A Search for Novel, Crystalline Nicotine Salts and Cocrystals

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Abstract

Nicotine salts have been described in the literature and have been used in consumer products such as pesticides, nicotine replacement therapy (NRT) pharmaceuticals for smoking cessation, and electronic cigarettes. A search for novel, crystalline forms of nicotine, including nicotine salts and cocrystals was done in an effort to find new materials with better physical properties than were available from commercial sources. The use of crystalline nicotine salts or cocrystals in consumer products would have manufacturing advantages, affording chemical stability, extending shelf life, and providing ease of material handling, thereby eliminating the need to handle pure nicotine as a neat liquid. A salt and cocrystal screen was initiated in which 38 organic acids and 10 coformers were investigated for crystalline nicotine salt or cocrystal formation. The search resulted in 13 crystalline nicotine salts, including four novel, crystalline salt forms. No nicotine cocrystals were obtained in this study. All salts were characterized by ^{1}H NMR, DSC, TGA, PLM, and GVS. Several nicotine salts, such as nicotine 2,3-dihydroxybenzoate, had promising solid state properties (high mp, low hygroscopicity) for use in consumer products and as a nicotine analytical reference standard. Preparation of these salts were easily scaled up (~5 g) by crystallization. The single crystal X-ray structure of the novel nicotine 3,5-dihydroxybenzoate confirmed a 1:1 nicotine:acid stoichiometry. The X-ray structure was of sufficient resolution to assign the absolute stereochemistry of nicotine as the (S) enantiomer, which is the naturally occurring stereoisomer in tobacco.

Introduction

Salts of nicotine (**Figure 1**) have been described in the literature[1,2] and have been used in consumer products such as pesticides,[3] nicotine replacement therapy (NRT) products such as Nicorette® gum,[4] and electronic cigarettes.[5] Other solid state forms, such as cocrystals for pharmaceutical applications, have been reported in the literature.[6] The use of crystalline nicotine salts or cocrystals in consumer products would be advantageous potentially imparting chemical stability, extending shelf life, and affording manufacturing ease in terms of material handling. Pure nicotine as a neat liquid would no longer need be handled. Even though nicotine ditartrate dihydrate and nicotine polacrilex are available in solid state forms, novel, crystalline nicotine salts with even better physical properties would be beneficial. Such crystalline salts or cocrystals, would represent new materials for potential use in nicotine lozenges, moist tobacco, snus, and electronic cigarettes.

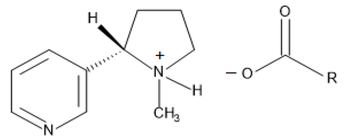

Figure 1. Generic Structure of an (S)-Nicotine Salt.

Materials and Methods

Materials

Tobacco-derived (S)-nicotine was sourced from Siegfried, Ltd (Zofingen, Switzerland) as the naturally occurring (S) enantiomer. The organic acids and coformers were commercially available (**Table 1**).

Methods

Crystallization methods involved nicotine combined with commercially available organic acids and coformers (**Table 1**). Solid state techniques included: (1) from neat nicotine, (2) from organic solvents and water, (3) from freeze dried solids/solvent maturation, (4) by ball-mill grinding, (5) by thermally mediated crystallization, and (6) by gum/oil maturation.

Table 1. Organic Acids and Coformers--Source and Purity

Organic Acid (Source) (% Purity)	Organic Acid (Source) (% Purity) (cont.)	Coformer (Source) (% Purity)
Levulinic acid (1) (99)	1-Hydroxy-2-naphthoic acid (Xinafoic acid) (1) (97)	Vanillin (1) (97)
(R,S)-Lactic acid, 85% in water (1) (85)	Ketoglutaric acid (1) (98.5)	Ethyl vanillin (1) (99)
Lactic acid (1) (98)	D-Glucuronic acid (1) (N/A)	Nicotinamide (1) (99.5)
Mucic acid (1) (97)	4-Aminosalicylic acid (1) (99)	Sulfacetamide (1) (98)
Citric acid (1) (99.5)	L-Pyroglutamic acid (1) (99)	Maltol (1) (99)
(S)-Malic acid (1) (97)	L-Ascorbic acid (1) (N/A)	Xylitol (1) (99)
(R)-Malic acid (2) (97)	Succinic acid (1) (99)	Caffeine (1) (N/A)
4-Hydroxybenzoic acid (1) (99)	Nicotinic acid (1) (98)	Saccharin (1) (99)
2,5-Dihydroxybenzoic acid (Gentisic acid) (1) (98)	4-Aminobenzoic acid (1) (99)	(-)-Menthol (1) (99)
Benzoic acid (1) (99.5)	3,5-Dihydroxybenzoic acid (1) (97)	4-Acetamidophenol (Acetaminophen) (1) (98)
2,4-Dihydroxybenzoic acid (1) (97)	2,3-Dihydroxybenzoic acid (1) (99)	
4-Acetamidobenzoic acid (1) (99)	3,4-Dihydroxybenzoic acid (1) (97)	
4-Fluorobenzoic acid (1) (98)	2,4-Dihydroxybenzoic acid (1) (97)	
2-Hydroxybenzoic acid (Salicylic acid) (1) (99)	Vanillic acid (1) (97)	
3-Hydroxybenzoic acid (1) (99)	Isonicotinic acid (1) (99)	
p-Toluenesulfonic acid (1) (98.5)	3,4,5-Trihydroxybenzoic acid (Gallic acid) (1) (98)	
L-Aspartic acid (1) (98)	2-Acetoxybenzoic acid (Aspirin) (1) (99)	
L-Glutamic acid (1) (99)	N-Acetyl-4-aminosalicylic acid (3) (N/A)	
Pyruvic acid (1) (99)	1,2-Benzenedicarboxylic acid (Phthalic acid) (1) (99)	

1 = Sigma-Aldrich; 2 = Fluka; 3 = Carbosynth; N/A = Not Available

Results

- The study produced 13 crystalline nicotine salts; four salts (mucate, 2,3-dihydrozybenzoate, 3,5-dihydroxybenzoate anhydrate and dihydrate) were novel and had not been previously reported (**Table 2** highlighted). Successful crystallization methods included: (1) Crystallization from neat nicotine ((S)-malate, gentisate, 4-acetamidobenzoate, mucate, xinafoate, salicylate, 4-aminosalicylate, 2,3-dihydroxybenzoate), (2) Crystallization from acetone (4-aminosalicylate) or THF ((S)-malate, 4-acetamidobenzoate, xinafoate, salicylate, 4-aminosalicylate), (3) Freeze-drying and IPA maturation ((S)-malate) and (4) Gum/oil maturation (3,5-dihydroxybenzoate from acetone). Unfortunately, no nicotine cocrystals were obtained. These salts were easily scaled up (~5 g) by crystallization from THF, except for the mucate (neat nicotine) and 2,3-dihydroxybenzoate (EtOH).
- The products were characterized by NMR, DSC, TGA, PLM, and GVS (**Table 2**). The nicotine:acid stoichiometry was found to be 1:1 by ^{1}H NMR with the exception of the mucate (1:0.72). Because of their good solid-state properties (high mp and low hygroscopicity), either the gentisate, 2,3-dihydroxybenzoate, xinafoate, or N-acetyl-4-aminosalicylate nicotine salt may be a better choice for use an analytical reference standard for USP nicotine analysis than the prescribed (S)-nicotine ditartrate dihydrate (1.4% weight gain, 0 to 90% RH GVS isotherm). In terms of solid-state properties, the 4-acetamidobenzoate and 3-hydroxybenzoate were also promising, though both salts were quite hygroscopic at >80% RH. The (S)-malate and mucate were rather hygroscopic solids, absorbing substantial amounts of moisture at >50% RH. The salicylate, 4-aminosalicylate, and phthalate showed relatively high hygroscopicity, but only >80% RH. The 4-aminosalicylate, salicylate, and phthalate all deliquesced upon exposure to high humidity (25 °C/96% RH). The 3,5-dihydroxybenzoate was shown to exist in multiple forms, including an anhydrate and a stable dihydrate form. The anhydrate form was found to be non-hygroscopic at <60% RH, but at ≥60% RH, hydration and the conversion to the dihydrate occurred.

Table 2. Characterization of Crystalline Nicotine Salts.

No. of Salt	Crystalline Nicotine Salt (1:1 Stoichiometry by NMR)	CAS Reg. No.	Stoich by SCXRD	Color of Solid	Mass Prep'd from THF(g)	DSC, Melting Onset (°C)	TGA	PLM	GVS (Water Uptake, 0 to 90% RH)
1	4-Acetamidobenzoate	110441-65-1 (1:1)	1:1	White	5.42	134, 143 (broad)	25-360 °C (64% mass loss)	Laths, up to 75 µm	~ 5%, 0-80%RH; ~20%, 80-90%RH§
2	3-Hydroxybenzoate	1644394-41-1 (1:1)		White	4.81	123	25-360 °C (89% mass loss)	Irregular particles	~ 5%, 0-80%RH; ~5%, 80-90%RH§
3	Gentisate	6012-21-1 (1:1)	1:1	White	7.20	149	25-280 °C (96% mass loss)	Laths, up to 100 µm	~0.3%, 0-90%RH§
4	L-Malate	253180-13-1 (1:1)		White	5.78	120, 168 (broad)	25-260 °C (91% mass loss)	Irregular particles, <25 µm	~70%, 0-90%RH (deliquesced)
5	Mucate* (1:0.72 Nicotine:Mucic Acid)♦	1835172-62-7 (1:0.5)		Pinkish	7.21‡	123, 133 (broad)	25-260 °C (91% mass loss)	Irregular particles, <10 µm	~60%, 0-90%RH (deliquesced)
6	2,3-Dihydroxybenzoate*	1835172-64-9 (1:1)		Off-white	7.90	157	2-stage total loss from 150 °C	Irregular plates, up to 150 µm	0.12%, 0-90%RH§
7	Xinafoate	856579-82-3 (1:1) 10047-35-5 (1:?)		Buff	6.49	111	2-stage total loss from 130 °C	Irregular particles, up to 100 µm	0.16%, 0-90%RH§
8	Salicylate	6012-21-1 (1:1)	1:1	Off-white	8.45	117	1-stage total loss from 150 °C	Square tablets, up to 50 µm	5%, 0-90%RH§
9	4-Aminosalicylate	20334-41-2 (1:1)		White	6.81	128	2-stage total loss from 130 °C	Laths, up to 50 µm	13%, 0-90%RH§
10	N-Acetyl-4-aminosalicylate	900789-26-6 (1:1)		Buff	6.17†	177	2-stage total loss from 150 °C	Irregular particles, <30 µm	0.30%, 0-90%RH§
11	Phthalate	88660-55-3 (1:1)		White	6.37	127	1-stage total loss from 130 °C	Lath-shaped plates, up to ~200 µm	Complex behavior
12	3,5-Dihydroxybenzoate (anhydrate)*	1835172-63-8 (1:1)	1:1	White	7.55	138	2-stage 39.4% loss from 100 °C to 300 °C	Irregular particles, <10 µm	10%, 0-90%RH; form change--hydration
13	3,5-Dihydroxybenzoate (dihydrate)*			White	~0.10 (by hydra-tion)	137 (endos at 50-100 °C	Mass losses from 65 °C		

Abbreviations: CAS Reg. No. = Chemical Abstracts Service Registry Number, Stoich = Stoichiometry, SCXRD = Single Crystal X-ray Diffraction, THF = Tetrahydrofuran, DSC = Differential Scanning Calorimetry, TGA = Thermal Gravimetric Analysis, PLM = Polarized Light Microscopy, GVS = Gravimetric Vapor Sorption

* = Novel salt form, ‡ = crystallized from neat nicotine, † = crystallized from EtOH, § = XRPD--form unchanged post GVS

♦ = The original preparation produced a solid with unknown true stoichiometry. A 2nd preparation from nicotine (4 eq) and crystallization from acetone-H_2O produced the hemimucate (nicotine:mucic acid (1:0.5)).

The study produced four nicotine salts (4-acetamidobenzoate, gentisate, salicylate, 3,5-dihydroxybenzoate (anhydrate)) with morphology acceptable for structure elucidation by single crystal X-ray diffraction (SCXRD). The SCXRD confirmed the 1:1 nicotine:acid stoichiometry. A single crystal X-ray structure was obtained for the anhydrate form of the 3,5-dihydroxybenzoate sample that was obtained from the initial screening experiments. The X-ray structure, including the hydrogen bonding present in the asymmetric unit and the crystal packing, is shown in **Figure 2**. The crystal packing shows a hydrogen-bonded head to tail arrangement of the acid counter-ion molecules with (S)-nicotine molecules attached to this chain at regular intervals. The X-ray structure was of sufficient resolution (with an absolute structure parameter (Flack parameter) of 0.02(7)) to assign the absolute stereochemistry of nicotine as the (S) enantiomer, which is the naturally occurring stereoisomer in tobacco. The DSC and TGA thermograms are shown in **Figure 3**.

SCXRD Results

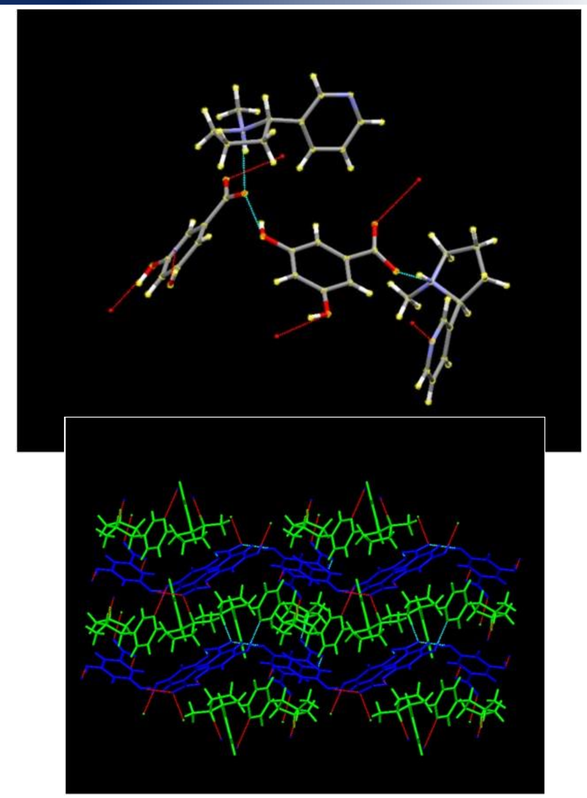

Figure 2. Hydrogen bonding in the asymmetric unit of nicotine 3,5-dihydroxybenzoate (anhydrate) (top) and crystal packing -- nicotine in green, acid in blue (bottom).

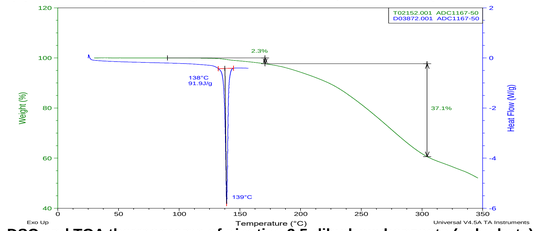

Figure 3. DSC and TGA thermograms of nicotine 3,5-dihydroxybenzoate (anhydrate).

Conclusions

The search resulted in 13 crystalline nicotine salts which were characterized using solid-state methods. No nicotine cocrystals were obtained in this study. Four novel, crystalline salt forms were discovered. One salt, the novel nicotine 2,3-dihydroxybenzoate, had very promising solid-state properties (high mp and low hygroscopicity) and could be used in consumer products and as a nicotine analytical reference standard for USP Monograph testing. The single crystal X-ray structure of the novel nicotine 3,5-dihydroxybenzoate (anhydrate) had a unique crystal packing arrangement and was of sufficient resolution to indicate that the nicotine in this study possessed the (S) configuration.

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