EXPERIC

CASE STUDY

Mitigate Risk by Conducting Filling Assessments During Formulation Development

Overview

A small-sized pharmaceutical company had worked with a variety of other contract manufacturing organizations (CMOs) and had no success achieving the necessary product yields to advance the development of their highly cohesive product formulation.

The client approached Experic to determine if one of the company's technologies could effectively and consistently fill their formulation with the goal of reproducibly metering powder into single dose containers and achieving an adequate yield.

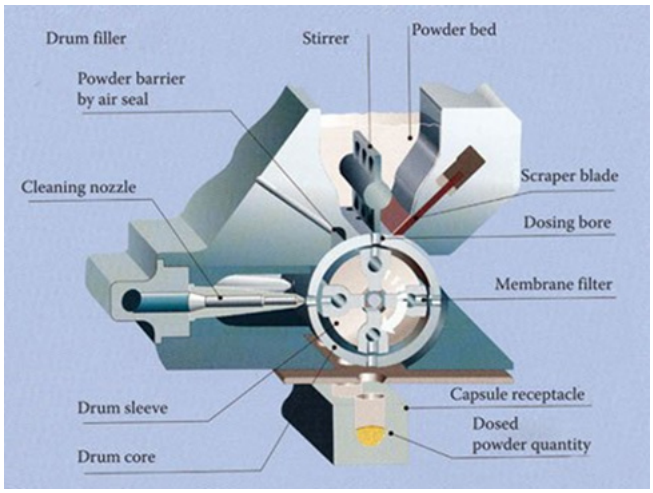
Understanding the Powder

Prior to coming to Experic, the client had invested a great deal of time developing a gravimetric filler that used a vibratory filling mechanism. Unsurprisingly, they found that their blended formulation segregated at certain parameter settings and they could only achieve, at best, a 70% yield of finished product.

Due to this experience, Experic recommended conducting a formulation filling feasibility study to gain the valuable information needed for the client to decide the course of action for future development of the product.

Experic also suggested a drum filling strategy since it is capable of handling cohesive powders without using vibration, which can lead to formulation segregation. Additionally, drum filling is a volumetric process which is generally favored over gravimetric filling for small doses due to its scalability. The Drum Lab was specifically selected because it does not require much formulation for each experiment and can be quickly cleaned and reassembled to increase the experimental throughput.

Harro Höfliger Drum Lab



Integrating the Technology

The Drum Lab features a single-dose volumetric filling drum with a set of precisely machined bores used for metering the powder. A hopper, which contains a powder bed, sits directly above the drum.

The system meters powder by drawing air by vacuum through the filter at the bottom of the bore of the drum as the powder bed is stirred. The dosing bore then rotates to a position above the target container and an impulse of air deposits the powder into a single-dose receptable such as a capsule. Dosing consistency is a function of filling the precise volume bore at a reproducible density. Net fill weight of each dose is measured to determine yield, which is critical in formulation and manufacturing development.

Filling Study Observations

Experic conducted several experiments to determine if the product formulation could be filled at its target weight of 6 milligrams. The highly cohesive nature of the powder resulted in significant fill weight variability. To observe the behavior that was causing fill weight variability under different filling conditions, a camera was positioned above the powder bed. We were able to capture a number of phenomena: bridging, which occurred at higher fill levels of the hopper at fast stir rates; rathole formation, which occurred after the volume in the hopper decreased; and stirrer adhesion, which was seen intermittently throughout the study.

Bridging

At fast stir rates, powder bridged across the top of the hopper, which was surprising because the initial charge of powder filled less than half of the hopper. As the stirrer turned, the powder was transported from the bottom of the powder bed to the hole above the stirrer where powder is typically added, leaving the powder bed starved for product. This lack of available powder resulted in inconsistent fill weights.

Bridging

Rathole Formation

Stirrer Adhesion

Rathole Formation

After the hopper volume was decreased, the powder bed remained at the bottom of the hopper; however, the fill weights were still inconsistent. This was caused by the formation of voids in the bed directly above the dosing bore. In this case, although the powder was directly adjacent to the bore, it did not flow into the bore due to its cohesiveness. Again, inconsistent powder availability led to inconsistent filling.

Stirrer Adhesion

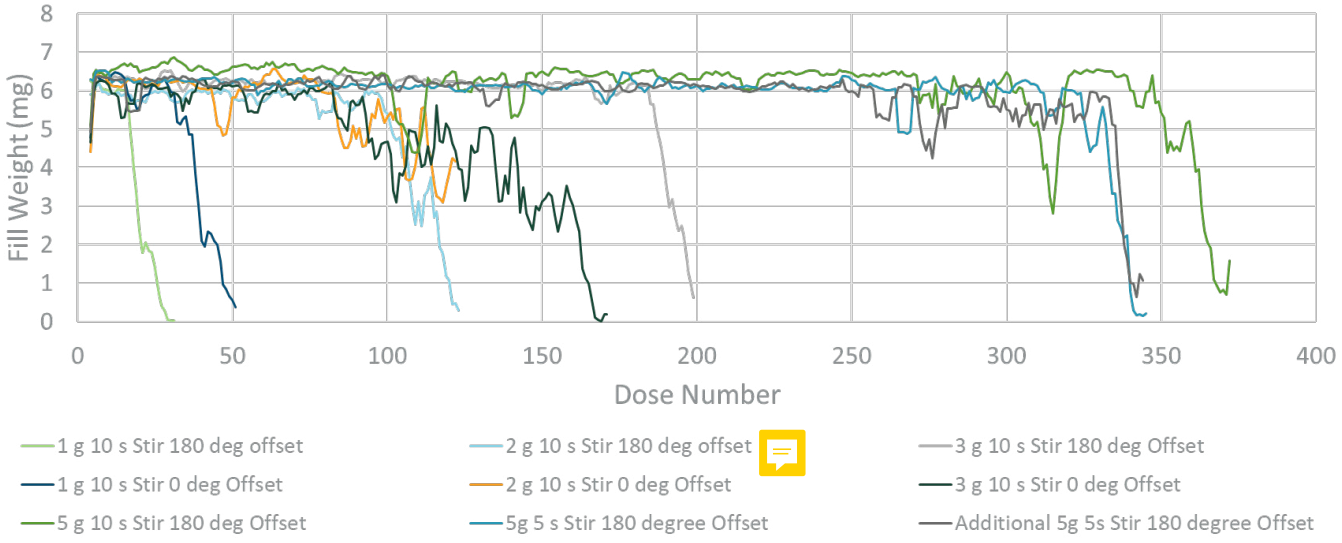
This phenomenon was observed when the stirrer passed through the powder bed and adhered to the powder, even though the stirrer was made from polished stainless steel. This effectively reduced the quantity available for filling and again showed the mechanism for creating cohesive bridges above the stirrer.

Filling Trial Results

Filling trials were conducted on the Drum Lab with varying stirrer speeds and hopper fill levels. Initial filling of the powders on the Drum Lab was done operating the stirrer at conventional speeds (0.5 revolution in 300 milliseconds). It was quickly learned that these fast stir speeds caused the bridging effects, mentioned above, leading to a nearly immediate loss of fill weight consistency (less than 30 doses). Due to this result, the other extreme was explored, reducing the speed of the stirrer to only 0.5 revolution in 5 to 10 seconds. This improved the consistency over the short term (60 doses).

After establishing that a consistent fill could be achieved for 60 doses, Experic turned its focus to trying to increase the total number of doses that could be consistently filled. This is largely influenced by the amount of powder that is added to the hopper and the rate at which powder is refreshed. Hopper fill levels of 1, 2, 3 and 5 grams were then tested, and results can be seen below. It was expected that the amount of material that remained in the hopper would be constant, filling in all dead zones of the hopper. This would mean that adding a larger amount to the hopper should result in less waste.

However, during the trial, a maximum of only 250 doses (~1.5 grams) could be consistently filled from a 5-gram hopper fill. This is only a 30% yield, meaning that 3.5 grams of formulation in the hopper were not available. This 30% yield was the same as the value seen at the 1-gram fill level, which was unexpected. Though the cause was not investigated further, it is hypothesized that it related to compression of the formulation resulting from stirring.



During filling trials for cohesive powders, varying the level of the powder bed typically can be used to control cohesive bridge effects that affect mixture segregation and the overall consistency of the filling process. However, in this case, powder bed management was not a primary determinant due to the highly compressible and cohesive nature of the powder.

Following these initial trials and analysis of the results, Experic suggested alternative filling experiments for the client to consider, including changing the powder bed geometry and type of stirring or filling technology. However, the client had already invested heavily trying to make this formulation work, and in the end, decided to reformulate the product.

Conclusion

While we were not able to find a perfect filling solution for the client's formulation, this case study demonstrates the importance of introducing filling studies during formulation development. Early filling trials can determine if there is a critical linkage between filling process parameters and the product design, assess the impact of lot variation and help in understanding the day-to-day variability in powder density and characteristics. These considerations can influence the robustness of filling and consequently the timelines of a development project as it transitions from lab scale to manufacturing.

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