Methods of Preparing the Crystalline Forms

[0416] In some aspects, the present disclosure features a method of preparing a crystalline form of Compound 1 or the pharmaceutically acceptable salt thereof described herein.

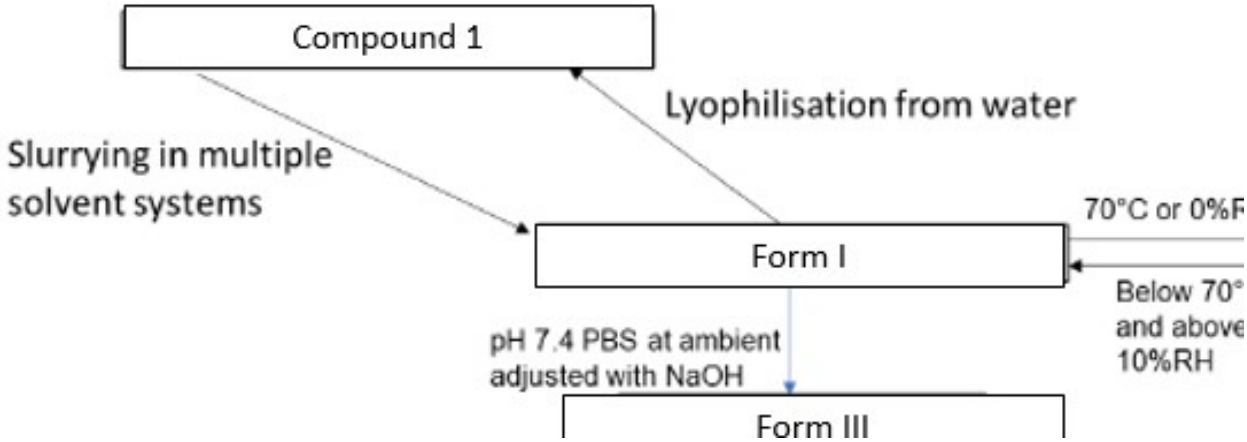
[0417] In some aspects, the present disclosure provides a method of preparing a crystalline form of Compound 1 or the pharmaceutically acceptable salt thereof, comprising one or more steps as described herein.

[0418] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, or directly obtained by a method for preparing a crystalline form of Compound 1 or the pharmaceutically acceptable salt thereof as described herein.

[0419] The crystalline form of Compound 1 or the pharmaceutically acceptable salt thereof can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

[0420] An exemplary preparation of a compound of the application is described in Scheme 1 herein.

Scheme 1



[0421] Scheme 1 demonstrates a general synthetic route to the Form I or II of the bis-tris salt of Compound 1 or Form III or IV of the mono-tris salt of Compound 1.

[0422] Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether,

Table 9 – Summary of Primary Salt Screen

Counterion	Solvent	Pattern	Polymorphism observed for counterion	TG/DSC	Remained pattern after 40°C	Remained pattern after 40°C/75%RH	NMR
N-methyl glucamine	All 6	1	No	N/A	Yes	No	N/A
Tromethamine	All 6	1	No	1.6% loss. Endothermic event onsets 27°C & 193°C.	Yes	Yes	0.3 equivalents of ethanol
Potassium	THF, isopropyl acetate, MEK & acetonitrile	1	Yes	10.1% loss. No defined thermal events.	Yes	No - Pattern 5 (6.5 eq. water)	Trace of isopropyl acetate (likely hydrated)
L-lysine	Isopropyl acetate & MEK	1, poorly crystalline	No	N/A	Not carried out poorly crystalline material	Not carried out poorly crystalline material	N/A
L- arginine	All 6	1, poorly crystalline	No	N/A	Predominantly unchanged, poorly crystalline	Predominantly unchanged, poorly crystalline	N/A
Ethanolamine	THF, isopropyl acetate, acetonitrile & IPA:water 95:5 v/v	1	No	N/A	Yes	Loss in crystallinity	N/A
N-(hydroxyethyl)pyrrolidine	THF, MEK & acetonitrile	1	Yes	N/A	Yes	No, Pattern 2	N/A
N-(hydroxyethyl)pyrrolidine	Isopropyl acetate	2	Yes	N/A	Yes	Yes	N/A
Ammonia	Ethanol, THF, isopropyl acetate, MEK & IPA:water 95:5 v/v	1	No	N/A	Predominantly unchanged	Predominantly unchanged	N/A
N-ethyl glucamine	Ethanol, isopropyl acetate, MEK & acetonitrile	1	Yes	N/A	Yes	No. Mixture Pattern 1 & 2	N/A

Form I (Pattern 1 of the tromethamine salt)

[0636] Form I was scaled-up, confirmed with XRPD analysis. PLM analysis (Figure 10) showed a rod-like morphology with slight birefringence. TG analysis (Figure 11) showed a loss of 2.0% from the outset up to ca. 60°C. This weight loss corresponded with 0.4 equivalents of ethanol. DSC analysis showed two endothermic events with onset ca. 35°C (peak at 45°C) and 192°C (peak at 197°C). The thermal analysis was found to be consistent with the primary screen data. DSC analysis (Figure 12) showed two endothermic events with onset ca. 55°C (peak at 77°C) and 197°C (peak at 200°C). DVS analysis (Figures 13A and 13B) showed Form I to be hydrated. Between 40%RH and 90%RH 0.5% uptake was observed. The total uptake at 90%RH (3.2%) corresponded with 1.2 equivalents of water. Between 10%RH and 0%RH 2.5% loss was observed. Post DVS XRPD analysis showed Form I to remain unchanged. FT-IR analysis showed some