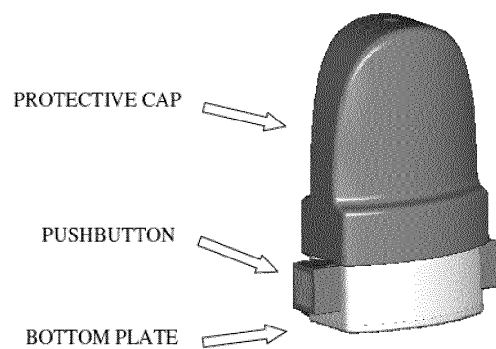
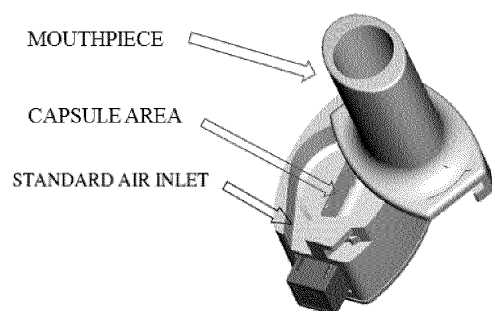


FIGURES**Fig. 1a:** capsule based single-unit dose inhaler**Fig. 1b:** capsule based single-unit dose inhaler

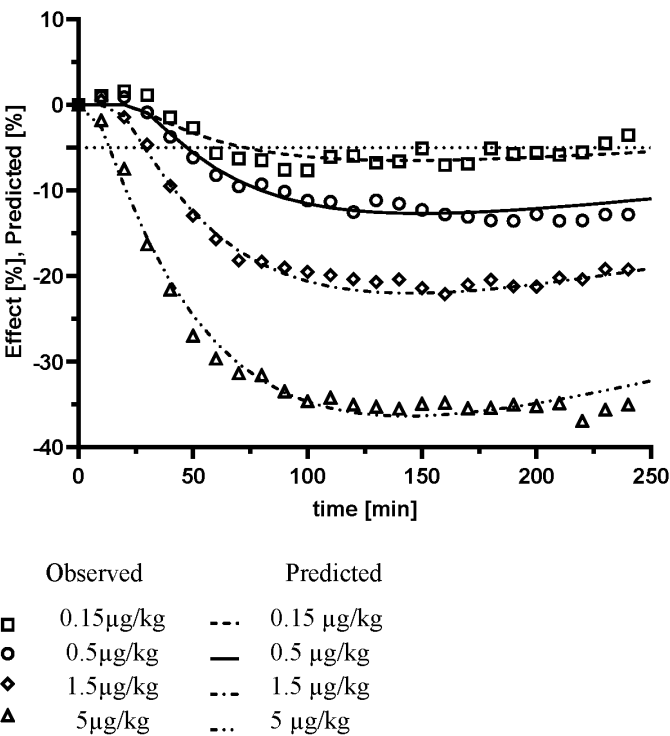


Fig. 2: Observed (symbols) and fitted (solid lines) PAP es after administration of 0.15, 0.5, 1.5 and 5 µg/kg Example 1 (doses expressed as lung deposited doses) to minipigs (7 min inhalation as liquid aerosol). Relevant PAP reduction of 5% indicated as dotted line

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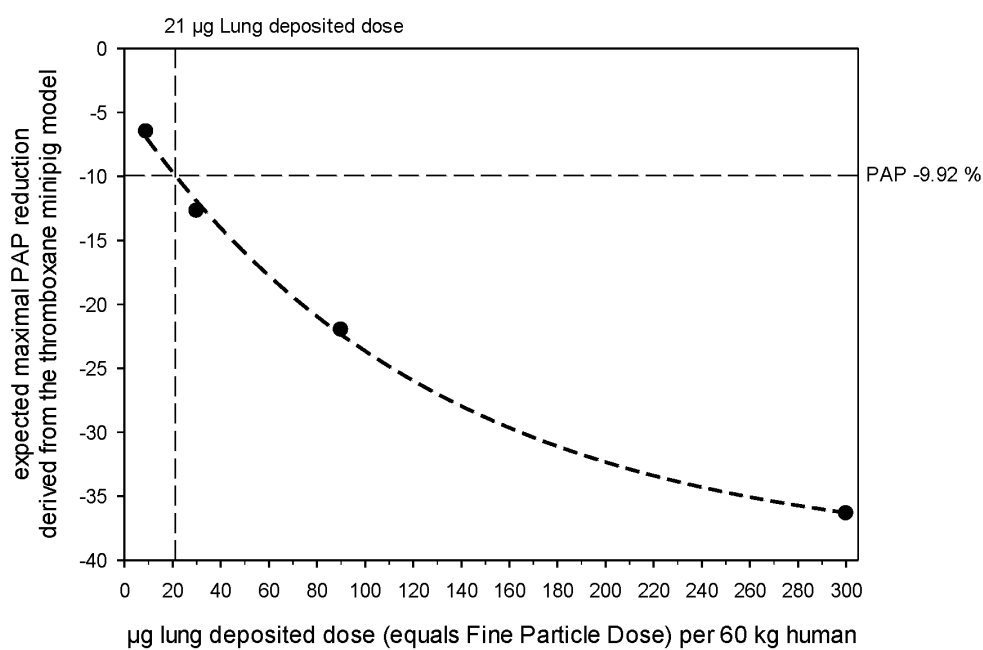


Fig. 3: Maximal expected PAP reduction for a 60 kg human at the corresponding lung deposited doses (FPD) based on the results of the anaesthetized thromboxane minipig model without considering interspecies differences in protein binding.

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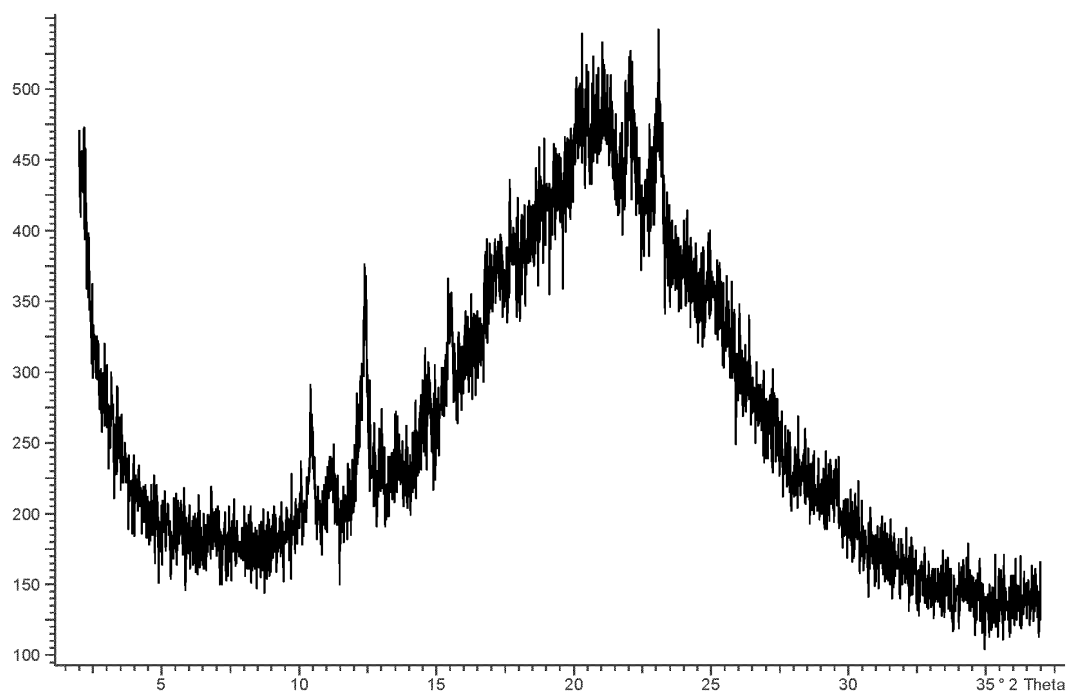


Fig. 4: X-Ray powder diffractogram of the amorphous residue build on salt screening experiments with L-arginine

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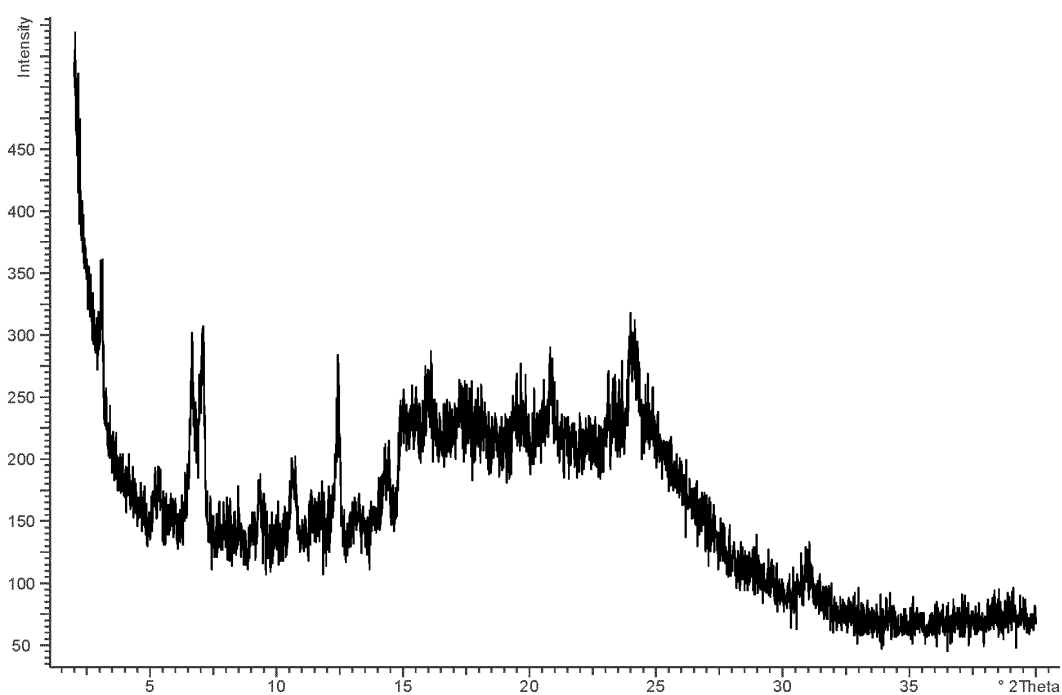


Fig. 5: X-Ray powder diffractogram of the Semihydrate, example 6a

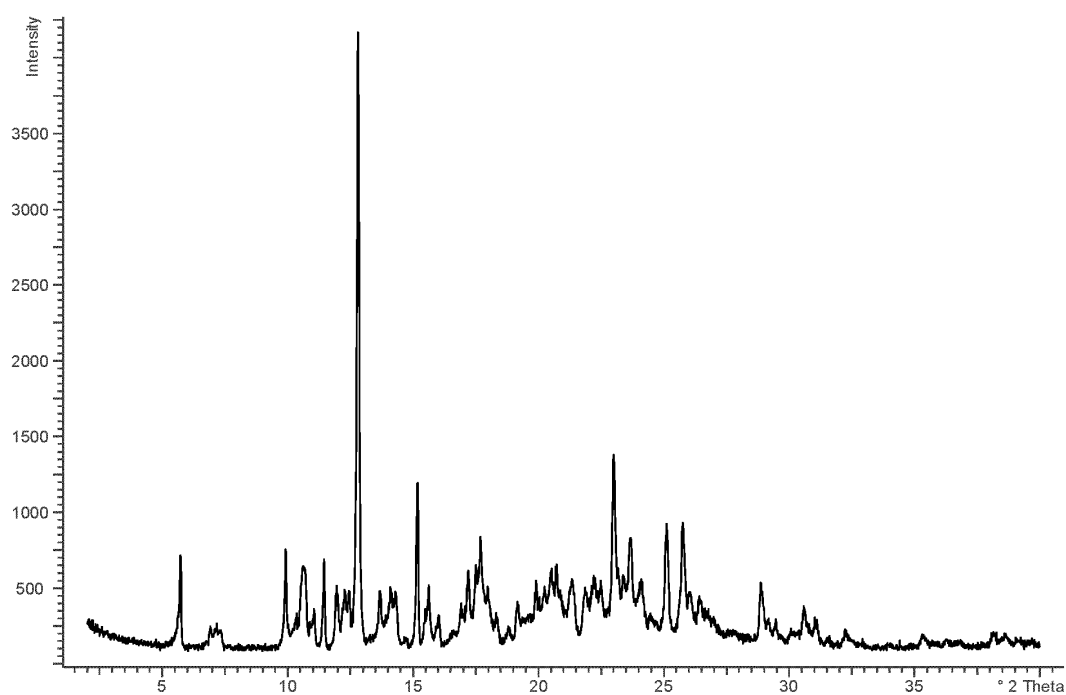


Fig. 6: X-Ray powder diffractogram of the Monohydrate I, example 6b

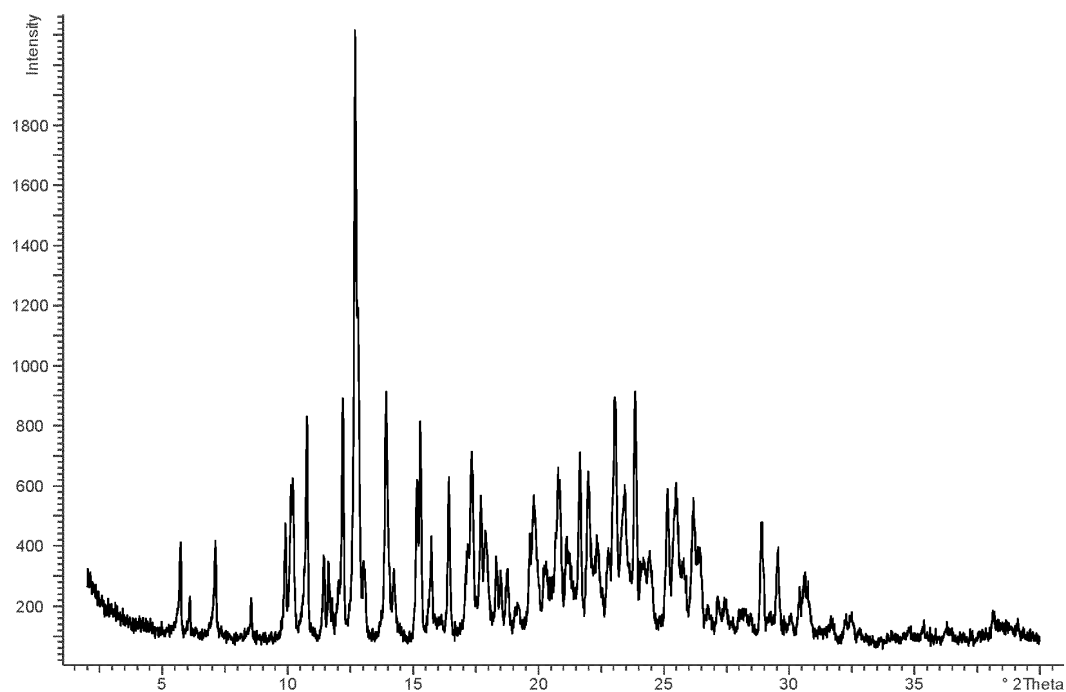


Fig. 7: X-Ray powder diffractogram of the Monohydrate II, example 6c

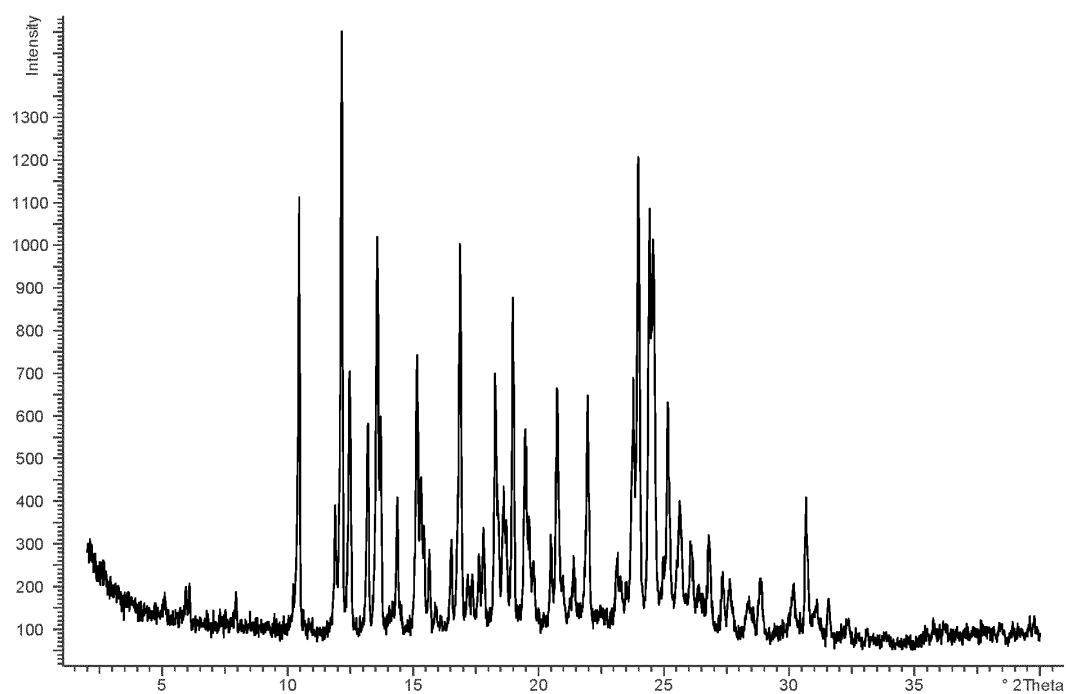


Fig. 8: X-Ray powder diffractogram of the 1,25-Hydrate, example 6d

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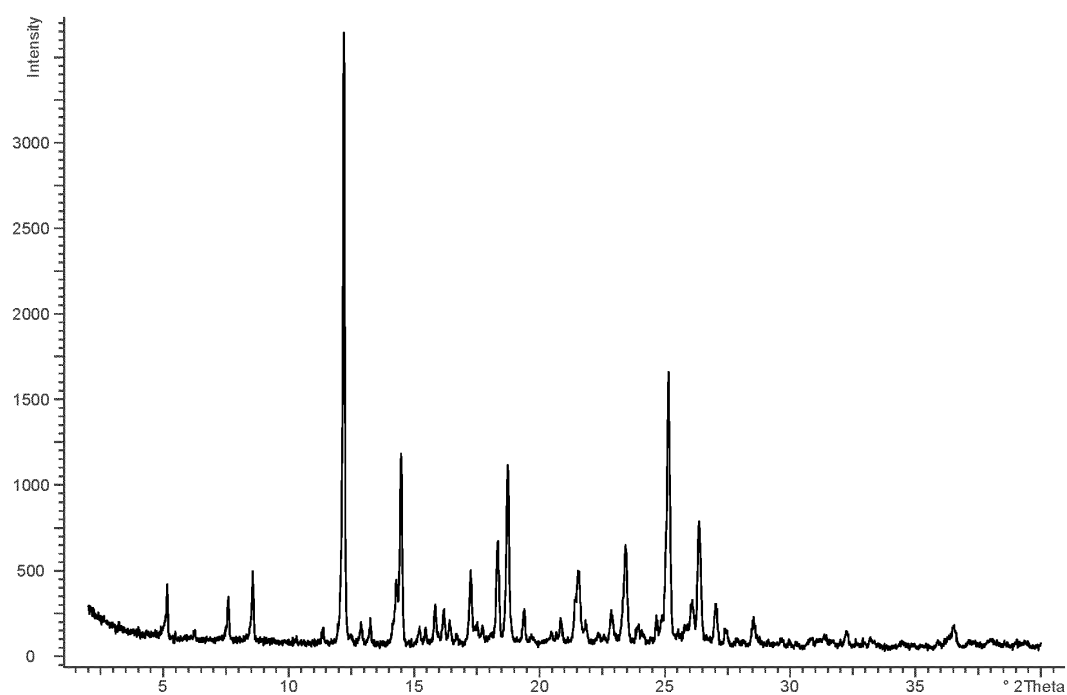


Fig. 9: X-Ray powder diffractogram of the Sesquihydrate, example 6e

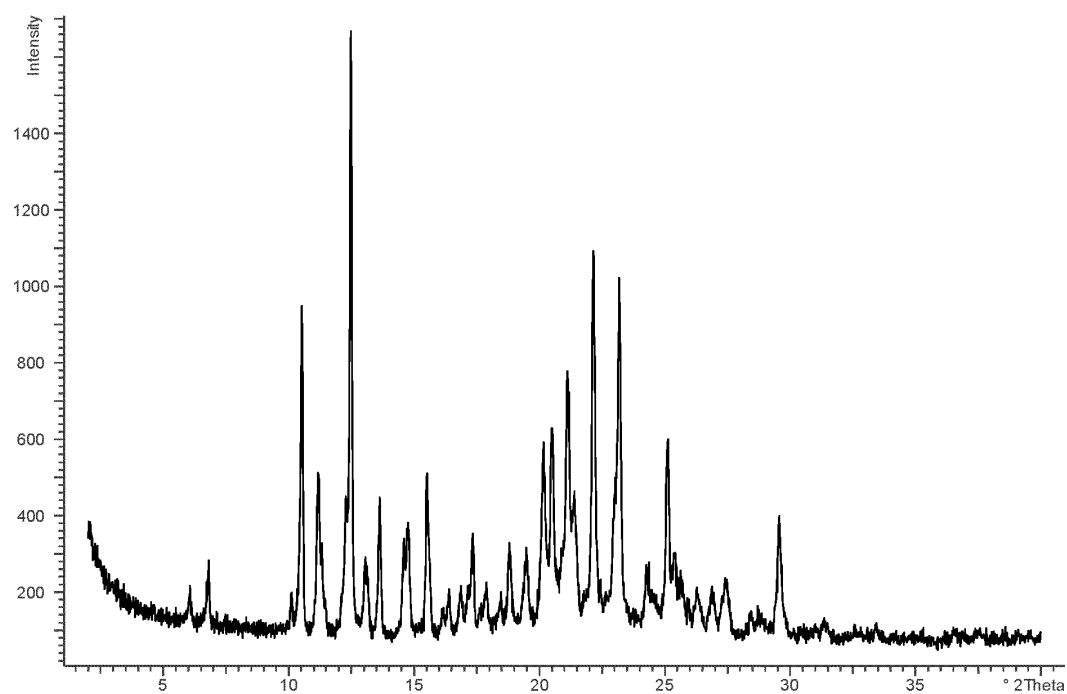
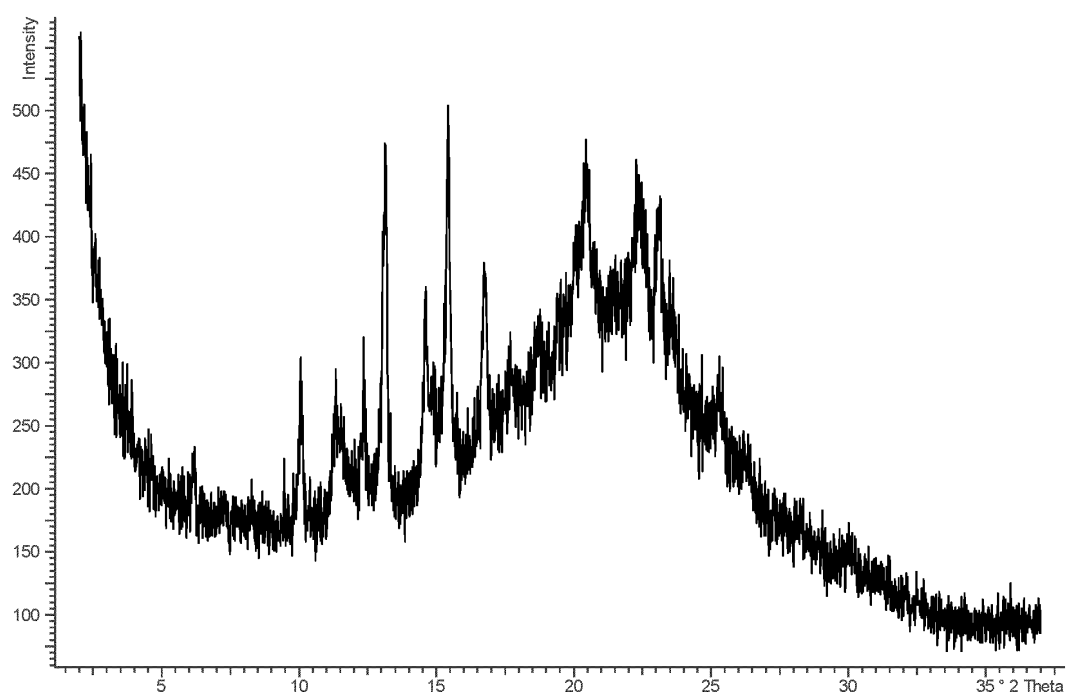
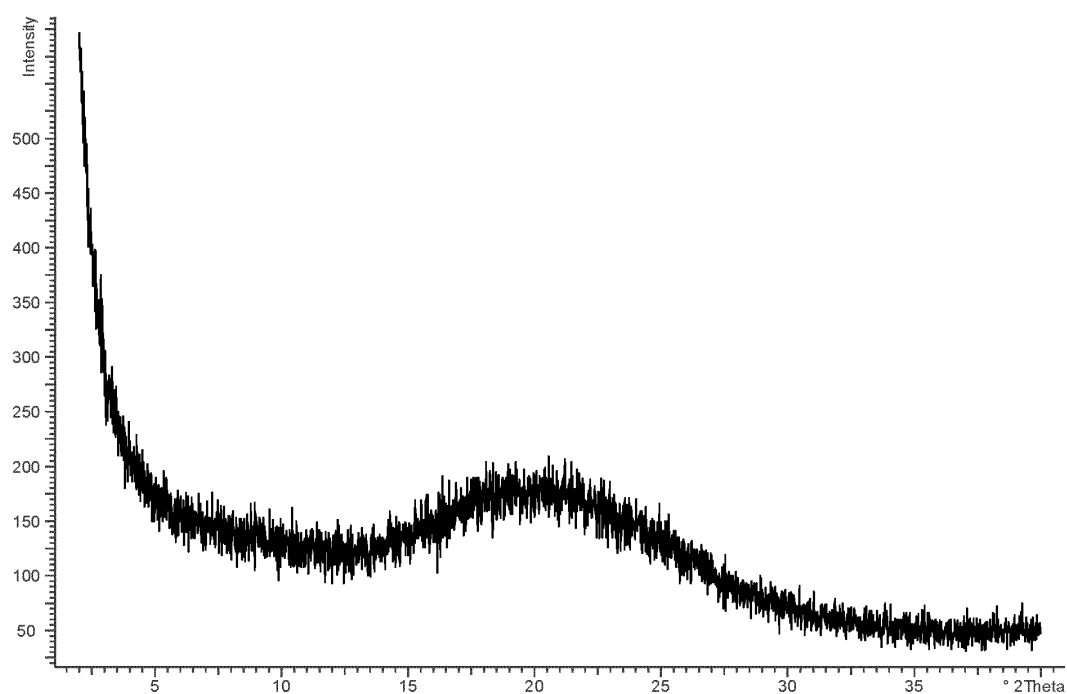


Fig. 10: X-Ray powder diffractogram of the Dihydrate, example 6f

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**Fig. 10a:** X-ray powder diffractogram of example 6f after drying**Fig. 11:** X-Ray powder diffractogram of the amorphous form, example 6g

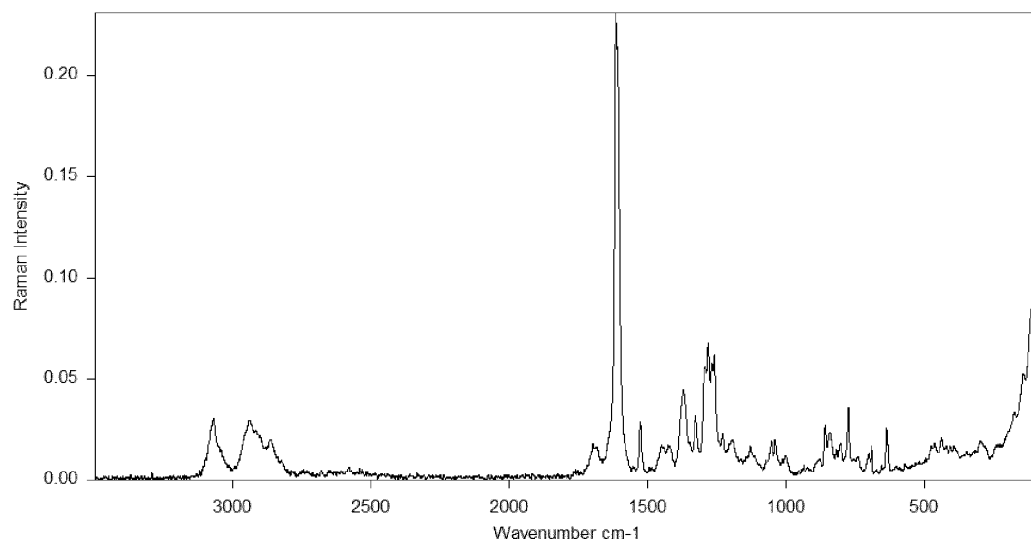


Fig. 12: Raman spectrum of the Semihydrate, example 6a

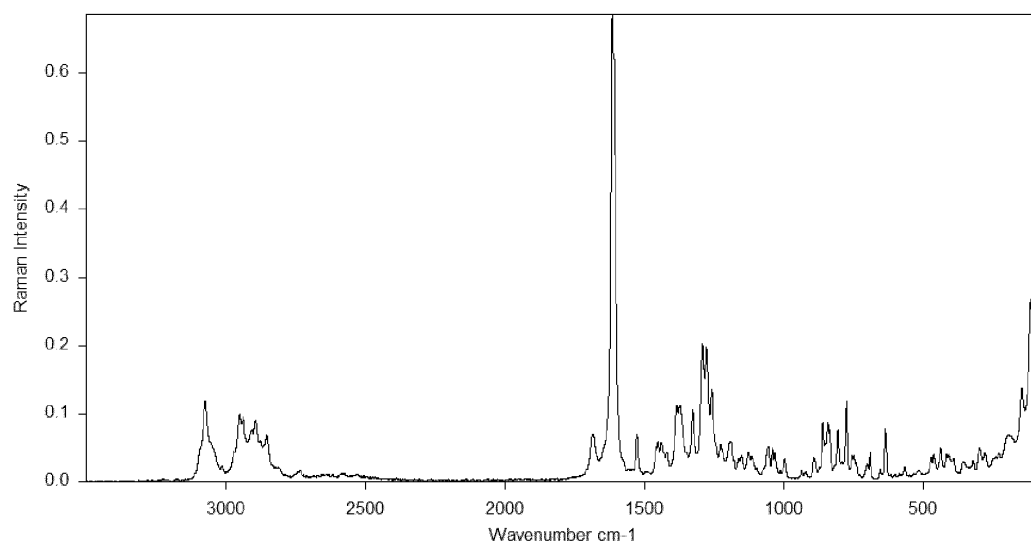
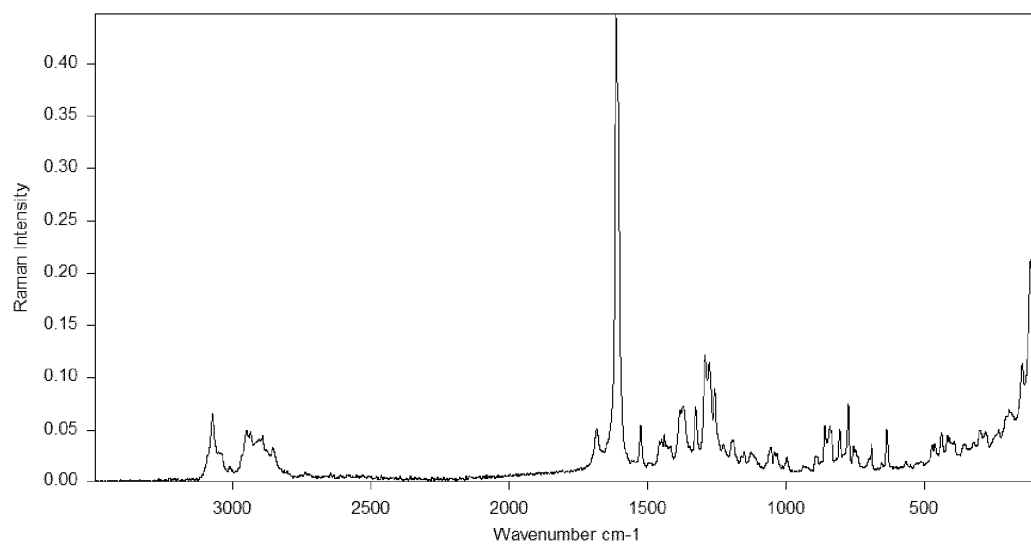
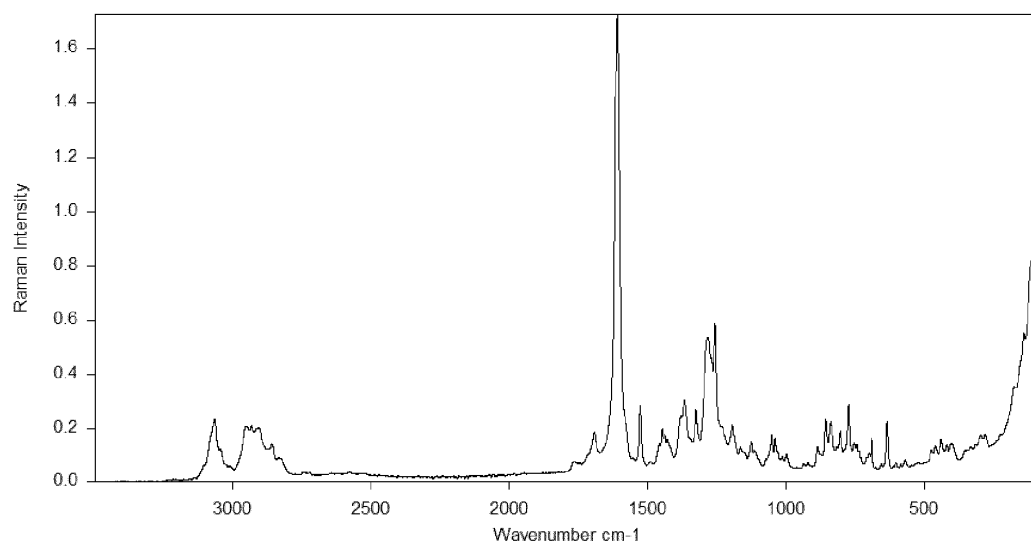
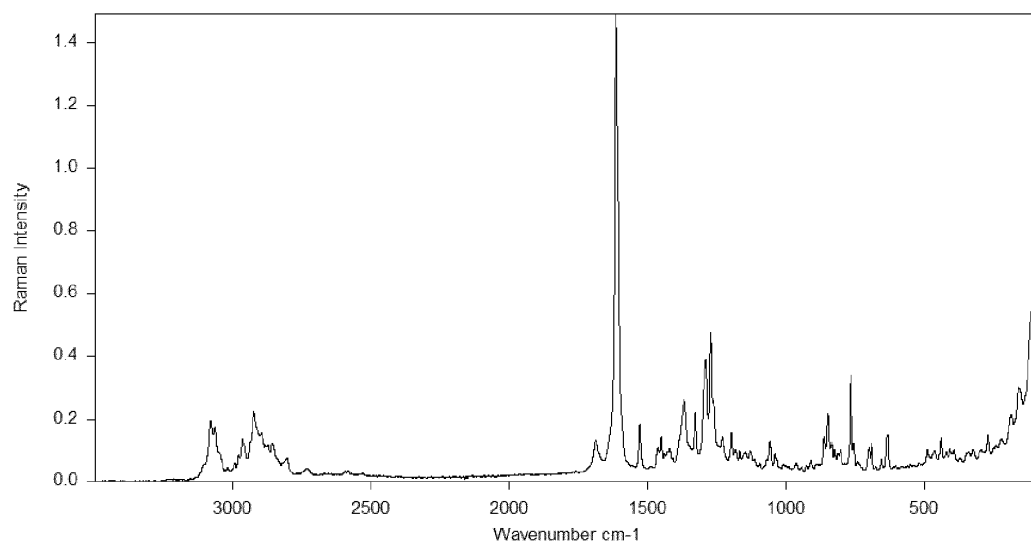
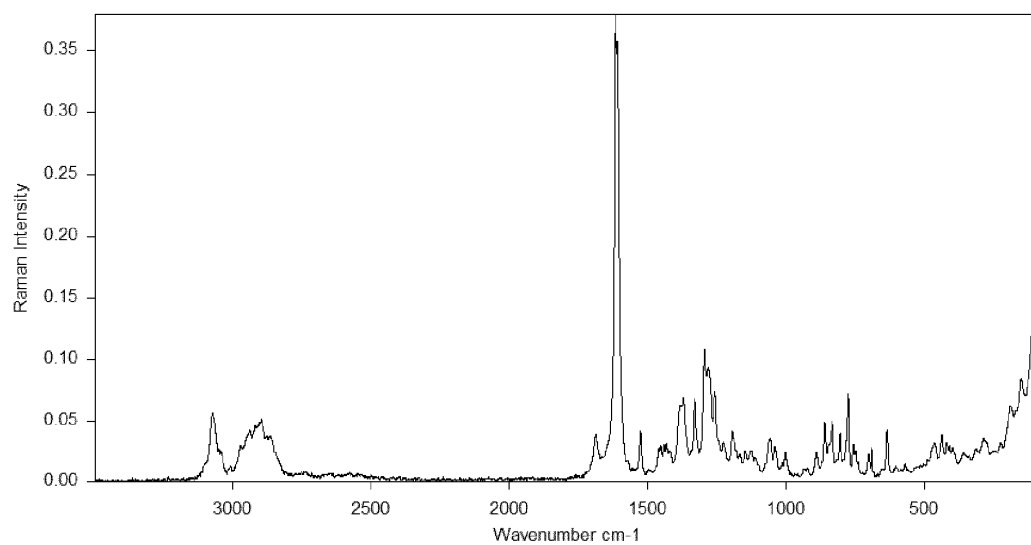


Fig. 13: Raman spectrum of the Monohydrate I, example 6b

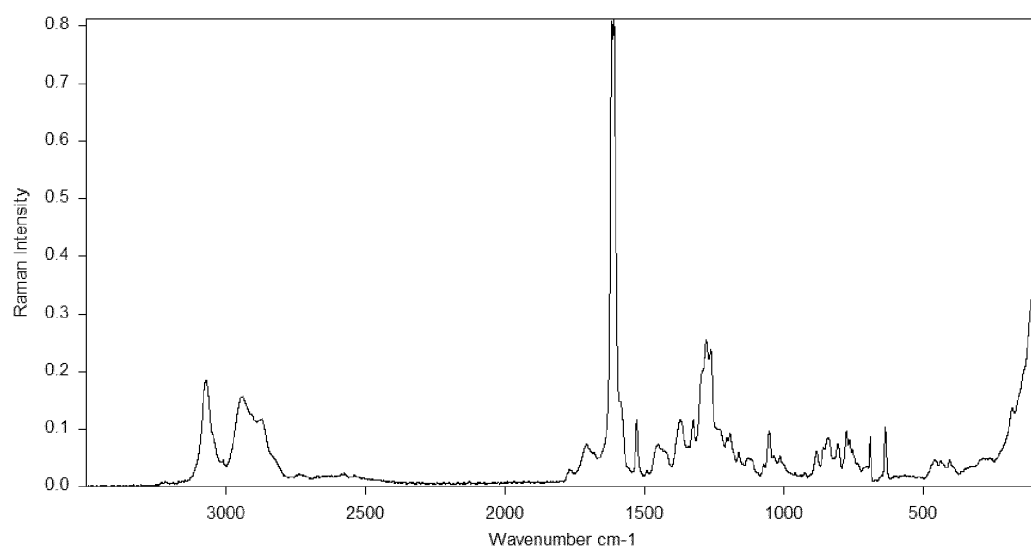
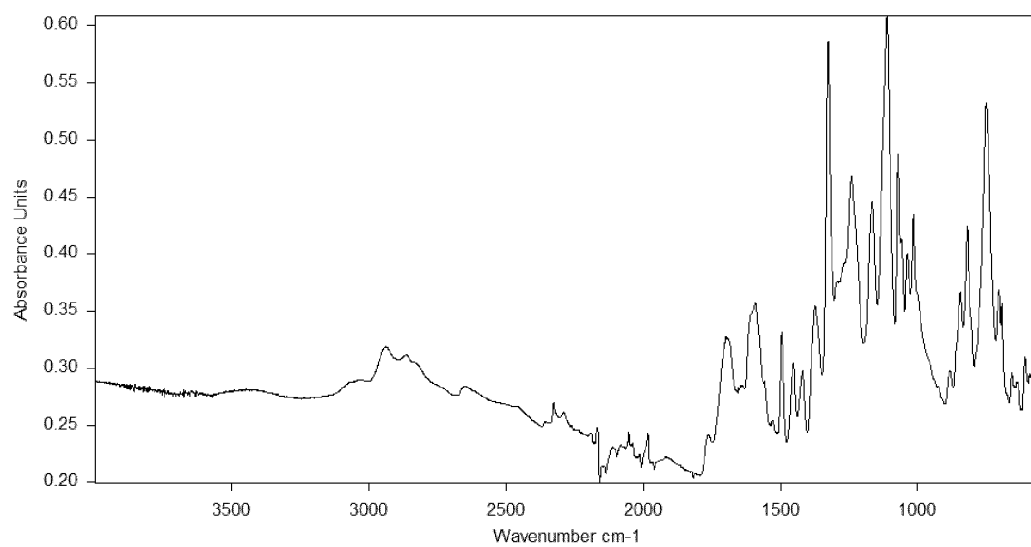
- 10/44 -

**Fig. 14:** Raman spectrum of the Monohydrate II, example 6c**Fig. 15:** Raman spectrum of the 1,25-Hydrate, example 6d

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**Fig. 16:** Raman spectrum of the Sesquihydrate, example 6e**Fig. 17:** Raman spectrum of the Dihydrate, example 6f

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**Fig. 18:** Raman spectrum of the amorphous form, example 6g**Fig. 19:** IR spectrum of the Semihydrate, example 6a

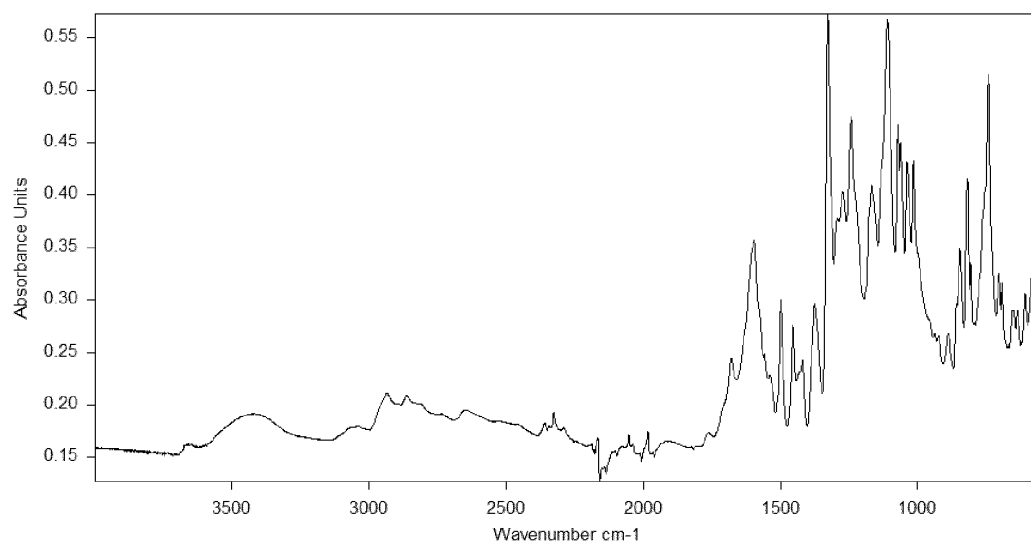


Fig. 20: IR spectrum of the Monohydrate I, example 6b

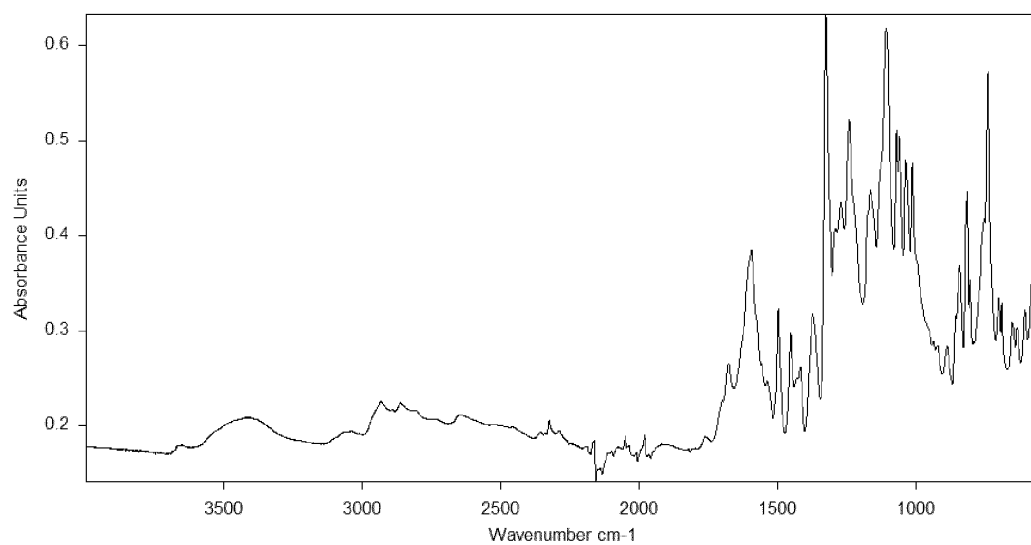


Fig. 21: IR spectrum of the Monohydrate II, example 6c

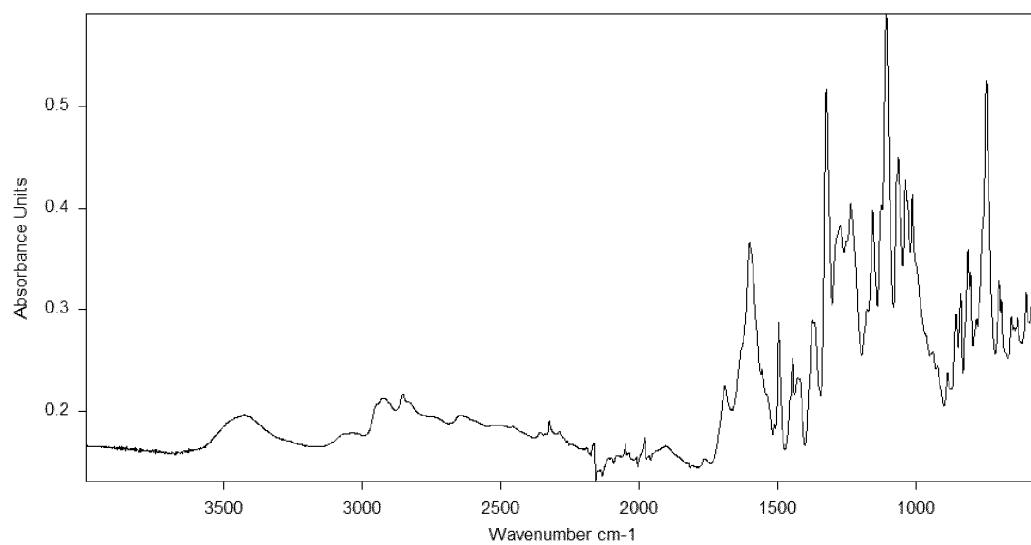


Fig. 22: IR spectrum of the 1,25-Hydrate, example 6d

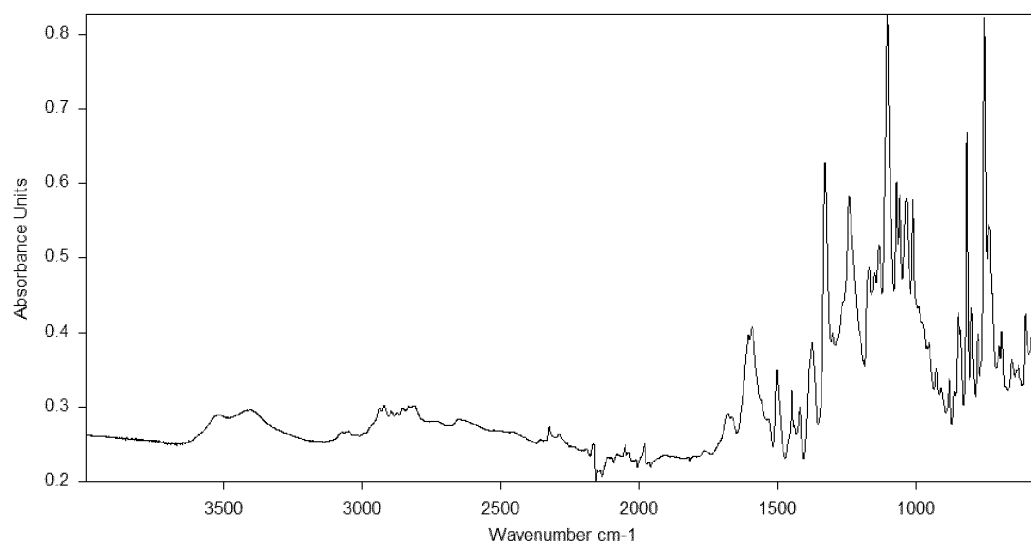
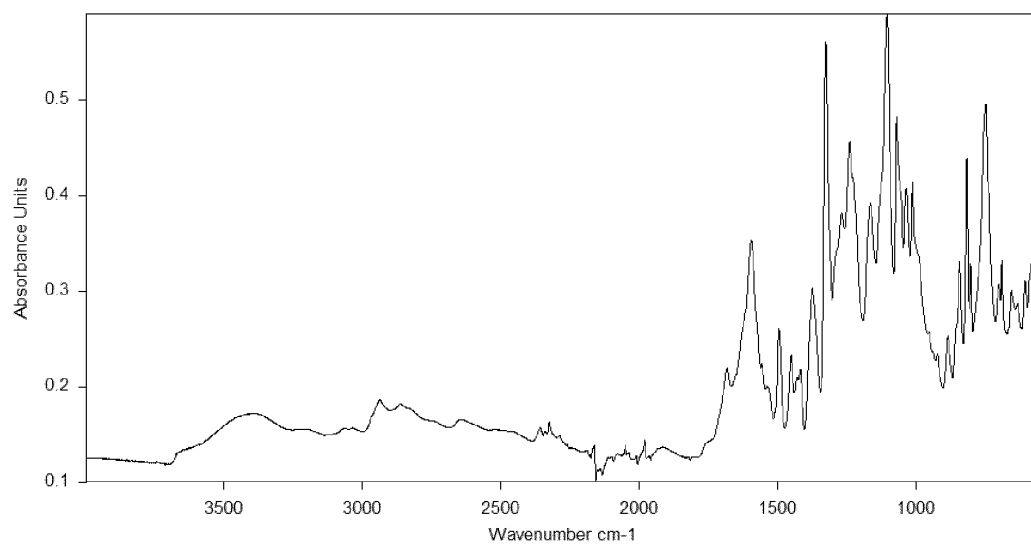
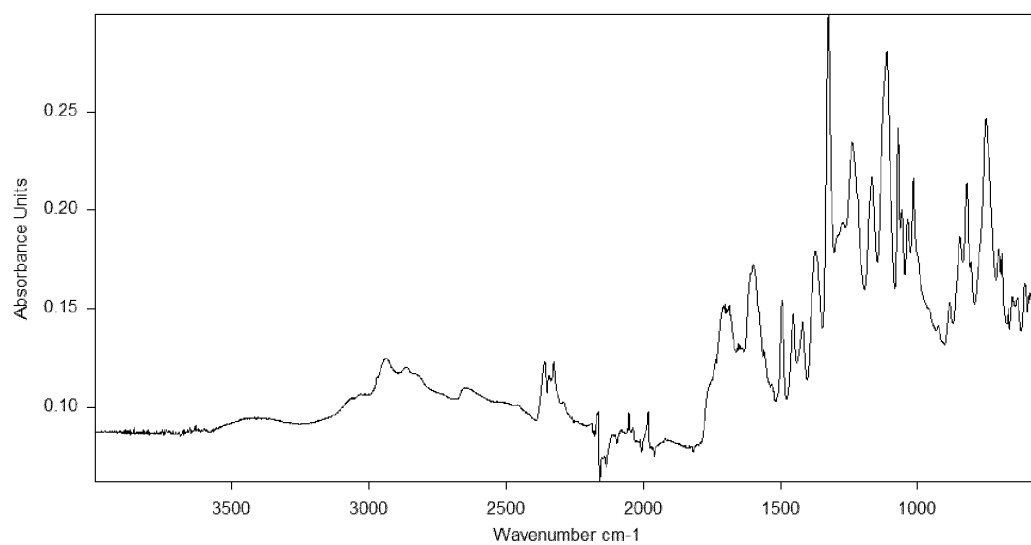
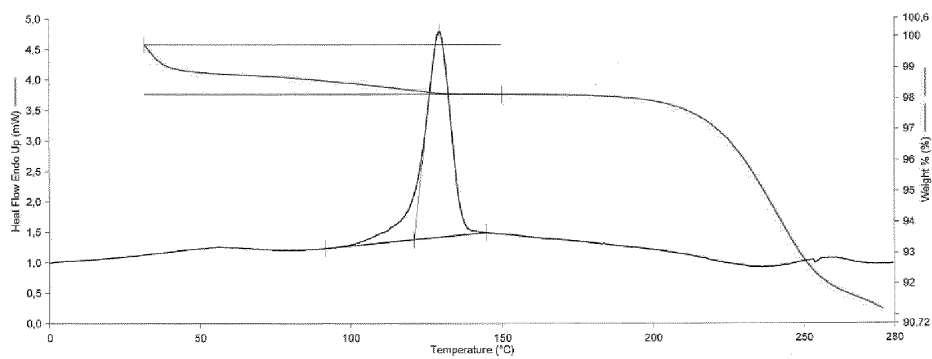
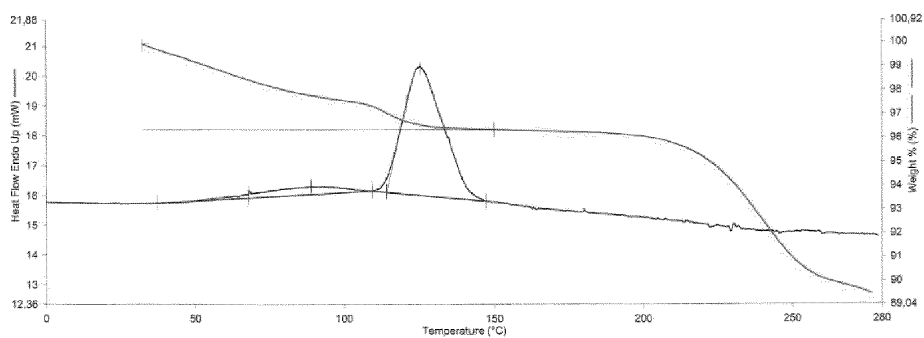


Fig. 23: IR spectrum of the Sesquihydrate, example 6c

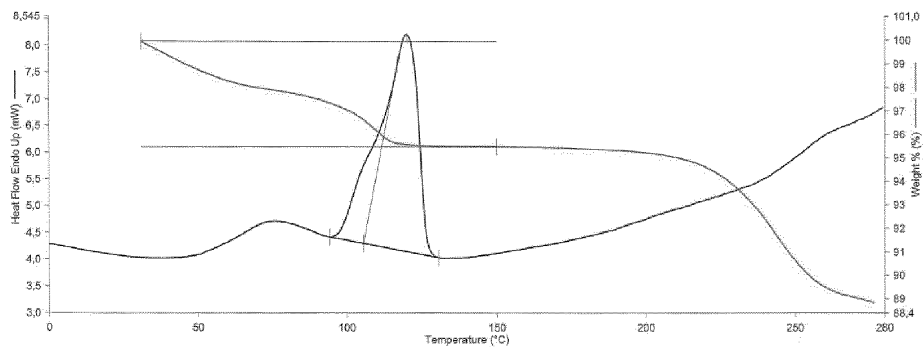
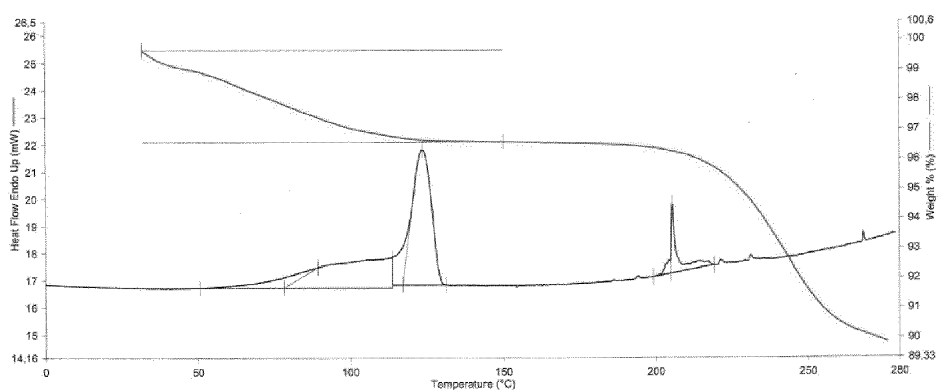
- 15/44 -

**Fig. 24:** IR spectrum of the Dihydrate, example 6f**Fig. 25:** IR spectrum of the amorphous form, example 6g

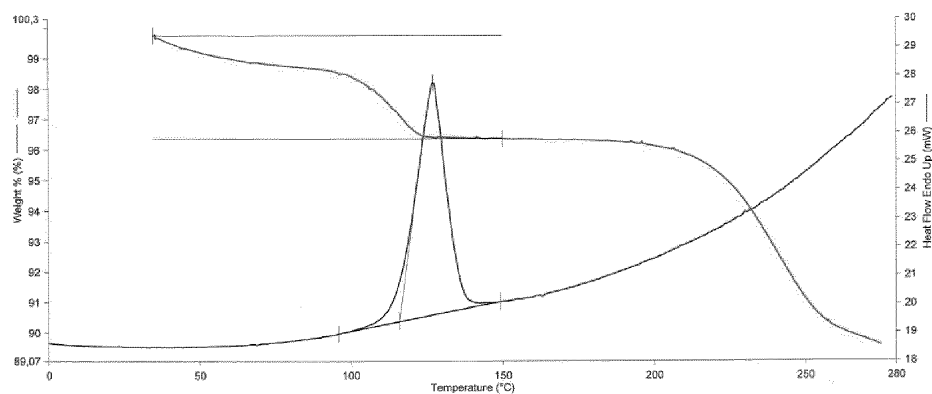
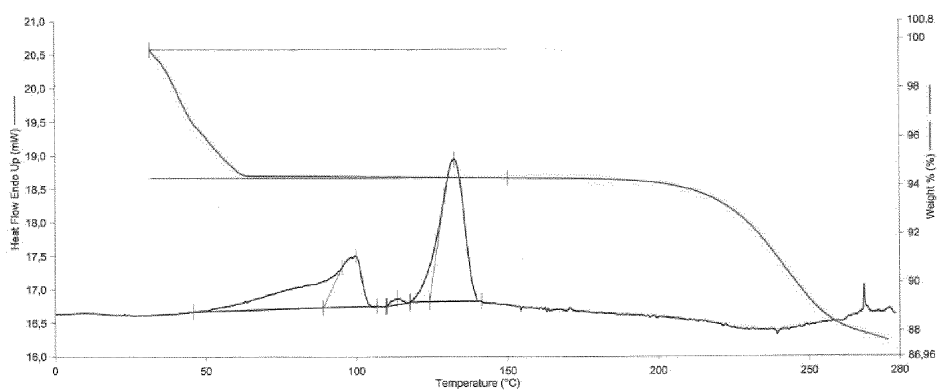
- 16/44 -

**Fig. 26:** DSC- and TGA-thermogram of the Semihydrate, example 6a**Fig. 27:** DSC- and TGA-thermogram of the Monohydrate I, example 6b

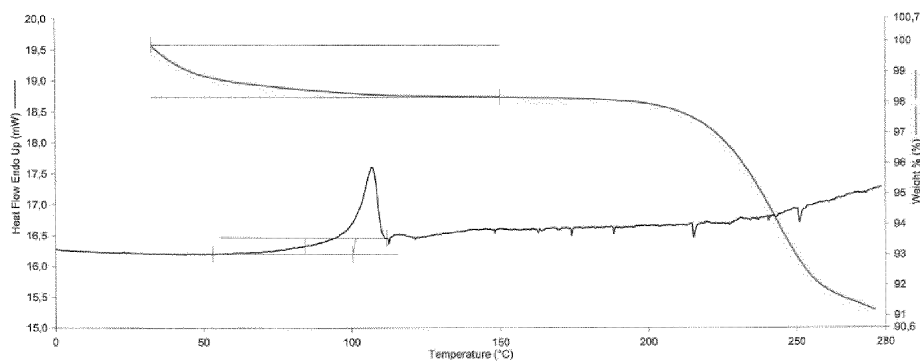
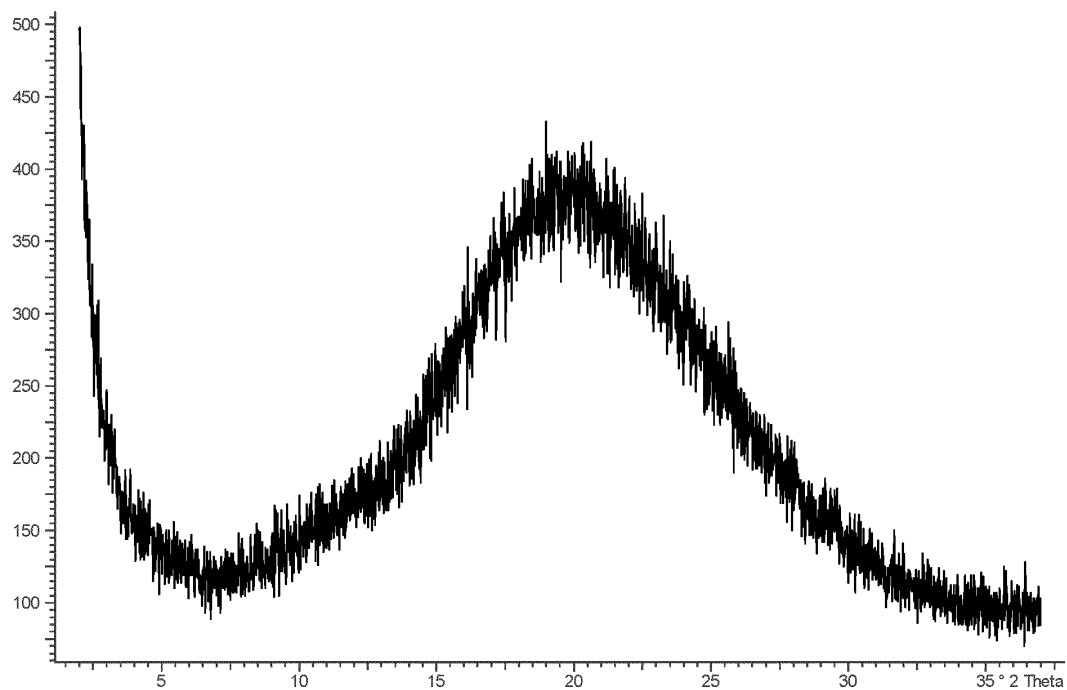
- 17/44 -

**Fig. 28:** DSC- and TGA-thermogram of the Monohydrate II, example 6c**Fig. 29:** DSC- and TGA-thermogram of the 1,25-Hydrate, example 6d

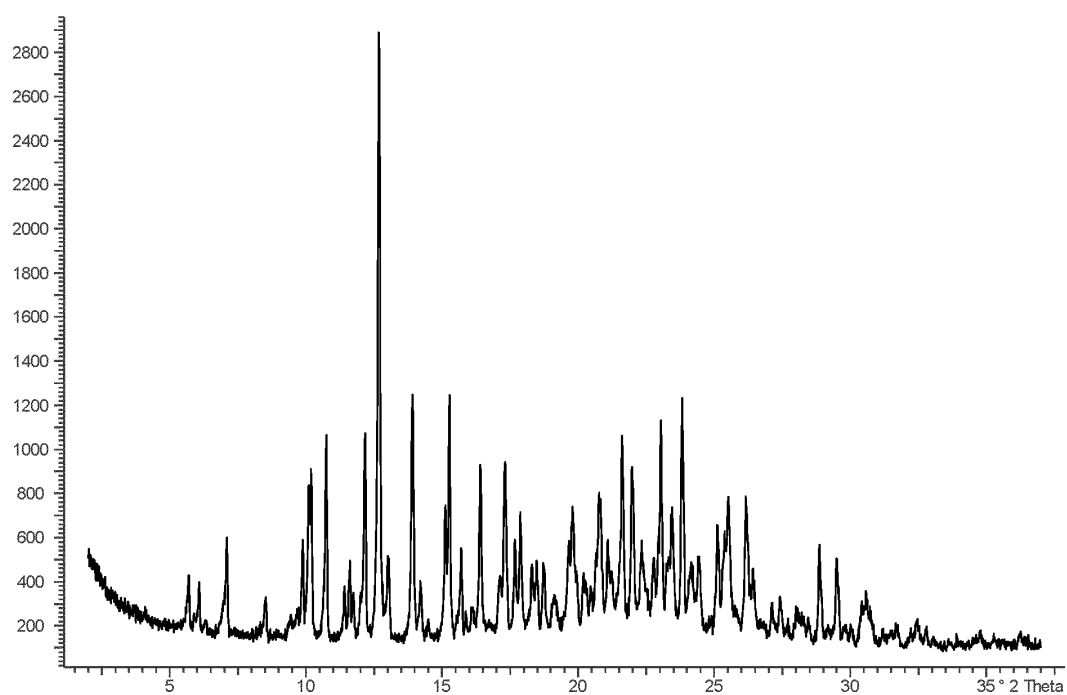
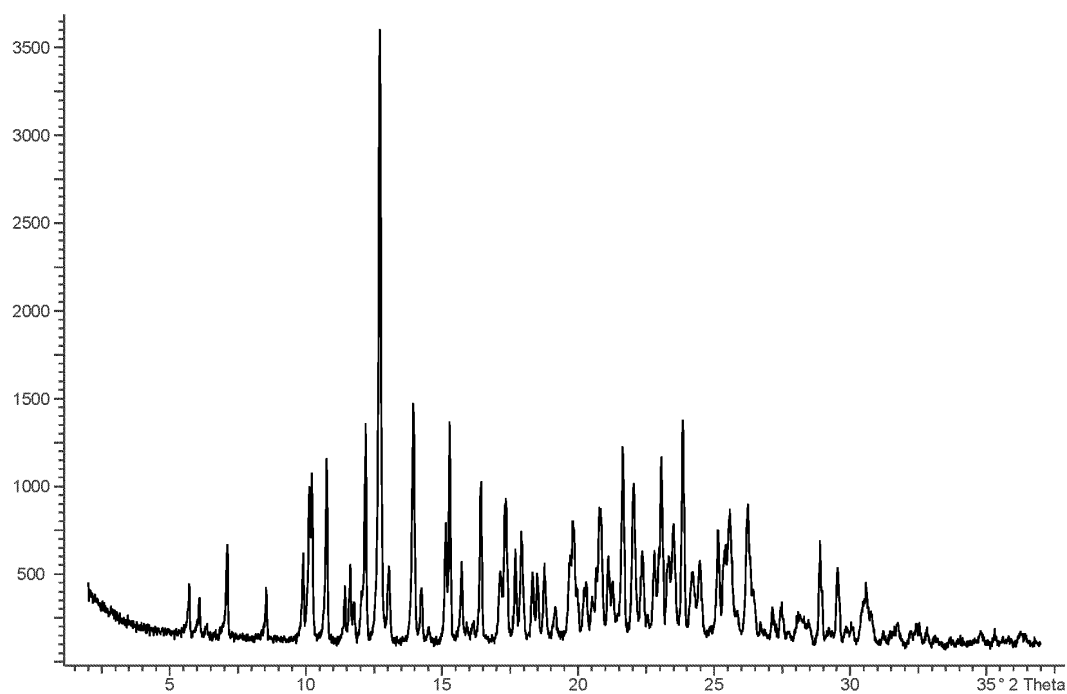
- 18/44 -

**Fig. 30:** DSC- and TGA-thermogram of the Sesquihydrate, example 6e**Fig. 31:** DSC- and TGA-thermogram of the Dihydrate, example 6f

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**Fig. 32:** DSC- and TGA-thermogram of the amorphous form, example 6g**Fig. 33:** X-Ray powder diffractogram of comparative example 11, amorphous form

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**Fig. 34:** X-Ray powder diffractogram of example 1, monohydrate II**Fig. 35:** X-Ray powder diffractogram of example 2 before micronization, monohydrate II

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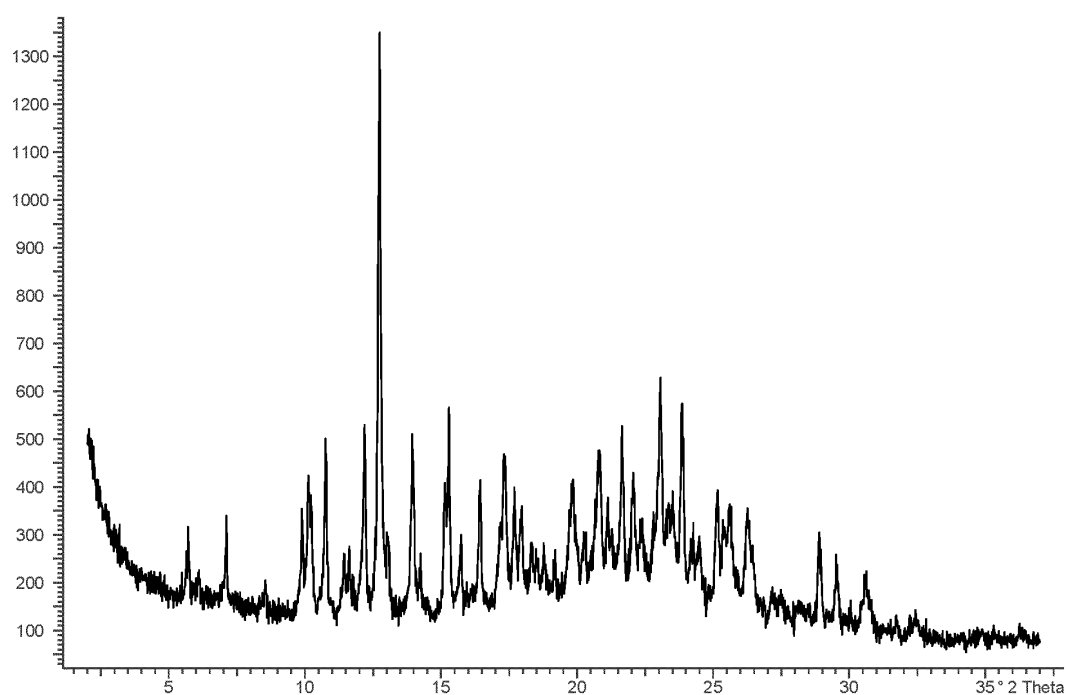


Fig. 36: X-Ray powder diffractogram of example 2 after micronization, monohydrate II, partial amorphization

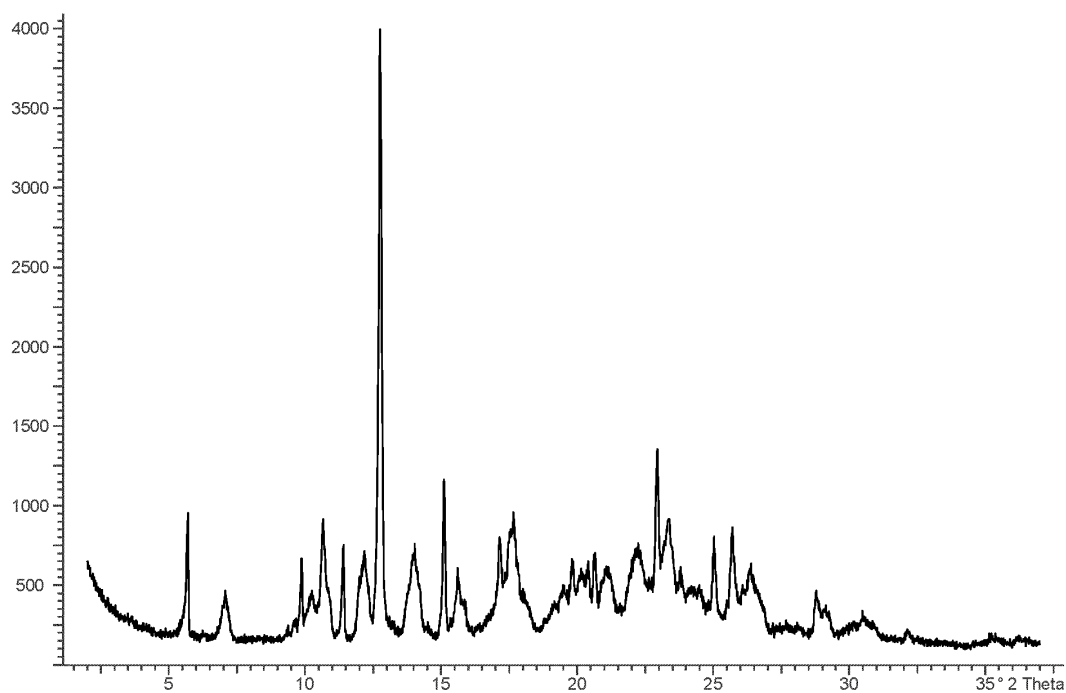
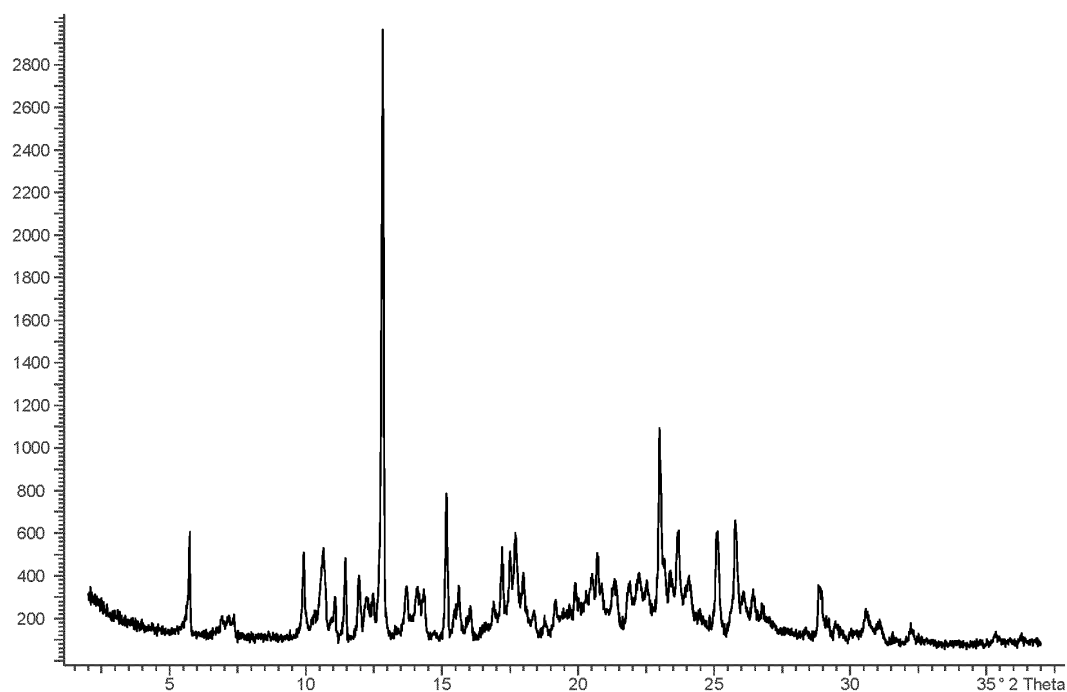
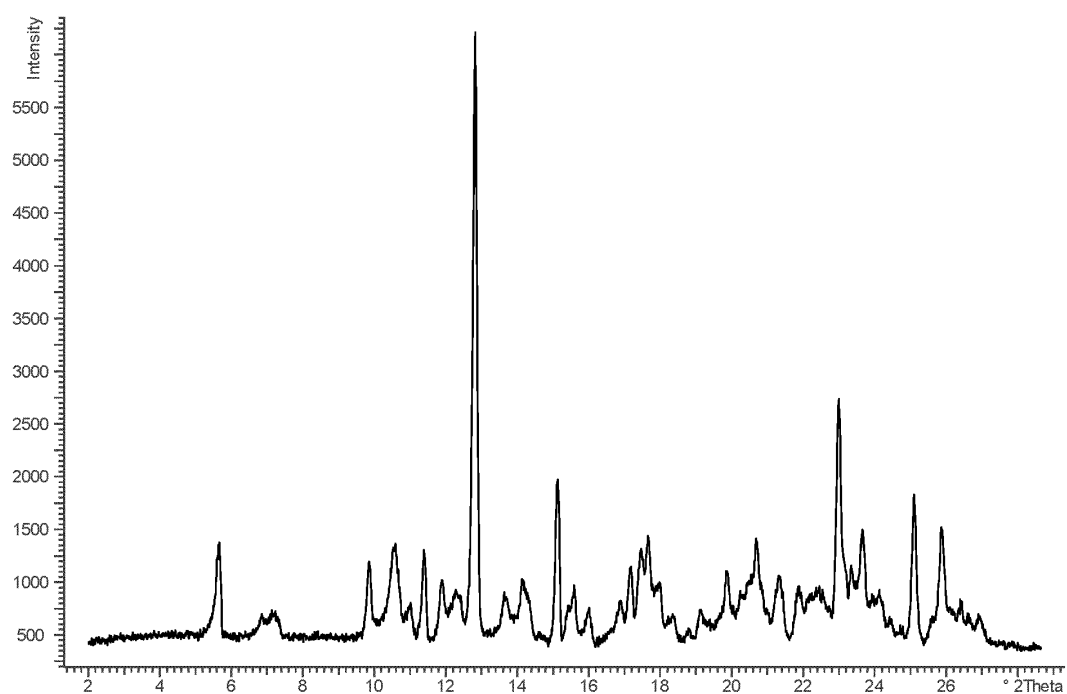


Fig. 37: X-Ray powder diffractogram of example 3, monohydrate I

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**Fig. 38:** X-Ray powder diffractogram of Example 4, monohydrate I**Fig. 39:** X-Ray powder diffractogram of example 5, monohydrate I

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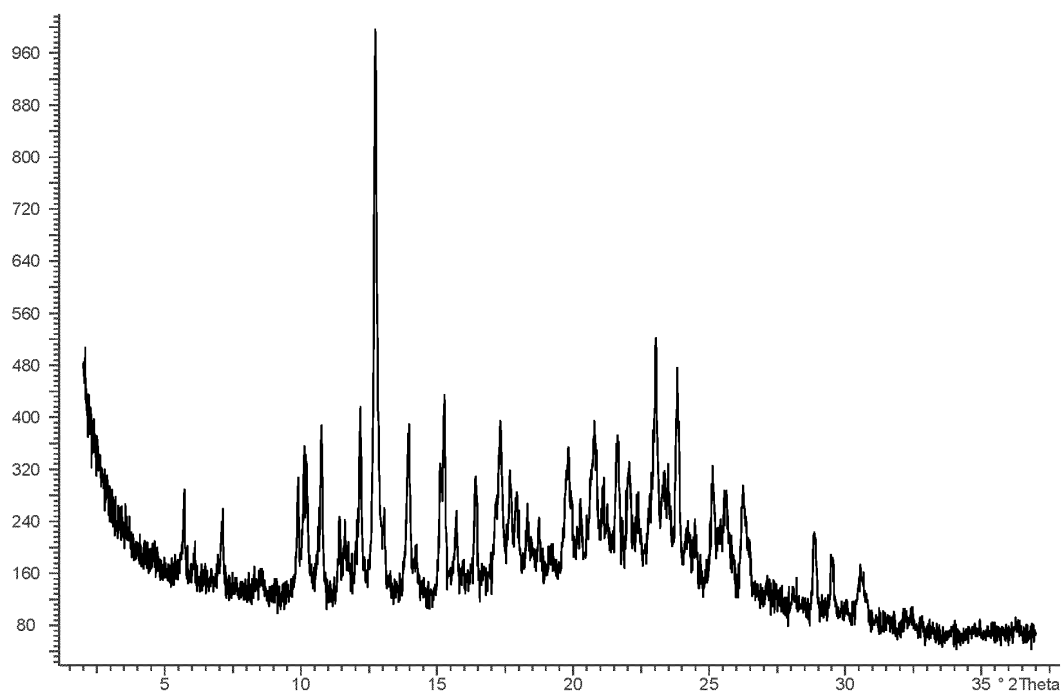


Fig. 40: X-Ray powder diffractogram of example 7 (storage stability): starting material for storage stability, monohydrate II

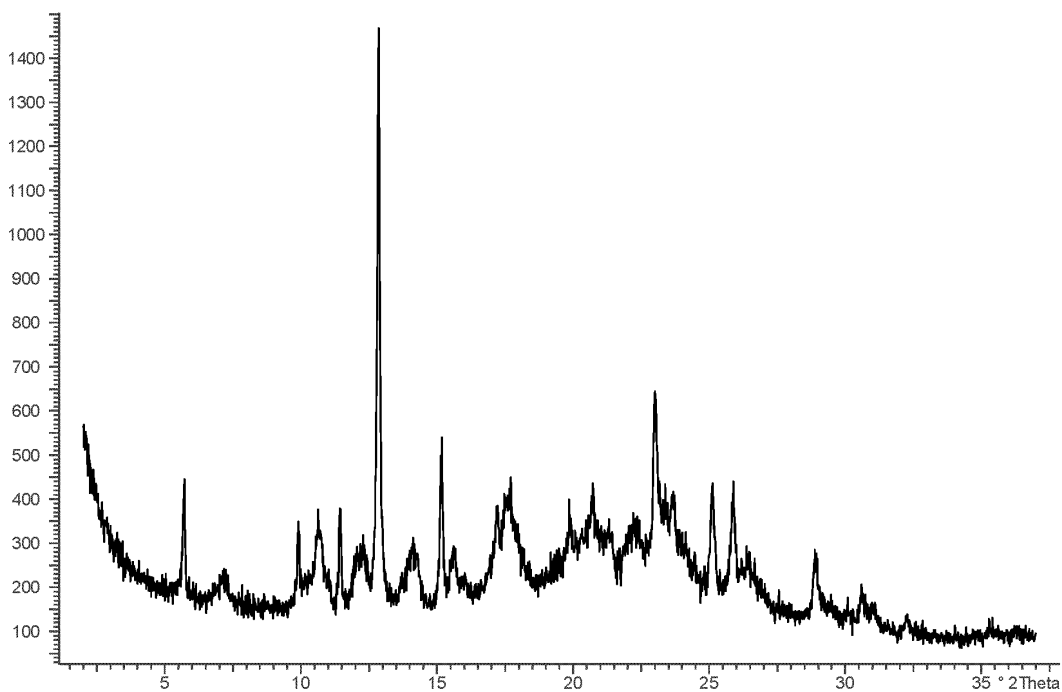


Fig. 41: X-Ray powder diffractogram of example 7b (storage stability): material after one month storage stability testing at 25°C and 60 % relative humidity in polyethylene, monohydrate I

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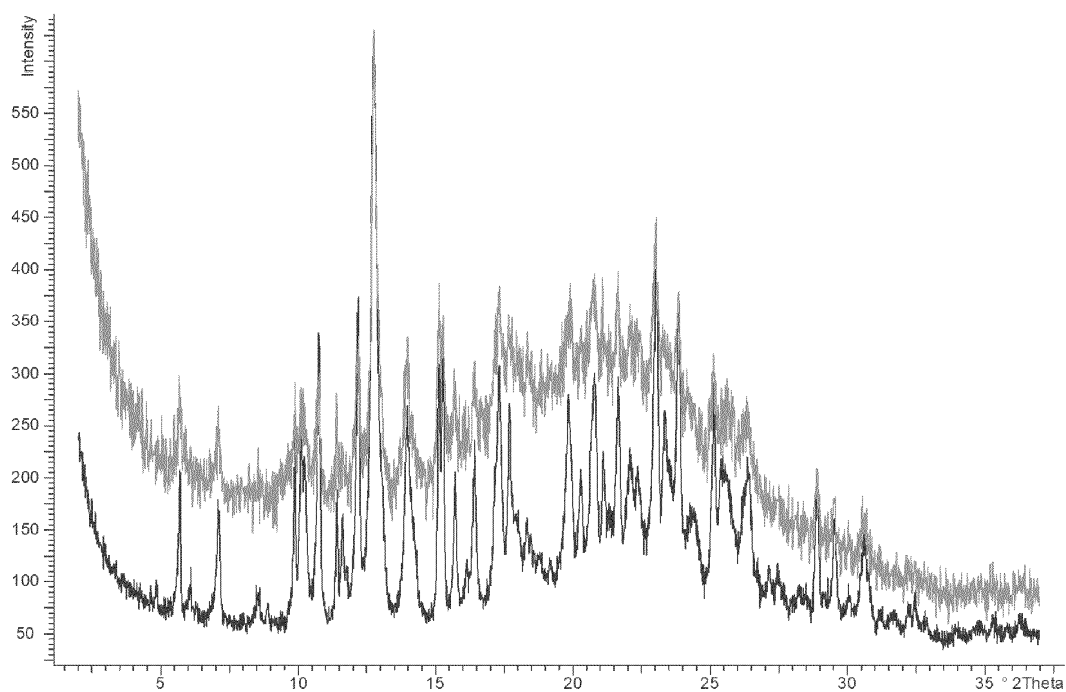


Fig. 42: Overlay of X-ray powder diffractograms of example 8b (micronization): starting material (monohydrate II) (bottom line) and material after micronization (monohydrate II with amorphous amounts, PTFE coated jet mill, 25°C) (top line)

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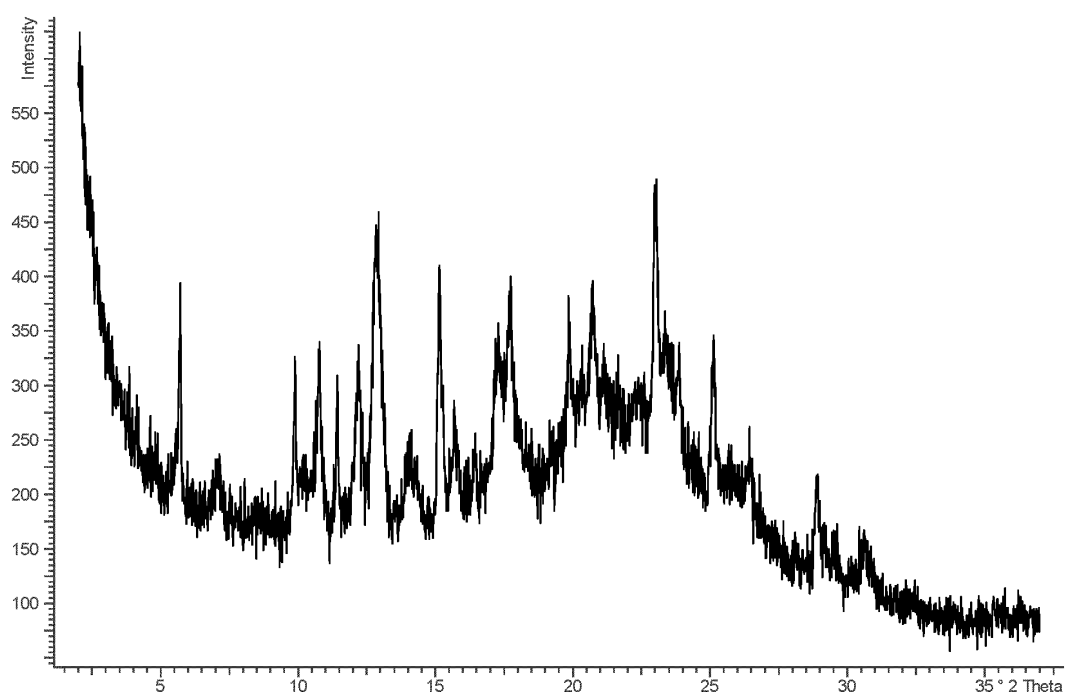


Fig. 43: X-ray powder diffractogram of example 8a: material after micronization (monohydrate I with amorphous amounts, VA jet mill, 25°C)

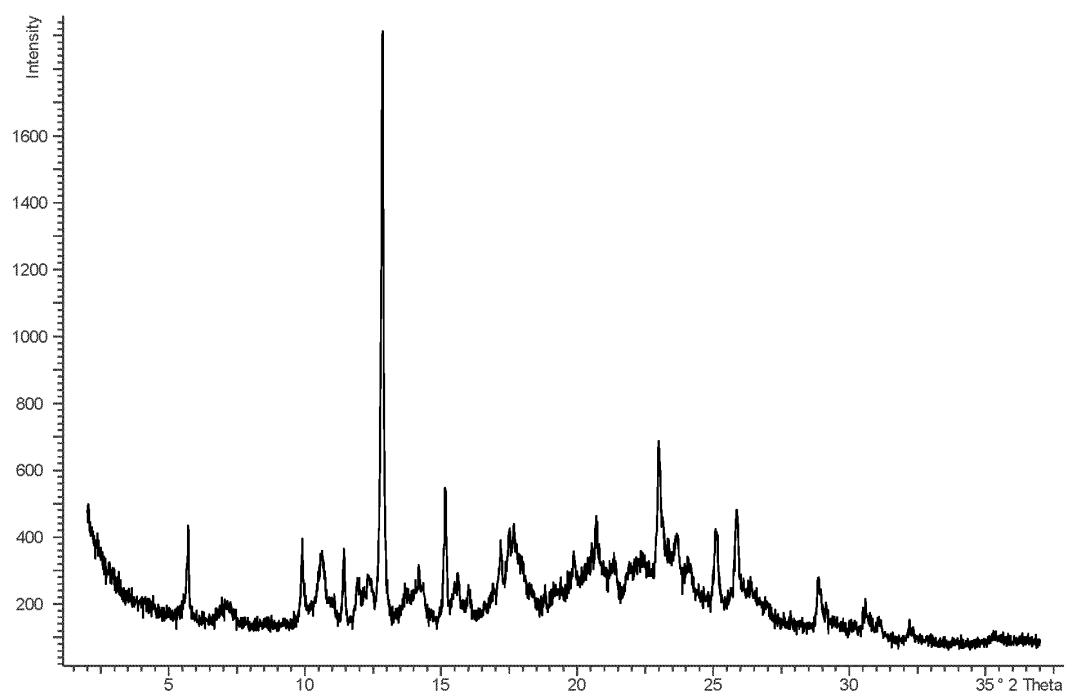


Fig. 44: X-ray powder diffractogram (example 8e): after micronization (monohydrate I)

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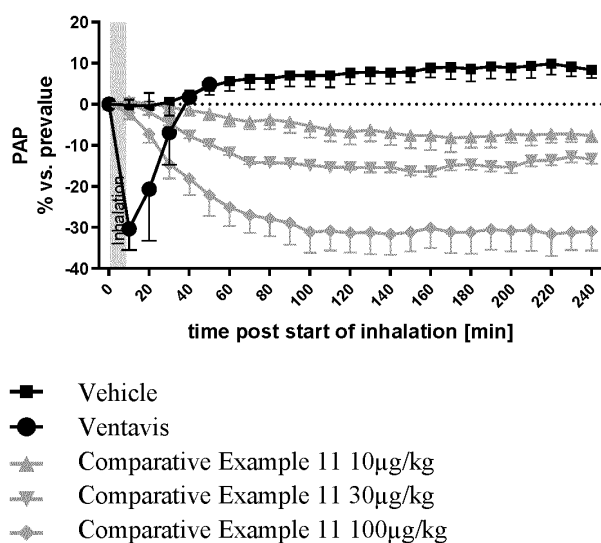
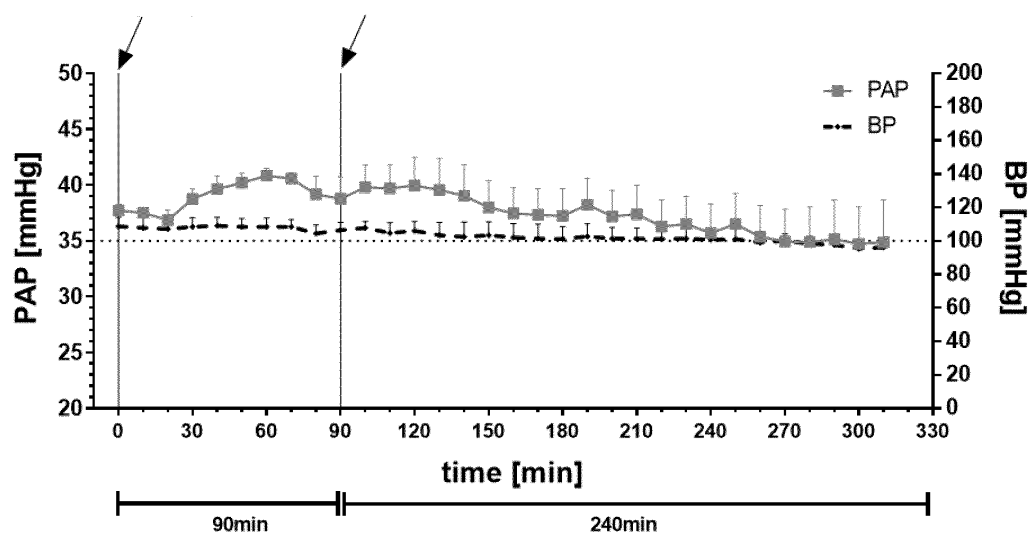


Fig. 45: Effects of vehicle solution, comparative example 11 (10, 30 and 100 µg/kg nominal dose) and Ventavis (10 µg/kg nominal dose) after inhaled application in the PAH minipigs model. Data are expressed as % changes in PAP and BP vs baseline (10 min interval prior to start of nebulization). Data are mean $\pm$ SEM. Nebulization interval took 5-7 min for all compounds (grey bar).

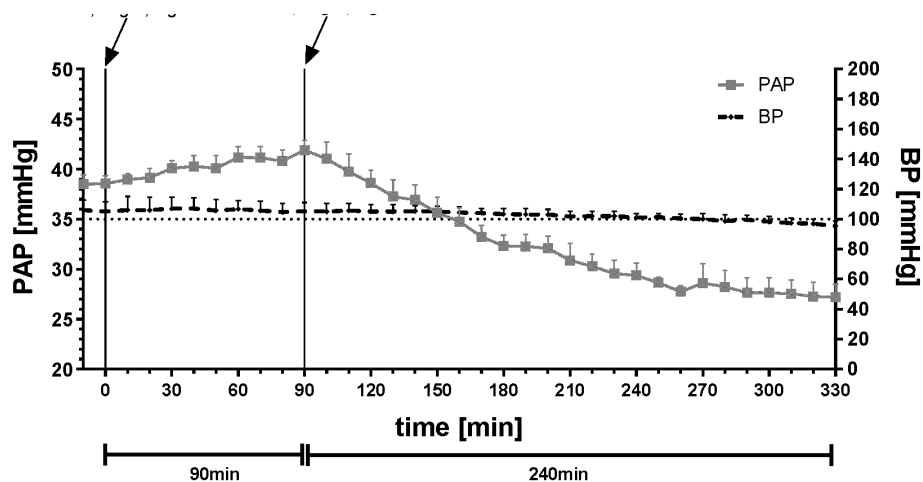
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↙ @0 min: Lactose 1.5mg/4kg; @90 min: Lactose formulation I (2%) 1.5mg/4kg

Fig. 46: Effects of lactose as well as lactose formulation I (7.5 μ g/kg) after intratracheal application. Data are mean $\pm$ SEM (n=3); Intratracheal application was conducted with PennCentury dry powder insufflator and Air Pump; BP: arterial blood pressure; PAP: pulmonary artery pressure; SEM: standard error of the mean

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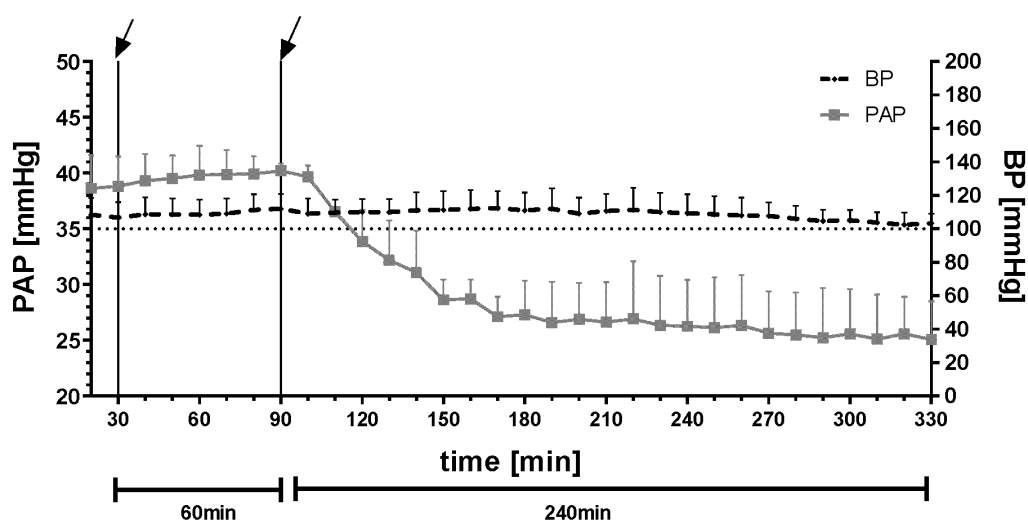


↙ @0 min: Lactose 1.5mg/4kg; @90 min: Lactose formulation II (6%) 1.5mg/4kg

Fig. 47: Effects of lactose as well as lactose formulation II (22.5 µg/kg) after intratracheal application.

Data are mean ± SEM (n=3); Intratracheal application was conducted with PennCentury dry powder insufflator and Air Pump; BP: arterial blood pressure; PAP: pulmonary artery pressure; SEM: standard error of the mean

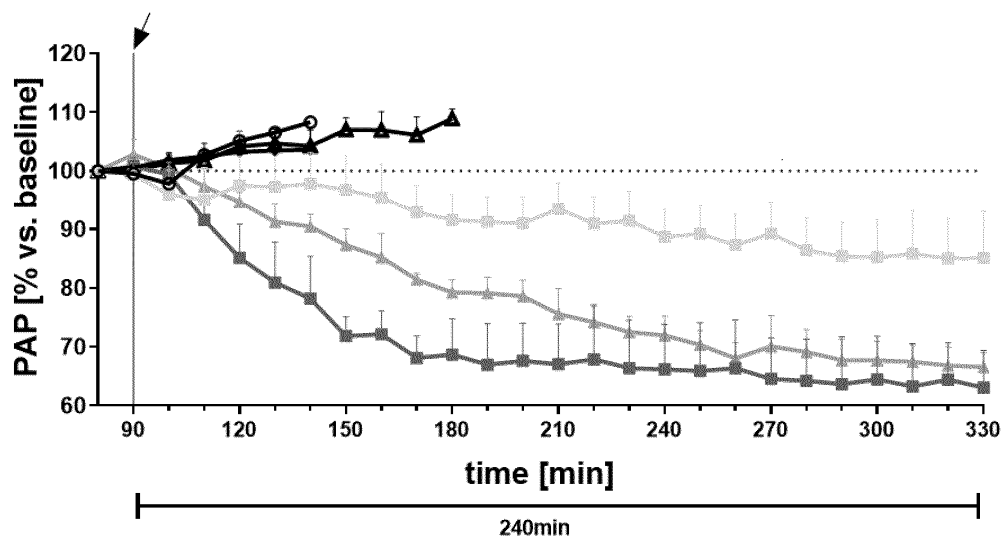
- 29/44 -



↙ @30 min: Lactose 1.5mg/4kg; @90 min: micronized example 6e 1.5mg/4kg

Fig. 48: Effects of lactose and micronized sesquihydrate, e.g. ex.. 6e (375 μ g/kg) after intratracheal application. Data are mean $\pm$ SEM (n=3) Intratracheal application was conducted with PennCentury dry powder insufflator and Air Pump; BP: arterial blood pressure; PAP: pulmonary artery pressure; SEM: standard error of the mean

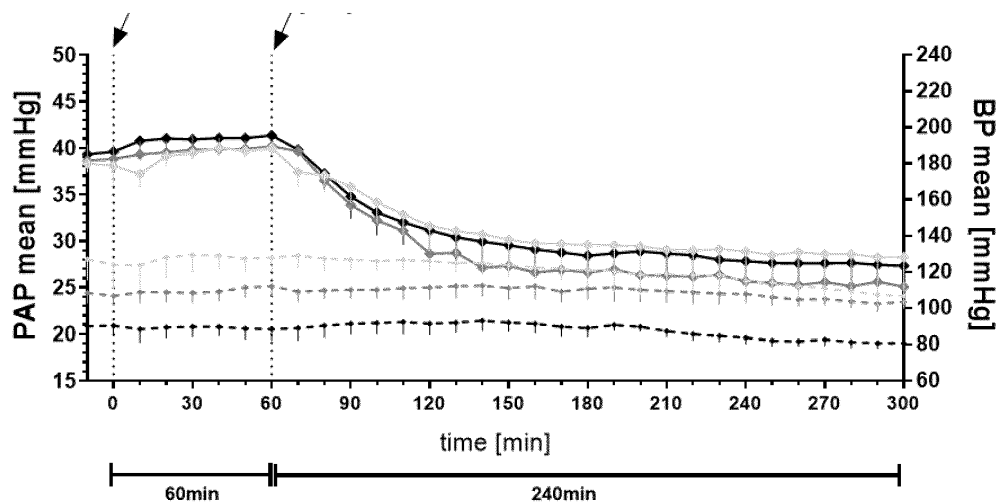
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↙ @90 min: Example 6e (mikro.) or lactose formulation I or II (2 or 6%) or Lactose 1.5mg/4kg

- PAP Lactose LH300/LH200 20:78m/m
- ▲ PAP Lactose LH300/LH200 20:80m/m
- PAP Lactose LH300/LH200 20:80m/m
- PAP Lactose formulation I (2%)
- PAP Lactose formulation II (6%)
- PAP Micronized example 6e

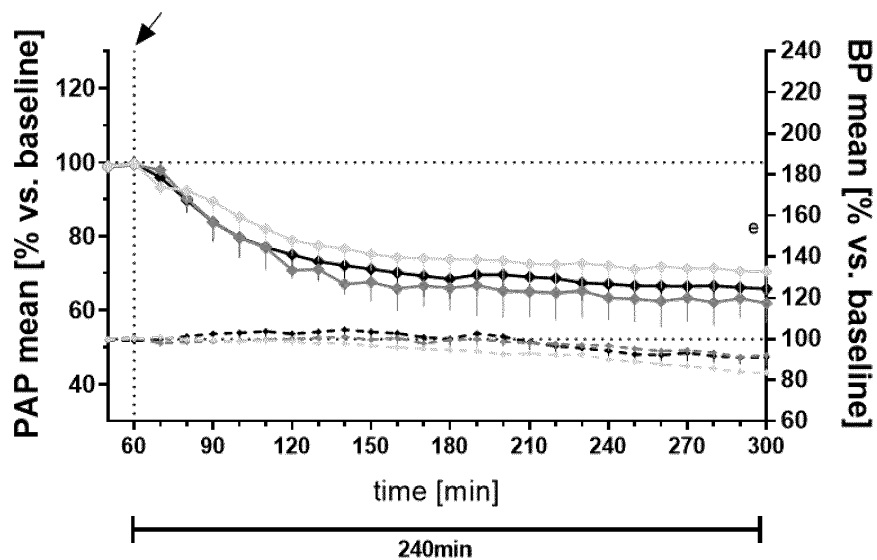
Fig. 49: Effects of intratracheal application of different lactose vehicles, lactose formulation I (7.5 $\mu\text{g/kg}$), lactose formulation II (22.5 $\mu\text{g/kg}$) and micronized sesquihydrate example 6e (375 $\mu\text{g/kg}$). Data are shown as %changes vs. prevalues as mean $\pm$ SEM (n=3)



↙ @0 min: Lactose LH300/LH200 1.5mg/4kg @60min: Hydrates of comparative example 11 micronized 1.5mg/4kg

- PAP mean Monohydrate II, example 2 (n=3)
- BP mean Monohydrate II, example 2 (n=3)
- ◆ PAP mean Semihydrate in analogy to example 6a (n=3)
- BP mean Semihydrate in analogy to example 6a (n=3)
- ◆ PAP mean Sesquihydrate in analogy to example 6e (n=3)
- BP mean Sesquihydrate in analogy to example 6e (n=3)

Fig. 50: Effects of comparative example 11 after intratracheal application of different hydrates micronized monohydrate II (example 2), micronized semihydrate (example 6a) and micronized sesquihydrate (example 6e), on BP and PAP. Data are shown as absolute values [mmHg] as mean $\pm$ SEM (n=3)



↙ @60 min: Hydrates of comparative example 11 micronized 1.5mg/4kg

- PAP mean Monohydrate II, example 2 (n=3)
- -○ BP mean Monohydrate II, example 2 (n=3)
- ◆—◆ PAP mean Semihydrate in analogy to example 6a (n=3)
- ◆- -◆ BP mean Semihydrate in analogy to example 6a (n=3)
- PAP mean Sesquihydrate in analogy to example 6e (n=3)
- -■ BP mean Sesquihydrate in analogy to example 6e (n=3)

Fig. 51: Effects of comparative example 11 after intratracheal application of different hydrates micronized monohydrate II (example 2), micronized semihydrate (example 6a) and micronized sesquihydrate (example 6e), on BP and PAP. Data are shown as absolute values [mmHg] as mean $\pm$ SEM (n=3)

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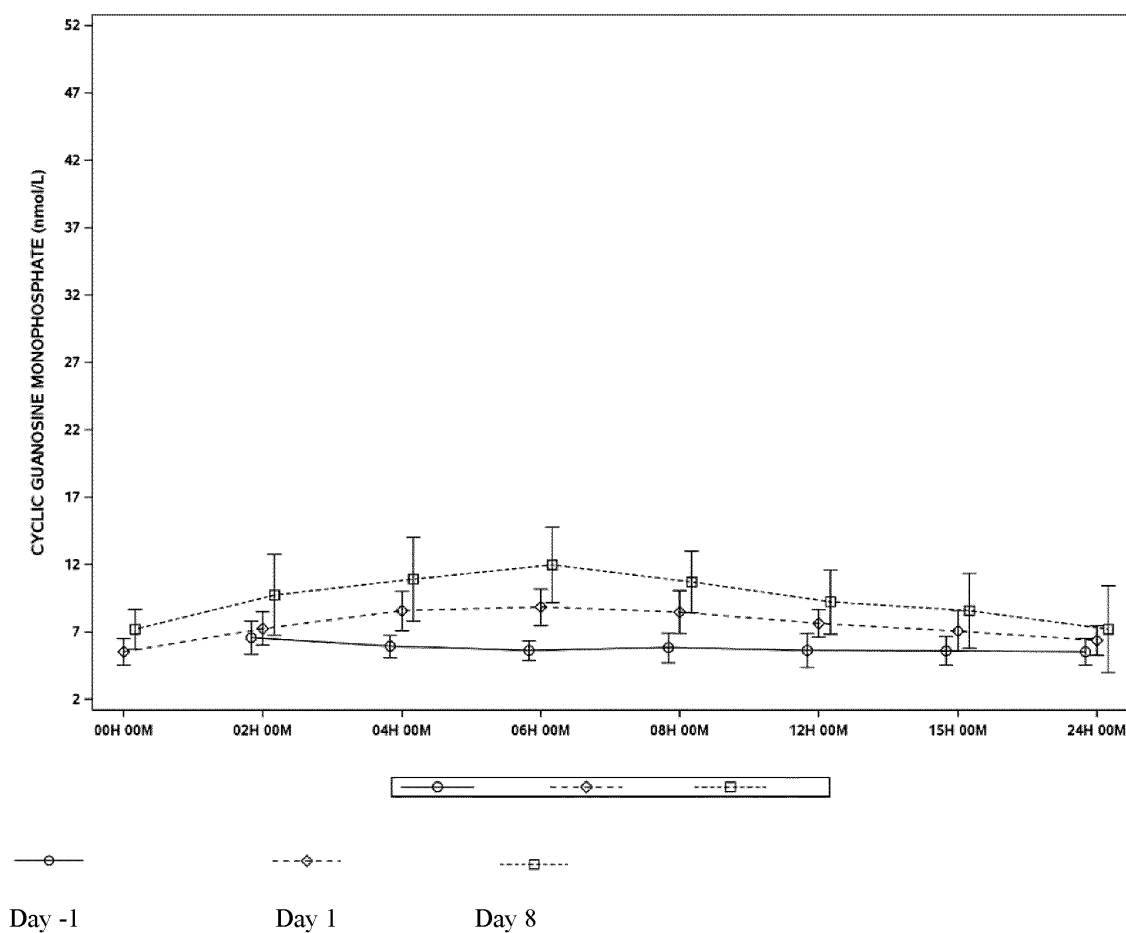


Fig. 52: Means $\pm$ SDs for cGMP (nmol/L) – comparison of pretreatment (day -1), first (day 1) and last (day 8) treatment days for the 480 μ g (example 2) dose group (SAF, N = 9)

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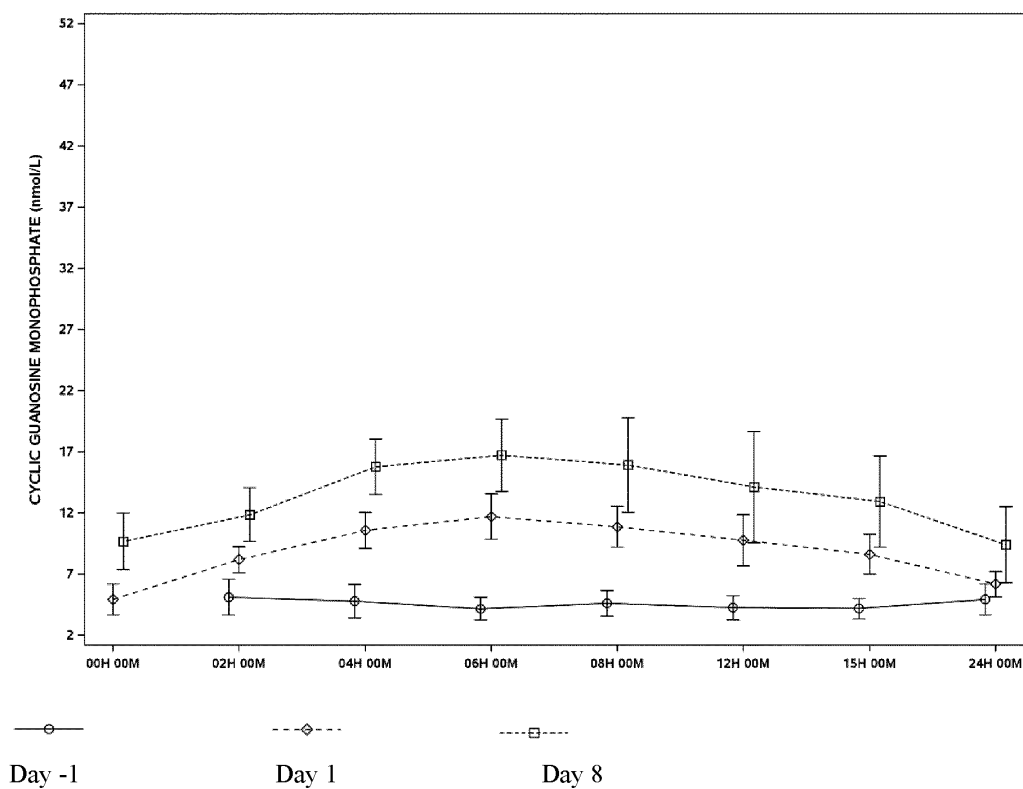


Fig. 53: Means $\pm$ SDs for cGMP (nmol/L) – comparison of pretreatment (day-1), first (day 1) and last (day 8) treatment days for the 1000 μ g (example 2) dose group (SAF, N = 9)

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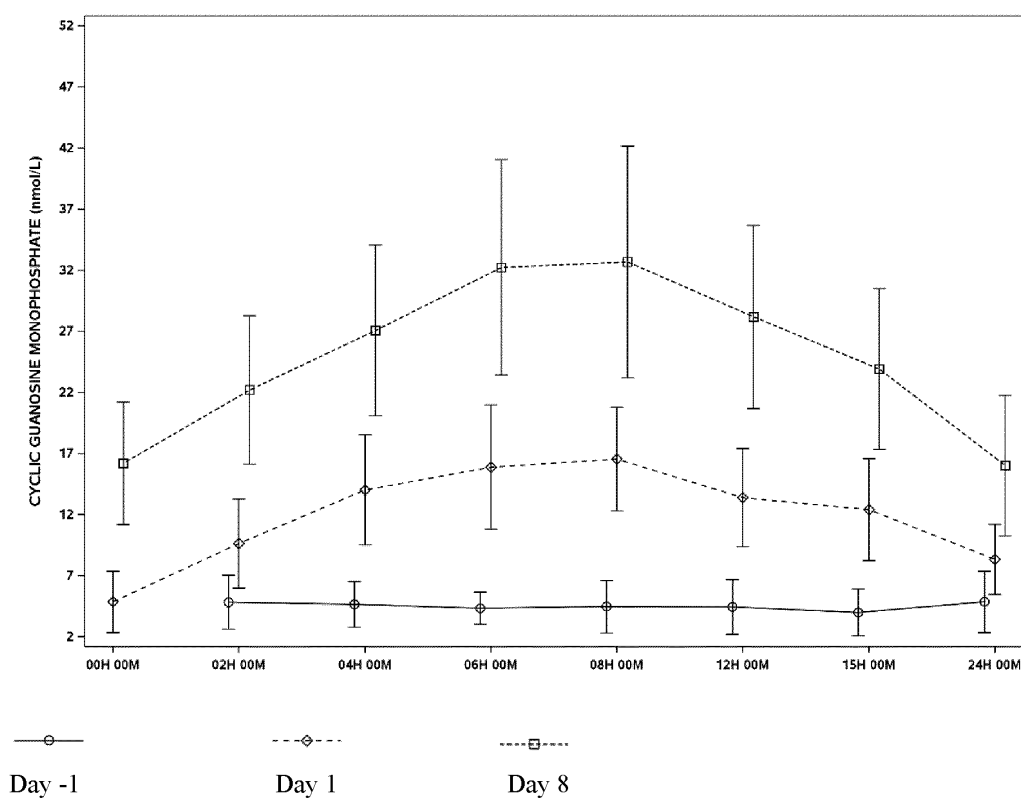


Fig. 54: Means $\pm$ SDs for cGMP (nmol/L) – comparison of pretreatment (day-1), first (day 1) and last (day 8) treatment days for the 2000 μ g (example 2) dose group (SAF, N = 9)

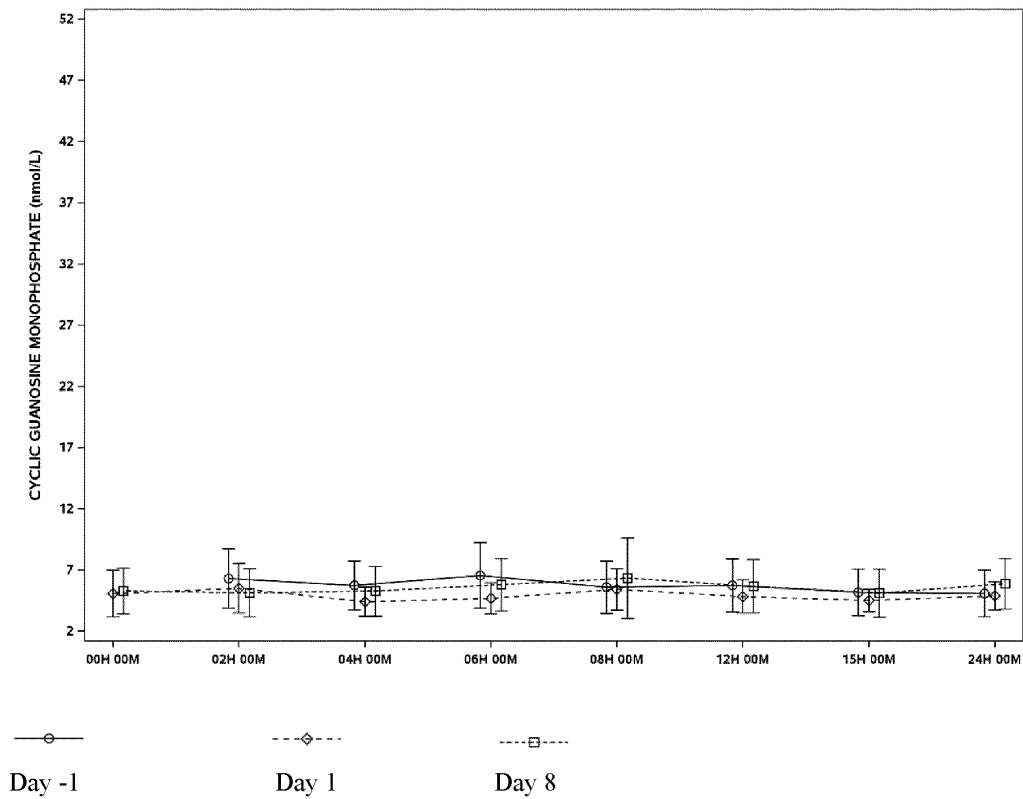


Fig. 55: Means $\pm$ SDs for cGMP (nmol/L) – comparison of treatment days for the placebo group (SAF, N = 9)

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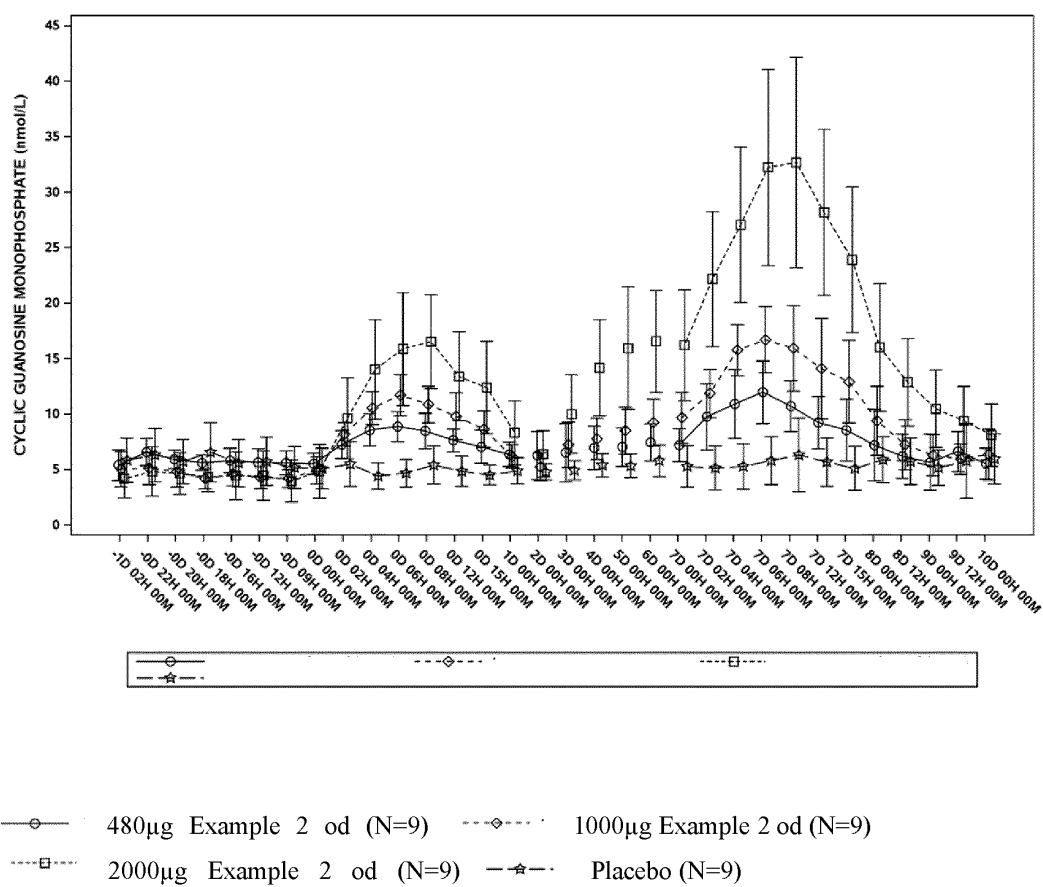


Fig. 56: Means (N = 9) $\pm$ SDs for cGMP in body liquids over time (nmol/L) on baseline day (-1d02h – 0d00h) first inhalation day (0d00h -2d00h), trough measurements 2d00h- 7d00h) and after 7 days inhalation (7d00h- 10d00h).

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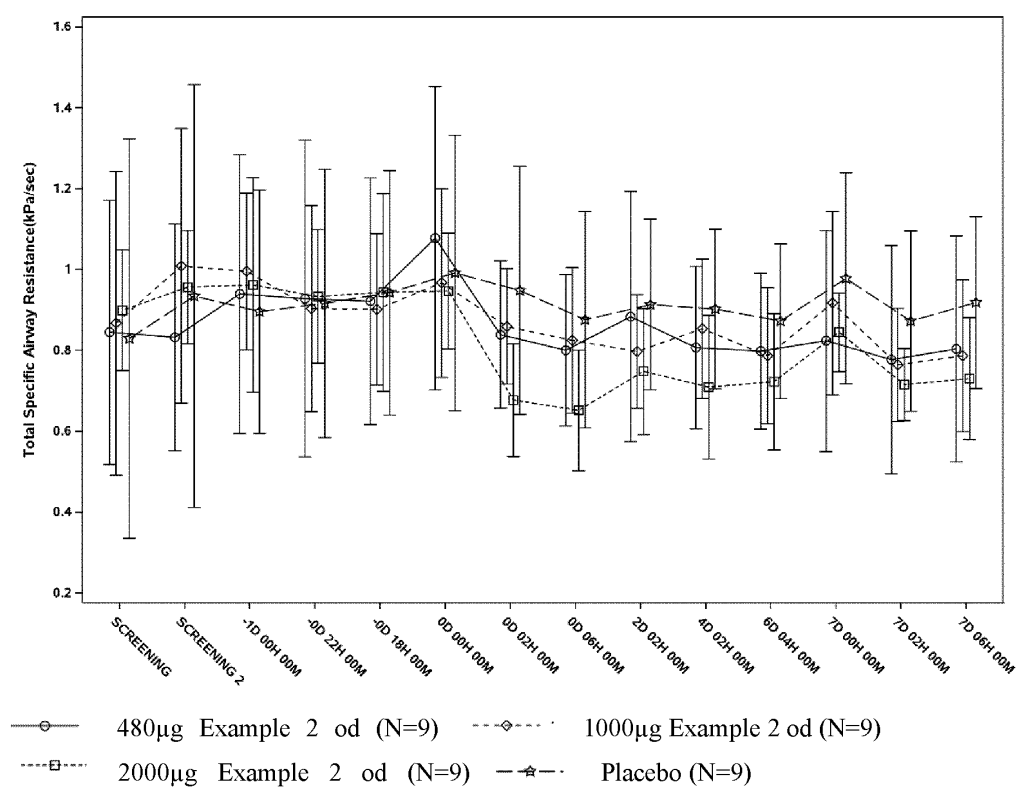


Fig. 57: Means (N = 36, 12 each for 480, 1000 and 2000 µg, example 2) and SDs for total specific airway resistance (kPa/sec) over time: screening 1/2, baseline day (-1d00h – 0d00h) first inhalation day (0d00h – 0d06h), measurements after inhalations 2d02h- 6d04h) and after 7 days inhalation (7d00h- 7d06h).

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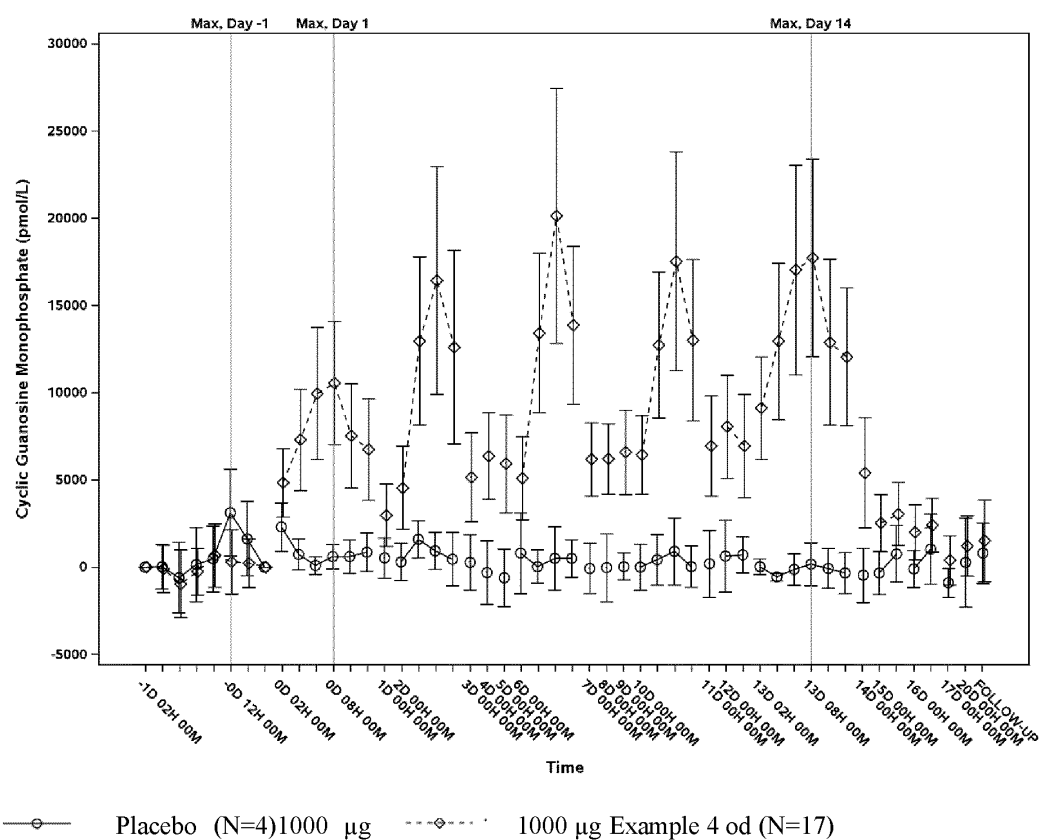


Fig. 58: Means for cGMP difference to baseline for Placebo (N = 4) and 1000 µg, (N = 17) example 4) over time (nmol/L) on pretreatment day (-1d00h – -0d09h) first inhalation day (-0d02h - 1d00h), measurements prior and after inhalations 2d00h- 2d12h, 6d00h- 6d12h, 10d00h- 10d12h) (profile days), at trough prior inhalation on days 3d – 5d, 7d-9d, 11d-12d) and for last of 14 days inhalation (12d22h- 20d00h).

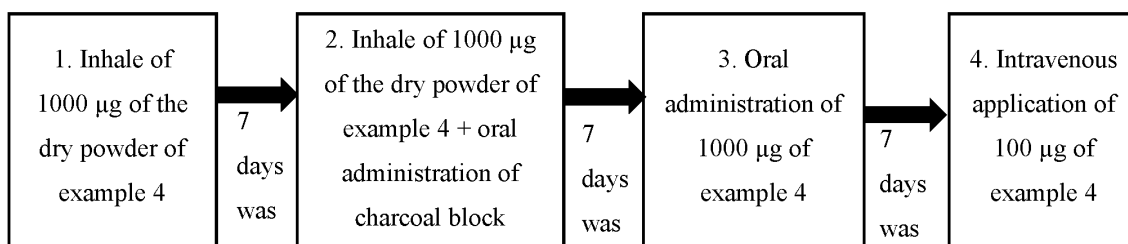
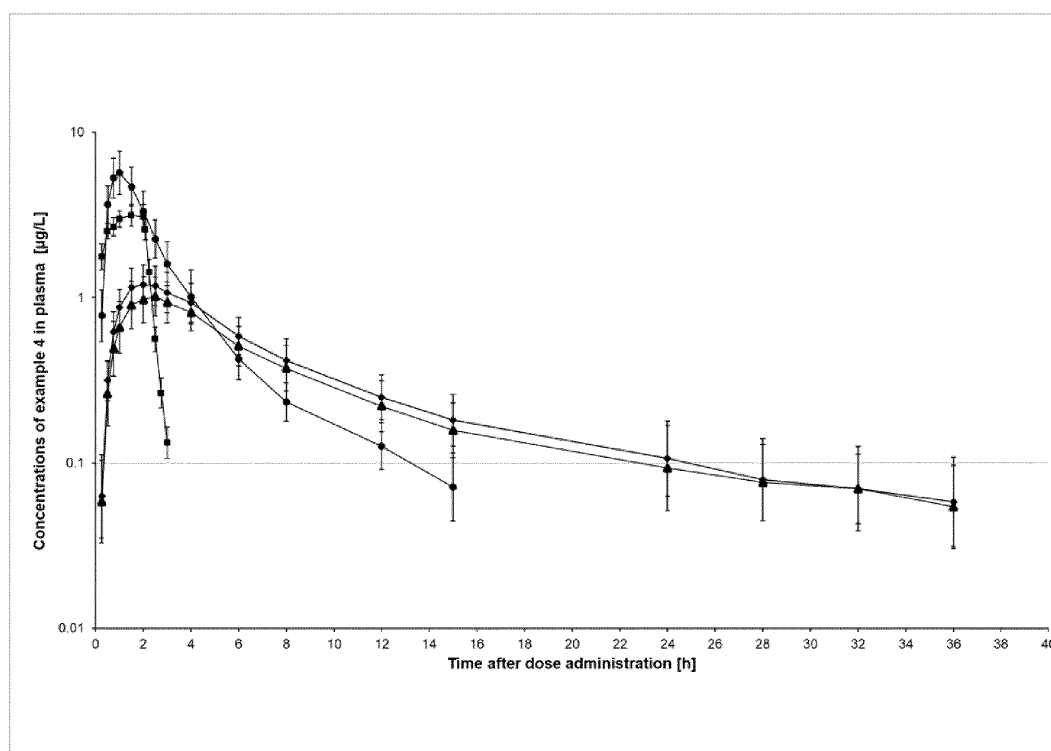


Figure 59: scheme of the treatments conducted to investigate lung deposition



■ 100 µg Example 4 intravenous, n= 15, ◆ 1000 µg inhale of example 4, n= 16
 ■ 1000 µg inhale of example 4 + charcoal, n=16, ◆ 1000 µg oral dose of example 4, n= 16

Figure 60: Geometric means and standard deviations for concentrations of example 4 (µg/L) in plasma, on semilogarithmic scale.

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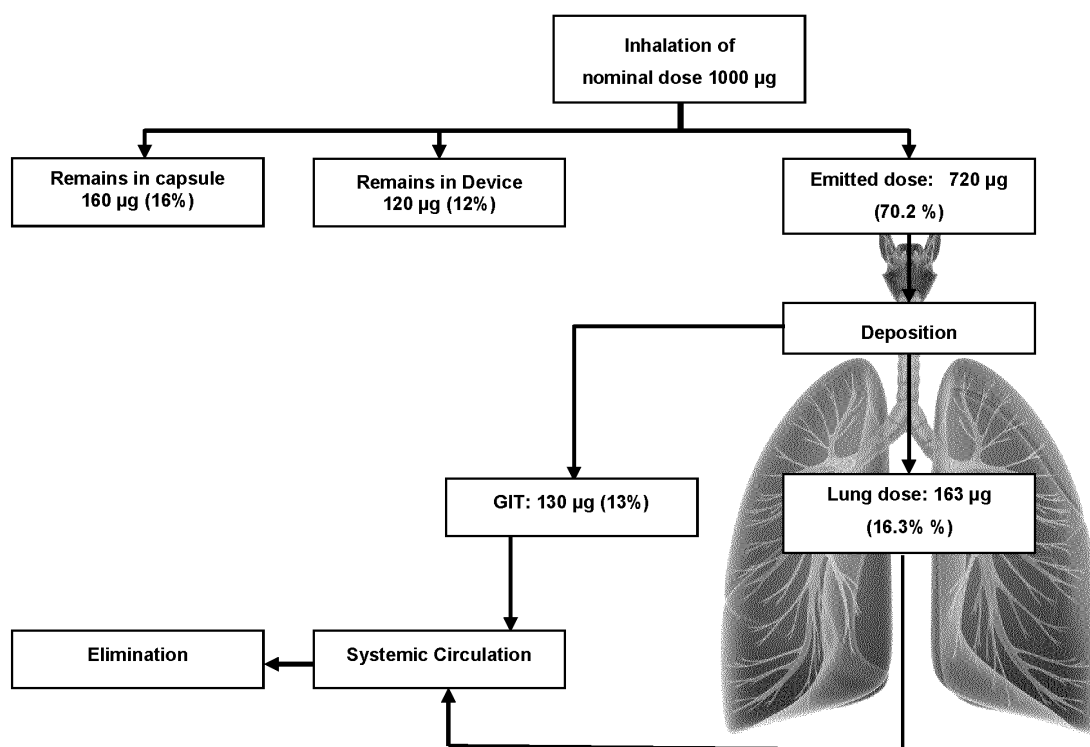


Figure 61: Part of the dose reached the mouthpiece (emitted dose) and parts of the dose remains in the capsule, in the device, the deposited lung dose and part of the dose reached the GIT tract

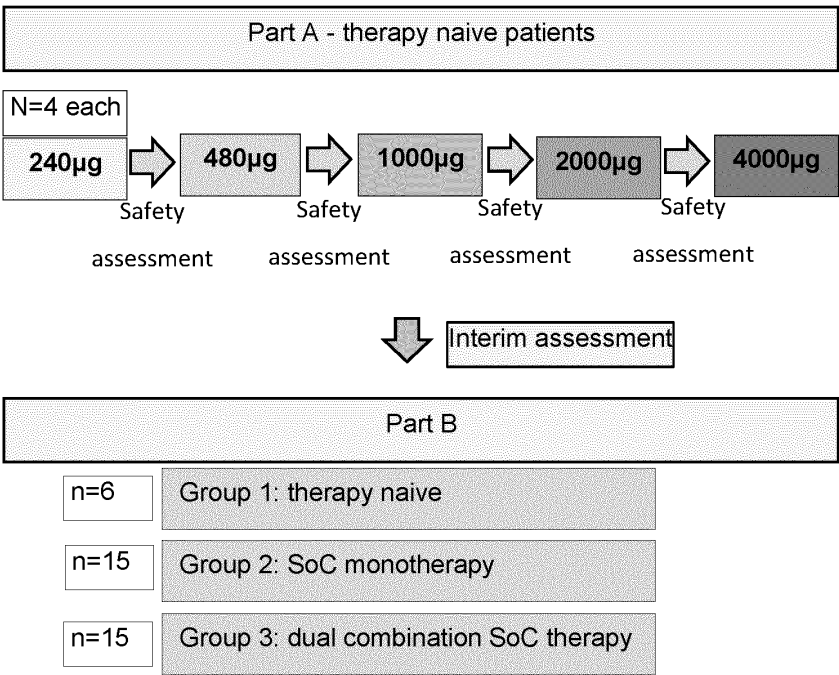
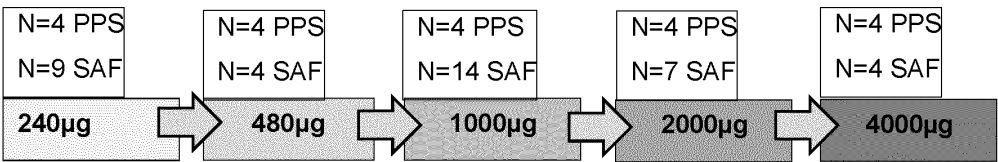


Figure 62: study design of clinical study in patients with PAH or CTEPH



*SAF: safety analysis set: all patients matching in- and exclusion criteria (IC/EC)

*PPS: per protocol set: IC/EC met + PVR > 400 dyn + PAP decrease during inhaled nitric oxide (NO) challenge < 10 mmHG (exclusion of vasoresponsivness)

Figure 63: summary of conducted Part A of clinical study in patients with PAH or CTEPH

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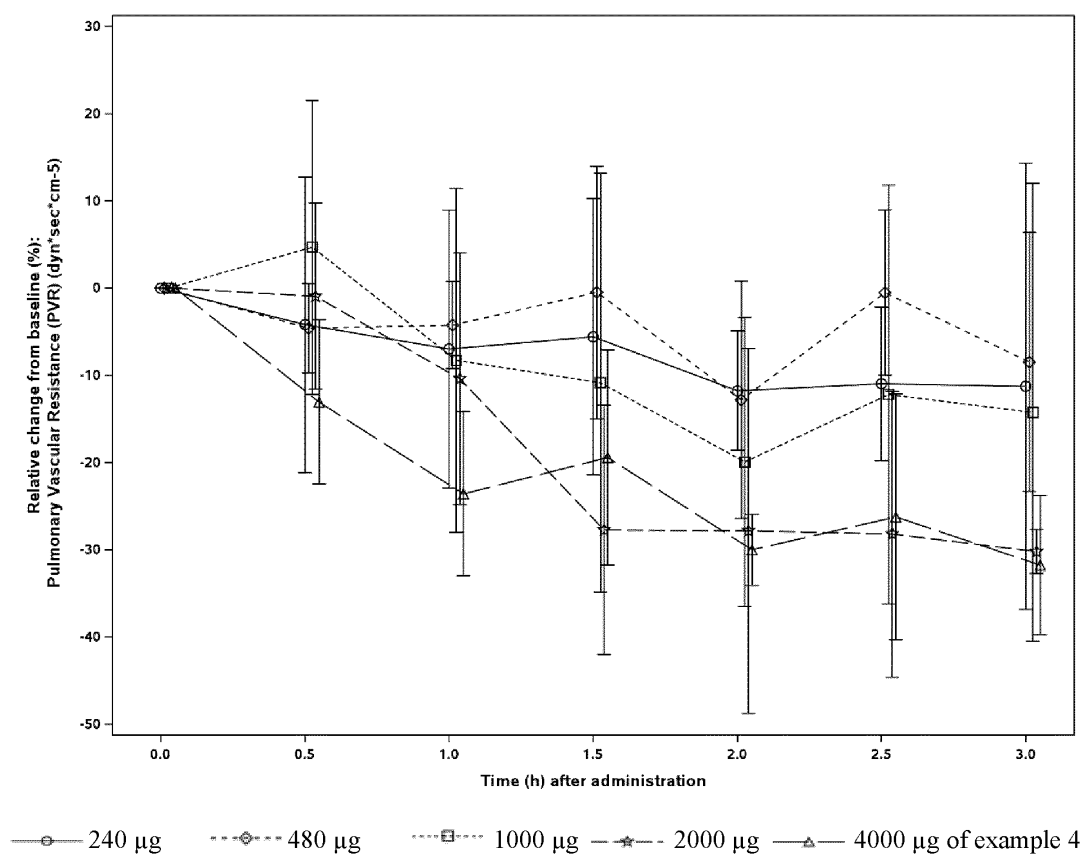


Figure 64: Means and SDs for relative changes (%) from baseline (0D00H00M) of pulmonary vascular resistance (PVR) over time after inhalation (0D00H30M until 0D03H00M) of example 4 in patients with PAH or CTEPH (N=4 each for 240, 480, 1000, 2000 and 4000 µg group, per protocol set)

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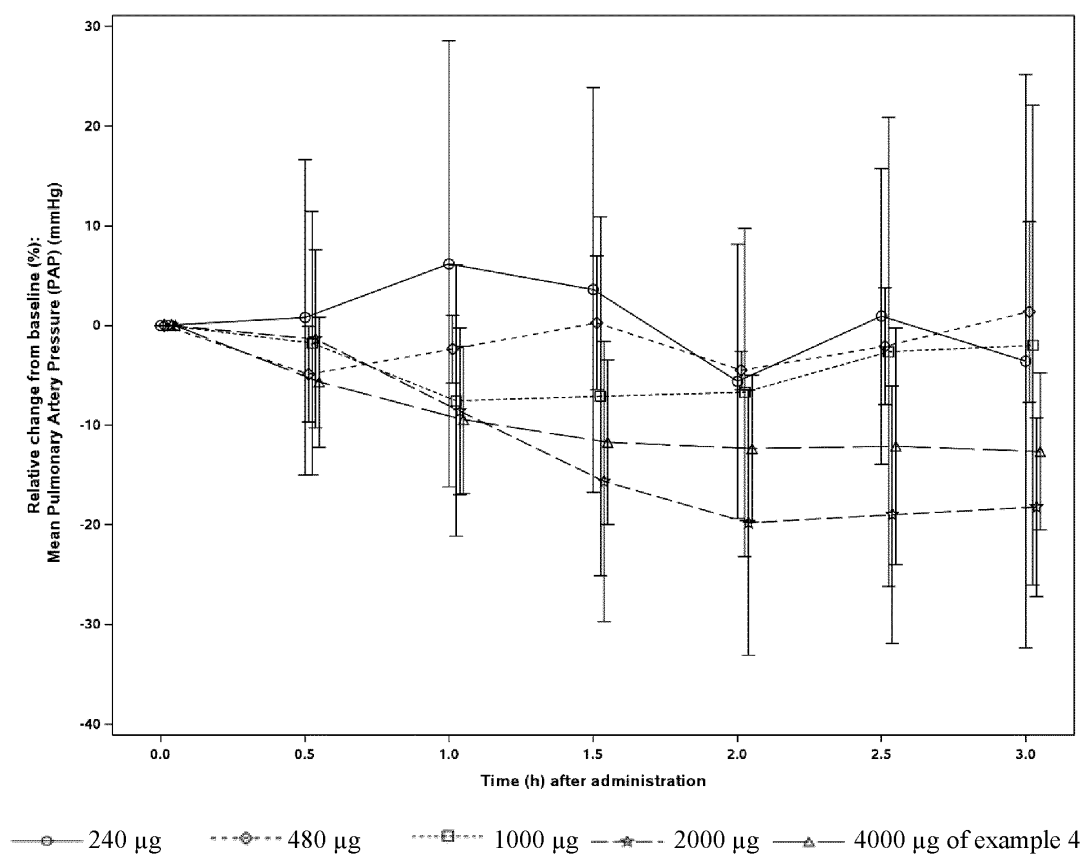


Figure 65: Means and SDs for relative changes (%) from baseline (0D00H00M) of mean pulmonary arterial pressure (mPAP) over time after inhalation (0D00H30M until 0D03H00M) of example 4 in patients with PAH or CTEPH (N=4 each for 240, 480, 1000, 2000 and 4000 µg group, per protocol set).