled administration of the drug.

The technical development of SIN-PFS combination products includes functionality testing over stability study as part of design verification. During the design of a combination product, consisting of a concentrated antibody formulation and a SIN-PFS, clogged needles were occasionally detected after mid-term storage at elevated temperatures (e.g. 25 °C/60% RH and 40 °C/25% RH [5]). Needle clogging is defined as the formation of an obstruction in the injection needle, which is the result of a change from liquid to highly viscous or even solid state. This obstruction limits or prevents the flow of the DPS from the barrel through the needle causing difficult or even impossible injections.

The needle of SIN-PFS is capped with a rigid needle shield (RNS) providing container closure integrity and protection of the injection needle. The RNS is composed of a soft elastomer core and an external rigid plastic protection. The soft elastomer may be slightly gas permeable, meaning that gas (i.e. air or water vapor) can be slowly exchanged through the rubber of the RNS. The gas transmission rate depends on the elastomer itself and it is a required property to facilitate steam or

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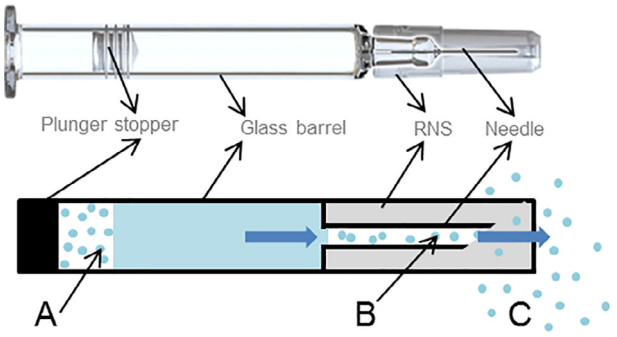

Fig. 1. Image of a PFS (upper) and a scheme (below) used to explain the system.

ethylene oxide sterilization of the empty syringe before filling. In our study, we considered the syringe as a system described in Fig. 1, with a constant inner volume. Here, the stopper is tight and does not move within the experimental conditions, whereas the gas inside needle still exchanges very slowly with the external environment.

Fig. 1 shows the presence of an air bubble in the barrel (A), an additional air bubble in the needle (B) and the environment outside of the PFS (C). For our consideration, only the relative pressure, which is described as the ΔP between pressure inside and outside the syringe, is relevant for the gas movement in the needle (B), whereas the absolute pressures P_A, P_B and P_C are not relevant. In this manuscript, a higher pressure inside the syringe compared to the outside will be referred to as the "positive ΔP" and an inner pressure lower than the external one will be referred to as the "negative ΔP". The ΔP is the driving force for gas movement through the elastomer of the needle shield.

The ideal gas law, also known as the general gas equation (Eq. (1), explains the state of a hypothetical ideal gas:

$$PV = nRT \quad (1)$$

However, it can be used with good approximation for describing a real gas, where P is the pressure of the gas (in N/m^2), V is the volume of the gas (in m^3), n is the amount of gas molecules (mol), R is the universal gas constant (8.314 Nm/K·mol) and T is the temperature (in K).

When a PFS is filled and stoppered at room temperature, the pressure in the inner compartments reaches an equilibrium with the environment, and temperature is identical both inside and outside of the syringe. When the ambient temperature increases, the temperature inside the syringe adapts to the new condition. According to Eq. (1) and on the assumption that the gas volume inside of the syringe is constant, the pressure inside of the syringe will increase. As the RNS rubber is slightly gas permeable, the overpressure inside the barrel will lead to gas diffusion through the needle shield driven by the difference of partial pressure. During this process, it is assumed that liquid can be pushed inside the needle. On the other hand, when the syringe is stored at colder temperatures, the temperature inside the syringe adapts to the new conditions and the inner gas pressure drops, leading to slow movement of liquid/air away from the needle tip. Therefore, external atmospheric pressure and temperature are two important variables of the system described in Fig. 1.

The analysis of a standard PFS supply chain from its filling to the final administration (Fig. 2) reveals that a PFS is exposed to several changes of environmental conditions such as temperature cycles as well as pressure changes. Additionally, syringes can be exposed to mechanical forces during stoppering, plunger rod assembly or transport-related agitation stress. Finally, the capillary nature of the needle may also contribute to the complexity of the system, acting as an additional factor promoting the entry of liquid in the needle [6].

The aim of this study is to investigate the causes of liquid entering the injection needle of SIN-PFS, as a prerequisite for needle clogging. Experiments were designed to confirm that pressure fluctuations, caused by the aforementioned external factors, will lead to both the presence and movement of liquid inside the needle. Hence, we investigated the capillary force, the influence of the stoppering method (vacuum and vent stoppering) and the effect of temperature and pressure fluctuations. Thereby, Neutron Imaging (NI) was applied as a tool to visualize the distribution of the original liquid inside the needle without manipulating the closure integrity of the syringe. The investigations continued by studying the role of liquid/air segments on the drying process inside of the needle.

2. Materials and methods

2.1. Materials

The SIN-PFS used in the experiments are 1 mL SIN-PFS, made of Type I borosilicate clear glass with a cut finger flange and a stainless steel 27 G regular-wall (RW) needle cannula (length of 19.5 ± 0.5 mm, inner diameter of 0.21 mm ± 0.02 mm), as shown in Fig. 1. The syringes were stoppered using PTFE-coated butyl rubber plunger stoppers. RNS were made of a soft core of synthetic polyisoprene type rubber and an external rigid molded plastic shield, as already described in a previous study (RNS 1 in [5]). The DP solution used for the experiment was a monoclonal antibody (mAb) solution (189 mg/mL buffered to pH 6 including both surfactants and stabilizers). SIN-PFS were filled with 1 mL of a concentrated antibody solution using a nested syringe filling line (Inova/Optima SV122). Each PFS had a head space of 3 ± 1.5 mm between liquid surface and syringe stopper.

2.2. Neutron imaging of PFS

Neutron imaging was used to investigate the presence of liquid in the needles of the intact SIN-PFS samples. The image acquisition is similar to conventional X-ray imaging where the irradiation penetrates into solids and is attenuated differently by each material. Neutrons, being electrically neutral, do not interact with electrons (as it is the case for X-rays) but with atomic nuclei. In contrast to X-rays, neutrons can penetrate through metals, whereas a high contrast is given for light atoms such as hydrogen (H) [7–9]. In the present work, neutron imaging is used to visualize drug product solution containing a high amount of H, inside a metal syringe needle emerging from the glass barrel (the total needle length is of 19.5 mm, the length outside of the glass barrel is of 12 mm). The RNS is kept in place during the measurement and hence the container closure integrity of the system is not compromised [10]. Experiments were carried out at the ICON beamline

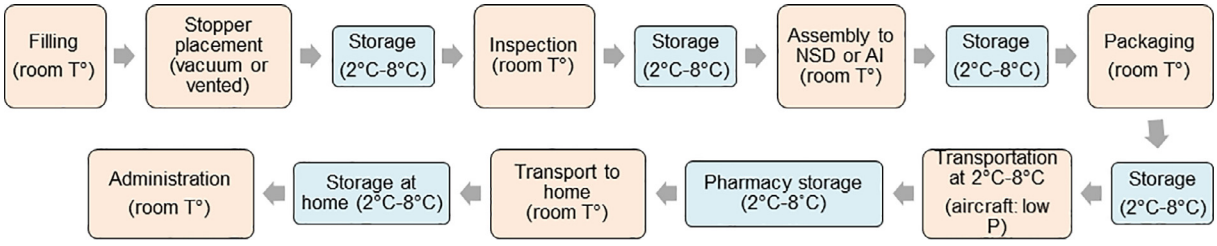

Fig. 2. Analysis of a PFS supply chain with emphasis on temperature and pressure changes.