Integrated Approach to Enhance Formulation Robustness in Multiparticulate Formulations

Authors - Vaibhav Ambudkar, Neha Velingkar, Jaydeep Nawale, Nitin Tayade, Prashant Thakker, Vishal Gogad, Shantanu Damle, Rahul Rane, and Ali Rajabi-Siahboomi

Colorcon, Inc. Harleysville, PA 19438, USA

AAPS

Poster Reprint 2024

Introduction

The dissolution of barrier membrane coated extended release (ER) multiparticulate formulations is influenced by several factors, including drug solubility, diffusional path length (determined by film thickness), and the diffusivity (film quality) of the functional coating. Achieving uniform film thickness is facilitated by factors such as narrow particle size distribution (PSD), high sphericity, and low friability of starting substrate, while coating composition and process parameters govern the film's diffusivity. Monitoring particle growth during the coating process is crucial for controlling coating thickness, ensuring consistent quality and performance. This study focuses on using the Spatial Filter Technique (Parsum probe) for in-line particle measurement to dynamically monitor particle growth during coating processes. The final PSD data from in-line measurement was compared with off-line data obtained via dynamic image analysis (Camsizer P4). The consistent film thickness is the key to dissolution robustness. Continuous particle growth monitoring and film thickness control during coating operations ensures a robust process and successful multiparticulate formulation.

Methods

Manufacturing of Venlafaxine HCl Extended Release Multiparticulate

Venlafaxine hydrochloride was layered onto two different sizes of sugar spheres: 710 to 850µm (Suglets® 20/25, Colorcon) and 500 to 600µm (Suglets® 30/35, Colorcon). Each size fraction was separately drug-layered using an HPMC-based Opadry® Clear (17% solids in purified water) as a binder in a GPCG 1.1 Wurster process at 100% weight gain (WG). This was followed by a seal coat using HPMC-based Opadry® Clear (8% solids in purified water) at 7% WG. The seal-coated multiparticulates were further coated with ethyl cellulose based fully formulated ready-to-coat, functional coating (Corelease EC™, Colorcon) in IPA: water (90:10) at 6% solids. For Suglets® 20/25, the functional coating weight gain was 25.5%, whereas for the Suglets® 30/35, it was 41.5% (Table 1). My Dosage Design™ (MDD), a proprietary theoretical modeling tool, was used to calculate target weight gains for both drug layered batches to achieve comparable functional coating thicknesses of 34.97 µm and 38.46 µm. This also resulted in relatively closer surface area / functional coating thickness ratios of 4.22 $cm^2/\mu m$ and 5.80 $cm^2/\mu m$ for the Suglets® 20/25 and Suglets® 30/35 size fractions, respectively. This was performed to ensure a target dissolution profile closely matching to Test 1 of the USP monograph. Table 2 shows the coating process parameters employed for drug layering, seal, and functional coatings. In the first set of experiments, coating for both Lot 1A of Suglets® 20/25 and Lot 2A of Suglets® 30/35 was performed without using an in-line particle size monitoring tool. PSD data at the end of each coating step were initially obtained using off-line Camsizer, which measures particle size based on the Feret max (length) of the particles. The PSD of coated pellets was further measured by fluidizing the pellets in GPCG 1.1 equipment connected to a Parsum probe (IPP 80-P, SOPAT GmbH) with an in-line disperser D12 (Figure 1).

In the second set of experiments, for Lot 1B of Suglets® 20/25 and Lot 2B of Suglets® 30/35 size fraction, the drug layering, seal coating, and functional coating processes were performed in the GPCG 1.1 equipment connected with Parsum's in-line particle size measuring probe. During this process, particle size growth was continuously measured in-line until the PSD was comparable with the PSD of corresponding first set of experiments (Lot 1A and Lot 2A). Pellets from the second set of experiments were also tested for PSD using Camsizer P4 to confirm the findings of the in-line measurements.

Evaluation of Venlafaxine HCl Multiparticulate

Multiparticulates from both Lot 1 and Lot 2 including core Suglets® were evaluated for PSD (D10, D50, and D90) employing both Camsizer as well as Parsum. The correlation (%R2) between the PSD values from the Camsizer and Parsum was calculated using statistical equation of Pearson's correlation coefficient. The film thickness of the functional coat for both Lot 1 and Lot 2 was determined using the D50 values from the PSD data of both Camsizer and Parsum.

Multiparticulates from both lots were evaluated for % assay of drug, using a HPLC (1200 infinity Series, Agilent) and dissolution performance (EDT-08LX, Electrolab) in 900mL of purified water, Apparatus I (Basket) at 100 rpm.

Table 1: Manufacturing of Venlafaxine HCl Extended Release Multiparticulates

Name of Ingredient	Manufacturer	Lot 1 (Suglets® 20/25)		Lot 2 (Suglets® 30/35)	
		%	mg/ multiparticulates	%	mg/ multiparticulates
Drug layering (100% WG)					
SUGLETS® PF010 [20/25	Colorcon	37.23	141.43	-	-
SUGLETS® PF006 [30/35	Colorcon	-	-	33.03	141.43
Venlafaxine HCl (~37.5mg Venlafaxine)	Anlon Healthcare	11.17	42.43	9.91	42.43
Opadry® 03A Clear	Colorcon	24.20	91.93	21.47	91.93
Glyceryl monostearate	Danisco	1.86	7.07	1.65	7.07
Water (17% solids)	-	-	-	-	-
Seal Coating (7% weight gain)					
Opadry® 03K Clear	Colorcon	5.21	19.80	4.62	19.80
Water (8% solids)	-	-	-	-	-
Functional Coat (25.5% & 41.5% WG)					
Corelease EC™ 505O	Colorcon	20.32	77.18	29.33	125.59
IPA: water (90:10) at 6% solids	-	-	-	-	-
Total		100.00	379.84	100.00	428.25

Results

Monitoring of Particle Size Growth and Its Impact on Film Thickness

The primary objective of this study was to evaluate the effectiveness of in-line particle size monitoring during fluid bed coating using the Parsum probe, and to compare the results with off-line measurements from the Camsizer, assessing their impact on achieving uniform film thickness and ensuring dissolution robustness. Despite the inherent differences in these methodologies, a high degree of correlation between the two measurement methods was observed across all process steps, with %R^2 values consistently around 97-98%. This finding suggests that although the PSD results from the Camsizer and Parsum are not directly interchangeable, their strong correlation supports good agreement between in-line and off-line measurements.

The PSD analysis of Lot 1A and 1B (Suglets® 20/25) showed that the drug loading, seal coating, and functional coating processes were highly consistent between the two lots. The D10, D50 and D90 values for each step were nearly identical, indicating that in-line monitoring in Lot 1B effectively mirrored the coating process of Lot 1A. Similarly, Lot 2A and 2B (Suglets® 30/35) exhibited strong consistency in PSD profiles throughout all the coating stages, further validating the efficacy of in-line monitoring for maintaining uniform particle size distribution and coating thickness.

The results demonstrate that the film thickness (D50) for Lot 1A was 51.5 µm (Camsizer) and 54.5 µm (Parsum), and for Lot 1B, 54.0 µm (Camsizer) and 50.5 µm (Parsum). For Lot 2A, the film thickness was 50.0 µm (Camsizer) and 50.5 µm (Parsum), while Lot 2B exhibited thicknesses of 55.0 µm and 54.0 µm, respectively. These results suggest that both methods consistently provided similar film thickness measurements, and that continuous in-line monitoring during the coating process effectively helped control the film thickness to ensure consistent drug release profiles.

Figures 2 and 3 compare particle size (D50) data of Lots 1A and 2A (bar graphs, without Parsum probe) and Lots 1B and 2B (line graphs, with Parsum probe). In both the cases, continuous particle size growth was observed for Lots 1B and 2B closely matching the endpoint D50 values of Lots 1A and 2A, demonstrating that in-line monitoring with the Parsum probe helps consistently track and control particle size growth throughout the coating process.

The % drug assay of Lot 1 and 2 multiparticulates yielded values close to 100%. Moreover, the drug release profiles produced a similarity factor (f2) of 84 and 94 for Lot 1 and 2 respectively (Figure 4 and 5). These results highlight consistent % assay and dissolution performance in the Corelease EC™ functional coating process, with similar particle size growth observed in both the trial lots.

Figure 1. In-line Monitoring Setup for Coating Trial with GPCG 1.1

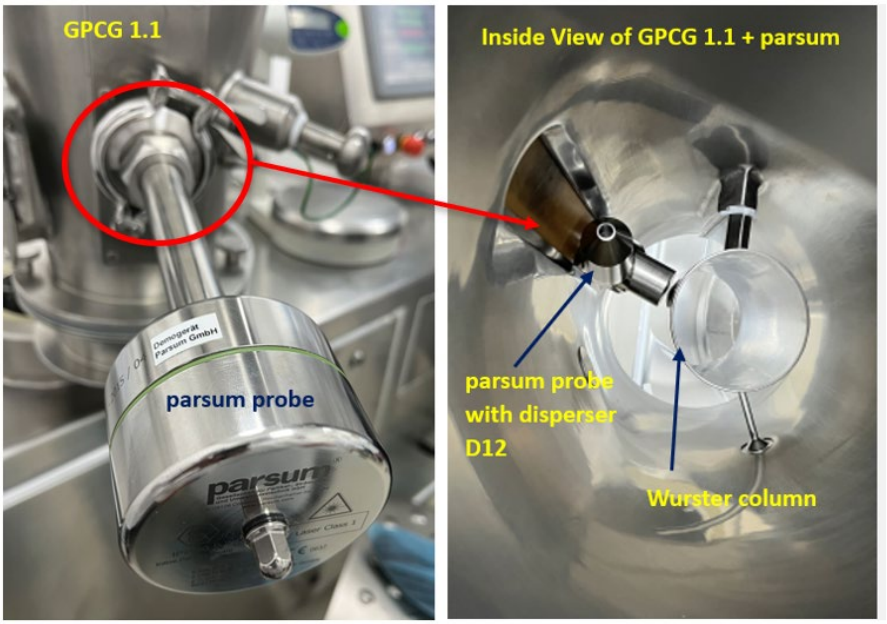


Figure 2. A Plot of Particle Size Growth: Functional Coating (D50) with Time of Lot 1A and Lot 1B

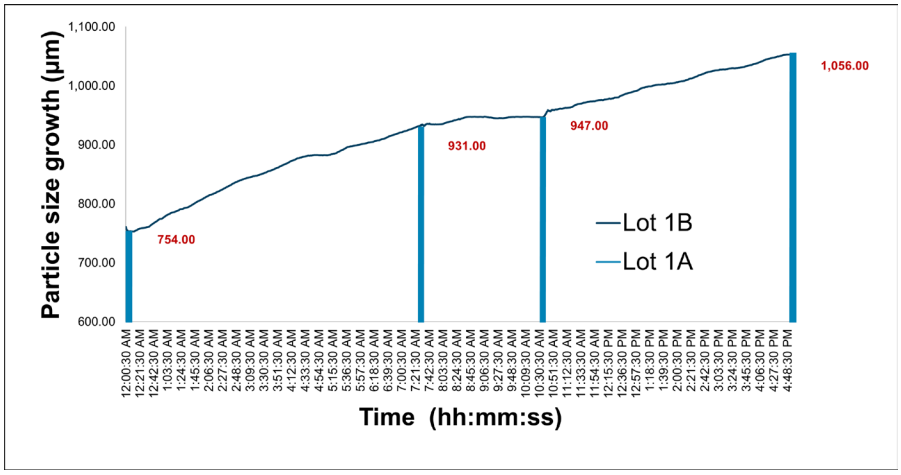


Figure 3. A Plot of Particle Size Growth: Functional Coating (D50) with Time of Lot 2A and Lot 2B

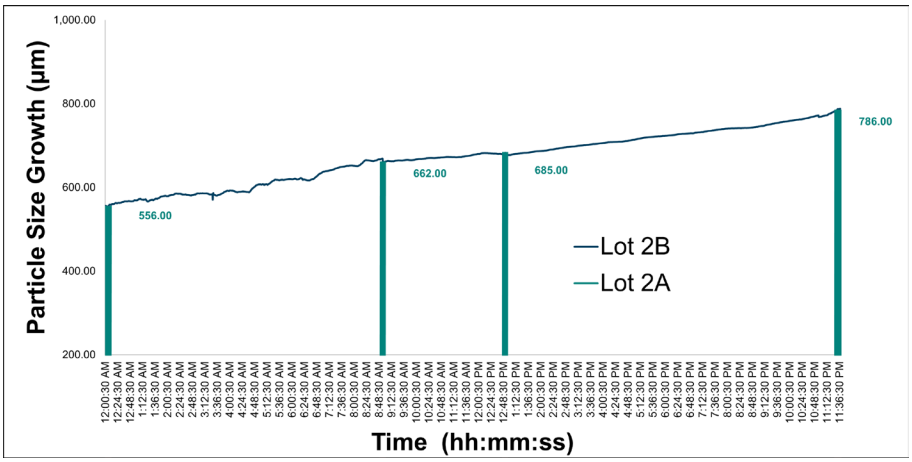


Figure 4. Drug Release Profile of Venlafaxine HCl Extended-Release Multiparticulates of Lot 1A and Lot 1B

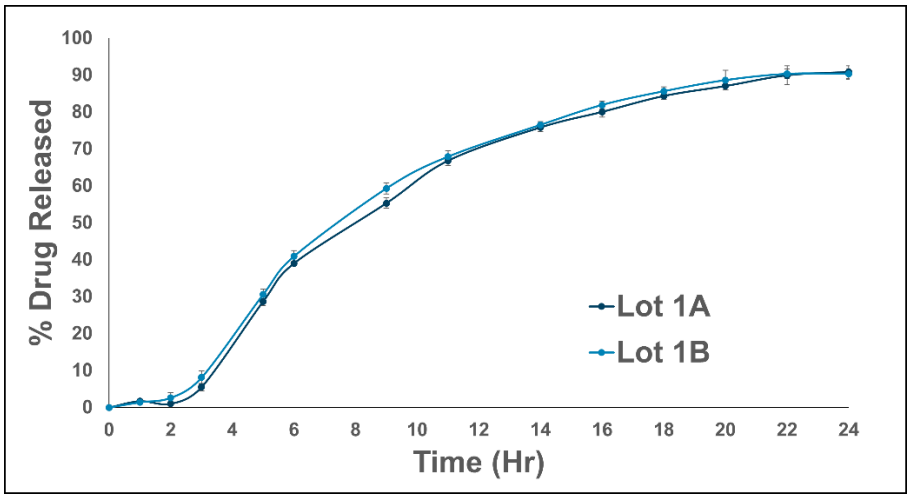
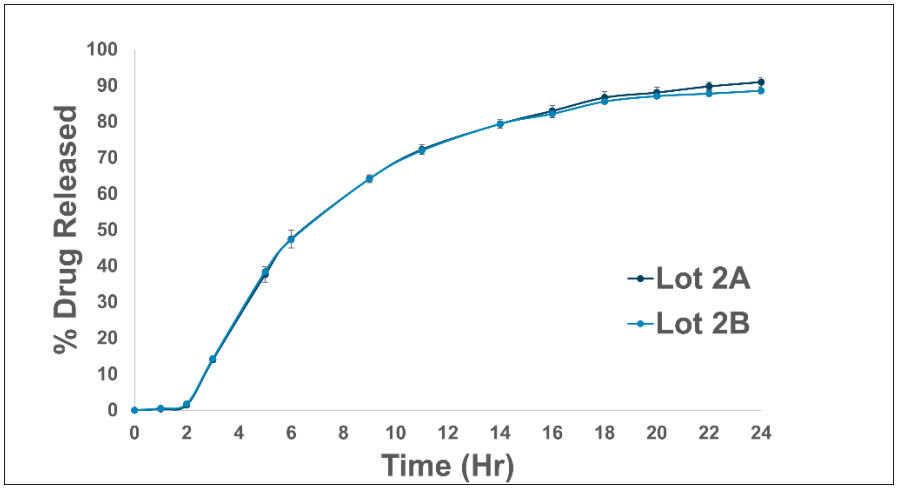


Figure 5. Drug Release Profile of Venlafaxine HCl Extended-Release Multiparticulates of Lot 2A and Lot 2B



Conclusions

The study demonstrated successful formulation of ER multiparticulates containing venlafaxine hydrochloride. The use of Suglets as consistent substrates, followed by an Opadry seal coat and Corelease EC functional coat, achieved consistent coating process and reproducible drug release profile. The MDD tool was used in predicting precise coating weight gains, ensuring uniform film thickness and consistent drug release across different multiparticulate sizes. Real-time particle growth monitoring with a Parsum probe enabled in-line process monitoring and control. Both the Camsizer and Parsum methods exhibited high correlation (%R^2 = 98%) in Lot 1 and 2, validating particle size growth measured by Parsum.

The information contained herein, to the best of Colorcon, Inc.'s knowledge is true and accurate. Any recommendations or suggestions of Colorcon, Inc. with regard to the products provided by Colorcon, Inc. are made without warranty, either implied or expressed, because of the variations in methods, conditions and equipment which may be used in commercially processing the products, and no such warranties are made for the suitability of the products for any applications that you may have disclosed. Colorcon, Inc. shall not be liable for loss of profit or for incidental, special or consequential loss or damages.

Colorcon, Inc. makes no warranty, either expressed or implied, that the use of the products provided by Colorcon, Inc., will not infringe any trademark, trade name, copyright, patent or other rights held by any third person or entity when used in the customer's application.

Colorcon is a global company located in North America, Europe, Middle East, Africa, Latin America, India, and China.

For more information website at **www.colorcon.com**

© BPSI Holdings LLC, 2023.

The information contained in this document is proprietary to Colorcon and may not be used or disseminated inappropriately.

All trademarks, except where noted, are property of BPSI Holdings, LLC.