Easy Scale-up of Wurster Processes for Pellet Drug Layering and Taste Masking

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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

Keep filling degree constant => proportional to working volume

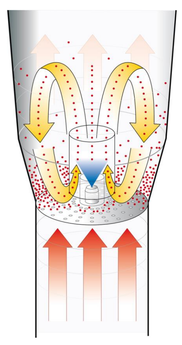
BS: adapt

PT / OAT: constant

Droplet size measurement

AAP: adapt

IAT: constant



SR: adapt

Keep energy balance constant => proportional to inlet air volume

IAV: adapt

Keep inlet air velocity constant => proportional to bottom plate area: $\frac{\frac{m^3}{h}}{m^2} = \frac{m^3}{m^2 * h} = \frac{m}{h}$

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

		Batch size kg	~ Working volume	Inlet air temperature °C	Product temperature °C	Inlet air velocity m/s	= const.	Inlet air volume m³/h	Spray rate g/min	~ Bottom plate area
Development batches 6" Wurster	**applied values**	**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

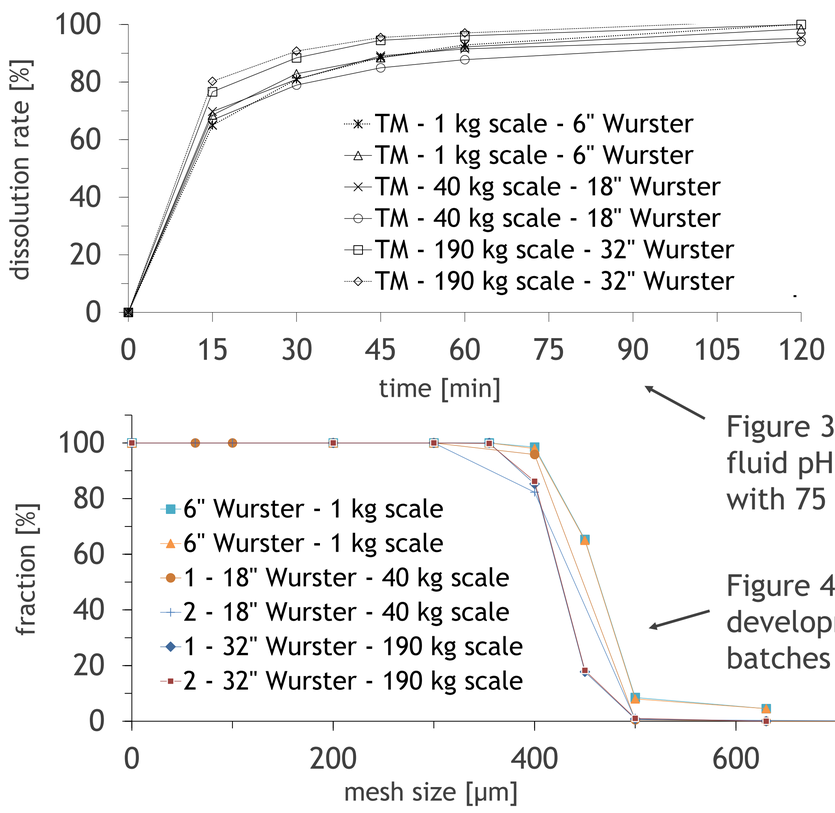


Figure 3: Dissolution in simulated gastric fluid pH 1.2 by using paddle apparatus with 75 rpm (n = 3)

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

			Bulk density g/mL	Residual moisture (LOD) %	Yield %	Assay rel. to theory %
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

- 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

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