The scientific approach of scale-up of a fluid be

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Objectives - Implementation of NIR in a fluid bed granulator

Case study

- The granulation of the API AXY should be transferred to the HDGC 600.
- The compressed tablets resulted in a longer dissolution time compared to the talets which were produced in the FBG.
- Different stabilities with regard to the dissolution of particles produced in the HKC and FBG
- OOS batches also with existing equipment

- A different humidity pattern during the granulation in the HKC and FBG is considered to be the reason for this.
- This leads to a different swelling of the starch which can be the cause of the different dissolutions.

Approach

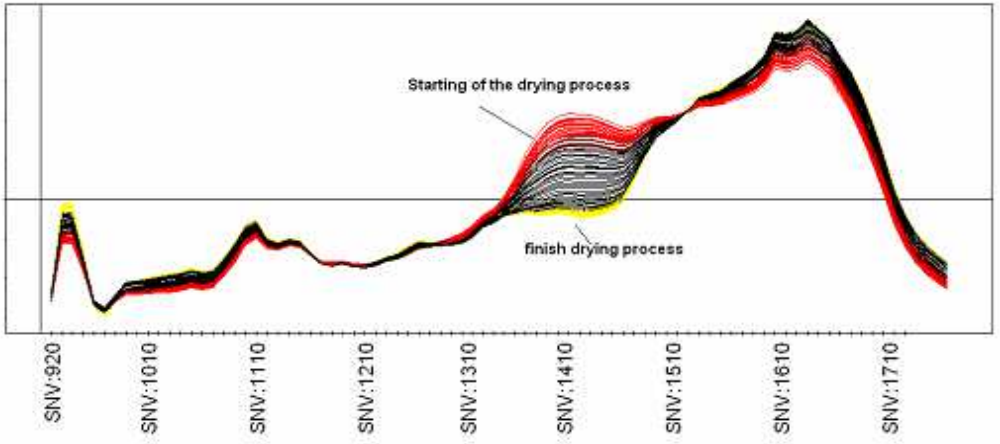
- Humidity pattern was monitored at existing product which was in spec
- The NIR-probe was calibrated during the trials with the Pilotlab (30 kg)
- The humidity pattern during the granulation was monitored by means of the NIR-probe.
- The process parameter were adapted in order to adjust the humidity pattern in the Pilotlab to the FBG
- Surprisingly the storage samples of trial with very dry conditions show no interference of the API release after the storage.

Scale up

- 30 kg (Pilotlab) to 600 kg (HDGC 600)
- Scale up of the granulation process by means of the Hüttlin scale up software to the HDGC 800.
- In-line monitoring of the humidity pattern by means of the NIR-probe.
- Adaption of the process parameters in order to adjust the humidity pattern in the Pilotlab to the HDGC 800.

Water detection during Granulation processes

- Absorbance spectroscopy
- based on the idea that different molecules in the product have frequencies at which they rotate or vibrate
- rotating molecules absorb a certain quanity of the given radiation
- OH- bonds are the specific molecules for water detection
- Typical water peek at 1450 nm



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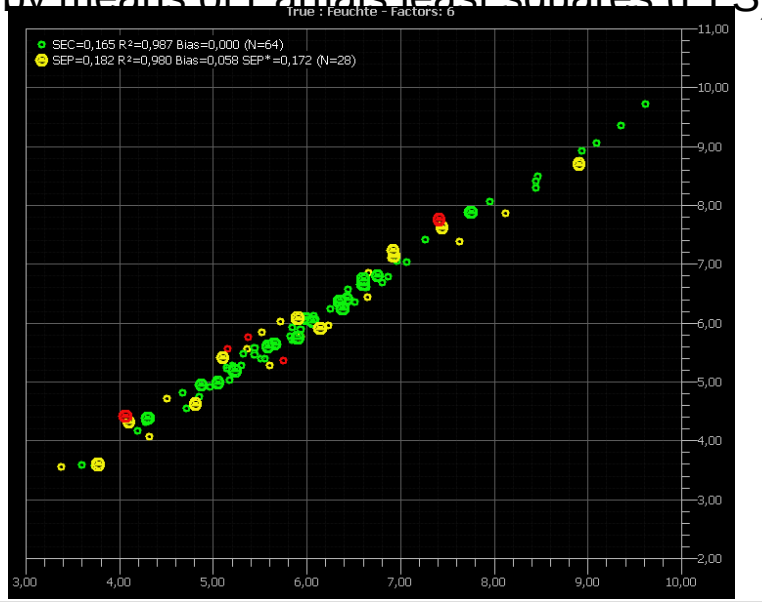
Model Development

- For the model development samples during the process were taken and the LOD was determined by means of a thermodynamic balance.
- Two trials (very dry & very moist conditions) were used as basic data set in order to cover a wide area of the moisture profile.
- Afterwards the determined LOD (%) was correlated with the measured spectra by means of Partials least squares (PLS).



Finished PLS-calibration
SEC= 0.165% (n=64) ; SEP = 0.172% (n=28).

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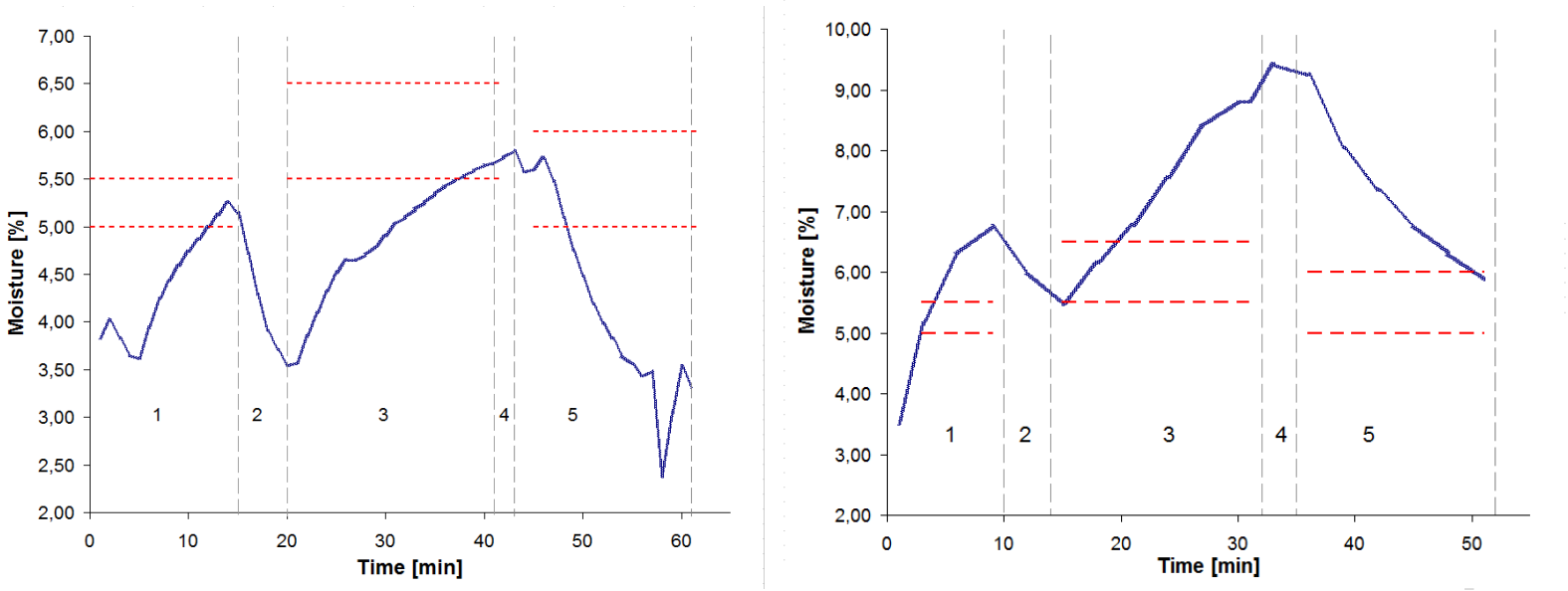
Basic data set –very dry and very moist conditions

- 5 Process steps which required specifized moisture conditions.
- Spraying of the colour (5.0-5.5%), Drying A, Spraying of the binder (5.5 - 6-5%), Water purging and Drying B (5.0+6.0%)



Inline measurements of the 2 batches for the basic data set,
Process steps; 1 Colouring spray, 2 Drying A, 2 Binder spray, 4 Water purging, 5 Drying B

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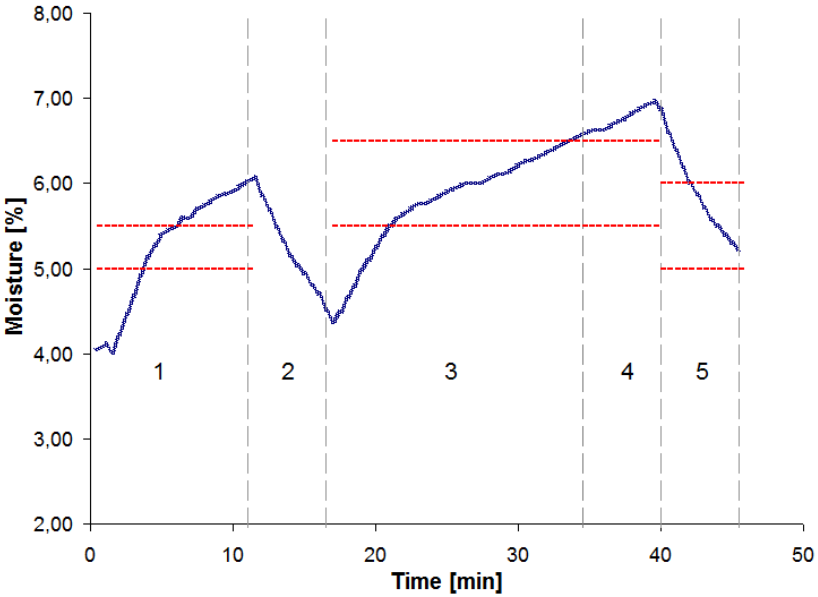
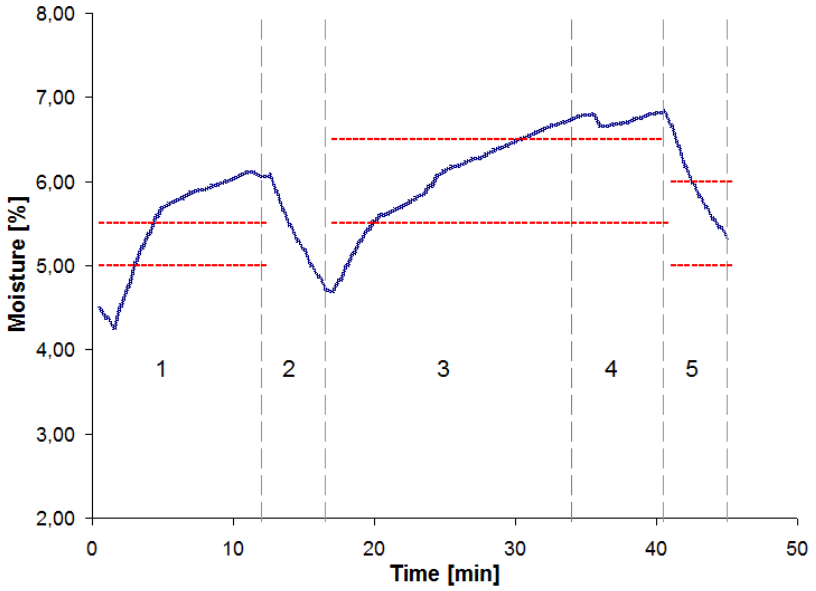
Adjustment of the desired profile





Inline measurements of batch,
Process steps; 1 Colouring spray, 2 Drying A, 2 Binder spray, 4 Water purging, 5 Drying B

NextStep Software

„All Models are wrong – some Models are useful“

Constant

Air velocity

Droplet Size

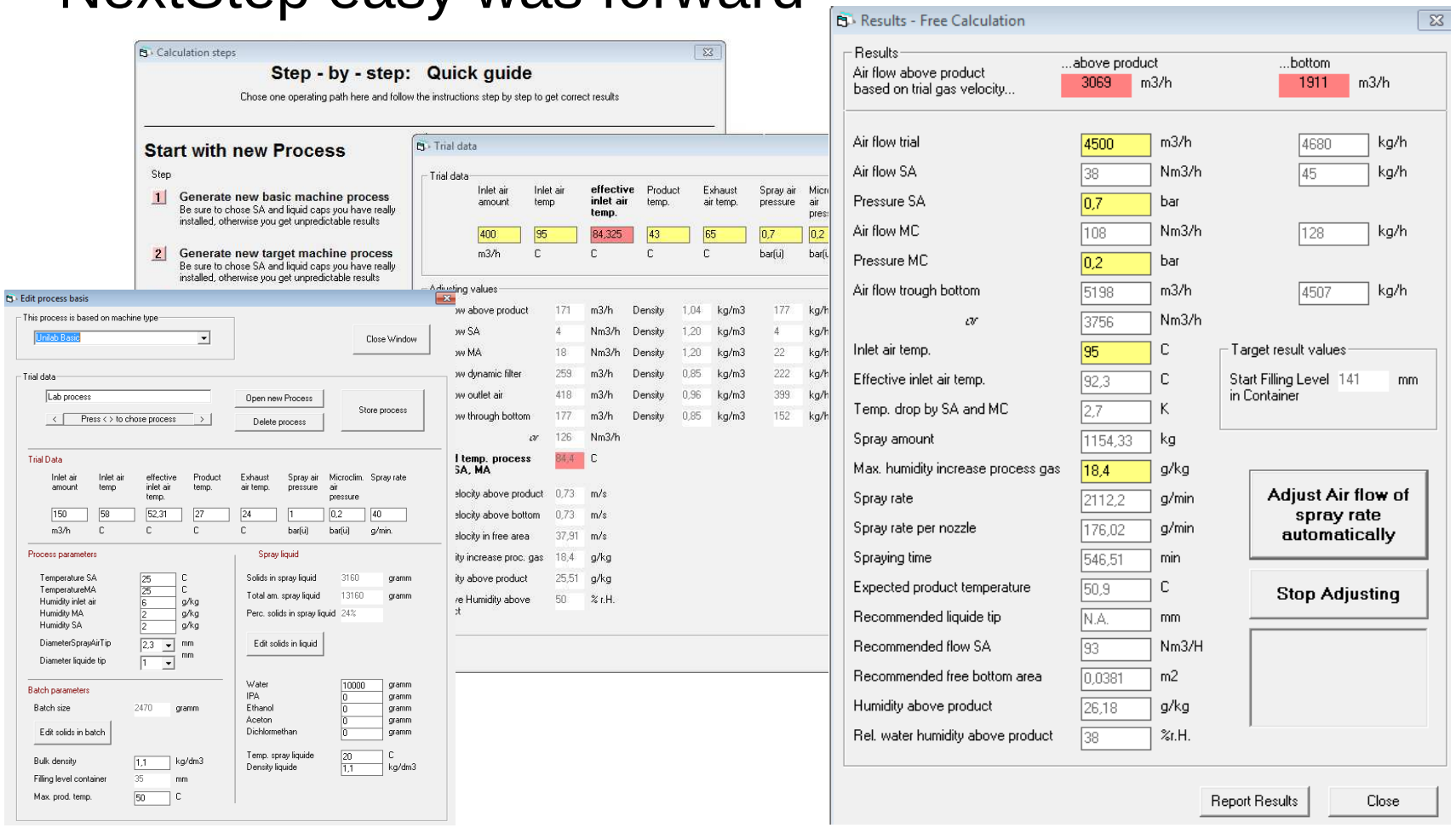
Product temperature

Solvent increase of the air

Constant Product

Box, G. (1979)“ Robustness in the Strategy of Scientific Model Building“, in (eds) Launer,R and Wilkinson, G, *Robustness in Statistics*

NextStep easy was forward



Scale up (Pilotlab to HDGC 800)

Calculated parameters by means of scale up software (Next step)

	Pilotlab	**HDGC 800**	Pilotlab &**HDGC 800**	Pilotlab **&HDGC 800**	Pilotlab	HDGC 800	Pilotlab	HDGC 800
Step type	**Air volume (m3/h)**		**Air Temperature (°C)**	**Microclimate (bar)**	**Spray pressure (bar)**		**Spray rate (g/min)**	
Preheat	530	**6000**	80/**50**	0.20/**0.10**	0.10	0.20	--	--
Charge	500	**5000**	80/**50**	0.20/**0.50**	0.10	1.10	--	--
Colour a	441	**4200**	80	0.20	0.80	2.90	220	2000
Colour b	530	**5300**	80	0.20	0.80	3.10	220	2100
Product dry	530	**6000**	80	0.20/**0.50**	0.10	1.10	--	--
Gel a	530	**4900**	80	0.20	0.80	2.90	220	2000
Gel b	574	**5500**	80	0.20	0.80	3.10	220	2100
Water	530	**5300**	80	0.20	0.80	3.20	180	1700
Dry/Cooling	530	**6000**	20/**50**	0.20/**0.30**	0.20	0.30	--	--
Dry/Cooling	530	**5000**	20/**40**	0.20/**0.30**	0.20	0.30	--	--
Dry/Cooling	530	**5000**	20/**35**	0.20/**0.30**	0.20	0.30	--	--
Discharging	480	**5500**	20	0.20/**0.30**	0.20	0.30	--	--
Discharging	335	**4000**	20	0.20/**0.30**	0.20	0.30	--	--
Discharging	100	1000	20	0.20	0.20	0.30	--	--

Adjustment of the desired profile

- During the process the humidity was monitored by means of the NIR-probe and the developed PLS. In order to match the humidity pattern of trial at the Pilotlab some parameters were changed during the process.

- During the spraying step colour b the inlet air volume was increased from **5300 to 5900m³/h** after a spraying amount of 23 l in order to match the humidity pattern.
- The drying step between the colour & gelatine spraying step was continued until a **moisture of 3.5%** was achieved
- During the spraying step Gel a the spray rate was increased from **2000 g/min to 2200g/min** after a spraying amount of 34.7 l. After 42 l the spray rate was decreased **to 2100g /min** and **to 2000 g/min** after 69 l.
- For the spraying step Gel b a spray rate of **2000g/min** was used. After a spraying amount of 13.5 l the inlet air volume was increased from **5500 to 6000 m3/h.**

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Adjustment of the desired profile

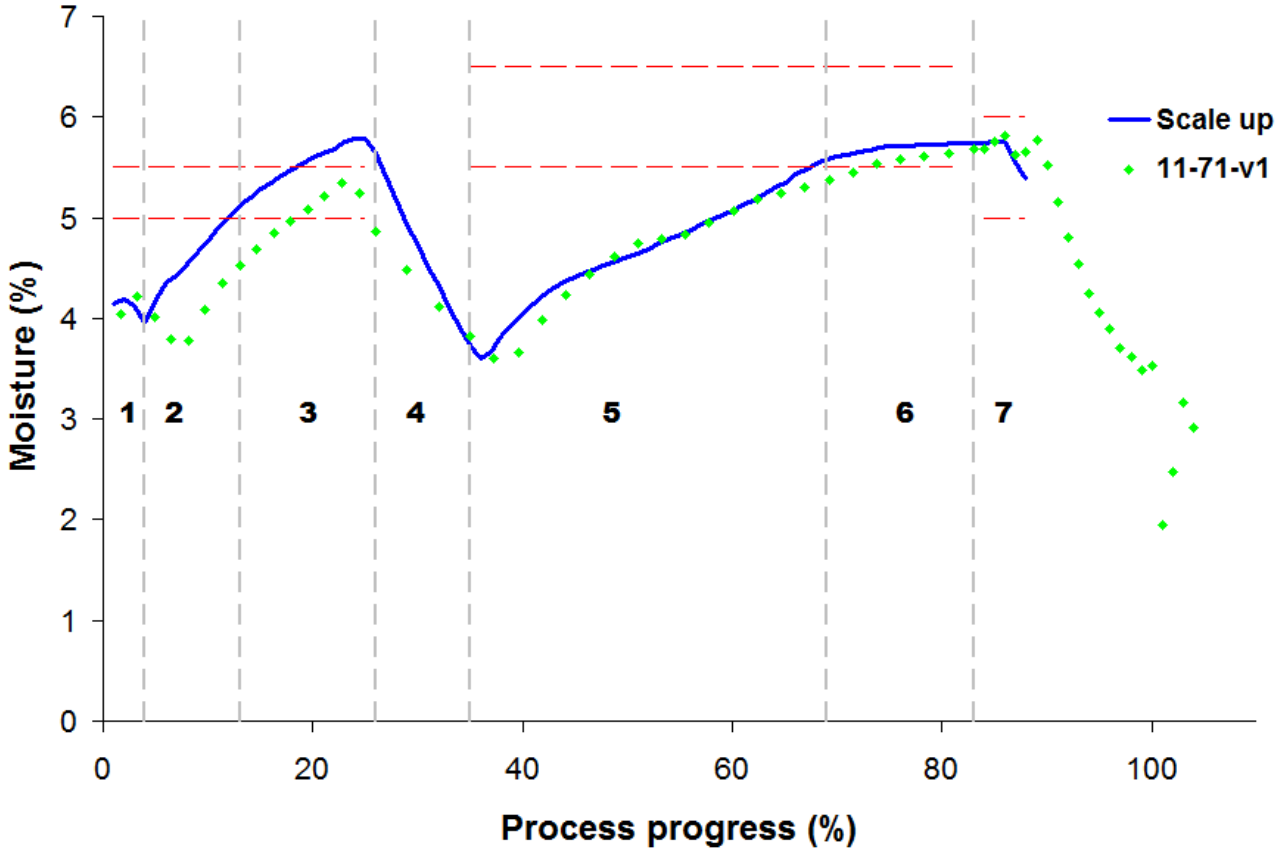

Figure 3: Inline measurements of the scale up process in comparison to 11-71-V1 Process steps; 1Preheat, 2 Colouring spray a, 3 Colouring spray b, 4 Drying A, 5 Gelatine spray a, 6 Gelatine spray b :7 Water purging