

The scientific approach of scale-up of a fluid be

Dr. Marcus Knöll

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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 tablets 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.

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- 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.

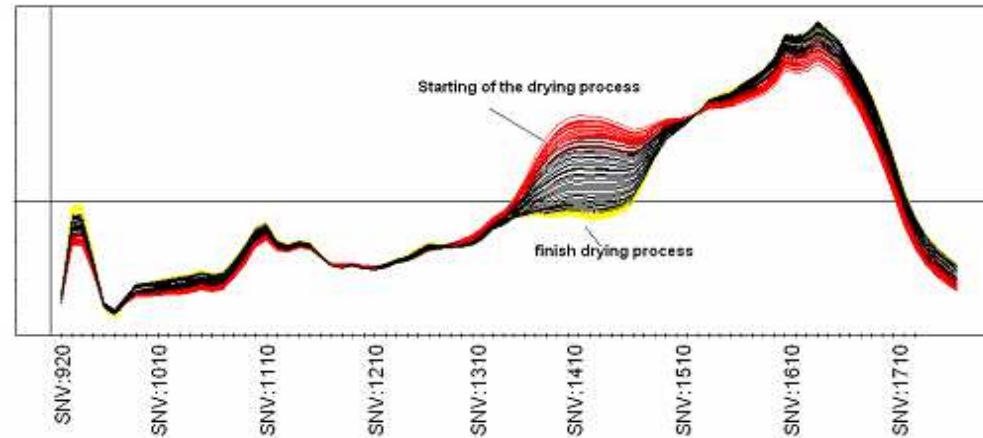
Scale up

- 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.



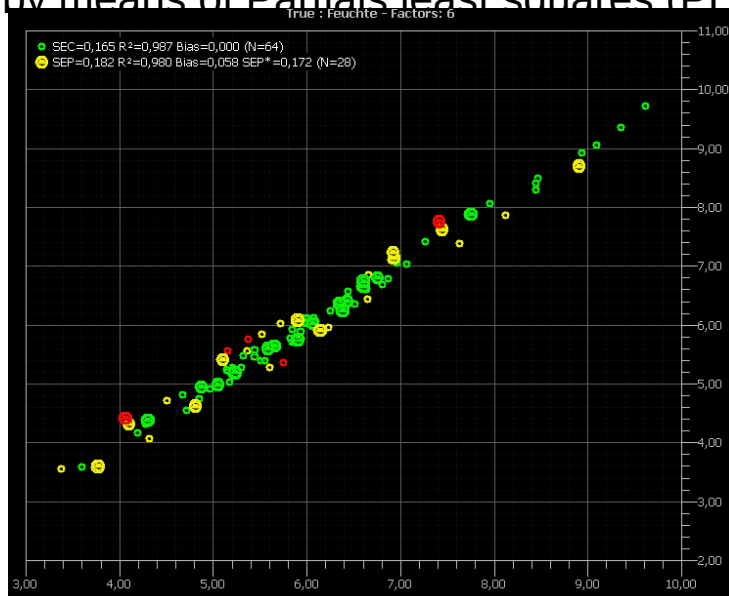
Water detection during Granulation processes

- 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 quantity of the given radiation
- OH- bonds are the specific molecules for water detection
- Typical water peak at 1450 nm



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- 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 Partial Least Squares (PLS).



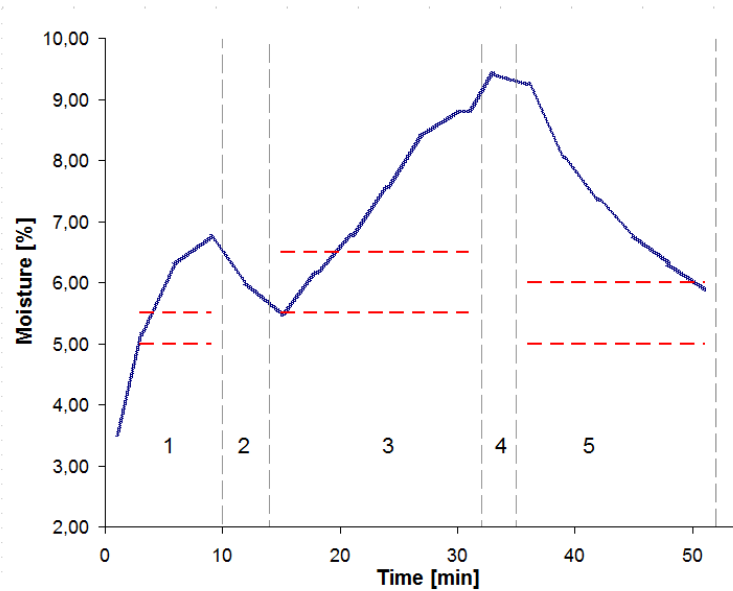
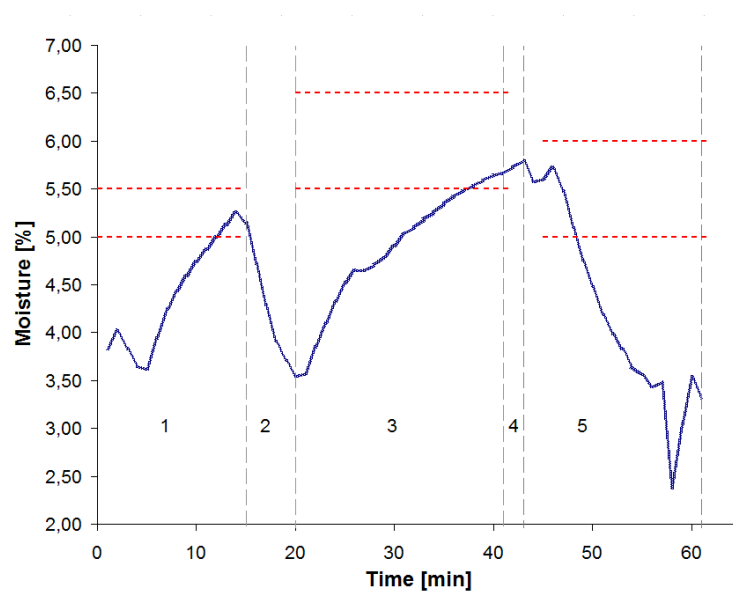
Finished PLS-calibration
SEC= 0.165% (n=64) ; SEP = 0.172% (n=28).



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Basic data set –very dry and very moist conditions

- 5 Process steps which required specified 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%)

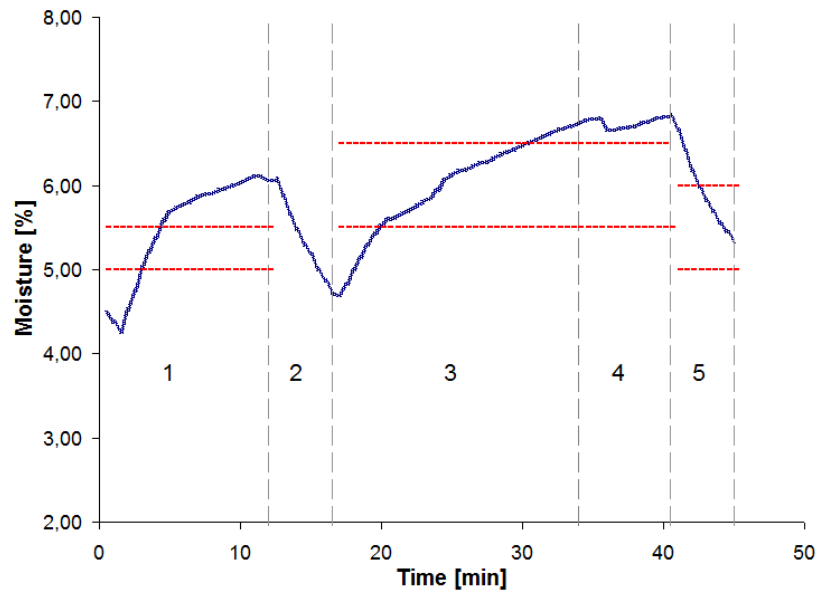
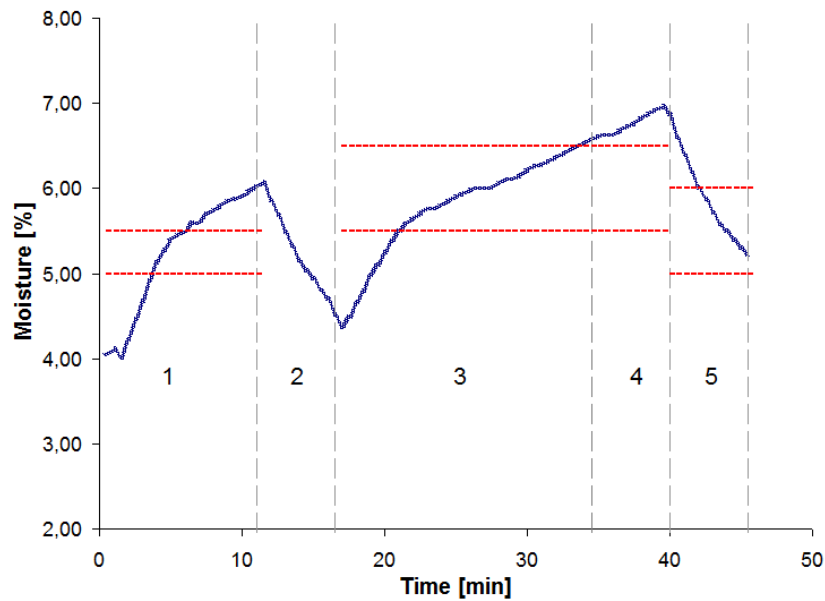


**Inline measurements of the 2 batches for the basic data set,
Process steps; 1 Colouring spray, 2 Drying A, 2 Binder spray, 4 Water purging, 5 Drying B**



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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*

Packaging Technology



NextStep easy was forward

Calculation steps

Step - by - step: Quick guide

Chose one operating path here and follow the instructions step by step to get correct results

Start with new Process

Step

- 1 Generate new basic machine process**
Be sure to chose SA and liquid caps you have really installed, otherwise you get unpredictable results
- 2 Generate new target machine process**
Be sure to chose SA and liquid caps you have really installed, otherwise you get unpredictable results

Edit process basis

This process is based on machine type: **Unilab Basic**

Close Window

Trial data

Trial data	Inlet air amount	Inlet air temp	effective inlet air temp.	Product temp.	Exhaust air temp.	Spray air pressure	Microclim. air pressure
	400 m3/h	95 C	84.325 C	43 C	65 C	0.7 bar(u)	0.2 bar(u)

Calculating values

	xw above product	171 m3/h	Density	1.04 kg/m3	177 kg/h
xw SA	4 Nm3/h	Density	1.20 kg/m3	4 kg/h	
xw MA	18 Nm3/h	Density	1.20 kg/m3	22 kg/h	
xw dynamic filter	259 m3/h	Density	0.85 kg/m3	222 kg/h	
xw outlet air	418 m3/h	Density	0.96 kg/m3	399 kg/h	
xw through bottom	177 m3/h	Density	0.85 kg/m3	152 kg/h	
or	126 Nm3/h				
t temp. process SA, MA	84.4 C				
slcity above product	0.73 m/s				
slcity above bottom	0.73 m/s				
slcity in free area	37.91 m/s				
ity increase proc. gas	18.4 g/kg				
ity above product	25.51 g/kg				
re Humidity above	50 % r.H.				

Process parameters

Process parameters	Spray liquid
Temperature SA	25 C
Temperature MA	25 C
Humidity inlet air	6 g/kg
Humidity MA	2 g/kg
Humidity SA	2 g/kg
Diameter SprayAirTip	2.3 mm
Diameter liquide tip	1 mm
Batch size	2470 gramm
Bulk density	1.1 kg/dm3
Filling level container	35 mm
Max. prod. temp.	50 C
Water	10000 gramm
IPA	0 gramm
Ethanol	0 gramm
Aceton	0 gramm
Dichlormethan	0 gramm
Temp. spray liquide	20 C
Density liquide	1.1 kg/dm3

Results - Free Calculation

Results

	...above product	...bottom
Air flow above product based on trial gas velocity...	3069 m3/h	1911 m3/h

Air flow trial

Air flow trial	4500 m3/h	4680 kg/h
Air flow SA	38 Nm3/h	45 kg/h
Pressure SA	0.7 bar	
Air flow MC	108 Nm3/h	128 kg/h
Pressure MC	0.2 bar	
Air flow trough bottom	5198 m3/h	4507 kg/h
or	3756 Nm3/h	

Inlet air temp.

Inlet air temp.	95 C
Effective inlet air temp.	92.3 C
Temp. drop by SA and MC	2.7 K

Spray amount

Spray amount	1154.33 kg
Max. humidity increase process gas	18.4 g/kg
Spray rate	2112.2 g/min
Spray rate per nozzle	176.02 g/min
Spraying time	546.51 min
Expected product temperature	50.9 C
Recommended liquide tip	N.A. mm
Recommended flow SA	93 Nm3/h
Recommended free bottom area	0.0381 m2
Humidity above product	26.18 g/kg
Rel. water humidity above product	38 % r.H.

Target result values

Start Filling Level in Container	141 mm
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Adjust Air flow of spray rate automatically

Stop Adjusting

Report Results Close



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	--	--

- 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**.



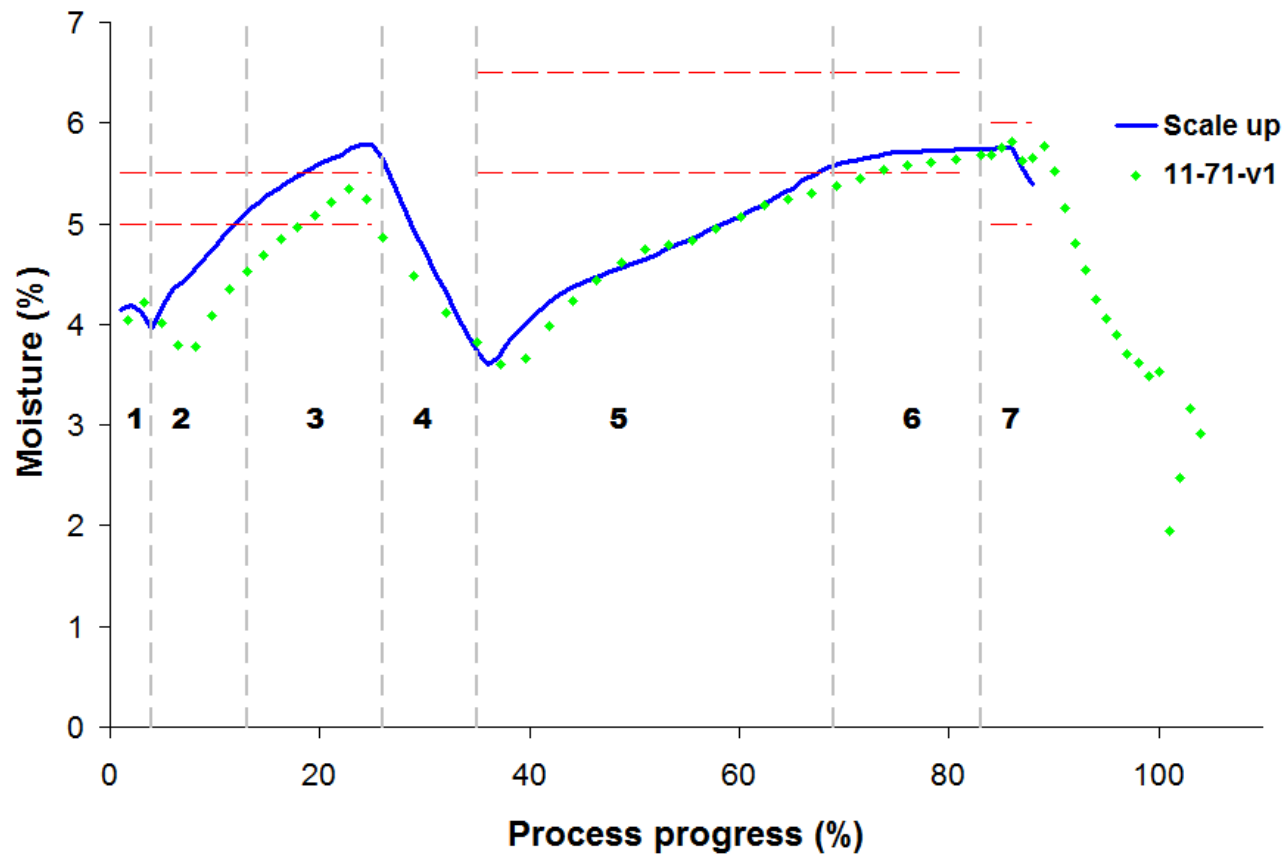


Figure 3: Inline measurements of the scale up process in comparison to 11-71-V1
Process steps; 1Preheat, 2 Colouring spray a, 3 Colouring spray b, 4 Drying A,
5 Gelatine spray a, 6 Gelatine spray b :7 Water purging