



OPTIMISING A PROLONGED RELEASE FIXED DOSE COMBINATION PRODUCT

Ensuring dose uniformity by optimising the coating process for a prolonged release antihistamine – decongestant combination tablet

A sponsor company tasked Recipharm to develop a scalable process for manufacturing a generic version of a fixed dose combination (FDC) brand product containing an antihistamine and a decongestant with different release profiles.



THE OVERVIEW

Recipharm was approached to support in the development of a new FDC product that had to contain a low dose of an antihistamine agent within a tablet coating designed for immediate release, as well as a high dose of a decongestant within the tablet matrix designed for extended release.

Recipharm was challenged by the product sponsor to optimise the coating process to ensure uniform distribution of the low-dose antihistaminic agent, while allowing the successful scale-up of registration batches.

THE DETAILS

As this was a technology transfer project from the sponsor to Recipharm, the initial scale-up batches were manufactured according to the process developed by the sponsor.

However, during initial trial stages, Recipharm found that this process did not meet the content uniformity criteria for the antihistamine agent contained within the immediate release tablet coating. In fact, uniformity varied from between 68% to 121%, with a percentage relative standard deviation (%RSD) of more than 7%.

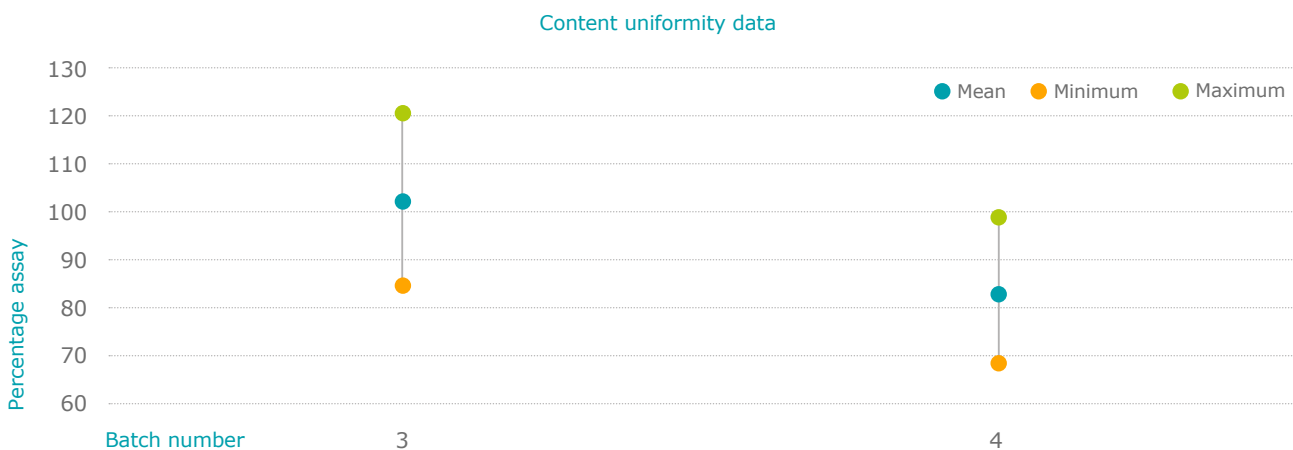


Coating machine: Neocota-60A | Pan load: 190.0 kg

Table 1: Initial trial details.

Batch number	API dispersion concentration (%)	Pan rpm	Spray rate (gm/min)	Gun to bed distance (cm)	Atomisation pressure (kg/cm ²)
03	10.0	06-08	219-253	21.0	3.5-4.5
04	5.0	04	214-300	25.0	3.5-4.5

Figure 1: Antihistamine dose uniformity varied considerably under the initial process designed by the sponsor.



Based on the results of this trial, it was clear that the critical process parameters for applying the immediate release tablet coating needed to be redesigned and refined. This was crucial to ensure the uniform distribution of the antihistamine agent over the tablet's decongestant-containing matrix core.

The issue was discussed with the sponsor, and Recipharm's technical team consisting of a lead scientist, formulation scientist and a project manager was formed to devise a new, more effective process. This team stayed in regular touch with the sponsor to explore options to address the challenge.

Generally, during pan coating processes, a number of parameters play a critical role in coating uniformity:

- ▶ Pan rotation speed

- ▶ Atomisation air pressure
- ▶ Spray rate
- ▶ Gun-to-bed distance

Harnessing the coating experience of its expert team, Recipharm identified that the principal issues in this case were with pan rotation speed and atomising pressure.

This was verified by designing experiments in 30kg scale batches by employing the One Factor At a Time (OFAT) method, where it was shown that an acceptable content uniformity could be achieved by adjusting these parameters.

Following this, Recipharm took a Quality by Design (QbD) approach to optimise the critical process parameters.

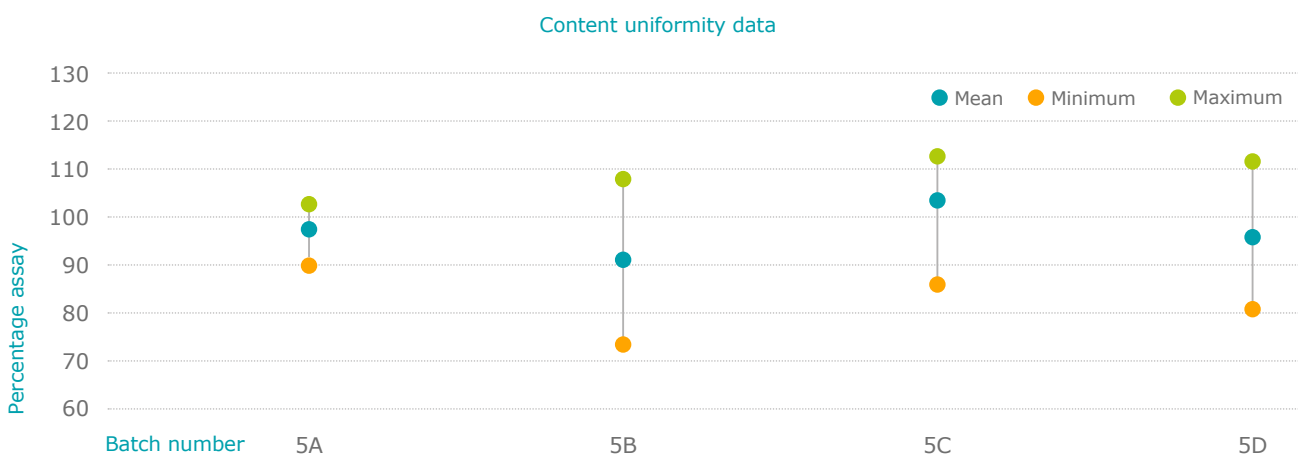


Coating machine: Neocota-40D | Pan Load: 30.0 kg

Table 2. Second trial details.

Batch number	Pan rpm	Spray rate (gm/min)	Gun to bed distance (cm)	Atomisation pressure (kg/cm ²)
05A	8	60-90	10-15	1.5
05B	4	60-90	10-15	1.5
05C	8	60-90	10-15	2.5
05D	4	60-90	10-15	2.5

Figure 2: Recipharm's new process significantly improved the dose uniformity of the tablet coating.



Following the trial of Recipharm's new process, content uniformity of the tablet coating was found to meet the requirements of the product sponsor, with a %RSD of less than 5%.

Recipharm manufactured a scale-up batch using the new coating process parameters to ensure that the new process was scalable and suitable for commercialisation.

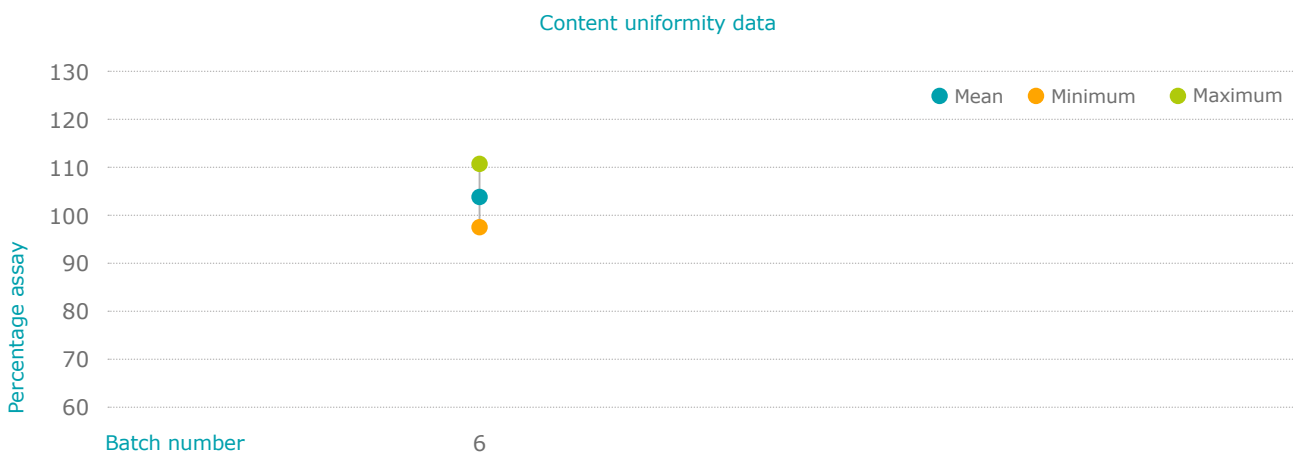


Coating machine: Smart Coater-Gci 700 | Pan Load: 198.0kg

Table 3. Scale-up trial details.

Batch number	API dispersion concentration (%)	Pan rpm	Spray rate (gm/min)	Gun to bed distance (cm)	Atomisation pressure (kg/cm ²)
6	10.0	6	210–218	27.0	2.0

Figure 3: The new process was found to deliver results even at commercial scale.



THE OUTCOME

Results of the scale-up batch demonstrated the effectiveness of the new process at achieving optimum content uniformity of the antihistamine agent within the tablet coating of the sponsor’s FDC product.

Stability studies for the product are ongoing, however, the product sponsor is highly satisfied with the

performance of the Recipharm team. Team members’ problem-solving capabilities, flexible approach and willingness to coordinate closely with the client have all made it possible to successfully complete the manufacture of the registration batches on time and exceed the sponsor’s expectations.



ABOUT RECIPHARM

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 9,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 25 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, we conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do. That's the Recipharm way.

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