SPOTLIGHT

Optimising the pre-filled syringe filling process for biological molecules using innovative single-use technologies: a design of experiments approach

Innovation in the parenteral landscape is key to ensure that pre-filled syringes can continue to remain at the forefront of treatments. We hear from experts at Aenova Group about what an experiment into good practices for pre-filled syringes revealed

In the last few years, the market demand for user-friendly injectable delivery systems has increased. Among them, pre-filled syringes (PFS) have attracted considerable interest from pharmaceutical companies, mainly due to their advantages over traditional pharmaceutical dosage forms.[1]

The Aenova Group's Latina site has dedicated a fill-finish suite to the production of PFS and vials for small and large molecules such as active pharmaceutical ingredients (API) and biologics, respectively. The drawbacks related to parenteral administration such as lack of convenience, affordability and accuracy, can be easily overcome by using PFS.[2] It is considered an efficient, reliable and convenient method for drug administration, possessing countless advantages such as simplicity, suitability for home use, reduction in waste, greater dose precision and

convenience for emergency use.[3,4] General knowledge about PFS is abundant, but information regarding PFS manufacturing as well as technical aspects regarding filling is still relatively unknown.[5]

Among the currently available fill-finish technologies, peristaltic pump dosing and single-use filling assemblies have garnered significant interest due to their features related to cleaning, gentle product transfer and shear stress minimisation on formulations. For this study, a custom-designed, single-use filling assembly made of ePTFE (expanded polytetrafluoroethylene) and silicone was chosen.

The primary objective of this study was to investigate the performance of the liquid filling machine installed in the fill-finish department of Aenova's Latina site, applied to a single-use filling assembly made of ePTFE and silicone. The focus was to study the filling line parameters and the geometry of the filling assembly to evaluate its efficiency and effectiveness in pharmaceutical production. The selected assembly, which is high-temperature resistant, may be cleaned in place (CIP) and sterilised in place (SIP), which is an advantage when products cannot be exposed to gamma irradiation or hydrogen peroxide and which also minimises operator handling and connection in an aseptic environment. In addition, it is highly resistant to mechanical stress and minimises the spallation phenomenon.

To achieve this, we adopted a design of experiments (DoE) approach. By manipulating inputs such as needle diameter, needle length and filling speed, DoE could identify the optimal combination in terms of filling profile and filling speed.

Materials and methods

Liquid filling machine

The filling machine installed in the fill-finish department of Aenova's Latina site is an automatic high-speed filling machine for nested syringes and vials, capable of processing vials and syringes supplied as nest/tub or nested trays. The syringes are taken from the nests and transported to the weighing station (tare).

According to the in-process control (IPC), the syringes are filled using ten peristaltic pumps and the filled syringes pass from the weighing station downstream of the filling station (gross). The linear vibrator guides the plungers to the grippers, which transfer the plunger into the syringe. The filling step is done by a set of peristaltic pumps.

The syringe filling process is carried out using a custom-designed, single-use filling assembly (**Figure 1**). This assembly, made of high-quality ePTFE and silicone (tubing) and stainless steel (y-connections and filling needles), ensures the precision and reliability of the filling process.

The PFS used in the study were 1mL sterile and ready-to-use syringes composed of type I glass and included four components: plunger, stopper, barrel and needle. The needle was pre-attached and protected by a needle shield. For the study, nine runs were conducted according to the experimental plan. Given the machine's capacity to fill syringes with ten peristaltic pumps/filling needles (ten syringes at a time), the complexity of the experimental activities necessitated a comprehensive approach.

A thorough preliminary study on a single run (single needle) was conducted, enabling a comprehensive evaluation of the entire process through an overall study of nine runs. This meticulous approach, which included a detailed examination of each run, ensured the reliability and robustness of our findings.

To optimise the experimental timing and evaluate any possible interaction between the three factors considered (average weight, drops presence and filling profile), a full factorial experimental design was chosen in which the factors were varied together instead of one at a time.

Approximately 30,000 syringes were used for each experimental run, and in-process control was performed on each syringe.

IPC

The process controls on syringes were carried out through visual check and weight IPC. A visual analysis of the profile of the syringe during its filling was made through a camera installed in front of the needle filling system.

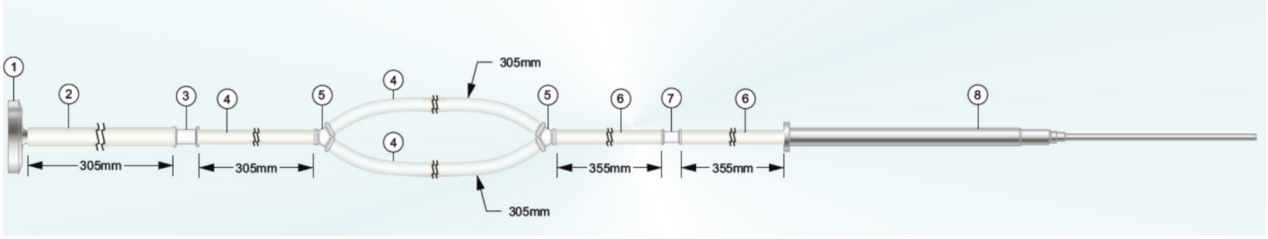

Figure 1: Filling assembly (Source: Aenova)

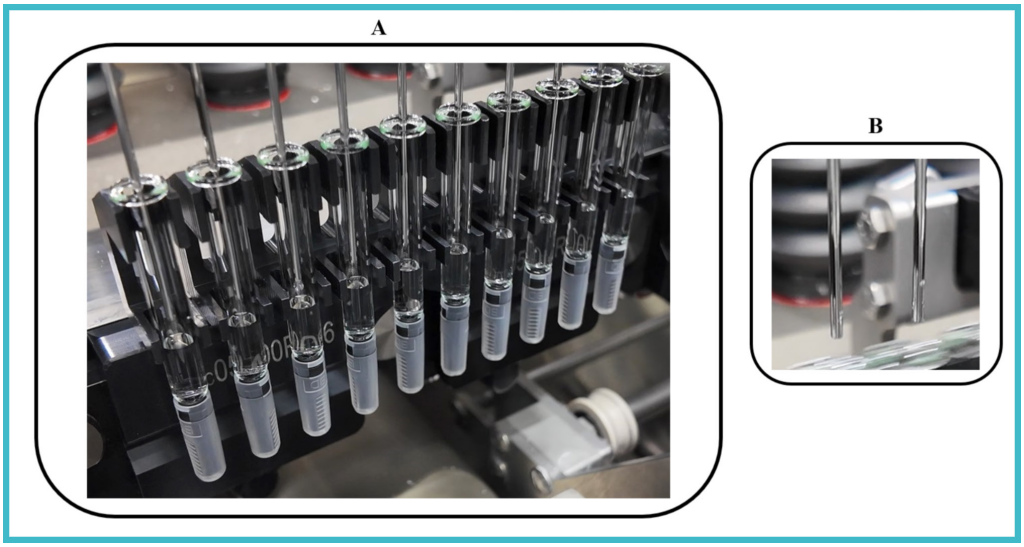

Figure 2: Laminar filling profile (A) and absence of drop on needle (B) (Source: Aenova)

Run	Needle diameter (mm)	Needle length (mm)	Filling speed (pfs/min)	Average Weight (g)	Weighing Range (g)	CV%	Cpk	Drops presence	Filling profile
1	1.7	111	300	0.517480	0.0342	1.21	2.36	0	3
2	1.7	111	580	0.520700	0.0432	1.73	2.27	1	2
3	1.7	61	580	0.520866	0.0340	1.15	2.32	1	3
4	1.7	61	300	0.519149	0.0306	0.81	3.48	0	3
5	1.3	111	580	0.523964	0.0266	0.90	2.76	1	1
6	1.3	111	300	0.519016	0.0428	1.38	1.89	0	3
7	1.3	61	300	0.520610	0.0370	0.89	2.52	0	3
8	1.3	61	580	0.518136	0.0320	1.32	2.00	0	1
9	1.7	61	520	0.520487	0.0336	1.10	2.26	0	4

Table 1: Filling machine parameters set and respective results (Source: Aenova)

The visual check was focused on the detection of the absence/presence of liquid on the needle's outer walls, the absence/presence of liquid drops on the tip of the needle and the performance of the filling profile. In addition, the dosing accuracy of each syringe was evaluated by weight IPC. The weight IPC was checked during the process since the filling machine automatically weighs the syringes before and after filling using weighing stations. For each experimental run, the filling weights were collected on 2% of the total syringes filled.

Statistical analysis

Data obtained during the IPCs were subjected to statistical analysis. Minitab software was used for statistical analysis during the present study. Minitab allowed decision-making to be based on data obtained during the filling step. In particular, it was used for the analysis of capability.[5] The results of the weights obtained from each run were used to understand the capability of our process and the probability of the process producing defects. The purpose of using this analysis was to evaluate, through the two parameters, Cp and Cpk, the variation and the process capability.[5]

In fact, for each run, these two parameters were used as a metric for comparison.

DoE

For this purpose, a DoE approach was chosen. This method allowed us to systematically vary parameters such as needle diameter, needle length and filling speed, while monitoring resulting responses such as filling weights (dosage), presence of drops on the needle tip (dripping) and filling profile (needle diameter and length).

The DoE approach was instrumental in our quest to understand the influence of the assembly geometry and filling speed on the filling profile and dosage performances.

Results and discussion

The quality of the filling profile is of the utmost importance as it directly impacts the dosing. The turbulence within the liquid during the syringes filling must be kept to a minimum, and dripping and splash formation should be avoided as much as possible.

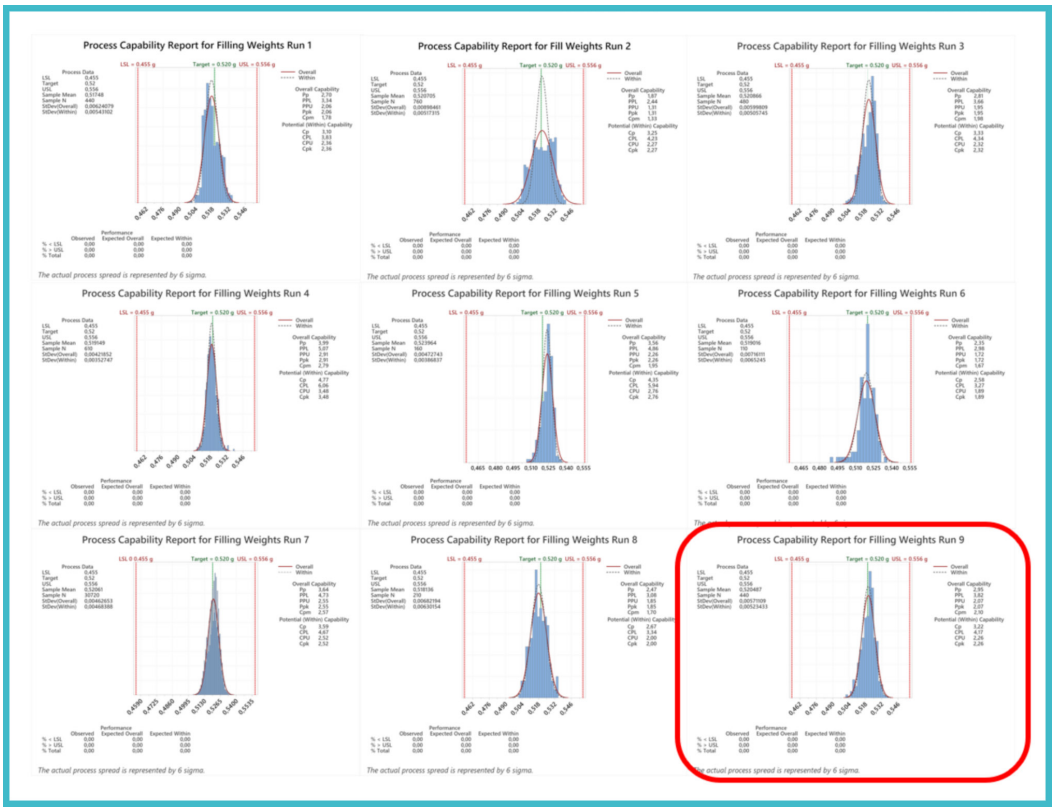

Figure 3: Process capability (Source: Aenova)

Dripping can cause unwanted variation in the syringe's weight and, consequently, loss of precision in filling dosing accuracy.

Table 1 presents the culmination of our study, showcasing all nine runs with the machine parameters set (needle diameter, needle length and filling speed) and the respective results obtained during the present study.

The filling profile was represented by numerical values. The numerical values from one to five that appear in the table correspond to the following situations:

1. Presence of turbulent flow with splashing
2. Bubble formation during filling operations
3. Dripping at the end of the dose
4. Slightly turbulent filling profile with some bubbles
5. Filling profile without bubbles and turbulence.

Simultaneously, the presence or absence of drops on each needle at each time point was numerically converted to one and zero, respectively.

The study carried out on the nine experimental runs showed the best run, combining efficiency with reduced machine time and the best possible filling profile.

According to our results (**Table 1**), the best run was the number nine, performed at a filling speed of 520pfs/min using 61mm short and with a needle diameter of 1.7mm. **Table 1** shows this run's filling profile having superior characteristics to previous runs (runs one through eight), especially with respect to turbulence as well as the absence of drops (see **Figure 2**), while the quantitative dosing data as well as weighing range of the ninth run does not significantly differ from the average weights of previous runs.

The capability analysis of the nine experiments was also evaluated and the results, shown in **Figure 3**, depict some relevant information. The process conducted in the operating conditions selected during the ninth run compared to the other runs, shows that the overall capability metrics and the potential capability metrics are practically identical, which indicates the consistency of the process in the short and long term. The overall capability metrics are in fact, based on all variations seen in the analysis (the long-term) and reflect the process' current performance.

The potential capability metrics are based on the short-term variation. These reflect how good the process could be. Moreover, Cpk and Ppk values are satisfactory and observed and expected performance statistics, which are predictions of the proportions that will fail the specification limits, are both equal to zero.

Conclusion

Based on the data obtained in the present study, all runs envisaged by the experimental design have in fact, led to similar situations with respect to quantitative dosing as evidenced by average weights and weighing range.

Based on these observations, the ninth run, whose quantitative dosing data is in line with those of the previous runs, presents a filling profile with superior characteristics compared to those that preceded it in the experimentation, especially with regard to turbulence and the absence of drops.

Since the productivity of this process is also significant (filling speed 520 pfs/min), it represents a potential candidate of industrial interest. Therefore, the ninth run has highlighted an optimal combination of the best possible filling profile and a filling speed sustainable for business purposes.

The study demonstrates that the geometry and material type of the single-use assembly, together with the optimisation of the filling parameters, represent a viable alternative for the production of injectable biological products sensitive to gamma-irradiated materials or high levels of hydrogen peroxide concentration.

References:

1. *Visit: https://rb.gy/m6b2rj*
2. *Makwana S et al (2011), 'Pre-filled syringes: An innovation in parenteral packaging', Int J Pharm Investig, Oct;1(4), 200-206*
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5. *Visit: https://rb.gy/wu6n6k*

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