Discovery of a new stable polymorph of 4-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)quinazolinium methanesulfonate using near-infrared spectroscopy to monitor form change kinetics †

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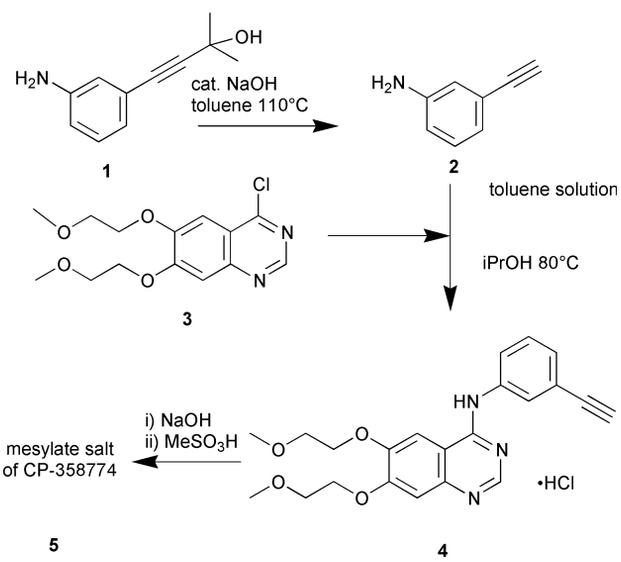
Polymorphism is an important property of crystalline organic molecules, particularly when used to develop medicines. Discovery of all the polymorphs in a series is often difficult. This paper highlights the use of near-infrared spectroscopy to monitor the kinetics of form changes of polymorphs and solvates (hydrates). In the case of mesylate salt **5**, this led to the discovery of a new preferred form. Identification and confirmation of unique polymorph crystal states are determined using X-ray powder diffraction patterns. This complements and confirms the kinetic change observed in the near-infrared. The technique is generally applicable to the study of two-phase solid–liquid crystal slurries under isothermal conditions.

Introduction

Polymorphism is an important property of organic compounds, especially when they are used as pharmaceutical drug substances. Areas of concern to the pharmaceutical manufacturer, depending on the polymorphic form used, include variations in the biological availability of the drug to the patient, and stability or shelf-life of the drug substance when formulated as a medicine or when stored as a bulk drug substance prior to formulation. During manufacture, control of the polymorphic form is essential in order to ensure reproducible performance of the bulk drug substance.

The compound ‡ 4-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)quinazolinium methanesulfonate **5** is a new drug that is being investigated for use as a specific inhibitor of epidermal growth factor receptor (EGFR) tyrosinase kinase activity in human cancers. The synthesis of the mesylate salt **5** is outlined in Scheme 1. When originally investigated, **5** was found to exist as a crystalline monohydrate and as an anhydrous crystal with two distinct polymorphic forms, A and B. The characteristic properties of these polymorphs are noted in the tables of physical data collected for **5**. Polymorphs A and B have distinct melting points and characteristic X-ray diffraction patterns as illustrated. Initially, it was thought that polymorph B was the most thermodynamically stable anhydrous crystalline form. In order to verify the stability of form B and to study the kinetics of its formation from the monohydrate form, we used the near-infrared spectroscopy technique we had developed to monitor polymorphic transformations.[1]



Scheme 1

Results

We monitored isothermally changes in the near-infrared region of the spectrum taken of crystal slurries in propan-2-ol of both the monohydrate form of **5** and the anhydrous polymorph B form. A transformation from one form to the other typically takes many hours in this system, somewhere between 18–48 h. The time taken for a polymorph or solvate conversion to occur in crystal–solvent slurry is not fixed for a given system because particle size is a factor in the rate of conversion. This is often quite characteristic of these types of transformations and one of the reasons why it is useful to monitor the kinetic behaviour with an on-line technique. The change is quite distinct to the observer and can be modelled graphically by chemometric methods similar to those described in our earlier work on reaction monitoring[2] using near-infrared spectroscopy. The experimental methodology used in this work has previously been described in detail.[1]

Fig. 1 shows the spectra for the initial crystal slurry of form B and the new form C that started to form after about 22.5 h. Form C was independently characterized and distinguished as a new polymorphic form by its unique X-ray powder diffraction pattern and melting point (see Tables and XRPD patterns). Intermediate spectra are omitted for simplicity (see supplementary data). Initially the spectra are essentially superimposed and when the new form starts to proliferate throughout the system each spectrum changes and continues to change until the transformation is complete and the system has reached equilibrium. At this point the spectra start to superimpose because no further changes are occurring. It should be noted that the time for an interconversion to occur depends upon the size of the crystals in the slurry. The rate in solid–liquid

† Spectral diagrams and data files relating to the polymorph conversion kinetics are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b003531i/
‡ Known as Pfizer compound CP-358774.

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Near-infrared crystal solvent matrix spectra

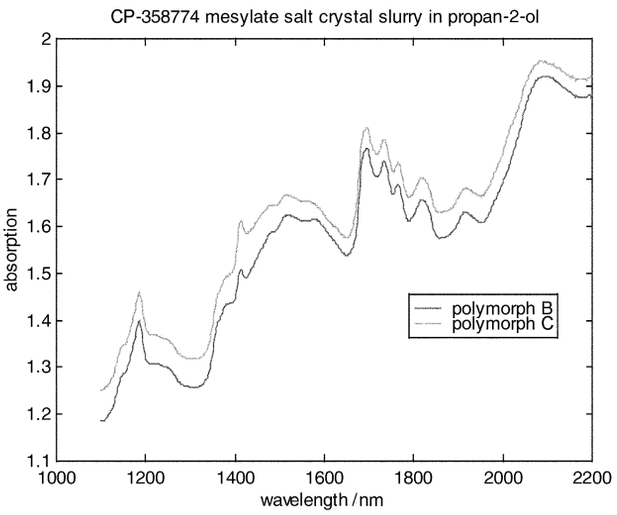


Fig. 1 Conversion of polymorph B into polymorph C (a new thermodynamically stable form) in propan-2-ol at 60 °C.

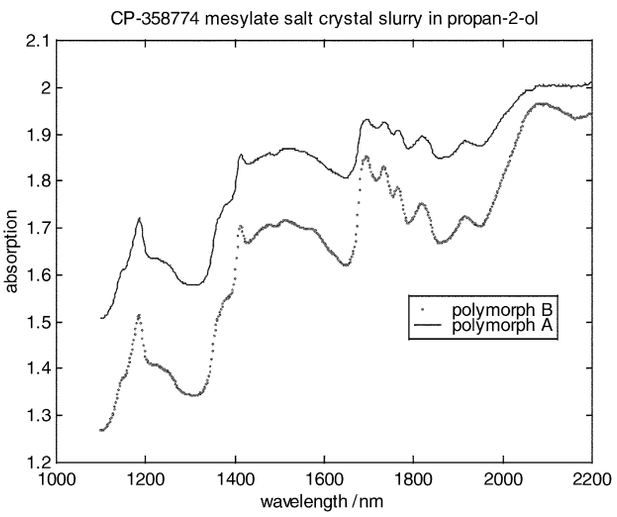


Fig. 2 Conversion of polymorph B into polymorph A in propan-2-ol at 70 °C.

two-phase systems is dependent on the surface area of the solid. Thus fine particles convert more quickly than large particles. This is a typical observation made when studying polymorph changes in crystal slurries.

Fig. 2 Shows the start and finish of the conversion of anhydrous form B into form A in propan-2-ol at 70 °C. The conversion was monitored for 24 h, but was essentially completed after 16 h, as shown by the chemometric modelling that was taking place in real time as the transformation was occurring.

Fig. 3 shows the transformation of the monohydrate form into the anhydrous form B at 72 °C in propan-2-ol. This transformation was monitored over 22 h and was completed after 4.5 h. Again intermediate spectra have been omitted for clarity.

X-Ray powder diffraction diagrams and tables

The anhydrous **5** polymorphs A, B and C, and **5** monohydrate are characterized by the principal peaks found in the X-ray powder diffraction patterns shown below.

Discussion

Solvents and crystalline organic compounds can be mixed to form chemically stable slurries in which essentially no chemical

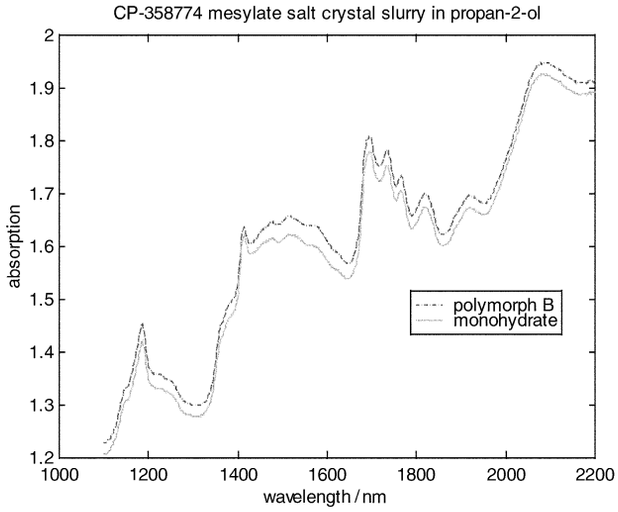
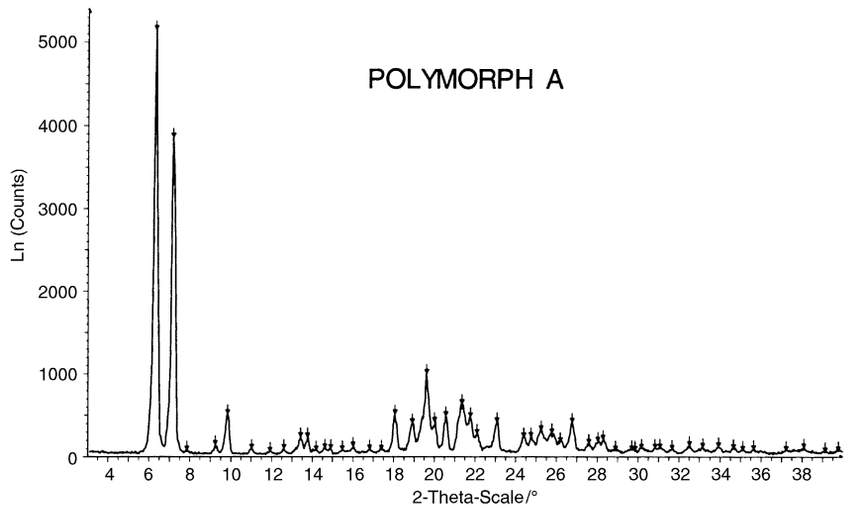


Fig. 3 Conversion of monohydrate form into anhydrous polymorph B in propan-2-ol at 72 °C.

reactions occur. When this type of crystal and solvent slurry mixture is monitored on-line under isothermal conditions, changes in the near-infrared region of the spectrum are sometimes observed. These spectral changes arise from changes in the crystalline structure due to polymorph or form changes in the crystal lattice. The noticeable baseline shift occurs because of changes in the physical nature of the crystal in the solvent, which cause increases or decreases in the light path travelled by the near-infrared radiation. In addition subtle changes occur in the spectroscopic curve due to crystal form variations within the matrix that are reflected in the vibrations that comprise the spectral measurement, in the case of **5** its crystal slurry in propan-2-ol. This type of change in the spectral information was most notable in the range 1300–1450 nm. Near-infrared spectral changes such as these have been used to successfully monitor the kinetics of polymorph and form changes under isothermal conditions.[1]

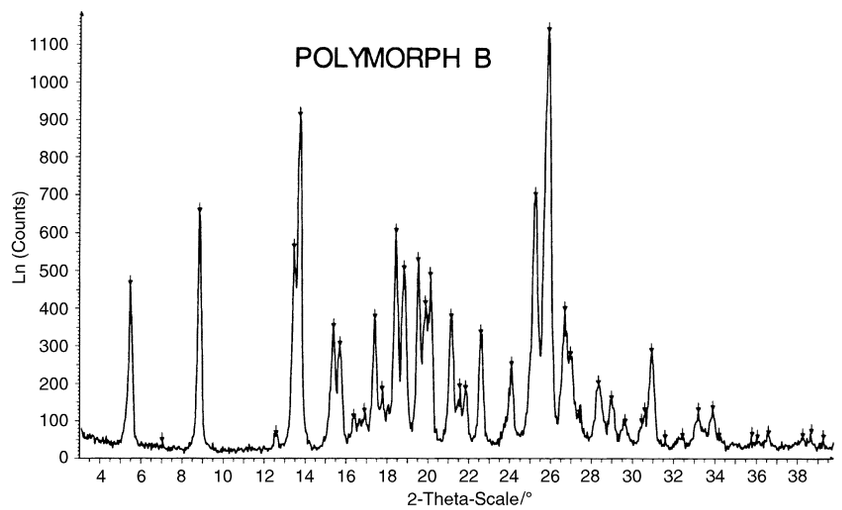
In the case of **5** three forms were known from initial observations made during routine morphology examinations; these were the monohydrate, anhydrous form A and anhydrous form B. Each is characterized by a distinct melting point and a distinct X-ray powder diffraction pattern (Table and XRPD pattern). During a study to understand the interconversion kinetics of various forms we discovered a new form, C. While monitoring the behaviour of form B slurries under isothermal conditions at various temperature points to verify its stability as a suitable form for development as a medicine we expected to see no change in the near-infrared region between 1100–2200 nm over time. Unexpectedly, while monitoring form B at various isothermal points in the range 60–70 °C, we observed a spectral change that corresponded to a transition to a new form, C. The new form was identified and characterized by a distinct melting point and a distinct X-ray powder diffraction pattern (Table). A useful guide and recent synopsis on the use of X-ray powder in the pharmaceutical industry for determination and characterization of polymorphic forms has been published.[3] The form change associated with this conversion could be detected consistently by changes in the near-infrared which initially led us to its discovery. In a series of seeding experiments, hygroscopic and thermal stability studies at elevated temperature it was determined that form C was the preferred form of **5** for formulation development. Thus by observing the changes in the near-infrared in an experiment designed to measure the form changes kinetically we were able to find a new form of the crystalline compound under investigation. The synthetic process to synthesize mesylate salt **5** is shown in Scheme 1 and the conversion of crystal forms of the three polymorphs and monohydrate is



Characteristic peaks found in X-ray diffraction pattern of **5** polymorph A, mp 160–161 °C

Peak no.	1[a]	2[a]	3	4	5	6	7	8	9	10
2θ/° Cu	6.3	7.15	9.8	13.4	13.7	18.05	18.9	19.6	20.0	21.35
d space/Å	14.1	12.3	9.0	6.6	6.4	4.9	4.7	4.5	4.4	4.15
Peak no.	11	12	13	14	15	16	17	18	19	20
2θ/° Cu	21.8	23.1	26.8							
d space/Å	4.1	3.85	3.3							

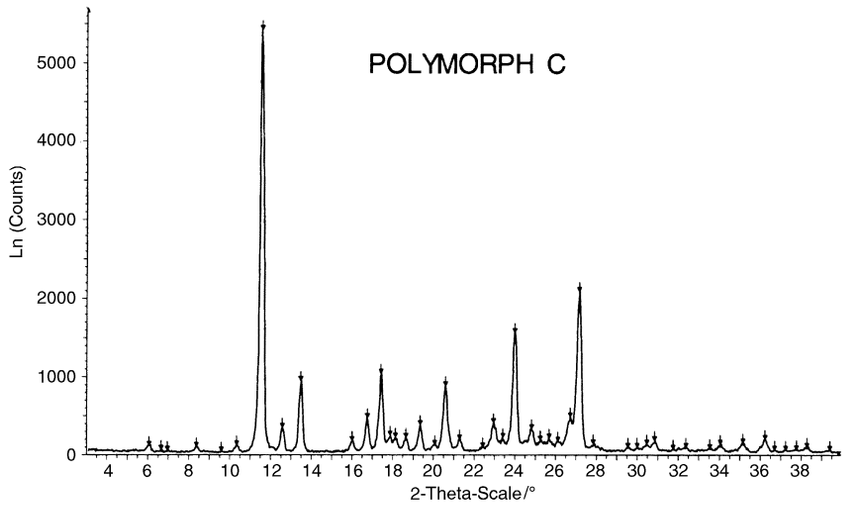
[a] Intense peaks.



Characteristic peaks found in X-ray diffraction pattern of **5** polymorph B, mp 142–144 °C

Peak no.	1[a]	2[a]	3[a]	4[a]	5	6	7	8	9	10
2θ/° Cu	5.4	8.8	13.4	13.7	15.3	15.7	17.4	17.8	18.4	18.8
d space/Å	16.3	10.1	6.6	6.5	5.8	5.65	5.1	5.0	4.8	4.7
Peak no.	11	12	13	14	15	16	17	18	19	20
2θ/° Cu	19.5	19.85	20.1	21.1	21.8	22.6	24.1	25.2[a]	25.9[a]	26.7
d space/Å	4.55	4.5	4.4	4.2	4.1	3.9	3.7	3.5	3.4	3.3
Peak no.	21	22	23	24	25	26	27	28	29	30
2θ/° Cu	28.3	30.9								
d space/Å	3.1	2.9								

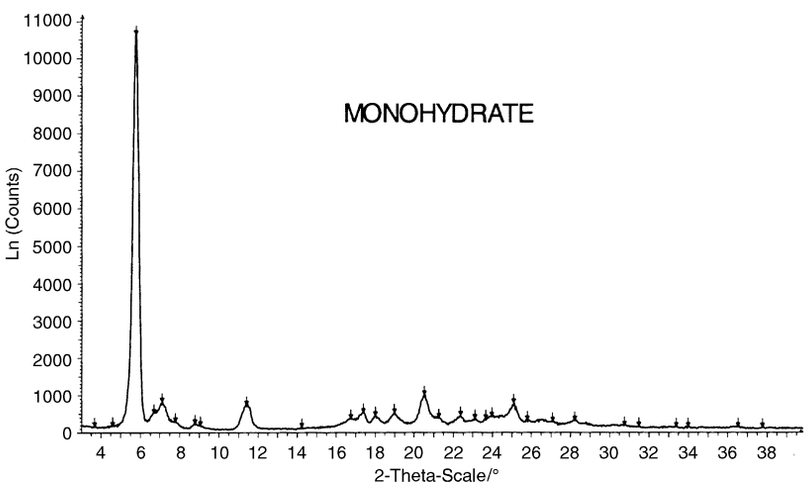
[a] Intense peaks.



Characteristic peaks found in X-ray diffraction pattern of **5** polymorph C, mp 153–154 °C

Peak no.	1	2	3	4[a]	5	6[a]	7	8	9[a]	10
2θ/° Cu	6.0	8.3	10.3	11.5	12.55	13.45	16.0	16.75	17.4	17.9
d space/Å	14.7	10.6	8.6	7.7	7.05	6.6	5.5	5.3	5.1	4.95
Peak no.	11	12	13	14[a]	15	16[a]	17	18	19[a]	20
2θ/° Cu	18.1	18.65	19.35	20.6	23.0	24.0	24.8	26.75	27.2	36.3
d space/Å	4.9	4.75	4.6	4.3	3.9	3.7	3.6	3.3	3.3	2.5

[a] Intense peaks.



Characteristic peaks found in X-ray diffraction pattern of **5** monohydrate, mp 98–100 °C

Peak no.	1[a]	2	3	4	5	6	7	8	9	10
2θ/° Cu	5.7	7.0	11.3	20.5	25.1					
d space/Å	15.5	12.5	7.8	4.3	3.5					

[a] Intense peak.

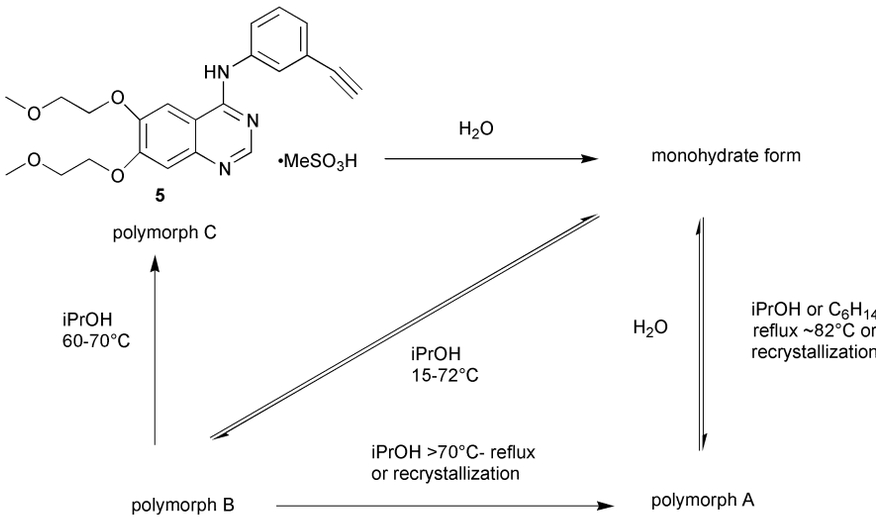
shown in Scheme 2. Other undiscovered interconversions may be possible.

Conclusions

Classical static approaches for evaluation of crystal forms do not always give the optimum result. We have shown that by monitoring the form change kinetics with an on-line near-infrared spectroscopy technique we were able to discover a new stable crystalline form for the EGFR tyrosine kinase inhibitor **5**. This approach has general applicability and could be applied generically to crystal form evaluations of other important medicines.

Experimental

NIR crystal slurry spectra were recorded on an NIRSystems 6500 spectrometer fitted with a variable pathlength fibre optic probe and an auto-gain adapter manufactured by Perstorp Analytical Inc. (Silver Spring, MD 20904, USA). The gap between the probe lens and the mirror was set at a maximum, 1.0 cm, so the crystal slurry could be probed to its fullest extent



Scheme 2

using an indeterminate light path. Crystal slurry concentrations were monitored in the range 9.5–10.5 ml propan-2-ol g^{-1} mesylate salt **5**. The apparatus setup was as noted in a previous publication.[1] This was found to be the convenient mode of operation for heterogeneous systems, such as crystal slurries. Powder X-ray data were collected using a Siemens D5000 spectrometer. Infrared spectra were measured using a Nicolet Magna 500 spectrometer with a DRIFTS autosampler accessory.

Synthesis of quinazoline hydrochloride salt 4

A mixture of the aniline **1** (8.80 g, 50.22 mmol) in toluene[4] (19.4 ml) under nitrogen, was treated with NaOH pellets (0.114 g, 2.85 mmol). The mixture was heated at reflux for 1 h, acetone–toluene was allowed to distil from the reaction. The solution containing NaOH pellets was allowed to cool to room temperature, filtered and concentrated by evaporation to give **2** as a pale yellow oil. The oil in i-PrOH (125 ml)§ was treated with the chloro compound[5] **3** (12.5 g, 39.97 mmol) and heated at reflux for 18 h. The mixture was cooled to room temperature and the solid collected by filtration. The solid was washed with i-PrOH (60 ml) and dried *in vacuo* at 45 °C overnight to give **4** (16.78 g, 98%) as a white solid (mp 225° dec.); ^{1}H 300 MHz NMR (d_6-DMSO) δ 3.36 (s, 6H), 3.77–3.80 (m, 4H), 4.30 (s, 1H), 4.31–4.33 (m, 2H), 4.32–4.40 (m, 2H), 7.39 (s, 1H), 7.41 (d, 1H, J = 7.8 Hz), 7.50 (t, 1H, J = 7.9 Hz), 7.79 (d, 1H, J = 8.1 Hz), 7.88 (s, 1H), 8.40 (s, 1H), 8.86 (s, 1H), 11.48 (br s, 1H); ^{13}C 100 MHz NMR (d_6-DMSO) δ 58.4 (2C), 68.7, 69.2, 69.7, 70.0, 81.3, 83.0, 100.3, 105.2, 107.2, 121.9, 125.4, 127.6, 128.9, 129.2, 135.5, 137.7, 148.3, 149.2, 155.4, 158.0; IR (neat) 3271, 2955, 2931, 2908, 2880, 2829, 2700, 1634, 1610, 1575, 1533, 1515, 1485, 1451, 1405, 1368, 1326, 1309, 1280 cm^{-1}; *m/z* 394 $(M + H)^+$ (Calc. for $C_{22}H_{23}N_3O_4$·HCl (MW 429.90) C, 61.46; H, 5.63; N, 9.77; Cl, 8.25. Found: C, 61.23; H, 5.81; N, 9.55; Cl, 8.06%).

Synthesis of quinazoline mesylate salt hydrate form of 5

A mixture of the quinazoline hydrochloride **4** (100 g, 0.233 M) in water (500 ml)–ethyl acetate (2 l) was warmed to 50 °C (internal temperature) and treated with 50% NaOH aqueous solution (200 ml). The layers were stirred vigorously for 15 min, giving two clear layers. The aqueous layer (pH 7) was removed and the warm organic solution washed with water (330 ml). The organic layer was filtered through a short pad of Celite and the resultant solution warmed to 50 °C to redissolve precipitated free base. The solution (50 °C) was treated with methanesulfonic acid (15.1 ml, 0.233 M) giving a white precipitate (temperature 53 °C) which was stirred while cooling for 4 h. The solid was collected by filtration, washed with ethyl acetate (40 ml) and dried under vacuum at 50 °C overnight to give the product (111.76 g, 98%) as a pale yellow–white solid (mp 93–98 °C).

Synthesis of quinazoline mesylate salt 5, polymorph A

A slurry of the mesylate salt hydrate form (2.00 g) in hexanes (20 ml) was heated at reflux, under Dean and Stark conditions, for 4 h. The mixture was cooled to room temperature and the solid collected by filtration, washed with hexanes (10 ml) and dried under vacuum at 30 °C overnight to afford polymorph A (1.69 g, 84%) as a white solid (mp 161–162 °C).

Synthesis of quinazoline mesylate salt 5, polymorph B

A slurry of the mesylate salt hydrate form (20.0 g) in propan-2-ol (200 ml) was stirred at 72 °C (internal temperature) for 22 h.¶ The mixture was allowed to cool to approximately 40 °C, the solid collected by filtration, washed with propan-2-ol (30 ml) and dried under vacuum at 38 °C overnight to afford polymorph B (17.62 g, 88%) as a white–pale yellow solid (mp 141–143 °C). This conversion may be performed in the temperature range 15–72 °C; at lower temperatures the conversion is slower.

Synthesis of quinazoline mesylate salt 5, polymorph C

A slurry of the mesylate salt form B (10.0 g) in propan-2-ol (100 ml) was stirred at 60 °C (oil bath temperature) for three days. The mixture was allowed to cool to room temperature, the solid collected by filtration, washed with propan-2-ol (15 ml) and dried under vacuum at 30 °C overnight to afford polymorph C (8.08 g, 81%) as a white–pale yellow solid (mp 152–154 °C).

§ Acetonitrile may be used in place of propan-2-ol.

¶ The conversion time is in part dependent on the crystal particle size.

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