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ARTICLE *in* CRYSTAL GROWTH & DESIGN · JUNE 2015

Impact Factor: 4.89 · DOI: 10.1021/acs.cgd.5b00074

CRYSTAL GROWTH & DESIGN

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Sulfonic Acid Salts of Donepezil and Stabilization of Amorphous Donepezil via Formation of Amorphous Salts

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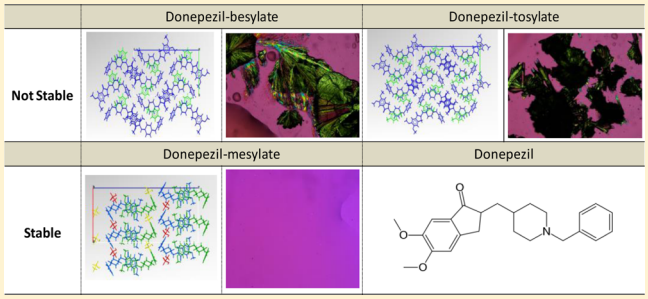
Supporting Information

ABSTRACT: Three crystal structures of donepezil salts formed with sulfonic acids were obtained. Interestingly, donepezil-besylate and donepezil-tosylate share similar crystal molecular conformations and crystal packing. On the basis of PXRD patterns, donepezil-mesylate and donepezil-esylate are likely to share similar crystal structures. The sulfonyl hydroxides of all three sulfonic acids form an intermolecular hydrogen bond with the piperidyl amine of donepezil. Solid state characterization showed that the T_g's of all four amorphous donepezil salts are similar to each other and increase significantly compared to T_g of donepezil. Stability analysis found that the amorphous salts of donepezil formed with mesylate and esylate led to significantly improved physical stability under accelerated stability conditions, but the other donepezil-sulfonic acid salts did not. Solubility data showed that mesylate/esylate salts of donepezil significantly increase the solubility of donepezil that is not shown by other salt forms. Solubility analysis indicated that the solubility of donepezil-mesylate and donepezil-esylate is extremely high compared to that of donepezil-besylate and donepezil-tosylate. We concluded that the extremely high solubility is responsible for delaying the rate of nucleation and thus improving the physical stability of amorphous donepezil. This study highlights that the aqueous solubility of amorphous material is an important factor when considering the physical stability of amorphous material under high relative humidity.



INTRODUCTION

Several commercially available acetylcholinesterase inhibitors, including tacrine, galantamine, rivastigmine, and donepezil, are used to improve cognition, functional ability, and behavior in patients with dementia resulting from Alzheimer's disease.[1,2] Donepezil is usually prescribed in the form of orally disintegrating tablets, sustained release tablets, or immediate release tablets.[3] However, because oral administration can have an adverse effect on the gastrointestinal system and lead to fluctuations in the level of the drug in the plasma,[4] there remains a need for the development of an alternative route of administration. Transdermal patches have been identified as a suitable alternative because a transdermal delivery system can avoid the aforementioned disadvantages of oral delivery, while improving patient compliance by reducing the dosing frequency. The physicochemical properties of donepezil—a low molecular weight and high lipophilicity—are also particularly suited to a transdermal drug delivery system.

However, for the production of transdermal patches, the target drug is required to remain amorphous and be molecularly dispersed in a matrix consisting of pressure-sensitive adhesives.[5] An important task is to prevent phase separation or crystallization of the drug when the patch is applied to the skin, because amorphous solids can be at the unstable or metastable state even in a miscible system. Many factors affect the physical stability of amorphous solids,[6] the most well-known being water and temperature.[7,8]

The presence of water is known to reduce the physical stability of amorphous solids.[9] The most plausible explanation is that water reduces the glass transition temperature (T_g), thus increasing molecular mobility; molecular mobility subsequently plays an important role in increasing the rate of crystallization. Sorbed water from environment or water introduced during process such as lyophilization, polymer film coating, wet granulation, and so forth can significantly reduce the physical stability of the drug. In addition, skin perspiration can expose drug molecules to water upon application on the skin in a transdermal drug delivery system. There is a need to develop physical forms that are stable during storage and use.

Received: August 14, 2014
Revised: May 21, 2015
Published: June 3, 2015

DOI: 10.1021/acs.cgd.5b00074
Cryst. Growth Des. 2015, 15, 3123−3130

A general rule of thumb is that amorphous material stored at 50 K or more below the T_g will not have the molecular mobility necessary for crystallization.[10,11] In other words, any amorphous material with a T_g that is at least 50 K higher than the normal operating temperature can be regarded as stable. The crystal structures and thermal behavior of polymorphs of donepezil have been reported.[12] The T_g of donepezil was about 18 °C, so it is expected to be unstable at room temperature.

Salt formation is a desirable approach to improve physicochemical properties of drugs, including stability. Salt forms of donepezil produced from oxalic acid and from salicylic acid and methyl-substituted salicylic acid have been reported.[13,14] The donepezil oxalate salt crystallized as a tertiary amine salt with an oxalate anion containing three molecules of water, thus forming a trihydrate. Various hydrogen-bonding interactions stabilize the crystal structure of donepezil, such as cation−anion, water−cation, water−anion, and water−water.[14] Some salicylic acid/methyl-substituted salicylic acid salts of donepezil are known to form methanol solvates.[13] However, others crystallize as nonsolvated crystals.

The use of sulfonic acid salts has become more common as they tend to be more advantageous in terms of physicochemical properties such as melting point, solubility, bioavailability, hygroscopicity, polymorph number, and stability.[11,15−18] In many instances, sulfonic acid salts increased the solubility and the melting point of the free form.[16] An increase in the melting point of the corresponding salt is often accompanied by an increase in T_g, and thus improving the physical stability of the amorphous salt. There are a number of preferred sulfonic acid counterions: mesylate, camsylate, and tosylate are the top three most frequently used sulfonic acids in the production of pharmaceutical salts.[15]

The aim of this study is to explore the physical stability enhancement of donepezil via the formation of amorphous sulfonic acid salts. We used four sulfonic acid salts—methanesulfonic acid (mesylate), ethanesulfonic acid (esylate), benzenesulfonic acid (besylate), and *p*-toluenesulfonic acid (tosylate)—to obtain crystalline sulfonic acid salts of donepezil (Figure 1). We also produced amorphous sulfonic acid salts of donepezil by cooling the corresponding molten crystalline salt. Mesylate and esylate are closely related, with the latter differing only in the presence of an additional methyl group. Besylate and tosylate are also structurally related, though tosylate has a methyl group attached to the benzene ring. After the crystal forms of four donepezil-sulfonic acid salts were obtained, their solid-state properties were characterized, and the accelerated physical stability of the amorphous salts was evaluated at 40 °C/75% RH for three months. The solubility of the amorphous and crystalline donepezil-sulfonic acid salts was also measured.

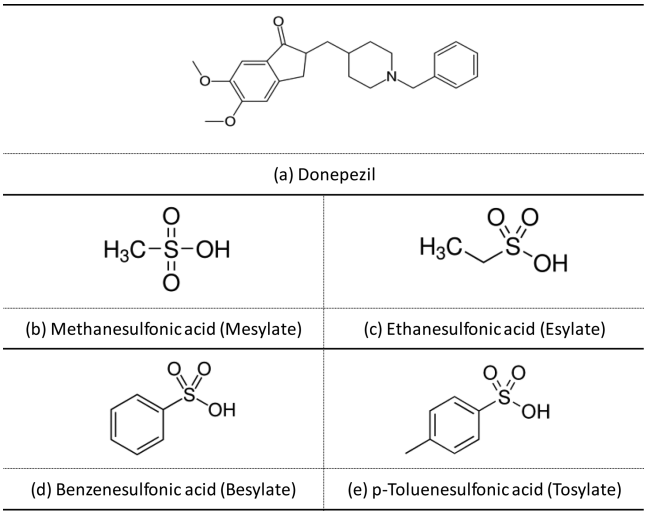


Figure 1. Molecular structures of (a) donepezil, (b) methanesulfonic acid (mesylate), (c) ethanesulfonic acid (esylate), (d) benzenesulfonic acid (besylate), and (e) *p*-toluenesulfonic acid (tosylate).

EXPERIMENTAL SECTION

Materials. The hydrochloride salt of donepezil (donepezil HCl) was purchased from Cangzhou Senary Chemical S. & T. Co., Ltd. (Hebei, China). The neutral form of donepezil was prepared following a procedure used previously.[12] Mesylate, esylate, besylate, tosylate, and isopropyl alcohol (IPA) were purchased from Sigma-Aldrich (St. Louis, MO). Sodium hydroxide was obtained from Jin Chemical Pharmaceutical Co., Ltd. (Gyunggi-do, Republic of Korea). Ethanol was obtained from Pharmco (Brookfield, CT). Water was double-distilled and filtered with a Milli-Q ultrapure water purification system (Billerica, MA).

Preparation of the Crystalline Donepezil-Sulfonic Acid Salts. The crystalline sulfonic acid salts were prepared by adding donepezil powder and the stoichiometric amount of the corresponding sulfonic acid (1/1) to isopropyl alcohol. The suspension was slurried for 1 week, and the resulting solids were filtered and dried at room temperature for 24 h.

Preparation of the Amorphous Donepezil-Sulfonic Acid Salts. The amorphous salts were obtained by heating the crystalline donepezil-esylate and donepezil-tosylate salts to 180 °C and the crystalline donepezil-mesylate and donepezil-besylate salts to 200 °C and subsequently cooling them at room temperature.

Physical Stability Assessment of the Amorphous Donepezil-Sulfonic Acid Salts. The amorphous forms of the sulfonic acid salts were stored in a jar equilibrated with a saturated solution of sodium chloride to maintain 75% RH at 40 °C. The jar was stored in a 40 °C oven, and microscopic observations were made at predetermined time intervals (1 day, 1 week, 1 month, and 3 months).

Powder X-ray Diffraction (PXRD). The physical stability of the amorphous salts of donepezil was evaluated using a D8 ADVANCE with Davinci (Bruker AXS Inc., GmbH, Germany) equipped with Cu K_α radiation and a high speed LynxEye detector. Samples were analyzed over a 2θ range of 4−40° with an increment of 0.02° at a rate of 6°/min. Data were analyzed using DIFFRAC^{plus} Eva (Bruker AXS Inc., GmbH, Germany).

Differential Scanning Calorimetry (DSC). Thermal analysis was conducted using a Q2000 DSC (TA Instruments, New Castle, DE). The Q2000 DSC was calibrated with indium for the cell constant and temperature. The donepezil-sulfonic acid salts were carefully weighed and placed in a low mass pan, before undergoing two sequential scans. Each sample was equilibrated at 0 °C and then heated to 200 °C at a heating rate of 10 °C/min. It was then cooled to 0 °C at a rate of 10 °C/min and reheated to 150 °C. Data were acquired and analyzed using Universal Analysis 2000 software v 4.1D (TA Instruments).

Thermogravimetric Analysis (TGA). Changes in the weights of the amorphous donepezil salts were measured using the TA Instruments thermogravimetric analysis system (TGA Q50 Thermogravimetric Analyzer; TA Instruments, New Castle, DE). A sample weighing approximately 10 mg was placed on a sample pan. The heating rate was 10 °C/min, from room temperature to 350 °C. Data were acquired and analyzed using Universal Analysis 2000 software v 4.1D (TA Instruments).

High Performance Liquid Chromatography (HPLC). The stoichiometric composition of the donepezil-sulfonic acid salts and the purity of crystalline and amorphous donepezil-sulfonic acid salts were determined by the 1260 infinity HPLC system (Agilent Technologies, Inc., Santa Clara, CA) with a diode array detector. HP Chemstation (Agilent Technologies, Inc.) was used for data

DOI: 10.1021/acs.cgd.5b00074
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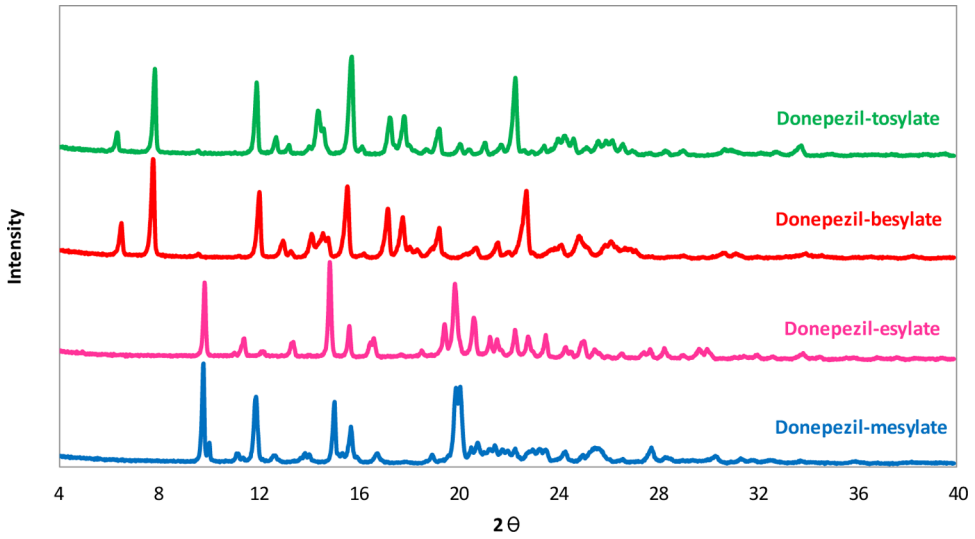

Figure 2. Powder X-ray patterns of the sulfonic acid salts of donepezil (from top to bottom: donepezil-tosylate, donepezil-besylate, donepezil-esylate, and donepezil-mesylate).

Table 1. Crystallographic Data for Three Donepezil-Sulfonic Acid Salts Obtained from Single Crystal X-ray Analysis

parameter	donepezil-mesylate	donepezil-besylate	donepezil-tosylate
chemical formula	$C_{24}H_{30}NO_3{\cdot}CH_3O_3S$	$C_{24}H_{30}NO_3{\cdot}C_6H_5O_3S$	$C_{24}H_{30}NO_3{\cdot}C_7H_7O_3S$
temperature	173 (2) K	296 (2) K	296 (2) K
space group	$Pna2_1$	$P2_1/n$	$P2_1/n$
crystal system	orthorhombic	monoclinic	monoclinic
a (Å)	15.1035 (3)	8.2183 (8)	8.4004 (13)
b (Å)	9.3287 (2)	12.4764 (12)	12.2217 (18)
c (Å)	34.9631 (6)	27.310 (3)	27.844 (4)
α (deg)	90.00	90.00	90.00
β (deg)	90.00	92.638 (7)	92.110 (3)
γ (deg)	90.00	90.00	90.00
V (Å^3))	4926.16	2800.05	2856.73
Density (mg/m^3)	1.282	1.275	1.283
Z	8	4	4
Reflections Collected/unique	53908/12217 [R_{int} (%) = 5.83]	24899/4956 [R_{int} (%) = 15.5]	36714/5620 [R_{int} (%) = 9.58]
R_1-Factor (%)	5.62	7.46	5.87
wR_2-Factor (%)	12.51	16.93	12.69

analysis. A Phenomenex Luna C18 5 μm, 4.6 × 250 mm analytical column (Phenomenex Inc., Torrance, CA) was used at 30 °C. The mobile phase consisted of A (0.01 M KH_2PO_4 with pH 3.0) and B (Acetonitrile) (A:B = 65:35, v/v).[12] The flow rate was 1 mL/min. The injection volume was 5 μL. The samples were analyzed at UV λ = 240 nm.

Solubility Measurements. A known amount of crystalline or amorphous donepezil-sulfonic acid salts was weighed and added to a vial. A known amount of water was gradually added to the vial with constant stirring. The water addition was kept at a very slow rate to minimize any excess water beyond what is needed to fully dissolve the solids. In order to cross-check the solubility, a small amount of salt was added to the vial to confirm that the solution became turbid. The duration of stirring before measurement varied: The solutions containing donepezil-mesylate and donepezil-esylate salt were stirred at least 10 h before the final measurement, while for the donepezil-besylate and donepezil-tosylate salts, stirring lasted less than 1 h before the final measurement. At least triplicate samples were used for each measurement.

X-ray Data Collection and Structure Determination. X-ray intensity data were collected on a Bruker SMART APEX-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at a temperature of 296 or 173 K. The structures were solved by applying the direct method using a SHELXS-97 and refined by full-matrix least-squares on F^2 using SHELXL-97.[19] All non-hydrogen atoms were refined anisotropically. The structures were solved by applying the direct method using a SHELXS-97 and refined by full-matrix least-squares on F^2 using SHELXL-97.[19] All non-hydrogen atoms were refined anisotropically. Amine H atoms (N−H) were located in a difference map and refined freely (refined distances; N−H = 0.95 (5) − 1.01 (3) Å). Other H atoms were positioned geometrically and refined using a riding model, with C−H = 0.93−0.98 Å, and with 1.5 U_{eq} (C) for methyl H atoms and 1.2 U_{eq} (C) for other H atoms.

RESULTS AND DISCUSSION

Crystalline Donepezil-Sulfonic Acid Salts. *Powder X-ray Diffraction (PXRD).* The powder patterns of the donepezil-sulfonic acid salts are shown in Figure 2. It is noted that the donepezil-benzenesulfonic acid (donepezil-besylate) and donepezil-*p*-toluenesulfonic acid (donepezil-tosylate) salts share similar powder patterns, as do the donepezil-ethanesulfonic acid (donepezil-esylate) and donepezil-methanesulfonic acid (donepezil-mesylate) salts. This implies that the unit cell parameters of donepezil with besylate are similar to those with tosylate, and that those with esylate are similar to those with

DOI: 10.1021/acs.cgd.5b00074
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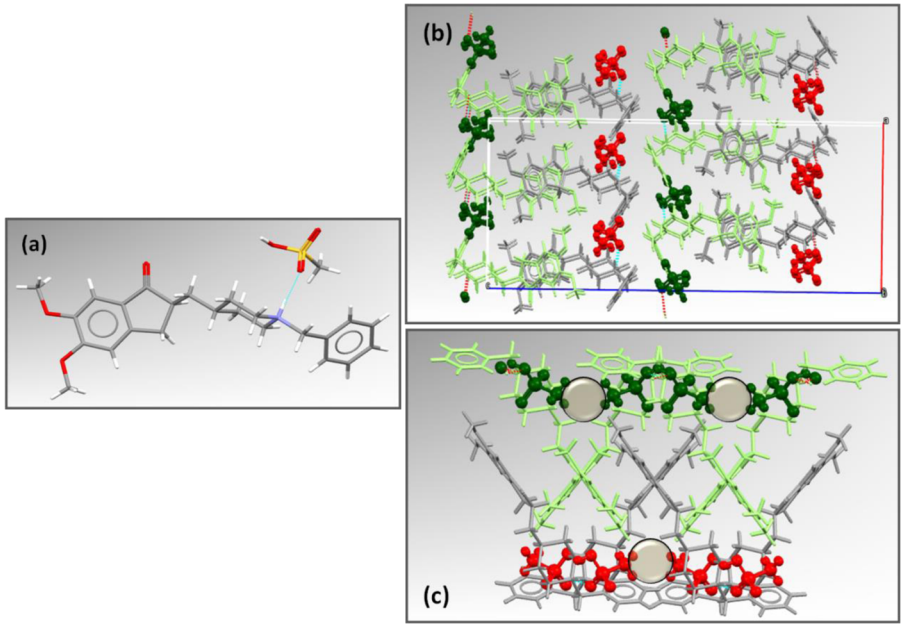

Figure 3. Hydrogen bonding motif and crystal packing diagrams of donepezil-mesylate salt: (a) hydrogen bonding motif of donepezil-mesylate consisting of one molecule of donepezil and one molecule of mesylate, and crystal packing diagram of donepezil-mesylate salt viewed (b) perpendicular to the *ac* plane and (c) perpendicular to the *bc* plane. The black circles illustrate void spaces in the crystal structure.

Table 2. Distribution of Bond Lengths and Bond Angles for the Donepezil-Sulfonic Acid Salts

Donepezil salts	N−H···O	*d*(N−H)	*d*(H···O)	*d*(N···O)	<(NHO)
Donepezil−mesylate	N^+6-H(6)···O^-2	0.95 (5)	1.71 (5)	2.648 (5)	168 (4)
	N^+39-H(39)···O^-35	0.95 (5)	1.74 (5)	2.685 (5)	174 (4)
Donepezil−besylate	N^+11-H(11)···O^-2	0.96 (5)	2.51 (5)	3.179 (6)	126 (5)
	N11−H(11)···O4 (S═O)	0.96 (5)	1.84 (5)	2.791 (5)	168 (4)
Donepezil−tosylate	N^+11-H(11)···O^-2	1.01 (3)	1.85 (4)	2.821 (3)	161 (3)
	N11−H(11)···O4 (S═O)	1.01 (3)	2.40 (3)	3.150 (5)	131 (2)

mesylate. The crystallographic data are discussed in detail in the single crystal X-ray analysis section.

Single Crystal Structure Analysis of Donepezil-Sulfonic Acid Salts. The tertiary amine donepezil salts were crystallized with pairs of the structurally related sulfonic acids including mesylate, esylate, besylate, and tosylate. However, crystals of donepezil-esylate suitable for single crystal X-ray analysis were unobtainable. Crystallographic data for the remaining three donepezil-sulfonic acid salts are shown in Table 1.

Donepezil-Mesylate Salt. Donepezil-mesylate crystallizes in the orthorhombic space group $Pna2_1$. The hydrogen bonding motif of donepezil-mesylate consists of one molecule of donepezil and one molecule of mesylate (Figure 3). Only one sulfonyl hydroxide of the mesylate forms an intermolecular hydrogen bond with the piperidyl amine of the donepezil. The piperidyl amine serves as a proton acceptor while the sulfonyl hydroxide from the mesylate serves as a proton donor. Therefore, this complex is a 1:1 salt of donepezil and mesylate. In a previous study conducted in our laboratories,[12] donepezil did not form any hydrogen bonds when its neutral form crystallized in different polymorphs. However, the proton transfer occurring between the piperidyl amine of the donepezil and the sulfonyl hydroxide of the mesylate contributes to the formation of a salt ($SO^-\cdots H-N^+$) as evidenced by the bond lengths of $H-N^+$ (<0.98 Å) and $SO^-\cdots H$ (>1.73 Å). Information regarding the bond length and bond angles is summarized in Table 2. The bond angles of <NHO are 168° and 174°, indicating strong hydrogen bonds between donepezil and mesylate. Figure 3b,c illustrates the crystal packing diagrams of donepezil-mesylate salt. Symmetrically inequivalent molecules are colored differently. The two hydrogen bonding motifs of donepezil-mesylate tend to stack in an antiparallel manner with respect to the indanone ring system, which results in the formation of a layered structure (Figure 3b).

On the basis of the PXRD patterns shown in Figure 2, we expect donepezil-mesylate and donepezil-esylate salts to be isostructural. Figure 3b, and c illustrates the mesylate in red or green using a ball and stick model. The way mesylate molecules reside in a crystal is similar to the way solvent molecules reside in channel solvates. Normally, a wide variety of solvents with similar sizes and structures can be easily replaced in a channel solvate crystal. The same analogy can be applied to donepezil-mesylate crystals. Because esylate is structurally similar to mesylate, donepezil-mesylate, and donepezil-esylate can be expected to have similar crystal structures. The black circles in Figure 3c represent void spaces that are large enough to accommodate esylate molecules instead of mesylate molecules.

Donepezil-Besylate and Donepezil-Tosylate Salts. Both donepezil-besylate and donepezil-tosylate crystallize in the monoclinic space group, $P2_1/n$ (Table 1). As expected from the powder patterns, the cell parameters of donepezil-besylate and donepezil-tosylate are similar to each other. Only slight variations in unit cell length ($-2\% < a, b, c < 2\%$) and β

DOI: 10.1021/acs.cgd.5b00074
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(<0.6%) are observed. The crystal molecular conformation of donepezil-besylate is superimposable on that of donepezil-tosylate (Figure 4). The hydrogen bonding motif of donepezil-

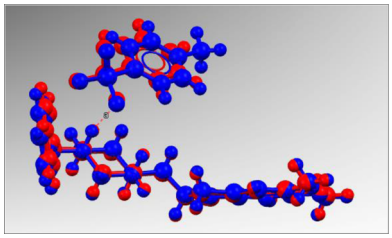

Figure 4. Superimposed molecular structures of donepezil-besylate and donepezil-tosylate; the crystal molecular conformations of the two compounds are superimposable.

besylate and donepezil-tosylate consists of one molecule of donepezil and one molecule of besylate or tosylate. As with donepezil-mesylate, only one sulfonyl hydroxide of the besylate or the tosylate forms an intermolecular hydrogen bond with the piperidyl amine of the donepezil. As shown in Figure 5, the crystal packing diagrams of both compounds look similar.

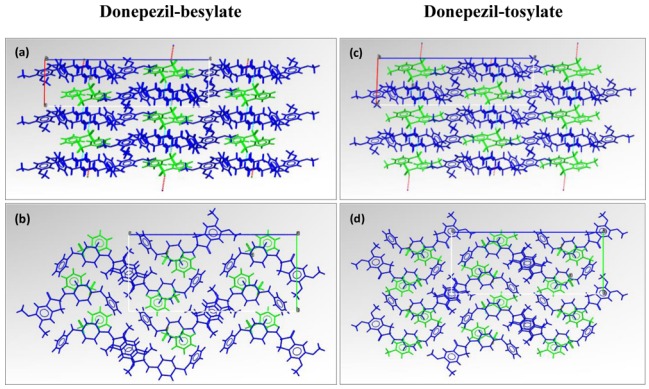

Figure 5. Crystal packing diagrams of donepezil-besylate and donepezil-tosylate: projection of donepezil-besylate on (a) the *ac* plane and (b) the *bc* plane, and projection of donepezil-tosylate on (c) the *ac* plane and (d) the *bc* plane.

Proton transfer from the sulfonyl hydroxide of the besylate or the tosylate to the piperidyl amine of the donepezil was also observed, contributing to the formation of a salt ($SO^{-}\cdots H-N^{+}$). However, it is observed that in both cases, the bond distance of one S═O···H is significantly larger than the other. The corresponding bond angles of <NHO are also large, indicating that only one sulfonyl hydroxide is involved in hydrogen bonding between donepezil and besylate or tosylate.

It is interesting to note that donepezil-besylate and donepezil-tosylate salts are nearly isostructural in terms of molecular conformation and crystal packing. As can be seen in Figure 5a and c, donepezil molecules and besylate or tosylate molecules alternate along the *c* axis. As with donepezil-mesylate salt, the two hydrogen bonding motifs of donepezil-besylate and donepezil-tosylate tend to stack in an antiparallel manner with respect to the centrosymmetrically related indanone ring. For donepezil-besylate and donepezil-tosylate salts, the hydrogen bonding motifs are stacked in a way that forms a herringbone pattern when projected on the *bc* plane. It is noticeable that the degree of overlap between the indanone moieties of the two hydrogen bonding motifs is higher for donepezil-tosylate than for donepezil-besylate. It seems to reduce the unit cell length of the *b* axis for donepezil-tosylate in comparison to donepezil-besylate.

Thermal Behavior of the Four Crystalline Donepezil-Sulfonic Acid Salts. The DSC thermograms of the four donepezil-sulfonic acid salts are shown in Figure 6; they melted as pure phases in the following descending order: donepezil-mesylate (181.76 °C), donepezil-besylate (175.28 °C), donepezil-tosylate (169.20 °C), and donepezil-esylate (153.17 °C; see also Table 3). The formation of sulfonic acid salts led to a significant increase in the T_g of donepezil, from 18.84 °C to at least 76.04 °C. The difference in melting points between donepezil-besylate and donepezil-tosylate is approximately 6 °C, while the melting point of donepezil-mesylate is almost 20 °C higher than that of donepezil-esylate. The heat of fusion of donepezil-esylate (81.21 J/g) is smaller than that of donepezil-mesylate (99.80 J/g). It is interesting that these isostructural compounds exhibit very different melting points and heats of fusion. The salts with smaller counterions, donepezil-mesylate and donepezil-besylate, exhibit higher melting points and larger heats of fusion than do the salts with larger counterions, donepezil-esylate and donepezil-tosylate.

Amorphous Donepezil-Sulfonic Acid Salts. *Thermal Behavior of the Four Amorphous Donepezil-Sulfonic Acid Salts.* Figure 7 shows the glass transition temperatures (T_g) of amorphous donepezil and four amorphous sulfonic acid salts of donepezil. The presence of a single T_g confirms the formation of an amorphous salt rather than a physical mixture of an amorphous acid and an amorphous compound. The melting points of the four solvent-free polymorphic forms of donepezil range from 89 to 94 °C, and the T_g is 18.84 °C.[12] Thus, amorphous donepezil is expected to be a supercooled liquid and show poor physical stability at both room temperature and in accelerated stability test conditions. When donepezil is prepared in the form of a sulfonic acid salt, the melting point increases by approximately 56−89 °C, and T_g increases by 55−63 °C. It is therefore expected that the amorphous donepezil-sulfonic acid salts will demonstrate greater stability in accelerated stability test conditions than will amorphous donepezil. The nearly isostructural salts including donepezil-besylate and donepezil-tosylate showed closer alignment of T_g's and melting points as expected. However, one might not expect that the difference in T_g's and the melting points between donepezil-mesylate and donepezil-esylate is clear. In this case, different degrees of lattice energy between donepezil-mesylate and donepezil-esylate can be attributed to the difference in T_g's and the melting points. Flexibility of esylate induced by one rotatable bond[20] as well as the difference in intermolecular interactions[21] between mesylate/esylate and donepezil might affect the crystal lattice energy despite of isostructural property between donepezil-mesylate and donepezil-esylate and result in difference in T_g's and the melting points.

Physical Stability of the Four Amorphous Donepezil-Sulfonic Acid Salts in Accelerated Stability Conditions. The physical stability of amorphous donepezil and the four amorphous donepezil-sulfonic acid salts was evaluated using a polarized microscope and PXRD. In addition, the purity of crystalline and amorphous donepezil-sulfonic acid salts was evaluated by using HPLC to exclude the effect of impurity on physical stability as well as solubility of donepezil-sulfonic acid salts, and confirmed (Supporting Information). Donepezil-besylate and donepezil-tosylate crystallized within 24 h when stored in accelerated stability conditions (40 °C/75% RH).

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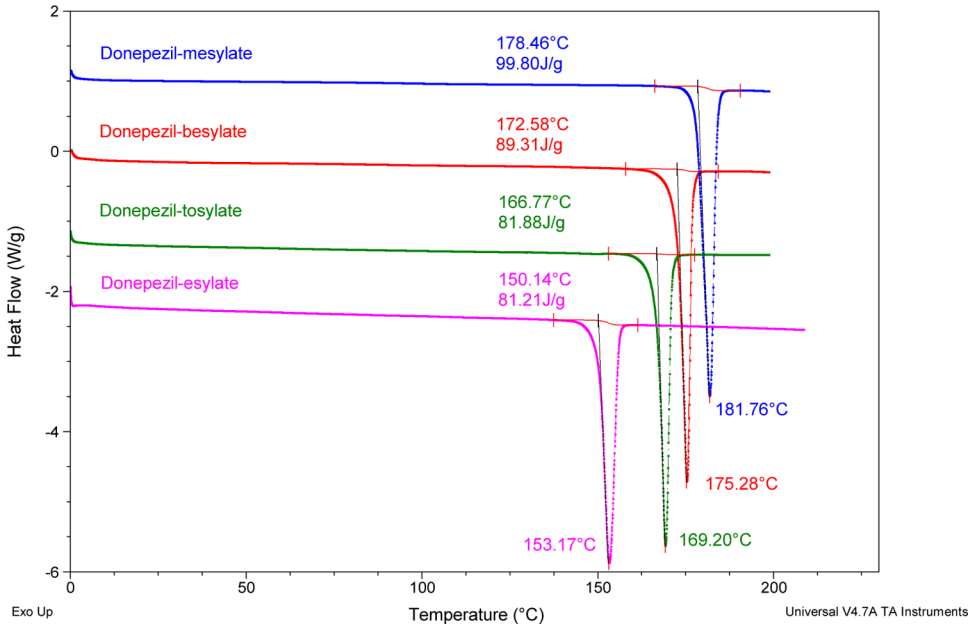

Figure 6. Overlaid DSC thermograms of four donepezil-sulfonic acid salts (from top to bottom: donepezil-mesylate, donepezil-besylate, donepezil-tosylate, and donepezil-esylate).

Table 3. Thermal Behavior of Donepezil-Sulfonic Acid Salts Measured by DSC

Donepezil salts	melting point (onset temp., °C)	heat of fusion (J/g)	melting point (°C)	T_g (°C)
Donepezil[12]	89–94	72–88	92–98	18.84
Donepezil-mesylate	178.46	99.80	181.76	81.82
Donepezil-esylate	150.14	81.21	153.17	73.48
Donepezil-besylate	172.58	89.31	178.28	76.04
Donepezil-tosylate	166.77	81.88	169.20	77.62

Neither donepezil-mesylate nor donepezil-esylate crystallized under the same conditions for 3 months (Supporting Information). During the study, it was noted that donepezil-mesylate and donepezil-esylate sorbed water. The sorbed water does not seem to facilitate the crystallization of both compounds as long as the amorphous form remains intact. However, the amorphous forms of both donepezil-mesylate and donepezil-esylate tend to crystallize when physical disturbance, such as scratching by a spatula, is introduced to the system.

It is well-known that the molecular mobility necessary for crystallization is negligible when the amorphous form is stored 50 K below T_g.[10,11] A T_g of 76–81 °C is not high enough to restrict the molecular motion of amorphous forms. In addition, water present in the amorphous form acts as a plasticizer.

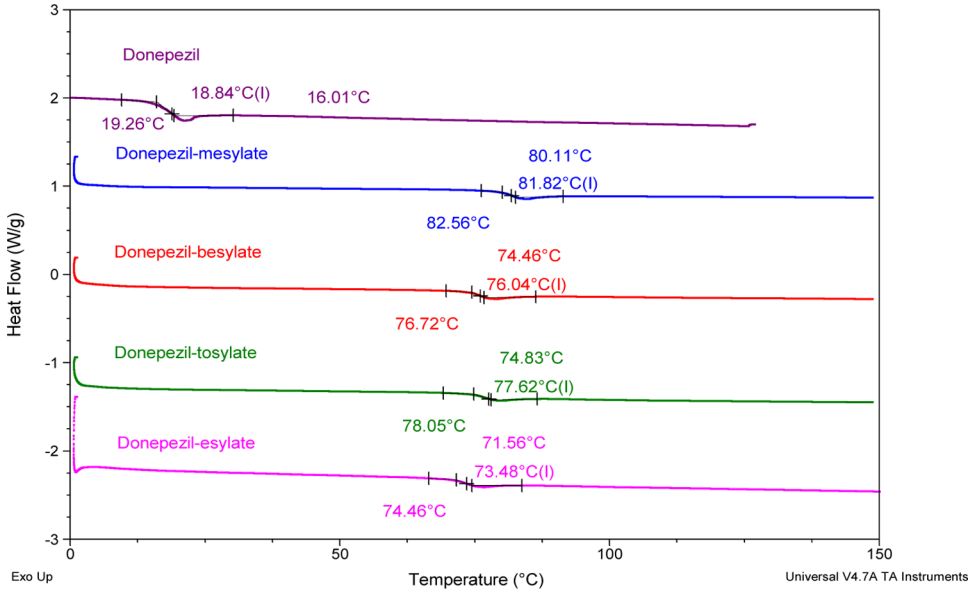

Figure 7. Overlaid DSC thermograms of amorphous donepezil and amorphous donepezil-sulfonic acid salts (from top to bottom: donepezil, donepezil-mesylate, donepezil besylate, donepezil-tosylate, and donepezil-esylate).

DOI: 10.1021/acs.cgd.5b00074
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However, the structural disorder is retained well even when water is retained in the amorphous system for donepezil-mesylate and donepezil-esylate.

Solubility Analysis. The solubility of amorphous/crystalline donepezil-esylate and donepezil-mesylate is extremely high, while that of amorphous/crystalline donepezil-besylate and donepezil-tosylate is low (Table 4). It was difficult to accurately evaluate the solubility of amorphous/crystalline donepezil-esylate and amorphous donepezil-mesylate since the solubility was extremely high (>4200 mg/g). For donepezil-besylate and donepezil-tosylate, the conversion from crystalline salt to an amorphous form occurred spontaneously. In practice, it was difficult to determine the exact solubility of the crystalline and amorphous salts. As a result, the measured solubility of crystalline and amorphous salts appears similar.

Table 4. Solubility of the Four Donepezil-Sulfonic Acid Salts in Water

	solubility (mg/g of water)	
Donepezil salts	amorphous	crystal
Donepezil-mesylate	>4295.71	2650.71 ± 104.78
Donepezil-esylate	>4789.35	>4227.10
Donepezil-besylate	5.68 ± 0.12	2.58 ± 0.14
Donepezil-tosylate	7.31 ± 0.40	6.27 ± 0.22

According to classical nucleation theory, the rate of nucleation increases exponentially as supersaturation increases. However, early work by Tamman suggested that viscosity also plays an important role in determining the rate of nucleation during cooling of the melt.[8] For example, a sharp increase in viscosity due to rapid cooling following a melt reduces the rate of nucleation by restricting the molecular mobility necessary for crystallization.[8] Practically, the first step in crystallization is to find a solvent that can dissolve material ranging from 2 to 200 mg/mL. It is difficult for crystallization to occur when the solubility of a particular material is over 200 mg/mL in a given solvent. The high solubility of a material in a solvent suggests that the solution will become viscous after complete solubilization, and this viscosity will prevent rapid crystallization. In other words, the strong interaction between the material and the solvent forms a viscous liquid and thus delays nucleation. Table 4 shows the solubility of the amorphous and crystalline donepezil-sulfonic acid salts. The solubility of amorphous and crystalline donepezil-mesylate and donepezil-esylate are extremely high while the solubility of amorphous and crystalline donepezil-besylate and donepezil-tosylate is very low. It is possible that the extremely high solubility of the crystalline/amorphous salts of donepezil delays the rate of nucleation by increasing the viscosity. The amounts of absorbed water in amorphous donepezil-mesylate and donepezil-esylate are approximately 10−12% w/w by TGA analysis (data not shown). Significant weight loss was observed around 100−150 °C indicating that water is actually absorbed in amorphous forms. It needs to be pointed out that the water present in the amorphous form reduces the physical stability of the amorphous salts of donepezil because physical disturbance induces crystallization. In this study, the water present in the amorphous salts of donepezil with mesylate and esylate increases the viscosity of the system and thus delays the rate of nucleation. Crystallization induced by physical disturbance also supports our hypothesis that water reduces physical stability, but the high degree of viscosity achieved by the high solubility of amorphous/crystalline forms in water delays the rate of nucleation and thus devitrification. It is also possible that physical disturbance causes the local environment of the amorphous form to become heterogeneous, such as water-rich or water-deficient. Water-rich or water-deficient local regions could be susceptible to crystallization.

CONCLUSION

Three crystal structures of donepezil-sulfonic acid salts were obtained. Donepezil-besylate and donepezil-tosylate were nearly isostructural in terms of their crystal molecular conformation and crystal packing. On the basis of their PXRD patterns, donepezil-mesylate and donepezil-esylate are likely to share similar crystal structures. The sulfonyl hydroxides of all three sulfonic acids form an intermolecular hydrogen bond with the piperidyl amine of donepezil. Solid state characterization found that the T_g's of all four amorphous salts of donepezil are similar to each other and are significantly higher compared to that of donepezil. Stability analysis found that the amorphous salts of donepezil with mesylate and esylate led to a significantly improved physical stability under accelerated stability conditions but the other sulfonic acid salts of donepezil did not. Solubility data showed that sulfonic acid salts of donepezil significantly increase the solubility of donepezil that are not shown by other salt forms except hydrochloride salt. Solubility analysis found that the solubility of amorphous/crystalline donepezil-mesylate and donepezil-esylate is extremely high compared to that of donepezil-besylate and donepezil-tosylate. We concluded that the extremely high solubility in water is responsible for delaying the rate of nucleation and thus improving the physical stability of donepezil. This study highlights that the aqueous solubility of amorphous material can be an important factor when considering the physical stability of amorphous material under high relative humidity.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data files (cif format) for donepezil-mesylate, donepezil-besylate, and donepezil-tosylate salts, the physical stability data, the comparisons of calculated vs experimentally obtained PXRD patterns of donepezil-sulfonic acid salts, HPLC data of amorphous/crystalline donepezil-sulfonic acid salts. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b00074.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by a grant (14172MFDS189) from the Ministry of Food and Drug Safety in 2014 and the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2014R1A1A1006429).

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DOI: 10.1021/acs.cgd.5b00074
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