Example 25: stability and dissolution experiments hydrate vs amorphous

In this experiment, the thermal characteristics (by DSC – differential scanning calorimetry) and powder dissolution are determined for (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate ("Compound") in the hydrate crystalline form and in the amorphous form, with reference to storage under defined conditions.

Sample Preparation

Compounds to be tested are stored in a closed container at 25°C, in which a relative humidity (RH) of 93% is installed by means of a saturated $(NH_4)H_2PO_4$ solution. The same set up is used also at 40°C (RH>93%). Compounds are stored in the specified conditions for 1 day, 1 week, 2 weeks and 1 month. Subsequently the samples are analyzed using DSC and powder dissolution.

DSC

DSC experiments are carried out using a DSC-7 (Perkin-Elmer, Norwalk, CT) using N_2 as purge gas. Liquid N_2 is used as a coolant. Samples (approximately 5 mg) are analyzed using aluminum hermetic pans (TA Instruments, Brussels, Belgium). Temperature calibration is performed using indium and tin standards, enthalpic calibration is carried out using indium standards. Validation of temperature and enthalpic response is performed using tin and indium standards. All samples are scanned at 10°C/min from 15°C to 140°C.

The results are indicated in Table 27. In view of the different solid state nature of Compounds in the samples tested, the temperature characteristics necessarily are also different: the temperature values indicated are the onset of a melting peak (for the crystalline hydrate form) and the Tg (for the amorphous form). Rather than being based on a comparison of the absolute temperature values, conclusions are drawn from comparing the temperature changes depending on the sample history.

Dissolution

Dissolution (Hanson Dissolution test station SR8 PLUS) is performed according to the rotating paddle method (USP 24) at 37°C and 50 rpm in 1000 ml of 0.01N HCl to which was added 0.1% sodium laurylsulfate. The dissolution test was performed on 50.0 mg of Compound (in either form), which was placed between filter paper at the bottom of the vessel. Two ml of the samples are taken a t0.6, 12, 20, 30, 60 and 120 minutes and immediately filtered over a 0.45µm PVDF membrane filter (Acrodica, USA) into a vial. The samples are analyzed using HPLC. The peak of Compound in the chromatogram is integrated and the concentration of Compound in the samples is calculated using a calibration curve, made of standards of known concentrations.

The results are depicted in Figures 27 to 30. Each of these figures is a graph representing the percentage of Compound dissolved (Y-axis) over time (X-axis).

Example 26: dissolution experiments ethanolate vs amorphous

In this experiment, the dissolution is tested of(3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate ("Compound") in the ethanolate crystalline form and in the amorphous form.

The results are depicted in Figures 31 to 33. In each figure, a graph indicates the percentage of Compound dissolved (Y-axis) over time (X-axis).

Figure 31 relates to samples at zero storage time. Samples 1-6 all represent the amorphous form.

The mean dissolution percentage of the amorphous form is 75.16% at 120 minutes, whilst for the ethanolate crystalline form this is 99.98%. After 90 minutes, the dissolution level of the ethanolate crystalline form is more or less stable and complete (100%), while the dissolution level of the amorphous form is still increasing after 120 minutes.

Figure 32 relates to samples that were subjected to 1 month of storage at 25°C. Samples 1-6 all represent the amorphous form.

The mean dissolution percentage of the amorphous form after one month of storage is 81.07% (which is 107.87% compared to the value found at zero storage time). For the ethanolate crystalline form, the dissolution percentage is 97.28% (which is 97.29% as compared to the value found at zero storage time). All these observations are extracted at time point 120 minutes.

As at zero storage time, the dissolution level of the ethanolate crystalline form is more or less stable and complete after 90 minutes dissolution (97%), while the dissolution level of the amorphous form is still increasing after 120 minutes.

Figure 33 relates to samples that were subjected to 3 months of storage at 25°C. Samples 1-4 all represent the amorphous form.

The mean dissolution percentage of the amorphous form after three month of storage is 87.92% (which is 116.99% compared to the value found at zero storage time). For the ethanolate crystalline form, the dissolution percentage is 102.67% (which is 102.69% as compared to the value found at zero storage time). All these observations are extracted at time point 120 minutes.

As at zero storage time, the dissolution level of the ethanolate crystalline form is more or less stable and complete after 90 minutes dissolution (103%), while the dissolution level of the amorphous form is still increasing after 120 minutes.

Table 27[1]

Thermal characteristics of (3R,3aS,6aR)-hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate (crystalline hydrate and amorphous)

Sample history		**T hydrate (°C)**	**T amorphous (°C)**
Untreated		70.38 (0.23)	63.87 (3.01)
after storage 25°C/93% RH:	1 day	69.80 (0.92)	63.37 (6.71)
after storage at 25°C/93% RH:	1 week	71.10 (1.09)	45.19 (1.19)
after storage at 25°C/93% RH:	2 weeks	70.64 (0.16)	44.45 (0.41)
after storage at 25°C/93% RH:	1 month	69.49 (0.21)	n.d.
Δ °C after 1 month of storage at 25°C/93% RH		***- 0.89***	***≥ -19.42***
after storage 40°C/93% RH:	1 day	70.37 (1.52)	49.16 (4.18)
after storage at 40°C/93% RH:	1 week	68.48 (0.07)	32.01 (single value)
after storage at 40°C/93% RH:	2 weeks	70.15 (0.82)	31.83 (3.67)
after storage at 40°C/93% RH:	1 month	67.77 (0.89)	32.38 (0.17)
Δ °C after 1 month of storage at 40C/93% RH		***- 2.61***	***-31.49***

[1] Each of the reported values is the mean of two measurements. In parentheses the difference between the two measurements is indicated (with one exception where a single value was available).

Figure 27: dissolution of Compound crystalline hydrate after storage at 25°C/93% RH

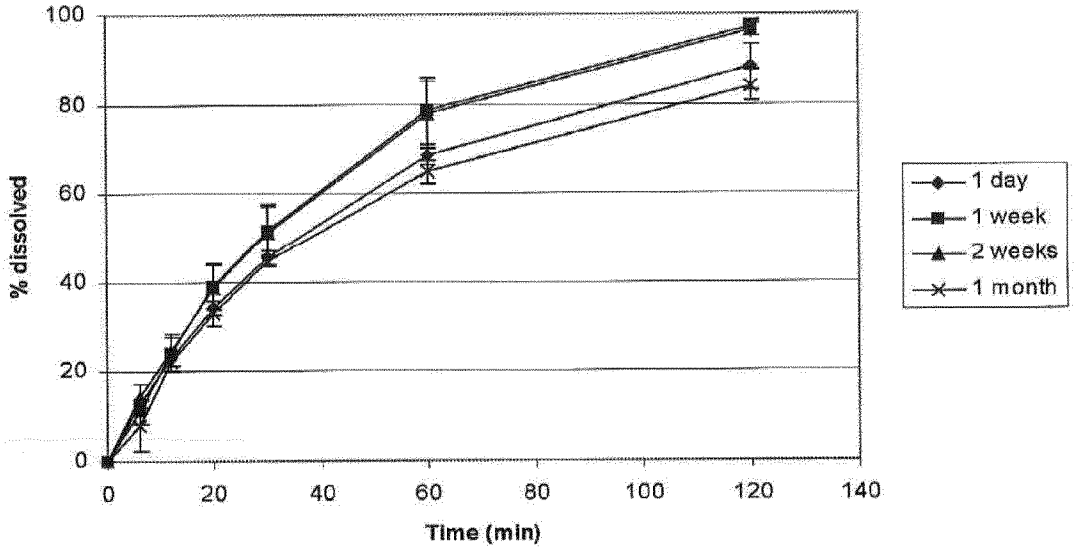


Figure 28: dissolution of amorphous Compound after storage at 25°C/93% RH

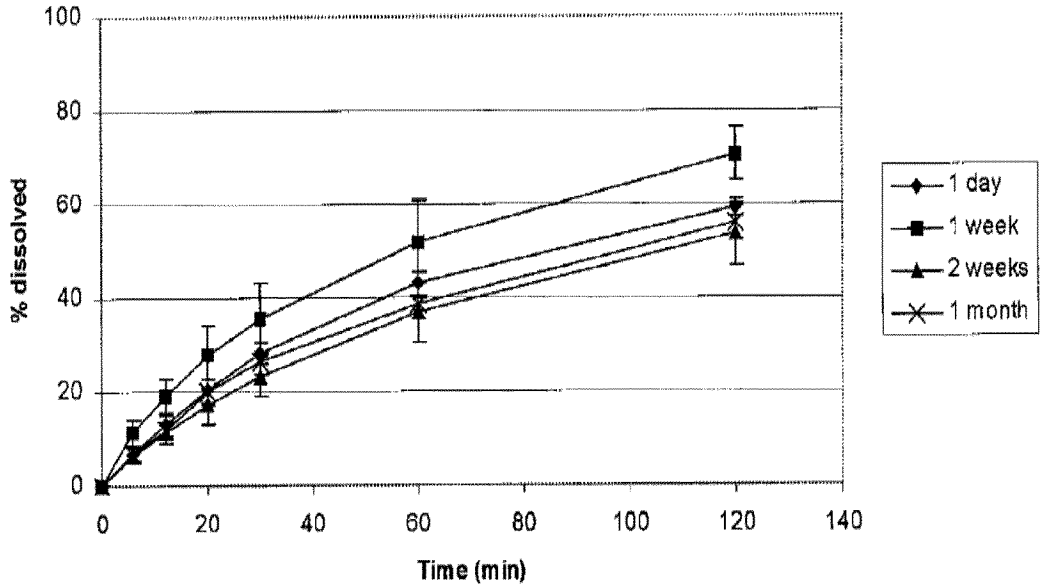


Figure 29: dissolution of Compound crystalline hydrate after storage at 40°C/93% RH

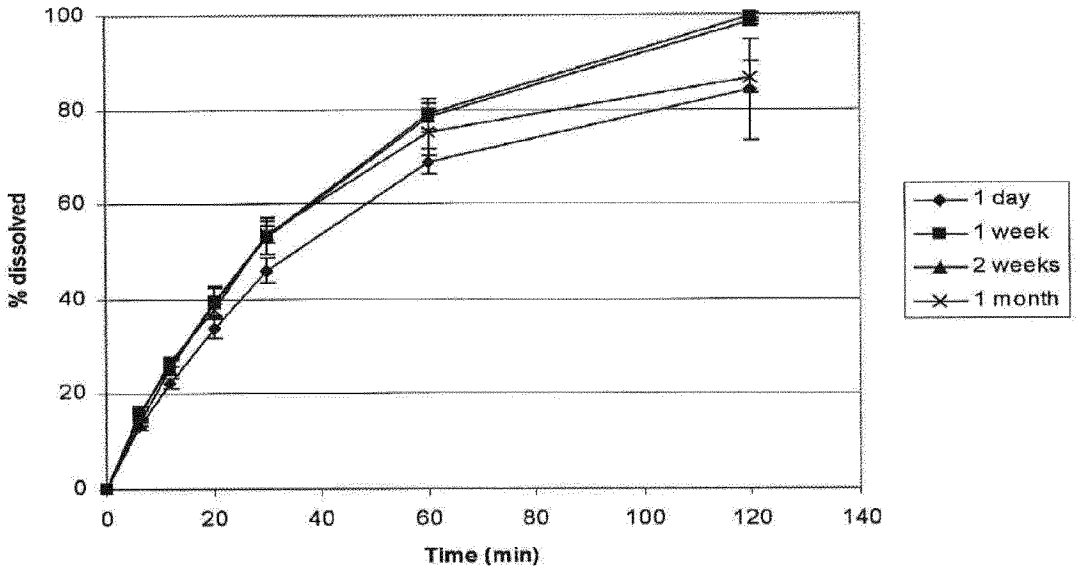
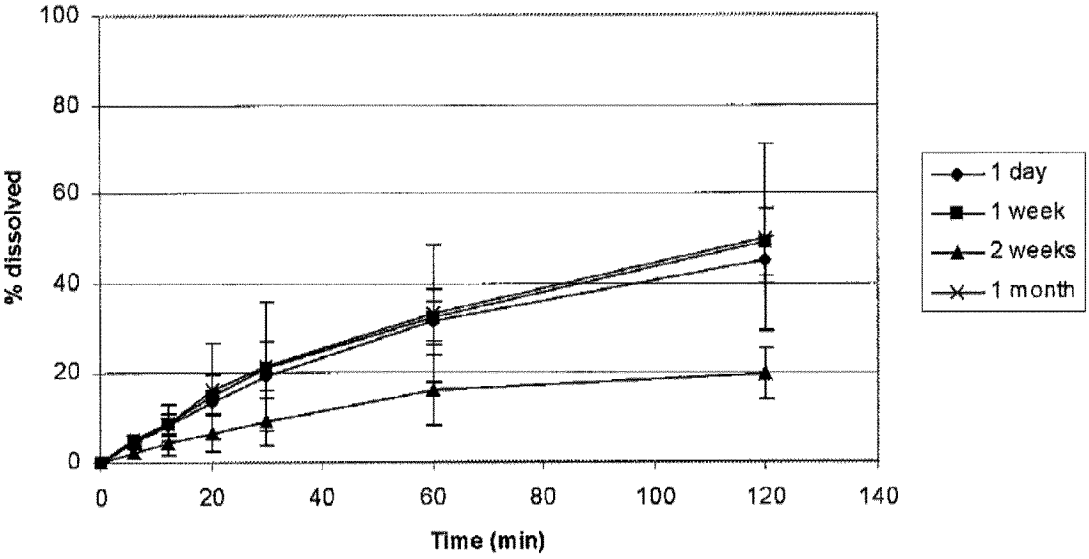


Figure 30: dissolution of amorphous Compound after storage at 40°C/93% RH



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