



Engineering of Highly Drug Loaded, Free-Flowing Mini-Particles via Tangential Spray Fluid Bed Granulation

Florian Engelsing¹, Jochen Thies², Annette Grave², Julian Quodbach¹

1. Department of Pharmaceutics, Utrecht University, Universiteitsweg 99, 3584CG Utrecht, f.n.f.engelsing@uu.nl

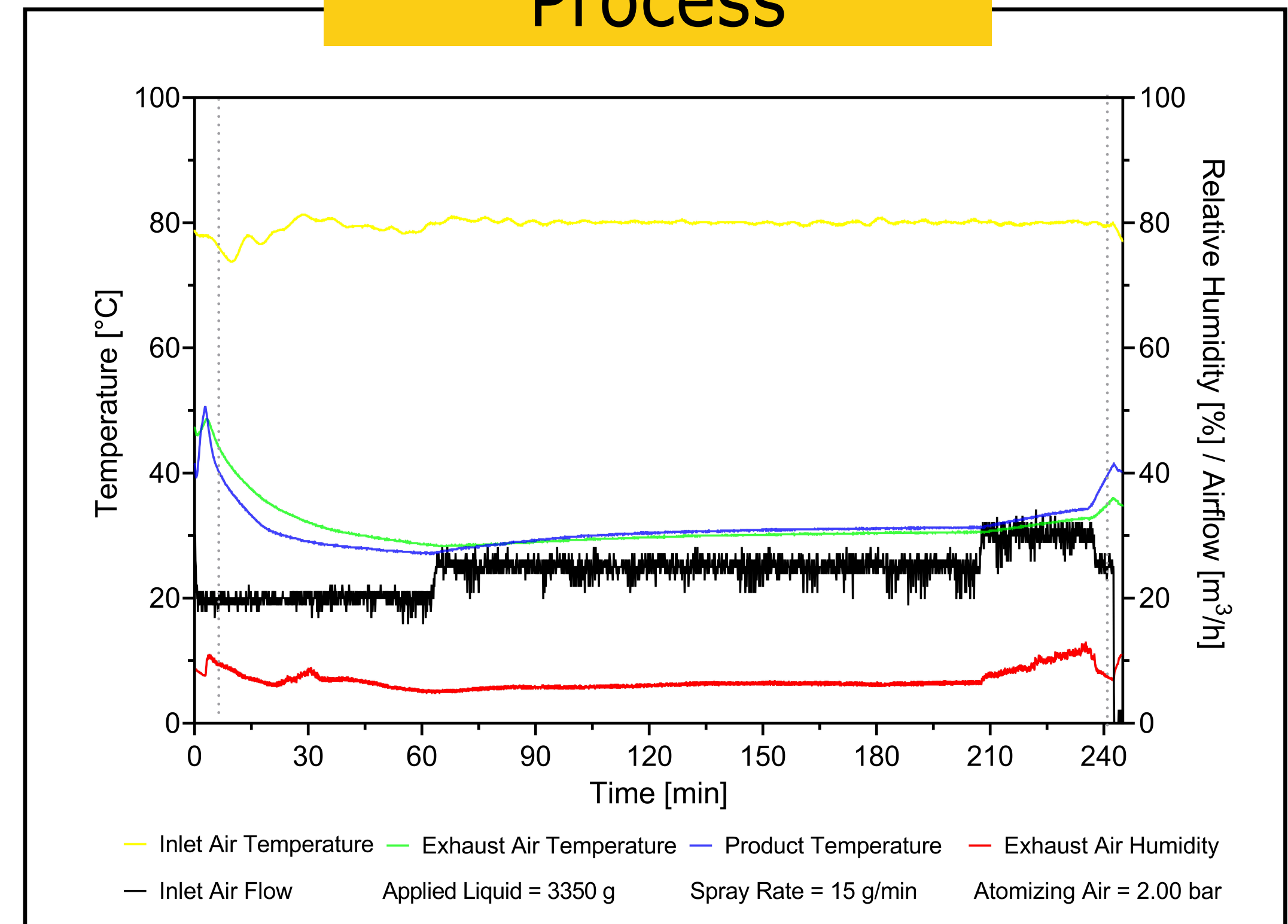
2. Glatt GmbH & Co. KG, Werner-Glatt-Strasse 1, 79539 Binzen

Introduction

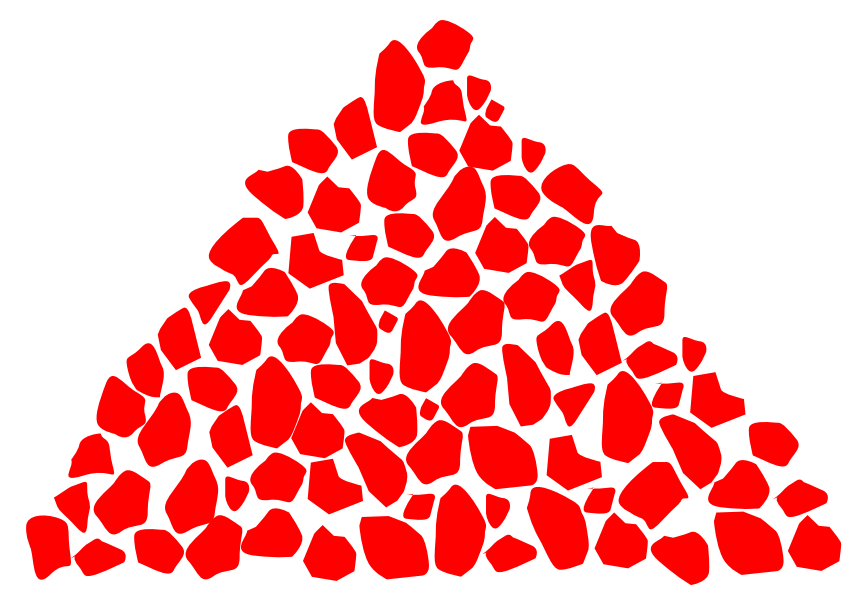
Personalized medicine combines various approaches to establish therapy regimens that are tailored to individual patients. In oral drug delivery, this involves providing patients with customized dosages, dosage forms, and potentially drug release kinetics to minimize adverse drug reactions and optimize therapy outcomes. Traditionally, compressed tablets do not allow this flexibility. Thus, alternative approaches, such as drug loaded pellets, mini-tablets or 3D printed tablets, have been explored. These alternatives offer improved dosing and release options, making them also suitable for use in pediatric or geriatric populations¹. However, a challenge in producing highly drug-loaded tablets is the frequent poor flowability of active pharmaceutical ingredients (APIs). Fluid bed granulation presents an opportunity to control particle shape, size, and size distribution, thereby improving flowability.

The objective of this study was to investigate the use of a tangential spray fluid bed system for the preparation of small-sized, highly drug-loaded, free-flowing particles. Poorly flowing Metoprolol succinate (MTP) was selected as model drug. Due to its high pharmacokinetic variability, it necessitates individualized dose adjustments for patients². Kollidon VA 64 (KVA) was chosen as excipient based on its high water solubility and its thermoplastic properties. The process conditions were chosen so that a dry process was possible in order to prevent excessive particle growth. Five batches with varying amount of KVA (10-30%) were produced to investigate its influence on flowability and particle morphology. In subsequent trials, these batches will be used for the production of 3D printed tablets via Selective Laser Sintering.

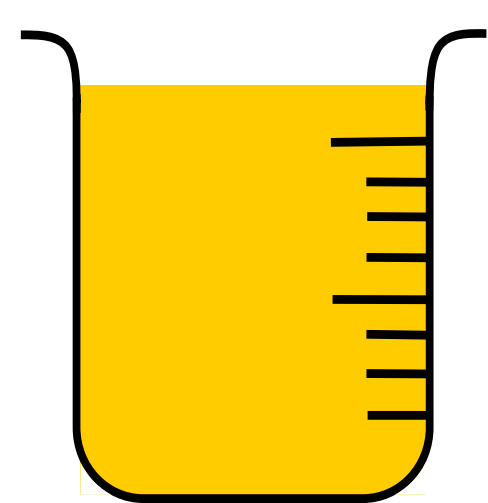
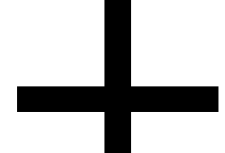
Process



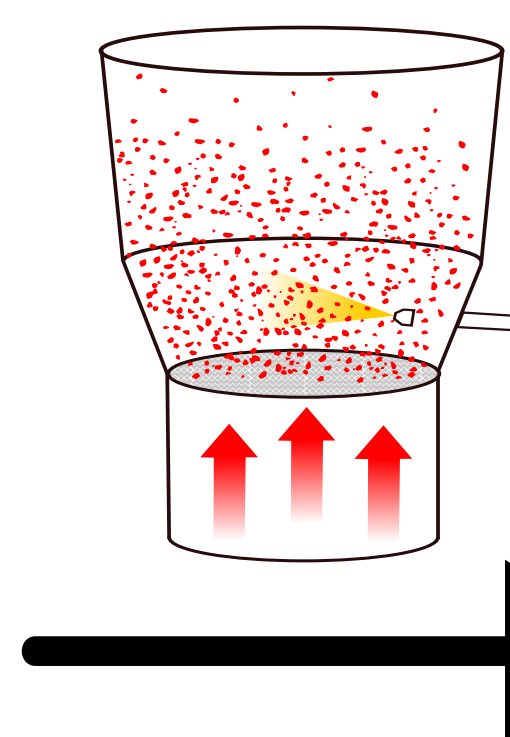
Method



MTP start material

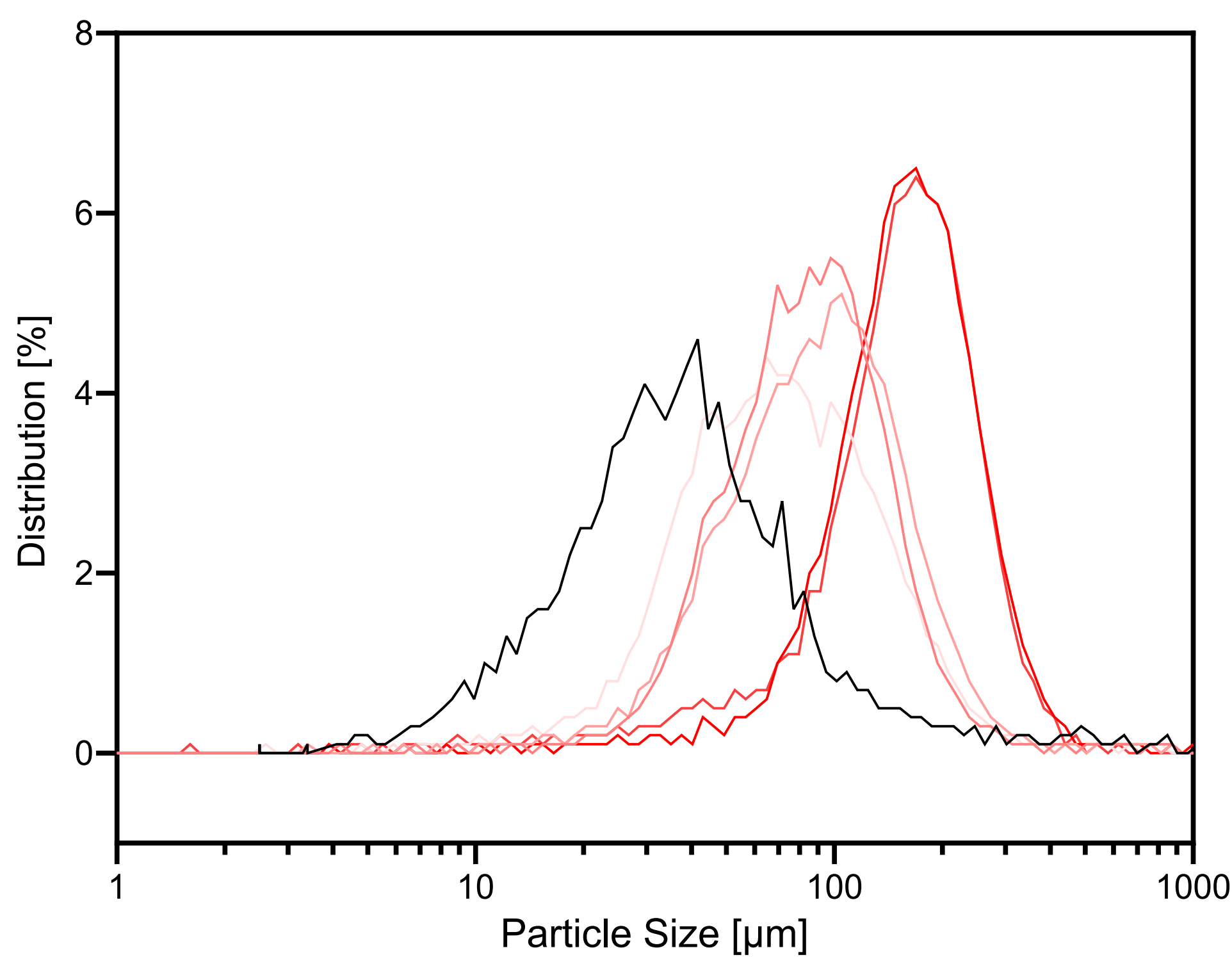


KVA dissolved in water



- Dynamic Image Analysis
- Light Microscopy
- UPLC
- Bulk & Tapped Density
- Angle of Repose
- Loss on Drying
- DSC and TGA

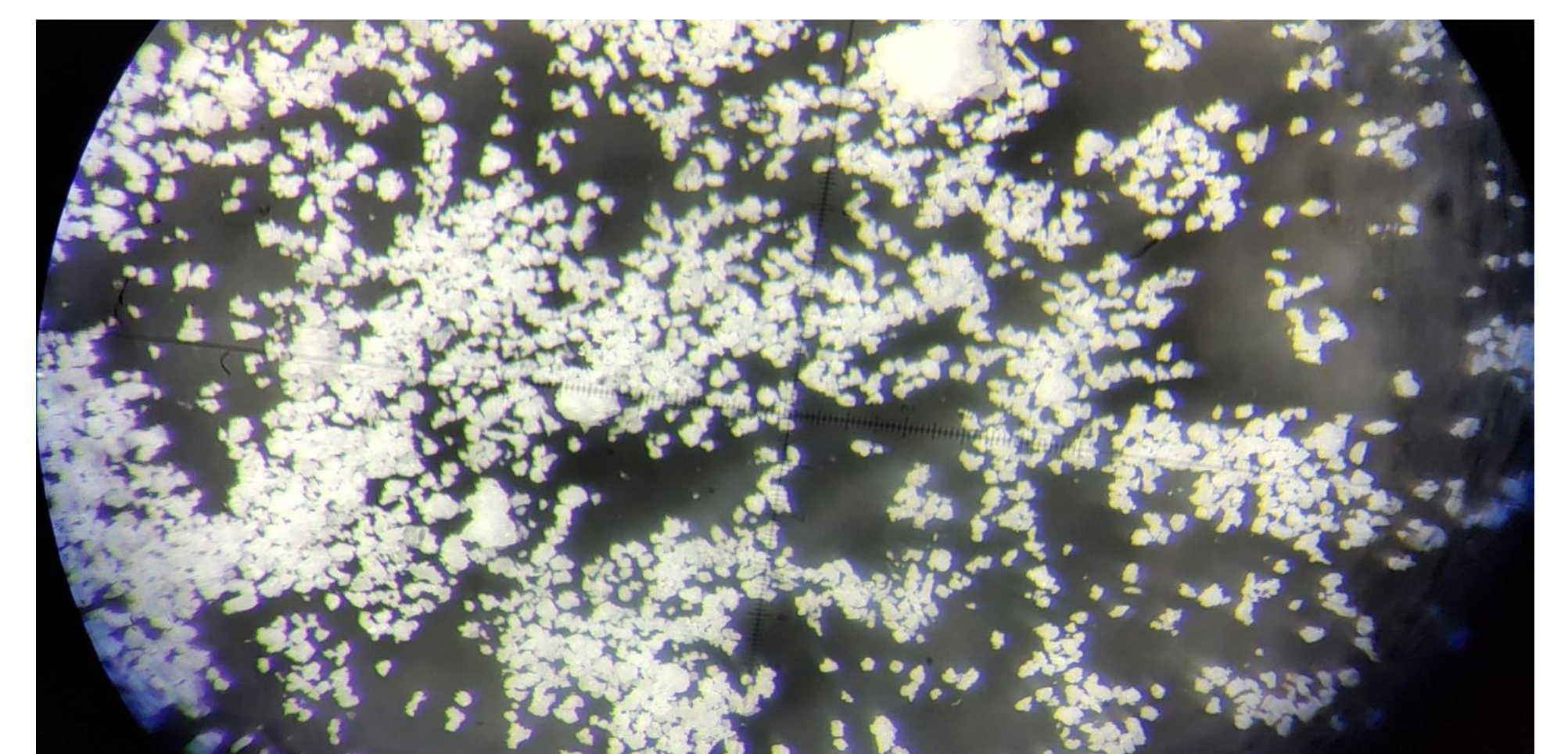
Results



- Monomodal particle size distributions were obtained.
- Particle size increased with increasing KVA load.

• Light microscopic images revealed granular structures of varying sizes. Individual excipient particles can still be clearly distinguished.

- The span was reduced with increasing KVA percentage.
- Index of sphericity increased with increasing KVA load (with a value of 1 representing a perfect sphere).
- Bulk density increased while approaching tapped density.
- Metoprolol flowability was drastically improved, with all granulated batches possessing fair or good flowability.



KVA load	x10 [µm]	x50 [µm]	x90 [µm]	span	Sphericity [0-1]	Bulk density [g/ml]	Tapped density [g/ml]	Angle of repose [°]	Flowability Ph. Eur.
0% (pure MTP)	14	35	84	1.99	0.70	0.31	0.52	54	Poor
10%	33	72	159	1.77	0.77	0.35	0.46	36	Fair
15%	72	94	180	1.48	0.79	0.35	0.42	33	Good
20%	44	88	159	1.32	0.79	0.35	0.44	32	Good
25%	66	164	270	1.25	0.81	0.42	0.49	33	Good
30%	89	167	279	1.14	0.82	0.42	0.50	31	Good

Conclusion

A stable and reproducible tangential spray fluid bed granulation process was developed to produce highly drug-loaded particles. Pure Metoprolol particles were granulated with the KVA to enable further processability for compaction into mini-tablets. The process successfully converted poor-flowing Metoprolol into free-flowing particles, partly due to the increase in particle size. While the x50 values increased from 35 µm of pure MTP to 167 µm to granules containing 30 % binder, the size increase could be limited by the developed process. Additionally, it is hypothesized that spraying KVA under dry process conditions smoothed the surface of uneven particles, thereby reducing interparticulate interactions. This hypothesis is supported by the increased sphericity values. Future investigations will explore the effect of KVA load on printing process during the production of personalized 3D printed tablets.

References:

1. Münch, J.; Kloft, C.; Farhan, M.; et al. Acceptability, swallowability, palatability, and safety of multiple film-coated mini-tablets in children aged ≥2-<7 years: results of an open-label randomised study. *Pharmaceutics*, 15 (2) (2023).
2. Swen, J. J.; van der Wouden, L. E. N.; Manson H.; et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *The Lancet*, 401, 347-356 (2023)

