

Introduction

- Bitter tasting active pharmaceutical ingredients (API) for children require effective taste masking.
- Pellets are ideal dosage forms:
 - A pre-defined dose of API can be applied by layering
 - Small spherical particles, with uniform and smooth surface, and a narrow particle size distribution can be further coated with functional excipients [1] to achieve e.g. taste masking, enteric protection or the controlled release of the API in defined parts of the gastro-intestinal tract.
 - Production of different dosages appropriate for children by adapting the amount of pellets to be filled into capsules or sachets is easily possible.
 - Formulations of small-sized pellets offer a valuable base for increased compliance and improved age-appropriate dosage forms.

Objectives

- Manufacturing processes for pellet layering and coating are often considered as challenging, especially the scale-up from development scale to pilot and production scale [2, 3].
- **In this work, a proven and established scale-up concept for pellet layering and coating applying the Wurster technology is presented.**

Materials

- The poorly soluble API was layered on CELLETS® 350, followed by a seal coat (HPMC) and a taste masking coat (EC / HPMC), using Glatt's Wurster technology.
- The process was developed at the 0.5 - 1 kg scale (GPCG 1 / 2 / 3, 6" or 7" Wurster), scaled-up to the 40 kg pilot scale in **two trials** (GPCG 60, 18" Wurster) and then to the final production scale of 190 kg (GPCG 60, 32" Wurster) in **two trials**.
- Important scale-up parameters are
 - batch size (BS),
 - inlet air volume (IAV),
 - spray rate (SR),
 - temperatures (inlet air (IAT), product (PT), outlet air (OAT)),
 - and atomisation air pressure (AAP) [Figure 1].
- Process parameters for the next process step were determined with a scale-up model equation, maintaining the inlet air velocity and evaporation capacity (product humidity) in the process [Table 1]. The final pellets were characterised for bulk density, residual moisture, yield, assay, [Table 2] dissolution [Figure 3], particle size [Figure 4] and ICH stability.

Scale-up concept - theory

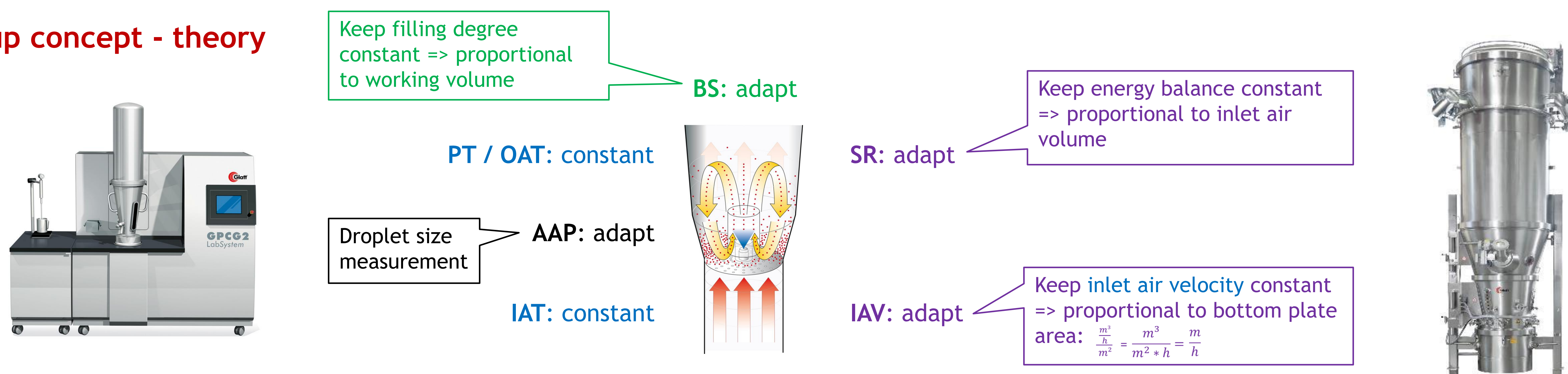


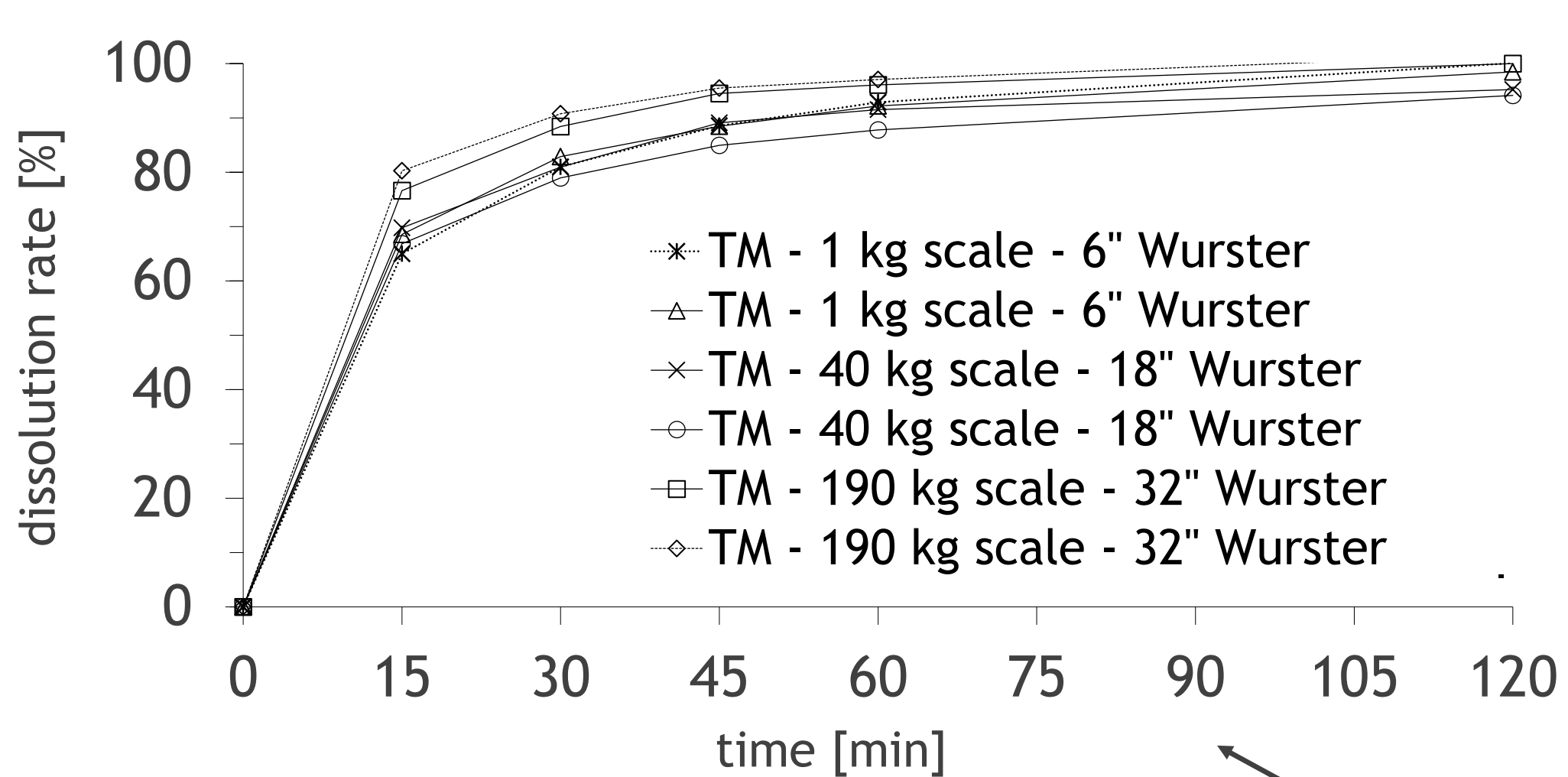
Figure 1: Illustration of relevant process parameters and their scale-up-concept (batch size (BS), inlet air volume (IAV), spray rate (SR), inlet air temperature (IAT), product temperature (PT), outlet air temperature (OAT), and atomisation air pressure (AAP))

Scale-up concept - process parameters

Development batches 6" Wurster	applied values	Batch size	~ Working volume	Inlet air temperature	Product temperature	Inlet air velocity	= const.	Inlet air volume	Spray rate	~ Bottom plate area
		kg		°C	°C	m/s		m³/h	g/min	
		1.1	↓	47 - 48	36 - 37	1.17	↓	80	5.3	↓
Pilot batches 18" Wurster	calculated values	32		47 - 48	36 - 37	1.17		657	36 - 50	
	applied values	39		45 - 48	36 - 38	1.16		650	47 - 54	

Table 1: Applied and calculated process parameters for development, pilot and production scale batches

Results



Development batches	6" Wurster	1st batch	Bulk density	Residual moisture (LOD)	Yield	Assay rel. to theory
			g/mL	%	%	%
Development batches	6" Wurster	1st batch	1.0	1.9	99.3	99.5
		2nd batch	1.0	1.8	99.8	99.7
Pilot batches	18" Wurster	1st batch	0.9	0.7	98.1	99.9
		2nd batch	0.9	1.0	99.6	100.0
Production batches	32" Wurster	1st batch	0.9	1.3	99.4	101.7
		2nd batch	0.9	1.5	99.5	101.6

Table 2: Results for bulk density, residual moisture, yield and assay

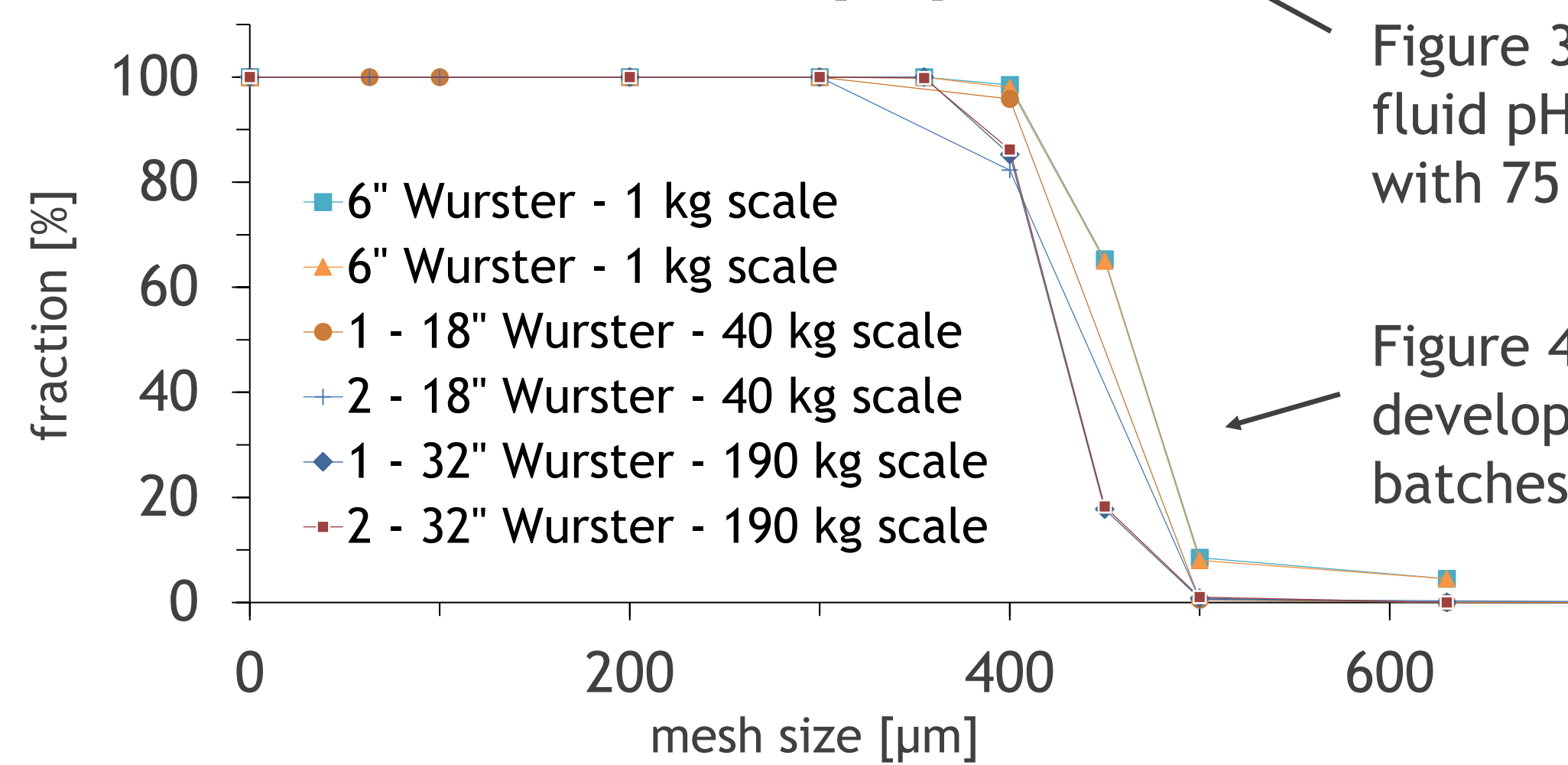


Figure 3: Dissolution in simulated gastric fluid pH 1.2 by using paddle apparatus with 75 rpm (n = 3)

Figure 4: Particle size distribution of development, pilot and production scale batches

- Two scale-up trials were performed in the 40 kg-pilot scale with yields of 98 - 99 %, assay values of 99 - 100 % and reproducible dissolution profiles within the specification.
- The scale-up to the production batch size of 190 kg was performed in two trials with comparable results.
- All batches were within specification; product stability was proven by ICH stability testing (data not shown).
- Taste masking efficiency is demonstrated by dissolution testing in phosphate buffer pH 7,0 for 5 min (data not shown).

Conclusion

- Taste masking of pellets by Wurster technology was successfully scaled-up to the production scale of 190 kg maintaining good yields, assay values and the intended dissolution profile.
- Scale-up parameters for fluid bed processes can be efficiently pre-calculated.
- The basis for scale-up and reliable processes in the production scale is a founded process development and optimisation in the development scale (e. g. 1 - 4 kg).

References

- Palugan, L., Cerea, M.; Zema, L., Gazzaniga, A., Maroni, A. Coated pellets for oral colon delivery, Journal of Drug Delivery Science and Technology 25, (2015) 1-15.
- Gavi, E., Dischinger, A., Scale-up of fluid bed granulation of an active formulation with a scale independent parameter and process model, Poster presentation, 4th European Conference on Pharmaceutics, 20 - 21 March 2023
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