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(71) Applicant: ZAKLADY FARMACEUTYCZNE POLPHARMA SA [PL/PL]; Ul. Pelpinska 19, Starogard, 83-200 Gdansk (PL).

(72) Inventors: ORACZ, Monika; ul. Kotarbinkiego, 40, 97-360 Kamienik (PL). GARCZAREK, Piotr; Os Podzamcze sektor C 16/7, 48-300 Nysa (PL). SKOCZEN, Przemyslaw; ul. Jana Kasprowicza 37, 83-010 Straszyn (PL). PODWYSOCKA, Dominika; ul. Beniowskiego 5c/21, 83-000 Pruszcz Gdansk (PL). SZULC, Marcin; Os. Konstytucji 3-go Maja 22/16, 83-200 Starogard Gdansk (PL). MAJEWSKI, Arkadiusz; ul. Janusza Melssnera 10A/4, 80-462 Gdansk (PL).

(74) Agent: CHMURZYNSKI, Sedzimir; Zaklady Farmaceutyczne Polpharma S.A., Ul. Pelpinska 19, 83-200 Starogard Gdansk (PL).

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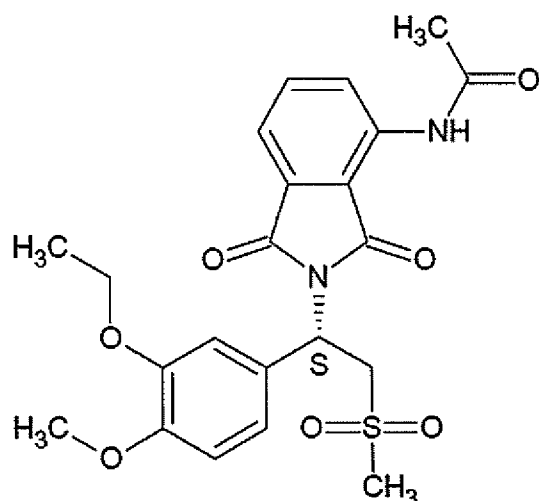
(57) Abstract: The invention particularly relates to crystalline (solid) forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1 H-isoindol-4-yl]acetamide, i.e. Form N, Form M, Form O and Form P. It also refers to a pharmaceutical composition or dosage form comprising said crystalline forms. The invention also concerns said pharmaceutical composition or dosage form for use in a method of treating a disease or disorder defined in the claims. Finally, the invention pertains to the use of said novel crystalline forms for the preparation of a pharmaceutical composition or dosage form.

CRYSTALLINE FORMS OF APREMILAST

The invention relates to novel crystalline forms of Apremilast and pharmaceutical compositions/dosage forms containing same. It also refers to processes for preparing said dosage forms and the use thereof for treating patients. Finally, the invention pertains to the use of said novel crystalline forms for the preparation of a pharmaceutical composition or dosage form.

Background art

Apremilast, i.e. N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), also referred to herein as "APM", has the following chemical formula, wherein "S", if not connected via a chemical bond in the formula, denotes the S-form of the chiral center.



[Formula 1]

Apremilast is a phosphodiesterase 4 inhibitor and blocks the action of an enzyme inside cells called phosphodiesterase 4 (PDE4). This enzyme plays a role in triggering the production of messenger molecules in the immune system called cytokines, which are involved in inflammation and other processes that cause psoriasis and psoriatic arthritis. By blocking PDE4, Apremilast reduces the level of these cytokines in the body, and so reduces the inflammation and other symptoms of psoriasis and psoriatic arthritis. Apremilast is the active ingredient of the medicament Otezla®, distributed by Celgene, Ltd, for the treatment of adults with psoriatic arthritis (inflammation of the joints associated with psoriasis) and moderate to severe plaque psoriasis (a disease causing red, scaly patches on the skin).

EP2276483 B1 discloses various polymorphic forms of Apremilast, i.e. Forms A, B, C, D, E, F and G. Regarding the characterization of these Forms A, B, C, D, E, F and G, in particular their XRPD peak locations and intensity, reference is made to EP2276483 B1. The stability, interconversion and equilibration studies in EP2276483 B1 show that most of these crystalline forms have a high tendency of interconversion, i.e. one polymorphic form converts into another polymorphic form in the presence of solvents.

Summary of the invention

The invention particularly relates to crystalline (solid) forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), i.e. Form N, Form M, Form O and Form P. It also refers to pharmaceutical compositions and dosage forms comprising said crystalline forms. The invention also concerns said pharmaceutical compositions or dosage forms for use in a method of treating a disease or disorder defined in the claims. Finally, the invention pertains to the use of said novel crystalline forms for the preparation of pharmaceutical compositions and dosage forms.

Although Form B is the commercially available form of Apremilast (Otezla®) and has quite good properties, there is a constant need for improvement of existing dosage forms.

Accordingly, one objective underlying the present invention was to improve the existing dosage forms.

List of figures

Figure 1: The figure shows the preparation of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (Apremilast, APM).

Figure 2: The figure shows the crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (APM).

Figure 3: The figure shows a representative XRPD pattern of Form N of Apremilast.

Figure 4: The figure shows a representative DSC plot of Form N of Apremilast.

Figure 5: The figure shows a representative thermogravimetric analysis (TGA) plot of Form N of Apremilast.

Figure 6: The figure shows a representative Dynamic Vapour Sorption (DVS) plot of Form N of Apremilast.

Figure 7: The figure compares the dissolution profile of Apremilast Form N that of prior art Form B.

Figure 8: The figure shows the crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (APM),
5 Form M. "EA" means ethyl acetate.

Figure 9: The figure shows a single crystal structure of Form M of Apremilast.

Figure 10: The figure shows a representative XRPD pattern of Form M of Apremilast.

Figure 11: The figure shows a representative differential scanning calorimeter (DSC) plot of Form M of Apremilast.

10 Figure 12: The figure shows a representative TGA plot of Form M of Apremilast.

Figure 13: The figure shows a representative DVS plot of Form M of Apremilast.

Figure 14: The figure shows the crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (APM) as a hemi dimethylacetamide solvate (Form O).

15 Figure 15: The figure shows a representative XRPD pattern of Form O of Apremilast.

Figure 16: The figure shows a representative DSC plot of Form O of Apremilast.

Figure 17: The figure shows a representative TGA plot of Form O of Apremilast.

Figure 18: The figure shows the crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (APM),
20 as a hemi dimethylformamide solvate (Form P). "DMF" means dimethylformamide.

Figure 19: The figure shows a representative XRPD pattern of Form P of Apremilast.

Figure 20: The figure shows a representative DSC plot of Form P of Apremilast.

Figure 21: The figure shows a representative TGA plot of Form P of Apremilast.

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Detailed description

It has unexpectedly been found that it is possible to provide new valuable polymorphic forms of Apremilast, designated Forms N, M, O and P herein. The crystalline forms described herein may have various benefits over the known crystalline forms.

In particular, it has been found that tablets comprising Form N show an improved dissolution profile as compared with tablets comprising Form B, wherein Form B is the commercially available form of Apremilast (Otezla®), see Experiment 9 and Figure 7. That is, when compared with prior art Form B, Form N exhibits a higher dissolution rate by more than 50% at 30 minutes.

- 5 The comparison with Form B is of greatest interest, since the marketed drug form represents the "gold standard" for any further pharmaceutical development. In addition, it has unexpectedly been found that Form N is a stable crystalline polymorph of Apremilast, which is non-solvated and non-hygroscopic, and has good flow characteristics.

- 10 Since EP2276483 B1 already discloses various polymorphic forms of Apremilast, it was not foreseeable, whether further polymorphic forms exist and can be prepared at all. In view of the high interconversion tendency of the known polymorphic forms, it was particularly unexpected that a new, substantially non-hygroscopic and stable (with respect to humidity) polymorph can be prepared (e.g. Form N). It is worth noting that EP2276483 B1 already describes 3 unsolvated or anhydrous crystalline forms, i.e. Forms A, B and F. Therefore, one could not have expected
- 15 that a further unsolvated, anhydrous form can be prepared, let alone a stable form. Accordingly, there was no reasonable expectation of success that the problems underlying the present invention can indeed be solved by investigating the possible existence of further stable polymorphs. Rather, a skilled person seeking to improve the existing dosage forms would have modified the composition (type and amounts of excipients) of the marketed dosage form or
- 20 would have improved the structure/type of said final drug dosage forms.

- Furthermore, unexpectedly, crystalline Form M of Apremilast has been found, which is also substantially non-hygroscopic. In particular, Form M of Apremilast has superior solubility, particularly compared to prior art Form B. Water solubility of prior art Form B according to literature findings and experimental data is about 7-12µg/ml, while water solubility of Form M is
- 25 almost 3 times greater at the same conditions, i.e. is 29µg/ml. Form B crystallizes as needle-like crystals. Needle-like crystal morphology can cause problems with filterability and flow characteristic. Form M crystallizes as prismatic crystals that have good flow characteristics and filterability and do not form aggregates.

Accordingly, the objective underlying the present invention has been solved.

- 30 The invention is further described with respect to the following items:

Items related to crystal Form N

- 5 N1. Crystalline (solid) form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isindol-4-yl]acetamide) (Form N),
having an X-ray powder diffraction pattern with peaks at 2-theta angles of 9.9 ± 0.2 degrees 2theta, 12.7 ± 0.2 degrees 2theta, 18.8 ± 0.2 degrees 2theta, 20.2 ± 0.2 degrees 2theta, 22.1 ± 0.2 degrees 2theta, 24.0 ± 0.2 degrees 2theta, and 29.4 ± 0.2 degrees 2theta when using Cu-K α radiation.
- 10 N2. The crystalline form of item N1, having a single endothermic event in a differential scanning calorimeter (DSC) plot. The applied temperature range is 25-250°C.
- 15 N3. The crystalline form of item N1 or N2, having an endothermic event in a differential scanning calorimeter plot with an onset temperature of about $139^\circ\text{C} \pm 6^\circ\text{C}$, about $139^\circ\text{C} \pm 4^\circ\text{C}$, or about $139^\circ\text{C} \pm 2^\circ\text{C}$.
- N4. The crystalline form of any of items N1-3, having an X-ray powder diffraction pattern, wherein the peak at 22.1 ± 0.2 degrees 2theta has the highest intensity (set to 100).
- 20 N5. The crystalline form of any of items N1-4, wherein the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at 18.8 ± 0.2 degrees 2theta.
- 25 N6. The crystalline form of any of items N1-5, wherein the X-ray powder diffraction pattern has further peaks at 2-theta angles of 11.7 ± 0.2 degrees 2theta, 11.9 ± 0.2 degrees 2theta, 13.7 ± 0.2 degrees 2theta, 14.4 ± 0.2 degrees 2theta, 14.6 ± 0.2 degrees 2theta, 15.3 ± 0.2 degrees 2theta, 16.7 ± 0.2 degrees 2theta, 21.4 ± 0.2 degrees 2theta, 23.0 ± 0.2 degrees 2theta, 23.7 ± 0.2 degrees 2theta, 24.8 ± 0.2 degrees 2theta, 25.6 ± 0.2 degrees 2theta, 26.8 ± 0.2 degrees 2theta, and 29.8 ± 0.2 degrees 2theta, when using Cu-K α radiation.
- 30 N7. The crystalline form of any of items N1-6, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of intensities of the peaks defined in items N1 and N6, in particular the X-ray powder diffraction pattern is

free of further peaks having an intensity which is higher than the intensity of the peak at 29.8 ± 0.2 degrees 2θ .

N8. The crystalline form of any of items N1-7, which is substantially polymorphically pure, i.e. contains less than 5 wt.-%, or less than 1 wt.-% of other crystalline, non-crystalline or amorphous forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2- (methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide.

N9. The crystalline form of any of items N1-8, which is substantially pure, i.e. contains less than 1 area-%, or less than 0.5 area-%, preferably less than 0.1 area-%, of compounds other than N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2- (methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) as determined by quantitative ^{13}C NMR measurement or high performance liquid chromatography (HPLC).

N10. The crystalline form of any of items N1-9, which is unsolvated, preferably has a solvent content of less than 1 wt.-%, or less than 0.5 wt.-%, preferably less than 0.2 wt.-%, or even less than 0.15 wt.-%, wherein the solvent content is determined by gaschromatographic (GC) analysis and the water content is determined by the method according to Karl Fischer. Form N is free of any solvent including water.

N11. The crystalline form of any of items N1-10, having a mass loss of less than 0.5% of the total mass of the sample in a thermogravimetric analysis (TGA) upon heating from 25°C to 250°C with the gradient of $7^\circ\text{C}/\text{min}$.

N13. The crystalline form of any of items N1-12, having an X-ray powder diffraction pattern with peaks and/or intensities as shown in Table 5 (below) or Figure 3.

N14. The crystalline form of any of items N1-13, wherein the peaks recited in item N1 and/or item N6 have intensities as shown in the following Table 1:

2-theta(deg)	Rel. int. I(a.u.)	Preferred intensities
		Rel. int. I(a.u.)
9.9	7-20	12.95
10.34	2-13	6.93
10.8	1-8	1.53
11.7	20-35	26.45

11.9	9-20	13.80
12.7	20-32	25.49
13.7	20-32	25.29
14.4	11-21	15.85
14.6	8-20	14.71
15.3	10-22	16.73
16.1	1-7	1.93
16.7	15-27	20.64
16.9	2-12	6.38
18.1	2-12	6.84
18.8	25-40	31.17
20.2	20-38	27.84
20.6	2-12	6.89
21.4	5-16	10.52
22.1	100	100.00
23.0	10-22	15.78
23.7	9-21	14.79
24.0	30-55	43.66
24.8	8-20	14.19
25.6	17-36	25.33
26.2	1-10	5.25
26.8	10-23	17.14
28.1	4-16	9.92
29.4	10-28	17.25
29.8	4-17	10.04
31.4	1-14	6.44
32.3	1-12	7.26

Items related to Form M

- 5 M1. Crystalline (solid) form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (Form M), containing 0.3-0.7 moles of ethyl acetate per of mole N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide),
- 10 having an X-ray powder diffraction pattern with peaks at 2-theta angles of 7.5 ± 0.2 degrees 2theta, 9.1 ± 0.2 degrees 2theta, 11.3 ± 0.2 degrees 2theta, 12.0 ± 0.2 degrees 2theta, 16.4 ± 0.2 degrees 2theta, 17.7 ± 0.2 degrees 2theta, 19.3 ± 0.2 degrees 2theta, 21.4 ± 0.2 degrees 2theta, 22.5 ± 0.2 degrees 2theta, 24.7 ± 0.2 degrees 2theta, 25.4 ± 0.2 degrees 2theta, 26.3 ± 0.2 degrees 2theta, 27.5 ± 0.2 degrees 2theta, and 34.3 ± 0.2 degrees 2theta, when using Cu-K α radiation.
- 15

The solvent molecules, i.e. ethyl acetate, are contained in the crystal lattice.

- M2. The crystalline form of item M1, having a single endothermic event in a differential scanning calorimeter (DSC) plot. The applied temperature range is 25-250°C.
- M3. The crystalline form of item M1 or M2, having an endothermic event in a differential scanning calorimeter plot with an onset temperature of about 103°C±6°C, about 103°C±4°C, or about 103°C±2°C.
- M4. The crystalline form of any of items M1-3, having an X-ray powder diffraction pattern, wherein the peaks at 2-theta angles of 7.5±0.2 degrees 2theta, 11.3±0.2 degrees 2theta, 16.4±0.2 degrees 2theta, 17.7±0.2 degrees 2theta, 19.3±0.2 degrees 2theta, 21.4±0.2 degrees 2theta, 22.5±0.2 degrees 2theta, 24.7±0.2 degrees 2theta, 25.4±0.2 degrees 2theta, 26.3±0.2 degrees 2theta, and 27.5±0.2 degrees 2theta represent the peaks with highest intensity, and/or wherein the peak at 26.3±0.2 degrees 2theta has the highest intensity (set to 100).
- M5. The crystalline form of any of items M1-4, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of the intensities of the peaks defined in item M4, in particular the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at 27.5±0.2 degrees 2theta.
- M6. The crystalline form of any of items M1-5, wherein the X-ray powder diffraction pattern has further peaks at 2-theta angles of 14.0±0.2 degrees 2theta, 15.2±0.2 degrees 2theta, 15.3±0.2 degrees 2theta, 20.2±0.2 degrees 2theta, 20.7±0.2 degrees 2theta, 22.8±0.2 degrees 2theta, 23.2±0.2 degrees 2theta, 23.4±0.2 degrees 2theta, and 29.0±0.2 degrees 2theta, when using Cu-Kα radiation.
- M7. The crystalline form of any of items M1-6, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of the intensities of the peaks defined in items M1 and M6, in particular the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at 22.8 degrees 2theta.
- M8. The crystalline form of any of items M1-7, which is substantially polymorphically pure, i.e. contains less than 5 wt.-%, or less than 1 wt.-% of other crystalline, non-crystalline or

amorphous forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide.

M9. The crystalline form of any of items M1-8, which is substantially pure, i.e. contains less than 1 area-%, or less than 0.5 area-%, preferably less than 0.1 area-%, of compounds other than N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) as determined by quantitative ^{13}C NMR measurement or high performance liquid chromatography (HPLC).

M10. The crystalline form of any of items M1-9, which is an ethyl acetate solvate, preferably containing 0.4-0.6 moles of ethyl acetate per mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), preferably it is a hemi-ethyl acetate solvate, i.e. N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) $\cdot$ 0.5 $\text{C}_4\text{H}_8\text{O}_2$.

M11. The crystalline form of any of items M1-10, having a mass loss of more than 8%, e.g. about 8.5%, of the total mass of the sample, corresponding to a loss of ethyl acetate, in a thermogravimetric analysis (TGA) upon heating from 25°C to 220°C with the gradient of 7°C/min.

M12. The crystalline form of any of items M1-11, having a mass change of less than 0.8%, less than 0.5%, or less than 0.2% of the total mass of the sample in a moisture sorption analysis from close to 0% relative humidity to 90% relative humidity.

M14. The crystalline form of any of items M1-13, having an X-ray powder diffraction pattern with peaks and/or intensities as shown in Table 6 (below) or Figure 10.

M15. The crystalline form of any of items M1-14, wherein the peaks recited in item M1 and/or item M6 have intensities as shown in the following Table 2:

2-theta(deg)	Rel. Int. I(a.u.)	Preferred intensities
		Rel. Int. I(a.u.)
7.5	50-75	64.05
9.1	8-22	14.28
9.7	1-12	5.10

11.3	30-55	46.19
12.0	8-20	12.88
14.0	10-27	18.37
15.2	10-22	15.09
15.3	5-16	10.72
16.4	30-55	45.72
17.7	55-90	70.79
19.3	25-40	32.37
20.2	14-28	19.62
20.7	8-22	14.84
21.4	25-45	34.11
22.5	24-43	32.68
22.8	5-16	10.32
23.2	10-22	15.25
23.4	15-32	22.12
24.7	25-45	34.29
25.4	23-43	32.30
26.3	100	100.00
27.5	23-40	30.53
29.0	15-30	20.37
29.7	2-14	7.97
30.5	1-12	4.70
34.3	8-20	14.62

Items related to Form O

O1. Crystalline (solid) form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (Form O), containing 0.3-0.7 moles of dimethylacetamide per mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) and

having an X-ray powder diffraction pattern with peaks at 2-theta angles of 7.5 ± 0.2 degrees 2theta, 11.2 ± 0.2 degrees 2theta, 15.3 ± 0.2 degrees 2theta, 16.4 ± 0.2 degrees 2theta, 17.7 ± 0.2 degrees 2theta, 21.4 ± 0.2 degrees 2theta, 22.5 ± 0.2 degrees 2theta, 23.5 ± 0.2 degrees 2theta, 24.8 ± 0.2 degrees 2theta, 25.5 ± 0.2 degrees 2theta, 26.4 ± 0.2 degrees 2theta, and 27.5 ± 0.2 degrees 2theta, when using Cu-K α radiation.

The solvent molecules, i.e. dimethylacetamide, are contained in the crystal lattice.

O2. The crystalline form of item O1, having a single endothermic event in a differential scanning calorimeter (DSC) plot. The applied temperature range is 25-250°C.

- O3. The crystalline form of item O1 or O2, having an endothermic event in a differential scanning calorimeter plot with an onset temperature of about $124^{\circ}\text{C}\pm 6^{\circ}\text{C}$, about $124^{\circ}\text{C}\pm 4^{\circ}\text{C}$, or about $124^{\circ}\text{C}\pm 2^{\circ}\text{C}$.
- 5 O4. The crystalline form of any of items O1-3, having an X-ray powder diffraction pattern, wherein the peaks recited in item O1 represent the peaks with highest intensity, and/or wherein the peak at 26.4 ± 0.2 degrees 2theta has the highest intensity (set to 100).
- 10 O5. The crystalline form of any of items O1-4, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of the intensities of the peaks defined in item O1, in particular the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at 21.4 ± 0.2 degrees 2theta.
- 15 O6. The crystalline form of any of items O1-5, wherein the X-ray powder diffraction pattern has further peaks at 2-theta angles of 9.1 ± 0.2 degrees 2theta, 11.9 ± 0.2 degrees 2theta, 13.8 ± 0.2 degrees 2theta, 14.0 ± 0.2 degrees 2theta, 19.4 ± 0.2 degrees 2theta, 20.3 ± 0.2 degrees 2theta, and 29.8 ± 0.2 degrees 2theta, when using Cu-K α radiation.
- 20 O7. The crystalline form of any of items O1-6, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of the intensities of the peaks defined in items O1 and O6, in particular the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at 14.0 ± 0.2 degrees 2theta.
- 25 O8. The crystalline form of any of items O1-7, which is substantially polymorphically pure, i.e. contains less than 5 wt.-% or less than 1 wt.-% of other crystalline, non-crystalline, or amorphous forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2- (methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide.
- 30 O9. The crystalline form of any of items O1-8, which is substantially pure, i.e. contains less than 1 area-%, or less than 0.5 area-%, preferably less than 0.1 area-%, of compounds other than N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2- (methylsulfonyl)ethyl]-1,3-dioxo-

2,3-dihydro-1H-isoindol-4-yl]acetamide) and dimethylacetamide as determined by quantitative ^{13}C NMR measurement or high performance liquid chromatography (HPLC).

O10. The crystalline form of any of items O1-9, which is a dimethylacetamide (DMA) solvate, preferably containing 0.4-0.6 moles of dimethylacetamide per mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), further preferred comprising about 0.5 of molar equivalents of DMA, e.g. the crystalline form is N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) · 0.5 $\text{C}_4\text{H}_9\text{NO}$.

O11. The crystalline form of any of items O1-10, having a mass loss of more than 7%, e.g. about 7.8%, which corresponds to the loss of dimethylacetamide as confirmed by gaschromatographic analysis, of the total mass of the sample in a thermogravimetric analysis (TGA) upon heating from 25°C to 220°C with the gradient of 7°C/min.

O12. The crystalline form of any of items O1-11, which does not contain any amorphous form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide).

O13. The crystalline form of any of items O1-12, wherein the peaks recited in item O1 and/or item O6 have intensities as shown in the following Table 3:

2-theta(deg)	Rel. int. I(a.u.)	Preferred intensities Rel. int. I(a.u.)
7.5	40-70	56.54
9.1	4-18	11.02
9.7	2-16	9.57
10.1	1-9	3.10
11.2	30-60	45.57
11.9	5-22	12.37
13.2	1-12	5.17
13.8	5-22	11.97
14.0	5-22	10.67
15.3	25-50	35.90
16.4	35-60	44.85
17.7	70-95	87.42
19.2	2-16	9.21
19.4	15-28	20.61
20.3	10-23	16.88
20.8	1-12	5.83

21.4	15-35	24.81
22.5	22-45	33.63
22.8	2-16	8.80
23.5	22-40	29.97
23.9	1-9	3.30
24.8	27-50	38.26
25.5	20-37	25.94
26.4	100	100.00
27.5	25-50	34.55
28.5	1-12	5.62
29.0	15-30	21.83
29.8	2-16	9.96

O14. The crystalline form of any of items O1-13, having an X-ray powder diffraction pattern with peaks and/or intensities as shown in Table 12 or Figure 15.

5

Items related to Form P

P1. Crystalline (solid) form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (Form P),
 10 containing 0.1-1.0 moles of dimethylformamide per mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) and
 having an X-ray powder diffraction pattern with peaks at 2-theta angles of 7.4 ± 0.2 degrees 2theta, 11.2 ± 0.2 degrees 2theta, 15.3 ± 0.2 degrees 2theta, 16.3 ± 0.2 degrees
 15 2theta, 17.7 ± 0.2 degrees 2theta, 19.3 ± 0.2 degrees 2theta, 20.3 ± 0.2 degrees 2theta, 21.3 ± 0.2 degrees 2theta, 22.5 ± 0.2 degrees 2theta, 23.5 ± 0.2 degrees 2theta, 24.7 ± 0.2 degrees 2theta, 25.5 ± 0.2 degrees 2theta, 26.3 ± 0.2 degrees 2theta, 27.3 ± 0.2 degrees 2theta, 27.5 ± 0.2 degrees 2theta, and 28.9 ± 0.2 degrees 2theta, when using Cu-K α radiation.

20 The solvent molecules, i.e. dimethylformamide, are contained in the crystal lattice.

P2. The crystalline form of item P1, having a single endothermic event in a differential scanning calorimeter (DSC) plot. The applied temperature range is 25-250°C.

25 P3. The crystalline form of item P1 or P2, having an endothermic event in a differential scanning calorimeter plot with an onset temperature of about $94^\circ\text{C} \pm 6^\circ\text{C}$, about $94^\circ\text{C} \pm 4^\circ\text{C}$, or about $94^\circ\text{C} \pm 2^\circ\text{C}$.

- P4. The crystalline form of any of items P1-3, having an X-ray powder diffraction pattern, wherein the peaks recited in item P1 represent the peaks with highest intensity, and/or wherein the peak at 26.3 ± 0.2 degrees 2theta has the highest intensity (set to 100).
- 5
- P5. The crystalline form of any of items P1-4, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of the intensities of the peaks defined in item P1, in particular the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at
- 10 15.3 ± 0.2 degrees 2theta.
- P6. The crystalline form of any of items P1-5, wherein the X-ray powder diffraction pattern has further peaks at 2-theta angles of 9.0 ± 0.2 degrees 2theta, 11.8 ± 0.2 degrees 2theta, 14.0 ± 0.2 degrees 2theta, 19.0 ± 0.2 degrees 2theta, 20.8 ± 0.2 degrees 2theta, and
- 15 23.7 ± 0.2 degrees 2theta, when using Cu-K α radiation.
- P7. The crystalline form of any of items P1-6, wherein said X-ray powder diffraction pattern is free of further peaks which have an intensity which is in the range of the intensities of the peaks defined in items P1 and P6, in particular the X-ray powder diffraction pattern is
- 20 free of further peaks having an intensity which is higher than the intensity of the peak at 19.0 ± 0.2 degrees 2theta.
- P8. The crystalline form of any of items P1-7, which is substantially polymorphically pure, i.e. contains less than 5 wt.-% or less than 1 wt.-% of other crystalline, non-crystalline or
- 25 amorphous forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2- (methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide.
- P9. The crystalline form of any of items P1-8, which is substantially pure, i.e. contains less than 1 area-%, or less than 0.5 area-%, preferably less than or 0.1 area-%, of compounds other than N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-
- 30 (methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) and dimethylformamide as determined by quantitative ^{13}C NMR measurement or high performance liquid chromatography (HPLC).

- P10. The crystalline form of any of items P1-9, which is a dimethylformamide (DMF) solvate, which preferably comprises 0.7 or less; further preferred 0.4-0.6 moles of DMF per mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), e.g. the crystalline form is N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) · 0.5 C₃H₇NO.
- P11. The crystalline form of any of items P1-10, having a mass loss of more than 7%, e.g. about 7.4%, which corresponds to the loss of dimethylformamide as confirmed by gaschromatographic analysis, of the total mass of the sample in a thermogravimetric analysis (TGA) upon heating from 25°C to 220°C with the gradient of 7°C/min.
- P12. The crystalline form of any of items P1-11, which does not contain any amorphous form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide).
- P13. The crystalline form of any of items P1-12, having an X-ray powder diffraction pattern with peaks and/or intensities as shown in Table 13 or Figure 19.
- P14. The crystalline form of any of items P1-13, wherein the peaks recited in item P1 and/or item P6 have intensities as shown in the following Table 4:

2-theta(deg)	Rel. int. I(a.u.)	Preferred intensities
		Rel. int. I(a.u.)
7.4	40-70	54.31
9.0	5-22	13.80
9.7	1-14	4.28
11.2	40-70	51.06
11.8	5-22	14.59
13.1	2-12	6.81
13.7	2-12	8.46
14.0	10-28	19.62
15.3	20-40	31.07
16.3	20-50	39.11
17.7	65-95	83.78
18.1	1-14	4.14
19.0	5-20	10.30
19.3	18-40	28.62
20.3	15-32	21.45
20.8	5-22	10.15

21.3	25-50	38.78
22.5	25-50	37.15
22.7	2-16	8.84
22.9	2-12	4.65
23.5	25-50	41.81
23.7	6-22	12.41
24.7	25-50	41.49
25.5	20-40	31.97
26.3	100	100.00
27.3	15-35	22.14
27.5	15-35	21.75
28.9	15-35	23.03

Items related to all crystalline Forms N, M, O and P

- 5 1. Pharmaceutical composition or dosage form comprising a crystalline form of any of items N1-N14, M1-M15, O1-O14 and P1-P14, preferably any of items N1-N14 and M1-M15, most preferably any of items N1-N14, or a mixture of any of the aforementioned crystalline forms.
- 10 2. The pharmaceutical dosage form of item 1, wherein the pharmaceutical dosage form is a solid oral dosage form, preferably a tablet.
3. The pharmaceutical composition or dosage form of item 1 or 2, which comprises at least one pharmaceutically acceptable excipient.
- 15 4. Pharmaceutical composition or dosage form of any of items 1-3, particularly preferred dosage forms/compositions with Form N or Form M, most preferably with Form N, for use in a method of treating a disease or disorder selected from the group consisting of: psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex aphthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymyositis; dermatomyositis; inclusion body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.
- 20 5. Pharmaceutical composition or dosage form of any of items 1-3, particularly preferred dosage forms/compositions with Form N or Form M, most preferably with Form N, for
- 25

use in a method of treating or preventing a disease or disorder selected from the group consisting of: HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic re perfusion injury; meningitis; psoriasis; psoriatic arthritis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury. Preferably, the pharmaceutical compositions or dosage forms described herein are used for treating psoriatic arthritis or plaque psoriasis.

6. Use of a crystalline form of any of items N1-N14, M1-M15, O1-O14 and P1-P14 or a mixture of said crystalline forms for the preparation of a pharmaceutical composition or dosage form.
7. The use of item 6, wherein the crystalline form is Form N, which is used as the starting material for preparing an oral solid pharmaceutical dosage form comprising Form N.
8. Process for preparing an oral solid pharmaceutical dosage form of any of items 1-3, comprising a step of compressing (i) a mixture of Form N with one or more pharmaceutical acceptable excipients (e.g. by applying direct compression techniques), or (ii) granules including Form N, optionally in admixture with one or more excipients, in order to provide a tablet. The granules can e.g. be prepared by dry granulation such as (roller) compaction, or slugging.

By way of example, the dosage form can be prepared by using a process comprising or consisting of the following steps:

- (i) Pass Apremilast, e.g. Form N, and one or more pharmaceutically acceptable excipients, preferably one or more (further preferred all) of lactose monohydrate, microcrystalline cellulose, and croscarmellose sodium through a sieve, e.g. a 0.425 mm sieve;
- (ii) Mix the ingredients from step (i), e.g. in a blender, e.g. for 15 min at 25 RPM;

- (iii) Optionally, add a lubricant, e.g. magnesium stearate, and mix for e.g. 5 min at 12 RPM; and
- (iv) Compress the blend of step (iii) using e.g. a single punch machine equipped with oval punch (14x8mm), e.g. at a compression force of 7 kN, in order to prepare a tablet.

5

9. Process for preparing an oral solid pharmaceutical dosage form comprising an amorphous form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), wherein the process comprises a step of dissolving a crystalline form of APM as described herein, preferably Form M, and optionally one or more pharmaceutically acceptable excipients, in a solvent or mixture of solvents, preferably in acetone, and (i) spraying the resulting solution onto pharmaceutical acceptable excipients, e.g. particles, granules, or a tablet core, or (ii) spray drying the resulting solution, while performing a drying step during and/or after the spraying step. The spraying and drying process provides an amorphous form of Apremilast.

15

By way of example, the dosage form can be prepared by using a process comprising or consisting of the following steps:

- i) Dissolve Apremilast (Form M) in a solvent, preferably acetone;
- 20 ii) Pass one or more pharmaceutically acceptable excipient(s), preferably one or more (further preferred all) of lactose monohydrate, microcrystalline cellulose, croscarmellose sodium through a sieve, e.g. a 0.425 mm sieve;
- iii) Place the ingredients from step (ii) in a fluid bed granulator (e.g. equipped with top spray nozzle) and granulate it by spraying the solution from step (i);
- 25 iv) Dry the obtained granulate;
- v) Add a lubricant, e.g. magnesium stearate, and mix for e.g. 5 min at 12 RPM; and
- vi) Optionally compress the blend from step (v), e.g. by using a single punch machine equipped with oval punch (14x8mm) at a compression force of 7 kN, in order to prepare a tablet. The blend of step (v) can also be used as is, e.g. can be filled in sachets.

30

10. Use of a crystalline form of any of items N1-N14, M1-M15, O1-O14 and P1-P14, preferably the crystalline Form N of items N1-N14, as a starting material for preparing an oral solid pharmaceutical dosage form comprising said crystalline form or a different crystalline or an amorphous form.

35

11. Method of treating a patient by administering an effective amount of any of the crystalline Forms M, N, O or P, or a pharmaceutical composition or dosage form disclosed herein.

Definitions:

- 5 Within the meaning of the present invention, the term "solvent" refers to any solvent such as water and organic or inorganic solvents.

The term "room temperature" as used herein is understood to mean temperatures of about 15 °C to about 25 °C.

- 10 Herein, the X-ray powder diffraction peaks of the crystalline Apremilast forms are described by their 2theta angles with a tolerance of " ± 0.2 ". In the context of the present invention, it is also possible to use a smaller tolerance of " ± 0.1 " or even " ± 0.0 ".

Herein, Forms M and N are preferred, wherein Form N is most preferred.

- 15 Regarding the synthesis of Apremilast, reference is made to Example 1 herein, as well as to EP2276483 B1 and US 6,962,940. Apremilast as the starting material for crystallizing any of Forms N, M, O and P of the present invention can be prepared by using any method.

Measuring instruments, conditions and protocols:

UPLC

- 20 Purity and assay analysis were carried out using Ultra Performance Liquid Chromatograph Waters Acquity I-Class equipped with PDA detector. The analysis were conducted using Waters Acquity UPLC BEH C18 1.7 μ m, 2.1x100 mm column, at a temperature of 60°C. The mobile phases were acetonitrile and 0.1%(v/v) ortho-phosphoric acid in water used in gradient.

GC

- 25 Determination of residual solvents were carried out using Perkin Elmer Clarus 680 Gas Chromatograph with flame-ionization detector (FID) with carrier gas split, equipped with TurboMatrix 110 Trap a headspace autosampler. The capillary column 60 m x 0.32mm ID x 1.8 μ m and stationary phase (6%)-cyanopropyl-phenyl-(94%)-dimethylsiloxane DB-624 Agilent Technologies at the temperature gradient were used.

30

KE

Water content in samples of Apremilast were determined using Mettler Toledo V30 Karl Fisher Titrator. The analysis were carried out using acetonitrile:methanol (50:50) solution and the Combi Titrant 2 Merck titrant.

5

XRPD

The analysis of the crystals by X-Ray diffraction was performed using X-ray Diffractometer Rigaku MiniFlex 600 in Bragg-Brentano geometry Cu K α radiation, D/teX Ultra Detector in a range of 3-36° of 2 θ angle. The wavelength of the Cu-K α radiation used herein is $\lambda=1.5406$ Angstrom. The patterns were recorded at a tube voltage of 40 kV, tube current of 15 mA, applying a step size of 0.013° 2° with 80s per step.

10

DSC

DSC analysis were carried out using DSC 1 Mettler Toledo Stare thermal analysis system at the temperature range of 25-250°C with the gradient of 5°C/min. Melting, aluminum crucible with the capacity of 40 μ l were used. Nitrogen was used as carried gas with the flow of 50ml/min.

15

TGA

TGA analysis were carried out using TGA/SDTA85 Mettler Toledo Stare thermal analysis system at the temperature range of 25-220°C with the gradient of 7°C/min. Melting, aluminum crucible with the capacity of 100 μ l were used. Nitrogen was used as carried gas with the flow of 50ml/min.

20

DVS

Water Vapour Sorption isotherms were obtained using a Dynamic Vapour Sorption apparatus (model: DVS - Advantage, supplier: Surface Measurement Systems Limited). The DVS apparatus consists of an ultra-microbalance housed inside a temperature-controlled cabinet. The sample was placed into a DVS sample pan under a stream of nitrogen (200 sccm) at 25°C. The humidity was increased ramping in 10% RH (relative humidity) steps from close to 0% RH to 90% RH (sorption phase). Next the humidity was decreased in a similar fashion for the desorption phase. The sample was held at each RH step for mass stabilization (dm/dt 0.02 %/min) but not less than 10 minutes. Two cycles of sorption and desorption were investigated.

25

30

Dissolution studies

Dissolution studies were performed using a Hanson SR8PLUS dissolution apparatus, according to European Pharmacopoeia apparatus, paddle method. The samples were tested in 900mL pH 6.8 with 0.3% SLS at 37.0°C +/- 0.5°C and the paddle rotation speed was set at 75 rpm. Dissolution study was conducted for 60min and samples were analyzed using HPLC method.

Stability test

A test for stability against humidity can be performed as follows: The sample is exposed to a relative humidity of 75% (+/- 5%) at 50°C (+/- 2°C) for 2 weeks. The expression "polymorphically stable" means that no conversion to another crystalline form occurs, as determined by XRPD.

The equilibrium relative humidity of a sample is measured by determining the relative humidity in % in the air above a test sample, after establishment of a humidity equilibrium in a closed/open system at a constant temperature.

The step of formulating the crystalline forms into a dosage form may be carried out by applying techniques known in the art, in particular as described herein. For example, the crystalline forms can be formulated into tablets by using direct compression, granulation processes, and spraying processes as described above. Examples are also given in the experimental part herein.

Exemplary pharmaceutically acceptable excipients which can be contemplated for use in the present invention are described in the following:

Binding agents are excipients which increase the adhesion of the active agents and excipients during granulation. Examples of binding agents are: sugars, such as sorbitol, glucose, fructose, disaccharides as saccharose, polysaccharides; acacia gum; cellulose derivatives, such as soluble celluloses like microcrystalline cellulose, methylcellulose, hydroxypropylmethylcellulose and hydroxypropylcellulose; tragacanth; polyvinylpyrrolidone, such as polyvinylpyrrolidone-vinyl acetate copolymer, or N-vinylpyrrolidone; sodium alginate and alginate derivatives and gelatin.

Disintegrants are excipients which can take up water and swell and thus improve disintegration of a tablet or granules. Examples of disintegrants are: croscarmellose sodium; starch (paste and pre-gelatinized), such as sodium starch glycolate, methacrylic acid polymer with divinylbenzene, potassium salt, Maltodextrin; croscarmellose sodium and low substituted hydroxypropylcellulose and croscopovidone.

Lubricants are excipients which reduce the friction between excipients and compression tooling surfaces. Examples of lubricants are magnesium stearate, magnesium fumarate, fumaric-acid, talc, stearic acid and sodium stearyl fumarate.

5 Fillers are excipients which increase the volume of e.g. tablets. Examples of fillers are mannitol, celluloses such as microcrystalline cellulose, synthetic polymers, Ca-phosphate, inorganic calcium salts, maize starch, polyols and pregelatinized starch.

10 A polymer, or a plurality of polymers may be used for coating tablets, including for example cellulose derivatives, e.g. hydroxypropylmethylcellulose, polyvinylpyrrolidones, polyethyleneglycols, polyvinylalcohols, acrylates, such as polymethacrylate, cyclodextrins and copolymers and derivatives thereof, including for example polyvinylpyrrolidone-vinylacetate. In some preferred embodiments the polymer or the plurality of polymers are pH dependent enteric polymers. Such polymers include cellulose derivatives, e.g. cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalates, hydroxypropyl methyl acetate succinate, hydroxypropyl methyl cellulose acetate, carboxymethylcellulose or a salt thereof, e.g. the sodium
15 salt, cellulose acetate trimellitate, hydroxypropylcellulose acetate phthalate, or polymethylacrylates, e.g. Eudragit®S.

Surfactants include but are not limited to, sorbitan fatty esters, polyoxyethylene sorbit esters, sodium laurylsulfate, sodium docedylbenzenesulfate, dioctyl sodium sulfosuccinate, sodium stearate, EDTA or vitamin E or tocol derivatives.

20 Most preferred for preparing pharmaceutical compositions/dosage forms is the use of one or more, preferably all, of lactose monohydrate, microcrystalline cellulose, magnesium stearate and croscarmellose sodium.

Other excipients are known in the art and can be chosen by a skilled person depending on their function.

25 Characterization of unsolvated Form N of Apremilast

The preparation of Form N is described in Example 1. Crystalline Form N of Apremilast can be characterized as already described above. It has an X-ray powder diffraction pattern as depicted in Figure 3 and as listed in Table 5 below, which shows the peak positions and their
30 intensities.

Table 5.

No.	2-theta(deg)	Rel. int. I(a.u.)
1	9.9	12.95
2	10.34	6.93
3	10.8	1.53
4	11.7	26.45
5	11.9	13.80
6	12.7	25.49
7	13.7	25.29
8	14.4	15.85
9	14.6	14.71
10	15.3	16.73
11	16.1	1.93
12	16.7	20.64
13	16.9	6.38
14	18.1	6.84
15	18.8	31.17
16	20.2	27.84
17	20.6	6.89
18	21.4	10.52
19	22.1	100.00
20	23.0	15.78
21	23.7	14.79
22	24.0	43.66
23	24.8	14.19
24	25.6	25.33
25	26.2	5.25
26	26.8	17.14
27	28.1	9.92
28	29.4	17.25
29	29.8	10.04
30	31.4	6.44
31	32.3	7.26

Form N of Apremilast may also (further) be characterized by thermal analysis. A representative DSC plot for Form N of Apremilast is shown in Figure 4. The DSC plot of Form N comprises an endothermic event with an onset temperature of about 139°C, e.g. about 139°C±2°C.

A representative TGA plot for Form N of Apremilast is shown in Figure 5. The TGA plot of Form N shows a mass loss of less than about 0.5%, e.g., less than 0.1%, of the total mass of the sample upon heating from about 25°C to about 220°C. Form N of Apremilast does not contain substantial amounts of either water or other solvent (confirmed by GC analysis, solvent content below 0.15%) in the crystal lattice, meaning that is at least substantially or completely unsolvated, in particular anhydrous.

Form N of Apremilast may be characterized by moisture sorption analysis. A representative moisture sorption isotherm plot is shown in Figure 6. When RH is increased from about 0% to about 95% RH, it exhibits a mass change of less than about 0.2%, e.g., about 0.14%, of the starting amount at about 0% RH. Form N is substantially non-hygroscopic and stable with respect to humidity.

Crystalline Form N of Apremilast can be characterized by having a dissolution profile as shown in Figure 7.

Characterization of Form M (containing ethyl acetate solvent molecules) of Apremilast

The preparation of Form M is described in Example 2 (see also Figure 8). Form M can be characterized by Single Crystal X-ray Crystallography Method. Figure 9 shows an X-ray structure for Form M of Apremilast with the numbering scheme being used. Solvated Form M of Apremilast with ethyl acetate crystallizes in the tetragonal crystal system, in the P41212 space group. The asymmetric unit cell consists of one molecule of Apremilast and 0.5 molecule of ethyl acetate. Crystallographic data with unit cell parameters, atomic coordinates, equivalent isotropic temperature parameters for non-hydrogen atoms, bond lengths and angles are listed in the below tables.

The crystalline Form M of Apremilast can be characterized as described above and has an X-ray powder diffraction pattern as depicted in Figure 10 and below Table 6.

Table 6.

No.	2-theta(deg)	Rel. int. I(a.u.)
1	7.5	64.05
2	9.1	14.28
3	9.7	5.10
5	11.3	46.19
6	12.0	12.88
7	14.0	18.37
8	15.2	15.09
9	15.3	10.72
10	16.4	45.72
11	17.7	70.79
12	19.3	32.37
13	20.2	19.62
14	20.7	14.84
15	21.4	34.11
16	22.5	32.68
17	22.8	10.32
18	23.2	15.25

19	23.4	22.12
20	24.7	34.29
21	25.4	32.30
22	26.3	100.00
23	27.5	30.53
24	29.0	20.37
25	29.7	7.97
26	30.5	4.70
27	34.3	14.62

Form M of Apremilast may be also (further) characterized by thermal analysis. A representative DSC plot for Form M of Apremilast is shown in Figure 11. The DSC plot of Form M comprises an endothermic event with an onset temperature of about 103°, e.g. about 103°C±2°C.

- 5 A representative TGA plot for Form M of Apremilast is shown in Figure 12. The TGA plot of Form M shows a mass loss of more than 2%, e.g., about 2%, of the total mass of the sample upon heating from about 25°C to 110°C and about 8.5% of the total mass of the sample upon heating from about 25°C to 220°C. The TGA mass loss event comprises the loss of the solvent ethyl acetate, as indicated, e.g., by GC analysis. Form M hemi-ethyl acetate is a solvated
10 modification of Apremilast. The crystal lattice of Form M comprises 0.5 molar equivalent of ethyl acetate per one mole of Apremilast (as confirmed by SC-XRD method).

Form M of Apremilast may be characterized by moisture sorption analysis. A representative moisture sorption isotherm plot is shown in Figure 13. When RH is increased from about 0% to about 95% RH, it exhibits a mass change of less than about 0.5%, e.g., about 0.2%, of the
15 starting amount at about 0% RH.

Table 7. Crystal data of form M

Crystallographic data	
Empirical formula	C ₂₂ H ₂₄ N ₂ O ₇ S · 0.5C ₄ H ₈ O ₂
Formula weight	504.54 g/mol
Temperature	100 K
Crystal system	tetragonal
Space group	P4 ₁ 2 ₁ 2
Unit cell dimensions	a = b = 12.8568(2) Å
	c = 29.5578(4) Å
	α = β = γ = 90°
F(000)	2128
Volume	4885.8(2) Å ³

Z	8
Calculated density	1.372 g/cm ³
Theta range for data collection	3° - 67,0°
R index	R = 2.17 %
Flack's parameter	0.002(2)
CuK α radiation	1.54178 Å
Crystal size	0.08 x 0.15 x 0.15 mm

Table 8 shows the atomic coordinates and equivalent isotropic temperature parameters for non-hydrogen atoms.

Table 8.

Atom	x	y	z	U _(eq)
S1	0.83730(3)	0.59584(3)	0.03680(2)	0.0169(1)
O1	0.76019(9)	0.51831(10)	0.16683(4)	0.0195(3)
O2	0.52954(9)	0.59614(10)	0.05373(4)	0.0203(4)
O3	0.67987(10)	0.80017(10)	0.28944(4)	0.0236(4)
O4	0.45702(10)	0.24102(9)	-0.01799(4)	0.0213(4)
O5	0.43894(10)	0.10382(10)	0.04670(4)	0.0241(4)
O6	0.78901(10)	0.68947(10)	0.05381(4)	0.0230(4)
O7	0.92439(10)	0.55422(10)	0.06169(4)	0.0245(4)
N1	0.65426(11)	0.53560(11)	0.10364(4)	0.0156(4)
N2	0.70488(12)	0.67896(12)	0.23418(5)	0.0176(4)
C1	0.70188(13)	0.45355(13)	0.07554(5)	0.0156(4)
C2	0.69084(13)	0.56304(13)	0.14650(5)	0.0154(4)
C3	0.63399(13)	0.71095(13)	0.20106(6)	0.0162(5)
C4	0.56458(14)	0.79512(13)	0.20505(6)	0.0186(5)
C5	0.49557(14)	0.81876(14)	0.17024(6)	0.0210(5)
C6	0.49049(14)	0.76071(14)	0.13025(6)	0.0199(5)
C7	0.57478(13)	0.60225(14)	0.08976(5)	0.0160(5)
C8	0.55921(13)	0.67855(14)	0.12680(5)	0.0167(5)
O8 [*]	0.4686(3)	0.4457(3)	0.18671(13)	0.0537(12)
O9	0.4558(13)	0.5428(15)	0.2516(13)	0.034(3)
C9	0.62940(13)	0.65449(13)	0.16096(6)	0.0159(5)
C10	0.72204(14)	0.72079(14)	0.27633(6)	0.0185(5)
C11	0.79494(15)	0.65812(15)	0.30524(6)	0.0235(5)
C12	0.62969(13)	0.36120(13)	0.06785(6)	0.0169(5)
C13	0.57627(13)	0.34662(13)	0.02698(6)	0.0173(5)
C14	0.51267(13)	0.26071(14)	0.02067(6)	0.0177(5)
C15	0.50207(14)	0.18718(13)	0.05566(6)	0.0188(5)
C16	0.55460(15)	0.20242(14)	0.09619(6)	0.0206(5)
C17	0.61802(14)	0.28928(14)	0.10212(6)	0.0192(5)
C18	0.46104(15)	0.31989(14)	-0.05253(6)	0.0219(5)
C19	0.38534(18)	0.29084(17)	-0.08938(7)	0.0316(6)
C20	0.41835(19)	0.03591(15)	0.08380(7)	0.0321(7)
C21	0.74102(13)	0.49802(13)	0.03055(5)	0.0162(4)

C22	0.87563(16)	0.61725(15)	-0.01960(6)	0.0265(6)
C23 [*]	0.4981(4)	0.4676(3)	0.22374(15)	0.0337(14)
C24 [*]	0.5890(16)	0.4185(15)	0.2521(9)	0.045(3)
C25 [*]	0.4036(4)	0.6321(4)	0.27060(18)	0.0423(17)
C26 [*]	0.3346(9)	0.6785(7)	0.2613(3)	0.075(4)

Table 9 shows the Bond lengths (Å) in Form M of Apremilast.

Table 9.

5	S1 -O6	1.445(1)
	O9 -C25	1.44(2)
	S1 -O7	1.443(1)
	O9 -C23	1.38(3)
	S1 -C21	1.774(2)
10	C10 -C11	1.503(3)
	S1 -C22	1.760(2)
	C12 -C17	1.380(2)
	O1 -C2	1.219(2)
	C12 -C13	1.402(2)
15	O2 -C7	1.216(2)
	C13 -C14	1.387(2)
	O3 -C10	1.219(2)
	C14 -C15	1.408(2)
	O4 -C14	1.372(2)
20	C15 -C16	1.389(3)
	O4 -C18	1.440(2)
	C16 -C17	1.394(3)
	O5 -C15	1.370(2)
	C18 -C19	1.508(3)
25	O5 -C20	1.427(2)
	N1 -C1	1.476(2)
	N1 -C2	1.397(2)
	N1 -C7	1.395(2)
	N2 -C3	1.399(2)
30	N2 -C10	1.375(2)
	C1 -C12	1.524(2)
	C1 -C21	1.533(2)
	C2 -C9	1.480(2)
	C3 -C9	1.391(2)
35	C3 -C4	1.408(2)
	C4 -C5	1.392(3)
	C5 -C6	1.399(3)
	C6 -C8	1.381(3)
	C7 -C8	1.484(2)
40	C8 -C9	1.389(2)
	O8 -C23	1.192(6)
	C23 -C24	1.57(2)
	C25 -C26	1.104(12)

Table 10 shows the Bond Angles ($^{\circ}$) in Form M of Apremilast.

Table 10.

	O6	-S1	-O7	117.72(8)	N1	-C7	-C8	106.73(13)
	O6	-S1	-C21	109.09(8)	C6	-C8	-C7	130.29(15)
5	O6	-S1	-C22	108.64(8)	C7	-C8	-C9	107.55(15)
	O7	-S1	-C21	109.37(8)	C6	-C8	-C9	122.16(15)
	O7	-S1	-C22	108.89(9)	C2	-C9	-C8	108.29(15)
	C21	-S1	-C22	101.98(8)	C2	-C9	-C3	129.65(15)
	C14	-O4	-C18	116.23(13)	C3	-C9	-C8	122.05(16)
10	C15	-O5	-C20	116.11(14)	C23	-O9	-C25	166(3)
	C1	-N1	-C2	123.47(13)	O3	-C10	-C11	123.07(16)
	C1	-N1	-C7	125.27(12)	O3	-C10	-N2	122.97(16)
	C2	-N1	-C7	110.99(13)	N2	-C10	-C11	113.93(15)
	C3	-N2	-C10	128.57(15)	C13	-C12	-C17	119.32(16)
15	N1	-C1	-C12	112.84(13)	C1	-C12	-C17	118.61(15)
	N1	-C1	-C21	110.97(13)	C1	-C12	-C13	122.07(15)
	C12	-C1	-C21	111.17(13)	C12	-C13	-C14	120.74(16)
	O1	-C2	-N1	125.04(15)	C13	-C14	-C15	119.54(16)
	O1	-C2	-C9	128.52(15)	O4	-C14	-C15	115.95(15)
20	N1	-C2	-C9	106.44(14)	O4	-C14	-C13	124.51(16)
	O5	-C15	-C14	116.14(15)	C14	-C15	-C16	119.46(16)
	N2	-C3	-C4	125.47(16)	O5	-C15	-C16	124.40(16)
	C4	-C3	-C9	116.47(16)	C15	-C16	-C17	120.39(16)
	N2	-C3	-C9	118.06(15)	C12	-C17	-C16	120.55(16)
25	C3	-C4	-C5	120.66(16)	O4	-C18	-C19	108.34(15)
	C4	-C5	-C6	122.52(16)	S1	-C21	-C1	113.78(11)
	C5	-C6	-C8	116.13(16)	O2	-C7	-N1	124.62(15)
	O2	-C7	-C8	128.64(16)	O8	-C23	-O9	126.0(13)
	O8	-C23	-C24	129.2(9)	O9	-C23	-C24	104.8(15)
30	O9	-C25	-C26	135.0(14)				

The crystal structure is additionally stabilized by the presence of strong N—H...O hydrogen bonds and many weaker C—H...O interactions (Table 11). Table 11 shows the inter- and intramolecular hydrogen bonds ($\text{\AA}$, $^{\circ}$).

35

Table 11.

Donor	--- H....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
N(2)	--H(2) ..O(1)	[]	0.81(2)	2.29(2)	2.956(2)	139.3(19)
C(4)	--H(4) ..O(3)	[]	0.95	2.30	2.902(2)	120

	C(13) --H(13) ..O(2)	[6555.01]	0.95	2.41	3.360(2)	176
	C(16) --H(16) ..O(7)	[7645.01]	0.95	2.41	3.334(2)	163
	C(17) --H(17) ..O(6)	[7645.01]	0.95	2.52	3.287(2)	138
	C(20) --H(201) ..O(3)	[4454.01]	0.98	2.48	3.424(2)	163
5	C(21) --H(211) ..O(2)	[6555.01]	0.99	2.28	3.137(2)	145
	C(21) --H(212) ..O(3)	[7645.01]	0.99	2.45	3.433(2)	172
	C(22) --H(221) ..O(1)	[4564.01]	0.98	2.35	3.062(2)	129
	C(22) --H(222) ..O(6)	[6555.01]	0.98	2.55	3.410(2)	147

Symmetry code [ARU]

=====

[6555.] = [7_555] = y,x,-z

[7645.] = [5_645] = 3/2-x,-1/2+y,1/4-z

[4564.] = [3_564] = 1/2+y,3/2-x,-1/4+z

[4454.] = [3_454] = -1/2+y,1/2-x,-1/4+z

Characterization of Form O (containing dimethyl acetamide solvent molecules) of Apremilast

The preparation of Form O is described in Example 3 (see also Figure 14). Crystalline Form O of Apremilast can be characterized as already described above. It has an X-ray powder diffraction pattern as depicted in Figure 15 and as listed in Table 12 below.

Table 12. Peak positions and their intensities

No.	2-theta(deg)	Rel. int. I(a.u.)
1	7.5	56.54
2	9.1	11.02
3	9.7	9.57
4	10.1	3.10
5	11.2	45.57
6	11.9	12.37
7	13.2	5.17
8	13.8	11.97
9	14.0	10.67
10	15.3	35.90
11	16.4	44.85
12	17.7	87.42
13	19.2	9.21
14	19.4	20.61
15	20.3	16.88
16	20.8	5.83
17	21.4	24.81
18	22.5	33.63
19	22.8	8.80
20	23.5	29.97

21	23.9	3.30
22	24.8	38.26
23	25.5	25.94
24	26.4	100.00
25	27.5	34.55
26	28.5	5.62
27	29.0	21.83
28	29.8	9.96

Form O of Apremilast may be also (further) characterized by thermal analysis. A representative DSC plot for Form O of Apremilast is shown in Figure 16. The DSC plot of Form O comprises an endothermic event with an onset temperature of about 124°C, e.g. about 124°C±2°C.

- 5 A representative TGA plot for Form O of Apremilast is shown in Figure 17. The TGA plot of Form O comprises a mass loss of more than about 7%, e.g., 7.8%, of the total mass of the sample upon heating from about 25°C to about 220°C. The TGA mass loss event comprises the loss of the solvent dimethyl acetamide, as indicated, e.g., by GC analysis. Form O is the DMA solvated modification of Apremilast. The crystal lattice of Form O comprises about 0.5 molar
10 equivalent of DMA per one mole of Apremilast.

Characterization of Form P (containing DMF solvent molecules) of Apremilast

- The preparation of Form P is described in Example 4 and Figure 18. Crystalline Form P of Apremilast can be characterized as already described above. It has an X-ray powder diffraction
15 pattern as depicted in Figure 19 and as listed in Table 13 below. Table 13 shows the peak positions and their intensities.

Table 13.

No.	2-theta(deg)	Rel. int. I(a.u.)
1	7.4	54.31
2	9.0	13.80
3	9.7	4.28
5	11.2	51.06
6	11.8	14.59
7	13.1	6.81
8	13.7	8.46
9	14.0	19.62
10	15.3	31.07
11	16.3	39.11
12	17.7	83.78
13	18.1	4.14
14	19.0	10.30

15	19.3	28.62
16	20.3	21.45
17	20.8	10.15
18	21.3	38.78
19	22.5	37.15
20	22.7	8.84
21	22.9	4.65
22	23.5	41.81
23	23.7	12.41
24	24.7	41.49
25	25.5	31.97
26	26.3	100.00
27	27.3	22.14
28	27.5	21.75
29	28.9	23.03

Form P of Apremilast may be also (further) characterized by thermal analysis. A representative DSC plot for Form P of Apremilast is shown in Figure 20. The DSC plot of Form P comprises an endothermic event with an onset temperature of about 94°C, e.g. about 94°C±2°C.

- 5 A representative TGA plot for Form P of Apremilast is shown in Figure 21. The TGA plot of Form P comprises a mass loss of more than about 7%, e.g., 7.4%, of the total mass of the sample upon heating from about 25 °C to about 220 °C. The TGA mass loss event comprises the loss of the solvent DMF, as indicated, e.g., by GC analysis. Form P is the DMF solvated modification of Apremilast. The crystal lattice of Form P comprises about 0.5 or less molar
- 10 equivalents of DMF per one mole of Apremilast.

The following examples describe the present invention in detail, but are not to be construed to be in any way limiting for the present invention.

15 Example 1 – Preparation of unsolvated Form N of Apremilast

1.1 Preparation of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-indol-4-yl]acetamide) (APM)

The below preparation serves as a non-limiting example for preparing APM. Any other method for preparing APM is also suitable in the context of the present invention.

- 20 Reference is made to Figure 1. APM-1 (9.65g) was dissolved in dimethylacetamide (100ml) at ambient temperature. Then APM-2 (20g) was suspended and dimethylacetamide (100 ml) was charged. After warming up of the suspension to the temperature 110-120°C under flow of inert gas the reaction mixture was stirred between 2-4 hours.

When the reaction was finished (after 2-4h at 110-120°C) the solution was cooled down to a temperature of 20-25°C. Ethyl acetate (180ml) and water (180ml) were added to the reaction mixture and the reaction mass was stirred for 10 min at 20-30°C. After separation, the ethyl acetate phase was left and the water phase was extracted with ethyl acetate (2x50ml). The combined ethyl acetate phases were washed with 8% NaHCO₃ solution (2x50ml), 1N HCl (2x50ml), and water (1x50ml). The organic solvent was evaporated under reduced pressure (200-30mbar) at 35°C giving compound APM (as an oil residue left after ethyl acetate distillation).

1.2 Crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (APM)

Crystallization – Option I

Reference is made to Figure 2. For crystallization, APM in any form and prepared by any method (e.g. any known literature method), for example the method of above Example 1.1, can be used.

10g of Apremilast were suspended in diethyl ether (200ml) and stirred for 12h at 25±5°C to give a white to cream color suspension. Obtained solid was filtered under reduced pressure and dried at 85°C and gave product APM Form N (as confirmed by XRPD, DSC and TGA) with purity above 99.90% (80-90% yield).

Crystallization – Option II

Reference is made to Figure 2. 10g of Apremilast were dissolved in dichloromethane (30ml) and stirred for 30 min at 25±5°C until a clear solution was obtained. Then, methyl tert butyl ether (200ml) was added under stirring and seeds of Form N were added. The mass was stirred for 12h at 25±5°C to give a white to cream color suspension. Obtained solid was filtered under reduced pressure and dried at 85°C gave product APM Form N (as confirmed by XRPD, DSC and TGA) with purity above 99.90% (90-95% yield).

Crystallization – Option III

Reference is made to Figure 2. The product 10g (APM as an oil residue left after ethyl acetate distillation) was suspended in methyl tert-butyl ether (MTBE) (1000ml) at 20±5°C and 0.5g of Apremilast N seeds was charged. Crystallization mixture was vigorously stirred for 16h at 20±5°C to give a white to cream color suspension. Obtained solid was filtered under reduced pressure and dried at 85°C gave product APM form N (as confirmed by XRPD, DSC and TGA) with purity above 99.90% (80-90% yield)

Example 2 – Preparation of Form M of Apremilast

Crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (APM) Form M as the hemi ethyl acetate solvate is shown in Figure 8:

10 g Apremilast were dissolved in ethyl acetate (52ml) and heated to 77°C. The solution was stirred for 30 min at boiling temperature and then cooled down to -5 to -10°C. The mass was stirred for 3-6h at about -5 to -10°C to give a white to cream color suspension. The obtained solid was filtered under reduced pressure and the cake was washed with cold ethyl acetate (2x 5ml). Drying at reduced pressure at 50°C gave product APM hemi-ethyl acetate form (as confirmed by XRPD, DSC, GC and TGA) with a purity of above 99.90% (88-92% yield).

Example 3 – Preparation of Form O of Apremilast

Crystallization of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) (APM) Form O as the hemi DMA solvate is shown in Figure 14.

10 g of Apremilast were dissolved in dimethyl acetamide (40ml) and stirred for 30 min at 25±5°C until a clear solution was obtained. The solution was stirred for 72h at 25±5°C to give a white to cream color suspension. The obtained solid was filtered under reduced pressure and dried at 50°C, which gave product APM Form O (as confirmed by XRPD, DSC and TGA) with purity above 99.90% (70-80% yield).

Example 4 – Preparation of Form P of Apremilast

Reference is made to Figure 18. 10 g of Apremilast were dissolved in dimethyl formamide (30ml) and stirred for 30 min at 25±5°C until a clear solution was obtained. The solution was stirred for 72h at 25±5°C to give a white to cream color suspension. The obtained solid was filtered under reduced pressure and dried at 50°C, which gave product APM Form P (as confirmed by XRPD, DSC and TGA) with a purity of above 99.90% (70-80% yield).

Example 5 – Stability testings with tablets containing Form B (prior art)

Tablets comprising Form B were prepared as follows:

- 5 Apremilast, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium were passed through a 0.425 mm sieve. The ingredients from the sieving step are mixed in a blender for 15 min at 25 RPM (rotations per minute). Magnesium stearate is added and the mixture is mixed for 5 min at 12 RPM. The resulting blend is compressed using a single punch machine equipped with an oval punch (14x8mm) at a compression force of 7 kN. The composition of the tablets is shown in Table 14.

Table 14. (Sample 001)

Ingredient	mg/tabl	%/tabl
Apremilast (Form B)	30.00	10.00
Lactose monohydrate	171.00	57.00
Microcrystalline cellulose	85.50	28.50
Croscarmellose sodium	11.25	3.75
Magnesium stearate	2.25	0.75
total:	300.00	100.00

- 10 Stability results after 2 weeks (conditions either closed or open):

Table 15.

Sample 001	
initial	Form B
50°C/75%RH close	not changed
50°C/75%RH open	not changed
RT/70-75%RH open	not changed

Example 6 – Stability testings with tablets containing an amorphous form

Tablets comprising an amorphous form of APM were prepared as follows:

- 5 Apremilast (Form M) was dissolved in acetone. Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium were passed through a 0.425 mm sieve. The ingredients from the previous step were added to a fluid bed granulator (equipped with top spray nozzle) and granulated by spraying the solution. The obtained granulate was dried. Magnesium stearate was added and mixed for 5 min at 12 RPM. The blend was compressed using a single punch machine equipped with oval punch (14x8mm) at a compression force of 7 kN.

10 **Table 16 (Sample 002)**

Ingredient	mg/tabl	%/tabl
Apremilast (amorphous form)	30,00	10,00
Lactose monohydrate	171,00	57,00
Microcrystalline cellulose	85,50	28,50
Croscarmellose sodium	11,25	3,75
Magnesium stearate	2,25	0,75
total:	300,00	100,00

Stability results after 2 weeks (conditions closed or open):

Table 17.

Sample 002	
initial	Amorphous
50°C/75%RH close	changed into B
50°C/75%RH open	changed into B
RT/70-75%RH open	not changed

Example 8 – Stability testings with tablets containing Form N

Sample 004 comprising Form N was prepared as follows:

5 Apremilast Form N, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium were passed through a 0.425 mm sieve. The ingredients from the previous step were mixed in a blender for 15 min at 25 RPM. Magnesium stearate was added and the resulting mixture was mixed for 5 min at 12 RPM. The resulting blend was compressed using a single punch machine equipped with oval punch (14x8mm) at a compression force of 7 kN

Table 18.

Ingredient	mg/tabl	%/tabl
Apremilast (Form N)	30,00	10,00
Lactose monohydrate	171,00	57,00
Microcrystalline cellulose	85,50	28,50
Croscarmellose sodium	11,25	3,75
Magnesium stearate	2,25	0,75
total:	300,00	100,00

Stability results after 2 weeks:

10 Table 19.

Sample 004	
initial	Form N
50°C/75%RH close	not changed
50°C/75%RH open	not changed
RT/70-75%RH open	not changed

Example 9 – Dissolution properties of tablets with Form B (prior art) and Form N

The dissolution profile of Apremilast Form N and Form B, prepared above, in buffer at pH 6.8 + 0.3% SLS is shown in Table 20 (see also Figure 7).

5 **Table 20.**

	APREMILAST			
Tablets	Sample 001 (Form B)		Sample 004 (Form N)	
	Assay:	95.1%	Assay:	93.7%
n=3	Mean	RSD	Mean	RSD
Time [min]				
5	38.6	4.3	63.3	3.3
10	47.8	4.5	81.4	4.6
15	52.5	4.0	87.3	5.3
20	55.4	5.0	89.6	5.4
30	60.3	4.8	91.2	5.4
45	65.4	6.3	91.6	5.5
60	68.9	6.4	91.8	5.7

When compared with prior art Form B, Form N exhibits a higher dissolution rate by more than 50% at 30 minutes.

10 **Cited literature**

EP2276483 B1; US 6,962,940

Claims

1. Crystalline Form N of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide),
having an X-ray powder diffraction pattern with peaks at 2-theta angles of 9.9 ± 0.2 degrees 2theta, 12.7 ± 0.2 degrees 2theta, 18.8 ± 0.2 degrees 2theta, 20.2 ± 0.2 degrees 2theta, 22.1 ± 0.2 degrees 2theta, 24.0 ± 0.2 degrees 2theta, and 29.4 ± 0.2 degrees 2theta when using Cu-K α radiation.
2. The crystalline form of claim 1,
 - (i) having a single endothermic event in a differential scanning calorimeter plot, preferably with an onset temperature of about $139^{\circ}\text{C}\pm 6^{\circ}\text{C}$, about $139^{\circ}\text{C}\pm 4^{\circ}\text{C}$, or about $139^{\circ}\text{C}\pm 2^{\circ}\text{C}$; and/or
 - (ii) wherein the X-ray powder diffraction pattern has further peaks at 2-theta angles of 11.7 ± 0.2 degrees 2theta, 11.9 ± 0.2 degrees 2theta, 13.7 ± 0.2 degrees 2theta, 14.4 ± 0.2 degrees 2theta, 14.6 ± 0.2 degrees 2theta, 15.3 ± 0.2 degrees 2theta, 16.7 ± 0.2 degrees 2theta, 21.4 ± 0.2 degrees 2theta, 23.0 ± 0.2 degrees 2theta, 23.7 ± 0.2 degrees 2theta, 24.8 ± 0.2 degrees 2theta, 25.6 ± 0.2 degrees 2theta, 26.8 ± 0.2 degrees 2theta, and 29.8 ± 0.2 degrees 2theta, when using Cu-K α radiation; and/or
 - (iii) which contains less than 5 wt.-% of other crystalline, non-crystalline or amorphous forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide.
3. The crystalline form of claim 1 or 2, which
 - (i) is unsolvated, preferably has a solvent content of less than 1 wt.-%, wherein the solvent content is determined by gaschromatographic (GC) analysis; and/or
 - (ii) has a mass loss of less than 0.5% of the total mass of the sample in a thermogravimetric analysis (TGA) upon heating from 25°C to 220°C with the gradient of $7^{\circ}\text{C}/\text{min}$.
4. The crystalline form of any of claims 1-3, wherein the X-ray powder diffraction pattern is free of further peaks having an intensity which is higher than the intensity of the peak at 18.8 ± 0.2 degrees 2theta.

5. Crystalline Form M of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide) containing 0.3-0.7 moles of ethyl acetate per of mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), and having an X-ray powder diffraction pattern with peaks at 2-theta angles of 7.5 ± 0.2 degrees 2theta, 9.1 ± 0.2 degrees 2theta, 11.3 ± 0.2 degrees 2theta, 12.0 ± 0.2 degrees 2theta, 16.4 ± 0.2 degrees 2theta, 17.7 ± 0.2 degrees 2theta, 19.3 ± 0.2 degrees 2theta, 21.4 ± 0.2 degrees 2theta, 22.5 ± 0.2 degrees 2theta, 24.7 ± 0.2 degrees 2theta, 25.4 ± 0.2 degrees 2theta, 26.3 ± 0.2 degrees 2theta, 27.5 ± 0.2 degrees 2theta, and 34.3 ± 0.2 degrees 2theta, when using Cu-K α radiation.
6. The crystalline form of claim 5,
 - (i) having a single endothermic event in a differential scanning calorimeter plot, preferably with an onset temperature of about $103^{\circ}\text{C}\pm 6^{\circ}\text{C}$, about $103^{\circ}\text{C}\pm 4^{\circ}\text{C}$, or about $103^{\circ}\text{C}\pm 2^{\circ}\text{C}$; and/or
 - (ii) wherein the X-ray powder diffraction pattern has further peaks at 2-theta angles of 14.0 ± 0.2 degrees 2theta, 15.2 ± 0.2 degrees 2theta, 15.3 ± 0.2 degrees 2theta, 20.2 ± 0.2 degrees 2theta, 20.7 ± 0.2 degrees 2theta, 22.8 ± 0.2 degrees 2theta, 23.2 ± 0.2 degrees 2theta, 23.4 ± 0.2 degrees 2theta, and 29.0 ± 0.2 degrees 2theta, when using Cu-K α radiation; and/or
 - (iii) which contains less than 5 wt.-% of other crystalline, non-crystalline or amorphous forms of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide.
7. The crystalline form of claim 5 or 6, which
 - (i) contains 0.4-0.6 moles of ethyl acetate per mole of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide); and/or
 - (ii) has a mass loss of more than 8% of the total mass of the sample, corresponding to a loss of ethyl acetate, in a thermogravimetric analysis (TGA) upon heating from 25°C to 220°C with the gradient of $7^{\circ}\text{C}/\text{min}$; and/or
 - (iii) has a mass change of less than 0.8% of the total mass of the sample in a moisture sorption analysis from close to 0% relative humidity to 90% relative humidity.
8. Pharmaceutical composition or dosage form comprising a crystalline form of any of claims 1-7.

9. The pharmaceutical composition or dosage form of claim 8, which comprises at least one pharmaceutically acceptable excipient and/or which is a tablet.
10. Pharmaceutical composition or dosage form of claim 8 or 9 for use in a method of treating a disease or disorder selected from the group consisting of: psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex aphthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymyositis; dermatomyositis; inclusion body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.
11. Pharmaceutical composition or dosage form of claim 8 or 9 for use in a method of treating or preventing a disease or disorder selected from the group consisting of: HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic re perfusion injury; meningitis; psoriasis; psoriatic arthritis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.
12. Use of a crystalline form of any of claims 1-7 for the preparation of a pharmaceutical composition or dosage form.
13. The use of claim 12, wherein the crystalline form is Form N, which is used for preparing an oral solid pharmaceutical dosage form comprising Form N.
14. Process for preparing an oral solid pharmaceutical dosage form of claim 8 or 9, comprising a step of compressing (i) a mixture of Form N with one or more pharmaceutical acceptable excipients, or (ii) granules including Form N, optionally in admixture with one or more pharmaceutical acceptable excipients.

15. Process for preparing an oral solid pharmaceutical dosage form comprising an amorphous form of N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide), wherein the process comprises a step of dissolving Form M or Form N of any of claims 1-7, and optionally one or more pharmaceutically acceptable excipients, in a solvent or mixture of solvents and (i) spraying the resulting solution onto pharmaceutical acceptable excipients, or (ii) spray drying the solution.

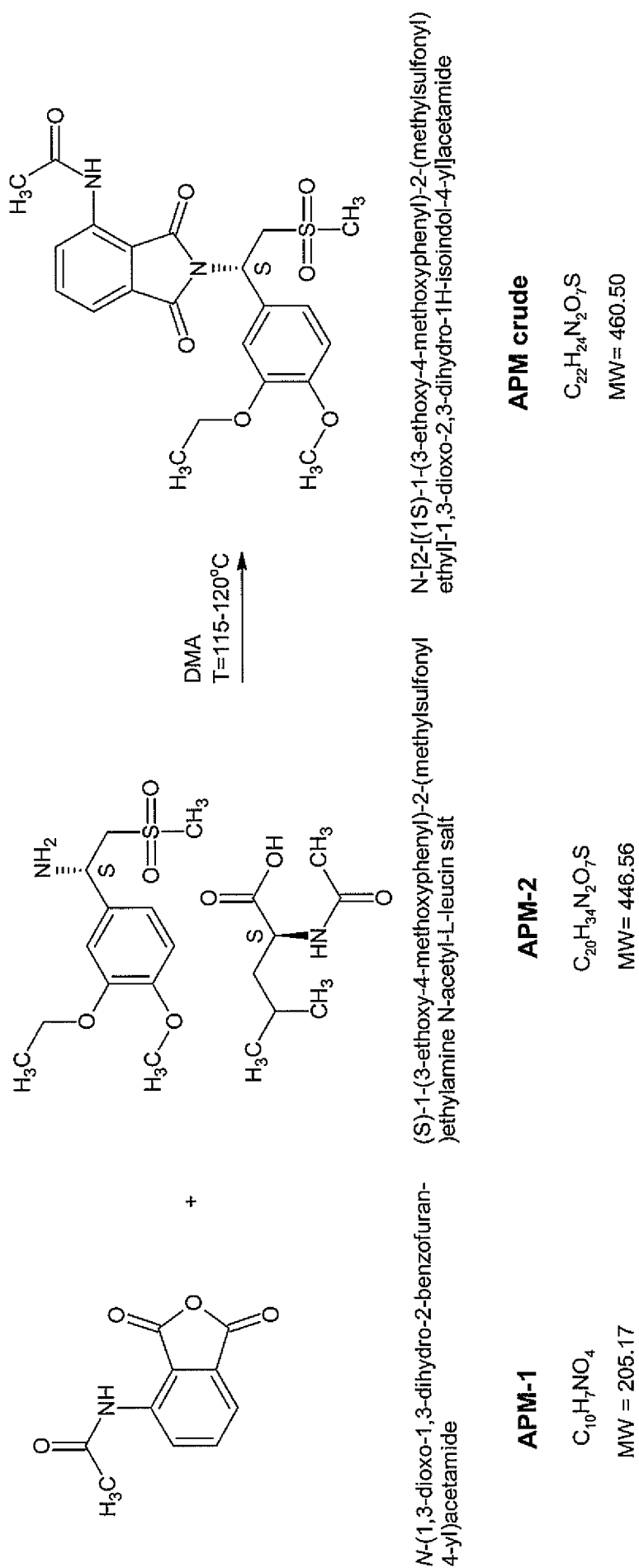


Figure 1

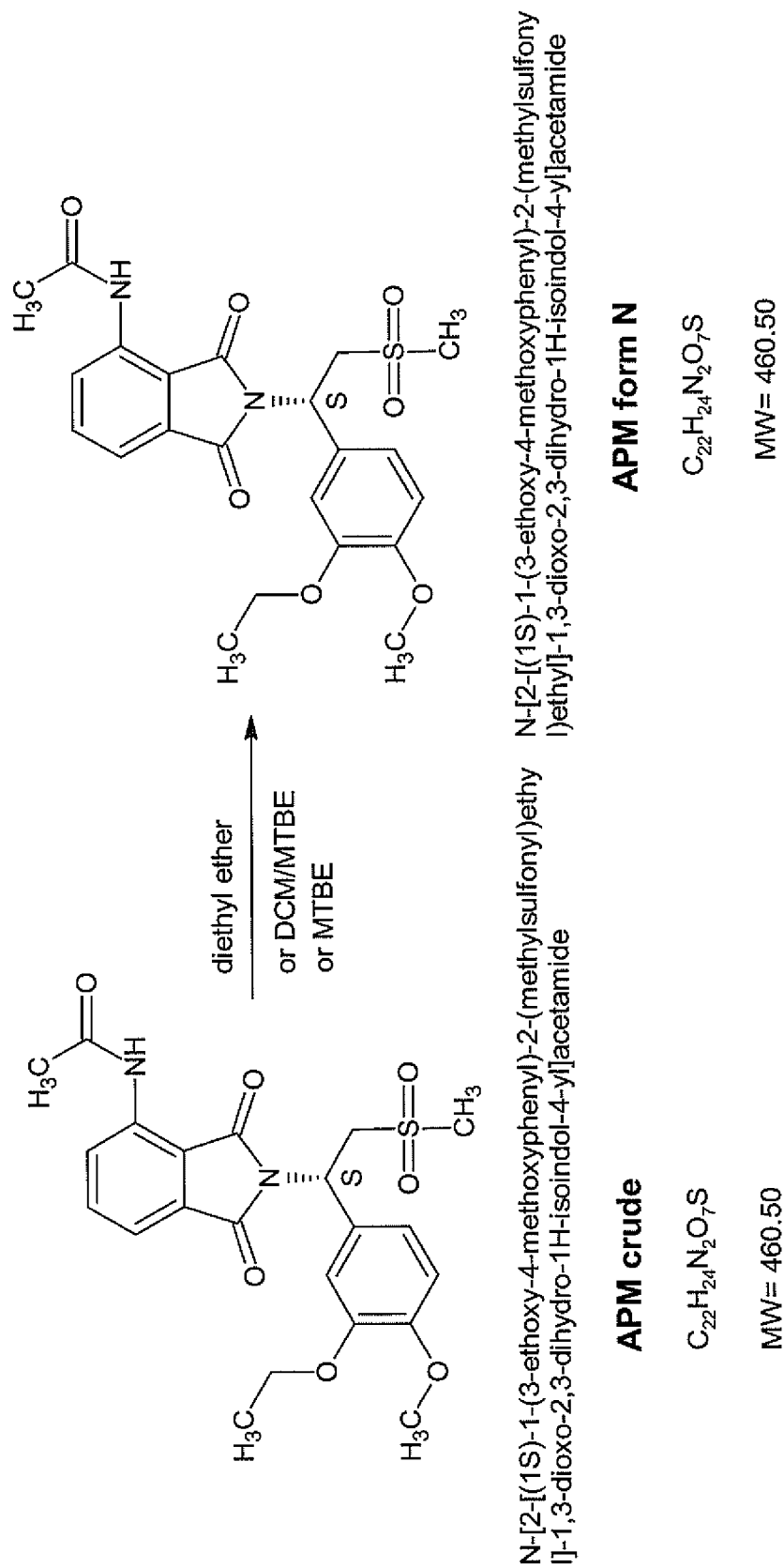


Figure 2

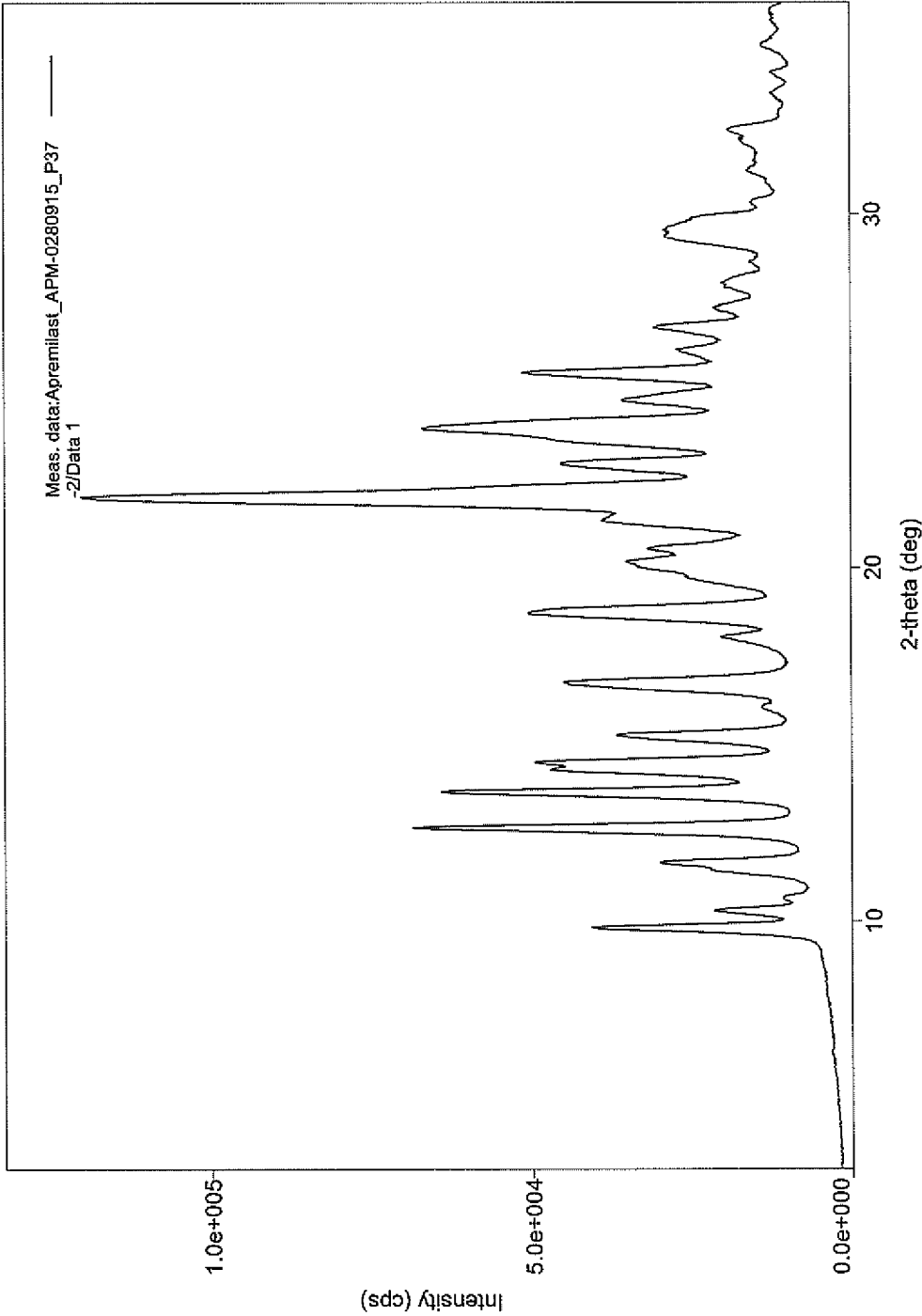


Figure 3

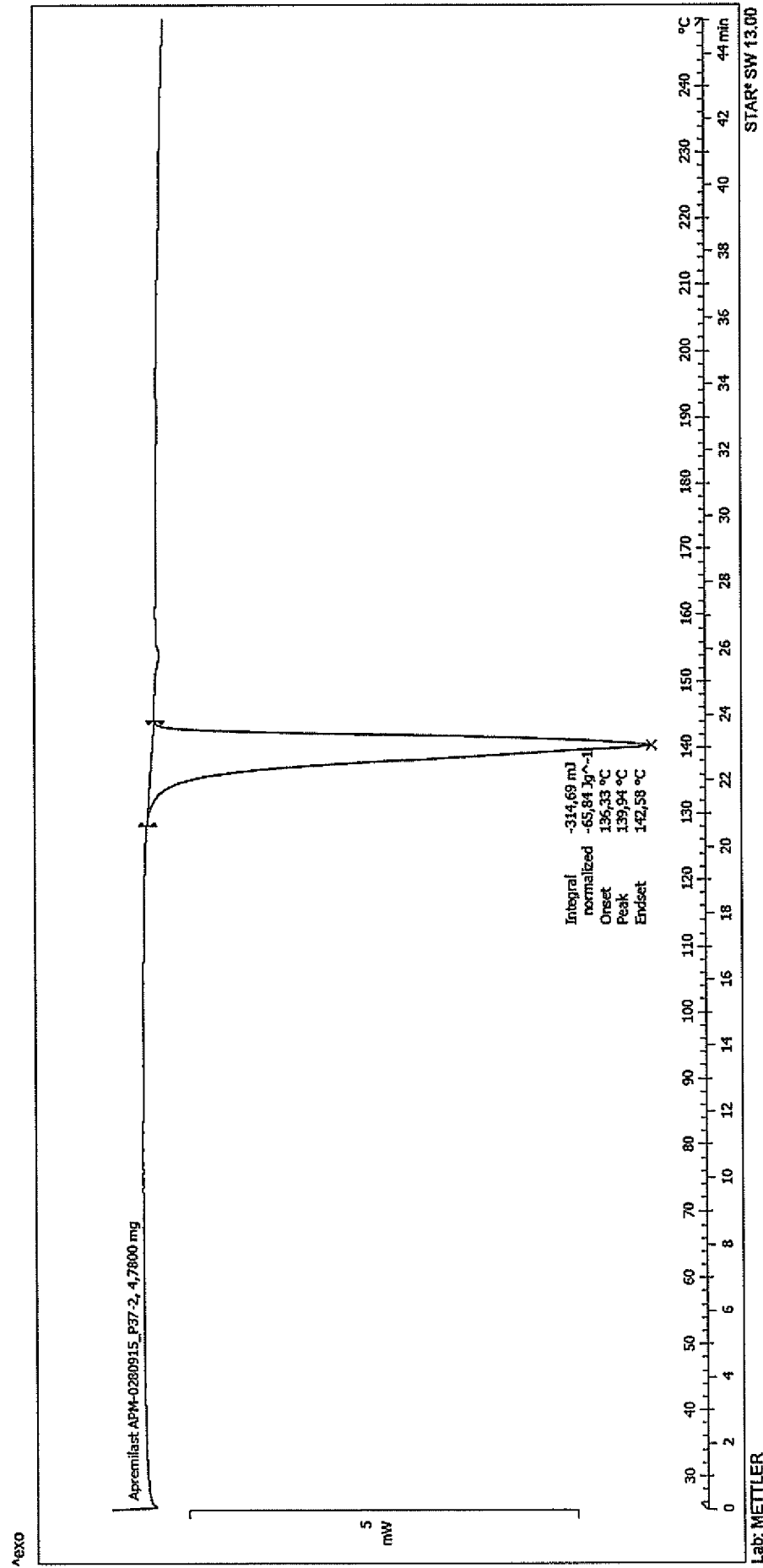


Figure 4

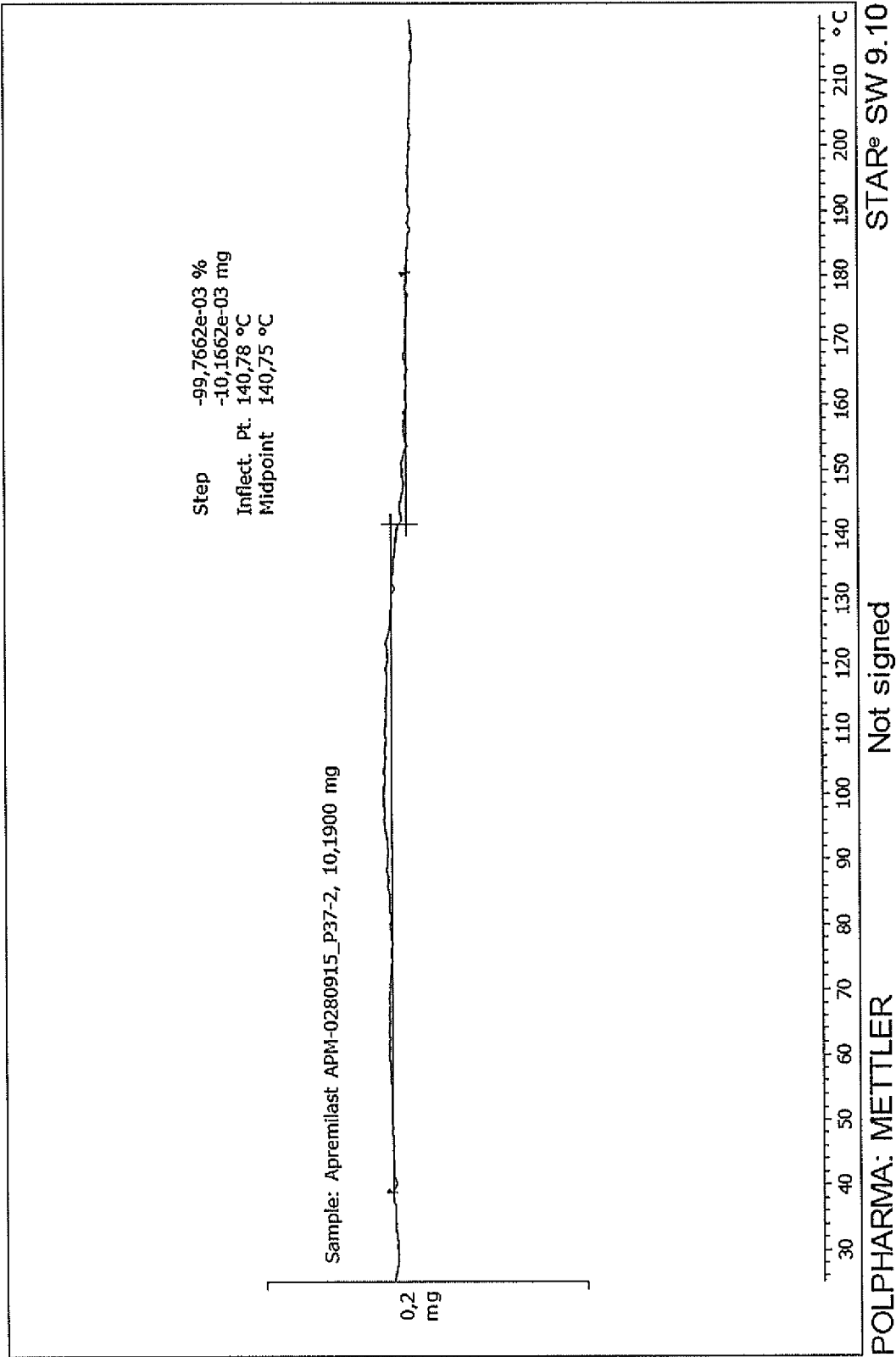


Figure 5

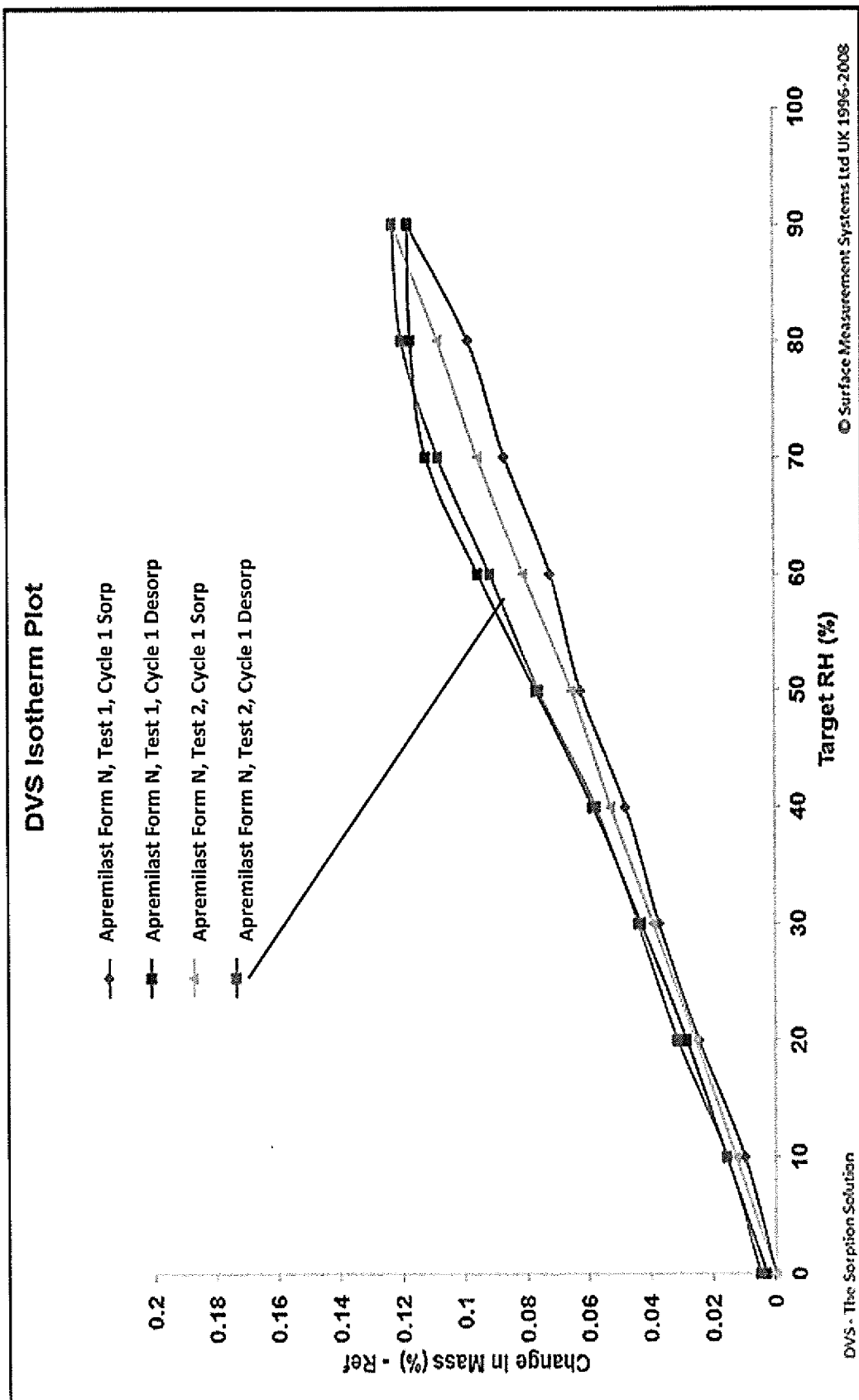


Figure 6

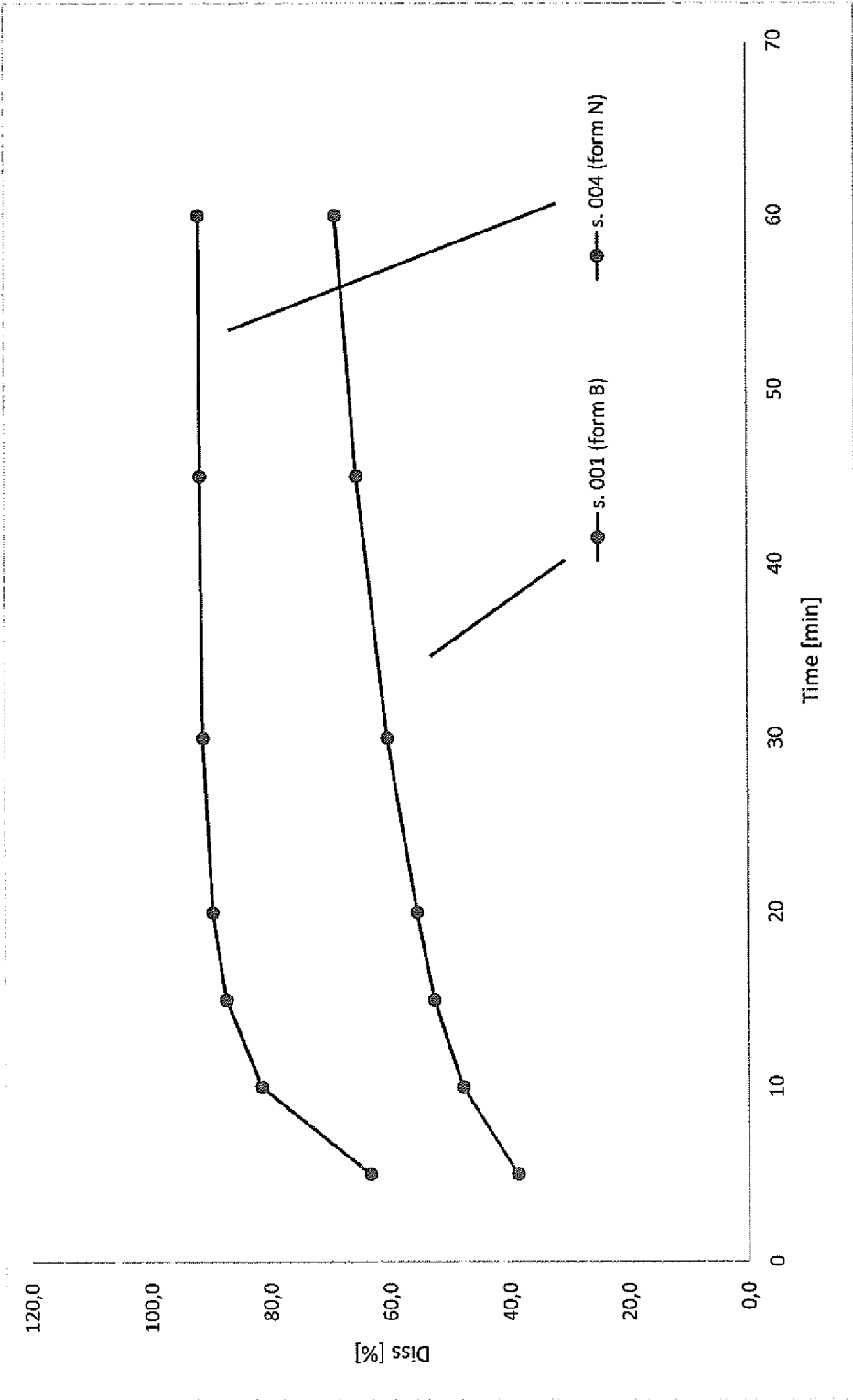


Figure 7

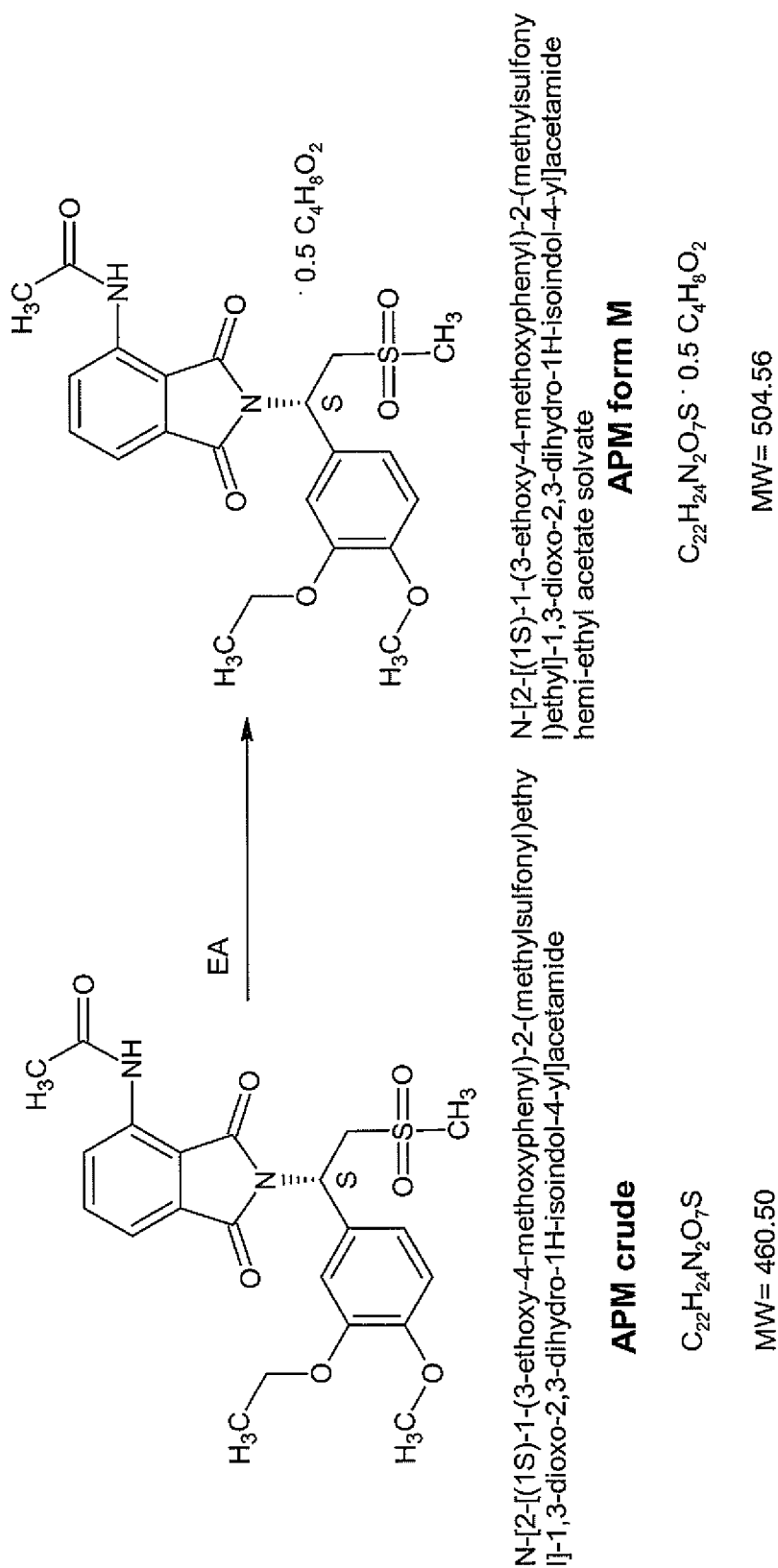


Figure 8

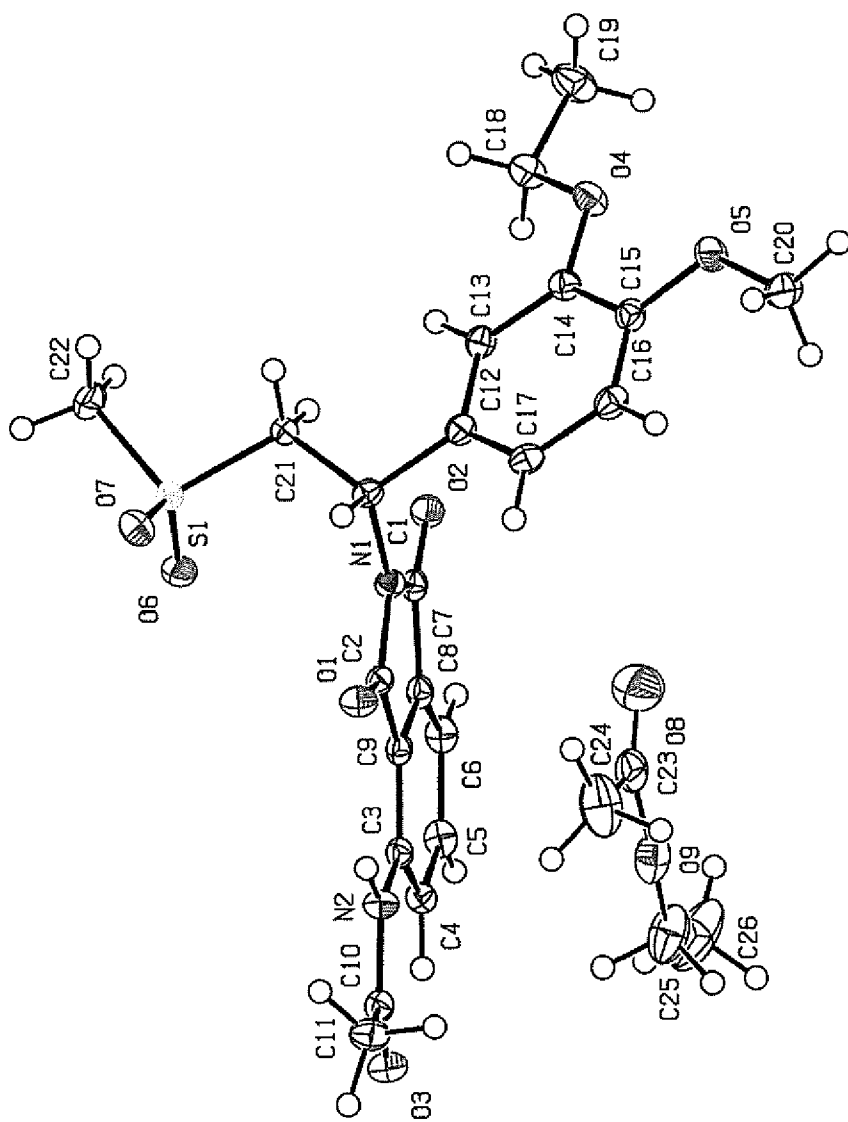


Figure 9

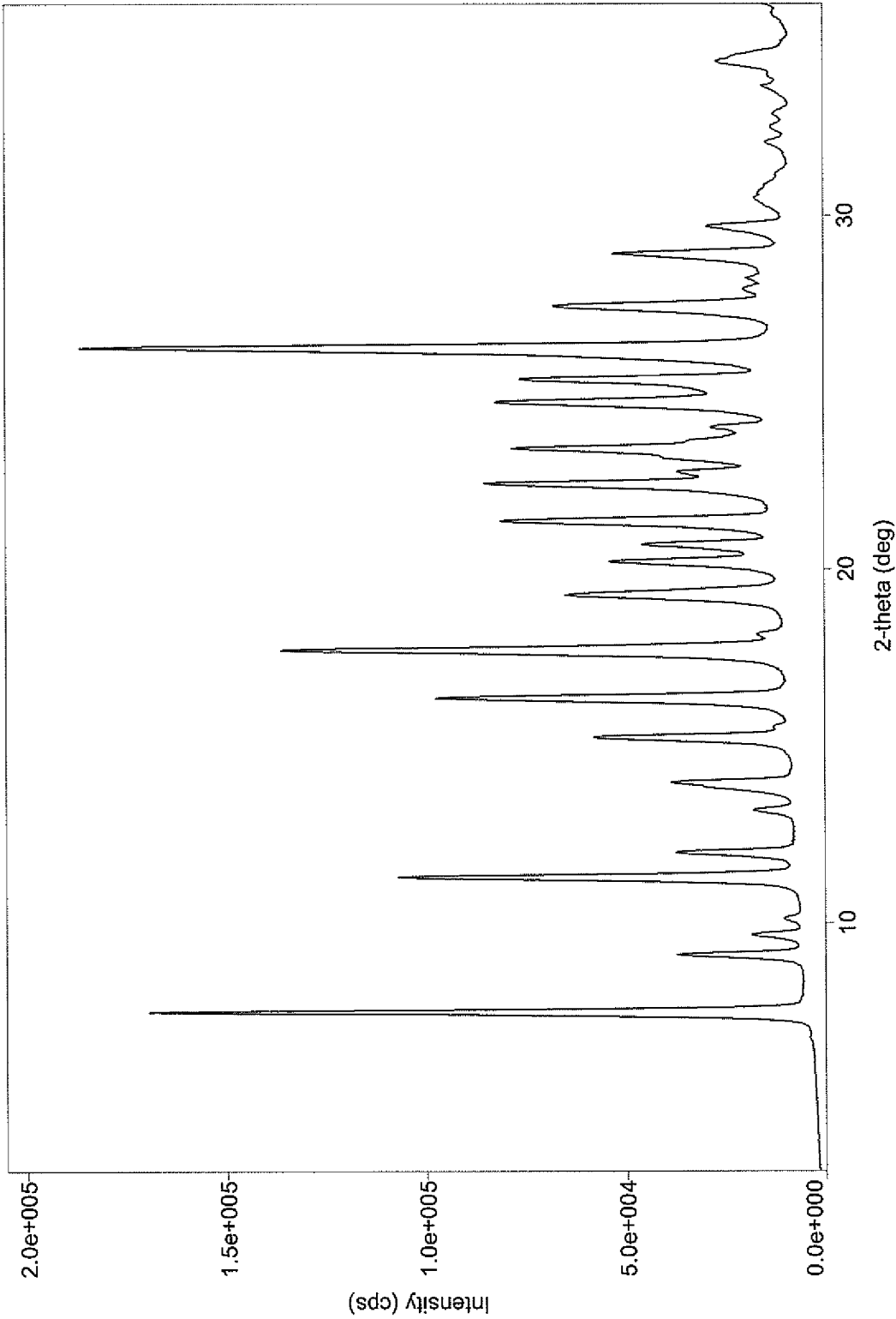


Figure 10

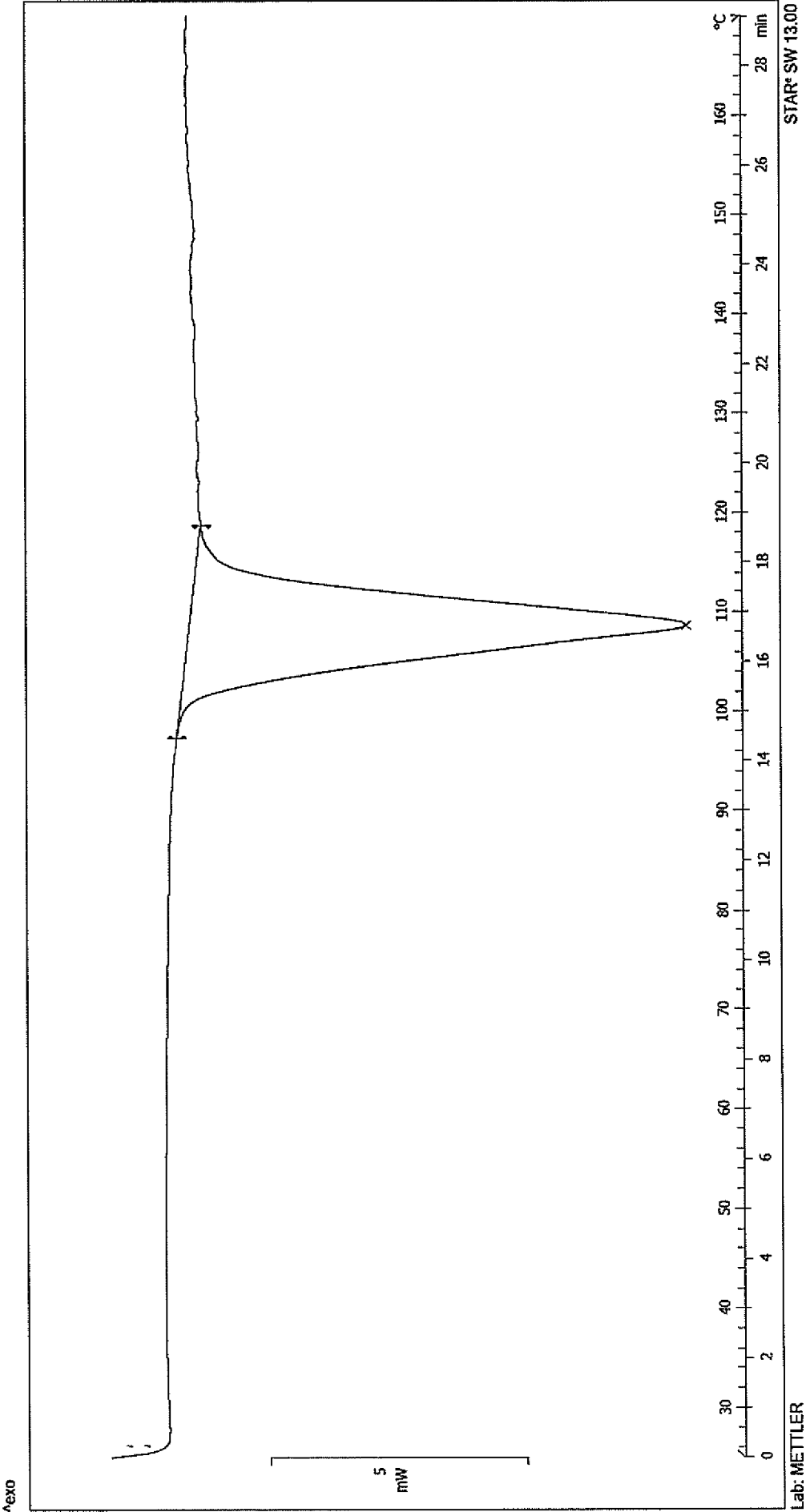


Figure 11

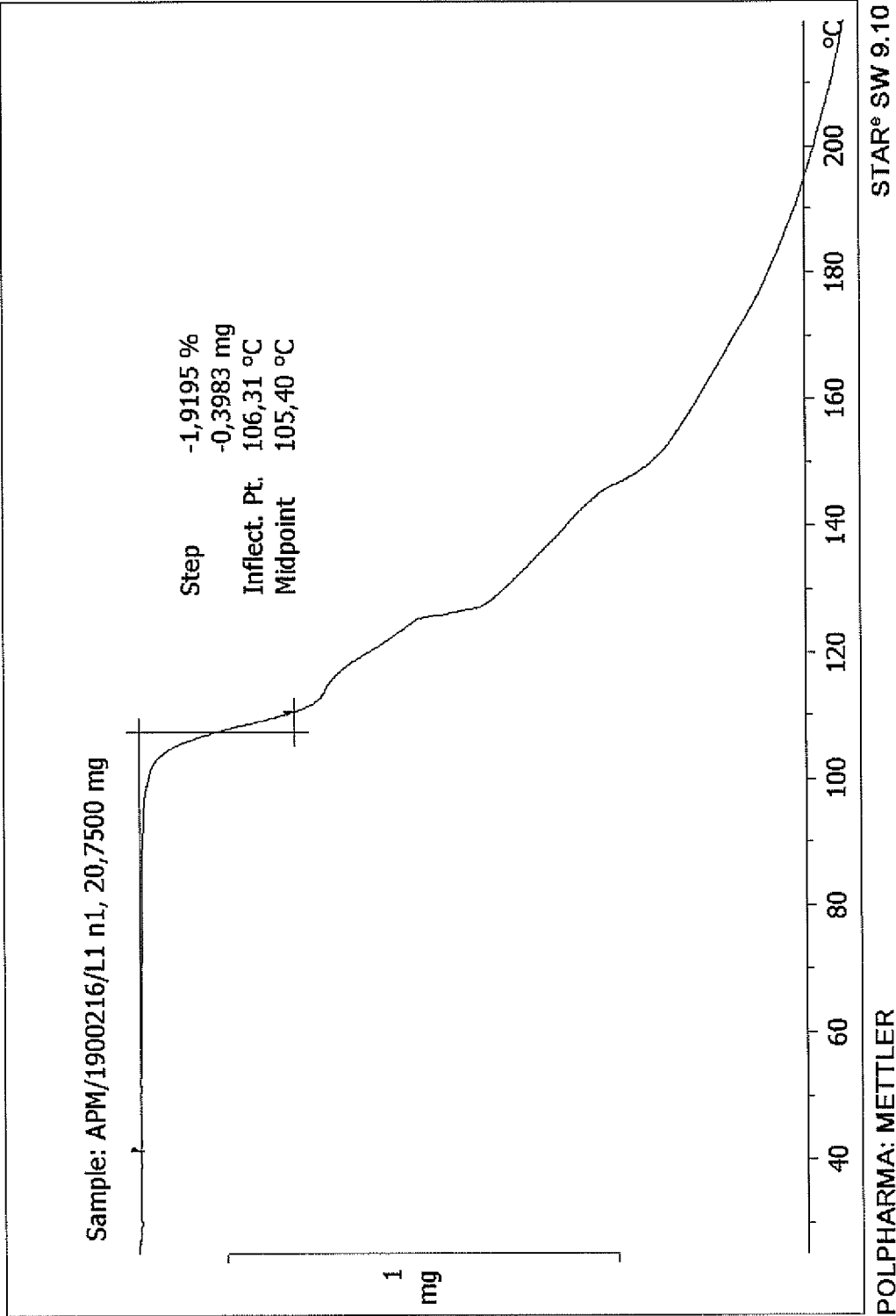


Figure 12

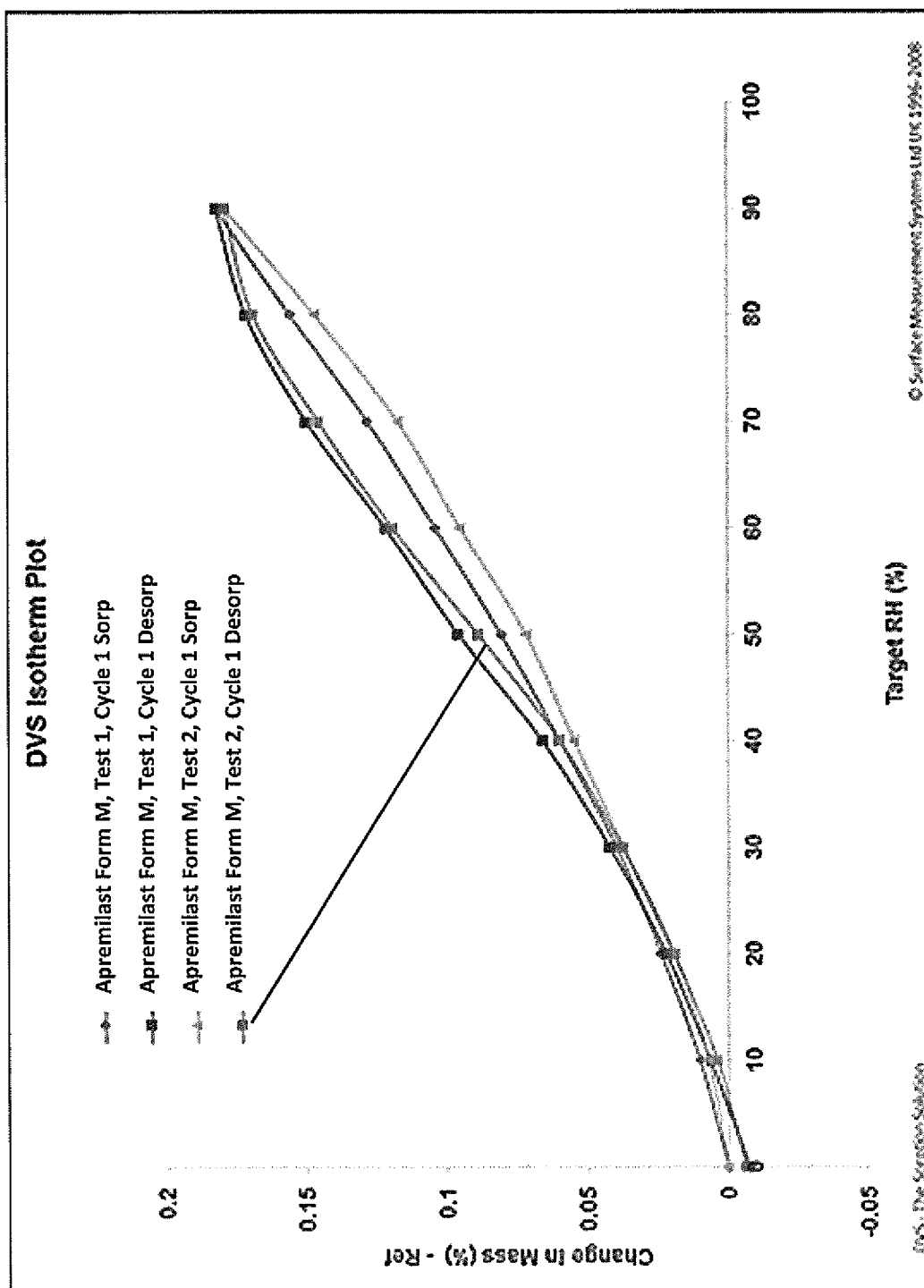


Figure 13

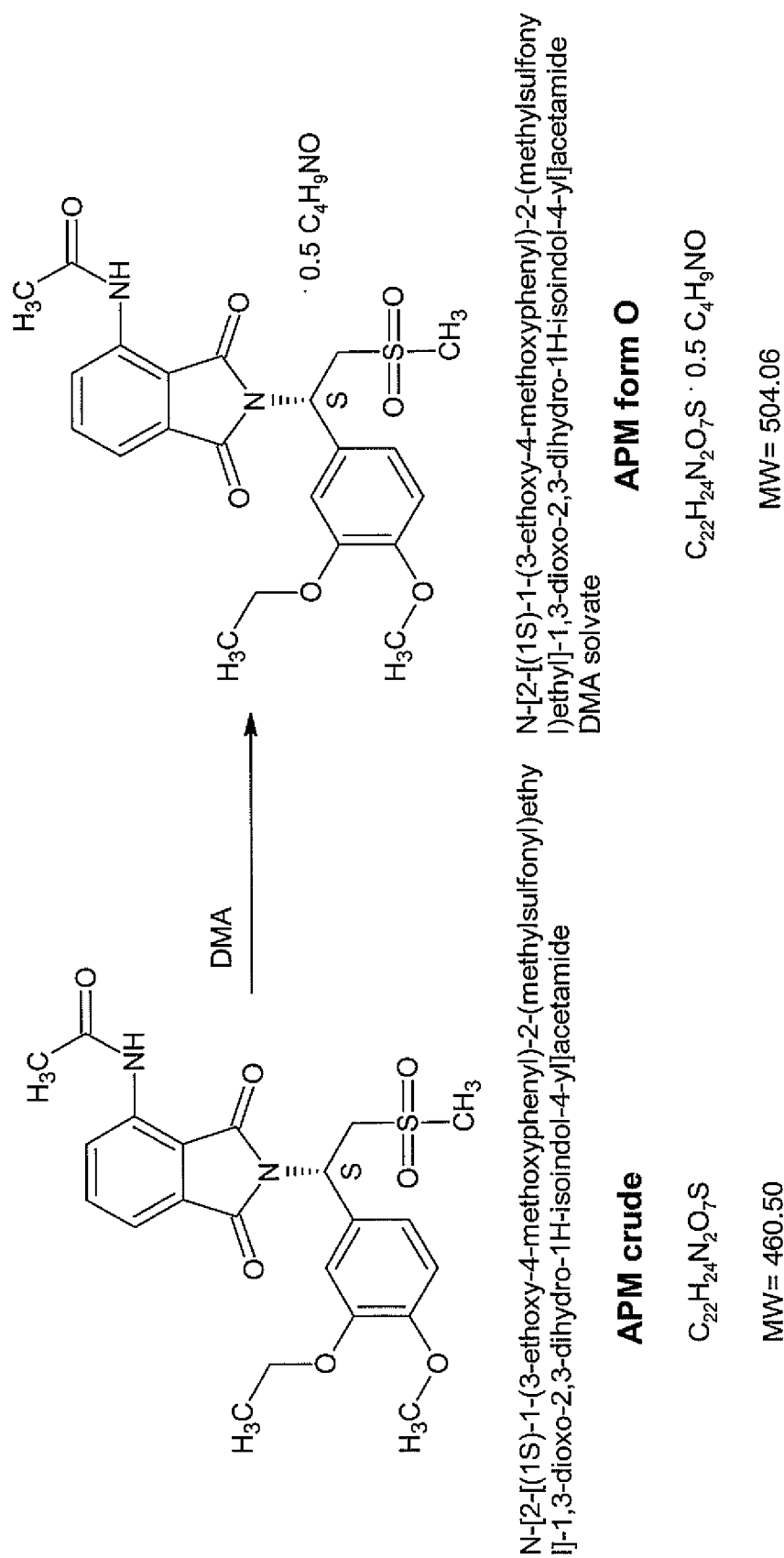


Figure 14

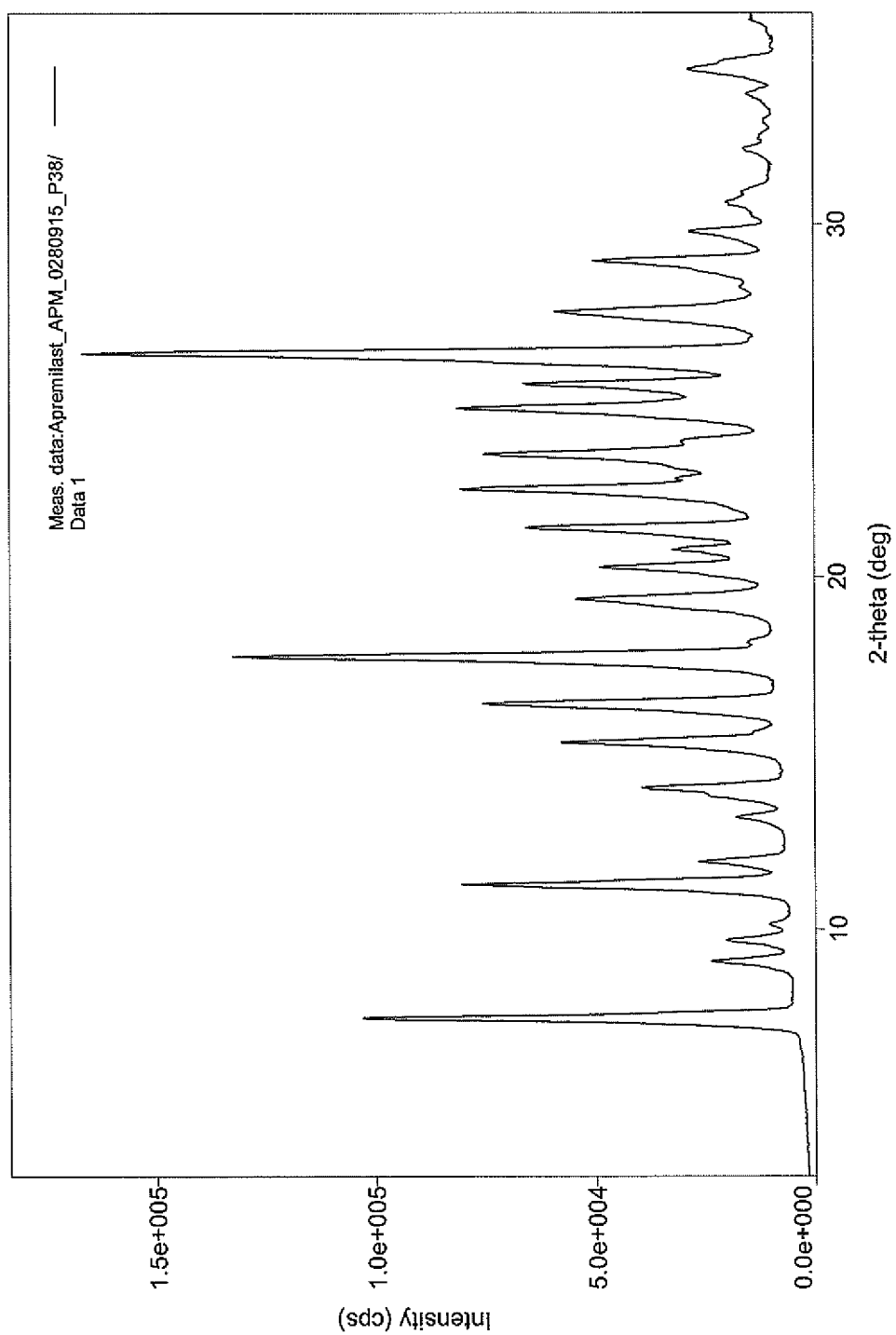


Figure 15

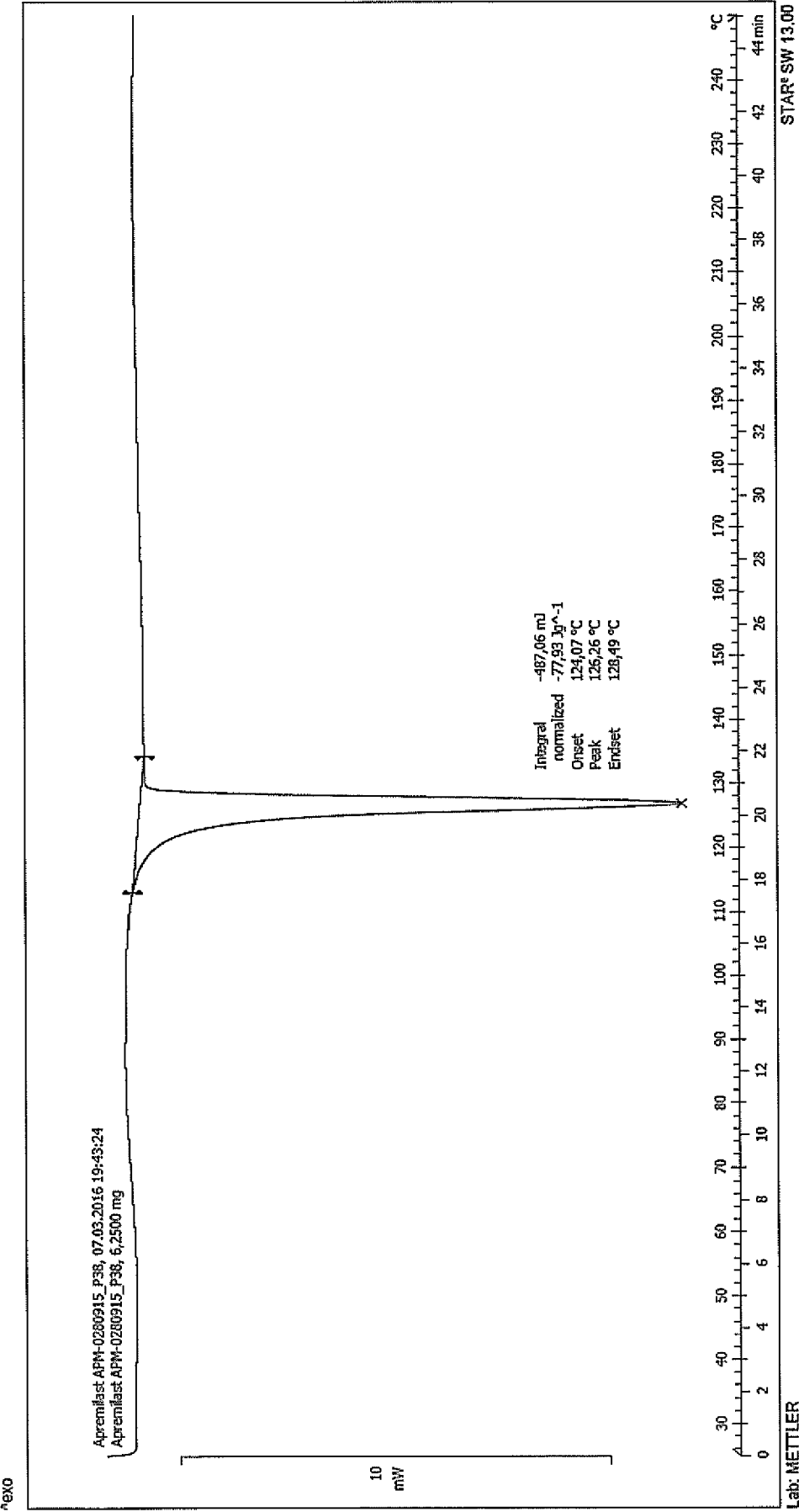


Figure 16

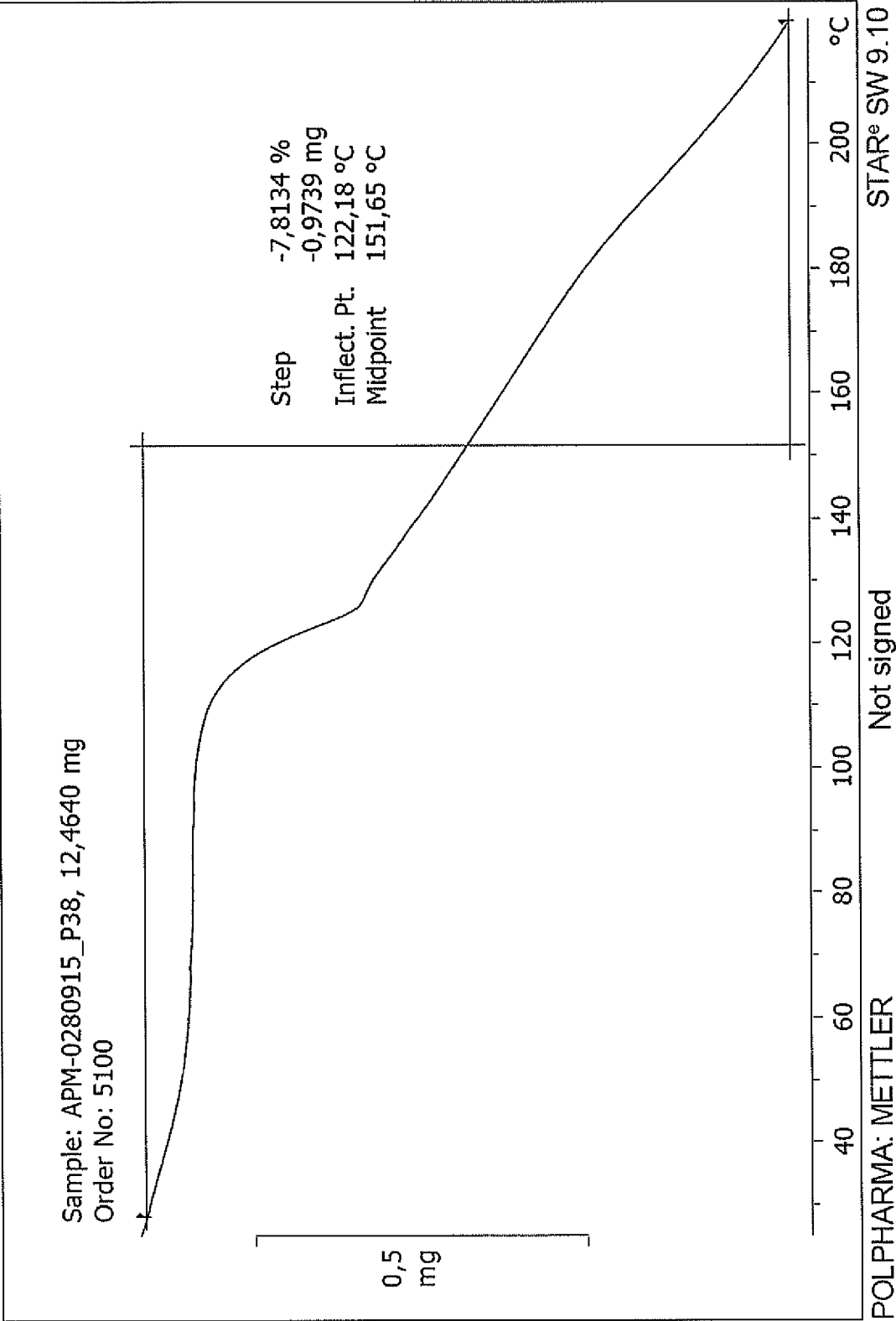


Figure 17

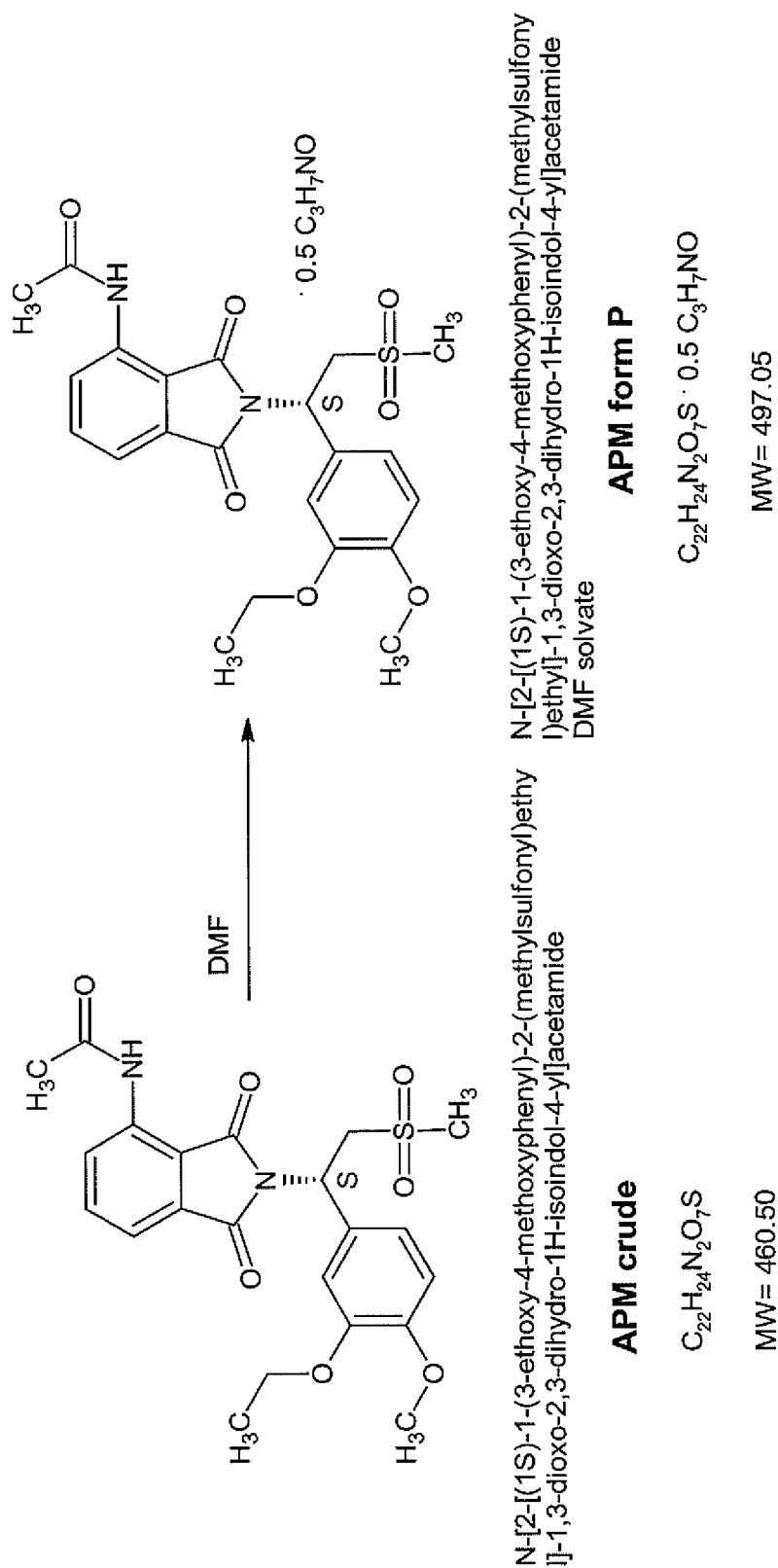


Figure 18

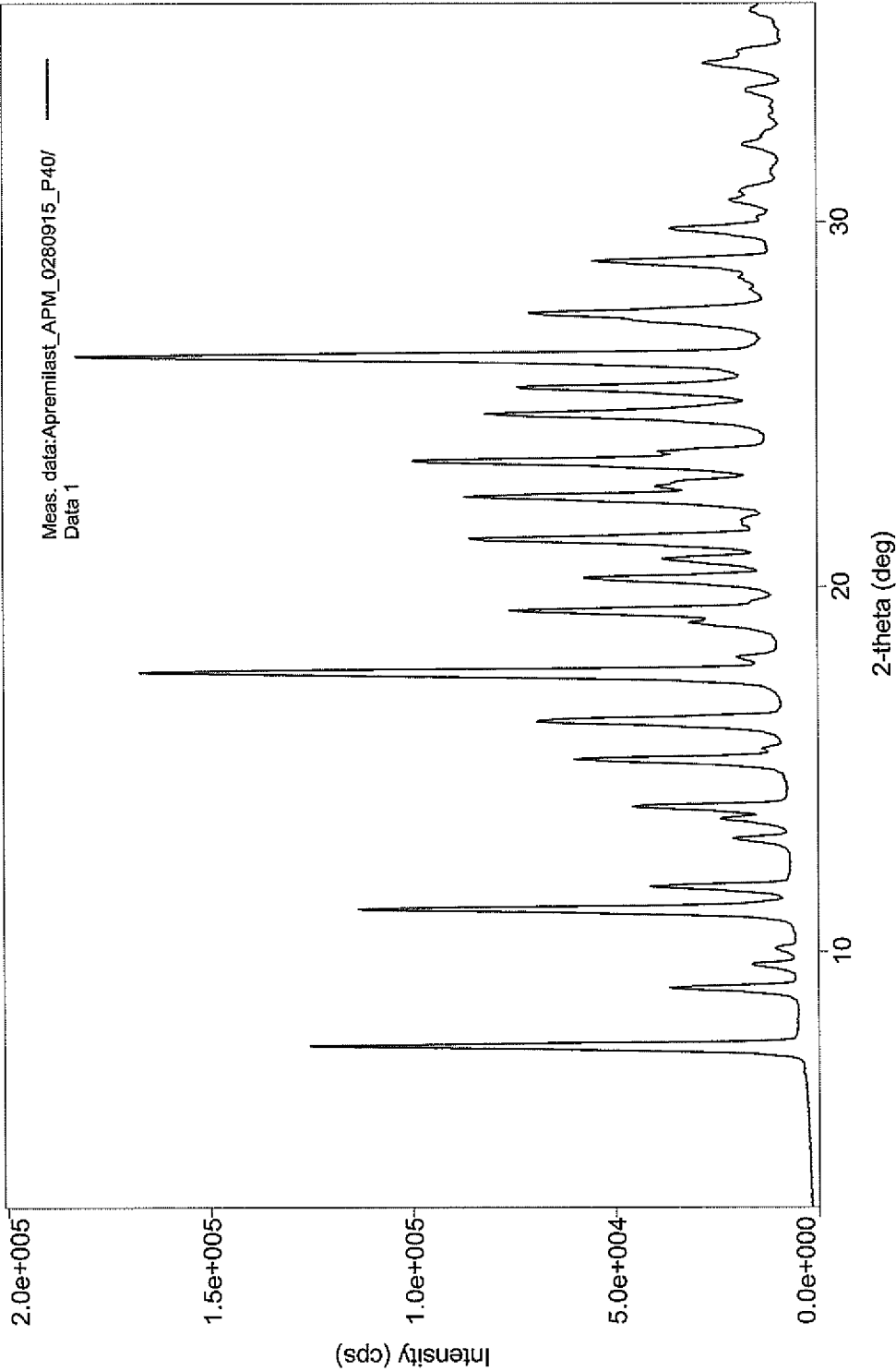


Figure 19

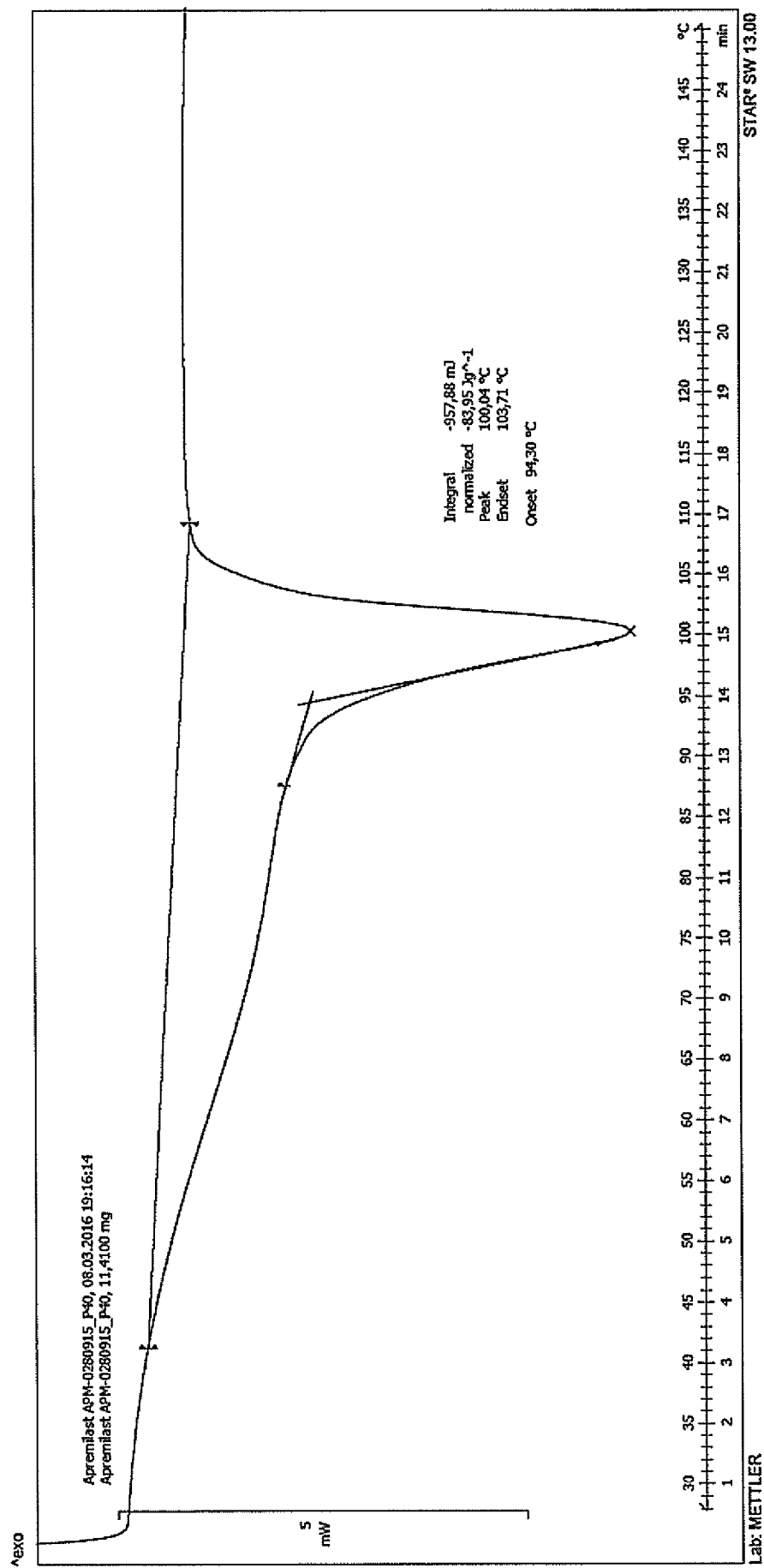


Figure 20

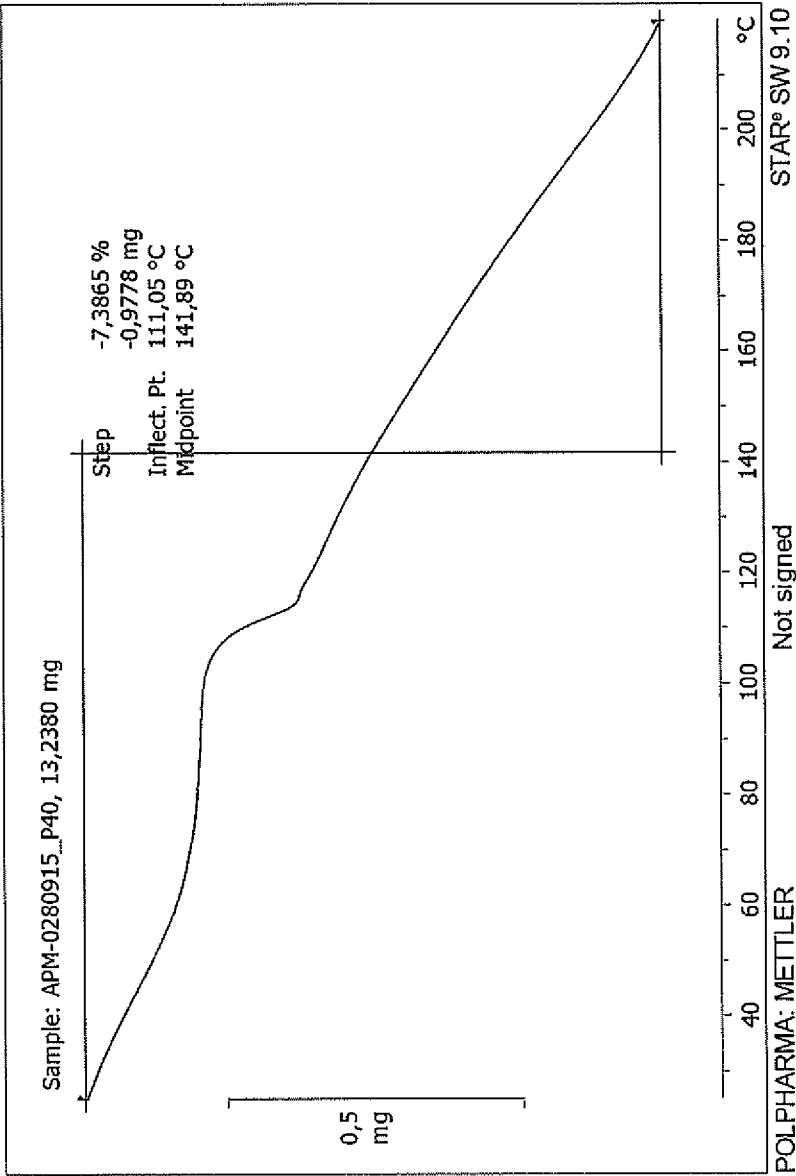


Figure 21

INTERNATIONAL SEARCH REPORT

International application No

PCT/PL2016/000129

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/48

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/234359 A1 (MULLER GEORGE W [US] ET AL) 25 September 2008 (2008-09-25) cited in the application forms A, B and F; forms C-E and, in particular, form G; claims	1-4,8-15
Y	----- HILFIKER R (EDITOR) ED - HILFIKER R: "Polymorphism in the Pharmaceutical Industry", 1 January 2006 (2006-01-01), 20060101, PAGE(S) 1 - 19, XP002528052, ISBN: 978-3-527-31146-0 Chapters 1 and 1.4.2 ----- -/-	1-4,8-15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 2017

Date of mailing of the international search report

11/04/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/PL2016/000129

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 Paragraph bridging pages 165-166; chapter 3.1 -----	1-4,8-15
Y	WO 2015/173792 A1 (MAPI PHARMA LTD [IL]) 19 November 2015 (2015-11-19) claims 16, 23 -----	15
Y	BERNSTEIN J: "Polymorphism of pharmaceuticals", POLYMORPHISM IN MOLECULAR CRYSTALS, XX, XX, 1 January 2002 (2002-01-01), pages 253-255, XP002308143, First sentence of second paragraph on page 254 -----	15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/PL2016/000129

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4, 14(completely); 8-13, 15(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4, 14(completely); 8-13, 15(partially)

Crystalline form N of Apremilast and related subject-matter

2. claims: 5-7(completely); 8-13, 15(partially)

Crystalline form M of Apremilast and related subject-matter

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/PL2016/000129

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008234359 A1	25-09-2008	US 2008234359 A1	25-09-2008
		US 2011112307 A1	12-05-2011
		US 2012101144 A1	26-04-2012
		US 2014100259 A1	10-04-2014
		US 2015196535 A1	16-07-2015

WO 2015173792 A1	19-11-2015	EP 3143004 A1	22-03-2017
		WO 2015173792 A1	19-11-2015
