Enhancing the Solubility and Dissolution Performance of Safinamid Using Salts

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Abstract: Safinamide (SAF) is an anti-Parkinson’s disease (PD) drug that has selective monoamine oxidase type-B (MAO-B) inhibition activity. In 2017, SAF was approved by the U.S. Food and Drug Administration (FDA) as safinamide mesylate (SAF-MS, marketed as Xadago). Owing to its poor solubility in water, SAF is a Biopharmaceutics Classification System BCS Class II compound. In this study, four salts of safinamide (with hydrochloric acid (HCl), hydrobromic acid (HBr), and maleic acid (MA)) were obtained and characterized using single crystal X-ray diffraction (SCXRD), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetry (TG). The solubility and dissolution rate of all salts were systematically studied in water and phosphate buffer (pH 6.86) solutions. The accelerated stability tests indicated that all salts, except SAF-MA, had good stability under high humidity conditions.

Keywords: safinamide; salts; X-ray diffraction; solubility; dissolution rate

1. Introduction

Approximately 40% of drug candidates fail during the late stages of drug discovery owing to their poor water solubility and intrinsic dissolution rate (IDR) [1,2]. Recently, many methods have been developed, such as solid dispersion [3], nanocrystals [4], cocrystal [5–7], salts [8–10], to improve the water solubility of poorly soluble drugs [11]. One of the key challenges is to improve the solubility of poorly soluble drugs without changing their other properties, including stability, covalent bonding structures, mechanical properties, and pharmacological behaviors. The formation of salts is a well-established approach for tailoring the physicochemical properties of drugs without altering the drug molecule [12–21].

Safinamide (SAF, Figure 1) is an anti-Parkinson’s disease drug with selective monoamine oxidase type-B inhibition activity [22–26]. Safinamide is a Biopharmaceutics Classification System (BCS) II drug with low solubility and high permeability, and it has been commercialized in its salt form, safinamide mesylate (marketed as Xadago) and was approved, in 2017, by the U.S. Food and Drug Administration. To date, there have been no relevant studies undertaken on the crystal structure and physicochemical properties of cocrystals and salts of safinamide. In the present study, a series of conformers containing organic and inorganic acids were used to interact with safinamide (Supplementary Materials Table S1), and four novel salts of safinamide with hydrochloric acid (HCl), hydrobromic acid (HBr), and maleic acid (MA) were prepared and characterized, and their solubilities, IDRs and stability were evaluated. The results indicated that all novel salts had improved solubilities and IDRs.
2. Materials and Methods

2.1. Instrumentations and Materials

Safinamide (SAF) was purchased from Shanghai BioChemPartner Co. Ltd (Shanghai, China). The coformers HCl, HBr, and MA were purchased from Aladdin Biochemical Technology Co. Ltd (Shanghai, China). All solvents used were purchased from Ghtech Co. Ltd (Guangzhou, China). The data from the X-ray diffraction of the powdered chemicals were measured using a powder diffractometer model D8 ADVANCE (Karlsruhe, Germany) with a tube of Cu Kα radiation (λ = 1.5418 Å) at 40 mA and 40 kV and data were collected within the range of 3–60°. Differential scanning calorimetry (DSC) was performed on a Mettler-Toledo machine at a rate of heating of 10 °C/min within the range of 25–250 °C under nitrogen flow at a rate of 20 mL/min. Thermogravimetric (TG) analysis was performed on a Perkin-Elmer TGA 4000 (Shanghai, China) equipment with a heating rate of 10 °C/min in the 25–500 °C range under nitrogen flow at a rate of 20 mL/min. All single crystal X-ray diffraction (SCXRD) data were collected on a Bruker Apex II CCD diffractometer (Karlsruhe, Germany) with Mo Kα radiation (λ = 0.71073 Å) at 293 K. The X-ray generator was operated at 50 kV and 30 mA. All the structures were solved by direct methods and refined using SHELX-97 (SHELX97 version) [27,28]. All atoms were placed at the geometrically calculated positions, except for the O-H and N-H hydrogen atoms. The crystallographic parameters of all the salts are summarized in Table 1 and the hydrogen bonds are listed in Table 2.

Table 1. Crystallographic parameters of safinamide and its pharmaceutical salts.

| Title                      | SAF-HCl         | SAF-HBr         | SAF-MA          | SAF-MA·H2O       |
|----------------------------|-----------------|-----------------|-----------------|-----------------|
| Chemical formula           | C_{17}H_{20}N_{2}O_{2}F^{+}, Cl^{-} | C_{17}H_{20}N_{2}O_{2}F^{+}, Br^{-} | C_{21}H_{24}N_{2}O_{6}F | C_{21}H_{25}N_{2}O_{7}F |
| Molecular formula          | C_{17}H_{20}N_{2}O_{2}FCl | C_{17}H_{20}N_{2}O_{2}FBr | C_{17}H_{25}N_{2}O_{6}F | C_{17}H_{25}N_{2}O_{6}F |
| Formula weight             | 338.80          | 383.26          | 418.41          | 443.63          |
| Crystal system             | orthorhombic    | orthorhombic    | orthorhombic    | triclinic       |
| Space group                | P2_1 2_1       | P2_1 2_1       | P2_1 2_1       | P1              |
| a [Å]                      | 5.2766(8)       | 5.2340(4)       | 5.7326(5)       | 5.9202(8)       |
| b [Å]                      | 12.174(2)       | 13.8352(11)     | 9.2498(12)      | 8.5781(11)      |
| c [Å]                      | 26.389(5)       | 24.0985(17)     | 38.155(4)       | 11.8413(15)     |
| α[°]                       | 90              | 90              | 90              | 105.072(11)     |
| β[°]                       | 90              | 90              | 90              | 101.299(11)     |
| γ[°]                       | 90              | 90              | 90              | 105.145(11)     |
| Z                           | 4               | 4               | 4               | 1               |
| V (Å³)                     | 1695.2(5)       | 1745.1(2)       | 2023.2(4)       | 537.57(12)      |
| D calc (g cm⁻³)            | 1.327           | 1.459           | 1.374           | 1.348           |
| μ (mm⁻¹)                   | 0.246           | 2.376           | 0.107           | 0.107           |
Table 2. Hydrogen bond distances (Å) and angles (°) of safinamide and its salts.

| H-Bond    | d(D–H) | d(H···A) | d(D···A) | \(\angle(DHA)\) | Symmetry Code |
|-----------|--------|---------|---------|----------------|---------------|
| SAF-HCl   |        |         |         |                |               |
| N1\(^+\)--H1A···Cl1 | 0.97  | 2.46   | 3.366(4) | 156           | \(-x, y-1/2, -z+1/2\) |
| N1\(^+\)--H1B···Cl1 | 0.89  | 2.36   | 3.219(4) | 164           | \(-x, y-1/2, -z+1/2\) |
| N2--H2A···Cl1 | 0.86  | 2.37   | 3.228(4) | 175           | \(x, y-1, z\)   |
| N2--H2B···Cl1 | 0.89  | 2.56   | 3.332(4) | 145           | \(x-1, y-1, z\) |
| SAF-HBr   |        |         |         |                |               |
| N1\(^+\)--H1A···Br1 | 0.89  | 2.54   | 3.436(4) | 176           | \(-x+1, y+1/2, -z+1/2\) |
| N1\(^+\)--H1B···Br1 | 1.04  | 2.45   | 3.410(4) | 152           | \(-x+1, y+1/2, -z+1/2\) |
| N2--H2A···Br1 | 0.86  | 2.79   | 3.503(4) | 141           | \(x+1, y+1, z\)   |
| N2--H2B···Br1 | 0.86  | 2.59   | 3.443(4) | 170           | \(x, y+1, z\)   |
| SAF-MA    |        |         |         |                |               |
| N1\(^+\)--H1A···O3 | 0.87  | 1.89   | 2.760(5) | 174           | \(x, y, z\)   |
| N1\(^+\)--H1B···O4 | 1.01  | 2.05   | 3.049(5) | 169           | \(x-1, y, z\)   |
| N2--H2A···O2 | 0.96  | 1.97   | 2.908(5) | 163           | \(-x+1, y-1/2, -z+1/2\) |
| N2--H2B···O5 | 0.90  | 2.35   | 3.066(5) | 137           | \(-x+1, y-1/2, -z+1/2\) |
| O5--H5···O4 | 0.94  | 1.51   | 2.439(5) | 173           | \(x, y, z\)   |
| SAF-MA-H2O|        |         |         |                |               |
| N1\(^+\)--H1A···O7 | 0.90  | 1.92   | 2.787(3) | 161           | \(x, y-1, z\)   |
| N1\(^+\)--H1B···O6 | 0.90  | 1.99   | 2.825(3) | 153           | \(x, y, z\)   |
| N2--H2A···O3 | 0.86  | 2.07   | 2.909(3) | 166           | \(x+1, y, z+1\) |
| N2--H2B···O4 | 0.87  | 2.19   | 3.000(3) | 155           | \(x, y, z+1\)   |
| O7--H7C···O6 | 0.90  | 2.09   | 2.846(3) | 141           | \(x-1, y+1, z\)   |
| O4--H4···O5 | 0.90  | 1.62   | 2.402(3) | 142           | \(x, y, z\)   |

2.2. Preparation of Safinamide Salts

**SAF-HCl (1:1) salt:** In a 25 mL round-bottom flask, SAF (40 mg) and HCl (30 μL) were dissolved in 4 mL of ethyl-acetate-water saturated solution and stirred constantly for 1 h. The flask was, then, kept at room temperature to slowly evaporate, and needle single crystals were obtained after 7–10 days.

**SAF-HBr (1:1) salt:** In a 25 mL round-bottom flask, SAF (40 mg) and HBr (50 μL) were dissolved in 5 mL of methanol/water (9:1, v/v) and stirred constantly for 1 h. The flask was, then, kept at room temperature to slowly evaporate, and block single crystals were obtained after 7–10 days.

**SAF-MA (1:1) salt:** In a 25 mL round-bottom flask, SAF (20 mg) and MA (7.7 mg) were dissolved in 4 mL of methanol and stirred constantly for 1 h. The flask was, then, kept at room temperature to slowly evaporate, and needle single crystals were obtained after 4–5 days.

**SAF-MA-H2O (1:1:1) salt:** In a 25 mL round-bottom flask, SAF (40 mg) and MA (15.4 mg) were dissolved in 6 mL of acetone/water (4:1, v/v) and stirred constantly for 1 h. The flask was, then, kept at room temperature to slowly evaporate, and needle single crystals were obtained after 2–3 days.
2.3. Solubility and Intrinsic Dissolution Rate (IDR) Studies

Previous studies on the solubility of SAF and related salts have been conducted using the excessive powder dissolution method [29]. SAF absorbance was determined at a wavelength $\lambda_{\text{max}} = 225$ nm in water and phosphate buffer (pH 6.86) solutions. The curve of intensity versus the concentration calibration was plotted using this absorbance value for the SAF and related salts. For the solubility experiments, excessive safinamide and its salts were placed in water and pH 6.86 phosphate buffer medium, respectively. In all solubility experiments, the solutions were stirred at a speed of 500 rpm using a magnetic stirrer at a temperature of 37 °C and the stirring process lasted for 24 h. During the process, subsamples (5 mL) were removed and filtered using membrane filters (0.22 μm). Then, based on UV-spectroscopy, the absorbance was determined. The undissolved residues were vacuum dried and further characterized by powder X-ray diffraction (PXRD). All tests were repeated six times.

The IDRs of the SAF and its related salts were determined using a PJ-3 LAB Tablet Four-Usage Tester (Tianjin Guoming Medical Equipment Co. LTD (Tianjin, China)). A total of 150 mg sample (SAF and its salts) was compressed with a smooth surface by applying a pressure of 1.8 MPa for 5 min in an area of 1.3 cm². The pellets were dipped in a dissolution medium (500 mL), i.e., water or pH 6.86 phosphate buffer medium. The temperature was set at 37 °C and a rotating paddle was used to stir the medium at 100 rpm. The dissolution medium (5 mL) was withdrawn at the following intervals: 5, 10, 15, 20, 30, 45, 60, 90, and 120 min, and replaced each time with the same amount of fresh medium. Samples were filtered through 0.22 μm membrane filters, and then the absorbance was determined using a UV-spectroscopy. All tests were performed in triplicate.

2.4. Stability Studies

The stability studies of SAF and its salts was performed under different humidity environments at 25 °C. The different relative humidity treatments were 75% (sodium chloride in saturated state), 85% (potassium chloride in saturated state), and 97% (potassium sulfate in saturated state). The samples were placed in an incubator after 14 days and assessed using PXRD data.

3. Results

3.1. Crystal Structure Analysis

3.1.1. Crystal Structure of SAF-HCl (1:1) Salt

The SAF-HCl salt crystallize in an orthorhombic space group $P2_12_12_1$. The asymmetric unit of SAF-HCl contained one SAFH+ cation and one Cl- anion, which were connected by N1−H1B···Cl1 (3.219(4) Å) and N2−H2A···Cl1 (3.228(4) Å) charge-assisted hydrogen bond forming a one-dimensional zigzag chain structure (Figure 2).
3.1.2. Crystal Structure of SAF-HBr (1:1) Salt

Similar to SAF-HCl, the SAF-HBr salt crystallize in an orthorhombic space group $P2_12_12_1$ with one SAFH$^+$ cation and one Br$^-$ anion in the asymmetric unit. A one-dimensional zigzag chain structure was observed between SAF cations and HBr anions through $N1^+\cdots H1A\cdots Br1$ (3.436(4) Å), $N1^+\cdots H1B\cdots Br1$ (3.410(4) Å), $N1^+\cdots H2A\cdots Br1$ (3.503(4) Å), and $N2^+\cdots H2B\cdots Br1$ (3.443(4) Å) charge-assisted hydrogen bonds (Figure 3).

3.1.3. Crystal Structure of SAF/MA (1:1) Salt

The SAF-MA salt crystallize in an orthorhombic space group $P2_12_12_1$. The asymmetric unit of SAF-MA contained one SAFH$^+$ cation and one MA$^-$ anion, which were connected by $N1^+\cdots H1B\cdots O4$ (3.049(5) Å), $O5-H5\cdots O4$ (2.439(5) Å), $N2^+\cdots H2B\cdots O5$ (3.066(5) Å), and $N2^+\cdots H2A\cdots O2$ (2.908(5) Å) charge-assisted hydrogen bond forming a trimerical $R_4^4(11)$ two-dimensional sheet structure (Figure 4). The two-dimensional sheet was further linked through $N1^+\cdots H1A\cdots O3$ (2.760(5) Å) charge-assisted hydrogen bond forming a three-dimensional structure.
3.1.4. Crystal Structure of SAF/MA/H₂O (1:1:1) Salt Hydrate

The SAF-MA-H₂O salt hydrate crystallize in a triclinic space group P1. The asymmetric unit of SAF-MA-H₂O contained one SAFH⁺ cation, one MA⁻ anion, and one water molecule, which were connected by N1⁻H1A···O7 (2.787(3) Å), N1⁻H1B···O6 (2.825(3) Å), N2⁻H2A···O3 (2.909(3) Å), N2⁻H2B···O4 (3.000(3) Å), O4-H4···O5 (2.402(3) Å), and O7⁻H7C···O6 (2.846(3) Å) charge-assisted hydrogen bond forming a closely linked R⁷/² (20) two-dimensional sheet structure (Figure 5).

3.2. Powder X-ray Diffraction (PXRD) Analyse

The PXRD diffractograms of SAF, SAF-HCl, SAF-HBr, SAF-MA and SAF-MA-H₂O are shown in Figure 6. The results demonstrated that the experimental patterns were consistent with the simulated patterns calculated by Mercury using the refined single crystal X-ray data.
3.3. Thermal Analyses

Differential scanning calorimetry and thermogravimetry methods are usually employed to assess the thermodynamic stability of solid forms. Herein, the DSC and TG curves of SAF and all salts are shown in Figures 7 and S1. The DSC curves of SAF, SAF-HCl, SAF-HBr, and SAF-MA showed an endothermic peak at 136 °C, 231 °C, 228 °C, and 182 °C, respectively, with the temperature attributed to the melting point of the solid forms. The DSC curve of SAF-MA-H2O exhibited a broad peak in the range of 50–110 °C, which may be attributed to the release of water in the crystal cell. Another endothermic peak at 182 °C was observed, which was assigned to the melting point of SAF-MA-H2O. The TG curves of SAF, SAF-HCl, SAF-HBr, and SAF-MA began to decompose with the formation of volatile compound(s) at 200 °C, 224 °C, 222 °C, and 177 °C, respectively. The TG curves of SAF-MA-H2O showed a weight loss of 4.38% at the range of 50–110 °C, which was attributed to water loss (calculated 4.13%). SAF-MA-H2O began to decompose at 177 °C, which meant that the melting observed was a melting/degradation due to the fact that the baseline was not reached after the phase transition, and then we continued the TGA experiments that confirmed the decomposition phenomenon.
3.4. Solubility and Dissolution Studies

Solubility is the intrinsic property of a drug and affects its absorption in the body, whereas the dissolution rate is a dynamical parameter that is a measure within a specific time. The solubility and IDR at 37 °C for the SAF and its salts are listed in Table 3. PXRD analyses of the undissolved residue at the completion of the solubility experiments indicated that SAF, SAF-HCl, SAF-HBr, and SAF-MA-H2O salts were stable in water and phosphate buffer (pH 6.86) solution (Figures S2–S5), whereas SAF-MA salt was completely transformed to SAF-MA-H2O (Figure S6).

The solubility profiles for SAF and its salts are shown in Figure 8 and the result showed the SAF-HCl, SAF-HBr, and SAF-MA-H2O salts exhibited a significant solubility advantage over that of SAF either in water or phosphate buffer (pH 6.86). The solubility values followed the order of SAF-HCl > SAF-HBr > SAF-MA-H2O > SAF in water and pH 6.86 phosphate buffer. Interestingly, the IDR values followed the order of SAF-HBr > SAF-HCl > SAF-MA > SAF-MA-H2O > SAF in water and phosphate buffer (pH 6.86) (Figures S7 and S8). The IDR results indicated that SAF-HBr showed better dissolution dynamics than that of SAF-HCl, although SAF-HCl had a higher solubility. The intrinsic dissolution profiles in water and phosphate buffer (pH 6.86) are shown in Figures 9 and 10. The results confirmed that the dissolution rates of the four salts produced in the present study were superior to that of SAF. The SAF-HBr salt exhibited the best dissolution enhancement as compared with the others in water and phosphate buffer (pH 6.86). Thus, SAF-HCl salt had a better dissolution rate that that of SAF-HBr salt from 90 min to 120 min. This may be attributed to the solubility advantage of SAF-HCl.
Table 3. Solubility and intrinsic dissolution rate (IDR) of safinamide and its new salts in water and pH 6.86.

| Compound      | Aqueous Solubility (mg/mL) | Solubility at pH 6.86 (mg/mL) | IDR in Aqueous Medium (mg/cm²/min) | IDR at pH 6.86 (mg/cm²/min) |
|---------------|-----------------------------|-------------------------------|-----------------------------------|-----------------------------|
| SAF           | 0.19                        | 0.39                          | 0.013                             | 0.024                       |
| SAF-HCl       | 30.86                       | 26.59                         | 4.16                              | 0.14                        |
| SAF-HBr       | 24.93                       | 16.69                         | 6.03                              | 1.49                        |
| SAF-MA        | Unstable                    | Unstable                      | 0.67                              | 0.037                       |
| SAF-MA-H₂O    | 6.66                        | 5.18                          | 0.64                              | 0.035                       |

Figure 8. Solubility studies in water and pH 6.86 media. SAF, SAF-HCl, SAF-HBr, and SAF-MA-H₂O (n = 6).
Figure 9. Dissolution profiles for SAF, SAF-HCl, SAF-HBr, SAF-MA, and SAF-MA-H2O in water at 37 °C.

Figure 10. Dissolution profiles for SAF, SAF-HCl, SAF-HBr, SAF-MA and SAF-MA-H2O in phosphate buffer pH 6.86 at 37 °C.

3.5. Stability Studies

Drug stability is an important index for evaluating drug shelf life. The accelerated stability tests of SAF and all four salts under different humidity conditions (25 °C/75%, 25 °C/85%, 25 °C/97%) were tested for 14 days. The results from the PXRD analysis indicated that all salts except SAF-MA had good stability under the three humidity conditions (Figures S9–S12). However, the SAF-MA salt was not stable at high humidity (Figure S13) and some of this salt transformed to SAF-MA-H2O. The evidence for this was the characteristic peaks at 7.96, 11.16, 15.76 and 16.22°, which were attributed to the SAF-MA-H2O salt.

4. Conclusions

In summary, four pharmaceutical salts of anti-Parkinson's disease drug safinamide were successfully synthesized and characterized using slow solvent evaporation techniques. The crystal structures and physicochemical properties of these salts were investigated. The solubility studies revealed that SAF-HCl, SAF-HBr, and SAF-MA-H2O salts improved the solubility of this API in water and phosphate buffer (pH 6.86). All salt forms exhibited better dissolution rates than that of SAF. Furthermore, SAF-MA salt completely transformed to SAF-MA-H2O in water and phosphate buffer (pH 6.86). The accelerated stability tests indicated that all salts, except SAF-MA, had good stability. Considering the solubility, dissolution rate, and stability advantages, SAF-HCl, SAF-HBr, and SAF-MA-H2O salts have the potential to be developed into effective oral preparations.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4352/10/11/989/s1, Figure S1: Thermogravimetry (TG) curves of SAF, SAF-HCl, SAF-HBr, SAF-MA, and SAF-MA-H2O salts, Figure S2: PXRD analysis of the residual materials of SAF after 24 h solubility in aqueous and pH 6.86 phosphate buffer medium, Figure S3: PXRD analysis of the residual materials of SAF-HCl after 24 h solubility in aqueous and pH 6.86 phosphate buffer medium, Figure S4: PXRD analysis of the residual materials of SAF-HBr after 24 h solubility in aqueous and pH 6.86 phosphate buffer medium, Figure S5: PXRD analysis of the residual materials of SAF-MA-H2O after 24 h solubility in aqueous and pH 6.86 phosphate buffer medium, Figure S6: PXRD analysis of the residual materials of SAF-MA after 24 h solubility in aqueous and pH 6.86 phosphate buffer medium.
medium, Figure S7: IDR profiles for SAF, SAF-HCl (20 min shown), SAF-HBr (20 min shown), SAF-MA and SAF-MA-H2O salts in water at 37 °C, Figure S8: IDR profiles for SAF, SAF-HCl (30 min shown), SAF-HBr (30 min shown), SAF-MA, and SAF-MA-H2O salts in phosphate buffer pH 6.86 at 37 °C, Figure S9: PXRD profiles for SAF after storage at 25 °C under various RH conditions for 14 days, Figure S10: PXRD profiles for SAF-HCl salt after storage at 25 °C under various RH conditions for 14 days, Figure S11: PXRD profiles for SAF-HBr salt after storage at 25 °C under various RH conditions for 14 days, Figure S12: PXRD profiles for SAF-MA salt after storage at 25 °C under various RH conditions for 14 days. Crystallographic data, deposition number 2010646-2010649, were deposited with the Cambridge Crystallographic Data Centre. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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