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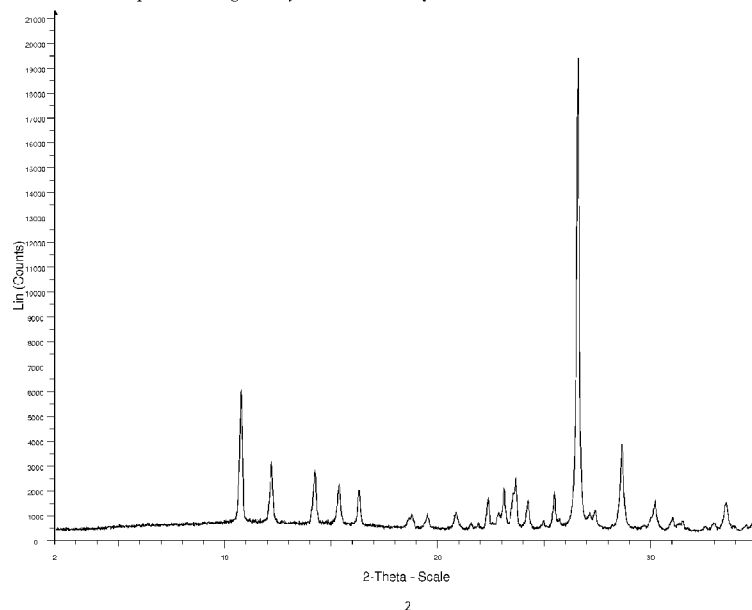
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- (54) **Title:** CRYSTALLINE FORM II OF ANAGRELIDE HYDROCHLORIDE MONOHYDRATE

FIGURE 2: XRPD pattern of anagrelide hydrochloride monohydrate form II



- (57) **Abstract:** The present invention relates to crystalline form II of anagrelide hydrochloride monohydrate, processes for making it, and pharmaceutical compositions comprising it.

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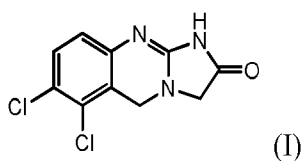
CRYSTALLINE FORM II OF ANAGRELIDE HYDROCHLORIDE MONOHYDRATE

5 BACKGROUND OF THE INVENTION

The present invention relates to crystalline form II of anagrelide hydrochloride monohydrate.

Anagrelide is a pharmaceutically active compound useful for the treatment of (essential) thrombocythaemia. It is represented by formula (I).

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The commercially marketed products Xagrid® and Agrylin® contain the hydrochloride monohydrate salt of the compound (I). Anagrelide hydrochloride monohydrate is an off-white powder that is very slightly soluble in water.

20

Anagrelide was disclosed in US 3932407. Preparation of crystalline anagrelide hydrochloride is described in Example 25. No melting point, IR or XRPD data are disclosed. In this patent, acetonitrile/ethereal HCl is used as solvent/salt forming acid system to produce anagrelide hydrochloride from anagrelide free base. The use of ether is not suitable for large scale production due to the risk for explosion. Acetonitrile is not preferred as it is a less acceptable class 2 solvent.

25

US 4146718 teaches in Example 4 the preparation of crystalline anagrelide hydrochloride monohydrate from anagrelide base in boiling methanol by adding concentrated HCl. Precipitation was effected by adding ether as an anti-solvent. According to a comparative example, anagrelide hydrochloride was prepared by means of recrystallisation of anagrelide hydrochloride from an ethanolic HCl solution. There is no reference as to which crystalline form is obtained.

30

US 5391737 discloses a process to make anagrelide hydrochloride semihydrate. It makes use of methanol as the solvent and ethanolic HCl as the salt forming agent. This process is not desired as methanol is a pharmaceutically less acceptable solvent. Furthermore, the reaction is performed at reflux temperature.

In Example 6 of WO 2009/087673, a preparation route for crystalline anagrelide hydrochloride monohydrate was disclosed using concentrated HCl as the salt forming agent and ethanol as the solvent. Furthermore, the salt preparation was performed at reflux temperature.

- 5 As anagrelide hydrochloride monohydrate is an important pharmaceutical, any improvement in the state of the art relevant to this salt, particularly with the aim to identify stable crystalline forms with improved physical properties, is needed.

BRIEF DESCRIPTION OF THE DRAWINGS

- 10 Figure 1: XRPD pattern of form I of anagrelide hydrochloride monohydrate
Figure 2: XRPD pattern of form II of anagrelide hydrochloride monohydrate
Figure 3: XRPD pattern of form III of anagrelide hydrochloride monohydrate
Figure 4: Overlay of the XRPD patterns of anagrelide hydrochloride monohydrate forms I to III
15 Figure 5: Solubility curves of form II of anagrelide hydrochloride monohydrate compared with form I

DETAILED DESCRIPTION OF THE INVENTION

- The present invention is based on the discovery of polymorphism and the identification
20 of a specific useful polymorphic form of anagrelide hydrochloride monohydrate for incorporation into a pharmaceutical composition. After repeating the prior art processes for making anagrelide hydrochloride monohydrate in solid state as indicated in the comparative examples, it was found that these processes yielded a certain crystalline form of anagrelide hydrochloride monohydrate, herein denoted as form I. The crystalline anagrelide
25 hydrochloride monohydrate form I can generally be characterized by an XRPD pattern as shown in Figure 1, and has characteristic diffraction peaks at the following angles: 5.4°, 9.6°, 13.4°, 15.8°, 16.1°, 16.7°, 17.0°, 17.8°, 18.2°, 19.2°, 20.7°, 24.0°, 26.4°, 28.2°, and 31.8° degrees 2 theta (± 0.2 degrees 2 theta). For clarity, whenever the expression “ ± 0.2 degrees 2 theta” is used herein it refers to the variance for each peak angle listed.

- 30 In the present invention, a particularly useful crystalline polymorph of anagrelide hydrochloride monohydrate was discovered. This polymorph has a crystal structure different from form I. This polymorph is characterized by a distinctly different X-ray powder diffraction (XRPD) pattern comprising signals at diffraction angles at 14.2°, 15.3°, 16.3°,

18.7°, 19.5°, 22.4°, 23.1°, 23.5°, 23.7°, 24.2°, 26.6°, and 33.6° degrees 2 theta (± 0.2 degrees 2 theta), at which angles form I shows no or just tiny peaks.

Typically, the XRPD pattern of the new polymorph substantially corresponds to that as shown in Figure 2. "Substantially corresponds" is meant to cover variations/differences in the pattern that would be understood by a worker skilled in the art not to represent a difference in the crystal structure, but rather differences in the technique, equipment, sample preparation, impurities, etc. Differences in a pattern or spectra that are not attributable to these factors indicate that the pattern in question does not "substantially correspond" to the reference pattern. For clarity, the XRPD pattern of Figure 1 does not substantially correspond to that of Figure 2 or Figure 3 as can be clearly seen in the overlay in Figure 4. Conversely, a pattern or spectrum may "substantially correspond" to e.g., Figure 2, even though it is not an identical/superimposable image. Further, the XRPD pattern of an actual sample of anagrelide hydrochloride monohydrate may differ from the pattern as shown in any one of Figures 1 to 4 with respect to intensities of the respective peaks due to preferred orientation of the crystal lattices in the powder sample.

This new polymorph of anagrelide hydrochloride monohydrate of the above XRPD pattern shall be denoted in this application as "anagrelide hydrochloride monohydrate form II," or simply "form II".

The present invention includes anagrelide hydrochloride monohydrate Form II as an isolated species (i.e. after removal of the residual solvents used in the method of making it), especially in an essentially (chemically) pure form and/or essentially polymorphically pure form. "Essentially pure" refers to at least 70% pure, preferably at least 80% pure, more preferably at least 90% pure, and still more preferably at least 95%, including at least 98% pure, at least 99% pure, and at least 99.8% pure, with respect to the presence of anagrelide hydrochloride monohydrate in a sample. "Essentially polymorphically pure" refers to at least 70% pure, preferably at least 80% pure, more preferably at least 90% pure, and still more preferably at least 95%, including at least 98% pure, at least 99% pure, and at least 99.8% pure, with respect to the presence of form II in a sample. Typically in order for a sample of anagrelide hydrochloride monohydrate to have an XRPD pattern that substantially corresponds to Figure 2, the Form II sample must be in essentially (chemically) pure form (typically at least 90% pure) and essentially polymorphically pure form (typically at least 90% polymorphically pure).

The form II of the present invention is polymorphically stable at ambient temperature and even more stable than form I, at least in solvents as ethanol, 2-propanol, acetone, and ethyl acetate as shown in the examples.

Form II is also more stable against aqueous hydrolysis than form I as shown in the
5 stability experiments in which both crystal forms were stirred in demi-water for up to 180 minutes.

Surprisingly, besides being more polymorphically stable than form I, at room temperature form II is also more soluble in USP acetate buffer pH 4.5, USP phosphate buffer pH 6.8, Milli-Q water and 0.1 M HCl than form I. One possible explanation for this higher
10 solubility of the more stable form II could be a better wettability. As a result, form II has at least the following advantages over form I:

- 1) Better thermodynamic stability at temperatures below 70°C;
- 2) Better stability against aqueous hydrolysis; and
- 3) Higher solubility, despite thermodynamic stability.

15 Accordingly, the form II of anagrelide hydrochloride monohydrate offers a potentially superior crystalline form of anagrelide for storing or making pharmaceutical compositions.

Anagrelide hydrochloride monohydrate form II may be obtained by various processes. In essence, the procedures may be sorted into two groups:

a] Stirring a suspension of crystalline form I of anagrelide hydrochloride
20 monohydrate in an alcoholic, ester, or ketone solvent (solvent-mediated polymorphic transition).

The alcoholic solvent is an aliphatic C₁-C₄ alcohol, preferably chosen from ethanol, 2-propanol, or a mixture thereof. An example of a suitable ester is ethyl acetate. An example of a suitable ketone is acetone. The temperature of stirring is preferably at an ambient
25 temperature; typically, the temperature of stirring is lower than 70°C, preferably from 15 to 35°C. The stirring time is typically at least 30 minutes, preferably of from 30 to 180 minutes.

In an advantageous arrangement, a seeding crystal of form II may be used to facilitate the transformation.

b] Suspending anagrelide free base in a suitable solvent and contacting the
30 suspension with a solution of hydrochloric acid in 2-propanol at an ambient temperature.

The anagrelide free base is preferably contacted with HCl by suspending anagrelide base in a solvent followed by contacting the formed suspension with an aqueous solution of HCl in 2-propanol under stirring. In one embodiment, an aqueous solution of HCl in 2-propanol is added to the anagrelide free base suspension under stirring. In another

embodiment, the suspension of anagrelide base in a solvent is added to the aqueous solution of HCl in 2-propanol under stirring. The suitable solvent is selected from acetonitrile, ethanol, acetone, ethyl acetate, or a mixture thereof.

Anagrelide free base may be used in an isolated form, which advantageously is a solid form. Alternatively, a reaction mixture comprising anagrelide free base as a result of a chemical reaction may be used.

The temperature of stirring is preferably at an ambient temperature; typically, the temperature of stirring is from 15 to 35°C. The stirring time is typically at least several hours, preferably at least 2 hours.

In an advantageous arrangement, a seeding crystal of form II may be used to facilitate the transformation.

When anagrelide free base was suspended in 2-propanol and subsequently contacted with a solution of hydrochloric acid in 2-propanol, a third, solvated form III was identified. Alternatively, this form III is also obtained when a suspension of anagrelide hydrochloride monohydrate is stirred at reflux, filtered and vacuum-dried at ambient temperatures.

A characteristic XRPD pattern of form III is depicted in Figure 3. This polymorph is characterized by a distinct X-ray powder diffraction (XRPD) pattern comprising signals at diffraction angles of about 3.7°, 7.4°, 10.2°, 11.0°, 15.9°, 19.1°, 19.4°, 20.5°, 22.1°, 23.9°, 24.7°, 25.3°, 25.6°, 25.9°, 26.9°, 27.7°, 29.0°, 30.9°, 31.9°, 32.4°, 33.3°, and 34.4° degrees 2 theta (± 0.2 degrees 2 theta). This form III is unstable as it converts into form I or a mixture of forms I and II when exposed to air, and thus unsuitable for use in a pharmaceutical composition.

In any of the above processes, form II of anagrelide hydrochloride monohydrate may be advantageously isolated from the suspension thereof in a liquid by conventional techniques such as filtration or centrifugation, washed by a suitable liquid and dried. Air-drying of form II at ambient temperature does not cause any polymorphic change.

It is preferred that the formed crystals have an average particle size of 1,000 µm or smaller, preferably smaller than 250 µm, and more preferably smaller than 100 µm. The known particle size analysis methods can be used for determining the particle size, for example particle size measurement using light, like light-scattering methods, in particular Malvern Mastersizer.

The crystalline product of smaller particle size is, in general, easier to process in forming pharmaceutical compositions than that having a larger particle size. If such particle

size is not obtainable by the process itself, conventional operations like sieving or milling can be performed to achieve a desired particle size (distribution).

The known processes for making crystalline anagrelide hydrochloride monohydrate are performed at reflux temperature. The processes of the present invention are performed at an ambient temperature; typically, the temperature of stirring is from 15 to 35°C, wherein anagrelide hydrochloride monohydrate form II is directly obtained.

Anagrelide hydrochloride monohydrate is unstable in water, and it converts into anagrelide free base within 30-180 minutes. This will also (partially) occur in a wet granulation process using water. It is apparent from the above that form II is a more stable and yet more soluble form of anagrelide hydrochloride monohydrate, at least in a suspension with ethanol, 2-propanol, or a mixture thereof. This represents an advantage, e.g. in a wet granulation processes using either of these solvents for making granulates, tablets or in pelletization processes. The physical stability of form II under contact with the granulation or pelletization liquid minimizes the danger of a polymorphic change of anagrelide hydrochloride monohydrate during the process, which could cause changes in properties of the resulting granulate, tablet or pellet. As no conversion or decomposition into the free base takes place, ethanol, 2-propanol, or a mixture thereof could also be suitable coating solvents.

Anagrelide hydrochloride monohydrate form II can be formulated into various pharmaceutical compositions with one or more pharmaceutically acceptable excipients. The pharmaceutical composition can be in a unit dosage form, such as a solid oral dosage form (i.e. a tablet or capsule), or a bulk precursor thereof, such as a pre-blended mixture ready for further blending/addition of ingredients, or a blend ready for tableting or filling into capsules. Making a pharmaceutical composition from anagrelide hydrochloride monohydrate form II by a process which comprises combining it with said at least one pharmaceutically acceptable excipient is a specific aspect of the present invention.

Thus, the invention includes pharmaceutical compositions, preferably solid oral pharmaceutical compositions, comprising a therapeutically effective amount of the form II of anagrelide hydrochloride monohydrate, in admixture with one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients may include, without limitation, carriers, diluents, fillers, binders, lubricants, disintegrants, glidants, colorants, pigments, taste masking agents, sweeteners, flavorants, plasticizers, etc. The proper excipient(s) are selected based in part on the dosage form, the intended mode of administration, the intended release rate, and manufacturing reliability.

Examples of common types of excipients include various polymers, waxes, calcium phosphates, sugars, etc. Polymers include cellulose and cellulose derivatives such as HPMC, hydroxypropyl cellulose, hydroxyethyl cellulose, microcrystalline cellulose, carboxymethyl-cellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and
5 ethylcellulose; polyvinylpyrrolidones; polyethylenoxides; polyalkylene glycols such as polyethylene glycol and polypropylene glycol; and polyacrylic acids including their copolymers and crosslinked polymers thereof, e.g., Carbopol[®] (B.F. Goodrich), Eudragit[®] (Rohm), polycarbophil, and chitosan polymers. Waxes include carnauba wax, hydrogenated castor oil, glyceryl behenate, glycerylpalmito stearate, and saturated polyglycolized
10 glycerate. Calcium phosphates include dibasic calcium phosphate, anhydrous dibasic calcium phosphate, and tribasic calcium phosphate. Sugars include simple sugars, such as lactose, maltose, mannitol, fructose, sorbitol, saccharose, xylitol, isomaltose, and glucose, as well as complex sugars (polysaccharides), such as maltodextrin, amyloextrin, starches, and modified starches.

15 Form II of anagrelide hydrochloride monohydrate may preferably be formulated into compositions for oral administration. The compositions for oral administration may be solid or liquid, such as in the form of an oral solution or suspension, oral capsule, or an oral tablet, and may exhibit immediate release or modified and/or extended release of the active substance from the composition.

20 The pharmaceutical compositions comprising form II of anagrelide hydrochloride monohydrate may be formulated, for instance, into conventional oral tablets. The tablets may be monolithic tablets, i.e. tablets that upon ingestion do not disintegrate into a plurality of smaller units from which the active ingredient is finally released, or may be disintegrable tablets. The tablets may be produced by any standard tableting technique, e.g. by wet
25 granulation, dry granulation, or direct compression. The wet granulation procedure comprises mixing anagrelide hydrochloride monohydrate and excipients with a granulation liquid and forming a solid granulated mass, which is then optionally dried, screening the granulate, mixing with remaining excipients, in particular with a lubricant, and compressing into a tablet. The dry granulation procedure typically comprises mixing the solid excipients (except
30 lubricants), compacting the mixture in a compactor (e.g., a roller compactor), milling the compacted mass, screening the milled granules, mixing with a lubricant, and compressing the mixture into tablets. The direct compression procedure generally comprises mixing the solid excipients and compressing the uniform mixture into tablets.

In an alternative arrangement, the above produced wet or dry granulates or the direct mix of the solid excipients may be directly filled into capsules.

Anagrelide hydrochloride monohydrate form II may also be blended into compositions that are suitable for being formulated into pellets by known pelletization techniques. A plurality of pellets comprising a single dose of anagrelide may be encapsulated into capsules made from pharmaceutically acceptable material, such as hard gelatin. In another mode, a plurality of pellets may be compressed together with suitable binders and disintegrants to a disintegrable tablet that, upon ingestion, decomposes and releases the pellets. In yet another mode, the plurality of pellets may be filled into a sachet.

The relative amount of anagrelide hydrochloride monohydrate form II in the granulate, tablet or pellet mass is not particularly limited but typically may range from 0.1 to 10 wt%, such as 0.3 to 3.0 wt%.

The solid oral compositions and dosage forms comprising form II of anagrelide hydrochloride monohydrate are advantageously of an immediate release of anagrelide from the composition after ingestion. In some embodiments, they have the following release profile: more than 80% of the active is released in 30 minutes, preferably in 15 minutes, when measured by the paddle method of Ph.Eur. at 50 rpm in 0.01 M HCl.

Tablets or pellets may be coated by a suitable film coat, which may be a film coat (dissolvable in the stomach) or an "enteric coat" (not dissolvable in the stomach). The film coat may protect the tablet against the environment (light, air, moisture) during storage and handling. Any conventional film coat may be used. The enteric coat retards or inhibits the release of anagrelide in the stomach.

The unit dose in tablet form may comprise a single tablet but it may also comprise a divided tablet or several smaller tablets (minitabets) administered at the same time. The unit dose of pellets in capsule form may comprise a single capsule. Solutions for oral administration may be packed in a multidose package, the unit dose being packaged in a calibrated vessel.

The pharmaceutical dosage forms formulated from the compositions of the present invention may comprise a unit dose of anagrelide, i.e., a therapeutically effective amount of anagrelide hydrochloride monohydrate for a single dose administration. The amount of form II of anagrelide hydrochloride monohydrate, expressed as anagrelide base, in the daily unit dose may range from 0.1 to 15 mg, typically from 0.3 to 5.0 mg.

Form II of anagrelide hydrochloride monohydrate of the present invention or pharmaceutical compositions comprising it may be used in medicine, for instance in the

treatment of (essential) thrombocythaemia. It may be used in monotherapy or in combination therapy.

The invention will be further described with reference to the following non-limiting examples.

5

EXAMPLES

Comparative example 1: Example 25 of US 3932407

0.16 g of anagrelide base was suspended in 7 ml acetonitrile (no clear solution at RT) and stirred at RT. To the suspension, 0.9 ml 1N HCl in diethyl ether was added. The
10 suspension was stirred at RT for about 3 hours. The suspension was filtered over a P3-glass filter (reduced pressure). The solid was air-dried overnight at RT. An off-white solid with lumps was obtained.

XRPD showed all peaks characteristic of form I cf. Figure 1.

15 Comparative example 2: based on Example 1 of US 5391737

Example 1 of US 5391737 does not give sufficient details as to the actual conduction of the experiment.

1.0 g of anagrelide base was suspended in 8.5 ml methanol, stirred and heated to reflux. No clear solution was obtained. To the hot suspension, 8.5 ml ethanol with 10-20% HCl was
20 added and stirring at reflux was continued for about 15 minutes. The suspension slowly became thinner, but no clear solution was observed at all.

The suspension was allowed to cool to RT and filtered over a P3-glass filter (reduced pressure). The solid was washed with little ethanol, analysed with XRPD and air-dried overweekend at RT. An off-white powder with lumps was obtained.

25 XRPD showed unknown peaks. NMR indicated significant degradation into at least four impurities.

Comparative example 3: Example 6 of WO 2009/087673

30 ml ethanol was heated up with an oilbath, while stirring. At 75°C, 1 gram of
30 anagrelide base was added and the suspension was allowed to reflux. Reflux and stirring was maintained for 10 minutes. To the suspension, 0.3 ml demi-water was added and reflux/stirring was continued for an additional 5 minutes. To the white, thick suspension, 1 ml concentrated HCl (37% aq) was added in a 3-minute period. As a result, the suspension became more yellowish and much thinner. After an additional 5 minutes at reflux, the

suspension was cooled to 10-15°C taking about 15 minutes. The suspension was stirred for 15 min at 10-15°C. The suspension was filtered over a P3-glass filter (reduced pressure). The solid was washed with 2 ml ethanol and vacuum-dried at 30°C for about 4 hours. An off-white powder was obtained.

5

XRPD showed peaks pointing to a mixture of form I and form II cf. Figures 1 and 2.

Example 1: Preparation of form II from anagrelide free base

0.5 g of anagrelide base was suspended in 20 ml ethanol (no clear solution at RT) and stirred at RT. To the suspension, 0.8 ml 5-6 N aqueous HCl in 2-propanol was added. The
10 suspension was stirred at RT for about 2 hours. Then, the suspension was filtered over a P3-glass filter (reduced pressure). The solid was air-dried overnight at RT. An off-white powder with lumps was obtained.

XRPD showed all peaks characteristic of form II cf. Figure 2.

15

Example 2: Preparation of form II from form I

~0.5 g of anagrelide hydrochloride monohydrate form I was suspended in 5 ml ethanol and stirred at RT for about 2 days. The suspension was filtered over a P3-glass filter (reduced pressure). The solid was air-dried overweekend at RT. An off-white, fine powder was obtained.

20

XRPD showed all peaks characteristic of form II cf. Figure 2.

2.0 g of anagrelide hydrochloride monohydrate (a mixture of forms I and II), was suspended in 20 ml ethanol. The mixture was stirred overnight at RT in a closed flask. The suspension was filtered over a P3-glass filter (reduced pressure). The solid was washed with ethanol and air-dried overweekend at RT. An off-white to pale-beige, fine powder was
25 obtained.

XRPD showed all peaks characteristic of form II cf. Figure 2.

Example 3: Preparation of form III

15.0 g anagrelide hydrochloride monohydrate was suspended in 150 ml 2-propanol,
30 heated to reflux and stirred at reflux for 2 hours. Then, 1 ml 5-6 N aqueous HCl in 2-propanol was added and the suspension was cooled down to luke-warm. The suspension was filtered over a P3-glass filter (reduced pressure). The solid was washed with 2-propanol and air-dried at RT. An off-white to yellowish, fine powder was obtained.

XRPD showed all peaks characteristic of form III cf. Figure 3.

Stability data of forms I and II

Stability of form I

- 5 0.5-15 g of anagrelide hydrochloride monohydrate form I was suspended in 5-25 ml of solvent and stirred at RT for 0.5-24 hours. The suspension was filtered over a P3-glass filter (reduced pressure), washed with solvent and dried. Details and results are provided in the table below.

Solvent	Stirring time	Stirring temperature	XRPD
Demi-water	30 min	RT*	Anagrelide base
	180 min	RT	Anagrelide base
Ethanol	30 min	RT	Form II
	16 hours	RT	Form II
2-propanol	16 hours	RT	Form I + II
Acetone	2 days	RT	Form II
Ethyl acetate	2 days	RT	Form II

- 10 * RT “means room temperature” (between 15-25°C, typically between 20-21°C).

Stability of form II

- 2.0 g of anagrelide hydrochloride monohydrate form II was suspended in 20 ml solvent. The mixture was stirred at RT in a closed flask. At certain time points, a small amount of the suspension was filtered over a P3-glass filter (reduced pressure). The solids were air-dried overnight at RT. Details and results are provided in the table below.
- 15

Solvent	Stirring time	Stirring temperature	XRPD
Demi-water	30 min	RT*	Form II + anagrelide base
	60 min	RT	Form II + anagrelide base
	120 min	RT	Form II + anagrelide base
	180 min	RT	Anagrelide base

Ethanol	30 min	RT	Form II
	60 min	RT	Form II
	120 min	RT	Form II
	overnight	RT	Form II
	3 hours	reflux	Form I
2-propanol	30 min	RT	Form II
	60 min	RT	Form II
	120 min	RT	Form II
	overnight	RT	Form II

* RT “means room temperature” (between 15-25°C, typically between 20-21°C).

Conversion study in ethanol

0.25 g of anagrelide hydrochloride monohydrate (a mixture of forms I and II) was suspended in 5 ml of ethanol and stirred at a specified stirring temperature for 22-24 hours. The suspension was filtered over a P3-glass filter (reduced pressure), washed with solvent and dried. Experimental details and results are provided below.

Stirring temperature (°C)	Crystal form (XRPD)
30	II
35	II
40	II
45	II
50	II
55	II
60	II
65	II
67.5*	II
70*	II
72.5*	I + II
75*	mostly I, some II left

* Stirring time 2 hours only.

Form II is stable at temperatures below 70°C, but is not stable at reflux. The transition point lies around 72.5°C.

Thus, at temperatures below 72.5°C form II will crystallise, whereas at temperatures above 72.5°C form I will preferentially be formed.

5

In the above examples, the XRPD patterns were recorded on a Bruker-AXS D8 vario ($\Theta/2\Theta$ geometry, reflection mode, Vantec PSD detector) operating at the following settings:

	Start angle (2θ):	2.0°
10	End angle (2θ):	35.0°
	Scan step width:	0.02°
	Scan step time:	between 0.7-5.5 seconds
	Radiation type:	Cu
	Radiation wavelengths:	1.54060 Å ($K\alpha_1$), primary monochromator used
15	Exit slit:	6.0 mm
	Focus slit:	0.2 mm
	Divergence slit:	Variable (V20)
	Antiscatter slit:	11.8 mm
	Receiving slit:	20.7 mm

20

Solubility experiments

The instant solubility of anagrelide hydrochloride monohydrate form II, form I and free base was determined in USP acetate buffer pH 4.5, USP phosphate buffer pH 6.8, Milli-Q water (herein below “MQ”) and 0.1 M HCl. About 30 mg of the drug substance was

25 transferred into a clear 50 ml sample jar and a stirring bar was added. Subsequently 30 ml of test medium was added; the vial was closed and placed on a magnetic stirrer. Under constant stirring at room temperature samples of 2 ml were taken at $t=0$, 10, 20, 30, 40, 50, and 60 minutes. The samples were immediately filtered through a 0.45 μm syringe disk filter (first ml was discarded) and analyzed at once with the HPLC-UV method described in Table 1.

30 The solubility was calculated in mg/ml anagrelide free base against an external standard (AGL.hcl.mhy.120310) dissolved in acetonitrile/milli-Q (ACN/MQ) (50:50).

Table 1 HPLC-UV parameters used for instant solubility testing

Column:	Xbridge Shield RP18, 50x4.6mm, 3.5µm (Waters)
Column temperature:	30°C
Auto sampler temp.:	Room temperature
Flow:	1.2 ml/min, isocratic
Detection:	UV, 254 nm
Injection volume:	3 µl
Mobile phase:	50 mM KH ₂ PO ₄ to pH=2.5 / ACN (75:25)
Run time:	3.5 min.
Next injection delay:	0 min.

The results are shown in Figure 5. In general, the instant solubility curves of form II are higher compared to form I indicating a higher instant solubility.

CLAIMS

1. Crystalline form II of anagrelide hydrochloride monohydrate characterized by an XRPD pattern that includes the following peaks at 2θ : 14.2, 15.3, 16.3, 18.7, 19.5, 22.4, 23.1, 23.5, 23.7, 24.2, 26.6, and 33.6 ± 0.2 degrees, when measured with $\text{CuK}\alpha 1$ radiation ($\lambda = 1.54060 \text{ \AA}$).
5
2. The crystalline form II of anagrelide hydrochloride monohydrate according to claim 1 having an average particle size of $1,000 \text{ }\mu\text{m}$ or smaller.
3. The crystalline form II of anagrelide hydrochloride monohydrate according to claim 1 or 2 having a polymorphic purity of at least 70%.
- 10 4. A process for making the crystalline form II of anagrelide hydrochloride monohydrate according to any one of claims 1 to 3 from crystalline form I of anagrelide hydrochloride monohydrate comprising:
 - a) suspending crystalline form I in an aliphatic $\text{C}_1\text{-C}_4$ alcohol, ester, or ketone solvent;
 - 15 b) stirring at an ambient temperature for at least 30 minutes, preferably of from 30 to 180 minutes; and
 - c) isolating the obtained crystals of form II.
5. The process according to claim 4, wherein the aliphatic $\text{C}_1\text{-C}_4$ alcohol solvent of step a) is selected from ethanol, 2-propanol, or a mixture thereof.
- 20 6. The process according to claim 4 or 5, wherein the ambient temperature is between 15 and 35°C .
7. The process according to any one of claims 4 to 6, wherein the suspension of step a) is seeded with crystals of form II according to any one of claims 1 to 3.
8. A process for making the crystalline form II of anagrelide hydrochloride monohydrate according to any one of claims 1 to 3 comprising:
25
 - a) suspending anagrelide free base in a solvent at an ambient temperature;
 - b) contacting the suspension of step a) with a solution of hydrochloric acid in 2-propanol at an ambient temperature;
 - c) stirring at an ambient temperature for several hours, preferably more than 2
30 hours; and
 - d) isolating the obtained crystals of form II according to any one of claims 1 to 3; wherein the solvent in step a) is selected from acetonitrile, ethanol, acetone, ethyl acetate, or a mixture thereof.

9. The process according to claim 8, wherein the suspension of step c) is seeded with crystals of form II according to any one of claims 1 to 3.
10. A pharmaceutical composition comprising the crystalline form II of anagrelide hydrochloride monohydrate according to any one of claims 1 to 3 and a
5 pharmaceutically acceptable excipient.
11. A process for making the pharmaceutical formulation according to claim 10 by wet granulation using a solvent selected from ethanol, 2-propanol, or a mixture thereof.
12. The crystalline form II of anagrelide hydrochloride monohydrate according to any one of claims 1 to 3 or the pharmaceutical composition according to claim 10 for use as a
10 medicament.
13. The crystalline form II of anagrelide hydrochloride monohydrate according to any one of claims 1 to 3 or the pharmaceutical composition according to claim 11 for use in the treatment of (essential) thrombocythaemia.

FIGURE 1: XRPD pattern of anagrelide hydrochloride monohydrate form I

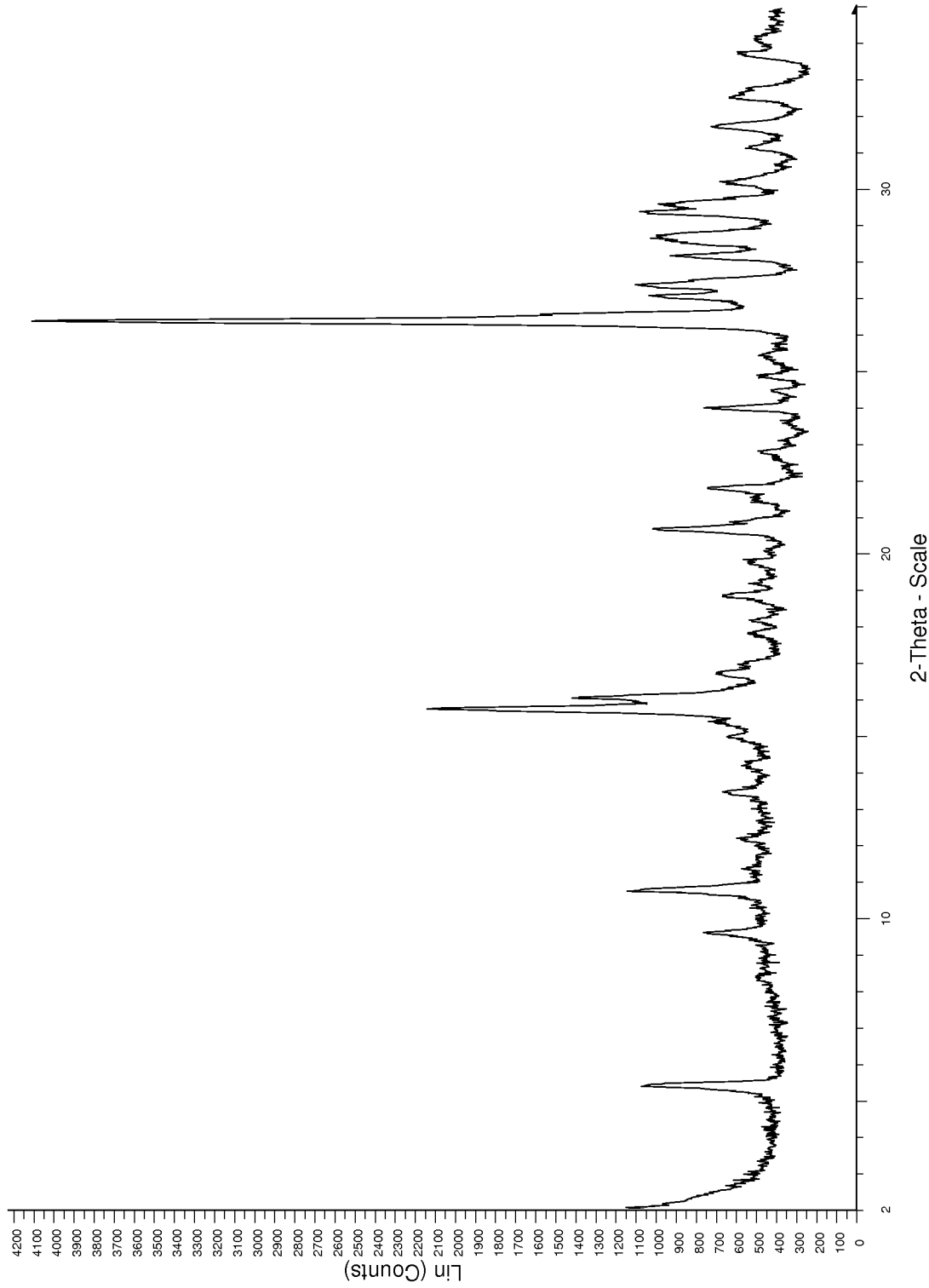


FIGURE 2: XRPD pattern of anagrelide hydrochloride monohydrate form II

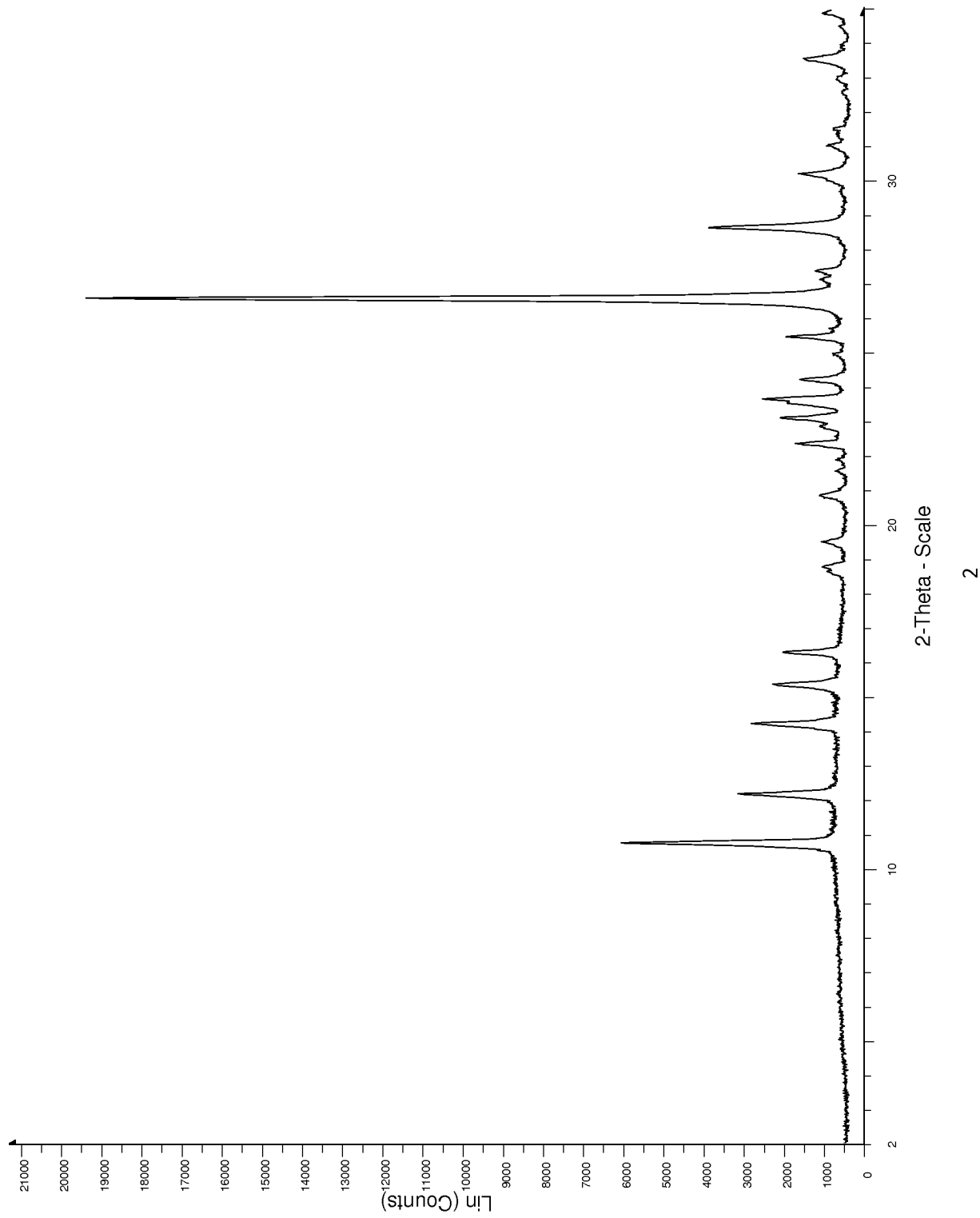


FIGURE 3: XRPD pattern of anagrelide hydrochloride monohydrate form III

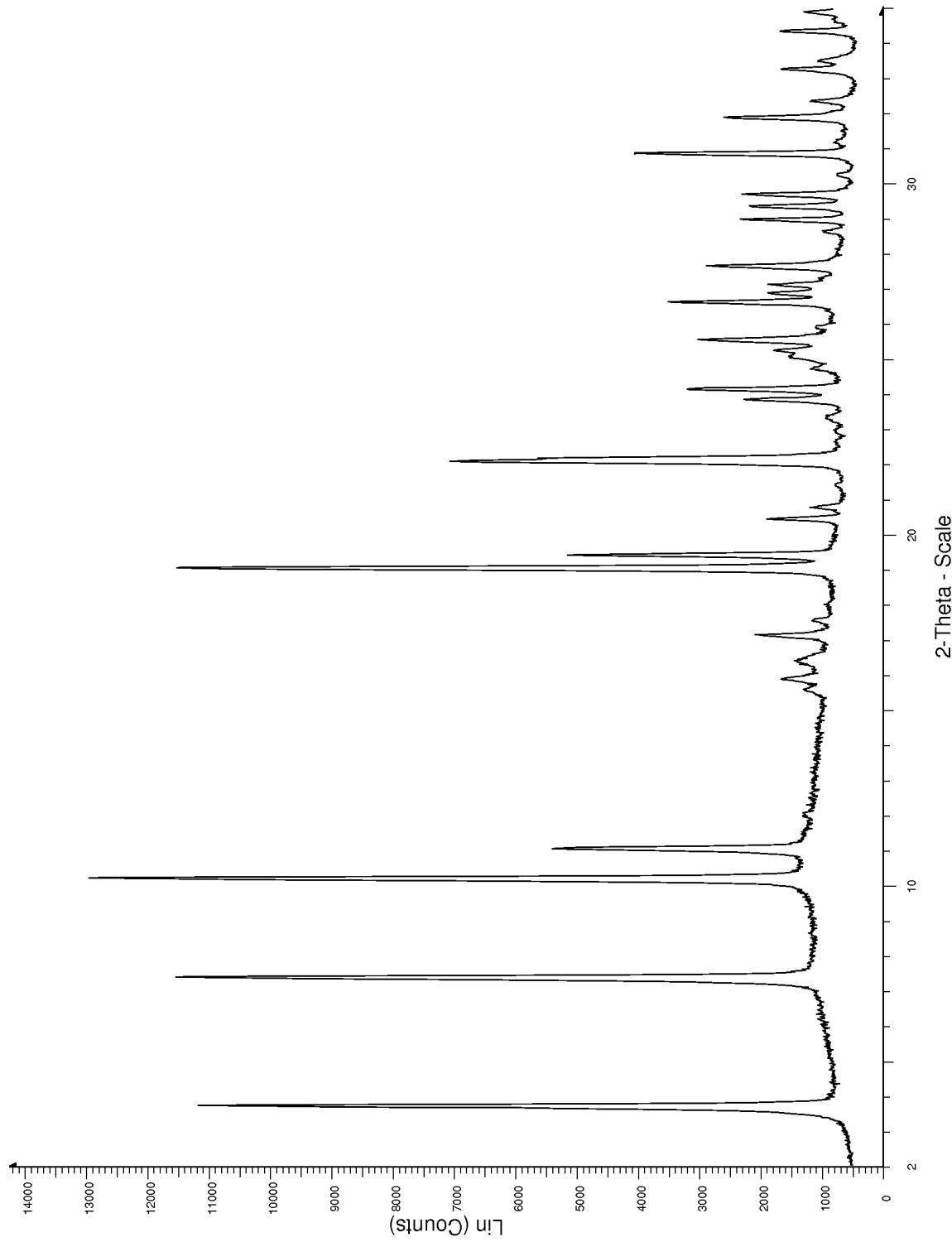


FIGURE 4: Overlay of the XRPD patterns of anagrelide hydrochloride monohydrate forms I to III

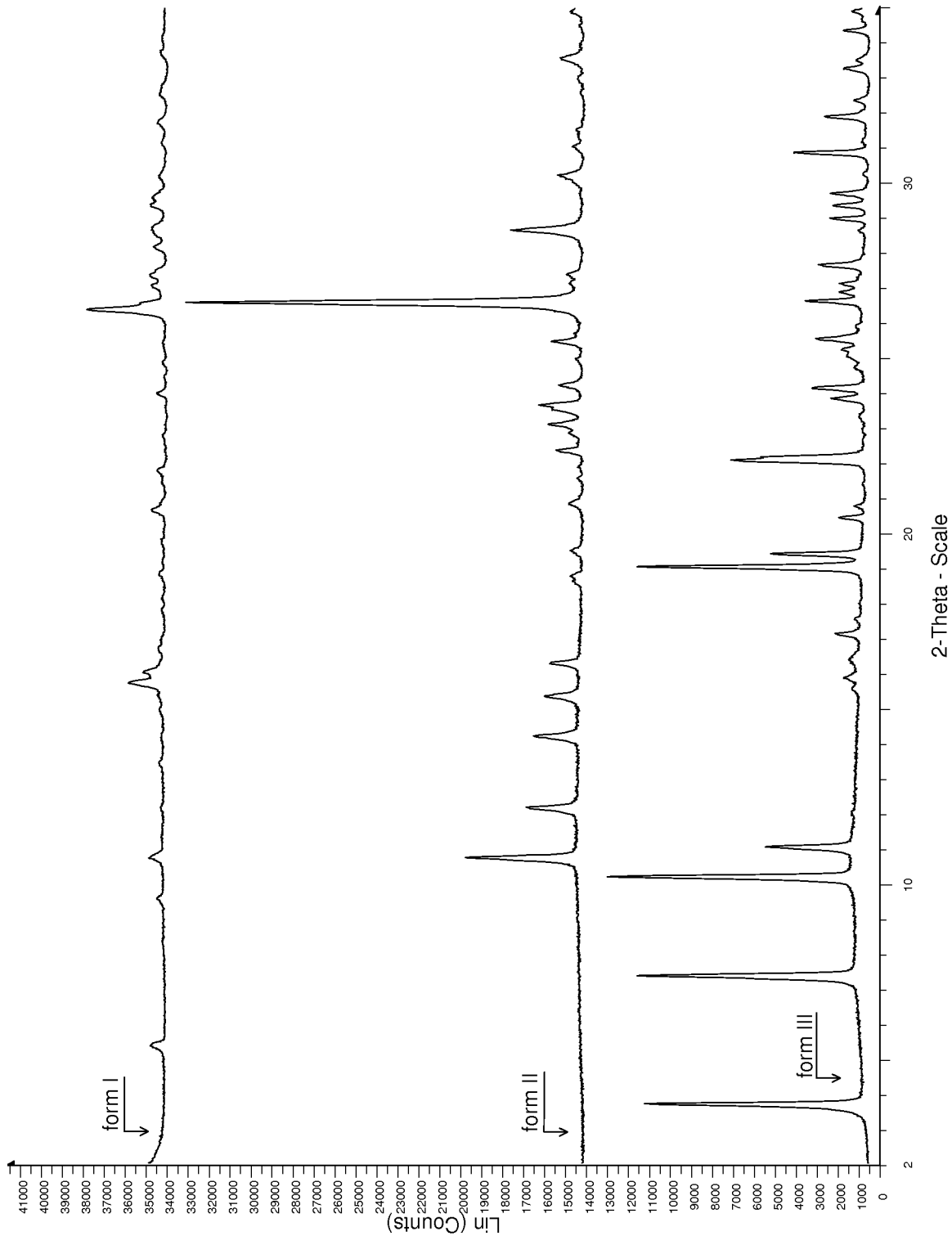
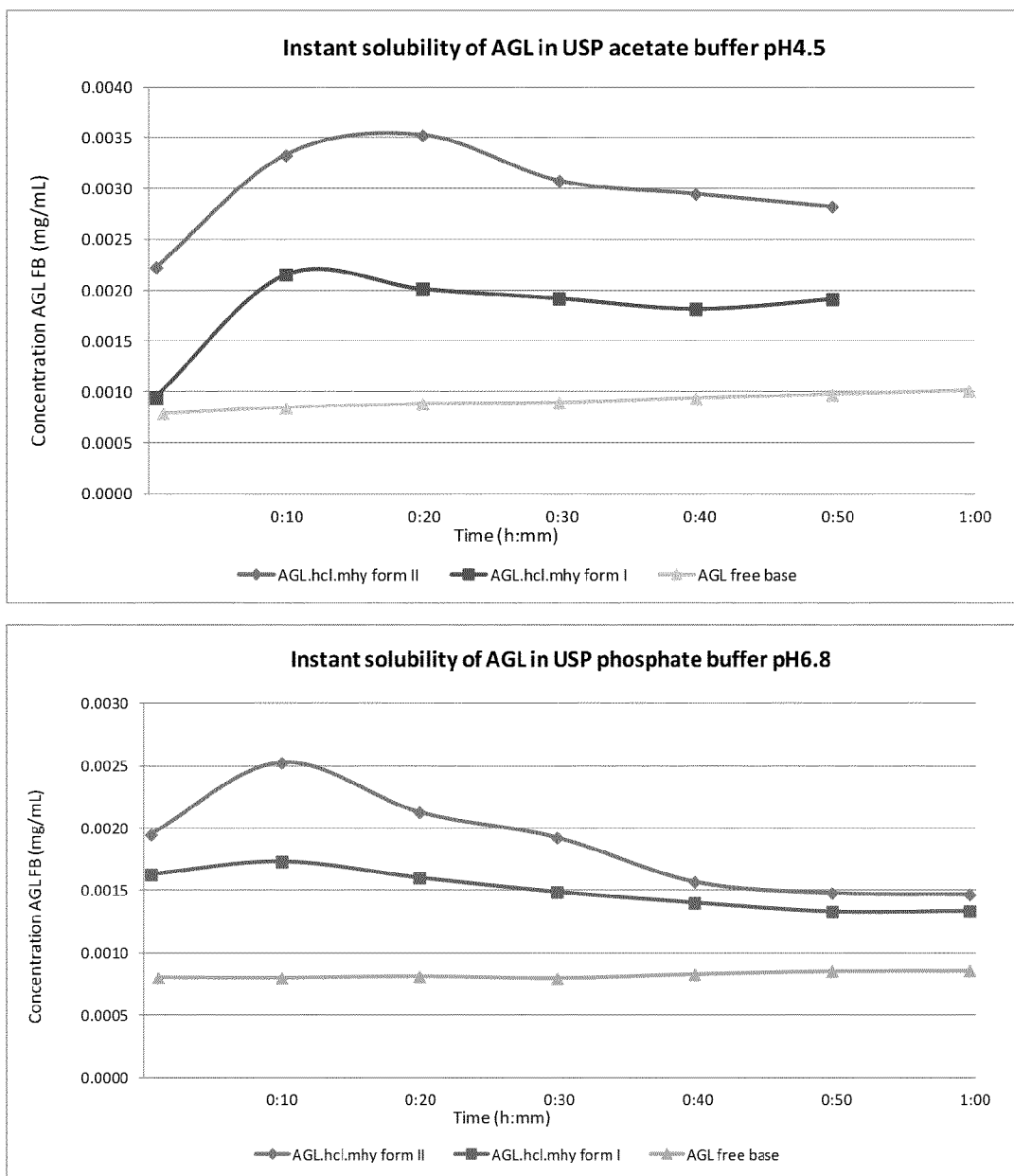
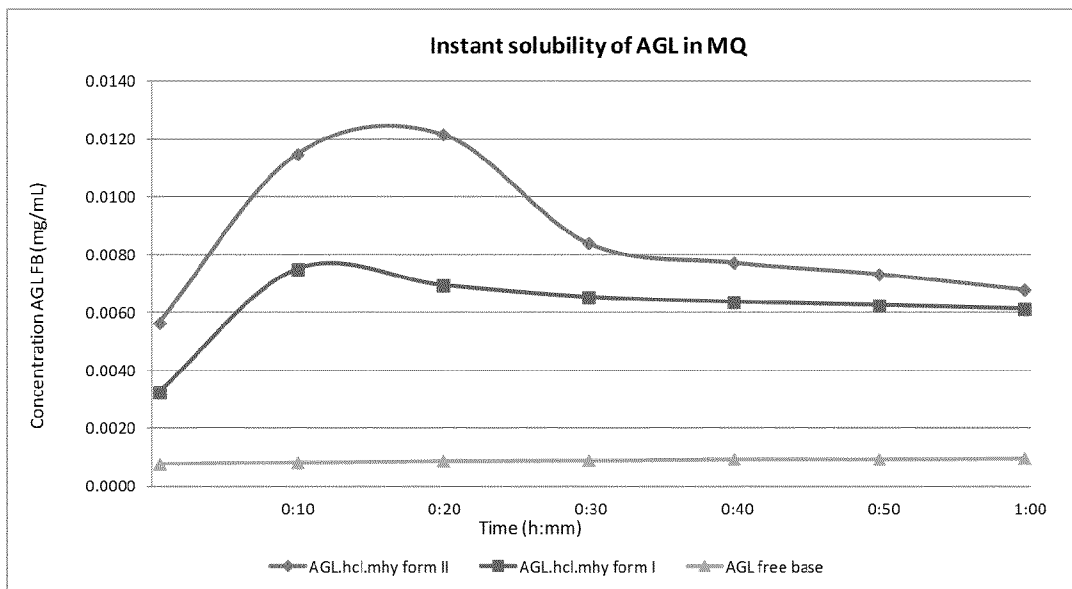
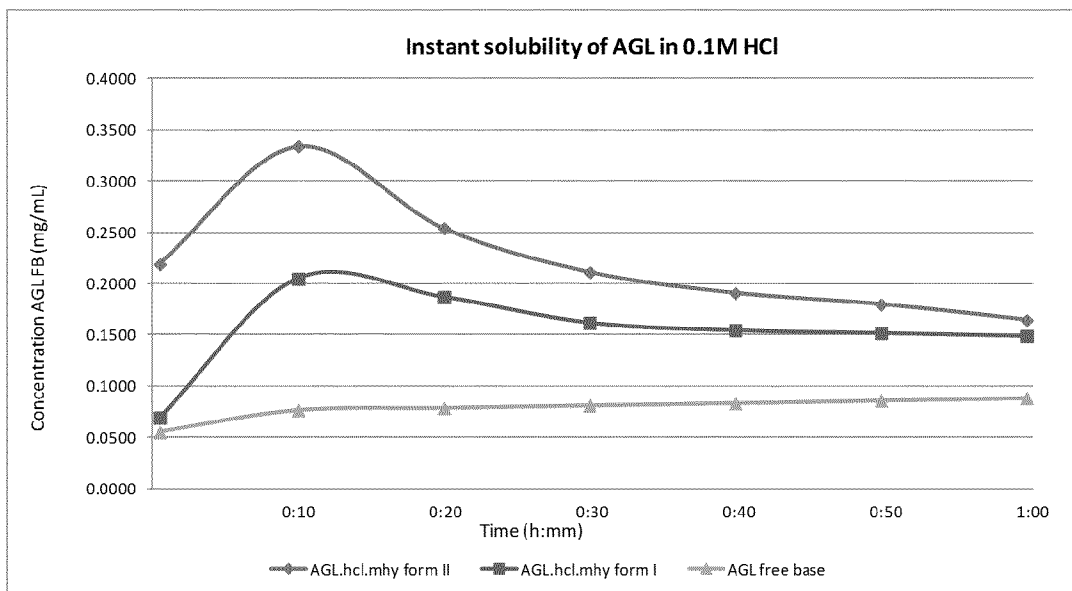


FIGURE 5: Solubility curves of form II of anagrelide hydrochloride monohydrate compared with form I





AGL.hcl.mhy form I

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/050759

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61P7/02
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)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 3 932 407 A (BEVERUNG JR WARREN NEIL ET AL) 13 January 1976 (1976-01-13) cited in the application example 25	1-13
X	----- US 4 146 718 A (JENKS THOMAS A ET AL) 27 March 1979 (1979-03-27) cited in the application column 1, line 8 - line 11 example 4 comparative preparation 1	1-13
A	----- US 5 391 737 A (REITER JOZSEF [HU] ET AL) 21 February 1995 (1995-02-21) cited in the application column 1, line 30 - line 34 claims 1-3, 5-9, 12, 13, 16-21 ----- -/-	1-13



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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Date of the actual completion of the international search

12 February 2014

Date of mailing of the international search report

21/02/2014

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/050759

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/087673 A1 (WATSON PHARMA PRIVATE LTD [IN]; BHANU MANJUNATH NARAYAN [IN]; NAIK SAM) 16 July 2009 (2009-07-16) cited in the application example 6 2nd paragraph; page 1 -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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